



Evidence submitted to the Royal College of Physicians working party on the lifelong impact of air pollution

February 2016

Overview – organisations that submitted evidence

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1 Blizard Institute

Submitted evidence:

- Changing personal exposure to air pollution within a city – PowerPoint
- Changing personal exposure to air pollution within a city – abstract

Changing Personal Exposure to Air Pollution Within a City

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Black carbon

- Main constituent of inhalable fossil fuel-derived particulate matter (<math><10\mu\text{m}</math> in aerodynamic diameter) (PM_{10})
- Taken up by airway macrophages (AMs)
- Inverse relationship between amount of AM black carbon and lung function¹ and mortality²

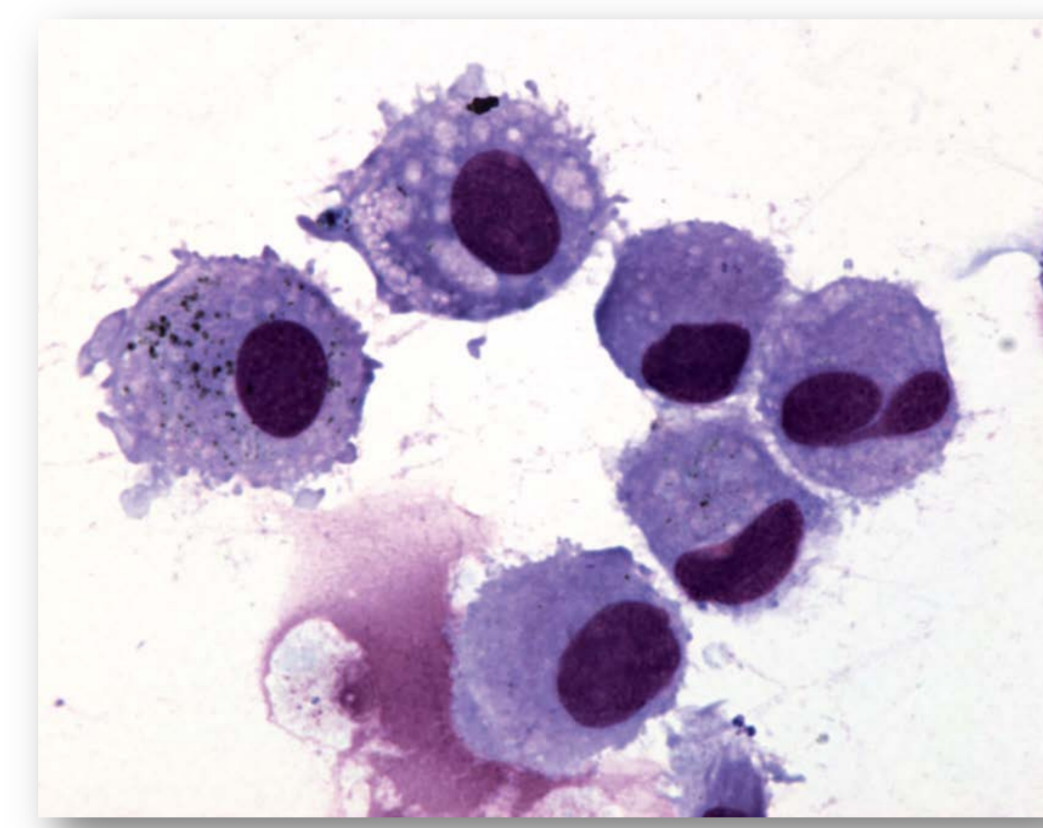


Figure 1: Airway macrophages (AMs) imaged under light microscopy. The black areas on the cytoplasm show uptake of black carbon by the AMs. Figure taken from Nwokoro, C., et al. (2012).

Start



There is currently no data on how much of a reduction in personal exposure to carbon black can be achieved by choosing to regularly move through cities via routes with lower levels of locally generated pollutants.

Methodology

- Two 3rd year medical students were selected to complete a pre-determined route in London

Student Y: Main road (Figure 2)

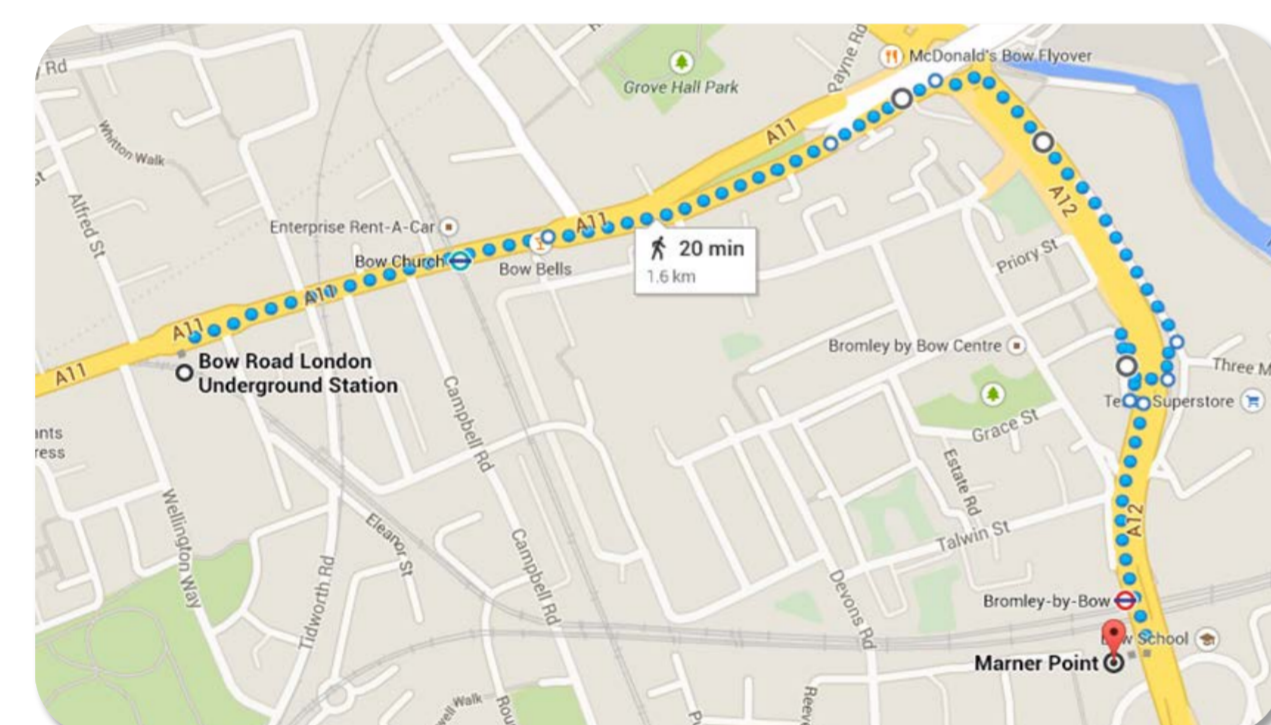


Figure 2: Main road route for Student Y with a total walking distance of 2.98km and a total walking time of approximately 44 minutes. Figure taken from Google Maps.

Student K: Side road (Figure 3)

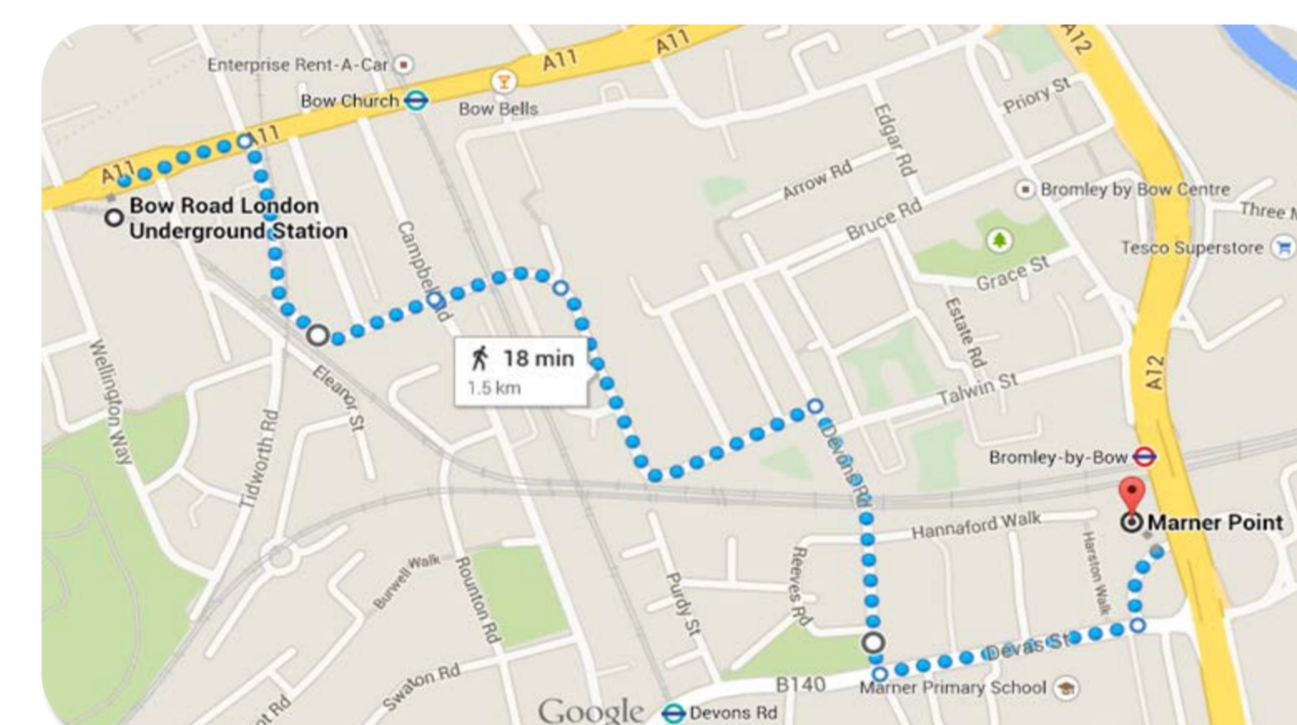


Figure 3: Side road route for Student K with a total walking distance of 3.06km and a total walking time of approximately 46 minutes. Figure taken from Google Maps.

Routes were completed by both students on the same day, within 2 hours of each other. Both routes have similar distance, time taken to complete and weather conditions. Progress was tracked by using *MapMyTracks* application on a smartphone.

Monitoring short-term Black Carbon exposure

Both subjects were given a pocket-sized portable aethalometer (*Magee Scientific AE51*) to monitor personal exposure to BC during the walks.

Airway Macrophage Carbon count

AM samples were collected using sputum induction, processed and placed on slides which were analysed for AM carbon by measuring the area of BC (μm^2) within the AMs.



Figure 4: AE-51 Aethalometer – world's first real time, portable Black Carbon aerosol monitor. The measurement accuracy is of +/- 0.1 $\mu\text{g Eq.C/m}^3$ at 150 ml/min. Figure taken from Ecomasure (2015).

Results

Mean exposure to Black Carbon

Each student did 11 walks over 60 days. Mean exposure to BC walking on a side road (N=11 trips) was 11974 ± 3741 ng per m^3/min as compared to the main road of 38415 ± 35301 ng per m^3/min . $p=0.0226$.

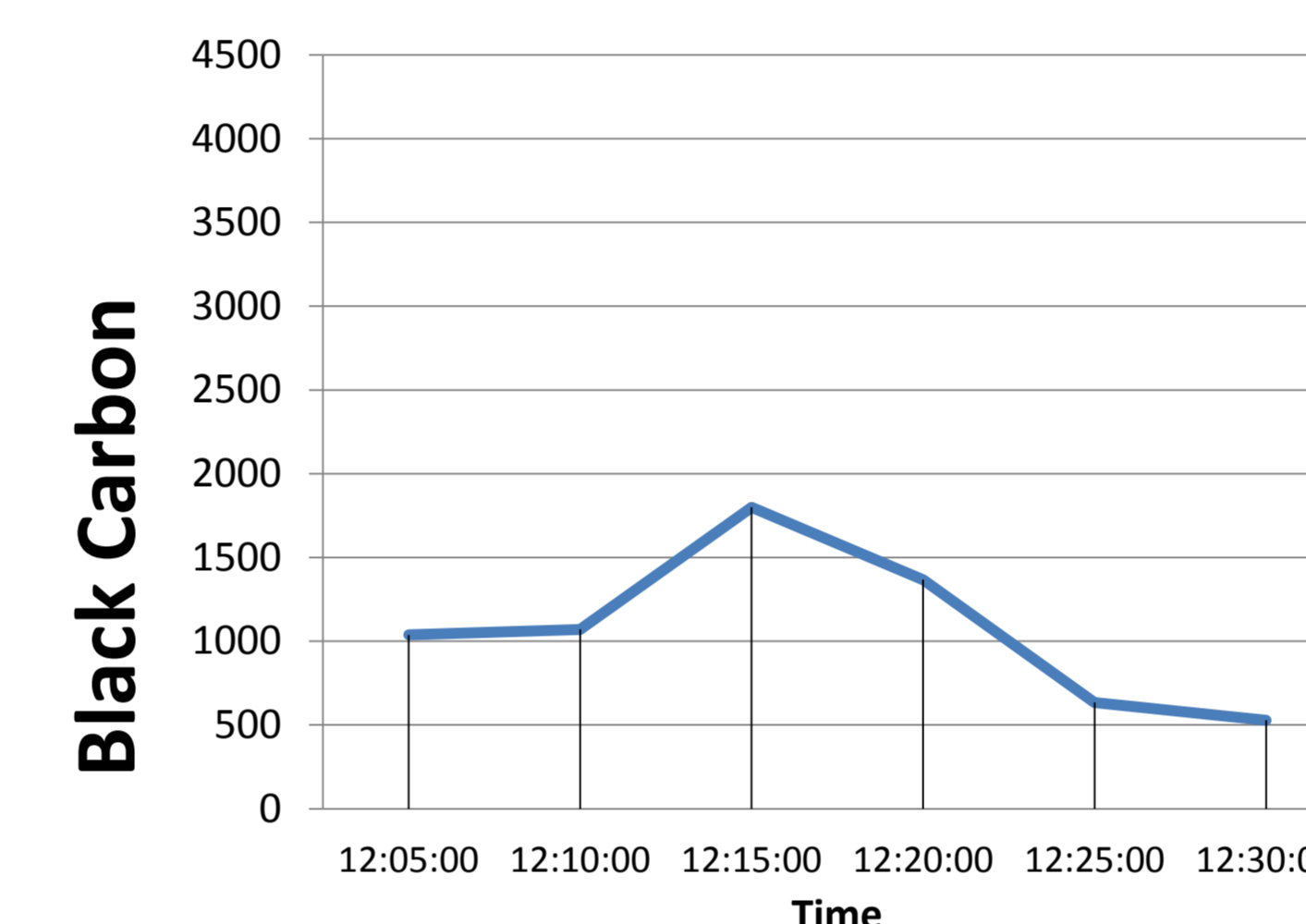


Figure 6: Amount of Black Carbon exposure along the side road measured by the aethalometer on 13/08/14

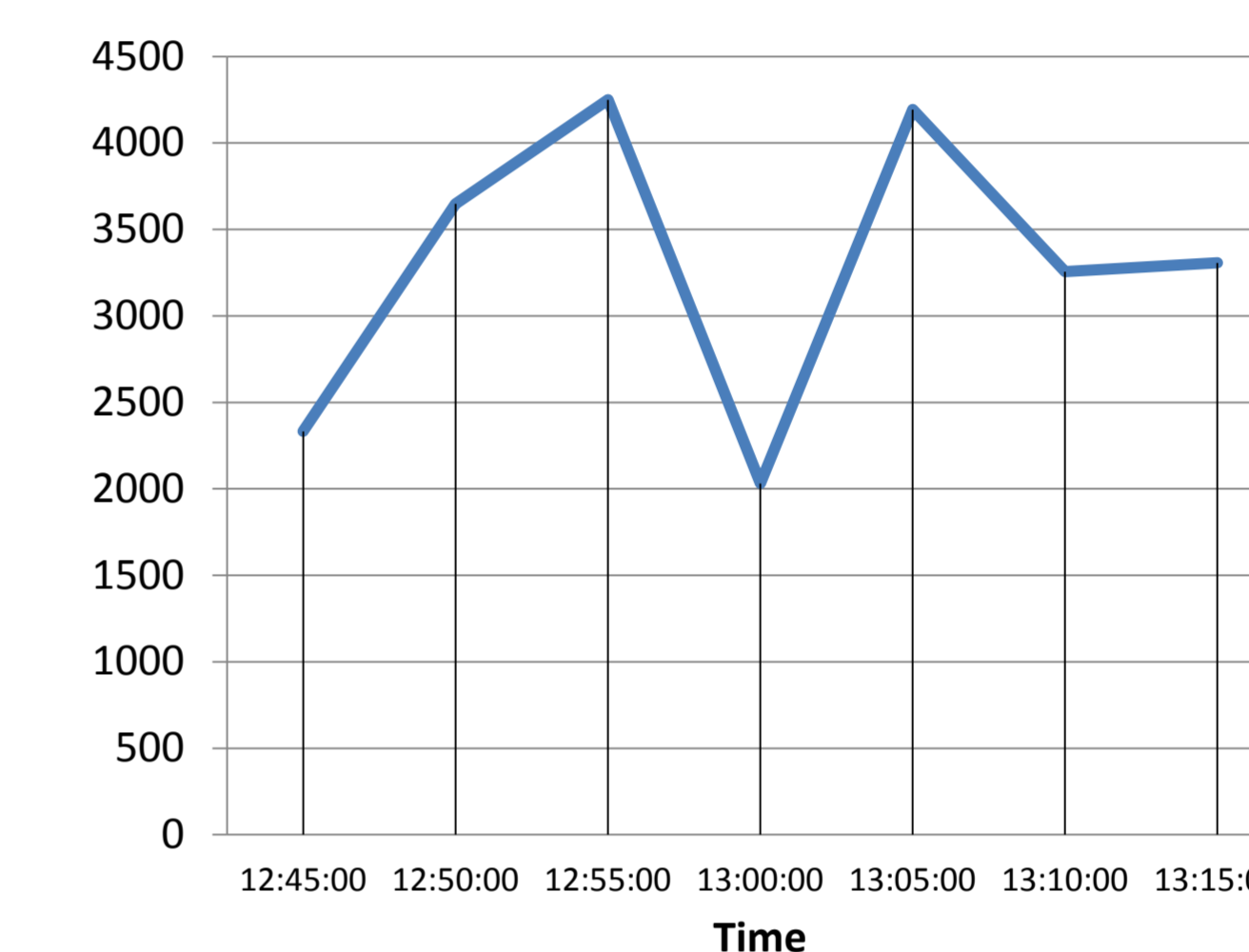


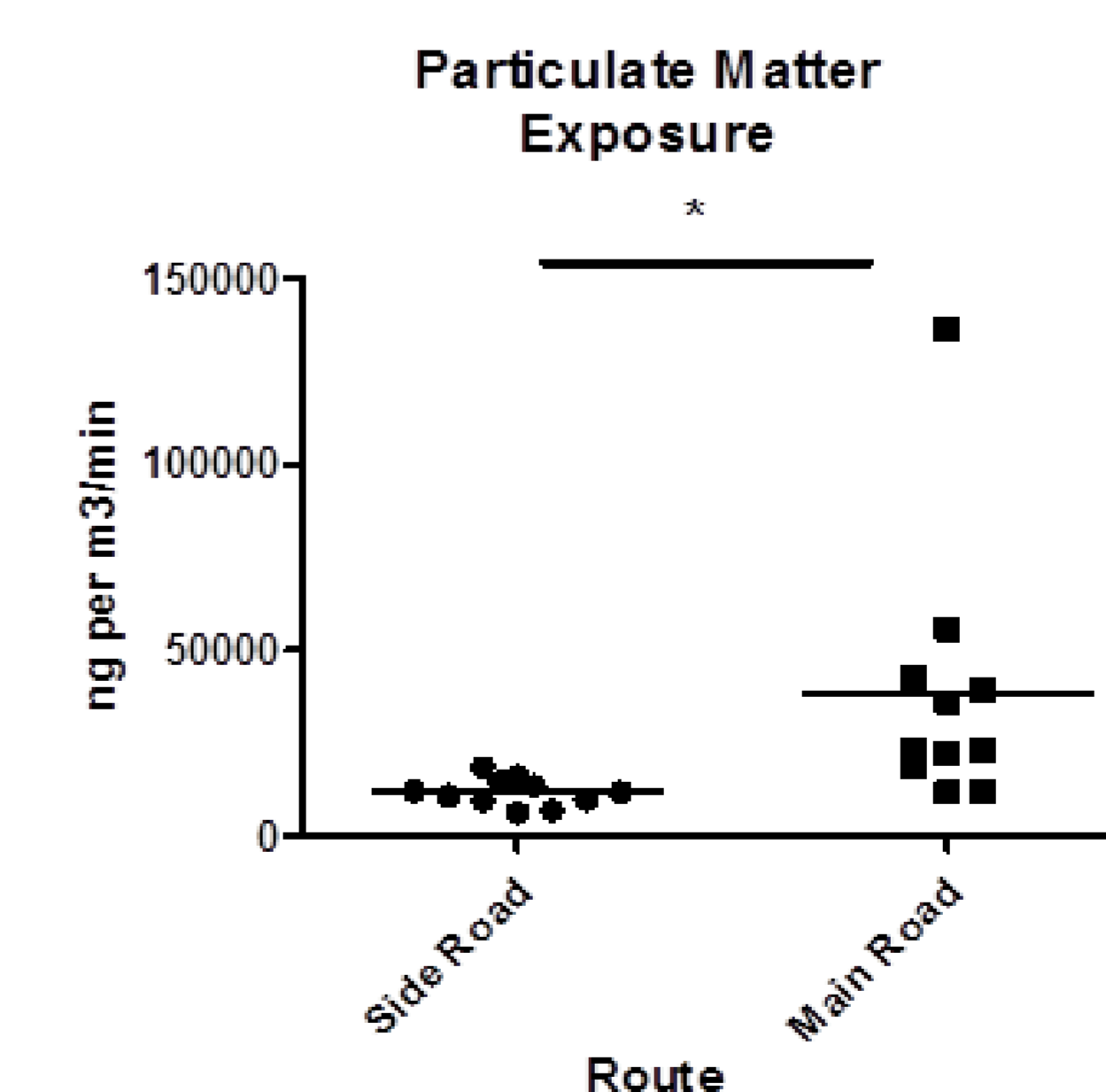
Figure 7: Amount of Black Carbon exposure along the main road measured by the aethalometer on 13/08/14



Side Road

Macrophage black carbon

Main road student: increased from 0.27 to 0.39 μm^2
Side road student: decreased from 0.37 to 0.30 μm^2



Conclusion

We have shown that a **simple intervention** in changing your route can **significantly affect personal pollution exposure** and this is reflected in the macrophage black carbon levels.

We speculate that macrophage black carbon is a useful marker when assessing personalised interventions to improve negative health effects of pollution levels and that interventions to reduce peak PM exposure can be effective on an individual level.



End

References
1. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med.* 2004;351(11):1057-67.
2. Brunekreef B, Beelen R, Hoek G, Schouten L, Bausch-Goldbohm S, Fischer P, et al. Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: the NLCS-AIR study. *Res Rep Health Eff Inst.* 2009(139):5-71; discussion 3-89.

Images
Figure 1: Nwokoro C, Ewin C, Harrison C, Ibrahim M, Dundas I, Dickson I, et al. Cycling to work in London and inhaled dose of black carbon. *Eur Respir J.* 2012;40(5):1091-7.
Figures 2 and 3: GoogleMaps. Google Maps: Google; [cited 2015 27/02]. Available from: <https://www.google.co.uk/maps>.
Figure 4: Ecomasure. AE-51 Aethalometer <http://www.ecomasure.com>; Ecomasure; 2015 [cited 2015 27/02]. Available from: <http://www.ecomasure.com/en/product/ae-51-aethalometer>.

Changing personal exposure to air pollution within a city

Kelvin Miu, Yunshu Ma, Abigail Whitehouse, Naseem Mushtaq, Jonathan Grigg

Background:

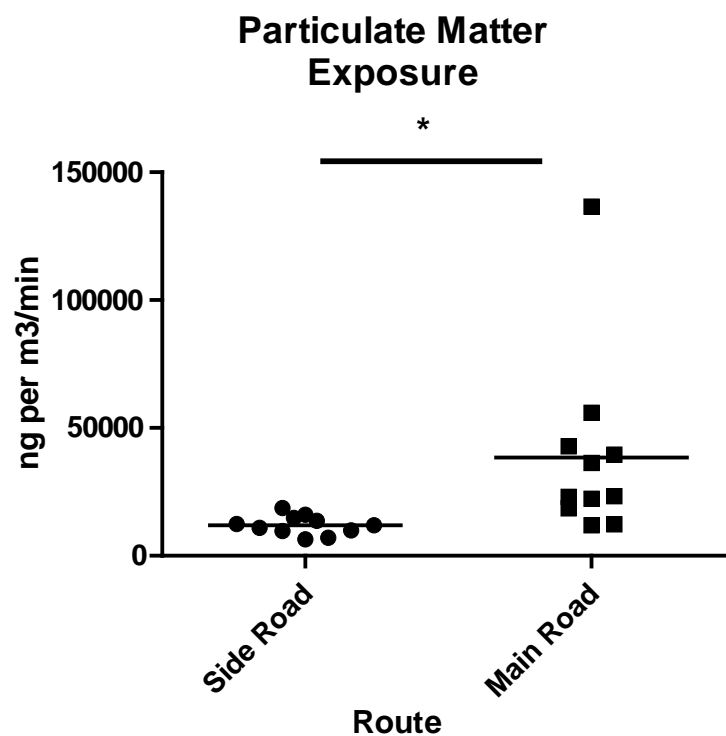
There is currently no data on how much of a reduction in personal exposure to carbon black can be achieved by choosing to regularly move through cities via routes with lower levels of locally generated pollutants. We sought to assess the effect of 2 regular routes to work (high and low) on airway macrophage black carbon – a marker of long term exposure to inhaled fossil-fuel derived particulate matter (PM).

Methods:

Two medical students were recruited living at the same address. One of the students walked on the route along the main road while the other walked on the route along the side road over a 12 week period. Personal exposure was assessed by repeated 24 h personal black carbon. Internal black carbon was assessed by sputum induction and expressed as μm^2 .

Results:

Each student did 11 walks over 60 days. Mean exposure to BC walking on a side road (N=11 trips) was 11974 ± 3741 ng per m^3/min vs 38415 ± 35301 ng per m^3/min . $p=0.0226$. Macrophage black carbon increased from 0.27 to 0.39 μm^2 in the student walking on the main road and decreased from 0.37 to 0.30 in the student walking on the side road. There was no associated change in lung function. There was no difference in the mean time taken to walk the routes (35.27 minutes vs 35 minutes)



Conclusions:

We have shown that a simple intervention in changing your route to and from work can impact on your pollution exposure and this is demonstrated in the macrophage black carbon levels. Personal monitoring is therefore an innovative way to create personalized interventions to improve the impact of pollution on health.

1. Nwokoro, C., et al., *Cycling to work in London and inhaled dose of black carbon*. Eur Respir J, 2012. **40**(5): p. 1091-7.
2. Nwokoro, C., R. Brugha, and J. Grigg, *Alveolar macrophages carbon load: a marker of exposure?* Eur Respir J, 2013. **41**(3): p. 763.

2 British Heart Foundation

Submitted evidence:

- RCP air pollution and health: response from the BHF
- Articles highlighted by BHF-funded researchers



Royal College of Physicians; Air pollution and health

Response from the British Heart Foundation
December 2014

The British Heart Foundation (BHF) is the nation's leading heart charity. We are working to achieve our vision of a world in which people do not die prematurely or suffer from cardiovascular disease. In the fight for every heartbeat we fund ground breaking medical research, provide support and care to people living with cardiovascular disease and advocate for improvement in care and services.

Research shows that air pollution can make existing heart conditions worse and cause cardiovascular events in vulnerable groups. Recent studies have linked air pollution to both increased incidence of heart attacks and an increased rate of hospitalisation of those living with heart failure. There are 2.3 million people in the UK living with coronary heart disease¹ and 7 million living with cardiovascular disease.² Given this large number and the likelihood of their exposure to air pollution, principally from diesel vehicles, therefore the BHF consider this to be a salient issue that must be improved to best support heart patients and the wider UK public. The BHF is therefore calling for the UK Government to reduce the UK's air pollution in as shortest time as possible, with the end goal of meeting the World Health Organization's lower thresholds for emissions.

Since 2010 the BHF has provided £3.2 million for medical research that will help us better understand the link between air pollution and cardiovascular disease and joined the Healthy Air Campaign in the summer of 2013.

Please find below the BHF's policy statement on air pollution which considers the evidence base regarding exposure to air pollution and cardiovascular disease, our advice to heart patients and our policy calls.

¹ CHD GP Register, Quality and Outcomes Framework (4 nations, 2012/13)

² BHF estimate based on latest UK Health Surveys containing CVD fieldwork (2011/12)



Policy statement

Air pollution

Introduction

Research shows that air pollution can make existing heart conditions worse and cause cardiovascular events in vulnerable groups. Recent studies have linked air pollution to both increased incidence of heart attacks and a worsening of heart failure. The association between elevated levels of air pollution and increased cardiac death rates was first recognised in the early 1950s. Since this time scientists have been researching the nature of the link, and the growing evidence confirms a causal relationship.

Policy statement

Background

Research shows that both long-term and short-term exposure to air pollution can make existing heart conditions worse and can cause cardiovascular events including heart attacks amongst vulnerable groups. Given the large number of people living in the UK with cardiovascular disease and the likelihood of their exposure to air pollution, it is imperative the governments and administrations around the UK ensure they are meeting European Union air quality limits and targets as soon as possible to improve air quality.

BHF Research

Since 2010 the BHF has provided £3.2 million for medical research that will help us better understand the link between air pollution and cardiovascular disease. Most of this research has focused on how small particles known as PM_{2.5} can be easily inhaled and affect the function of blood vessels consequently triggering cardiovascular events. Additional research is urgently needed to investigate the independent health impacts of several gaseous pollutants e.g. ozone and nitrogen dioxide.

Government action needed

In light of the growing evidence implicating air pollution as a cause of cardiovascular disease the BHF is calling on the UK Governments to:

- Explore a range of policy options to act quickly to improve UK air quality and meet all EU air quality targets whilst working towards the lower World Health Organisation guidelines.
- Retain legal duty for local authorities to monitor local air quality.
- Make it mandatory for all diesel powered vehicles, regardless of age, to be fitted with a diesel particulate filter (DPF) that meets Euro 6/VI Standards to reduce the harmful high levels of traffic related particle emissions
- Include within MOT test a physical check of all existing DPFs to ensure they are working properly and have not been tampered with.
- Improved warning systems for public about elevated pollution levels

BHF is aware that a by-product of DPFs is increased nitrogen dioxide emissions and of the debate surrounding independent health effects of nitrogen dioxide. We are maintaining a watching brief on the development of academic evidence linking this pollutant to cardiovascular health.

Current advice for heart patients on air pollution

The Department for Food, Environment and Rural Affairs website [UK-AIR](#) provides advice which classifies daily pollution levels as „low,“ „moderate,“ „high“ or „very high.“ At the extreme end of the scale, when air pollution is „very high,“ at risk individuals are advised to „avoid strenuous physical activity“ compared to the general population who are advised to „reduce physical exertion outdoors.“ The BHF support this advice, as well as continuing to advocate the importance of being physically active and run fundraising events such as runs and cycles. Current evidence shows that healthy individuals with no prior history of cardiovascular disease have a low risk of suffering a cardiovascular event following exposure to high levels of air pollution. However, we do advise that those living with heart conditions monitor air pollution levels and amend their physical activity accordingly, such as exercising indoors when air quality is poor. Members of the public can use the UK-AIR postcode finder service to monitor air pollution levels in their area as well as follow [@DefraUKAir](#) Twitter feed and sign up for text alerts. The BBC weather forecast also provides an air quality rating on its online forecast service. However, we do not believe that this advice is currently reaching the population as widely as is needed. Current systems place the onus on individuals to understand the health impacts of pollution and rely heavily on online technology for this information. We would like to see this system improved to ensure advice reaches down to the community level and is easily accessible to the population as a whole.

Background

What is air pollution?

There are two types of air pollution: indoor and outdoor. Indoor pollution is caused by cooking fumes and heating using solid fuels on open fires or traditional stoves. Outdoor air pollution is caused by emissions from industries such as fuel burning for power, households and vehicles.³ Road transport is a major source of outdoor pollution, as vehicle engines release nitrogen oxides, carbon monoxide and particles into the atmosphere. Pollution is made up of many different components, including;

- **Particulate matter (PM)**, consisting of solid and liquid particles such as soot and dust, suspended in air. PM is a component of black carbon.
- **Gases**, such as nitrogen dioxide (NO₂), ozone, sulphur dioxide and carbon monoxide
- **Semi-volatile liquids**, such as methane and benzene.

Particulate Matter

³ Excluding cigarette smoke. Health impacts from cigarette smoke are not included in these definitions. For more information please see our policy statement on [passive smoking](#)

Particles are grouped according to their size, which ranges from clusters of molecules called ultrafine particles (UFPs) with a diameter of 0.1µm or less, through to fine particles with a diameter of 2.5µm or less (PM_{2.5}), and coarse particles with a diameter between 2.5µm and 10µm (PM₁₀).

The majority of research has focused on fine particles and cardiovascular disease, and there is now enough evidence to support a causal link.^{4,5,6} The association with cardiovascular disease and exposure to PM is strongest for exposure to PM_{2.5} and ultrafine particles derived from diesel vehicle exhausts.^{7,8}

Studies suggest that traffic pollution is specifically associated with cardiovascular risk due to the high level of fine and ultrafine particulate matter emitted.⁹ Experts believe this is one of the major public health burdens today because we're all exposed to traffic pollution so often.^{10,11} This is exacerbated by two factors. Firstly, the number of cars on UK roads has risen from 19 to 34.5 million vehicles between 1980 and 2012^{12,13} Secondly, following Government promotion of diesel cars through favourable tax rates based on carbon dioxide emissions, registrations of diesel cars now outstrip petrol.¹⁴

The link to cardiovascular disease

The cardiovascular effects of air pollution were first observed after the major smog that occurred in London in 1952. Based on available data from the previous year, it was estimated that there were 4,000 extra premature deaths attributed to respiratory and cardiovascular disease during the three weeks after the smog began.^{15, 16}

Since the 1970s hundreds of epidemiological studies have demonstrated an association between PM and adverse health effects.¹⁷

Research suggests there are three potential mechanisms by which PM may contribute to cardiovascular disease (CVD):

- PM may stimulate receptors in the lung that then alter the function of our nervous system, causing deleterious changes to our heart rhythm
- Inhaled particles produce inflammation of the lung and inflammatory chemicals may pass into the blood and damage the cardiovascular system

⁴ Committee on the Medical Effects of Air Pollutants (2009) *'The mortality effects of long-term exposure to particulate air pollution in the UK.'*

⁵ American Heart Association (2010) 'Particulate matter air pollution and cardiovascular disease. An update to the scientific statement from the American Heart Association.' <http://europepmc.org/abstract/MED/20458016>

⁶ Pope & Dockery (2006) "Health effects of fine particulate air pollution: Lines that connect." *Air & Waste Management Association* 56:709-742

⁷ Brook et al (2008) „Cardiovascular effects of air pollution." *Clinical science* 115, 175-187

⁸ *ibid*

⁹ Hart JE et al. (2013) „Changes in traffic exposure and the risk of incident myocardial infarction and all-cause mortality." *Epidemiology* 24(5) <http://www.ncbi.nlm.nih.gov/pubmed/23877047>

¹⁰ American Heart Association (2010) 'Particulate matter air pollution and cardiovascular disease. An update to the scientific statement from the American Heart Association.' <http://europepmc.org/abstract/MED/20458016>

¹¹ Dr Nawrot T S et al (2011) „Public health importance of triggers of myocardial infarction: a comparative risk assessment." *The Lancet* Volume:377(9767) [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(10\)62296-9/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)62296-9/abstract)

¹² House of Commons Environmental Audit Committee (2010) „Air Quality Fifth report of the session 2009-10 Vol 1." <http://www.publications.parliament.uk/pa/cm200910/cmselect/cmenvaud/229/22902.htm>

¹³ UK Government (2013) 'Vehicle licensing statistics 2012.' <https://www.gov.uk/government/publications/vehicle-licensing-statistics-2012>

¹⁴ Society of Motor Manufacturers and Traders (2014) 'New Car CO2 Report 2014 The 13th Report' <http://www.smmt.co.uk/co2report/>

¹⁵ Wilkins, E.T. (1954). „Air pollution and the London fog of December, 1952" *J.R. Sanit. Instit.* 1-21

¹⁶ Greater London Authority (2002) "50 years on: The struggle for air quality in London since the great smog of December 1952" http://legacy.london.gov.uk/mayor/environment/air_quality/docs/50_years_on.pdf

¹⁷ For example: Wold, L E. (2010) „Cardiovascular effects of ambient particulate air pollution exposure." *Circulation* 121(25) <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2924678/pdf/nihms-213443.pdf>

- Very small particles may be able to pass into the blood and directly affect blood vessels.¹⁸

The pathways are thought to affect the cardiovascular system by making the fatty deposits in the arteries less stable, narrowing the blood vessels, causing cardiovascular inflammation, and increasing coagulation, blood clots and sensitising the heart to damage. The effects of this include hypertension, atherosclerosis, arrhythmias, myocardial ischemia, heart attacks, heart failure, and strokes.¹⁹

The three mechanisms are not mutually exclusive. They may overlap temporally or be activated at different time points, for example within minutes, hours or days of exposure.²⁰ The types, size and chemical composition of pollutants inhaled may also determine their toxicity and importance of each pathway.²¹

Both long-term and short-term exposure to air pollution has been associated with cardiovascular risk. Short-term exposure to elevated concentrations of particulate matter has been linked with an increase in the risk of heart attacks within a few hours to one day after exposure.²² In 2013 BHF-funded research also found a link between increased hospitalisation rates and poor short-term air quality in those with heart failure, with the highest effects a result of PM_{2.5} from traffic exhaust fumes.²³ A link between short-term exposure and atrial fibrillation (AF) has also been suggested. Research conducted in Boston found that the relative risk of an episode of AF in patients with dual chamber implantable cardioverter-defibrillators (ICDs) increased by 26 per cent for each 6 µg/m³ increase in PM_{2.5} two hours prior to the episode.²⁴

In 2014, the European Study of Cohorts for Air Pollution Effects (ESCAPE) found that long-term exposure to PM_{2.5} is strongly linked to heart attacks and angina.²⁵ Researchers found that a 5 µg/m³ increase in PM_{2.5} was associated with a 13 per cent increased relative risk of coronary events and a 10µg/m³ increase in PM₁₀ was associated with a 12 per cent increased risk of coronary events. The study involved over 100,000 participants with no prior history of heart disease over a ten year period (1997-2007). Worryingly, this study found that the risk of heart attack and angina increased at levels of PM_{2.5} exposure below current EU limit thresholds [see below for EU limits and UK guidelines].²⁶ This mirrors findings from a study conducted in Italy which found that long-term exposure to both PM_{2.5} and NO₂ had a negative association on mortality from coronary heart disease.²⁷

Impacts of air pollution

In 2012 the Global Burden of Disease study stated that outdoor air pollution was the ninth leading cause and indoor air the fourth leading cause of morbidity and mortality worldwide;

¹⁸ Brook et al (2008) 'Cardiovascular effects of air pollution.' *Clinical science* 115, 175-187

¹⁹ Brook et al (2008) 'Cardiovascular effects of air pollution.' *Clinical science* 115, 175-187

²⁰ Langrish JP et al. (2012) „cardiovascular effects of particulate air pollution exposure: time course and underlying mechanisms." *Journal of International Medicine*. 272:224-39.

²¹ Brook et al (2008) *Cardiovascular effects of air pollution*. *Clinical science* 115, 175-187

²² Peters A et al (2001) „Increased particulate air pollution and the triggering of myocardial infarction." *Circulation* 103:2810-2815

²³ Mills, NL et al. (2013) „Global association of air pollution and heart failure: a systematic review and meta-analysis." *The Lancet*, Volume 382 [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(13\)60898-3/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60898-3/fulltext)

²⁴ Link MS et al (2013) 'Acute exposure to air pollution triggers atrial fibrillation.' *Journal of the American College of Cardiology* 62(9) <http://www.ncbi.nlm.nih.gov/pubmed/23770178>

²⁵ Peters A et al (2014) „Long-term exposure to ambient air pollution and incidence of acute coronary events: perspective cohort study and meta-analysis in 11 European cohorts from the ESCAPE project." *British Medical Journal* <http://www.bmj.com/content/348/bmj.f7412>

²⁶ Peters A et al (2014) „Long-term exposure to ambient air pollution and incidence of acute coronary events: perspective cohort study and meta-analysis in 11 European cohorts from the ESCAPE project." *British Medical Journal* <http://www.bmj.com/content/348/bmj.f7412>

²⁷ Cesaroni G. (2013) „Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome." *Environmental Health Perspective* 121(3) <http://www.ncbi.nlm.nih.gov/pubmed/23308401>

estimating that over 3.5million deaths worldwide each year can be attributed to indoor and outdoor pollution.²⁸

According to the Organisation for Economic Co-operation and Development, urban air pollution is set to become the top environmental cause of mortality worldwide by 2050, ahead of dirty water and lack of sanitation.²⁹ At a European level the European Commission's *Clean Air Programme 2013* names air pollution as the number one environmental cause of premature death in the UK, responsible for ten times the toll of road traffic accidents, contributing to over 400,000 premature deaths across the EU in 2010 as well as costing between €330-940 billion when taking into consideration avoidable sickness and decreased productivity.³⁰

In England, the House of Commons Environmental Audit Committee reported that a reduction in man-made PM_{2.5} would increase life-expectancy by 7-8 months—more than the elimination of traffic accidents and passive smoking. (Results are below)³¹

	Reduction in PM_{2.5} (reduction of 10 µg/m3)	Elimination of road traffic accidents	Elimination of passive smoking
Expected gain in life expectancy	7-8 months	1-3 months	2-3 months

Who is at risk?

Increases in acute cardiovascular morbidity and mortality as a result of exposure to high levels of air pollution, are mainly amongst susceptible, but not critically ill, individuals such as older people with existing coronary artery disease.³² Obese people may also be at higher risk.³³ Factors that increase the risk of a heart attack, such as high blood pressure and high cholesterol, may also increase the risk from particles.³⁴

Children are at risk because their lungs are still developing. They also spend more time at high activity levels and can be more likely to have asthma.³⁵ A study in Mexico found that the heart begins to show adverse effects of air pollution in young adults. Researchers believe this may be due to an inflammatory response which leads to chronic inflammation in the heart, although they note that this inflammation doesn't appear to create any immediate harm.³⁶

The BHF has recently funded research to help us understand the impact exposure to pollutants has on fire-fighters' cardiovascular health. We know that fire-fighters are at an increased risk of heart attack during rescue and duties. The research findings are expected to be published later this year.

Policy Context

²⁸ Lim S et al. (2012) „A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010): a systematic analysis of the Global Burden of Disease Study 2010." *The Lancet* 380: 2224-60 <http://download.thelancet.com/pdfs/journals/lancet/PIIS0140673612617668.pdf?id=baaZsePJpxz4l-p3zKhsu>

²⁹ The OECD Environment Outlook 2050 available at http://www.oecd.org/document/11/0,3746,en_2649_37465_49036555_1_1_1_37465,00.html.

³⁰ European Commission (2013) „A Clean Air Programme for Europe" <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2013:0918:FIN:EN:PDF>

³¹ House of Commons Environmental Audit Committee (2010) „Air Quality Fifth report of the session 2009-10 Volume 1." <http://www.publications.parliament.uk/pa/cm200910/cmselect/cmenvaud/229/22902.htm>. Evidence provided by Department of Health

³² Ibid

³³ Ibid

³⁴ Air Now. „Particle pollution and your health." Accessed at http://www.airnow.gov/index.cfm?action=particle_health_page1#3

³⁵ Ibid

³⁶ Federation of American Societies for Experimental Biology (2010, April 28). *Mexico City air pollution adversely affects the hearts of young people.* *ScienceDaily*. Retrieved May 19, 2010, from <http://www.sciencedaily.com/releases/2010/04/100428153256.htm>

As air pollution is a global issue the World Health Organisation sets recommended limits for levels in its Air Quality Guidelines.³⁷ The limits recommended by WHO are substantially lower than the current limits set by the European Union (EU) and implemented in UK legislation. It is estimated that some 40 million people in the 115 largest cities in the EU are exposed to air exceeding WHO guideline values for at least one pollutant.³⁸ The United Nations Economic Commission for Europe also plays a key role in legislating for better air quality under the Convention on Long Range Transboundary Air Pollution. This acknowledges that as a global issue States must co-operate to achieve better air quality. This body also convenes the Gothenburg Protocol. This important piece of legislation sets targets that guides European law on emission limits. A review of the Gothenburg Protocol took place in 2012 and the ratification of this review has been included in the European Commission's 2013 Clean Air Quality Package.³⁹

The EU regulates air quality through a number of directives. The Ambient Air Quality Directive (2008/50/EC) and the Fourth Daughter Directive (2004/107/EC) are the key pillars of EU legislation which govern air quality. The National Emission Ceilings Directive (2001/81/EC) sets emission limits that the UK is required to meet.⁴⁰

Current EU targets and limits for key pollutants⁴¹

Pollutant	Concentration	Averaging period	Timeline	Permitted exceedances (per annum)	UK compliance 2012 ⁴²
PM _{2.5}	25 µg/m ³	1 year	Target from 2010 Limit from 2015	n/a	<input checked="" type="checkbox"/>
PM ₁₀	50 µg/m ³	24 hours	Limit from 2005	35	<input checked="" type="checkbox"/>
	40 µg/m ³	1 year	Limit from 2005	n/a	<input checked="" type="checkbox"/>
NO ₂	200 µg/m ³	1 hour	Limit value from 2010	18	2 zones failed
	40 µg/m ³	1 year	Limit value from 2010	n/a	34 failed zones

The responsibility to comply with EU targets is devolved in the UK. As well as having responsibility for compliance in England the Department for Environment, Food and Rural Affairs (DEFRA) also co-ordinates the assessment of air quality plans for the UK as a whole. Each local authority in the UK is responsible for monitoring and reporting compliance with EU regulations. This is then fed back to the EU annually. The UK Government is answerable overall to the EU for failure to comply with the EU's limits and deadlines. In 2013 DEFRA launched a consultation

³⁷ World Health Organisation (2005) „WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide.“ http://whqlibdoc.who.int/hq/2006/WHO_SDE_PHE_OEH_06.02_eng.pdf

³⁸ World Health Organisation. „Data and Statistics“ <http://www.euro.who.int/en/what-we-do/health-topics/environment-and-health/air-quality/data-and-statistics>

³⁹ European Commission (2013) 'A Clean Air Programme for Europe' <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2013:0918:FIN:EN:PDF>

⁴⁰ European Commission (2013) 'New Air Quality Directive' <http://ec.europa.eu/environment/air/quality/legislation/directive.htm>

⁴¹ European Commission. „Air Quality Standards.“ <http://ec.europa.eu/environment/air/quality/standards.htm>

⁴² Department for Environment Food and Rural Affairs. (2013) 'Air pollution in the UK 2012.' http://uk-air.defra.gov.uk/library/annualreport/air_pollution_uk_2012_Compliance_Assessment_Summary.pdf

proposing the removal of the duty on local authorities to perform this monitoring function, but were forced to reconsider as a result of strong opposition.⁴³

The most recent UK Air Quality Strategy was published in 2007 and is now vastly out of date. The Strategy document outlines current policies along with proposed new measures. These focus on reducing emissions from transport. For example, by designing transport infrastructure to improve air quality, providing duty incentives for cleaner fuels, and promoting the uptake of less polluting vehicles. The document describes an „exposure reduction“ strategy to tackle PM exposure. Whereas other pollutants will be tackled in local hotspots of high concentrations, PM is to be reduced nationally. This is because there is no safe threshold for this pollutant and driving improvement across the UK will help maximise the benefits to public health.⁴⁴ Similarly, the European Clean Air Quality Package is focused towards reducing emission at the source. In May 2014 the Environment Audit Commission announced an inquiry to assess the steps taken by the UK Government following the Committee’s recommendations of 2010 and 2011. After initially refusing to give oral evidence at the Inquiry, Boris Johnson, Mayor of London, finally agreed to attend. The Inquiry is due to commence on 25 June. The BHF submitted written evidence to this Inquiry.

In May 2013 the European Supreme Court ruled that the UK Government were in breach of EU regulations for NO₂ as 40 of the 43 air quality zones in Britain exceeded the EU NO₂ limits. Furthermore Government plans meant that 16 of the 43 areas would not meet limits until 2020 and London until 2025, a full 15 years after the EU deadline. The European Commission launched legal proceedings against the UK Government on 20 February 2014, the outcome of which could amount to a substantial multi-million pound fine.⁴⁵

2013 was the EU’s „Year of Air“ which aimed to review existing evidence on the link between air pollution and health and subsequently review their air quality policy.

In December 2013 the European Commission launched their Air Quality Package which proposed the following; The „Clean Air Programme for Europe“ document, which outlines key problems and sets new interim objectives up to 2030; a revised National Emission Ceilings Directive containing updated national ceilings for key air pollutants (including PM_{2.5} and nitrogen oxides) for 2020 and 2030; a new directive for medium-sized Combustion Plants and a ratification proposal for the 2012 amended Gothenburg Protocol.

NGO’s including Client Earth, European Environmental Bureau and AirClim have criticised the package as „too little too late“ arguing that in prolonging the deadline to 2030 for compliance and failing to propose a revised Ambient Air Quality Directive, the EU have bowed to industry pressure.⁴⁶ This package is now being negotiated by member states which could take up to three years.

Diesel Particulate Filters

A diesel particulate filter (DPF) is a device that filters PM from exhaust fumes. It does this by trapping solid particles while letting gases escape. Like any other filter DPFs need to be emptied regularly, this is done by a process called regeneration. This involves burning the soot to a gas at

⁴³ Department for Environment Food and Rural Affairs. (2013) *Local Air Quality Management Review: Summary of responses and government reply* https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/265819/laqm-sum-resp-20131213.pdf

⁴⁴ Department for Environment Food and Rural Affairs. (2007) *Air Quality Strategy*

<http://archive.defra.gov.uk/environment/quality/air/airquality/strategy/documents/air-qualitystrategy-vol1.pdf>

⁴⁵ European Commission (2014) „Commission takes action against UK for persistent air pollution problems.“

http://europa.eu/rapid/press-release_IP-14-154_en.htm

⁴⁶ European Environment Bureau (2014) *NGO Assessment of the European Year of Air: Achievements, failures and next steps.* <http://www.eeb.org/?LinkServID=13110E1F-5056-B741-DB5B8C89AC46D071&showMeta=0&aa>

a high temperature, which leaves behind only a small amount of residue. Failure to do so can lead to DPFs being less effective.⁴⁷

Under Euro Standards it has been mandatory for all new buses and HGVs to be fitted with a DPF since 2006 and for all new diesel cars since 2011.⁴⁸ From February 2014 a visual check for modification or removal of DPFs will be included as part of the MOT test. However, no efficiency or physical examination is included; meaning modification and inefficient DPFs can be missed. This is a watering down of the Department for Transport's original proposal of a full efficiency check.⁴⁹ Importantly older vehicles which are still on the UK's roads that were manufactured under previous Euro Standards do not have to be fitted with a DPF.

Research funded by BHF has recommended that DPFs are a highly efficient method of reducing particle emissions from diesel engines. As there is no threshold below which PM is deemed safe, further reduction below EU limits could help prevent several adverse cardiovascular effects.⁵⁰ DPFs would significantly reduce the levels of PM_{2.5} and ultra-fine particles in the atmosphere close to busy roads. **The BHF therefore believes that all diesel vehicles regardless of age should be fitted with a DPF that meets Euro Standard 6/VI requirements. We believe that this should be enforced over the next 3 years as a mandatory part of the MOT test to ensure road worthiness of vehicles.** Euro 6 Standards count total particle emission numbers rather than measuring by mass. This ensures the smallest particles, which are most easily inhaled, are included within the Standards. DPFs are expensive to fit therefore the Government should investigate options to subsidise retrofitted DPFs as an effective part of their Air Quality Strategy.

The BHF acknowledges that a side effect of the regeneration process is an increased production of NO₂. There is currently a debate on the health impact of NO₂, with some academic studies likening the impact to that of PM_{2.5}.⁵¹ However there is also contradictory evidence that disputes an independent health impact on the cardiovascular system from NO₂.⁵² This is an area where greater research is urgently needed to further understand the independent health impact on the cardiovascular system of this pollutant. The UK Government's Committee of the Medical Effects of Air Pollution is currently considering this and a report is expected late 2014/early 2015. The BHF will monitor the emerging evidence.

BHF Activity

- We are funding research to establish the mechanistic link between long and short-term exposure and cardiovascular disease and the effect that air pollution has on the blood vessels. This research is currently focusing on the public health questions raised by this and identifying novel solutions to reduce the harmful effects such as removing toxic constituents from fuels, interventions, alternative fuels and susceptible populations. This is led by BHF Chair of Cardiology Professor David Newby at the University of Edinburgh.
- In 2010 BHF-funded research found some evidence that wearing a highly efficient facemask may help protect against the harmful effects of pollution for people with existing coronary heart disease.⁵³ However, the research was carried out in Beijing where levels

⁴⁷ UK Government (2013) 'Diesel Particulate Filters'

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/263018/diesel-particulate-filters-guidance.pdf

⁴⁸ Client Earth 'Reducing Particulate Matter Emissions from Diesel Vehicles and Equipment.'

<http://healthyair.org.uk/documents/2013/10/black-carbon-retrofit-guidance.pdf>

⁴⁹ The Telegraph (2014) 'DPF removal; the facts' <http://www.telegraph.co.uk/motoring/10573720/DPF-removal-the-facts.html>

⁵⁰ Newby, D, E. (2011) „Particle traps to prevent adverse vascular and prothrombotic effects of diesel engine exhaust inhalation in men.“ *Circulation* April.

⁵¹ Faustini, A et al (2014) „Nitrogen dioxide and mortality: review and meta-analysis of long-term studies.“ *European Respiratory Journal* Feb

⁵² Langrish, J P et al. (2010) „Exposure to nitrogen dioxide is not associated with vascular dysfunction in man.“ *Inhalation Toxicology*, 22(3)

⁵³ British Heart Foundation (2010) *Press release*: <http://www.bhf.org.uk/media/news-from-the-bhf/news-archive/pollution.aspx>

of pollution are very high. At present there is not enough evidence to advise the use of face masks in the UK.

- In 2013 the BHF joined the Healthy Air Campaign, a coalition of organisations including Client Earth, Clean Air for London, Asthma UK and the Climate and Health Council. This campaign group is focused on improving air quality across the UK.

Case study

“I try to live a heart healthy lifestyle and being physically active is an important part of that.

I love getting out and about on my bike but I hate the pollution.

When you’re cycling you are exposed to everything. There’s nothing worse than being hit straight in the face with warm exhaust fumes, especially knowing the harm that they can do your health.

I do what I can to avoid it, using smaller roads and cycling in parks and green spaces as much as I can. But sadly you can’t always avoid the busy roads and this put me off taking the kids out cycling.

The Government need to step up and improve our air quality as soon as possible.”



Graham, Cyclist

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 13, 2007

VOL. 357 NO. 11

Ischemic and Thrombotic Effects of Dilute Diesel-Exhaust Inhalation in Men with Coronary Heart Disease

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ABSTRACT

BACKGROUND

Exposure to air pollution from traffic is associated with adverse cardiovascular events. The mechanisms for this association are unknown. We conducted a controlled exposure to dilute diesel exhaust in patients with stable coronary heart disease to determine the direct effect of air pollution on myocardial, vascular, and fibrinolytic function.

METHODS

In a double-blind, randomized, crossover study, 20 men with prior myocardial infarction were exposed, in two separate sessions, to dilute diesel exhaust (300 μ g per cubic meter) or filtered air for 1 hour during periods of rest and moderate exercise in a controlled-exposure facility. During the exposure, myocardial ischemia was quantified by ST-segment analysis using continuous 12-lead electrocardiography. Six hours after exposure, vasomotor and fibrinolytic function were assessed by means of intraarterial agonist infusions.

RESULTS

During both exposure sessions, the heart rate increased with exercise ($P < 0.001$); the increase was similar during exposure to diesel exhaust and exposure to filtered air ($P = 0.67$). Exercise-induced ST-segment depression was present in all patients, but there was a greater increase in the ischemic burden during exposure to diesel exhaust (-22 ± 4 vs. -8 ± 6 millivolt seconds, $P < 0.001$). Exposure to diesel exhaust did not aggravate preexisting vasomotor dysfunction, but it did reduce the acute release of endothelial tissue plasminogen activator ($P = 0.009$; 35% decrease in the area under the curve).

CONCLUSIONS

Brief exposure to dilute diesel exhaust promotes myocardial ischemia and inhibits endogenous fibrinolytic capacity in men with stable coronary heart disease. Our findings point to ischemic and thrombotic mechanisms that may explain in part the observation that exposure to combustion-derived air pollution is associated with adverse cardiovascular events. (ClinicalTrials.gov number, NCT00437138.)

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N Engl J Med 2007;357:1075-82.

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THE WORLD HEALTH ORGANIZATION (WHO) estimates that air pollution is responsible for 800,000 premature deaths worldwide each year.¹ Short-term exposure to air pollution has been associated with increases in cardiovascular morbidity and mortality, with deaths due to ischemia, arrhythmia, and heart failure.² In a large cohort study from the United States, Miller et al. recently reported that long-term exposure to air pollution increases the risk of death from cardiovascular disease by 76%.³ These associations are strongest for fine particulate air pollutants (particulate matter of less than 2.5 μm in aerodynamic diameter [$\text{PM}_{2.5}$]), of which the combustion-derived nanoparticulate in diesel exhaust is an important component.⁴ Substantial improvements in air quality have occurred in the developed world over the past 50 years, yet the association between $\text{PM}_{2.5}$ and mortality has no apparent threshold and is evident below current air-quality standards.⁵

Preclinical models of exposure to particulate air pollution demonstrate accelerated atherosclerotic plaque development⁶ and increased *in vitro*⁷ and *in vivo*⁸ platelet aggregation. Epidemiologic and observational clinical studies suggest that exposure to air pollution may worsen symptoms of angina,⁹ exacerbate exercise-induced myocardial ischemia,^{10,11} and trigger acute myocardial infarction.^{12,13} These clinical findings are limited by imprecision in the measurement of pollution exposure, the effect of potential confounding environmental and social factors, and the lack of mechanistic data.¹⁴ Controlled exposures to air pollutants can help address these shortcomings by providing a precisely defined exposure in a regulated environment that facilitates investigation with validated biomarkers and surrogate measures of cardiovascular health. Using a carefully characterized exposure system, we have previously shown that exposure to dilute diesel exhaust in healthy volunteers causes lung inflammation,¹⁵ depletion of airway antioxidant defenses,¹⁶ and impairment of vascular and fibrinolytic function.¹⁷

To our knowledge, there have been no controlled exposures in patients with coronary heart disease, an important population that may be particularly susceptible to the adverse cardiovascular effects of air pollution. We assessed the effect of inhalation of dilute diesel exhaust on myocardial, vascular, and fibrinolytic function in a population of patients with stable coronary heart disease.

METHODS

SUBJECTS

Twenty men with stable coronary artery disease participated in this study, which was performed with the approval of the local research ethics committee, in accordance with the Declaration of Helsinki, and with the written informed consent of all participants.

All the men had proven coronary heart disease, with a previous myocardial infarction (>6 months before enrollment) treated by primary angioplasty and stenting, and were receiving standard secondary preventive therapy. Men with angina pectoris (Canadian Cardiovascular Society class ≥ 2), a history of arrhythmia, diabetes mellitus, uncontrolled hypertension, or renal or hepatic failure, as well as those with unstable coronary disease (acute coronary syndrome or symptoms of instability 3 months before enrollment), were excluded. All eligible volunteers were invited to a prestudy screening for exercise stress testing; subjects who were unable to achieve stage 2 of the Bruce protocol or who had marked changes on an electrocardiogram (left bundle-branch block, early ST-segment depression >2 mm) and those in whom hypotension developed were excluded. Current smokers and men with asthma, substantial occupational exposure to air pollution, or an intercurrent illness were also excluded from the study.

STUDY DESIGN

Using a randomized, double-blind, crossover study design, we evaluated the subjects in two 8 a.m. sessions at least 2 weeks apart. In each session, the subjects were exposed to controlled amounts of dilute diesel exhaust or filtered air. Each subject was exposed for 1 hour in an exposure chamber, as previously described.¹⁵ During each exposure, the subjects performed two 15-minute periods of exercise on a bicycle ergometer separated by two 15-minute periods of rest. For each subject, the ergometer workload was calibrated to achieve a ventilation of 15 liters per minute per square meter of body-surface area to ensure a similar exposure on both occasions. The workload was constant for both exposures and was equivalent to stage 2 of the Bruce protocol (range, 110 to 150 watts; 5 to 7 metabolic equivalents). All subjects were fitted with 12-lead Holter electrocardiographic monitors (Medical Lifecard 12 Digital Holter Recorder, Del Mar Reynolds). In accordance with

previous exposure studies in healthy volunteers, vascular assessments were made 6 to 8 hours after exposure to diesel exhaust or filtered air.¹⁷

DIESEL-EXHAUST EXPOSURE

The diesel exhaust was generated from an idling Volvo diesel engine (Volvo TD45, 4.5 liters, 4 cylinders, 680 rpm) from low-sulfur gas-oil E10 (Preem), as described previously.¹⁵ More than 90% of the exhaust was shunted away, and the remainder diluted with filtered air heated to 20°C (relative humidity approximately 50%) before being fed into a whole-body exposure chamber (3.0 m by 3.0 m by 2.4 m) at a steady-state concentration.

The chamber was monitored continuously for pollutants, with exposures standardized with the use of nitrogen oxide concentrations to deliver a particulate matter concentration of 300 μg per cubic meter (median particle diameter, 54 nm; range, 20 to 120). There was little variation between exposures in the mean (\pm SE) number of particles ($1.26\pm 0.01\times 10^6$ particles per cubic centimeter) or in the concentrations of nitrogen oxide (4.45 ± 0.02 ppm), nitrogen dioxide (1.01 ± 0.01 ppm), nitric oxide (3.45 ± 0.03 ppm), carbon monoxide (2.9 ± 0.1 ppm), and total hydrocarbon (2.8 ± 0.1 ppm). The predominant polycyclic aromatic hydrocarbons (approximately 90% of the total) were phenanthrene, fluorene, 2-methylfluorene, dibenzothiophene, and different methyl-substituted phenanthrenes. Only a minor fraction of polycyclic aromatic hydrocarbons (3.5%) was associated with particulate matter: 0.04% total particulate matter and 0.06% particulate-matter organic fraction. The concentration of particulate matter of less than 10 μm in aerodynamic diameter (PM_{10}) in the exposure chamber exceeded the WHO air-quality standard of 50 μg per cubic meter by a factor of 6, and the nitrogen dioxide concentration exceeded the WHO standard of 0.105 ppm by a factor of 10.¹⁸

VASCULAR STUDY

All subjects underwent brachial-artery cannulation with a 27-standard wire-gauge steel needle. After a 30-minute baseline saline infusion, subjects were given infusions of acetylcholine at rates of 5, 10, and 20 μg per minute (endothelium-dependent vasodilator, Clinalfa), bradykinin at rates of 100, 300, and 1000 pmol per minute (endothelium-dependent vasodilator that releases tissue plasminogen activator [t-PA], Clinalfa), and sodium nitroprusside at rates of 2, 4, and 8 μg per minute

Table 1. Baseline Characteristics of the 20 Subjects with Coronary Heart Disease.*

Characteristic	Value
Age (yr)	60 \pm 1
Smoking history (no. of subjects)	
Nonsmoker	12
Former smoker	8
Current smoker	0
Hypertension (no. of subjects)	8
Height (cm)	173 \pm 6
Weight (kg)	79 \pm 3
Body-mass index	27 \pm 1
Time since index infarction (mo)	35 \pm 4
Coronary angiographic findings	
No. of diseased vessels	
1	13
2	6
3	1
Culprit lesion (no. of subjects)	
Left anterior descending coronary artery	14
Circumflex coronary artery	4
Right coronary artery	2
Cholesterol (mg/dl)	
Total	173 \pm 6
LDL	100 \pm 8
HDL	48 \pm 2
Triglycerides (mg/dl)	128 \pm 23
Fasting glucose (mg/dl)	102 \pm 6
Medications (no. of subjects)	
Aspirin	20
Statin	18
Beta-blocker	15
ACE inhibitor or angiotensin-receptor blocker†	4

* Plus–minus values are means \pm SE. The body-mass index is the weight in kilograms divided by the square of the height in meters. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, and ACE angiotensin-converting enzyme. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

† ACE inhibitor therapy was withdrawn 7 days before each vascular study. All other regular medications were continued throughout the study.

(endothelium-independent vasodilator, David Bull Laboratories); each infusion was given for 6 minutes. Infusions of the three vasodilators were separated by 20-minute saline infusions and given in a randomized order. Therapy with angiotensin-converting-enzyme inhibitors was withdrawn

Table 2. Effect of Exercise on Heart Rate and ST Segment in the 20 Subjects during Exposures to Filtered Air and Diesel Exhaust.*

Characteristic	Filtered Air	Diesel Exhaust	P Value†
Exercise phase 1			
Heart rate — bpm			
Baseline	63±2	61±2	0.24
Maximum	87±3	86±3	0.67
Maximum ST-segment change (μV)			
Lead II	-28±13	-56±10	0.03
Lead V ₂	-28±10	-41±12	0.18
Lead V ₅	-14±8	-33±9	0.04
Change in ischemic burden (mVsec)			
Lead II	-11±5	-23±4	0.004
Lead V ₂	-13±5	-21±6	0.04
Lead V ₅	-4±3	-12±4	0.01
Exercise phase 2			
Heart rate (bpm)			
Baseline	67±2	65±2	0.35
Maximum	91±3	87±3	0.12
Maximum ST-segment change (μV)			
Lead II	-17±15	-49±12	0.006
Lead V ₂	-18±12	-41±13	0.04
Lead V ₅	-7±9	-28±10	0.02
Change in ischemic burden (mVsec)			
Lead II	-8±6	-22±4	0.0007
Lead V ₂	-11±5	-20±6	0.02
Lead V ₅	-2±3	-12±5	0.006

* Plus-minus values are means ±SE; mVsec denotes millivolt seconds.

† P values were calculated with Student's t-test.

7 days before each vascular study, because it augments bradykinin-induced release of endothelial t-PA.¹⁹ All other medications were continued throughout the study.

Forearm blood flow was measured in both arms by venous occlusion plethysmography with the use of mercury-in-Silastic strain gauges, as described previously.²⁰ Heart rate and blood pressure in the noninfused arm were monitored at intervals throughout each study while the subject was in the supine position, with the use of a semi-automated, noninvasive oscillometric sphygmomanometer.

FIBRINOLYTIC AND INFLAMMATORY MARKERS

Blood (10 ml) was withdrawn into acidified buffered citrate (Stabilyte tubes, Biopool International)

for t-PA assays and into citrate (BD Vacutainer) for plasminogen activator inhibitor type 1 (PAI-1) assays. Plasma t-PA and PAI-1 antigen concentrations were determined by means of enzyme-linked immunosorbent assays (TintElize t-PA, Biopool EIA; Coaliza PAI-1; and Chromogenix AB). Serum C-reactive protein concentrations were measured with an immunonephelometric assay (BN II nephelometer, Dade Behring).

DATA ANALYSIS

Electrocardiographic recordings were analyzed with the use of the Medical Pathfinder Digital 700 Series Analysis System (Del Mar Reynolds). ST-segment deviation was calculated by comparing the ST segment during each 15-minute exercise test with the average ST segment for the 15-minute period immediately before the start of the exposure. The ST-segment amplitude was determined at the J point plus 80 msec. The ischemic burden during each exercise test was calculated as the product of the change in ST-segment amplitude and the duration of exercise. Leads II, V₂, and V₅ were selected a priori for ST-segment analysis to reflect separate regions of myocardium. The maximum ST-segment depression and ischemic burden were determined for these leads individually and as a composite.

Plethysmographic data and net t-PA release were determined as described previously.^{20,21}

STATISTICAL ANALYSIS

Continuous variables are reported as means ±SE. Analysis of variance with repeated measures and a two-tailed Student's t-test were performed as appropriate with the use of GraphPad Prism software. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Subjects were all middle-aged men with predominantly single-vessel coronary artery disease (Table 1). They reported no symptoms of angina and had no major arrhythmias during exposure or in the subsequent 24 hours.

MYOCARDIAL ISCHEMIA

The heart rate increased with exercise during exposures to diesel exhaust and filtered air (P<0.001 for both comparisons with the baseline rates; P=0.67 for the comparison of rates during exposure to diesel exhaust and during exposure to filtered

air) (Table 2). Myocardial ischemia was detected during exercise in all subjects, with greater maximum ST-segment depression during exposure to diesel exhaust than during exposure to filtered air (Table 2 and Fig. 1A and 1B) ($P<0.05$). The ischemic burden induced by exercise was greater during exposure to diesel exhaust (Fig. 1C).

VASOMOTOR FUNCTION

There were no significant differences in resting heart rate, blood pressure, or baseline blood flow in the noninfused forearm between or during the two study visits. Although there was a dose-dependent increase in blood flow with each vasodilator ($P<0.001$ for all comparisons), neither endothelium-dependent nor endothelium-independent vasodilatation was affected by inhalation of diesel exhaust (Fig. 2). Comparison of these data with the findings in a contemporary reference population of healthy male volunteers (mean age, 53 ± 4 years) showed impaired vasodilatation in response to acetylcholine ($P=0.02$) but not to sodium nitroprusside (Fig. 2).

FIBRINOLYTIC AND INFLAMMATORY MARKERS

There were no significant differences in basal plasma concentrations of t-PA (10.5 ± 1.0 and 9.5 ± 1.0 ng per milliliter, respectively) or its endogenous inhibitor, PAI-1 (18.8 ± 3.0 and 17.0 ± 2.0 ng per milliliter, respectively), 6 hours after exposure to either diesel exhaust or filtered air. Likewise, leukocyte, neutrophil, and platelet counts and serum C-reactive protein concentrations were not altered at 6 or 24 hours by exposure to diesel exhaust or filtered air. Bradykinin caused a dose-dependent increase in plasma t-PA concentrations (data not shown) and net t-PA release (Fig. 3) in the infused arm ($P<0.001$ for both comparisons) that was suppressed after exposure to diesel exhaust ($P=0.009$; 35% decrease in the area under the curve).

DISCUSSION

We have demonstrated that transient exposure to dilute diesel exhaust, at concentrations occurring in urban road traffic, exacerbates exercise-induced myocardial ischemia and impairs endogenous fibrinolytic capacity in men with coronary heart disease. These findings provide a plausible explanation for the epidemiologic observation that exposure to air pollution is associated with adverse cardiovascular events.

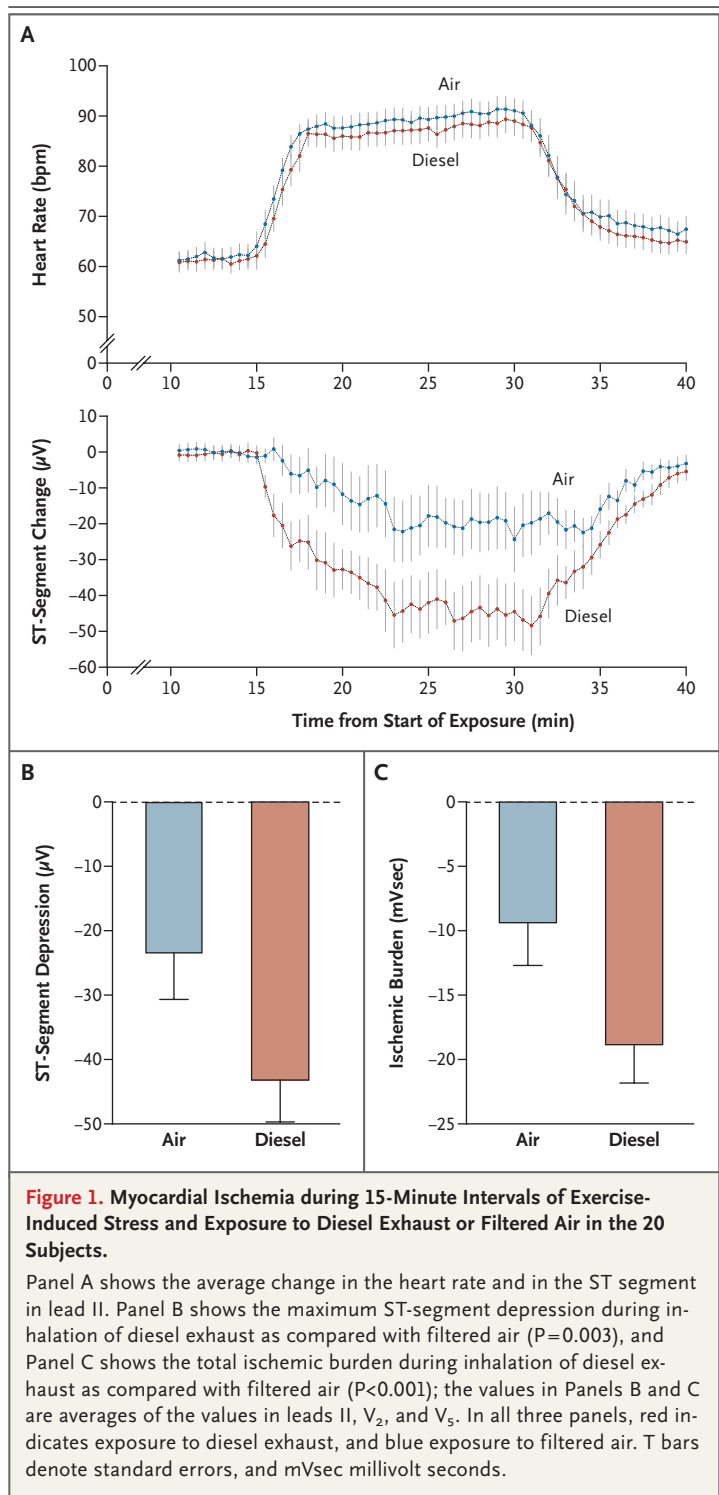


Figure 1. Myocardial Ischemia during 15-Minute Intervals of Exercise-Induced Stress and Exposure to Diesel Exhaust or Filtered Air in the 20 Subjects.

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 ischemic 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, V_2 , and V_5 . In all three panels, red indicates exposure to diesel exhaust, and blue exposure to filtered air. T bars denote standard errors, and mVsec millivolt seconds.

Concentrations of particulate matter can regularly reach levels of $300 \mu\text{g}$ per cubic meter in heavy traffic, in occupational settings, and in the world's largest cities.²² A major proportion of this

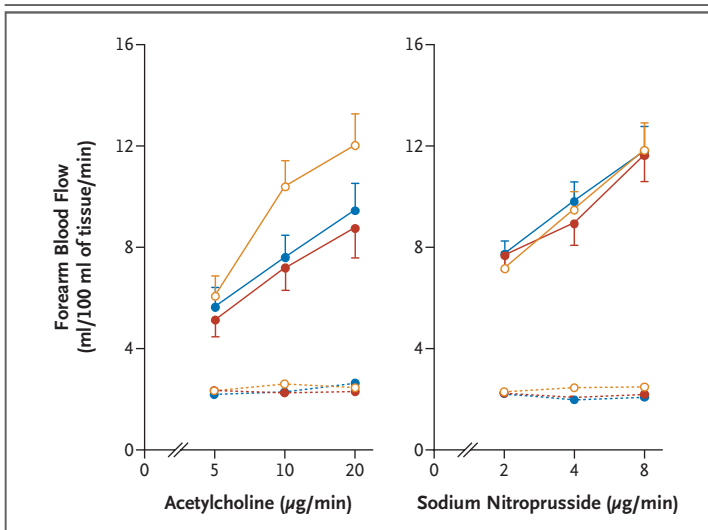


Figure 2. Forearm Blood Flow 6 to 8 Hours after Exposures to Diesel Exhaust and Filtered Air.

Values for infused (solid lines) and noninfused (dashed lines) forearm blood flow are shown for 17 subjects after exposure to diesel exhaust (red) and after exposure to filtered air (blue), as well as for a reference population of matched healthy controls (orange), during intrabrachial infusion of acetylcholine or sodium nitroprusside. $P < 0.001$ for dose response to both drugs in the infused arm. Among the 17 subjects, $P = 0.54$ for exposure to diesel exhaust versus filtered air during infusion of acetylcholine, and $P = 0.56$ during infusion of sodium nitroprusside. For the comparison of the subjects with healthy controls, $P = 0.02$ during acetylcholine infusion, and $P = 0.72$ during sodium nitroprusside infusion.

mass is attributable to combustion-derived nanoparticles from traffic, ranging from 20% at remote monitoring sites²³ to 70% in a road tunnel.²⁴ Exposure to 300 µg of particulate matter per cubic meter for 1 hour increases a person's average exposure over a 24-hour period by only 12 µg per cubic meter. Changes of this magnitude occur on a daily basis, even in the least polluted cities, and are associated with increases in the rate of death from cardiorespiratory disorders.²⁵ Our model is therefore highly relevant, in terms of both the composition and the magnitude of exposure, to the assessment of short-term health effects in men.

Given potential safety concerns, we recruited patients who had stable and symptomatically well-controlled coronary heart disease, with good exercise tolerance on formal stress testing. The study participants were closely monitored throughout the exposure and reported no adverse effects. Despite similar changes in the heart rate during exposure to diesel exhaust and to filtered air, we documented asymptomatic myocardial ischemia that was increased by a factor of up to three after

inhalation of diesel exhaust. This reproducible effect was present despite extensive use of maintenance beta-blocker therapy in patients without limiting angina. Thus, we have established that inhalation of diesel exhaust has an immediate, proischemic effect, and we believe this provides an important mechanism for the observed increase in myocardial infarction in the hour after exposure to traffic.¹³

Small areas of denudation and thrombus deposition are common findings on the surface of atheromatous plaques and are usually subclinical. Rosenberg and Aird have postulated that vascular-bed-specific defects in hemostasis exist and that propagation of coronary thrombosis is critically dependent on the local fibrinolytic balance.²⁶ The magnitude and rapidity of t-PA release from the vascular endothelium regulate the generation of plasmin and thus determine the efficacy of endogenous fibrinolysis.

We have previously reported impaired t-PA release in healthy volunteers 6 hours after inhalation of diesel exhaust, although this effect was not seen 2 hours after exposure.¹⁷ We have now confirmed similar reductions in acute t-PA release 6 hours after inhalation of diesel exhaust in patients with coronary heart disease. This delayed effect on endogenous fibrinolysis cannot explain our findings of immediate myocardial ischemia but is consistent with the observations of Peters and colleagues, who reported a second peak in the incidence of myocardial infarction 5 to 6 hours after exposure to traffic.¹³ Preclinical thrombotic models also lend support to our findings. Nemmar and colleagues reported that in a hamster model, instillation of diesel-exhaust particulate into the lungs increases venous and arterial thrombus formation at sites of vascular injury.²⁷ Taken together, these findings indicate an important thrombotic effect of diesel-exhaust inhalation that may promote coronary thrombosis.

Although we found important adverse effects of diesel exhaust on vascular fibrinolytic function, we did not detect an effect on vasomotor function. However, vasomotor function was assessed 6 hours after exposure and 5 hours after we documented an increase in the ischemic burden. We have previously demonstrated that exposure to diesel exhaust impairs vasomotor function in healthy volunteers.¹⁷ This effect was most marked at 2 hours but was still present 6 hours after exposure. Therefore, we cannot exclude the possibil-

ity of a detrimental vasomotor effect in patients at an earlier point in time.

Patients with coronary heart disease are known to have impaired endothelial function,²⁸ and we confirm the presence of endothelial dysfunction in our patients. This may have hindered our ability to demonstrate a further impairment of vascular function after exposure to diesel exhaust. In addition, we performed our assessments while the subjects were taking medications that are known to influence endothelial vasomotor function.²⁹ Furthermore, Brook and colleagues reported that air pollution does not have an effect on endothelium-dependent vasodilatation.³⁰

We have identified two distinct and potentially synergistic adverse cardiovascular effects of air pollution in patients with coronary heart disease. These effects may contribute to the increased incidence of myocardial infarction after exposure to traffic. However, the precise mechanisms by which diesel-exhaust inhalation induces these ischemic and thrombotic effects have not been established in our study and will need to be determined in future work.

Our findings are consistent with epidemiologic studies showing associations between ambient particulate air pollution and increased myocardial ischemia during formal exercise testing.^{10,11} Myocardial ischemia occurs as a consequence of reduced myocardial oxygen supply, increased demand, or both. We hypothesize that oxidative stress and microvascular dysfunction in the resistance vessels of the myocardium may, in part, explain the adverse ischemic effects of exposure to dilute diesel exhaust. In vitro studies, animal models, and studies of exposures in humans have clearly established the oxidant and proinflammatory nature of combustion-derived particulate matter.³¹ Indeed, the pattern of vascular dysfunction in our previous studies suggested that oxidative stress and reduced nitric oxide availability may play a role in mediating the adverse vascular effects of diesel-exhaust inhalation.¹⁷

Diesel exhaust is a complex mixture of gases and particles, and from our findings, we cannot rule out a nonparticulate cause of the adverse cardiovascular effects. However, on the basis of epidemiologic studies,³² particulate matter is thought to be responsible for the majority of the adverse health effects of air pollution.³³ This view is supported by the recent observations of Miller and colleagues, who found that cardiovascular out-

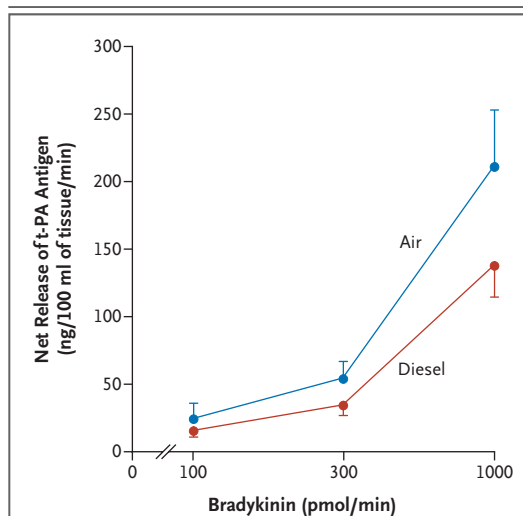


Figure 3. Release of Tissue Plasminogen Activator (t-PA) Antigen 6 to 8 Hours after Exposures to Diesel Exhaust and Filtered Air in 17 Subjects.

As compared with filtered air (blue), inhalation of diesel exhaust (red) reduced the net release of t-PA antigen (calculated as the product of forearm plasma flow and the difference in t-PA concentrations between the two arms) by 35% ($P=0.009$).

comes were strongly associated with long-term exposure to particulate matter but not with gaseous pollutants.³ Ambient nitrogen dioxide can be considered a surrogate for pollution from traffic, but it has little adverse effect in controlled-chamber studies, even at the exposure levels in our study.³⁴ We therefore suggest that the cardiovascular effects described here are mediated primarily by the particulates in diesel exhaust and not by its other components. This argues for the use of diesel-exhaust particle traps to limit the adverse health effects of traffic emissions. However, the causative role of particulates must first be definitively established, and the efficacy of particle traps confirmed.

Brief exposure to dilute diesel exhaust increases myocardial ischemia and impairs endogenous fibrinolytic capacity in men with stable coronary heart disease. Our findings suggest mechanisms for the observation that exposure to combustion-derived air pollution is associated with adverse cardiovascular events, including acute myocardial infarction. Environmental health policy interventions targeting reductions in urban air pollution should be considered in order to decrease the risk of adverse cardiovascular events.

Supported by a Michael Davies Research Fellowship from the British Cardiovascular Society (to Dr. Mills) and by grants from the British Heart Foundation (program grant RG/05/003); the Swedish Heart Lung Foundation; the Swedish Research Council for Environment, Agricultural Sciences, and Spatial Planning; the Swedish National Air Pollution Program; the Swedish Emission Research Program; the Heart and Lung Associations in Sollefteå and Örnsköldsvik; the County Council of Västerbotten; and the Colt Foundation (to Dr. Donaldson).

No potential conflict of interest relevant to this article was reported.

We thank Christopher Ludlam, Pamela Dawson, William MacNee, Joan Henderson, Chris Llewellyn, Frida Holmström, Annika Johansson, Margot Johansson, Veronica Sjögren, Maj-Cari Ledin, Jamshid Pourazar, and the staff in the Department of Respiratory Medicine and Allergy, Umeå, and the Wellcome Trust Clinical Research Facility, Edinburgh, for their assistance; and Peter Bloomfield, for his critical appraisal and review of the manuscript.

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Adverse cardiovascular effects of air pollution

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SUMMARY

Air pollution is increasingly recognized as an important and modifiable determinant of cardiovascular disease in urban communities. Acute exposure has been linked to a range of adverse cardiovascular events including hospital admissions with angina, myocardial infarction, and heart failure. Long-term exposure increases an individual's lifetime risk of death from coronary heart disease. The main arbiter of these adverse health effects seems to be combustion-derived nanoparticles that incorporate reactive organic and transition metal components. Inhalation of this particulate matter leads to pulmonary inflammation with secondary systemic effects or, after translocation from the lung into the circulation, to direct toxic cardiovascular effects. Through the induction of cellular oxidative stress and proinflammatory pathways, particulate matter augments the development and progression of atherosclerosis via detrimental effects on platelets, vascular tissue, and the myocardium. These effects seem to underpin the atherothrombotic consequences of acute and chronic exposure to air pollution. An increased understanding of the mediators and mechanisms of these processes is necessary if we are to develop strategies to protect individuals at risk and reduce the effect of air pollution on cardiovascular disease.

KEYWORDS air pollution, atherothrombosis, endothelium, inflammation, risk

REVIEW CRITERIA

The PubMed search terms used to identify relevant references for this Review on the cardiovascular effects of exposure to air pollution included the following: "air pollution", "particulate matter", "atherosclerosis" and "cardiovascular risk."

CME

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Received 30 April 2008 Accepted 3 October 2008 Published online 25 November 2008

www.nature.com/clinicalpractice
doi:10.1038/ncpcardio1399

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Identify the component of air pollution most associated with adverse health effects in humans.
- 2 Describe the distribution of particulate matter.
- 3 Specify associations between particulate matter and atherogenesis.
- 4 List cardiovascular outcomes associated with greater exposure to air pollution.

Competing interests

The authors and the Journal Editor B Mearns declared no competing interests. The CME questions author CP Vega declared that he has served as an advisor or consultant to Novartis, Inc.

INTRODUCTION

The adverse effects of air pollution on cardiovascular health have been established in a series of major epidemiologic and observational studies.¹⁻⁴ Even brief exposures to air pollution have been associated with marked increases in cardiovascular-related morbidity and deaths from myocardial ischemia, arrhythmia, and heart failure.⁵⁻⁷

The WHO estimates that air pollution is responsible for 3 million premature deaths each year.⁸ This pathologic link has particular implications for low-income and middle-income countries with rapidly developing economies in which air pollution concentrations are continuing to rise. In developed nations, major improvements in air quality have occurred over the last 50 years, yet the association between air pollution

and mortality is still evident, even when pollution levels are below current national and international targets for air quality. No apparent threshold exists below which the association no longer applies.⁹

The breadth, strength, and consistency of the evidence provides a compelling argument that air pollution, especially traffic-derived pollution, causes cardiovascular disease.^{10–12} However, these epidemiologic and observational data are limited by imprecise measurements of pollution exposure, and the potential for environmental and social factors to confound the apparent associations. For a causal association to have scientific credence, a clear mechanism must be defined. In this Review, we discuss potential pathways through which air pollution mediates these adverse cardiovascular effects. We also explore the preclinical and clinical evidence for the main mechanisms that link air pollution with cardiovascular disease.

PATHWAY OF EXPOSURE

Causative components

Air pollutants implicated as potentially harmful to health include particulate matter (PM), nitrogen dioxide, ozone, sulphur dioxide, and volatile organic compounds. We will restrict our discussion to the effects of PM, as this component of the air pollution 'cocktail' has been most consistently associated with adverse health effects.³ Furthermore, both the WHO and the United Nations have declared that PM poses the greatest air pollution threat globally.

Large particles (diameter >10 µm) are mostly derived from soil and crustal elements, whereas smaller particles are primarily produced from the combustion of fossil fuels by motor vehicles and power generators, or from atmospheric chemistry. Only particles less than 10 µm in diameter can be inhaled deep into the lungs. National air quality standards have been based on the mass concentration of such 'inhalable' particles, which are typically defined as having an aerodynamic diameter below 10 µm (PM₁₀), 2.5 µm (PM_{2.5}) or 0.1 µm (nanoparticles). These thresholds are based on the distribution of PM in ambient air. Of note, the nanoparticulate fraction does not contribute substantially to the mass of PM and is not currently regulated by national air quality standards. Typical background concentrations of PM₁₀ in North America or Western Europe are between 20 and 50 µg/m³; these concentrations increase to

between 100 and 250 µg/m³ in industrialized areas and in the developing world.

Many of the individual components of atmospheric PM are not especially toxic at ambient levels and some major constituents, such as sodium chloride, are harmless. By contrast, combustion-derived nanoparticles carry soluble organic compounds, polycyclic aromatic hydrocarbons, and oxidized transition metals on their surface¹³ and can generate oxidative stress and inflammation.¹⁴ Thus, the toxicity of PM primarily relates to the number of particles encountered, as well as their size, surface area, and chemical composition. Although nanoparticles have a greater surface area and, therefore, potency than larger particles, important effects of the coarse fraction (PM_{2.5–10}) should not be ruled out.¹⁵

Potential effector pathways

The precise pathway through which PM influences cardiovascular risk has not yet been determined, but two hypotheses have been proposed (Figure 1) and assessed experimentally. These studies principally used exposure to either concentrated ambient PM or dilute diesel exhaust. The findings from studies that used diesel exhaust exposure have been the most consistent, in part because the concentration and composition of these exposures are easily reproducible between studies. By contrast, the composition of ambient particles is less predictable and is dependent on the local environment, prevailing weather, and atmospheric conditions.

Classical pathway: indirect pulmonary-derived effects

The original hypothesis proposed that inhaled particles provoke an inflammatory response in the lungs, with consequent release of prothrombotic and inflammatory cytokines into the circulation.¹⁶ PM causes lung inflammation in animal models after intrapulmonary instillation¹⁷ and after inhalation of roadside ambient particles.¹⁸ In clinical studies, evidence of pulmonary inflammation has been demonstrated after inhalation of both concentrated ambient PM¹⁹ and dilute diesel exhaust.²⁰ Such exposures led to elevated plasma concentrations of cytokines such as interleukin (IL)-1β, IL-6, and granulocyte–macrophage colony-stimulating factor,²¹ all of which could be released as a consequence of interactions between particles, alveolar macrophages, and airway epithelial cells.²²

Indeed, inhalation of concentrated ambient PM has been shown to induce the release of bone-marrow-derived neutrophils and monocytes into the circulation in both animal models²² and clinical studies.²³

Increases in plasma or serum markers of systemic inflammation have been reported after exposure to PM. In animal studies, plasma fibrinogen concentrations are raised in both normal²⁴ and hypertensive rats exposed to PM.²⁵ In panel and population studies, exposure has been associated with evidence of an acute phase response, namely increased serum C-reactive protein²⁶ and plasma fibrinogen²⁷ concentrations, enhanced plasma viscosity,²⁸ and altered leukocyte expression of adhesion molecules.²⁹

Alternative pathway: direct translocation into the circulation

This hypothesis proposes that inhaled, insoluble, fine PM or nanoparticles could rapidly translocate into the circulation, with the potential for direct effects on hemostasis and cardiovascular integrity. The ability of nanoparticles to cross the lung–blood barrier is likely to be influenced by a number of factors including particle size and charge, chemical composition, and propensity to form aggregates. Translocation of inhaled nanoparticles across the alveolar–blood barrier has been demonstrated in animal studies for a range of nanoparticles delivered by inhalation or instillation.^{30–32} Convincing demonstration of translocation has been difficult to achieve in humans;^{33,34} however, given the deep penetration of nanoparticulate matter into the alveoli and close apposition of the alveolar wall and capillary network, such particle translocation seems plausible—either as a naked particle or after ingestion by alveolar macrophages (Figure 1).

Once in the circulation, nanoparticles could interact with the vascular endothelium or have direct effects on atherosclerotic plaques and cause local oxidative stress and proinflammatory effects similar to those seen in the lungs. Increased inflammation could destabilize coronary plaques, which might result in rupture, thrombosis, and acute coronary syndrome.³⁵ Certainly, injured arteries can take up blood-borne nanoparticles,³⁶ a fact exploited by the nanotechnology industry for both diagnostic and therapeutic purposes in cardiovascular medicine. Indeed, uptake of nanoparticulate matter into the vessel wall underlies the fundamental

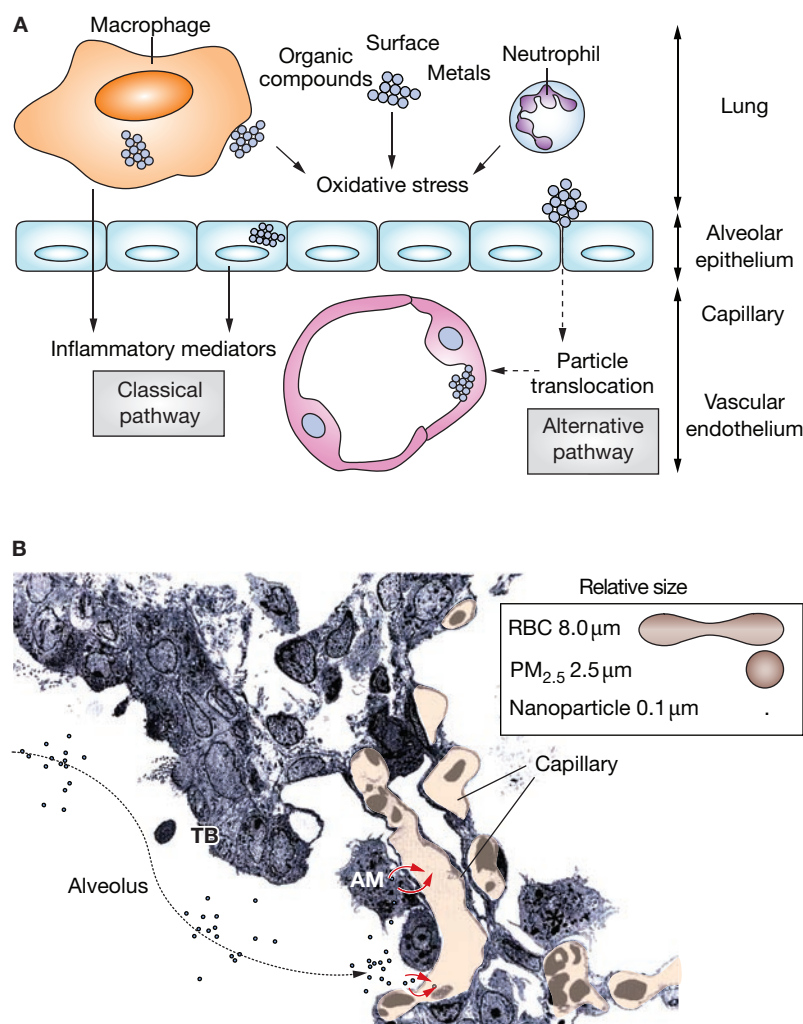


Figure 1 The hypothetical effector pathways through which airborne particulate matter influences cardiovascular risk. **(A)** Classical and alternative pathways through which combustion-derived nanoparticulate matter induces cardiovascular effects. **(B)** Transmission electron micrograph of the alveolar-duct-terminal bronchiolar region that demonstrates the close proximity between the alveolar wall and capillary network. Particle translocation from the airways into the circulation may occur directly or after ingestion by alveolar macrophages. Abbreviations: AM, alveolar macrophages; PM, particulate matter; RBC, red blood cell; TB, the alveolar-duct-terminal bronchiolar region. Part B adapted from Lehnert BE (1992) *Environ Health Perspect* **97**: 17–46, which is published under an open-access license by the US Department of Health, Education, and Welfare.⁶⁹

pathogenesis of atherosclerosis, with the accumulation of LDL particles (diameter 20 nm) into the intima.

MECHANISMS OF DISEASE

Epidemiologic data suggest that air pollution can promote both chronic atherogenesis and acute atherothrombosis (Figure 2).

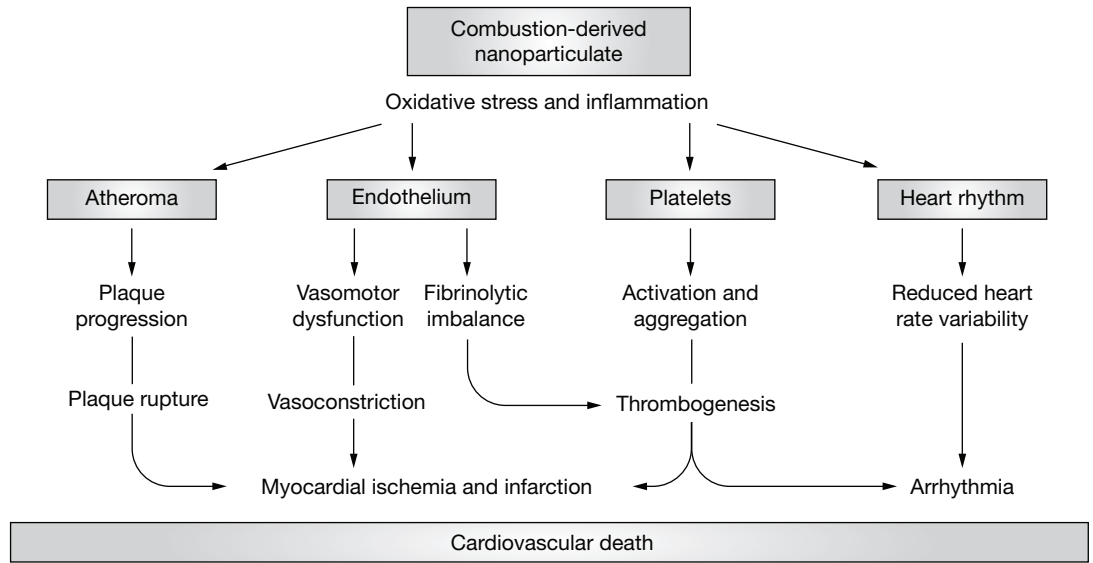


Figure 2 The mechanisms through which combustion-derived nanoparticulate matter causes acute and chronic cardiovascular disease.

Atherogenesis

In one of the largest case series to date, which incorporated 350,000 patient-years of follow-up, Miller *et al.* reported that long-term exposure to air pollution increases the risk of cardiovascular events by 24% and cardiovascular-related death by 76% for every 10 µg/m³ increase in PM_{2.5}.³ Repeated exposure to air pollution could plausibly induce vascular inflammation, oxidative stress, and promote atherosclerotic plaque expansion or rupture. Although defining the atherogenic potential of air pollution experimentally is a challenge, two approaches have been used to good effect: animal models of atheroma given controlled exposures to pollutants, and cross-sectional, clinical studies.

Prolonged exposure to concentrated ambient PM_{2.5} increases aortic plaque area and burden, when compared with filtered air, in apolipoprotein-E-knockout mice fed a high-fat diet.³⁷ The ultrafine component of PM_{2.5} could have a greater atherogenic effect than the fine fraction—exposure to ultrafine particulate matter rich in polycyclic aromatic hydrocarbons produced more inflammation, systemic oxidative stress, and atheroma formation than the fine fraction or filtered air in apolipoprotein-E-knockout mice.³⁸ In the Watanabe hyperlipidemic rabbit model, repeated instillation of ambient PM₁₀ was associated with the development of more-advanced, ‘vulnerable’ coronary

and aortic atherosclerotic plaques than those seen in control rabbits.³⁹ Although the precise role of different fractions of PM requires further study, taken together these preclinical data suggest that not only is the atherosclerotic burden increased by exposure to PM, but that the resultant lesions might be more vulnerable to plaque-rupture events.

In a cross-sectional, population-based study, Künzli and colleagues examined carotid intima-media thickness measurements in nearly 800 residents of Los Angeles, CA.⁴⁰ Personal air pollution exposures were estimated with a geostatistical model that mapped their area of residence to PM values recorded by local pollution-monitoring stations. For every 10 µg/m³ increase in PM_{2.5}, carotid intima-media thickness increased by 6%, a figure which fell to 4% after adjustment for potential confounding variables. Similar effects have also been reported for coronary artery calcium scores, a marker of coronary atherosclerosis. In a prospective, cohort study of 4,944 individuals, Hoffmann and colleagues demonstrated that living in close proximity to a major urban road increased coronary artery calcium scores by 60%.⁴¹

Atherothrombosis

Short-term exposure to PM is associated with acute coronary events, ventricular arrhythmia, stroke, and hospitalizations and death caused by

both heart failure and ischemic heart disease.³⁵ Peters and colleagues performed a detailed survey of 691 patients with acute myocardial infarction and found that the time spent in cars, on public transport, or on motorcycles or bicycles was consistently linked to the onset of symptoms, which suggests that exposure to road traffic is a risk factor for myocardial infarction.⁴²

Atherothrombosis is characterized by disruption of an atherosclerotic plaque and thrombus formation, and is the major cause of acute coronary syndromes and cardiovascular death. The association between environmental air pollution and acute cardiovascular events could, therefore, be driven by alterations in either thrombus formation or behavior of the vessel wall (Figure 2).

Thrombosis

PM can induce a variety of prothrombotic effects including enhanced expression of tissue factor on endothelial cells both *in vitro*⁴³ and *in vivo*,⁴⁴ and accumulation of fibrin and platelets on the endothelial surface.⁴⁵ In addition to altering the properties of endothelial cells and platelets, nanoparticles could themselves act as a focus for thrombus formation. Scanning electron microscopy was used to evaluate explanted temporary vena caval filters and revealed the presence of foreign nanoparticulate within the thrombus itself.⁴⁶

In 2008, long-term exposure to particulate air pollution was linked to an increase in the risk of venous thromboembolic disease.⁴⁷ In pre-clinical models, overall thrombotic potential is enhanced by exposure to PM, especially under circumstances of vascular injury. Intratracheal instillation of diesel exhaust particles augmented thrombus formation in a hamster model of both venous and arterial injury.⁴⁸ This increase in thrombotic potential seems to be mediated, at least in part, by enhanced platelet activation and aggregation.⁴⁸

Clinical investigations of thrombosis are difficult to conduct, partly because of the ethical implications of assessing thromboses *in vivo*. *Ex vivo* thrombus formation has been assessed, with the use of a Badimon chamber, after controlled exposures to dilute diesel exhaust in healthy volunteers.⁴⁹ The Badimon chamber measures thrombus formation—triggered by exposure to a physiologically-relevant substrate—in native (no anticoagulation), whole blood, under flow conditions that mimic those

found in diseased coronary arteries. Within 2 h of dilute diesel exhaust exposure, thrombus formation was enhanced and associated with increased platelet activation. These findings are consistent with previous *in vitro* investigations, which demonstrated that the addition of diesel exhaust particles to human blood resulted in platelet aggregation and enhanced glycoprotein IIb/IIIa receptor expression.⁵⁰ In support of this mechanism, an observational study published in 2006 reported an increase in platelet activation and platelet–leucocyte aggregation in women from India who were regularly exposed to indoor air pollution from the combustion of biomass fuels.⁵¹

Vascular dysfunction

Epidemiologic and observational clinical studies indicate that exposure to air pollution could worsen symptoms of angina,⁵² exacerbate exercise-induced myocardial ischemia,⁵³ and trigger acute myocardial infarction.⁶ Many of these effects could be mediated through direct effects on the vasculature.

Both preclinical and clinical assessments have demonstrated alterations in vascular vasomotor function after controlled exposures to air pollution. In their proatherogenic mouse model, Sun and colleagues reported enhanced vasoconstriction and reduced endothelium-dependent vasodilatation in the aorta after chronic exposure to concentrated ambient PM.³⁷ Similar vasoconstrictor effects of PM have been reported by Brook and colleagues in clinical studies of forearm conduit vessels, although they observed no effects on endothelium-dependent vasodilatation.⁵⁴ When exposed to dilute diesel exhaust, healthy volunteers demonstrated an early and persistent (up to 24 h) impairment of vascular function.^{55,56} This vascular dysfunction seems to involve nitric oxide pathways, and reduced nitric oxide bioavailability secondary to oxidative stress has been postulated as one potential mechanism.⁵⁷ Experimental studies have confirmed a role for increased levels of superoxide in mediating the adverse vascular effects of air pollution and indicate that exposure to PM could contribute to a hypertensive phenotype.⁵⁸ A number of clinical studies provide indirect support for this mechanism through the observation that PM exposure is associated with small, but significant, increases in both diastolic and systolic blood pressures.^{59–61}

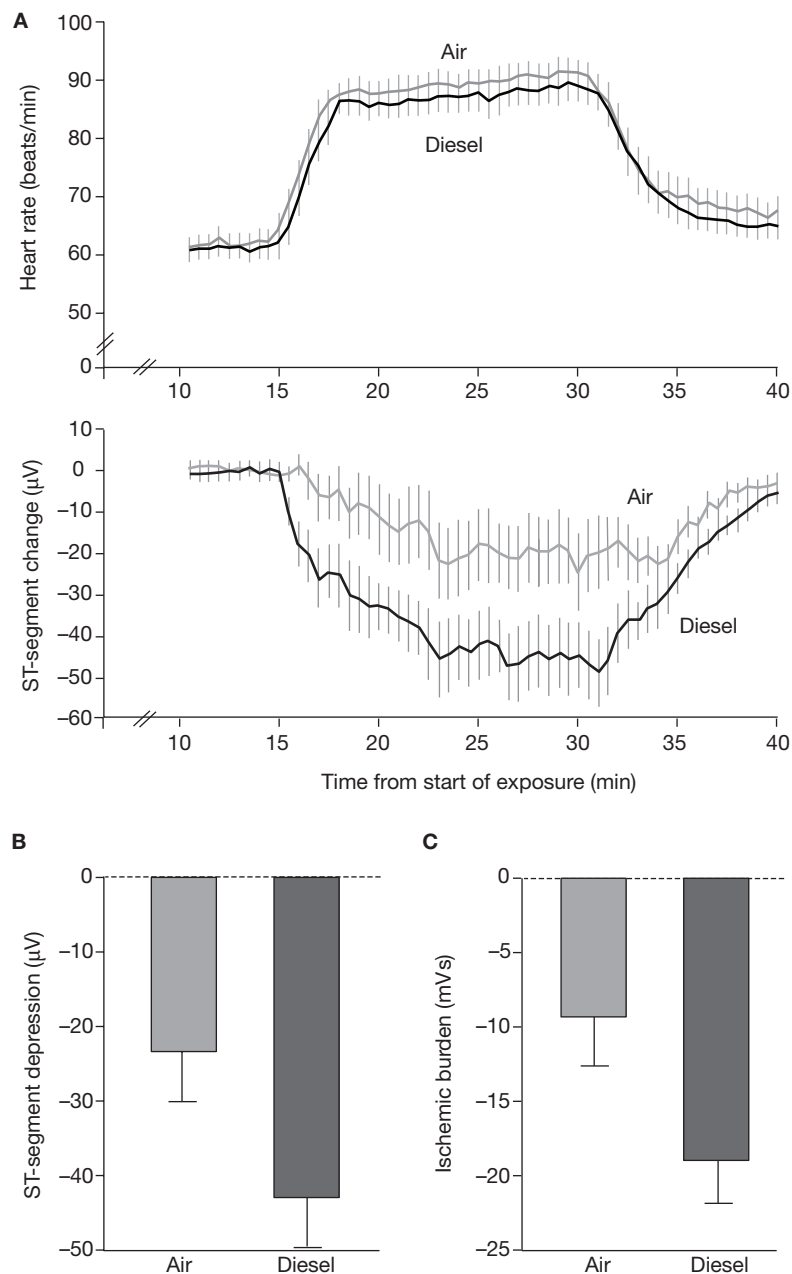


Figure 3 Clinical consequences of diesel exhaust inhalation in patients with coronary heart disease. Electrocardiographic ST-segment depression occurs during exercise in patients with coronary heart disease exposed to filtered air (solid line) or dilute diesel exhaust (dashed line). **(A)** Average change in heart rate and ST-segment in lead II. **(B)** Maximal ST-segment depression ($P=0.003$, diesel exhaust versus filtered air), and **(C)** total ischemic burden ($P<0.001$, diesel exhaust versus filtered air) as an average of leads II, V2, and V5. Reproduced from Mills NL *et al.* (2007) Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *N Engl J Med* **357**: 1075–1082. Copyright © 2007 Massachusetts Medical Society. All rights reserved.⁶²

and patients with stable coronary artery disease were exposed to dilute diesel exhaust ($300\ \mu\text{g}/\text{m}^3$ PM concentration) or filtered air for 1 h during intermittent exercise.^{55,62} In these studies, the acute release of tissue plasminogen activator, a key regulator of endogenous fibrinolytic capacity, was reduced after diesel exhaust inhalation. This effect persisted for 6 h after initial exposure,⁵⁵ and the magnitude of this reduction is comparable with that seen in cigarette smokers.⁶³ This antifibrinolytic effect further underscores the prothrombotic potential of air pollution, especially under circumstances of vascular injury.

The clinical effect of these alterations in vascular function was evaluated further in our study, which assessed diesel exhaust inhalation in patients with coronary heart disease.⁶² While patients were exposed to diesel exhaust, myocardial ischemia was quantified by ST-segment analysis using continuous 12-lead electrocardiography. Exercise-induced ST-segment depression was present in all patients, but a threefold greater increase in ST-segment depression and ischemic burden was evident during exposure to diesel exhaust than during exposure to filtered air (Figure 3). Thus, reductions in vasomotor reserve have serious consequences for myocardial ischemia in this at-risk population.

Arrhythmogenesis

Although arrhythmias are unlikely to account for many manifestations of the adverse cardiovascular effects of air pollution, nonetheless dysrhythmias can be implicated in hospitalization for cardiovascular disease and the incidence of sudden cardiac death. To date, most studies in this area have examined the effects of PM on heart rate variability because of its association with an increased risk of cardiovascular morbidity and mortality in both healthy individuals⁶⁴ and survivors of myocardial infarction.⁶⁵

Liao and colleagues were the first to report an association between $\text{PM}_{2.5}$ and heart rate variability in a panel of elderly individuals (mean age 81 years).⁶⁶ Although the authors considered their finding somewhat exploratory, the analysis revealed an inverse correlation between same-day $\text{PM}_{2.5}$ concentrations and cardiac autonomic control response. They hypothesized that the association between inhaled PM and adverse cardiovascular outcomes might be explained by the effect of PM exposure on the autonomic control of heart rate and rhythm. How inhaled

Abnormalities of vascular function are not only restricted to vasomotion. In a series of double-blind, randomized crossover studies, healthy men

PM would modulate autonomic functions remains unclear, but some investigators have postulated that deposited particles could stimulate irritant receptors in the airways and directly influence heart rate and rhythm via reflex activation of the nervous system.³⁵ Numerous panel studies have since explored this mechanistic hypothesis and have studied the associations between levels of different air pollutants and changes in heart rate variability or incidence of cardiac arrhythmia. The current literature is, however, inconsistent in the magnitude, type, and direction of changes elicited by PM, which makes firm conclusions impossible.

Direct evidence that air pollution could trigger arrhythmia has been further assessed in studies of high-risk patients with implanted cardioverter-defibrillators. In a pilot study, estimated community-acquired exposures to fine particulate and other traffic-derived air pollutants were associated with an increase in the number of defibrillator-detected tachyarrhythmias amongst 100 patients with these devices.⁶⁷ However, in a large analysis with extended follow-up, the risk of ventricular arrhythmia did not increase with air pollution exposures unless the analysis was restricted to a subgroup of patients with frequent arrhythmias.⁶⁸ Of note, acute myocardial ischemia secondary to an acute coronary syndrome is the most common trigger for life-threatening arrhythmias. Overall, the proarrhythmic potential of air pollution remains uncertain and has yet to be definitively established.

CONCLUSIONS

The robust associations between air pollution and cardiovascular disease have been repeatedly demonstrated and have even withstood legal challenge by the automotive industry. The mechanisms that underlie this association have yet to be definitively established, but clear evidence exists that many of the adverse health effects are attributable to combustion-derived nanoparticles. Either through direct translocation into the circulation or via secondary pulmonary-derived mediators, PM augments atherogenesis and causes acute adverse thrombotic and vascular effects, which seem to be mediated by proinflammatory and oxidative pathways. Improving air quality standards, reducing personal exposures, and the redesign of engine and fuel technologies could all have a role in reducing air pollution and its consequences for cardiovascular morbidity and mortality.

KEY POINTS

- Exposure to air pollution is associated with increased cardiovascular morbidity and deaths from myocardial ischemia, arrhythmia, and heart failure
- Fine particulate matter derived from the combustion of fossil fuels is thought to be the most potent component of the air pollution cocktail
- Particulate matter upregulates systemic proinflammatory and oxidative pathways, either through direct translocation into the circulation or via secondary pulmonary-derived mediators
- Exposure to particulate matter has the potential to impair vascular reactivity, accelerate atherogenesis, and precipitate acute adverse thrombotic events
- In patients with coronary heart disease, exposure to combustion-derived particulate can exacerbate exercise-induced myocardial ischemia
- Improving air quality standards, reducing personal exposures, and the redesign of engine and fuel technologies could all have a role in reducing air pollution and its consequences for cardiovascular morbidity and mortality

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Acknowledgments

NL Mills is supported by a Michael Davies Research Fellowship from the British Cardiovascular Society. This work was supported by a British Heart Foundation Programme Grant (RG/05/003) and the Swedish Heart Lung Foundation.

Charles P Vega, University of California, Irvine, CA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the Medscape-accredited continuing medical education activity associated with this article.

Competing interests

The authors declared no competing interests.

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2005;112:3930-3936

DOI: 10.1161/CIRCULATIONAHA.105.588962

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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Diesel Exhaust Inhalation Causes Vascular Dysfunction and Impaired Endogenous Fibrinolysis

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Background—Although the mechanisms are unknown, it has been suggested that transient exposure to traffic-derived air pollution may be a trigger for acute myocardial infarction. The study aim was to investigate the effects of diesel exhaust inhalation on vascular and endothelial function in humans.

Methods and Results—In a double-blind, randomized, cross-over study, 30 healthy men were exposed to diluted diesel exhaust (300 $\mu\text{g}/\text{m}^3$ particulate concentration) or air for 1 hour during intermittent exercise. Bilateral forearm blood flow and inflammatory factors were measured before and during unilateral intrabrachial bradykinin (100 to 1000 pmol/min), acetylcholine (5 to 20 $\mu\text{g}/\text{min}$), sodium nitroprusside (2 to 8 $\mu\text{g}/\text{min}$), and verapamil (10 to 100 $\mu\text{g}/\text{min}$) infusions 2 and 6 hours after exposure. There were no differences in resting forearm blood flow or inflammatory markers after exposure to diesel exhaust or air. Although there was a dose-dependent increase in blood flow with each vasodilator ($P < 0.0001$ for all), this response was attenuated with bradykinin ($P < 0.05$), acetylcholine ($P < 0.05$), and sodium nitroprusside ($P < 0.001$) infusions 2 hours after exposure to diesel exhaust, which persisted at 6 hours. Bradykinin caused a dose-dependent increase in plasma tissue plasminogen activator ($P < 0.0001$) that was suppressed 6 hours after exposure to diesel ($P < 0.001$; area under the curve decreased by 34%).

Conclusions—At levels encountered in an urban environment, inhalation of dilute diesel exhaust impairs 2 important and complementary aspects of vascular function in humans: the regulation of vascular tone and endogenous fibrinolysis. These important findings provide a potential mechanism that links air pollution to the pathogenesis of atherothrombosis and acute myocardial infarction. (*Circulation*. 2005;112:3930-3936.)

Key Words: air pollution ■ endothelium ■ blood flow ■ fibrinolysis

Air pollution is a major cause of cardiovascular morbidity and mortality. Short-term increases in air pollution exacerbate cardiorespiratory disease, leading to hospitalization for conditions including acute myocardial infarction.¹ Long-term repeated exposure increases the risk of cardiovascular mortality, with deaths attributable to ischemic heart disease, arrhythmias, and heart failure.² These associations are strongest for fine particulate air pollutants (PM_{2.5}),³ of which the combustion-derived nanoparticles of diesel exhaust are an important component.⁴ Although significant improvements in air quality have occurred during the last 50 years, the association between PM_{2.5} and mortality is evident below current air quality standards.⁵

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Despite the strength of the epidemiological evidence and the emergence of promising hypotheses,^{6,7} the important

constituents and biological mechanisms responsible for the cardiovascular effects of air pollution are largely unknown. It was recently reported that transient exposure to road traffic may increase the risk of acute myocardial infarction.⁸ Long-term exposure to traffic in those living within 100 m of a major road significantly increased cardiopulmonary mortality.⁹ These important observations suggest that the combustion-derived particulates in PM_{2.5} may be critical in determining the cardiovascular effects of air pollution.

Abnormal endothelial function has been widely recognized in patients with atherosclerosis and its risk factors.^{10,11} Endothelial dysfunction can also predict the likelihood of future cardiovascular events and death in patients with coronary artery disease¹² and in at-risk individuals with normal coronary arteries.¹³ We have previously demonstrated endothelial dysfunction in both the peripheral and coronary circulations

Received December 14, 2004; de novo received August 12, 2005; revision received September 14, 2005; accepted October 7, 2005.

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.105.588962

of cigarette smokers.^{10,11} Given the potential for common etiologic factors contained within polluted air and cigarette smoke, we hypothesized that the adverse cardiovascular effects of air pollution are a result of combustion-derived particulates and are mediated by an impairment of normal vascular function. Using a carefully characterized exposure system, we sought to assess the effect of diluted diesel exhaust inhalation on endothelial vasomotor and fibrinolytic function in humans.

Methods

Subjects

Thirty healthy, male nonsmokers between 20 and 38 years old participated in these studies, which were performed with the approval of the local research ethics committee, in accordance with the Declaration of Helsinki, and the written, informed consent of all volunteers. Subjects taking regular medication and those with clinical evidence of atherosclerotic vascular disease, arrhythmias, diabetes mellitus, hypertension, renal or hepatic failure, asthma, significant occupational exposure to air pollution, or an intercurrent illness likely to be associated with inflammation were excluded from the study. Subjects had normal lung function and reported no symptoms of respiratory tract infection for at least 6 weeks before or during the study.

Study Design

Subjects attended the experimental sessions on 2 occasions 2 weeks apart and received either filtered air or diesel exhaust in a randomized, double-blind, cross-over design. Each subject was exposed for 1 hour in a specially built diesel exposure chamber according to a previously described standard protocol.¹⁴ During each exposure, they performed moderate exercise (minute ventilation, $25 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) on a bicycle ergometer that was alternated with rest at 15-minute intervals.

Based on previous exposure¹⁵ and systemic inflammatory¹⁶ studies, vascular assessments were performed in 15 subjects at 6 to 8 hours after diesel or air exposure. In light of our findings from this 6- to 8-hour study, we subsequently determined vascular function in another 15 subjects at an earlier time point of 2 to 4 hours after exposure to diesel exhaust or air. All subjects abstained from alcohol for 24 hours and from food, tobacco, and caffeine-containing drinks for at least 4 hours before each vascular study. Studies were carried out in a quiet, temperature-controlled room maintained at 22°C to 24°C with subjects lying supine. All subjects remained indoors between the exposure and vascular assessment to minimize additional exposure to particulate air pollution.

Diesel Exposure

The diesel exhaust was generated from an idling Volvo diesel engine (Volvo TD45, 4.5 L, 4 cylinders, 680 rpm) as described previously.¹⁵ More than 90% of the exhaust was shunted away, and the remaining part was diluted with air and fed into the exposure chamber at a steady-state concentration. The air in the exposure chamber was continuously monitored for nitrogen oxides (NO, NO₂), carbon monoxide (CO), particulates (number/cm³), and total hydrocarbons. The exposures were standardized by keeping the particulate concentration at 300 μg/m³ and were associated with concentrations of NO₂ of 1.6 ppm; of NO, 4.5 ppm; of CO, 7.5 ppm; of total hydrocarbons, 4.3 ppm; of formaldehyde, 0.26 μg/m³; and of suspended particles, 1.2 × 10⁶/cm³. The temperature and humidity in the chamber were controlled at 20°C and 50%, respectively.

Vascular Studies

All subjects underwent brachial artery cannulation with a 27-standard wire gauge steel needle under controlled conditions. After a 30-minute baseline saline infusion, acetylcholine at 5, 10, and 20 μg/min (endothelium-dependent vasodilator that does not release

tissue plasminogen activator [t-PA; Merck Biosciences); bradykinin at 100, 300, and 1000 pmol/min (endothelium-dependent vasodilator that releases t-PA; Merck Biosciences); and sodium nitroprusside at 2, 4, and 8 μg/min (endothelium-independent vasodilator that does not release t-PA; David Bull Laboratories) were infused for 6 minutes at each dose. The 3 vasodilators were separated by 20-minute saline infusions and given in a randomized order. In the second cohort with the early (2- to 4-hour) vascular assessment, verapamil at 10, 30, and 100 μg/min (endothelium- and NO-independent vasodilator that does not release t-PA) was infused at the end of the study protocol.¹⁷

Forearm blood flow (FBF) was measured in infused and noninfused arms by venous occlusion plethysmography with a mercury-silicone elastomer strain gauges as described previously.¹⁸ Supine heart rate and blood pressure in the noninfused arm were monitored at intervals throughout each study with a semiautomated, noninvasive, oscillometric sphygmomanometer.

Venous cannulas (17 gauge) were inserted into large subcutaneous veins of the antecubital fossae of both arms. Blood (10 mL) was withdrawn simultaneously from each arm at baseline and during infusion of each dose of bradykinin and collected into acidified buffered citrate (Stabilyte tubes, Biopool International) for t-PA assays and into citrate (BD Vacutainer) for plasminogen activator inhibitor type 1 (PAI-1) assays. Samples were kept on ice before being centrifuged at 2000g for 30 minutes at 4°C. Platelet-free plasma was decanted and stored at -80°C before assay. Plasma t-PA and PAI-1 antigen concentrations were determined by ELISAs (TintElize t-PA, Biopool EIA; Coaliza PAI-1, Chromogenix AB). Hematocrit was determined by capillary tube centrifugation at baseline and during infusion of bradykinin at 1000 pmol/min.

Blood samples were taken immediately before and at 2 and 6 hours after exposure and analyzed for total cells, differential cell counts, and platelets by an autoanalyzer. Plasma interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured with commercially available ELISAs (Quantikine, R&D Systems). Plasma immunoreactive big endothelin (ET)-1 and ET-1 concentrations were measured according to an acetic acid extraction technique by use of a modified commercial radioimmunoassay with rabbit anti-human big ET-1 or ET-1 (Peninsula Laboratories Europe), as described previously.¹⁹ Serum C-reactive protein (CRP) concentrations were measured with an immunonephelometric assay (Behring BN II nephelometer).

Data Analysis and Statistics

Plethysmographic data were analyzed as described previously.¹⁰ The estimated net release of t-PA antigen was defined as the product of the infused forearm plasma flow (based on the mean hematocrit and the infused FBF) and the concentration difference between the infused and noninfused arms.¹⁰ Continuous variables are reported as mean ± SEM. Statistical analyses were performed with GraphPad Prism (Graph Pad Software) by ANOVA with repeated measures and 2-tailed Student *t* test, where appropriate. The area under the curve was calculated for the estimated net release of t-PA during the forearm study period. Statistical significance was taken at *P* < 0.05.

Results

There were no differences in resting heart rate, blood pressure, or baseline FBF after exposure to diesel exhaust or air in either cohort (Table 1). Leukocyte, neutrophil, and platelet counts; plasma IL-6, TNF-α, big ET-1, and ET-1; and serum CRP concentrations were not altered by diesel or air exposure (Table 2).

Bradykinin, acetylcholine, and sodium nitroprusside caused dose-dependent increases in FBF after both air and diesel exhaust exposure (*P* < 0.0001; Figure 1). The increase in blood flow was blunted 2 hours after exposure to diesel exhaust in response to infusion of bradykinin (*P* < 0.05), acetylcholine (*P* < 0.05), and sodium nitroprusside (*P* < 0.001), and this dimin-

TABLE 1. Baseline Hemodynamics Variables

	Air	Diesel	Significance
2 Hours, n=15			
Heart rate, bpm	64±3	65±2	P=0.64
Systolic blood pressure, mm Hg	140±4	148±4	P=0.13
Diastolic blood pressure, mm Hg	71±3	77±4	P=0.08
Infused FBF, mL/100 mL tissue per min	3.3±0.6	3.1±0.4	P=0.45
Noninfused FBF, mL/100 mL tissue per min	2.3±0.2	2.6±0.4	P=0.30
6 Hours, n=15			
Heart rate, bpm	61±2	60±2	P=0.66
Systolic blood pressure, mm Hg	138±5	138±3	P=0.39
Diastolic blood pressure, mm Hg	75±2	76±4	P=0.87
Infused FBF, mL/100 mL tissue per min	3.1±0.5	2.5±0.2	P=0.25
Noninfused FBF, mL/100 mL tissue per min	2.2±0.1	2.4±0.3	P=0.65

Values are reported as mean±SEM, 2-tailed paired *t* test.

ished response persisted at 6 hours (Figure 2). In contrast, verapamil-induced vasodilatation was unaffected after exposure to air or diesel exhaust (*P*=NS).

Bradykinin caused a dose-dependent increase in plasma t-PA antigen concentrations (*P*<0.0001; Table 3) that was reduced 6 hours after diesel exposure (*P*<0.001). The estimated net t-PA antigen release was reduced by 34% 6 hours after exposure to diesel (*P*<0.05; Figure 3) but was unaffected at the earlier time point of 2 hours.

TABLE 2. Systemic Effects of Exposure to Diesel Exhaust

	Before Exposure	2 Hours	6 Hours
Air			
Leucocytes, ×10 ⁹ cells/L	5.1±0.2	5.6±0.3	5.3±0.3
Neutrophils, ×10 ⁹ cells/L	2.8±0.2	3.3±0.2	3.0±0.2
Platelets, ×10 ⁹ cells/L	217±12	216±9	218±12
IL-6, pg/mL	2.6±1.3	...	3.4±0.8
TNF-α, pg/mL	16.9±1.1	...	17.8±1.2
CRP, mg/L	0.9±0.3	...	0.8±0.2
PAI-1 antigen, ng/mL	20.2±3.9	19.2±2.8	18.5±3.7
t-PA antigen, ng/mL	6.6±0.6	7.0±0.6	6.0±0.5
ET-1, pg/mL	4.9±0.5	4.9±0.5	4.9±0.4
Big ET-1, pg/mL	28.8±1.5	29.6±2.5	32.2±2.5
Diesel			
Leucocytes, ×10 ⁹ cells/L	5.6±0.3	5.7±0.4	5.1±0.3
Neutrophils, ×10 ⁹ cells/L	2.8±0.2	3.4±0.3	2.9±0.3
Platelets, ×10 ⁹ cells/L	228±14	227±11	221±12
IL-6, pg/mL	2.7±0.7	...	4.3±2.2
TNF-α, pg/mL	15.3±0.5	...	16.0±0.8
CRP, mg/L	1.0±0.4	...	0.7±0.4
PAI-1 antigen, ng/mL	16.1±3.0	15.7±3.6	12.8±2.6
t-PA antigen, ng/mL	6.0±0.6	5.9±0.6	5.3±0.6
ET-1, pg/mL	4.5±0.4	4.8±0.3	4.8±0.5
Big ET-1, pg/mL	30.2±2.3	31.9±3.7	28.1±2.6

Values are reported as mean±SEM.

Discussion

This is the first study to demonstrate that inhalation of diesel exhaust, a common urban air pollutant, can impair vascular function in humans. Using a robust and powerful study design, we have assessed 2 important and complementary aspects of vascular function: the regulation of vascular tone and endogenous fibrinolysis. Both are impaired and plausibly related to the well-documented cardiovascular effects of air pollution. These important findings provide a plausible mechanism that links air pollution to the pathogenesis of atherosclerosis and acute myocardial infarction.

Vasomotor Function

Impaired endothelium-dependent and -independent vasomotor function in the forearm vascular bed is associated with an increased risk of acute cardiovascular events, including cardiac death.¹² We have demonstrated that inhalation of diesel exhaust impairs vasomotor responses to both endothelium-dependent and -independent vasodilators at 6 hours. On the basis of this initial study, it is unclear whether the impairment is primarily mediated by the vascular endothelium or is a result of smooth muscle dysfunction. However, reduced NO bioavailability in the presence of increased systemic or vascular oxidative stress is an attractive hypothesis.

The endothelium is a major target of oxidative stress, and this interaction plays an important role in the pathophysiology of vascular disease.²⁰ Superoxide radicals, produced as a consequence of oxidative stress, combine with NO to form peroxynitrite, thus reducing NO bioavailability in the vessel wall and shifting the balance toward vasoconstriction. In vascular smooth muscle cells, superoxide inhibits the activity of enzymes such as soluble guanylyl cyclase²¹ and cGMP-dependent protein kinase,²² thereby reducing both endothelium-dependent and -independent NO-mediated vasodilation.

We hypothesized that our initial findings were due to the oxidative effects of diesel exhaust, and as such, vascular impairment would occur early. In the subsequent study, we have demonstrated an acute impairment to endothelium-dependent and -independent vasodilators, but we were also

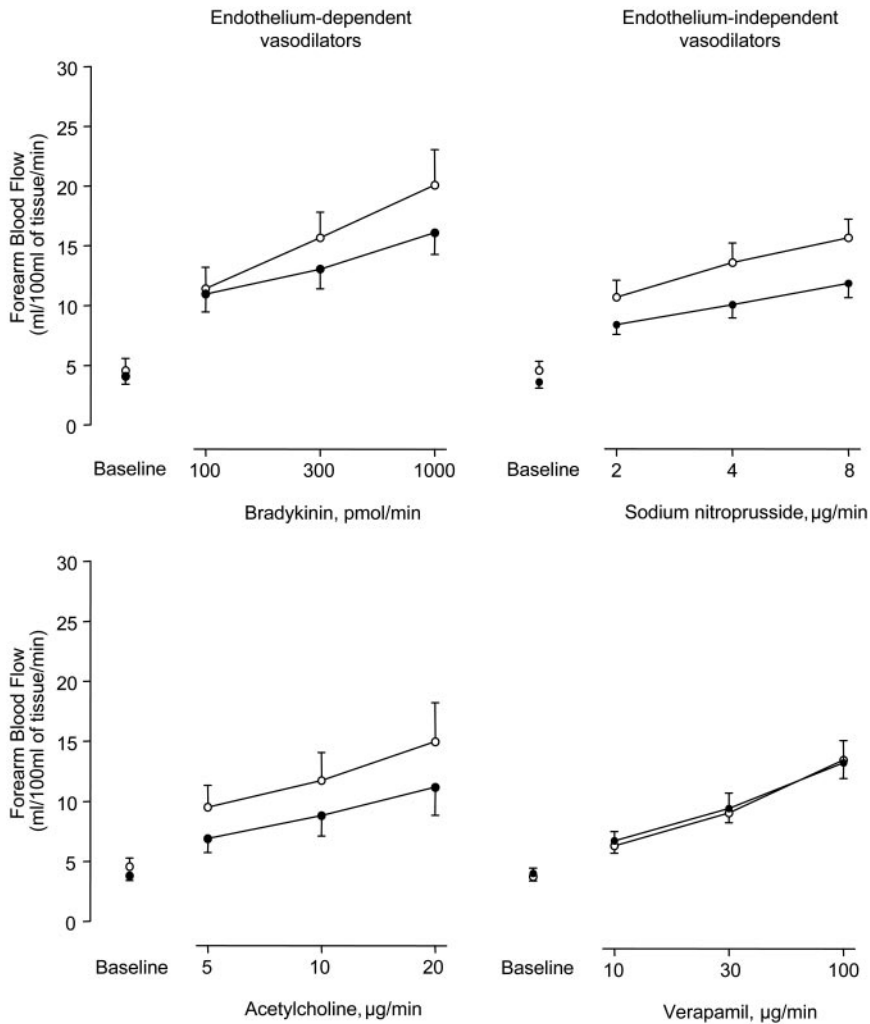


Figure 1. Infused FBF in subjects 2 to 4 hours after diesel exposure (●) and air (○) during intrabrachial infusion of bradykinin, acetylcholine, sodium nitroprusside, and verapamil. For all dose responses, $P < 0.0001$. For diesel exposure (●) vs air (○), bradykinin $P < 0.05$, acetylcholine $P < 0.05$, sodium nitroprusside $P < 0.001$, and verapamil $P = \text{NS}$.

able to show that vasodilation to the calcium channel antagonist verapamil was unaffected. This suggests that the mechanism of vascular dysfunction involves increased consumption of NO, whether it be endogenously derived from endothelial NO synthase or from an exogenous source, such as sodium nitroprusside. Indeed, *in vitro* studies provide support for this mechanism, with Ikeda et al²³ demonstrating that incubation of aortic ring preparations with diesel exhaust particles resulted in a dose-dependent inhibition of acetylcholine-mediated relaxation, an effect abolished by coincubation with superoxide dismutase.

Our findings of an acute effect of exposure to air pollution are consistent with recent epidemiological studies that report a significant increase in risk of acute myocardial infarction as little as 2 hours after exposure to road traffic⁸ or an increase in $\text{PM}_{2.5}$.¹ Our studies add to those of Brook et al,²⁴ who demonstrated a reduction in brachial artery diameter immediately after exposure to a mixture of concentrated ambient particles and ozone. In contrast, they did not find an effect on endothelium-dependent or -independent vasodilation by flow-mediated and nitroglycerine-induced dilation. This may reflect differences in the potency of the pollution models used or the technique used to assess vascular function. Exposures to concentrated ambient particulates are inherently variable in

magnitude and composition, whereas in our study, each volunteer received a standard exposure to combustion-derived particulates of known toxicity. Alternatively, it is possible that the vascular effects of particulate matter are mediated primarily in the resistance vessels, as assessed by plethysmography, rather than in the conduit arteries, as assessed by ultrasound of the brachial artery.

Fibrinolytic Function

Acute endogenous t-PA release from the endothelium regulates the dissolution of intravascular thrombus and is a critical determinant of cardiovascular outcome. This is exemplified by the clinical observation that in $\approx 30\%$ of patients with acute myocardial infarction, spontaneous reperfusion occurs within 12 hours of vessel occlusion. The increased risk of atherothrombosis and myocardial infarction in cigarette smokers is at least in part explained by impaired fibrinolytic capacity.^{10,11}

We have described an impairment in acute endogenous fibrinolytic capacity after diesel exhaust inhalation. This abnormality may have prothrombotic consequences that could plausibly result in acute cardiovascular events.⁸ t-PA release was reduced 6 hours after exposure but not at the earlier time point, suggesting that this impairment is mediated by an inducible pathway or a change in protein synthesis.

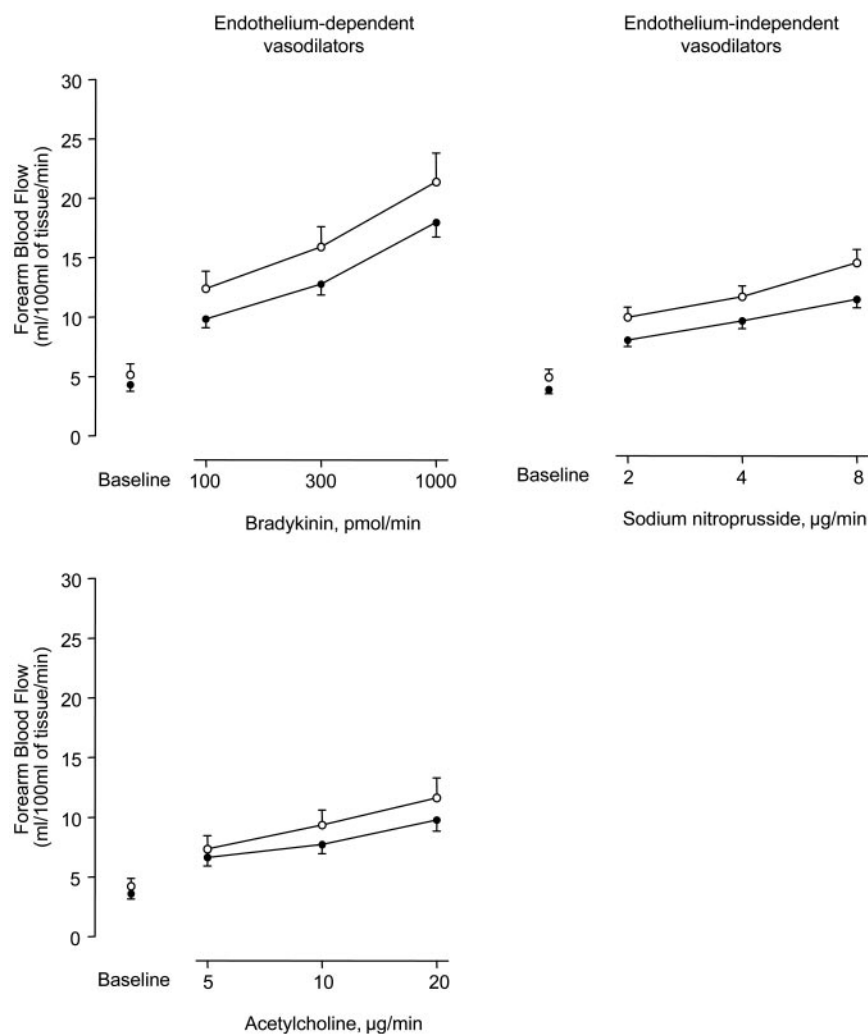


Figure 2. Infused FBF in subjects 6 to 8 hours after diesel exposure (●) and air (○) during intrabrachial infusion of bradykinin, acetylcholine, and sodium nitroprusside. For all dose responses, $P < 0.0001$. For diesel exposure (●) vs air (○), bradykinin $P < 0.05$, acetylcholine $P = 0.07$, and sodium nitroprusside $P < 0.001$.

Indeed, culture of human umbilical vein endothelial cells with particulate matter for 6 hours inhibits both the synthesis and release of t-PA in a dose-dependent manner.²⁵ Given that cigarette smoking and air pollution share common toxicolog-

ical properties, the present findings are consistent with previous observations in the peripheral¹⁰ and coronary¹¹ circulations of cigarette smokers and suggest a potential common etiologic factor.

TABLE 3. Plasma t-PA Antigen Concentrations After Air and Diesel Exposure

	Air (Bradykinin, pmol/min)				Diesel (Bradykinin, pmol/min)			
	0	100	300	1000	0	100	300	1000
2 Hours								
tPA antigen, ng/mL								
Noninfused arm	7.0±0.6	7.0±0.7	7.7±0.8	9.4±1.2	7.2±0.8	7.5±0.8	8.0±0.8	8.9±0.8
Infused arm	6.5±0.5	8.8±1.4	12.2±1.9	17.1±1.3*	6.6±0.7	9.8±1.5	13.7±0.9	18.7±2.7*
Difference	-0.5±0.3	1.7±0.8	4.6±1.2	9.3±1.1*	-0.3±0.4	2.2±0.8	5.3±1.4	9.9±2.2*
Net t-PA release, ng/100 mL of tissue per min	-3.3±2.2	6.6±2.7	27.3±4.3	81.3±10.7*	-0.2±1.0	8.9±3.0	29.4±6.1	82.5±17.8*
6 Hours								
tPA antigen, ng/mL								
Noninfused arm	5.8±0.5	7.1±1.1	7.0±0.6	7.7±0.6	5.5±0.6	5.6±0.5	5.7±0.4	7.1±0.5
Infused arm	6.0±0.5	9.6±1.7	12.0±1.3	18.6±2.5*	5.3±0.6	7.4±0.9	10.0±1.0	14.5±1.3*‡
Difference	0.2±0.2	2.6±1.7	5.4±1.1	11.7±2.5*	-0.2±0.2	2.0±0.6	4.6±0.8	8.0±1.1*†
Net t-PA release, ng/100 mL of tissue per min	0.7±0.9	15.8±9.4	42.9±7.3	138.2±27.8*	-1.0±0.5	10.6±2.9	33.2±5.1	82.5±11.5*†

Values are reported as mean±SEM.

ANOVA (dose response), * $P < 0.0001$; ANOVA (air vs diesel), † $P < 0.05$, ‡ $P < 0.001$.

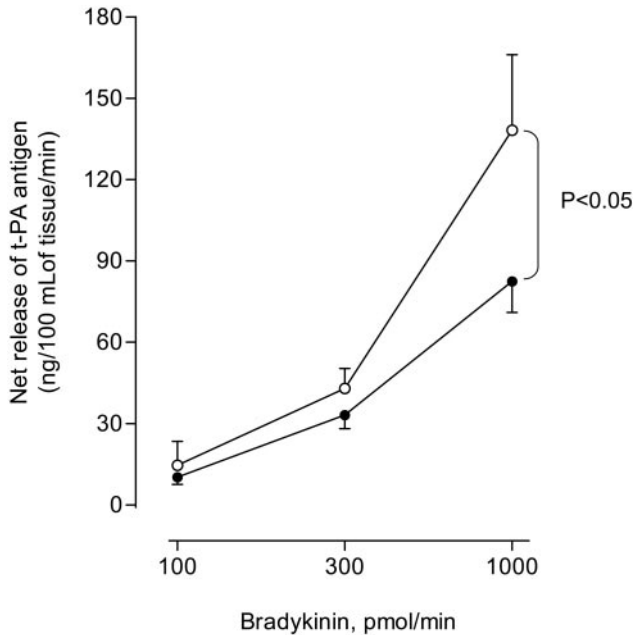


Figure 3. Net release of t-PA antigen in subjects 6 hours after diesel exposure (●) and air (○) during intrabrachial infusion of bradykinin. For both dose responses, $P < 0.0001$. For diesel exposure (●) vs air (○), $P < 0.05$.

Air Pollution, Oxidative Stress, and Inflammation

A substantial body of evidence supports a role for oxidative stress in determining the toxicity of ambient pollution²⁶ and in the proinflammatory effects of diesel exhaust particles.^{27,28} Reactive oxidant species arise not only from the redox potential of the pollutants themselves but also from the activation of alveolar epithelial cells or resident macrophage and the recruitment of circulating neutrophils.

The potential for inhaled nanoparticulate air pollution to cause local inflammation is not in doubt, and airway neutrophilia has been demonstrated in a healthy volunteer study with the same concentration of diesel particulate and exposure system.¹⁵ In our study, inhaled diesel exhaust was not associated with an increase in blood leukocytes, plasma IL-6 and TNF- α , or serum CRP concentrations, but this does not rule out the influence of other circulating inflammatory factors, oxidized lipids, or proteins.

Population Risk and Exposure

As an important source of combustion-derived particulate, diesel exhaust is strongly implicated in the observed adverse effects of air pollution.^{4,29,30} Particulate matter concentrations can regularly reach levels of 300 $\mu\text{g}/\text{m}^3$ in heavy traffic, occupational settings, and the world's largest cities.³¹ Exposure to 300 $\mu\text{g}/\text{m}^3$ for 1 hour increases a person's average exposure during a 24-hour period by only 12 $\mu\text{g}/\text{m}^3$. Changes of this magnitude occur on a daily basis in even the least polluted of cities and are associated with increases in cardiorespiratory mortality.³ Our model is therefore relevant in both the composition and magnitude of exposure for the assessment of short-term health effects in humans.

Diesel exhaust is a complex mixture of gases and particles, and from our findings, we cannot exclude a nonparticulate

cause of the adverse vascular effects. However, in epidemiological studies, particulate matter has been held responsible for the majority of the adverse health effects of air pollution.³² Ambient NO₂ can be considered a surrogate for traffic-derived pollution,²⁹ but it has little adverse effect in controlled chamber studies, even at the exposure levels seen here.³³ There are no reports of the potential adverse cardiovascular effects of toxins such as hydrocarbons or formaldehyde. We therefore suggest that the vascular effects described herein are mediated primarily by diesel exhaust particulates and not its other components, but this needs to be more definitively addressed.

Conclusions

Exposure to increased levels of combustion-derived air pollution for as little as 1 hour can impair vasomotor function and endogenous fibrinolysis in humans. We provide evidence that this may be the result of reduced NO bioavailability in the vasculature and postulate that this effect is mediated by oxidative stress induced by the nanoparticulate fraction of diesel exhaust. These data provide a plausible mechanistic link to explain the association between air pollution and acute myocardial infarction.

Acknowledgments

This work was supported by British Heart Foundation Project (03/017/15071) and Programme (PG/05/003) Grants; a Small Project grant from the National Health Service Research and Development Fund; the Swedish Heart-Lung Foundation; the Swedish Research Council for Environment, Agricultural Sciences, and Spatial Planning (FORMAS); Front Research; the County Council of Västerbotten; and the Swedish National Air Pollution Programme. We thank David Webb, Neil Johnston, Ian Megson, Mike Crane, Pamela Dawson, Frida Holmström, Annika Johansson, Maj-Cari Ledin, Jamshid Pourazar, and all the staff in the Department of Respiratory Medicine and Allergy, Umeå, and the Wellcome Trust Clinical Research Facility, Edinburgh, for their assistance with the studies.

Disclosures

None.

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CLINICAL PERSPECTIVE

Air pollution is a serious problem in the world's major cities owing to the combustion of fossil fuels such as diesel oil. In particular, there has been recent interest in the consistent association between increased levels of air pollution and cardiovascular morbidity and mortality. The World Health Organization estimates that a quarter of the world's population is exposed to unhealthy concentrations of air pollutants. The American Heart Association recently issued a scientific statement highlighting the increased cardiovascular risk associated with exposure to air pollution and emphasized the importance of establishing a mechanistic link to explain these epidemiological observations. We have previously demonstrated vascular dysfunction in cigarette smokers. Because combustion products and particulate matter are common to both polluted air and cigarette smoke, we hypothesized that air pollution would cause detrimental vascular effects. This is the first study to demonstrate that inhalation of diesel exhaust, a common urban air pollutant, can impair vascular function in humans. Using a double-blind, randomized, cross-over study design, we have assessed the effects of diesel exhaust inhalation on 2 important and complementary aspects of vascular function: the regulation of vascular tone and endogenous fibrinolysis. We were able to demonstrate that both are impaired and plausibly related to the well-documented adverse cardiovascular effects of air pollution. These important findings provide a plausible mechanism that links air pollution to the pathogenesis of atherothrombosis and acute myocardial infarction.

Particle Traps Prevent Adverse Vascular and Prothrombotic Effects of Diesel Engine Exhaust Inhalation in Men

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Circulation. 2011;123:1721-1728; originally published online April 11, 2011;
doi: 10.1161/CIRCULATIONAHA.110.987263

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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Particle Traps Prevent Adverse Vascular and Prothrombotic Effects of Diesel Engine Exhaust Inhalation in Men

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Background—In controlled human exposure studies, diesel engine exhaust inhalation impairs vascular function and enhances thrombus formation. The aim of the present study was to establish whether an exhaust particle trap could prevent these adverse cardiovascular effects in men.

Methods and Results—Nineteen healthy volunteers (mean age, 25 ± 3 years) were exposed to filtered air and diesel exhaust in the presence or absence of a particle trap for 1 hour in a randomized, double-blind, 3-way crossover trial. Bilateral forearm blood flow and plasma fibrinolytic factors were assessed with venous occlusion plethysmography and blood sampling during intra-arterial infusion of acetylcholine, bradykinin, sodium nitroprusside, and verapamil. Ex vivo thrombus formation was determined with the use of the Badimon chamber. Compared with filtered air, diesel exhaust inhalation was associated with reduced vasodilatation and increased ex vivo thrombus formation under both low- and high-shear conditions. The particle trap markedly reduced diesel exhaust particulate number (from 150 000 to 300 000/cm³ to 30 to 300/cm³; $P < 0.001$) and mass (320 ± 10 to 7.2 ± 2.0 $\mu\text{g}/\text{m}^3$; $P < 0.001$), and was associated with increased vasodilatation, reduced thrombus formation, and an increase in tissue-type plasminogen activator release.

Conclusions—Exhaust particle traps are a highly efficient method of reducing particle emissions from diesel engines. With a range of surrogate measures, the use of a particle trap prevents several adverse cardiovascular effects of exhaust inhalation in men. Given these beneficial effects on biomarkers of cardiovascular health, the widespread use of particle traps on diesel-powered vehicles may have substantial public health benefits and reduce the burden of cardiovascular disease.

Clinical Trial Registration—<http://www.clinicaltrials.gov>. Unique identifier: NCT00745446. (*Circulation*. 2011;123:1721-1728.)

Key Words: air pollution ■ endothelium ■ thrombosis

There is a robust and consistent association between air pollution and cardiorespiratory morbidity and mortality.¹⁻⁴ These harmful effects are most strongly associated with exposure to traffic-derived fine particles (particulate matter [PM] with a mean diameter < 2.5 μm [PM_{2.5}]) that originate predominantly from diesel engine exhaust emissions.⁵ Diesel engines are popular because of their reliability, efficiency, and relatively low running costs. However, they generate up to 100 times more fine particles than petroleum engines of a similar size and contribute substantially to the global burden of PM air pollution.

Editorial see p 1705 Clinical Perspective on p 1728

According to the World Health Organization, air pollution is responsible for at least 800 000 premature deaths worldwide each year, with an average loss of life of 1 year.⁶ The long-term risk of cardiovascular death rises by 76% for each 10- $\mu\text{g}/\text{m}^3$ increase in PM_{2.5}.^{7,8} Short-term exposure has been linked to the triggering of acute myocardial infarction,⁹ with patients 3 times more likely to be exposed to traffic-derived air pollution in the hours before their acute myocardial

Received September 1, 2010; accepted January 24, 2011.

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The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.110.987263/DC1>.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.110.987263

infarction.¹⁰ Despite the strength and consistency of observational studies, the underlying pathophysiological mechanisms remain unclear. Using well characterized and controlled diesel engine exhaust exposure studies in healthy volunteers, we have previously demonstrated impaired vascular vasomotor and fibrinolytic function,¹¹ increased arterial stiffness,¹² and enhanced *ex vivo* thrombus formation.¹³ Furthermore, in patients with coronary heart disease, we have shown that diesel engine exhaust inhalation exacerbates exercise-induced ST-segment depression during light exercise.¹⁴ Taken together, these adverse cardiovascular effects provide important mechanisms that help to explain the detrimental health effects of air pollution exposure.

One approach to limit traffic emissions has been the introduction of diesel engine exhaust particle traps or filters. Although the efficiency of particle traps to reduce particle emission is >90%, particles are not completely eliminated, and traps have the potential to create new and potentially more toxic particles that may outweigh the benefits of reducing the emitted particle mass.¹⁵ We therefore sought to determine whether the introduction of a particle trap would attenuate or worsen the adverse cardiovascular effects of diesel engine exhaust inhalation.^{11–14}

Methods

Twenty-one subjects were screened, and 1 subject was excluded at the initial screening. A further subject was excluded after randomization because of inability to complete all exposures, leaving 19 healthy nonsmoking men who completed the full study protocol (see Figure I in the online-only Data Supplement). The study was approved by the local research ethics committee and conducted in accordance with the Declaration of Helsinki and with the written informed consent of all volunteers.

All subjects had normal lung function and no symptoms of upper airway infection for the 4 weeks before or during the study. Exclusion criteria were regular medication, clinical evidence of atherosclerotic vascular disease, arrhythmias, diabetes mellitus, hypertension, renal or hepatic failure, asthma, significant occupational exposure to air pollution, or intercurrent illness. All subjects abstained from caffeine-containing drinks or food for at least 4 hours and from alcohol for 24 hours before each assessment.

Study Design

The primary end points were endothelial vasomotor and fibrinolytic function and *ex vivo* thrombus formation. Secondary end points were soluble markers of inflammation and platelet activation. Exploratory end points were markers of arterial stiffness and airway inflammation. Sample size was determined a priori and based on power calculations for the primary end points derived from our previous studies (see the online-only Data Supplement).^{11,13}

In a randomized, double-blind, 3-way crossover design, subjects were exposed to filtered air, unfiltered dilute diesel engine exhaust, and dilute diesel engine exhaust that had passed through a particle trap. The order of the exposures was randomized, with an independent predetermined exposure sequence. Exposures were performed at a separate dedicated exposure facility by technical staff with no involvement in the clinical studies. Clinical studies were performed in a dedicated clinical research facility by clinical staff blinded to exposure allocation. Exposures were separated by at least 1 week and performed in a purpose-built exposure chamber, according to a previously described standard protocol.¹¹ During each 1-hour exposure, subjects performed moderate exercise (minute ventilation, 25 L/min per m² body) on a bicycle ergometer for 15 minutes alternated with 15 minutes of rest.

Diesel Exhaust

A Volvo diesel engine (Volvo TD40 GJE, 4.0 L, 4 cylinders) running on Volvo standard diesel fuel (SD-VSD-10) was used to generate the diesel exhaust. The specification of the Volvo diesel fuel is similar to the European automotive standard diesel (EN590), with a sulfur content of 5 to 7 mg/kg and polycyclic aromatic hydrocarbon content of 2% to 6% by mass. The engine worked under transient speed and load conditions in accordance with the standardized European transient cycle that mimics real-world urban driving conditions.¹⁶ More than 90% of the exhaust was shunted away, and the residual exhaust was mixed with filtered air (Figure 1).

The concentrations of nitrogen oxides (NO, NO₂, and other nitrogen oxides) in the chamber were monitored continuously together with total gaseous hydrocarbons. During diesel exhaust exposures, we sought to generate a PM mass concentration of 300 μg/m³. This PM mass concentration was maintained for the inlet conditions of the particle trap. Actual exposure was measured gravimetrically with standard glass fiber filter sampling together with the use of a tapered element oscillating microbalance online instrument and in accordance with a well-established protocol, as described previously.¹⁷ In addition, a scanning mobility particle sizer system was used to determine fine (<1 μm) particle number concentration.

Particle Trap

The particle trap (diesel particulate filter—continuously regenerating trap [DPF-CRT], Johnson Matthey, Royston, UK) used is an unmodified, continuously regenerating trap filter, available commercially throughout the world as a factory-fit option or as a retrofit unit to buses and heavy goods vehicles. It is similar in design to filters produced by a number of manufacturers. It consists of a honeycomb-like complex of channels through which the exhaust is passed. A catalyst at the front of the filter oxidizes part of the NO gas in the exhaust into NO₂, which flows through the particle filter and subsequently reacts with trapped carbonaceous particles to generate CO₂ and N₂. This increases NO₂ levels in the exhaust after the particle trap, without causing significant changes in total nitrogen oxide concentrations, while achieving an efficient reduction in particle emissions.

Vascular Studies

On the basis of data from previous exposure studies,^{13,14,16,18} vascular assessment was performed 6 to 8 hours after each exposure. Assessments were performed with subjects resting supine in a quiet temperature-controlled (22°C to 24°C) room. Venous cannulas (17 gauge) were inserted into large subcutaneous veins in the antecubital fossae of both arms. The brachial artery of the nondominant arm was cannulated with a 27-standard-wire-gauge steel needle. After a baseline 30-minute saline infusion, bradykinin at 100, 300, and 1000 pmol/min (endothelium-dependent vasodilator that releases tissue-type plasminogen activator [tPA]; Merck Biosciences, Nottingham, UK); acetylcholine at 5, 10, and 20 μg/min (endothelium-dependent vasodilator that does not release tPA; Merck Biosciences); and sodium nitroprusside at 2, 4, and 8 μg/min (endothelium-independent vasodilator that does not release tPA; David Bull Laboratories, Warwick, UK) were infused for 6 minutes at each dose. The 3 vasodilators were given in random order, separated by a 20-minute saline infusion. Verapamil was infused at 10, 30, and 100 μg/min (endothelium-independent and NO-independent vasodilator that does not release tPA) at the end of the study protocol. The infusion of these vasodilators was undertaken to allow the assessment of distinct aspects of vascular function, including NO, endothelium, fibrinolysis, and vasomotion.

Forearm blood flow was measured in both infused and noninfused arms with venous occlusion plethysmography incorporating mercury-in-silicone elastomer strain gauges as described previously.¹¹ Heart rate and blood pressure were monitored in the noninfused arm throughout each study with a noninvasive, semiautomated oscillometric sphygmomanometer (Boso Medicus, Jungingen, Germany). Blood was drawn simultaneously from the venous cannulas in each arm at baseline and during infusion of each dose of bradykinin. Samples were collected into acidified buffered citrate

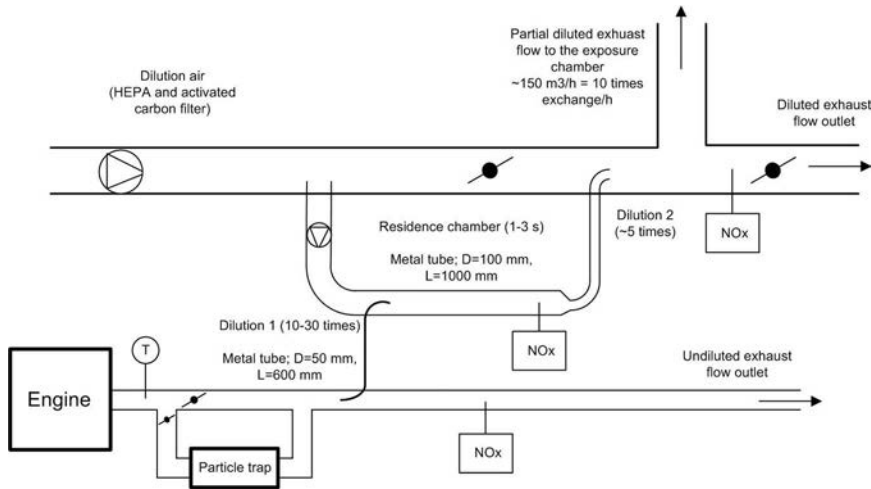


Figure 1. Schematic illustration of the diesel exhaust setup from the engine to the flow of diluted exhaust to the chamber. HEPA indicates high-efficiency particulate air; NO_x, nitrogen oxides.

(Stabilyte, Biopool International) for tPA assays and into citrate (BD Vacutainer) for plasminogen activator inhibitor type 1 assays. Samples were kept on ice before being centrifuged at 2000g for 30 minutes at 4°C. Platelet-free plasma was decanted and stored at -80°C before assay. Plasma tPA and plasminogen activator inhibitor type 1 antigen concentrations were determined by enzyme-linked immunosorbent assay (TintElize tPA, Biopool EIA, Trinity Biotech, Ireland; Coaliza plasminogen activator inhibitor type 1, Chromogenix AB, Milan, Italy). Hematocrit was determined by capillary tube centrifugation of samples collected at baseline and during infusion of bradykinin at 1000 pmol/min.

Inflammatory Measures

Venous blood samples were obtained before and at 2, 6, and 8 hours after exposure. Samples were analyzed for total and differential cell count with an autoanalyzer. Plasma interleukin-6, tumor necrosis factor-α, soluble CD40 ligand, soluble P-selectin, intercellular adhesion molecule-1, and C-reactive protein were measured with commercially available enzyme-linked immunosorbent assays (R&D Systems, Abingdon, UK).

Ex Vivo Thrombosis Studies

On the basis of previous studies,¹³ ex vivo thrombus formation was determined with the use of the Badimon chamber 2 hours after each exposure. In brief, a pump was used to draw blood from an antecubital vein through a series of 3 cylindrical perfusion chambers maintained at 37°C in a water bath. Carefully prepared strips of porcine aorta, from which the intima and a thin layer of media had been removed, acted as the thrombogenic substrate. The rheological conditions in the first chamber simulate those of patent coronary arteries (low-shear rate, ≈212 s⁻¹), and those in the second and third chambers simulate those of mildly stenosed coronary arteries (high-shear rate, ≈1690 s⁻¹). The model thus acts as one of deep coronary arterial injury. Each study lasted for 5 minutes, during which flow was maintained at a constant rate of 10 mL/min. All studies were performed with the same perfusion chamber, by the same operator, and according to a well-established protocol.¹³

Immediately after each study, porcine strips with thrombus attached were removed and fixed in 4% paraformaldehyde. Strips were paraffin-wax embedded, sectioned, and stained with Masson’s trichrome. Images were acquired at ×20 magnification, and thrombus area was measured with a semiautomated image acquisition system (Ariol, Applied Imaging) by a blinded operator. Results from at least 6 sections were averaged to determine thrombus area for each chamber as described previously.^{19,20}

Assessment of Arterial Stiffness

Please see the online-only Data Supplement.

Assessment of Airway Inflammation

Please see the online-only Data Supplement.

Data Analysis and Statistics

Plethysmographic data were analyzed as described previously.¹¹ Estimated net release of tPA antigen was defined as the product of the infused forearm plasma flow (based on the mean hematocrit and the infused forearm blood flow) and the concentration difference between the infused and noninfused arms, as described previously.^{11,14} Continuous variables are reported as mean±SEM. Statistical analyses were performed with GraphPad Prism (Graph Pad Software, CA). All studies, data analysis, and data exclusion were performed before the data were unblinded.

To address our primary hypothesis, the analysis plan required 2 independent assessments of the responses in the 3 randomized arms of the study. First, to confirm our previous findings, we assessed whether the inhalation of diesel engine exhaust impaired vascular function and promoted thrombogenesis. Second, we assessed whether the particle trap improved these surrogate measures of cardiovascular health. Comparisons between exposures were undertaken with a 2-sided paired *t* test and 2-way ANOVA with repeated measures, as appropriate. Factors assessed in the 2-way ANOVA were exposure and vasodilator dose. Exposure data were analyzed with a 2-sided unpaired *t* test. Statistical significance was taken at *P*<0.05.

Results

The 19 healthy male volunteers were young and normotensive, and had normal lung function (Table 1). All volunteers

Table 1. Baseline Subject Characteristics (n=19)

Age, y	25±3
Height, cm	181±5
Weight, kg	75±8
Body mass index, kg/m ²	23.4±2
Pulse, bpm	54±8
Systolic blood pressure, mm Hg	113±6
Diastolic blood pressure, mm Hg	73±8
FEV ₁ , L	4.6±0.6
% Predicted FEV ₁	100±12
FVC, L	5.6±0.8
% Predicted FVC	103±14

Data shown are mean±SEM (n=19). FEV₁ indicates forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2. Exposure Conditions in the Chamber

	Filtered Diesel Exhaust	Diesel Exhaust	<i>P</i>
NO, ppm	2.09±0.15	5.72±0.33	<0.001
NO ₂ , ppm	3.44±0.33	0.69±0.02	<0.001
NO _x , ppm	5.53±0.44	6.40±0.34	0.049
Total gaseous hydrocarbons, ppm	0.84±0.06	0.91±0.05	0.387
Total PM mass concentration, μg/m ³	7.2±2.0	320±10	<0.001
Fine particle number concentration, n/cm ³	30–300	150 000–200 000	<0.001

Data shown are mean±SEM (n=19) unless indicated otherwise. Data were analyzed by 2-tailed unpaired *t* test. NO indicates nitric oxide; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; and PM, particulate matter.

completed the 3 study visits. Exposures were well tolerated, with no adverse symptoms reported.

The particle trap reduced the total particle mass concentration in the chamber by ≈98% and the fine (<1 μm) particle number concentration by >99.8%. As anticipated, the particle trap, with an integrated oxidation catalyst, altered the composition of nitrogen oxides (ie, increased NO₂ and decreased NO) (Table 2). However, it had no significant effect on the concentrations of gaseous hydrocarbons.

There were no changes in blood pressure, resting heart rate, baseline forearm blood flow, or markers of arterial stiffness in between the 3 study visits (Tables II and III in the online-only Data Supplement). Hematologic variables, markers of inflammation, and soluble markers of platelet activation did not differ between exposures (Tables IV and V in the online-only Data Supplement). Markers of airway inflammation did not differ between exposures (Table VI in the online-only Data Supplement).

Vascular Studies

Vasomotor Function

There was a dose-dependent increase in forearm blood flow with both endothelium-dependent (bradykinin and acetylcholine) and endothelium-independent (sodium nitroprusside and verapamil) vasodilators after each exposure (*P*<0.0001 for all; Figure 2).

Compared with filtered air, vasodilatation was impaired after diesel engine exhaust exposure in response to bradykinin (*P*=0.009), acetylcholine (*P*=0.01), and verapamil (*P*=0.03; Figure 2). There was no significant difference in response to sodium nitroprusside (*P*=0.15; Figure 2). However, with the introduction of the particle trap, vasodilatation increased in response to all vasodilators: bradykinin (*P*<0.0001), acetylcholine (*P*<0.0001), verapamil (*P*=0.001), and sodium nitroprusside (*P*=0.04; Figure 2). Indeed, there were no differences in vasomotor responses between filtered air and filtered diesel engine exhaust except for acetylcholine, with which vasodilatation was lower with filtered air (*P*=0.02).

Fibrinolytic Function

There were no differences in baseline plasma tPA and plasminogen activator inhibitor type 1 concentrations between exposures

(Table VI in the online-only Data Supplement). There was a dose-dependent increase in tPA release in response to bradykinin infusion after each exposure (*P*<0.0001 for all; Figure 3). Although numerically lower, there was no statistical difference in tPA release after exposure to diesel engine exhaust inhalation compared with filtered air (*P*=0.30; Figure 3). However, application of the particle trap was associated with an improvement in the net release of tPA compared with unfiltered diesel engine exhaust (*P*=0.03; Figure 3). There was no difference in tPA release between filtered air and filtered diesel engine exhaust (*P*=0.22).

Ex Vivo Thrombosis

Compared with filtered air, inhalation of diesel exhaust was associated with an increase of thrombus formation in the low-shear (21.8%; *P*<0.001; Figure 4) and high-shear (14.8%; *P*=0.02; Figure 4) chambers. Compared with unfiltered exhaust, the introduction of the particle trap was associated with a reduction in thrombus formation in the low-shear chamber (−15.7%; *P*=0.02; Figure 4), whereas the apparent reduction in the high-shear chamber did not reach statistical significance (*P*=0.11; Figure 4). There were no differences in thrombus formation between filtered air and filtered diesel exhaust (*P*=0.78 and *P*=0.76 for the low- and high-shear chambers, respectively).

Discussion

Short-term exposure to traffic-derived air pollution is associated with acute cardiovascular events.^{9,10,21} In the present study, using complementary and relevant measures of cardiovascular health, we have reconfirmed the adverse effects of exposure to diesel engine exhaust on endothelial function and ex vivo thrombosis. In addition, for the first time, we demonstrate that reducing the particulate component of diesel exhaust with the use of a commercially available particle trap can prevent these detrimental cardiovascular effects. Our study provides support for the application of particle traps to diesel-powered vehicles to reduce urban particulate concentrations and limit a range of adverse cardiovascular effects of exposure to traffic-derived air pollution.

In a series of controlled exposure studies in human subjects, we have previously shown an impairment of vasomotor responses to endothelium-dependent and endothelium-independent vasodilators after diesel exhaust exposure.¹⁸ These observations are consistent with other reports of brachial artery vasoconstriction shortly after exposure to dilute diesel exhaust²² and concentrated ambient particles.²³ Such vascular impairment is not restricted to vasomotor function. We have also demonstrated increased thrombogenicity with reduced tPA release from the endothelium,¹¹ enhanced platelet activation,¹³ and increased ex vivo thrombus formation.¹³

In the present study, we used a range of these complementary measures of cardiovascular function in a comprehensive assessment of the potential for particle traps to improve human health. We were able to confirm our earlier findings that diesel exhaust inhalation causes detrimental vascular and prothrombotic effects. On this occasion, we did not observe a statistically significant reduction in tPA release from the

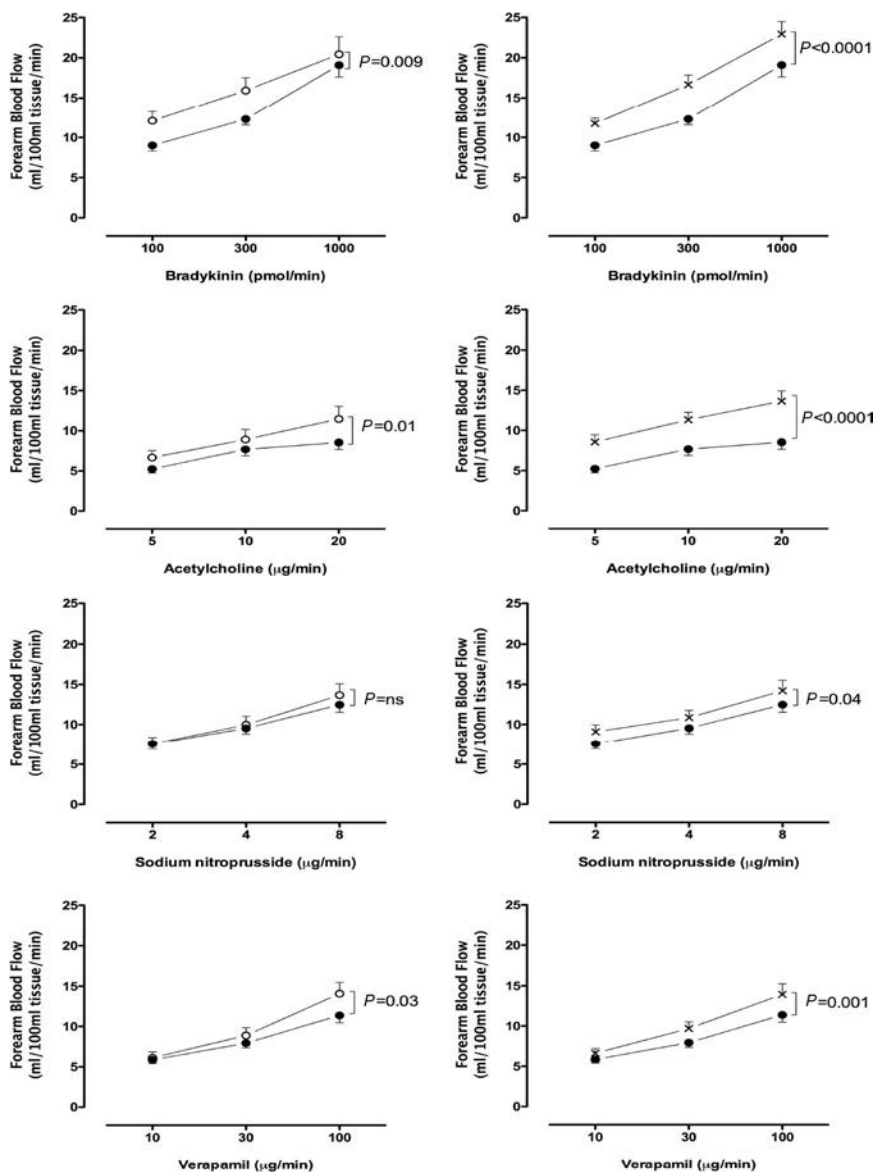


Figure 2. Infused forearm blood flow 4 to 6 hours after exposure, during intra-brachial infusion of bradykinin, acetylcholine, sodium nitroprusside, and verapamil. The left panel displays vasomotor response after exposure to air and diesel exhaust, confirming the vascular effects from previous investigations. Filtered air exposure is shown by open circles, and diesel engine exhaust exposure by filled circles. The right panel displays the main comparison of vasomotor function after exposure to unfiltered diesel exhaust (filled circles) and filtered diesel exhaust (crosses).

endothelium after diesel exhaust exposure, and this may represent a type II error or reflect the subtle differences between study protocols. However, more importantly, we were able to demonstrate that the introduction of a particle trap not only improved vasomotion, endogenous fibrinolysis, and ex vivo thrombosis but appeared to normalize them.

Although there are many potentially harmful components in ambient air pollution, traffic-derived fine and ultrafine particles are most closely and consistently linked to acute cardiovascular events. This has been the rationale for the development of, and legislation for, targeted interventions to reduce the particulate matter content of vehicle emissions.²⁴

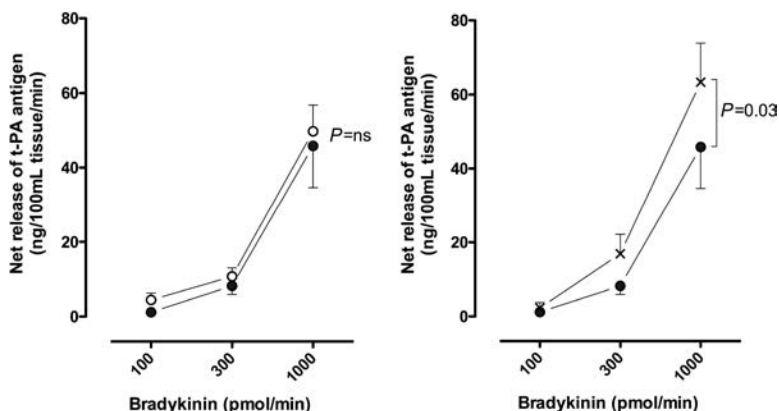


Figure 3. Tissue-type plasminogen activator (tPA) release from the forearm endothelium 4 to 6 hours after exposure, during intrabrachial infusion of bradykinin. The left panel displays fibrinolytic response after exposure to air and diesel exhaust. Filtered air exposure is shown by open circles and diesel engine exhaust exposure by filled circles. The right panel displays the main comparison of fibrinolytic function after exposure to unfiltered diesel exhaust (filled circles) and filtered diesel exhaust (crosses).

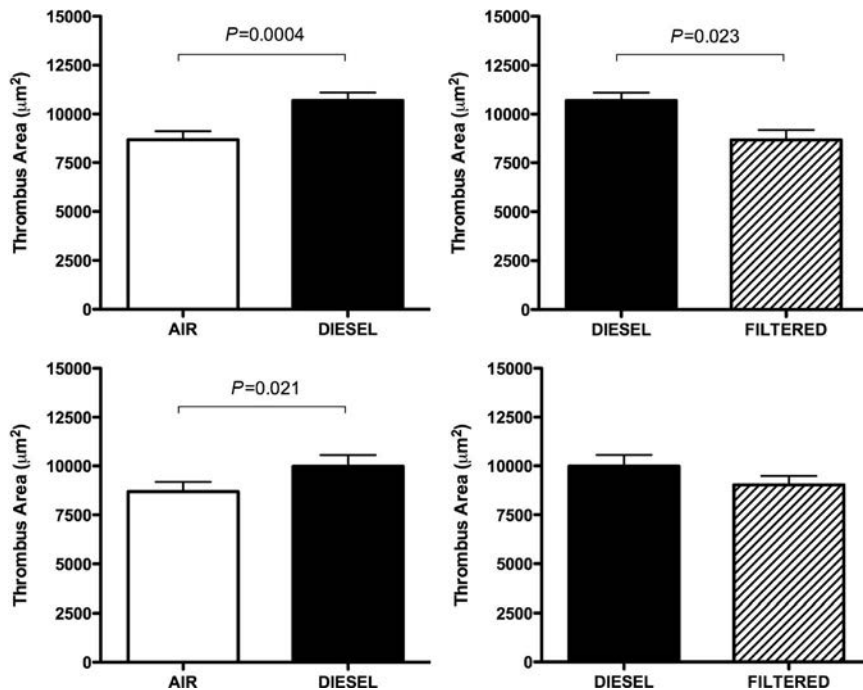


Figure 4. Ex vivo thrombus formation assessed with the Badimon chamber at 2 hours after exposure. Data from the low-shear chamber are shown in the top panels. Data from the high-shear chamber are shown in the bottom panels. Filtered air exposure is shown in white, diesel engine exhaust exposure in black, and filtered diesel exposure in hatched bars.

Although there is little doubt that particle traps are effective in reducing PM mass and number, concerns have been raised regarding the oxidation catalysts required to regenerate and maintain filter efficiency, because they may alter the toxicity of particulate and gaseous emissions. For example, soot particles generated from a low-emission diesel engine appear to have greater cytotoxic and proinflammatory effects.¹⁵ The potential for particle traps to reduce the adverse cardiovascular effects of diesel exhaust emissions therefore needs to be assessed in humans. In the present study, we observed no adverse cardiovascular effects arising from the use of a particle trap. In fact, the only difference between filtered air and filtered diesel exhaust observed for any variable we assessed was an enhancement of vasodilatation in response to acetylcholine after exposure to filtered diesel exhaust. Although this difference was statistically significant, it was numerically small, and unlikely to be of major physiological significance. In light of these factors, we suspect that this may be a result of a type I error, although we cannot rule out an effect related to alterations in 1 or more unmeasured gaseous components.

We used a commercially available particle trap to reduce particle emissions from a heavy-duty diesel engine operating under the transient cycling conditions used as the standard for engine testing across the European Union. Particle filtration markedly reduced the mass and number of particle emissions. Taken together with our previous findings and data from observational studies, we believe that this reduction is responsible for rectifying the adverse cardiovascular effects of diesel engine exhaust inhalation. As expected, oxidation catalysts within the particle trap altered the composition of nitrogen oxides, with an increase in NO₂ and decrease in NO concentrations. However, we have recently assessed the effects of NO₂ on healthy volunteers, and did not identify any adverse effects on vascular or fibrinolytic function.²⁵ Al-

though we did not observe an effect on the other gaseous components of the exposure, we acknowledge that the particle trap may have altered the composition of the exposures beyond those variables assessed during this study.

Consistent with previous studies,^{11,16,18} vasodilatation was impaired after exposure to diesel engine exhaust in response to bradykinin and acetylcholine. However, there was also a reduction in vasodilatation to verapamil, implying an additional calcium flux-dependent impairment of vascular smooth muscle function. A reduction in vasodilatation in response to verapamil has been demonstrated previously after exposure to diesel exhaust generated under transient engine speed and load,¹⁶ but not when generated under idling conditions.¹¹ We have speculated previously that, in exhaust generated under transient running conditions, the higher diesel-related soot content and its associated (adsorbed) organic material may cause these additional vascular smooth muscle effects, and we believe that this observation warrants further investigation.¹⁶ Interestingly, impaired vasodilatation in response to verapamil was also normalized by the introduction of a particle trap. Although variations in responses between studies with different exposure protocols might provide insights into the pathophysiological mechanisms responsible for the adverse vasomotor effects of diesel exhaust exposure, these studies were designed and powered to detect differences within rather than between studies. Thus, although tempting, we believe that we should be cautious and circumspect in drawing conclusions from comparisons made between studies and that any such differences should be regarded as hypothesis generating and the subject of future investigations.

The exact mechanisms underlying the vascular and prothrombotic effects we observed in the current and previous studies remain only partially understood. Regarding the increase in ex vivo thrombosis seen after diesel exhaust

exposure, data from previous *in vitro*²⁶ and animal studies,²⁷ as well as our own previous controlled exposure studies in humans,¹³ suggest that platelet activation plays a central role. Platelets are key components of arterial thrombosis, a process that underpins acute coronary syndromes, including myocardial infarction. Platelet-leukocyte aggregates, increasingly recognized as the gold standard measure of *in vivo* platelet activation,²⁸ were increased after tracheal instillation of carbon nanotubes in a murine model of vascular injury²⁹ and after diesel exhaust exposure in humans.¹³ Debate remains regarding whether inhaled components of diesel exhaust can translocate into the systemic circulation to mediate direct effects on blood and vascular components,^{30,31} or whether the induction of pulmonary inflammation and the subsequent generation of free radicals may activate platelets by reducing endothelium- and platelet-derived nitric oxide and antioxidants. Although a single observational study reported a small reduction in prothrombin time associated with ambient exposure to PM₁₀,³² the authors are not aware of any controlled exposure study demonstrating an effect of pollution exposure on plasma concentrations of coagulation factors.

The potential mechanisms underlying the adverse vasomotor effects observed in response to diesel exhaust exposure remain only partly understood,³³ and a full discussion is beyond the scope of this article. However, on the basis of data from our earlier studies in which the exposure was generated by an idling diesel engine,^{11,18} we have speculated previously that oxidative stress and impaired NO-dependent signaling play a central role in the adverse vasomotor effects. Given the broader impairment of vasomotor function we observed here and in a previous study in which a transient cycling diesel engine was used,¹⁶ we acknowledge that we cannot discount upregulation of other circulating or cellular vasoconstrictor mediators (such as Rho kinase³⁴) or activation of the sympathetic nervous system as an alternative explanation for the general blunting of vasodilator responses observed.

Limitations

Our principal objective was to assess the impact of a commercially available particle trap on markers of cardiovascular health by comparing the effects of unfiltered and filtered diesel exhaust. In this regard, we clearly demonstrate that vasodilatation, endothelial tPA release, and thrombus formation are improved by particle filtration. However, we acknowledge that our approach has limitations. The use of multiple and complementary surrogates of cardiovascular health is both a strength and a weakness of this study. Replication of previous observations suggests that the findings are real and provides a clear and consistent message: Diesel exhaust impairs vascular function^{11,16,18} and increases *ex vivo* thrombus formation.¹³ The use of multiple end points with 3 exposure conditions requires multiple comparisons and increases the possibility of type I and II errors. We have not adjusted for multiple comparisons because the initial comparison between diesel exhaust and filtered air was made simply to confirm our previous findings. Both the direction and magnitude of the changes seen here are consistent with our previous findings, although the differences in net tPA release failed to achieve statistical significance. Although the

study was powered prospectively on the basis of measurements of the primary end points made during previous diesel exposure studies, we acknowledge that the sample size is modest. Although we are confident that we have not missed effects on endothelial function or *ex vivo* thrombosis, we acknowledge that we may have insufficient power to detect changes in some of the secondary end points (Table I in the online-only Data Supplement), and thus cannot exclude the possibility of false-negative findings confounding their assessment. In addition, the study cohort consisted exclusively of young, healthy men. Although one might postulate that the benefit of particle traps may actually be greater in those with preexisting cardiovascular disease, we concede that further studies are required to assess the role of particle traps in mitigating cardiovascular effects in women and the broader population.

Conclusion

With the use of several surrogate measures, a range of adverse cardiovascular effects of diesel exhaust inhalation in men appears to be prevented by the introduction of a particle trap. Given these beneficial effects on biomarkers of cardiovascular health, the widespread use of particle traps on diesel-powered vehicles may have substantial public health benefit and reduce the burden of cardiovascular disease.

Acknowledgments

We thank Annika Johansson, Frida Holmström, Ann-Britt Lundström, Ester Roos-Engstrand, Maj-Cari Ledin, and the Department of Respiratory Medicine and Allergy (University Hospital, Umeå, Sweden). We thank the staff at Svensk Maskinprovning AB (Umeå, Sweden) for conducting the exposures and Cat Graham (Wellcome Trust Clinical Research Facility, Edinburgh, Scotland) for statistical advice. Studies were performed at the Department of Respiratory Medicine and Allergy, Umeå University, Umeå, Sweden, and the Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK.

Sources of Funding

This research was supported by a British Heart Foundation program grant (BHF RG/10/9/28286) and the Swedish Heart Lung Foundation. Prof Blomberg is the holder of the Lars Werkö Distinguished Research Fellowship from the Swedish Heart Lung Foundation. Dr Mills is supported by an Intermediate Clinical Research Fellowship from the British Heart Foundation (FS/10/024/28266).

Disclosures

None.

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CLINICAL PERSPECTIVE

There is a robust and consistent association between air pollution and cardiovascular morbidity and mortality. These harmful effects are most strongly associated with exposure to traffic-derived fine particles that predominantly originate from diesel engine exhaust emissions. Using a purpose-built exposure chamber, we have demonstrated previously the adverse vascular and prothrombotic effects of exposure to diesel exhaust in healthy men. In the present study, using complementary and relevant measures of cardiovascular health, we have reconfirmed the adverse effects of exposure to diesel engine exhaust on endothelial function and ex vivo thrombosis. In addition, for the first time, we demonstrate that reducing the particulate component of diesel exhaust with a commercially available particle trap can prevent these detrimental cardiovascular effects. Our study provides support for the application of particle traps to diesel-powered vehicles to reduce urban particulate concentrations and limit a range of adverse cardiovascular effects related to exposure to traffic-derived air pollution.

SUPPLEMENTAL MATERIAL

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Power Calculations

The studies were prospectively powered based on measurements of the primary endpoints (endothelial vasomotor function and endogenous fibrinolysis assessed by forearm venous occlusion plethysmography; and *ex vivo* thrombus formation assessed using the Badimon Chamber). Based on our previous studies of endothelial vasomotor function and endogenous fibrinolysis, to detect a 20% difference in forearm blood flow and a 16% difference in t-PA release, we require sample sizes of n=18 at 90% power and two-sided P<0.05. Based on previous studies by our own and Professor Badimon's group, to detect differences of 10% in thrombus area, we require sample sizes of n=18 at 90% power and two-sided P<0.05. Power calculations for the secondary and other endpoints are presented in Table 1.

Arterial Stiffness

All measurements were performed by a single operator who was unaware of the nature of exposure. Studies were performed in a quiet, temperature controlled room with subjects resting in a supine position. Systolic and diastolic blood pressures were measured using a semi automated non-invasive oscillometric sphygmomanometer (Omron HEM-705CP, Omron, Matsusaka, Japan). Pulse wave analysis was performed using applanation tonometry (Millar Instruments, Texas, USA) of the radial artery and the SphygmoCor[®] system (AtCor Medical, Sydney, Australia) in accordance with the manufacturer's recommendations. Briefly, pulse wave analysis derives an aortic pulse pressure waveform from the radial artery wave via a mathematical transfer function. The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave

generated by peripheral vascular resistance. The augmentation pressure is the difference between the second and first systolic peaks. The augmentation index (augmentation pressure as a percentage of the pulse pressure) is a measure of systemic arterial stiffness and wave reflection. The time to wave reflection is reduced with increasing arterial stiffness, and provides a surrogate of aortic pulse wave velocity.¹ At least two independent waveform analyses were obtained from each subject, with measurements only accepted upon meeting SphygmoCor[®] quality control criteria. Pulse wave velocity was calculated by measuring the time for the pulse wave to travel between the carotid and femoral arteries.

Fraction of Exhaled Nitric Oxide

All measurements were performed by a single blinded operator. Fraction of exhaled nitric oxide (FE_{NO}) concentrations were evaluated pre exposure, 2 and 6 hours post-exposure, using a nitric oxide analyzer (NIOX[®], Aerocrine AB, Stockholm, Sweden). Two different exhalation flow rates; 10 and 50 mL×s⁻¹ (± 10%), during a slow exhalation against an oral pressure of 2 cm H₂O for 8 seconds were examined. The measurements were conducted in triplicate and the mean concentration of exhaled NO (ppb) was registered according to ERS/ATS guidelines.²

Data Analysis and Statistics

All studies, data analysis and data exclusion were performed prior to the data being unblinded. Continuous variables are reported as mean ± standard error of the mean (SEM). Statistical analyses were performed with GraphPad Prism (Graph Pad Software, California, USA).

Comparisons between exposures were undertaken using one- and two-way analysis of variance (ANOVA) with repeated measures, as appropriate. Factors assessed in the two-way ANOVA were exposure and time. Statistical significance was taken at $P < 0.05$.

Supplemental Results

There were no differences in resting heart rate, blood pressure or arterial stiffness following exposure to diesel exhaust, filtered exhaust or filtered air (Tables 2 and 3). Haematological variables, plasma markers of inflammation and platelet activation, baseline markers of fibrinolytic function and markers of airway inflammation were not different between exposures (Tables 4-7).

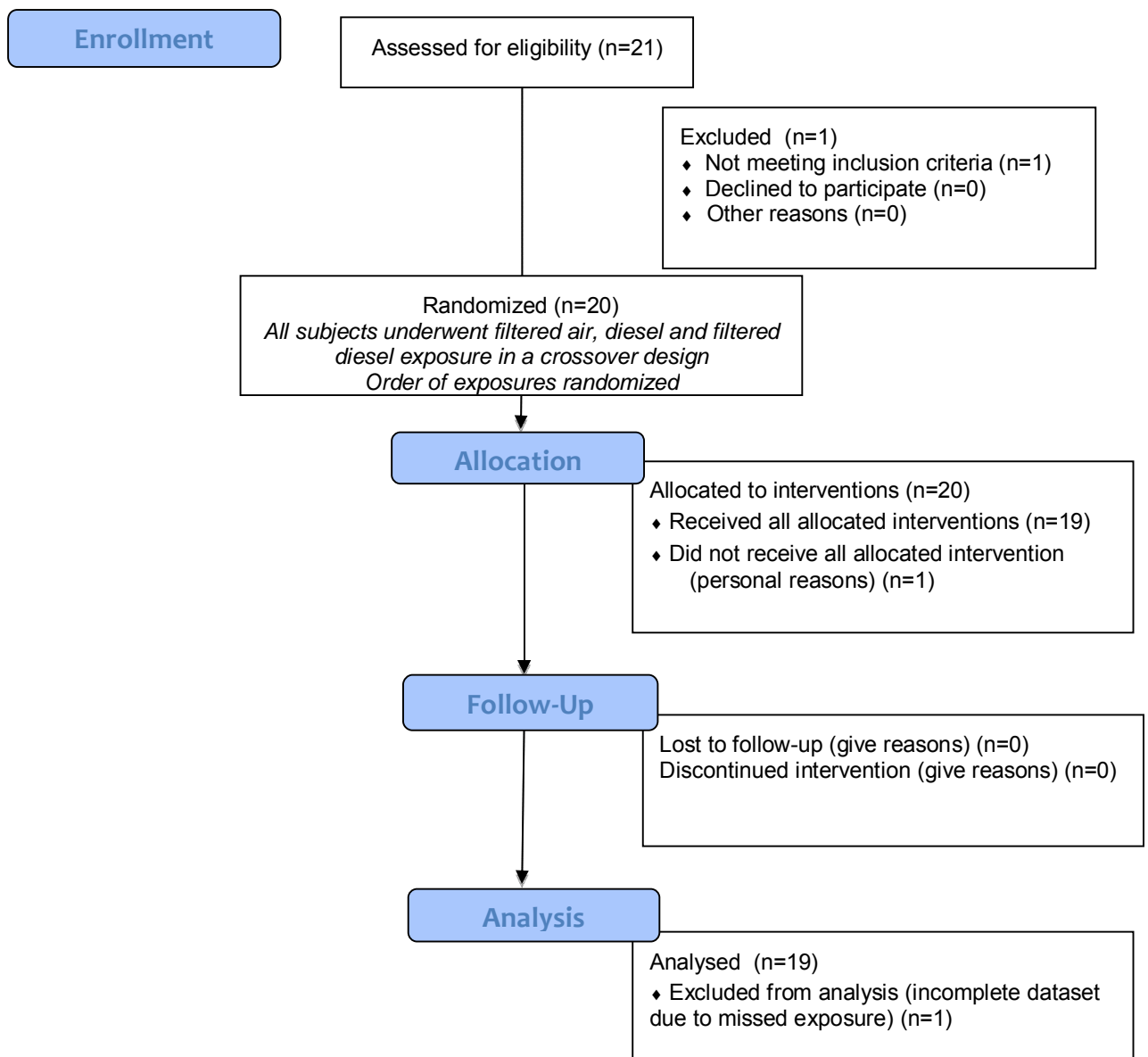
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Supplemental Figure

Figure 1

CONSORT diagram



Supplemental Tables

Table 1. Power calculations for the secondary endpoints

	<i>n</i>	mean	SD	SD ²	<i>Effect size detectable at:</i>	
					80% power	90% power
Systolic blood pressure (mmHg)	19	136	14	190	13	14
Diastolic blood pressure (mmHg)	19	70	9.9	100	9.0	10
Pulse (bpm)	19	64	12	132	10	12
TNF-a (pg/mL)	19	0.63	0.31	0.10	0.28	0.32
IL-6 (pg/mL)	19	0.28	0.21	0.04	0.19	0.22
CRP (mg/mL)	19	0.56	0.28	0.08	0.25	0.29
Soluble CD40L (pg/mL)	19	61	18	339	17	19
Soluble P-selectin (mg/mL)	19	39	11	110	9.5	11
Soluble ICAM-1 (mg/mL)	19	231	41	1658	37	43
Baseline t-PA (ng/mL)	19	5.0	3.9	15	3.5	4.0
Baseline PAI-1 (ng/mL)	19	6.3	3.8	14	3.4	4.0
Augmentation Pressure (mmHg)	19	-0.70	3.9	15	3.5	4.1
Augmentation Index (%)	19	-2.6	12	142	11	12
Time to Wave reflection (ms)	19	179	28	784	25	29
FE_{NO} 50 (ppb)	19	13	5.2	27	4.7	5.4
FE_{NO} 10 (ppb)	19	44	19	375	18	20

Table 2. Haemodynamic variables

	<i>Before Exposure</i>	<i>After Exposure</i>	<i>6 Hours</i>	<i>8 Hours</i>
FILTERED AIR				
Systolic Blood Pressure (mmHg)	135 ± 3	139 ± 3	141 ± 3	139 ± 3
Diastolic Blood Pressure (mmHg)	73 ± 3	66 ± 2	66 ± 2	71 ± 3
Pulse (bpm)	73 ± 3	64 ± 2	63 ± 2	59 ± 3
Infused FBF (mL/100mL tissue/min)	-	-	2.1 ± 0.1	-
Noninfused FBF (mL/100mL tissue/min)	-	-	2.0 ± 0.1	-
DIESEL EXHAUST				
Systolic Blood Pressure (mmHg)	133 ± 3	131 ± 3	132 ± 3	135 ± 3
Diastolic Blood Pressure (mmHg)	75 ± 2	66 ± 2	66 ± 2	69 ± 2
Pulse (bpm)	72 ± 2	63 ± 3	59 ± 2	57 ± 2
Infused FBF (mL/100mL tissue/min)	-	-	2.1 ± 0.1	-
Noninfused FBF (mL/100mL tissue/min)	-	-	2.1 ± 0.2	-
FILTERED DIESEL EXHAUST				
Systolic Blood Pressure (mmHg)	132 ± 3	137 ± 3	138 ± 4	137 ± 3
Diastolic Blood Pressure (mmHg)	77 ± 2	70 ± 2	69 ± 3	72 ± 2
Pulse (bpm)	74 ± 2	63 ± 2	59 ± 2	59 ± 2
Infused FBF (mL/100mL tissue/min)	-	-	2.1 ± 0.1	-
Noninfused FBF (mL/100mL tissue/min)	-	-	2.1 ± 0.2	-

Data shown are mean ± standard error of the mean (n=19)

There were no significant differences between exposures (2 way ANOVA with repeated measures)

FBF = Forearm blood flow

Table 3. Pulse wave analysis and pulse wave velocity

<i>Time after exposure</i>	<i>+5 mins</i>	<i>+20 mins</i>	<i>+30 mins</i>	<i>+50mins</i>
FILTERED AIR				
Augmentation Pressure (mmHg)	0.9 ± 1.4	0.0 ± 1.1	-1.1 ± 0.8	0.1 ± 1.0
Augmentation Index (%)	2.0 ± 3.8	-0.8 ± 3.3	-4.7 ± 2.5	-0.2 ± 3.1
Time to Wave Reflection (ms)	178 ± 10	175 ± 8	184 ± 7	165 ± 7
Systolic Blood Pressure (mmHg)	141 ± 3	137 ± 2	139 ± 3	137 ± 3
Diastolic Blood Pressure (mmHg)	71 ± 2	69 ± 3	66 ± 3	69 ± 3
Pulse (bpm)	63 ± 3	63 ± 3	62 ± 2	63 ± 2
DIESEL EXHAUST				
Augmentation Pressure (mmHg)	-0.6 ± 0.7	-0.6 ± 0.9	-0.8 ± 0.9	-0.6 ± 1.1
Augmentation Index (%)	-1.8 ± 2.2	-2.3 ± 2.9	-2.7 ± 2.9	-2.9 ± 3.7
Time to Wave Reflection (ms)	174 ± 8	188 ± 7	180 ± 7	185 ± 8
Systolic Blood Pressure (mmHg)	136 ± 3	138 ± 3	142 ± 4	138 ± 3
Diastolic Blood Pressure (mmHg)	69 ± 3	70 ± 2	70 ± 2	67 ± 2
Pulse (bpm)	58 ± 2	58 ± 3	59 ± 2	59 ± 2
FILTERED DIESEL EXHAUST				
Augmentation Pressure (mmHg)	-0.9 ± 0.9	-1.9 ± 1.0	-2.1 ± 1.0	-1.5 ± 1.1
Augmentation Index (%)	-2.5 ± 2.9	-7.1 ± 3.2	-7.1 ± 3.0	-5.9 ± 3.3
Time to Wave Reflection (ms)	177 ± 8	183 ± 7	181 ± 7	186 ± 7
Systolic Blood Pressure (mmHg)	144 ± 3	139 ± 3	140 ± 2	140 ± 3
Diastolic Blood Pressure (mmHg)	74 ± 2	70 ± 2	74 ± 3	72 ± 2
Pulse (bpm)	63 ± 2	60 ± 3	61 ± 2	62 ± 2
Pulse wave velocity, m/s				
<i>Time after exposure</i>	<i>+10 mins</i>	<i>+40 mins</i>		
Filtered air	5.6 ± 0.4	5.2 ± 0.1		
Diesel exhaust	5.0 ± 0.1	5.0 ± 0.1		
Filtered diesel exhaust	4.9 ± 0.1	5.0 ± 0.1		

Data shown are mean ± standard error of the mean (n=19)

There were no significant differences between exposures (2 way ANOVA with repeated measures)

Table 4. Haematological variables

	<i>Before Exposure</i>	<i>2 Hours</i>	<i>6 Hours</i>	<i>8 Hours</i>
FILTERED AIR				
Haemoglobin (g/L)	143±2	137±2	137±2	135±2
Leucocytes (×10 ⁹ cells/L)	4.9±0.3	5.2±0.4	5.1±0.4	5.3±0.4
Lymphocytes (×10 ⁹ cells/L)	1.8±0.1	1.7±0.1	1.6±0.1	1.8±0.1
Neutrophils (×10 ⁹ cells/L)	2.4±0.2	2.9±0.3	2.9±0.3	2.8±0.3
Monocytes (×10 ⁹ cells/L)	0.5±0.0	0.5±0.0	0.4±0.0	0.5±0.0
Platelets (×10 ⁹ cells/L)	202±11	203±10	205±11	201±9
DIESEL EXHAUST				
Haemoglobin (g/L)	141±2	137±2	135±2	134±2
Leukocytes (×10 ⁹ cells/L)	5.0±0.3	5.3±0.3	5.2±0.3	5.5±0.3
Lymphocytes (×10 ⁹ cells/L)	1.8±0.1	1.8±0.1	1.7±0.1	1.9±0.1
Neutrophils (×10 ⁹ cells/L)	2.4±0.2	2.9±0.2	2.9±0.2	2.9±0.2
Monocytes (×10 ⁹ cells/L)	0.5±0.0	0.5±0.0	0.4±0.0	0.5±0.0
Platelets (×10 ⁹ cells/L)	201±9	204±10	207±9	201±9
FILTERED DIESEL EXHAUST				
Haemoglobin (g/L)	141±2	137±2	135±2	133±2
Leukocytes (×10 ⁹ cells/L)	4.9±0.2	5.2±0.3	5.1±0.2	5.3±0.2
Lymphocytes (×10 ⁹ cells/L)	1.9±0.1	1.8±0.1	1.7±0.1	1.9±0.1
Neutrophils (×10 ⁹ cells/L)	2.3±0.1	2.8±0.2	2.9±0.2	2.7±0.2
Monocytes (×10 ⁹ cells/L)	0.5±0.0	0.4±0.0	0.4±0.0	0.5±0.0
Platelets (×10 ⁹ cells/L)	200±8	190±8	201±8	194±8

Data shown are mean±standard error of the mean (n=19)

There were no significant differences between exposures (2 way ANOVA with repeated measures)

Table 5. Markers of inflammation and platelet activation

	<i>Before Exposure</i>	<i>2 Hours</i>	<i>6 Hours</i>
FILTERED AIR			
TNF- α (pg/mL)	0.59 \pm 0.07	0.63 \pm 0.08	0.65 \pm 0.06
IL-6 (pg/mL)	0.29 \pm 0.05	0.32 \pm 0.06	0.23 \pm 0.04
CRP (mg/L)	0.55 \pm 0.06	0.55 \pm 0.06	0.58 \pm 0.07
Soluble CD40L (pg/mL)	62 \pm 2	57 \pm 3	63 \pm 7
Soluble P-selectin (mg/mL)	40 \pm 3	40 \pm 2	37 \pm 2
Soluble ICAM-1 (mg/mL)	228 \pm 10	241 \pm 8	223 \pm 11
DIESEL EXHAUST			
TNF- α (pg/mL)	0.61 \pm 0.06	0.65 \pm 0.07	0.65 \pm 0.06
IL-6 (pg/mL)	0.35 \pm 0.08	0.40 \pm 0.08	0.31 \pm 0.08
CRP (mg/L)	0.60 \pm 0.11	0.52 \pm 0.08	0.56 \pm 0.07
Soluble CD40L (pg/mL)	67 \pm 3	60 \pm 2	60 \pm 2
Soluble P-selectin (mg/mL)	42 \pm 2	38 \pm 3	40 \pm 2
Soluble ICAM-1 (mg/mL)	254 \pm 10	220 \pm 13	234 \pm 10
FILTERED DIESEL EXHAUST			
TNF- α (pg/mL)	0.61 \pm 0.06	0.58 \pm 0.07	0.61 \pm 0.07
IL-6 (pg/mL)	0.33 \pm 0.06	0.33 \pm 0.07	0.36 \pm 0.07
CRP (mg/L)	0.61 \pm 0.10	0.60 \pm 0.08	0.64 \pm 0.10
Soluble CD40L (pg/mL)	63 \pm 4	61 \pm 4	62 \pm 4
Soluble P-selectin (mg/mL)	39 \pm 2	39 \pm 2	39 \pm 2
Soluble ICAM-1 (mg/mL)	242 \pm 11	243 \pm 14	238 \pm 10

Data shown are mean \pm standard error of the mean (n=19)

There were no significant differences between exposures (2 way ANOVA with repeated measures)

TNF- α = Tumour necrosis factor- α

IL-6 = Interleukin-6

CRP = C reactive protein

CD40L = CD40 ligand

ICAM-1 = Intercellular adhesion molecule-1

There were no significant differences between exposures (1 way ANOVA with repeated measures)

Table 6. Markers of airway inflammation

	<i>Before Exposure</i>	<i>2 Hours</i>	<i>6 Hours</i>
FILTERED AIR			
FE _{NO} 50 (ppb)	13 ± 1.2	16 ± 2.1	16 ± 2.3
FE _{NO} 10 (ppb)	46 ± 4.9	51 ± 8.6	54 ± 8.1
DIESEL EXHAUST			
FE _{NO} 50 (ppb)	13 ± 1.2	14 ± 1.3	15 ± 2.1
FE _{NO} 10 (ppb)	44 ± 4.4	47 ± 4.7	48 ± 7.1
FILTERED DIESEL EXHAUST			
FE _{NO} 50 (ppb)	12 ± 0.9	13 ± 1.1	13 ± 1.0
FE _{NO} 10 (ppb)	41 ± 3.3	45 ± 3.3	44 ± 3.6

Data shown are mean ± standard error of the mean (n=19)

There were no significant differences between exposures (2 way ANOVA with repeated measures)

FE_{NO} 50 = Fraction of exhaled nitric oxide at exhalation rate 50 mL/s

FE_{NO} 10 = Fraction of exhaled nitric oxide at exhalation rate 10 mL/s

Table 7. Markers of fibrinolytic function

	<i>Six Hours</i>
FILTERED AIR	
Tissue plasminogen antigen (ng/mL)	2.9 ± 0.5
Plasminogen activator inhibitor type 1 (ng/mL)	4.8 ± 0.5
DIESEL EXHAUST	
Tissue plasminogen antigen (ng/mL)	2.9 ± 0.5
Plasminogen activator inhibitor type 1 (ng/mL)	5.4 ± 0.6
FILTERED DIESEL EXHAUST	
Tissue plasminogen antigen (ng/mL)	3.4 ± 0.6
Plasminogen activator inhibitor type 1 (ng/mL)	5.1 ± 0.5

Data shown are mean ± standard error of the mean (n=19)



Diesel exhaust inhalation increases thrombus formation in man[†]

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Received 28 February 2008; revised 18 September 2008; accepted 29 September 2008

Aims

Although the mechanism is unclear, exposure to traffic-derived air pollution is a trigger for acute myocardial infarction (MI). The aim of this study is to investigate the effect of diesel exhaust inhalation on platelet activation and thrombus formation in men.

Methods and results

In a double-blind randomized crossover study, 20 healthy volunteers were exposed to dilute diesel exhaust (350 µg/m³) and filtered air. Thrombus formation, coagulation, platelet activation, and inflammatory markers were measured at 2 and 6 h following exposure. Thrombus formation was measured using the Badimon *ex vivo* perfusion chamber. Platelet activation was assessed by flow cytometry. Compared with filtered air, diesel exhaust inhalation increased thrombus formation under low- and high-shear conditions by 24% [change in thrombus area 2229 µm², 95% confidence interval (CI) 1143–3315 µm², *P* = 0.0002] and 19% (change in thrombus area 2451 µm², 95% CI 1190–3712 µm², *P* = 0.0005), respectively. This increased thrombogenicity was seen at 2 and 6 h, using two different diesel engines and fuels. Diesel exhaust also increased platelet–neutrophil and platelet–monocyte aggregates by 52% (absolute change 6%, 95% CI 2–10%, *P* = 0.01) and 30% (absolute change 3%, 95% CI 0.2–7%, *P* = 0.03), respectively, at 2 h following exposure compared with filtered air.

Conclusion

Inhalation of diesel exhaust increases *ex vivo* thrombus formation and causes *in vivo* platelet activation in man. These findings provide a potential mechanism linking exposure to combustion-derived air pollution with the triggering of acute MI.

Keywords

Air pollution • Particulate matter • Thrombosis • Platelet activation

Introduction

Chronic exposure to air pollution is a major cause of cardiovascular morbidity and mortality worldwide.¹ Recently, exposure to traffic-derived air pollution has been associated with the triggering of acute myocardial infarction (MI).^{2,3} Although air pollution consists of a heterogeneous mixture of gaseous and particulate matter, adverse cardiovascular events are most strongly associated with exposure to fine particulate matter (diameter <2.5 µm,

PM_{2.5}).^{4,5} An important component of PM_{2.5} is nanoparticulate matter generated during the combustion of diesel fuel.⁶ These particles, with an aerodynamic diameter ≤100 nm, readily deposit within human alveoli and possess a considerable surface area that may contribute to their biological toxicity.⁷

Despite the strength and consistency of observational data, the pathophysiological mechanisms linking air pollution with adverse cardiovascular events remain unclear. They have been proposed to include endothelial dysfunction,^{8–10} myocardial ischaemia,¹⁰

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altered autonomic function,¹¹ systemic inflammation,⁹ and platelet activation.¹² Thrombosis plays a central role in the pathogenesis of atherosclerosis. As well as contributing to atherogenesis, thrombosis at the site of a disrupted coronary arterial plaque may cause acute vessel occlusion, resulting in an acute coronary syndrome (ACS). In pre-clinical studies employing a thrombotic vascular injury model, tracheal instillation of diesel exhaust particles caused platelet activation and increased arterial and venous thrombus formation.¹² Given that exposure to combustion-derived pollutants appears to act as a trigger for MI and that the majority of such events are due to thrombus formation at the site of an atherosclerotic plaque, we hypothesized that exposure to diesel exhaust would increase *in vivo* platelet activation and enhance thrombus formation in an *ex vivo* clinical model of arterial injury.

Methods

Subjects

Twenty healthy non-smokers aged between 21 and 44 years were enrolled into the study (Table 1). The study was performed with the approval of local research Ethics Committees, in accordance with the Declaration of Helsinki and the written informed consent of all volunteers. Volunteers were recruited using advertisements and from local healthy volunteer databases. Exclusion criteria were the use of regular medication or clinical evidence of atherosclerosis, arrhythmias, diabetes mellitus, hypertension, renal or hepatic impairment, asthma, occupational exposure to air pollution, intercurrent infective disease, or any other clinically significant illness. Subjects had normal lung function and reported no symptoms of respiratory tract infection within the 6-week period preceding the study.

Study design

Subjects attended on two occasions at least one week apart and received either filtered air or dilute diesel exhaust in a double-blind randomized crossover design. Exposures were performed at separate dedicated exposure facilities by technical staff with no involvement in the clinical studies. The order of the exposures was randomized based on an independently determined exposure protocol. Subjects

remained indoors following exposures to minimize confounding effects of ambient air pollution. The primary endpoint was *ex vivo* thrombus formation. Secondary endpoints were *in vivo* platelet activation assessed by flow cytometry and changes in haematological and coagulation variables and soluble markers of inflammation.

Clinical studies were performed in dedicated clinical research facilities by clinical staff blinded to exposure allocation. Based on previous vascular and inflammatory studies,⁸ initial thrombosis studies were performed 6 h after exposure in eight subjects (protocol 1). In light of the findings, further thrombosis and flow cytometric studies were performed at 2 and 6 h in a separate cohort of 12 subjects (protocol 2). The second protocol was designed to confirm the initial findings, to assess temporal effects, to investigate potential mechanisms, and to determine whether the initial findings were reproducible with a different type of diesel exposure.

Protocol 1

Exposures were performed for 2 h in a mobile ambient particle concentrator exposure laboratory in Edinburgh, UK. During exposures, subjects performed moderate exercise (minute ventilation 25 L/min/m²) on a bicycle ergometer for 15 min alternated with 15 min rest periods. Temperature and humidity in the chamber were controlled at 22°C and 50%, respectively. Diesel exhaust was generated by an idling engine (type F3M2011, 2.2 L, 500 rpm; Deutz, Germany) using gas oil (Petroplus Refining, UK). Over 90% of the exhaust fumes were shunted away, with the remainder being diluted with air and fed into the exposure chamber at a steady-state concentration. Air in the chamber was continuously monitored with exposures standardized using continuous measurement of nitrogen oxide (NO_x) concentrations to deliver a particulate concentration of 350 µg/m³. There was little variation in particle mass (348 ± 68 µg/m³), particle number (1.2 ± 0.1 × 10⁶/cm³), NO_x (0.58 ± 0.03 ppm), NO₂ (0.23 ± 0.02 ppm), NO (0.36 ± 0.02 ppm), CO (3.54 ± 0.76 ppm), and total hydrocarbon (2.8 ± 0.1 µg/m³) concentrations between exposures.

Protocol 2

In Umeå, Sweden, subjects were exposed for 1 h in a purpose-built diesel exposure chamber according to a standard protocol, as described previously.^{8,13} Diesel exhaust was generated by an idling Volvo engine (TD45, 4.5 L, 680 rpm) using Gasoil E10 (Preem, Sweden), as described previously.^{8,13} During exposures, subjects performed periods of exercise as described earlier. Exposures were standardized using continuous measurement of NO_x to deliver a particulate concentration of 350 µg/m³. There was little variation in particle mass (330 ± 12 µg/m³), particle number (1.26 ± 0.01 × 10⁶/cm³), NO_x (2.78 ± 0.03 ppm), NO₂ (0.62 ± 0.01 ppm), NO (2.15 ± 0.03 ppm), CO (3.08 ± 0.12 ppm), and total hydrocarbon (1.58 ± 0.16 µg/m³) concentrations between exposures.

Ex vivo thrombosis studies

Thrombus formation was measured using the Badimon chamber. This technique has principally been used previously to assess the efficacy of novel antithrombotic agents.^{14–16} In brief, a pump was used to draw blood from an antecubital vein through a series of three cylindrical perfusion chambers maintained at 37°C in a water bath. Carefully prepared strips of porcine aorta, from which the intima and a thin layer of media had been removed, acted as the thrombogenic substrate. The rheological conditions in the first chamber simulate those of patent coronary arteries (low-shear rate, ~212 s⁻¹), whereas those in the

Table 1 Baseline volunteer characteristics

	Value
Age (years)	26 ± 5
Height (m)	1.8 ± 0.1
Weight (kg)	73 ± 3
Body mass index (kg/m ²)	22 ± 1
Pulse (bpm)	58 ± 2
Systolic blood pressure (mmHg)	120 ± 3
Diastolic blood pressure (mmHg)	71 ± 2
Forced expiratory volume in 1 s (FEV ₁ , L)	4.9 ± 0.1
% Predicted FEV ₁	108 ± 3
Forced vital capacity (FVC, L)	5.8 ± 0.2
% Predicted FVC	103 ± 3

Data are presented as mean ± standard deviation. Pooled data from protocols 1 and 2 (n = 20).

second and third chambers simulate those of mildly stenosed coronary arteries (high-shear rate, $\sim 1690 \text{ s}^{-1}$). The model thus acts as one of the deep coronary arterial injury. Each study lasted for 5 min during which flow was maintained at a constant rate of 10 mL/min. All studies were performed using the same perfusion chamber and by the same operator.

Immediately after each study, porcine strips with thrombus attached were removed and fixed in 4% paraformaldehyde. Strips were wax-embedded, sectioned, and stained with Masson's Trichrome. Images were acquired at $\times 20$ magnification, and the thrombus area was measured using an Ariol image acquisition system (Applied Imaging, USA) and Image-Pro Plus software (Media Cybernetics, USA) by a blinded operator. Results from at least six sections were averaged to determine thrombus area for each chamber, as described previously.^{14–16}

Flow cytometry

Samples were obtained at 2 and 6 h, immediately prior to each thrombosis study, and processed according to previously described protocols.¹⁷ In brief, blood was taken from an antecubital vein using a 21-gauge cannula and anticoagulated with D-phenylalanyl-L-prolyl-L-arginine chloromethylketone (75 μm ; Cambridge Biosciences, UK). Samples were not analysed unless venesection achieved rapid and uninterrupted blood flow. Five minutes after sample collection, samples were stained with the following conjugated monoclonal antibodies: phycoerythrin (PE)-conjugated CD14 (Dako, Denmark), PE-conjugated CD62P, and PE-conjugated CD154 (Becton-Dickinson, UK); PE-conjugated CD11b, PE-conjugated CD40, fluorescein isothiocyanate (FITC)-conjugated CD42a, and FITC-conjugated CD14 (Serotec, USA); and appropriate control isotypes. All antibodies were diluted 1:20. Once stained, samples were incubated for 20 min at room temperature to identify P-selectin and CD40L on the platelet surface and CD40 on the monocyte surface. Monocyte and platelet-leucocyte samples were fixed with FACS-Lyse (Becton-Dickinson). Platelet samples were fixed with 1% paraformaldehyde. Samples were analysed within 24 h using a FACScan flow cytometer (Becton-Dickinson). Platelet-monocyte and platelet-neutrophil aggregates were defined as monocytes or neutrophils positive for CD42a. Data analysis was performed using FlowJo (Treestar, USA).

Blood sampling

Samples were obtained before exposure and at 2 and 6 h. Samples were analysed for total white cell count, differential cell count, and platelets by an autoanalyser. Plasma interleukin-6 (IL-6), tumour necrosis factor- α (TNF- α), soluble CD40 ligand (sCD40L), soluble P-selectin, intercellular adhesion molecule-1 (ICAM-1), and C-reactive protein were measured with commercially available ELISAs (R&D Systems, UK). Prothrombin time (PT, reagents from Medirox, Sweden) and activated partial thromboplastin time (aPTT, reagents from Dade Behring, USA) were measured using a CA-7000 analyser (Sysmex, Japan).

Statistical analysis

Data presented are pooled from protocols 1 and 2 unless otherwise stated. Continuous variables are reported as mean \pm standard deviation. Statistical analysis was performed in Excel (Microsoft Corporation, USA), using a modified *t*-test (two-sided) to account for potential period effects.¹⁸ Statistical significance was taken at *P*-value less than 0.05.

Results

Exposures and clinical studies were well tolerated with no adverse symptoms reported. All volunteers completed both study visits.

Total leucocyte, monocyte and platelet counts, PT, and aPTT were unaltered following dilute diesel exhaust and filtered air (Table 2). Although neutrophil count appeared to increase and lymphocyte count appeared to decrease following both exposures, there were no differences in the magnitude of these changes following dilute diesel exhaust compared with filtered air (Table 2).

Markers of inflammation and platelet activation

There was a heterogeneous cytokine response following both dilute diesel exhaust and filtered air exposures (Table 3, data from protocol 2). Changes in plasma TNF- α , IL-6, C-reactive protein, and soluble ICAM-1 concentrations were similar following both exposures. Following dilute diesel exhaust exposure, plasma sCD40L concentrations were increased at 2 h ($P = 0.003$ vs. filtered air), and the fall at 6 h following filtered air exposure was attenuated ($P = 0.011$ vs. filtered air). Similarly, the fall in plasma soluble P-selectin concentration at 6 h following filtered air exposure was attenuated following diesel exhaust exposure ($P = 0.003$).

Flow cytometry

Monocyte surface expression of CD40 and platelet surface expression of CD40L and P-selectin were similar following dilute diesel exhaust and filtered air exposure (data on file). Compared with filtered air, diesel exhaust exposure increased platelet-neutrophil and platelet-monocyte aggregates at 2 h by 52% [absolute change 6%, 95% confidence interval (CI) 2–10%, $P = 0.01$] and 30% (absolute change 3%, 95% CI 0.2–7%, $P = 0.03$), respectively (Figure 1, data from protocol 2). There was a trend towards similar increases at 6 h, although these were not statistically significant.

Thrombus formation

Thrombus formation increased following dilute diesel exhaust by 23% in the low-shear chamber (change in thrombus area 1941 μm^2 , 95% CI 873–3008 μm^2 , $P = 0.002$) and by 21% in the high-shear chamber (change in thrombus area 2916 μm^2 , 95% CI 1365–4466 μm^2 , $P = 0.001$), compared with filtered air at 6 h (Figure 2).

In protocol 2, thrombus formation at 2 h increased by 27% in the low-shear chamber and 21% in the high-shear chamber following dilute diesel compared with filtered air (change in thrombus area 2772 μm^2 , 95% CI 879–4721 μm^2 , $P = 0.04$ and change in thrombus area 2312 μm^2 , 95% CI 597–4026 μm^2 , $P = 0.014$, respectively; Figure 3). Likewise, thrombus formation at 6 h was increased by 22% (change in thrombus area 2254 μm^2 , 95% CI 244–3924 μm^2 , $P = 0.033$) in the low-shear chamber and appeared to increase (13%; change in thrombus area 1467 μm^2 , 95% CI –230–3163 μm^2 , $P = 0.083$) in the high-shear chamber (Figure 3, data from protocol 2).

Table 2 Effects of dilute diesel exhaust on haematological and coagulation variables

	Before exposure	2 h	6 h	Δ 2 h	Δ 6 h	P-values	
						2 h	6 h
Filtered air							
Leucocytes ($\times 10^9$ cells/L)	5.44 \pm 1.42	5.27 \pm 1.16	5.75 \pm 1.07	-0.18 \pm 1.08	0.26 \pm 1.19	—	—
Lymphocytes ($\times 10^9$ cells/L)	2.17 \pm 0.67	1.92 \pm 0.52	1.68 \pm 0.43	-0.48 \pm 0.46	-0.51 \pm 0.53	—	—
Neutrophils ($\times 10^9$ cells/L)	2.62 \pm 0.69	3.00 \pm 0.75	3.51 \pm 0.91	0.42 \pm 0.68	0.89 \pm 0.86	—	—
Monocytes ($\times 10^9$ cells/L)	0.47 \pm 0.16	0.42 \pm 0.14	0.41 \pm 0.16	-0.06 \pm 0.11	-0.06 \pm 0.10	—	—
Platelets ($\times 10^9$ cells/L)	223 \pm 38	221 \pm 35	223 \pm 30	-1.80 \pm 18	1.79 \pm 22	—	—
INR ^a	1.00 \pm 0.06	1.03 \pm 0.07	1.04 \pm 0.07	0.02 \pm 0.04	0.03 \pm 0.05	—	—
aPTT ^a (sec)	28.9 \pm 0.91	29.1 \pm 0.89	28.7 \pm 0.90	0.28 \pm 0.47	-0.20 \pm 0.58	—	—
Diesel exhaust							
Leucocytes ($\times 10^9$ cells/L)	5.45 \pm 1.22	5.51 \pm 1.54	5.53 \pm 1.31	0.06 \pm 1.34	0.07 \pm 1.41	0.54	0.52
Lymphocytes ($\times 10^9$ cells/L)	2.20 \pm 0.73	1.67 \pm 0.55	1.61 \pm 0.42	-0.53 \pm 0.36	-0.59 \pm 0.58	0.60	0.30
Neutrophils ($\times 10^9$ cells/L)	2.60 \pm 0.64	3.26 \pm 1.42	3.38 \pm 1.17	0.68 \pm 1.27	0.81 \pm 1.17	0.90	0.90
Monocytes ($\times 10^9$ cells/L)	0.49 \pm 0.11	0.45 \pm 0.12	0.45 \pm 0.13	-0.07 \pm 0.09	-0.08 \pm 0.08	0.69	0.60
Platelets ($\times 10^9$ cells/L)	227 \pm 38	223 \pm 47	218 \pm 31	-4.15 \pm 21	-3.74 \pm 16	0.72	0.32
INR ^a	1.02 \pm 0.06	1.02 \pm 0.08	1.03 \pm 0.08	0.01 \pm 0.03	0.01 \pm 0.03	0.55	0.26
aPTT ^a (s)	29.3 \pm 1.39	29.22 \pm 0.87	29.2 \pm 0.89	-0.07 \pm 0.86	-0.06 \pm 0.74	0.22	0.83

Data are presented as mean \pm standard deviation.

P-values are for comparison of diesel exhaust vs. filtered air.

aPTT, activated partial thromboplastin time; INR, international normalized ratio of prothrombin time.

Pooled data from protocols 1 and 2, (n = 20, except ^aunavailable for protocol 1).

Table 3 Effects of dilute diesel exposure on markers of inflammation and platelet activation

	Before exposure	2 h	6 h	Δ 2 h	Δ 6 h	P-values	
						Δ 2 h	Δ 6 h
Filtered air							
TNF- α (pg/mL)	0.62 \pm 0.73	—	0.36 \pm 0.32	—	-0.26 \pm 0.30	—	—
IL-6 (pg/mL)	0.60 \pm 0.76	—	0.88 \pm 0.80	—	0.28 \pm 1.1	—	—
C-reactive protein (mg/L)	1.02 \pm 0.66	1.09 \pm 1.42	1.13 \pm 1.64	0.07 \pm 0.17	0.12 \pm 0.16	—	—
Soluble CD40L (pg/mL)	66 \pm 29	75 \pm 8	41 \pm 14	9.00 \pm 29	-20 \pm 26	—	—
Soluble P-selectin (mg/mL)	61 \pm 27	37 \pm 8	44 \pm 18	-25 \pm 22	-18 \pm 26	—	—
Soluble ICAM-1 (mg/mL)	278 \pm 65	170 \pm 25	271 \pm 69	-109 \pm 56	-6.40 \pm 66	—	—
Diesel exhaust							
TNF- α (pg/mL)	0.55 \pm 0.41	—	0.57 \pm 0.44	—	0.06 \pm 0.44	—	0.11
IL-6 (pg/mL)	0.27 \pm 0.19	—	0.78 \pm 0.61	—	0.52 \pm 0.66	—	0.51
C-reactive protein (mg/L)	0.67 \pm 0.65	0.66 \pm 0.94	0.65 \pm 0.85	-0.01 \pm 0.10	-0.02 \pm 0.04	0.48	0.30
Soluble CD40L (pg/mL)	48 \pm 16	78 \pm 8	42 \pm 10	30 \pm 15	-0.85 \pm 18	0.01	0.01
Soluble P-selectin (mg/mL)	51 \pm 18	37 \pm 10	54 \pm 14	-14 \pm 13	2.89 \pm 16	0.11	0.003
Soluble ICAM-1 (mg/mL)	263 \pm 56	181 \pm 33	280 \pm 58	-82 \pm 37	17 \pm 59	0.49	0.64

Data are presented as mean \pm standard deviation.

Data from protocol 2 (n = 12).

P-values are for the comparison of diesel exhaust vs. filtered air.

TNF- α , tumour necrosis factor- α ; IL-6, interleukin-6; CD40L, CD40 ligand; ICAM-1, intercellular adhesion molecule-1.

Discussion

Short-term exposure to traffic-derived air pollution is associated with acute cardiovascular events.^{2,3} This is the first study to demonstrate

that inhalation of diesel exhaust, a common urban air pollutant, causes platelet activation and enhances thrombus formation in men. This provides a plausible mechanism linking exposure to particulate air pollution with acute cardiovascular events including MI.

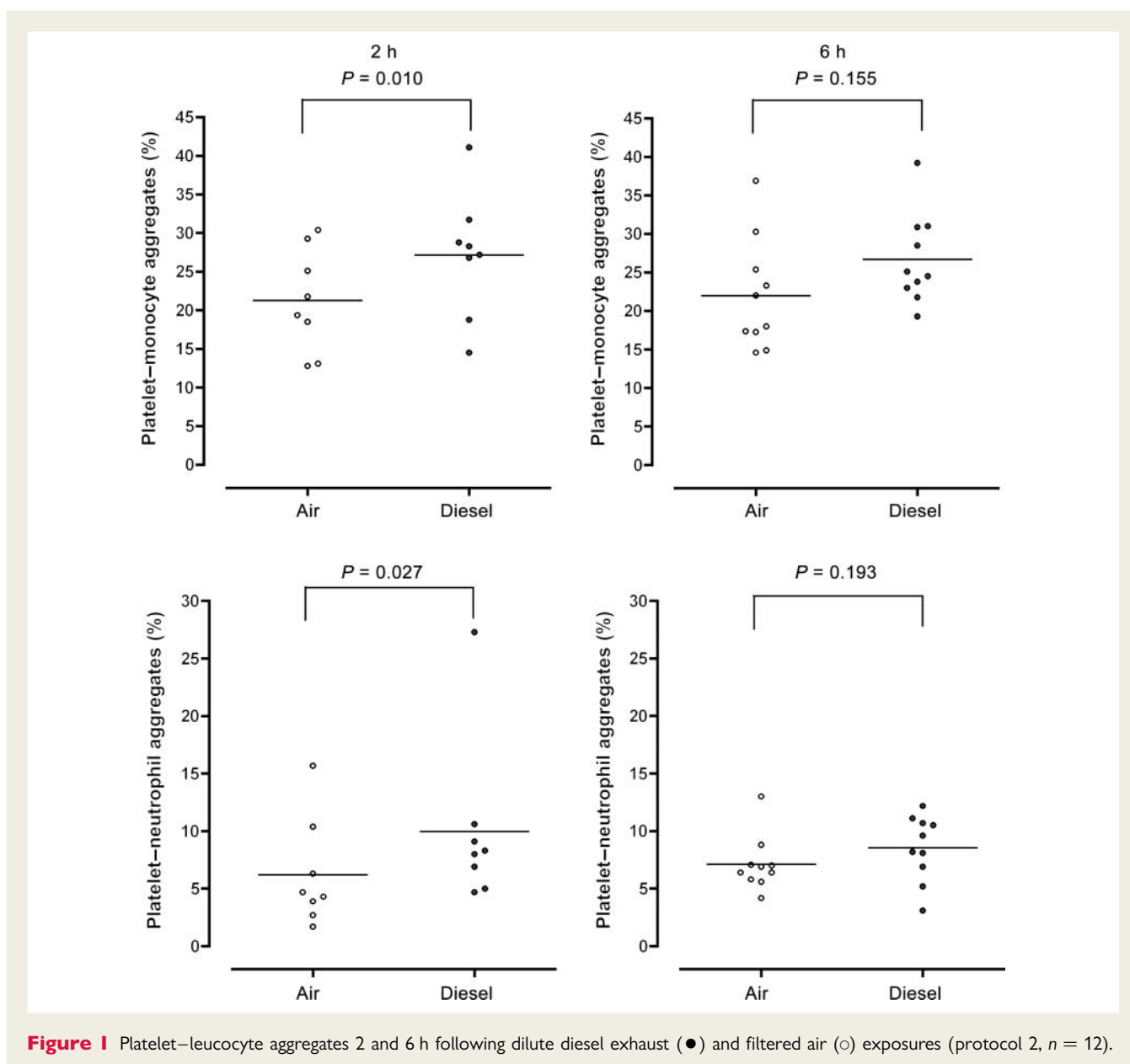


Figure 1 Platelet–leucocyte aggregates 2 and 6 h following dilute diesel exhaust (●) and filtered air (○) exposures (protocol 2, $n = 12$).

Effect of diesel exhaust on thrombosis

Despite the suggestion from observational studies that exposure to combustion-derived air pollution is associated with MI, few studies have examined whether controlled exposure alters thrombotic potential. Developing a reproducible *in vivo* model of thrombosis for use in human studies is challenging. We therefore used the Badimon chamber as a validated *ex vivo* model of arterial injury and thrombosis.¹⁴ It has previously been used to evaluate the effects of novel antithrombotic regimens and has a number of advantages over other techniques.^{14–16} It allows the measurement of thrombus formation in native (non-anticoagulated) whole blood triggered by exposure to a physiologically relevant substrate and under flow conditions mimicking those in diseased coronary arteries. Thus, this is a particularly relevant model as it broadly

simulates the intra-arterial conditions following spontaneous or iatrogenic plaque disruption within the coronary vasculature.

Taken together with our previous finding that dilute diesel exhaust exposure impairs endothelial t-PA release,⁸ we suggest that enhanced thrombus formation is an important mechanism that may explain the association of MI shortly after traffic pollution exposure.

Effect of diesel exhaust on platelet activation

Platelets are key components of arterial thrombosis. Shortening of closure times in a platelet function analyser have been observed following tracheal instillation of diesel exhaust particles in hamsters¹² and their addition to human blood enhances platelet

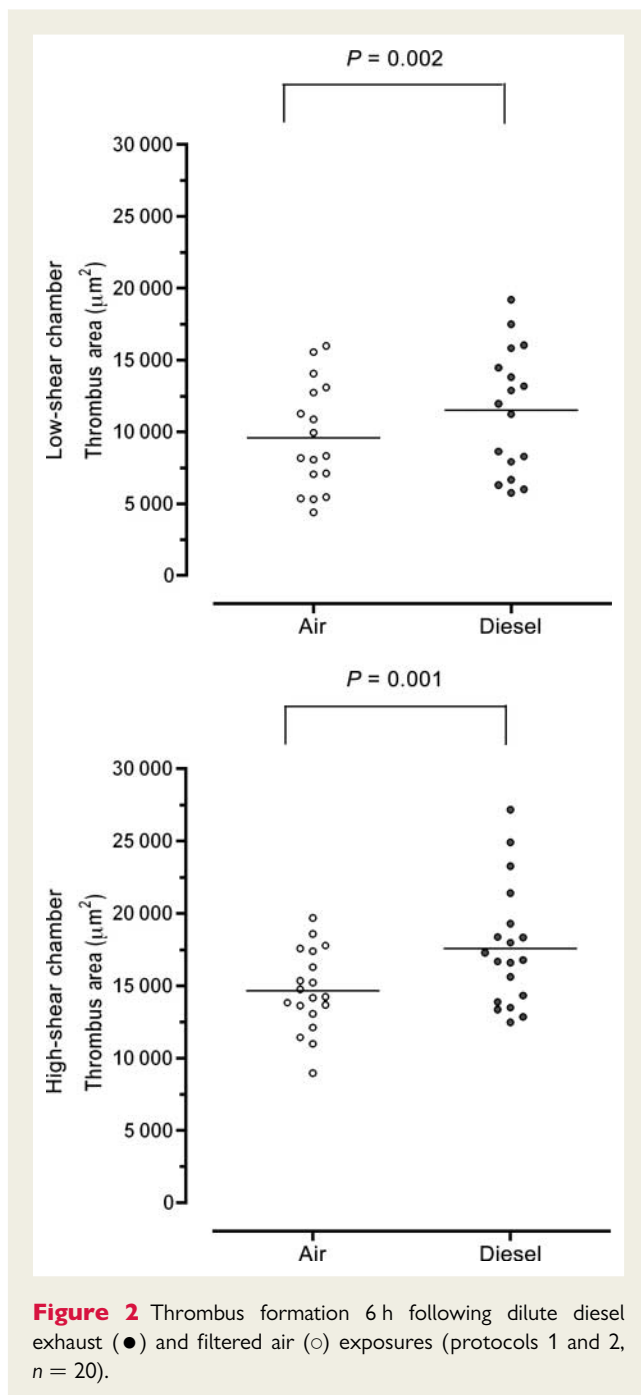


Figure 2 Thrombus formation 6 h following dilute diesel exhaust (●) and filtered air (○) exposures (protocols 1 and 2, $n = 20$).

aggregation.¹⁹ Here, we used flow cytometry to measure the surface expression of platelet and leucocyte activation markers as well as platelet–leucocyte aggregates, a technique increasingly recognized as the gold standard measure of *in vivo* platelet activation, including in patients with ACS.²⁰

We observed an increase in platelet–neutrophil and platelet–monocyte aggregates after dilute diesel exhaust exposure, suggesting that enhanced thrombus formation was mediated through platelet activation. These findings are consistent with an increase in circulating platelet–leucocyte aggregates observed in women exposed to biomass smoke.²¹ In addition, tracheal instillation of carbon nanotubes increased platelet–leucocyte aggregates

and thrombus formation in a murine model of vascular injury.²² Interestingly, blockade of P-selectin abrogated platelet–leucocyte aggregation and thrombus formation, suggesting that P-selectin serves as a link between pulmonary inflammation, systemic inflammation, and enhanced thrombogenicity. Although platelet–monocyte binding is principally dependent on P-selectin, we did not observe an increase in the platelet surface expression of P-selectin. However, in patients with MI, platelet–monocyte aggregates have been shown to be a more sensitive marker of platelet activation than P-selectin,²³ as P-selectin is rapidly shed from the platelet surface.²⁴ Exposure to dilute diesel exhaust also increased plasma sCD40L levels. This is in keeping with studies that demonstrated upregulation of the CD40/CD40L pathway in cigarette smokers²⁵ and following exposure to ultrafine particles.^{26,27} As platelets contain large amounts of CD40L that is released following activation,²⁸ the increase in sCD40L we observed further strengthens the argument that the enhanced thrombus formation observed was driven principally by platelet activation.

It is not possible from our study to determine the mechanism of platelet activation. Debate remains as to whether inhaled components of diesel exhaust can translocate into the systemic circulation^{29,30} to mediate direct effects on blood and vascular components. A substantial body of evidence supports a role for oxidative stress and inflammation in mediating the adverse effects of air pollution.³¹ Although we did not observe an increase in cellular or soluble inflammatory markers, this does not preclude a role for factors not assessed here. The ability of diesel exhaust exposure to cause pulmonary inflammation is not in doubt,³² and we have demonstrated previously that diesel particles are capable of generating free radicals,³³ which may activate platelets by reducing endothelial and platelet-derived nitric oxide and antioxidants.

Effect of diesel exhaust on coagulation

A number of previous ambient and controlled exposure studies have evaluated the association between plasma concentrations of coagulation factors and particulate air pollution with mixed results. Although some have demonstrated increased levels of fibrinogen^{34–36} and von Willebrand factor,³⁷ other studies measuring the same factors have failed to show any association with particulate exposure.^{37–39} This apparent disparity may well be explained by variations in study design and perhaps, more importantly, the type of exposure investigated. Two previous studies have investigated the effect of controlled diesel exhaust exposure on coagulation factors in men, with neither demonstrating a significant effect.^{40,41} Although a recent observational study reported a small reduction in PT associated with ambient exposure to PM₁₀,⁴² we found no effect on PT or aPTT following exposure to diesel exhaust. Despite higher effective particulate matter concentrations, our findings are in keeping with previous controlled diesel exposure studies that failed to demonstrate changes in fibrinogen, von Willebrand factor, D-dimer, pro-thrombin fragments 1 and 2, tissue-plasminogen activator, and plasminogen activator inhibitor-1.^{40,41}

Population risk and diesel exposure

Diesel exhaust is an important source of combustion-derived air pollution. We have now performed a large number of inhalation

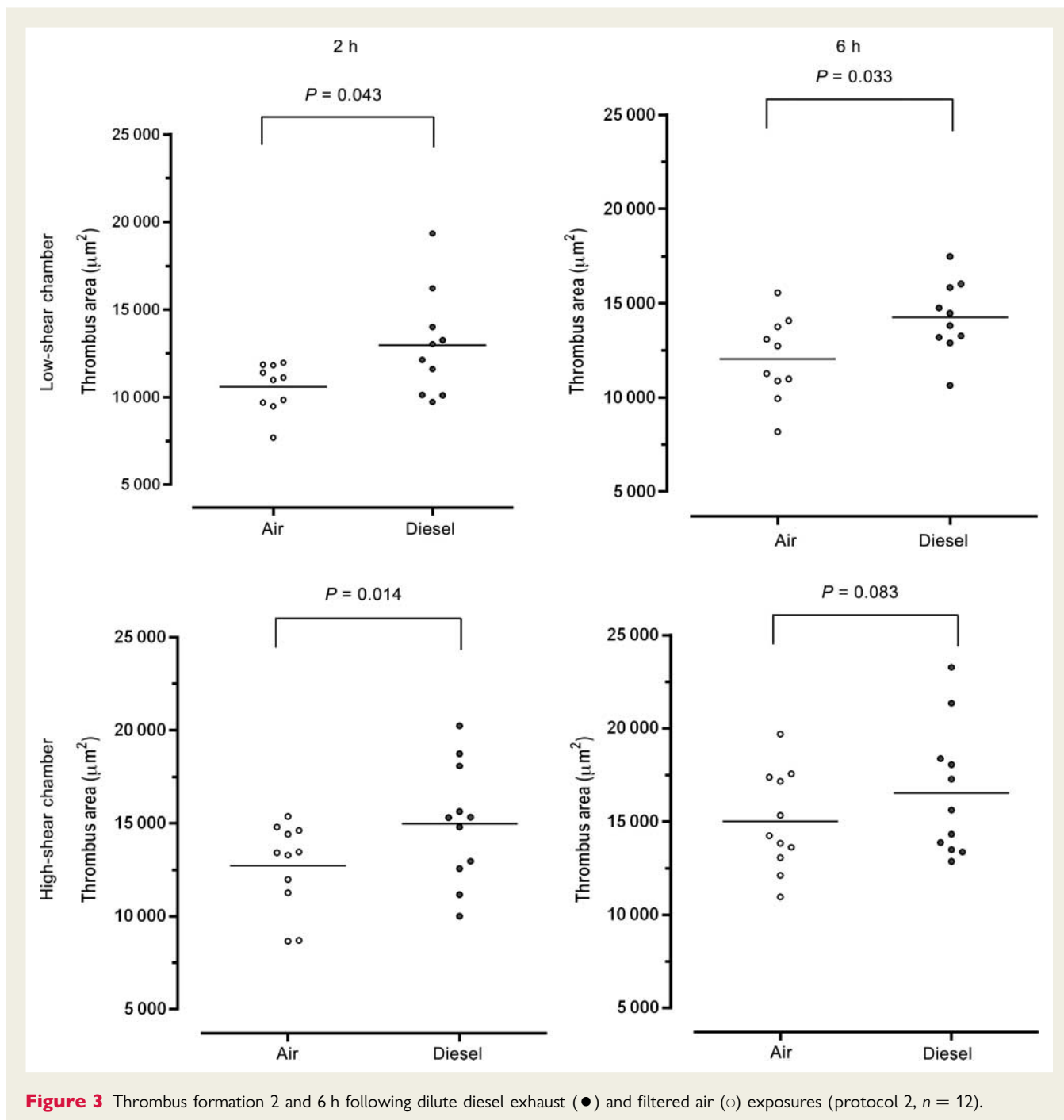


Figure 3 Thrombus formation 2 and 6 h following dilute diesel exhaust (●) and filtered air (○) exposures (protocol 2, n = 12).

exposures in healthy subjects and patients with cardiovascular disease using well-characterized systems. Particulate levels during these exposures are comparable with those in heavy traffic and occupational settings in large cities. Here, we used two types of diesel engines and two different commercially available fuels. The particulate component was similar in both protocols. Despite differences in the method of diesel exhaust generation and the gaseous component, prothrombotic effects were consistent.

Although the overall implications of exposure to traffic-derived pollution are significant from a population perspective, individual risk is modest. Observational data support the notion that risk

is greatest in those with pre-existing cardiovascular disease. Indeed, we have recently demonstrated that dilute diesel exhaust inhalation has pro-ischæmic effects in patients with prior MI.¹⁰ In the present study, we have extended these findings using a clinical model of severe arterial injury that is reflective of the intravascular conditions in a patient with a ruptured or denuded atheromatous plaque. Our findings of enhanced platelet activation and thrombus formation further highlight the potential-increased propensity of ‘at-risk’ populations to suffer adverse cardiovascular consequences following exposure to air pollution, although it is not possible from this study to determine

whether diesel exhaust exposure enhances thrombogenicity in patients on antiplatelet therapies.

Conclusions

Inhalation of dilute diesel exhaust causes platelet activation and increased thrombus formation in men. This study provides a plausible pathophysiological link that may explain the association between combustion-derived air pollution and acute cardiovascular events. Further work is required to clarify more precisely the mechanism of enhanced thrombogenicity and to investigate how this potentially harmful effect may be abrogated.

Funding

British Heart Foundation Project (PG/04/131) and Programme (PG/05/003) Grants; the Swedish Heart–Lung Foundation; and the Swedish Research Council for Environment, Agricultural Sciences, and Spatial Planning (FORMAS).

Acknowledgements

We thank Frida Holmström, Annika Johansson, Maj-Cari Ledin, and all staff in the Departments of Respiratory Medicine/Allergy and the Clinical Research Facility, Umeå, Sweden; Finny Patterson, Laura Flint, and all staff at the Wellcome Trust Clinical Research Facility, Edinburgh, UK; John Bartlett at the Cancer Research Centre, Edinburgh, UK; and Paul Fokkens, John Boere, and Daan Leseman from the Dutch National Institute of Public Health and Environment.

Conflict of interest: none declared.

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Reducing Personal Exposure to Particulate Air Pollution Improves Cardiovascular Health in Patients with Coronary Heart Disease

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BACKGROUND: Air pollution exposure increases cardiovascular morbidity and mortality and is a major global public health concern.

OBJECTIVES: We investigated the benefits of reducing personal exposure to urban air pollution in patients with coronary heart disease.

METHODS: In an open randomized crossover trial, 98 patients with coronary heart disease walked on a predefined route in central Beijing, China, under different conditions: once while using a highly efficient face mask, and once while not using the mask. Symptoms, exercise, personal air pollution exposure, blood pressure, heart rate, and 12-lead electrocardiography were monitored throughout the 24-hr study period.

RESULTS: Ambient air pollutants were dominated by fine and ultrafine particulate matter (PM) that was present at high levels [74 $\mu\text{g}/\text{m}^3$ for PM_{2.5} (PM with aerodynamic diameter <2.5 μm)]. Consistent with traffic-derived sources, this PM contained organic carbon and polycyclic aromatic hydrocarbons and was highly oxidizing, generating large amounts of free radicals. The face mask was well tolerated, and its use was associated with decreased self-reported symptoms and reduced maximal ST segment depression (−142 vs. −156 μV , $p = 0.046$) over the 24-hr period. When the face mask was used during the prescribed walk, mean arterial pressure was lower (93 \pm 10 vs. 96 \pm 10 mmHg, $p = 0.025$) and heart rate variability increased (high-frequency power: 54 vs. 40 msec², $p = 0.005$; high-frequency normalized power: 23.5 vs. 20.5 msec, $p = 0.001$; root mean square successive differences: 16.7 vs. 14.8 msec, $p = 0.007$). However, mask use did not appear to influence heart rate or energy expenditure.

CONCLUSIONS: Reducing personal exposure to air pollution using a highly efficient face mask appeared to reduce symptoms and improve a range of cardiovascular health measures in patients with coronary heart disease. Such interventions to reduce personal exposure to PM air pollution have the potential to reduce the incidence of cardiovascular events in this highly susceptible population.

KEY WORDS: air pollution, blood pressure, face mask, heart rate variability, myocardial ischemia. *Environ Health Perspect* 120:367–372 (2012). <http://dx.doi.org/10.1289/ehp.1103898> [Online 3 January 2012]

Air pollution exposure is an established risk factor for cardiovascular morbidity and mortality (Brook et al. 2010), especially exposure derived from traffic and industrial sources (Laden et al. 2000; Lall et al. 2011; Lipfert et al. 2006; Pope et al. 2002; Sarnat et al. 2008). Acute exposure to combustion-derived particulate matter (PM) is associated with the onset of myocardial infarction and admissions to hospital in survivors of myocardial infarction and has been proposed as a trigger for acute cardiovascular events (Peters et al. 2004; von Klot et al. 2005). Although estimates vary, chronic exposure to air pollution has been estimated to increase all-cause mortality by 2–4% per 10- $\mu\text{g}/\text{m}^3$ increase in PM (Dockery et al. 1993; Pope et al. 2002), with most deaths due to cardiovascular disease (Miller et al. 2007). The World Health Organization estimates that outdoor urban air pollution results in around 800,000 deaths worldwide each year (United Nations Environment Programme 2006).

In controlled exposure studies, inhalation of PM air pollution affects blood pressure and causes abnormalities in vascular function, coagulation, and myocardial perfusion (Mills et al. 2009). These responses provide a plausible mechanism to explain the observed increase in acute cardiovascular events and cardiovascular mortality after exposure to PM air pollution. However, although acute exposure induces these adverse effects, whether improvements in cardiovascular health can be achieved by interventions targeted to reduce exposure in those living and working in highly polluted urban environments is unclear.

Major environmental health policy interventions can have a substantial impact on the health of populations, as evidenced by major reductions in cardiovascular events after the banning of bituminous coal in Dublin, Ireland, in 1990 (Clancy et al. 2002) and, more recently, with the restriction of smoking in public places (Pell et al. 2008). However, such environmental interventions may be

difficult to implement in rapidly developing countries where economic growth is dependent on road traffic and heavy industry (Smith et al. 2009). More practical solutions to reduce individual exposure and protect susceptible persons are urgently required. Therefore, we investigated the effects of a simple face mask intervention to reduce PM air pollution exposure on measures of cardiovascular health in patients with coronary heart disease.

Methods

Subjects. One hundred and two patients were recruited from the Fuwai Hospital, Beijing, China, in March 2009. All patients were nonsmokers and had a history of coronary heart disease. Exclusion criteria were a history of arrhythmia, severe coronary artery disease without revascularization, resting conduction abnormality, digoxin therapy, uncontrolled hypertension, renal or hepatic failure, or an acute coronary syndrome within the previous 3 months. Patients' medical histories were recorded from the case notes, and baseline anthropometric and biochemical measures were performed on recruitment. All subjects gave their written informed consent, and the

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Supplemental Material is available online (<http://dx.doi.org/10.1289/ehp.1103898>).

We thank the research nurses and laboratory staff at the Fuwai Cardiovascular Institute for their work during the study, the Chinese Academy of Meteorological Sciences for their assistance with filter processing, and the National Institute for Public Health and the Environment (RIVM), the Netherlands, for their invaluable assistance with particulate sample collection and processing.

This research was supported by a British Heart Foundation (BHF) program grant (RG/10/9/28286) and U.K. National Health Service (NHS) Lothian Endowments. J.P.L. and N.L.M. are supported by a BHF clinical Ph.D. studentship (FS/07/048) and a BHF intermediate clinical research fellowship (FS/10/026/28266), respectively. Trial registration: <http://www.ClinicalTrials.gov/NCT00809653>.

The authors declare they have no actual or potential competing financial interests.

Received 5 May 2011; accepted 3 January 2012.

study was reviewed and approved by the local research ethics committee.

Study design. Subjects attended the Fuwai Hospital or the ChaoYang Hospital in Beijing on two occasions, with at least a week between visits (median time between visits was 9 days), between March and May 2009. Each subject attended the same hospital on each visit. In a prospective randomized open blinded end point (PROBE) crossover study, subjects walked for 2 hr between 0900 hours and 1100 hours along prescribed city center routes [see Supplemental Material, Figure S1 (<http://dx.doi.org/10.1289/ehp.1103898>)] in Beijing, using a highly efficient face mask on one study visit but not the other (Dust Respirator 8812; 3M, St. Paul, MN, USA). This mask consists of a lightweight polypropylene filter, which is effective at removing airborne PM without affecting ambient gases. The mask has an expiration valve, complies with EN149:2001 FFP1 European Standard (British Standards Institute 2001), and has an assigned protection factor of 4 [i.e., it can be worn in atmospheres containing up to four times the workplace exposure limit (WEL) as defined by the U.K. Health and Safety Executive (2011). [The WEL for respirable carbon particles (carbon black), is 3.5 mg/m³ over an 8-hr time weighted average.] Mask use was randomly assigned to the first or second visit using balanced computer-generated randomization. In order to maximize the difference in PM air pollution exposure, subjects wore the mask for 24 hr before the mask study day, in addition to wearing it during the 24 hr study day, and were given instructions to wear the mask at all times while outdoors and as much as possible when indoors. Subjects' activities after the prescribed walk were not restricted, and they were instructed to continue their normal daily routines.

Personal pollution exposure and activity monitoring. Personal air pollutant exposure was determined using monitoring equipment contained within a backpack. Fine particulate matter (PM_{2.5}; PM with aerodynamic diameter ≤ 2.5 μm) was determined using a DataRAM monitor (model pDR-1500; Thermo Scientific, Franklin, MA, USA), and particle number was measured using a condensation particle counter (model CPC 3007; TSI Instruments Ltd., High Wycombe, UK). Ambient temperature and relative humidity were recorded using an external sensor (Omegattem[®] model HH-314; Omega Engineering Ltd., Stamford, CT, USA). Gaseous pollutants were measured using a multigas analyzer with electrochemical sensors for carbon monoxide, sulfur dioxide, and nitrogen dioxide (model X-am 7000; Dräger Safety, Lübeck, Germany). During the prescribed walk, physical activity was measured using global positioning system (GPS) tracking (eTrex Summit HC GPS unit; Garmin, Olathe, KS, USA), and energy expenditure was

estimated using activity data and anthropometric data as described previously (Langrish et al. 2009). The estimated PM exposure when wearing the mask was determined based on measurements of mask filter efficacy as described previously (Langrish et al. 2009).

Background pollution monitoring. Background exposure was recorded from permanent monitoring stations in the district where the patients walked on the study day (Beijing Municipal Environmental Protection Bureau 2009). Airborne PM was collected onto Teflon filters (Pall Corp., Ann Arbor, MI, USA) in three size fractions: coarse (mean aerodynamic diameter, 2.5–10 μm), fine (0.18–2.5 μm), and ultrafine (< 0.18 μm) using a MOUDI cascade impactor (MSP Corp., Shoreview, MN, USA).

PM mass was determined gravimetrically for each size fraction from the above filters after temperature and humidity conditioning and subsequently analyzed for elemental and organic carbon fractions, metals and cations, nitrate and sulfate anions, and organic matter.

Chemical and toxicological analysis of collected PM. Collected PM samples were analyzed for total carbon content, as well as elemental and organic carbon fractions, using the Sunset method (National Institute for Occupational Safety and Health 2003). Metals and cations were determined using inductively coupled plasma mass spectrometry (ICP-MS) after pretreatment with nitric acid. Nitrate and sulfate anions were determined after extraction with water using liquid chromatography paired with ICP-MS. Organic matter was extracted from filters by ultrasonication with toluene and analyzed using gas chromatography/mass spectrometry.

The oxidative potential of PM was assessed using electron paramagnetic resonance (EPR) (Miller et al. 2009). EPR was used to establish oxygen-centered free radical generation from the collected PM in the absence of tissue. Filters for all size fractions were pooled and sonicated in phosphate-buffered saline to give a final concentration of 1 mg particles/mL. Solutions were incubated with the spin-trap 1-hydroxyl-2,2,6,6,-tetramethyl-4-oxopiperidine (Tempone-H; 1 mM) (Enzo Life Sciences, Exeter, UK), loaded into a capillary tube and assessed at 37°C in an X-band EPR spectrometer (model MS-200; Magnettech, Berlin, Germany) as described previously (Miller et al. 2009). Pyrogallol (100 μM) was used as a positive control, and samples were compared with the National Institute of Standards and Technology (NIST; Gaithersburg, MD, USA) standard reference materials for urban dust (SRM-1649a; 1 mg/mL) and diesel exhaust PM (SRM-2975; 10 μg/mL).

Electrocardiography and blood pressure monitoring. Continuous 12-lead electrocardiography (ECG) was assessed with a

digital Holter recorder (Lifecard 12; Spacelabs Healthcare Ltd., Hertford, UK) using the Pathfinder automated arrhythmia analysis package (version 8.701, DelMar Reynolds' Pathfinder Digital; Spacelabs Healthcare Ltd.). Identified arrhythmias were individually inspected and verified or deleted as appropriate, and heart rate variability was assessed using the DelMar Reynolds' HRV Tools software package as described previously (Langrish et al. 2009). ST segment analysis was performed at the J-point +80 msec in three representative leads (II, V2, and V5) that were analyzed separately for each subject. Maximal ST segment depression and ischemic burden (product of the change in ST segment amplitude and the duration of the recording) were determined for each lead and as a composite (Mills et al. 2007).

Ambulatory blood pressure was measured automatically (model 90217 ultralite ambulatory blood pressure monitor; Spacelabs Healthcare Ltd.) every 15 min during the 2-hr walk and then every 30 min during the day and every hour overnight (i.e., 2200 hours to 0700 hours).

Symptom questionnaire. Subjects completed a symptom questionnaire at the beginning of the study day, after the 2-hr walk, and at the end of the 24-hr visit. They were asked to report physical symptoms (e.g., headaches, dizziness, nausea), their perception of the pollution, their perceived workload, and the tolerability of the mask after the prescribed walk using a visual analog scale.

Data analysis and statistical methods. In our previous study of healthy volunteers, we demonstrated a difference (mean ± SD) in systolic blood pressure of 7 ± 5 mmHg after a 2-hr walk when a face mask was used (Langrish et al. 2009). Based on the assumption that the effect size in the present study would be considerably smaller because of the use of cardiac medications, we powered the study to detect a 2-mmHg difference in systolic blood pressure, giving a sample size of 101 at 80% power and two-sided $p < 0.05$.

Blood pressure and ECG end points were analyzed by investigators unaware of treatment allocation. All data are expressed as medians (interquartile ranges) or means ± SD unless otherwise stated. Treatment × period (order in which the mask intervention was used) interactions were assessed as described previously (Hills and Armitage 1979), before data were compared using paired Student's t -tests or Wilcoxon matched pairs signed rank test as appropriate. Occurrence of arrhythmias, reported symptoms, and ST segment event frequency, were compared using the chi-squared analysis. All data were analyzed using GraphPad Prism (version 4 for Macintosh; GraphPad Software, San Diego, CA, USA). Statistical significance was taken as a two-sided $p < 0.05$.

Results

Subjects and face mask intervention. Ninety-eight patients (87% male; mean age, 62 years) completed the study protocol (Table 1). Four of those originally enrolled did not complete the protocol because of withdrawn consent, cataract extraction, or withdrawal by investigators because of smoking or failure to walk the prescribed route. All subjects tolerated the mask intervention well, scoring the comfort of the mask as 0.64 ± 1.06 on a 0–10 scale (0 represents completely comfortable, and 10, intolerable). The mask intervention reduced self-reported general symptoms (Figure 1) and patients' perceived effort of work, as well their perception of the level of ambient air pollution (2.46 ± 1.67 vs. 2.73 ± 1.64 on the 0–10 visual analog scale; $p = 0.03$). There were no significant treatment \times period interactions for any outcome measure.

Air quality and pollutants. Personal levels of ambient air pollutants were similar on both study days (Table 2), although we predict

from previous studies of filter efficacy (97% reduction in particle number) that the PM exposure in the presence of the mask would be reduced from $89 \mu\text{g}/\text{m}^3$ and 43,900 particles/ cm^3 to approximately $2 \mu\text{g}/\text{m}^3$ and 1,200 particles/ cm^3 (Langrish et al. 2009). Temperature (17.3°C vs. 16.8°C) and ambient relative humidity (30% vs. 35%) were similar on both visits. Airborne PM was predominantly ($> 99\%$ by particle number) in the fine and ultrafine fractions (Figure 2) and contained a large amount of organic carbon and high concentrations of polycyclic aromatic hydrocarbons, nitrates, hopanes, and steranes, suggesting that much of the PM was combustion derived and related to traffic sources [see Supplemental Material, Table S1 (<http://dx.doi.org/10.1289/ehp.1103898>)]. These collected particles were highly oxidizing and generated large amounts of free radicals as detected by EPR, exceeding the signal seen with both the standard reference NIST urban dust material at an equivalent

concentration and the intense free-radical-generating oxidant pyrogallol (Figure 2).

Effect of the face mask on cardiovascular health. Over the 24-hr period, the maximal ST segment depression recorded was lower [median (interquartile range), $-142 \mu\text{V}$ (-179 to -110) vs. $-156 \mu\text{V}$ (-202 to -123); $p = 0.046$] when the face mask was used. However, measures of myocardial ischemic burden were similar during the 2-hr walk and over the entire 24-hr period between visits (Table 3).

During the 2-hr prescribed city center walks, subjects walked a comparable distance (6.37 ± 1.44 km vs. 6.40 ± 1.51 km), at a similar average speed (4.25 ± 0.96 km/hr vs. 4.27 ± 1.01 km/hr), and expended the same amount of energy [2.32 ± 0.52 metabolic equivalent tasks (METs) vs. 2.33 ± 0.55 METs] between visits when the face mask was or was not used. Despite this similar workload, mean ambulatory arterial blood pressure was significantly lower (93 ± 10 mmHg

Table 1. Baseline characteristics of subjects ($n = 98$) completing the study.

Characteristic	Measure
Age (years)	62 ± 7
Male	85
Height (cm)	169 ± 6
Weight (kg)	75 ± 10
BMI (kg/m^2)	26 ± 3
Risk factors	
Hypertension	79
Diabetes mellitus	45
Stroke	15
Peripheral vascular disease	5
Previous myocardial infarction	68
Previous PCI	60
Previous CABG	38
LV ejection fraction (%; $n = 31$)	62 ± 9
Angina status	
CCS class I	67
CCS class II	31
Seattle angina score (maximum, 500)	387 ± 34
Clinical biochemistry	
Random glucose (mmol/L)	5.5 ± 1.8
Triglycerides (mmol/L)	1.5 ± 0.7
Cholesterol (mmol/L)	3.9 ± 0.9
HDL cholesterol (mmol/L)	1.2 ± 0.3
LDL cholesterol (mmol/L)	2.0 ± 0.8
Medication use	
Aspirin	92
Clopidogrel	17
Warfarin	1
ACE inhibitor or ARB	54
Beta blocker	73
Calcium channel blocker	42
Statin (fibrate, or ezetimibe)	83
Nitrate	45
Other antianginal	5
Diabetic medication	42
Traditional Chinese medicine	19

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; HDL, high density lipoprotein; LDL, low density lipoprotein; LV, left ventricle; PCI, percutaneous coronary intervention. Data are mean \pm SD, or n .

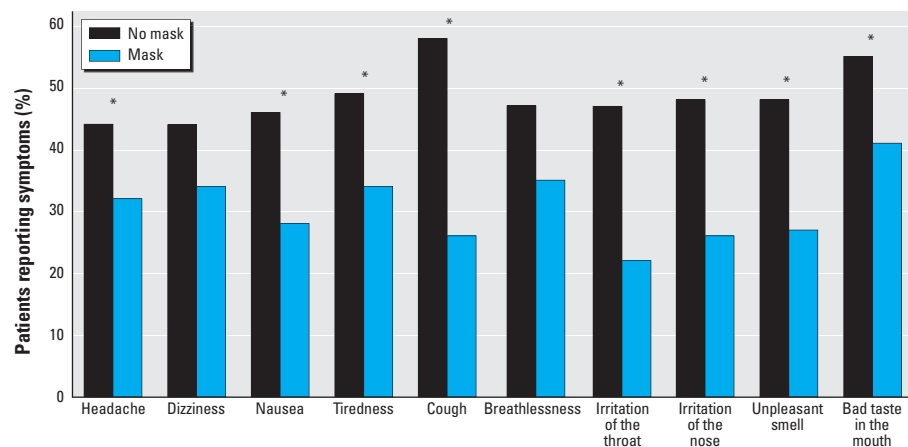


Figure 1. Self-reported symptoms of well-being in the presence or absence of the face mask. * $p < 0.05$.

Table 2. Personal ambient pollution exposures and background pollution levels on days defined according to mask use.

Parameter	Mask	No mask
Personal PM_{2.5} exposure ($\mu\text{g}/\text{m}^3$)		
Measured	61 (20–88)	89 (25–170)
Estimated	~ 2 (0.6–2.6)	89 (25–170)
Personal particle count ($\times 10^4$ particles/cm^3)		
Measured	4.19 ± 1.29	4.39 ± 1.45
Estimated	$\sim 0.12 \pm 0.04$	4.39 ± 1.45
Personal temperature ($^\circ\text{C}$)	17.3 ± 5.2	16.8 ± 5.8
Personal relative humidity (%)	30.4 ± 14.0	34.8 ± 18.2
Personal peaks > 1 ppm (number)		
NO ₂	None	None
SO ₂	None	None
CO	5 (2–7.5)	4 (2–8)
Background exposure		
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	92 (70–117)	103 (83–180)
SO ₂ (ppb)	38 (29–53)	54 (32–77)
NO ₂ (ppb)	36 (29–42)	36 (32–47)

Abbreviations: CO, carbon monoxide; NO₂, nitrogen dioxide; SO₂, sulfur dioxide. Data are mean \pm SD or median (interquartile range). Personal monitoring data were collected using portable monitoring equipment during the 2-hr walk. Background data were collected from permanent monitoring stations for the whole 24-hr period. Estimated PM exposure is calculated based on filter efficacy studies where 97% of fresh diesel exhaust PM were removed (Langrish et al. 2009).

vs. 96 ± 10 mmHg) when the face mask was used, although heart rate was similar (Table 3). During the 2-hr walk, heart rate variability [high-frequency (HF) power, high-frequency normalized power (HF_n), HF:low-frequency (LF) ratio, and root mean square successive differences (RMSSD)] was higher when wearing the face mask (Table 3). There were no significant differences in overall 24-hr ambulatory blood pressure or heart rate variability. There were no significant differences in the incidence of arrhythmias between the two visits (Table 4).

Discussion

PM air pollution is a major public health concern and is associated with increases in cardiovascular morbidity and mortality. In this study, we demonstrated that reducing personal exposure to urban airborne PM by means of a simple face mask is associated with a reduction in self-reported symptoms and improvements in objective measures of myocardial ischemia, blood pressure, and heart rate variability in patients with coronary heart disease. Reducing personal exposure to PM air pollution has the potential to reduce the incidence of cardiovascular events in patients with coronary heart disease living and working in industrialized or urban environments.

Using a robust PROBE design, we conducted a randomized controlled trial to assess the impact of reducing personal air pollution exposure in patients with coronary heart disease in a polluted urban environment. Through the use of portable monitoring devices and sample collection, we completed a detailed characterization of air pollutant exposure that demonstrated the remarkably

complex and toxic composition and extremely high prooxidative potential of ambient air PM in Beijing. We combined individualized pollution monitoring with a comprehensive cardiovascular assessment that incorporated hemodynamic and electrophysiological monitoring in conjunction with GPS tracking. Despite reducing exposure only for a 48-hr period in patients chronically exposed to a polluted urban environment, we observed evidence of consistent beneficial effects on a range of biomarkers of cardiovascular health after the introduction of this simple but highly efficient face mask intervention.

Myocardial ischemia. In a cohort of 20 men with stable asymptomatic coronary disease, we previously demonstrated greater exercise-induced maximum ST segment depression during exposure to diesel exhaust (Mills et al. 2007). However, although acute air pollution exposure exacerbates myocardial ischemia, many persons around the world are chronically exposed to high levels of air pollution, and it is unknown whether interventions targeted at reducing exposure will decrease myocardial ischemia.

In the present study, we showed that decreasing personal exposure to ambient air pollution reduces maximal ST segment depression over a 24-hr period in patients with coronary heart disease. The significance of silent myocardial ischemia is still debated, but it has been associated with major cardiac events in the general population (Fleg et al. 1990). Moreover, in patients with recent myocardial infarction or unstable angina, the occurrence of silent ischemia is a poor prognostic factor and is associated with a significant increase (relative risk ~ 3 – 4) in major

cardiac events and death (Cohn et al. 2003). It seems plausible, therefore, that the modest reduction in silent myocardial ischemia seen in this study might, if sustained, result in significant reductions in major cardiac events and cardiovascular mortality.

Blood pressure. Chronic exposure to air pollution is associated with increases in blood pressure in large epidemiological studies (Auchincloss et al. 2008). Similarly controlled exposure to concentrated ambient PM and ozone in healthy volunteers results in an acute increase in diastolic blood pressure (Urch et al. 2005). Hypertension is a major risk factor for atherosclerosis, and acute increases in blood pressure may trigger plaque rupture leading to an acute cardiovascular event. Consistent with this, exercise-related increases in blood pressure are predictive of the incidence of myocardial infarction (Mundal et al. 1996), stroke (Kurl et al. 2001), and cardiovascular mortality (Kikuya et al. 2000).

We recently reported that use of a face mask that decreased personal PM air pollution exposure reduced systolic blood pressure in healthy volunteers during a 2-hr walk by 7 mmHg (Langrish et al. 2009). The more modest 3-mmHg difference in mean arterial blood pressure after a 2-hr walk observed in the present study may be explained at least in part by the lower workload during walking in this older population with heart disease (estimated energy expenditures of 2.32 METs vs. 3.61 METs in the previous study population), coupled with the modifying effects of antihypertensive medications (Barclay et al. 2009), which were used by most of the present study population. However, interventional trials of blood pressure reduction

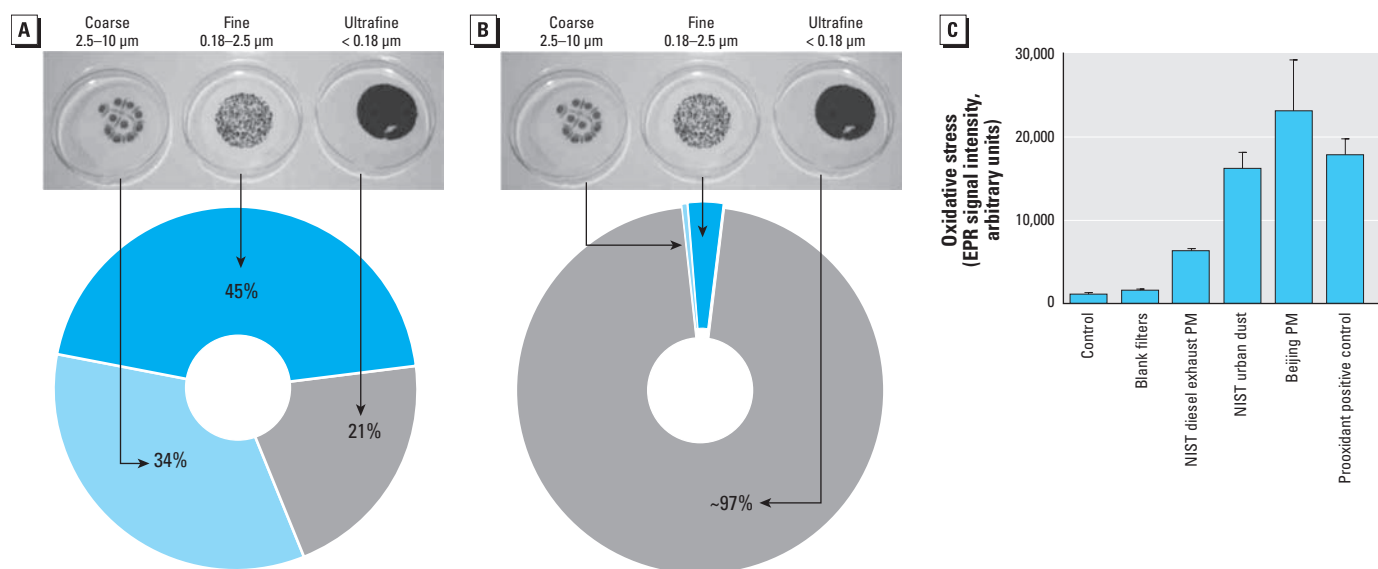


Figure 2. (A) Representative filter samples collected showing contribution by mass of the three size fractions averaged over 3 days. (B) Estimated contribution of each size fraction collected on filters by particle number. (C) Oxidative potential of the collected Beijing PM (1 mg/mL) using EPR to assess oxygen-centered free radical generation, compared with NIST diesel exhaust PM (10 μg/mL) and urban dust (1 mg/mL) and the prooxidant positive control (pyrogallol 100 μM) as described previously (Miller et al. 2009). Data are mean \pm SD ($n = 2$ – 4).

suggest that even modest changes in blood pressure would reduce the incidence of major cardiovascular events at the population level (Williams 2005).

Heart rate variability. Heart rate variability is a reflection of the autonomic control (a balance of the sympathetic and parasympathetic nervous systems) of the heart and is a measure of the variation in the RR intervals on a continuous electrocardiogram. A reduction in heart rate variability has been demonstrated in patients with a variety of pathophysiological conditions, including hypertension, heart failure, and diabetes mellitus (Task Force 1996). Indeed, reduced heart rate variability has been linked to increased cardiovascular mortality (Nolan et al. 1998), and a large number of studies link exposure to air pollutants with a reduction in heart rate variability (Brook et al. 2010).

In the present study, we have shown that reducing personal exposure to PM air pollution in patients with coronary heart disease is associated with an improvement in heart rate variability during exercise, based on general measures of variability and variability in specific frequency bands. In this study, the changes demonstrated were predominantly in the HF-power band, which is associated with changes in parasympathetic tone, and an improvement may suggest an increased contribution of parasympathetic (vagal) tone to heart rate control. In our previous healthy volunteer study (Langrish et al. 2009), heart rate variability also increased after the face mask intervention, but changes were seen predominantly in the LF-power band, suggesting effects on sympathetic nervous system control. We suggest that this difference (HF-power vs. LF-power changes) may be

related to the high use of beta-blocker therapy (74% of patients) in the present study population, which is likely to blunt any effects of exposure on sympathetic tone. The clinical relevance of acute changes in heart rate variability is not clear, although it has been demonstrated that the higher the variability, the lower the cardiovascular mortality (Kikuya et al. 2000). We suggest that a sustained improvement in heart rate variability has the potential to improve patients' prognosis and reduce the impact of air pollution on cardiovascular morbidity and mortality.

Symptoms. Patients perceived fewer self-reported symptoms, a reduction in effort of work, and lower background pollution levels when they wore the face mask. Although we observed no change in the occurrence of self-reported anginal symptoms, this is perhaps not surprising given that we recruited a highly selected population with stable coronary disease,

without significant clinical angina, and who were maintained on optimal medical therapy.

Limitations. We chose a PROBE study design because we wanted to determine the acceptability of wearing a face mask, as well as its potential beneficial effects on both symptoms and objective measures of cardiovascular health. We recognize that a double-blind approach incorporating a sham mask would reduce the potential for subjective bias and would therefore be considered more scientifically robust (Smith et al. 2007). In addition, we acknowledge that such an intervention may be more readily accepted in Chinese and Asian societies, where use of face masks is commonplace because of concerns over airborne diseases, pollution, and even fashion, and furthermore, that this may have affected patients' reporting of symptom improvement. However, even a sham mask will filter air pollutants to some degree (Langrish et al. 2009),

Table 4. Cardiac arrhythmias during 24-hr electrocardiographic monitoring periods among 98 coronary heart disease patients according to face mask use.

Arrhythmia	No. patients		Median no. of events per patient (interquartile range)	
	Mask	No mask	Mask	No mask
Dropped beat	2	2	1 (1–1)	1 (1–1)
VT	1	2	2 (2–2)	1 (1–1)
Salvo	1	2	4 (4–4)	2 (1–3)
Bigeminy	15	18	4 (1–33)	6 (2–36)
Triplet	1	0	11 (11–11)	0 (0–0)
Couplet	9	4	2 (1–5)	2 (1–10)
Bradycardia	20	19	52 (3–275)	89 (9–347)
SVT	2	5	1 (1–1)	1 (1–1)
Trigeminy	3	4	12 (6–134)	10 (6–230)
Premature aberrant	79	77	17 (3–122)	22 (3–181)
Isolated aberrant	52	54	3 (1–16)	5 (1–25)
Premature normal	81	84	12 (3–56)	12 (3–42)

Abbreviations: SVT, supraventricular tachycardia; VT, ventricular tachycardia. Bradycardia defined as heart rate < 50 bpm. $p > 0.05$ for all using chi-squared (number of patients) and Mann-Whitney U -tests (number of events).

Table 3. Ambulatory blood pressure, heart rate variability during the 2-hr city center walk and the 24-hr study period, and myocardial ischemia measured as ischemic burden, in each individual territory and as a composite according to face mask use.

Parameter	Walk		24 hr	
	Mask	No mask	Mask	No mask
Systolic blood pressure (mmHg)	126.9 ± 15.9	128.1 ± 16.5	121.2 ± 11.9	120.8 ± 12.4
Diastolic blood pressure (mmHg)	78.0 ± 9.3	79.5 ± 8.6	73.8 ± 7.2	74.0 ± 7.3
Mean arterial pressure (mmHg)	93.3 ± 9.7*	95.7 ± 10.0	89.8 ± 7.5	90.0 ± 7.9
Heart rate (bpm)	81.5 ± 8.7	81.5 ± 10.1	77.6 ± 11.3	76.7 ± 11.1
LF power (msec ²)	133 (68–97)	136 (52–227)	81 (40–172)	93 (46–208)
HF power (msec ²)	54 (27–108)*	40 (20–69)	27 (11–77)	31 (11–68)
LFn (msec)	58.4 (45.6–69.1)*	62.9 (51.1–75.5)	67.2 (55.5–78.0)	71.1 (59.4–81.1)
HFn (msec)	23.5 (18.0–32.4)*	20.5 (13.5–27.9)	21.4 (15.0–31.6)	20.9 (12.7–30.1)
HF:LF ratio	0.418 (0.258–0.712)	0.328 (0.207–0.573)	0.301 (0.190–0.554)	0.306 (0.161–0.492)
pNN50 (%)	1.2 (0.2–2.8)	0.7 (0.0–2.3)	0.5 (0.0–3.1)	0.6 (0.0–2.6)
RMSSD (msec)	16.7 (13.2–22.5)*	14.8 (10.9–19.6)	15.5 (11.0–22.6)	14.4 (10.3–20.3)
SDNN (msec)	59.8 (46.4–79.1)	60.1 (41.0–79.3)	45.6 (30.8–70.4)	48.2 (30.0–66.3)
Ischemic burden (mV-sec)				
Inferior (II) territory	–66 (–118 to –26)	–52 (–149 to –21)	–641 (–767 to –504)	–615 (–820 to –473)
Anterior (V2) territory	–66 (–142 to –16)	–50 (–124 to –13)	–597 (–859 to –435)	–632 (–905 to –489)
Lateral (V5) territory	–37 (–104 to –8)	–43 (–85 to –18)	–604 (–811 to –429)	–586 (–790 to –412)
Sum (II + V2 + V5)	–189 (–382 to –90)	–188 (–340 to –112)	–1,930 (–2,306 to –1,541)	–1,934 (–2,391 to –1,575)

Abbreviations: LFn, low frequency-normalized; pNN50, percentage of successive RR intervals that differ by > 50 msec; SDNN, standard deviation of RR intervals. Data are mean ± SD, or median (interquartile range). LFn and HFn are normalized units to account for variation in the total power and very low-frequency components. LF and SDNN reflect mainly sympathetic nervous stimulation; HF, pNN50, and RMSSD reflect parasympathetic tone.

* $p < 0.05$ from Wilcoxon matched pairs signed rank test or Student's paired t -tests as appropriate, mask versus no mask.

and true blinding is difficult to achieve given that large differences in mask efficiency would be readily apparent to trial participants, and differences in mask design would be obvious to investigators. It would also be anticipated that the greater effort of breathing through a mask during exercise would lead to an increase in blood pressure rather than the reverse.

We have assessed an acute intervention, and it remains to be seen whether wearing a face mask for more prolonged periods would have sustained benefits that could affect clinical outcomes.

Conclusions

In this randomized controlled crossover intervention trial, we observed that reducing personal exposure to PM air pollution was associated with small but consistent improvements in objective measures of myocardial ischemia, exercise-related increases in blood pressure, and heart rate variability in patients with coronary heart disease. Although efforts to reduce emissions are critical to reducing exposures to the population as a whole, use of a face mask may be an effective individual-level intervention for high-risk populations. The use of a face mask has the potential to reduce the incidence of acute cardiovascular events, as well as improving patients' general well-being, particularly in developing countries where pollutant exposures are high and resources to reduce emissions are limited.

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RESEARCH ARTICLE

Exposure to nitrogen dioxide is not associated with vascular dysfunction in man

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Abstract

Background: Exposure to air pollution is associated with increased cardiorespiratory morbidity and mortality. It is unclear whether these effects are mediated through combustion-derived particulate matter or gaseous components, such as nitrogen dioxide.

Objectives: To investigate the effect of nitrogen dioxide exposure on vascular vasomotor and six fibrinolytic functions.

Methods: Ten healthy male volunteers were exposed to nitrogen dioxide at 4 ppm or filtered air for 1 h during intermittent exercise in a randomized double-blind crossover study. Bilateral forearm blood flow and fibrinolytic markers were measured before and during unilateral intrabrachial infusion of bradykinin (100–1000 pmol/min), acetylcholine (5–20 µg/min), sodium nitroprusside (2–8 µg/min), and verapamil (10–100 µg/min) 4 h after the exposure. Lung function was determined before and after the exposure, and exhaled nitric oxide at baseline and 1 and 4 h after the exposure.

Results: There were no differences in resting forearm blood flow after either exposure. There was a dose-dependent increase in forearm blood flow with all vasodilators but this was similar after either exposure for all vasodilators ($p > .05$ for all). Bradykinin caused a dose-dependent increase in plasma tissue-plasminogen activator, but again there was no difference between the exposures. There were no changes in lung function or exhaled nitric oxide following either exposure.

Conclusion: Inhalation of nitrogen dioxide does not impair vascular vasomotor or fibrinolytic function. Nitrogen dioxide does not appear to be a major arbiter of the adverse cardiovascular effects of air pollution.

Keywords: Air pollution; endothelial function; fibrinolysis; nitrogen dioxide; NO₂

Introduction

Exposure to air pollution is a major public health problem, and is associated with an increased risk of cardiorespiratory morbidity and mortality. Epidemiological studies have consistently shown a strong association of cardiorespiratory illness and fine particulate matter (Dockery et al., 1993; Miller et al., 2007; Pope et al., 2002), although similar positive associations have been shown for long-term exposure to nitrogen dioxide (Anderson et al., 1996; Hoek et al., 2001; Rosenlund et al., 2008). Nitrogen dioxide and other oxides of nitrogen are major constituents of combustion-derived

air pollution, such as diesel exhaust, and the associations of nitrogen dioxide with adverse outcomes have usually been attributed to the close association of fine particulate with nitrogen dioxide concentrations (Sarnat et al., 2001). However, isolated real life exposures to nitrogen dioxide have been linked to increases in respiratory illness and susceptibility to airway infection (Guidotti, 1978; Mostardi et al., 1981; Love et al., 1982). Controlled exposure to nitrogen dioxide induces airway inflammation and modifies antioxidants in the respiratory tract lining fluid (Kelly et al., 1996).

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(Received 06 April 2009; revised 23 June 2009; accepted 24 June 2009)

ISSN 0895-8378 print/ISSN 1091-7691 online © 2010 Informa UK Ltd
DOI: 10.3109/08958370903144105

<http://www.informahealthcare.com/iht>

The cardiovascular effects of inhaled diesel exhaust are well documented. We have demonstrated that controlled exposures to diesel exhaust, as a model of combustion-derived fine particulate air pollution, causes acute vascular endothelial effects (Mills et al., 2005; Törnqvist et al., 2007). In these models, the actual exposure is a complicated mixture of carbon-centered particulate matter, volatile organic compounds, and gaseous pollutants (Scheepers & Bos, 1992). The predominant gaseous components are nitrogen dioxide and other oxides of nitrogen, with NO_x concentrations reaching around 4 ppm in previous controlled exposures to diesel exhaust (Mills et al., 2005; Salvi et al., 1999; Behndig et al., 2006). These models have consistently demonstrated an impairment of vascular endothelial function and endogenous fibrinolysis following exposure to diesel exhaust that appears to be mediated through increased oxidative stress and reduced nitric oxide bioavailability (Mills et al., 2005; Miller et al., 2009). Although particulate matter appears to be a major arbiter of these adverse vascular effects, the question remains as to the independent effect of a pure exposure to nitrogen dioxide. Nitrogen dioxide is itself a powerful oxidizing species, and this is proposed to underlie the airway inflammatory and antioxidant responses, as well as the vascular dysfunction previously described (Blomberg et al., 1997; Patel & Block, 1986).

The aim of this study was to explore the effect of a pure exposure to 4 ppm of nitrogen dioxide on vascular endothelial and fibrinolytic function, and to test the hypothesis that the previously demonstrated adverse effects are driven by nitrogen dioxide.

Methods

Subjects

Ten healthy male volunteers were recruited into the trial. Women were not included to avoid the potential confounding influence of cyclical changes in estrogen on vascular endothelial function (Ganz, 2002). One subject developed a respiratory tract infection during the study and was excluded and replaced. All subjects were nonsmokers, had no intercurrent illness, took no regular medication, and all had normal lung function. All subjects had been free of symptoms of upper airway infection for at least 6 weeks prior to the study. All subjects gave their written informed consent, and the trial was approved by the local research ethics committee in accordance with the Declaration of Helsinki.

Exposure protocol

The exposures to nitrogen dioxide or filtered air took place at the Medical Division of the National Institute for Working Life in Umeå as described previously (Kelly et al., 1996). Briefly, ambient air was drawn continuously through a large exposure chamber at a constant rate of 30 m³/h, which was maintained at a temperature of 20°C and relative humidity of 50%. Nitrogen dioxide (AGA Special Gas, Lidingö, Sweden) was passed through a mass flow controller (Model 5850TR, Brooks Instrument B.V., Veenendaal, Netherlands) and a

flow meter (Rota, Hannover, Germany) to control the gas flow, and was introduced to the ventilating duct just before reaching the chamber. Air was sampled in the breathing zone of the subjects and analyzed continuously for nitrogen dioxide, nitric oxide, and total NO_x using a CSI 1600 oxides of nitrogen analyzer (Columbia Scientific Industries, Austin, TX, USA). The concentration of nitrogen dioxide within the chamber was maintained at 4 ppm, a concentration selected to match that of NO_x concentrations seen in controlled exposures to diesel exhaust as described previously (Mills et al., 2005; Salvi et al., 1999; Behndig et al., 2006). Filtered air exposures were performed by HEPA filtration of air prior to introduction into the exposure chamber without introduction of additional nitrogen dioxide.

Study design

Subjects attended the clinical research facility at Umeå University Hospital on two occasions, each at least 1 week apart. In a randomized double-blind crossover trial, subjects were exposure to either filtered air or nitrogen dioxide at 4 ppm for 1 h with intermittent exercise. Subjects performed exercise on a bicycle ergometer while in the chamber at a predesignated workload to achieve a mean ventilation rate of 25 L/min, based on a prestudy screening exercise ventilation stress test. Subjects then returned to the clinical research facility for forearm vascular plethysmography studies with active drug infusions commencing 4 h after the exposure.

Outcome measures

Vascular assessments

Subjects underwent forearm venous occlusion plethysmography as described previously (Wilkinson & Webb, 2001). The brachial artery of the nondominant arm was cannulated with a 27-gauge steel needle under aseptic technique and local anaesthesia. After a 30-min baseline saline infusion, forearm blood flow was recorded during infusion of the endothelial-dependent (acetylcholine, 5, 10, and 20 µg/min; bradykinin, 100, 300, and 1000 pmol/min) and -independent (sodium nitroprusside, 2, 4, and 8 µg/min; verapamil, 10, 30, and 100 µg/min) vasodilators. The vasodilators were infused for 6 min at each dose, with the blood flow determined for last 3 min of the infusion. Vasodilators were administered in a random order, except for verapamil, which was always administered last given its prolonged vascular action, and were separated by a washout period of 20 min during which saline was infused.

Biochemical analyses

Peripheral venous blood samples were obtained at baseline and at 4 and 6 h after exposure for total and differential cell counts. Analysis was performed on an autoanalyzer by the local hematology reference laboratory (Department of Clinical Chemistry, University Hospital, Umeå). Blood samples were obtained during the forearm vascular study from indwelling 17-gauge venous cannulae inserted into a large antecubital vein on both arms before and after each dose of bradykinin. Bradykinin is an endothelial-dependant

vasodilator that also stimulates the release of stored tissue-plasminogen activator (t-PA) from the vascular endothelium (Brown et al., 1999, 2000). Samples were collected into acidified buffered citrate (Stabilyte, Biopool International) for analysis of t-PA and into citrate (BD Vacutainer) for plasminogen-activator inhibitor type 1 (PAI-1) assays to assess the activity of the endogenous fibrinolytic pathway.

t-PA and PAI-1 antigen concentrations were determined by commercially available enzyme-linked immunosorbent assays (ELISAs) (t-PA combi Actibind, Technoclone, Vienna, Austria; Elitest PAI-1, Hyphen BioMed, Neuville-sue-Oise, France). As much of the t-PA present in the circulation is bound to PAI-1, thus rendering both inactive and leading to hepatic clearance (Chandler et al., 1997), both t-PA and PAI-1 activity were assessed using enzymatic assays (t-PA combi Actibind, Zymutest PAI-1) as described previously (Mills et al., 2005).

Exhaled nitric oxide and lung function

The standardized fractional exhaled nitric oxide (FENO) was measured in duplicate at expiratory flow rates of 10, 50, 100, and 250 ml/s at baseline, 1 h, and 4 h after both exposures using a chemiluminescence analyzer (NiOX; Aerocrine AB, Stockholm, Sweden) (ATS/ERS 2005). Lung function was measured using simple spirometry (Vitalograph, Bucks, UK) at baseline and after the exposure, recording forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and slow vital capacity (VC).

Statistical analysis

We calculate, based on previous studies (Mills et al., 2005), that a sample size of 10 gives an 80% power of detecting a difference in forearm blood flow responses of 20% at a two-sided statistical significance level of 5%. All investigators were blinded to the exposure received. Plethysmography data were analyzed as described previously (Newby et al., 1999). Data were analysed using two-way analysis-of-variance (ANOVA) with repeated measures. The variables included in the ANOVA were dose and exposure for the forearm blood flow data, and time and exposure for the other outcome measures. All data are expressed as mean ± standard deviation unless otherwise stated. Statistical significance was taken as a two-sided *p* value of .05. Data were analyzed using GraphPad Prism (Version 4 for Macintosh; GraphPad Software, San Diego, USA) on a Macintosh personal computer.

Results

Ten subjects, median age 24 years, completed the study (Table 1). There were no changes in any indices of lung function seen following the nitrogen dioxide exposure (Table 2). Exhaled nitric oxide (FENO), measured as a surrogate of airway inflammation, was unchanged at all time points following either nitrogen dioxide or filtered air exposure (Table 2).

The forearm vascular studies revealed a dose-dependent increase in blood flow in the infused arm compared to the

Table 1. Baseline characteristics of the 10 subjects completing the study.

Age, years (median, range)	24 (22–28)
Male sex, %	100%
Height, cm	181 ± 5
Weight, kg	79 ± 10
BMI, kg m ⁻²	24 ± 2
FEV ₁ , L	4.95 ± 0.33
FVC, L	5.99 ± 0.52
VC, L	5.91 ± 0.47
Systolic blood pressure, mm Hg	136 ± 11
Diastolic blood pressure, mm Hg	67 ± 8
Heart rate, bpm	60 ± 12
Hemoglobin, g/L	146 ± 7
White cell count, × 10 ⁹ /L	4.9 ± 1.5
Platelet count, × 10 ⁹ /L	224 ± 53
PAI-1 antigen, ng/mL	6.87 ± 4.04
PAI-1 activity, U/mL	0.27 ± 0.22
t-PA antigen, ng/mL	2.82 ± 1.85
t-PA activity, U/mL	1.25 ± 0.54

Note: Data expressed as mean ± standard deviation unless otherwise stated. VC, Slow vital capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity. Plasminogen activator type 1 (PAI-1) and tissue plasminogen activator (t-PA) concentrations measured during forearm study on control air day before infusion of bradykinin.

Table 2. Basic spirometry and exhaled nitric oxide (FENO) at flow rates of 10, 50, 100 and 250 ml/s after 1 h of nitrogen dioxide (4 ppm) or filtered air exposure with intermittent exercise.

	Time	NO ₂	Air	<i>p</i> values	
				Time	Exposure
VC, L	Pre-exposure	5.82 ± 0.41	5.91 ± 0.47	.9586	.1525
	Post-exposure	5.88 ± 0.44	5.87 ± 0.48		
FEV ₁ , L	Pre-exposure	4.95 ± 0.24	4.95 ± 0.33	.9758	.9200
	Post-exposure	4.95 ± 0.33	4.94 ± 0.33		
FVC, L	Pre-exposure	5.93 ± 0.47	5.99 ± 0.52	.8824	.5704
	Post-exposure	5.93 ± 0.49	5.92 ± 0.54		
FENO 250 ml/s, ppm	Pre-exposure	6.28 ± 2.77	6.49 ± 2.36	.7960	.4244
	1 hour	5.80 ± 2.31	6.14 ± 2.10		
	4 hours	6.27 ± 1.69	6.83 ± 2.53		
FENO 100 ml/s, ppm	Pre-exposure	10.23 ± 5.62	10.53 ± 3.22	.8667	.8194
	1 hour	10.33 ± 5.45	10.52 ± 5.32		
	4 hours	11.28 ± 4.44	11.44 ± 5.43		
FENO 50 ml/s, ppm	Pre-exposure	16.55 ± 9.67	15.71 ± 9.02	.8628	.7003
	1 hour	16.94 ± 9.71	16.34 ± 8.32		
	4 hours	18.25 ± 9.01	17.81 ± 9.48		
FENO 10 ml/s, ppm	Pre-exposure	51.15 ± 32.65	51.87 ± 32.59	.8292	.9924
	1 hour	55.74 ± 32.00	54.28 ± 33.16		
	4 hours	58.57 ± 27.16	59.48 ± 35.41		

Note: Data shown as mean ± standard deviation. *p* values shown from two-way ANOVA with repeated measures showing effect of time and exposure. VC, Slow vital capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity, FVC.

noninfused arm in all subjects after each infused vasodilator. There was no difference in the vascular responses to any of the vasodilators (endothelium-dependent or -independent) following air or nitrogen dioxide exposure (Figure 1). Bradykinin stimulated a dose-dependent increase in release of plasma tissue-plasminogen activator (t-PA),

although the response was similar following each exposure (Table 3). Plasma plasminogen-activator inhibitor 1 (PAI-1) concentrations were unchanged ($p > .05$ for both infused and noninfused arms (data not shown) following infusion of bradykinin, with no differences following either exposure ($p > .05$ for all, data not shown).

There was no difference in white cell count, differential cell count, or platelet count through the study following either exposure (Table 4). We did observe a small fall in systemic hemoglobin concentrations through the study period consistent with repeated venesection, although

there was no difference between the study exposures (Table 4).

Discussion and conclusions

We have demonstrated for the first time that direct exposure to nitrogen dioxide is not associated with vascular vasomotor or fibrinolytic dysfunction. This suggests there are components other than nitrogen dioxide that are responsible for the previously documented adverse cardiovascular effects of air pollution.

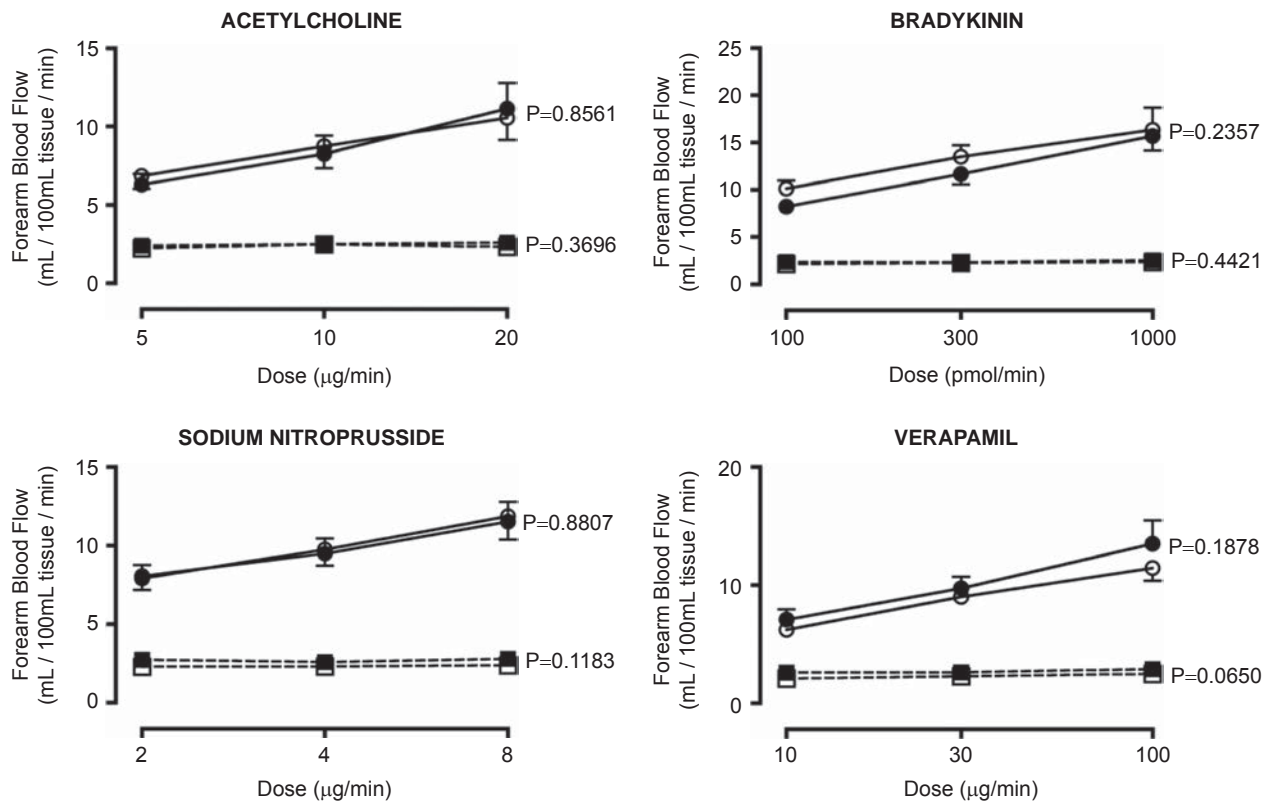


Figure 1. Forearm venous occlusion plethysmography with intra-arterial infusion of vasodilators performed 4 h after exposure. Data plotted as mean and T-bars show standard error of the mean. Solid lines show infused arm, dotted lines show noninfused arm after exposure to air (open symbols) or nitrogen dioxide (solid symbols) at 4 ppm. p values shown from two-way ANOVA with repeated measures showing effect of exposure for both infused and noninfused arms.

Table 3. Plasma tissue-plasminogen activator (t-PA) antigen concentrations and activity and estimated net t-PA release following infusion of bradykinin after 1 hour of nitrogen dioxide (4 ppm) or filtered air exposure with intermittent exercise.

Bradykinin (pmol/min)		Air				NO ₂				p Value	
		Baseline	100	300	1000	Baseline	100	300	1000	Time	Exp.
t-PA antigen ng/ml	Infused arm	2.82±1.85	2.46±1.26	4.22±2.78	8.52±4.74	3.01±1.98	2.67±3.32	3.32±2.42	5.98±3.10	.0005	.0982
	Noninfused arm	2.50±1.54	1.81±1.01	2.08±1.16	2.24±1.23	2.82±1.88	1.99±1.44	2.17±1.35	2.36±1.51	.6724	.2562
	Estimated net t-PA release (ng/100ml tissue/min)	0.43±0.67	3.78±1.87	16.54±13.90	54.27±30.52	0.33±0.64	2.93±4.59	8.89±12.29	36.71±25.87	<.0001	.0833
t-PA activity U/ml	Infused arm	1.25±0.54	1.81±0.55	2.60±0.72	3.48±1.57	1.25±0.43	1.82±0.77	2.11±1.11	2.95±1.01	<.0001	.2130
	Noninfused arm	0.98±0.49	1.08±0.32	1.20±0.36	1.54±0.49	1.00±0.34	1.04±0.44	1.13±0.42	1.53±0.54	.0009	.8191
	Estimated net t-PA activity release (U/100ml tissue/ min)	0.43±0.42	4.82±2.66	12.24±6.59	17.29±10.14	0.39±0.26	3.97±3.23	7.60±5.73	15.09±10.20	<.0001	.2158

Note: Data shown as mean ± standard deviation. p values shown from two-way ANOVA with repeated measures showing effect of time and exposure (Exp.).

Table 4. Differential cell count and hemoglobin concentrations before and after a 1-hour nitrogen dioxide (4 ppm) or filtered air exposure with intermittent exercise.

	Time	NO ₂	Air	<i>p</i> values	
				Time	Exposure
Haemoglobin (g/L)	Pre-exposure	148±8	146±7	.0124	.2842
	4 hours	142±8	143±7		
	6 hours	139±7	137±7		
White cell count (×10 ⁹ /L)	Pre-exposure	4.8±0.9	4.9±1.5	.2434	.4340
	4 hours	5.6±1.5	5.7±1.6		
	6 hours	6.2±2.1	5.7±1.5		
Platelet count (×10 ⁹ /L)	Pre-exposure	209±44	224±53	.8358	.2365
	4 hours	214±55	226±50		
	6 hours	209±46	209±45		
Neutrophils (×10 ⁹ /L)	Pre-exposure	2.37±0.75	2.34±1.14	.1580	.2961
	4 hours	3.14±1.10	3.15±1.21		
	6 hours	3.57±1.78	3.00±1.22		
Lymphocytes (×10 ⁹ /L)	Pre-exposure	1.89±0.34	1.91±0.47	.6226	.6763
	4 hours	1.91±0.55	1.92±0.44		
	6 hours	2.12±0.54	2.04±0.48		
Monocytes (×10 ⁹ /L)	Pre-exposure	0.39±0.11	0.40±0.10	.6687	.9647
	4 hours	0.41±0.15	0.43±0.13		
	6 hours	0.45±0.16	0.43±0.12		

Note: Data shown as mean ± standard deviation. *p* values shown from two-way ANOVA with repeated measures showing effect of time and exposure.

Vascular effects

In this study we have employed a robust and well-validated technique to assess vascular endothelial function following a short-term exposure to nitrogen dioxide. Exposure to nitrogen dioxide, a major component of combustion-derived air pollution, has been linked to cardiovascular morbidity and mortality in epidemiological studies. Why then did we not observe adverse vascular effects? Many workers have attributed the epidemiological link with nitrogen dioxide to a bystander association or epi-phenomenon rather than a casual relationship. Nitrogen dioxide is a copollutant that correlates tightly with fine and ultrafine particulate matter (Sarnat et al., 2001). Our current and previous findings are in agreement with this hypothesis. Using controlled exposures to dilute diesel exhaust, we have previously demonstrated marked adverse effects on vascular endothelial function (Mills et al., 2005) that are present 2 and 6 h after the exposure but have largely resolved by 24 h (Törnqvist et al., 2007). In the present study, performed 4 h after the exposure and well within the time window of the previously demonstrated adverse vascular effects, we aimed to separate the effects of the major gaseous copollutant, nitrogen dioxide, by using a pure gaseous exposure.

It is important to note that the nitrogen dioxide concentration employed in this study has been previously demonstrated to cause airway inflammatory responses (Blomberg et al., 1997; Sandstrom et al., 1991). In homes with gas stoves and in certain industries, nitrogen dioxide concentrations may peak at 1–2 ppm (Samet et al., 1987). Alongside busy roads, nitrogen dioxide concentrations may reach 0.6 ppm (WHO, 1999). Whereas the concentration of nitrogen dioxide

chosen for this study was matched to the overall concentration of oxides of nitrogen from previous diesel exhaust exposure studies (Mills et al., 2005; Salvi et al., 1999), in these studies nitrogen dioxide concentrations reached an average of 1.6 ppm. Therefore, even at levels above those encountered in dilute diesel exposures, when pronounced adverse vascular effects were demonstrated, we have clearly demonstrated that short-term exposure to pure nitrogen dioxide is not associated with vascular endothelial dysfunction in healthy young male subjects, although we cannot rule out a small effect in women or elderly people with comorbidities who may be more sensitive to environmental pollutants.

Nitrogen dioxide is a powerful oxidizing species, and we have demonstrated that its inhalation is associated with mild airway inflammation (Blomberg et al., 1997) and changes in airway antioxidant responses (Kelly et al., 1996; Blomberg et al., 1997). Moreover, after exposure to nitrogen dioxide in *in vitro* studies, porcine pulmonary artery and aortic endothelial cells have been shown to suffer a significant oxidant injury, with lipid peroxidation and impaired cell membrane function (Patel & Block, 1986). We have suggested that the vascular effects of air pollution exposure are mediated by oxidative stress (Miller et al., 2008), so why has inhalation of nitrogen dioxide failed to have an effect on vascular function? Nitrogen dioxide is relatively insoluble, and does not easily diffuse across to the bloodstream from the lungs. In fact, its penetration of the alveolar space is further inhibited by the normal respiratory tract lining fluid (Postlethwait et al., 1991). Therefore it is likely that inhaled nitrogen dioxide is confined mainly to the lungs where it exerts a localized and specific pulmonary inflammatory stimulus (Blomberg et al. 1997), without any significant vascular or systemic oxidative insult. In light of these findings, we suggest that the vascular endothelial effects we have previously demonstrated following exposure to diesel exhaust are driven by exposure to fine and ultrafine particulate matter, rather than any gaseous component.

Thrombotic effects

Thrombosis plays a central role in coronary heart disease. Formation of thrombus on disrupted atherosclerotic plaques may cause acute vessel occlusion, and acute coronary syndromes. Exposure to air pollution is proposed to be procoagulant. Exposure to ambient nitrogen dioxide and carbon monoxide has been associated with increased plasma fibrinogen (Pekkanen et al., 2000) and a reduced prothrombin time (Baccarelli et al., 2007), and ambient sulfur dioxide with plasma viscosity (Peters et al., 1997), but again the question of whether exposure to nitrogen dioxide and carbon monoxide is a surrogate for exposure to combustion-derived particulate matter arises. We have previously demonstrated that short-term exposure to dilute diesel exhaust results in increased platelet activation and enhanced thrombus formation (Lucking et al., 2008), and at the same time impairs vascular release of tissue-plasminogen activator (t-PA), an endogenous fibrinolytic enzyme (Mills et al., 2005) responsible for local dissolution of formed blood clot.

In this study we have not shown impaired release of tissue-plasminogen activator, or any increase in its endogenous inhibitor plasminogen-activator inhibitor type 1 (PAI-1), following exposure to nitrogen dioxide. Therefore we propose that the previously demonstrated procoagulant and antifibrinolytic effects of air pollution exposure are primarily driven by exposure to fine and ultrafine particulate matter rather than the gaseous copollutants.

Pulmonary effects

Our study demonstrated no change in exhaled nitric oxide (FENO) or simple spirometry following exposure to nitrogen dioxide. Spirometry provides a basic measure of lung function, assessing airway restriction and obstruction, and forms a critical part of the diagnosis of chronic lung conditions such as asthma and chronic obstructive pulmonary disease. Small effects on lung function have been demonstrated in patients with asthma following exposure to inhaled ambient air pollution (McCreanor et al., 2007). In light of this, we chose to assess changes in airway reactivity using simple spirometry in this group of healthy volunteers. Our study findings of no change in spirometry indices are in concordance with similar studies performed after exposure to diesel exhaust in healthy volunteers (Nightingale et al., 162).

Exhaled nitric oxide is proposed as a marker of airway inflammation, especially in asthmatic patients (ATS/ERS, 2005), and is closely correlated with eosinophilic inflammation (Lim & Mottram, 2008). As a marker, it is helpful in obtaining a diagnosis of asthma (Dupont et al., 2003) and may be used to track response to treatment (Yates et al., 1995). Although FENO has been used in other airway conditions, such as chronic obstructive pulmonary disease, interstitial lung diseases, and allergic rhinitis (2005), its usefulness as a marker of airway inflammation in healthy volunteers is unclear. Although exposure to the strong oxidative air pollutant ozone does not affect exhaled nitric oxide concentrations at an ozone dose known to induce a pronounced neutrophilic airway inflammation (Olin et al., 2001), we have recently demonstrated a significant increase in FENO following a 1-h exposure to dilute diesel exhaust in young healthy volunteers (Barath et al., 2007) and for this reason we chose FENO as a marker of airway inflammation in this study. In healthy volunteers we have previously demonstrated a mild airway inflammatory response, with increases in interleukin-8 (IL-8) concentrations in bronchial washings 90 min after a 4-h exposure to nitrogen dioxide (2 ppm). At 6 h after the exposure, we demonstrated increased IL-8 concentrations and neutrophil counts within bronchial washings but no signs of inflammatory cell recruitment into the endobronchial mucosa (Blomberg et al., 1997). We therefore believe that our measurements of FENO were performed within the established timeframe of an early airway inflammatory response.

Allowing for the limitations of FENO as a sensitive marker of airway inflammation as a result of air pollution exposure, we suggest that our study provides no strong evidence for an early marked airway inflammatory response following short-

term nitrogen dioxide exposure. However, we also acknowledge that measurements of FENO can be highly variable (Olin et al., 2001), and therefore that our small study may be underpowered to detect a clinically significant change. We therefore suggest that further investigation into the ability of short-term high-dose nitrogen dioxide to cause an inflammatory response is warranted.

Using a robust controlled study design, we have demonstrated for the first time that exposure to nitrogen dioxide is not associated with any vascular vasomotor or fibrinolytic dysfunction. The adverse cardiovascular effects of combustion-derived air pollution appear to be mediated via components other than nitrogen dioxide, and it is plausible that these vascular effects are rather driven by the fine and ultrafine particle fractions.

Acknowledgements

Dr. Langrish is supported by a British Heart Foundation clinical PhD studentship (FS/07/048). Dr. Blomberg is the holder of the Lars Werkö distinguished research fellowship from the Swedish Heart Lung Foundation. We would like to thank our research nurses Annika Johansson and Frida Holmström; Jamshid Pourazar, Ann-Britt Lundström, Neil Johnston, and the Clinical Pharmacology Department, Edinburgh, for their laboratory work; and the Department of Respiratory Medicine and Allergy, Umeå.

Trial Registration: www.ClinicalTrials.gov; NCT00774514.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Hypertension 2009;54;910-915; originally published online Aug 17, 2009;

DOI: 10.1161/HYPERTENSIONAHA.109.135947

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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Contribution of Endothelin 1 to the Vascular Effects of Diesel Exhaust Inhalation in Humans

Jeremy P. Langrish, Magnus Lundbäck, Nicholas L. Mills, Neil R. Johnston, David J. Webb, Thomas Sandström, Anders Blomberg, David E. Newby

Abstract—Diesel exhaust inhalation impairs vascular function, and, although the underlying mechanism remains unclear, endothelin (ET) 1 and NO are potential mediators. The aim of this study was to identify whether diesel exhaust inhalation affects the vascular actions of ET-1 in humans. In a randomized, double-blind crossover study, 13 healthy male volunteers were exposed to either filtered air or dilute diesel exhaust ($331 \pm 13 \mu\text{g}/\text{m}^3$). Plasma concentrations of ET-1 and big-ET-1 were determined at baseline and throughout the 24-hour study period. Bilateral forearm blood flow was measured 2 hours after the exposure during infusion of either ET-1 (5 pmol/min) or the ET_A receptor antagonist, BQ-123 (10 nmol/min) alone and in combination with the ET_B receptor antagonist, BQ-788 (1 nmol/min). Diesel exhaust exposure had no effect on plasma ET-1 and big-ET-1 concentrations ($P > 0.05$ for both) or 24-hour mean blood pressure or heart rate ($P > 0.05$ for all). ET-1 infusion increased plasma ET-1 concentrations by 58% ($P < 0.01$) but caused vasoconstriction only after diesel exhaust exposure (-17% versus 2% after air; $P < 0.001$). In contrast, diesel exhaust exposure reduced vasodilatation to isolated BQ-123 infusion (20% versus 59% after air; $P < 0.001$) but had no effect on vasodilatation to combined BQ-123 and BQ-788 administration ($P > 0.05$). Diesel exhaust inhalation increases vascular sensitivity to ET-1 and reduces vasodilatation to ET_A receptor antagonism despite unchanged plasma ET-1 concentrations. Given the tonic interaction between the ET and NO systems, we conclude that diesel exhaust inhalation alters vascular reactivity to ET-1 probably through its effects on NO bioavailability. (*Hypertension*. 2009;54:910-915.)

Key Words: air pollution ■ particulate matter ■ endothelial function ■ endothelin receptor antagonists ■ ET-1 ■ endothelin-1 ■ blood pressure

Exposure to combustion-derived fine particulate air pollution is a recognized risk factor for cardiorespiratory mortality and morbidity.^{1,2} There is a strong relationship between acute exposure to traffic-derived particulate matter and the incidence of acute myocardial infarction³ and hospital readmission in survivors of myocardial infarction.⁴ The World Health Organization estimates that annually ≈ 3 million deaths worldwide can be attributable to air pollution.⁵

Recent controlled exposure studies have demonstrated that inhalation of concentrated ambient particles and ozone causes acute arterial vasoconstriction 2 hours after the exposure.⁶ Inhalation of diesel exhaust, a major component of fine particulate air pollution in urban environments, impairs vasomotor function and endogenous fibrinolysis.⁷ The fundamental mechanisms underlying these detrimental vascular endothelial effects remain poorly understood. Furthermore, the exact components of air pollution responsible for these effects have not been defined, although it is proposed that airborne particulate matter is likely to be the major arbiter.²

Endothelin (ET) 1, an endogenous vasoconstrictor 100-fold more potent than norepinephrine,⁸ is a 21-amino acid peptide

produced by the vascular endothelium in response to stress. It is produced initially as preproendothelin-1, which is processed to form big-ET-1, before being cleaved by ET-converting enzyme into ET-1. The actions of ET-1 are mediated by 2 G protein-coupled receptors, the ET_A and ET_B receptors. Stimulation of either the ET_A or ET_B receptor causes vasoconstriction, although the ET_B receptor is also expressed on endothelial cells where it releases NO. The ET system plays a major role in cardiovascular and renal physiology,⁹ and although its actions are complex, ET-1 contributes to the maintenance of basal vascular tone and blood pressure in humans.^{10,11}

Recent work has suggested that plasma ET-1 concentrations are increased by exposure to air pollution. Rats raised with daily exposure to diesel exhaust particles and urban particulate matter have increased blood pressure, plasma ET-1 concentrations,¹² and ET-1 expression in cardiac tissue.¹³ In children from Mexico City, Mexico, plasma ET-1 concentrations correlated with the degree of air pollution exposure.¹⁴ Peretz et al¹⁵ recently demonstrated elevated

Received May 11, 2009; first decision May 26, 2009; revision accepted July 18, 2009.

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00745693).

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Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.109.135947

plasma ET-1 concentrations in a heterogeneous population of healthy volunteers and patients with the metabolic syndrome 3 hours after a controlled 2-hour resting exposure to diesel exhaust.

The aims of this study were to assess the effect of diesel exhaust inhalation on plasma ET-1 and big-ET-1 concentrations, ET-1-mediated vasoconstriction, and the contribution of ET-1 to basal vascular tone.

Methods

Subjects

Fifteen healthy male volunteers were recruited between February and March 2008 at Umeå University Hospital. All of the subjects had normal lung function, were nonsmokers, and took no regular medication. Those with a significant occupational exposure to air pollution and those with an intercurrent illness were excluded. The trial was performed with the approval of the local research ethics committee, in accordance with the Declaration of Helsinki, and with the written informed consent of each participant.

Study Design

Subjects attended for 2 consecutive days on 4 occasions ≥ 1 week apart. In a double-blind, randomized crossover study, subjects were exposed to either filtered air or dilute diesel exhaust at $300 \mu\text{g}/\text{m}^3$ for 1 hour in a specially built diesel exposure chamber, as described previously.¹⁶ During the exposure, subjects performed 15-minute periods of exercise on a bicycle ergometer (minute ventilation: 25 L/min per meter squared) alternated with 15-minute periods of rest.

On the basis of previous studies,⁷ vascular assessments and intra-arterial infusions were commenced 2 hours after the exposure. All of the subjects abstained from alcohol for 24 hours and caffeine-containing drinks for ≥ 8 hours and fasted for ≥ 4 hours before commencement of the vascular study. All of the subjects remained indoors at rest between the exposure and the vascular assessment to minimize additional exposure to air pollution. A validated ambulatory blood pressure monitor (model 90217, SpaceLabs Healthcare) was applied to the right arm 2 hours before the start of the exposure, and monitoring was continued for a total of 24 hours.

Diesel Exposure

Diesel exhaust emissions were generated using an idling Volvo (Volvo TD45, 4.5 L, 4 cylinders, 680 rpm) diesel engine. More than 90% of the exhaust was shunted away, and the remaining part was diluted with air and fed into the exposure chamber at steady-state concentration. During the exposure, air was sampled in the breathing zone of the subjects and monitored for nitrogen oxides, particle number, and total hydrocarbons (measured as propane). Filter samples were collected and analyzed for mass concentration. The exposures were standardized by keeping the particle (diameter: $< 10 \mu\text{m}$) mass concentration at $\approx 300 \mu\text{g}/\text{m}^3$. Temperature and humidity in the chamber were controlled at 22°C and 50%, respectively.

Vascular Studies

All of the subjects underwent brachial artery cannulation in the nondominant arm using a 27-gauge steel needle under controlled conditions. After a 30-minute baseline infusion of 0.9% saline, subjects received either a 60-minute infusion of ET-1 (American Peptide) at $5 \text{ pmol}/\text{min}$ ¹⁷ or infusion of BQ-123 (an ET_A receptor antagonist, American Peptide) at $10 \text{ nmol}/\text{min}$ for 60 minutes,¹⁸ followed by coinfusion of BQ-123 ($10 \text{ nmol}/\text{min}$) and BQ-788 (an ET_B receptor antagonist, American Peptide; $1 \text{ nmol}/\text{min}$)^{19,20} for a further 60 minutes.

Forearm blood flow was measured in the infused and noninfused arms by venous occlusion plethysmography with mercury-silicone elastomer strain gauges, as described previously.²¹ Supine heart rate and blood pressure were determined in the noninfused arm

Table. Baseline Characteristics of the 13 Subjects Who Completed the Study

Parameter	Data (N=13)
Age, median (range), y	23 (21 to 28)
Height, cm	181 ± 2
Weight, kg	79 ± 3
Body mass index, kg/m^2	24 ± 1
Hemoglobin concentration, g/L	153 ± 3
White blood cell count, $\times 10^9/\text{L}$	5.1 ± 0.4
Neutrophil count, $\times 10^9/\text{L}$	2.5 ± 0.3
Lymphocyte count, $\times 10^9/\text{L}$	2.0 ± 0.1
Monocyte count, $\times 10^9/\text{L}$	0.40 ± 0.03
Platelet count, $\times 10^9/\text{L}$	209 ± 11

Data show the mean \pm SEM unless otherwise stated.

at intervals throughout the study using the ambulatory blood pressure monitor.

Venous cannulae (17-gauge) were inserted into large subcutaneous veins in the antecubital fossae of both arms. Blood (10 mL) was drawn simultaneously from each arm at the end of the baseline saline infusion and at the end of each 60-minute infusion period. Blood samples were also obtained by separate venipuncture at baseline, immediately, and 6 and 24 hours after the exposure.

Biochemical Analyses

Blood samples taken at baseline and 6 and 24 hours after the exposure were analyzed for total and differential cell counts by an autoanalyzer. Plasma samples were collected into ethylene diamine tetra-acetic acid and kept on ice until centrifuged at 3000 rpm for 30 minutes. Plasma samples were immediately frozen and stored at -80°C . Plasma ET-1 and big-ET-1 concentrations were measured according to an acetic acid extraction technique using a commercial radioimmunoassay with rabbit antihuman ET-1 or big-ET-1 (Peninsular Laboratories Europe Ltd), as described previously.²²

Data and Statistical Analysis

Nursing staff at the clinical research facility at the Umeå University Hospital randomized exposure type and the associated vascular study protocol. The investigators were blinded to the exposure received. Plethysmography data were analyzed as described previously.²³ Data are expressed as mean \pm SEM unless otherwise stated. Statistical analyses were performed using paired Student *t* tests and 2-way ANOVA with repeated measures, including time and exposure as variables, where appropriate. Statistical significance was taken at the 5% level. All of the analyses were performed using GraphPad Prism (version 4 for Macintosh, GraphPad Software) on a Macintosh personal computer.

Results

Thirteen subjects, with a median age of 23 years (Table), completed the study (Figure 1). The diesel exposure generated a mean particle mass concentration of $331 \pm 13 \mu\text{g}/\text{m}^3$, and this was associated with concentrations of NO_2 of $1.0 \pm 0.04 \text{ ppm}$, NO of $3.3 \pm 0.13 \text{ ppm}$, and total hydrocarbons of $1.4 \pm 0.04 \text{ ppm}$. There were no differences in 24-hour mean systolic or diastolic blood pressures or mean heart rate after exposure to air or diesel exhaust ($P > 0.05$ for all), although there was a slightly lower nocturnal diastolic blood pressure after diesel exhaust exposure (62 ± 1 versus $65 \pm 1 \text{ mm Hg}$; $P < 0.01$). There was a rise in blood pressure after exercise on both study visits, although there was no difference between the 2 exposures (data not shown; $P > 0.05$).

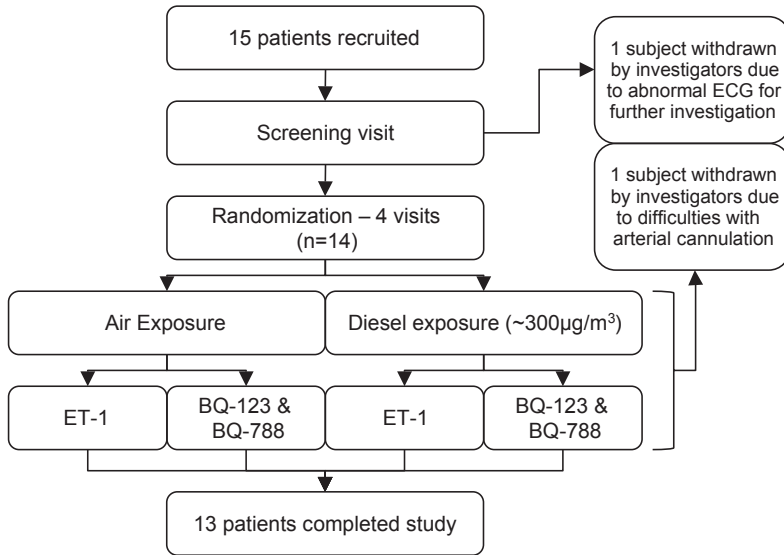


Figure 1. Consort flowchart of study participants.

Infusion of ET-1 caused a slow-onset vasoconstriction after diesel exhaust inhalation ($17 \pm 10\%$ peak reduction in blood flow), although there was little effect after filtered air (Figure 2; ANOVA, $P < 0.001$ for exposure effect). Infusion of the ET receptor antagonists, BQ-123 and BQ-788, caused a slow-onset vasodilatation ($77 \pm 14\%$ peak increase in blood flow after filtered air; Figure 3). This vasodilatation was greater after filtered air compared with the diesel exhaust exposure (Figure 3; ANOVA, $P < 0.001$). The difference was greatest at 60 minutes, but, after infusion of the BQ-788, there was little difference in blood flow by 120 minutes ($P > 0.05$).

Plasma ET-1 and big-ET-1 concentrations were unchanged at all of the time points after diesel exhaust or filtered air exposure ($P > 0.05$ for both). Comparison of the infused and noninfused arm plasma ET-1 concentrations confirmed that the ET-1 infusion increased local plasma ET-1 concentrations by $58 \pm 9\%$ (Figure 2; $P < 0.01$ for infused arms and $P > 0.05$ for noninfused arms for both exposures).

Discussion

Although diesel exhaust inhalation had no effect on plasma ET-1 or big-ET-1 concentrations, there was an increase in vascular sensitivity to ET-1 associated with a reduced ET_A induced vasodilatation. These apparently contradictory findings can be explained by impaired ET-1-induced NO release and are consistent with preclinical evidence of NO-mediated alterations in vascular reactivity to ET-1.²⁴ We conclude that diesel exhaust inhalation, at levels commonly encountered in the urban environment, does not affect plasma ET-1 concentrations but alters vascular reactivity to ET-1 probably through effects on NO release and bioavailability.

Endothelin 1

We did not demonstrate any change in plasma concentrations of ET-1 or its immediate precursor, big-ET-1, after exposure to filtered air or diesel exhaust. Although this is consistent with our own previous work,⁷ it is at odds with other reports.

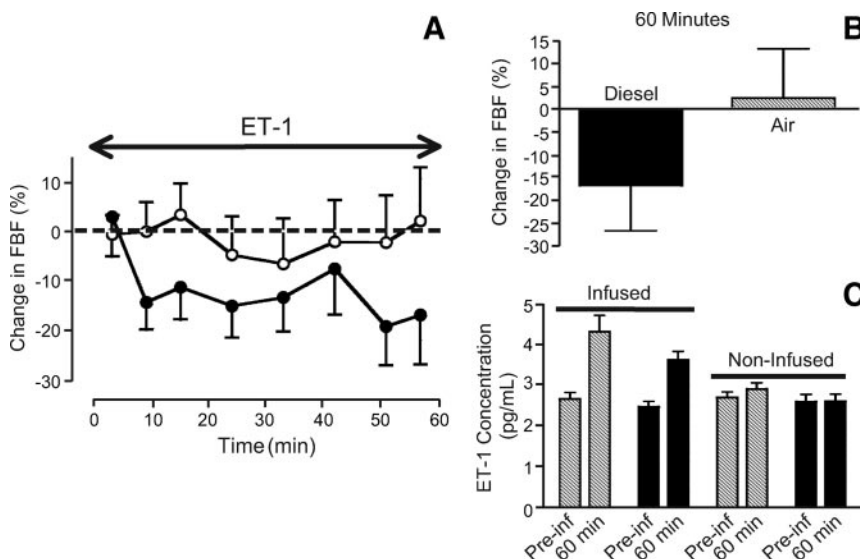


Figure 2. A, Forearm blood flow (FBF) during infusion of ET-1 (5 pmol/min) after exposure to air (○) and diesel exhaust (●; ANOVA, $P < 0.001$). B, Maximal effect at 60 minutes and (C) comparison of plasma ET-1 concentrations in infused and noninfused arms before and at the end of the forearm vascular study after air (□; $P < 0.001$ for infused and $P > 0.05$ for noninfused) and diesel exhaust inhalation (■; $P < 0.0001$ for infused and $P > 0.05$ for noninfused). Data are from a paired Student *t* test of air vs diesel.

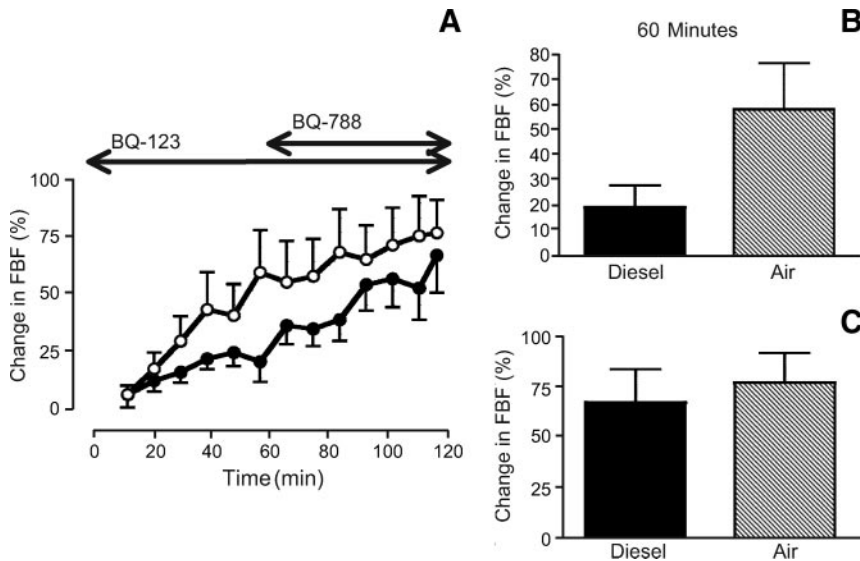


Figure 3. A, Forearm blood flow (FBF) during infusion of BQ-123 (10 nmol/min) and BQ-788 (1 nmol/min) after exposure to air (○) and diesel exhaust (●; ANOVA, $P < 0.001$). B, Maximal effect after BQ-123 infusion alone and (C) after dual endothelin receptor antagonism.

In rodent studies, plasma ET-1 (and ET-3) concentrations were upregulated after exposure to diesel exhaust and concentrated urban particles.^{12,13} It is possible that there are species differences in the response to diesel exhaust inhalation, and upregulation of ET-1 in rats may not translate to humans. However, Peretz et al¹⁵ studied a heterogeneous group of individuals composed of patients with metabolic syndrome and healthy volunteers and showed an increase in plasma ET-1 concentrations 3 hours after diesel exhaust exposure. Their study was not designed specifically to look at ET-1 and was limited by missing data and small numbers in a heterogeneous population in whom vascular endothelial function may not be equivalent.²⁵ In contrast, our study was specifically designed to address the ET hypothesis and used a robust crossover study design, in a homogenous group of healthy volunteers, with samples optimally collected to assess plasma ET-1 and big-ET-1 concentrations.²² Taken together with our previous study, our experience represents the largest sample size to date ($n=43$). Therefore, we think it is unlikely that diesel exhaust inhalation causes major changes in plasma ET concentrations.

We recognize that plasma ET-1 concentrations may not reflect the activity of the ET system because 90% of ET-1 synthesized by the vascular endothelium is secreted abluminally and acts locally on vascular smooth muscle in a paracrine manner.⁸ Therefore, in addition to measuring plasma ET-1 concentrations, we assessed the effects of ET agonism and antagonism on peripheral vascular tone.

ET Agonism

We demonstrated increased vasoconstriction after exposure to diesel exhaust, but little effect after exposure to filtered air, suggesting an increased vascular sensitivity to ET-1. We were surprised to see little vasoconstriction with ET-1 after exposure to filtered air, having previously reported $\approx 30\%$ to 40% reductions in forearm blood flow during infusions of 5 pmol/min.^{10,26} In the present study, we used an alternative preparation of ET-1 and suggest that the disparity in vascular effects is attributable to differing potencies of the prepara-

tions. Because of this, we measured plasma ET-1 concentrations in both forearms and demonstrated a selective 60% increase in plasma ET-1 concentrations in the infused arm. Assuming a forearm blood flow of 25 mL/min, we achieved an end-organ concentration approximately one tenth of that anticipated. However, this simple calculation does assume that there is no clearance or extraction of ET-1 across the forearm, but we do not believe that the modest increase in venous ET-1 concentrations can be solely accounted for by clearance, and conclude that it reflects a reduced activity of the infused peptide preparation. Although the reduced activity of ET-1 limits comparisons with other studies, this was perhaps fortuitous, because it enabled us to assess the vasoreactivity to ET-1 at the threshold for vasoconstriction and to observe an alteration in ET-1 sensitivity.

ET_A Receptor Antagonism

The reduction in vasodilatation to BQ-123 infusion after diesel exhaust inhalation has several potential explanations. First, this may relate to reduced production or increased clearance of active ET-1 from the vasculature. However, this seems unlikely given that plasma ET-1 and big-ET-1 concentrations were unchanged, although we acknowledge that an effect on the abluminal release of ET-1 cannot be excluded. Second, a reduced sensitivity of the vascular smooth muscle ET_A receptor could have occurred, but this is at odds with the increased ET-1 vasoconstriction and is, therefore, unlikely. We believe that there is a third, more likely, explanation.

Looking closely at ET_A receptor antagonism, it is clear that the mechanism of vasodilatation is complex. This reflects the distribution and basal activity of both the ET_A and ET_B receptors. Both receptors contribute to the maintenance of basal vascular tone but have differing actions and vascular distributions: ET_A receptors are present on vascular smooth muscle cells only and mediate vasoconstriction, whereas ET_B receptors are present on both vascular smooth muscle and endothelial cells, where they mediate vasoconstriction and vasodilatation, respectively. Moreover, selective ET_A receptor antagonism leads not only to inhibition of the ET_A

receptor but potentially to hyperstimulation of the ET_B receptor. Indeed, we have demonstrated that BQ-123-induced vasodilatation can be markedly attenuated by concomitant blockade of NO release,¹⁸ suggesting that selective ET_A receptor antagonism does indeed lead to significant ET_B receptor-mediated vasodilatation through endothelial NO release. Given the central role of NO in modulating and balancing the effects of the ET system, we propose that changes in the L-arginine-NO pathway offer the most plausible hypothesis for the impaired vasodilatation to BQ-123. This would also explain the enhanced vasoconstriction to ET-1 with a reduction in the opposing vasodilatory actions of NO. Moreover, we have shown previously that diesel exhaust impairs NO bioavailability^{7,27} and suggest that the observed effects on ET-1 vasoreactivity can be explained by the reduction in ET-induced NO release and bioavailability.

The finding of reduced vasodilatation in response to ET_A receptor blockade is at odds with previous studies demonstrating enhanced response in patients with conditions such as hypertension and hypercholesterolemia who have preexisting endothelial dysfunction mediated by reduced NO bioavailability.^{28,29} The reason for this discrepancy is unclear, but here we have induced an acute and brief episode of endothelial dysfunction in an otherwise healthy population of volunteers. Chronic dysfunctional states are likely to invoke compensatory mechanisms that may result in important differences in these vascular responses.

Combined ET_A and ET_B Receptor Antagonism

Previous data, including our own work,¹⁸ would suggest that combined ET_A/ET_B receptor antagonism should produce less vasodilatation than selective ET_A receptor antagonism. We were, therefore, surprised to observe the continued further modest vasodilatation when ET_B receptor antagonism was superimposed on ET_A receptor antagonism. We believe that the explanation for this observation is 3-fold. First, vasodilatation to ET agonism and antagonism is of slow onset and offset. In our own hands, BQ-123-induced vasodilatation appears to reach a peak effect by 60 minutes¹⁸ but may take up to 90 minutes.¹⁰ The continued vasodilatation may, therefore, reflect further and more complete ET_A receptor antagonism. Second, we chose this study design to minimize the number of visits given the invasive nature of the studies. We attempted to assess both ET_A receptor antagonism and combined ET_A/ET_B receptor antagonism on the same visit. This approach has been used once before by Cardillo et al³⁰ in a small subgroup of patients with diabetes mellitus. Here, they demonstrated a brisk vasodilatation to BQ-123 of ≈65% with maximal vasodilatation by 60 minutes. Importantly, the predicted "tailing off" of the response when BQ-788 was added did not occur, and the vasodilatation plateaued rather than fell. This is consistent with the findings in our study. Finally, there may be an interaction when ET_A receptor antagonism precedes combined ET_A/ET_B receptor antagonism. This may reflect alterations in ET_B receptor expression on both the endothelium and vascular smooth muscle cells in the face of ET_A receptor antagonism. Indeed, there is considerable cross-talk between the receptors, as we have described previously.³¹ Thus, the differing profile of responses may

reflect the dynamic interaction of the 2 receptors over the course of the study.

This altered profile of vasodilatation does not detract from the comparison between the filtered air and diesel exhaust exposure. Combined ET_A and ET_B receptor antagonism appears to be unaffected by diesel exhaust exposure, whereas selective ET_A receptor antagonism is impaired. This is likely to reflect the greater and marked dependence of ET_A receptor antagonism on NO release in comparison with combined ET_A and ET_B receptor antagonism.

Conclusions

Our data demonstrate that the previously documented impairment of endothelium-dependent vasodilatation after a 1-hour exposure to combustion-derived air pollutants is not mediated by an upregulation of the ET system. Furthermore, we have shown that diesel exhaust inhalation has no effect on plasma ET-1 concentrations or systemic blood pressure. Our data are consistent with the hypothesis that the diesel exhaust-induced vascular effects are predominantly driven by reduced endothelial NO bioavailability. However, we cannot exclude a role for other vasoactive mediators, such as endothelium-derived hyperpolarizing factor, and further studies are warranted to investigate the L-arginine:NO and other pathways in more detail.

Perspectives

Air pollution exposure is associated with increased cardiovascular morbidity and mortality and is thought to lead to ≈3 million deaths worldwide each year. Understanding the underlying mechanism for these detrimental effects is crucial in trying to reduce this significant disease burden. In this study, we show that the well-established adverse vascular endothelial effects demonstrated after inhalation of diesel exhaust are not directly mediated through the ET system. We propose instead that these may be driven by changes in NO bioavailability. Additional studies are warranted to investigate this hypothesis in more detail.

Acknowledgments

We thank Annika Johansson, Frida Holmström, Margot Johansson, Jamshid Pourazar, Ann-Britt Lundström, Ester Roos-Engstrand, Maj-Cari Ledin, and the Department of Respiratory Medicine and Allergy (Umeå). Thanks also to the staff at Svensk Maskinprovning (Umeå) and the Clinical Pharmacology Unit (Edinburgh) for their assistance with the studies.

Sources of Funding

This research was supported by a project grant from Chest, Heart, and Stroke Scotland (08/A116); the Swedish Heart Lung Foundation; the County Council of Västerbottens, Sweden; the Swedish National Air Pollution Programme; a British Heart Foundation Programme grant (RG/03/005); and the University of Umeå. J.P.L. is supported by a British Heart Foundation Clinical PhD Studentship (FS/07/048). A.B. is the holder of the Lars Werkö Distinguished Research Fellowship from the Swedish Heart Lung Foundation.

Disclosures

None.

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Cardiovascular effects of particulate air pollution exposure: time course and underlying mechanisms

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Abstract. Langrish JP, Bosson J, Unosson J, Muala A, Newby DE, Mills NL, Blomberg A, Sandström T (University of Edinburgh, Edinburgh, UK; and Ume University, Umeå, Sweden). Cardiovascular effects of particulate air pollution exposure: time course and underlying mechanisms. *J Intern Med* 2012; doi: 10.1111/j.1365-2796.2012.02566.x

Air pollution is now recognized as an important independent risk factor for cardiovascular morbidity and mortality and may be responsible for up to

3 million premature deaths each year worldwide. The mechanisms underlying the observed effects are poorly understood but are likely to be multifactorial. Here, we review the acute and chronic effects of air pollution exposure on the cardiovascular system and discuss how these effects may explain the observed increases in cardiovascular morbidity and mortality.

Keywords: air pollution, atherosclerosis, cardiovascular disease, thrombosis, vascular function.

Introduction

It has long been recognized that air pollution is potentially detrimental to health. In 1661, John Evelyn, one of the founding members of the Royal Society, proposed that almost half of the deaths observed from 'phthisical and pulmonic distempers' may be attributed to poor air quality and that inhabitants of polluted urban areas should 'move into the country... where [the air] is excellent' [1]. Well-documented episodes of air pollution, such as the Great Smog of London in December 1952 [2], are associated with marked increases in cardiorespiratory deaths. This has led to the implementation of legislation to improve air quality and has stimulated scientific study of the health effects associated with inhaling commonly found air pollutants.

Epidemiology

Large epidemiological studies have repeatedly demonstrated the association between exposure to air pollution and increased morbidity and mortality. In 1993, Dockery and colleagues reported the results of a landmark study (the Harvard Six Cities Study). In a prospective cohort of 8111 adults living in six major US cities, they demonstrated an odds ratio of mortality of 1.26, after adjustment for baseline differences, between subjects living in the least-polluted and those in the most-polluted cities [3]. These findings were strengthened by an analysis of the American

Cancer Society prospective cohort study of 1.2 million adults across the 50 states of the USA which demonstrated strong associations between air pollution exposure and all-cause, cardiorespiratory and lung cancer mortality [4]. Estimates of the size of this effect vary widely, but it is now accepted that the increase in mortality is a robust and reproducible finding [5] (Table 1).

Air pollution is a complex mixture of gaseous, volatile, semi-volatile and particulate matter, and its exact composition varies widely. Indeed, the composition in a single location will vary depending on the meteorological conditions, time of the day, day of the week, industrial activity and traffic density. Some of the commonly measured components of the air pollution mixture are illustrated in Fig. 1. Airborne particulate matter can vary widely in its chemical composition, depending on its source. For instance, crustal particles (e.g. soil and sand) are predominantly silica based, whereas particles from industrial sources and traffic, which are derived from the burning of fossil fuels, largely contain carbon.

Epidemiological evidence suggests that the strongest associations between air pollution exposure and morbidity and mortality are found for particulate matter, especially the fine and ultrafine particulate fractions that can easily be inhaled deep into the lungs [6]. In a re-analysis of the Harvard Six Cities Study, the association between mortality and air

Table 1 Summary of key epidemiological studies to investigate the link between air pollution exposure and mortality

Study	Percentage increase in mortality (95% CI) per 10 $\mu\text{g m}^{-3}$ $\text{PM}_{2.5}$		
	All-cause	Cardiopulmonary	Cardiovascular
Harvard Six Cities, original (Dockery <i>et al.</i> , 1993) [3]	13 (4–23)	18 (6–32)	–
Harvard Six Cities, HEI re-analysis (Krewski <i>et al.</i> , 2004) [123]	14 (5–23)	19 (7–33)	–
Harvard Six Cities, extended (Laden <i>et al.</i> , 2006) [124]	16 (7–26)	–	28 (13–44)
American Cancer Study, original (Pope <i>et al.</i> , 1995) [125]	7 (4–10)	12 (7–17)	–
American Cancer Study, HEI re-analysis (Krewski <i>et al.</i> , 2004) [123]	7 (4–10)	12 (7–17)	13 (8–18)
American Cancer Study, extended (Pope <i>et al.</i> , 2002, 2004) [4, 126]	6 (2–11)	9 (3–16)	12 (8–15)
Women's Health Initiative Study (Miller <i>et al.</i> , 2007) [127]	–	–	76 (25–247)
American Cancer Study, extended (Krewski <i>et al.</i> , 2009) [128]	6 (4–8)	13 (10–16)	–
California Teachers Study (Lipsett <i>et al.</i> , 2011) [129]	–	–	20 (2–41)
Harvard Six Cities, extended (Lepeule <i>et al.</i> , 2012) [130]	14 (7–22)	–	26 (14–40)

HEI, Health Effects Institute.

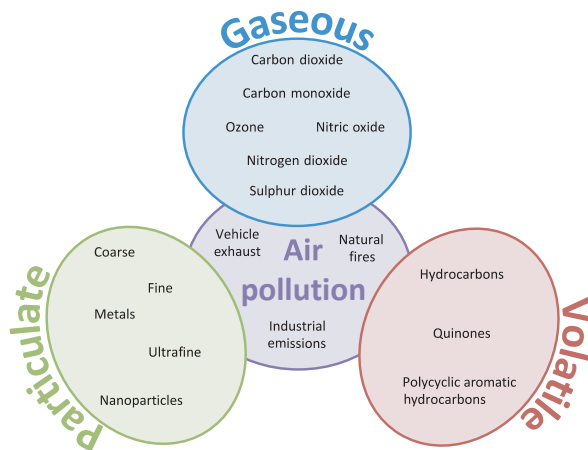


Fig. 1 Schematic diagram demonstrating that air pollution is a complex mixture of gaseous, volatile and particulate matter.

pollution exposure was found to be specifically linked to particles derived from combustion-based sources, such as industry and traffic, but not for crustal particles [7].

Although the exposure to air pollution is associated with the incidence of pulmonary diseases such as chronic obstructive pulmonary disease and asthma [8, 9], what is perhaps unexpected is that the associations between air pollution exposure and morbidity and mortality are strongest for cardiovascular diseases, such as myocardial infarction. This finding is

supported by a number of meta-analyses and multicity studies of daily changes in exposure to particulate air pollution exposure that has demonstrated an increase of 0.5–2% in cardiovascular mortality with each 10–20 $\mu\text{g m}^{-3}$ increase in particulate air pollution exposure [10–16].

The association between air pollution exposure and acute cardiovascular events has a close temporal relationship. Peters and colleagues reported a retrospective cohort study of 772 adults who presented with acute myocardial infarction in Boston, USA, during 1995 and 1996. They found that subjects who suffered an acute myocardial infarction were three times more likely to have been exposed to traffic in the hour before the onset of symptoms, suggesting a causal link between high levels of acute exposure to combustion-derived particulate air pollution and the onset of myocardial infarction [17]. An analysis of 80 000 cases of myocardial infarction from the Myocardial Infarction National Audit Project database in the UK similarly demonstrated an increase in the onset of myocardial infarction in the first 6 h following exposure to traffic-derived air pollution. Detailed meta-analyses have demonstrated a 2.5% (95% confidence interval [CI] 1.5–3.6%) increase in the risk of acute myocardial infarction with each 10 $\mu\text{g m}^{-3}$ increase in exposure to particulate matter with a mean aerodynamic diameter of $<2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) [18]. Such meta-analyses have also shown that on a population level, traffic exposure is, in fact, the highest attributable risk factor to precipitate nonfatal myocardial infarction,

with a similar magnitude of risk as well-accepted factors such as physical exertion [19].

The epidemiological links between exposure to air pollution and cardiovascular morbidity and mortality are compelling. However, well-designed and carefully controlled observational studies, whilst of undeniable importance, are limited to describing associations and by definition cannot prove causation. At best, such studies provide the basis for speculation and hypothesis generation regarding the potential pathophysiological mechanisms. To test these hypotheses, there is now a wealth of data derived from controlled exposure studies assessing underlying pathophysiological mechanisms.

Controlled human exposure studies

Controlled exposure studies have several important benefits in assessing the pathophysiological mechanisms underlying the association between exposure to air pollution and cardiovascular morbidity and mortality. First, unlike studies in 'real-world' environments, exposures are predictable and controllable, and as such are ideal for performing toxicological studies [20]. Furthermore, exposure studies can be used to separate the various effects of different components of the air pollution mixture. In general, these studies have focused on the effects of combustion-derived particulate matter with exposure to either dilute diesel exhaust or concentrated ambient particles. Diesel exhaust is an important component of urban outdoor air pollution in which it may account for up to 40% of the airborne particulate matter [21]; this fraction is likely to increase given the current drive for 'green taxation' on vehicles linked to carbon dioxide emissions. Diesel engines emit less carbon dioxide, but particulate emissions are around 100-fold higher compared to gasoline engines [22–24].

In this review, we discuss the acute and chronic effects of pollution exposure on the cardiovascular system and describe the complex mechanisms underlying the observed responses, focusing on human exposure studies, but including animal data where such studies cannot be performed in humans.

Acute cardiovascular effects

Vasoconstriction and arterial stiffness

In the first studies of controlled human exposure to air pollutants to assess vascular function, Brook *et al.* [25] demonstrated vasoconstriction of the brachial artery immediately following exposure to con-

centrated ambient particles in combination with ozone. Similar acute vasoconstriction was shown in a heterogeneous population of healthy volunteers and subjects with metabolic syndrome [26] after controlled exposure to dilute diesel exhaust. In a recent real-world cardiovascular substudy within the Detroit Exposure and Aerosol Research Study, exposure to air pollution was measured in individuals using portable monitoring equipment, and exposure to particulate matter was found to be associated with increasing vasoconstriction [27]. Using applanation tonometry, we have demonstrated that there is an immediate and transient increase in central arterial stiffness immediately after exposure to dilute diesel exhaust, which is consistent with an increase in arterial tone and vasoconstriction [28]. Similarly, in a small real-world panel study of children living in Italy, central arterial stiffness was found to be significantly higher in children living near than in those living further from major roads [29].

Blood pressure

Following on from their observation that exposure to a combination of concentrated ambient particles and ozone caused arterial vasoconstriction, Brook *et al.* assessed the systemic haemodynamic response to a similar combined exposure and demonstrated an increase in diastolic and mean arterial blood pressure 2 h after the exposure [30, 31]. This increase in blood pressure was strongly associated with the concentration of airborne particulate matter, but not with the ozone concentration, suggesting that the blood pressure changes are attributable to the particulate matter alone and not the gaseous components of the exposure [31]. Furthermore, the magnitude of the increase in blood pressure was strongly associated with the organic carbon fraction of the particulate air pollution exposure, reflecting combustion-derived matter [30]. In real-world studies in Beijing, China, which is known to have a high level of urban air pollution, exercise-related increases in blood pressure were exaggerated in healthy volunteers [32] and in patients with coronary heart disease [33]. It is interesting that this effect could be reversed when subjects were protected from inhaling particulate air pollution by the use of a highly efficient facemask.

Myocardial ischaemia

Exposure to particulate air pollution has been shown to be associated with an increased risk of ST-segment depression during submaximal exercise tolerance

testing in elderly patients with coronary heart disease [34–36]; the risk was strongly associated with exposure to combustion-derived particulate matter [36]. Similarly, using continuous electrocardiographic recordings before, during and after exercise outdoors, Gold *et al.* [37] showed that black carbon exposure (a measure of traffic-derived particulate air pollution) increased the risk of ST-segment depression in elderly patients. Black carbon and PM_{2.5} exposure increased ST-segment depression during repeated continuous 24-h electrocardiographic recordings in elderly subjects with coronary heart disease [38] and in survivors of acute coronary syndromes [39]. Furthermore, in patients with coronary heart disease, maximal ST-segment deviation was reduced when walking in the centre of Beijing by using a highly efficient facemask to reduce personal exposure to particulate air pollution exposure [33].

In a controlled human exposure study, men with coronary heart disease were assigned to exposure to dilute diesel exhaust and filtered air in a double-blind, randomized, crossover manner. Throughout the exposure period, subjects performed bouts of standardized exercise on an exercise bicycle. During exercise, ST-segment depression and ischaemic burden were increased when exposed to the dilute diesel exhaust as compared to the filtered air [40].

Heart rate variability and cardiac arrhythmias

Epidemiological studies have demonstrated that short-term exposure to particulate air pollution is associated with an increase in hospital admissions with conditions including myocardial infarction, heart failure and arrhythmias [5]. In addition, there appears to be a positive association between exposure to airborne particulate matter and the incidence of ventricular arrhythmias in patients with automated implantable defibrillators [41, 42]. The incidence of ventricular arrhythmias and sudden cardiac death is closely associated with the activity of the autonomic nervous system [43]; this can be readily measured using heart rate variability [44, 45]. Indeed, heart rate variability is recognized as a prognostic marker following myocardial infarction and is reduced prior to the development of ventricular arrhythmias in patients with this condition [46, 47]. Moreover, reduced heart rate variability may predict the likelihood of developing ventricular arrhythmias in susceptible patients [48]. A number of panel studies have demonstrated a reduction in heart rate variability with increased exposure to particulate air pollution [49–52].

This relationship has been explored in more detail in controlled human exposure studies. Heart rate variability was reduced immediately following a 2-h exposure to concentrated ambient particles in healthy elderly subjects and remained impaired up to 24 h after the exposure [53]. Similar changes in autonomic control of the heart have been shown in younger healthy volunteers, patients with asthma [54, 55] and those with chronic obstructive pulmonary disease [56] following concentrated ambient particle exposure. In real-world studies in Beijing, we recently demonstrated an increase (improvement) in indices of heart rate variability in healthy volunteers [32] and patients with coronary heart [33] when participants were protected from the exposure to particulate air pollution by the use of a highly efficient facemask.

Samet and colleagues exposed healthy volunteers to concentrated ambient particles separated into size fractions and assessed changes in heart rate variability. They found no relationship between heart rate variability and exposure to ultrafine or fine particulate air pollution – including combustion-derived particulate matter – but a reduction in indices of heart rate variability following exposure to the coarse fraction containing particles between 2.5 and 10 µm in diameter [57]. In line with these findings, we did not observe any changes in heart rate variability following exposure to dilute diesel exhaust in either healthy volunteers or patients with coronary heart disease [58]. This suggests that the changes in autonomic control of the heart may be mediated by components of the air pollution mixture other than the combustion-derived particulate matter such as transition metals.

Early cardiovascular effects

Vascular endothelial vasomotor function

Vascular vasomotor function may be assessed in a variety of ways, but the most commonly used techniques are forearm venous occlusion plethysmography and flow-mediated vasodilatation (FMD). Forearm venous occlusion plethysmography enables forearm blood flow to be assessed safely and reproducibly, whilst also allowing pharmacological intervention by means of intra-arterial infusion of drugs at sub-systemic doses [59]. FMD evaluates vasodilatation of the brachial artery in response to reperfusion after a period of ischaemia, which is driven predominantly by the release of nitric oxide (NO) from the endothelium [60].

Whereas vasoconstriction of the brachial artery has been demonstrated immediately following exposure to concentrated ambient particulate matter in combination with ozone [25] and dilute diesel exhaust [26], FMD of the brachial artery seems to remain unaffected at this early time-point. However, in further studies, Brook *et al.* [31] have demonstrated impaired FMD 24 h after the exposure to concentrated ambient particulate matter. A similar impairment in FMD has been demonstrated in a small panel study in Paris, France; FMD was negatively correlated with average exposure to ambient air pollution (measured as sulphur dioxide and nitrogen dioxide, which can be considered surrogate markers of combustion-derived particulate matter [61]) over the 5 days before measurement [62]. Dales *et al.* [63] measured both local air pollution concentrations and FMD in the forearm in people waiting at bus stops in Ottawa, Canada. They demonstrated a similar negative association between FMD and airborne particulate matter (PM_{2.5}) in these healthy volunteers, underlining the fact that these are important responses even at the relatively low concentrations of particulate matter seen in such real-world studies. The same investigators, however, found a reversed (positive) relationship between particulate air pollution exposure and FMD in patients with diabetes mellitus [64]. Such patients are known to have impaired vascular endothelial vasomotor function, and this may underlie the differing effects in these two populations.

Underlying differences in the chemical composition of the particles appear to be important for these vascular endothelial effects, as FMD was impaired following exposure to concentrated ambient particles from Toronto, Canada, but not to those from Ann Arbor, USA [31]. Similarly, exposure to concentrated ambient particulate matter in Edinburgh, UK, had no effect on vascular vasomotor responses measured using forearm venous occlusion plethysmography [65]. Real-time chemical analysis of the concentrated particles revealed that they were composed predominantly of inert sodium chloride, reflecting the maritime location of the city, and very little combustion-derived matter, which is known to be most closely associated with cardiovascular effects [66].

Attenuated responses to the endothelium-dependent vasodilators acetylcholine and bradykinin as well as the endothelium-independent vasodilator sodium nitroprusside have been shown as early as 2 h following exposure to dilute diesel exhaust, and responses persisted at 6 h [67]. The endothelium-

dependent vasomotor responses were still blunted 24 h after the exposure [68], although the response to sodium nitroprusside was no longer evident. These vascular endothelial effects were seen after exposure to dilute diesel exhaust, but not after exposure to the gaseous phase of diesel exhaust (with the particles filtered out), pure carbon nanoparticles or filtered air [69].

The endothelial mechanisms underlying these impaired responses are still the source of some debate. Observational studies have demonstrated that exposure to air pollution is associated with an increase in plasma concentrations of endothelin-1 [70], a potent endogenous vasoconstrictor, which has also been implicated in the vascular endothelial dysfunction observed in cigarette smokers [71] and patients with hypertension [72] or hypercholesterolaemia [73]. Experimental studies in apolipoprotein E-deficient (ApoE^{-/-}) mice and in rats and humans have confirmed an increase in plasma endothelin-1 following exposure to dilute diesel exhaust [26, 74, 75]. By contrast, we failed to demonstrate an increase either in endothelin-1 or in its precursor following diesel exhaust exposure, and the vasomotor responses to infusion of endothelin-1, and the endothelin receptor antagonists BQ-123 and BQ-788, were consistent with alterations in vascular NO bioavailability rather than a direct effect on the endothelin pathway [76].

Consistent with the hypothesis that changes in NO bioavailability are responsible for the vascular vasomotor effects of air pollution exposure, recent studies have shown that rats exposed to diesel exhaust by inhalation have increased expression of endothelial NO synthase along with an increase in plasma nitrate and nitrite concentrations, suggesting a disturbance of the NO pathway [77]. Consistent with this hypothesis, we have demonstrated an increase in plasma nitrite concentration 2 h after diesel exhaust inhalation in man [78]. After eliminating endogenous NO using an NO clamp, vascular vasomotor responses following diesel exhaust exposure were no longer attenuated, compared to the control filtered air exposure, underlining the central role of NO in these effects.

Oxidative stress

It has been proposed that oxidative stress, or the generation of reactive oxygen species (ROS), over and above that which the body's defences can remove by means of endogenous antioxidant defence pathways,

underlies the observed cardiovascular effects of exposure to particulate air pollution [5]. Indeed, atherosclerosis, the formation of plaques on the inner surface of arteries, is driven by the accumulation of oxidized lipids within the intimal layer and subsequent inflammation. Furthermore, ROS within the vasculature can react with NO forming peroxynitrite and limiting the beneficial effects of NO such as vasodilatation, inhibition of platelet activation and regulation of inflammatory cells.

There is now substantial epidemiological and experimental evidence to suggest a key role for oxidative stress in the adverse pulmonary effects of traffic-related air pollution. Animal models and *in vitro* studies have clearly demonstrated the presence of oxidative stress within the lung, associated with increased expression of heme oxygenase-1 and oxidative DNA damage [79, 80], following exposure to diesel exhaust particles. Exposure studies in human subjects have demonstrated antioxidant changes in bronchoalveolar lavage fluid together with upregulation of the redox-sensitive transcription factors, nuclear factor kappa-light-chain-enhancer of activated B cells and activator protein 1 in the bronchial mucosa [81]. Furthermore, deposition of particulate matter in the lung triggers activation of NADPH oxidase within the lung, causing stimulation of the bone marrow by alveolar macrophages and a subsequent systemic inflammatory response [82–84]. This pulmonary and systemic inflammatory response may then translate into an increase in vascular oxidative stress, stimulating local cytokine and superoxide generation via toll-like receptor 4 and NADPH oxidase 2-dependent mechanisms and generating ROS [84] which may then act within the vasculature to limit the bioavailability of NO [85]. Another important oxidative pathway that has been implicated in vascular oxidative stress is the generation of oxidized low-density lipoproteins (oxLDL), which can directly stimulate and activate endothelial cells increasing atherosclerosis through macrophage lipid accumulation in the vessel wall [86, 87]. Increased concentrations of oxLDL are seen in ApoE^{-/-} mice exposed to vehicle exhaust [88], and *in vitro* studies have demonstrated upregulation of important genes involved in vascular inflammation and atherosclerosis in human microvascular endothelial cells [89], highlighting the likely importance of this pathway. Although the physicochemical properties that mediate these reactions are unresolved, emerging evidence indicates that adsorbed chemicals on the particle surface are responsible and not the carbon core itself [90, 91].

The clinical evidence for vascular oxidative stress is limited, largely because of difficulties in measuring oxidative stress *in vivo* because of the short lifespan of ROS, the numerous pathways involved and the limited availability of biological tissues. In a recent meta-analysis, studies addressing the issue of oxidative stress following exposure to particulate matter were reviewed, and the evidence from controlled exposures, panel studies and cross-sectional investigations were analysed [92]. The authors concluded that there is a consistent and reliable relationship between exposure to combustion-derived particulate matter and oxidative DNA adducts and lipid peroxidation markers in urine, blood and exhaled breath condensate. Although further studies are required to determine a causal relationship, this analysis clearly demonstrates the importance of oxidative stress as a central mediator of the adverse systemic effects of inhaled particulate matter.

Thrombosis and endogenous fibrinolysis

Exposure to air pollution is associated with an increase in admission to hospital because of venous thromboembolic disease [93, 94] as well as acute cardiovascular events, which are predominantly driven by arterial thrombosis [95] complicating atheromatous plaque rupture. Furthermore, some studies have demonstrated increases in plasma viscosity [96], plasma fibrinogen concentrations [97–99] and a shortening in prothrombin time, consistent with an increased thrombotic tendency [100].

For ethical and practical reasons, experimental *in vivo* studies of thrombosis are difficult to conduct in man, and therefore, much evidence is derived from animal models. Nemmar and colleagues found in a hamster model that thrombus formation in response to a photochemical injury to the vascular endothelium was enhanced in a dose-dependent manner following the intratracheal instillation of diesel exhaust particles [101]. They demonstrated that the increase in thrombus formation was associated with an increase in platelet activation, without any increase in total platelet concentration.

Studies of the effects on systemic thrombotic tendency of inhalation of dilute diesel exhaust have been inconclusive. Carlsten *et al.* [102] found no effect on C-reactive protein, von Willebrand factor, plasminogen activator inhibitor type 1 or platelets in healthy subjects at 3, 6 or 22 h after exposure, whereas Salvi *et al.* [103] reported small but significant

increases in platelet concentration in peripheral blood 6 h after exposure to dilute diesel exhaust in healthy volunteers.

The Badimon chamber can be used to assess the thrombotic potential of native whole blood *ex vivo* in physiologically relevant conditions and in a reproducible manner [104]. Using this method, we reported increased thrombus formation in healthy volunteers 2 and 6 h after exposure to dilute diesel exhaust, compared to air exposure as a control [105]. An increase in thrombus formation was seen both in low- and high-shear conditions representing patent and mildly stenosed coronary vessels, respectively. Increases were also seen in levels of soluble P-selectin and soluble CD40L as well as platelet-monocyte aggregates, suggesting that platelet activation as a likely mechanism underlying the increased thrombotic tendency.

Although the formation of a clot within the arterial system following endothelial injury or plaque rupture is clearly important, thrombus formation is a highly dynamic process; formation is counterbalanced by turnover and breakdown. This process is controlled by the vascular endothelium by the release of the endogenous fibrinolytic enzyme tissue-plasminogen activator (t-PA). Indeed, t-PA is used clinically to lyse a thrombus in the context of acute myocardial infarction or pulmonary embolism. The ability of the endothelium to release t-PA can be measured during venous occlusion plethysmography by the infusion of bradykinin or substance P [106]. Using this approach, we have demonstrated that inhalation of dilute diesel exhaust reduces t-PA release in healthy volunteers and men with stable coronary artery disease 6-h postexposure to diesel exhaust inhalation [40, 67]. However, no difference in t-PA release was found in the healthy volunteers when assessed 2- or 24-h postexposure, suggesting a maximal effect a few hours after exposure [68].

Late cardiovascular effects

Atherosclerosis

Much of the evidence linking the development of atheroma to ambient air pollution is necessarily derived from controlled exposure studies in animal models and epidemiological data. Sun *et al.* [107] exposed ApoE^{-/-} mice fed on high-fat chow to concentrated ambient particles or filtered air for 6 h per day, 5 days per week for 6 months. At the end of the exposure period, the animals were killed, and atheroma burden was measured in the aortic arch. Animals exposed to

the concentrated ambient particles had a 1.5-fold increase in aortic atheroma measured using oil red-O staining and an increase in abdominal aorta atheroma measured using magnetic resonance imaging. Suwa *et al.* [108] conducted an experiment in Ottawa using another animal model of atherosclerosis, the Watanabe heritable hyperlipidaemic rabbit. The animals were exposed to urban particulate matter or saline by intratracheal instillation twice a week for 4 weeks; at the end of the exposure period, animals were killed, and coronary atherosclerotic lesions were measured histologically. There was a 14% increase in atheroma volume in the animals exposed to particulate matter, compared to the control animals. Furthermore, the lesions in the animals exposed to the particulate matter appeared to be more advanced with an increase in cellularity and lipid content, as seen in vulnerable plaques. High-fat chow-fed ApoE^{-/-} mice exposed to dilute diesel exhaust for 6 h per day, 5 days per week for 7 weeks did not have an increased plaque volume compared to control mice, although plaque cellularity was increased and lipid content increased 8-fold, with a concomitant increase in markers of oxidative stress, which is again consistent with more advanced and vulnerable plaques [109].

Künzli *et al.* examined data from two randomized, double-blind, placebo-controlled clinical trials conducted at the University of Southern California, Los Angeles, USA, in which carotid artery intima-media thickness (CIMT) was assessed. CIMT measured using high-resolution B-mode ultrasonography [110] is a surrogate of carotid atheroma burden, and changes in CIMT were found to be strongly correlated with progression of coronary atheroma measured using conventional coronary angiography [111]. Furthermore, measurement of CIMT is robustly associated with cardiovascular risk and the occurrence of cardiovascular events and, as such, is a valid surrogate end-point for cardiovascular events in clinical trials [112]. Künzli *et al.* [113] calculated background exposure to particulate air pollution using a geostatistical model based on subjects' home addresses. After correction for conventional cardiac risk factors, they demonstrated a 4% increase in CIMT with each increase of 10 $\mu\text{g m}^{-3}$ in background air pollution exposure. Similarly, in the Multi-Ethnic Study of Atherosclerosis, CIMT was found to be weakly associated with the 20-year estimated particulate air pollution exposure amongst 5172 US subjects with no history of cardiovascular disease [114], although there was no similar association with coronary artery calcification. Amongst 4494 subjects enrolled in the German

Table 2 Air pollution exposure and atherogenesis. A summary of the published human clinical studies and animal model data

Study	Model	Design	Country	Participants	Pollution measure	Primary outcome	Effect
Clinical studies							
Lambrechtsen <i>et al.</i> , 2012 [116]	Human	Cohort study	Denmark	1225 adults	Urban versus rural residence	Coronary artery calcification by CT	Increased CAC score in urban versus rural dwellers: OR 1.8 (95% CI 1.3 to 2.4)
Hoffman <i>et al.</i> , 2007 [115]	Human	Cohort study (Heinz Nixdorf Recall)	Germany	4494 adults	Residential proximity to major highway		Strong association between distance of residence from road and CAC – 50% reduction in distance to road increased CAC by 7% (95% CI 0.1 to 14.4%)
Allen <i>et al.</i> , 2009 [131]	Human	Cohort study (MESA)	USA	1147 adults	Background PM _{2.5} exposure	Abdominal aortic calcification by CT	6% (95% CI –4 to 16%) increased risk of abdominal aortic calcification per 10 µg m ⁻³ increase in PM _{2.5} exposure
Bauer <i>et al.</i> , 2010 [132]	Human	Cohort study	Germany (Heiz-Nixdorf Recall)	3380 adults	Background PM _{2.5} exposure	CIMT by B-mode ultrasonography	4.3% (95% CI 1.9 to 6.7%) increased CIMT per 10 µg m ⁻³ increase in PM _{2.5} exposure
Künzli <i>et al.</i> , 2010 [117]	Human	Cohort study	USA	1483 adults	Residential proximity to major highway		Accelerated progression of CIMT: 5.5 µm per year (95% CI 0.13 to 10.79)
Künzli <i>et al.</i> , 2005 [113]	Human	Cohort study	USA	798 adults	Background PM _{2.5} exposure		5.9% (95% CI 1 to 11%) increased CIMT per 10 µg m ⁻³ increase in PM _{2.5} exposure

Table 2 (Continued)

Study	Model	Design	Country	Particles	Primary outcome	Effects in exposed animals
Animal models						
Tranfield <i>et al.</i> , 2010 [133]	Watanabe Rabbits	Instillation study	Canada	Urban particles (Ottawa)	Histological changes in atherosclerotic plaque	Increased macrophage-derived foam cells, reduced extracellular matrix, type IV collagen. Increased plaque vulnerability
Suwa <i>et al.</i> , 2002 [108]	Watanabe Rabbits	Instillation study	Canada	Urban particles (Ottawa)	Plaque volume, plaque turnover and systemic inflammation	Approximately 50% increased plaque volume, increased lipid accumulation in plaque and increased cell turnover. Increased neutrophils in circulation
Bai <i>et al.</i> , 2011 [109]	ApoE-/- mice	Inhalation study	Canada	Inhaled diesel exhaust	Plaque volume, cellularity, lipid content and systemic oxidative stress	No change in plaque volume, but large increase in cellularity, foam cell content and lipid accumulation in plaque and increased markers of oxidative stress
Campen <i>et al.</i> , 2010 [134]	ApoE-/- mice	Inhalation study	USA	Inhaled diesel exhaust	Plaque volume, cellularity, matrix metalloproteinase expression and oxidative stress	No change in plaque volume, but increased macrophage infiltration and collagen staining. Increased expression of MMP-9 and reduction in MMP-13 and induction of oxidative stress
Floyd <i>et al.</i> , 2009 [135]	ApoE-/- mice	Inhalation study	USA	Inhaled concentrated ambient particles	Gene expression in plaque by mRNA microarray	Alterations in genes linked to inflammation, cell proliferation, cell cycle and haematological and cardiovascular pathways
Araujo <i>et al.</i> , 2008 [136]	ApoE-/- mice	Inhalation study	USA	Inhaled concentrated ambient particles	Plaque volume, cellularity and lipid content. Systemic oxidative stress.	Approximately 50% increase in plaque volume with increased macrophage infiltration and lipid accumulation. Increased systemic lipid peroxidation and expression of hepatic malonaldehyde, consistent with increased oxidative stress

Table 2 (Continued)

Study	Model	Design	Country	Particles	Primary outcome	Effects in exposed animals
Sun <i>et al.</i> , 2005 [107]	ApoE ^{-/-} mice	Inhalation study	USA	Inhaled concentrated ambient particles	Plaque volume by MRI and composition by histology and immunohistochemistry	Approximately 50% increase in plaque burden, with upregulation of iNOS, nitrotyrosine and macrophage CD68 in plaque
Soares <i>et al.</i> , 2009 [137]	LDLR ^{-/-} mice	Inhalation study	Brazil	Inhalation of ambient air compared with filtered air	Plaque volume and cellularity. Lipid peroxidation	Increased plaque volume, but no increase in lipid content. Increased systemic lipid peroxidation

CT, computed tomography; CAC, coronary artery calcium; CIMT, carotid intima medial thickness; MMP, matrix metalloproteinase; MRI, magnetic resonance imaging; iNOS, inducible nitric oxide synthase; LDLR, low-density lipoprotein receptor.

Heinz Nixdorf Recall Study, coronary artery calcium scores (recognized as a surrogate marker for coronary atherosclerosis) were increased in subjects living close to a major road, compared to those living further away [115]. Similarly, amongst 1225 subjects recruited in Denmark, coronary artery calcium scores were significantly higher in those living in a city centre environment (odds ratio 1.8, 95% CI 1.3–4) compared to those living outside the city (estimated residential PM₁₀ – particulate matter with a mean aerodynamic diameter of <10 µm – exposure approximately 30–40% lower), after correction for conventional risk factors and demographics [116]. These findings suggest that long-term residential exposure to traffic-derived air pollution is a risk factor for developing coronary atherosclerosis as well as increased carotid atheroma.

Further to these cross-sectional studies, Künzli and colleagues assessed the progression of atheroma by measuring annual change in CIMT and linked this both to the estimated background exposure to particulate matter using their geostatistical model and to the proximity of a major highway as a surrogate for exposure to traffic-derived air pollution. Consistent with the cross-sectional data, CIMT progression was accelerated in those living in more highly polluted areas and those living close (within 100 m) to major highways [117]. The clinical and preclinical evidence for increased atherosclerotic plaque burden following exposure to air pollution is summarized in Table 2.

Systemic inflammation

It has been proposed that many of the systemic effects of exposure to particulate air pollution may be mediated by local and systemic inflammatory responses, in turn driven by oxidative stress. Indeed, following controlled exposures to concentrated ambient particulate matter [97] and dilute diesel exhaust [118], local inflammation within the lungs has been demonstrated along with changes in the local antioxidant response [81]. These exposures are associated with increases in the cytokines interleukin (IL)-1β, IL-6, granulocyte-macrophage colony-stimulating factor [83] and tumour necrosis factor-α [68]. Recent studies of controlled exposure to concentrated ambient particulate matter have demonstrated increases in total white blood cell and neutrophil counts immediately following a 2-h exposure [31], whilst panel studies have shown associations between particulate air pollution exposure and the acute phase response, as evidenced by increases in C-reactive protein [119], fibrinogen [99], plasma

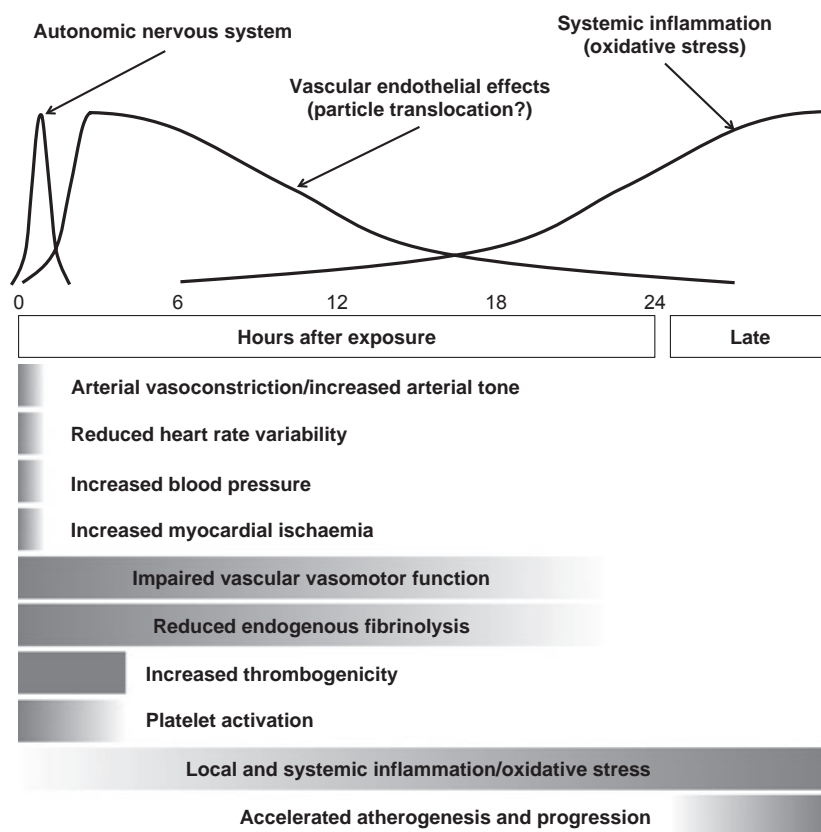


Fig. 2 Acute vascular, thrombotic and inflammatory effects of exposure to particulate air pollution and proposed underlying mechanisms.

viscosity [96] and altered leucocyte expression of adhesion molecules [120].

Summary

Air pollution is a complex heterogeneous mixture of particulate, volatile and gaseous components, and as such is difficult to study and define. It is now well established that exposure to ambient air pollution causes an increase in cardiovascular events, and these events are most closely linked to the fine and ultrafine particulate matter in the air pollution mixture, especially that associated with the combustion of fossil fuels.

In epidemiological, panel and controlled exposure studies, exposure to air pollution has a variety of important and adverse effects on the cardiovascular system that, when combined, may help to explain the observed increase in cardiovascular events. These adverse effects appear to change over time and sug-

gest that at least three main underlying mechanisms may be involved (Fig. 2).

Systemic inflammation and oxidative stress are key steps in early atherogenesis and atheroma progression [121], which appear to promote the development and accelerate the progression of atheroma in both animals and humans chronically exposed to increased levels of particulate air pollution. Short-term exposure to particulate air pollution can increase blood pressure and cause arterial vasoconstriction and changes in vascular tone which may in turn result in plaque rupture [95]. These immediate effects are probably driven by the changes in activation of the autonomic nervous system, as indicated by the coincident changes in heart rate variability. At the same time, platelet activation is enhanced, and blood becomes more prothrombotic following exposure, which may accelerate the formation of a thrombus over the ruptured plaque. Because of impaired endothelial vasomotor responses, arteries cannot

dilate to compensate for the impending obstruction, and endogenous fibrinolytic systems – which normally limit clot progression – are also impaired so limiting the ability of the vascular system to fight this threat. The end result of this cascade of effects is occlusion of the coronary artery and acute myocardial infarction. Furthermore, because of proarrhythmogenic changes in the autonomic control of the heart, patients may become more prone to developing ventricular arrhythmias in conjunction with acute myocardial infarction.

It is difficult to attribute this vascular endothelial dysfunction either to activation of the autonomic nervous system, as these changes appear to be immediate and transient, or to systemic inflammation, as studies have failed to demonstrate any changes in the inflammatory cascade for at least 18 h following exposure to pollutants. This suggests that a third mechanism may be responsible for these important effects. It has been proposed that fine and ultrafine particles, which are of a similar physical size to LDL-cholesterol particles, are able to translocate from the lungs into the systemic circulation [122]. Although only a small fraction of the inhaled mass may cross into the circulation, this represents a huge number of particles that may have a direct impact on the vascular endothelium.

A better understanding of the mechanisms underlying the adverse effects of air pollution is key in helping to inform environmental health policy and also in providing advice for individuals at risk, which is an important recommendation of the recently updated American Heart Association scientific statement on particulate matter air pollution and cardiovascular disease [5]. This is especially important given that combustion-derived particulate air pollution is now recognized as the single most important trigger for acute myocardial infarction at a population level [19].

Acknowledgements

The authors would like to acknowledge financial support from the British Heart Foundation (RG/10/9/28286 and CH/09/002 held by DEN) and the Swedish Heart Lung Foundation (held by TS). NLM is supported by a British Heart Foundation Intermediate Clinical Research Fellowship (FS/10/024/28266).

Conflict of interest statement

None of the authors has any conflicts of interest to declare.

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3 Cancer Research UK

Submitted evidence:

- Epidemiological evidence
- Indoor air pollution and cancer

Epidemiological evidence

IARC's classification of air pollution as a Group I carcinogen in 2013 confirmed the strength of the evidence base which had been building for several years¹. There is now clear evidence that air pollution contributes to the UK's lung cancer mortality, as well as to cardiovascular and other respiratory diseases². Evidence from a range of long-term epidemiological studies now exists, showing the contribution air pollution is making to lung cancer mortality. Though the increase observed is often relatively modest, the lack of preventative action the public themselves can take as well as its ubiquitous presence makes air pollution a classic public health problem.

Air pollutants

The meta-analysis by Hamra et al consolidated 18 large, well-designed studies and concluded that there was evidence to support PM_{2.5} as a cause of lung cancer.³ Further European studies have also shown similar results, with increased measures of air pollution correlating with increased adverse health outcomes, including cases of lung cancer: including the ESCAPE meta-analysis, which found correlation between PM₁₀ and lung cancer incidence.⁴

It is important to keep in mind that there are several difficulties involved in measuring PM_{2.5} levels. In addition to this there are difficulties in measuring small changes in risk individually, and to meaningfully study it requires large cohorts.

Studies in the US have shown an association between PM_{2.5} and lung cancer mortality, and help contribute to the overall body of evidence.^{5,6} The low heterogeneity between US studies, where larger cohorts contribute to research, further strengthen the evidence between air pollution and lung cancer³. Agreement from IARC and others points to the convincing evidence that that PM_{2.5} is contributing to lung cancer incidence.¹

Though less consistent for NO₂ than for PM_{2.5}, there is gathering evidence to suggest NO₂ contributes to adverse health effects associated with air pollution. The Carey et al paper showed a significant association between NO₂ and lung cancer mortality⁷. These results have also been replicated more widely in other European studies.⁸

Public health actions

Government and local authorities should work together to develop a comprehensive strategy to reduce air pollution. A network of low emission zones and increased funding for active travel options such as cycling should be considered as part of a wider package of measures to cut air pollution.

Further research is needed to clarify which groups of people are most at risk, and how we can best mitigate adverse health outcomes. In addition clarity on potential confounders; socio-economic status, smoking etc is needed to fully understand the modulatory effect they may have on lung cancer risk from air pollution.

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Indoor air pollution and cancer: epidemiological evidence

There are several pollutants that contribute to indoor air pollution in the UK, which are distinct from those found in outdoor air pollution. Indoor pollutants have a negative impact on public health, with limited options for intervention– though more than is available to alleviate outdoor air pollution. The main sources of indoor air pollution in the UK are radon, environmental tobacco smoke, and potential indoor contamination with particulate matter and other outdoor pollutants – these are briefly summarised below.

Radon

Largely due to occupational studies, the evidence surrounding lung cancer and radon is longstanding, with IARC classifying it as a group one carcinogen in 1988¹. More recently, research looking at radon in residential settings has concluded that at concentrations found within homes in some parts of the UK radon can increase the risk of lung cancer²³. Although in absolute terms, radon-related risk of lung cancer in current and recent ex-smokers is substantially higher than for never smokers, this is due to the underlying cancer risk associated with smoking². Radon levels vary throughout the UK, but homes in high radon areas can be built or modified to minimise radon levels, information is available to the public through UKradon.

Environmental tobacco smoke

The long history of research into tobacco and cancer has given a wealth of high quality studies on the link between active smoking and lung cancer as well as environmental tobacco smoke (ETS), also known as passive or secondhand smoke, and lung cancer. Studies have measured the effects of ETS exposure in non-smoking spouses; a 2007 meta analysis of ETS showed their relative risk of lung cancer was 1.27⁴. Studies examining workplace exposure to ETS found that for the most highly exposed workers the risk was doubled⁵. Second hand smoke can have a large impact on the health of those exposed to it, significantly increasing the risk of lung cancer⁶⁷⁸. Children are particularly susceptible to ETS; 165,000 cases of disease in children each year are linked to ETS exposure⁹. Measures such as the 2007 UK ban on smoking in public places have gone a long way to tackling this problem.

Air flow: allowing 'outdoor' pollutants into buildings

Though very difficult to study, air flow between indoor and outdoor areas can distribute 'outdoor' air pollutants, such as particulate matter, indoors. Air flow into buildings and dwellings has not been well studied, though there is evidence that this occurs, the implications for public health are unclear¹⁰. For further information on the known health effects of outdoor air pollutants, see Cancer Research UK's first evidence submission.

Other potential sources

Evidence from developing countries whose use of solid-fuel cooking is high, such as China, shows the substantial contribution solid-fuel cooking makes to indoor air pollution¹¹. But less research has been done in developed countries, such as the UK. There is some, more limited, research on the use of solid fuels for heating; research in the US has found that approximately 2.5 million US households use solid fuel as their main heating source, despite the US being a developed country¹². Use of solid fuels as primary or secondary fuel sources in the home is a complex issue and may affect groups

disproportionately: for example lower socioeconomic groups potentially using solid fuels as a primary source, and higher socioeconomic groups supplementing other heating sources with solid fuels such as log fires. This potential source of indoor air pollution needs further research, but could give valuable insight into appropriate and targeted interventions.

Public health actions

Government and local authorities should work together to ensure children in particular are not exposed to cancer-causing second-hand smoke in any environment, particularly one in which they may be confined for long periods of time.

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4 Client Earth

Submitted evidence:

- Healthy Air Campaign – summary of health impacts on air pollution

The health impacts of air pollution

Clean air is considered to be a basic requirement of human health and well-being. However, air pollution continues to pose a significant threat to health worldwide¹ as one of the top ten risk factors for death and disability.²

Every year, it is estimated that 29,000 deaths are linked with poor air quality in the UK³ and 4,300 in London.⁴ This figure is based on particulate pollution, and is set to rise - the first studies of premature mortality related to nitrogen dioxide are due to be released in Dec 2014/2015.⁵

The UK Government estimates the cost of the health impacts of air pollution at £15 billion each year, within the range of £8-17 billion⁵. To put this in comparison the estimated costs of other public health issues are: smoking £3.3 billion, alcohol £3.3 billion, and obesity £5.1 billion.⁶

Air pollution is associated with a myriad of health problems including respiratory diseases such as emphysema, bronchitis and asthma, impaired lung development in children, premature births and low birth weight, lung cancer and heart disease. A pan-European study found that fine particulate air pollution was associated with natural-cause mortality, even within concentration ranges well below the present European annual mean limit value.⁷

While the evidence for the health effects of PM_{2.5} has been more firmly established, there is a growing body of evidence indicating independent, equally as bad health effects for NO₂ as for PM_{2.5}.³⁴

Cardiovascular disease

Air pollution is now strongly linked with heart (cardiovascular) disease and increases the risk of mortality.

Studies indicate that particulate matter can make existing heart conditions worse and can cause cardiovascular events, including heart attacks and strokes, among vulnerable people.^{7,8,9,10} The association with these incidences persists at levels of exposure below the current legal limits.⁷

- Air pollution is strongly linked to Coronary Heart Disease (CHD)/Ischaemic Heart Disease.^{10,11}
- Air pollution is linked to an increased risk of having a heart attack.¹²
- Air pollution has been linked to reduced survival rates following acute coronary syndrome (ACS/heart attack).¹³
- Air pollution has been linked to heart failure resulting in hospitalisation or death.¹⁴
- Exposure to air pollution increases the risk of nonfatal and fatal strokes.^{10,15,16}

Cancer

Air pollution is a leading environmental cause of cancer deaths.¹⁷ Outdoor air pollution,¹⁸ particulate matter,¹⁷ and diesel engine exhausts¹⁸ have been found to increase the risk of lung cancer and bladder cancer.^{17,18}

Respiratory disease

Air pollution is linked to a number of adverse respiratory effects overall.¹⁰

- Air pollution is associated with decreased lung function,¹⁹ increases the risk of childhood asthma,²⁰ triggers responses in children and adults with asthma²⁰ and increases the number of hospital admissions for asthma.¹⁹
- Exposure to air pollution increases the frequency of respiratory infections in children.¹⁰
- Air pollution is linked to development of chronic obstructive pulmonary disease (COPD), such as bronchitis and emphysema, the aggravation of symptoms^{20,21,22,23} and increase of mortality.²⁴
- The link between air pollution and the development of COPD has been observed, in particular, in people who have diabetes and asthma.²⁵ Air pollution has also been linked to bronchitis symptoms in children and chronic bronchitis in adults.¹⁰

Lung capacity

Air pollution has been reported to reduce lung development and function in children^{10,20,26,27} and adults.^{10,20,26}

Pregnancy and birth

Exposure to air pollution during pregnancy is linked to low birth weight,^{10,28} and premature births.^{10,29,30}

There is also a suggested link between air pollution and high blood glucose levels in pregnant women.³¹ Exposure to ozone in the first three months of pregnancy has been reported to increase the risk of pre-eclampsia.³²

Other negative health effects

Studies have been published that suggest links between air pollution and a number of other health effects such as:

- atherosclerosis¹⁰
- diabetes¹⁰
- impairment of cognitive functions in adults and children¹⁰
- neurological development in children,¹⁰ such as autism spectrum disorder (ASD)³³
- neurological disorders in adults.¹⁰

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5 Improvement Academy, Bradford

Submitted evidence:

- Air pollution survey monkey questions
- Air and health
- References

Air pollution survey monkey questions

Page 1

The following survey is aimed to help raise awareness of the health impact of air pollution, as well as determine how much of this knowledge is already out there.

I was appalled at my ignorance when learning about this subject. Ill health has a resultant burden on our society and our NHS. The magnitude of this is highlighted by an estimate that PM2.5 (a road pollutant) reduces average life expectancy in the UK by around six months, worth £16 billion a year.

Thank you for taking a couple of minutes to find out about this important issue and answer these questions.

Emma

Page 2

What is your age? (drop down list)

What is your gender?

Female

Male

What County do you live in? (drop down list)

Which of the following categories best fits your current or most recent occupation? (drop down list)

Page 3

If select Healthcare Practitioner or Technician get the following three questions:

What type of healthcare practitioner are you? (drop down list)

What level are you? (drop down list)

Which is your main specialty area? (drop down list)

Page 4

Did you know...

...currently London, Leeds and Birmingham will not meet the new lower EU air pollution targets until 2030?

...that 2/3 of asthma patients find that air pollution makes their asthma worse? Ref Asthma UK

...that if pollution levels are high asthma patients should avoid strenuous exercise outside?

...that air pollution is higher when it is sunny?

...that levels of air pollution are higher in the afternoon?

Reference Asthma UK <http://www.asthma.org.uk/knowledge-bank-pollutants> and <http://www.asthma.org.uk/News/surge-in-reported-asthma-attacks-as-pollution-levels-remain-high> last accessed 8/9/14

Page 5

Are you surprised that...

...during a spike in air pollution in April 2014 Asthma UK did a survey and found out that inhaler use was up by 86%?

...during that same period the London Ambulance Service reported a rise on one day in 999 calls related to breathing difficulties by 14%?

Did you know that particulate matter, ozone and nitrous oxide are the important particles in air related with adverse health outcomes?

Particulate matter 2.5 (PM2.5) are the deadliest form of air pollution due to their ability to penetrate deep into the lungs and blood streams unfiltered, causing permanent DNA mutations, heart attacks and premature death.

Page 6

Did you know that air pollution is known to be linked with the following conditions...

...ischaemic heart disease (angina and heart attacks)?

...stroke?

...lung cancer?

...bladder cancer?

...chronic obstructive pulmonary disease (COPD, bronchitis and emphysema)?

...acute lower respiratory tract infections (chest infections) in children?

...childhood asthma development and wheeze symptoms?

...low birth weight of babies born?

...deficits in neurobehavioral development in children (lower IQ)?

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The ESCAPE study (European Study of Cohorts for Air Pollution Effects) has shown that PM_{2.5} (particulate matter size 2.5micrometers or below) causes a 7% increase in natural cause mortality with each 5 µg/m³ increase in PM_{2.5} concentration (hazard ratio [HR] 1.07, 95% CI 1.02–1.13). This reveals an adverse health effect even at the EU target

concentration of 25 µg/m³. The study also reported an 18% increase in lung cancer incidence for each 5 µg/m³ increase in PM_{2.5} concentration in this cohort.

The percentage of low birth weight babies attributable to PM_{2.5} has been shown to be 22%, above the 15% attributable to smoking (Pederson, 2013) as many more women are exposed to particulate pollution than smoke.

Pedersen M, Giorgis-Allem L, Bernard C, et al. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). *Lancet Respir Med* 2013; 1(9): 695-704.

Page 7

Are you surprised that ...

... in 2012 the World Health Organisation reports 7 million people died from air pollution exposure?

...the burden due to fine particulate matter alone has been estimated to be 29,000 deaths per year in the UK? Ref COMEAP 2010

To put this in context, in 2012 in the UK there were estimated 100,000 deaths caused by smoking, 8,700 attributable to alcohol, 1,800 due to road fatalities, and 1,200 deaths related to psychoactive drug misuse in 2012.

The World Health Organization (WHO) estimates that "... fine particulate air pollution (PM_{2.5}), causes worldwide about 3% of mortality from cardiopulmonary disease, 5% of mortality from cancer of the trachea, bronchus, and lung and about 1% of mortality from acute respiratory infections in children under 5 yr."

Page 8

Measures that can be used to cut air pollution include:

- Avoid using cars for short journeys – combine trips or, alternatively, walk, cycle, or take a bus (in 2005 69% of all car journeys were under 5 miles)
- Share journeys
- Changing diesel cars to petrol/hybrid electric
- Turning off your engine while idling
- Putting catalytic converters on buses and HGVs
- Use of Low Emission Zones in cities
- Use of noise barriers on motorways Ref Dutch Air Quality Innovation Programme
- Cutting congestion and slow moving traffic
- Reducing use of woodburners/biomass boilers (further information http://uk-air.defra.gov.uk/assets/documents/reports/cat18/0806261519_methods.pdf last accessed 22/9/14)

For years drivers have been encouraged to buy diesels to help fight climate change with reduced carbon emissions without recognition of the resulting local air pollution and health impact. Diesels emit less CO₂ than petrol vehicles, but more local pollutants harmful to health. Today 10 million cars in Britain are powered by diesel engines - a third of the total.

The Highways agency schemes to cut air pollution along the M1 include the erection of high barriers along the relevant sections of the motorway to funnel fumes away from ground level. These have been found to cut pollution and noise in large-scale tests in Holland. Also the road-widening schemes aim to cut congestion by reducing queuing time.

Do you own a diesel car?

Has the information in this survey meant that in the future you are less likely to buy a diesel car? (rating scale)

Do you think health practitioners should receive more information about the health risks of air pollution? (rating scale)

Should responsible authorities (e.g. Government and local Councils) use policies to discourage diesel cars in the same way they discourage smoking? (rating scale)

Page 9

Thank you very much for taking your time to fill in this survey. If you feel that the Government should act to reduce the health impact of air pollution please consider signing this e-Petition <https://you.38degrees.org.uk/petitions/clean-our-air-it-s-killing-us-1>.

If you would be happy for us to contact you with further information in the future please leave your email address.

If you have any questions please email emma.ryland@nhs.net or leave comments below.

AIR & HEALTH

Around 90 % of Europeans living in cities are exposed to levels of air pollution deemed damaging for human health.

Although air pollution is rarely visible nowadays, Europe's air quality is still a huge problem. Air pollution is responsible for more than 400,000 early deaths in the EU each year [1]. Sensitive and vulnerable groups such as pregnant women, children, the elderly and those already suffering from respiratory and other serious illnesses or from low income groups are particularly affected [2].

The health effects of air pollution are well documented: not only is poor air quality a risk factor for heart and respiratory diseases such as asthma and chronic bronchitis, but it is also

increasingly linked with harm to children's nervous systems and brain development, and even with diabetes.

The World Health Organization's Cancer Agency (IARC) also confirmed that outdoor air pollution can cause lung cancer [3].

Clearly the quality of indoor and outdoor air plays a major role in many chronic diseases in Europe with high costs for the individuals affected, national health services and the economy at large.

FACTS AND FIGURES

1ST
2 3

Air pollution will become the top cause of environmental-related deaths worldwide by 2050 if no action is taken [5].



AIR POLLUTION KILLS

over 10 times more people than road traffic accidents in the EU [6].



9 OUT OF 10

European city dwellers still breathe air that the World Health Organisation (WHO) considers to be harmful to health [7].



HEALTH DAMAGE

In the year 2010 alone, the health damage from air pollution in the EU amounted to between €330 and €940 billion, that is 3-9% of the EU's GDP [4].



FINANCIAL BENEFIT

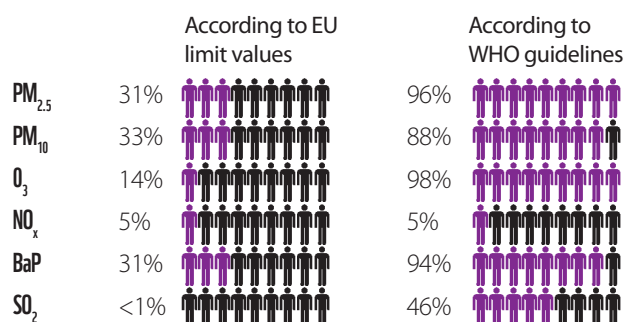
Reducing concentrations of fine particulate matter (PM_{2.5}) to WHO recommended levels in 25 European cities would add up to 22 months to the average life expectancy of their inhabitants, resulting in financial benefits of €31 billion per year [8].

ASSESSING THE HEALTH COSTS OF AIR POLLUTION

One method for putting a price tag on the health effects of air pollution has been developed under the Clean Air for Europe Programme [9]. First, emissions of air pollutants and concentrations are assessed, using modelled and monitored data. Second, people's exposure and the associated health impacts are quantified. Third, these impacts are valued using agreed amounts (see Air & the Economy factsheet).

Such assessments draw on hundreds of studies that are published on the health effects of air pollution. New evidence is now available from large population-based assessments, such as ESCAPE [10]. These epidemiological studies trace the effects of one or more pollutants in people over a certain time. Researchers make sure that health impacts are due to air pollution and not to other factors such as smoking or physical inactivity.

EU urban population exposed to harmful levels of air pollution

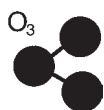
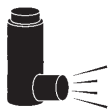


Source: EEA Report, 2013

HEALTH EFFECTS OF AIR POLLUTANTS



PARTICULATE MATTER (PM): short and long-term exposure to PM causes respiratory and cardiovascular disease, atherosclerosis (thickening of the arteries), adverse birth outcomes, impacts on children's development of the brain and nervous system, diabetes, and can result in death. PM is also linked to respiratory infections and asthma in young children. Depending on their size, PM are referred to as either PM₁₀, which are coarser particles, or PM_{2.5}, which are finer particles. The smaller the particles, the greater the harm to human health.



OZONE: short-term exposure can lead to more frequent hospital admissions and increases the risk of death from heart and respiratory disease. Ozone is also suspected to harm children's cognitive development and contribute to premature births.



NO₂: short and long-term exposure has impacts on mortality and morbidity (mainly through cardiovascular and respiratory disease). NO₂ also contributes to the formation of ozone and PM.



SO₂: impacts respiratory function and contributes to PM formation.



METHANE (CH₄): a powerful climate gas which also contributes to the formation of ozone which is harmful to health.



MERCURY: a highly toxic pollutant damaging the nervous system at even relatively low levels of exposure, and of particular concern for children.



BLACK CARBON (BC): a major component of PM_{2.5} and a short-lived climate pollutant. Has similar health effects to PM.

EU LEGISLATION

Current EU air quality standards to limit harmful air pollution were agreed in the late 1990s. However, in many places in Europe, especially in cities, people are exposed to concentrations that are above the legal limits. These EU limit values are 'informed' by World Health Organisation guidelines, but in some cases are much less stringent [11]. For example, allowing Member States to exceed the daily PM concentrations up to 35 times a year has no scientific basis at all. The WHO also recently announced that they will make their guidelines even stricter, following a comprehensive review of the scientific evidence. This assessment showed that serious health effects occur at levels lower than current guidelines and that the range of effects is broader than previously thought.

EU HEALTH STANDARDS LAGGING BEHIND

25µg/m³

EU PM_{2.5} ANNUAL LIMIT

15µg/m³

JAPAN PM_{2.5} ANNUAL LIMIT

12µg/m³

US PM_{2.5} ANNUAL LIMIT

10µg/m³

WHO PM_{2.5} RECOMMENDATION



RECOMMENDATIONS

- Adopt ambitious emission reduction commitments in the revised National Emissions Ceilings Directive. Emission reduction commitments must go beyond the Gothenburg Protocol and aim to achieve the health and environmental objectives of the EU's 6th and 7th Environment Action Programmes by 2030.
- Control emissions from medium combustion installations by setting limits in line with current best available techniques, ensure their rapid entry into force and an adequate permitting and monitoring regime.
- Adopt sector legislation to cut emissions from all major sources of air pollution. Surveillance of compliance is also critical, as shown with road vehicles.
- Enforce current EU ambient air quality limit values so they are met throughout the EU as soon as possible.
- Align EU ambient air quality limit values with the most recent WHO recommendations and health research by 2020.

More information

- World Health Organization Europe: <http://www.euro.who.int/en/health-topics/environment-and-health/air-quality>
- European Environment Agency: <http://www.eea.europa.eu/themes/air>
- APHEKOM project: www.aphekom.org
- Health and Environment Alliance (HEAL): <http://www.env-health.org/policies/air-quality/>

For footnotes, please refer to separate reference sheet and to the EEB website.

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6 Global Action Plan (GAP)

Submitted evidence:

- GAP evidence to RCP inquiry into air pollution



‘EVERY BREATH WE TAKE: THE LIFELONG EFFECTS OF AIR POLLUTION’

**EVIDENCE TO THE RCP WORKING
PARTY ON AIR POLLUTION**

INTRODUCTION

Air pollution has a significant impact on health and the environment, the Mayor of London recognises that it could contribute to 4,000 premature deaths in London each year.¹ Global Action Plan is working with Barts Health NHS Trust, the City of London and the London boroughs of Newham, Tower Hamlets and Waltham Forest to deliver the Barts Health Cleaner Air project.

The project is pioneering an approach to understand how the influence of clinicians delivering messages and advice to patients around air pollution can reduce emissions from NHS patients, visitors, staff and the wider community. The project also tests how these messages can protect the most vulnerable from the impacts of air pollution. Over three years the project will test a number of behaviour change interventions:

1. Warm and Well – community clinicians providing energy packs to patients in their homes to reduce boiler emissions
2. Protecting Patients – Pharmacists and specialist clinical staff providing advice to patients on how to reduce their exposure to air pollution to prevent exacerbation of respiratory and cardiovascular
3. Clean Air Zones – reducing emissions from and around hospital sites through anti-idling, building upon green spaces, and increasing car travel to hospital sites.
4. Trust Transport – Working with hospital vehicles, suppliers and influencing local fleets to adopt cleaner driving behaviours through a NHS recognition programme or ‘Healthy Vehicle award’.
5. Active Travel – reduce car travel to sites by working with staff to adopt active or ‘clean air travel behaviours’

The project is funded by the Mayor’s Air Quality Fund and Defra and is a three year project. You can read more information on our website here <http://www.globalactionplan.org.uk/barts-health-cleaner-air-programme>

While it is early days yet for results, over 1,000 patients have so far been engaged and provided with a Breathe Better Plan (by completing the [Cleaner Air for London survey](#)) through Barts Health Cleaner Air Week. Given the number of excess deaths as a result of poor air quality, we believe that alongside emissions reduction programmes focused on hospital fleets and vehicles at NHS sites, that using clinicians to engage vulnerable patients in particular may offer a route to improved public health protection from poor air quality.

¹ <http://www.london.gov.uk/sites/default/files/MAQS%20Executive%20Summary%20FINAL.pdf>

In addition to the Barts Health Cleaner Air Project, Global Action Plan is working with City of London to trial Air Quality Action Days to engage local drivers with anti-idling messages.

We are keen to keep you updated on the results and findings of our Cleaner Air projects. For further information please contact:

Caroline Watson
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caroline.watson@globalactionplan.org.uk
0207 420 4435

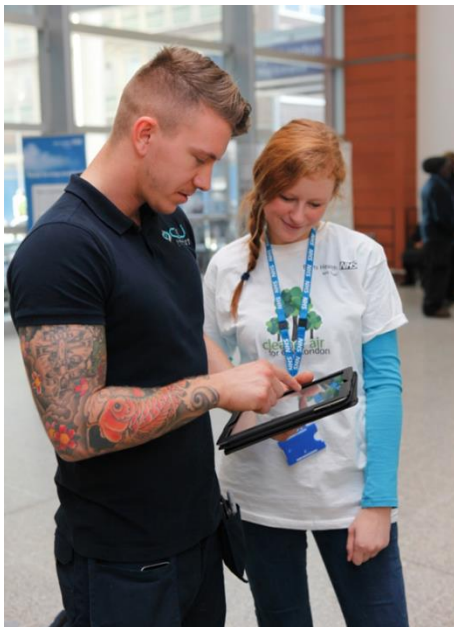


Photo: Global Action Plan team member engaging a visitor with the Cleaner Air for London survey at Royal London Hospital, during Barts Health Cleaner Air Week in February 2014. Over 1000 people completed the survey and received a Breathe Better Plan with advice on how to reduce their exposure and their own impact on air pollution.

DELIVERING AND TESTING BEHAVIOUR CHANGE INTERVENTIONS:

WARM AND WELL: REDUCING DOMESTIC BOILER EMISSIONS THROUGH CLINICAL ADVICE TO PATIENTS

As part of the Barts Health NHS Trust Cleaner Air Project we are working in the London Borough of Tower Hamlets to trial an approach for community nurses to reach patients in their homes with messages and tools to stay warm and well. This winter community clinicians are giving 1,000 energy packs to patients to reduce their energy bills, increase comfort in their homes and cut boiler emissions that contribute to air pollution in London. Domestic gas boilers account for 7% of NO₂ in London, a main cause of air pollution. We are testing the effectiveness of

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community clinicians as a trusted messenger to change behaviour of patients to reduce domestic gas emissions. Results from the project should be available in early summer 2015.

PROTECTING PATIENTS: ENABLING THE MOST VULNERABLE TO REDUCE THEIR EXPOSURE TO AIR POLLUTION

Air pollution is the second biggest public health issue in the UK in terms of premature deaths. We are working with medical specialists to provide information to patients whose health is particularly vulnerable to the effects of air pollution, giving messages on key behaviours patients can take to reduce their exposure to air pollution.

This programme will help to raise the profile of this important issue and test a behaviour change approach to a patient information campaign on air pollution.

We will be testing the following assumptions:

- Patients and their families are likely to take seriously the advice and information provided to them by medical specialists.
- Patients who have a particular vulnerability to air pollution are more likely to be interested in how this issue affects their health and motivated to change their behaviour.
- Each clinical speciality has to demonstrate how it is working towards public health aims; this intervention will provide a simple and effective way for them to meet those goals.

We will work with one department at Barts Health to initially test this intervention with a single type of at risk patients. The ideal patient group would:

- Have a health condition that can be improved or managed through reduced exposure to air pollution
- Have several interactions with Barts Health to allow for ongoing support and follow-up

We are currently engaging with a range of cardiology and respiratory department leads to investigate the most suitable patient cohort for the pilot and designing relevant messages to give to patients. Part of this approach will be to include air pollution advice in patient asthma plans. Results from this intervention will be published in the autumn 2015.

Key messages we are testing:

- Avoid travelling in rush hour
- Avoid busy roads and take low pollution routes
- Stay informed of air pollution levels through [Air Text](#)

A second approach is to test the effectiveness of delivering air pollution exposure reduction messages through pharmacists to patients receiving prescriptions over the counter for their

respiratory problems. Results from this approach in the London Borough of Waltham Forest will be published in June.

CLEAN AIR ZONES

The project is aiming to reduce emissions from hospital sites by creating Clean Air Zones around hospitals to protect the most vulnerable and reduce emissions that impact the local community. We are trialling:

BREATHING SPACES

- We are building upon and improving existing green spaces at the five hospital sites within Barts Health NHS Trust, through planting air quality plants to create a “Breathing Space” area where staff, patients and visitors can enjoy the surroundings, breathe cleaner air and find out more about air quality issues and what they can do.
- We will be planting particular species of plants and trees (e.g. ivy, silver birch) that have been shown to have made significant improvements to local air quality.
- Adding signage to the Breathing Spaces on air quality and actions that can be taken providing an excellent engagement opportunity and building the profile of Cleaner Air messages.
- We will engage Barts Health volunteers to assist with planting days to help build the profile of the programme and gain buy in from volunteers.
- Improvement of green spaces provides additional social and environmental benefits e.g. carbon absorption, staff and visitor relaxation, patient rehabilitation, biodiversity etc.
- This intervention will provide an opportunity to feed into wider research on the benefits to ambient air quality that plants can contribute.

The Breathing Spaces intervention will take place in spring with results published in summer 2015.

TRUST TRANSPORT

- Transport, alongside domestic and commercial boilers, is the largest single source of air pollution in London.ⁱⁱ The Mayor of London has proposed an Ultra-Low Emission Zone to come into force in 2020 which is sending market signals for future vehicle purchasing decisions. However, there is much that can be achieved through behaviour led engagement well in advance of the 2020 date.

ⁱⁱ Mayor’s Air Quality Strategy, 2010 http://www.london.gov.uk/sites/default/files/Air_Quality_Strategy_v3.pdf

- The Barts Health Cleaner Air project is working with the Trust’s own fleet to reduce emissions through efficient driving behaviours, introducing no-idling zones around hospital grounds, and developing a Cleaner Vehicle recognition scheme which aims to reduce emissions from Trust suppliers and fleets in the local community.
- This intervention is a great opportunity to reduce the emissions Barts Health contributes and to influence other sector vehicles to reduce their emissions through a Barts-branded “health” message. This is currently in the development phase with results over the next year.
- Passing traffic significantly contributes to air pollution at the hospital sites, especially at inner London sites. Therefore influencing other sector vehicles as well as Trust vehicles will increase the programme impact.

The Trust Transport interventions will take place throughout 2015 with results published in spring 2016.

ACTIVE TRAVEL

To reduce emissions from vehicles travelling to and from outer London hospital sites we will be delivering an Active Travel programme with Barts Health staff at Whipps Cross and Newham hospitals. Following an initial pilot month-long Challenge, we will work with the Barts Health public health team to embed the ongoing activities e.g. an annual Challenge event.



- Active travel is a topic that clearly links environmental improvements (reducing emissions through modal shift) to health benefits (through physical exercise)
- Potential reach of the programme is large; even if only offered to staff, Barts Health NHS Trust directly employs 15,000 people
- The Barts Health Public Health Team have ambitions to get more staff travelling actively, increasing the likelihood for the programme to be successfully embedded internally following the end of the two years’ support.
- There is the potential to add on additional air quality messages around using cleaner, safer routes when cycling or walking. This element is important not only to ensure that participants’ exposure is not increased by travelling actively, but also provides an innovative messaging approach to trial.

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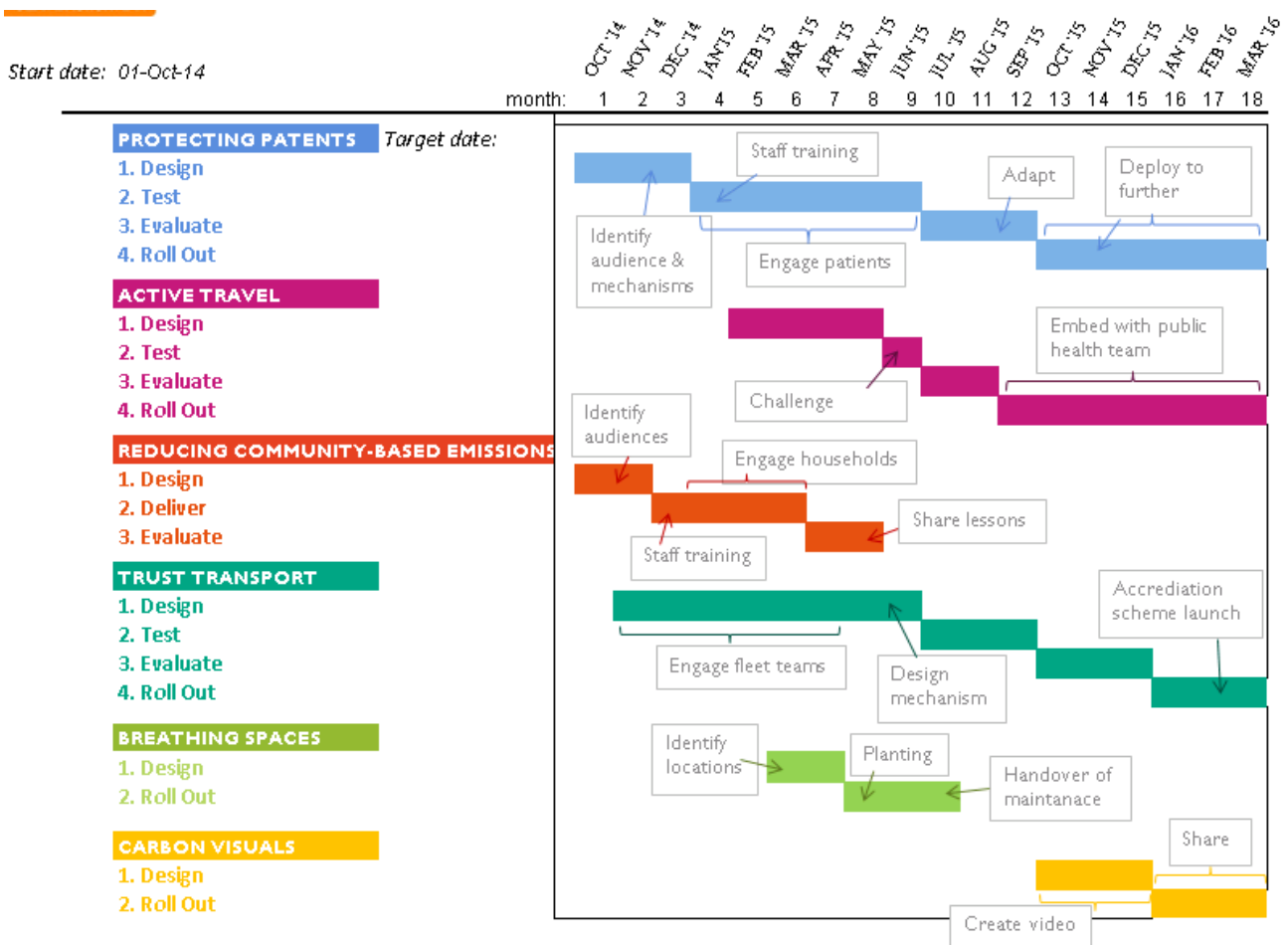
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We aim to:

- Deliver a replicable engagement process to motivate staff to switch to active travel and away from driving where possible.
- Increase numbers of staff travelling actively and as a result having improved health and wellbeing
- Cut individual vehicles travelling to the outer London sites by up to 4-8%
- Integration of the staff active travel programme into the wider Public Health work of the Trust e.g. embedding the programme support internally, integrating with patient active lifestyle campaigns

The month long Active Travel campaign will take place in summer 2015 with results available autumn/winter 2015.

TIMELINE FOR THE BARTS HEALTH CLEANER AIR PROJECT



CITY OF LONDON AIR QUALITY ACTION DAYS

We are working with the City of London Corporation to deliver two Air Quality Action Days to engage drivers around the benefits of turning their engine off when stationary to reduce air pollutants.

The first Air Quality Action Day was held on 17th March, with the second day planned for 31st March. The campaign aims to show drivers that it is better for health, better for wallets and better for vehicle engines to turn off, and not idle, if stopping for more than 60 seconds.

Key messages we are testing on the days are:

- **OTHER DRIVERS ARE SWITCHING OFF:** “Businesses in the City of London are asking drivers to switch their engines off while parked today. Will you join them?”
- **BETTER FOR YOUR HEALTH:** “London’s air pollution contributes to thousands of premature deaths every year. Stopping unnecessary idling is an easy way to help improve air quality and improve the respiratory and cardiovascular health of everyone (including your own)”
- **BETTER FOR YOUR WALLET:** “Excessive idling is a waste of fuel and money”
- **BETTER FOR YOUR CAR:** “An idling engine will leave fuel residues that can cause oil contamination and damage engine components. Idling also causes spark plugs to become dirtier more quickly, leading to an increase in fuel consumption. Idling also lets water condense in the vehicles exhaust system, which can lead to corrosion.
- **IMPACT OPPORTUNITY:** “If all drivers in central London switched off engines instead of idling unnecessarily, for one minute each day, this would reduce ‘particulate matter’ emissions by 90kg a year.”

Our Air Quality Champions engaged approximately 170 drivers face to face on the day with anti-idling messages. Over 30 local businesses pledged their support to the Air Quality Action Day, and engaged their own drivers with anti-idling messages and their wider staff and customers through flyers and posters. We are currently compiling results from the companies involved in the first Action Day, the first two companies to share results with us engaged between 22 and 64 drivers each on the day. So we estimate local businesses will have engaged about 1200 drivers. We aim for the second Air Quality Action Day next week to have a larger impact and gain some further press coverage to raise the issue of air quality and empower drivers to take action to reduce their own impacts on local air pollution.

7 Greater London Authority

Submitted evidence:

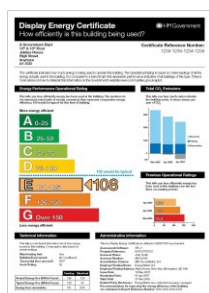
- All clean air zones – the indoor environment
- All clean air zones – the outdoor environment
- All clean air zones – the learning environment

CLEAN AIR ZONES PILOT - THE INDOOR ENVIRONMENT

In order to improve energy efficiency and lower the emission of air pollutants locally and on a wider scale, measures to reduce building emissions from the schools were considered. An energy audit was undertaken or used at each school to assess what measures could be implemented.

WHAT COULD BE DONE?

Possible ways of reducing building emissions include:



- ❖ Replacing old boilers with newer more efficient ultra low NO_x boilers - this has the added benefit of contributing to the improvement of air quality in the immediate area
- ❖ Thermostatic radiator control valves to control the temperature of the radiators, thus reducing boiler use and emissions
- ❖ Draught proofing/excluders around windows and doors (chimney's, floors and skirting boards in older schools)
- ❖ Energy saving light bulbs, power down switches and timer switches to reduce energy use e.g. classroom lighting and computers
- ❖ Solar (heat rejection) film/solar shading for windows to cut down on over-heating from solar heat gain and the need to use a cooling system
- ❖ Radiator reflector panels behind radiators to reduce heat loss
- ❖ Improved classroom ventilation practices to encourage openable windows above radiators to remain closed to reduce heat loss and alternative classroom windows or ventilation extracts to be used instead



CASE STUDIES

BOTWELL HOUSE RC PRIMARY SCHOOL, HAYES

- ☞ **Power down timer switches** - for the computer room - this was particularly effective at this school as they also had a server cabinet serving a number of schools which had to be maintained at the right temperature. Turning off computers promptly would also reduce the heat from these sources which also meant the air conditioning did not have to work as hard to keep the room cool when the computers were not in use
- ☞ **Solar (heat rejection) film** - there were a few classrooms in the new school building that were too hot due to solar heat gain. The solar film applied to the affected windows reduced the heat gain, and reduced the need to use energy to cool the classrooms

WHAT WAS THE OUTCOME: A more comfortable classroom environment was created whilst also saving energy and cutting down on pollutant emissions (NO_x as well as CO₂). The school's energy efficient operational rating was 101 in band E. Department of Energy & Climate Change (DECC) indicate 100 would be typical for a building. Just these simple measures have reduced the school's operational rating to 83 in band D.

SIR JOHN CASS'S FOUNDATION PRIMARY SCHOOL, CITY OF LONDON

- ☞ **Lighting management system** – Lights remained permanently on in various areas of the school and there was no way of isolating lighting systems when parts of the school were not in use. The schools lighting control system was repaired and upgraded to ensure better control and efficiency.

☞ **LED Lights** – Within the gymnasium area, new, robust LED lights were installed to save energy and create an additional indoor play area which could be fully utilised by children during wet play and pollution episodes.

WHAT WAS THE OUTCOME: A lighting audit identified the scope for improvement. The repaired lighting control system means that any member of staff closing the school is able to shut down the entire lighting system and lights no longer remain on overnight. The gymnasium had been out of action for ball games due to the outdated lighting system which could be damaged. The replacement system will improve energy efficiency and provides a fully versatile indoor play area.

OXFORD GARDENS SCHOOL AND ST CUTHBERT WITH ST MATTHIAS, KENSINGTON AND CHELSEA

☞ **Reflective panels** – The addition of reflective panels behind radiators were encouraged.

☞ **Openable windows** – Openable windows above radiators and adjacent to roadside emissions were encouraged to remain closed and alternative ventilation methods used instead.

☞ **Radiator valves** – Broken thermostatic temperature valves were replaced.

WHAT WAS THE OUTCOME: In both schools there were limited opportunities to make changes to the indoor environment. Alternative ventilation advice was welcomed particularly in the schools adjacent to busy and very noisy roads. This also benefitted by reducing the roadside emissions entering the classrooms from adjacent roads. Energy loss from radiators under windows was reduced whilst reflective radiator panels ensured efficient retention of heat within the classrooms.

<i>Do's</i>	&	<i>Don'ts</i>
<ul style="list-style-type: none"> ☑ undertake a detailed audit if needed ☑ ensure any measures implemented have maximum/long term benefits ☑ form a good relationship with school's maintenance team ☑ gain approval and agree on scheduling of works with school maintenance team and head teacher e.g. during holidays ☑ establish if future changes to the premises are planned and how energy efficiency measures can be introduced ☑ discuss changes to be made with school representatives to determine benefits and establish permissions for changes e.g. listed building / planning issues ☑ ensure the school is kept updated ☑ inform all staff of energy efficiency measures undertaken and the reasons why changes have been made ☑ ensure adequate training and maintenance of any new installations ☑ use assemblies and newsletters to inform children and parents of changes 		<ul style="list-style-type: none"> ☒ don't forget to check the building energy certificate to identify if improvement is actually needed ☒ don't forget low cost options such as staff training and awareness ☒ don't proceed without consulting with the school to identify areas where they feel emission reduction / energy savings can be made, for example, they know if classrooms are too hot or draughty ☒ don't forget to identify problem areas with school buildings, for example, areas to avoid due to structural issues ☒ don't introduce measures that the school consider unachievable or are unwanted , for example, lights which automatically shut down if there is no movement can be scary for children if introduced in areas which would become totally dark ☒ don't forget to provide updates of when energy efficiency measures will be installed/made

CLEAN AIR ZONES PILOT – THE OUTDOOR ENVIRONMENT

As well as increasing biodiversity and absorbing nitrogen, plants can play a role in trapping fine particulate matter (PM₁₀ and PM_{2.5}) found in the air we breathe. Research by Imperial College London indicates that plants with small leaves (which disrupt the flow of air) and fine hairs on their surface work best; however, leaves which cover a large surface or are grooved also provide surfaces upon which particles can be trapped. It is therefore thought that to help improve air quality, trees and plants which have these characteristics can be planted.

WHAT COULD BE DONE?

- ❖ Installation of green screens (pre-grown hedges/screens or plants trained to climb fences) and plants around the school to create 'air quality gardens' which can trap PM₁₀ and NO₂
- ❖ Air quality monitoring before and after the installation to see the effect of planting and for the monitoring results to be used as a pupil engagement tool
- ❖ Outdoor air quality engagement projects such as monitoring, planting and designing signs to raise awareness regarding air quality matters (see The Learning Environment)

CASE STUDIES

BOTWELL HOUSE RC PRIMARY SCHOOL, HAYES

- ☞ **NO₂ Monitoring** - Air quality modelling data from CERC indicated nitrogen dioxide (NO₂) levels at the school are over the EU limit value. NO₂ tubes were used to monitor the air quality on Botwell Lane and at the boundary of the infants' playground; this monitoring is ongoing



- ☞ **Green screen** - a mature hedge was planted at the front of the school along the stretch of the infants' playground, adjacent to a busy main road and near a junction. Available monitoring data indicates green screens reduce PM₁₀ levels compared to roadside levels and whilst Hillingdon does not have PM₁₀ levels above the EU limit value, no level of PM is considered *safe*.

☞ **Green screen and planters** - A planted 'quiet area' was created in the rear playground, to replace the previous one that would be lost as part of the school redevelopment. Climbing plants, including *ivy* and *Virginia creeper*, were planted in the quiet area along the fence line adjacent to residential garages creating an attractive green screen. Lost seating was replaced, the greening included raised planters with 'air quality' plants such as *lamb's ear* and *wild geranium*.



WHAT WAS THE OUTCOME: Monitoring data collected indicates the NO₂ annual mean may just exceed at the roadside, although it is likely to drop a little under the limit value by the boundary to the infants' playground. The EU limit value (NO₂ annual mean) is set for the facade of buildings with a sensitive use and the results indicate it is unlikely the EU limit value will be exceeded at the school building. It is hoped the hedge adjacent to the main road and the green screen in the rear playground will be effective in reducing the PM reaching the playground once they have fully matured. Once it is fully grown, the hedge will have the additional benefit of providing some visual screening to the infants'

playground. The 'quiet area' provides much needed greening for the school and an attractive environment for the children to learn about air quality and enjoy.

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☞ **Monitoring and Alerting** - The school already had a continuous air quality monitoring system, but the Clean Air Zones project allowed a diffusion tube monitoring network to be set up in the school. The pupils are also able to use the results to look at how levels vary in and around the school. Additional particulate monitoring equipment was also installed in the front playground to look at the effects of changes to the road system outside the school. An air quality reporting and alerting system was established and using the Defra Daily Air Quality Index, the school are notified when pollution is predicted to be moderate or above.

☞ **Planting:** 45m² of pre-grown green ivy screens were installed in the rear playground and roof garden. Pupils also planted 170 'air quality' plants with the help of a local community group. Six mobile green ivy screens with chalkboards were made to create unique play areas within the playground. In addition, the shed roofs in the front and rear playground had sedum roofs containing *succulents* installed.



WHAT WAS THE OUTCOME: The screening in the back playground has turned a concrete, unwelcoming area into a green vibrant space which is engaging for the children. The mobile screens are used in the front playground to create a unique sheltered space for the children to play and plant vegetables. Monitoring as part of the wider project indicates that greening improves air quality and with monitoring at the school demonstrating that the NO₂ annual mean EU limit value is exceeded, it is hoped that simple greening measures will help with improvements and raise awareness. Monitoring will continue, providing data for the alerting system, for the children to use and for the effectiveness of the planting and road changes outside the school to be monitored.



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☞ **Green Screen Installation** - *Oxford Gardens School:* An elevated series of pre-grown green screens were installed to a wall in the rear playground, adjacent to the Westway dual carriageway (A40), an area where NO₂ is shown to exceed the EU limit values. PM₁₀ is also in high concentrations around major road sources.



St Cuthbert with St Matthias: A 51 metre pre-grown green screen was installed to a wall in the front playground area adjacent to a busy road where NO₂ has been shown to exceed the EU limit values and roadside levels of PM₁₀ have been shown to be high. The green screens comprised of built-in benching and a drip feed irrigation system to ensure appropriate plant maintenance. Plant species within the green screen were selected for their air quality improvement properties.



A planter bed was also installed to the rear playground area to facilitate the teaching of planting and the benefits of certain plant species to the reduction of air pollutants.

☞ **Monitoring-** At *St Cuthbert with St Matthias* school a temporary (12 months) air quality monitoring station was installed into the school playground with continuous NO_x and PM₁₀ monitors positioned either side of a green screen located between the school playground and busy roadside location. Results from the monitoring station were used in teaching sessions to demonstrate how effective the green screens were at reducing NO₂ and PM levels in the school playground environment. At *Oxford gardens school*, NO₂ diffusion tubes were deployed by the children during a practical exercise followed by the collection of tubes and analysis of results. Sample location maps were created and graphs of results used to demonstrate changes in NO₂ in the local environment.

☞ **Surface wipe test** - A surface wipe test experiment was undertaken in a practical exercise to demonstrate PM₁₀ and PM_{2.5} air pollution. The exercise was used to demonstrate the difference between particulate pollution at roadside locations in comparison to locations away from roadside locations. A traffic count was undertaken to demonstrate the volume of traffic along the busy road outside the school and the different types of vehicles contributing the poor air quality.

☞ **Gardening Sessions** - To continue the legacy of air pollution teaching, existing gardening sessions run at St Cuthbert with St Matthias school will use the green screen installation and planter beds and plants with air pollutant trapping properties to explain what air pollution is and demonstrate how plants can be used to improve local air quality.

WHAT WAS THE OUTCOME: An aesthetically pleasing environment with the addition of plant species with NO₂ absorption and particle trapping and air quality improving properties was created. A bare stark tarmac and brick playground area was transformed into a green area with benching and planter bed

space to facilitate a continued legacy of air pollution engagement. The twelve month monitoring programme enabled the scientific assessment of the effectiveness of the green installation to reduce local air pollution in a school environment. Results were presented in a poster presentation at the 2014 Monitoring Ambient Air conference and a research paper produced to promote the benefits of greening to the wider scientific community. Articles

ACTION PLANS

Green screen benefits claimed

Monitoring of pollutants near a playground suggests a green screen may be reducing pollution.

A green screen was installed on the boundary wall along the Warwick Road at St Cuthbert with St Matthias Primary School in Kensington and Chelsea.

This is one of the busiest and most congested roads in the borough and has been identified as an area that has high background levels of NO₂ and PM₁₀ pollution.

A temporary air quality monitoring station was also installed into the school comprising two NO₂ analysers and two PM analysers. The analysers have provided concentration data for NO₂ and PM on the road side of the green screen and the



Before and after: the green screen is being monitored

playground side of the green screen installation.

The monitoring so far has shown early indications that the concentrations of NO₂ and PM on the playground side of the green screen are “markedly” lower than concentrations on the road side of the green screen.

An air quality education programme was also designed and delivered to year 5 and 6

pupils within the school in conjunction with the installation of the green infrastructure and monitoring station.

The project was funded by the GLA receiving funding through INTERREG IVB, the Royal Borough of Kensington and Chelsea Council and Defra and was run in collaboration with King’s College London and the Transport Research Laboratory.

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were also published in the Air Quality Bulletin in October 2014 and January 2015. Once the green screen foliage had matured the difference between the roadside and playground side of the screen was 35% for NO₂ and 30-40% for PM₁₀.

<i>Do's</i>	<i>&</i>	<i>Don'ts</i>
<ul style="list-style-type: none"> ✔ ensure the screening is located where it will be of most benefit, including for non-air quality reasons ✔ ensure the planting is attractive, and includes 'air quality' plants which can be used to educate children about air quality ✔ as tailored planting will be required, do undertake a site visit with green infrastructure contractors and site maintenance staff and school representatives at the design stage to assess suitability ✔ ensure that the plant species selected to make up the green infrastructure have known NO₂ absorption and particle trapping properties ✔ seek permissions from all levels of the school such as head teacher, diocese, school/parent governors ✔ identify water and electrical sources early on in programme of works and decide with the school the best solution to the provision of water for the planting ✔ include a minimum of 12 months green infrastructure maintenance into the contract for the installers, to include cut back, soil fertilising and irrigation system servicing and ensure the school agree (at the design stage) to take on the work after this time ✔ ensure adequate parking is available for the green infrastructure installer vehicles and ask for low emission vehicles to be used where possible ✔ work closely with school site maintenance staff and teachers to schedule the green infrastructure installation during school holidays or when children are least present ✔ ensure the green installation is a manageable size and design for the school to be able to maintain ✔ compile a green infrastructure care plan for the school to follow when they take over the maintenance programme 	<p><i>&</i></p>	<ul style="list-style-type: none"> ✘ Don't implement a greening scheme without ensuring the school is able to maintain it in the long term ✘ Don't forget to check if it is feasible to plant straight into the ground, where a suitable depth of soil is available or can be created ✘ Don't forget to check with the planning department (and others, e.g. Building Control) whether permissions are required for the intended installation ✘ Don't forget to keep school site maintenance staff updated of changes to the installation schedule / design ✘ Don't forget to ensure the school site maintenance staff are available during installation works to assist with any queries ✘ Don't forget to keep the school children informed of the proposed installation through updates in the school newsletter and by teachers at whole of school assemblies ✘ Don't forget to maintain contact with the school after installation is complete to assist with any queries, problems or alterations ✘ Don't forget to get the relevant health and safety documentation and insurance information from the installers ✘ Don't forget to get a competent person to pre-approve installations where there are potential structural and weight restriction issues e.g. roof garden additions or sedum roof tile installation ✘ Don't forget to engage the children with the installation design, where possible, and advertise the work conducted

CLEAN AIR ZONES PILOT – THE LEARNING ENVIRONMENT

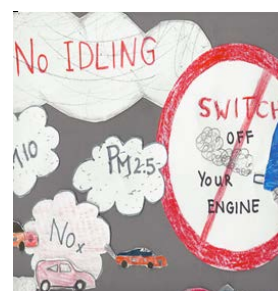
Engaging children with air quality messages is important because they can help spread the messages and drive behaviour change today and deliver change in the future. Engaging children with the green infrastructure helps them understand why the greening is there and gain a practical understanding of solutions.

WHAT COULD BE DONE?

- ❖ Use the **Cleaner Air 4 Primary Schools Toolkit** ([click here](#)) to get lesson and activity ideas, for example, the use of traffic counts and surface wipes
- ❖ Use the green infrastructure in the school to engage the children, for example, help with planting and conducting experiments to see which types of leaves are better at trapping particles



- ❖ Establish project outputs to raise awareness for example: signage around the school ('no engine idling' and 'clean air garden' signs), animations and videos, newsletters, webpage development, plays, whole school assembly, an air quality notice board, walking maps, air quality posters and leaflets
- ❖ Organise whole class and school workshops for children to learn about air quality messages



- ❖ Establish an 'eco-club' and 'air quality champions' in the school to maintain air quality messages and to help look after the greening once installed

CASE STUDIES

BOTWELL HOUSE RC PRIMARY SCHOOL, HAYES

- ☞ **Cleaner Air 4 Primary Schools Toolkit** - teachers used materials provided to ensure the children had an understanding of the importance of air quality. The children created posters, drew pictures and wrote poems about what they had learnt.
- ☞ **The Pollution Solution Workshop** - 6 interactive theatre workshops were run by the Big Wheel Theatre Company for Year 3, covering air pollution and climate change.
- ☞ **Planting Day** - about 50 children helped out on planting day, run by



'Groundwork'. All the planting in the 'quiet area' was done on this day. They learnt about 'air quality' plants and herbs and worked on designs for 5 themed panels that were installed later in the planters.

☞ **The School Children's Council** have been involved in shaping the school and got involved in the project. A presentation was made to the Council on air quality and what the school was trying to achieve. The children's Council were involved in the building audit and design of the 'quiet area'.



WHAT WAS THE OUTCOME: The children produced a wonderful junior assembly about air quality and the participation of the school in the Clean Air Zones project on the official open day for the 'quiet area'. This included a factual presentation and a skit on the Mayor of London and the project. The school choir also sang a song about looking after environment. The fun filled theatre workshops showed what could be done to improve air quality locally, suggesting using good air quality routes and also how addressing air quality could have a positive impact on reducing carbon emissions and so help with climate change. The teachers and the children enjoyed themselves and gave very positive feedback about the workshops.

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Over the course of the project various engagement programmes were implemented with the help of an external provider and a local volunteer group helped the pupils with 'air quality' planting.

☞ **Class engagement programme** - the year 6 class took part in a six week engagement programme where they found out about the causes and effects of air pollution, monitored air pollution around the school; investigated 'pollution loving/hating' lichen and produced no engine idling signs, air quality posters and webpages. Some work was presented at the leavers' assembly.



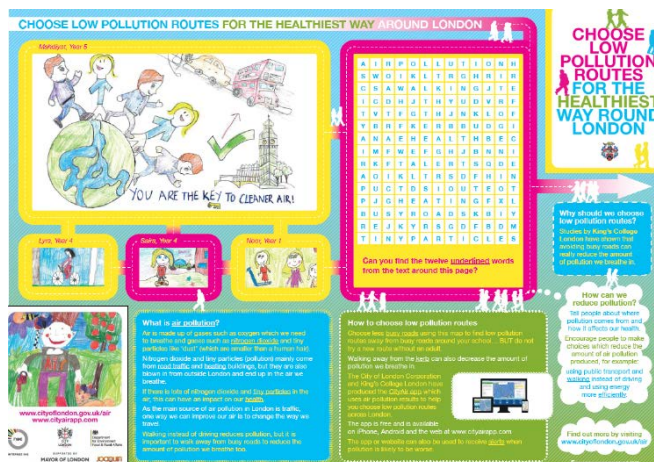
☞ **Workshop and project outputs** - all classes took part in air quality workshops where the pupils identified ways in which they could reduce their 'air quality footprint'. Some classes followed with projects, including using the air quality monitoring results, writing articles and producing artwork for signs and a walking map. The project finished with a whole school assembly presented by nine air quality champions who prepared mini sketches, a short play and a song about air pollution.



☞ **eco club** – A year 4 eco-club was established and they learned about air pollution and monitoring in weekly sessions. They helped plant 170 air quality plants on the roof garden and in the playground with a local volunteer group.

☞ **Planting** – the pupils were actively encouraged to help with planting and looking after the 'air quality greening' by watering the plants during break-time. A 'green team' has been set up and the local volunteer group will continue to help the school with care of the greening.

WHAT WAS THE OUTCOME: The children produced signs for around the school and a competition was run to design the artwork for a fold out walking map and a giant door sticker for the air quality monitoring station. The walking map explains how children can reduce their exposure by travelling via less busy roads. It also lets them know about the CityAir app which uses real time air quality data to show low pollution routes. The school are kept informed about air quality in the area via termly reports and alerts when pollution levels are moderate or above.



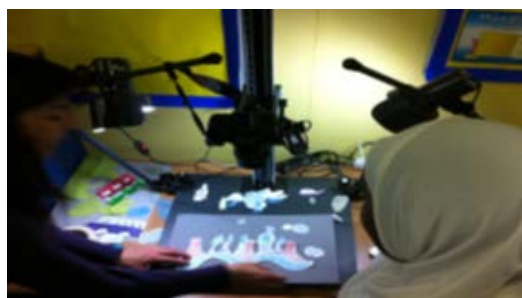
OXFORD GARDENS SCHOOL AND ST CUTHBERT WITH ST MATTHIAS, KENSINGTON AND CHELSEA

☞ **Education programme** - An education programme was designed for each schools' curriculum requirements using the Cleaner Air for Primary Schools toolkit and the Healthy Air education

toolkit. Air pollutants NO₂, PM₁₀ and PM_{2.5} were highlighted in teaching sessions and practical exercises.

☞ **Practical Experiments** - NO₂ diffusion tubes deployment was undertaken as a practical exercise with each class, followed by the collection of tubes and analysis of results. Sample location maps were created and graphs of results used to demonstrate changes in NO₂ in the local environment. A *surface wipe test* experiment was undertaken to demonstrate PM₁₀ and PM_{2.5} air pollution. The exercise was used to demonstrate the difference between roadside locations and locations away from the roadside. A traffic count was undertaken to demonstrate the volume of traffic along the busy road outside the school and the different types of vehicles contributing the poor air quality.

☞ **Monitoring station Installation** – To facilitate the schools teaching programme and further the understanding of the effectiveness of green screens to reduce local air pollution, at St Cuthberts with St Matthias school, a temporary (12 months) air quality monitoring station was installed. Continuous NO_x and PM₁₀ monitors positioned either side of a green screen located between the school playground and busy roadside location. Results from the monitoring station were used in teaching sessions to demonstrate how effective the green screens were at reducing NO₂ and PM levels in the school playground environment.



☞ **Animation/film creation** - Each class held a brainstorming session on air pollution and were given the task to create drawings about the sources and impact of air pollution on their health. The children then used their drawings to create a story board and create a script for their animation/ film. Sessions were held with the children and a team of animators to create the animation/film.

☞ **Gardening Sessions** - Existing gardening sessions

which ran at St Cuthbert with St Matthias School used the green screen installation to carry on a legacy of air pollution teaching in the school after the education programme came to an end.

WHAT WAS THE OUTCOME: During the teaching sessions children made no idling engine posters to place outside of the school along the busy road locations. Children also produced maps of low pollution walking routes to school using Walk-it.com. The final animation/film was premiered at the end of project school assembly. The classes led on presenting a summary of their work and showing their animation/film to the rest of the school, parents, governors and councillors. The animations were uploaded to You Tube and the Royal Borough of Kensington and Chelsea website. Gardening sessions at St Cuthbert with St Matthias School carried on the legacy of air pollution teaching by using the green screen installation as an example of how planting can improve local air quality. A research poster and paper were written using the results from the air quality monitoring station. Results were presented at the Monitoring Ambient Air 2014 conference and an article was published in Air Quality Bulletin (October 2014). Links to You Tube animation/films can be found on the Schools Projects link:

Green wall for London school



St Cuthbert with St Matthias School in the Royal Borough of Kensington and Chelsea has held a special assembly to celebrate the installation of a living green screen, made up of ivy, clematis, jasmine and Ionicera.

The green wall aims to "significantly" reduce the pupils' exposure, whilst at school, to nitrogen dioxide and particulate matter vehicle pollution at the roadside location in Earl's Court. King's College London is monitoring air quality at the site (inset).

An air quality education programme has seen pupils from year six map their lowest pollution routes to school, create images for no-idling engine posters and script and produce an animated film. To see the film go to <http://youtu.be/T4kpqIYBNI>

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Results were presented at the Monitoring Ambient Air 2014 conference and an article was published in Air Quality Bulletin (October 2014). Links to You Tube animation/films can be found on the Schools Projects link:

<http://www.rbkc.gov.uk/environmentandtransport/airquality/airqualityprojects.aspx>

Do's	&	Don'ts
<ul style="list-style-type: none"> ✔ meet the school needs by engaging with staff to see what the priorities are ✔ ensure the school understands the commitment required and establish a Letter of Agreement, which the teacher(s) and school sign ✔ do work with partner organisations who are already involved with schools and already know what works and is required ✔ have a single point of contact at the school to champion the project ✔ highlight how air quality fits across the curriculum: maths, sciences, geography, English, social studies, art and design ✔ use existing materials e.g. Cleaner Air 4 Primary Schools Toolkit, creating a comprehensive plan in advance ✔ be aware of holidays and activities at the school before agreeing timeframes ✔ establish early on with the school how the education programme will fit in with their curriculum requirements and schedule ✔ ensure the teachers are engaged with and informed of the programme lesson plans, exercises and practical session(s) ✔ provide teachers with an air quality information pack ✔ ensure that you have teachers assistance with the handing out and collection of homework and worksheets ✔ try to ensure that the sessions take place during similar school themes such as environment week, geography week etc. ✔ do book in use of school halls for assemblies early on and ensure time is made available to practice the assembly ✔ if using educational delivery agents, work with them to design the educational programme ensuring lessons plans, exercises and practical experiments are suitable for the air pollution educational programme and undertake regular updates and progress meetings 		<ul style="list-style-type: none"> ✘ Do not leave it too late to contact the school. Ideally contact the school well before the new school year so the engagement can be programmed ✘ Do not overwhelm teachers with work or tasks. Keep the messages simple ✘ Do not forget to keep the school and teachers updated on the progress of the educational programme ✘ Do not forget to work with the school to publicise the programme through the school website and any school/governors newsletter to reach a wider audience/community ✘ Do not forget to send event and assembly invites early to parents, school and parent governors and where possible provide incentives such as 'freebies' to ensure they attend so as to spread the messages ✘ Do not forget to record each stage of the project, through written summaries, videos footage, photographs etc. but get school and parent/carer permissions for the use of photos etc. ✘ Do not forget that teachers are REALLY busy and so don't worry if some teachers do not want to be involved. It is better to work with teachers who have time and can commit ✘ Do not forget pre and post leaning evaluation sheets to understand what the children have learnt and what, if any behaviour change has occurred ✘ Don't forget copyright issues for materials produced on behalf of the school. Be sure the matters are finalised and agreed before proceeding

8 Royal College of Obstetricians and Gynaecologists

Submitted evidence:

- Scientific Impact Paper on [Chemical Exposures During Pregnancy](#)

9 Royal College of Physicians of Edinburgh

Submitted evidence:

- Long-term effects of air pollution on children and adults – RCPE response

Royal College of Physicians of Edinburgh

Royal College of Physicians of London and Royal College of Paediatrics and Child Health call for evidence on the long term effects of air pollution on children and adults

The Royal College of Physicians of Edinburgh (the College) is pleased to respond to the call for evidence on the on the long term effects of air pollution on children and adults.

Overview

Children and young people are affected, as adults are, by levels of all aero pollutants. There is evidence of adverse effects on respiratory health from high environmental levels of tobacco smoke, particulates and chemical fumes. However, young children are particularly at risk from inflammatory responses in the growing lung, and so the younger the child the greater the risk. This is particularly relevant for children with atopia, as research suggests that their susceptibility to asthma may be increased, and reversibility compromised, by the effect of early remodelling associated with aero pollutant exposure.

Although the long term physiology of the respiratory system in infants and children who are born preterm or have respiratory problems and suffer neonatal lung disease is poorly understood, it may be that an early inflammatory process may compromise later function, resulting in reduced potential for recovery from exposure to airborne toxins.

Focus has widened from the obvious environmental hazards of antenatal effects of smoking to the impact of tobacco smoke in the home or car, diesel fumes from vehicle exhausts, chlorine and disinfectant by-products in swimming pools, toxic fumes from chemical products and waste disposal. As different particulates and airborne fumes vary in density the exposure of small children or infants in buggies to more dense particles may be greater than to taller adults but this is rarely emphasised in environmental studies.

The complex interaction between particle size and chemical composition is often unclear, but the combined risks to the growing airway and lung and to its maturing immune and inflammatory response point to the need for sustained environmental vigilance and atmospheric protection.

Literature review

A recent literature reviewⁱ has highlighted evidence from historical recordsⁱⁱ showing a link between air pollution and an increase in death rate, and has stated that the body of evidence from scientific studies confirms a strong causal link between air pollution and health. There does not appear to be a level below which health effects are not seenⁱⁱⁱ therefore to protect health there must be a continual attempt to lower air pollution to as low as reasonably practicable, and support improvements in general health thereby reducing the population of vulnerable people. Research is required to find mechanisms to engage with communities to reduce vehicle use and increase sustainable forms of transport.

Reviews have shown an increased risk of infant mortality as a result of elevated particulate matter (PM) exposure^{iv}. There is also evidence of increased morbidity in the first year of life^v and an increase in asthma in 8-12 year olds linked to exposure to particulate matter (PM₁₀) and nitrous oxide^{vi} (NO₂).

The literature review found that evidence for the association between air pollution and health has been provided in many studies and summarized in robust reviews^{vii viii ix x} and that pollutants from traffic are associated with an increase in all-cause mortality, morbidity from cardiovascular and pulmonary disease, cancer and have a detrimental impact in pregnancy and the neonate.

Conclusion

In summary, therefore, the College wishes to highlight the growing body of evidence which suggest a strong relationship between levels of air pollution and respiratory health. This relationship may be particularly important to consider in the prevention of childhood respiratory disease, which has the potential to then manifest as chronic adult lung disease.

All College responses are published on the College website www.rcpe.ac.uk.

Further copies of this response are available from Lesley Lockhart (tel: 0131 225 7324 ext 608 or email: l.lockhart@rcpe.ac.uk)

9 January 2014

ⁱ Hyland J. The impact of traffic-related air pollution on the health of Scottish residents living adjacent to busy roads. Literature Review. St Andrews University MD Thesis - in progress. January 2014
([Dr Jackie Hyland](#), Consultant in Public Health Medicine, NHS Tayside. Personal Communication based on MD thesis submission)

ⁱⁱ Met Office Education. The Great Smog of 1952. <http://www.metoffice.gov.uk/education/teens/case-studies/great-smog>

ⁱⁱⁱ World Health organization Europe. Review of evidence on health aspects of air pollution –REVIHAAP Project. Technical Report. 2013

http://www.euro.who.int/_data/assets/pdf_file/0004/193108/REVIHAAP-Final-technical-report.pdf

^{iv} World Health Organisation. Health aspects of air quality in Europe. Results from the WHO project; “Systematic review of health aspects of air pollution in Europe”. Copenhagen, WHO Regional Office for Europe, 2004 <http://www.euro.who.int/document/E83080.pdf>

^v Gehring, U.; [Cyrus, J.](#) [Sedlmeir, G.](#) [Brunekreef, B.](#) [Bellander, T.](#) [Fischer, P.](#) [Bauer, C.P.](#) [Reinhardt, D.](#) [Wichmann, H.E.](#) [Heinrich, J.](#) Traffic-related air pollution and respiratory health during the first 2 yrs of life. *European Respiratory Journal* 2002, 19(4):690-698

^{vi} Gruzieva, O; Bergström, A; Hulchiy, O; Kull, I; Lind, T; Melén, E; Moskalenko, V; Pershagen, G; Bellander, T. Exposure to Air Pollution from Traffic and Childhood Asthma Until 12 Years of Age. *Epidemiology*. Volume 24(1), January 2013, p 54–61

^{vii} World Health Organisation Regional Office for Europe Copenhagen. Air Quality Guidelines for Europe. Second Edition. WHO Regional Publications, European Series, No. 91. WHO 2000

http://www.euro.who.int/_data/assets/pdf_file/0005/74732/E71922.pdf

^{viii} World Health Organisation Europe. Air quality guidelines. Global update 2005. Particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Germany Druckpartner Moser 2005

http://www.euro.who.int/_data/assets/pdf_file/0005/78638/E90038.pdf

^{ix} World Health Organisation Working Group. Health Aspects of Air Pollution with Particulate Matter, Ozone and Nitrogen Dioxide. WHO. Bonn, Germany 2003

http://www.euro.who.int/_data/assets/pdf_file/0005/112199/E79097.pdf

^x World Health Organisation. Health aspects of air quality in Europe. Results from the WHO project; “Systematic review of health aspects of air pollution in Europe”. Copenhagen, WHO Regional Office for Europe, 2004 <http://www.euro.who.int/document/E83080.pdf>

10 Sustrans

Submitted evidence:

- Environmental Audit Committee inquiry into air quality
- Local air pollution: the role of active travel

Environmental Audit Committee inquiry into air quality

Submission from Sustrans

May 2014

1. Summary

1.1 Sustrans would like to urge the Committee to keep three matters in mind, when carrying out the inquiry. These all relate to issues raised in the invitation to give evidence, around the scope for transport policies (and in our view, practice also) to contribute to cutting air pollution. They are:

- **the co-benefits achievable by addressing our over-use of private motorised transport in urban and peri-urban areas, and the logic of cross-government and cross-sector action to maximise these**
- **the scale of travel behaviour change achievable, to deliver these benefits**
- **the unlikelihood that technology advances can make the problem disappear as quickly as its urgency demands.**

1.2 And we make three recommendations:

- **transport investment priorities need to change: local air quality improvement should be a priority objective in the fundamental planning of government spending on transport**
- **specifically, a significant, dedicated investment programme should be created for cycling and walking, to build on the successful Local Sustainable Transport Fund, and with a still clearer focus on shifting local transport choices from motorised to active travel**

- **existing and planned developments and infrastructure should be ‘health-checked’ , to ensure they are supportive of active travel, will not generate additional motor trips, and in particular will lead to improved local air quality.**

2. Introduction

- 2.1 Sustrans is a leading UK charity enabling people to travel by foot, bike or public transport for more of the journeys we make every day. We work with families, communities, policy-makers and partner organisations so that people are able to choose healthier, cleaner and cheaper journeys, with better places and spaces to move through and live in.
- 2.2 Our practical work includes a major national programme of environmental interventions – working with many partners to create or improve walking and cycling infrastructure – including the National Cycle Network. We also run national programmes of behavioural interventions, working with one in ten English schools, for example, doubling cycling to school, increasing scooting by over fifty per cent, and sustaining walking levels.
- 2.3 The scale of behaviour change engendered by our work is enough to make a real difference to local travel, including air quality. In 2012, over 3 million individuals made half a billion trips on the National Cycle Network, roughly half walking and half cycling. Usage has increased every year since systematic monitoring began in 2000, and we expect further growth when the 2013 figures have been validated.
- 2.4 We believe this practical experience of creating travel behaviour change makes the Sustrans viewpoint particularly relevant and important to the Committee' s inquiry. Our comments below relate to our field of expertise, transport and travel choice, although some may have wider relevance.

3. Sustrans evidence

3.1 Members of the Committee will already be fully informed about the embarrassing struggle between the European Commission and the UK Government, caused by our failure to tackle air quality in some of our cities. They will have studied the Public Health England local air quality impact modelling, and no doubt turned in shock to the figures around their own constituencies. None will need to be told about the new WHO database on ambient air pollution in cities. We do not propose to weary them by reiterating evidence they already know. Rather, we want to address three areas of evidence which may be useful:

- **the co-benefits achievable by addressing our over-use of private motorised transport in urban and peri-urban areas, and the logic of cross-government and cross-sector action to maximise these**
- **the scale of travel behaviour change achievable, to deliver these benefits**
- **the unlikelihood that technology advances can make the problem disappear as quickly as its urgency demands.**

3.2 Co-benefits

3.2.1 In Sustrans' view, policies and measures to address the problem of local air pollution can and should be developed with an eye to objectives in other, associated policy areas. In our field, successful intervention to change travel behaviour contributes to numerous policy objectives, offering therefore exceptional value for money.

3.2.2 In the first place, motorised transport is a major contributor to local toxic air pollution. Therefore we should take immediate and decisive action to reduce it, by promoting alternatives and by restraint measures, such as reallocating road space from motor traffic to pedestrians and cyclists. This is an imperative in its own right.

3.2.3 This modal shift to active travel will also reduce climate change emissions and noise, improve road safety, increase social interaction, and above all by promoting physical activity it will cut cardio-vascular disease, various forms of cancer and type 2 diabetes, improve mental health and contribute to other health objectives.

3.2.4 The evidence on disease prevention through active travel is not at issue. There is a strong consensus, led by the four Chief Medical Officers of England, Scotland, Wales and Northern Ireland who state that *“for most people, the easiest and most acceptable forms of physical activity are those that can be incorporated into everyday life. Examples include walking or cycling instead of travelling by car, bus or train”* ⁽¹⁾. This is backed up by the Government’s Foresight obesity team⁽²⁾, The British Medical Association⁽³⁾, the public health profession as a whole⁽⁴⁾, and the National Institute for Health and Care Excellence (NICE) which offers a list of practical interventions in favour of walking and cycling, including road space reallocation, traffic calming, road user charging and network improvements⁽⁵⁾ as well as a range of motivational and information approaches⁽⁶⁾. NICE says that *“walking and cycling should become the norm for short journeys”* ⁽⁷⁾.

3.2.5 At the national policy level, a shift from motorised to active travel for local trips offers a reduction in our dependence on fossil fuel imports, sometimes from unstable nations or regions, and an improvement in the balance of payments through lower energy import demand.

3.2.6 On top of all these benefits, investment in active travel is far, far better value for money than other transport spending. Using the Department for Transport’s assessment methodology, it offers much higher benefit to cost ratios (BCR) than traditional road schemes. DfT regards a BCR of 2:1 as a good return on investment: walking and cycling schemes regularly return BCR of over 10:1.

3.2.7 A review of published transport analyses, carried out in 2010 for the South West regional government office and the Department of Health, found that, *“almost all of the studies identified report economic benefits of walking and cycling interventions which are highly significant. The median result for all data identified is 13:1 and for UK data alone the median figure is higher, at 19:1”* ⁽⁸⁾.

3.3 The potential for change in travel behaviour

3.3.1 The scale of potential change in local travel behaviour, modelled by Sustrans and others, is really significant: there is an opportunity to transform local air quality, along with the associated benefit areas described above.

- 3.3.2 Sustrans' own work for the DfT has shown that in representative UK cities 47% of car trips could be replaced by walking, cycling or public transport, without major changes to existing infrastructure⁽⁹⁾.
- 3.3.3 Even greater potential exists where significant investment is made in infrastructure to support these modes. Sustrans has called for a doubling of the share of trips made by walking, cycling and public transport⁽¹⁰⁾: this is achievable, and would have very significant public health impact.
- 3.3.4 This is not a view unique to Sustrans: the Cabinet Office has calculated that people could replace 78% of their local car trips under five miles with walking, cycling or public transport⁽¹¹⁾.

3.4 Will technology save us?

- 3.4.1 Sustrans is cautious about the idea that technological advances can solve problems associated with vehicle emissions, be they climate change gases or local pollutants. The motor industry has historically fought a successful rearguard action against tighter engine emission standards, but even were this to change the scale and severity of the air pollution problem is such that, put simply, we cannot wait. Technology may promise cleaner exhaust gases in the future, but people are dying now.
- 3.4.2 The other weakness of a tech-based approach to air quality policy is that it fails to deliver on many of the co-benefits listed above. If the UK vehicle fleet magically became all-electric tomorrow, it would still be sedentary transport, still severing communities and suppressing social interaction, and still creating road danger. This illustrates very well that an integrated approach to policy is desirable.
- 3.4.3 The technological solutions which we would support would be those which have a part to play in tackling the air quality problem by addressing the motor traffic which causes it. Real-time air quality monitoring, linked to variable traffic messaging to close roads to traffic when limits are breached, for example, would be appropriate use of technology. But the real issue illustrated here is one of national and local policy – this example is about having the courage and compassion to stop the traffic when the air is toxic, not particularly about the technology.

4. Sustrans recommends

4.1 The committee will no doubt identify urgently needed changes to policy and practice in a number of areas. As regards transport, we suggest:

- **transport investment priorities need to change: local air quality improvement should be a priority objective in the fundamental planning of government spending on transport**
- **specifically, a significant, dedicated investment programme should be created for cycling and walking, to build on the successful Local Sustainable Transport Fund, and with a still clearer focus on shifting local transport choices from motorised to active travel**
- **existing and planned developments and infrastructure should be ‘health-checked’ , to ensure they are supportive of active travel, will not generate additional motor trips, and in particular will lead to improved local air quality.**

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References

¹ **Department of Health, 2011** Start active, stay active: A report on physical activity for health from the four home countries’ Chief Medical Officers

² **Government Office for Science, 2007** Foresight Tackling Obesities: Future Choices

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- ³ **British Medical Association, 2012** Healthy transport = Healthy lives
- ⁴ **Sustrans, 2013** Is England taking action on active travel?
- ⁵ **National Institute for Health and Care Excellence, 2008** Promoting and creating built or natural environments that encourage and support physical activity
- ⁶ **National Institute for Health and Care Excellence, 2012** Walking and cycling: local measures to promote walking and cycling as forms of travel or recreation
- ⁷ **National Institute for Health and Care Excellence, 2012**
<http://www.nice.org.uk/newsroom/pressreleases/NoTimeForPhysicalActivityTheAnswersOnYourdoors>
tepSaysNICE.jsp
- ⁸ **Government Office Southwest / Department of Health, 2010** Value for Money: An Economic Assessment of Investment in Walking and Cycling
- ⁹ **Sustrans, 2005** Travel Behaviour Research Baseline Survey 2004: Sustainable Travel Demonstration Towns
- ¹⁰ **Sustrans, 2010** More Haste Less Speed
- ¹¹ **Cabinet Office, 2009** An analysis of urban transport

Local air pollution: the role of active travel

Submission from Sustrans to the Royal College of Physicians working party

September 2014

Key points

Sustrans would like to urge the working party to keep three matters in mind:

- **the co-benefits achievable by addressing our over-use of private motorised transport in urban and peri-urban areas, and the logic of cross-government and cross-sector action to maximise these**
- **the scale of travel behaviour change achievable, to deliver these benefits**
- **the unlikelihood that technology advances can make the problem disappear as quickly as its urgency demands.**

And we make four recommendations:

Transport investment priorities need to change: local air quality improvement should be a priority objective in the fundamental planning of government spending on transport.

A significant, dedicated investment programme should be created for cycling and walking, to build on the successful Local Sustainable Transport Fund, and with a still clearer focus on shifting local transport choices from motorised to active travel.

Existing and planned developments and infrastructure should be ‘health-checked’, to ensure they are supportive of active travel, will not generate additional motor trips, and in particular will lead to improved local air quality.

NICE should be commissioned to deliver guidance on local strategies and measures to tackle air pollution and improve air quality.

Introduction

Sustrans is a leading UK charity enabling people to travel by foot, bike or public transport for more of the journeys we make every day. We work with families, communities, policy-makers and partner organisations so that people are able to choose healthier, cleaner and cheaper journeys, with better places and spaces to move through and live in.

Our practical work includes a major national programme of environmental interventions – working with many partners to create or improve walking and cycling infrastructure – including the National Cycle Network. We also run national programmes of behavioural interventions, working with one in ten English schools, for example, doubling cycling to school, increasing scooting by over fifty per cent, and sustaining walking levels.

The scale of behaviour change engendered by our work is enough to make a real difference to local travel, including air quality. In 2013, almost 5 million individuals made 423 million walking and 325 million cycling trips on the National Cycle Network. 150 million of these trips could have been made by car. Usage has increased every year since systematic monitoring began in 2000.

We believe this practical experience of creating travel behaviour change makes the Sustrans viewpoint relevant and important to your working party.

We have noted that the working party will focus primarily on how air pollution damages health. Nonetheless, we hope you will be able to touch on some of the practical things that can be done to tackle it. This submission is to look at some of those.

Overarching considerations

We hope members of the working party can keep in mind three overarching considerations while considering evidence and developing recommendations. These relate to transport in the context of strategies and measures to address the air pollution problem: there may be others relevant to other fields. They are introduced below.

The co-benefits achievable by addressing our over-use of private motorised transport in urban and peri-urban areas, and the logic of cross-government and cross-sector action to maximise these

In Sustrans' view, policies and measures to address the problem of local air pollution can and should be developed with an eye to the gains that can be made on objectives in other, associated policy areas. Transport is a good example: change in travel behaviour contributes to numerous policy objectives, offering therefore exceptional value for money.

In the first place, private motorised transport is a major contributor to local toxic air pollution. Therefore we should take immediate and decisive action to reduce it, by promoting alternatives and by restraint measures, such as reallocating road space from motor traffic to pedestrians and cyclists. This is an imperative in its own right.

We have noted the working party's commitment to consider the relationship between climate change and air pollution and we very much welcome this. The Royal College has been a leader on climate change policy for some time, and this too is welcome: medical

professionals, and your expert views, are trusted by the public and your leadership is valuable.

A shift to active travel will reduce climate change emissions as well as local toxic air pollution. At the same time, it reduces noise, improves road safety, increases social interaction, and above all by promoting physical activity it will cut cardio-vascular disease, various forms of cancer and type 2 diabetes, improve mental health and contribute to other health objectives.

The evidence on disease prevention through active travel is not at issue. There is a strong consensus, led by the four Chief Medical Officers of England, Scotland, Wales and Northern Ireland who state that *“for most people, the easiest and most acceptable forms of physical activity are those that can be incorporated into everyday life. Examples include walking or cycling instead of travelling by car, bus or train”*⁽¹⁾. This is backed up by the Government’s Foresight obesity team⁽²⁾, The British Medical Association⁽³⁾, the public health profession as a whole⁽⁴⁾, and the National Institute for Health and Care Excellence (NICE) which offers a list of practical interventions in favour of walking and cycling, including road space reallocation, traffic calming, road user charging and network improvements⁽⁵⁾ as well as a range of motivational and information approaches⁽⁶⁾. NICE says that *“walking and cycling should become the norm for short journeys”*⁽⁷⁾.

At the national policy level, a shift from motorised to active travel for local trips offers a reduction in our dependence on fossil fuel imports, sometimes from unstable nations or regions, and an improvement in the balance of payments through lower energy import demand.

On top of all these benefits, investment in active travel is far, far better value for money than other transport spending. Using the Department for Transport’s assessment methodology, it offers much higher benefit to cost ratios (BCR) than traditional road schemes. DfT regards a BCR of 2:1 as a good return on investment: walking and cycling schemes regularly return BCR of over 10:1.

A review of published transport analyses, carried out in 2010 for the South West regional government office and the Department of Health, found that, *“almost all of the studies identified report economic benefits of walking and cycling interventions which are highly significant. The median result for all data identified is 13:1 and for UK data alone the median figure is higher, at 19:1”*⁽⁸⁾.

The scale of travel behaviour change achievable, to deliver these benefits

The scale of potential change in local travel behaviour, modelled by Sustrans and others, is really significant: there is an opportunity to transform local air quality, along with the associated benefit areas described above.

Sustrans’ own work for the DfT has shown that in representative UK cities 47% of car trips could be replaced by walking, cycling or public transport, without major changes to existing infrastructure⁽⁹⁾.

Even greater potential exists where significant investment is made in infrastructure to support these modes. Sustrans has called for a doubling of the share of trips made by walking, cycling and public transport⁽¹⁰⁾: this is achievable, and would have very significant public health impact.

This is not a view unique to Sustrans: the Cabinet Office has calculated that people could replace 78% of their local car trips under five miles with walking, cycling or public transport⁽¹¹⁾.

The unlikelihood that technology advances can make the problem disappear as quickly as its urgency demands

Sustrans is cautious about the idea that technological advances can solve problems associated with vehicle emissions, be they climate change gases or local pollutants. The motor industry has historically fought a successful rearguard action against tighter engine emission standards, but even were this to change the scale and severity of the air pollution problem is such that, put simply, we cannot wait. Technology may promise cleaner exhaust gases in the future, but people are dying now.

The other weakness of a tech-based approach to air quality policy is that it fails to deliver on many of the co-benefits listed above. If the UK vehicle fleet magically became all-electric tomorrow, it would still be sedentary transport, still severing communities and suppressing social interaction, and still creating road danger. This illustrates very well that an integrated approach to policy is desirable.

The technological solutions which we would support would be those which have a part to play in tackling the air quality problem by addressing the motor traffic which causes it. Real-time air quality monitoring, linked to variable traffic messaging to close roads to traffic when limits are breached, for example, would be appropriate use of technology. But the real issue illustrated here is one of national and local policy – this example is about having the courage and compassion to stop the traffic when the air is toxic, not particularly about the technology.

Sustrans recommends

The working party will no doubt identify urgently needed changes to policy and practice in a number of areas. As regards transport, we suggest:

Transport investment priorities need to change: local air quality improvement should be a priority objective in the fundamental planning of government spending on transport.

A significant, dedicated investment programme should be created for cycling and walking, to build on the successful Local Sustainable Transport Fund, and with a still clearer focus on shifting local transport choices from motorised to active travel.

Existing and planned developments and infrastructure should be ‘health-checked’, to ensure they are supportive of active travel, will not generate additional motor trips, and in particular will lead to improved local air quality.

NICE should be commissioned to deliver guidance on local strategies and measures to tackle air pollution and improve air quality.

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- ¹ **Department of Health, 2011** Start active, stay active: A report on physical activity for health from the four home countries' Chief Medical Officers
- ² **Government Office for Science, 2007** Foresight Tackling Obesities: Future Choices
- ³ **British Medical Association, 2012** Healthy transport = Healthy lives
- ⁴ **Sustrans, 2013** Is England taking action on active travel?
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- ⁶ **National Institute for Health and Care Excellence, 2012** Walking and cycling: local measures to promote walking and cycling as forms of travel or recreation
- ⁷ **National Institute for Health and Care Excellence, 2012**
<http://www.nice.org.uk/newsroom/pressreleases/NoTimeForPhysicalActivityTheAnswersOnYourdoorstepSaysNICE.jsp>
- ⁸ **Government Office Southwest / Department of Health, 2010** Value for Money: An Economic Assessment of Investment in Walking and Cycling
- ⁹ **Sustrans, 2005** Travel Behaviour Research Baseline Survey 2004: Sustainable Travel Demonstration Towns
- ¹⁰ **Sustrans, 2010** More Haste Less Speed
- ¹¹ **Cabinet Office, 2009** An analysis of urban transport

11 UK Health Forum

Submitted evidence:

- UK Health Forum's submission of evidence to the RCP/RCPCH Working Party for Air Pollution



**UK Health Forum's submission of evidence to the RCP/RCPC Working Party for Air
Pollution**

Date: 9 January 2015

Contact: Hannah Graff, Senior Policy Researcher
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Air Pollution and NCDs

The UK Health Forum (UKHF) has become increasingly interested in both outdoor and indoor air quality and air pollution, in particular the impact on non-communicable diseases (NCDs). We recognise that the impact of polluted air on population health has been relatively overlooked - particularly the impact on chronic as well as acute disease - and it is time for public health and environmental policies to reflect this link. As the evidence base grows, air pollution should be incorporated into the broader NCD prevention agenda - globally, nationally and locally.

Citing the importance of air pollution on health, UKHF undertook a research update on outdoor air quality and NCDs in 2014. This update looked specifically at direct effects of air quality and air pollution on NCDs, primarily respiratory and cardiovascular disease. UKHF will incorporate air pollution evidence and policy development into our work particularly on active travel, the built environment, sustainable development and climate change. Our evidence submission and recommendations for policy action are based on the research update.

Summary of evidence

The UKHF research update looked specifically at the links between outdoor air quality and NCDs, in particular cardiovascular and respiratory diseases. For example, the UKHF update does not incorporate new evidence linking tobacco smoke and near-roadway air pollution to the development of childhood obesity.¹ Indoor air quality, socio-economic inequalities, issues around pregnancy and other aspects of the RCP/RCPC scope of inquiry are not included in our update.

- Air pollutants including NO₂, other combustion pollutants and particle pollutants such as PM_{2.5} have the greatest impact on health.
- Near-roadway or “road proximity” appear to be the largest contributing factor for exposure to pollutants. However, other sources besides road traffic including space heating and air conditioning contribute to overall exposure.
- To date, the evidence supports effect on respiratory and cardiovascular disease to be the greatest burden on health from air pollution. However, there is a small amount of evidence to support additional risk for other NCDs.
- Research suggests that air pollutants both trigger and exacerbate the development of both cardiovascular and respiratory conditions, primarily due to long-term exposure.
- With regards to children, evidence points to a number of specific factors on air pollutants and the development of NCDs. These include: seasonal variations; proximity (of homes and schools) to roadways; interactions with other allergens; children’s activity levels; and the age of children.

¹ McConnell, R., Shen, E., Gilliland, F.D., Jerrett, M., Wolch, J., Chang, C., Lurmann, F., Berhane, K. (2014). A Longitudinal Cohort Study of Body Mass Index and Childhood Exposure to Secondhand Tobacco Smoke and Air Pollution: The Southern California Children’s Health Study. *Environmental Health Perspectives*. Published online: Nov. 12, 2014.

- Younger children seem to be disproportionately affected by both chronic and acute conditions with acute respiratory illness, asthma and gastro enteric illness being the most common.
- For adults, long-term exposure to road traffic has the biggest impact on those with pre-existing conditions. This is particularly apparent for cardiac risk, with hospital admissions due to myocardial infarction (MI) cited in several studies.
- There is evidence to support a stronger correlation between particles and ill health, however long term exposure to gas emissions is also a risk.
- It should be noted that inconsistencies and difficulties in interpreting the evidence, such as assessing relative risk and exposure, must be acknowledged when considering the links between air pollution and NCDs.

The full research update can be found in Appendix 1.

Recommendations for action

Given the evidential links between poor outdoor air quality and both the development and exacerbation of NCDs, UKHF recommends the following policy actions:

- Change transport investment priorities. Local air quality improvement should be a priority objective in the fundamental planning of government spending on transport. Investment in air quality improvement and active travel will have a dual-benefit of reducing air pollution and increasing levels of physical activity across the population.
- There needs to be a significant, dedicated investment programme created for walking and cycling, to build on the successful Local Sustainable Transport Fund, and with a clearer focus on shifting local transport choices from motorised to active travel.
- Active Travel bills, appropriate to national context and powers, should be introduced for England, Scotland and Northern Ireland, similar in aim to the Active Travel (Wales) Act passed in 2013 and building on the experience of the Welsh Government.²
- Existing and planned developments and infrastructure should be ‘health-checked’, to ensure they are supportive of active travel, will not generate additional motor trips, and in particular will lead to improved local air quality.
- NICE should be commissioned to deliver guidance on local strategies and measures to tackle air pollution and improve air quality.
- The UK needs to ensure it meets its legal duty to protect the population from the harmful affects of air pollution under EU regulation. Current levels of particle pollution and gas

² National Assembly for Wales. 2013. *Active Travel (Wales) Act 2013*. Accessed 15 March 2014: <http://www.senedd.assemblywales.org/mgIssueHistoryHome.aspx?IId=5750>

emissions, particularly in urban centres, undermine the health benefits of time spent outdoors being physically active.³

- Geographic and socio-economic inequalities in exposure to air pollution have been documented in the UK and across Europe, however funding for updated research in this area is needed for improved, evidence based policy development.^{4,5,6}
- There should be investment in research to improve our understanding of the impact of air pollution on NCDs, and in modelling studies to help indicate the likely health, social and economic benefits of policies to reduce air pollution.

About the UK Health Forum

The UK Health Forum (UKHF), a registered charity, is both a UK forum and an international centre for the prevention of non-communicable diseases (NCDs) including coronary heart disease, stroke, cancer, diabetes, chronic kidney and liver diseases, and dementia through a focus on up-stream measures targeted at the four shared modifiable risk factors of poor nutrition, physical inactivity, tobacco use and alcohol misuse. UKHF undertakes policy research and advocacy to support action by government, the public sector and commercial operators. As an alliance, the UKHF is uniquely placed to develop and promote consensus-based healthy public policy and to coordinate public health advocacy.

UKHF's vision is of a society where public policy and effective regulation supports the social, economic and environmental conditions in which everyone has equal access to good health and the opportunity to enjoy a life free from disability or preventable death caused by non-communicable diseases. www.ukhealthforum.org.uk

³ King's College London. 2014. *London Air: What is the Government doing?* Accessed 21 March 2014: <http://www.londonair.org.uk/LondonAir/guide/GovernmentAction.aspx>

⁴ Wheeler, B. M. and Ben-Shlomo, Y. 2005. Environmental equity, air quality, socioeconomic status, and respiratory health: a linkage analysis of routine data from the Health Survey for England. *Journal of Epidemiology and Community Health*. 59(11): 948-54.

⁵ Forastiere, F. et al. 2007. Socioeconomic status, particulate air pollution, and daily mortality: differential exposure or differential susceptibility. *American Journal of Industrial Medicine*. 50(3): 208-16.

⁶ Pearce, J. et al. 2013. *Geographical and Social Inequalities in Particulate Matter (PM10) and Ozone Air Pollution in the EU: 2006 to 2010*. Centre for Research on Environment, Society and Health.

Appendix 1 - Research update on air quality and NCDs

Over the summer of 2014 the UKHF Research and Information Services and Policy teams undertook an internal research update on air quality and NCDs. This section provides an overview of the search criteria and findings. The evidence here is organised into sub-sections by focus of the specific research.

Search criteria

Objectives of the research: To find existing research and data sources around what is already known about air pollution and its impact on non-communicable diseases.

Methodology:

Search terminology

(Air pollution OR air quality OR clean air OR particulate matter OR black carbon OR emission*OR fine particles OR coarse particles OR carbon monoxide OR sulphur dioxide OR lead OR greenhouse gases OR nitrogen dioxide OR volatile organic compounds)

AND

(Chronic disease OR respiratory disease OR heart attack OR myocardial infarction OR asthma* OR death OR cardiovascular OR emphysema OR cardiac disease OR cancer OR bronchitis OR obstructive pulmonary disease OR heart disease)

Limits

- Years: 2005- present
- Human
- Language: English only
- Geography: EU focus (Could include global information if there are a low number of references.)

Types of evidence:

- Journal articles, reports, data sets
- Bibliographic databases and other sources of evidence
- Pubmed, NHS Evidence, Cochrane
- WHO, European Commission, PHE, Defra
- Health & Social care information centre, Office of National Statistics,

Output: All references will be imported in Mendeley into a closed group for appraisal and sifting

Air quality search strategy:

Pubmed:

```
((("Air Pollution"[Majr:NoExp]) OR "Vehicle Emissions"[Majr:NoExp])) AND (((("Chronic Disease"[Majr:NoExp]) OR "Myocardial Infarction"[Majr:NoExp]) OR "Asthma"[Mesh]) OR "Respiratory Tract Diseases"[Majr:NoExp]) OR "Mortality, Premature"[Majr:NoExp]) OR "Neoplasms"[Majr:NoExp])
```

NHS Evidence:

“air pollution” AND (“chronic disease” OR respiratory disease OR asthma OR mortality OR neoplasm OR “myocardial infarction”)

Cochrane:

(air pollution) AND “chronic disease” OR respiratory OR asthma OR “myocardial infarction” OR neoplasm

NICE:

Air pollution or air quality

Defra:

air pollution

WHO Europe (IRIS):

“air pollution”

Office of National Statistics:

“air pollution” OR “air quality”

European Commission:

air pollution

HSCIC:

Air pollution

Air pollution and health effects⁷

[Brunekreef B. \(2007\) Health effects of air pollution observed in cohort studies in Europe. Journal of Exposure Science & Environmental Epidemiology; 17: s61-65](#)

In recent years, several studies in Europe have associated within-city contrasts in air pollution with various health end points including mortality in cohort studies of adults, and respiratory morbidity in cross-sectional and cohort studies of children. Many of these studies have used NO₂ contrasts as the primary exposure variable, which raises the issue of whether such associations are uniquely found for NO₂ *per se*, or whether NO₂ acts as a surrogate for a complex mixture of combustion pollutants primarily derived from vehicular traffic. Exposure assessment in these studies has been based on dispersion modelling, on data from routine monitoring networks, on stochastic models developed from dedicated spatially resolved monitoring, or some combination of these. The results of a number of recent European studies are discussed.

⁷ Please note: Links for each citation are live when connected to the internet.

[Heinrich J, Slama R. \(2007\) **Fine particles, a major threat to children.** Int J Hyg Environ Health; 210\(5\): 617-22.](#)

This is a strategic review of children's susceptibility to ambient fine particles and characteristics of infant and children which underlie their increased susceptibility to PM. The authors found ambient fine PM is associated with intra-uterine growth retardation, infant mortality; it is associated with impaired lung function and increased respiratory symptoms, particularly in asthmatics.

[Henschel S, Chan G. \(2013\) **Health risks of air pollution in Europe – HRAPIE project: New emerging risks to health from air pollution – results from a survey of experts.** WHO Regional Office for Europe, Copenhagen.](#)

This document presents the results of a survey of experts developed and conducted as part of the WHO "Health risks of air pollution in Europe – HRAPIE" project. The survey's objective was to assess and document the views of expert stakeholders regarding "evidence of new emerging issues on risks to health from air pollution, either related to specific source categories, specific gaseous pollutants or specific components of particulate matter. The main findings are that the majority of respondents identified "road traffic", "space heating and air conditioning" and "shipping" as the top emission sources and felt that fine and ultrafine particles are the greatest concern in relation to health effects.

[Perez L, Declercq C, Iniguez C, Aguilera I, Badaloni C. \(2013\) **Chronic burden of near-roadway traffic pollution in 10 European cities \(APHEKOM network\).** Eur Respir Journal; 42\(3\): 594-605.](#)

Recent epidemiological research suggests that near road traffic-related pollution may cause chronic disease, as well as exacerbation of related pathologies, implying that the entire "chronic disease progression" should be attributed to air pollution, no matter what the proximate cause was. The researchers estimated the burden of childhood asthma attributable to air pollution in 10 European cities by calculating the number of cases of 1) asthma caused by near road traffic-related pollution, and 2) acute asthma events related to urban air pollution levels. They then expanded their approach to include coronary heart diseases in adults.

Air pollution and respiratory disease

Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Loft S, Sørensen M, Tjønneland A, Overvad K, Raaschou-Nielsen, O. (2011) [Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study.](#) Am J Respir Crit Care Med; 183 (4): 455-61.

Short-term exposure to air pollution has been associated with exacerbation of chronic obstructive pulmonary disease (COPD), whereas the role of long-term exposures on the development of COPD is not yet fully understood. The authors assessed the effect of exposure to traffic-related air pollution over 35 years on the incidence of COPD in a prospective cohort study. They found that long-term exposure to traffic-related air pollution may contribute to the development of COPD with possibly enhanced susceptibility in people with diabetes and asthma.

[Guarnieri M, Balmes JR. \(2014\) **Outdoor air pollution and asthma.** The Lancet; 383 \(9928\): 1581-92.](#)

In this Series paper, the authors discuss the effects of particulate matter (PM), gaseous pollutants (ozone, nitrogen dioxide, and sulphur dioxide), and mixed traffic-related air pollution. They focus on clinical studies, both epidemiological and experimental, published in the previous 5 years.

[Kelly FJ, Fussell JC. \(2011\) Air pollution and airway disease. Clin Exp Allergy; 41 \(8\): 1059-71](#)

Epidemiological and toxicological research continues to support a link between urban air pollution and an increased incidence and/or severity of airway disease. Not only do we have strong epidemiological evidence of a relationship between air pollution and exacerbation of asthma and respiratory morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD), but recent studies, particularly in urban areas, have suggested a role for pollutants in the development of both asthma and COPD.

[Strak M, Janssen NA, Godri KJ, Gosens I, Mudway IS, Cassee FR, Lebret E, Kelly FJ, Harrison RM, Brunekreef B, Steenhof M, Hoek G. \(2012\) Respiratory health effects of airborne particulate matter: the role of particle size, composition, and oxidative potential0 the RAPTES project. Environmental Health Perspectives, 120\(8\): 1183-9.](#)

Specific characteristics of particulate matter (PM) responsible for associations with respiratory health observed in epidemiological studies are not well established. High correlations among, and differential measurement errors of, individual components contribute to this uncertainty. The authors investigated which characteristics of PM have the most consistent associations with acute changes in respiratory function in healthy volunteers.

By age-groups

Child

[Altug H, Gaga EO, Dogeroglu T, Ozden O, Ornektekin S, Brunekreef B, Meliefste, K., Hoek, G., Van Doorn, W. \(2013\) Effects of air pollution on lung function and symptoms of asthma, rhinitis and eczema in primary school children. Environ Sci Pollut Res Int; 20 \(9\): 6455-67.](#)

Health effects of ambient air pollution were studied in three groups of schoolchildren living in areas (suburban, urban and urban-traffic) with different air pollution levels in Eskişehir, Turkey. Significant association between ambient ozone concentrations and impaired lung function (for an increase of 10 µg m⁻³) was found only for girls for the summer season evaluation [OR = 1.11 (95 % CI 1.03-1.19)]. No association was found for boys and for the winter season evaluation.

[Brown, MS., Sarnat, SE., DeMuth, KA., Brown, LA., Whitlock, DR., Brown, SW., Tolbert, PE., Fitzpatrick, AM. \(2012\) Residential proximity to a major roadway is associated with features of asthma control in children. PLoS One; 7\(5\).](#)

The authors determined the spatial relationship between the distance from a major roadway and clinical, physiologic and inflammatory features of asthma in a highly characterized sample of asthmatic children 6-17 years of age across a wide range of severities. They hypothesized that a closer residential proximity to a major roadway would be associated with increased respiratory symptoms, altered pulmonary function and a greater magnitude of airway and systemic inflammation. Asthmatic children living in closer proximity to a major roadway had an increased frequency of wheezing associated with increased medication requirements and more hospitalizations even after controlling for potential confounders.

[Buonanno, G., Marks, G.B., Morawska, L. \(2013\) Health effects of daily airbourne particle dose in children: Direct associations between personal dose and respiratory health effects. Environmental Pollution; 180: 246-250.](#)

Air pollution is a widespread health problem associated with respiratory symptoms. Continuous exposure monitoring was performed to estimate alveolar and tracheobronchial dose, measured as deposited surface area, for 103 children and to evaluate the long-term effects of exposure to airborne particles through spirometry, skin prick tests and measurement of exhaled nitric oxide (eNO). The mean daily alveolar deposited surface area dose received by children was $1.35 \times 10^3 \text{ mm}^2$. The lowest and highest particle number concentrations were found during sleeping and eating time. A significant negative association was found between changes in pulmonary function tests and individual dose estimates. Significant differences were found for asthmatics, children with allergic rhinitis and sensitive to allergens compared to healthy subjects for eNO. Variation in a child's activity over time appeared to have a strong impact on respiratory outcomes, which indicates that personal monitoring is vital for assessing the expected health effects of exposure to particles.

[Ghosh R, Joad J, Benes I, Dostal M, Radim J. \(2012\) Ambient nitrogen oxides exposure and early childhood respiratory illnesses. Environmental International. 39\(1\): 96-102.](#)

Acute respiratory infections are common in children below 5 years and recent studies suggest a possible link with air pollution. In this study, this study investigated the association between ambient nitrogen oxides (NO_x) and bronchitis or upper airway inflammation. The results demonstrate an association between NO_x and respiratory infections that are sufficiently severe to come to medical attention. The evidence, if causal, can be of public health concern because acute respiratory illnesses are common in preschool children.

[Gul H, Gaga EO, Dogeroglu T, Ozden O, Ayyaz O, Ozel S, Gungor G. \(2011\) Respiratory health symptoms among students exposed to different levels of air pollution in a Turkish City. Int J Environ Res Public Health; 8\(4\): 1110-1125.](#)

In this study the authors aimed to investigate the frequency of respiratory health symptoms among high school students attending schools at industrial, urban and rural areas in a Turkish city. Chronic pulmonary disease, tightness in the chest and morning cough were higher among students in the industrial zone where nitrogen dioxide and ozone levels were also highest.

[Orazio F, Nespoli L, Ito K, Tassinari D, Giardina D et al. \(2009\) Air pollution, aeroallergens, and emergency room visits for acute respiratory diseases and gastroenteric disorders among young children in six Italian cities. Environ Health Perspect; 117 \(11\): 1780-5](#)

Few studies have examined associations between air pollution and emergency room (ER) visits for wheezing, and even fewer for gastroenteric illness. These researchers conducted a multicity analysis of the relationship between air pollution and ER visits for wheezing and gastroenteric disorder in children 0-2 years of age. CO and SO₂ were most strongly associated with wheezing, with a 2.7% increase [95% confidence interval (CI), 0.5-4.9] for a 1.04-microg/m³ increase in 7-day average CO and a 3.4% (95% CI, 1.5-5.3) increase for an 8.0-microg/m³ increase in SO₂. Air pollution is associated with triggering of wheezing and gastroenteric disorders in children 0-2 years of age.

Adult

[Lindgren A, Bjork J, Stroh E, Jakobsson K. \(2010\) **Adult asthma and traffic exposure at residential address, workplace address, and self-reported daily time outdoor in traffic. A two-stage case-control study.** BMC Public Health, 10 \(716\)](#)

Most epidemiologic studies use traffic at residential address as a surrogate for total traffic exposure when investigating effects of traffic on respiratory health. This study used GIS (Geographical Information Systems) to estimate traffic exposure, not only on residential, but also on workplace address, in addition to survey questions on time spent in traffic during commuting or other daily activities. The aim was to investigate 1) if there is an association between traffic exposure and prevalence of adult asthma and asthma symptoms, and 2) if so, does this association become stronger using more complete traffic exposure information.

[McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E et al.\(2007\) **Respiratory effects of exposure to diesel traffic in persons with asthma.** NEJM; 357: 2348-58.](#)

Air pollution from road traffic is a serious health hazard, and people with preexisting respiratory disease may be at increased risk. The authors investigated the effects of short-term exposure to diesel traffic in people with asthma in an urban, roadside environment. 60 adults with either mild or moderate asthma participated in a randomized, crossover study. Each participant walked for 2 hours along a London street (Oxford Street) and, on a separate occasion, through a nearby park (Hyde Park). The authors performed detailed real-time exposure, physiological, and immunologic measurements. Our observations serve as a demonstration and explanation of the epidemiologic evidence that associates the degree of traffic exposure with lung function in asthma.

[Migliaretti G, Dalmaso P, Gregori D. \(2007\) **Air pollution effects on the respiratory health of the resident adult population in Turin, Italy.** Int J Environ Health Res; 17 \(5\): 369-79.](#)

A case-control study was employed to investigate the relationship between atmospheric pollution and emergency hospital attendance for respiratory causes among adult and elderly patients resident in Turin in the period 1997 – 1999. A significant association was found between the increase in emergency hospital attendance for respiratory causes and exposure to sulfur dioxide, total suspended particulate and carbon monoxide in Turin during the study period. This easy to use and manage case-control study produced results in line with those reported for other Italian and European cities.

[Nomeo, A., Tiwart, A., Farrow, E. \(2011\) **Estimation of age-related vulnerability to air pollution: assessment of respiratory health at local scale.** Environ Int; 37 \(5\): 829-37.](#)

This paper demonstrates association of short-term variation in pollution and health outcomes within the same geographical area for a typical urban setting in the northern part of the UK from time series analysis. It utilises publicly available datasets for regulated air pollutants (PM₁₀, NO₂, SO₂, CO and O₃), meteorology and respiratory hospital admissions (and mortality) between April 2002 and December 2005 to estimate the respiratory health effect of pollution exposure, mainly in the elderly. The results show that PM₁₀ and O₃ are positively associated with respiratory hospital admissions in the elderly, specifically in the age group 70-79.

Air pollution and cardiovascular disease

[Brugge D, Durant JL, Rioux C. \(2007\) **Near-highway pollutants in motor vehicle exhaust: A review of epidemiologic evidence of cardiac and pulmonary health risks.** Environmental Health; 6\(23\).](#)

There is growing evidence of a distinct set of freshly-emitted air pollutants downwind from major highways, motorways and freeways that include elevated levels of ultrafine particulates (UFP), black carbon (BC), oxides of nitrogen (NO_x), and carbon monoxide (CO). The paper reviewed studies that described measurement of near-highway air pollutants, and epidemiologic studies of cardiac and pulmonary outcomes as they relate to exposure to these pollutants and/or proximity to highways. The authors concluded that those most susceptible to serious health effects from air pollution may be those who live very near major regional transportation routes.

[Cesaroni G, Forastiere F, Stafoggia M, Anderson ZJ, Bafaloni C. et al.\(2014\) **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; 348.](#)

The aim of this paper was to study the effect of long term exposure to airborne pollutants on the incidence of acute coronary events in 11 cohorts participating in the European Study of Cohorts for Air Pollution Effects (ESCAPE). Modelled concentrations of particulate matter <2.5 µm (PM_{2.5}), 2.5-10 µm (PM_{coarse}), and <10 µm (PM₁₀) in aerodynamic diameter, soot (PM_{2.5} absorbance), nitrogen oxides, and traffic exposure at the home address based on measurements of air pollution conducted in 2008-12. The authors concluded that long term exposure to particulate matter is associated with incidence of coronary events, and this association persists at levels of exposure below the current European limit values.

[Chang, CC., Kuo, CC., Liou, SH., Yang, CY. \(2013\) **Fine particulate air pollution and hospital admissions for myocardial infarction in a subtropical city. Taipei, Taiwan.** J Toxicol Environ Health; 76 \(7\): 440-8.](#)

This study was undertaken to determine whether there was a correlation between fine particles (PM_{2.5}) levels and hospital admissions for myocardial infarction (MI) in Taipei, Taiwan. Hospital admissions for MI and ambient air pollution data for Taipei were obtained for the period 2006-2010. For the single-pollutant model (without adjustment for other pollutants), increased numbers of MI admissions were significantly associated with higher PM_{2.5} levels both on warm days (>23°C) and on cool days (<23°C).

[Mustafic, H., Jabre, P., Caussin, C., Murad, MH., Escolano, S., Tafflet, M et al. \(2012\) **Main air pollutant and myocardial infarction: a systematic review and meta-analysis.** JAMA; 307 \(7\).](#)

The objective of this study was to assess and quantify the association between short-term exposure to major air pollutants (ozone, carbon monoxide, nitrogen dioxide, sulfur dioxide, and particulate matter ≤10 µm [PM₁₀] and ≤2.5 µm [PM_{2.5}] in diameter) on MI risk. All the main air pollutants, with the exception of ozone, were significantly associated with an increase in MI risk.

[Nawrot, TS., Perez, L., Kunzli, N., Munters, E., Nemery, B. \(2011\) **Public health importance of triggers of myocardial infarction: a comparative risk assessment.** The Lancet; 377 \(9767\): 732-40.](#)

The researchers compared triggers of myocardial infarction at an individual and population level. In view of both the magnitude of the risk and the prevalence in the population, air pollution is an important trigger of myocardial infarction, it is of similar magnitude (PAF 5—7%) as other well accepted triggers such as physical exertion, alcohol, and coffee. The work shows that ever-present small risks might have considerable public health relevance.

[Nichols, JL., Owens, EO., Dutton, SJ., Luben, TJ. \(2013\) **Systematic review of the effects of black carbon on cardiovascular disease among individuals with pre-existing disease.** Int J Public Health; 58 \(5\): 707-24.](#)

Recent interest has developed in understanding the health effects attributable to different components of particulate matter. This review evaluates the effects of black carbon (BC) on cardiovascular disease in individuals with pre-existing disease using evidence from epidemiologic and experimental studies. Evidence across studies suggested ambient BC is associated with changes in subclinical cardiovascular health effects in individuals with diabetes and coronary artery disease (CAD). Limited evidence demonstrated that chronic respiratory disease does not modify the effect of BC on cardiovascular health.

[Nuvolone, D., Balzi, D., Chini, M., Scala, D., Giovannini, F., Barchielli, A. \(2011\) **Short-term association between ambient air pollution and risk of hospitalization for acute myocardial infarction: results of the cardiovascular risk and air pollution in Tuscany \(RISCAT\) study.** Am J Epidemiol; 174 \(1\): 63-71.](#)

Air pollutant levels have been widely associated with increased hospitalizations and mortality from cardiovascular disease. In this study, the authors focused on pollutant levels and triggering of acute myocardial infarction (AMI). Data on AMI hospitalizations, air quality, and meteorologic conditions were collected in 6 urban areas of Tuscany (central Italy) during 2002-2005. More susceptible subgroups were elderly persons (age ≥ 75 years), females, and older patients with hypertension and chronic obstructive pulmonary disease.

[Rosenlund M, Bellander T, Nordquist T, Alfredsson L. \(2009\) **Traffic-generated air pollution and myocardial infarction.** Epidemiology; 20\(2\): 265-71.](#)

The aim of this study was to investigate the association between long-term residential exposure to air pollution from traffic and the risk of nonfatal and fatal myocardial infarction. Long-term exposure to traffic-generated air pollution is associated with fatal myocardial infarction but not with nonfatal infarction.

[Teng TK, Williams TA, Bremner A, Tohira H, Franklin P et al. \(2014\) **A systematic review of air pollution and incidence of out-of-hospital cardiac arrest \(OHCA\).** J Epidemiol Community Health; 68: 37-43](#)

The aim of this paper was to examine the association of air pollution with the occurrence of OHCA. Larger studies suggested that an increased risk of OHCA with air pollution exposure from PM_{2.5} and ozone.

Air pollution and mortality

[Anderson HR, Atkinson RW, Bremner SA, Carrington J, Peacock J. \(2007\) **Quantitative systematic review of short term associations between ambient air pollution \(particulate matter, ozone, nitrogen dioxide, sulphur dioxide and carbon monoxide\), and mortality and morbidity.** University of London, London.](#)

All peer-reviewed papers with quantitative results from time series and panel studies of ambient air pollution published up to 2006 were obtained. Estimates of effects were extracted and standardized for meta-analysis. Meta-analyses were done for all pollutant/outcome/diagnosis/age groups for which there were 4 or more estimates. While the evidence was fairly similar for the various pollutants, there were some variations in the level of evidence between them and between various outcomes. Overall, we consider that our results largely support the position that ambient air pollution is a hazard to health. However, the inconsistencies and difficulties in interpreting the evidence must also be acknowledged.

[Committee on the Medical Effects of Air Pollutants \(2009\) **Long-term exposure to air pollution: effect on mortality.** Health Protection Agency, London.](#)

The Committee on the Medical Effects of Air Pollutants (COMEAP) produced in 2001 a report on the long-term effects of particulate air pollution on mortality. Research in this field has progressed rapidly since then and COMEAP present in this report a summary of the new evidence and quantitative estimates of the impact of the long-term effects of particulate pollution on mortality. Long term exposure to sulphur dioxide, nitrogen dioxide, carbon monoxide and ozone on mortality is thought to be weaker than that regarding particles.

[Dockery DW, Rich DQ, Goodman PG, Clancy L, Ohman-Strickland P et al. \(2013\) **Effect of air pollution control on mortality and hospital admissions in Ireland.** Research Report \(Health Effects Institute\); 176.](#)

During the 1980s the Republic of Ireland experienced repeated severe pollution episodes. This study explores and compares the effectiveness of sequential 1990, 1995 and 1998 bans in reducing community air pollution and improving public health. The bans were associated with reductions in respiratory mortality but no detectable improvement in cardiovascular mortality. The changes in hospital admissions for respiratory and cardiovascular disease were supportive of these findings but cannot be considered confirming.

[Forastiere F, Stafoggia M, Tasco C, Picciotto S, Agabiti N, Cesaroni G, Perucci, CA. \(2007\) **Socioeconomic status, particulate air pollution, and daily mortality: differential exposure or differential susceptibility.** American Journal of Industrial Medicine 50\(3\): 208-16.](#)

Short-term increases in particulate air pollution are linked with increased daily mortality and morbidity. Socioeconomic status (SES) is a determinant of overall health. This paper investigated whether social class is an effect modifier of the PM(10) (particulate matter with diameter <10 micron)-daily mortality association, and possible mechanisms for this effect modification. The results confirm previous suggestions of a stronger effect of particulate air pollution among people in low social class. Given the uneven geographical distributions of social deprivation and traffic emissions in Rome, the most likely explanation is a differential burden of chronic health conditions conferring a greater susceptibility to less advantaged people.

[Jimenez E, Linares C, Martinez D, Diaz J. \(2011\) **Particulate air pollution and short-term mortality due to specific causes among the elderly in Madrid \(Spain\): seasonal differences.** Int J Environ Health Res; 21\(5\): 372-90.](#)

A time-series study was conducted to ascertain the short-term effects of different-sized airborne particulate matter (PM) on daily respiratory and cardiovascular cause-specific mortality in winter and summer, among subjects aged over 75 years in Madrid. The results indicated an association between coarser PM fractions (PM10 and PM10-2.5) and respiratory-specific mortality on the one hand, and between PM2.5 and cardiovascular-specific mortality on the other. While the risk of mortality due to exposure to particulate matter was greater in summer than in winter, this difference was statistically significant solely for total organic-cause mortality.

Further reading

[Department for Environment, Food & Rural Affairs \(2014\) **Air quality statistics in the UK, 1987 to 2013.** Department for Environment, Food & Rural Affairs, London.](#)

This statistical release covers annual average concentrations in the UK of two pollutants thought to have the greatest health impacts: particulate matter and ozone. The statistical release also covers the number of days when air pollution was 'moderate or higher'. The indicator is intended to provide a summary measure of air pollutants that affect health.

Department for Environment, Food & Rural Affairs (2007) **The Air Quality Strategy for England, Scotland, Wales and Northern Ireland: Volume 1& 2.** Department for Environment, Food and Rural Affairs, London.

These documents provides an overview and outline of the UK Government and devolved administrations' ambient (outdoor) air quality policy. It sets out a way forward for work and planning on air quality issues, details objectives to be achieved, and proposes measures to be considered further to help reach them. The strategy is based on a thorough and detailed analysis of estimating reductions in emissions and concentrations from existing policies and proposed new policy measures, and quantification and valuation of benefits and estimated costs (the analysis is set out in more detail in Volume 2 of the strategy and the updated Third Report by the Interdepartmental Group on Costs and Benefits (IGCB). [Volume 1](#) [Volume 2](#)

[Le ND, Sun L, Zidek JV. \(2010\) **Air pollution.** Chronic Diseases in Canada. 29\(Supp 2\): 144-63.](#)

Literature review of research on air pollution and health impacts. The paper discusses strengths and limitations of previous research.

[European Public Health Association \(2011\) **Report 2011-1 Environment and Health.** EUPHA, The Netherlands](#)

For several decades, environmental changes have impacted the health of Europeans. Over the last two decades, the environment has become increasingly more complex. Today, the links between health and environment have never been so evident and the time to act is here and now. In this report the European Public Health Association highlight what has been done so far and who has been active at European level in the field of environment and health. At the end of the report, we formulate some conclusions in our strategic four pillars.

[Public Health England \(2014\) **Air pollution in London in the last 2 years to April 2014.** Public Health England, London.](#)

Air pollution EIRs: air quality and air pollution in London in the last 2 years to April 2014, including copies of minutes of Secretary of State's meetings with the Mayor of London and copies of correspondence between them.

[Schweizer C, Racioppi F, Nemer L. \(2014\) **Developing national action plans on transport, health and environment: A step-by-step manual for policy-makers and planners.** World Health Organization Regional Office for Europe, Denmark.](#)

A national transport, health and environment action plan (NTHEAP) is a key tool and mechanism for developing sustainable and healthy transport in a country. NTHEAPs provide a comprehensive and intersectoral way of planning and implementing transport, environment and health action at the national level. This manual was developed to guide NTHEAP development at the country level. It proposes four phases: planning, development, implementation and evaluation.