Combustion-derived air pollution and cardiovascular disease

Air pollution is a modifiable risk factor for cardiovascular disease that affects the entire population and is thus a major public health concern. It is important to understand how air pollution increases cardiovascular risk to develop strategies to protect susceptible individuals and reduce the effect of air pollution on cardiovascular health.

Specific historical events initially highlighted the detrimental health effects of air pollution. During the London fog episode of December 1952, between 3500 and 4000 excess deaths from respiratory and cardiovascular causes were attributed to air pollution (UK Ministry of Health, 1954). Since these early observations, a series of major epidemiological and observational studies have consistently demonstrated the adverse effects of air pollution on health (Dockery et al, 1993; Pope et al, 1995; Hoek et al, 2002; Miller et al, 2007; Langrish et al, 2009).

The World Health Organization (2006) estimates that urban air pollution contributes to 5% of all cardiopulmonary deaths which translates into around 100 000 premature deaths in Europe and 1.3 million deaths worldwide each year. Low and middle-income countries disproportionately experience this burden because air pollution levels are on the increase as a result of the industrialization and urbanization accompanying their rapidly developing economies. However, the association between air pollution and mortality still persists even below current national and international standards, and remains a major problem even in high-income countries (Miller et al, 2007).

This review focuses on the clinical effects of combustion-derived air pollution which is widely regarded as the main mediator of adverse cardiovascular effects of air pollution. In addition, it identifies those persons and patient groups most susceptible to the effects of air pollution.

What is combustion-derived air pollution?

Air pollution is a heterogenous and dynamically changing mixture of gases and particulate matter that makes it difficult to study any individual component in isolation. Over 98% of combustion-derived pollutant mass is from gases or vapour phase compounds such as carbon monoxide, volatile organic carbons, the nitrogen oxides and sulphur dioxide. However, particulate matter is the most strongly associated with adverse health effects. Particulate matter is categorized, monitored and regulated on the basis of its aerodynamic diameter. Particles with a diameter of less than 10 μm can be inhaled deep into the lungs and are quantified by mass as PM_{10}. Smaller particles of less than 2.5 μm diameter are referred to as $PM_{2.5}$ or fine particulate matter, while particles of less than 0.1 μm diameter are ultrafine, nanoparticles or $PM_{0.1}$.

Current World Health Organization (2006) air quality guideline targets for annual mean exposure of $PM_{2.5}$ and PM_{10} are 10 and 20 μg/m^3 respectively. Typical background concentrations of PM_{10} in North America and Western Europe are between 20 and 50 μg/m^3 while in industrialized areas and in the developing world are between 100 and 250 μg/m^3. *Tables 1* and *2* show the mean levels of air pollution, in the form of PM_{10}, in the UK and in a selection of cities worldwide. The toxicity of particulate matter relates to the number of particles encountered, together with size, surface area and chemical composition.

The major source of particulate matter throughout the world is human combustion of fossil fuels among which traffic-derived particulate matter appears to be most dan-

Table 1. Particulate matter air pollution concentrations in the UK (hourly measured PM_{10} (μg/m^3)*)

	Mean	Max
London	49	317
Birmingham	30	285
Glasgow	34	664
Liverpool	19	121
Manchester	23	176
Edinburgh	15	85
Newcastle	16	69
Nottingham	21	174

From MacCarthy et al (2008). * World Health Organization recommended levels of PM_{10} (PM_{10} = articulate matter with a diameter less than 10 μm)= 50 μg/m^3

Dr Amanda L Hunter *is Clinical Research Fellow and Specialty Registrar in Cardiology,* **Dr Nicholas L Mills** *is British Heart Foundation Intermediate Clinical Research Fellow and Consultant Cardiologist and* **Professor David E Newby** *is British Heart Foundation John Wheatley Professor of Cardiology and Consultant Cardiologist in the British Heart Foundation/University of Edinburgh Centre for Cardiovascular Science, The University of Edinburgh, Edinburgh EH16 4SU*

Correspondence to: Dr AL Hunter (amanda.hunter@ed.ac.uk)

gerous (Hoek et al, 2002). Combustion-derived particulate matter carries soluble organic compounds, polycyclic aromatic hydrocarbons and oxidized transition metals on their surface. While $PM_{2.5}$ is most consistently associated with cardiovascular morbidity and mortality, there is some epidemiological evidence that $PM_{0.1}$ may be associated with an even higher cardiovascular risk but studies remain challenging to conduct because there are few regional monitoring sites and personal exposure may be very different to monitored exposure as a result of spatial heterogeneity. Moreover, the toxicity of any single pollutant is not homogenous.

A novel cardiovascular risk factor

Air pollution is increasingly being recognized as an important and modifiable risk factor for cardiovascular disease. Owing to the pervasive nature of air pollution, millions of susceptible individuals are unknowingly at greater cardiovascular risk: hence its rightful position as a major public health concern. Indeed, Nawrot et al (2011) evaluated potential triggers of myocardial infarction revealing that both exposure to traffic and to a 30 $\mu g/m^3$ change in PM_{10} had the greatest population effect in triggering cardiovascular events.

In addition to the effects of air pollution as an independent cardiovascular risk factor, it also appears to adversely effect other traditional risk factors. Brook et al (2008) demonstrated a relationship between long-term traffic exposure and the odds of having a diagnosis of diabetes mellitus, while Zanobetti et al (2004) reported acute increases in systolic blood pressure in relation to higher daily ambient particulate matter concentrations.

Effects of combustion-derived air pollution

The public health burden of air pollution is sizable. Combustion-derived air pollution and more specifically traffic-derived air pollution has been implicated in acute cardiovascular events such as myocardial infarction, arrhythmia, heart failure, the hospitalization for these events and cardiovascular death. Compelling evidence from a large cohort of 65 893 post-menopausal women living in metropolitan areas of the USA reported that an increase of 10 $\mu g/m^3$ in $PM_{2.5}$ was associated with a 24% increase in the risk of a cardiovascular event and 76% increase in risk of cardiovascular death (Miller et al, 2007).

There are two widely accepted hypotheses as to how particulate matter air pollution may increase cardiovascular risk. The original hypothesis proposed that inhaled particles provoke an inflammatory response in the lungs, with consequent release of pro-inflammatory cytokines into the circulation (Seaton et al, 1995). Alternatively inhaled, insoluble ultrafine particulate matter or nanoparticles could rapidly translocate to the circulation via the alveolar–blood barrier and interact directly with the vascular endothelium or atherosclerotic plaques, causing local oxidative stress and pro-inflammatory effects similar to those seen in the lungs (*Figure 1*). Experimental studies in man and animal models demonstrate direct translocation of a small fraction of ultrafine particles from the alveoli into the circulatory system (Oberdorster et al, 2005). Langrish et al (2011) demonstrated the translocation of inhaled nanoparticles of gold, a model particle chosen with a distinct signal that could be tracked into blood and urine, following inhalation in healthy male volunteers.

Myocardial infarction

In a large observational study, Peters et al (2004) reported that exposure to traffic while travelling in cars, buses and riding on bicycles or motorcycles was strongly associated with onset of a myocardial infarction within the following hour. Overall, there have been mixed results from studies looking at short-term exposure to air pollution and myocardial infarction, which likely reflects the discrepancy between exposure levels monitored regionally

Table 2. Particulate matter air pollution concentrations in residential areas worldwide (annual PM_{10} ($\mu g/m^3$)*)

Continent	Most populated cities†	Mean
Europe	Paris, France	12
	Istanbul, Turkey	62
	Moscow, Russian Federation	27
	London, UK	23
Africa	Lagos, Nigeria	65
	Cairo, Egypt	178
	Alexandria, Egypt	163
	Casablanca, Morocco	30
North America	New York, New York	23
	Los Angeles, California	38
	Chicago, Illinois	27
	Washington DC	21
South America	Mexico City, Mexico	69
	Buenos Aires, Argentina	107
	Sao Paolo, Brazil	46
	Lima, Peru	74
Asia	Mumbai, India	79
	Calcutta, India	153
	Tokyo, Japan	43
	Karachi, Pakistan	220
Australia	Sydney	22
	Melbourne	14
	Brisbane	19
	Perth	14

From Pandey et al (2006) * World Health Organization recommended levels of PM_{10} (PM_{10} = articulate matter with a diameter less than 10 μm) = 50 $\mu g/m^3$. † Four most populated cities per continent (in descending order).

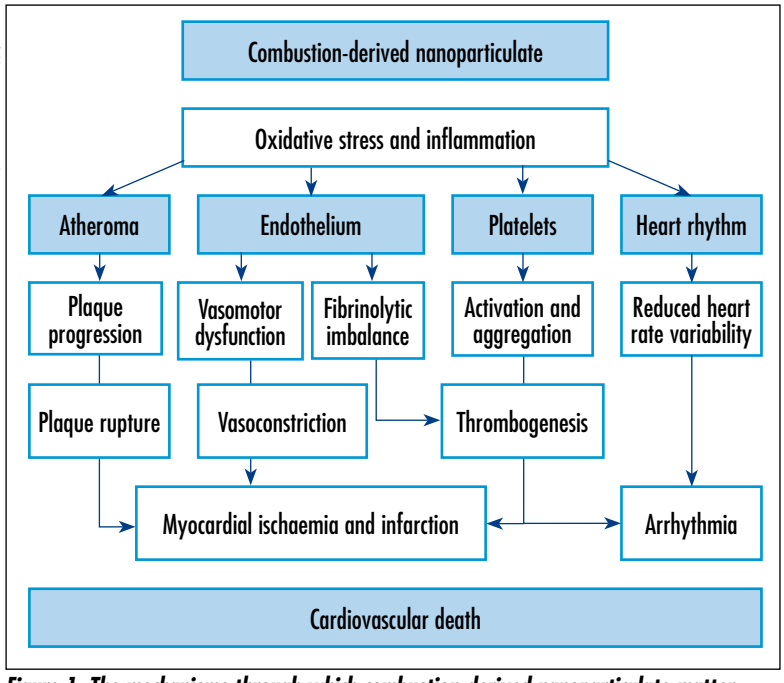

Figure 1. The mechanisms through which combustion-derived nanoparticulate matter causes acute and chronic cardiovascular disease. From Mills et al (2009).

and personal exposure. However, a recently published meta-analysis of 34 studies investigating the relationship between short-term exposure (up to 7 days) to one or more air pollutants and subsequent risk of myocardial infarction reported a significant increase in myocardial infarction with combustion-related air pollutants such as carbon monoxide, nitrogen dioxide, $PM_{2.5}$ and PM_{10} (Mustafic et al, 2012).

Myocardial infarction, secondary to short-term exposure to air pollution, is likely to be mediated in the acute phase by an impairment of vascular function. Diesel exhaust, a major source of combustion-derived air pollution, has been extensively studied in both animal and controlled human exposure studies. When exposed to dilute diesel exhaust (PM_{10} concentration 300 $\mu g/m^3$), healthy volunteers demonstrated an early impairment of vascular vasomotor and fibrinolytic function that persisted for up to 24 hours (Mills et al, 2005; Tornqvist et al, 2007). In addition to vascular dysfunction, ex-vivo thrombus formation was increased within 2 hours of dilute diesel exhaust exposure and associated with platelet activation (Lucking et al, 2008)

Long-term exposure to ambient air pollution increases the risk of death from acute myocardial infarction (Brook et al, 2010). Overall, the evidence of ischaemic heart disease events in response to long-term air pollution exposure is more robust, supporting accelerated atherosclerosis as a potential mechanism. Moreover, air pollution exposure is linked more strongly to fatal, out-of-hospital events than non-fatal events (Rosenlund et al, 2006; Miller et al, 2007). In light of this, it may be that air pollution may affect the severity of response to a predetermined cardiovascular event rather than actually initiating it (Rosenlund et al, 2009). It has been postulated, therefore, that in the short term, air pollution may trigger ventricular arrhythmias or promote more extensive myocardial ischaemia.

Long-term air pollution exposure causes accelerated atherosclerosis in animal (Suwa et al, 2002) and human studies. Kunzli et al (2005) observed a 4% increase in carotid intima media thickness for every 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration. Furthermore, living in close proximity to a major urban road was associated with a 60% higher coronary calcium score (Hoffmann et al, 2007). These changes are likely to be mediated by long-term, low-grade inflammation and indeed increases in systemic markers of inflammation have been reported following exposure to air pollution (Woods et al, 2000; Brook et al, 2010). Factors involved in inflammation and infection are widely regarded as pro-atherogenic and, additionally, increased inflammation could destabilize coronary plaques resulting in rupture, thrombosis and acute coronary syndrome (Ross, 1999).

Arrhythmias

Arrhythmias may precipitate hospitalization and death from cardiovascular events. Implantable cardioverter defibrillators offer the ideal opportunity to study the effect of air pollution on cardiac rhythm with continuous monitoring of the heart rate. Peters et al (2000) estimated exposures to fine particulate matter and other traffic-derived air pollutants, and reported an association between increased exposure and tachyarrhythmias among 100 patients with these devices. However, many of the studies reporting a pro-arrhythmic effect of air pollution have included small numbers of participants and in a larger analysis with extended follow-up, the risk of ventricular arrhythmia was limited to a subgroup of patients with frequent arrhythmias (Dockery et al, 2005).

The autonomic nervous system is likely to play a key role in the development of arrhythmia. Some postulate that dysfunction of the autonomic nervous system is mediated via a reflex from irritant receptors in the lungs directly influencing heart rate and rhythm (Schulz et al, 2005). Following inhalation of fine and ultrafine particulate matter, acute changes have been reported in heart rate variability. Secondarily, arrhythmia may well be precipitated by myocardial ischaemia and more work is required in this area to confirm the pro-arrhythmic effect of air pollution.

Heart failure

Hospitalization with acute heart failure has been associated with short-term increases in particulate matter (Brook et al, 2010). Additionally, exposure to traffic-related air pollution is associated with increased mortality risk following admission with acute heart failure (Medina-Ramon et al, 2008). In an analysis of 11.5 million individuals older than 65 years, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with three times more admis-

sions for heart failure than for ischaemic heart disease (Dominici et al, 2006). Heart failure and admissions following arrhythmia occurred on the same day as the increase in $PM_{2.5}$ concentrations. The timing of these events suggests a mechanism with rapid onset such as the upregulation of the sympathetic nervous system or oxidative stress. Interestingly a reduction in $PM_{2.5}$ concentration by 10 $\mu g/m^3$ was estimated to reduce heart failure admissions by 3156 cases per year (Dominici et al, 2006).

Susceptible groups

Air pollution is omnipresent, especially traffic-derived pollutants, with a sizeable portion of the population, particularly those from a lower socioeconomic class, living close to major roads and chronically exposed to elevated concentrations (Brook et al, 2010). This in itself may explain the link between low socioeconomic status and higher risk of adverse health effects following exposure to air pollution (Brook et al, 2010). Additionally, the daily commute, whether by car or bus, brings most people closer to the source. Low levels of air pollutant exposure can have minor effects on healthy people, but seem to trigger more serious events in susceptible groups.

The elderly

The elderly have been identified as being particularly susceptible to the effects of air pollution, but it is unclear whether age independently carries an increased risk or whether this is caused by the presence of other cardiovascular risk factors that are more common in the elderly. The APHENA study, which combined and analysed data from other major air pollution studies in Europe and North America, reported the estimated effects of PM_{10} on cardiovascular mortality in the elderly (age > 75 years old) were greater than those in the overall population (Samoli et al, 2008). In this analysis a 10 $\mu g/m^3$ increase in PM_{10} concentration increased the number of cardiovascular deaths among the elderly by 1.30% (95% confidence interval=0.19–2.40%) in Canadian cities, 0.47% (95% confidence interval=0.23–0.70%) in European cities and 0.51% (95% confidence interval=0.29–0.73%) in American cities.

Pre-existing coronary artery disease

Pope et al (2006) reported that exposure to $PM_{2.5}$ increases the risk of an acute cardiovascular event within a few days of exposure principally among individuals with pre-existing coronary artery disease even if they are asymptomatic and seemingly healthy. Patients without obstructive disease on coronary angiography were not at risk of acute coronary syndrome following a transient increase in $PM_{2.5}$ concentration. This is perhaps not surprising given that most acute cardiovascular events occur among individuals with underlying vulnerable or unstable plaque and not in individuals with normal coronary arteries.

Diabetics

Zanobetti and Schwartz (2001) reported that the acute risk for cardiovascular events in patients with diabetes mellitus may be two-fold higher than for non-diabetics. It is plausible that both diabetes itself and the high incidence of concomitant cardiovascular disease may explain this relationship. Diabetes is associated with low-grade systemic inflammation providing a further link between inflammation and atherogenesis. Furthermore, exposure to particulate matter has been implicated in the development of type 2 diabetes mellitus. In a diet-induced obesity mouse model, Sun et al (2010) demonstrated a marked whole-body insulin resistance, systemic inflammation and an increase in visceral adiposity among mice exposed to $PM_{2.5}$.

Occupational groups

Occupational exposures to air pollution differ from those of the general population in both composition and concentration of air pollution, exposure frequency and duration of exposure (i.e. shift work). Occupational exposures are generally higher than ambient levels. Hence this group may be most at risk. Indeed an increase in risk of death as a result of ischaemic heart disease has been documented in particular occupational groups exposed to traffic, such as police officers who regulate traffic (Forastiere et al, 1994).

A number of studies have assessed the risk of myocardial infarction among 'at risk' occupational groups. Males employed in occupations exposed to traffic-related particles such as bus drivers, taxi drivers and long distance lorry drivers had an increased risk of myocardial infarction compared to employed men in the general population while controlling for age and other potential confounders (Gustavsson et al, 1996).

Male and female workers exposed to high levels of combustion-related particulate matter as determined from a lifetime occupational history questionnaire experienced a more than two-fold increased risk of myocardial infarction compared to unexposed individuals, while controlling for smoking and a number of other covariates, including age, diabetes and increased body mass index (Gustavsson et al, 2001). However, Bigert and colleagues (2007) assessed subway drivers exposed to underground particulate matter and found no increased risk of myocardial infarction when workers were compared to employed men in the general population or other manual workers. The authors were, however, unable to control for a number of covariates, and the particulate matter present in subways is not combustion derived but arises from ambient dust and particles released during mechanical contact such as brake blocks.

Another at-risk occupational group are fire-fighters, with an extremely high-risk of on-duty cardiovascular death (45% of all deaths on-duty). This is specifically related to certain occupational exposures with fire suppression carrying the highest risk (Kales et al, 2007). This

risk may be mediated in part by exposure to air pollution in the form of structural or forest fires although sudden physical and emotional stresses also play a role.

Potential interventions

Reducing exposure to second-hand tobacco smoke in Scotland following the implementation of a smoking ban in public places (Pell et al, 2008) and reductions in combustion-derived air pollution following the ban of bituminous coal in Dublin, Ireland (Clancy et al, 2002) both resulted in a reduction in the number of cardiac events. Indeed, life expectancy has improved since effective legislation has reduced air pollution levels in the developed world (Sun et al, 2010).

Strategies to limit the adverse cardiovascular effects of air pollution by reducing emissions are clearly critically important. However, other interventions can be applied at a more local level to limit exposure by measures aimed at filtering out the particulate matter either at the source of generation or by preventing inhalation. The merit of simple interventions, such as facemasks and fitting cars with particle traps, has been assessed. Langrish and colleagues (2009) demonstrated that blood pressure falls and heart rate variability rises if healthy individuals who wear a high efficiency particulate-filter facemask when walking around central Beijing in China. Moreover, reducing particulate matter concentrations by fitting a particle trap to the exhaust of a diesel engine prevents the adverse prothrombotic and vascular effects of diesel exhaust inhalation (Lucking et al, 2011). Together this suggests limiting the spread and inhalation of particulate matter may afford further benefits in preventing the development of cardiovascular disease.

Conclusions

Despite current strategies to improve air quality, there remains an excess of cardiovascular disease attributable to air pollution. The cardiovascular system seems to be very sensitive to fine and ultrafine particulate matter (Pope et al, 2009) and further improvements in air quality are necessary. It is conceivable that the next generation of vehicle engines and new fuel technologies along with smoking bans and simple interventions, such as filter masks, will improve cardiovascular health in our urban environment. Furthermore, identifying and targeting specific at-risk populations, in an attempt to reduce personal exposure, may help more targeted interventions prevent cardiovascular morbidity and mortality. **BJHM**

KEY POINTS

- Air pollution is an important and modifiable risk factor for cardiovascular disease, associated with increased cardiovascular morbidity and deaths from myocardial ischaemia, arrhythmia and heart failure.
- There appears to be no threshold below which the effects of air pollution on cardiovascular health are no longer seen.
- Exposure to air pollution and in particular particulate matter has the potential to impair vascular reactivity, accelerate atherogenesis and precipitate acute cardiovascular events.
- Specific sub-groups are more vulnerable to the cardiovascular effects of air pollution for example those with pre-existing heart disease, the elderly and diabetics.
- Certain occupational groups have higher exposure to air pollution than the general population and this may be implicated in the excess risk of cardiovascular events among some of these occupations, e.g. fire-fighters.

Dr AL Hunter (PG/11/27/28842), Dr NL Mills (FS/10/024) and Professor DE Newby (CH/09/002) are supported by the British Heart Foundation. Professor DE Newby holds a Programme Grant with the British Heart Foundation exploring the adverse cardiovascular effects of air pollution (RG/10/9).

Figure 1 *is reprinted from Mills et al (2009) by kind permission of Macmillan Publishers Ltd.*

Conflict of interest: none.

Bigert C, Klerdal K, Hammar N, Gustavsson P (2007) Myocardial infarction in Swedish subway drivers. *Scand J Work Environ Health* **33**(4): 267–71

Brook RD, Jerrett M, Brook JR, Bard RL, Finkelstein MM (2008) The relationship between diabetes mellitus and traffic-related air pollution. *J Occup Environ Med* **50**(1): 32–8

Brook RD, Rajagopalan S, Pope CA, 3rd et al (2010) Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* **121**(21): 2331–78

Clancy L, Goodman P, Sinclair H, Dockery DW (2002) Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *Lancet* **360**(9341): 1210–14

Dockery DW, Pope CA 3rd, Xu X et al (1993) An association between air pollution and mortality in six U.S. cities. *N Engl J Med* **329**(24): 1753–9

Dockery DW, Luttmann-Gibson H, Rich DQ et al (2005) Association of air pollution with increased incidence of ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators. *Environ Health Perspect* **113**(6): 670–4

Dominici F, Peng RD, Bell ML et al (2006) Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* **295**(10): 1127–34

Forastiere F, Perucci CA, Di Pietro A et al (1994) Mortality among urban policemen in Rome. *Am J Ind Med* **26**(6): 785–98

Gustavsson P, Alfredsson L, Brunnberg H et al (1996) Myocardial infarction among male bus, taxi, and lorry drivers in middle Sweden. *Occup Environ Med* **53**(4): 235–40

Gustavsson P, Plato N, Hallqvist J et al (2001) A population-based case-referent study of myocardial infarction and occupational exposure to motor exhaust, other combustion products, organic solvents, lead, and dynamite. Stockholm Heart Epidemiology Program (SHEEP) Study Group. *Epidemiology* **12**(2): 222–8

Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA (2002) Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet* **360**(9341): 1203–9

Hoffmann B, Moebus S, Mohlenkamp S et al (2007) Residential exposure to traffic is associated with coronary atherosclerosis. *Circulation* **116**(5): 489–96

Kales SN, Soteriades ES, Christophi CA, Christiani DC (2007) Emergency duties and deaths from heart disease among firefighters in the United States. *N Engl J Med* **356**(12): 1207–15

Kunzli N, Jerrett M, Mack WJ et al (2005) Ambient air pollution and atherosclerosis in Los Angeles. *Environ Health Perspect* **113**(2): 201–6

Langrish JP, Mills NL, Chan JK et al (2009) Beneficial cardiovascular effects of reducing exposure to particulate air pollution with a simple facemask. *Part Fibre Toxicol* **6**: 8

Langrish JP, Raftis JB, McSheaffrey S et al (2011) Inhaled gold nanoparticles translocate to the bloodstream in man. *Am J Respir*

Crit Care Med **183**: A2281
Lucking AJ, Lundback M, Mills NL et al (2008) Diesel exhaust inhalation increases thrombus formation in man. *Eur Heart J* **29**(24): 3043–51
Lucking AJ, Lundback M, Barath SL et al (2011) Particle traps prevent adverse vascular and prothrombotic effects of diesel engine exhaust inhalation in men. *Circulation* **123**(16): 1721–8
MacCarthy J, Li Y, Murrells TP (2008) Air quality pollutant inventories for England, Scotland, Wales and Northern Ireland: 1990-2008. http://uk-air.defra.gov.uk/reports/cat07/1010130853_DA_AQI_2008_main_text_Issue_1.pdf (accessed 10 March 2012)
Medina-Ramon M, Goldberg R, Melly S, Mittleman MA, Schwartz J (2008) Residential exposure to traffic-related air pollution and survival after heart failure. *Environ Health Perspect* **116**(4): 481–5
Miller KA, Siscovick DS, Sheppard L et al (2007) Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* **356**(5): 447–58
Mills NL, Tornqvist H, Robinson SD et al (2005) Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. *Circulation* **112**(25): 3930–6
Mills NL, Donaldson K, Hadoke PW et al (2009) Adverse cardiovascular effects of air pollution. *Nat Clin Pract Cardiovasc Med* **6**(1): 36–44
Mustafic H, Jabre P, Caussin C et al (2012) Main air pollutants and myocardial infarction: a systematic review and meta-analysis. *JAMA* **307**(7): 713–21
Nawrot TS, Perez L, Kunzli N, Munters E, Nemery B (2011) Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet* **377**(9767): 732–40
Oberdorster G, Oberdorster E Oberdorster J (2005) Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect* **113**(7): 823–39
Pandey KD, Wheeler D, Ostro B, Deichmann U, Hamilton K, Bolt K (2006) Ambient Particulate Matter Concentrations in Residential and Pollution Hotspot areas of World Cities: New Estimates based on the Global Model of Ambient Particulates (GMAPS), The World Bank Development Economics Research Group and the Environment Department Working Paper. The World Bank. Washington DC. (http://siteresources.worldbank.org/INTRES/Resources/AirPollutionConcentrationData2.xls accessed 10 March 2012)
Pell JP, Haw S, Cobbe S (2008) Smoke-free legislation and hospitalizations for acute coronary syndrome. *N Engl J Med* **359**(5): 482–91
Peters A, Liu E, Verrier RL et al (2000) Air pollution and incidence of cardiac arrhythmia. *Epidemiology* **11**(1): 11–17
Peters A, von Klot S, Heier M et al (2004) Exposure to traffic and the onset of myocardial infarction. *N Engl J Med* **351**(17): 1721–30
Pope CA 3rd, Thun MJ, Namboodiri MM et al (1995) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am J Respir Crit Care Med* **151**(3 Pt 1): 669–74
Pope CA 3rd, Muhlestein JB, May HT, Renlund DG, Anderson JL, Horne BD (2006) Ischemic heart disease events triggered by short term exposure to fine particulate air pollution. *Circulation* **114**(23): 2443–8
Pope CA 3rd, Burnett RT, Krewski D (2009) Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. *Circulation* **120**(11): 941–8
Rosenlund M, Berglind N, Pershagen G, Hallqvist J, Jonson T, Bellander T (2006) Long-term exposure to urban air pollution and myocardial infarction. *Epidemiology* **17**(4): 383–90
Rosenlund M, Bellander T, Nordquist T, Alfredsson L (2009) Traffic-generated air pollution and myocardial infarction. *Epidemiology* **20**(2): 265–71
Ross R (1999) Mechanisms of disease: atherosclerosis - an inflammatory disease. *N Engl J Med* **340**: 115–26
Samoli E, Peng R, Ramsay T et al (2008) Acute effects of ambient particulate matter on mortality in Europe and North America: results from the APHENA study. *Environ Health Perspect* **116**(11): 1480–6
Schulz H, Harder V, Ibald-Mulli A et al (2005) Cardiovascular effects of fine and ultrafine particles. *J Aerosol Med* **18**(1): 1–22
Seaton A, MacNee W, Donaldson K, Godden D (1995) Particulate air pollution and acute health effects. *Lancet* **345**(8943): 176–8
Sun Q, Hong X, Wold LE (2010) Cardiovascular effects of ambient particulate air pollution exposure. *Circulation* **121**(25): 2755–65
Suwa T, Hogg JC, Quinlan KB, Ohgami A, Vincent R, van Eeden SF (2002) Particulate air pollution induces progression of atherosclerosis. *J Am Coll Cardiol* **39**(6): 935–42
Tornqvist H, Mills NL, Gonzalez M et al (2007) Persistent endothelial dysfunction in humans after diesel exhaust inhalation. *Am J Respir Crit Care Med* **176**(4): 395–400
UK Ministry of Health (1954) *Mortality and morbidity during the London fog of December 1952.* In: Reports on public health and medical subjects. Ministry of Health, London
Woods A, Brull DJ, Humphries SE, Montgomery HE (2000) Genetics of inflammation and risk of coronary artery disease: the central role of interleukin-6. *Eur Heart J* **21**(19): 1574–83
World Health Organization (2006) Air Quality Guidelines: Global Update 2005. http://whqlibdoc.who.int/hq/2006/WHO_SDE_PHE_OEH_06.02_eng.pdf (accessed 10 March 2012)
Zanobetti A, Schwartz J (2001) Are diabetics more susceptible to the health effects of airborne particles? *Am J Respir Crit Care Med* **164**(5): 831–3
Zanobetti A, Canner MJ, Stone PH et al (2004) Ambient pollution and blood pressure in cardiac rehabilitation patients. *Circulation* **110**(15): 2184–9