Cardiovascular Disease and Air Pollution

A report by the Committee on the
Medical Effects of Air Pollutants

DH Department of Health

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Chairman: Professor JG Ayres

Chairman of the Sub-Group on Cardiovascular Disease and Air Pollution: Professor JG Ayres

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Foreword

Recognition that air pollution might impact on cardiovascular disease, the commonest cause of death in the UK, came as a surprise to most when first identified. Since that time, a huge amount of research has been undertaken to ensure that these initial findings were supported and to define potential mechanisms for these effects. Because of these findings, this Committee decided to undertake an extensive review of the evidence for these effects, to assess possible mechanisms and identify areas for future research. Clearly, an understanding of the size of the effect of air pollution on cardiovascular disease is very important in terms of the contribution to public health and this report will contribute to a formal quantification of the effects of air pollution currently being undertaken by the Committee.

This report required an immense amount of work over the last eighteen months, particularly from members of the Sub-Group, responsible for producing a series of drafts and responding to comments from the main Committee and from the Secretariat, who have produced a report which is state of the art in all respects. To them all, I am extremely grateful.

Cardiovascular disease is very common and, as exposure to air pollution, both in the long and short term, contributes to initiation and exacerbation of disease, it is likely that even modest reductions in exposure will result in significant health gain. We hope this report helps in assessing the importance of this area and welcome any comments that you may have.

Professor Jon Ayres
Chairman of the Committee on the Medical Effects of Air Pollutants

Acknowledgements

Contents

Executive Summary

i. The Department of Health (DH) asked the Committee on the Medical Effects of Air Pollutants (COMEAP) to advise on the possible effects of outdoor air pollutants on cardiovascular disease in the UK. The Committee formed a Sub-Group which reviewed the literature in detail and drafted this report. The report has been agreed by the Committee.

ii. The terms of reference of the Sub-Group were to:

   (a) advise on the current state of knowledge on effects of outdoor air pollutants on cardiovascular disorders;

   (b) to comment on the likelihood that the reported associations between concentrations of outdoor air pollutants and cardiovascular disorders, often represented by deaths and acute episodes of disease, represent causal associations;

   (c) to comment specifically on the evidence that associates long-term exposure to outdoor air pollutants with an increase in deaths from cardiovascular disorders and a consequent reduction in average life expectancy;

   (d) to identify gaps in knowledge and to recommend research to close these gaps.

iii. The Sub-Group agreed that as systematic an approach as possible should be taken in reviewing the available literature. In the epidemiological field, systematic review and meta-analyses formed the main approaches. In some areas, for example the literature relating occupational exposure to pollutants, a narrative review based on literature searching was undertaken because the systematic/meta-analytical approach proved not to be feasible. A narrative review of *in vitro* and *in vivo* studies, the latter involving both experimental animals and human volunteers, was also undertaken.

iv. The principal conclusions of the report are that:

   (a) Clear associations have been reported between both daily and long-term average concentrations of air pollutants and effects on the cardiovascular system, reflected by a variety of outcome measures including risk of death and of hospital admissions.

(b) It is our broad conclusion that many of these associations are likely to be causal in nature. Because of the implications for public health, a precautionary approach should be adopted in future planning. Details of our views regarding individual pollutants are provided in Chapter 4.

(c) It is not possible to be certain which components of the ambient pollution mixture are responsible for these effects but it is likely that fine particles play an important part.

v. Further details regarding the conclusions reached by the Sub-Group and agreed by the Committee are set out in the following paragraphs.

Effects of short-term exposure

vi. Evidence from epidemiological studies of the association between daily average concentrations of a number of classical air pollutants and the number of deaths occurring daily from cardiovascular causes is convincing. This conclusion is based upon the large number of studies that have yielded positive and statistically significant associations and is supported by the results of formal meta-analysis.

vii. The question of publication bias in the epidemiological data has been specifically examined and though there is some evidence of bias in favour of publication of large and statistically significant associations we do not feel that this undermines our conclusions.

viii. In terms of the strength and statistical significance of the associations referred to in iv(a) above, the evidence linking daily cardiovascular deaths with concentrations of particles (measured as PM_{10} or as Black Smoke), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), ozone (O_3) and carbon monoxide (CO) are similar.

ix. Associations between daily measurements of the pollutants mentioned above and daily admissions to hospital for a variety of diagnostic conditions or categories relating to cardiovascular disease are also generally positive and significant. The associations with cardiac endpoints are generally clearer than those with cerebrovascular incidents. There is no convincing evidence for an association between day-to-day changes in concentrations of ozone and hospital admissions for cardiovascular disorders.

x.   Though the meta-analysis has revealed variations in the strengths and statistical significance of associations between daily measures of pollutants and different diagnostic categories of admissions to hospital, no clear patterns which support either of the two major mechanistic hypotheses that have been proposed (see below) have emerged.

Effects of long-term exposure

xi.   Evidence from epidemiological studies of associations between long-term exposure to particulate air pollution ($PM_{2.5}$ and sulphate) and sulphur dioxide shows positive and statistically significant associations with a reduction in life expectancy. This was noted in the COMEAP Statement and Report on the Long Term Effects of Particles on Mortality (Department of Health, 2001). Re-analysis of these studies by the US Health Effects Institute has confirmed the initial findings and has extended them by showing that the reduction in life expectancy is due to increased deaths from cardiovascular rather than respiratory disease, a most important finding. The long-term studies have not shown convincing associations with nitrogen dioxide, ozone or carbon monoxide.

xii.   Studies of the effects of occupational exposure to relevant air pollutants have not shown an unequivocal association with either deaths from cardiovascular disorders or an increased prevalence of these disorders, though the evidence, particularly from better studies, points in that direction. The possibility that such effects could be obscured in these studies by other more important factors is noted.

Mechanisms

xiii. Two major mechanistic hypotheses have been put forward to explain the associations between particles and effects on the cardiovascular system reported above. It should be appreciated that it is likely that more than one mechanistic process may result in these effects and that it is plausible that mechanisms may act in concert – the hypotheses should not be regarded as mutually exclusive. One suggests that particles set up an inflammatory response in the interstitium of the lung and that this, in time, provokes an increase in the likelihood of the blood to clot and/or atheromatous plaques to rupture. Experimental data bearing on this and the results of epidemiological studies as have been reported are suggestive but not yet wholly consistent or convincing. An alternative hypothesis points to a reflex effect on the heart, the effect being provoked by the interaction of pollutants, or secondary factors produced by inflammation, with receptors in the airways and lung. It has been suggested that the autonomic control of the heart beat is subtly affected but, here too, though some study results are suggestive, the evidence is neither consistent nor convincing. It is noted that species differences may reduce the value of studies of this

hypothesis in animal models and that these changes may simply be physiological rather than pathophysiological.

xiv.   The above hypotheses were developed with particles in mind. There has been less work on possible mechanisms of effect for the gaseous pollutants.

General conclusions

xv.   The findings discussed in this report persuade us that daily variations in concentrations of several air pollutants and long-term average concentrations of fine particles, sulphate particles and sulphur dioxide are associated with a range of effects on the cardiovascular system. Consideration of the accepted features of causal associations leads us to think that many of the associations are likely to be causal. Furthermore, we think that the impacts on public health implied by these associations, though not as large as those arising from factors such as family history, active smoking and hypertension, are important and that a precautionary approach should be adopted in future planning and policy development.

xvi.   We see no reason to conclude that the effects described above, especially those relating to day-to-day changes in concentrations of air pollutants, are unlikely to be occurring, now, in the UK. On the contrary, though studies undertaken in the UK are few they lend support to these conclusions.

xvii.   It is clear that much remains to be discovered and explained regarding the association between exposure to air pollutants and cardiovascular disease. One aspect that is intriguing is the clear heterogeneity that exists in results obtained for some pollutants between different geographical locations. Though this is at present not well understood we feel that it offers scope for further study that may well be valuable.

xviii.   COMEAP will soon be undertaking a revision of its earlier work on quantification of the effects of air pollutants in the UK. The findings from this report support the need for further analyses of the quantitative effects of air pollutants on hospital admissions for treatment of cardiovascular diseases, of deaths from cardiovascular causes and of reductions in life expectancy. We make no recommendations as to which specific coefficients linking measures of pollutants and effects should be used for this work but draw attention to the likely value of the original meta-analytical work included in this report.

Need for further research

xix.   The discovery that exposure to levels of air pollutants has important effects on the cardiovascular system is a recent one and more research in this area is urgently needed. A number of approaches could usefully be adopted and we have outlined some ideas below under headings indicating different techniques.

Epidemiological

xx.   Further time-series studies designed to look at associations between different indices of the ambient aerosol and effects on the cardiovascular system are needed. We draw attention to the need to include indices of fine and ultrafine particles and suggest that $PM_{2.5}$, $PM_{1.0}$ and number concentration should be studied. Collaborative studies between groups working in different countries to allow examination of the comparative effects of aerosols of differing composition are recommended.

xxi.   As has already been mentioned, heterogeneity between results obtained in differing geographical locations should be pursued. It is strongly recommended that studies designed to separate the effects of different components of traffic-generated pollution should be undertaken. These could include studies in areas where there are significant contributions from sources other than vehicles.

xxii.   Confusion regarding the roles of nitrogen oxides and particles remains and this should be resolved. Work on multi-pollutant models may be a useful approach to this problem and we recommend that such work should be undertaken: we note with some concern the preponderance of single-pollutant models in the work we have reviewed. Work using oxides of nitrogen (NOx) as a better marker for traffic-generated pollutants than NO_2 is recommended.

xxiii.   There is a need for research which considers the different components of particles with relation to toxicity.

xxiv.   There is a need for research using better exposure assessment, particularly for work examining associations between personal exposure and acute effects on health.

xxv.   In addition to time-series studies, further work on the effects of long-term exposure to air pollutants with respect to possible effects on the cardiovascular system is needed in the UK. It is appreciated that such studies are inevitably costly and do not yield rapid results but the importance of such work cannot be over-emphasised. A European study would be a very powerful study as it would accommodate variations in air pollutant exposures both qualitatively and quantitatively. Work looking at

historical data on air pollution and the effect of smoke control policies on heart disease rates is also needed.

xxvi.   Epidemiological studies designed to test current and new mechanistic hypotheses are needed. We have noted inconsistencies in the findings of such studies as have been undertaken and see this as a strong reason for further work. We note that the number of epidemiological studies designed to relate measures of ultrafine particles (e.g. number and surface area concentrations) to physiological variables recorded at an individual level remains remarkably small. Liaison with research workers in the general fields of cardiovascular physiology and medicine is recommended: this is likely to be especially valuable in understanding the importance of changes in such physiological variables as heart rate variability.

xxvii.   Additionally, work on potentially susceptible subgroups in the population is needed. A focus on gene-environmental interactions would be helpful here.

xxviii.   Perhaps, most importantly, it needs to be shown whether or not short term fluctuations in 'inflammation' and in autonomic control in humans with coronary artery disease (CAD) can result in adverse coronary events/sudden death/arrhythmia. A large prospective cohort study examining markers of inflammation and of autonomic control and possibly arterial stiffness/endothelial function on a regular basis, perhaps even every week, is needed. Over a longer period of time this would tell us:

a.   whether or not the variation in these markers is associated with rises and falls in pollutant levels or whether other factors 'drown' this effect;

b.   whether or not acute events – death/MI – are preceded by changes in the markers and with what time lag.

It is appreciated that this would be a large and expensive study.

Laboratory based studies

xxix.   Work is needed both in animal models and in human volunteer subjects. Much work is underway in these fields in the United States and we recommend that a detailed appraisal of current research programmes be undertaken before launching studies in the UK. It is suggested that the Department of Health might commission such an appraisal. We note that more work has been done on particles than on gaseous pollutants with regard to the mechanistic hypotheses discussed in this report. This we see as in need of correction and work on nitrogen dioxide and on nitric oxide, a known vasoactive compound, is recommended. Work on the possible effects

of sulphur dioxide and carbon monoxide is also needed in view of the associations reported in epidemiological studies.

xxx.   Further whole animal work examining the nature of any inflammatory response to inhaled pollutants is needed. This should be in two parts. The first, a detailed examination of the response to 'whole' pollutants such as diesel exhaust and concentrated ambient particles (CAPS) at a range of concentrations. The nature of any pulmonary and systemic inflammatory response needs to be described more precisely in terms of the cytokine profile, time of onset and duration, etc. With this information one could re-look at the observational studies and concentrate on appropriate lag times. The second, an examination of the effects of administering pollutants via non-pulmonary routes, would give insight into whether the pulmonary inflammatory response is the initiator of a systemic reaction or whether the lungs are simply the portal of entry and the response is initiated in the circulation. It would be helpful if mechanistic studies used a range of pollutants within the same experimental system to aid consideration of the relative plausibility of the associations found for the different pollutants in the epidemiological studies.

xxxi.   Further work designed to discover which components are active in the pollutant mix is needed. This is easier for gases than for particles, although again, the nature and duration of any response needs to be detailed. For particles, the responses to components such as metals, salts, even bacterial cell wall components in a range of particle sizes/solubilities needs to be defined.

xxxii.   More whole animal work is required on the autonomic response to inhaled pollutants. Work to identify whether this is receptor mediated and if so, to define the identity and location of the receptors is needed.

xxxiii.   Further studies of the development of atherosclerotic plaques and the effect upon them of oxidative stress is needed.

xxxiv.   As far as possible this work requires duplication in human subjects. The animal work should point the way so that needless experimentation in humans is avoided. Similar information is needed about the inflammatory/autonomic responses and also whether or not the response to pollutants varies with the presence of atherosclerosis and/or chronic lung disease.

Chapter 1
Introduction

Background

1.1 Pollution of air as a result of man's activity has been a feature of the urban environment for centuries, probably since the introduction of fire as a means of heating and cooking. Urban air pollution increased rapidly with the use of wood and later coal for domestic heating and, later again, for industrial processes. Pollution arising from the latter was regarded for many years as a necessary or unavoidable evil, the inevitable price of provision of work for the population.

1.2 In the United Kingdom, the London smog of December 1952 proved a turning point in the history of air pollution and attempts at its control. As a result of a dense fog lasting nearly a week, when Black Smoke levels reached a daily average concentration of in excess of 4000 μg/m³ and sulphur dioxide concentrations (daily averages) reached 3000-4000 μg/m³, at least 4000 deaths occurred in excess of those expected in a two week period. All age groups were affected, although infants and the elderly were found to be most at risk. The main causes of death were respiratory and cardiac disease. Recent analyses have stressed that the effects of the smog on health persisted for longer than two weeks and that the total number of deaths may have significantly exceeded 4000. This was, in fact, noted in the original report on the effects of the 1952 smog, it being pointed out that the cut off at two weeks used in calculating the excess deaths was arbitrary (Logan, 1953).

1.3 As a direct consequence of this event the UK Clean Air Act, which aimed to control both industrial and domestic emissions, was passed in 1956. It was very effective: the mean urban Black Smoke concentration in the UK fell from more than 200 μg/m³ in the 1950s to 20 μg/m³ in 1980 (Department of the Environment, 1996). Similar legislation appeared in other countries and had the same effect. In the late 1980s research from the United States suggested that even at levels of pollution then considered to be low, there appeared to be effects on daily death rates and hospital admissions (Department of Heath, 1995). The coefficients linking particle concentrations and effects were small, but over the subsequent decade or so, a large body of published research has been broadly consistent in confirming these initial findings. The potential methodological concerns around the analytical methods used, which might have explained the findings, were addressed and it is now accepted that current concentrations of air pollutants have effects on health that are both measurable and important.

1.4   The effects of short-term average concentrations of pollutants on a day-to-day basis (acute effects) were studied using the recently applied and very powerful time-series methods. A range of health indicators including daily deaths and hospital admissions were studied. The effects of long-term exposure to pollutants (chronic effects) proved less easy to study, but large cross-sectional cohort studies undertaken in the United States have demonstrated their existence (Dockery *et al*, 1993; Pope *et al*, 1995). Chronic effects can be considered either as triggers of new cases of protracted disease (either due to air pollution alone or in conjunction with other causal agents), as worsening of the severity of disease over time reflected as an increase in symptoms (morbidity) or as acceleration in progression of disease over time. Recent work has shown that a significant reduction in life expectancy may be produced by long-term exposure to fine particles. A similar association with long-term average concentrations of sulphur dioxide has also been demonstrated (Department of Health, 1998; Department of Health, 2001a). It is now believed that these chronic effects of air pollution are substantial and may have a greater overall impact on the public health than acute effects.

1.5   There are thus two potential uses of the word "cause" in the context that air pollutants cause ill health or death: day-to-day variations in exposure causing (i.e. resulting in) day-to-day increases in, say, mortality, and long term exposures causing disease in previously disease-free individuals.

1.6   A large volume of research undertaken over more than fifty years has identified many potential causes of, or risk factors for, cardiovascular disease (Oxford Textbook of Medicine, 1996). There is considerable discussion as to whether the causal factors that operate over a long period are the same as those which can precipitate a fatal attack in a susceptible individual in whom relevant disease processes are well developed. Are precipitants true causes of disease process, or do they simply determine the when and where of an event rather than whether it occurs at all? The mechanism of precipitation may be the same as, or different from, that of causation. If a precipitant were not a cause of the disease process it would imply that the event would have occurred anyway, but not necessarily at the time it did. On the other hand, if a fatal event were to be postponed by removing the precipitant, it is possible that the subject might live long enough to die from some other cause and it might be said that a death from heart disease had been prevented. The term "prevented" in this case would refer to avoidance of precipitation of death and not to an effect on slowly developing cardiovascular dysfunction.

1.7   Exercise provides an interesting example of how a "factor" – in this case, exercise – can act in two ways. Coronary insufficiency and a myocardial infarction (heart attack) can be *caused* by severe exercise in a patient with underlying coronary artery disease.

But the long-term practice of taking exercise does not *cause* coronary artery disease; on the contrary, it prevents it.

1.8   Deciding whether an association between some putatively causative factor and a health outcome is actually causal is a common problem in environmental medicine. Whereas in the laboratory carefully controlled experiments may provide firm evidence for causality, in epidemiological studies causation is often not so easily inferred. We have considered the evidence discussed in this report in terms of Bradford Hill's characteristics of causal associations (Hill, 1965). These characteristics or features are set out in Box 1.1.

Box 1.1

Bradford Hill's characteristics of causal associations

Bradford Hill, a distinguished English medical statistician was involved in early work on the association between cigarette smoking and premature death. Involvement in such work led him to define a number of characteristics which experience had shown him to be often found with truly causal associations. **(Hill, 1965)**.

1. Strength

2. Consistency

3. Specificity

4. Temporality (temporal plausibility)

5. Biological gradient (dose-response)

6. Plausibility (biological plausibility)

7. Coherence

8. Support from experiment

9. Support from analogy

1.9   In the late 20th and early 21st century, the main sources of air pollution in Western countries have been and continue to be motor vehicles and industry, including the power industry (non-nuclear). The pollutant mix is complex and this complexity is magnified because of variation in the components of the mix between places and over time. The major primary pollutants in ambient air which are of concern regarding effects on health are particles and the gases sulphur dioxide, the oxides of nitrogen and carbon monoxide. Ozone is a secondary pollutant produced by the action of UV

light on oxides of nitrogen and hydrocarbon moieties emitted from vehicles. Concentrations of air pollutants are monitored at a range of sites throughout the UK: details of which can be found on the defra website (http://www.airquality.co.uk). Nitrogen dioxide is both a primary and secondary pollutant, being emitted directly by motor vehicles and formed by oxidation of emitted nitric oxide. Ozone plays an important part in this oxidation and concentrations of ozone are thus reduced in urban areas close to traffic sources.

Table 1.1: Average concentrations of the main air pollutants in the UK in 2004

Site Type/Pollutant	Annual Mean in 2004 ($\mu g\ m^{-3}$)						
	NO_2	O_3	PM_{10} grav. equiv.	$PM_{2.5}$ TEOM	SO_2	CO ($mg\ m^{-3}$)	Black Smoke
Kerbside	89	25	39	19	8.0	1.0	n/a
Roadside	49	43	24	n/a	6.0	0.5	n/a
Urban/Suburban	32	57	22	13	6.3	0.3	6.5
Rural	11	72	20	11	3.7	n/a	n/a

Ozone concentrations are annual average of maximum daily 8-hour average.

PM_{10} based on TEOM* multiplied by 1.3 to approximate gravimetric values.

$PM_{2.5}$ are TEOM values and not gravimetric values.

1.10 Air pollutants such as carbon monoxide and ozone are simple inorganic compounds. The ambient aerosol (small solid particles or liquid droplets suspended in air and forming a relatively stable suspension) is much more complex and comprises dozens, or more likely hundreds of different chemical compounds: some simple and some very complicated. Particles can be characterised by their chemical composition and by their mass or number per unit volume. Urban air, for example, might contain about 20 μg of suspended material per cubic metre and tens of thousands of individual particles per cubic centimetre. Because particles larger than about 10 μm in diameter usually do not pass the upper airways (nose, mouth, pharynx, larynx) to reach the air passages of the lung, it has become conventional to measure the mass of particles of diameter of less than about 10 μm per cubic metre of air and to describe this measurement as PM_{10}. Details of the conventions for measurement of particle concentrations can be found in the COMEAP report on Non Biological Particles and Health (Department of Health, 1995).

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*   (see Glossary).

Figure 1.1: Scanning electron micrograph of carbon particles
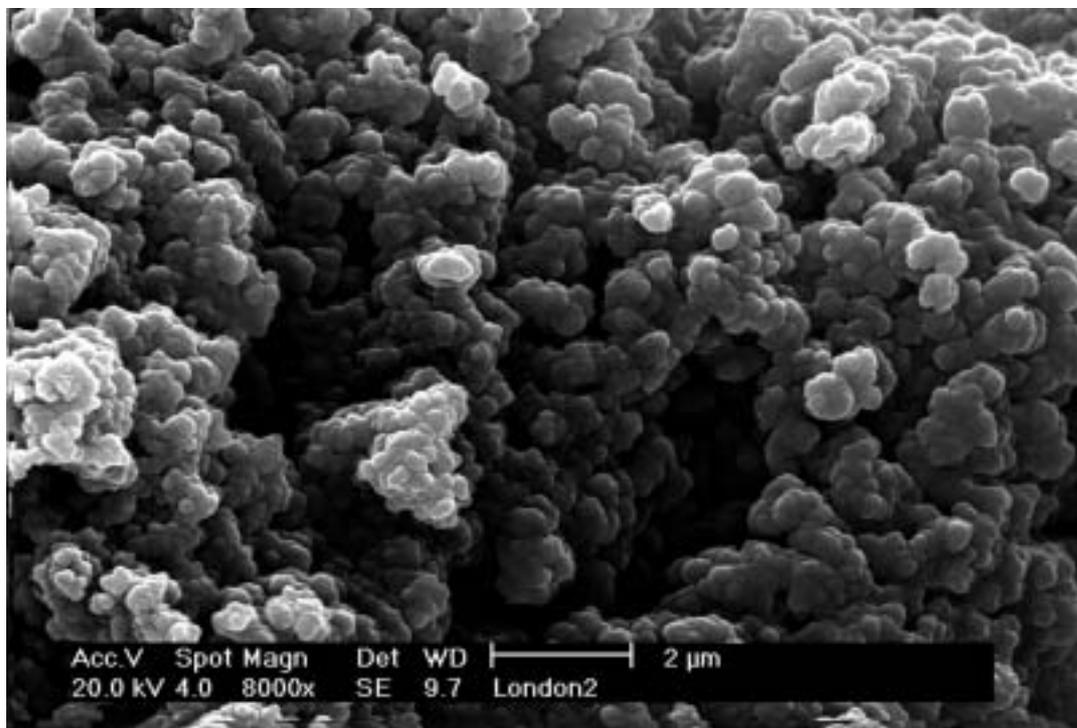
(Figure supplied by Prof. RJ Richards, University of Wales, Cardiff)

1.11 Small particles penetrate more deeply into the air passages of the lungs than larger particles. As particles pass along the airways they are deposited by the processes of impaction, sedimentation and diffusion: the latter affects only the very small particles in the mixture. Deposition at the alveolar level has always been seen as important because vital gas exchange occurs here, because the barrier separating the air from the blood is thin (< 0.5 µm) and because clearance of particles from this area is slower than from the conducting airways. In terms of particle diameter, two peaks for deposition at the alveolar level can be defined: 2 µm and 20 nm (i.e. 0.02 µm). The latter particles are so small that they contribute but little to measurements of the mass concentration of the ambient aerosol: their presence is, however, dominant in measurements of number concentrations i.e. how many individual particles there are in a given volume of air. Particles of less than 100 nm (0.1 µm) diameter are often referred to as ultrafine particles or, because their diameter can be conveniently expressed in nanometres (nm), as nanoparticles. Recent work has focused on such particles (The Royal Society and The Royal Academy of Engineering, 2004) and their possible effects will be discussed further in Chapter 3. It has also been shown that ultrafine particles disappear rather rapidly from the alveoli – they are to some extent cleared to the blood and probably to the lymphatic system as well as being removed by the ciliary escalator of the conducting airways after uptake by macrophages. The science of aerosols is complex and the reader is referred to a recent report Particulate

Matter in the United Kingdom (Defra, 2005) and to Hinds' standard work "Aerosol Technology" for details (Hinds, 1998).

1.12 Air quality in the UK is managed by the Air Quality Strategy for England, Scotland, Wales and Northern Ireland (Defra, 2000). This strategy sets objectives for concentrations of air pollutants which are based on EC Directives on Air Quality and on Air Quality Standards recommended by the UK Expert Panel on Air Quality Standards (EPAQS). Whilst the standards recommended by EPAQS do not take account of cost-benefit relationships, the objectives in the Air Quality Strategy do and it is thus important to calculate as completely as possible the benefits that will accrue from reductions in levels of pollutants. In 1998, COMEAP advised on the impact of certain pollutants on mortality and on respiratory admissions to hospital (Department of Health, 1998) and in 2001 added to this with a statement dealing with admissions for cardiovascular disorders (Department of Health, 2001b). In addition, advice on the health impacts of long-term exposure to particles has been provided (Department of Health 2001a). Recent work has suggested a link between air pollution and cardiovascular morbidity and mortality (Health Effects Institute, 2003). This report sets out to examine this assertion and to prepare the ground for quantification of this effect.

Cardiovascular disease

1.13 The term cardiovascular disease includes all diseases of the heart and blood vessels including stroke. It accounts for 40% of deaths in the United Kingdom and a large proportion of hospital admissions. Most cardiovascular disease occurs in middle and old age – comparatively little occurs in young people. But, because it is common, the proportion of persons in the age range 45-65 years dying of cardiovascular disease is high. The proportion of deaths from cardiovascular disease is the same in the two sexes but women tend to die at a more advanced age than men, particularly from heart disease.

1.14 The most common cardiovascular disease in the United Kingdom, as in other industrialised countries, is coronary artery disease (CAD), also known as ischaemic or atherosclerotic heart disease. Coronary artery disease is the most frequent single cause of death in the UK and is caused by atheromatous plaques occurring in the walls of the coronary arteries, the arteries which supply blood to the heart. These plaques appear first in young people and are widely distributed in the large and medium sized arteries of the body. The occurrence of plaques in the coronary arteries is particularly important as growth of these lesions can lead to progressive narrowing and eventually obstruction of the vessels in some cases. In addition, the plaques may rupture or fissure leaving an ulcer in the wall of the artery on which a thrombus (blood clot) forms. This may lead to complete blockage of the artery (coronary thrombosis or

heart attack). Such events may cause death if the blood supply to the heart is seriously impaired and the heart ceases to function, or the area of heart muscle served by the artery may itself die and be replaced by scar tissue. Death of a portion of the muscle of the heart wall is referred to as a myocardial infarction. Repeated non-occluding thromboses can lead to enlargement of the plaque in layers. In older people, coronary heart disease is a leading cause of heart failure, associated with disability, breathlessness and fluid retention. Aneurysmal dilatation of coronary arteries can also be caused by atheromatous plaques. For our purposes, coronary artery disease can be seen as the underlying cause of many cases of coronary heart disease: the latter implying malfunction of the heart itself.

1.15   Atheromatous disease occurring in the blood vessels supplying the brain causes cerebrovascular disease (stroke), the second most common cardiovascular cause of death. Strokes can also be caused by bleeding (haemorrhage) into the brain substance. Atheroma can also occur in the arteries supplying the legs, causing peripheral vascular disease, and in the main artery of the body, the aorta, where it is a major cause of aortic aneurysms. Atheroma formation is, therefore, the common factor in the majority of cardiovascular diseases. Material can break off from the surface of the thrombus associated with atheromatous plaques and form loose fragments which block downstream blood vessels. This is called embolism. The growth and breakdown of the atheromatous plaque determines the clinical consequences.

Figure 1.2: Atheromatous plaque rupture
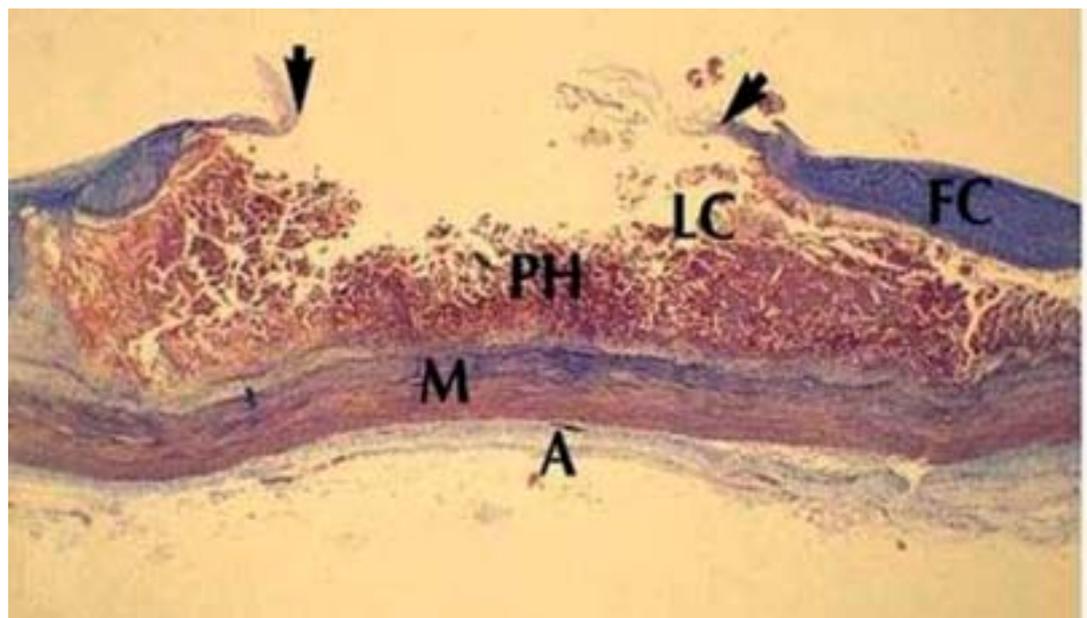
A – Adventitia; M – Media; FC – Fibrous Cap; LC – Lipid Core; PH – Plaque Haemorrhage

1.16 Up to 50% of deaths from coronary disease are sudden and occur outside hospital (Callans, 2004; Virmani *et al*, 2001; Wannamethee *et al*, 1995). In a significant proportion of these deaths, greater in younger people, there is no previous history of heart disease, so the deaths are sudden and unexpected (Tunstall-Pedoe *et al*, 1975; Tunstall-Pedoe *et al*, 1996; Callans, 2004; Wannamethee *et al*, 1995; Bowker *et al*, 2003). With increasing age, a greater proportion of coronary deaths occur in those who are known to have had a heart attack previously, or in those who suffer from and have been treated for the chronic symptoms of angina pectoris, or of heart failure. Many of these deaths can also occur quite suddenly but a greater proportion of the victims in this, the older category, than in the younger age group reach hospital alive when they have an attack.

1.17 As the population ages, an increasing proportion of older people have diagnosed heart disease often caused by coronary artery disease. They may also have chronic diseases of other organ systems such as chronic obstructive pulmonary disease (COPD). Such patients can be frail, surviving under normal conditions, but are more likely to die if exposed to a sudden stress, such as influenza or a sudden spell of cold weather.

1.18 There are problems with the diagnosis and recording (coding) of death from cardiovascular disease. Heart disease deaths in younger people are likely to be accurately diagnosed either because they have occurred in hospital, or because the cause is identified at post mortem examination. With increasing age, attribution of death to a specific cause may become more problematic. The coding rules for death certificates mean that each death is ultimately assigned to one primary cause even in someone known to be suffering from more than one condition, for example coronary heart disease and chronic lung disease. Pre-existing coronary heart disease increases the risk of death whether or not death is due to coronary heart disease. Therefore, even if death is actually precipitated by influenza, or an exacerbation of COPD for example, a diagnosis of coronary disease recorded on the death certificate is more probable in someone known to be suffering from this condition. Coronary disease is therefore a very commonly reported cause of death in the elderly, but may be the immediate cause, a contributing cause, or be unrelated to the death. Conversely, it may be the true immediate cause whilst another disease is recorded as the cause of death. Consequently, mortality statistics relating to cause need to be interpreted with great care.

1.19 Whereas attribution of death to specific causes can be problematic, this is less true of hospital admissions. Victims of heart attacks (myocardial infarctions), who live long enough to reach hospital are subjected to standardised investigations and management designed to confirm or refute the presumptive diagnosis of myocardial infarction. Patients with chest pain are investigated in a conventional manner to find the cause of

the pain; this may be due to myocardial ischaemia but can be caused by a number of other processes. Commonly, a proportion of people seen in an accident and emergency department with chest pain are not admitted. Of those admitted some have myocardial infarction and some have what is called unstable angina (acute coronary syndromes), and some have non-cardiac chest-pain. The differentiation between severe angina and myocardial infarction is sometimes not clear-cut, although newer tests such as the troponin assay (see glossary) make this easier.

1.20   It is possible therefore, to imagine circumstances in which an environmental change could produce a true increase in admissions from myocardial infarction, or others where there was an exacerbation of angina symptoms leading to an increase of admissions for 'acute coronary syndromes' short of myocardial infarction itself, or, again, where it proved difficult to tell the difference between the two.

1.21   A similar argument applies to stroke and to heart failure, both common causes of hospital admission. Patients admitted for the first time for these conditions include a significant proportion of chronically incapacitated and frail patients, who are admitted for an exacerbation or deterioration of their pre-existing condition or conditions. Statistics for hospital admissions are complicated and require careful interpretation if they record the same patient more than once, or fail to distinguish re-admissions from first admissions.

1.22   The following is a deliberately short list of some of the risk factors generally recognised as "causes" of cardiovascular disease and which satisfy most or all of Bradford Hill's characteristics of causal associations. Some of them have been included because they have been raised as illustrating potential mechanisms of action of air pollutants, others because they might confound analyses involving air pollution as a factor.

   (i)   **Cigarette smoking.** Smoking has been long recognised as increasing the risk of cardiovascular disease. Although the mechanism by which smoking acts has not been definitely established, inflammation (see below) may be a factor. Initially rejected because the measured exposure was so low, passive smoking has many similarities to air pollution as a candidate risk factor.

   (ii)   **Diabetes/Obesity/Lack of exercise.** These are all closely linked together, to the 'metabolic syndrome' and to excess coronary risk particularly in South Asians.

   (iii)   **Family history.** Some genetic and some shared lifestyle and dietary habits.

   (iv)   **Diet.** Originally thought to operate largely through serum cholesterol, mechanisms of effects of dietary factors are now known to be more complicated. Although the vitamin/antioxidant hypothesis is now less persuasive than it was a

few years ago, there are a number of mechanisms by which a balanced diet, rich in vegetables, fruit and fish are thought to lower coronary risk.

(v) **Lipids including serum cholesterol.** It is now known that the cholesterol accumulates in and is damaging to the arterial wall.

(vi) **Blood pressure.** Mechanisms are not quite so well established as for cholesterol.

(vii) **Social status.** Excess coronary risk is associated with low social status and socio-economic factors in many studies, even when conventional risk factors are accounted for.

(viii) **Inflammation.** Coronary risk is known to be associated with higher levels of blood constituents associated with inflammation, such as white blood cells, fibrinogen and C-reactive protein. It is postulated that factors that precipitate an inflammatory response could precipitate coronary events, both by changing the composition of atheromatous plaques in a manner that increases the likelihood of their rupture (see 1.14) and by increasing platelet activation and coagulation.

1.23 Cardiovascular disease is the commonest worldwide cause of death and disability. It is estimated that, together, coronary artery disease and stroke account for about 12 million of the 56 million deaths that occur in the world each year. Although age-adjusted rates are falling in the UK, cardiovascular disease remains the single leading cause of death accounting for about 40% of total mortality. Worryingly, rates have risen steeply in low and middle income developing nations, which now account for about 80% of the world-wide burden of cardiovascular disease (Yusuf *et al*, 2001). As has been emphasised strongly in recent years, many of the causes of this epidemic of cardiovascular disease are well known. At least 75% of cases can be explained by inappropriate diet and physical inactivity (as expressed by plasma lipids, obesity and high blood pressure) and tobacco use (Beaglehole, 2001). A recent case control study of myocardial infarction in 52 countries suggested that 90% of the population attributable risk could be accounted for by such well-recognised risk factors (Yusuf *et al*, 2004). Efforts are being made around the world to reduce the prevalence of the disease chiefly by concentrating on reducing individual risk rather than by population-wide primary prevention.

Purpose of the report and the approach taken

1.24 COMEAP has been asked to review the reported association between air pollution and cardiovascular disease, to consider whether the evidence is strong, what the potential mechanisms might be and to comment on possible impacts on public health. Our findings are provided in this report.

1.25 We begin in Chapter 2 by considering the epidemiological evidence for an association between ambient concentrations of air pollutants and indices of cardiovascular disease. The latter includes deaths from cardiovascular diseases and the occurrence of symptoms of disease. The latter are, in part, represented by hospital admissions.

1.26 The epidemiological evidence divides naturally into two unequal groups. The first, and larger body of data relates to studies looking at the effects of daily changes in concentrations of pollutants; the second, and smaller body of data relates to studies of the effects of long-term exposure to air pollutants.

1.27 Having established a number of associations, we examine in Chapter 3 the available evidence regarding mechanisms of effect. This leads us to the major current hypotheses of the effects of air pollutants and we have considered these in some detail. The evidence presented in Chapter 3 is less detailed as regards original studies than that provided in Chapter 2. This is in part due to the lack of mechanistic studies and, also, because these do not lend themselves to formal meta-analysis as do some groups of the epidemiological studies.

1.28 We then return in Chapter 4 to the question of causality. Accepting that definitive proof of causality is unlikely to be available, we weigh the evidence against the advice provided by Bradford Hill – see Box 1.1 above. From this analysis we draw our conclusions. That there will be gaps in the chain of evidence is accepted from the outset and we put forward a number of research recommendations to close these gaps.

1.29 It will be noted that emphasis has been placed on the possible role of particles rather than of gaseous air pollutants though such evidence as bears on the latter has been considered. This emphasis on particles is not due to any *a priori* decision to downplay the possible role of gaseous pollutants but, rather, reflects the interest of the international air pollution research community in particles – and especially in fine and ultrafine particles.

References

Bowker, T.J., Wood, M.J., Davies, M.J., Sheppard, M.N., Cary, N.R., Burton, J.D., Chambers, D.R., Dawling, S., Hobson, H.L., Pyke, S.D., Riemersma, R.A. and Thompson, S.G. (2003) Sudden, unexpected cardiac or unexplained death in England: a national survey. *Q.J.Med.* **96**, 269-279.

Beaglehole R. (2001) Global cardiovascular disease prevention: time to get serious. *Lancet* **358**, 661-663.

Callans, D. (2004) Out-of-hospital cardiac arrest – the solution is shocking. *N.Engl.J.Med.* **351**, 632-634.

Department for Environment, Food and Rural Affairs. (2000) *The Air Quality Strategy for England, Scotland, Wales and Northern Ireland. Working together for clean air.* London: Defra.

Department of the Environment. (1996) *Airborne Particulate Matter in the United Kingdom. Third Report of the Quality of Urban Air Review Group.* London: Department of the Environment.

Department for Environment, Food and Rural Affairs. (2005) Air Quality Expert Group. *Particulate Matter in the UK.* London: defra.
http://www.defra.gov.uk/environment/airquality/aqeg/particulate-matter/index.htm

Department of Health. (1998) Committee on the Medical Effects of Air Pollutants. *Quantification of the Effects of Air Pollution on Health in the United Kingdom.* London: The Stationery Office.

Department of Health. (1995) Committee on the Medical Effects of Air Pollutants. *Non-biological Particles and Health.* London: HMSO.

Department of Health. (2001a) Committee on the Medical Effects of Air Pollutants. *Statement and Report on Long-term Effects of Particles on Mortality.* London: The Stationery Office. http://advisorybodies/doh.gov.uk/comeap/statementsreports/longtermeffects.pdf

Department of Health. (2001b) Committee on the Medical Effects of Air Pollutants. *Statement and Report on Short-term Associations Between Ambient Particles and Admissions to Hospital or Cardiovascular Disorders.*
http://www.advisorybodies/doh.gov.uk/comeap/statementsreports/statement.htm

Dockery, D.W., Pope, C.A., Xu, X., Spengler, J.D., Ware, J.H., Fay, M.E., Ferris, B.G. and Speizer, F.E. (1993) An association between air pollution and mortality in six US cities. *N.Engl.J.Med.* **329**, 1753-1759.

Health Effects Institute. (2003) *Revised Analyses of Time-series Studies of Air Pollution and Health. Special Report.* Boston, MA: Health Effects Institute.

Hill, A.B. (1965) The environment and disease: association or causation? *Proc.R.Soc.Med.* **58**, 295–300.

Hinds, W.C. (1998) *Aerosol Technology: Properties, Behavior, and Measurement of Airborne Particles*. Washington DC: Wiley-Interscience.

Logan, W.P.D. (1953) Mortality in the London fog incident, 1952. *Lancet*, **i**, 336-338.

Oxford Textbook of Medicine. (1996) Weatherall, D.J., Ledingham, J.G.G. and Warrell. D.A. editors. *Cardiovascular Disease*. Oxford: Oxford University Press.

Pope, C.A., Thun, M.J., Namboodiri, M.M., Dockery, D.W., Evans, J.S., Speizer, F.E. and Heath, C.W. (1995) Particulate air pollution as a predictor of mortality in a prospective study of US adults. *Am.J.Respir.Crit.Care Med.* **151**, 669-674.

The Royal Society and The Royal Academy of Engineering. (2004) *Nanoscience and Nanotechnologies: Opportunities and Uncertainties*. London: The Royal Society and The Royal Academy of Engineering.

Tunstall-Pedoe, H., Clayton, D., Morris, J.N., Brigden, W. and McDonald, L. (1975) Coronary heart-attacks in East London. *Lancet* **1**, 833-838.

Tunstall-Pedoe, H., Morrison, C., Woodward, M., Fitzpatrick, B. and Watt G. (1996) Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment, and 28-day case fertility of 3991 events in men and 1551 events in women. *Circulation* **93**, 1981-1992.

Virmani, R., Burke, A. and Farb, A. (2001) Sudden cardiac death. *Cardiovasc. Pathol.* **10**, 211-218.

Wannamethee, G., Shaper, A., Macfarlane, P. and Walker, M. (1995) Risk factors for sudden cardiac death in middle-aged British men. *Circulation* **91**,1749-1756.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen. M., Budaj, A., Pais, P., Varigos, J., Lisheng, L., and INTERHEART Study Investigators. (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries. (The INTERHEART study): case-control study. *Lancet* **364**, 937-952.

Yusuf, S., Reddy, S., Ounpuu, S. and Anand, S. (2001) Global burden of cardiovascular diseases, part 1: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* **104**, 2746-2753.

Chapter 2
Epidemiological evidence for an association between air pollutants and cardiovascular disease

Lay summary

2.1 This chapter examines the evidence that air pollution is associated with cardiovascular disease in human populations. Broadly, two research approaches have been used. One, the time-series approach, investigates whether air pollution is accompanied by short term changes in the incidence of cardiovascular events such as heart attacks. This method generally uses available data on daily counts of deaths or hospital admissions and relates these to ambient concentrations of air pollution on the same or previous days, measured by monitors situated in the study area – usually a city. Evidence from a large number of time-series studies show very clearly that, with few exceptions, all of the commonly measured pollutants (particles, ozone, sulphur dioxide, nitrogen dioxide and carbon monoxide) are positively associated with increased mortality and hospital admissions for cardiovascular disease. These associations are likely to be explained by air pollution making existing disease worse or by precipitating an acute event such as a heart attack in one who is already vulnerable to this possibility. Though there are exceptions, the various air pollutants tend to be correlated with one another because they have common sources (e.g. traffic) and are affected by weather conditions. For this reason, it is difficult to disentangle their individual effects.

2.2 The other main research approach is to compare the incidence of cardiovascular diseases between populations with different long-term exposures to pollution. These studies usually follow groups of subjects (cohorts) for a number of years and provide important information about the amount of life lost due to air pollution. Because large numbers of subjects are required and because the cohorts must be followed up for a number of years, few cohort studies have been done. The evidence from two American studies suggests that cardiovascular deaths are increased by living in areas with higher levels of particulate air pollution. This effect seems to be modified by socio-demographic and regional factors.

Introduction

2.3 Observational studies relating air pollution to cardiovascular disease lack the simplicity of interpretation, associated with clinical trials or experiments. Controlled long-term exposure experiments are neither feasible nor ethical. As in the study of long-term effects of cigarette smoking on cardiovascular disease, as distinct from short-term studies of possible mechanisms, studies in humans have to be by observation, rather than deliberate exposure, or withdrawal. It is, however, worth

considering what ideal, but hypothetical, studies of the rôle of air pollution in cardiovascular disease would involve. Considering these hypothetical studies would clearly illustrate the unavoidable problems which plague observational studies, irrespective of the fact that these 'ideal' studies are completely unfeasible.

- Anything from thousands up to millions of subjects would have to be studied for long periods of time (years) to detect differences in disease rates.

- Subjects would need to be randomly allocated into different exposure groups, so that any differences between the groups at the start would be small, and determined only by chance, rather than by any systematic factors or biases.

- Levels of exposure to pollutants in each group would need to be carefully controlled, standardized and measured, so that each individual would have a known level of exposure to one or more pollutants over a measured period of time.

- Pathophysiological indicators would have to be monitored using standardized definitions applied over the duration of the study.

2.4 Clearly, such studies are extraordinarily difficult but this does highlight the problems with observational studies. Nevertheless, epidemiological studies of air pollution and cardiovascular disease are important in showing how both vary in the real world, and in providing the potential to dissect out any inter-relationship. Epidemiological studies of air pollution and cardiovascular disease can be classified into four main types:

(i) **Studies of fixed populations with fluctuating air pollution levels.** In these, fluctuating levels of pollution are related to very short term variation in numbers of acute cardiovascular episodes.

(ii) **Studies of different occupational groups with different occupational exposures to pollutants.** Here estimated long-term differences in exposure are related to differences in disease rates. The unit of investigation is the occupational group. Such studies do not deal with ambient air pollution but may involve studies of the effects of mixtures of pollutants not dissimilar from the ambient mixture albeit, perhaps, at different concentrations.

(iii) **Studies of fixed populations with long-term changes in exposure to air pollution.** Before and after differences in pollution are related to before and after differences in cardiovascular disease rates. Each population contributes two observations of the presumed cause and effect.

(iv) **Studies of different populations with different levels of long-term exposure to air pollutants.** Each population provides one observation on exposure and one on cardiovascular disease rates.

2.5 Another way of looking at the epidemiological studies is to distinguish between those that look at the effect of temporal variations in concentrations of air pollutants and also those that look at the effects of spatial variations. The former group includes time-series studies which capitalise on day-to-day fluctuations in concentrations and those that look at the impact of short-lived air pollution episodes. Spatial patterns are addressed mainly by the cross sectional cohort studies.

2.6 All these different types of study have problems to a greater or lesser extent:

- observations are made at a population rather than an individual level. This means that the number of units of observation is limited and, as a result, the statistical power of most studies is rather small;

- measurement of exposure to pollutants is extrapolated to a whole population from observations or observation sites that may be limited in number and representativeness;

- common forms of pollution involve a mixture of possible harmful components that show a degree of association with each other and with other factors (such as temperature, barometric pressure and rainfall) in their excess levels or their rise and fall. Disease association with a particular pollutant could therefore be indirect. In some historical studies, the pollutants now under suspicion may not have been measured, or they may have been measured by a method which has now been superseded by more refined techniques;

- people who are exposed over long periods to different levels of air pollution are not going to be identical in all other respects. Apart from smokers, most people prefer not to be exposed to smoke and dust, and if they are financially able, will choose homes and occupations providing clean or fresh air in preference to polluted or smokey surroundings. Observations of cardiovascular disease differences between persons exposed to different levels of air pollution are therefore likely to be confounded by all the other socio-economic and cultural differences that might also explain different levels of disease. These will involve other environmental factors – such as climate, temperature, rainfall, drinking-water, housing quality, overcrowding and the hundreds of personal risk-factor and lifestyle factors which have previously been related to risk of cardiovascular disease which also relate to where people live and which jobs they choose or are chosen for;

- causes of death in large population studies tend not to be subjected to meticulous checking as to accuracy. This is particularly so as the majority of deaths occur in the elderly and very elderly. Such people may have a number of disease conditions simultaneously when they die, and though the death certificate may record these, it is the underlying cause of death which is generally analysed in epidemiological studies.

2.7 Short-term exposure studies, discussed later in this chapter, have a great advantage in that the study design utilises hundreds or thousands of fluctuations in the daily counts of a health outcome and concurrent ambient air pollution. This is a powerful statistical design which enables precise estimates of effect and close control for potential confounders such as season. This contrasts with episode analyses in which only one fluctuation, albeit large, is available for analysis. The large populations at risk during short-term exposure are relatively constant, as will be their personal characteristics or risk-factors (e.g. smoking) which confound geographical comparisons. The exposure of individuals is extrapolated from one or more community based monitoring stations, but even in a large city, dependence on atmospheric conditions will mean that pollution levels will tend to rise and fall relatively synchronously from day-to-day over a wide area even though the absolute levels of exposure may be at different levels in different places in town. Associations with daily mortality observed by such techniques do not provide information about the amount of life that is lost but only that the time of death has been "brought forward" by an unknown period of time. Associations that are observed with daily hospital admissions do not distinguish between added admissions and those that would have occurred anyway but which have been brought forward by, perhaps, a short period. Time-series studies are useful for identifying the likelihood of an effect of air pollution but are significantly less useful for estimating the health impact in terms of amount of life lost or about the number of additional admissions to hospital.

2.8 For this reason, it is important to examine whether long-term exposure to pollutants is also associated with an increased risk of cardiovascular disease. This can only be answered by a different sort of study. Study types ii, iii and iv (para 2.4) have been used for this purpose.

2.9 Studying the effects of occupational exposure to air pollutants may help us interpret studies on the effects of ambient air pollution. However, these need to be assessed with caution. Occupation does not involve initial random allocation to different groups. Entry to some occupations is competitive, whereas others recruit whom they can – for example, security guards are often drawn from older age groups and are thus more likely to have underlying cardio-pulmonary disease. Differing disease experience in different occupations may therefore involve differing degrees of fitness at the time

of recruitment, quite apart from subsequent socio-economic differences, exposures and lifestyles. Such factors can only be partially controlled for in the analysis. Occupational studies may explore specific varieties and intensities of exposure to pollutants, but it cannot be assumed that those adopting or recruited into different occupations have the same risk of cardiovascular disease at recruitment. Nevertheless, there is value in considering these analogous exposures when determining whether effects do exist rather than trying to define a quantitative estimate of effect size.

2.10 There are two main issues with occupational studies which need to be considered – exposure assessments and the fact that the studies were not necessarily designed to address the exposures and outcomes which concern us in the air pollution field. Many early studies were concerned with diesel exhaust and cancer, particularly lung cancer; analysis of cardiovascular mortality was incidental. Some later studies were concerned with workers' exposure to carbon monoxide, but if this was generated by heavy traffic it would have been correlated with other components of diesel exhaust fumes. However, many of the studies assumed the occupational exposure to pollution without being able to measure it in any way. This is not a fatal analytical problem as some help can be obtained from an exposed/not exposed classification rather than seeking different levels of exposure to define a possible dose response relationship. Equally, if a consistent pattern can be found from occupational studies even though the outcomes we are interested in were secondary outcomes, this does help in assessing whether an effect is likely to exist – they provide support for the concept. One final problem with occupational studies is that they usually only analyse the data with respect to the individual's current occupation and do not consider past occupations which might have provided either higher or lower putative pollutant exposures.

2.11 The third type of study involves observing whether a long-term change in pollution is associated with a change in cardiovascular disease rates. Such studies are described as natural experiments. The number of such published studies is very limited. Cardiovascular mortality rates are not stable, indeed they are increasing or decreasing in many countries for reasons probably unconnected with air pollution, so analysis needs to account for the effect of these other factors. This is not always possible.

2.12 A similar problem applies to the fourth type of study, of residential populations such as cities with different levels of air pollution. The latter is very unlikely to be the only factor relevant to cardiovascular disease rates that varies between them. In this context the importance of cohort studies lies in the availability of relevant information about potential confounding factors such as smoking, which can be controlled for at an individual level. The great advantage of such studies is that the mortality risks

obtained can be transformed, using life-tables into years of life lost (Miller and Armstrong, 2001).

Interpreting the results of epidemiological associations between air pollutants and health effects

2.13   Studies of short term changes in concentrations of air pollutants and daily counts of events such as deaths or hospital admissions, provide information on the number of people likely to be affected by such changes. However, in their simplest form, they fail to provide information on the extent to which such events are advanced and cannot distinguish, in the case of non-lethal events, between extra events and events brought forward. This is important because when we try to estimate impacts on public health we would, for example, like to distinguish between deaths brought forward by a short period in the already seriously ill and frail and deaths brought forward by perhaps many years in apparently healthy individuals.

2.14   Recent work has shown that the results of studies of the associations between long-term exposure to air pollutants on the risk of death can be converted, by means of life tables, into an estimate of the average extent by which life expectancy in a population is reduced. But these studies do not tell us how this loss of life expectancy is distributed among the population.

2.15   To oversimplify: short term (time-series) studies tell us the number of people whose deaths are advanced and long-term studies tell us the extent of advancement on an 'all population' or average basis. In principle these two approaches should be able to be combined, but for various reasons – some discussed below and some discussed in our earlier report (Department of Health, 2001; Miller and Armstrong, 2001), this has proved to be difficult.

Evidence from short term exposure studies

2.16   This body of evidence is based on analyses which examine the relationship between cardiovascular outcomes and levels of air pollution on the same or immediately preceding days. The earliest studies were of air pollution episodes in which the number of disease events occurring during and shortly after an air pollution episode was compared with that expected in normal circumstances. Over the last 20 years, as statistical techniques, computing power and routine health data have developed, there has been an enormous growth in studies of daily time series. In this type of study, the relationship between an outcome such as daily counts of cardiovascular mortality deaths is related to an indicator of exposure to air pollution using regression techniques. These analyses take into account confounding factors that are potentially related to both air pollution and the cardiovascular outcome. In practical terms, time-

series studies may be carried out in two ways. The first is at an individual level by following panels of subjects: an example would be the study of heart rate variability in panels of elderly patients. More frequently, the outcome is measured at a population level in what are described as "ecological" or "population" time-series studies: an example would be the study of daily hospital admissions for acute myocardial infarction in a whole city. Here the analysis is carried out at a group level, the dependent variable being daily counts of admissions for this diagnosis. A variant of this design is the "case-crossover" study in which pollution levels immediately preceding the event are compared with those in a control period in which the event did not occur. This is conceptually similar to the time-series approach, with the advantage that individual level factors can be incorporated into the analysis, if available.

2.17 A full review of this area needs to address the following questions:

(i) Is there evidence of short-term associations between air pollution and cardiovascular mortality and morbidity?

(ii) Do associations differ for different pollutants?

(iii) Which cardiovascular conditions are most affected?

2.18 This section will deal only with ecological time-series studies which have studied clinical cardiovascular outcomes. Time-series techniques have also been used to study the relationship between ambient air pollution and outcomes that may be relevant to mechanisms; these include heart rate variability, ECG changes, haematological and clotting indices, but these will be reviewed in a subsequent chapter dealing with mechanisms.

2.19 Reviewing this literature presents difficulties because of its scale and complexity. Previous COMEAP reviews have usually relied on summarisation of studies in tables and narrative description. In this review we have adopted a meta-analytic approach to describing the literature. Following the guidance of a WHO report (WHO Working Group, 2000), we have used a protocol to conduct a systematic literature search to identify all relevant papers. This should have avoided some sources of reviewing bias which might have otherwise occurred and has enabled us to carry out a meta-analysis.

2.20 The main aim of this analysis was to enable the results of the studies to be visually inspected using forest plots (see Glossary) so that a judgement could be made about the overall direction of the evidence. For pollutant-outcome pairs with a sufficient number of estimates, we tested for heterogeneity (variation between cities in individual studies) and calculated combined (or summary) estimates. We also looked

for evidence of publication bias (the possibility that negative studies might not be published) using funnel plots (see Glossary) and statistical tests.

2.21 The evidence is presented in three sections. The first deals with episode studies, the second (and largest) with the systematic review of ecological daily time-series studies, and the third with some additional important studies that could not, for various reasons, be included in the meta-analysis. Before reviewing the evidence however, we discuss some important general aspects of the measurement of health outcomes and air pollution exposure in ecological time series studies.

Outcomes

2.22 Daily mortality counts are available from death registration systems that are primarily intended to serve civil and legal functions. The medical certificate of cause of death which is included in this process records the cause of death according to the current version of the World Health Organization International Classification of Diseases (ICD) (World Health Organization, 1977). Part 1 of the certificate contains three lines for the recording of 1(a) the disease or condition directly leading to death, 1(b) other disease or condition, if any, leading to 1(a); and 1(c) other disease or condition, if any, leading to 1(b). The diagnosis on the lowest line is coded as the underlying cause of death and most time-series studies use this. Only recently have some studies begun to take account of other diseases recorded on the certificate. This information is linked with other registration data including date of death, place of death, address, sex, and date of birth. From these data, it is possible to construct time-series studies comprising, for each day over a number of years, the numbers of deaths stratified by diagnostic group and other relevant variables, such as age and sex. These are then merged with daily data on air pollution and potential confounding factors such as temperature, to provide an analytic data set which is then analysed using regression techniques.

2.23 In the ICD, cardiovascular diseases comprise one rubric (or grouping) and the various conditions are coded down to 4 digits though most ecological time-series studies use 3 digit codes. Those found in time-series studies are shown in Table 2.1. The ICD is revised periodically and the 10th Revision was introduced in the late 1990s. However, most studies described here have used the 9th Revision of the ICD (World Health Organization, 1977).

Table 2.1: Number of studies (and estimates) in the APED database with a given outcome-pollutant estimate

Outcome	ICD (9th rev)	PM$_{10}$	PM$_{2.5}$	BS	TSP	NO$_2$	O$_3$	SO$_2$	CO
Mortality									
Cardiovascular	390-459	37 (52)	11 (12)	19 (36)	22 (28)	41 (52)	36 (58)	49 (78)	19 (19)
Admissions									
Cardiovascular	390-459	6 (12)	2 (2)	5 (11)	1 (1)	8 (8)	13 (20)	10 (16)	6 (6)
Cardiac	390-429	17 (72)	4 (4)	4 (12)		13 (21)	11 (11)	10 (22)	11 (11)
AMI	410	2 (2)		1 (1)		2 (2)	3 (4)	2 (2)	3 (3)
Angina Pectoris	413			1 (1)		1 (1)	1 (1)	1 (1)	1 (1)
IHD	410-413/414	11 (23)	4 (4)	4 (16)	1 (1)	9 (10)	11 (13)	11 (12)	8 (9)
Dysrhythmias	427	7 (8)	4 (4)	1 (1)		4 (4)	6 (7)	3 (3)	4 (4)
Heart Failure	428	8 (8)	3 (3)	1 (1)		9 (9)	10 (18)	10 (10)	4 (4)
Cerebrovascular	430-438	8 (12)	4 (5)	4 (9)		9 (10)	7 (8)	6 (8)	6 (7)
Circulatory	440-459	1 (1)	1 (1)			1 (1)	1 (1)	2 (3)	1 (1)

APED = Air Pollution Epidemiology Database (see Appendix 2 for more details of the database)

2.24 For cardiovascular mortality, the majority of studies have only looked at conditions coded under the whole cardiovascular rubric of the WHO International Classification of Disease (ICD) (ICD9 390-459). For hospital admissions the use of the whole cardiovascular rubric of the ICD is also common, but various subgroupings may be used, the most frequent being all conditions affecting the heart (390-429), ischaemic heart disease (410-414), dysrhythmias (427), heart failure (428), and cerebrovascular disease (430-438). The various aggregations clearly include some conditions that might not be susceptible to air pollution and these will dilute any effect on susceptible subgroups.

2.25 The diagnosis of hospital admissions is also coded using the ICD. However, it is the immediate cause of admission that is usually coded, rather than the underlying cause. It is likely to be more accurate than the diagnosis of cause of death because the diagnosis of a hospital admission is made at the end of the hospital stay and is made with the benefit of the information provided by clinical examination, investigations, and response to treatment. One potential problem is that some hospital information systems (Paris, for example) do not distinguish elective admissions from emergency admissions. If total admissions are used in the analysis, the effect is to dilute the estimate of effect on the emergency admissions within the total. Some studies try to minimise this problem by excluding ICD codes that are known to include mainly elective admissions, such as for elective coronary artery surgery.

2.26 As discussed in Chapter 1 (para 1.18 *et seq*), the true underlying cause of death is often difficult to determine and the certification of cardiovascular causes of death is especially subject to considerable inaccuracy and variation between certifying doctors (Coady *et al*, 2001; Lloyd-Jones *et al*, 1998). For a particular time-series study, the

consequence of misclassification of diagnosis will be to bias the estimates of effect downward because it is increasing the random variation or background noise in the data. It does not lead to confounding however, because it is not plausible that the level of misclassification would vary according to pollution levels in the short term. In the unlikely event that a seasonal correlation was present (e.g. more misclassification in the summer, when pollution levels are different from those in winter) this would be corrected by the standard modelling processes which adjust for season. However, if there were a systematic difference in classification, which might occur, for example, between two cities in different countries having different diagnostic fashions, this might contribute to heterogeneity of the effect estimates. Misclassification problems can be largely overcome by analysing large diagnostic aggregations (e.g. all cardiovascular diseases) if the diagnostic transfer is within the cardiovascular group.

Air pollution measurement

2.27　Daily concentrations of ambient pollution are almost always obtained from fixed site monitors. For ecological time-series studies the most suitable monitors are those designed to measure background concentrations rather than local sources such as roadsides. Daily concentrations of air pollutants are mostly analysed as 24-hour averages, but ozone may be expressed as a fixed 8-hour or rolling 8-hour averages and ozone and nitrogen dioxide may also be expressed as maximum 1-hour concentrations, in order to capture the peak exposure during a 24-hour period.

2.28　Community monitors provide an imprecise indicator of the exposure of individuals to outdoor pollution, since many other factors affect the concentration of pollutants in the breathing zone. The population spends most of their time indoors where they may be exposed to other sources of pollutants, such as gas cooking and cigarette smoke. Also, the penetration of outdoor pollutants into the indoor environment and their deposition there will vary. The effect of this misclassification of exposure is likely to bias any estimate of effect downwards. In contrast, if the exposure of an individual is systematically over- or under-estimated by the community monitor, any association can be biased in either direction[1]. For example, if the ozone relationships were to be based on an inner urban monitor, the pollution effect estimate would be different from those observed if a suburban monitor were to be used because the inner urban monitor will record lower values due to scavenging of ozone by nitric oxide. This would be true even if the suburban and urban monitors were perfectly correlated day-to-day. Neither differential nor non-differential sources of bias are likely to lead to a spurious positive association through confounding.

1　For further discussion, see Environmental Epidemiology Ed. Steenland, K, and Savitz, D.A. Oxford University Press 1997 pages 23-27.

2.29 Ambient air pollution is a mixture of gases and various types and sizes of particles. Because of common sources and dispersal factors, these are commonly correlated. This means that an association between a particular pollutant and a health outcome may reflect the presence of that pollutant as part of the mixture, rather than an effect of the pollutant *per se*. Time series studies often attempt to disentangle these relationships with multi-pollutant models, but this may not resolve the problem for various reasons. These include the fact that these are small associations already difficult to identify against the other sources of variation, that correlations between pollutants may be too close, and that pollutants vary in their degree of measurement error. We shall be presenting a limited range of analyses of multi-pollutant estimates. This is mainly because of an absence of published evidence. However, we note that studies that have investigated multi-pollutant models have not generally been successful in disentangling the separate effects of correlated pollutants. An exception is provided by the case of ozone and particles. Here the majority of studies have found the effects to be independent. (Department of Health, 1995; Stieb *et al*, 2002).

Evidence from air pollution episodes

London 1952

2.30 The earliest evidence for cardiovascular effects of air pollution is provided by investigations of the health effects of air pollution episodes. Winter episodes had been known to be associated with increased cardiovascular mortality since the early 20th century but this was attributed to the accompanying cold weather (Russell, 1924; Russell, 1926). The major smog that occurred in London from the 5th to 9th December, 1952 was the first in a large city to be thoroughly investigated (Logan, 1953; Ministry of Health, 1954; Wilkins, 1954) although two previous episodes, in Belgium and Pennsylvania, had been recognised and studied prior to this time (Firket, 1936; Schrenk *et al*, 1949). Based on predictions from the previous year in London, it was estimated that during the three weeks following the onset of the smog there were 4000 extra deaths.

2.31 Figure 2.1 shows that compared with the prior four days, cardiovascular deaths during the episode increased from 111 to 305 (175% increase) and respiratory deaths from 49 to 207 (322% increase). Cardiovascular deaths fell more rapidly than respiratory deaths. When deaths in the week ending the 6th December were compared with those in the week ending the 13th, an increase in deaths from "myocardial degeneration" from 308 to 653 (112%) and of coronary heart disease from 88 to 244 (177%) was found. By contrast, there was only a small increase in stroke deaths from 102 to 128 (26%).

Figure 2.1: London air pollution episode, December 1952. Changes in deaths for respiratory and cardiovascular disease
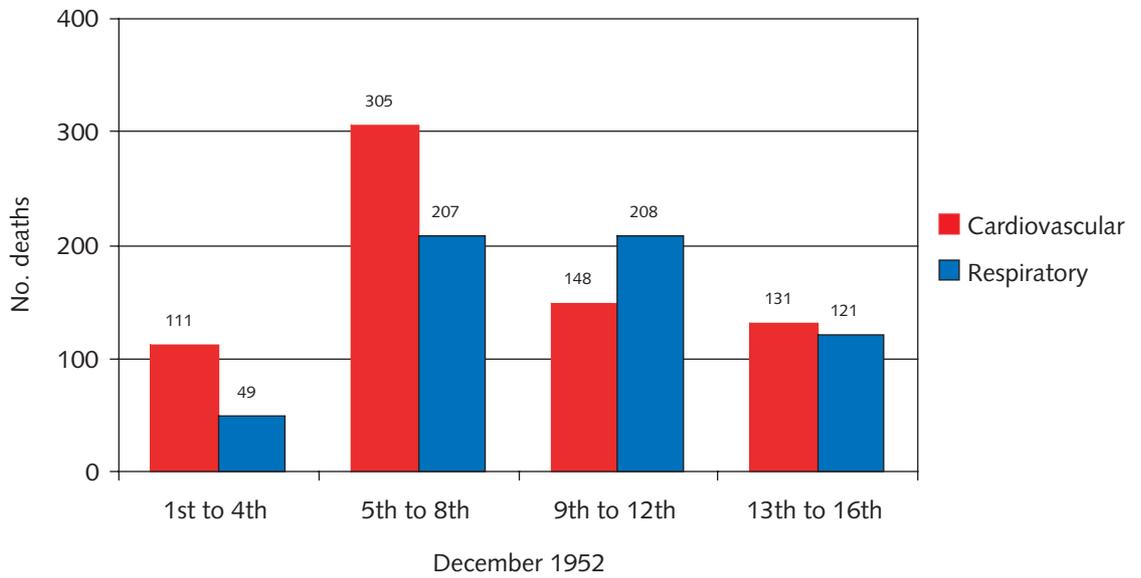
2.32 The trends in hospital admissions are shown in Figure 2.2. The trends are presented using a log scale to enable rates of change in respiratory and cardiac admissions to be more easily compared.

Figure 2.2: London air pollution episode, December 1952. Trends in hospital admissions for respiratory and cardiac conditions
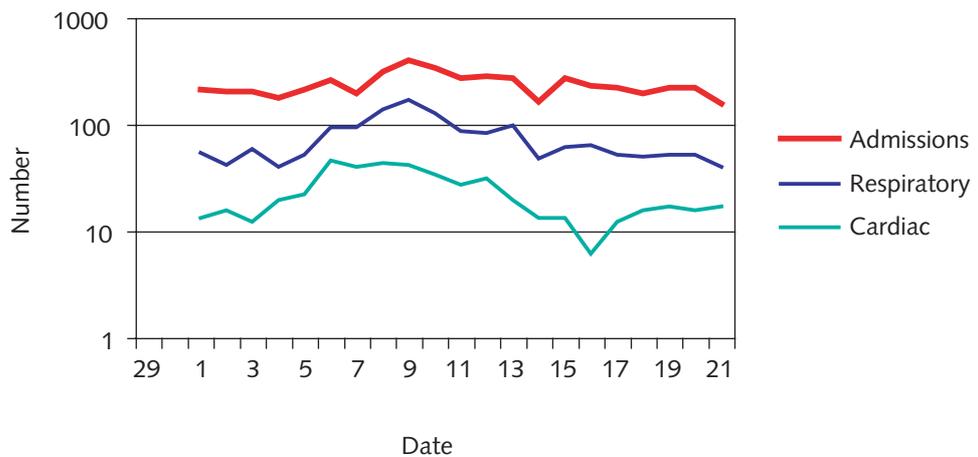
2.33 Cardiac admissions were lower than respiratory in absolute terms, but increased initially at the same rate as the respiratory admissions. Cardiac admissions peaked and began to fall a little earlier than respiratory admissions. Probably because a link between cardiac disease and air pollution was not suspected at the time, it has been asserted that some of the cardiac deaths were in fact due to respiratory problems. This is not borne out by the results of post mortem examinations of deaths attributed to myocardial (mainly ischaemic heart) disease (Ministry of Health, 1954; Wilkins, 1954) the results of which are illustrated in Figure 2.3. Only a small proportion of myocardial deaths were thought to be associated with significant respiratory disease and this did not increase during the episode period.

Figure 2.3: London air pollution episode, December 1952. Numbers of autopsies on deaths from myocardial disease showing additional evidence of respiratory disease
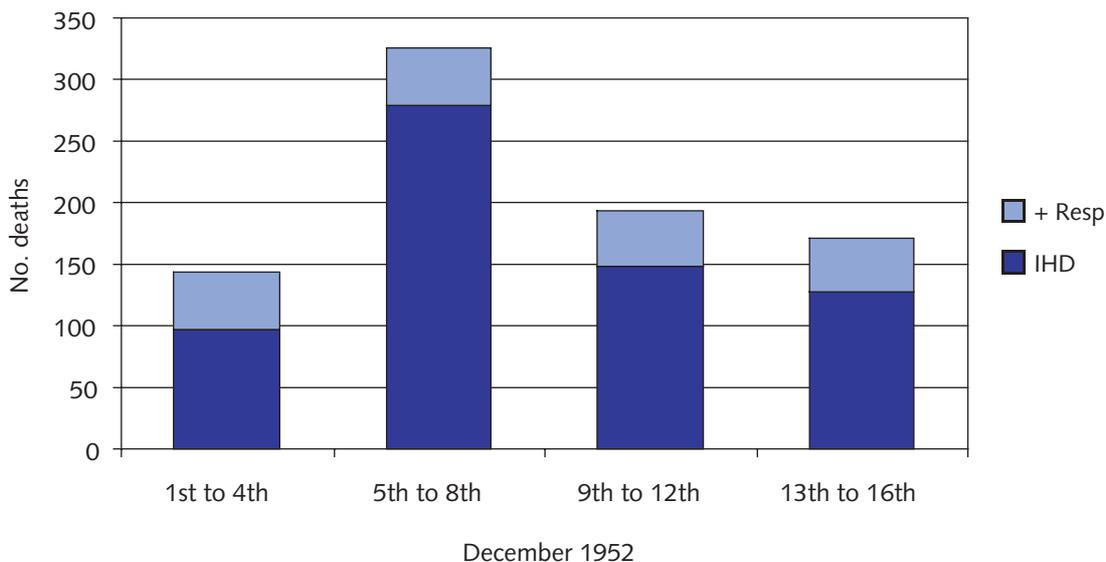
The Ruhr, Germany 1985

2.34 In January 1985, there was a severe air pollution episode lasting 5 days characterised by high levels of particles and SO_2. Mortality increased by 15% (Wichmann *et al*, 1989). Effects were greater for cardiovascular than respiratory disease.

London 1991

2.35 In December 1991, London experienced still, cold weather associated with a temperature inversion. One-hour NO_2 levels rose to 423 ppb and remained elevated for four days. Black Smoke rose to 150 µg/m³. These levels were about 4 to 5 times the seasonal average. The main sources were traffic followed by space heating. The numbers of deaths, admissions and GP consultations during the episode were

compared with those at that time of year in previous years and with those in the equally cold but less polluted rural areas of the South East. In the first reported analysis, cardiovascular deaths rose by 14 % and respiratory deaths by 22% (Anderson *et al*, 1995). These data were reanalysed with more extensive control periods and areas (Anderson *et al*, 2001) (Figure 2.4).

Figure 2.4

London air polution episode, December 1991.
Percentage changes of various outcomes during the episode week,
compared with the rest of the South East

Percentage change per 10 unit increase in concentration
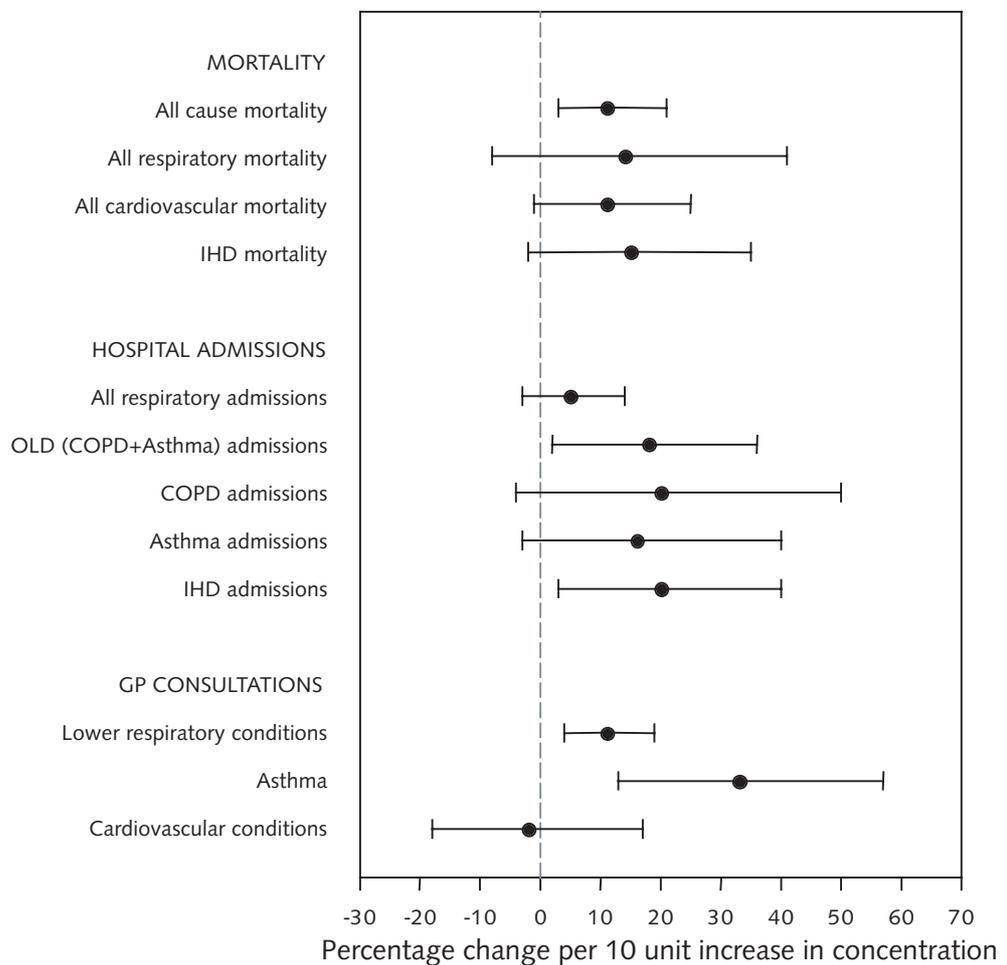
IHD= ischaemic heart disease;
OLD= obstructive lung disease;
COPD= chronic obstructive pulmonary disease.

2.36 For mortality, the proportionate increase in risk for IHD mortality was equal to that for respiratory infections (odds ratio 1.14, 95% CI 0.97 to 1.34). The relative increase in risk for all cardiovascular deaths was similar (odds ratio 1.10 95% CI 0.98 to 1.24). The relative increase in risk of hospital admission for IHD was significant 1.20 (95% CI 1.03 to 1.40) and equalled or exceeded the estimates for respiratory diagnoses. In contrast, there was no relation between the episode and GP consultations for cardiovascular disease 0.98 (95% CI 0.82 to 1.17). This may be explained by the dilution of the relatively few GP contacts for severe acute heart disease by the much larger number of visits for routine and chronic disease, such as blood pressure control.

Conclusions from episode studies

2.37 There is strong evidence that adverse cardiovascular effects occur in air pollution episodes. This was observed both in air pollution episodes characterised by particles and SO_2 from coal burning, and those characterised by particles and NO_2 from vehicle exhaust. It is unlikely that these effects can be explained entirely by the cold weather that typically accompanies winter episodes. The increase in cardiovascular outcomes is not explained by an increase in those that are closely related to respiratory problems (such as cor pulmonale); acute problems due to ischaemic heart disease appear to be important. In the study of the 1952 episode there was an analysis of cerebrovascular mortality and this showed little association with the episode.

Evidence from daily time-series studies

2.38 The weaknesses of evidence based on episode analyses include low statistical power and difficulties in distinguishing the effects of air pollution from those of weather or coincidental factors such as unrelated influenza epidemics. Daily time-series studies provide a way of examining the association with air pollution while controlling for these and other factors. The statistical techniques, computing power and routine data systems for recording health outcomes and air pollution concentrations were largely lacking in earlier years, but this type of analysis began to be used in the 1980s and is now used world-wide. The usual analytic approach is to use regression techniques, usually from the family of Poisson models. The approach favoured in the latter part of the 1990s used non-parametric smoothing techniques to control for time-dependent and weather variables. This was found to have problems (Dominici *et al*, 2002; Ramsay *et al*, 2003). However, an extensive re-analysis of existing data sets using alternative methods of confounder modelling has established that while there is a degree of sensitivity to the model used, significant positive effects of air pollution on daily mortality and hospital admissions remain. The study that showed the most sensitivity to the statistical method was a large US multi-city study of daily mortality, but even in this case, significant positive associations remained (Health Effects Institute, 2003).

2.39 Large numbers of time-series studies have been done in cities around the world and provide the main basis of this review. In the mid 1990s, it was recognised that there were benefits in conducting multi-city studies with standardised protocols. These would provide combined estimates of effect that were less affected by random variation, would help to avoid problems of reporting and publication bias and be a more secure basis for investigating the reasons for any heterogeneity.

2.40 The assessment of research evidence on the effects of environmental factors on health should be systematic, comprehensive and transparent (World Health Organization Working Group, 2000). This is a difficult task where time-series studies are concerned because the literature is now very large and contains complex results presented in varying degrees of detail. The usual approach, in which the studies are summarised in a large table which is then discussed in a narrative form, while it has its place, now presents an enormous task and even if it could be achieved would be difficult for the reviewer to interpret and the reader to assimilate. The individual relative risks found in these reports are typically small and may not be statistically significant in a particular study. However, it may be possible to achieve a more coherent picture when the evidence is assembled and presented using meta-analytic techniques.

2.41 In order to address the need for a feasible and systematic method for evaluating time-series evidence, the Department of Health established an Air Pollution Epidemiology Database (APED), of population time-series and panel studies at the Department of Community Health Sciences at St George's Hospital Medical School, London. The database and its methods are described in Appendix 2. Briefly, the steps are as follows:

(i) Systematic search of the literature (all languages) supplemented by inspection of bibliographies of reviews and other articles.

(ii) Sift of papers to identify those that are suitable for including in a database of relative risks.

(iii) Extraction of data from each paper into an Access relational database with two levels. The first level is that of the paper, the second level is at the level of the pollution-health outcome effect estimate.

Overview of studies and estimates

2.42   The number of studies of cardiovascular effects in the database, as updated to January 2003, is shown in Table 2.1, by pollutant and diagnostic category. For the purpose of this analysis, the smaller number of papers reporting emergency room visits or admissions were also included. Some papers reported more than one estimate and the number of estimates is shown in parentheses. For cardiovascular mortality the largest number of studies is for SO_2 (49), followed by NO_2 (41) and PM_{10} (37). Only 11 studies reported estimates for $PM_{2.5}$. For hospital admissions, a range of cardiovascular diagnoses and diagnostic groupings were reported, the most common being "cardiac" followed by "ischaemic heart disease" and "all cardiovascular" (cardiac plus cerebrovascular). The most represented pollutant was PM_{10}, followed by O_3, SO_2 and NO_2, depending on the particular diagnostic group. Fewer studies reported the effects of $PM_{2.5}$. The overview in this part of the chapter does not cover sulphate as a pollutant as there were too few time-series studies examining sulphate and cardiovascular outcomes for any conclusions to be drawn using quantitative meta-analysis. The small number of studies, some of which do not provide confidence intervals, are tabulated in Appendices 3a and 3b.

2.43   The estimates for each pollution-outcome pair are tabulated in Appendix 3a and 3b. They are presented as the percentage increase in deaths or admissions predicted by the regression equation for a change of 10 units of pollution ($\mu g/m^3$) for all pollutants (except for CO, which is per 1 unit of pollution in mg/m^3). These estimates are presented as forest plots to provide a visual representation of the relationship between each pollutant and cardiovascular mortality and admissions, respectively. The 95% confidence limits accompany each estimate except those for which none was found in the original paper.

Cardiovascular mortality and PM$_{10}$

Figure 2.5a

Cardiovascular mortality and PM$_{10}$
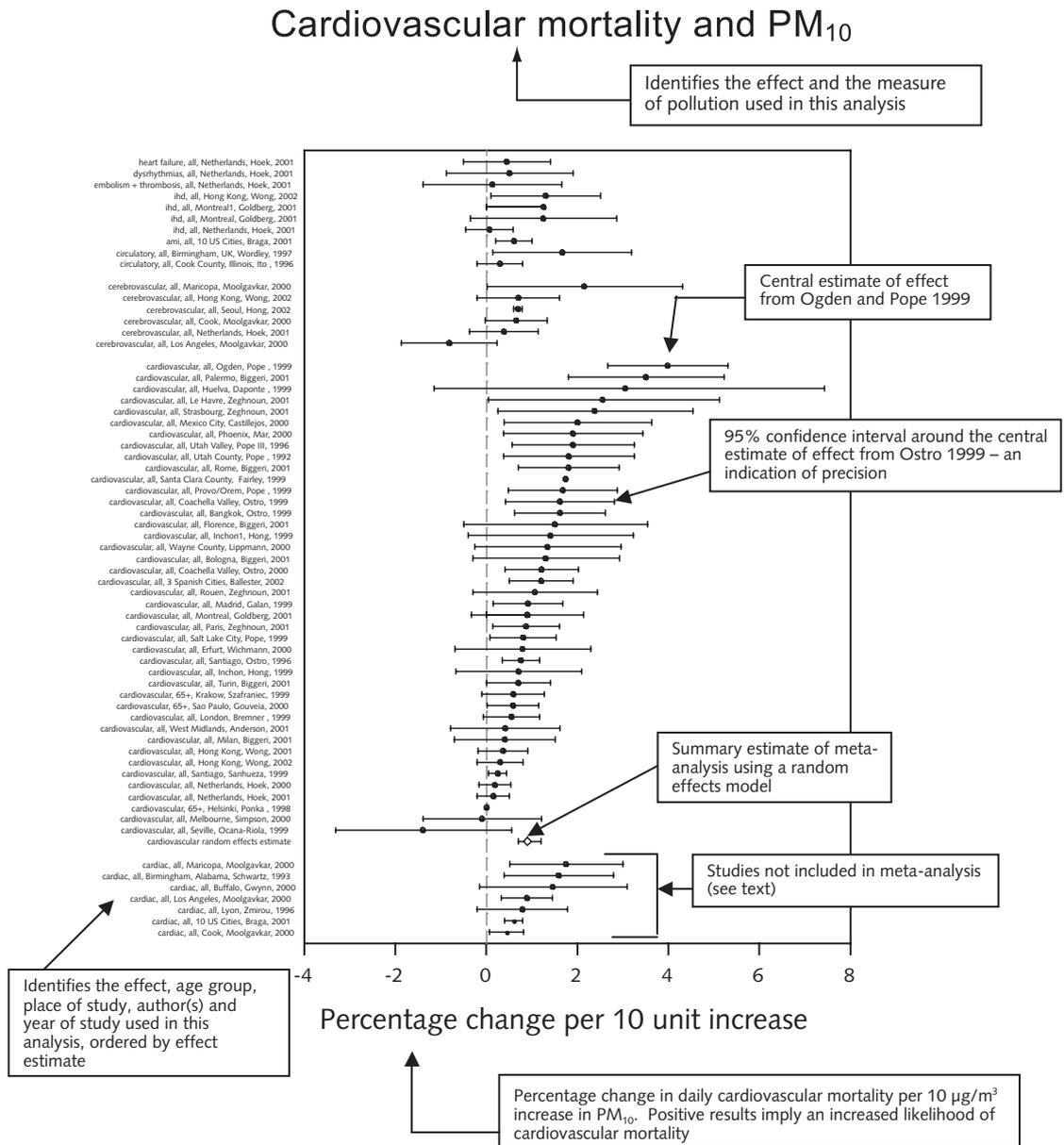
2.44 The y (vertical) axis contains the identifying data for each study in the order of: diagnosis, age-group, city, first author and year of publication. This enables more details about the estimate to be obtained by consulting Appendices 3a and 3b. Studies are ordered by effect estimate size within diagnoses. The black dots in the body of the graph represent the effect estimates for the given diagnosis/age/city combination. The ends of the horizontal arms from these dots represent the 95% confidence limits, which are an indication of the precision of an estimate. They represent the range

within which we are 95% confident that the underlying true estimate lies. If one of the arms of the confidence interval crosses zero (the no-effect point), there is a stronger possibility that there is no real effect and that the result is due to chance. If the confidence interval does not cross the zero point, the estimate is regarded as unlikely to be due to chance. Wider confidence intervals indicate estimates with lower precision; this is usually due to greater random variation in studies with smaller sample sizes. Some publications did not give confidence limits or standard errors to calculate confidence limits; these are represented by a black dot with no horizontal arms. Some papers do not give effect estimates, but make it clear from the paper that the given analysis was carried out; these are represented on the forest plots by a black dot on zero with no confidence interval. Zero (0) is the point where there is no effect on the diagnosis/age/city combination by the given pollutant, shown with a vertical dashed line. The open diamonds are the summary estimates from random effects meta-analytical models for the diagnosis displayed immediately above it (excluding those studies which do not have confidence intervals). The x (horizontal) axis shows the percentage change for a 10-unit ($\mu g/m^3$) increase in pollutant ($1mg/m^3$ for CO). A positive estimate indicates that there is a given percentage increase in the given diagnosis/age/city combination associated with a 10 unit increase in the given pollutant (with the associated confidence interval). A negative estimate indicates that there is a given percentage reduction in the given diagnosis/age/city combination associated with a 10 unit increase in the given pollutant (with the associated confidence interval).

2.45   For those pollution/outcome pairs for which there were 5 or more estimates, a summary (or combined) estimate was calculated using a procedure which gives more weight to studies with more statistical power. (DerSimonian and Laird, 1986). A test of heterogeneity was done and both random and fixed effects models were fitted. Where there is evidence of heterogeneity (a p value of < 0.1 is a generally accepted guide), the random effects estimate is more appropriate as it reflects the greater uncertainty surrounding the estimate.

2.46   We tested for asymmetry using a funnel plot (Light and Pillemer, 1984) and used both Egger's and Begg's tests to examine whether this bias was statistically significant (Egger *et al*, 1997; Begg and Mazumdar, 1994). In the forest plots which follow, the summary estimate is represented as an open diamond at the end of the block of outcomes. Where there was evidence of asymmetry, we calculated an adjusted estimate using the "trim and fill" technique (Duval and Tweedie, 2000). Further details can be found in Appendix 2.

Cardiovascular mortality

2.47 Figures 2.5 to 2.15 show the association between cardiovascular mortality and PM_{10}, $PM_{2.5}$, Black Smoke, TSP, NO_2, O_3 (three averaging times), SO_2 and CO. These data are in corresponding tables in Appendix 3a, which also contains the relevant references. Where estimates have been reported for both all age mortality and mortality in those 65 or over, we have chosen the all-ages estimate. Combined estimates for those outcomes with 5 or more studies are shown in Tables 2 to 9 and are also displayed in the forest plots as open diamonds.

Cardiovascular mortality and particles

2.48 **PM_{10} (Figure 2.5b, Table 2.2).** There were nearly 70 estimates for PM_{10} and mortality from a cardiovascular diagnosis. The vast majority of these studies have produced positive associations, with only three studies having negative estimates. The quantitative meta-analysis was confined to those with cardiovascular mortality (as a whole category, not a sub group). There was significant heterogeneity and the random effects summary estimate was 0.9% (95% CI 0.7% to 1.2%)[2] for a 10-unit increase in PM_{10}.

Table 2.2: Combined estimates for PM_{10} and various cardiovascular outcomes (% change per 10 μg/m³)

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	40	<0.001	0.5 (0.4, 0.7)	0.9 (0.7, 1.2)	0.005	<0.001
CV admission	6	0.003	0.5 (0.2, 0.7)	0.3 (-0.4, 0.9)	0.851	0.847
Cardiac admission	51	<0.001	0.9 (0.8, 1.0)	0.9 (0.7, 1.0)	0.666	0.545
IHD admission	19	0.076	0.8 (0.6, 0.9)	0.8 (0.6, 1.1)	0.021	0.023
Dysrhythmias	7	0.174	0.6 (0.2, 1.0)	0.8 (0.1, 1.4)	0.051	0.122
Heart Failure	7	<0.001	1.0 (0.7, 1.3)	1.4 (0.5, 2.4)	0.652	0.656
Cerebrovascular	9	0.041	0.3 (0.1, 0.6)	0.4 (0.0, 0.8)	0.458	0.492

Notes: IHD includes the diagnosis acute myocardial infarction (AMI) where the analysis of IHD is not given.

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2   The full expression of the summary estimate and its confidence intervals has been abbreviated in the tables of this chapter and is presented, for example, as 0.9 (0.7, 1.2)

Figure 2.5b

Cardiovascular mortality and PM$_{10}$

Percentage change per 10 unit increase
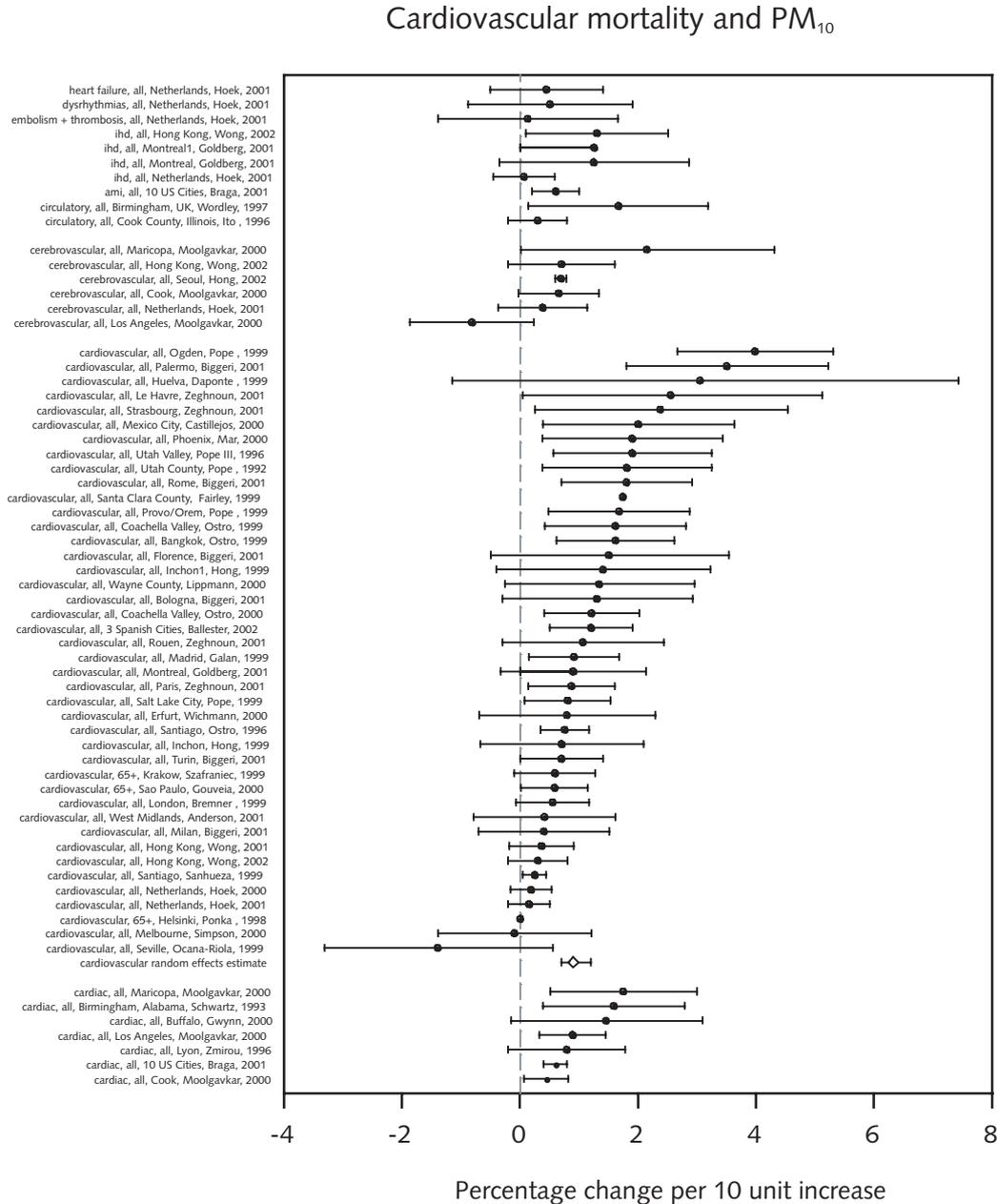
2.49 There was strong evidence of publication bias in the funnel plot (Figure 2.6) according to both Begg's test and Egger's test. When the "trim and fill" analysis was done, the number of "missing" studies was estimated at 15. Re-estimation to allow for these led to a reduction of the random effects estimate to 0.5% (95% CI 0.3% to 0.8%) and of the fixed effects estimate to 0.4% (95% CI 0.3% to 0.5%). The adjusted random effects estimate is probably the best estimate of the association available from published studies.

Figure 2.6: Funnel plot of cardiovascular mortality and PM$_{10}$
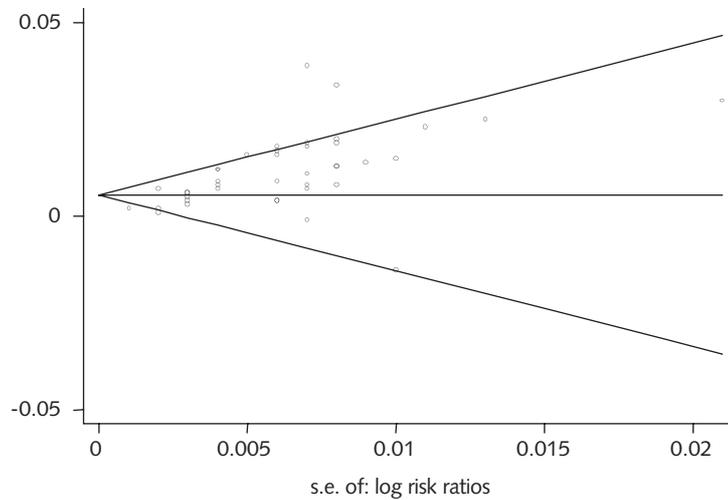
Random effects meta analysis percentage change for a 10 unit increase is 0.9 (0.7 to 1.2), fixed effect estimates are 0.5 (0.4 to 0.7) based on 40 estimates. Heterogeneity p<0.001. Begg p=0.005, Egger p<0.001.

Begg's funnel plot with pseudo 95% confidence limits
Log risk ratios for 10 µg/m³ increase in PM$_{10}$

2.50 **PM$_{2.5}$ (Figure 2.7, Table 2.3).** There were 17 estimates and all were positive in direction. For the 9 estimates for all cardiovascular mortality there was no evidence of heterogeneity and the combined estimate was 1.4% (95% CI 0.7% to 2.2%). There was no evidence of publication bias.

Figure 2.7

Cardiovascular mortality and PM$_{2.5}$
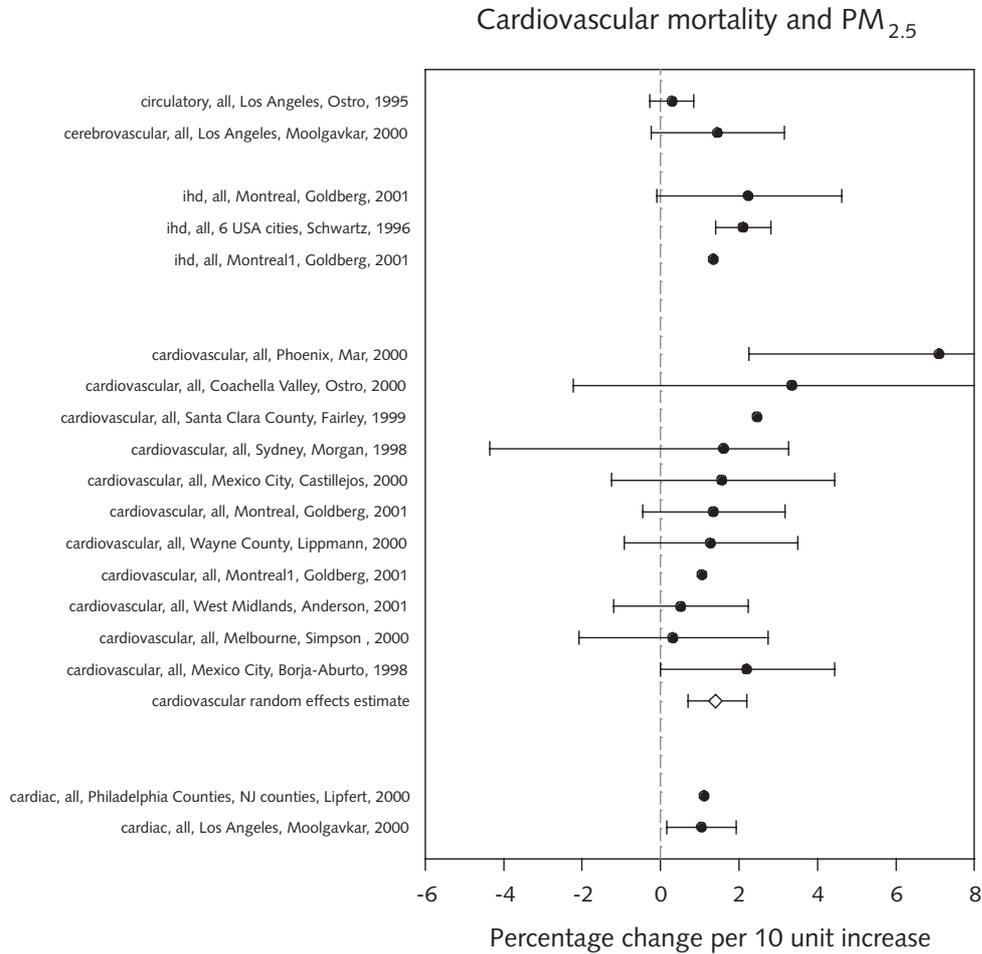
Table 2.3: Combined estimates for PM$_{2.5}$ and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	9	0.414	1.4 (0.7, 2.2)	1.4 (0.7, 2.2)	0.297	0.059

2.51 **Black Smoke (Figure 2.8, Table 2.4)**. A similar pattern was observed for the 37 estimates for Black Smoke, with all but three estimates being positive. For cardiovascular mortality there was some evidence of heterogeneity and the combined random effects estimate was 0.6% (95% CI 0.4% to 0.7%). There was moderate evidence of publication bias.

Figure 2.8

Cardiovascular mortality and Black Smoke

Percentage change per 10 unit increase
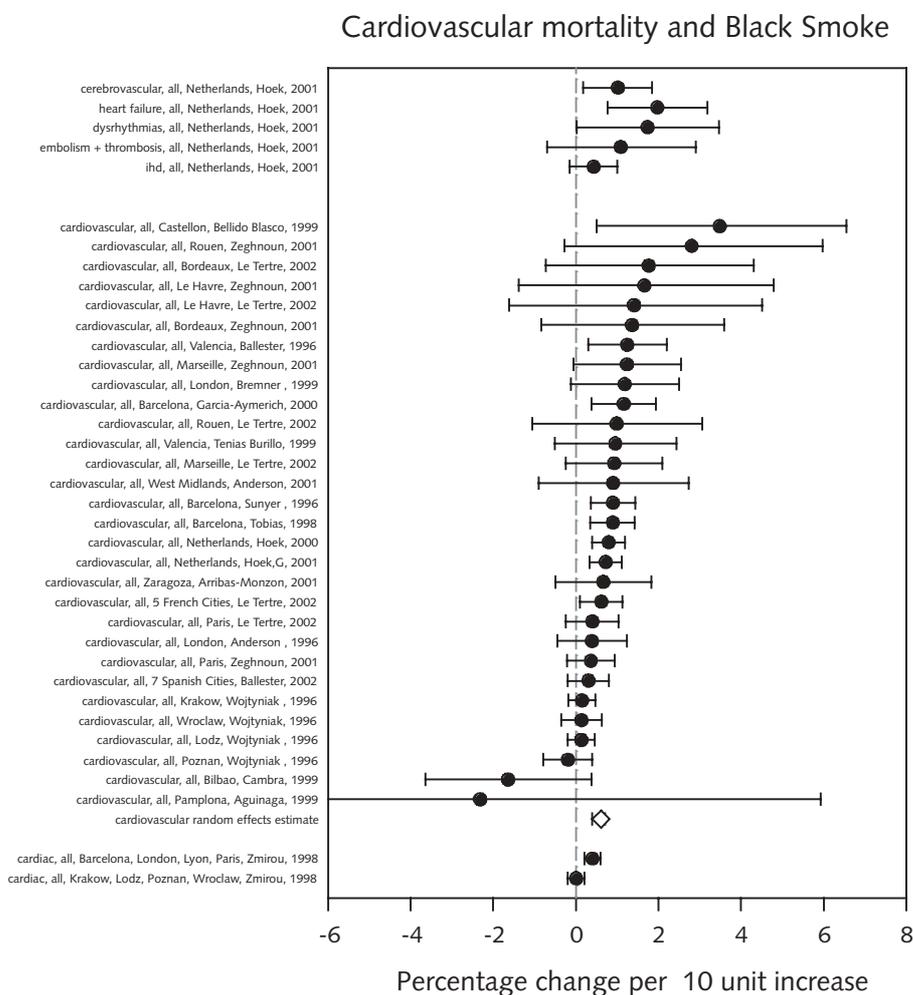
Table 2.4: Combined estimates for Black Smoke and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	29	0.030	0.5 (0.4, 0.6)	0.6 (0.4, 0.7)	0.280	0.056
CV admission	5	0.330	1.0 (0.5, 1.5)	1.0 (0.4, 1.5)	0.801	0.731
Cardiac admission	6	<0.000	0.1 (0.0, 0.1)	0.8 (0.2, 1.4)	0.573	0.028
IHD admission	8	0.124	1.1 (0.7, 1.5)	1.1 (0.4, 1.7)	0.621	0.663

2.52 **TSP (Figure 2.9, Table 2.5).** All but three of the 30 estimates for cardiovascular mortality and TSP were positive. The combined estimate was 0.4% (95% CI 0.3% to 0.5%). There was weak evidence of publication bias.

Figure 2.9

Cardiovascular mortality and TSP
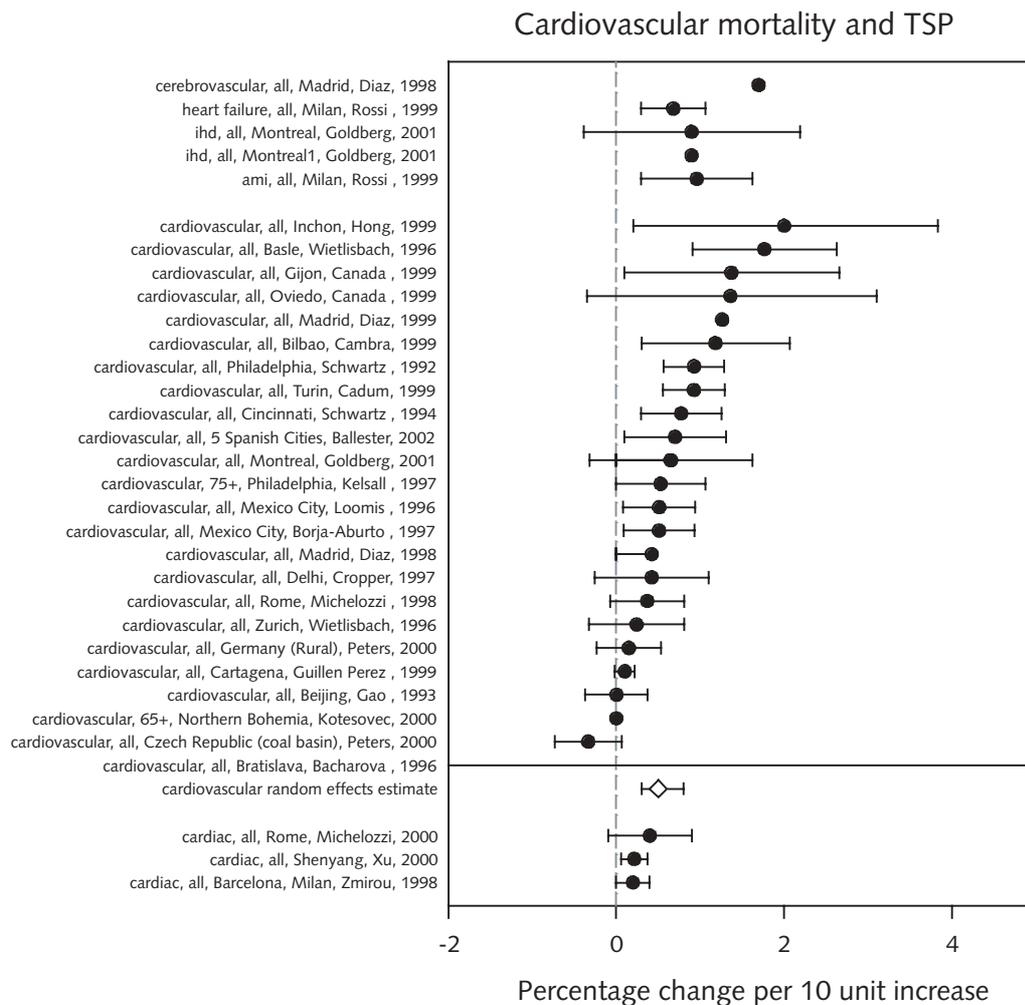
Table 2.5: Combined estimates for TSP and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	21	<0.001	0.4 (0.3, 0.5)	0.5 (0.3, 0.8)	0.205	0.022

Cardiovascular mortality and nitrogen dioxide (Figure 2.10, Table 2.6)

2.53   There were 67 estimates for cardiovascular mortality or sub groupings thereof.
The vast majority were positive and many had lower confidence intervals above zero.
The 44 estimates for the cardiovascular mortality diagnostic group were highly
heterogeneous. The random effects estimate was 1.0% (95% CI 0.8% to 1.3%).
There was moderate evidence of publication bias.

Figure 2.10

Cardiovascular mortality and NO_2

Percentage change per 10 unit increase
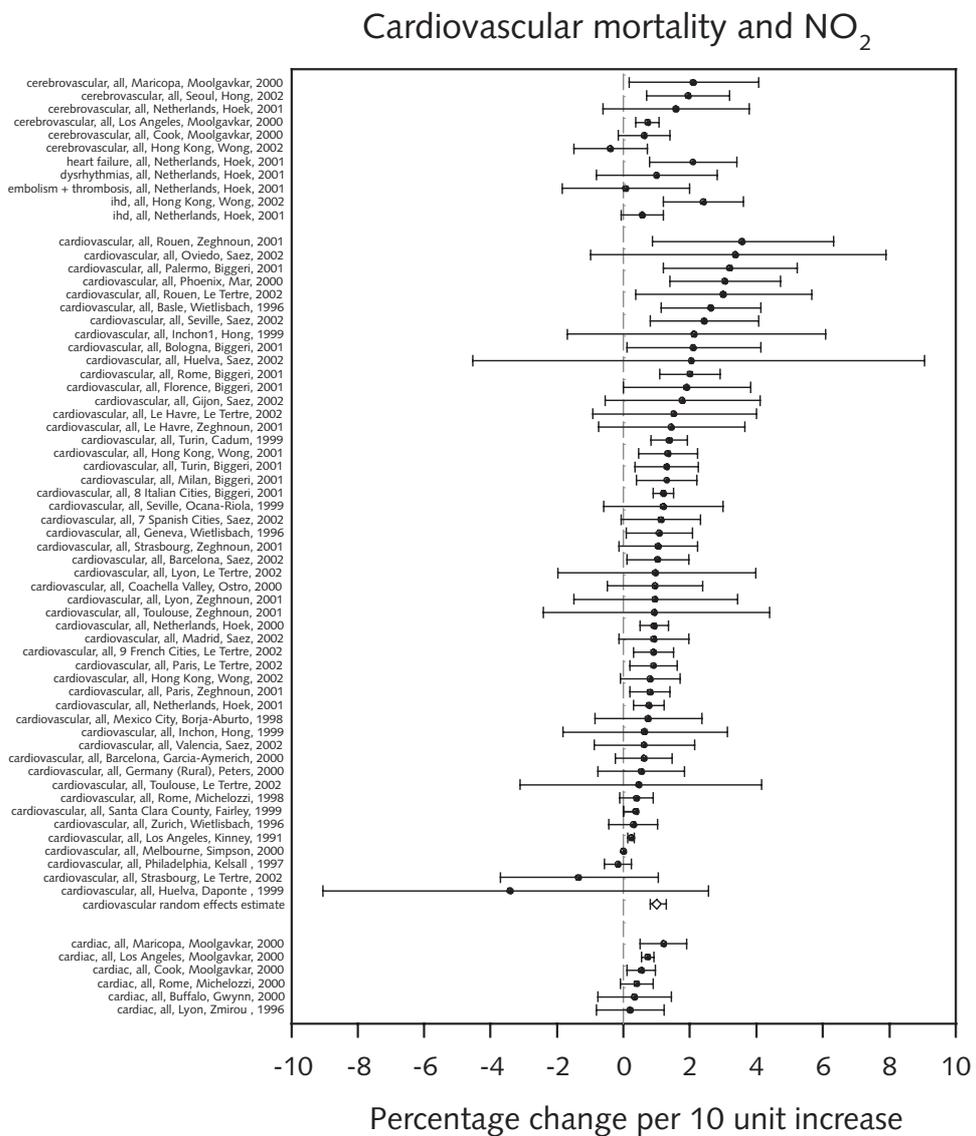
Table 2.6: Combined estimates for NO_2 and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	44	<0.001	0.4 (0.3, 0.5)	1.0 (0.8, 1.3)	0.321	<0.001
Cardiac admission	17	<0.001	1.2 (1.2, 1.3)	1.3 (1.0, 1.7)	0.707	0.763
IHD admission	9	<0.001	1.0 (0.8, 1.2)	0.6 (-0.1, 1.4)	0.276	0.136
Heart Failure	6	<0.001	0.7 (0.5, 1.0)	1.3 (0.4, 2.3)	0.421	0.158
Cerebrovascular	8	<0.001	0.5 (0.3, 0.6)	0.4 (0.0, 0.8)	0.899	0.670

Note: Madrid cardiac estimate missing because of misprint in the paper (Saez et al, 2002)

Cardiovascular mortality and ozone (Figures 2.11-2.13, Table 2.7).

2.54   The estimates for 1-hour ozone tended to be positive and the majority were significant. The largest number of estimates (38) were for 8 hour ozone. Unlike most of the other pollutant–outcome pairs, there was little evidence of heterogeneity and only weak evidence of publication bias. The combined estimate for 8-hour ozone was 0.4% (95% CI 0.3% to 0.5%). In contrast, the 13 estimates for 24-hour ozone were more variable and fewer were statistically significant. It should be noted that there are systematic regional differences in the averaging times used, with most 24-hour estimates coming from North America, and most 8-hour estimates coming from Europe.

2.55   The summary estimates differ slightly from those that will be found in the forthcoming Department of Health Report on ozone and a recent WHO report (World Health Organization, 2004b). This is because the APED database is continually evolving with the addition of new studies and because of differences in the criteria for selecting studies and cities according to the purposes at the time.

Figure 2.11

Cardiovascular mortality and 1-hour ozone

Forest plot showing, from top to bottom:
- cardiovascular, all, Brisbane, Simpson, 1997
- cardiovascular, all, Barcelona, Tobias, 1998
- cardiovascular, all, Barcelona, Sunyer, 1996
- cardiovascular, all, Sydney, Morgan, 1998
- cardiovascular, all, London, Anderson, 1996
- cardiovascular, 65+, Sao Paulo, Gouveia, 2000
- cardiovascular, all, Mexico City, Borja-Aburto, 1997
- cardiovascular, all, Mexico City, Loomis , 1996
- cardiovascular, all, Coachella Valley, Ostro, 2000
- cardiac, all,4 European Cities, Zmirou, 1998
- cardiac, all, Lyon, Zmirou, 1996

Percentage change per 10 unit increase

Figure 2.12

Cardiovascular mortality and 8-hour ozone

Percentage change per 10 unit increase
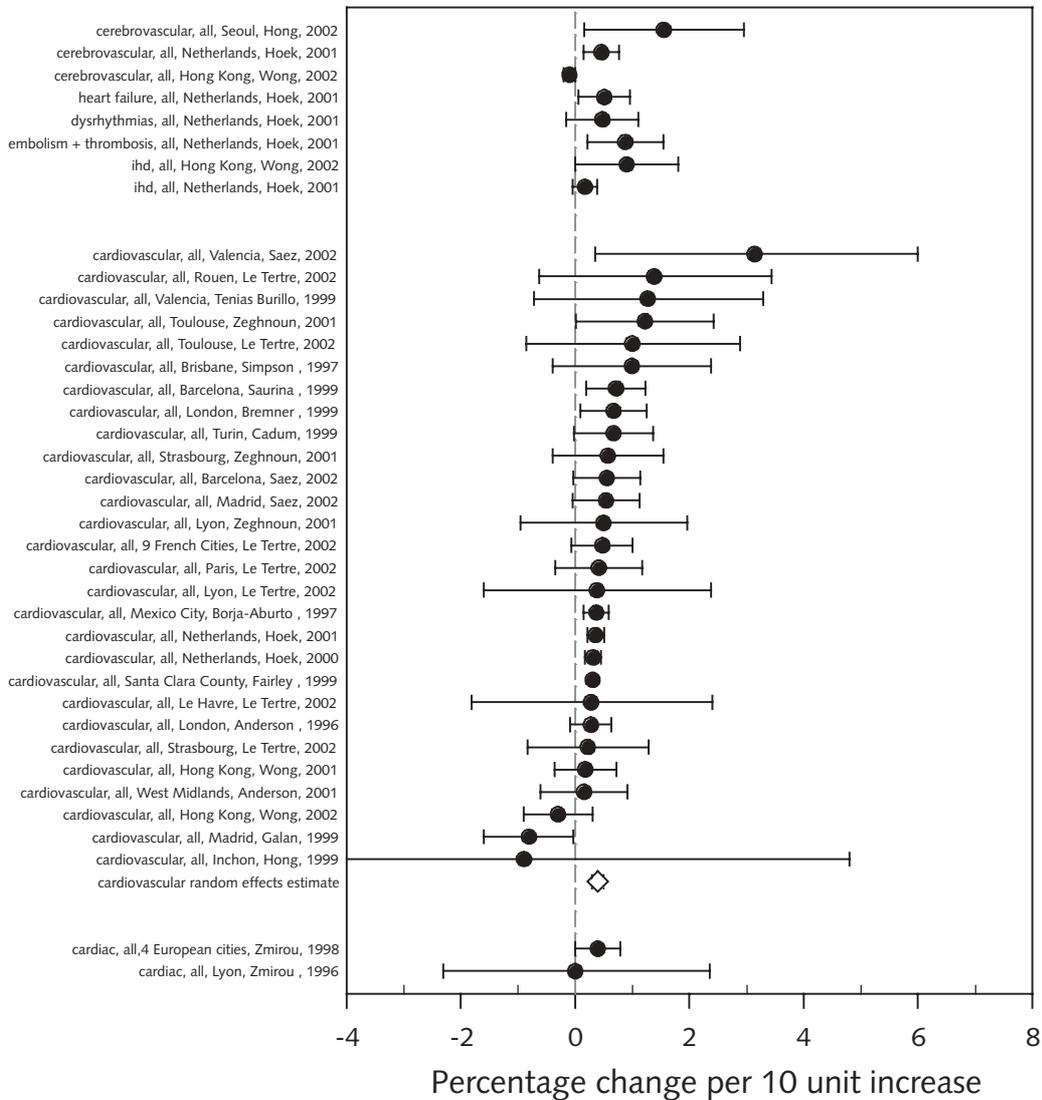
Table 2.7: Combined estimates for 8-hour ozone and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	26	0.298	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	0.212	0.250
CV admission	8	0.001	0.1 (-0.1, 0.3)	0.1 (-0.5, 0.4)	0.441	0.352
IHD admission	6	0.009	-0.2 (-0.4, 0.1)	-0.1 (-0.7, 0.4)	0.837	0.801

Figure 2.13

Cardiovascular mortality and 24-hour ozone

Percentage change per 10 unit increase
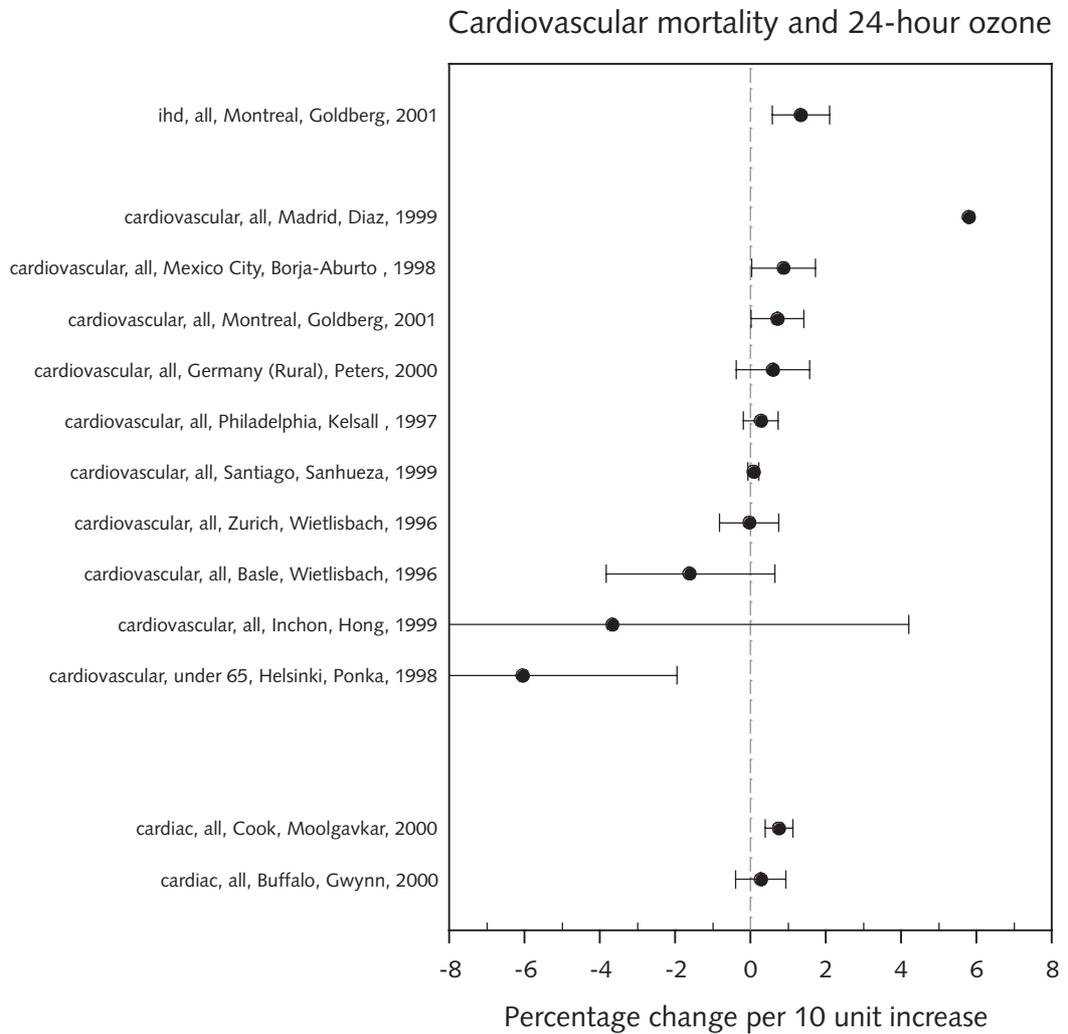
Cardiovascular mortality and SO$_2$ (Figures 2.14a and 2.14b, Table 2.8)

2.56   There were nearly 90 estimates for SO$_2$. The majority were positive and many were significant and relatively large. The 67 estimates of all cardiovascular mortality were highly heterogeneous. The combined estimate was 0.8% (95% CI 0.6% to 1.0%). There was moderately strong evidence of publication bias.

Figure 2.14a

Cardiovascular mortality and SO$_2$

Figure 2.14b

Other cardiovascular mortality diagnoses and SO$_2$

Percentage change per 10 unit increase
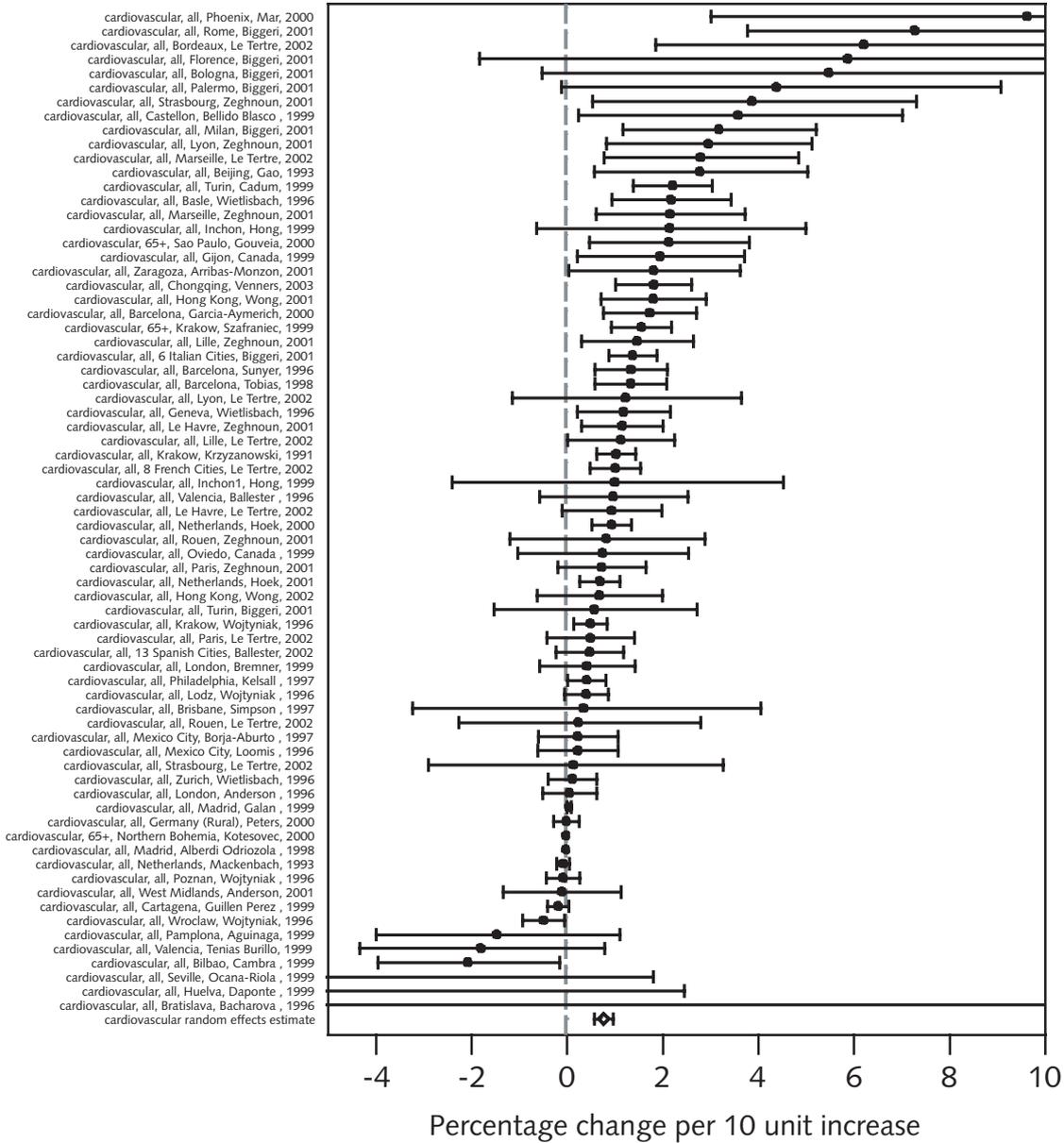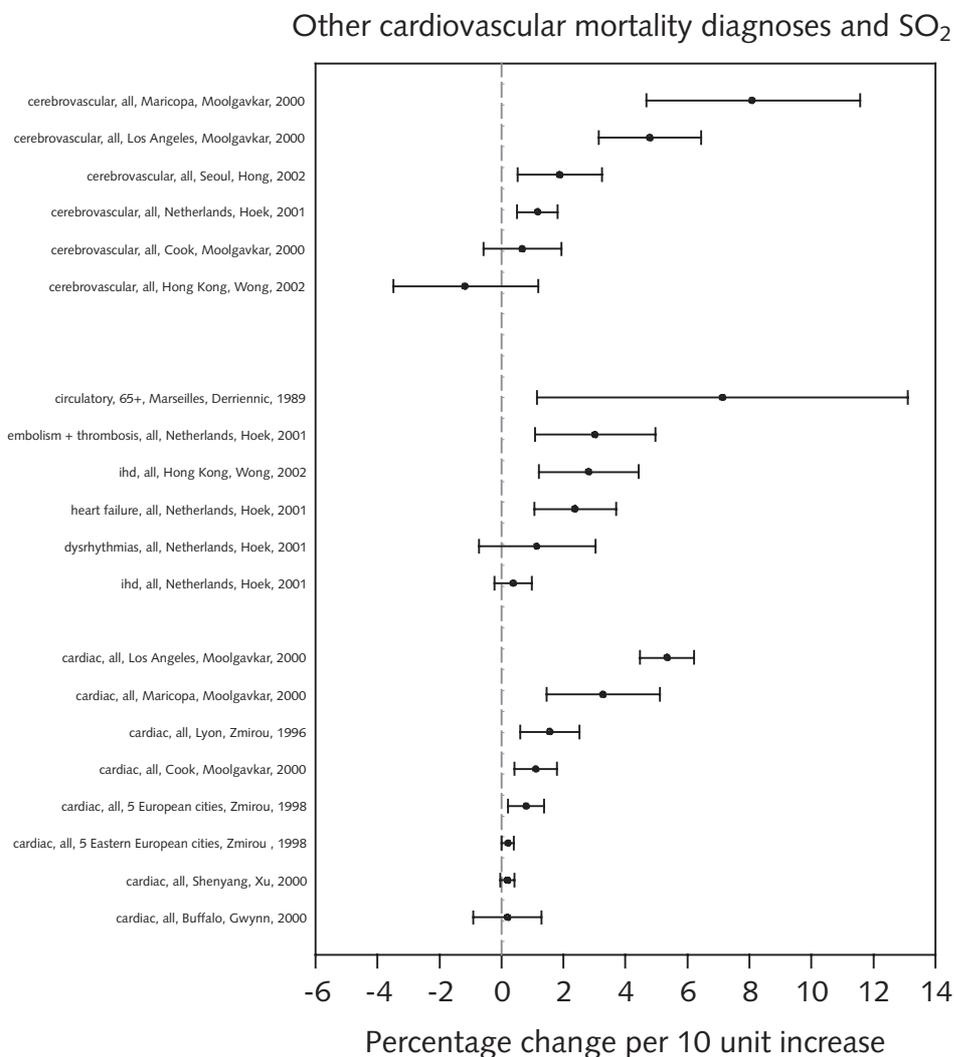
Table 2.8: Combined estimates for SO$_2$ and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	67	<0.001	0.1 (0.1, 0.2)	0.8 (0.6, 1.0)	0.741	<0.001
CV admission	7	0.013	0.5 (0.2, 0.8)	0.6 (0.1, 1.2)	0.215	0.341
Cardiac admission	18	<0.001	1.7 (1.5, 1.8)	2.4 (1.6, 3.3)	0.182	0.188
IHD admission	10	<0.001	0.9 (0.7, 1.2)	1.2 (0.5, 1.9)	0.468	0.163
Heart failure	5	<0.001	0.5 (0.2, 0.8)	0.9 (-0.1, 1.8)	0.327	0.413
Cerebrovascular	7	<0.001	0.3 (0.0, 0.6)	0.3 (-0.5, 1.1)	0.761	0.871

Cardiovascular mortality and CO (Figure 2.15, Table 2.9)

2.57   The 20 estimates for CO were generally positive and there was evidence of heterogeneity. The combined estimate for all cardiovascular mortality (12 observations) was 1.1% (95% CI 0.2% to 2.1% per 1 mg/m). Based on the p-values and inspection of the funnel plots, there was a suggestion of publication bias.

Figure 2.15

Cardiovascular mortality and CO
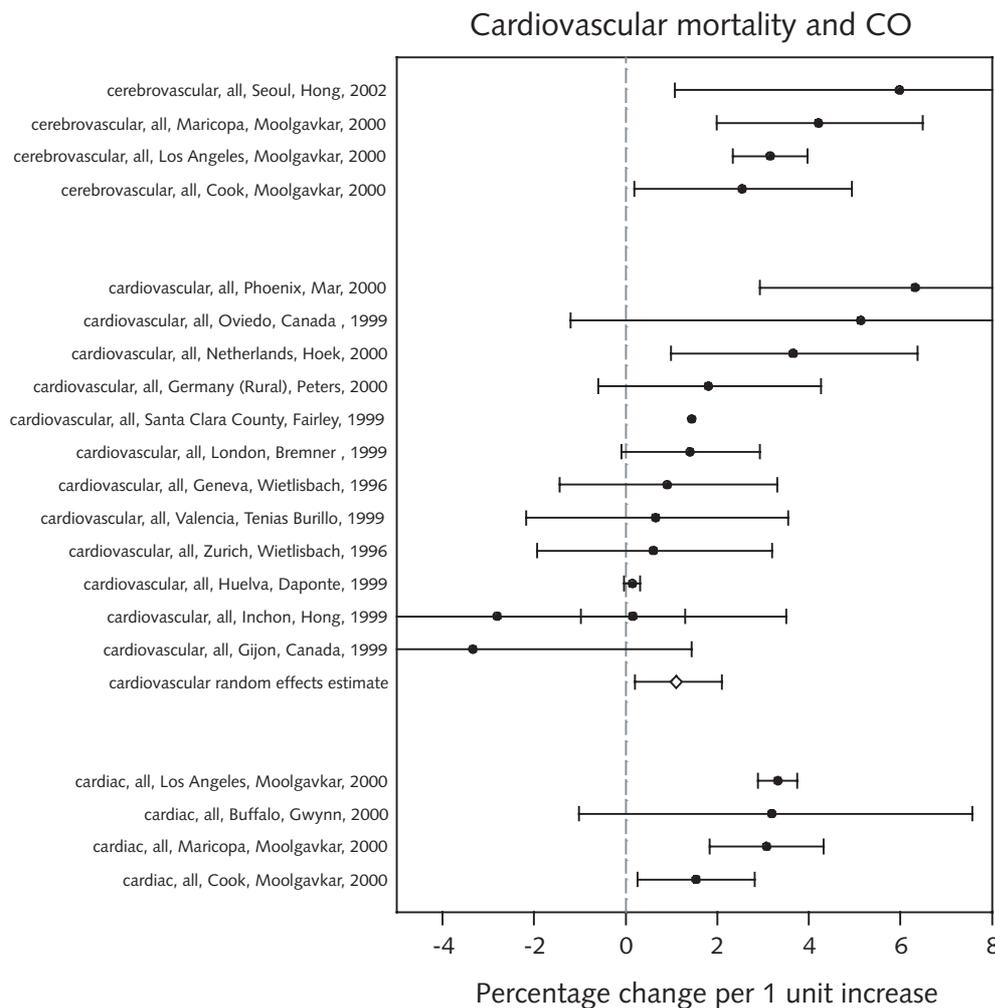
Table 2.9: Combined estimates for CO and cardiovascular mortality

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	12	0.002	0.2 (0.0, 0.4)	1.1 (0.2, 2.1)	0.730	0.076
Cardiac admission	8	<0.001	3.1 (2.8, 3.3)	2.5 (1.8, 3.3)	0.209	0.138
IHD admission	7	<0.001	0.4 (0.1, 0.8)	2.4 (0.2, 4.6)	0.645	0.071
Cerebrovascular	5	0.007	1.4 (1.0, 1.7)	0.8 (-0.1, 1.8)	0.782	0.151

Cardiovascular Hospital Admissions

Particles – PM$_{10}$ (Figures 2.16a and 2.16b, Table 2.10)

2.58 **PM$_{10}$ and cardiac admissions. Fig 2.16a** This category excludes cerebrovascular and circulatory causes. There were 51 estimates for PM$_{10}$ and the summary estimate was significant, 0.9% (95% CI 0.7% to 1.0%). There was no evidence of publication bias.

2.59 **PM$_{10}$ and all cardiovascular admissions. Fig 2.16b.** This group included both cardiac and cerebrovascular diagnoses. There were only six estimates for PM$_{10}$ and the random effects summary was non-significant, 0.3% (95% CI -0.4% to 0.9%).

2.60 **PM$_{10}$ and IHD admissions.** This category included studies which specifically examined acute myocardial infarction. There were 19 studies and the combined estimate was 0.8% (95% CI 0.6% to 1.1%). There was moderate evidence of heterogeneity and strong evidence of publication bias (Figure 2.17). When adjusted using the trim and fill technique, the fixed effect estimate changed from 0.8% (95% CI 0.6% to 0.9%) to 0.7% (95% CI 0.6% to 0.9%) but the random effects estimate remained at 0.8% (95% CI 0.5% to 1.0%).

2.61 **PM$_{10}$ and dysrhythmia admissions.** There were 8 estimates and the combined estimate was significant 0.8% (95% CI 0.1% to 1.4%). There was moderate evidence of publication bias.

2.62 **PM$_{10}$ and heart failure admissions.** There were eight estimates and all but one were positive. The combined estimate was 1.4% (95% CI 0.5% to 2.4%). There was no evidence of publication bias.

2.63 **PM$_{10}$ and cerebrovascular admissions.** There were 9 estimates, one of which was a combined estimate from 8 European cities. All but one were positive. The combined estimate bordered on significance 0.4% (95% CI 0.0% to 0.8%). There was no evidence of publication bias.

Figure 2.16a

Cardiac admissions and PM$_{10}$
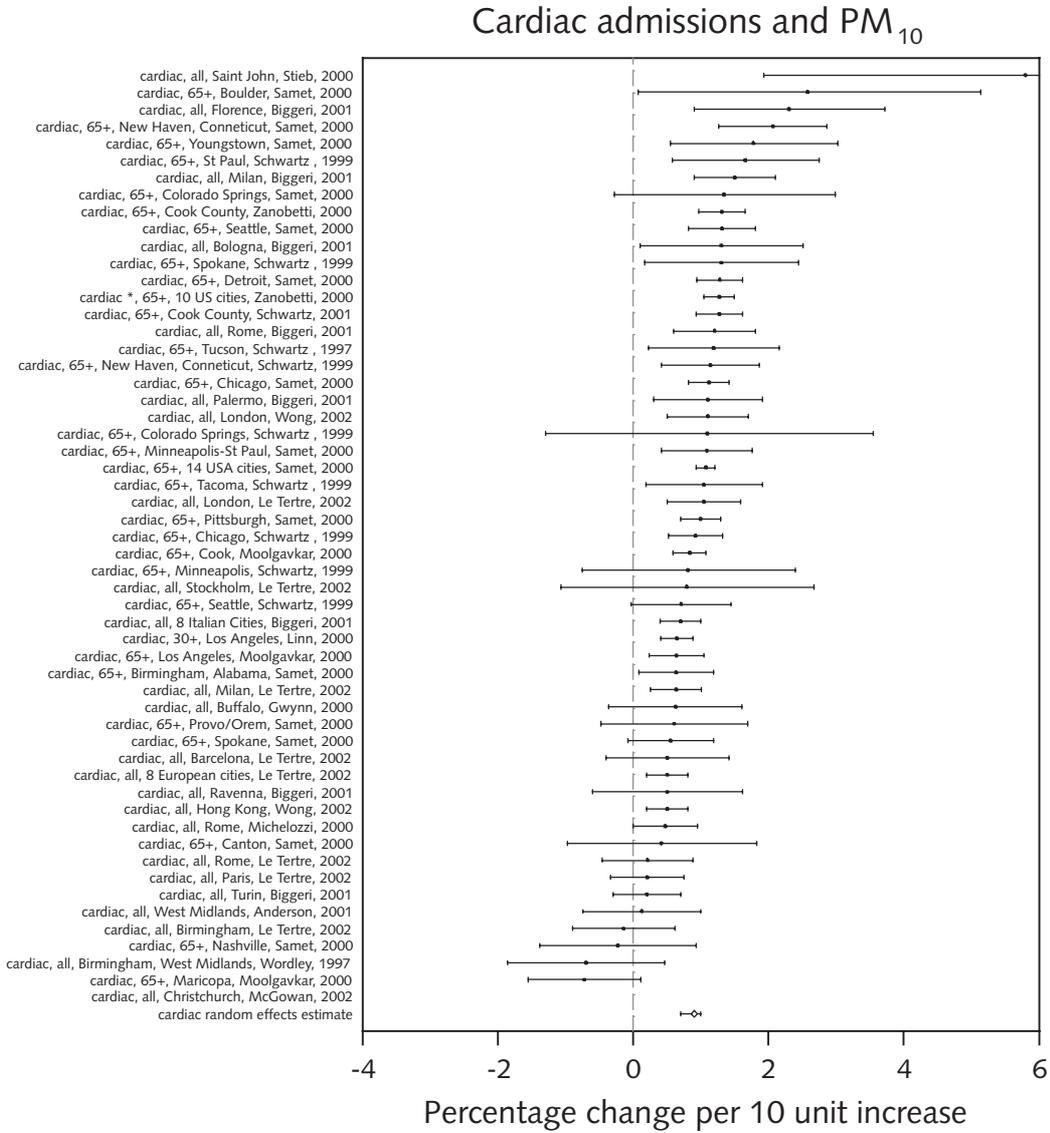
Figure 2.16b

Other cardiovascular admissions diagnoses and PM$_{10}$

Percentage change per 10 unit increase
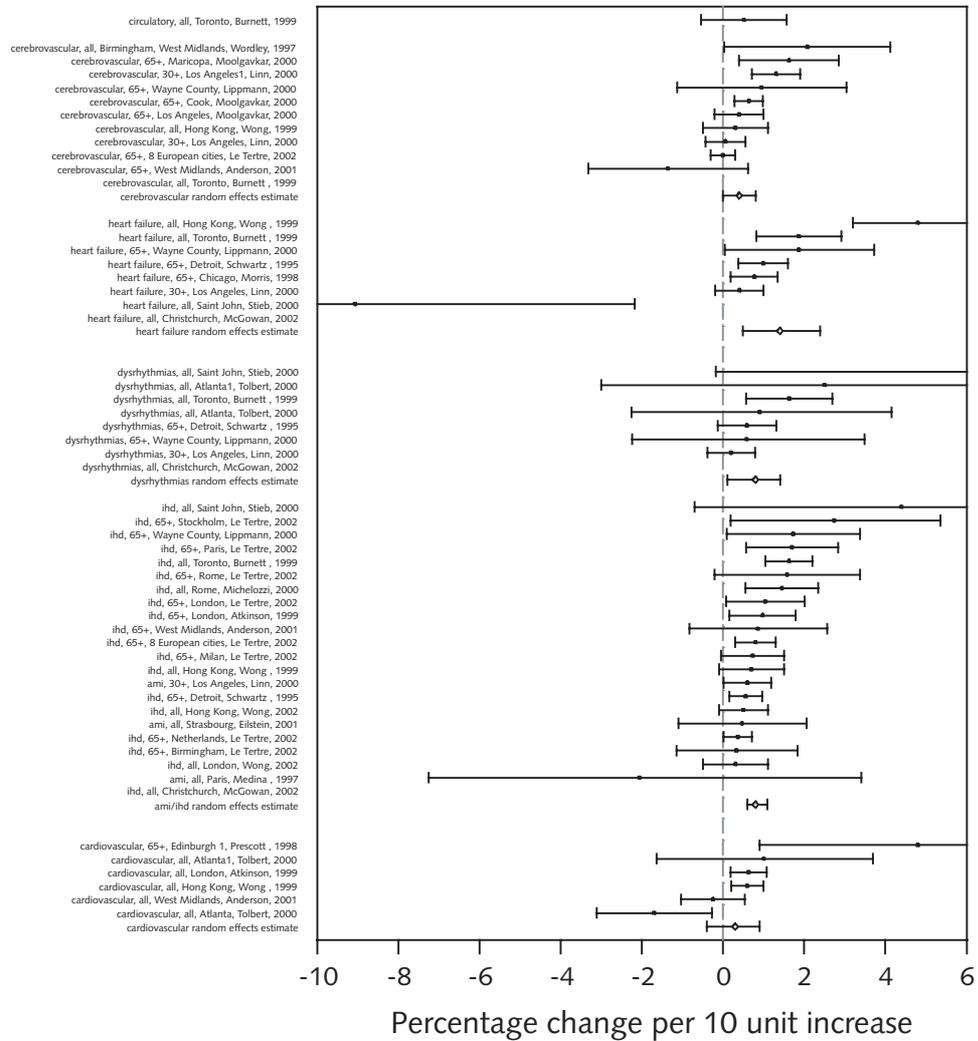
Table 2.10: Combined estimates for PM$_{10}$ and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	40	<0.001	0.5 (0.4, 0.7)	0.9 (0.7, 1.2)	0.005	<0.001
CV admission	6	0.003	0.5 (0.2, 0.7)	0.3 (-0.4, 0.9)	0.851	0.847
Cardiac admission	51	<0.001	0.9 (0.8, 1.0)	0.9 (0.7, 1.0)	0.666	0.545
IHD admission	19	0.076	0.8 (0.6, 0.9)	0.8 (0.6, 1.1)	0.021	0.023
Dysrhythmias	7	0.174	0.6 (0.2, 1.0)	0.8 (0.1, 1.4)	0.051	0.122
Heart failure	7	<0.001	1.0 (0.7, 1.3)	1.4 (0.5, 2.4)	0.652	0.656
Cerebrovascular	9	0.041	0.3 (0.1, 0.6)	0.4 (0.0, 0.8)	0.458	0.492

2.64 The funnel plot of IHD admissions and PM_{10} (Figure 2.17) revealed asymmetry and tests for publication bias were significant.

Figure 2.17: Funnel plot of IHD admissions and PM_{10}
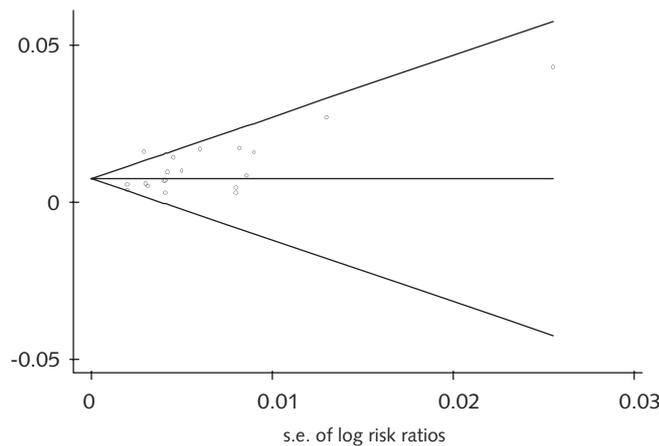
Begg's funnel plot with pseudo 95% confidence limits

Log risk ratios for 10 µg/m³ increase in PM_{10}

Random effects meta analysis percentage change for a 10 unit increase is 0.8 (0.6 to 1.1), fixed effect estimates are 0.8 (0.6 to 0.9) based on 19 estimates. Heterogeneity p=0.076. Tests for publication bias: Begg p=0.021, Egger p=0.023.

Heterogeneity of estimates for PM_{10} and cardiovascular admissions

2.65 The heterogeneity observed in most of these meta-analyses is not well understood but may, amongst other explanations, provide insights into the relative toxicity of the PM mixture in different cities. This was investigated in relation to PM and hospital admissions for cardiovascular diseases as part of the APHEA project (Le Tertre *et al*, 2002). While the small number of cities (8) was too small to give a clear result, there were indications that the effect of PM_{10} on cardiac admissions was higher in cities with a higher correlation between PM_{10} and NO_2. The effect of PM_{10} on ischaemic heart disease admissions for people over 65 was increased in cities with a higher correlation between PM_{10} and CO, and with lower annual concentrations of ozone. From this, it was tentatively concluded that the effects of PM_{10} were higher when associated with primary emission sources.

Particles – $PM_{2.5}$ (Figure 2.18)

2.66 There were 21 estimates for cardiovascular admissions, distributed fairly evenly among the various diagnostic categories. About one third were less than zero and about one third were significantly positive. There was no clear difference between the different diagnoses. In the largest European study, that of the West Midlands region in the UK, no associations were found with admissions for cardiac, cardiovascular, cerebrovascular or ischaemic heart disease.

Figure 2.18

Cardiovascular admissions and PM$_{2.5}$

Percentage change per 10 unit increase
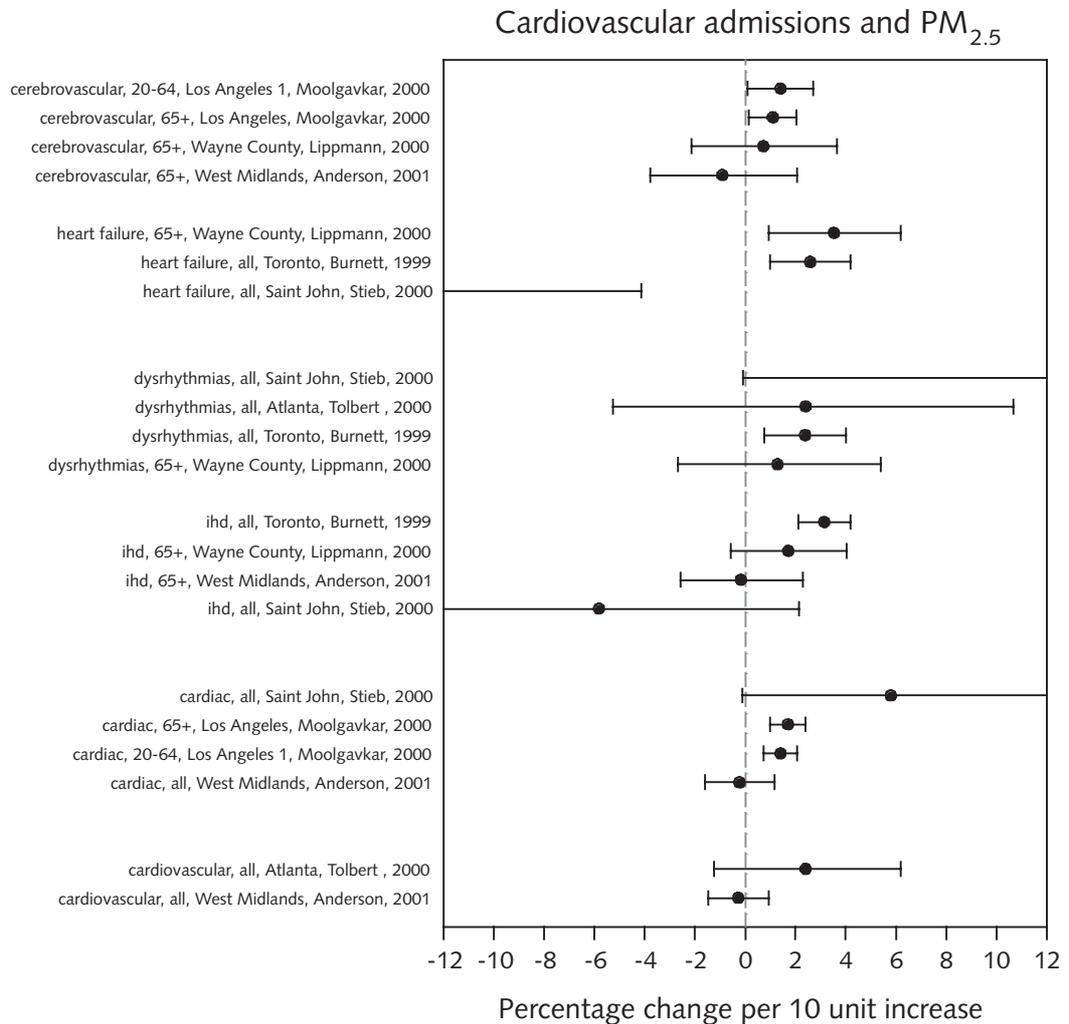
2.67 **Particles – Black Smoke (Figure 2.19, Table 2.11)** There were 28 estimates for Black Smoke and admissions for cardiovascular diagnoses.

2.68 **Black Smoke and admissions for all cardiovascular conditions.** There were 6 estimates and all but one were positive. The combined effect was 1.0% (95% CI 0.4% to 1.5%). There was no evidence of publication bias.

2.69 **Black Smoke and admissions for cardiac diagnoses.** There were 6 estimates, all of which were positive. There was strong evidence of heterogeneity. The combined estimate was 0.8% (95% CI 0.2% to 1.4%). There was moderate evidence of publication bias.

2.70 **Black Smoke and admissions for IHD diagnoses.** Most of the 10 estimates were positive and the combined estimates was 1.1% (95% CI 0.4% to 1.7%). There was no evidence of publication bias.

Figure 2.19

Cardiovascular admissions and Black Smoke
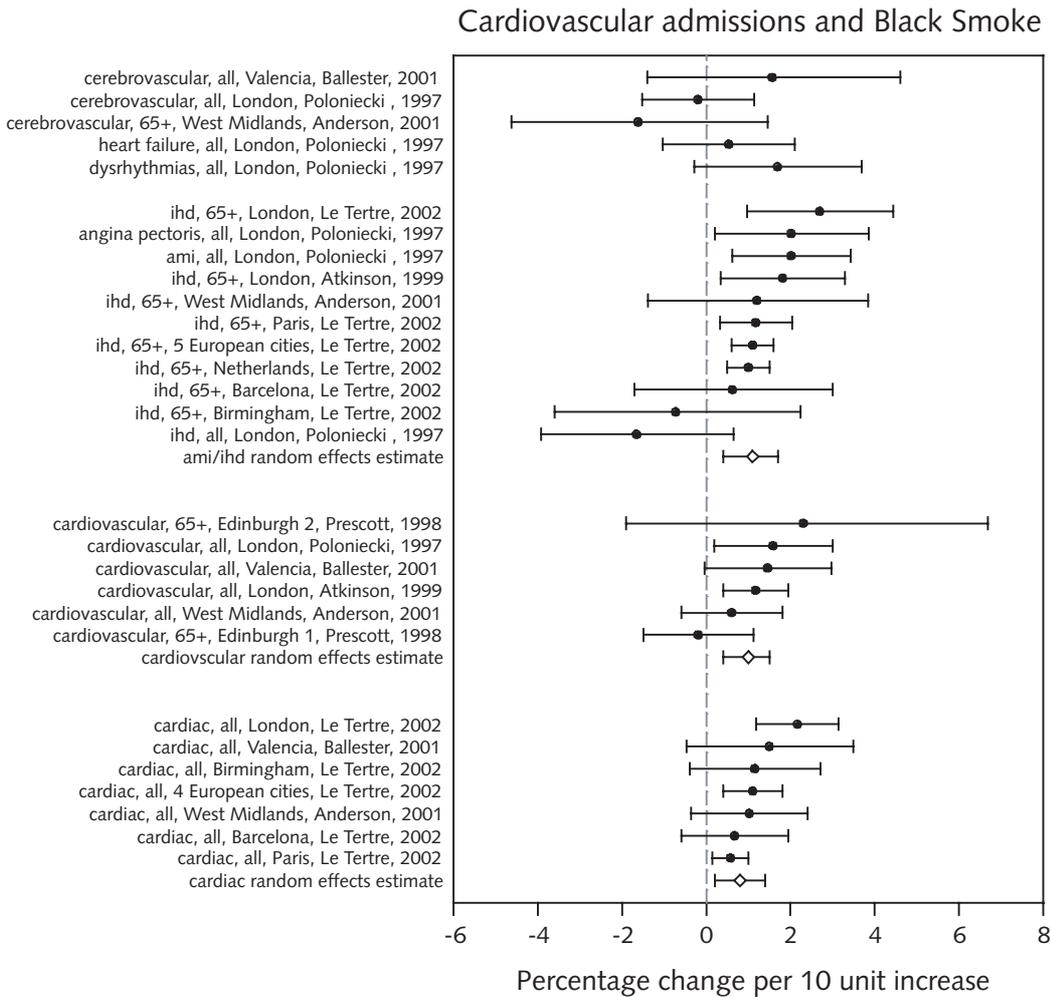
Table 2.11: Combined estimates for Black Smoke and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	29	0.030	0.5 (0.4, 0.6)	0.6 (0.4, 0.7)	0.280	0.056
CV admission	5	0.330	1.0 (0.5, 1.5)	1.0 (0.4, 1.5)	0.801	0.731
Cardiac admission	6	<0.000	0.1 (0.0, 0.1)	0.8 (0.2, 1.4)	0.573	0.028
IHD admission	8	0.124	1.1 (0.7, 1.5)	1.1 (0.4, 1.7)	0.621	0.663

2.71 **NO_2 and cardiovascular admissions (Figure 2.20, Table 2.12).** There were over 50 estimates and most were positive. Combined estimates were possible for cardiac, IHD, heart failure and cerebrovascular admissions.

2.72 **NO_2 and cardiac admissions.** There were 17 estimates including 8 from the Italian multi-city analysis. They showed considerable heterogeneity and the combined estimate was 1.3% (95% CI 1.0% to 1.7%). There was no evidence of publication bias.

2.73 **NO_2 and IHD admissions.** There were 11 estimates and most were positive. The combined estimate was not significant 0.6% (95% CI -0.1% to 1.4%). There was no evidence of positive reporting bias.

2.74 **NO_2 and heart failure admissions.** There were 6 estimates and 5 were positive. The combined estimate was 1.3% (95% CI 0.4% to 2.3%). There was weak evidence of publication bias.

2.75 **NO_2 and cerebrovascular admissions.** There were 8 estimates for cerebrovascular disease, of which 6 were positive. The combined estimate was borderline significant 0.4% (95% CI 0.0% to 0.8%). There was no evidence of publication bias.

Figure 2.20

Cardiovascular admissions and NO_2
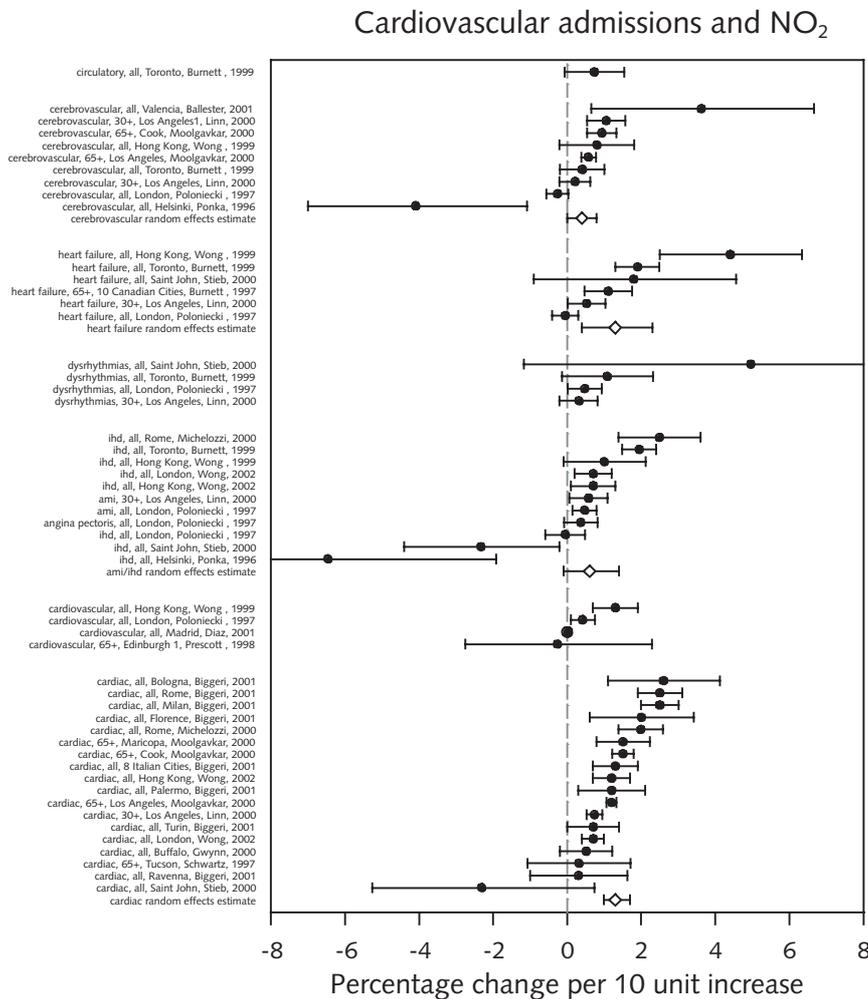
Table 2.12: Combined estimates for NO_2 and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	44	<0.001	0.4 (0.3, 0.5)	1.0 (0.8, 1.3)	0.321	<0.001
Cardiac admission	17	<0.001	1.2 (1.2, 1.3)	1.3 (1.0, 1.7)	0.707	0.763
IHD admission	9	<0.001	1.0 (0.8, 1.2)	0.6 (-0.1, 1.4)	0.276	0.136
Heart failure	6	<0.001	0.7 (0.5, 1.0)	1.3 (0.4, 2.3)	0.421	0.158
Cerebrovascular	8	<0.001	0.5 (0.3, 0.6)	0.4 (0.0, 0.8)	0.899	0.670

Note: Madrid cardiac estimate missing because of misprint in the paper (Saez *et al*, 2002)

2.76 **Ozone and admissions for cardiovascular diagnoses (Figures 2.21 to 2.23, Table 2.13).** There were 14 estimates for 1-hour ozone (including one Canadian combined estimate for 10 cities), 29 estimates for 8-hour ozone and 29 estimates for 24-hour ozone, including one combined estimate from 10 Canadian cities. Combined estimates were only calculated for 8-hour ozone in this review.

2.77 **1-hour ozone (Figure 2.21).** Of the 14 1-hour ozone estimates, most were from North America and were for heart failure. Most were positive but only one was statistically significant.

2.78 **8-hour ozone and admissions for all cardiovascular diagnoses (Figure 2.22).** There were 8 estimates, the majority of which were negative. The combined estimate was 0.1% (95% CI -0.5% to 0.4%). There was no evidence of positive publication bias.

2.79 **8-hour ozone and admissions for all ischaemic heart disease (Figure 2.22).** There were 8 estimates, the majority of which were negative. The combined estimate was –0.1% (95% CI -0.7% to 0.4%). There was no evidence of publication bias.

2.80 **8-hour ozone and admissions for other cardiovascular diagnoses (Figure 2.22).** There were too few for combination but it is notable that all four estimates for cerebrovascular disease were negative and none were significant.

2.81 **24-hour ozone (Figure 2.23).** There were too few studies for combination. About a quarter of the estimates were negative and there was a lot of scatter. Most of the studies with high precision (narrow confidence intervals) were not significant. The three estimates for cerebrovascular disease were not significant and were very close to zero.

Figure 2.21

Cardiovascular admissions and 1-hour ozone
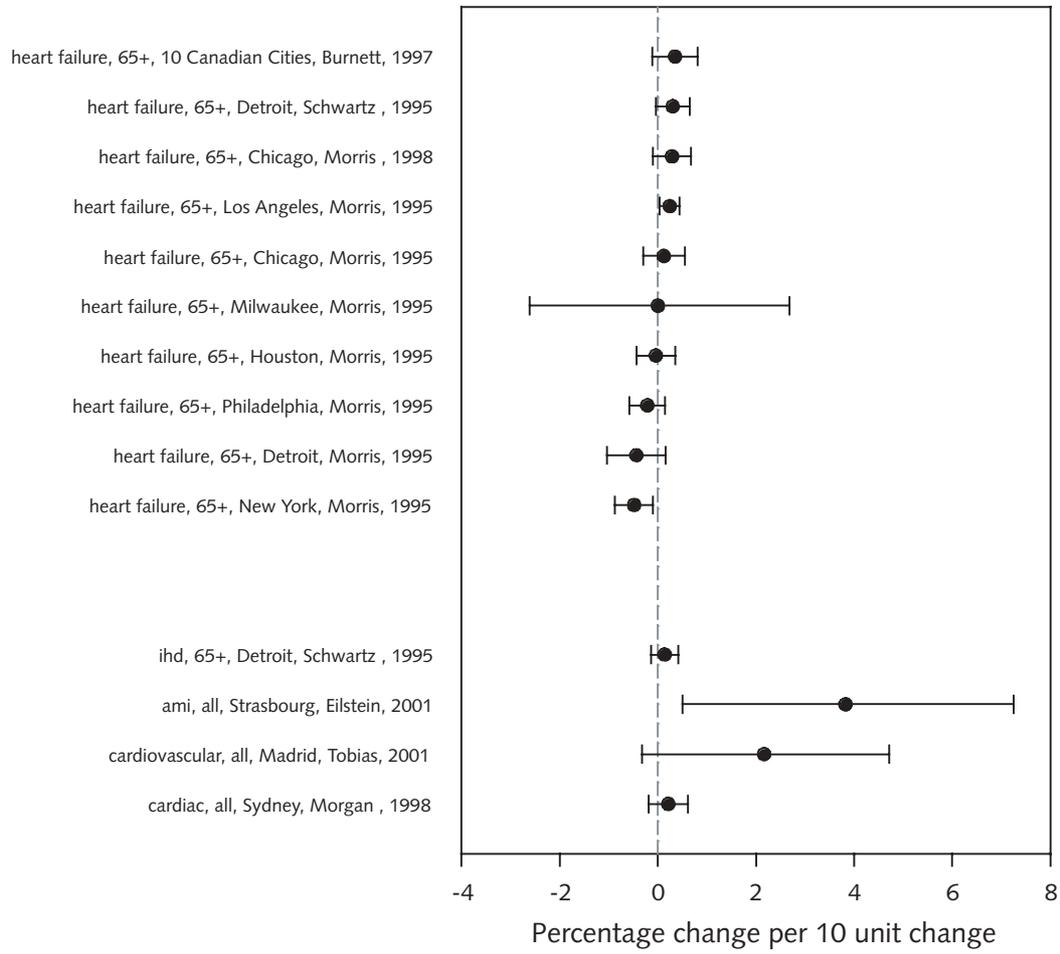
Figure 2.22

Cardiovascular admissions and 8 hour ozone

Percentage change per 10 unit increase

Figure 2.23

Cardiovascular admissions and 24-hour ozone

circulatory, all, Toronto, Burnett , 1999
cerebrovascular, 30+, Los Angeles, Linn, 2000
cerebrovascular, all, Toronto, Burnett , 1999
cerebrovascular, 65+, Hong Kong, Wong, 1999

heart failure, 65+, Hong Kong, Wong, 1999
heart failure, 65+, 10 Canadian Cities, Burnett , 1997
heart failure, all, Toronto, Burnett , 1999
heart failure, 30+, Los Angeles, Linn, 2000
heart failure, all, Saint John, Stieb, 2000

dysrhythmias, all, Saint John, Stieb, 2000
dysrhythmias, 65+, Hong Kong, Wong, 1999
dysrhythmias, all, Toronto, Burnett, 1999
dysrhythmias, 30+, Los Angeles, Linn, 2000

ihd, all, Saint John, Stieb, 2000
ihd, 65+, Hong Kong, Wong, 1999
ihd, all, Toronto, Burnett, 1999
ihd, all, Helsinki, Ponka, 1996
ami, all, Strasbourg, Eilstein, 2001
ami, 30+, Los Angeles, Linn, 2000

cardiovascular, all, Madrid, Diaz, 1999
cardiovascular, all, Madrid, Diaz, 2001
cardiovascular, 65+, Hong Kong, Wong, 1999
cardiovascular, 65+, Edinburgh 1, Prescott , 1998

cardiac, all, Saint John, Stieb, 2000
cardiac, 65+, Tucson, Schwartz, 1997
cardiac, all, Buffalo, Gwynn, 2000
cardiac, 30+, Los Angeles, Linn, 2000

Percentage change per 10 unit increase

Table 2.13: Combined estimates for 8-hour ozone and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	26	0.298	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	0.212	0.250
CV admission	8	0.001	0.1 (-0.1, 0.3)	0.1 (-0.5, 0.4)	0.441	0.352
IHD admission	6	0.009	-0.2 (-0.4, 0.1)	-0.1 (-0.7, 0.4)	0.837	0.801

2.82 **SO_2 and cardiovascular admissions (Figure 2.24, Table 2.14).** There were nearly 50 estimates for SO_2 of which 7 were negative.

2.83 **SO_2 and admissions for all cardiovascular diagnoses.** For 7 studies, the combined estimate was 0.6% (95% CI 0.1% to 1.2%) with some evidence of heterogeneity. There was weak evidence of publication bias.

2.84 **SO$_2$ and admissions for cardiac diagnoses.** All of the 18 estimates for cardiac diagnoses were positive. There was strong heterogeneity and the combined estimate was 2.4% (95% CI 1.6% to 3.3%). There was a slight suggestion of publication bias.

2.85 **SO$_2$ and admissions for all ischaemic heart disease.** All but one of the 11 estimates were positive and there was strong heterogeneity. The combined estimate was 1.2% (95% CI 0.5% to 1.9%). There was no evidence of publication bias.

2.86 **SO$_2$ and admissions for all heart failure.** All but one of the five estimates were positive and there was strong heterogeneity. The combined estimate was not significant 0.9% (95% CI -0.1% to 1.8%). There was no evidence of publication bias.

2.87 **SO$_2$ and admissions for cerebrovascular disease.** Most of the 7 estimates were positive and there was strong heterogeneity. The combined estimate was not significant 0.3% (95% CI -0.5% to 1.1%).

Figure 2.24

Cardiovascular admissions and SO$_2$

Percentage change per 10 unit increase
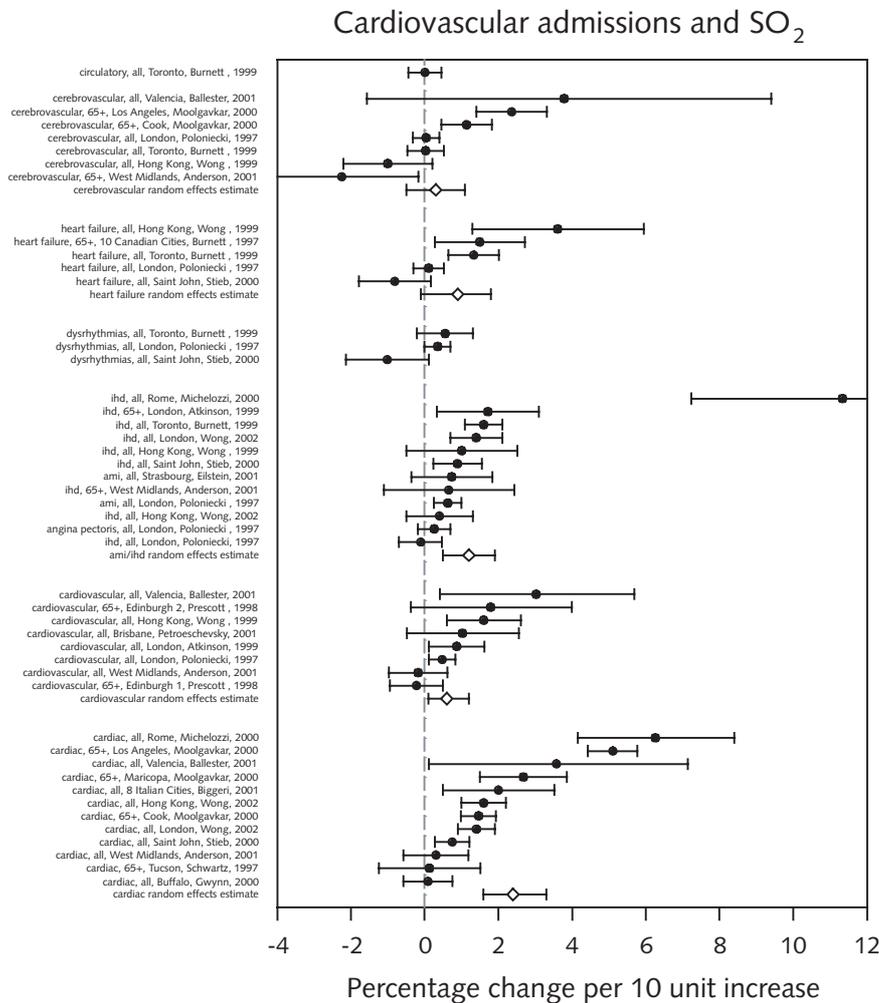
Table 2.14: Combined estimates for SO$_2$ and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	67	<0.001	0.1 (0.1, 0.2)	0.8 (0.6, 1.0)	0.741	<0.001
CV admission	7	0.013	0.5 (0.2, 0.8)	0.6 (0.1, 1.2)	0.215	0.341
Cardiac admission	18	<0.001	1.7 (1.5, 1.8)	2.4 (1.6, 3.3)	0.182	0.188
IHD admission	10	<0.001	0.9 (0.7, 1.2)	1.2 (0.5, 1.9)	0.468	0.163
Heart failure	5	<0.001	0.5 (0.2, 0.8)	0.9 (-0.1, 1.8)	0.327	0.413
Cerebrovascular	7	<0.001	0.3 (0.0, 0.6)	0.3 (-0.5, 1.1)	0.761	0.871

2.88 **CO and cardiovascular admissions (Figure 2.25, Table 2.15).** There were 33 estimates for CO of which all but 3 were positive. Meta-analysis was feasible for cardiac, IHD and cerebrovascular admissions

2.89 **CO and admissions for cardiac diagnoses.** The 8 estimates for cardiac diagnoses showed heterogeneity and moderate evidence of publication bias. The combined estimate was 2.5% (95% CI 1.8% to 3.3%).

2.90 **CO and admissions for ischaemic heart disease and acute myocardial infarction.** Most of these 9 estimates were positive and showed heterogeneity. There was moderate evidence of publication bias. The combined estimate was significant 2.4% (95% CI 0.2% to 4.6%).

2.91 **CO and admissions for cerebrovascular disease.** The five estimates tended to be positive and showed heterogeneity and moderate evidence of publication bias. The combined estimate was not significant 0.8% (95% CI -0.1% to 1.8%).

Figure 2.25

Cardiovascular admissions and CO
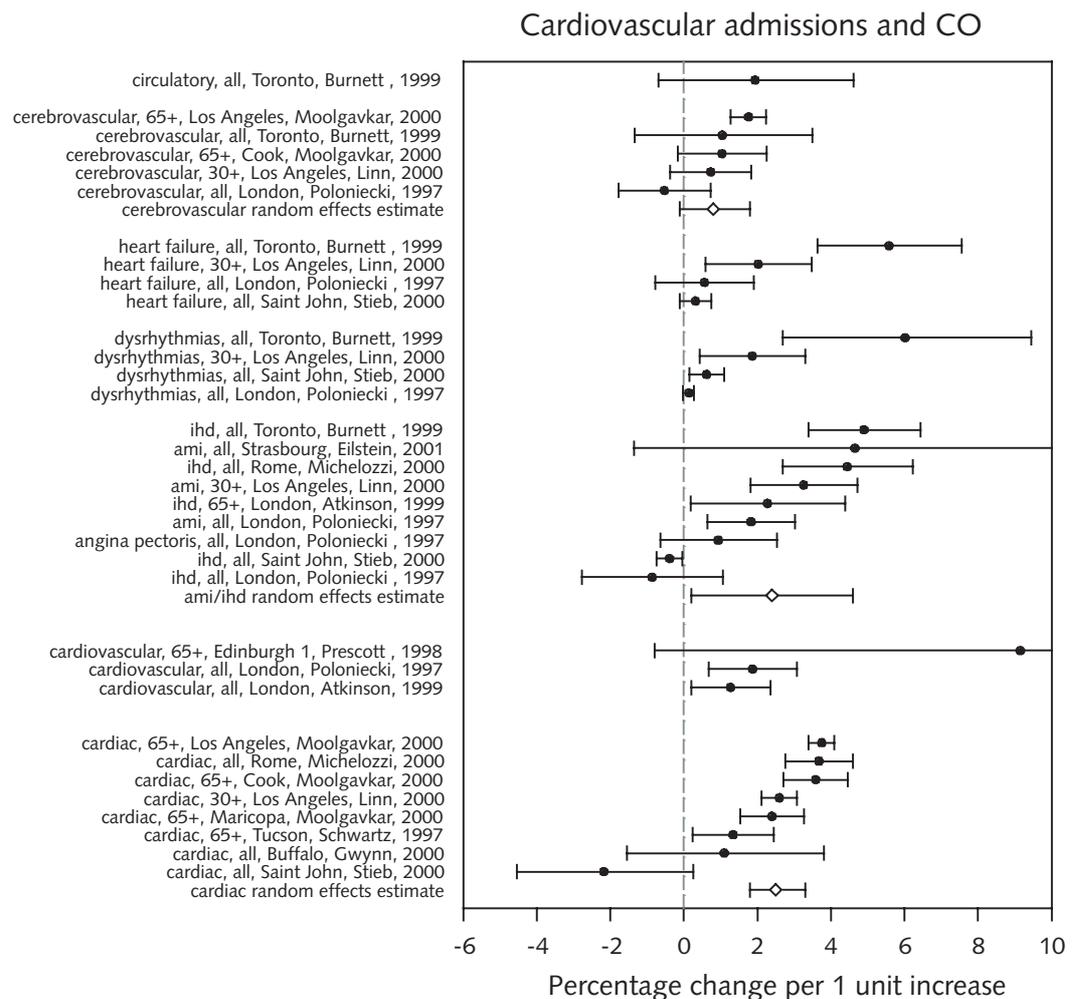
Table 2.15: Combined estimates for CO and various cardiovascular outcomes

Outcome	Number of Estimates	Heterogeneity p-value	Fixed Effects (95% CI)	Random Effects (95% CI)	Publication Bias (Begg) p-value	Publication Bias (Egger) p-value
CV mortality	12	0.002	0.2 (0.0, 0.4)	1.1 (0.2, 2.1)	0.730	0.076
Cardiac admission	8	<0.001	3.1 (2.8, 3.3)	2.5 (1.8, 3.3)	0.209	0.138
IHD admission	7	<0.001	0.4 (0.1, 0.8)	2.4 (0.2, 4.6)	0.645	0.071
Cerebrovascular	5	0.007	1.4 (1.0, 1.7)	0.8 (-0.1, 1.8)	0.782	0.151

Comparison of effects of air pollution on diagnostic subgroups.

2.92   For those pollutants which had sufficient estimates for a range of diagnoses it is possible to get some impression whether some diagnoses are more affected than others. The summary estimates described in Tables 2.2 to 2.15 are shown in Figure 2.26 by pollutant and diagnosis. For PM_{10} and SO_2, where there were estimates only for all cardiovascular disease and cardiac diagnoses, there was clearly a larger effect for cardiac diagnoses. For PM_{10}, the highest estimate was observed for heart failure and the lowest for cerebrovascular disease. For NO_2 the pattern was similar, the highest estimate being for heart failure and the lowest for cerebrovascular disease. For SO_2, the ranking was IHD, heart failure and cerebrovascular disease, with the latter two being non-significant. Lastly, for CO, the estimate for cerebrovascular disease was one third of that for IHD and was non-significant.

2.93   The problem with this approach is that differing sets of studies are being compared. To overcome this, the analysis was restricted to comparing the effects of a pollutant on IHD, heart failure, arrhythmias and cerebrovascular disease within each study.

Figure 2.26

Air pollution and cardiovascular diagnoses:
comparison of summary estimates for admissions
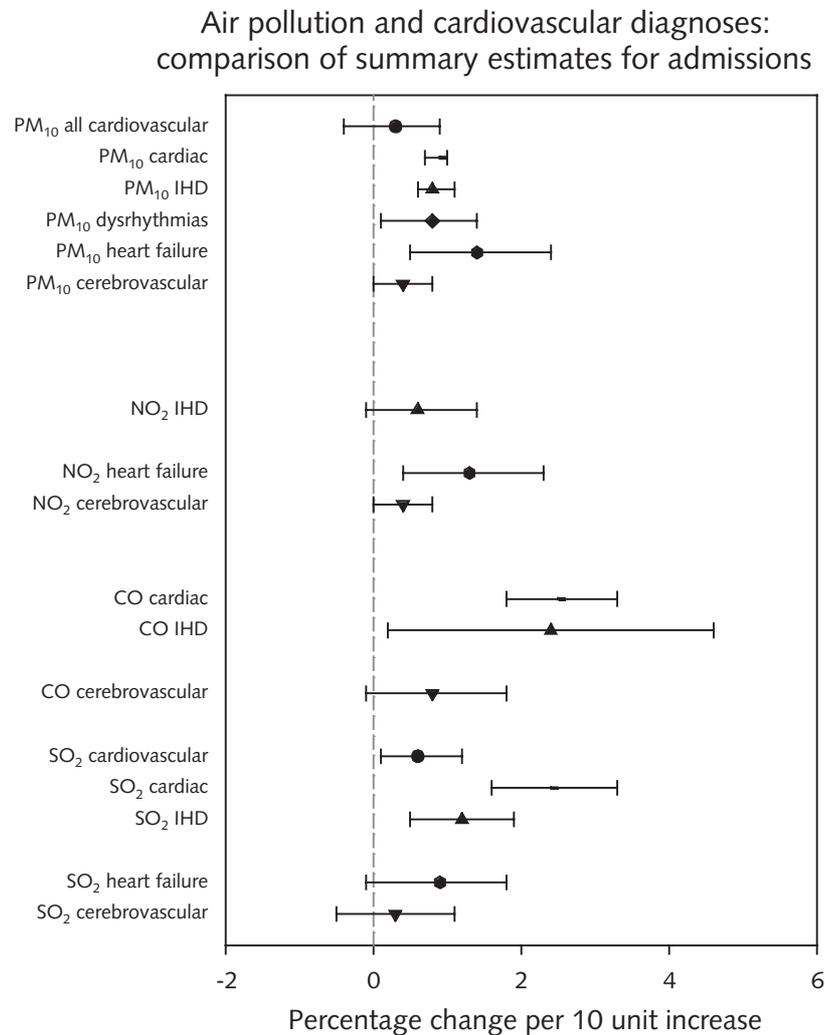
2.94 The results for PM_{10} are shown in Figure 2.27 to enable comparison of effects on different diagnoses within studies. This is hard to interpret because the confidence intervals tended to overlap but a crude assessment can be made as to the relative rankings. In the 5 studies where cerebrovascular disease was examined, it had the lowest estimate in 4, thus tending to confirm the impression given by the comparison of combined estimates in Figure 2.22. Where IHD was examined, it was the highest estimate in 7 out of 14 studies. In the studies of heart failure, it was the highest estimate in 4 out of 6 studies.

Figure 2.27

Comparison of effects of PM_{10} within studies
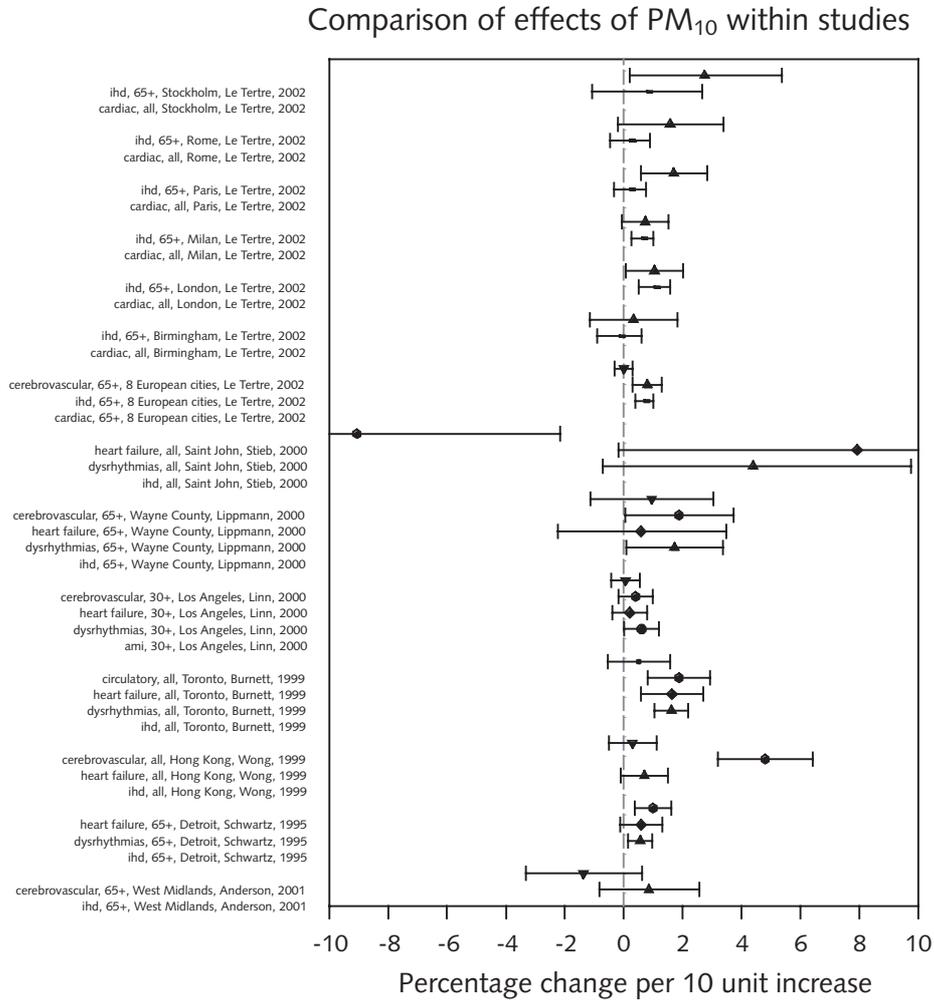
2.95 The effects of Black Smoke on various outcomes are shown in Figure 2.28. Admissions for cerebrovascular disease were ranked lowest in 6 of the nine comparisons. In contrast, IHD admissions were ranked highest in 6 out of 8 comparisons.

Figure 2.28

Comparison of effects of Black Smoke within studies
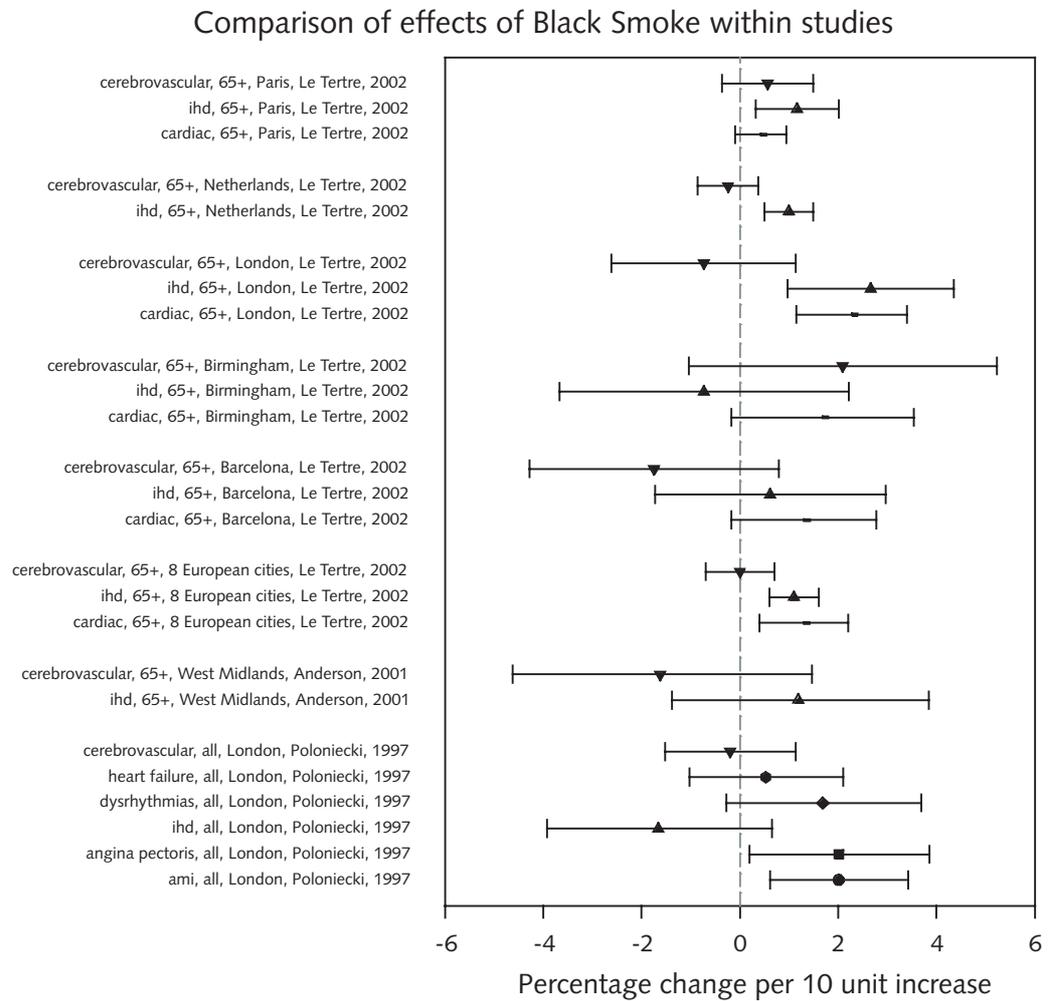
2.96 The effects of NO_2 on various outcomes is shown in Figure 2.29. In 5 comparisons the estimates for cerebrovascular disease ranked lowest. The rankings between IHD and heart failure did not show any consistent pattern.

Figure 2.29

Comparison of effects of NO$_2$ within studies
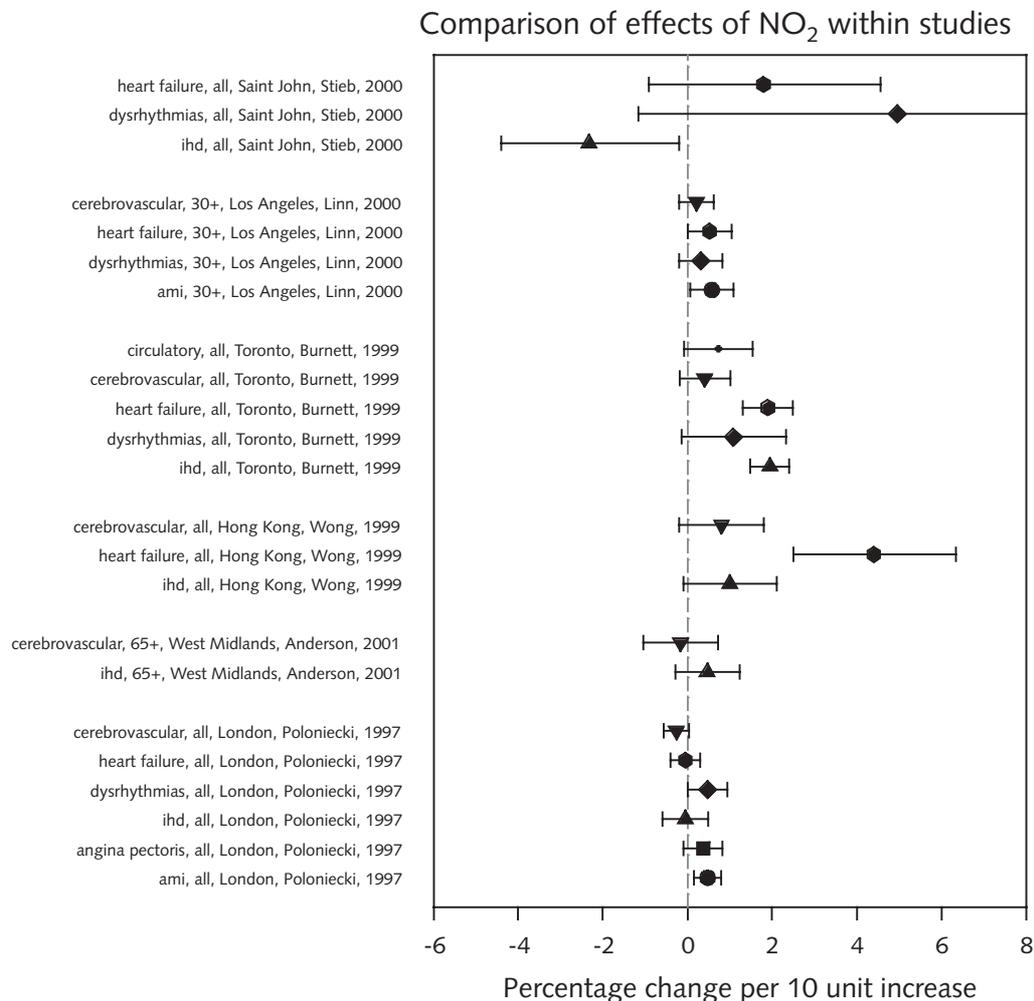
2.97 When all of the above is considered, it appears that the evidence for an effect of air pollution on admissions for cerebrovascular disease is the weakest of the various subgroups of cardiovascular disease. One study that has found positive associations with cerebrovascular mortality was reported from Seoul (Hong *et al*, 2002a). These authors did a further analysis comparing ischaemic with haemorrhagic stroke, as recorded using the ICD on the death certificates (Hong *et al*, 2002b) concluding that the increased risk was confined to ischaemic stroke. However, the authors report a positive association between TSP and haemorrhagic stroke, and the lack of full presentation of the results for the latter make it difficult to evaluate the conclusion that these two types of stroke might be affected differently.

Independent effects of particles on cardiovascular outcomes

2.98 Generally there is a strong and consistent correlation between most of the pollutants, the exception being ozone, which, being a secondary and regional pollutant is variably correlated with indicators of primary emissions depending on the balance between scavenging by nitric oxide (usually in the cool months) or photochemistry (during warm sunny weather). Two pollutant models were available from some studies and these have the potential to give some insight into which pollutant is likely to be more influential. The database was searched for two pollutant estimates and the results for PM_{10} and NO_2 are shown in Appendix 4. The effects of pollutants on PM_{10} estimates for cardiovascular mortality were reported for SO_2 (6 studies), NO_2 (6 studies), O_3 (6 studies) and CO (4 studies). PM_{10} was not affected by SO_2 or O_3 but was markedly reduced by NO_2 (single pollutant estimate 0.4% (95% CI 0.1% to 0.7%); two pollutant estimate -0.2% (95% CI -0.5% to 0.2%)) and CO (single pollutant estimate 0.3% (95% CI 0.1% to 0.6%); two pollutant estimate 0.1% (95% CI -0.2% to 0.4%)). In contrast, the effects of NO_2 were less affected by including PM_{10} in the model (single pollutant estimate 0.6% (95% CI 0.3% to 0.8%); two pollutant estimate 0.4% (95% CI -0.2% to 1.1%)). One explanation for this might be that NO_2 is a better marker of primary emissions than PM_{10}, which has both primary and secondary sources, and contains coarse as well as fine particle fractions.

Time-series evidence relating to air pollution and sudden death, incidence of acute myocardial infarction, and ventricular arrhythmias

2.99 Being essentially descriptive, quantitative meta-analysis concentrates on presenting the main single-pollutant evidence in a way that is easy to evaluate by inspection of plots and combined estimates. There is a wealth of detail in the large literature on short-term associations that is not captured by this approach. For example, some studies used outcomes that we did not include in the database, the most important being sudden death, the onset of acute myocardial infarction in the community and the occurrence of ventricular arrhythmias indicated by the discharge of implanted cardioverter defibrillators (also abbreviated to ICD – not to be confused with ICD as in International Classification of Diseases).

Acute myocardial infarction

2.100 Peters *et al* (2001) used a case-crossover approach to investigate risk factors for the onset of acute myocardial infarction in the Boston area. The risk of onset was increased in association with elevated fine particles two hours previously as well as the day before. This result is consistent with those of the studies of daily mortality and hospital admissions described earlier in this chapter, but in addition draws attention to the possibility of very short term (i.e. hours) effects. As the authors note, it requires replication.

2.101 In King County, Washington, the relationship between concentrations of fine particulate matter and the onset of myocardial infarction was investigated by case-crossover analysis in 5,793 confirmed cases registered with a community database (Sullivan *et al*, 2005). It was concluded that although a very small effect could not be excluded, there was no consistent association between fine particles and the onset of myocardial infarction. The authors also replicated the methods of Peters *et al* (2001) but found no association.

Sudden death and life-threatening arrhythmias

2.102 The association between air pollution and sudden death was investigated using a case-crossover design (Levy *et al*, 2001; Checkoway *et al*, 2000) in Seattle. The subjects, who had been part of a case-control study of out of hospital cardiac arrest, were eligible if they had a "sudden pulseless condition in the absence of a non-cardiac condition." Those with a history of clinically recognisable heart disease or a life-threatening co-morbidity were excluded. Concentrations of particles were compared at index times with those from reference days matched for day of week. No evidence of an association with fine particles over a range of lags up to 5 days was observed. At lag 1, for example, the relative risk for an inter-quartile change in nephelometry[3] was 0.89 (95% CI 0.78 to 1.02). The results do not support a role of particles and primary cardiac arrest in persons without clinical heart disease. Since sudden cardiac death is thought to be due to ventricular arrhythmia, these results are relevant to the results of studies of subjects with implanted cardioverter defibrillators.

2.103 Implanted cardioverter defibrillators detect the occurrence of ventricular fibrillation or tachycardia and treat this by pacing or defibrillation as appropriate. They may be triggered by some supra-ventricular arrhythmias. A record of the date, diagnosis triggering discharge and type of discharge is stored in the device and is downloaded at the clinic review. Peters *et al* investigated the association between air pollution and ICD discharges in 100 patients living in the Boston area (Peters *et al*, 2000). They reported that a 26 ppb increase in nitrogen dioxide was associated with increased defibrillator discharge 2 days later (OR 1.8 (95% CI 1.1 to 2.9)). The risk was increased with other lags of nitrogen dioxide but less convincingly. There was no association with PM_{10}, $PM_{2.5}$, black carbon, carbon monoxide, ozone or sulphur dioxide. When the 6 patients with at least 10 events were analysed, an association emerged for $PM_{2.5}$ lagged by two days and carbon monoxide lagged by 3 days while for the five day mean the associations with nitrogen dioxide were strengthened. The analysis used parametric approaches to controlling for confounding by season. In a sensitivity analysis using non parametric functions for season, it was noted that this improved the model fit and while this increased the odds ratio for $PM_{2.5}$ at lag 2 days

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3   Nephelometry is a light scattering technique for measuring particles

(OR 1.87 (95% 0.77 to 4.55)), that for nitrogen dioxide was reduced from 2.79 (95% CI 1.53 to 5.10) to 2.03 (95% CI 0.66 to 6.20). This study was, essentially an exploratory pilot study which found evidence consistent with an effect of pollution associated with vehicle emissions on ventricular arrhythmias.

2.104 Two further studies, both from the same clinics in Vancouver have also investigated this question. Thirty-four patients who had at least one discharge in a one year period were investigated using case-crossover techniques (Rich *et al*, 2004). The pollutants considered were elemental carbon, organic carbon, ozone, SO_2, NO_2 and CO. Some evidence of an increase in risk was observed for elemental carbon and for ozone. In the summer period, the risk was increased for all of the pollutants considered. No associations were statistically significant and considering the low power of the study, it must be concluded that it offers little positive evidence of an effect of air pollution on the incidence of arrhythmia. The second Vancouver study comprised 50 patients who had experienced discharges over a four year period (Vedal *et al*, 2004). No significant associations were observed overall, but when the analysis was restricted to 16 patients with frequent discharges, a significant association with SO_2 was found. This was unlikely to be causal because concentrations of SO_2 were very low. The authors concluded that the study provided "no compelling evidence" that low concentrations of outdoor pollutants increased the risk of ventricular arrhythmias.

2.105 When these studies of sudden death, myocardial infarction and ventricular arrhythmias are taken together, it is concluded that the evidence for an association between air pollution and acute cardiac events is insufficient to be confident that an association exists, though most results are in a positive direction. Further evidence from similar studies is required. It may be relevant that the cities where these studies have taken place (Boston, Seattle, Vancouver) all have low levels of pollution which, together with the low statistical power of some of the studies, made a real association difficult to detect. In favour of an effect however, is the substantial body of evidence from time-series studies of hospital admissions for myocardial infarction which shows convincingly consistent associations for all the main pollutants apart from O_3 and hospital admissions for cardiac causes (see above). The apparent difference between the results of studies of patients with myocardial infarction, arrhythmias and sudden death, and time-series studies based on hospital and death registries may be reconciled by the fact that time-series studies are more statistically powerful and can obtain more precise estimates of effects at lower risks than is possible in panels of patients with ICDs or myocardial infarction.

Conclusions

2.106 The aim of this review and meta-analysis was to ensure that all the time-series literature had been identified and to present the main results in a form that would enable COMEAP to make a judgment as to whether air pollution was a hazard for cardiovascular disease.

2.107 All in all, the evidence for a positive short-term association between ambient air pollution and cardiovascular outcomes is convincing.[4] In particular, that fraction of cardiovascular outcomes comprised by effects on the heart is convincing: this reflects an effect on patients with coronary heart disease. For most of the pollutant outcome pairs examined, the estimates were positive and often statistically significant. The combined estimates tended to be positive and significant (all summarized in Table 2.16). Although publication bias was present in some of the comparisons, it is unlikely that this will have led to a false conclusion as to whether an association exists. Because most of the pollutants studied are correlated, the existence of an association with a particular pollutant should not be interpreted as an effect of that pollutant *per se,* but as an effect of the mixture of which the pollutant could be regarded as an indicator. We have not carried out an extensive meta-analysis of estimates that have controlled for the effects of other pollutants. However, the impression obtained from those studies that have done this is that the effects of particles and ozone seem to be generally independent of one another. Our analyses suggested that effects of PM_{10} were not very robust to inclusion of other pollutants such as NO_2 or CO in the model, which is consistent with these being better markers of primary emissions. Consistent with this was the finding that NO_2 effects were quite robust to the inclusion of PM_{10}.

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4   The term 'convincing' is used here to reflect both statistical significance and the consistency of the findings.

Table 2.16: Combined estimates for various pollutants and various cardiovascular outcomes.

Outcome	Pollutant (24 hr average)	Number of Estimates	Heterogeneity[5] p-value	Fixed Effects (95% CI)	Random Effects (95% CI)
				% Change[6] per 10µg/m³	
CV mortality	PM_{10}	40	<0.001	0.5 (0.4, 0.7)	0.9 (0.7, 1.2)
CV admission	PM_{10}	6	0.003	0.5 (0.2, 0.7)	0.3 (-0.4, 0.9)
Cardiac admission	PM_{10}	51	<0.001	0.9 (0.8, 1.0)	0.9 (0.7, 1.0)
IHD admission	PM_{10}	19	0.076	0.8 (0.6, 0.9)	0.8 (0.6, 1.1)
Dysrhythmias	PM_{10}	7	0.174	0.6 (0.2, 1.0)	0.8 (0.1, 1.4)
Heart Failure	PM_{10}	7	<0.001	1.0 (0.7, 1.3)	1.4 (0.5, 2.4)
Cerebrovascular admissions	PM_{10}	9	0.041	0.3 (0.1, 0.6)	0.4 (0.0, 0.8)
CV mortality	$PM_{2.5}$	9	0.414	1.4 (0.7, 2.2)	1.4 (0.7, 2.2)
CV mortality	TSP	21	<0.001	0.4 (0.3, 0.5)	0.5 (0.3, 0.8)
CV mortality	black smoke	29	0.030	0.5 (0.4, 0.6)	0.6 (0.4, 0.7)
CV admission	black smoke	5	0.330	1.0 (0.5, 1.5)	1.0 (0.4, 1.5)
Cardiac admission	black smoke	6	<0.000	0.1 (0.0, 0.1)	0.8 (0.2, 1.4)
IHD admission	black smoke	8	0.124	1.1 (0.7, 1.5)	1.1 (0.4, 1.7)
CV mortality	NO_2	44	<0.001	0.4 (0.3, 0.5)	1.0 (0.8, 1.3)
Cardiac admission	NO_2	17	<0.001	1.2 (1.2, 1.3)	1.3 (1.0, 1.7)
IHD admission	NO_2	9	<0.001	1.0 (0.8, 1.2)	0.6 (-0.1, 1.4)
Heart Failure	NO_2	6	<0.001	0.7 (0.5, 1.0)	1.3 (0.4, 2.3)
Cerebrovascular admissions	NO_2	8	<0.001	0.5 (0.3, 0.6)	0.4 (0.0, 0.8)
CV mortality	8-hour ozone	26	0.298	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)
CV admission	8-hour ozone	8	0.001	0.1 (-0.1, 0.3)	0.1 (-0.5, 0.4)
IHD admission	8-hour ozone	6	0.009	-0.2 (-0.4, 0.1)	-0.1 (-0.7, 0.4)
CV mortality	SO_2	67	<0.001	0.1 (0.1, 0.2)	0.8 (0.6, 1.0)
CV admission	SO_2	7	0.013	0.5 (0.2, 0.8)	0.6 (0.1, 1.2)
Cardiac admission	SO_2	18	<0.001	1.7 (1.5, 1.8)	2.4 (1.6, 3.3)
IHD admission	SO_2	10	<0.001	0.9 (0.7, 1.2)	1.2 (0.5, 1.9)
Heart Failure	SO_2	5	<0.001	0.5 (0.2, 0.8)	0.9 (-0.1, 1.8)
Cerebrovascular admissions	SO_2	7	<0.001	0.3 (0.0, 0.6)	0.3 (-0.5, 1.1)
CV mortality	CO	12	0.002	0.2 (0.0, 0.4)	1.1 (0.2, 2.1)
Cardiac admission	CO	8	<0.001	3.1 (2.8, 3.3)	2.5 (1.8, 3.3)
IHD admission	CO	7	<0.001	0.4 (0.1, 0.8)	2.4 (0.2, 4.6)
Cerebrovascular admissions	CO	5	0.007	1.4 (1.0, 1.7)	0.8 (-0.1, 1.8)

2.108 The major exception to the pattern of positive associations was ozone and cardiovascular admissions, for which there was little or no evidence of an association. It should be noted that there was considerable heterogeneity in the size and direction of the effects. This might have many explanations, including variations in the toxicity of the air pollution mixture, measurement of community exposure and baseline susceptibility. The investigation of this was outside the scope of this descriptive review.

2.109 The meta-analytic estimates are presented to help clarify the evidence that air pollution is a hazard. They are not intended for health impact assessment purposes.

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5 This is the probability that the sample estimates come from populations with the same underlying mean. For small studies especially, if p <0.1, this suggests that they are from populations with different means.

6 In the case of CO, % change per 1mg/m³

It is, however, appropriate to comment on what time-series evidence does and does not tell us about the health impact, beyond estimating attributable deaths or hospital admissions. It is possible that air pollution brings forward by a small amount of time, deaths which would have been expected to occur in any case. This is sometimes referred to as "harvesting", but "short-term mortality displacement" is a more appropriate term. Some deaths are likely to have been brought forward by a few days in people who were dying of cardiovascular conditions such as heart failure. However, other causes of death such as acute myocardial infarction due to coronary thrombosis may occur during spells of temporary vulnerability to air pollution. If the infarction would not have occurred without the increase in air pollution at that time, the person may have lived for a considerable time before experiencing a problem. It has been suggested that not all deaths attributed to air pollution in time-series studies can be explained by short-term displacement and may represent a loss of months or even years of life. (Schwartz 2001; Zeger *et al*, 1999). These estimates apply to all-cause mortality, but since cardiovascular mortality is a major part of all-cause mortality, the argument is likely to hold for this subgroup of deaths as well.

2.110 With hospital admissions, the issue is more complicated because hospital admissions may occur more than once, or not at all – unlike death. Thus, hospital admissions attributable to air pollution may be either brought forward by a relatively short time, or be genuinely additional events that would not have occurred otherwise. Little is known about the relative contributions of these two possibilities.

2.111 The recent concern about the sensitivity of the results of time-series studies to the statistical methods used was referred to earlier and is relevant to the interpretation of these results. An extensive reanalysis of a range of existing datasets concluded that the use of linear, rather than non parametric methods (Generalised Additive Models (GAMs)) for controlling for confounders tended to reduce the size of the estimates, but that significant positive associations remained (Health Effects Institute, 2003). The most sensitive results were those of the large multi-city study of daily mortality (National Mortality and Morbidity Air Pollution Study (NMMAPS)) for which estimates were reduced by 40-50%. The associated NMMAPS study of hospital admissions found a smaller reduction (8-19%). A variety of other datasets were re-analysed including mortality and admissions from the multi-city European study (Air Pollution and Health a European Approach (APHEA)). These generally found smaller reductions in mortality estimates than in the NMMAPS study and the APHEA hospital admissions results were generally insensitive to the method used. In the APED database, the combined all-cause mortality estimates for studies using the GAM model were 50% higher than those using generalised linear models (World Health Organization, 2004a). Nevertheless, the lower estimates remained statistically significant. It can be concluded that while the size of the estimate may be sensitive to

the method of statistical analysis, there remains strong evidence of a short-term association between air pollution and health.

2.112 We attempted to see if estimates of effect varied by diagnosis since a degree of specificity would add credibility to the associations as well as giving insight into mechanisms. This was only possible with hospital admission studies because few studies have desegregated mortality data into diagnostic subgroups. Overall, associations with cardiac admissions were stronger than with all cardiovascular admissions, probably explained by the weak or absent association with cerebrovascular disease, which diluted the effect on all cardiovascular diagnoses. Among the cardiac diagnoses, there was an impression that IHD was affected more than heart failure and dysrhythmias from studies which compared these outcomes directly.

Evidence from long-term exposure studies

2.113 We will consider here the three main types of study which might inform on effects of long-term exposures – studies of occupational exposures, studies of the effect on populations of reductions in ambient pollution and longitudinal studies which consider populations in areas with differing levels of exposure over time.

Occupational exposure

2.114 It has often been considered that use could be made of data in which occupational exposure to particles might be associated with cardiovascular outcomes. For the purposes of this report we explored the literature using Medline and Embase searches for the whole period from 1966 to the current day. While this was not in the form of a formal systematic review we believe that we have covered, by use of this main search and then by identifying secondary papers from within the bibliography of each of those papers found, the greater part of the published work in this area. It soon became clear that a formal quantitative meta-analysis would not be possible and therefore we took the view that a qualitative approach was necessary whereby possible degrees of association could be identified and listed, making allowances for different assessments of exposure, different types of exposure and different population bases.

2.115 In the event a tabulation of studies was produced and from that a series of different work exposures were identified as general groups, notably those workforces exposed to vehicle emissions (e.g policemen, traffic wardens), those in whom particle generation was part of their work, such as welders and those in which there were continuing particulate exposures but which did not necessarily fall into either of the previous categories.

2.116 Some of the exposure estimates were rather crude (e.g. all or none) while occasionally there were some attempts made at estimating the extent of exposure although the quality of this assessment varied. Few studies had used a job exposure matrix to determine exposures over time.

2.117 With these caveats some broad general assessments can be made of cardiovascular outcomes from occupational exposure to particulates.

2.118 A review of the literature of mortality and morbidity in different occupations exposed to engine exhaust, traffic fumes or particle exposures similar in character to ambient air, revealed a range of approaches which considered indices of cardiovascular disease either as the main focus or as a secondary outcome (Table 2.17). Most studies were primarily concerned with cancer incidence. The majority used population norms as comparators and, indeed, were undertaken to identify health burden (i.e. to identify to what extent exposed sub-groups experienced greater mortality or morbidity than unexposed ones) rather than to explore potential causal pathways through exposure-response relationships. Nevertheless, some information can be obtained from these studies providing a number of shortcomings of this methodology are understood.

2.119 An important issue in assessing these studies is the ability of each study to deal with the "healthy worker effect" or the "unhealthy incomer effect". The "healthy worker effect" identifies the fact that on average, people who are fit enough to be in employment are also healthier than the general population of the same age. It is seen to act at time of recruitment to a company, when self-selection and/or pre-employment screening ensure that those starting employment are relatively healthy; and later, when affected workers leave their place of work, either because of disease severity or to avoid further exposures or both. Both processes leave an apparently healthier work force behind when surveys take place. This can lead to underestimation of the true effect of an occupational exposure when comparisons are made with the mortality or morbidity of the general population. The less well recognised "unhealthy incomer effect" is seen where an individual, say with coronary artery disease, moves from one occupation to another within an industry for reasons of health (e.g. a job with reduced stress or one which is less physically demanding) and thus lowers the average health status of the occupational group he has joined. If that group is used as a comparator (control), then differences between that group and any other will be less marked because of the increased prevalence of disease in the comparator (un-exposed) group. This applies in particular to within-industry comparisons of higher and lower exposed groups. It is difficult to quantify the size of these effects but movements of workers across work forces will affect how such occupational studies can be interpreted. It is generally accepted that studies of cardiovascular disease and mortality will be affected more severely than studies of, say, cancer.

2.120 Similarly, exposures change over time and estimated "average" exposures for a worker may not reflect improvements in work practice over time and consequent reductions in exposure (see Hense, 2004). Consequently, best estimates of exposure come from studies which either take into consideration these changes through effective estimation of exposures retrospectively or, even better, which obtain estimates of contemporaneous exposures prospectively.

2.121 One of the most important factors in assessing causality is identified when a dose-response relationship can be established (although lack of such a relationship does not refute a causal link between exposure and outcome). Attempts at identifying a dose-response relationship between cardiovascular disease or mortality and occupational exposure to air pollution are few as studies are often retrospective in nature with only very broad estimates of exposure (usually exposed or not, without differentiating according to intensity of exposure). The picture is also confused by the fact that a number of other occupational exposures (e.g. noise, stress, irregular working hours), are known to have an impact on cardiovascular disease both in the long- and short term and none of the published reports we reviewed was able to disentangle the effects of these other factors from each other, or from workplace air pollution exposures with respect to causality.

2.122 We have considered the occupational studies in three broad groups: those in which direct exposure to vehicle exhaust is a main component of their work (e.g. drivers), those who are exposed to exhaust in their work to some extent and those who have occupational exposures to particles or fume not generated by the internal combustion engine.

TABLE 2.17

Author, country, year	Outcome	Population studied	No. studied	Risk index Crude (95% CI)	Risk index Adjusted	Comments
DRIVERS						
Alfredsson et al Sweden (1993)	Incidence of MI[7] and mortality for a range of diagnoses	Bus drivers	9,446 Swedish bus drivers with MI and 17,400 individuals with MI in other occupations	50% increased risk of MI in drivers in urban areas but not in rural areas Risk of first MI increased in Stockholm drivers 1.6 (1.1 – 1.9)	When adjusted for socioeconomic status, no significant change in effect reported although no data provided.	Assessed over a 15 year period (1971-85) Case-control study (ratio 1:2) with data linkage. Unable to separate out the relevant factors from each other as main causal contributors.
Bigert et al Sweden (2003)	MI	All cases controls Studied more intensively: Bus drivers Taxi drivers Truck drivers	1,067 1,482 46 44 95	2.14 (1.34 to 3.41) 1.88 (1.19 to 2.98) 1.66 (1.22 to 2,26)	1.49 (0.9 to 2.45) 1.34 (0.82 to 2.19) 1.10 (0.79 to 1.53)	No direct measure of air pollutant exposure. ORs adjusted for socio-economic status, smoking alcohol, physical inactivity, overweight, diabetes and hypertension. Risks greater in bus drivers more than 10 years in their profession. Possible greater effect of psychological effects of work not accounted for in this analysis
Borgia et al Italy (1994)	Circulatory disease; Ischaemic heart disease	Taxi drivers	2,311	SMRs[8] Diabetes 1.73 (1.25 to 2.34) Lung cancer 1.23 (0.97 to 1.54) Ischaemic heart disease 0.97 (0.81 to 1.15)	Not done	Cohort study from 1965-1988. Set up to consider lung cancer. Lung cancer more marked in those registered as taxi drivers more recently. Multiple univariate analyses only undertaken.
Fleming & Charlton, UK (2001)	All circulatory disorders; asthma, COPD[9], acute respiratory infections	General Practice population using the UK National Morbidity Survey, 1991/2 Men aged 16-64	Employed 93 692 Unemployed 20 858		Prevalence ratios Goods vehicle drivers IHD 80 (50 – 110) All circ 85 (72 – 97) Bus & coach drivers IHD 68 (8 – 127) All circ 116 (84 – 148) Taxi drivers IHD 121 (50 – 193) All circ 114 (85 – 142)	Occupational grouping based on current job and retrospective. Numbers in each occupational group not given but expressed as person years in job. No exposure assessment. No estimate of survivor population effect.
Guberan et al Switzerland (1992)	Mortality and cancer incidence	Professional drivers	6,630 holding a licence between 1949 and 1961	SMRs All-cause mortality 115 (107 to 123) Lung cancer 150 (123 to 181) For those less exposed 121 (103 to 140) For those more exposed 161 (111 to 227) Ischaemic heart disease 104 (84 to 127)		Prospective cohort study followed from 1949 to 1986 with only a 3% loss. But could not allow for smoking, alcohol consumption or diet. Definition of those more or less exposed defined by job description but only analysed for cancers. Cerebrovascular disease also increased: 132 (99 to 174)

7   MI = Myocardial Infarction
8   SMR = Standardised Mortality Ratio
9   COPD = Chronic Obstructive Pulmonary Disease

Author, country, year	Outcome	Population studied	No. studied	Risk index Crude (95% CI)	Risk index Adjusted	Comments
Gustavsson P *et al* Sweden (2001)	Myocardial infarction	Stockholm community study of men and women between 45 and 70	937 men 398 women with MI (1,120 and 538 case referents)		RRs[10]: Myocardial infarction High exp: 2.11 (1.23 to 3.60) Intermediate exp: 1.42 (1.05 to 1.92) for exposure to combustion products	Lifetime occupational exposure by questionnaire. JEM approach to exposure to motor exhaust, combustion products, organic solvents and lead. Adjusted for smoking, alcohol consumption, hypertension, diabetes, overweight and physical inactivity.[11] No effects of solvent exposure.
Hannerz & Tüchsen Denmark (2001)	Hospital admissions for selective diagnoses	Professional drivers	1981 6,371 1986 8,105 1991 7,337 1994 7,002		RRs: Ischaemic heart disease Ranging from 1.30 to 1.80 Acute MI Ranging from 1.30 to 1.99	A series of 4 cohort studies of 20-59 year old male drivers. RRs raised for most causes for admission except diagnoses associated with heavy lifting/standing such as hernias and back pain, varicose veins.
Hansen Denmark (1993)	Cancer mortality	Truck drivers compared with unskilled male labourers	14,225 cases 43,024 controls	SMR Circulatory diseases 104 (90 to 119) Lung cancer 160 (126 to 200)		Control group unskilled male labourers. Census data with limited historical occupational information. Also found a relationship to myeloma. No direct allowance for smoking. Authors invoked diesel as the causal factor for lung cancer.
Hedberg *et al* Sweden (1993)	Ischaemic heart disease risk	Professional drivers	440 drivers and 1,000 referents from local population	OR[12] for having high cardiovascular risk score (drivers vs controls) 3.18 (2.41 to 4.20)	OR adjusted for age, heredity, shift work, educational level, marital status, SES 2.34 (1.70 to 3.21)	Assessed all risk factors including lipids and smoking. Specific exposure to diesel exposure was not allowed for, but this residual effect could be related to fume exposure.
Paradis *et al* Canada (1989)	Mortality from a range of causes	Bus drivers	2,134 men employed for at least 5y in 1962 Comparator group – male population of greater Montreal	SMRs Ischaemic heart disease 106 (95 to 118) Circulatory system disease: 109 (99 to 119)		Cohort followed for 23 years. 94% follow up data – 804 deaths No account of smoking or other relevant variables No excesses for lung or bladder cancer
WORKERS EXPOSED TO EXHAUST FUMES						
Forastiere *et al* Italy (1994)	Ischaemic heart disease Circulatory disease Cardiovascular disease Lung cancer	Policemen	3,868	SMRs Ischaemic heart disease 0.89 (0.73 to 1.0) Hypertension 1.23 (0.7 to 2.0)		Limited follow up period. Past exposure measurements not available so probable exposure misclassification. Non-significant excess risk for IHD amongst younger workers with short duration of employment. Very difficult to make anything of this.

10 RR = Relative Risk
11 JEM= Job Exposure Matrix
12 OR = Odds Ratio

Author, country, year	Outcome	Population studied	No. studied	Risk index Crude (95% CI)	Risk index Adjusted	Comments
Grandjean & Andersen Denmark (1991)	Mortality from Lung cancer Cardiovascular disease	Filling station attendants	4,055 men 1,195 women (529 deaths)		O/E[13] ratios: Respiratory cancer 1.58 (1.25 to 2.00) Cardiovascular disease 1.15 (1.00 to 1.31)	Linked census data (with occupation) to register of deaths. No information on past occupation and none on smoking status. O/E for ischaemic heart disease = 1.08 (Non-significant)
Herbert et al US (2000)	Prevalence of coronary heart disease	Bridge & tunnel workers	526	OR for CHD[14] 1.64 for each decade of employment Bridge and tunnel hours combined 1.98 (1.49 to 2.71)	Adjusted for BMI, job strain and sedentary lifestyle 1.61 (1.11 to 2.33)	Adjusted for other coronary heart disease risk factors all measured directly (e.g. exercise ECG etc). Exhaust particles and CO[15] amongst a number of potential candidates for this increase.
Park US (2001)	Mortality	Motor engine foundry and manufacturing workers	2,546 deaths	ORs Lung cancer 1.7 (1.15 to 2.4) Heart disease (in moulders) 1.6 (1.09 to 2.3) Stroke (in metalworking fluid exposed workers) 1.8 (1.22 to 2.7)		Assumed smoking comparable to reference population. Hypothesised that CO exposure might be relevant to the association with heart disease mortality but also suggested that carbon disulphide (partly contributed to by SO_2 exposures) might be implicated. No mention of possible role of particles.
Stern et al US (1981)	Mortality	Motor vehicle examiners	1,558 white males employed for at least 6 months between 1944 and 1973		SMR: (no CIs given) Resp system cancer 102 Circ. system disease 105 Circ. disease within 1st 10 y of employment: 134	Exposure estimated as CO (time weighted average) Modified life table approach used If observation that early years exposure might be the key period of exposure then this is an important observation. Survivor population issue may be relevant here.
Stern et al US (1988)	Mortality	Bridge and tunnel workers	5,529 men employed between 1952 and 1981 Compared to New York population rates		SMRs: Atherosclerotic heart disease in tunnel workers only 1.35 (1.09 to 1.68) For those employed >10y 1.88 (1.36 to 2.56)	Retrospective study Exposures estimated by knowledge of CO levels in their places of work. Lung cancer rates not increased and this fact used as "allowing" for smoking in this analysis. Effect seen mostly in those under the age of 40.
Wong et al US (1985)	Mortality	Heavy equipment operators with exposure to diesel	34,156	SMR for all circulatory disease 71.9 (no 95%CIs given but reported as statistically significantly reduced at the 1% level.) SMR very similar when considering those with a work exposure of >20 years		This paper tackles the issue of differences in outcomes when using SMRs compared to PMRs.

13 O/E = Observed/Expected
14 CHD = Coronary Heart Disease
15 CO = Carbon Monoxide

Author, country, year	Outcome	Population studied	No. studied	Risk index Crude (95% CI)	Risk index Adjusted	Comments
INDUSTRIAL PARTICLE EXPOSURES						
Guidotti Canada (1993)	Mortality	Urban firefighters	3,328 active between 1927 and 1987		SMRs Heart disease 110 (92 to 131) Lung cancer 142 (91 to 211)	Smoking not allowed for. Assumption made that rates are similar between firemen and the overall population. Rates compared to national data and used a weighted employment analysis to allow for differences in degree of work-related exposure to smoke. (See also his review in 1995 drawing a negative conclusion for IHD in firefighters).
Heyer et al US (1990)	Malignancies and heart disease	Firefighters	2,289	SMR Lung cancer (65+) 177 (105 to 279) Leukaemia (>30y service) 503 (104 to 1470) Myeloma (>30y service) 989 (120 to 3571) Circulatory disorders (>30y service) RR 1.84 (0.87 to 4.41)		Followed from 1949 – 1983. Only 383 deaths so some high RRs based on small numbers. Trend for increasing deaths from circulatory disorders with increasing time in service but SMRs not elevated even in that group.
Kales et al US (2003)	Death from coronary heart disease	Firefighters	52 firefighters with death from CHD Death compared to 51 firefighters dying from on-duty trauma and 310 living firefighters			Case control study. MI deaths are work related and invariably in those with underlying, often unrecognised CHD. Concentrated on stress as the main trigger and did not consider particle/smoke exposure as a possible contributory factor.
Koskela Finland (1994)	Cardiovascular morbidity and mortality	Foundry workers exposed to CO	2,857 hired between 1950 & 1972 and 931 still active in 1972 exposed for at least 4.2y		Age standardized incidence rate for medication for hypertension 4.7/1000 person yrs in non-exposed vs 9.4 in those exposed (Ratio 2.0 (1.28 to 2.92)) Mortality rate for exposed non-smokers in iron foundries 2.7/1000 yrs vs 9.2 for exposed smokers	Drew the conclusion that CO exposure affects cardiovascular outcomes but, while allowing to some extent for PAH exposure, did not in this analysis, allow for particle or heat exposure. COHb exceeded 6% in 28% of non-smokers. Smoking history only available for the 931 sub-cohort.

Author, country, year	Outcome	Population studied	No. studied	Risk index Crude (95% CI)	Risk index Adjusted	Comments
Matanoski & Tao US (2003)	Ischaemic heart disease	Styrene-butadiene rubber manufacturing workers	997 workers 498 cases dying from IHD	RH[16] of death from acute MI: For time weighted styrene conc. 0.2 to <0.3ppm 2.95 (1.02 to 8.57) >0.3ppm: 4.30 (1.56 to 11.84)		Workers employed 1943 – 1984. Relative hazards apply to the most recent 2 years of exposure in workers in the industry for >2y. Smoking history somewhat limited (n=424 overall) Exposure estimations good and job-based.
Menotti et al US (2004)	Cardiovascular mortality	Railroad employees	2,571 men aged 40-59 at recruitment in 1957-9 and 5 years later	No assessment of pollutant exposure related to job		Cohort followed for 40 years. Essentially an assessment of cardiovascular risk assessed at onset of employment but specific job exposures not addressed. Standard risk factors confirmed (blood pressure, cholesterol, smoking). Overall 32.9% of deaths due to coronary artery disease and 53.2% from all cardiovascular disease (incl. CAD[17]). (See also accompanying editorial by Hense which raises the issue of considering changes in hazard over time and factors which affect individual risk at any one time during follow up risk tracking.)
Schenker et al US (1984)	Mortality	Railway workers	2,519 white males aged 45-64 with at least 10 years service by 1967 Compared to US national rates	O/E Cancer respiratory system 0.85 (0.63 to 1.13) All circulatory diseases 0.78 (0.68 to 0.88) Rate ratio for death from resp. cancer in those exposed or not exposed to diesel 2.0 (> age 60) (no CIs given)		Follow up minimum 12 years. Significantly reduced risk of death from circulatory disease. No specific allowance for other risk factors.
Sjogren et al Sweden (2002)	Ischaemic heart disease mortality	Male welders and gas cutters	31,722 in the 1970 cohort 28,068 in the 1990 cohort	SMR for IHD mortality 1.35 (1.1 to 1.6)		Data linked to occupation as at 1970 and 1990 censuses, followed for 25 and 5 years respectively. Effect unlikely to be due to cigarette smoking which was well accounted for. Authors raise the possibility of particle and/or ozone exposure as contributory factors.
Sjogren et al Sweden (2003)	Ischaemic heart disease mortality	Female cleaners	1970 83,285 1990 90,271	SMRs for IHD 1970 1.25 (1.21 to 1.28) 1990 1.25 (1.02 to 1.51)	After allowance for socio-economic group 1.1 (0.9 to 1.4)	Review of literature 1990-2001. These data from a Swedish study. (Hammar et al 1992). Unable to identify possible cause but included potential exposure to air pollution.

16 RH = Relative Hazard
17 CAD = Coronary Artery Disease

Author, country, year	Outcome	Population studied	No. studied	Risk index Crude (95% CI)	Risk index Adjusted	Comments
Suadicani et al Denmark (2002)	Heart disease prevalence	Men without heart disease	3,321 men aged 53-74	ORs for lifetime risk of MI Solderers 3.0 (1.6 to 5.8) Welders 2.1 (1.05 to 4.2) Plastic fume exposed workers 8.3 (2.6 to 27.0)		Links occupational exposures to fume to heart disease events in men with the "O" blood group without known heart disease over 8 years. Copenhagen Heart Study.
Toren et al Sweden (1996)	Cardiovascular disease, obstructive airways disease	Pulp and paper industry				Review of published work from different countries Identified that most studies poorly addressed exposures Identified that some studies reported that workers with higher sulphate exposures had increased risk of coronary artery disease Recommended more studies which dealt with shift work, smoking and other potential risk factors
MISCELLANEOUS STUDIES						
Riediker et al US (2003)	HRV & inflammatory markers	Highway patrol officers	9	$PM_{2.5}$ increases HRV (as SDNN) and inflammatory markers by small amounts		Small numbers and no allowance for other factors which affect HRV such as activity and stress.
de Paula Santos et al Brazil (2005)	Blood pressure and HRV	Vehicle traffic controllers	48 non-smoking traffic controllers	IQR inc. in [CO] (1.1ppm) -> 2.6mmHg inc in systolic blood pressure IQR inc. in SO_2 (9.6_g/m³) >-7.93 ms decrease in SDNN (lag 4 and 5 days moving average)		SO_2 also some association with blood pressure No association with particles or NO_2.

Professional drivers

2.123 A number of studies have considered cardiovascular outcomes in workforces who drive as a part of their job such as truck or bus drivers. Paradis and colleagues (1989) compared mortality rates in 2,134 Montreal bus drivers exposed for at least 5 years to that of the rest of the population. They showed a small, but non-significant excess mortality from ischaemic heart disease and all cardiovascular disease (SMR 106). A later study of drivers with licences for driving heavy or light goods vehicles or public service vehicles from Switzerland (Gubéran *et al*, 1992) whose working exposure was largely in the 1950s, was designed to study potential carcinogenic effects but included assessment of other causes of death. Non-professional drivers less-exposed and those more exposed (exposure being based on job description) showed no increase in mortality from circulatory disease, but professional drivers did show a significantly increased rate (SMR 114 (CI 102 to128)). Allowing 15 years latency, a diagnosis of ischaemic heart disease, other heart disease, cerebrovascular disease or other circulatory disease was not increased in professional drivers. These findings were consistent with a large study of 14,225 Danish truck drivers identified at census in 1970 and followed for 10 years for cause-specific mortality compared with unskilled male labourers, which revealed a non-significant slight increase in SMR for circulatory disease (Hansen, 1993). No allowance was made for smoking in this study and while the authors conjectured that diesel exhaust was the cause of the increase in lung cancer, no exposure measures were made. Small, non-significant increases in SMRs would be of little interest except that the relevant baseline for a true comparison of the effect of exposure is not an SMR of 100, but some lower value which takes into account the healthy worker effect.

2.124 A study of Swedish men with myocardial infarction showed that urban bus drivers had an approximate 50% increased risk of MI compared to rural bus drivers (Alfredsson *et al* 1993). While the study design was elegant, it was unable to identify specific components of the drivers' exposures, other than urban driving, which contributed to the increase in fatal MI. Interpretation is difficult because it is likely that the urban-rural contrast captures not only differences in occupational exposures to particles and fumes, but also work-related differences in stress and non-occupational lifestyle differences.

2.125 A key study is that by Gustavsson and colleagues from Sweden (Gustavsson *et al*, 2001) who assessed occupational exposure using a job exposure matrix approach. This allowed estimation of degrees of exposure to combustion products from organic material. They showed a dose-response gradient when considering all exposure types (a doubled risk of MI in the high exposure group and 1.42 times increased risk in the low exposure group) but with a less suggestive dose-response effect when considering motor exhaust exposure alone. A later study from the same group, focusing on bus,

taxi and truck drivers, confirmed a non-statistically significant increased risk of MI in this occupational group, but again specific causal agents could not be identified (Bigert *et al*, 2003). Adjusting for job strain had little impact on the effect sizes – which in general were of the order of a 1.5 to 2-fold increased risk. As noted above, within-industry comparisons like this are relatively protected against the healthy worker effect and so provide stronger evidence than simple comparisons with general population mortality.

2.126 A Danish study showed increased hospital admission rates for a very wide range of diagnoses in professional drivers in a series of cohorts for whom individual level occupational information was available (Hannerz and Tuchsen, 2001). The strengths of this study are its size, its prospective nature and the occupational information, but there was no gradation of exposure which allowed assessment of a dose-response relationship. However, for a range of different cardiovascular diagnoses, relative risks ranged between 1.3 and 2.0. Again, specific components of the occupational exposures were not measured so it is not possible to state that exhaust exposure was or was not the implicated factor.

2.127 A case-referent study from Sweden (Hedberg *et al*, 1993), which specifically aimed at assessing cardiovascular risk in drivers, was able to obtain high levels of individual detail of cardiovascular risk factors in 440 drivers compared to 1000 controls. Drivers showed a 2.3-fold increased chance of having a high cardiovascular risk index although no dose-response analysis was possible. However, the degree of adjustment for other cardiovascular risk factors suggested that exposure to diesel exhaust may be an important contributor.

2.128 Taxi drivers might be considered to be at greater risk of exposure to vehicle emissions than other professional drivers because of constant exposure to pollutants generated by slow moving traffic. However, a study of 2,311 male taxi drivers in Rome (Borgia *et al*, 1994), registered between 1950 and 1975 and followed from 1965 through to 1988, had a significantly lower overall mortality for circulatory disease than expected compared with the general population, with an SMR of 78 (CI 69 to 88). Results for ischaemic heart disease showed a higher SMR of 97 (CI 81 to 115), i.e. very close to that expected based on general population rates (matched for age and gender). As noted above, this apparent protective effect for circulatory disease was not seen in the Bigert study (2003) of taxi drivers where the risks were positive albeit not statistically significantly so; the results from Borgia *et al* (1994), both for circulatory disease and for IHD, need to be interpreted in the context of the healthy worker effect.

2.129 A British study based in primary care (Fleming and Charlton, 2001) assessed self-reported occupational exposure to diesel fume and prevalence of asthma, respiratory

infections and ischaemic heart disease. This was a very large study but with limited data – it is difficult, for example, to ensure comparability of reporting of self-assessed exposures in a large scale study of General Practice records. Among the employed, Prevalence Ratios (PR) for IHD in all but one of the individual occupation groups examined did not differ from the average in a statistically significant way. However, among those not employed, the PR in the all-exposed group (PR 152 (95% CI 128 to 174)) exceeded that in controls (PR 112 (95% CI 104 to 120)) perhaps reflecting the unhealthy incomer effect, in this case coming into the unemployed group.

Other occupations with exhaust exposures

2.130 In addition to drivers, other occupational groups are also exposed to air pollution but in whom, for a variety of reasons, other cardiovascular risk factors may also vary. For instance, policemen and bridge and tunnel workers have much less sedentary jobs that are associated with varying levels and patterns of stress.

2.131 Four studies with more direct exposure to vehicle emissions show variable effects. A study of motor vehicle examiners with presumed exposure to carbon monoxide (for which exposure estimates were derived), diesel exhaust particles and NO_x (Stern *et al*, 1981) revealed a small but insignificant increase in cardiovascular deaths in the first ten years of work, but this was based on relatively small numbers of deaths (124). However, a greater effect size (SMR 134, CI not given) was seen for mortality from circulatory disorders in those in their last ten years of employment. This could be a real effect or it could be due to individuals changing to a more sedentary job because of underlying heart disease.

2.132 Conversely, in a study of over 34,000 engineers with potential exposure to diesel exhaust emissions (Wong *et al*, 1985), overall mortality and that from cardiovascular disease were substantially lower than for all US white men. Those exposed for less than 10 years had an SMR for cardiovascular disease of 57.3, those exposed for 10-19 years, 71.1 and those exposed for over 20 years, 76.3, all significantly reduced (compared to the general population) at the 1% level. Clearly, these reduced SMRs are not to be interpreted as evidence of a protective effect of diesel exhaust exposures; rather, as the benefits of employment in an occupation which incidentally includes such exposures, outweigh any detrimental effects of the exposures *per se*. It is unclear whether the apparent trend of increasing SMR with increasing duration of exposure indicates an adverse effect of exposure specifically. Another occupationally exposed group (urban policemen) also showed reduced SMRs relative to the general population, although the lack of exposure assessment and limited period of follow-up limits this study (Forastiere *et al*, 1994). A study of 2,519 railway workers in the USA exposed to diesel exhaust for ten years before 1967 revealed lower overall mortality than in the US male population with 532 deaths overall (odds ratio 0.87

(95% CI 0.80 to 0.95)) (Schenker *et al*, 1984). Circulatory diseases contributed nearly half the deaths, and with lower odds ratio (0.78 (95% CI 0.68 to 0.88)) than for mortality generally. The findings from the large US Railroad cohort (Menotti *et al*, 2004), with 40 years of follow up, were unusual in that cardiovascular risk had been assessed at time of first employment. These seemed to predict outcome much as one would expect but no attempt was made to unpick potential occupational exposures relevant to heart disease. However, overall these studies do not support the idea that diesel fume exposure predisposes workers to cardiovascular disease.

2.133 Bridge and tunnel workers have been found to be exposed to high levels of vehicle exhaust in studies of respiratory effects, one of which also considered effects on the cardiovascular system (Stern *et al*, 1988). In 5529 tunnel workers, 61 deaths from atherosclerotic heart disease were found compared to 45 expected from the New York city population (SMR 135 (90% CI 1.09 to 1.68)). There was excess cardiac mortality in tunnel workers compared with bridge workers (who have lower exposures), the excess declining after cessation of exposure. In addition, SMRs in those employed for more than 10 years were greater (188) than those employed for shorter periods having allowed for age, compatible with a dose-response effect for the development of chronic disease rather than acute episodes. A more recent study of these occupational groups (Herbert *et al*, 2000) was able to show an incremental increase in coronary artery disease risk by length of employment (OR 1.64 for each decade of employment), having allowed for a wide range of other cardiovascular risk factors. On this occasion, there was no difference in risk between the bridge and tunnel workers. While exhaust particles and CO exposures may have contributed to this effect, the lack of contemporaneous exposure measurements again leaves the question of causality open.

2.134 Motor engine foundry workers were studied by Park (2001) where, apart from CO and particles, the workers were also exposed to carbon disulphide (from sulphur dioxide production), a known cardiovascular risk factor. Park (2001) showed a 60% increase in cardiac mortality in moulders but also an 80% increase in the risk of death from stroke in metalworking fluid exposed workers. Population norms were used as comparators and the assumption was therefore made that smoking patterns were the same, which again makes interpretation difficult.

2.135 The study by Grandjean *et al* (1991) considered 4,055 men and 1,195 women aged 20-64, employed in selling oil and gasoline at the time of the Danish census in 1970, almost all at filling stations. 529 men died in the next 17 years. Respiratory cancer was the only cause of death, showing a significant increase in the exposed population, but cardiovascular disease, without any relationship to a specific diagnostic group, was also increased in men (OR 1.15 (95% CI 1.00 to 1.31)). Female mortality was as

expected but there were no measures of any pollutant given. Details of past employment and cigarette smoking were again missing from this study.

Occupations with relevant exposures not generated by the internal combustion engine

2.136 Some occupations are associated with very specific pollutant exposures, in particular particles, notably in the dusty trades and in occupations such as firefighters. The Swedish community study mentioned above (Gustavsson *et al*, 2001) showed a clear dose response relationship between exposure to combustion products and MI which, although less marked for exposure to diesel exhaust, strongly supports a causal relationship between particles generated by combustion and MI.

2.137 Sjögren (1997), in a review of populations with occupational exposure to dusts, addressed the hypothesis that occupational exposure to inhaled particulate dust could cause increased ischaemic heart disease events through the inflammatory pathway triggering changes in blood coagulability. He considered a range of occupations (e.g. gold miners to welders) and identified differing associations between these occupations and cardiovascular outcomes. He reported that the body of information did point towards an effect of particle exposure on cardiovascular endpoints, although many of the confounding issues we have discussed here were not addressed. Even accepting these caveats, the variation in the findings needs to be addressed. While the healthy worker effect might explain some of these inconsistencies, other factors such as inaccurate exposure classification and failing to account for relevant exposures during previous employments, could have contributed.

2.138 Firefighters can be intermittently exposed to very high particulate exposures although the correct use of personal protective equipment reduces this. Two thousand two hundred and eighty nine (2,289) Seattle firefighters were followed from 1945 through 1983 during which time 383 deaths occurred (Heyer *et al*, 1990). The authors stated that after 30 years there was a trend of increasing risk, with increasing exposure, for diseases of the circulatory system. However, the SMR for circulatory disease was 29 (CI 6 to 85) with less than 15 years from first exposure, 73 (CI 53 to 99) with 15-29 years from exposure, and 85 (CI 70 to 101) with 30 or more years exposure. Various re-calculations for subgroups produced SMRs above 100 for prolonged exposure; although the gradient was impressive, the final risk was not significantly greater than in the general population and may simply reflect an age effect.

2.139 Guidotti's study of mortality (Guidotti, 1993) also failed to show an increased risk of cardiovascular death from heart disease, subsequently reinforced in a later review (Guidotti, 1995).

2.140 A later, small case-control study of firefighters dying from MI while on duty identified unrecognised heart disease and the stress of the situation where death occurred, as the most critical factors (Kales *et al*, 2003). Curiously, no mention of the possible role of particle or gas exposure was made.

2.141 Foundry workers are exposed to high levels of carbon monoxide as well as particles. A large cohort study from Finland (Koskela, 1994) showed a markedly increased risk of treated hypertension in relation to measured CO exposure, although no measure of either particle or heat exposure was made. There was evidence of an interaction between exposure and cigarette smoking implying that foundry work is associated with increased cardiovascular risk perhaps related to CO or particle exposure.

2.142 Exposure to styrene in rubber manufacturing plants is associated with an increased risk of death from MI (Matanoski and Gao, 2003) in an exposure-response related manner. This very volatile compound is present in ambient air but measured levels in the vapour phase are low because of its rapid breakdown. However, near to sources of emission, levels are likely to be higher and it was this argument which led to this study. How relevant it may be to understanding the overall health impacts of air pollution on cardiovascular health is unclear as little attention to date has been paid to volatile compounds in this regard. These findings, however, merit attention but are difficult to fit into the established causal paradigms for air pollution-induced effects on the cardiovascular system.

2.143 A review of published studies of cardiovascular disease and COPD in workers in the pulp and paper industry (Toren *et al*, 1996) suggested that workers with higher sulphate exposures had an increased risk of ischaemic heart disease. However, the authors again identified that, in general, studies poorly addressed exposure estimation, shift work effects and the effects of cigarette smoking and other relevant exposures.

2.144 Welders are exposed to high concentrations of metal fume, many in the nanoparticle size range (Waldron, 1995). A Swedish study of welders and gas cutters (Sjögren *et al*, 2002), using census-linked data and which accounted well for cigarette smoking, revealed a 35% increased risk of death from ischaemic heart disease in welders although no dose-response relationship was shown as there were no measures of lifetime exposure or patterns of exposure. Metal fume has been shown to be associated with admission to hospital with pneumonia (Palmer *et al*, 2003) but only in relation to exposure within 6 months of admission. This suggests that metal fume can induce or permit airway inflammation and infection to occur but that this is a relatively short-lived effect, perhaps without longer term impacts. The most likely causal agents for these effects (both cardiovascular and pulmonary) are exposures to particles although ozone from the welding arc may also be a candidate.

2.145 It is likely that if there is an association between occupational air pollutant exposures and heart disease, susceptibility factors within the individual will play a part, as well as differences in exposures. Recently, findings from the Copenhagen Heart Study (Suadicani *et al*, 2002) identified a strong interplay between ABO blood group, air pollutant exposure and the risk of ischaemic heart disease. Apart from identifying an increased risk of heart disease prevalence in solderers (three-fold increased risk) and welders (two-fold increased risk), cardiac events in these fume exposed workers were limited to those with the O blood group when followed up over 8 years, an effect which was independent of smoking status or history. This suggests different pathways by which smoking and occupational air pollution affect coronary artery disease natural history.

2.146 Cleaners also appear to have an increased risk of death from ischaemic heart disease, although a review of published data (Sjögren *et al*, 2003) was unable to identify the causal components, which included air pollution, to which these workers are exposed, often for as long as one quarter of their working hours in some cases.

2.147 Overall, there is some evidence that occupational exposure to a range of agents is associated with adverse cardiovascular outcomes, although in many assessments, methodological issues allow only tentative statements of causality to be made. Workers obligatorily exposed to vehicle fumes at higher levels (e.g. drivers, tunnel workers) have up to a twofold increased risk of an adverse cardiovascular outcome, although the healthy worker effect and inadequate control for confounders might respectively either increase or reduce these effects.

2.148 Non-vehicle associated occupational exposures may be associated with adverse cardiovascular effects, notably in welders, but there are other occupations where formal assessment specifically exploring cardiac outcomes is needed.

Long-term changes in air pollution and cardiovascular mortality

2.149 In many westernised countries early air quality legislation was driven by concern about the effects on health of coal smoke smogs. In the UK, the Clean Air Act was passed in 1956 and over the next two decades there was a decline in all-cause mortality. This was attributed to the decline in levels of air pollutants in towns and cities and to the campaign against cigarette smoking: the relative impacts of these factors is unknown. At the time, much emphasis was put on the effects of air pollutants on the respiratory system though, as had been noted in the study of the 1952 London smog, there was evidence that episodes of severe air pollution increased deaths from heart disease (Ministry of Health, 1954). It does not seem to have been thought that long term exposure to air pollutants caused heart disease: the emphasis, such as it was, was placed on the triggering of deaths in patients with pre-existing

heart disease. Heart disease did not begin to decline in Britain until the 1970s or early 1980s and it is not clear whether reductions in levels of air pollutants contributed to this.

2.150 It is likely that any benefit of longer term reductions in exposure to air pollutants on health endpoints will not be as easy to determine as the benefits of reducing day-to-day variations of concentrations that will be reflected in changes in daily events (such as deaths or hospital admissions). The mechanisms behind worsening or initiation of disease over time are unlikely to be immediately switched off with reductions in levels of air pollutants. More likely is that there will be a delay, perhaps of some years, in such a benefit beginning to be measurable, although during that time there will likely be benefit from reductions in mortality and morbidity because of the impact on short term exposure effects. Distinguishing between an effect on causation of cardiovascular disease, on the rate of development of such disease and on the triggering of acute effects in patients with such disease is not easy. Debate continues about how these effects are reflected in studies of the effects of long-term exposure.

2.151 The number of studies of the effects on health of long-term exposure to air pollutants is small in comparison with that of studies of short-term effects. This is unsurprising: studies of long-term effects tend, themselves, to be long term and thus costly in terms of effort and money. Two groups of studies have been identified as bearing upon the identification and characterisation of the effects of long-term exposure:

- studies of natural experiments;

- cohort studies.

2.152 In the latter, carefully defined groups are studied over periods of varying length and their health status is related to long-term levels of air pollution. In a way the cohort studies are a refinement of simple ecological studies in which, for example, the death rate in a polluted town or city might be compared with that in a relatively unpolluted location. Such simple studies might, of course, be misleading as a host of factors besides air pollution affect mortality rates. Some of these factors exert a greater effect than air pollutants. The elegance of the cohort design is that such confounding factors may be controlled, i.e. allowed for, at an individual level. It follows that well designed cohort studies collect a wealth of data about the individuals in the studies. Such information is made use of in constructing mathematical models that relate long-term air pollutant concentrations to the risk of death. At the simplest level, two cohorts in two cities or towns characterised by long-term differences in levels of air pollutants would allow the relationship between this difference and any difference in death rates to be explored. Of course, a study of such simplicity would generate but two data

points: the unit of study is the city or town. More than two data points would clearly be desirable, though in the first of the studies to be discussed below, only six locations were studied, but to great effect.

2.153 Studies of natural experiments on the other hand, are conducted in single locations and advantage is taken of a sudden decline in long-term levels of air pollution. Such studies are unplanned in the sense that the reduction is not made to facilitate the study of the effects of air pollutants. On the contrary – studies of natural experiments involve capitalising on a fortuitous event. Knowing that such an event is coming does, of course, allow design of the study, though retrospective studies of the effects of such events are also feasible.

Studies of natural experiments

2.154 Studies of natural experiments are defined for our purposes as studies of the impact on health of policies deliberately designed to produce sudden changes in emissions of air pollutants – the policies are described as interventions and these studies are sometimes referred to as 'intervention studies'. This excludes changes produced over a longer time scale, for example those produced by the Clean Air Act in the UK in 1956 and by the Reunification of Germany. We have also excluded studies of the effects on health of events that have produced only a short-lived reduction in emissions of pollutants. An example of this sort of study is provided by the work by Pope and Dockery (1992) of the effects on health of the temporary closure of a steel mill in the Utah Valley as a result of industrial action.

2.155 Two studies are considered here: the study by Clancy *et al* (2002) of the effects of the banning of coal sales in Dublin (1990) and the study by Hedley *et al* (2002) of the effects of restricting power plants and road vehicles in Hong Kong to the use of fuel oil with a sulphur content of not more than 0.5% by weight.

The Dublin Study

2.156 Clancy *et al* (2002) studied the effects of the banning of coal sales in Dublin by comparing air pollution levels, weather and deaths, by season, in two, six year periods: 1984-1990 and 1990-1996. The ban on coal sales occurred in 1990. The effects on pollution levels, especially particles, were dramatic, the following data being six year averages.

Black Smoke
1984-1990:   50.2 μg/m^3
1990-1996:   14.6 μg/m^3

Sulphur dioxide
1984-1990:   33.4 μg/m³
1990-1996:   22.1 μg/m³

2.157 Unsurprisingly, the greatest effect was seen in the winter, reflecting the ban on coal for domestic heating.

Effects on mortality: methods and results

2.158 Statistical analyses used a generalised linear model with assumed Poisson distribution of Dublin death rates – age-standardised, to take account of demographic changes between 1984-90 and 1990-96, including changes in age-distribution. Analyses adjusted also for influenza epidemics; for temperature, humidity and day-of-the-week; and for unmeasured secular trends in death rates (assessed via changes in death rates in the rest of Ireland). Unadjusted mortality results overall for non-trauma deaths showed a clear and highly statistically significant reduction of 8% between the two 6-year periods, from 9.41 to 8.65 per 1000 person-years at risk. Reductions were found in all four seasons, most strongly in Winter, least strongly in Autumn. Adjustment via Poisson regression analyses lowered the estimated percent reduction to 5.7%; but this nevertheless was very highly statistically significant (P<0.0001; 95% CI 4.1% to 7.2%). It is interesting and relevant that in cause-specific analyses, the highest adjusted percent reduction was for respiratory causes (15.5%; 95% CI 11.6% to 19.1%); followed by cardiovascular causes (10.3%; CI 8.0% to 12.6%). (In terms of 'lives saved', the greatest impact was on cardiovascular deaths, from which many more people die than from respiratory causes.) On the other hand, deaths from other non-trauma causes showed a slight *increase* (of 1.7%; p = 0.17; 95% CI -0.07% to 4.2%) between 1984-90 and 1990-96. This cause-specific pattern is exactly consistent with what would be expected, based on ambient air pollution generally. The adjusted percent change was somewhat *higher* in younger people: in the three age groups reported (i) <60, (ii) 60-74, (iii) >75, the estimated adjusted percent reduction from 1984-90 to 1990-96 was 7.9, 6.2 and 4.5. The reduction was highly statistically significant in all three age-groups.

Interpretation and conclusion regarding the effect of the intervention

2.159 The authors discuss in some detail the adequacy of adjustment for non-pollution confounders. They reported that *'adjustment for respiratory epidemics and weather had a small effect'* on results for total deaths. Changes in underlying demography were substantial, but availability of 5-year census data helped in making reliable adjustments. There were very marked reductions in mortality in Ireland from cardiovascular causes over the years of the study, and some reductions in respiratory mortality also. These reductions appear to be traceable to reductions in risk factors.

The study took account of these by adjusting death rates in Dublin for those in the rest of Ireland. This was clearly a useful thing to do; but whether or not there remains important residual confounding depends on whether the lifestyle changes underlying the general Irish reductions in cardiovascular and respiratory mortality were similar in Dublin and in the rest of Ireland. Dublin being by far the largest city, there may be differences. Nevertheless, the adjusted results show very clear differences in age-standardised death rates before and after the coal ban in Dublin, and it is difficult to disagree with the authors' main conclusion – that, while non-pollution factors partly explained the overall reduction in non-trauma death rates between 1984-90 and 1990-96, the ban on coal and associated pollution also contributed clearly and identifiably to the reduction.

Other implications for our understanding of air pollution and health

2.160 The study gives some insights into other topics relevant to air pollution and health.

a. *Relative importance of various pollutants and sources.* The change was characterised by reduced Black Smoke and sulphur dioxide, from reduced coal burning. Much of modern Western urban air pollution is traffic-generated, where, as well as primary particles (which will appear as Black Smoke), the mixture includes oxides of nitrogen rather than sulphur dioxide, with consequent effects on ozone also.

b. *The time-series studies capture only some of pollution-related mortality.* Clancy *et al* (2002) make this point. The estimated adjusted effect on non-trauma deaths of 5.7% overall, per approximately 35 $\mu g/m^3$ reduction in Black Smoke, is substantially more than the estimate of about 0.5% per 10 $\mu g/m^3$ PM_{10} from APHEA, and lower estimates from the GAM-adjusted analyses of the US multi-city NMMAPS study. Clearly, the observed reductions cannot be explained by effects captured by these time series studies; i.e. effects that occur within a week of the relevant daily pollution.

c. *A substantial part of the effect of air pollution on mortality occurs within weeks or months: i.e., much of the benefits as assessed via cohort studies are not delayed long-term.* This point is a kind of mirror-image of b, above. By design, the Dublin study focused on changes in death rates that occurred within six years of the local ban. It is clear from Clancy *et al* (2002) that a great part of the reduction happened in the months immediately following the ban. The time-delay from pollution change to full impact on death rates is one of the important unknowns in the effects of air pollution on mortality – the cohort studies are uninformative about this aspect – and so the evidence from the present study of substantial and sudden benefits is important supplementary evidence.

The Hong Kong Study

2.161 Hedley *et al* (2002) examined cause-specific mortality and pollution in the 5 years after the intervention (restricting fuel oil to 0.5% sulphur content), taking account of baseline values in the years before the change. Mortality baseline rates were based on the 5 years prior to change; pollution baseline data from five monitoring stations referred to the 2 years before the change, data from a further three stations referred to data for 1 year only. The study examined differences in deaths over 5 years after the change between districts with and without sustained reductions in pollution (SO_2) relative to baseline – sustained being interpreted as the reductions measured as at 2.5 years after the change.

Effects on ambient air pollution

2.162 There was an immediate and marked decrease in ambient sulphur dioxide. Baseline levels (data from 5 stations, over 12 months) were 44.2 μg/m³. One year after intervention, they were 20.8 μg/m³, a reduction of 53%. Levels increased slowly over the following years, to 24.5 μg/m³ five years after intervention; a reduction of 44.7% on baseline. Sulphates within respirable particles showed an initial decrease of 23% (from 8.9 to 6.9 μg/m³) after 12 months, then rising to 7.9 μg/m³ (reduction of 11.7% on baseline) after 2.5 years and returning to 8.9 μg/m³ at 5 years after intervention (Hedley *et al*, 2002, Table 1; the text says that in years 3-5 after intervention, sulphate concentrations were 110% to114% of baseline). The authors reported that the rise was part of a regional pattern of sulphate pollution in Southern China. Ozone levels increased throughout the period. There was little change in either nitrogen dioxide or in PM_{10}.

Effects on mortality: methods and results

2.163 The main analyses compared mortality before and after the intervention, in terms of mortality overall, age-specific and cause-specific, and in terms of seasonal pattern. Excess risk of death was studied by Poisson regression on monthly death rates, with adjustment for time trend, seasonality and climate. In addition, analyses considered *change* in death rates between two groups of Districts – the high (sulphur dioxide) reduction area, served by 4 stations with an average sulphur dioxide reduction of 52.8% over 2.5 years; and the low (sulphur dioxide) reduction area, with an average increase of 8.7% over 4 other stations. There were two main findings. One concerned a marked change in seasonal pattern in year one after intervention – a marked reduction in deaths in the cool season. This reduction was found for deaths in all age-groups, and for respiratory and cardiovascular causes, but not for neoplasms and other causes. *'In the second 12 months a striking rebound in cool season deaths occurred, followed by a gradual return during years 3-5 to the seasonal pattern before intervention'.* Monthly deaths had been increasing on average by 3.5% per annum during 1985-90,

reflecting demographic changes. The second main finding was a clear and sustained reduction in this increase, for deaths from all causes and all ages, over the following five years. The change was greatest for respiratory causes and to a lesser extent for cardiovascular diseases, with a less marked reduction for lung cancer and for other non-cancer causes. Cancers other than lung cancer increased as before the intervention. The change was most marked in the high sulphur dioxide reduction areas; indeed, the low sulphur dioxide reduction areas showed a higher increase in mortality after the intervention than before. This general reduction in the rate of increase of mortality is also expressed by Hedley *et al* (2002) in terms of life expectancy.

Interpretation and conclusion regarding the effect of the intervention

2.164 This study is interesting because it examines mortality and air pollution in the context of little or no changes in ambient PM_{10}. The two pollutants showing changes were sulphates – with a sustained change for about two years – and sulphur dioxide, where the reduction was sustained for the full five years post-intervention studied. Hedley *et al* (2002) find effects on mortality associated with both pollutants. They interpret the marked seasonal changes of Year 1 post-intervention as being associated with the initial sulphate reductions, and the sustained mortality changes over the 5-year period as reflecting an effect of the sustained sulphur dioxide reductions.

2.165 Both these studies show that a reduction in some markers of particulate pollution is associated with a reduction in deaths from cardiovascular diseases. In the Dublin study a significant reduction in Black Smoke (particles of dark colour and of aerodynamic diameter generally less than about 4 μm) occurred. In the Hong Kong study the key effect was on sulphur dioxide and on particles monitored as sulphate. These findings support those of the ecological cohort studies i.e. long-term exposure to particles measured on a size basis (fine particles, $PM_{2.5}$) and as sulphate (a component of the fine particle aerosol) and sulphur dioxide which are both associated with deaths from cardiovascular disease.

Ecological cohort studies

2.166 The cohort studies we shall consider can be divided into two groups: the first group has had a greater impact on thinking than the second.

(a)   The major US studies: the Harvard Six Cities study (Dockery *et al*, 1993) and the American Cancer Society cohort study (Pope *et al*, 1995). The latter has been extended in a recent paper (Pope *et al*, 2002).

(b)   Other studies including the Seventh Day Adventists Study (Abbey *et al,* 1999) conducted in the US and a small number of European studies.

2.167 The studies listed under (a) above have been exposed to searching, indeed exceptional, review and reanalysis (Krewski *et al,* 2000). This has not only confirmed the original findings but has extended them. This review deserves detailed consideration for it is a study in itself. It should be acknowledged that the studies listed in group (a) above have not escaped criticism. Lipfert, for example, has recently published a commentary on the review and reanalysis noted above (Lipfert, 2003). This followed an earlier critique by Lipfert and Wyzga (1995). These critiques are worth close examination although a number of the points raised had been noted by the workers who reported the cohort studies and by those who undertook the reanalysis. The status of the US cohort studies and the HEI reanalysis is high – they are accepted as good studies and their findings have played a large part in the development of thinking about the effects of air pollutants on health. It is important to note that these studies reveal a significantly greater adverse effect of air pollutants on health than do studies of acute effects e.g. the time-series studies.

Harvard Six Cities Study (Dockery *et al*, 1993)

2.168 This was a planned study of mortality and air pollution, initially over the period 1974 to 1991. It formed a part of a long term series of studies of six US cities specially selected by academic departments at Harvard University. In addition to this cohort study the programme has generated important time-series studies. Additional follow-up data to the study were included in the HEI reanalysis. The study followed 8111 men and women aged 25-74, resident in the following cities: Steubenville (Ohio), St Louis (Missouri), Portage (Wisconsin), Topeka (Kansas), Watertown (Massachusetts) and Kingston-Harriman (Tennessee). Over the study period, 1,430 deaths occurred in the cohort and these were classified as being from cardiopulmonary causes, from lung cancer and from "all causes". The characteristics of the study population (the cohort) and the mean air pollution levels in the Six Cities are shown in Table 2.18 below.

Table 2.18. Characteristics of the study population and mean air pollution levels in six cities*

Characteristic	Portage (Wis)	Topeka (Kansas)	Watertown (Mass)	Kingston-Harriman (Tennessee)	St Louis (Missouri)	Steubenville (Ohio)
No. participants	1,631	1,239	1,336	1,258	1,296	1,351
Person-years of follow-up	21,618	16,111	19,882	17,836	17,715	17,914
No. of deaths	232	156	248	222	281	291
Deaths/1000 person-years	10.73	9.68	12.47	12.45	15.86	16.24
Female sex (%)	52	56	56	54	55	56
Smokers (%)	36	33	40	37	35	35
Former smokers (%)	24	25	25	21	24	23
Average pack-years of smoking						
Current smokers	24.0	25.6	25.2	24.5	30.9	28.0
Former smokers	18.0	19.7	21.8	21.1	22.0	25.0
Less than high-school education (%)	25	12	22	35	45	30
Average age (yr)	48.4	48.3	48.5	49.4	51.8	51.6
Average body-mass index	26.3	25.3	25.5	25.1	26.0	26.4
Job exposure to dust or fumes (%)	53	28	38	50	40	48
Total particles µg/m³	34.1	56.6	49.2	49.4	72.5	89.9
Inhalable particles (µg/m³)	18.2	26.4	24.2	32.5	31.4	46.5
Fine particles (µg/m³)	11.0	12.5	14.9	20.8	19.0	29.6
Sulphate particles (µg/m³)	5.3	4.8	6.5	8.1	8.1	12.8
Aerosol acidity (nmol/m³)	10.5	11.6	20.3	36.1	10.3	25.2
Sulphur dioxide (ppb)	4.2	1.6	9.3	4.8	14.1	24.0
Nitrogen dioxide (ppb)	6.1	10.6	18.1	14.1	19.7	21.9
Ozone (ppb)	28.0	27.6	19.7	20.7	20.9	22.3

* Air-pollution values were measured in the following years: total particles, sulphur dioxide, nitrogen dioxide and ozone, 1977 through 1985; inhalable and fine particles, 1977 through 1985; sulphate particles, 1979 through 1984; and aerosol acidity 1985 through 1988.

2.169 It will be noted that the cities were of similar size but differed with regard to their levels of pollution. Details of the methods used to measure pollutant concentrations may be found in the original paper: the figures given in Table 2.18 represent mean values over a six year period. Further details are provided in the footnote to the table. It will be noted that whilst some characteristics of the cohort were distinctly (indeed, deliberately) similar across the six cities, others were not.

2.170 Participants completed questionnaires starting in 1974 and follow-up questionnaires were completed at 3, 6 and 12 years after enrolment. Pollution was measured at one site in each city, especially for the study, but durations of measurement varied for different pollutants: the original paper should be consulted for details.

2.171 The Cox proportional-hazards model was used to analyse the data. The following description of the modelling is taken from the original paper.

Two approaches were used to evaluate the effects of air pollution in the Cox proportional-hazards models. First, indicator variables for the city of residence were included, with Portage, Wisconsin, the city with the lowest levels of particulate air pollution, as the

*reference category. Adjusted mortality-rate ratios for each of the six cities were then
compared graphically with the mean pollution levels in those cities. Next, adjusted
mortality-rate ratios were estimated by including city-specific pollution levels directly in the
Cox proportional-hazards models. Adjusted rate ratios were calculated and reported for a
difference in air pollution equal to that between the city with the highest levels of air
pollution and the city with the lowest levels – that is, the adjusted rate ratios across the
range of exposure for each pollutant among the six cities.*

2.172 Mortality was found to be strongly associated with concentrations of inhalable (PM_{15}, PM_{10}) particles, with fine particles ($PM_{2.5}$) and with sulphate particles. The authors stated that these associations were stronger than those with sulphur dioxide and nitrogen dioxide and with Total Suspended Particles but did not report coefficients for these pollutants. No clear association with ozone concentrations was found though it should be noted that the range of ozone concentrations across the cities was small. As expected, a strong association between cigarette smoking and lung cancer was found and a smaller association between smoking and cardiopulmonary disease excluding lung cancer. The key findings are shown in Table 2.19.

Table 2.19 Adjusted mortality-rate ratios for current and former cigarette smokers and for the most polluted city as compared with the least polluted, according to cause of death*

Cause of Death	Percentage of total	Current smokers†	Former smokers‡	Most vs least polluted city
		Rate Ratio (95% CI)		
All	100	2.00 (1.51-2.65)	1.39 (1.10-1.75)	1.26 (1.08-1.47)
Lung cancer	8.4	8.00 (2.97-21.6)	2.54 (0.90-7.18)	1.37 (0.81-2.31)
Cardiopulmonary disease	53.1	2.30 (1.56-3.41)	1.52 (1.10-2.10)	1.37 (1.11-1.68)
All others	38.5	1.46 (0.89-2.39)	1.17 (0.80-1.75)	1.01 (0.79-1.30)

* The city with the highest level of air pollution (indicated by the level of the particles) was Steubenville, Ohio, and that with the lowest was Portage, Wisconsin. CI denotes confidence interval. Rates have been adjusted for age, sex, smoking, education and body-mass index.
† The risk of death for a current smoker with approximately the average number of pack-years of smoking at enrolment (25 pack-years), as compared with that for a non-smoker.
‡ The risk of death for a former smoker with approximately the average number of pack-years of smoking at enrolment (20 pack-years), as compared with that for a non-smoker.

2.173 The authors focused on the effects of fine particles and reported their findings in terms of the mortality-rate ratio between the most polluted city (Steubenville) and the least polluted city (Portage). This ratio, with and without correction for confounding factors is shown in Table 2.20.

Table 2.20. Estimated mortality-rate ratios for the most polluted city as compared with the least polluted city, with fine particles used as the indicator of air pollution, in selected models*

Model No.	Variables included†	Rate Ratio (95% CI)‡
1	Fine particles	1.31 (1.13-1.52)
2	Model 1 + all smoking variables	1.29 (1.11-1.49)
3	Model 2 + high-school education	1.26 (1.08-1.47)
4	Model 3 + body-mass index	1.26 (1.08-1.47)
5	Model 4 + occupational exposure	1.26 (1.08-1.46)
6	Model 5, excluding 1439 subjects with hypertension	1.25 (1.04-1.50)
7	Model 5, excluding 561 subjects with diabetes	1.29 (1.09-1.52)

* The city with the highest level of fine-particulate air pollution was Steubenville, Ohio, and that with the lowest was Portage, Wisconsin. In addition to the variables specified, rates have been adjusted for age and sex.
† Subjects with hypertension were those who had been treated for high blood pressure within 10 years before enrolment; subjects with diabetes were those who had ever been told by a doctor they had diabetes, had glucose in their urine, or had too much glucose in their blood.
‡ CI denotes confidence interval.

2.174 The "bottom line" adjusted mortality-rate ratio for fine particles across a span of 11.0 to 29.6 μg/m^3 was 1.26 (CI 1.08 to 1.47). The equivalent figure for cardiopulmonary disease was 1.37 (CI 1.11 to 1.68) (see Table 2.19).

2.175 The authors also presented their data as a series of graphs: see Figure 2.30.

Figure 2.30

Estimated adjusted mortality-rate ratios and pollution levels in the Six Cities study
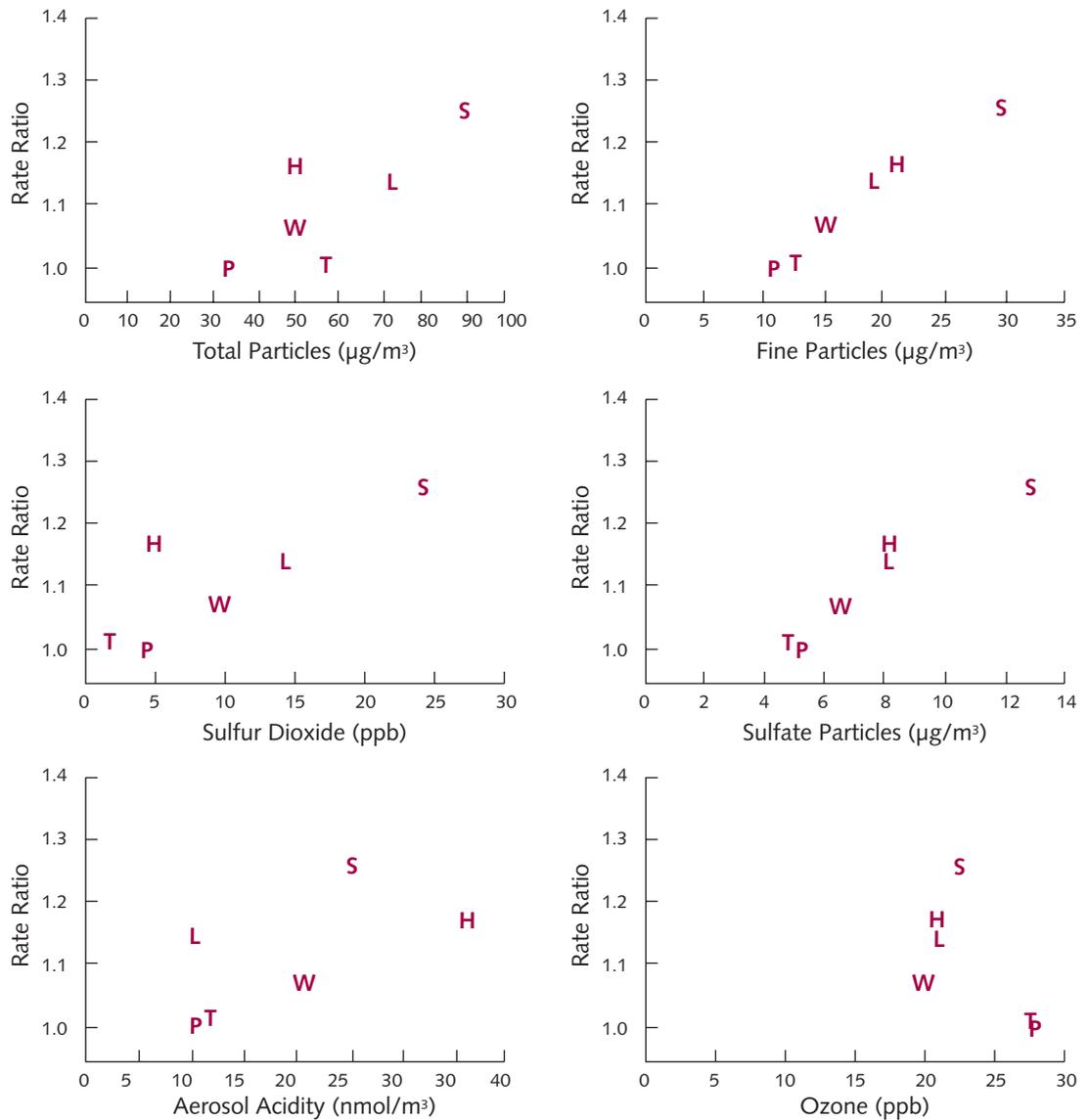
Mean values are shown for the measures of air pollution.
P= Portage, Wisconsin; T= Topeka, Kansas; W= Watertown, Massachusetts; L= St Louis, Missouri; H=Harriman, Tennessee; and S=Steubenville, Ohio.

2.176 It should be noted that the cleanest city (Portage, P) is always assigned a rate ratio of 1.0 in these graphs: the authors were comparing the mortality rates in the other cities with that in Portage. These results have had a considerable impact on thinking: the clearly closer association between fine particles and the rate ratio than in the case of total particles has focused attention on the fine fraction as being likely to contain or reflect the active components of the ambient aerosol. It should also be noted (see Table 2.18) that nitrogen dioxide concentrations appeared to be fairly well correlated with fine particle concentrations and yet any association between the rate ratio and nitrogen dioxide levels was unreported.

2.177 The authors of the Harvard Six Cities Study drew cautious conclusions:

In this prospective cohort study, the mortality rate, adjusted for other health risk factors, was associated with the level of air pollution. Mortality was more strongly associated with the levels of fine, inhalable, and sulphate particles than with the levels of total particulate pollution, aerosol acidity, sulphur dioxide, or nitrogen dioxide. As with all other epidemiologic studies, it is possible that the observed association was due to confounding – that is, that it resulted from a risk factor that was correlated with both exposure and mortality. Potential confounders of the effects of air pollution include cigarette smoking and occupational exposure to pollutants. In our study, however, the association of air pollution with mortality was observed even after we directly controlled for individual differences in other risk factors, including age, sex, cigarette smoking, education level, body-mass index, and occupational exposure.

2.178 It was also noted that the association between fine particles and all-cause mortality was unaffected by excluding from the analysis those treated for high blood pressure or for diabetes. These are risk factors for cardiovascular disease: the authors did not report the effect of such exclusions on the association with cardiopulmonary disease.

2.179 This study was the first to identify an effect of long-term exposure to fine particles on cardiopulmonary disease. No attempt to distinguish effects on cardiovascular disease from those on respiratory disease, with the exception of lung cancer, was reported.

The American Cancer Society Cohort Study (Pope *et al*, 1995)

2.180 This was a much larger and statistically more powerful study than the Harvard Six Cities Study: some 552,138 subjects from 151 metropolitan areas in the US formed the cohort. The study used data from the American Cancer Society (ACS) Cancer Prevention Study II – this is a prospective study of 1.2 million adults. The vital status of the participants was assessed from 1982 to 1989 both by personal inquiry (1984, 1986, 1988) and by interrogation of the US National Death Index. In all, 39,963 participants died in the period of the study. Personal details were acquired by

questionnaire. Only two indices of air pollution: fine particle and sulphate concentrations were used in the study. Unlike the Harvard Six Cities Study, data on sulphate concentrations were acquired from the US EPA's National Database and not from monitors set up especially for the study. Data on sulphate concentrations were available for all 151 metropolitan areas. Data on fine particle concentrations were derived from a study by Lipfert *et al* (1988). The sulphate data were calculated as means; the fine particle data as medians. A summary of the characteristics of the cohort and of the pollution ranges across the areas studied is given in Table 2.21.

Table 2.21. Summary characteristics of subjects in baseline analytic cohort derived from the ACS, CPS-II study cohort, 1982-1989

Characteristics	Analysis with sulphate particles	Analysis with fine particles
Number of metropolitan areas	151	50
Number of subjects	552,138	295,223
Number of deaths	38,963	20,765
Age at enrolment, mean	56.5	56.6
Sex, %female	56.0	55.9
Race % White % Black % Other	 94.2 4.1 1.7	 94.0 4.1 1.9
Current cigarette smoker, % Cigarettes/day, mean Years smoked, mean	22.0 22.0 33.5	21.8 22.1 33.5
Former cigarette smoker, % Cigarettes/day, mean Years smoked, mean	29.1 22.0 22.3	29.4 22.0 22.2
Pipe/Cigar smoker only, %	4.1	3.9
Passive smoke, hours/day, mean	3.2	3.2
Occupational exposure, %	20.0	19.5
Less than high school education, %	12.3	11.3
BMI, mean	25.1	25.0
Alcohol, drinks/day, mean	1.0	1.0
Sulphate particles, $\mu g/m^3$, mean (Standard Deviation)	11.0 (3.6)	–
Sulphate particles, $\mu g/m^3$, range Fine particles, $\mu g/m^3$, mean (Standard Deviation)	3.6-23.5 –	– 18.2 (5.1)
Fine particles, $\mu g/m^3$, range	–	9.0-33.5

2.181 In this study, as in the Harvard Six Cities Study, Cox Proportional-Hazards models were constructed. These allowed associations between pollutants and the risk of death from lung cancer, from cardiopulmonary disease and from "all causes" and "all other causes" to be studied. Correction for the many individual factors that might have affected such risks was also possible and a series of models including these factors were constructed. Once again, the mortality-risk ratios, for the three causes of death, were calculated across the range of long-term pollutant concentrations recorded in the areas studied. For sulphates, the concentration range across the areas studied was 19.9 μg/m³, for fine particles it was 24.5 μg/m³. Two tables are reprinted below: Table 2.22 being the inclusive table of results, Table 2.23 being a comparison of the effects of cigarette smoking with those of long-term exposure to sulphate and fine particles. The "bottom line" adjusted mortality-risk ratios for all-cause mortality were:

for sulphate (concentration range = 19.9 μg/m³)
   RR = 1.15 (1.09-1.22)

for fine particles (concentration range = 24.5 μg/m³)
   RR = 1.17 (1.09-1.26).

Table 2.22. Adjusted mortality-risk ratios* (and 95% CI) for the most polluted areas compared with the least polluted for all–cause and cardiopulmonary deaths separated by gender and smoking status

	Sulphate (19.9 μg/m³)			Fine particles (24.5 μg/m³)		
	All cause	Lung cancer	Cardio-pulmonary	All cause	Lung cancer	Cardio-pulmonary
All combined	1.15 (1.09-1.22)	1.36 (1.11-1.66)	1.26 (1.16-1.37)	1.17 (1.09-1.26)	1.03 (0.80-1.33)	1.31 (1.17-1.46)
Women	1.18 (1.06-1.30)	1.17 (0.80-1.72)	1.39 (1.20-1.61)	1.16 (1.02-1.32)	0.90 (0.56-1.44)	1.45 (1.20-1.76)
Men	1.14 (1.06-1.23)	1.43 (1.13-1.81)	1.20 (1.08-1.33)	1.18 (1.07-1.30)	1.10 (0.81-1.47)	1.24 (1.08-1.41)
Never-smokers	1.18 (1.06-1.30)	1.51 (0.73-3.11)	1.36 (1.19-1.58)	1.22 (1.07-1.39)	0.59 (0.23-1.52)	1.43 (1.18-1.72)
Women	1.20 (1.06-1.36)	1.61 (0.66-3.92)	1.44 (1.20-1.74)	1.21 (1.02-1.39)	0.65 (0.21-2.06)	1.57 (1.23-2.01)
Men	1.14 (0.97-1.34)	1.36 (0.40-4.66)	1.28 (1.03-1.58)	1.24 (1.00-1.54)	0.49 (0.09-2.66)	1.24 (0.93-1.67)
Ever-smokers	1.14 (1.06-1.23)	1.35 (1.10-1.66)	1.20 (1.08-1.33)	1.15 (1.05-1.26)	1.07 (0.82-1.39)	1.24 (1.08-1.42)
Women	1.14 (0.97-1.33)	1.10 (0.72-1.68)	1.30 (1.01-1.66)	1.10 (0.90-1.33)	0.95 (0.57-1.58)	1.27 (0.92-1.74)
Men	1.14 (1.05-1.24)	1.44 (1.14-1.83)	1.17 (1.05-1.32)	1.16 (1.05-1.29)	1.12 (0.83-1.52)	1.23 (1.06-1.43)

*Risk ratios have been adjusted for age, sex, race, cigarette smoking, exposure to passive cigarette smoke, body-mass index, drinks per day of alcohol, education and occupational exposure

Table 2.23. Adjusted mortality-risk ratios (and 95% CI) by cause of death for cigarette smoking and for a difference in pollution*

Cause of death	Current smoker†	Sulphate‡ (19.9 μg/m³)	Fine particles‡ (24.5 μg/m³)
All	2.07 (1.75-2.43)	1.15 (1.09-1.22)	1.17 (1.09-1.26)
Lung cancer	9.73 (5.96-15.9)	1.36 (1.11-1.66)	1.03 (0.80-1.33)
Cardiopulmonary	2.28 (1.79-2.91)	1.26 (1.16-1.37)	1.31 (1.17-1.46)
All other	1.54 (1.19-1.99)	1.01 (0.92-1.11)	1.07 (0.92-1.24)

* Difference in pollution equal to the most polluted areas compared with the least polluted using sulphates and fine particles as measures of combustion source air pollution.

† Risk ratios for cigarette smoking are estimated from the model using sulphate data and correspond to the risk of death for a current smoker with 25 years of smoking 20 cigarettes per day as compared with a never smoker. Risk ratios have been adjusted for age, sex, race, exposure to passive cigarette smoke, body-mass index, drinks per day of alcohol, education and occupational exposure.

‡ Risk ratios have been adjusted for age, sex, race, cigarette smoking, exposure to passive cigarette smoke, body-mass index, drinks per day of alcohol, education and occupational exposure.

2.182 The authors concluded in their abstract that:

> *"Particulate air pollution was associated with cardiopulmonary and lung cancer mortality but not with mortality due to other causes".*

2.183 This cautious conclusion is supported by their analysis. The authors then discussed their findings in conjunction with those of the Harvard Six Cities Study and with the findings of time-series studies that showed associations between daily concentrations of particulates and a range of endpoints including decrements in lung function, increased hospital admissions for respiratory diseases and increased daily respiratory and cardiovascular mortality. This discussion led them to a bolder conclusion:

> *"In combination with daily time-series mortality and morbidity studies, they (the findings of the ACS cohort study) suggest that combustion source air pollutants may be important contributing factors causing respiratory illness and early mortality due to cardiopulmonary diseases".* (Underlining added by present author).

2.184 Lipfert (2003) took issue with this statement, but selectively cites this omitting the words underlined in the above quotation from the original authors' work. It is true that the ACS study, *per se*, sheds no light on respiratory disease: only deaths from cardiorespiratory disease were studied. The authors (and those of the Harvard Six Cities Study) discussed this point and argued that errors in death certificate attributions of causes of death made distinguishing, in this sort of study, between deaths from these causes, difficult and liable to error. Thus, the combined category "cardiopulmonary deaths" was used.

2.185 It should be noted that this, the original publication of the ACS cohort study, tells us nothing of the possible effects of other pollutants such as nitrogen dioxide and sulphur dioxide.

2.186 It is possible that the reported coefficients may have been inflated as a result of the effects of the high concentrations of pollutants that occurred in the past being attributed to the lower concentrations found today. This possiblity is illustrated by Figure 2.31. Here the current range of pollutant concentrations is represented by "d" and ranges at times in the past by d_1, d_2, d_3.

2.187 It is also possible that misclassification errors have occurred. These would be expected to bias results towards a conclusion of no effect and may have caused the reported coefficient to be reduced in size.

2.188 A further possibility, though this is conjectural, is that the composition of ambient particles has changed significantly and that the ultrafine component may have increased or decreased as a fraction of $PM_{2.5}$. This, too, may have effected the coefficient. It is not possible to quantify the effect of the factors mentioned in this paragraph and in 2.186 and 2.189.

Figure 2.31
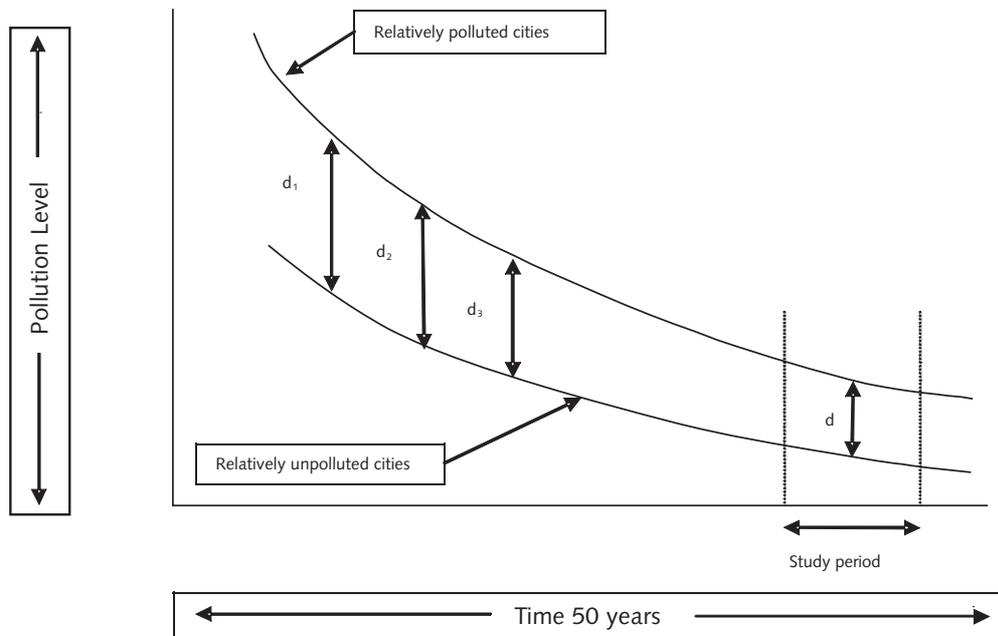
2.189 These, then, are the two major and fundamental US ecological cohort studies. We now turn to the HEI reanalysis and then consider the update of the ACS study (Pope, 2002).

The Health Effects Institute Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality

2.190 The Harvard Six Cities Study and the American Cancer Society cohort study have been exposed to searching examination. Both these studies caused controversy and widespread comment. In part this was because they reported unexpected findings and also because they provided encouragement for an Ambient Air Quality Standard based on fine particles ($PM_{2.5}$). Interest in the studies spread rapidly from the research community to industry and government and, in 1997, the proposal that the data used in the original studies should be validated and reanalysed was made. The task was taken on by the US Health Effects Institute which commissioned a group of distinguished research workers to undertake the Reanalysis. Their report was published in 2000, runs to 421 pages plus appendices and is remarkable for its depth and detail. Such a study was clearly intended to put to rest controversy about the original studies and has, to a large extent, done so. The authors of the original studies were invited to comment on the Reanalysis: their comments, both congratulatory and critical, merit attention (Dockery *et al*, 2003).

2.191 The Reanalysis can be divided into two parts:

(a)   replication and validation (88 pages);

(b)   sensitivity analyses and extension of the original work (108 pages).

2.192 Part (a) may be dealt with rapidly: the Reanalysis confirmed the original findings. Part (b) deserves more detailed comment. A number of the conclusions from this section including:

• examination of the importance of level of education in defining a potentially sensitive subgroup;

• the shape of the concentration-response relationship;

• the effect of allowing certain confounding factors such as smoking and body-mass index to vary over the period of analysis;

• the recognition that both pollutant variables and mortality appeared to be spatially correlated and that the development of statistical methods to deal with this led to some reduction in "bottom line" coefficients

need not concern us in detail. But some findings were important and perhaps unexpected.

2.193 The first is the clear finding that when the cardiopulmonary mortality group was subdivided into deaths from cardiovascular disease and deaths from respiratory disease, the association with the latter became small and statistically insignificant or

disappeared, whilst the former strengthened. This is shown in Table 2.24 which is extracted from Table 20 of the Reanalysis report.

Table 2.24. Relative risks of mortality by cause of death associated with an increase in fine particles or sulphate in risk models with alternative time axes in the ACS study[a] (Table adapted from Table 20 of Krewski *et al*, 2000)

	Calendar Year		Age	
Alternative risk model[b]	Fine particles	Sulphate	Fine particles	Sulphate
Cardiopulmonary disease [50%]				
Base	1.41 (1.27-1.56)	1.39 (1.28-1.50)	1.41 (1.27-1.56)	1.38 (1.27-1.49)
Original	1.30 (1.18-1.45)	1.27 (1.17-1.38)	1.30 (1.18-1.45)	1.27 (1.17-1.37)
Full	1.28 (1.15-1.42)	1.25 (1.15-1.35)	1.28 (1.15-1.42)	1.24 (1.14-1.34)
Extended	1.30 (1.17-1.44)	1.25 (1.16-1.36)	1.29 (1.17-1.43)	1.25 (1.15-1.35)
Cardiovascular disease [43%]				
Base	1.47 (1.32-1.65)	1.47 (1.35-1.60)	1.46 (1.31-1.63)	1.46 (1.34-1.59)
Original	1.36 (1.22-1.52)	1.36 (1.25-1.48)	1.36 (1.18-1.45)	1.35 (1.24-1.47)
Full	1.34 (1.20-1.49)	1.33 (1.22-1.45)	1.33 (1.19-1.48)	1.32 (1.21-1.43)
Extended	1.35 (1.21-1.51)	1.34 (1.23-1.46)	1.34 (1.20-1.50)	1.33 (1.22-1.44)
Respiratory disease [7%]				
Base	1.07 (0.80-1.42)	0.94 (0.76-1.17)	1.09 (0.82-1.45)	0.95 (0.76-1.18)
Original	1.00 (0.76-1.33)	0.83 (0.67-1.04)	1.01 (0.76-1.34)	0.85 (0.68-1.05)
Full	0.96 (0.72-1.27)	0.81 (0.65-1.01)	0.99 (0.74-1.31)	0.82 (0.66-1.03)
Extended	0.98 (0.74-1.30)	0.82 (0.65-1.02)	1.00 (0.76-1.33)	0.83 (0.66-1.03)

a Relative risks were calculated for a change in the pollutant of interest equal to the difference in mean concentrations between the most-polluted city and the least-polluted city; in the ACS Study, this difference for fine particles was 24.5 $\mu g/m^3$, and for sulphate was 19.9 $\mu g/m^3$. Causes of death are shown with percentage of all causes. Data are RRs with 95% CIs.

b See the Alternative Risk Models section under the ACS study for a description of models and Table 19 (of the HEI report) for a list of covariates included in each model.

2.194 The authors also report statistically significant risks if the underlying cause of death were restricted to ischaemic heart disease, with risks associated with sulphate of 1.32 (95% CI 1.20 to 1.44) and risks associated with fine particle exposures of 1.37 (95% CI 1.22 to 1.53). For the first time it became clear that long-term exposure to particulate air pollutants in the USA had a minor effect on mortality from respiratory disease but a significant effect on deaths from cardiovascular disease. Some workers have argued that, in retrospect, this is unsurprising: few advanced such views before the reanalysis was published. We regard this finding as very important: it forms a firm foundation for our conclusion that the fate of people with cardiovascular disease is affected by particulate air pollutants.

2.195 The Six Cities Study showed that fine particles ($PM_{2.5}$) were more strongly associated with cardiopulmonary deaths than were indices of particulate pollution that included particles of larger diameter (TSP, PM_{10}). The original American Cancer Society Study did not pursue this point but it was taken up again in the Reanalysis. The following table (Table 2.25) summarises the findings. It should be noted that in this table

cardiopulmonary disease occurs as a combined category: no division into cardiac and pulmonary deaths is made.

Table 2.25. Relative risks of mortality from all causes, cardiopulmonary disease, and lung cancer associated with various measures of air pollution from the Reanalysis of the American Cancer Society Study[a] (Table from Krewski *et al*, 2000)

| | | Cause of Death | | |
Pollutant[b]	Number of cities	All causes	Cardiopulmonary disease	Lung cancer
$PM_{2.5}$(OI, MD)[c]	50	1.18 (1.09-1.26)	1.30 (1.17-1.44)	1.00 (0.79-1.28)
$PM_{2.5}$(OI, MD) Denver omitted	49	1.18 (1.10-1.27)	1.30 (1.17-1.44)	0.99 (0.78-1.26)
$PM_{2.5}$(DC, MD)[d]	50	1.14 (1.06-1.22)	1.26 (1.14-1.39)	1.08 (0.88-1.32)
$PM_{2.5}$(DC, MD) Denver omitted	49	1.17 (1.09-1.26)	1.28 (1.15-1.42)	1.02 (0.81-1.30)
$PM_{2.5}$(DC)[e]	63	1.12 (1.06-1.19)	1.26 (1.16-1.38)	1.08 (0.88-1.32)
PM_{15}(DC)[f]	63	1.05 (1.01-1.09)	1.09 (1.04-1.15)	1.01 (0.90-1.13)
$PM_{15-2.5}$(DC)[g]	63	1.01 (0.97-1.06)	1.01 (0.95-1.08)	0.97 (0.83-1.13)
PM_{15}(SSI)[h]	59	1.02 (0.99-1.05)	1.07 (1.03-1.11)	0.98 (0.89-1.08)
TSP(IPMN)[i]	58	1.00 (0.98-1.02)	1.02 (0.99-1.05)	0.95 (0.89-1.02)
TSP[j]	156	0.99 (0.98-1.00)	0.99 (0.97-1.01)	0.94 (0.90-0.99)
SO_4^{2-}(DC)[k]	51	1.17 (1.10-1.23)	1.29 (1.19-1.40)	1.09 (0.90-1.33)
SO_4^{2-}(OI)[l]	151	1.15 (1.09-1.21)	1.25 (1.16-1.36)	1.33 (1.10-1.61)
SO_4^{2-}(cb-unadj)[m]	144	1.14 (1.07-1.20)	1.24 (1.15-1.35)	1.18 (0.97-1.44)
SO_4^{2-}(cb-adj US)[n]	144	1.18 (1.11-1.26)	1.31 (1.19-1.43)	1.18 (0.96-1.47)
SO_4^{2-}(cb-adj region)[o]	144	1.23 (1.16-1.30)	1.34 (1.23-1.45)	1.25 (1.03-1.52)
SO_4^{2-}(cb-adj season)[p]	144	1.17 (1.09-1.25)	1.29 (1.17-1.42)	1.16 (0.93-1.44)

a Risks were calculated for a change in the pollutant of interest equal to the difference in mean concentrations between the most-polluted city and the least-polluted city; in the American Cancer Society Study, this difference for fine particles was 24.5 µg/m³, and for sulphate was 19.9 µg/m³. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups, gender and race. See Table 19 of the Reanalysis report (Krewski *et al*, 2000) for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

b Refer to the Abbreviations and Other Terms section at the end of the Investigators Report for the specific meanings of these pollutant terms and to Table 29 of the Reanalysis report (Krewski *et al*, 2000) for the sources of pollutant data. All values are means unless indicated by MD (median).

c **Median** fine particle concentration used by the Original Investigators.

d **Median** fine particle mass concentration from dichotomous samplers.

e **Mean** fine particle fraction from dichotomous samplers.

f **Mean** inhalable particle fraction from dichotomous samplers.

g **Mean** coarse particle fraction from dichotomous samplers.

h **Mean** inhalable particle fraction from high volume samplers with size-selective inlets.

i **Mean** TSP mass concentrations based on inhalable particle monitoring network (IPMN) data.

j Total suspended particles.

k Sulphate data from PM15(DC).

l Sulphate data used by the Original Investigators.

m Sulphate data for 1980-1981 inclusive, unadjusted for artifactual sulphate.

n Sulphate data for 1980-1981 inclusive, with US-specific adjustment for artifactual sulphate.

o Sulphate data for 1980-1981 inclusive, with region-specific adjustment for artifactual sulphate.

p Sulphate data for 1980-1981 inclusive, with season-specific adjustment for artifactual sulphate.

2.196 It will be seen that though the number of cities providing data for the different categories of particles varied considerably, the coefficients (relative risks) linking fine particles ($PM_{2.5}$) and sulphate with the outcome were consistently larger than those for the indices that included larger particles as well as fine particles (PM_{15}) and than for those including larger particles but not fine particles ($PM_{15-2.5}$). Also all the relative risks related to fine particles and sulphate were statistically significant but this was not the case for all the other indices. Interestingly, the relative risks for TSP were statistically significant, as were those for PM_{15} but that for $PM_{15-2.5}$ was not. These findings support the findings of the Six Cities Study: it is likely that the fine particle fraction, as represented by $PM_{2.5}$ and by sulphate, is most likely associated with cardiopulmonary deaths.

Reanalysis – gaseous pollutants

2.197 The HEI Reanalysis collated additional data on gaseous pollutants and performed additional analyses to those described in the original publications of the Six Cities and ACS studies.

2.198 Table 2.26, extracted from Table 16 of Part II of the Reanalysis report, shows relative risks for cardiopulmonary disease and sulphur dioxide, nitrogen dioxide and ozone based on the Six City cohort. Increased relative risks were seen for both sulphur dioxide and nitrogen dioxide but the report also notes that both pollutants were closely correlated with fine particles (correlations with fine particles of 85% and 78% for sulphur dioxide and nitrogen dioxide, respectively). Ozone was not positively associated with cardiopulmonary disease but, as noted previously, the range of ozone concentrations across the cities in the Six Cities study was very small (only 8 ppb). As there were only six cities available, multi-pollutant models were not attempted.

Table 2.26. Relative risks of mortality from cardiopulmonary disease associated with various measures of air pollution from the Reanalysis of the Six Cities Study[a] (Table adapted from the HEI Reanalysis Report, Krewski *et al*, 2000)

Pollutant	Range[b]	Cause of death
		Cardiopulmonary disease
SO_2	22.4 ppb	1.25 (1.01-1.54)
SO_2 reconstructed[c]	22.1 ppb	1.24 (1.00-1.54)
NO_2	15.8 ppb	1.28 (1.04-1.59)
O_3	8.3 ppb	0.78 (0.64-0.95)

a Data are RRs with 95% CIs
b Unless otherwise noted: all ranges were calculated from the values in Table 17a in Part I of the Reanalysis report, which corresponds to Table 1 in Dockery *et al*, 1993.
c This range was reconstructed by the Original Investigators during the Reanalysis

2.199 The original 1995 publication of the ACS study focused on fine particles and sulphate. The reanalysis of the ACS study extended this to look at other pollutants and also examined the effect of adjusting the relative risk for fine particles or sulphate for other pollutants. Table 2.27 is extracted from Table 38 of the reanalysis.

Table 2.27. Relative risks of mortality from cardiopulmonary disease associated with an increase in fine particles after adjusting for selected ecologic covariates[a] (Taken from Table 38 of HEI Reanalysis Report, Krewski _et al_, 2000)

| | Relative Risk from Fine Particles | | Relative Risk from Ecologic Covariates | |
Ecologic covariate	Without ecologic covariate	With ecologic covariate	Without fine particles	With fine particles
Gaseous co-pollutants				
CO (range 36 ppm)	1.30 (1.17-1.45)	1.32 (1.19-1.47)	0.92 (0.85-1.00)	0.74 (0.61-0.90)
NO_2 (range 43.3 ppb)	1.32 (1.16-1.49)	1.39 (1.22-1.59)	0.99 (0.91-1.08)	0.91 (0.83-1.00)
O_3 (range 30.7 ppb)	1.29 (1.16-1.44)	1.30 (1.17-1.45)	0.96 (0.86-1.07)	0.93 (0.83-1.04)
SO_2 (range 45.2 ppb)	1.35 (1.21-1.51)	1.17 (1.03-1.33)	1.59 (1.39-1.81)	1.45 (1.25-1.69)

a Relative risks were calculated for a change in the pollutant of interest equal to the difference in mean concentrations between the most-polluted city and the least-polluted city. In the ACS Study, this difference for fine particles was 24.5 $\mu g/m^3$. Analyses are based on the Extended Model with calendar year as the time axis and the baseline hazard function stratified by 1-year age groups, gender and race. See Table 19 of the HEI Reanalysis Report for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

2.200 It will be seen that, (with the exception of sulphur dioxide) the relative risks for the gaseous pollutants alone, 3rd column, approximate to 1.0: they had no effect. It will also be seen, columns 1 and 2, that including the gaseous pollutants (again with the exception of sulphur dioxide) in a model for fine particles made little difference to the fine particle coefficients.

2.201 The lack of a positive association for nitrogen dioxide may seem surprising, given that nitrogen dioxide is usually closely correlated with particles, at least on a daily basis. However, it seems that the Pearson correlation between nitrogen dioxide and fine particles was low (-8%) overall in the ACS cities[18]. This is in contrast to the close correlation found in the Six Cities Study, probably accounting for the contrasting relative risk results for nitrogen dioxide between the two studies. The correlation of fine particles with ozone was also low (4%). In the ACS study the correlation between fine particles and sulphur dioxide was higher than for nitrogen dioxide at 50%. The relative risk for fine particles was substantially reduced (but remained positive) after adjustment for sulphur dioxide. The interpretation of this result is not clear cut given a certain amount of correlation between these pollutants – we intend to examine this

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18 Correlations between pollutants in the reanalysis of the ACS study are given in Appendix G of the Reanalysis report available on request from the Health Effects Institute. Appendix G also contains the range in concentrations of gaseous pollutants across cities – the relative risks in Table 38 of the Reanalysis report are quoted for the range from the least to the most polluted city for each pollutant.

issue in further detail in our forthcoming report on quantifying the effects of air pollutants on health.

2.202 The reanalysis report gives results for a substantial number of sensitivity analyses involving gaseous pollutants (for the pool of cities measuring sulphates, for the pool of cities measuring fine particles (described above) and for various statistical models with increasing levels of adjustment for spatial correlation). We will not discuss all these here but note that the qualitative conclusions were analogous to those above for sulphur dioxide, nitrogen dioxide and carbon monoxide. The qualitative conclusions were also analogous in most cases for ozone except that Table 48 of the reanalysis report gives a positive and statistically significant association for ozone and cardiopulmonary disease in the Regional Adjustment Model for the pool of cities with fine particle measurements.

2.203 The Reanalysis report also presented results for the ACS study analysed by season[19]. (Table 2.28).

Table 2.28. Relative risks of mortality from cardiopulmonary disease associated with gaseous copollutants by season from the Reanalysis of the ACS study[a] (Adapted from Table 32 the HEI Reanalysis Report, Krewski *et al*, 2000)

Pollutant	Season	Seasonal mean concentrations	Cardiopulmonary disease
SO_2 (ppb)	April-September	7.18	1.48 (1.33-1.64)
	October-March	11.24	1.29 (1.20-1.38)
NO_2 (ppb)	April-September	23.65	0.96 (0.88-1.04)
	October-March	27.20	0.94 (0.88-0.99)
CO (ppm)	April-September	1.33	1.00 (0.92-1.09)
	October-March	1.73	0.90 (0.84-0.97)
O_3 (ppb)	April-September	30.44	1.08 (1.01-1.16)
	October-March	15.07	0.82 (0.74-0.91)

a Analyses based on the Extended Model: see Table 19 of the HEI Reanalysis Report for a complete list of covariates included in the Extended Model. Data are RRs with 95% CIs.

2.204 There is a suggestion here that cities with higher levels of ozone between April and September may be associated with greater cardiopulmonary mortality. As with the all-year results, nitrogen dioxide and carbon monoxide do not show clear positive associations in either season. Sulphur dioxide is again clearly associated with cardio-pulmonary mortality.

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19 The pollutant ranges for the relative risks in the table are not given in the reanalysis report.

Reanalysis – consideration of spatial correlation

2.205 The risk analysis in the Reanalysis report (Krewski *et al*, 2000) assumes that each city forms an independent observation whereas, in fact, mortality rates in cities in the same geographic region are more likely to be similar than those of cities further away from each other. This is probably due to unknown regional factors affecting mortality. These unknown factors could act as confounders if they are also correlated with air pollution. The Reanalysis report developed complex new statistical models to account for this. The use of spatial analytic methods showed that, when the analyses controlled for correlations among cities located near to one another, the associations between mortality and fine particles or sulphate remained but were diminished. However, the findings need to be interpreted with caution as these statistical models are newly developed.

2.206 We conclude from the above that the findings reported in the Harvard Six Cities Study and the ACS cohort study are sound – indeed no other studies have been exposed to such searching reanalysis. For the purposes of this report the findings are clear:

- long-term exposure to particulate air pollutants represented by fine particles ($PM_{2.5}$) and sulphate is associated with an increased likelihood of death from cardiovascular disease;

- long-term exposure to ozone and carbon monoxide is not associated with an increased likelihood of death from cardiovascular disease. It is possible that there is a warm season (April – September) association between ozone and likelihood of death from cardiopulmonary disease but this, if true, is a weak association;

- long-term exposure to nitrogen dioxide is unlikely to be associated with increased cardiovascular deaths. Although a positive association was found in the reanalysis of the Six Cities study, nitrogen dioxide and fine particles concentrations were closely correlated. When nitrogen dioxide was less closely correlated with fine particles, as in the reanalysis of the ACS study, no positive association was found;

- long-term exposure to sulphur dioxide is associated with increased likelihood of death from cardiovascular disease;

- the above conclusions should all be qualified by the phrase "within the range of concentrations studied" and "in the United States".

Update of the ACS Cohort Study (Pope *et al*, 2002)

2.207 The updated study followed essentially the same design as the original ACS cohort study but:

(a) increased the follow-up time to more than 16 years and tripled the number of deaths recorded;

(b) expanded the pollutant database to include data on gaseous pollutants and data from an expanded $PM_{2.5}$ network;

(c) included some control for occupational exposure to dusts and fumes;

(d) incorporated dietary variables;

(e) used improved statistical modelling developed in the HEI reanalysis – discussed below.

2.208 For details of the analysis the reader is referred to the original paper; only a brief summary of the findings are provided here. The authors focused on fine particles, though a significant association between the mortality risk ratio and sulphate was found. Weaker and less consistent associations were found with PM_{10} and PM_{15}; associations with $PM_{15-2.5}$, TSP, nitrogen dioxide, ozone and carbon monoxide were not found to be significant. Sulphur dioxide was significantly positively associated with the mortality risk ratio. The adjusted mortality risk ratios for fine particles ($PM_{2.5}$) associated with a 10 μg/m³ differential in this pollutant are shown in Table 2.29.

Table 2.29. Adjusted mortality relative risk (RR) associated with a 10 μg/m³ change in fine particles measuring less than 2.5 μm in diameter

Cause of mortality	Adjusted RR (95% CI)*		
	1979-1983	1999-2000	Average
All-cause	1.04 (1.01-1.08)	1.06 (1.02-1.10)	1.06 (1.02-1.11)
Cardiopulmonary	1.06 (1.02-1.10)	1.08 (1.02-1.14)	1.09 (1.03-1.16)
Lung cancer	1.08 (1.01-1.16)	1.13 (1.04-1.22)	1.14 (1.04-1.23)
All other causes	1.01 (0.97-1.05)	1.01 (0.97-1.06)	1.01 (0.95-1.06)

*Estimated and adjusted based on the baseline random-effects Cox proportional-hazards model, controlling for age, sex, race, smoking, education, marital status, body-mass, alcohol consumption, occupational exposure and diet. CI indicates confidence interval.

2.209 Note that 10 µg/m^3 is the differential used: not the span or range of PM$_{2.5}$ concentrations across the study areas as was used in the original ACS cohort study. A number of points were stressed by the authors in their discussion. Some of these, for example a discussion of the shape of the concentration-response relationship as revealed by the use of non-parametric smoothing methods, need not concern us here, though we anticipate returning to this point in future work on quantification of the impact of air pollutants on health. The lack of an association with nitrogen dioxide was mentioned again.

Further examination of associations between long-term exposure to air pollutants and cardiovascular disease: Pope *et al*, 2004

2.210 In 2004, Pope and colleagues, including authors of the HEI Reanalysis discussed above, published an important paper which focused on subgroups of cardiovascular disease (Pope *et al*, 2004). The American Cancer Society cohort again provided the data for analysis. The analysis was designed to look for evidence bearing on the two leading hypotheses that have been put forward to explain the effect of long-term exposure to fine particles on the heart. These are discussed in detail in the following chapter but it is noted here that they were identified by Pope and his colleagues as:

(i) the inflammation-accelerated atherosclerosis hypothesis;

(ii) the altered cardiac autonomic function hypothesis.

2.211 A third hypothesis, suggesting that long-term exposure to fine particles led to accelerated progression of chronic obstructive pulmonary disease (COPD) was also examined. Little support for this was found, the authors pointing out that:

"In fact, COPD and related deaths were negatively associated with fine particulate air pollution exposure".

2.212 As would be expected, smoking had a significant effect on the risk of death from cardiovascular disease and respiratory disease. This is shown in the following tables taken from Pope *et al*, 2004.

Table 2.30. Adjusted RRs and 95% CIs for a 10 μg/m³ increase in PM$_{2.5}$ (average) and for former and current smoker (vs never smoker) for various cause-of-death categories (Table taken from Pope _et al_, 2004)

Cause of death	PM$_{2.5}$	Former smoker	Current smoker
All cardiovascular diseases plus diabetes	1.12 (1.08-1.15)	1.26 (1.23-1.28)	1.94 (1.90-1.99)
Ischemic heart disease	1.18 (1.14-1.23)	1.33 (1.29-1.37)	2.03 (1.96-2.10)
Dysrhythmias, heart failure, cardiac arrest	1.13 (1.05-1.21)	1.18 (1.12-1.24)	1.72 (1.62-1.83)
Hypertensive disease	1.07 (0.90-1.26)	1.21 (1.07-1.37)	2.13 (1.86-2.44)
Other atherosclerosis and aortic aneurysms	1.04 (0.89-1.21)	1.63 (1.45-1.84)	4.21 (3.71-4.78)
Cerebrovascular disease	1.02 (0.95-1.10)	1.12 (1.06-1.18)	1.78 (1.67-1.89)
Diabetes	0.99 (0.86-1.14)	1.05 (0.94-1.16)	1.35 (1.20-1.53)
All other cardiovascular diseases	0.84 (0.71-0.99)	1.22 (1.09-1.38)	1.78 (1.56-2.04)
Diseases of the respiratory system	0.92 (0.86-0.98)	2.16 (2.04-2.28)	3.88 (3.66-4.11)
COPD and allied conditions	0.84 (0.77-0.93)	4.93 (4.48-5.42)	9.85 (8.95-10.84)
Pneumonia and influenza	1.07 (0.95-1.20)	1.23 (1.13-1.34)	1.89 (1.70-2.09)
All other respiratory diseases	0.86 (0.73-1.02)	1.54 (1.36-1.74)	1.83 (1.57-2.12)

Note that as before in this section in the table Relative Risks are quoted and that a Relative Risk of 1.07 indicates a 7% increase in risk whereas a relative risk of 2.13 indicates a 113% increase in risk. Relative Risks of < 1.0 indicate a negative association. Stratification of the findings by smoking status and the results are shown in the following table.

Table 2.31. Adjusted RRs and 95% CIs stratified by smoking status for a 10 μg/m³ increase in PM$_{2.5}$ (average) (Table taken from Pope _et al_, 2004)

Cause of death	Never smokers	Former smokers	Current smokers
All cardiovascular diseases plus diabetes	1.11 (1.07-1.16)	1.09 (1.04-1.15)	1.16 (1.09-1.23)
Ischemic heart disease	1.22 (1.14-1.29)	1.15 (1.07-1.23)	1.16 (1.07-1.27)
Dysrhythmias, heart failure, cardiac arrest	1.04 (0.95-1.15)	1.14 (1.00-1.29)	1.31 (1.12-1.52)
Hypertensive disease	0.88 (0.69-1.12)	1.05 (0.76-1.44)	1.57 (1.12-2.19)
Other atherosclerosis and aortic aneurysms	1.18 (0.90-1.55)	0.91 (0.70-1.19)	1.08 (0.84-1.40)
Cerebrovascular disease	1.03 (0.93-1.15)	1.01 (0.88-1.17)	1.01 (0.86-1.20)
Diabetes	1.01 (0.83-1.23)	0.86 (0.66-1.12)	1.26 (0.91-1.74)
All other cardiovascular diseases	0.86 (0.67-1.09)	0.83 (0.61-1.13)	0.83 (0.59-1.15)
Diseases of the respiratory system	1.03 (0.91-1.17)	0.89 (0.80-1.00)	0.85 (0.76-0.96)
COPD and allied conditions	0.96 (0.73-1.24)	0.86 (0.73-1.00)	0.81 (0.70-0.93)
Pneumonia and influenza	1.20 (1.02-1.41)	0.98 (0.80-1.20)	0.90 (0.69-1.18)
All other respiratory diseases	0.74 (0.56-0.97)	0.88 (0.68-1.16)	1.10 (0.76-1.60)

2.213 The authors concluded, cautiously, that the results provided:

"intriguing, but inconclusive, insights into the general pathophysiological pathways that may link exposure to fine particulate air pollution and cardiovascular disease mortality".

2.214 The association with death from ischaemic heart disease supports the inflammation-accelerated atherosclerosis hypothesis; the association with deaths attributed to dysrhythmias and heart failure and cardiac arrest supports the hypothesis of disordered cardiac autonomic control. For a valuable and detailed discussion of supporting evidence for these ideas the reader is referred to the original paper (Pope _et al_, 2004).

Other studies of the effects of long-term exposure to air pollutants

2.215 Abbey *et al* (1999) studied 6,338 non-smoking Seventh-Day Adventists in California from 1977 to 1992. Air pollution concentrations were obtained as monthly averages from 1966 to 1992, interpolated to subjects' work or home locations, cumulated and then averaged over time. Adjustment was made for several other risk factors such as smoking, education, occupation, exercise and body-mass index. Sex-specific adjusted mortality relative risks were estimated using Cox proportional-hazard regression models. Positive associations (RRs from 1.01 to 1.10 per inter quartile range of pollutant) were found in men between cardio-pulmonary mortality and all pollutants examined (particles (as PM_{10}), sulphate, sulphur dioxide, ozone and nitrogen dioxide) but none was statistically significant and no positive associations were found in women. (This study found some significant positive associations with respiratory mortality and several significant strong positive associations with lung cancer mortality, but some commentators have expressed concern that smoking might be under-reported as Seventh-Day Adventists are not supposed to smoke).

2.216 The same cohort and general methodology were used to examine the association between PM_{10} or $PM_{2.5}$ and incidence of fatal or non-fatal coronary heart disease (CHD). (Chen *et al*, 2005). In men, the relative risk for fatal CHD was positive and statistically significant for both PM_{10} (RR 1.43 (95% CI 1.13 to 1.81)) and $PM_{2.5}$ (RR 1.88 (95% CI 1.07 to 1.31)) (relative risks given for the inter quartile range). In women, the relative risk was positive for both pollutants but only significant for $PM_{2.5}$ (PM_{10} RR 1.16 (95% CI 0.94 to 1.42); $PM_{2.5}$ RR 1.67 (95% CI: 1.04 to 2.27)). The risk of non-fatal CHD was only examined for PM_{10} – the association was found to be positive and statistically significant in both men (RR 1.75 (95% CI: 1.07 to 2.88)) and women (RR 2.90 (95% CI: 1.22 to 6.91)). The same point as that made above about possible under-reporting of smoking applies also to this study.

2.217 Jerrett *et al* (2005) reports on a study in Los Angeles with 22,905 subjects (5891 deaths) from the ACS Cancer Prevention II study cohort. $PM_{2.5}$ concentrations were interpolated from 23 monitoring locations giving concentrations at a more local scale than with the previous ACS study. A larger effect for all-cause mortality was found than in the previous ACS study – RR 1.17 (95% CI 1.05 to 1.30) per 10 μg/m³ after control for 44 individual variables, although the association just lost statistical significance with maximal control for individual and ecological confounders RR 1.11 (95% CI 0.99 to 1.25). Larger relative risks were found for ischaemic heart disease deaths (RRs in the range 1.24 to 1.46). This study indicates that long-term effects can also be shown when pollutant concentrations are compared within a city rather than across cities, lessening concerns that the associations found in the ACS study might be an artefact of unknown between-city differences. The study also indicates an effect of traffic-related pollution since this is the dominant source of pollution in Los Angeles.

European mortality studies

2.218 A random sample of 5000 people in the Netherlands aged 55-69 years was investigated from 1986 to 1994. Exposure to traffic-related air pollution (Black Smoke and nitrogen dioxide) was estimated for the 1986 home address (Hoek *et al*, 2002). Eleven percent of the people died during the follow-up period. Adjustment was made for a range of possible confounders including age, sex, smoking, passive smoking, level of education, occupation type (e.g. blue collar, white collar), regional indicators of poverty, bodyweight and intake of alcohol, fat, vegetables and fruit. Data on occupational exposure to dust and fumes were not available. Cardiopulmonary mortality was associated with living near to a major road, RR 1.95 (95% CI 1.09 to 3.52). All-cause mortality showed a weaker relationship with a RR of 1.41 (95% CI 0.94 to 2.12) but non-cardiopulmonary, non-lung-cancer deaths were unrelated to pollution, so the excess in all-cause mortality was largely due to cardiopulmonary disease. This study is important in that, although of a slightly different design to the Six Cities Study and ACS study discussed in the previous section, it confirmed that similar results to those found in the US also applied to the European mix of pollution. The study is ongoing.

2.219 Another European study has recently been published (Nafstad *et al*, 2004). A sample of 16,209 Norwegian men aged 40-49 in 1972-1973 were studied through to 1998, during which period there were 4227 deaths. These were linked to average yearly air pollution levels from 1974 to 1998. The air pollution levels were modelled using air pollution monitoring and emissions data and modelled concentrations linked to individual home addresses. The pollutants addressed were sulphur dioxide and nitrogen oxides (NO_x). These were regarded as markers of the air pollution mixture with the latter better representing traffic exposure. The relative risks were adjusted for education, occupation, smoking, exercise, cardiovascular disease risk group and age. NO_x exposure was associated with all-cause mortality RR 1.08 (95% CI 1.06 to 1.11). It was also associated with deaths from ischaemic heart disease RR 1.08 (95% CI 1.03 to 1.12), although the exposure-response pattern in this case was not very clear when categorical ranges of exposure were considered rather than exposure as a continuous variable. The association with cerebrovascular disease was smaller and not statistically significant RR 1.04 (95% CI 0.94 to 1.15). In this study, relative risks for respiratory mortality and lung cancer were larger than for ischaemic heart disease mortality. Sensitivity analysis adding adjustment for height, weight, blood pressure and cholesterol level did not affect the result. Sulphur dioxide, a pollutant which is less associated with traffic exposure, did not appear to increase mortality. This result for sulphur dioxide is in contrast to the results for the ACS study. The differences could be for a variety of reasons – the different spatial scale of modelling resulting in different correlations between different pollutants, differences in correlations between

pollutants between the US and Europe and differences in concentrations between the US and Europe.

2.220 An alternative approach is to consider residency near point sources of pollution. Populations within 7.5 km of 22 cokeworks in Great Britain in 1981 to 1992 were studied using a small area statistics approach (Dolk *et al*, 1999). Air pollution was not measured directly but was expected to be higher closer to cokeworks than further away. Expected deaths were adjusted for age, sex, deprivation quintile (Carstairs index) and region. There were 18,973 observed all-cause deaths, 8872 cardiovascular deaths and 5628 ischaemic heart disease deaths within 2 km of the selected cokeworks. Overall, within 2 km, an excess all-cause mortality of 3% was found over the calculated expected numbers of deaths. A 5% excess for mortality from all cardiovascular causes (Observed/Expected ratio 1.05 (95% CI 1.03 to 1.07)) was found and a 6% excess for ischaemic heart disease mortality (O/E 1.06 (95% CI 1.03 to 1.09)). Smaller excesses were found within 7.5 km compared with within 2 km of cokeworks. Although the expected deaths were adjusted for deprivation, the authors noted that the effect of deprivation alone was strong (an 8.6% excess within 2 km of cokeworks). Thus, the authors could not rule out the possibility that the small excess, assumed to be due to air pollution, could be due to residual confounding by socioeconomic deprivation.

European morbidity studies

2.221 There has been one study of historic Black Smoke levels in the UK in relation to diagnosed ischaemic heart disease. 1166 women over the age of 45 who had lived within 5 miles of their current address for 30 years answered a short postal questionnaire which covered diagnosis of heart and lung disease (Solomon *et al*, 2003). Ischaemic heart disease was reported by 137 women. Black Smoke levels in 11 electoral wards were available from 1966 to 1997. Black Smoke levels in 1966-1969 were used to classify wards into high (mean Black Smoke 122-180 $\mu g/m^3$) or low (Black Smoke 40-47 $\mu g/m^3$) particulate pollution wards. After adjusting for potential confounders (smoking, passive smoking in childhood, tenancy, social class, diabetes and body-mass index), there was no increase in the frequency of ischaemic heart disease in areas of high compared with low particulate pollution wards RR 1.0 (95% CI 0.7 to 1.4). The authors suggested that this finding, different from the US studies (albeit in a smaller sample and limited to women only) requires further, more detailed study in the UK. The authors noted that the results did not rule out a shorter term effect as the wards had rather similar Black Smoke levels by 1994-1997 (range 4-14 $\mu g/m^3$).

2.222 A case-control study of non-fatal myocardial infarction was performed in Kaunas, Lithuania (Grazuleviciene *et al*, 2004). Cases were men aged 25-64 hospitalised with a first time myocardial infarction between 1997 and 2000. There were 448 cases and 1777 age and sex matched population based controls without ischaemic heart disease.

Annual mean nitrogen dioxide exposure from 12 residential districts with their own monitoring sites was used to characterise exposure to traffic pollution. Odds ratios were adjusted for potential confounding factors collected by interview with medical staff. The factors were age, education, smoking, blood pressure, body-mass index, marital status and psychological stress. Using a continuous exposure variable, incidence of myocardial infarction increased from the lowest tertile (< 17 $\mu g/m^3$) to the highest tertile (> 19 $\mu g/m^3$) of nitrogen dioxide exposure – OR 1.17 (95% CI 1.01 to 1.35) for the full 25-64 year old age group. This association was driven by an increase in myocardial infarction incidence in the 55-64 year old age group – OR 1.34 (95% CI 1.08 to 1.67) from the lowest to the highest tertile of nitrogen dioxide exposure.

2.223 The statistically significant positive association between PM_{10} and non-fatal coronary heart disease in Seventh-Day Adventists in California, with possible under-reporting of smoking, was discussed in paragraph 2.215.

2.224 Thus, the results on air pollution and cardiovascular morbidity are mixed. There are very few studies and the populations studied and the study designs were different. The pollution mixtures were also different. It is not possible to come to a firm conclusion on the effect of long-term exposure to air pollution on cardiovascular morbidity at present.

Lead and cardiovascular disease

2.225 It has been suggested that lead exposure is linked to increases in blood pressure, and, thus, potentially to cardiovascular disease (IPCS, 1995; Prüss-Üstün *et al*, 2004). We have not considered this evidence for this report as levels of lead in air in the UK are now generally very low and lead in air makes only a minor contribution to blood lead levels (Department of the Environment, Transport and the Regions, 1998). We mention it here as lead levels in air were higher in the past and, if correlated with other pollutants, could act as a potential confounder for the results attributed to other pollutants. However, it is unclear whether, even in the past, airborne lead exposures would have been high enough to have a measurable impact on cardiovascular disease. For the ACS study, control for spatial autocorrelation (systematic regional differences) may have to some extent controlled for potential confounders, such as lead, which had not been included. In addition, Pope *et al* (2004) only found a small raised relative risk for $PM_{2.5}$ deaths from hypertensive disease which was not statistically significant (Table 2.30) and was less marked than the statistically significant increased relative risk for ischaemic heart disease. In summary, although a contribution cannot be completely ruled out, it seems unlikely that lead levels in air could account for the findings in the ACS study.

Conclusion from studies of effects of long-term exposure to air pollutants

2.226 Three types of study have been considered; occupational, intervention and the cohort studies. The conclusions from each are considered, briefly, in turn.

Conclusions on studies of occupational exposures

2.227 Studies of vehicle drivers are to an extent conflicting but those with the strongest methodology (Gustavsson *et al*, 2001; Hedberg *et al*, 1993) show positive effects. However, there remains some doubt about the components of work as a driver that causally contribute to heart disease, although there is reasonable evidence to support the hypothesis that air pollution is a causal factor.

2.228 In a range of occupations where exhaust exposure is common but to a varying extent, the findings suggest no effect on cardiovascular outcomes in groups with likely lower exposures (policemen, engineers, gasoline salesmen) but positive and dose-related effects in tunnel workers with higher exposures. Intriguingly, the study by Wong *et al* (1985), while apparently showing an overall protective effect, did show a positive relationship with degree of exposure which would be compatible with a healthy worker effect overlaying a true health impact.

2.229 Other occupations which involve exposure to particles, fumes or gases analogous to those found in ambient air, also offer some supportive evidence for causation, bearing in mind the range of differing exposures. Firefighters show no association (if anything cardiovascular risk is decreased) but this may reflect recruiting requirements and the benefits of regular health-checks. Nevertheless, it is possible that in some individuals with, perhaps, unsuspected heart disease, an acute exposure to fire smoke might precipitate an acute cardiac event. Both foundry workers and welders have increased cardiovascular risk (hypertension and ischaemic heart disease, respectively) and of interest is that metal particles are an important component of their exposures.

2.230 Overall, the evidence from the occupational literature is limited by inadequacy of study design – poor characterisation of exposure, lack of adjustment for confounding factors, comparisons with the general population only. This makes the evidence difficult to interpret. There is sufficient evidence from the better studies, i.e. those that estimate exposure-response relationships, to support the viewpoint that occupational exposure to exhaust or particulate pollution contributes to cardiovascular morbidity and mortality. On the other hand the strength of evidence from occupational studies alone is unlikely to convince the sceptical.

Studies of natural experiments

2.231 The studies in Dublin and in Hong Kong both show that sudden and sustained reductions in concentrations of air pollutants are associated with long-term reductions in deaths from cardiovascular causes (Clancy *et al*, 2002; Hedley *et al*, 2002). In the Dublin study, coal smoke was the pollutant reduced and the association was found to link Black Smoke and deaths. In the Hong Kong study, sulphur dioxide and sulphate particles were the pollutants reduced and the association was found with these. Our primary conclusion from these studies is that reductions in concentrations of particles and sulphur dioxide are associated with a decline in deaths from cardiovascular diseases. It is unlikely that this effect is due, solely, to a reduction in the effects of daily changes in concentrations of particles and sulphur dioxide (though peak concentrations would have been reduced) and a longer term effect on perhaps the rate of development of cardiovascular disease rather than its initial causation seems likely to us.

Cohort studies

2.232 In considering the findings of the cohort studies we draw attention to the points made in the introduction to this chapter. The major US cohort studies provide convincing evidence of an association in the US between long-term exposure to fine particles and the risk of death from cardiovascular disease. Little or no effect on deaths from respiratory disorders was produced. The association is most clearly seen when fine particles ($PM_{2.5}$) or sulphate are considered. Of the gaseous pollutants, there is a clear association with sulphur dioxide but less clear evidence of effects with the other pollutants studied: ozone, carbon monoxide and nitrogen dioxide. We discuss these findings and their implications at some length in Chapter 4.

2.233 Other US cohort studies provide some support for the above conclusions and studies in Europe and in the UK are also indicative of an association between long-term exposure to air pollutants and an increased risk of death from cardiovascular disease. But the pollutants most likely to be responsible for this effect are less easy to discern from the European studies. Traffic-related pollutants, however, seem likely to be playing a part.

2.234 The question of transferability of the results of the US cohort studies to the UK is an important one and was considered by COMEAP in 2001 (Department of Health, 2001). The points raised then about the lack of UK and European studies and about the differences in concentrations of pollutants between the US and the UK have, to some extent, been resolved: European studies are appearing and concentrations are not very different between the US and the UK. But one point raised in 2001 remains and we reproduce it here:

'Where there are several causes leading to death from particular diseases, the competing causes can modify the proportion of deaths affected by the cause of interest. This 'causal field' could vary in different places, as can the proportion of people in particular susceptible groups. The quantitative impact of pollution could therefore vary between countries with different cultures and lifestyles. In fact, the HEI reanalysis found evidence of regional heterogeneity in the effect of air pollution on mortality within the United States.'

This point needs further attention.

2.235 Studies of the effect of long-term exposure to air pollutants and cardiovascular morbidity have produced mixed results. But it is noted that such studies are very few in number and inconsistent in terms of the mixture of pollutants studied. No clear conclusion emerges from these studies.

References – Short-term exposure studies

Anderson, H.R., Limb, E.S., Bland, J.M., Ponce de Leon, A., Strachan, D.P. and Bower, J. S. (1995) Health effects of an air pollution episode in London, December 1991. *Thorax* **50**, 1188-1193.

Anderson, H.R., Limb, E.S., Bland, J.M. and Strachan, D.P. (2001) *The health effects of Smog Episodes in London in December 1991 and in the Manchester and Birmingham conurbations in December 1992*. Report to the Department of Health. London: St George's Hospital Medical School.

Begg, C.B. and Mazumdar, M. (1994) Operating characteristics of a rank correlation test for publication bias. *Biometrics* **50**, 1088-1101.

Checkoway, H., Levy, D., Sheppard, D., Kaufman, J., Koenig J.Q. and Siscovick, D. (2000) A case-crossover analysis of fine particulate matter air pollution and out-of-hospital sudden cardiac arrest. *Res.Rep.Health Eff.Inst.* **99**, 5-32.

Coady, S.A., Sorlie, P.D., Cooper, L.S., Folsom, A.R., Rosamond, W.D. and Conwill, D.E. (2001) Validation of death certificate diagnosis for coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. *J.Clin.Epidemiol.* **54**, 40-50.

Department of Health Committee on the Medical Effects of Air Pollutants. (1995) *Non-Biological Particles and Health.* London: HMSO.

Department of Health. (2001) Committee on the Medical Effects of Air Pollutants. Statement and Report on the Long-term Effects of Particles on Mortality. London: The Stationery Office. http://www.advisorybodies.doh.gov.uk/comeap/statementsreports/longtermeffects.pdf

DerSimonian, R. and Laird, N. (1986) Meta-analysis in clinical trials. *Control. Clin. Trials* **7**, 177-188.

Dominici, F., McDermott, A., Zeger, S.L. and Samet, J.M. (2002) On the use of generalized additive models in time-series studies of air pollution and health. *Am. J. Epidemiol.* **156**, 93-203.

Duval, S. and Tweedie, R. (2000) Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **56**, 455-463.

Egger, M., Davey, S.G., Schneider, M. and Minder, C. (1997) Bias in meta-analysis detected by a simple, graphical test. *Br. Med. J.* **315**, 629-634.

Firket, J. (1936) Fog along the Meuse Valley. *Trans. Faraday Soc.* **32**, 1192-1197.

Health Effects Institute. (2003) *Revised Analyses of Time-Series Studies of Air Pollution and Health. Special Report.* Boston, MA: Health Effects Institute.

Hong, Y.-C., Lee, J.-T., Kim, H., Ha, E.-H., Schwartz, J. and Christiani, D.C. (2002a) Effects of air pollutants on acute stroke mortality. *Environ. Health Perspect.* **110**, 187-191.

Hong, Y.-C., Lee, J.-T., Kim, H. and Kwon, H.-J. (2002b) Air pollution: A new risk factor in ischemic stroke mortality. *Stroke* **33**, 2165-2169.

Le Tertre, A., Medina, S., Samoli, E., Forsberg, B., Michelozzi, P., Boumghar, A., Vonk, J.M., Bellini, A., Atkinson, R., Ayres, J.G., Sunyer, J., Schwartz, J. and Katsouyanni, K. (2002) Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. *J. Epidemiol. Community Health* **56**, 773-779.

Levy, D., Sheppard, L., Checkoway, H., Kaufman, J., Lumley, T., Koenig, J. and Siscovick, D. (2001) A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. *Epidemiology* **12,** 193-199.

Light, R.J. and Pillemer, D.B. (1984) *Summing Up: the Science of Reviewing Research.* Cambridge: Harvard University Press.

Lloyd-Jones, D.M., Martin, D.O., Larson, M.G. and Levy, D. (1998) Accuracy of death certificates for coding coronary heart disease as the cause of death. *Ann.Intern.Med.* **129**, 1020-1026.

Logan, W.P.D. (1953) Mortality in the London fog incident, 1952. *Lancet* **i**, 336.

Miller, B.G. and Armstrong, B. (2001) *Quantification of the Impacts of Air Pollution on Chronic Cause-Specific Mortality.* (IOM Research Report TM/01/08). Edinburgh: Institute of Occupational Medicine.

Ministry of Health. (1954) *Mortality and Morbidity During the London Fog of December 1952. Reports on Public Health and Medical Subjects No. 95.* London: HMSO.

Peters, A., Liu, E., Verrier, R. L., Schwartz, J., Gold, D.R., Mittleman, M., Baliff, J., Oh, J.A., Allen, G., Monahan, K. and Dockery, D.W. (2000) Air pollution and incidence of cardiac arrhythmia. *Epidemiology* **11**, 11-17.

Peters, A., Dockery, D.W., Muller, J.E. and Mittleman, M.A. (2001) Increased particulate air pollution and the triggering of myocardial infarction. *Circulation* **103**, 2810-2815.

Ramsay, T.O., Burnett, R.T. and Krewski, D. (2003) The effect of concurvity in generalized additive models linking mortality to ambient particulate matter. *Epidemiology* **14**, 18-23.

Rich, K.E., Petkau, J., Vedal, S. and Brauer, M. (2004) A case-crossover analysis of particulate air pollution and cardiac arrhythmia in patients with implantable cardioverter defibrillators. *Inhalation Toxicol.* **16**, 363-372.

Russell, W.T. (1924) The influence of fog on mortality from respiratory diseases. *Lancet* **ii**, 335-339.

Russell, W.T. (1926) The relative influence of fog and low temperature on the mortality from respiratory disease. *Lancet* **ii**, 1128-1130.

Schrenk, H.H., Heim, H., Clayton, G.D., Gafafer, W.M. and Wexler, H. (1949) Air pollution in Donora, PA. Epidemiology of the unusual smog episode of October 1948. Preliminary Report. *Public Health Bull. No 306.*

Schwartz, J. (2001) Is there harvesting in the association of airborne particles with daily deaths and hospital admissions? *Epidemiology* **12**, 55-61.

Steenland, K. and Deddens, J.A. (1997) In: Steenland, K. and Savitz, D.A., editors. *Topics in Environmental Epidemiology.* Oxford: Oxford University Press.

Stieb, D.M., Judek, S. and Burnett, R.T. (2002) Meta-analysis of time-series studies of air pollution and mortality: effects of gases and particles and the influence of cause of death, age, and season. *J.Air Waste Manage.Assoc.* **52**, 470-484.

Sullivan, J., Sheppard, L., Schreuder, A., Ishikawa, N., Siscovick, D. and Kaufman, J. (2005) Relation between short-term fine-particulate matter exposure and onset of myocardial infarction. *Epidemiology* **16**, 41-48.

Vedal, S., Rich, K., Brauer, M., White, R. and Petkau, J. (2004) Air pollution and cardiac arrhythmias in patients with implantable cardioverter defibrillators. *Inhalation Toxicol.* **16**, 353-362.

World Health Organization. (1977) *International Classification of Diseases. 9th Revision.* Geneva: World Health Organization.

World Health Organization. (2004a) *Health Aspects of Air Pollution - Answers to Follow-Up Questions from CAFE. Report on a WHO working group. EUR/04/5046026.* Bonn: World Health Organization.

World Health Organization. (2004b) *Meta-analysis of Time Series Studies and Panel Studies of Particulate Matter (PM) and Ozone (O$_3$). EUR/04/5042688.* Copenhagen: World Health Organization Regional Office for Europe.

World Health Organization Working Group. (2000) Evaluation and use of epidemiological evidence for environmental health risk assessment: WHO Guideline Document. *Environ.Health Perspect.* **108**, 997-1002.

Wichmann, H.E., Mueller, W., Allhoff, P., Beckmann, M., Bocter, N., Csicsaky, M.J., Jung, M., Molik, B. and Schoeneberg, G. (1989) Health effects during a smog episode in West Germany in 1985. *Environ Health Perspect.* **79**, 89-99.

Wilkins, E.T. (1954) Air pollution and the London fog of December, 1952, *J.R. Sanit. Inst.* **74**, 1-21.

Zeger, S.L., Dominici, F. and Samet, J. (1999) Harvesting-resistant estimates of air pollution effects on mortality. *Epidemiology* **10**, 171-175.

References – Long-term exposure studies

Abbey, D.E., Nishino, N., McDonnell, W.F., Burchette, R.J., Knutsen, S.F., Beeson, L.W. and Yang, J.X. (1999) Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am.J.Respir.Crit.Care Med.* **159**, 373-382.

Alfredsson, L., Hammar, H. and Hogstedt, C. (1993) Incidence of myocardial infarction and mortality from specific causes among bus drivers in Sweden. *Int.J.Epidemiol.* **22**, 57-61.

Bigert, C., Gustavsson, P., Hallqvist, J., Hogstedt, C., Lewne, M., Plato, N., Reuterwall, C. and Scheele, P. (2003) Myocardial infarction among professional drivers. *Epidemiology* **14**, 333-339.

Borgia, P., Forastiere, F., Rapiti, E., Rizzelli, R., Magliola, M.E., Perucci, C.A. and Axelson, O. (1994) Mortality among taxi drivers in Rome: a cohort study. *Am.J.Ind.Med.* **25**, 507-517.

Clancy, L., Goodman, P., Sinclair H. and Dockery, D.W. (2002) Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *Lancet*, **360**, 1210-1214.

Department of the Environment, Transport and the Regions. (1998) Expert Panel on Air Quality Standards. Lead. London: The Stationary Office.

Department of Health. (2001) *Statement and Report on Long-Term Effects of Particles on Mortality.* London: The Stationery Office. Also available at the following website address: http://www.advisorybodies.doh.gov.uk/comeap/statementsreports/longtermeffects.pdf

De Paula Santos, U., Braga, A.L., Giorgi, D.M., Pereia, L.A., Grupi, C.J., Lin, C.A., Bussacos, M.A., Zanetta, D.M., do Nascimento Saldiva, P.H. and Filho, M.T. (2005) Effects of air pollution on blood pressure and heart rate variability: a panel study of vehicular traffic controllers in the city of Sao Paulo, Brazil. *Eur.Heart* J. **26,** 193-200.

Dockery, D.W., Pope, A., Speizer, F.E. and Thun, M.J. (2003) Comments on the Reanalysis project. *J.Toxicol.Environ.Health A* **66**, 1689-1696.

Dockery, D.W., Pope, C.A., Xu, X., Spengler, J.D., Ware, J.H., Fay, M.E., Ferris, B.G. and Speizer, F.E. (1993) An association between air pollution and mortality in six US cities. *N.Engl.J.Med.* **329**, 1753-1759.

Dolk, H., Thakrar, B., Walls, P., Landon, M., Grundy, C., Saez, L.I., Wilkinson, P. and Elliott, P. (1999) Mortality among residents near cokeworks in Great Britain. *Occup.Environ.Med.* **56**, 34-40.

Fleming, D.M. and Charlton, J.R. (2001) The prevalence of asthma and heart disease in transport workers: a practice-based study. *Br.J.Gen.Pract.* **51**, 638-643.

Forastiere, F., Perucci, C., Di Pietro, A., Meceli, M., Rapiti, E., Bargagli, A. and Borgia, P. (1994) Mortality among urban policemen in Rome. *Am.J.Ind.Med.* **26**, 785-798.

Grandjean, P. and Andersen, O. (1991) Lung cancer in filling station attendants. *Am.J.Ind.Med.* **20**, 763-768.

Grazuleviciene, R., Maroziene, L., Dulskiene, V., Malinauskiene, V., Azaraviciene, A., Laurinaviciene, D. and Jankauskiene, K. (2004) Exposure to urban nitrogen dioxide pollution and the risk of myocardial infarction. *Scand.Work Environ.Health* **30**, 293-298.

Guberan, E., Usel, M., Raymond, L., Bolay, J., Fioretta, G. and Puissant, J. (1992) Increased risk for lung cancer and for cancer of the gastrointestinal tract among Geneva professional drivers. *Br.J.Ind.Med.* **49**, 337-344.

Gustavsson, P., Plato, N., Hallqvist, J., Hogstedt, C., Lewne, M., Reuterwall, C. and Scheele, P. (2001) A population-based case-referent study of myocardial infarction and occupational exposure to motor exhaust, other combustion products, organic solvents, lead and dynamite. *Epidemiology* **12**, 222-228.

Guidotti, T.L. (1993) Mortality of urban firefighters in Alberta, 1927-1987. *Am.J.Ind.Med.* **23**, 921-940.

Guidotti, T.L. (1995) Occupational mortality among firefighters: assessing the association. *J.Occup.Environ.Med.* **37**, 1348-1356.

Hannerz, H. and Tuchsen, F. (2001) Hospital admissions among male drivers in Denmark. *Occup.Environ.Med.* **58**, 253-260.

Hansen, E.S. (1993) A follow-up study on the mortality of truck drivers. *Am.J.Ind.Med.* **23**, 811-821.

Hedberg, G.E., Jacobsson, K.A., Janlert, U. and Langendoen, S. (1993) Risk indicators of ischemic heart disease among male professional drivers in Sweden. *Scand.J.Work Environ.Health* **19**, 326-333.

Hedley, A.J., Wong, C.-M., Thach, T.Q., Ma, S., Lam, T.-H. and Anderson, H.R. (2002) Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. *Lancet* **360**, 1646-1652.

Hense, H.W. (2004) Once at risk – forever at risk? The long-term impact of cardiovascular risk factors on death. *Eur.J.Epidemiol.* **19**, 409-410.

Herbert, R., Schecter, C., Smith, D.A., Phillips, R., Diamond, J., Carroll, S., Weiner, J., Dahms, T.E. and Landrigan, P.J. (2000) Occupational coronary heart disease among bridge and tunnel officers. *Arch.Environ.Health* **55**, 286.

Heyer, N., Weiss, N., Demers, P. and Rosenstock, L. (1990) Cohort mortality study of Seattle fire fighters: 1945-1983. *Am.J.Ind.Med.* **17**, 493-504.

Hoek, G., Brunekreef, B., Goldbohm, S., Fischer, P. and van den Brandt, P.A. (2002) Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet* **360**, 1203-1209.

International Programme on Chemical Safety. (1995) *Inorganic Lead*. Environmental Health Criteria 165. Geneva: World Health Organization.

Jerrett, M., Burnett, R. T., Ma, R., Pope, C.A.3rd., Krewski, D., Newbold, K.B., Thurston, G., Shi, Y., Finkelstein, N., Calle, E.E. and Thun, M.J. (2005) Spatial analysis of air pollution and mortality in Los Angeles. *Epidemiol.* **16**, 727-736.

Kales, S.N., Soteriades, E.S., Christoudias, S.G. and Christiani, D.C. (2003) Firefighters and on-duty deaths from coronary heart disease: a case-control study. *Environ.Health Perspect.* **2**, 14.

Koskela, R.S. (1994) Cardiovascular diseases among foundry workers exposed to carbon monoxide. *Scand.J.Work Environ.Health* **20**, 286-293.

Krewski, D., Burnett, R.T., Goldberg, M.S., Hoover, K., Siemiatycki, J., Abrahamowicz, M., White, W.H. *et al* (2000) *Re-analysis of the Harvard Six-Cities Study and the American Cancer Society Study of Air Pollution and Mortality*. Cambridge, MA: Health Effects Institute. Also available at the following website address: http://www.healtheffects.org

Lipfert, F. (2003) Commentary on the HEI reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of particulate air pollution and mortality. *J.Toxicol.Environ.Health A* **66**, 1705-1722.

Lipfert, F.W., Malone, R.G., Daum, M.L, Mendell, N.R. and Yang, C.C. (1988) *A Statistical Study of the Macroepidemiology of Air Pollution and Total Mortality*. Report No BNL 52122. Upton, NY: Brookhaven National Laboratory.

Lipfert, F.W. and Wyzga, R.E. (1995) Air pollution and mortality: issues and uncertainties. *J.Air Waste Manage.Assoc.* **45**, 946-966.

Matanoski, G.M. and Tao, X.G. (2003) Styrene exposure and ischemic heart disease: a case-cohort study. *Am.J.Epidemiol.* **158**, 988-995.

Menotti, A., Kromhout, D., Blackburn, H., Jacobs, D. and Lanti, M. (2004) Forty-year mortality from cardiovascular diseases and all causes of death in the US Railroad cohort of the Seven Countries Study. *Eur.J.Epidemiol.* **19**, 417-424.

Ministry of Health. (1954) *Mortality and Morbidity During the London Fog of December 1952.* Reports on Public Health and Medical Subjects No 95. London: HMSO.

Nafstad, P., Haheim, L.L., Wisloff, T., Gram, F., Oftedal, B., Holme, I., Hjermann, I. and Leren, P. (2004) Urban air pollution and mortality in a cohort of Norwegian men. *Environ.Health Perspect.* **112**, 610-615.

Palmer, K.T., Poole, J., Ayres, J.G., Mann, J., Burge, P.S. and Coggon, D. (2003) Exposure to metal fume and infectious pneumonia. *Am.J.Epidemiol.* **157**, 227-33.

Paradis, G., Theriault, G. and Tremblay C. (1989) Mortality in a historical cohort of bus drivers. *Int.J.Epidemiol.* **18**, 397-402.

Park, R.M. (2001) Mortality at an automotive engine foundry and machining complex. *J.Occup.Environ.Med.* **43**, 483-493.

Pope, C.A. and Dockery, D.W. (1992). Acute health effects of symptomatic and asymptomatic children. *Am.Rev.Respir.Dis.* **145**, 1123-1128.

Pope, C.A., Thun, M.J., Namboodiri, M.M., Dockery, D.W., Evans, J.S., Speizer, F.E. and Heath, C.W. (1995) Particulate air pollution as a predictor of mortality in a prospective study of US adults. *Am.J.Respir.Crit.Care Med.* **151**, 669-674.

Pope, C.A., Burnett, R.T., Thun, M.J., Calle, E.E., Krewski, D., Ito, K. and Thurston, G.D. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA.* **287**, 1132-1141.

Pope, C.A., Burnett, R.T., Thurston, G.D., Thun, M.J., Calle, E.E., Krewski, D. and Godleski, J.J. (2004) Cardiovascular mortality and long-term exposure to particulate air pollution. Epidemiological evidence of general pathophysiological pathways of disease. *Circulation* **109**, 71-77.

Prüss-Üstün, A., Fewtrell, L., Landrigan, P.J. and Ayuso-Mateos, J. (2004) Lead exposure. In: Ezzati, M., Lopez, A.D., Rodgers, A. and Murray, J.L., editors. *Comparative Quantification of Health Risks. Global and Regional Burden of Disease Attributable to Selected Major Risk Factors.* Volume 2. Geneva: World Health Organization; pp1495-1542.

Riediker, M., Williams, R., Devlin, R., Griggs, T. and Bromberg P. (2003) Exposure to particulate matter, volatile organic compounds, and other air pollutants inside patrol cars. *Environ.Sci.Technol.* **37**, 2084-2093.

Schenker, M.B., Smith, T., Muñoz, A., Woskie, S.R. and Speizer, F.E. (1984) Diesel exposure and mortality among railway workers: results of a pilot study. *Br.J.Ind.Med.* **41**, 320-327.

Sjögren, B. (1997) Occupational exposure to dust: inflammation and ischaemic heart disease. *Occup.Environ.Med.* **54**, 466-469.

Sjögren, B., Fredlund, P., Lundberg, I. and Weiner, J. (2003) Ischemic heart disease in female cleaners. *Int.J.Occup.Environ.Health* **9**, 134-137.

Sjögren, B., Foddum, T., Lindh, T. and Weiner, J. (2002) Welding and ischemic heart disease. *Int.J.Occup.Environ.Health* **8**, 309-311.

Solomon, C., Poole, J., Jerup, L., Palmer, K. and Coggon, D. (2003) Cardio-respiratory morbidity and long-term exposure to particulate air pollution. *Int.J.Environ.Health Res.* **13**, 327-335.

Stern, F.B., Halperin, W.E., Hornung, R.W., Ringenburg, V.L and McCammon C.S. (1988) Heart disease mortality among bridge and tunnel officers exposed to carbon monoxide. *Am.J.Epidemiol.* **128**, 1276-1288.

Stern, F.B., Lemen, R.A. and Curtis, R.A. (1981) Exposure of motor vehicle examiners to carbon monoxide: a historical prospective mortality study. *Arch.Environ.Health* **36**, 59-65.

Suadicani, P., Hein, H.O. and Gyntelberg, F. (2002) Airborne occupational exposure, ABO phenotype and risk of ischaemic heart disease in the Copenhagen Male Study. *J.Cardiovasc.Risk* **9**, 191-198.

Toren, K., Hagberg, S. and Westberg, H. (1996) Health effects of working in pulp and paper mills: exposure, obstructive airways diseases, hypersensitivity reaction, and cardiovascular diseases. *Am.J.Ind.Med.* **29**, 111-122.

Waldron, H.A. (1995) Non-neoplastic disorders due to metallic, chemical and physical agents. In: Parkes, W.R., editor. *Occupational Lung Disorders*. 3rd Edition. New York, London: Butterworth–Heinemann.

Wong, O., Morgan, R.W., Kheifets, L., Larson, S.R. and Whorton, R.D. (1985) Mortality among members of a heavy construction equipment operators union with potential exposure to diesel exhaust emissions. *Br.J.Ind.Med.* **42**, 435-448.

Chapter 3
Potential mechanisms underlying the cardiovascular effects of air pollutants

Lay Summary

3.1   The epidemiological studies reviewed in the previous chapter show that air pollutants may have an effect on the cardiovascular system and that this can lead, in some instances, to death or hospital admission. These findings are remarkable in that the effects seem to be produced by exposure to low concentrations of air pollutants. In fact, the effects occur on exposure to concentrations of pollutants at which classical toxicology would not predict adverse effects. This has led some to doubt the validity of the epidemiological findings though the accumulation of studies, the reproducibility of the findings and the rigorous checking of the work has convinced most workers that the studies are indeed valid, albeit that the results are difficult to explain in terms of mechanisms of disease.

3.2   In the last few years two major hypotheses or theories have been put forward to explain the effects. The first suggests that inhaled particles, especially very small particles, may set up inflammation in the lung and that this can trigger changes in the control of blood clotting. It is also suggested that changes in chemical factors in the blood can affect the stability of the fatty deposits (atheromatous plaques) found in the walls of arteries in many people – especially those in the walls of the arteries which supply blood to the muscle of the heart itself. If this is true then a link between inhalation of particles and the likelihood of, for example, heart attacks will have been established. The following chapter presents evidence; some for and some against this idea.

3.3   A second important theory suggests that the inhalation of particles and perhaps some pollutant gases may trigger a reflex that leads to a subtle change in the rhythm of the heart. The triggering of a reflex begins when some stimulus is detected by a receptor, a message is sent along nerves to the spinal cord or brain and a response follows. Well known reflexes include the production of saliva on smelling appetising food and the forward kick of the leg when the tendon below the knee-cap is tapped smartly. Coughing is also a reflex: in this case the receptors are in the airways and the trigger is an irritant: perhaps a crumb of food. Air pollutants may stimulate receptors in the airways and though coughing may not be produced, reflex changes in the rhythm of the heart may occur. Such changes may lead to the heart being more susceptible to dangerous changes in rhythm: such changes can cause sudden death. Evidence for and against this theory is also presented in this chapter. Interestingly, this hypothesis links with the one above: inflammation may be involved in the early stages of both.

3.4   Work on these ideas is continuing and it is too early to say whether one or the other, or perhaps both, will come to be seen as the true explanation for the findings reviewed in the previous chapter. The fact that plausible hypotheses have been put forward and that some evidence in support of them has been produced, has strengthened our views of the importance of the findings of the epidemiological studies.

Introduction and the clotting hypothesis

3.5   When the cardiovascular effects of air pollution were first identified by epidemiological techniques, mechanisms explaining these effects were not immediately clear. Impacts were seen across a range of diagnostic categories (e.g. myocardial infarction (heart attack), heart failure and arrhythmias) but, as discussed earlier (see paragraph 2.22, Chapter 2), these diagnostic labels are not necessarily clear-cut. In addition, as there are sub-groups who may be especially susceptible, it is possible that different mechanisms operate in different clinical settings or clinical states. In recent years a number of helpful reviews of this topic have appeared (Chapman *et al*, 1997; Schwartz, 2001; Glantz, 2002; Brook *et al*, 2003).

3.6   Before discussing the evidence on air pollution and mechanisms of development or exacerbation of heart disease, we outline the physiological background to some of these mechanisms. The main interest has been in the role of abnormalities in the clotting mechanisms of the blood and in the induction of changes in cardiac autonomic control. We have separated consideration of these two largely independent mechanisms, but it should be realised that they are not mutually exclusive and that any overall consideration of these issues should embrace both. The possibility that other mechanisms are playing a part remains.

General background on ways in which the heart might be affected by air pollution

3.7   The heart and the lungs are closely integrated both functionally and structurally. The main function of the lung is gas exchange, oxygen being delivered to blood passing through the pulmonary circulation in the lungs, carbon dioxide being removed at the same time. The main function of the heart is to pump oxygenated blood around the body (the systemic circulation) and, in parallel, to pump de-oxygenated blood to the lungs.

3.8   The pulmonary circulation consists of a series of progressively smaller blood vessels beginning with the main pulmonary artery which leaves the right ventricle. This divides into the right and left pulmonary arteries, which pass to the lungs and divide progressively, to produce a mesh of capillaries which are closely related to the alveolar

air sacs of the lung. Capillaries have an internal diameter of less than 5 μm, so the red blood cells which carry the oxygen are literally squeezed through them, the outside wall of the red blood cell coming into intimate contact with the inside of the capillary wall (the endothelium) facilitating gas exchange (see figure 3.1).

Figure 3.1: Electronmicrograph showing the structural elements of the air-blood barrier of the lung
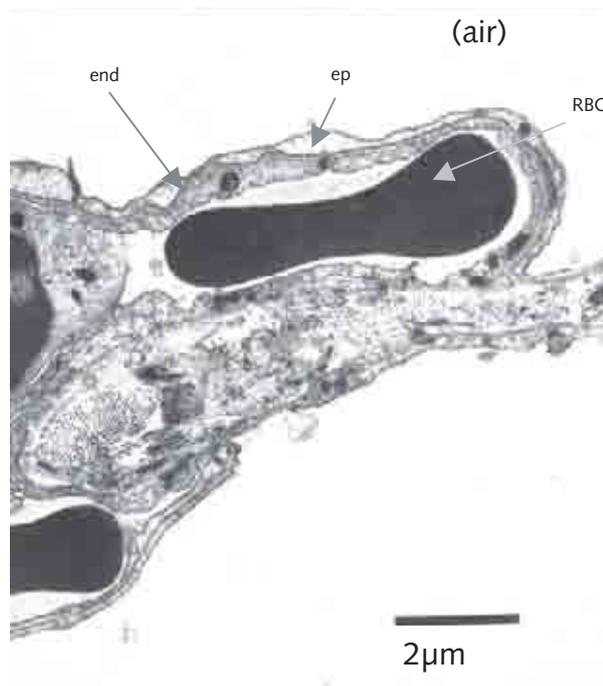
ep: epithelium, RBC: red blood cell, end: capillary endothelium
Illustration provided by Ann Dewar, NHLI, Imperial College, London

3.9   As the red blood cells pass along the length of a pulmonary capillary, oxygen diffuses across the alveolar epithelium, the capillary endothelium, plasma and the red cell membrane to bind to the oxygen-carrying protein haemoglobin, within the red blood cell. Diffusion occurs at a rapid rate at the beginning of the capillary, but diminishes along the length of the capillary as haemoglobin becomes nearly fully saturated and the alveolar-arterial difference in PO_2 falls. Diffusion of carbon dioxide from the blood plasma occurs in the opposite direction (Nunn, 1993).

Air flow and blood flow

3.10   It is essential for normal gas exchange, that there is an appropriate relationship between the amount of deoxygenated blood arriving in the pulmonary capillaries and the amount of air arriving at the alveoli. This can be expressed as the ratio of ventilation to perfusion: the VA/QC ratio[20] (Comroe *et al*, 1962; Nunn, 1993).

20 VA: alveolar ventilation; QC: pulmonary blood flow

Because both ventilation and perfusion vary differently from the apex of the lung to the base, the V_A/Q_C ratio also varies. It has been found that the range of V_A/Q_C ratios occurring within the lung follow a log-normal distribution centred on a ratio of about 0.8. In those parts (near the apex) where ventilation exceeds perfusion, the ratio exceeds 0.8. In any parts ventilated but not perfused (dead space), the ratio approaches infinity. Areas perfused but not ventilated form "shunts": the blood moves from the pulmonary artery to the pulmonary vein without being exposed to air, resulting in V_A/Q_C ratios approaching zero. In the normal lung the distribution of V_A/Q_C ratios is fairly narrow but this can be widened by disease with consequent impairment of gas transfer (Selkurt, 1976). It is not easy to determine the range of V_A/Q_C ratios occurring in the lung, though methods to do this have been developed, and the 3-compartment model introduced by Riley and Cournand (1949) is often used as a model for the distribution. In this model the lung is divided into dead space, shunt and entirely ideal gas exchange units. It will be appreciated that units with a high V_A/Q_C ratio tend towards dead space and those with low V_A/Q_C ratios tend towards shunts. Closure of an airway to a region of lung produces shunt; obstruction of a branch of the pulmonary artery produces dead space.

3.11   The blood vessels and airways of the lung are responsive to local concentrations of oxygen and carbon dioxide. In regions ventilated but not perfused, ventilation may be decreased by a narrowing of the airways (bronchoconstriction); similarly, blood vessels become constricted in regions perfused but not ventilated. This autoregulatory system acts to maintain as normal as possible a distribution of V_A/Q_C ratios (Nunn, 1993).

3.12   Disturbance of the normal distribution of V_A/Q_C ratios is a major cause of impaired gas transfer in the diseased or damaged lung. Both uptake of oxygen and release of carbon dioxide are impaired, though the latter is compensated for by an increase in ventilation and the approximate linearity of the curve linking blood CO_2 content with the partial pressure of CO_2 as compared with the sigmoid oxyhaemoglobin dissociation curve. A greater effect is thus seen on oxygen uptake than on carbon dioxide release (Nunn, 1993).

3.13   Pulmonary oedema (fluid within the alveoli) is a common cause of disturbance of the normal distribution of V_A/Q_C ratios: ventilation of oedematous regions is impaired and partial shunting occurs. The air-blood diffusion pathway is also lengthened in oedematous alveoli. The decrement in oxygen uptake is reflected in a reduced supply of oxygen to the body. If this occurs in a patient with an already impaired coronary circulation the myocardium may become hypoxic and heart failure may follow. Failure of the left ventricle leads to a 'backing-up' of blood and an increase of pressure in the left atrium and pulmonary veins. The pulmonary capillary pressure increases; further leakage of fluid into the alveolar spaces follows and a vicious circle is established.

3.14 It is possible that exposure to high concentrations of air pollutants could disturb the normal distribution of V_A/Q_C ratios in the lung. This effect is, perhaps, more significant in those with an already widened distribution, i.e. in those with cardiopulmonary disease. Evidence for this mechanism of effect of air pollutants is limited but the notable effect of the 1952 London smog, with an increase in deaths attributed to cardio-respiratory disease, makes it possible, perhaps likely, that effects on V_A/Q_C ratios played a part (Ministry of Health, 1954). Whether such an effect occurs at current levels of air pollution is unknown but it seems unlikely that a normal distribution of V_A/Q_C ratios would be sufficiently disturbed so as to produce significant impairment of oxygen uptake. However, people with severely disturbed distributions of V_A/Q_C ratios and who might be imagined as being close to the brink of significant failure of oxygen uptake, could be affected. Such a mechanism would account for deaths from a sudden worsening of cardio-pulmonary function during air pollution episodes. Individuals with chronic obstructive pulmonary disease (COPD), a disease largely of cigarette smokers, often have coronary artery disease which is also related to cigarette smoking. So, in theory, individuals with both these conditions may be particularly susceptible: the impaired uptake of oxygen in the lung combining with the impaired coronary circulation to put the heart at increased risk of an inadequate supply of oxygen.

The patho-biology of atherosclerosis and thrombus formation

3.15 Atherosclerosis, characterised by the formation of atheromatous plaques in the intima of arteries is the major current cause of arterial disease, particularly coronary artery disease. It is widely accepted that atheromatous changes in arteries begin, at least in Western populations, in childhood with the deposition of lipid in the innermost layer (tunica intima) of the arterial wall (Crawford, 1977). This gives rise to pale yellowish spots which are visible through the endothelium and are called fatty streaks. It is unknown whether endothelial dysfunction is the cause or consequence of lipid uptake. The development of lesions has been described in detail by Stary *et al* (1994) and has been divided into six stages. Stages I-III involve increasing uptake of lipid from the blood and the phagocytosis of this lipid by macrophages in the tunica intima. Uptake of lipid by macrophages gives these cells a foamy, vacuolated appearance and they are described as foam cells. The macrophage reaction to lipid leads to a release of cytokines (Libby *et al*, 1996). Smooth muscle cells of the intima, or which have, perhaps, migrated from the muscular layer of the vessel wall, take up lipid and undergo a change in form (phenotype) from a contractile to a synthetic type capable of producing collagen, which leads to the development of fibrosis (scarring). The endothelium remains intact in these early lesions but subtle changes occur, including rounding of endothelial cells, and the appearance of stomata and multi-nucleated cells. In addition to these morphological changes, the permeability of the endothelium increases and adhesion factors for white blood cells are increasingly

expressed. Production of nitric oxide (a vasodilator) is depressed and that of endothelins (potent vasoconstrictor molecules), is increased.

3.16 Progression of atheromatous deposits is uneven (Libby *et al*, 1996; Falk *et al*, 1995). Some develop to a stage II appearance and then stop: such lesions are commonly found in the coronary arteries by the time of puberty. Others progress and develop into stage III lesions, the transitional form between the essentially harmless stage I and II lesions and the progressive stages IV-VI. The key distinction between stage III and IV lesions is the presence of a free lipid core in the latter.

3.17 Stage IV lesions contain a lipid core that is extracellular in location. This lies deep to layers of lipid-containing macrophages which themselves show increasing lipid content as their location varies from close to the endothelium to close to the free lipid of the core. The lipid core results from the breakdown of lipid-loaded macrophages and also from lipid trapping in the intercellular matrix. The matrix shows an increased concentration of sulphated glycosaminoglycans such as chondroitin sulphate and a decrease in non-sulphated forms such as hyaluronic acid. The apoprotein, apo B, of low density lipoprotein reacts with components of the matrix and traps lipid molecules. At the same time as this is occurring, elastin of the internal elastic lamina (the outermost component of the tunica intima) begins to show damage, and elastin fragments which are highly chemotactic for macrophages are produced. The presence of a free lipid core provokes an inflammatory reaction and capillaries appear near its margins (Moreno *et al*, 2004). These are not components of the normal tunica intima and at later stages may break down producing intra-lesional haemorrhage.

3.18 Further development is characterised by fibrosis and stage V lesions are produced: narrowing of the vessel lumen, for the first time, becomes prominent. Collagen is deposited between the lipid core and the endothelium and layering of lipid and fibrous tissue may occur. Calcium salts are deposited in the lesion. Micro-haemorrhages are common in stage V lesions. Stage V lesions may be subdivided depending on the relative amounts of fibrosis, calcification and lipid present (Stary *et al*, 1994; Shanahan *et al*, 1994). Stage V lesions are also characterised by disarrangement of the muscle layer and infiltration of lymphocytes in the outer part of the arterial wall.

3.19 The stage V lesion is ripe for disruption and when this occurs the stage VI lesion is produced. Fracturing of the surface causes an efflux of highly thrombogenic lipid, and an influx of blood leads to thrombosis on the surface of the lesion which, if severe, may block the vessel completely (Fernández-Ortiz *et al*, 1994). Thrombosis may, however, be incorporated into the lesion and overgrowth by endothelial and modified smooth muscle cells may occur: the lesion begins to heal, but may break down again.

Role of clotting

3.20   A considerable number of blood components have been studied and identified as risk factors for myocardial infarction (Muller *et al*, 1994; Kullo *et al*, 2000). These factors include: homocysteine, fibrinogen, soluble intercellular adhesion molecule 1 (ICAM-1), C-reactive protein (CRP), lipoprotein A, and "small dense low-density lipoprotein". Impaired fibrinolysis, increased platelet reactivity and hyper-coagulability of the blood also play a part. Fibrinogen has been studied in some detail.

3.21   Fibrinogen is a soluble plasma protein which on losing two pairs of polypeptides becomes fibrin. Polymerisation of fibrin produces loose strands which cross-link to produce a dense aggregate, a process known as fibrin stabilisation. This process is catalysed by thrombin, one of the series of serine proteases that play key roles in the clotting process and which also activates platelets and endothelial cells. Clotting may occur as a result of activation of either the intrinsic or extrinsic clotting pathways. The former begins with the activation of factor XII as a result of contact of plasma with collagen. Kallikrein, itself a product of a short cascade of reactions, catalyses the activation of factor XII. The extrinsic pathway begins with tissue damage and the release of a protein-phospholipid mixture, thromboplastin, which activates factor VII. Activated factor VII, in the presence of calcium and platelet phospholipid, activates factor X which, in turn, and in the presence of factor V, converts prothrombin to thrombin. The intrinsic pathway also leads to the activation of factor X, the common factor of the two pathways, but via activated factor IX in the presence of factor VIII and, again, calcium and platelet phospholipids.

Breakdown of thrombus

3.22   If the pathways leading to the formation of stabilised fibrin are complex, the balancing processes that lead to inhibition of this process and clot-removal are equally complex. In recent years, the molecular biology of these processes has been intensively studied and detailed accounts are provided by Oliver *et al* (2005) and by Van de Wouwer *et al* (2004). The links between coagulation, fibrinolysis and the inflammatory response are becoming increasingly clear. Plasmin is the key factor that produces lysis of stabilised fibrin. But plasmin itself is formed in the plasma from an inactive precursor, plasminogen and the conversion of plasminogen to plasmin is controlled by tissue plasminogen activator (t-PA), itself a carefully regulated substance that is known to be stored in endothelial cells. Release of this activator is known to be impaired in those who smoke cigarettes and in those with atherosclerosis. Not only is the release of t-PA affected by a range of factors, but so is its synthesis: the paper by Oliver *et al* (2005) should be consulted for details and for further references.

3.23 That this system is complex is obvious. Potentially dangerous factors such as those inducing clotting are produced in an inactive state, activated when needed and deactivated by the other factors as quickly as possible. Complexity of this sort is found in other cascade processes including that controlling the formation of the kinins: these will not be discussed here.

3.24 Disruption of a plaque and its interaction with clotting mechanisms are clearly the potentially lethal events in its evolution and the causes of such disruption have been studied in detail. This process raises the following questions:

(a) What makes a plaque vulnerable to disruption?

(b) Once disruption has occurred what controls the extent of local thrombus formation? (See paragraph 3.26 *et seq*).

3.25 Plaque vulnerability may be considered in terms of intrinsic and extrinsic factors, not to be confused with intrinsic and extrinsic pathways controlling clot formation.

(i) Intrinsic factors

Many factors have been described and the following list is incomplete (Davies 1995; Mann and Davies 1996; Mann and Davies, 1999; Rothwell *et al*, 2000).

• Surface irregularities that activate platelets (Lendon *et al*, 1992).

• Macrophage infiltration causing weakening of the cap: especially in the so-called shoulder region (Lendon *et al*, 1991). Thinning of the fibrous cap may be a very important factor.

• Low levels of plaque fibrosis and calcification.

• Cap fatigue due to its anatomical location leading to repetitive strain produced by stretching: lesions in the left coronary artery are particularly susceptible to this.

• High cholesterol ester content of the core providing a softer core than is provided by cholesterol crystals (Davies *et al*, 1994; Felton *et al*, 1997; Shiomi *et al*, 2001; Shiomi *et al*, 2003).

• Increased levels of metalloproteinases including collagenase in the lesion perhaps due to a decrease in metalloproteinase inhibitor production.

• Local muscular spasm acting on an incompressible liquid core.

• Inflammatory reaction within plaque.

(ii)   Extrinsic factors

Again several have been described.

- Increases in sympathetic neural tone leading to an increase in blood pressure and heart rate.

- Winter or cold days at any time of the year causing reflex coronary vasoconstriction (Keatinge *et al*, 1984; Neild *et al*, 1994; Woodhouse *et al*, 1994; Donaldson and Keatinge, 1997).

- Hot days – though here the evidence bears on red cell counts, blood viscosity and plasma cholesterol levels, rather than plaque vulnerability (Keatinge *et al*, 1986).

Interaction between atheromatous plaques, the clotting process and inflammatory processes

3.26   The inter-relationship between inflammation, plaque composition and stability and coagulation is complex and the details are beyond the scope of this report. There is no doubt however, that these factors are related and that inflammation plays a central role in the natural history of athero-thrombosis and therefore in the events that link atherosclerosis to human mortality and morbidity. Inflammation may lead to plaque 'destabilisation' by mechanisms that include the secretion of monocyte chemoattractant protein-1 by endothelial cells in response to cytokines such as TNα. and IL-1 (Rollins *et al*, 1990) and an increase in endothelial selectin-dependent amonocyte adhesion. These factors promote the accumulation of monocytes and lymphocytes in atherosclerotic plaques which ultimately leads to necrosis and apoptosis of the stabilising vascular smooth muscle cells, and metalloproteinase mediated weakening and thinning of the fibrous cap.

3.27   In the event of plaque rupture, an increase in blood coagulability will increase the chances of a significant thrombus forming on the surface and thus of a clinical event. Inflammatory stimuli inevitably result in increased coagulation and reduced fibrinolysis as these mechanisms are intimately related (Becker, 2002). Fibrinogen is both an acute phase protein and a central factor in coagulation. In addition, tissue-factor bearing cells (monocytes and endothelial cells) are now recognised as the initiating sites of coagulation. In response to inflammatory cytokines these cells stimulate the release of tissue factor thereby both facilitating thrombin generation and impairing fibrinolysis by provoking release of plasminogen-activator inhibitor type 1 and thrombin-activatable fibrinolysis inhibitor. Further and more complex pro-coagulant effects of inflammatory cytokines are also described (Goel and Diamond, 2001). The importance of impaired endogenous fibrinolysis is emphasised by the results of the Northwick Park study which showed an important role of t-PA

and its inhibitor plasminogen-activator inhibitor type 1 (PAI-1) in myocardial infarction (Meade *et al*, 1986; Hamsten *et al*, 1987; Miller *et al*, 1991).

3.28 In another study, platelet reactivity (aggregability) was shown to be a marker for coronary artery disease (Harker and Ritchie, 1980) probably through thromboxane A$_2$, while aspirin, an inhibitor of cyclooxygenase which catalyses production of thromboxane A$_2$, has some effect in reducing the likelihood of myocardial infarction.

3.29 Two further molecules play an important role in thrombosis, C-reactive protein and the von Willebrand factor (Pepys, 1981; Danesh, 2004). The existence of CRP has been known for more than seventy years. It was named, in 1931, for its reactivity with the so-called Fraction C of the non-type-specific somatic polysaccharide fraction extracted from the pneumococcus bacterium. The functions of CRP are still debated, though once bound to ligands it is known to be a potent activator of the classical complement activation pathway. CRP is well established, along with fibrinogen, as an acute phase protein produced by the liver in response to stress – commonly inflammation and infection (Green and Humphries, 1989; Cook and Ubben, 1990; Cooper and Douglas, 1991; Woodhouse *et al*, 1994; Pearson *et al*, 1997). This raises an interesting point. Thompson *et al* (1995) argued that the increase in blood fibrinogen levels seen in patients with progressive atherosclerosis occurred, in part, as a consequence of the inflammatory reaction occurring in plaques. It was noted that both t-P$_A$ antigen and von Willebrand factor antigen also increased and were released by endothelial cells. The von Willebrand factor, produced by and stored in endothelial cells, promotes platelet adhesion and also acts as a carrier protecting factor VIII from premature destruction. Congenital lack of the von Willebrand factor causes a generally mild bleeding disorder. The conclusion that raised plasma fibrinogen levels may be *produced by* rather than being the *cause of* increased activity in atheromatous plaques needs careful consideration. But, however increased fibrinogen production is triggered, it will cause an increase in blood viscosity and this, too, has been shown to be associated with an increased likelihood of acute myocardial infarction (Yarnell *et al*, 1991).

3.30 So, events occurring in and close to an atheromatous plaque are extraordinarily complex and it will not be difficult to imagine that different investigators have stressed one or more aspects of the process above others. That such processes are linked with exposure to air pollutants, especially particles, is becoming increasingly clear and a number of hypotheses have been proposed: these and the evidence bearing upon them are discussed below.

How air pollution could affect blood clotting and plaque rupture

3.31 The following paragraphs put forward ideas linking exposure to air pollutants and effects on both the clotting process and the stability of atherosclerotic plaques. It will be noted that the possible effects of particles are emphasised in comparison with those of gaseous air pollutants. This is due to the emphasis put on particles by research workers in this area.

3.32 The epidemiological evidence clearly identifies associations between exposure to particulate air pollution and heart disease (Schwartz, 2001; Glantz, 2002; Brook *et al*, 2003). These associations, occurring as they do at what would be regarded, in toxicological terms, as very low concentrations of particles not known to contain substances of exceptional toxicity, affecting the function of an organ or tissues distant from the lung, raise serious questions as to their scientific plausibility. Is it likely that less than a milligram of particulate matter inhaled over 24 hours could cause death from a heart attack? Or is it possible that the associations observed are a consequence of some other environmental factors, such as temperature and adverse weather conditions, which are themselves associated with a rise in pollution? These confounding factors have been considered in Chapter 2.

3.33 In order to address this issue of biological plausibility, demonstration of mechanisms whereby a small mass of particles deposited in the lungs could, in the short term, cause cardiac dysfunction and, in the longer term, contribute to the development of atheroma in the coronary arteries, is necessary.

3.34 Two main hypotheses have provided the foundation upon which toxicological research has been based. One has proposed that the cardiac effects are a consequence of inflammation in the lung, leading to the release of cytokines with secondary effects on blood constituents interfering with coagulability and stability of atheromatous plaques (Seaton *et al*, 1995). This hypothesis further proposed that the lung inflammation was a consequence not of the mass but of the number of particles, particularly those in the ultrafine (<100 nm) size range. This hypothesis has the potential to explain both short-term morbidity and also longer-term atherogenesis. The second hypothesis, which suggests that inhalation of air pollutants might trigger reflex changes in the control of the heart, is discussed below. The possibility of transfer of particles by blood to the heart causing a direct effect has also been proposed (Bailey *et al*, 1988; Nemmar *et al*, 2001; Nemmar *et al*, 2002). While there is no doubt that some inhaled particles can reach the bloodstream and be widely distributed, it seems unlikely that such a small dose, either in number or mass terms could have a direct effect on the heart.

Evidence supporting the hypothesis that air pollutants affect the evolution of atherosclerotic plaques by mechanisms involving components of the clotting process

3.35 Any satisfactory mechanistic explanation must take account of three facts:

- Fine particles, those associated with the cardiac effects, are composed largely of carbon and of salts such as ammonium sulphate and ammonium nitrate. These substances would not be generally regarded as notably toxic to the heart, especially at the low mass doses likely to occur currently in the UK. Other chemical species, including a number of metals, are also present in trace amounts. Mechanisms of effect other than those associated with larger quantities of these substances will need to be proposed if it is to be argued that they play an important part in the process being discussed. It is suggested that the toxic effects of the inhaled particulate material cannot be predicted or explained by the mass of material inhaled nor, yet, by the identity of its major chemical components. The toxicity of the inhaled material must therefore depend on some other factor or factors: an idea concerning particle number concentrations is discussed below.

- The epidemiological associations suggest that although the particles deposit in the lungs, effects occur in the heart. It is thus necessary to invoke a mechanism that involves the transfer of a message from the lung to the coronary circulation or the heart muscle. Perhaps the most obvious routes by which events in the lung might be linked with events in the heart, or more precisely in the coronary arteries, are the humoral and neural pathways. These are discussed in some detail below. However, direct translocation of particles and increased cellular traffic from the lung to atheromatous plaques could also be involved. Arterial monocytes or macrophages could play a part in this process.

- In normal, everyday conditions, the lung is subjected to low mass concentrations of particles but high number concentrations (Seaton and Dennekamp, 2003). For example, on a relatively unpolluted day the air of a city may contain an average of about 10,000 particles per millilitre (ml). There are a million ml in a cubic metre and adults inhale about 20 cubic metres per day (200-500 ml per breath). Thus, in a day we may expect to inhale around 200 thousand million, or 200 billion[21] particles over 24 hours in urban conditions – without apparent harm occurring. About half of these particles are deposited in the lung. These huge numbers are contained in very little mass, about 20 µg per cubic metre, ie, 400 µg inhaled in 24 hours. In moderate pollution episodes where the average particle mass rises to 50 µg/m³, the mass of particles inhaled associated with adverse cardiac effects is still as low as 1mg over 24 hours (50 µg x 20 cubic

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21 1 billion = 1 thousand million i.e. 1×10^9

metres) but that mass may contain about 100,000 particles per ml, or a total of 2000 billion particles over 24 hours. In other words, the mass does not represent the numbers of very small, nanometre-sized (< 0.1 micron) particles.

3.36 It is also noted that as a given mass of material is divided into an increasing number of units, the total surface area of those units increases. It is possible that the total contact area (total area of inhaled material in contact with lung tissue) might play a part in controlling local and, secondarily, more distant pathophysiological responses.

3.37 Toxicological studies may be carried out on healthy or unhealthy humans, on animals in either a healthy state or suffering from some artificially induced pathological state, or on isolated cell preparations. A number of human studies have combined epidemiological design with methods to investigate possible toxicological mechanisms. These fall into two categories, those investigating secondary changes in the blood and those investigating reflex or neural cardiac responses.

Human Studies

3.38 Human studies of secondary changes in the blood have shown associations with particulate pollution. The case for inflammation occurring has been supported by findings of rises in CRP in the blood in association with exposure to particulates (Ghio *et al*, 2000; Seaton *et al*, 1999), though Pekkanen *et al* (2000) in an epidemiological study in London found associations between fibrinogen levels and NO_2 and CO but not with particles. This, as stated above, is an indicator of an acute-phase reaction, and its association with pollution is strong evidence that significant pulmonary inflammation follows exposure even to small masses of particles. The original hypothesis that fibrinogen concentrations would rise has been supported by several studies of both fibrinogen and its surrogate, plasma viscosity (Peters *et al*, 1997; Schwartz, 2001)[22] although the original proposers of the hypothesis found a fall in fibrinogen in their study and a rise in clotting factor VII (Seaton *et al*, 1999) and are thus not included in a later table (Table 4.2). These differences might be explained by a biphasic response involving production followed by consumption of fibrinogen as clotting proceeds. An intriguing finding in one study was an association between particle exposure and the red blood cell count (Seaton *et al*, 1999), the number of red cells falling as pollution rose and vice versa. This relationship was not lost when corrected for changes in plasma albumin concentration, and led the authors to suggest that red cell sequestration occurred as a consequence of particle-induced alveolar inflammation or, possibly, of direct effects on the vascular endothelium. Work by Salvi *et al* (1999) has shown that exposure to partially diluted diesel exhaust caused

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22 In the latter study no association between ambient ozone concentrations and increased plasma fibrinogen levels was found; associations with NO_2 and SO_2 were reported but these did not survive adjustment for particles.

an increase in the neutrophil count in the blood. It is not easy to say whether this was due to exposure to particles or NO_2.

3.39 These studies point towards pulmonary inflammation at low particle doses. This may be responsible for destabilisation of atheromatous plaques and changes in clotting factors that could lead to increased blood coagulability and thrombus formation. This mechanism, local inflammation, could also be the initial stimulus of a reflex neural discharge and this is discussed below. Some support for the possibility of two mechanisms acting in concert to cause significant effects on the heart comes from a study of the timing of onset of myocardial infarction in relation to air pollution, in which it was shown that two phases of response may be detected, an early one at about 2 hours and a later at 24 hours (Peters *et al*, 2001; Peters *et al*, 2004). The short term response speaks for a neural reflex, and consideration of the nature of this response leads to speculation that it is mediated via pharyngeal, nasal or olfactory receptors. The longer term response speaks for a humoral response to local lung inflammation. The neural response would be analogous to an animal's detection of danger or food by the sense of smell, initiating an excitatory response. Recent work has shown that ultrafine particles may penetrate the olfactory nerve, and it is not unreasonable to suppose that this could result in its stimulation. Recent work by Lewis *et al* (2005) has shown that particles can also be taken up by trigeminal nerve endings. Lewis quoted work to show that trans-synaptic transport of such particles could take place (Gianutsos *et al*, 1997; Henriksson *et al*, 1997; Tjälve *et al*, 1996). Early work on olfactory uptake was also quoted (Bench, 1991; Divine *et al*, 1999; Normandin *et al*, 2002). By the same token, it is possible to view the inflammatory response of the lung to inhaled particles as being similar to that which has evolved to deal with potentially dangerous micro-organisms. It is plausible to propose that the lung therefore not only mounts a local response but also initiates a systemic reaction (the acute phase response) in the expectation of invasion of the blood stream by organisms with the potential to multiply (Seaton and Dennekamp, 2003). Thought about in this way, it has been suggested that the response would be to the numbers of particles rather than to the total mass as it is the number of invading micro-organisms that predicts the severity of the infection and not the mass of the organisms. The challenge for toxicology is to demonstrate that these or other possible mechanisms could operate at the low doses to which humans appear to respond.

Animal studies

3.40 Purely toxicological studies in animals have confirmed that particulate air pollution can affect the cardiovascular system and that there are effects on other organs following exposure. Pollutant gases are also known to cause systemic effects but have been less well studied. Particles have been shown to produce a range of effects in animal models including heart injury (Kodavanti *et al*, 2000; Calderon-Garciduenas *et*

al, 2001), changes in blood parameters (van Eeden and Hogg, 2002; Gardner *et al*, 2000) and endothelial injury (Vincent *et al*, 2001). The area has been reviewed by Godleski *et al* (2000). However, none of these responses is seen with inhalation exposure to ambient levels of particles, with the key exception of a study in dogs that is discussed below. Normal healthy laboratory animals, rather like normal people, do not show any significant response to exposure to normal (ambient) levels of particles. Laboratory animals are constantly exposed to particle concentrations characteristic of animal facilities and have short life spans. Seeking evidence of acute or chronic effects of 'normal levels of PM_{10}' in these models is unlikely to be helpful.

3.41 The extra-pulmonary effects that are seen following exposure to particles in toxicological studies can often be explained by the fact that the exposure causes a severe inflammatory response in the lungs for a number of reasons:

- the particles are often delivered (instilled) to the lungs as a single dose of a suspension in a saline solution. This is a commonly used, less expensive alternative to inhalation exposure, the route by which exposure occurs in real life. Such a 'bolus' exposure delivers a large dose of particles instantaneously, probably representing the dose that would normally be spread over weeks if not months, if it were inhaled. This causes a rapid peak of severe inflammation, even in the case of dusts that are harmless by longer term inhalation;

- since investigators cannot always obtain PM_{10}, or wish to address specific hypotheses regarding the roles of the components of PM_{10}, they may use one of a range of alternative particles. These include residual oil fly-ash (ROFA – a particle type that is highly toxic by virtue of its high transition metal content) and various types of ultrafine particles. The dose is often composed entirely of the suggested harmful component of ambient particles and so the relationship that these surrogate exposures have to real-life PM_{10}, which contains a large proportion of apparently low toxicity material, is not clear;

- where the exposure is to concentrated real-life air pollution particles (Concentrated Ambient Particles (CAPs)), this can be up to 25 times or more the ambient concentration of PM_{10}.

3.42 Exposure to normal ambient levels of particles is very unlikely to cause severe lung inflammation, although it may cause a low degree of inflammation, as described above. A severe inflammatory response in the lungs, or indeed anywhere in the body, will have effects on the cardiovascular system and will cause an acute phase response, which could also have effects on cardiovascular disease. Therefore the toxicological studies with particles that produce a severe inflammatory response in the lungs leading to cardiovascular effects do not, necessarily, mean that exposure to ambient concentrations of PM_{10} has this effect.

3.43 Most toxicological studies have used normal rats, since animal models of the main conditions, such as COPD and coronary heart disease, that produce susceptibility to PM_{10} are only now being developed. However, technological advances suggest that better toxicological models mimicking aspects of susceptibility will eventually become available. Perhaps the most convincing animal study reported to date is that of Suwa *et al* (2002). The authors exposed Watanabe rabbits – a strain that develops atheroma (Shiomi *et al*, 2003; Rosenfeld *et al*, 1987; Watanabe *et al*, 1985) – to ambient particles collected in Ottawa (these particles are referred to as EH6-93). Each exposed animal was instilled with 5 mg of EH6-93 (99% by number < 3 μm diameter) in 1 ml saline twice a week for four weeks. Control animals were exposed only to saline. Animals were killed three days after the final instillation. Detailed arterial histopathology was undertaken and bone marrow activity was monitored using the 5'-bromo-2'-deoxyuridine (BrdU) labelling technique. An increased pool of actively dividing cells was found in the bone marrow of the exposed group: the bone marrow labelling being proportional to the number of macrophages found to have ingested particles in the lung. Even more interesting were the effects of particle exposure on the progression of atheromatous plaques. Table 3.1 uses the classification system described above and shows a shift towards more advanced plaques in the exposed group. In discussing their findings the authors proposed a multistage process.

Table 3.1 Effect of exposure to particles on staging of atheromatous plaques

Staging of atheromatous plaques	% Plaques at specified stages	
	Exposed group	Controls
I	–	–
II	13	50
III	27	19
IV	25	3
V	5	0

(Adapted from Suwa *et al*, 2002)

- Macrophages take up PM, are activated and produce TNFα, IL-1, IL-6 and GM-CSF.

- GM-CSF stimulates bone marrow.

- TNFα and IL-1 up-regulate secretion of monocyte chemoattractant protein-1 (MCP-1) by endothelial cells leading to a movement of macrophages and T lymphocytes into plaques. TNFα also stimulates endothelial cells to produce L-selectin leading to increased monocyte adhesion.

- IL-6 stimulates bone marrow to release leukocytes and platelets and stimulates the liver to increase production and release of fibrinogen and CRP.

3.44 Evidence supporting each of these steps is quoted by the authors: see paper by Suwa *et al* (2002) for detailed references.

3.45 This paper provides clear evidence that large doses of ambient particles can affect atheromatous plaques. If such a progression towards more advanced lesions occurred in man, the likelihood of thrombosis and myocardial infarction would certainly be increased. The relevance of this study to the effects of changes in ambient concentrations of particles may, however, be questioned. The large and repeated doses may have provoked a very significant inflammatory response in the lungs, a response far beyond that likely on exposure to ambient concentrations. However, the results suggest that the presence of particles in the lung can affect the progress of atheromatous lesions. This is an important and new finding.

3.46 Similarly, instilled ultrafine particles (Nemmar *et al*, 2002; Nemmar *et al*, 2003a) and diesel exhaust particles (Nemmar *et al*, 2003b) have been found to increase systemic thrombosis in a hamster model but there is still a question mark over whether PM_{10} has this effect when inhaled at ambient levels.

3.47 Some weight can be put on studies with CAPs, even though they may employ exposures at up to 25 times the ambient PM_{10} concentration, as they do expose animals, by inhalation, to particles found in the ambient air and personal exposures in man can include short lived peaks of very high concentrations. Studies with CAPs in rats have shown inflammatory effects (Saldiva *et al*, 2002) although this is not a consistent effect (Gordon *et al*, 1998), while increased levels of oxidative stress have been reported in the lungs and, interestingly the hearts of rats after CAPs exposure (Gurgeira *et al*, 2002).

3.48 Dogs with experimentally compromised coronary arteries showed changes in heart rate variability and ST segments following CAPs exposure (Godleski *et al*, 2000). Rats with experimental bronchitis caused by sulphur dioxide exposure showed increased small pulmonary artery vasoconstriction in response to CAPs exposure although the significance of this finding in this model is not clear (Batalha *et al*, 2002).

3.49 One study took a more tangential approach by relating outcomes in animals to ambient air pollution. In this study the lungs of stray dogs from low pollution and high pollution areas of Mexico were compared with regard to pathological changes in the cardiovascular system (Calderon-Garciduenas *et al*, 2001). This showed differences between the two groups, with evidence of damage and inflammation of the heart muscle and the coronary blood vessels in the animals from the polluted area. However, differences in nutritional status and infection between the animals from the

two areas could have confounded these observations and further carefully controlled work is necessary before this intriguing finding can be properly evaluated.

3.50 Much of the mass of ambient PM_{10} is of low toxicity (e.g. sea salt, soil particles) but there are components that toxicologists have identified as having the potential to cause toxicity. Toxicologists have focused on the combustion-derived, carbon-centred ultrafine (or nanoparticle) fraction and animal studies have clearly demonstrated that ultrafine, nanometre-sized particles cause more inflammation than larger particles of the same material, probably related to their high surface area (Ferin *et al*, 1992; Oberdörster *et al*, 1990; Oberdörster *et al*, 1992). Other experiments have demonstrated that chemically reactive transition metals (Costa and Dreher, 1997; Jimenez *et al*, 2000) and organics, (Squadrito *et al*, 2001) commonly present in combustion-derived nanoparticles, can cause both oxidative stress and inflammation and possibly, thereby, affect the regularity of the heart beat. Additionally bloodborne metal, following pulmonary deposition of metals has been shown to cause detrimental effects on heart rhythm and bradycardia (Campen *et al*, 2001).

3.51 An alternative explanation to the above is that particles may gain access to the blood and directly affect the heart and its circulation. Several studies with ultrafine particles have demonstrated that they do gain access to the blood (Bailey *et al*, 1988; Nemmar *et al*, 2001; Nemmar *et al*, 2002) although no toxicological studies have demonstrated convincingly that ambient particles can pass into the blood and have direct effects on the heart or cardiovascular system. However, it is likely that this will take place as it does in individuals exposed to silica and coal dust by inhalation where particles can be found in the reticuloendothelial cells (fixed macrophages) of the spleen and liver. However, the likely dose to any target organ such as the heart, even in terms of particle numbers, makes this a less likely explanation of the observed epidemiological associations.

Indoor air pollution and environmental tobacco smoke

3.52 Although this review deals with outdoor air pollution we note that indoor air pollution is experienced by the majority of the population for considerable lengths of time. Indoor air pollution in homes with smokers is dominated by secondary cigarette smoke and this has been reported to have several effects in various systems that may contribute to cardiovascular disease. These include platelet activation (Glantz and Parmley, 1995), promotion of atherosclerosis (Penn *et al*, 1994), reduction in heart rate variability (Pope *et al*, 2001) and damage to the endothelium (Zhu and Parmley, 1995). One mechanism for the enhancement of thrombosis that might occur in individuals exposed to PM has been identified in smokers. The fibrinolytic factor tissue plasminogen activator (t-PA) regulates the degradation of intravascular fibrin and is released from the endothelium through the translocation of a dynamic

intracellular storage pool (van den Eijnden-Schrauwen *et al*, 1995). If endogenous fibrinolysis is to be effective, then the rapid mobilisation of t-PA from the endothelium is essential because thrombus dissolution is much more effective if t-PA is incorporated during, rather than after, thrombus formation (Brommer, 1984). The efficacy of plasminogen activation and fibrin degradation is further determined by the relative balance between the acute local release of t-PA and its subsequent inhibition through formation of complexes with plasminogen activator inhibitor type 1. This dynamic aspect of endothelial function and fibrinolytic balance may be directly relevant to the pathogenesis of atherothrombosis. Newby *et al* (1999) have shown that cigarette smoking causes marked inhibition of substance P-induced t-PA release *in vivo* in the forearm circulation of healthy male volunteers. This model has recently been applied to the coronary circulation of patients undergoing diagnostic coronary angiography (Newby *et al*, 2001) confirming that cigarette smoking was also associated with a marked impairment of coronary t-PA release. These important findings provide evidence of a direct link between endogenous fibrinolysis, endothelial dysfunction and atherothrombosis in the coronary circulation of smokers. Such events may also occur in those exposed to increased levels of PM.

3.53 Mills *et al* (2005) have found a response to diesel exposure similar to that they reported in cigarette smokers. Exposure to 200 μg/m³ DEP for 1 hour caused inhibition of peripheral vasomotion and t-PA release in response to endothelial-dependent and endothelial-independent stimulation. Interestingly, exposure to Edinburgh CAPS at similar concentrations had no effect on these parameters.

Possible role of gaseous pollutants

3.54 A few findings regarding gaseous pollutants were mentioned earlier in paragraph 3.38. Nonetheless, thinking about the possible role of inhaled gaseous air pollutants is much less well developed than that regarding particles. This is perhaps surprising as regards the oxides of nitrogen. Nitrogen dioxide is one component of the ambient mixture of nitrogen oxides, nitric oxide is another and is known to be an important mediator of vasodilatation: indeed organic nitrates and nitrites are used to relieve angina – the chest pain caused by spasm of the coronary arteries. It is now known that nitric oxide is the messenger substance that passes between the endothelial cells of blood vessels and the smooth muscle in their walls. This factor, before it was known to be nitric oxide, was called endothelium-derived relaxing factor (EDRF). An enormous literature has grown up around nitric oxide and it is used, therapeutically, at concentrations of 5-80 ppm, to induce vasodilatation of the pulmonary blood vessels. Once nitric oxide enters the blood it is rapidly bound to haemoglobin and is thus prevented from having an effect on the systemic circulation. Appreciation of the physiological role of nitric oxide does not lead easily to hypotheses suggesting that exposure to this compound could lead to a reduction in coronary blood flow; indeed

the opposite, if anything, seems more likely. But this conclusion may be simplistic and more complex interactions may be important. For example, it is known that rapid withdrawal from high concentrations of nitric oxide used therapeutically can result in rebound pulmonary vasospasm (Weinberger *et al*, 2001). The authors noted that this may be the result of down-regulation of nitric oxide synthase activity in the presence of exogenous nitric oxide, such that endogenous nitric oxide production by vascular endothelial cells remains diminished after therapeutic nitric oxide is withdrawn. It may be exacerbated by the unopposed action of vasoconstrictors until endogenous nitric oxide production is re-established. Clinical protocols suggest a slow reduction in therapeutic inhaled nitric oxide to 1 ppm before withdrawal. A concentration of 1 ppm is higher than the concentrations of nitric oxide found in ambient air but is a concentration that can occur for short periods indoors during use of combustion appliances.

3.55 Another study (Barberà *et al* 1996) has found that, at high concentrations, inhaled nitric oxide worsened pulmonary gas exchange in patients with chronic obstructive pulmonary disease. In COPD patients, blood flow is diverted from the poorly ventilated areas of the lung to better ventilated areas to optimise oxygenation of the blood: matching of ventilation and perfusion. Diversion of blood flow away from the poorly ventilated areas is achieved by vasoconstriction of the supplying blood vessels. If this selective vasoconstriction is inhibited, oxygenation of the blood will be impaired. Although the inhaled nitric oxide is less likely to reach poorly ventilated areas and thus less likely to have a vasodilation effect in those areas, the authors showed that mismatching of ventilation and perfusion, and reduced oxygenation of the blood, did occur at 40 ppm inhaled nitric oxide in COPD patients. Reduced oxygenation of the blood may risk the development of hypoxia of the myocardium. Whether these mechanisms occur to any extent at the much lower concentrations of nitric oxide present in ambient air is unknown.

3.56 These paragraphs do not, of course, reflect the vast literature available on nitric oxide. We simply highlight these two aspects to make the point that nitric oxide should not be dismissed as an air pollutant not worth investigating for its possible cardiovascular effects. Further work is also needed on the role of oxidative stress in destabilisation of atheromatous plaques. It is known however, that exposure to ozone produces general oxidative stress.

3.57 Figure 3.2 illustrates how the hypotheses discussed above might interact to produce death or the need for admission to hospital as a result of secondary effects upon the heart.

Figure 3.2 Toxicological mechanisms involved in the cardiovascular effects of particles and gases – two current hypotheses
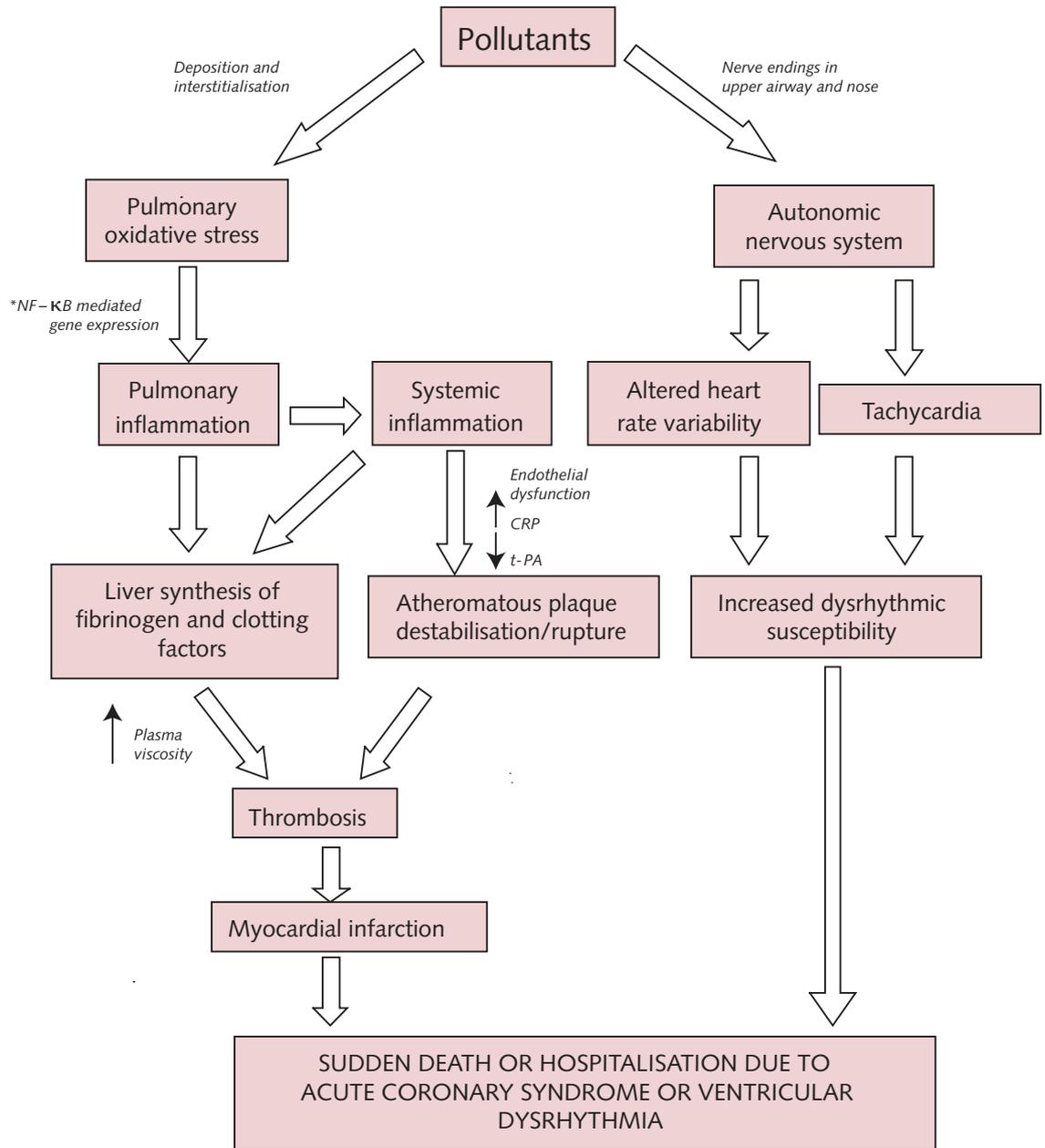
*NF-ĸB is a transcription factor that acts as an intracellular messenger and causes specific genes to be activated in response to, for example, oxidative stress.

The neural hypothesis

Neural reflexes linking the respiratory and cardiovascular systems and their relevance to understanding the effects of air pollutants

3.58   The respiratory and cardiovascular systems are closely linked by virtue of their innervation. Each is supplied with afferent fibres travelling in the autonomic nervous system and the centres controlling both respiratory and cardiovascular function are located close to each other in the brain stem. Detailed descriptions of the innervation of the heart and respiratory system have been provided (Krahl, 1964) and will not be reviewed in detail here. Three cranial nerves: the trigeminal (V), the glossopharyngeal (IX) and the vagus (X) contain afferent fibres from the nose, pharynx and the remainder of the respiratory system, respectively. Afferent fibres also pass along the sympathetic nerves and reach the upper thoracic spinal cord. Efferent fibres supplying the lung and heart travel in the vagus and sympathetic nerves, the former producing bronchoconstriction and slowing of the heart. Nerve fibres from the sympathetic ganglia ($T_2 - T_4$) join the vagi and form the pulmonary plexuses. Sympathetic control of the heart causes an increase in heart rate and secondary dilatation of coronary blood vessels. Interestingly, sympathetic activity actually causes constriction of the coronary vessels. The dilation from coronary sympathetic activation is an indirect effect due to metabolic vasodilation which over-rides the constriction. The importance of the efferent sympathetic supply to the airways has been disputed though bronchodilatation produced by the release of noradrenaline may occur. The presence of ß$_2$ adrenoreceptors in the airways, stimulation of which results in relaxation of smooth muscle, explains the efficacy of bronchodilator drugs such as salbutamol. A third system of airway innervation has been described, referred to as the Non Adrenergic Non Cholinergic (NANC) system. This is mediated by the release of neuropeptides such as Substance P from nerve terminals (Crystal *et al*, 1997) and can cause bronchodilatation.

3.59   The afferent fibres of the vagus nerve arise from three types of receptors within the lung. These have been classified by Widdicombe (2001) as stretch receptors, irritant receptors and C-fibre supplied nocioreceptors. The latter occur in the airways and in the alveolar walls close to capillaries and were originally described as juxtapulmonary capillaries or J receptors by Paintal (1983). A table showing a recent classification of respiratory receptors and stimuli is shown below in Table 3.2.

Table 3.2 Respiratory receptors and their stimuli (Widdicombe and Lee, 2001)

Site	Receptor	Stimulus
Nose	Touch	Mechanical
	Cold/flow	Cold
	Pressure	Mechanical
	C-fiber	Irritants
Epipharynx	Touch	Mechanical
	C-fiber	?Irritants
Larynx	Pressure	Mechanical
	Cold/flow	Cold
	Drive	Inspiratory drive
	RAR/Irritant	Touch, irritants
	C-fiber	Irritants
Trachea/bronchi	SAR	Lung inflation
	RAR	Touch, irritants
	C-fiber	Irritants
	NEB	Hypoxia
Alveoli	C-fiber	Irritants

Abbreviations: SAR, slowly adapting pulmonary stretch receptor; NEB, neuroepithelial body; RAR, rapidly adapting stretch receptor

3.60 Stimulation of the three types of receptor lead to reflex responses in both the lungs and the cardiovascular system. Widdicombe and Lee (2001) provided a table listing the reflex responses to stimulation of the different receptor. This is reproduced as Table 3.3.

Table 3.3 Respiratory and cardiovascular responses from different airway sites

Site	Respiration	Blood pressure	Heart rate
Nose	Sneeze/apnea	Increase	Decrease
Nasopharynx	Gasp/sniff	Increase	Increase
Larynx	Cough/apnea/expiration	Increase/decrease	Increase/decrease
Trachea/bronchi	Cough/apnea/hypernea	Increase/decrease	Increase/decrease
Alveoli	Apnea	Decrease	Decrease

3.61 Stimulation of irritant receptors is now thought to cause bradycardia. Stimulus of stretch receptors occurs cyclically during breathing and contributes to sinus arrhythmia, the increase of the heart rate during inspiration. Sinus arrhythmia was also thought to result from stimulation of stretch receptors in the right atrium during rapid filling from the vena cava as a result of the increasingly negative intrathoracic pressure produced during inspiration. Early work demonstrated that rapid infusion of fluid into the right atrium produced such an effect, the Bainbridge Effect, but later work cast doubt on this effect and its physiological importance is uncertain. The effects of reflexes from the lungs on the heart have been studied in detail and found to be very complex: the early work by Anrep and colleagues should be consulted for details (Anrep *et al*, 1936a, 1936b).

3.62 Air pollutants could affect two of three receptors within the lung: the irritant receptors and the C-fibre receptors. A detailed description of the effects of sulphur dioxide on these receptors has been provided by Widdicombe (1992). Stimulation of these receptors causes bradycardia as a result of increased vagal activity. Stimulation of mucosal sensory nerves leads to the release of neuropeptides in the airway wall, including, Substance P, neurokinins A and B and calcitonin gene related peptide (CGRP). These locally acting compounds lead to local vasodilation and transudation of plasma in addition to increased secretion by submucosal glands. The porosity of the surface epithelium is increased (Barnes and Lundberg, 1991; Barnes, 1986; Persson, 1991). There is, however, no evidence to suggest that these neuropeptides affect heart rate.

3.63 The control of the heart by the autonomic nervous system may be affected by exposure to particulate matter or gaseous pollutants leading to an increased risk of arrhythmia in susceptible patients. The current concept of ventricular arrhythmias not associated with acute ischaemia is one of substrate, triggers and modulating factors.

- The substrate is the presence of differential i.e., varying, intra-myocardial conduction velocities allowing the formation of a micro-re-entrant circuit (i.e. an abnormal pattern of conduction of impulses between heart muscle cells). For instance, any process that results in myocardial scarring including infarction or inflammation, can cause an area of slowed conduction.

- Triggers include ischaemia, electrolyte imbalance and mechanical stretch.

- Modulating factors increase or reduce susceptibility to a triggering factor, one of the most powerful of these modulating factors being cardiac autonomic control (i.e. the balance between sympathetic and parasympathetic outputs). In simple terms, while increased sympathetic activity increases susceptibility to arrhythmia, parasympathetic activity reduces the susceptibility both directly and indirectly via a sympatho-inhibitory action often referred to as "accentuated antagonism". Consequently, a range of influences on cardiac autonomic control can affect arrhythmic potential, often unpredictably.

Epidemiological evidence for disturbance in cardiac autonomic control in response to exposure to air pollution

3.64 Disturbances in the control of heart rate and rhythm in response to particulate pollution were originally suggested by two large observational studies. During an air pollution episode in Augsburg in Southern Germany in January 1985, hospital admissions for acute coronary syndromes and arrhythmia were substantially increased (Wichmann *et al*, 1989). Concurrently, resting electrocardiograms were recorded in a random sample of over 4000 subjects living in the area who were participating in the

MONICA survey. When heart rates were compared with those recorded at a later control period in over 3000 of these subjects, values were increased during the pollution episode (in men: +1.75 bpm (95% CIs 0.43 to 3.07) in women: +2.87 bpm (95% CI 1.42 to 4.32) mean change) (Peters *et al*, 1999). In addition, when concentrations of suspended particles and sulphur dioxide were considered as continuous variables throughout the whole study period, an association with heart rate remained even after adjusting for cardiovascular risk factors and meteorological parameters. In the same episode, arrhythmia admissions increased by 50% compared with the periods before and after the smog (Peters *et al*, 1999). This study provides strong evidence that air pollution can directly increase heart rate and precipitate cardiac arrhythmias.

3.65   In a panel study in Utah in the winter of 1995-96, oxygen saturation and heart rate using pulse-oximetry were measured daily in 90 elderly subjects (Pope *et al*, 1999a). While there was no evidence of pollution-related hypoxia, pulse rate and the likelihood of the pulse rate being elevated by 5 or 10 beats a minute were significantly associated with PM_{10} on the previous 1 to 5 days.

3.66   It is unlikely that the increase in heart rate *per se* could precipitate acute arrhythmic events but an increase in resting heart rate is likely to only be mediated by an increase in sympathetic, or a reduction in parasympathetic activity. Thus, these changes in heart rate suggest an alteration in cardiac autonomic control, an effect well recognised to influence the vulnerability to ventricular arrhythmia and sudden death (Schwartz *et al*, 1992; Wharton *et al*, 1992). It is notable that heart rate has long been recorded, albeit inconsistently, as an independent predictor of cardiovascular mortality, myocardial infarction and sudden death (Dyer *et al*, 1980; Hjalmarson *et al*, 1990). These observational studies therefore suggest a plausible link between exposure to particulate pollution and sudden cardiac death in susceptible individuals.

Cardiac autonomic control, heart rate variability and mortality

3.67   Although the study of heart rate allows a crude estimate of cardiac autonomic control, much more information is available from the study of heart rate variability (HRV). HRV measurement is a non-invasive technique that can be used to quantify cardiac autonomic control. The principle behind the technique is that variability in rate is not a property intrinsic to the heart but is instead determined by the effects of the autonomic nervous system on the sinus node.

3.68   The term "heart rate variability" is misleading as it refers not to changes in heart rate (beats per unit time), but to changes in the time interval between beats, usually referred to as heart period or, on an ECG, as the R-R interval. (To distinguish the intervals between normal sinus beats from those between abnormal, ectopic or artefactual ECG

activity, the term NN interval is often used). Unlike the study of heart rate, heart rate variability provides information on underlying sympathetic and parasympathetic neural influences that together control all aspects of cardiac performance including of course, heart rate. The vagus nerve exerts a dominant inhibitory influence on resting heart rate and fires phasically at a frequency that corresponds with the respiratory rate (Katona *et al*, 1982). The resulting oscillation in heart rate, known as respiratory sinus arrhythmia, constitutes the majority of HR variability. Measurement of beat-to-beat changes in heart periodicity thus predominantly reflects vagal influence on the heart.

### Figure 3.3 The Electrocardiogram (ECG)
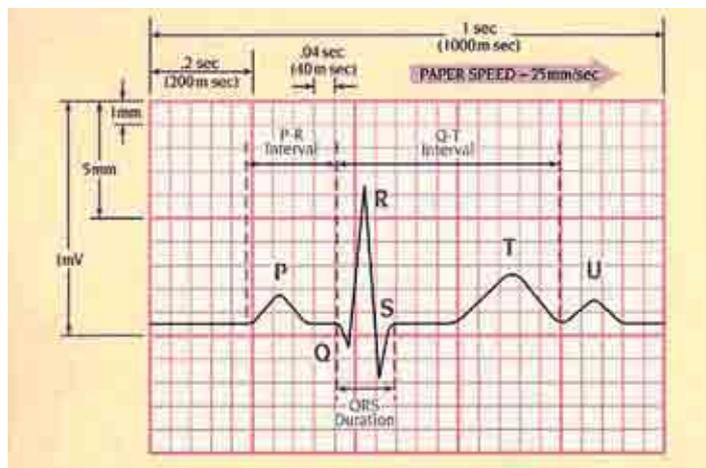
Figure 3.3 courtesy of London Ambulance Service.
The electrocardiogram (ECG) is a recording of the electrical activity of the heart taken from electrodes placed on the surface of the body. The variations in the potential differences between each of a series of electrodes and a neutral electrode are displayed on a paper trace. The potential difference (voltage) changes as the muscle of the heart depolarises and then repolarises during each heart beat. The diagram shows a trace recorded from one electrode during a single cardiac cycle. The electrical activity of the atria is shown by the P wave. This is followed by the QRS complex representing ventricular depolarisation and then by the T wave which represents repolarisation. The origin of the U wave is uncertain but it may represent repolarisation of a part of the impulse conducting pathway of the ventricles. The ECG trace is recorded on paper that moves at a standard speed and thus allows calculation of the heart rate. Disease states cause parts of the ECG trace to vary from the normal. For example the part of the trace between the S and T waves (the ST segment) may be depressed in myocardial ischaemia. In myocardial infarction the Q waves are enlarged and after a short delay the T wave may be inverted.

3.69 Standardised techniques are used to obtain a series of NN intervals from ECG recordings, i.e. the time intervals between consecutive normal beats. From these recordings, taken either over short periods with controlled respiration or over 24 hours using Holter monitoring, are derived a number of measures of variability, both in the time and in the frequency domains (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Time domain measures are statistical measures of the variability of NN intervals measured in units of time, while frequency domain measures quantify the power of

the individual component frequencies that together form the total power (or variability) of the signal under examination, in this case a period of ECG recording.

3.70 The standard deviation of NN interval differences (SDNN) is a simple time domain statistical measure that quantifies overall variability. Although this largely reflects cardiac vagal control there are also major influences from the sympathetic nervous system and a number of poorly understood lower frequency inputs including those related to thermoregulation and certain humoral factors. More specific time domain measures of cardiac vagal control can be derived using analysis of the variability of differences between successive NN intervals (interval difference variability) rather than the intervals themselves. These are measures of high frequency beat-to-beat variability and include RMSSD (the root mean square of successive NN interval differences) and pNN50 (the percentage of intervals varying by greater than 50 ms from their preceding interval). Because only the vagus nerve can modulate the sinus node at a sufficiently high frequency to alter discharge within one heart period, the NN interval difference variability is almost exclusively determined by vagal activity.

3.71 More information on the relative contributions of sympathetic and parasympathetic activity to heart rate control can be gained from analysis of HRV in the frequency rather than time domain. Power spectrum analysis using autoregressive modelling or Fast Fourier transformation can be applied to short, stationary periods of ECG recording and be used to quantify the power of component frequencies. The so-called 'high frequency' power, centred at the respiratory frequency – usually 0.25 Hz – is determined almost exclusively by respiratory sinus arrhythmia and is therefore a measure of cardiac vagal control. The low frequency power (0.1 Hz) component is determined by both parasympathetic and sympathetic nervous activity and is probably a result of resonant interaction between sympathetic and vagal responses to baroreceptor stimulation (Sleight *et al*, 1995). It is often used in a simplistic and in most cases erroneous fashion, as an index of sympathetic control. Normal ranges for time and frequency domain measures are available both for healthy individuals of all ages and for those with cardiovascular disease (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

3.72 Analysis of ECG recordings in apparently healthy subjects enrolled in the Framingham Heart Study has demonstrated that reduced heart rate variability is a powerful and independent predictor of mortality (Tsuji *et al*, 1994). Further analysis of a larger cohort (> 2500) of healthy Framingham patients showed that after adjustment for other cardiovascular risk factors, HRV measures in both time and frequency domains were significantly associated with risk of cardiac events including myocardial infarction, new onset angina, death due to coronary heart disease and heart failure onset (Tsuji *et al*, 1996). A recent large prospective study of healthy

subjects from Japan has confirmed an independent relationship of HRV and cardiovascular mortality in this ethnically distinct population, greatly strengthening the available data (Kikuya *et al*, 2000). Thus, even in a healthy population, cardiac autonomic control appears to be an important determinant of prognosis, perhaps as a reflection of factors as diverse as physical conditioning and occult heart disease. Decreased heart rate variability occurs in patients with established heart disease such as myocardial infarction and chronic heart failure (Mortara and Schwartz, 1998; Nolan *et al*, 1998). In both groups it has been shown to be an independent predictor of cardiac death. The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) investigators studied 1284 survivors of a recent myocardial infarction and found low values of HRV to be associated with a 2 year mortality of 10% compared with 2% when normal HRV was preserved (Mortara and Schwartz, 1998). Further analysis of these mortality data revealed specific associations between depressed HRV, sudden death and sustained ventricular tachycardia (La Rovere *et al*, 2001). In 433 patients with chronic heart failure followed for a mean of 482 days, SDNN was an independent predictor of mortality. The annual mortality for patients with an SDNN of < 50 ms was 51.4% compared with 12.7% for an SDNN of 50 to 100 ms and 5.5% for an SDNN of > 100 ms. This relationship between HRV and mortality was independent of conventional risk factors such as left ventricular function. Possible mechanisms by which preserved cardiac vagal activity might beneficially influence prognosis include a decrease in heart rate and myocardial oxygen demand, a reduction in sympathetic activity and of course, a decreased susceptibility of the ventricular myocardium to lethal arrhythmia.

3.73 The precise pathophysiology of the relationship between susceptibility to ventricular fibrillation (VF) and autonomic control is poorly understood. There is however, a strong body of animal evidence showing that in anaesthetised animals, increased sympathetic and reduced vagal activity increases the susceptibility of ischaemic myocardium to ventricular fibrillation (Lown and Verrier, 1976). In addition, a series of experiments using conscious exercising dogs with experimentally induced myocardial infarction and ischaemia showed that dogs with high baseline levels of markers of vagal control were relatively resistant to VF. In susceptible dogs, pharmacological and electrical stimulation of vagus nerve activity effectively prevented induced VF during exercise (Schwartz *et al*, 1992; Schwartz *et al*, 1988). It is unclear how cardiac vagal activity is able to prevent arrhythmia at a cellular level but at least part of this anti-arrhythmic action may be due to pre- and post-synaptic inhibition of elevated levels of sympathetic activity.

3.74 The factors contributing to impaired cardiac autonomic control in cardiac disease are poorly understood. Humoral rather than neural factors may be important. Catecholamines, angiotensin II and aldosterone all exert inhibitory effects on cardiac

vagal control while neurohormonal antagonists such as beta blockers, ACE inhibitors and spironolactone effectively increase HRV and vagal control. (These drugs reduce mortality in coronary artery disease and heart failure by multiple direct and indirect actions. The relative contribution of their effects on cardiac autonomic control is unknown, although in the case of beta blockers it is clearly important). Inherited factors and physical fitness may also be of importance. Environmental factors that may have a detrimental effect on cardiac autonomic control have only recently become the subject of investigation. The epidemiological evidence for an association between exposure to air pollutants, tachycardia and mortality from cardiac arrhythmia has however, led investigators to use non-invasive measures of cardiac autonomic control in a number of observational studies.

Observational studies of the association of pollution exposure to arrhythmia and heart rate variability

3.75   A number of studies have identified associations between day-to-day changes in air pollution and either arrhythmia or changes in HRV. During the Augsburg pollution episode referred to above, arrhythmia admissions were increased by 50% compared to control periods before and after the smog (Wichmann *et al*, 1989). A panel study provided some evidence for the hypothesis that an increase in the incidence of cardiac arrhythmia contributes to the rise in mortality associated with increases in ambient pollution levels (Peters *et al*, 2000). In 100 patients with implantable cardioverter defibrillators in Boston, USA, episodes of defibrillation were positively related to daily air pollution. The frequency of defibrillator discharges showed a significant correlation with increased levels of PM_{10} and $PM_{2.5}$ with a lag time of 2 days and an association with NO_2 levels on the previous day. In a sub-group of patients who had had at least 10 interventions to treat ventricular arrhythmia, the likelihood of a rectifying discharge being needed tripled with an increase in NO_2 from the 5th to 95th percentile and increased by 60% for an equivalent rise in $PM_{2.5}$. The possibility that NO_2 may be acting as a surrogate for some active component of the ambient aerosol has been discussed in the previous chapter and is noted again. Preliminary work in London has produced similar findings (Wilkinson P. Personal communication 2004). In 7 elderly US subjects undergoing ambulatory ECG monitoring before, during and after particulate pollution episodes from a steel mill in Utah, small but consistent negative associations between pollution (PM_{10}) levels and same day measures of HRV (SDNN) were found (Pope *et al*, 1999b). A later and larger study from Utah examined HRV from repeated 24 hour recording studies in 88 elderly Utah subjects. A 100 µg/m³ increase in $PM_{2.5}$ was associated with a 35 ms decline in SDNN and a 42 ms decline in RMSSD (Pope *et al*, 2004) In a further group of 26 elderly men (mean age 81) in urban Baltimore, the risk of an individual having low heart rate variability (SDNN, HF power) over a three week period was significantly increased on days when $PM_{2.5}$ levels were high. The largest associations were found for individuals

with pre-existing cardiovascular disease (Liao *et al*, 1999). In a repeated measures study in Boston, 21 subjects (aged 53-87) were observed intermittently over a period of 4 months with ambulatory ECG monitoring. Robust and significant negative associations between $PM_{2.5}$ and RMSSD were apparent. Inter-quartile increases in $PM_{2.5}$ and ozone in a multi-pollutant model resulted in a combined effect equivalent to a 33% reduction in the mean RMSSD[23] (Gold *et al*, 2000). More recently, studies examining HRV and the possible influence of air pollutants have been published from groups in Mexico and the US. In Mexico, 34 nursing home residents underwent a 5 minute ECG recording on alternate days for 3 months, which was analysed in the frequency domain (Holguin *et al*, 2003). Indoor and outdoor $PM_{2.5}$ were measured daily at the nursing home. After adjusting for age and heart rate, a strong inverse relationship between High Frequency (HF) power and same day total exposure to $PM_{2.5}$ was noted, this effect was largest in subjects with hypertension, suggesting a susceptible group. In the US, the population based Atherosclerosis Risk in Communities (ARIC) study examined associations between average 24-hour locally measured particulate and gaseous pollutant[24] levels and HRV from 5 minute recordings in over 5000 people (Liao *et al*, 2004). Values were adjusted for numerous risk factors and other variables and regression coefficients were calculated for one standard deviation increase in PM_{10}. Highly significant but small negative coefficients between PM_{10} and SDNN, high frequency power and heart rate were present. Of interest, no association was present for 2- and 3-day lagged values, suggesting an acute effect. Similar results were also found for gaseous pollutants. This study is the largest cross sectional study available and is perhaps the strongest evidence for an acute effect of air pollution on HRV. Most recently, a group from Taiwan studied the association between personal exposure to submicrometer particles (size range 0.02 – 1.0 μm) and HRV in small cohorts of young adult and elderly volunteer subjects (Chan *et al*, 2004). Increases of 10,000 particles/cm³ were associated with decreases in both time and frequency domain HRV measures of between 0.6 and 5% in both age groups with consistently larger effects in the elderly.

3.76 In an occupational setting, Magari and colleagues (2001) addressed one of the limitations to these earlier studies. Previously, estimation of personal exposure to pollutants had relied upon data obtained from regional monitoring stations. Magari used personal exposure monitors in a cohort of 40 boiler-makers, who wore 24-hour ambulatory ECG monitors at home and in the work place. In these young industrial workers, half of whom were current smokers, a significant negative association was found between 4-hour $PM_{2.5}$ exposure (increases of 100 μg/m³) and 5-minute measures of SDNN. This effect appeared to be biphasic with a short acting

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23 $PM_{2.5}$ and ozone were also separately positively associated with a reduction in mean RMSSD but CO, NO_2 and SO_2 were not.
24 Ozone, CO, NO_2 and SO_2

component (several minutes) and a longer effect over several hours. However, personal $PM_{2.5}$ levels were higher (mean 167 μg/m³ ± S.D 320 μg/m³) than ambient levels typically reported in Boston and there were differences in activity levels during and away from work, which make interpretation of alterations in HRV measures difficult. It also raises the issue of whether such changes are physiological as opposed to pathological.

Experimental evidence for adverse effects of air pollution on cardiac autonomic control: animal and human studies

3.77   Experimental exposure studies in this area are limited. Rats with pulmonary hypertension exposed to particulate matter showed a dose-related increase in incidence and duration of serious arrhythmia, with no preceding hypoxia (Watkinson *et al*, 1998). More recently, two groups have documented that both residual oil fly ash (ROFA) and concentrated ambient particles result in a decrease in heart rate and blood pressure in rats with drug induced pulmonary hypertension (Watkinson *et al*, 2001; Cheng *et al*, 2003). This bradycardia would suggest an increase in cardiac vagal activity which would be expected to result in a reduced susceptibility to ventricular arrhythmia in humans. Great caution is required in extrapolating effects of pollutants in rodents with pulmonary hypertension to humans with cardiovascular disease, but these results show that cardiac autonomic tone can be influenced by inhaled pollutants.

3.78   In a series of studies on dogs with partially ligated coronary arteries, exposure to CAPs (at about 20 times ambient concentration) via tracheostomy, caused a decrease in heart rate (Godleski *et al*, 2000). Using a paired crossover design Godleski also demonstrated increases in both high frequency (HF) and low frequency (LF) power and an increase in LF/HF ratio following a 3-hour exposure to CAPs, i.e. an increase in sympatho-vagal balance which might be expected to increase susceptibility to arrhythmia. Once again, these results are perhaps unexpected, but do provide evidence of the capacity of particulate pollution to influence cardiac autonomic control.

3.79   More recently, Devlin and colleagues challenged healthy adults with a 2-hour chamber exposure to CAPs (Devlin *et al*, 2003). Although no change in HRV occurred in young (< 40 years) adults, in 10 elderly subjects (60-80 years) significant decreases in both time and frequency domain measures of HRV occurred immediately on exposure and persisted for up to 24-hours.

3.80   There is evidence that chronic allergic airway inflammation in monkeys is associated with increased activity and amplitude of neural output from the nucleus ambiguus (Chen *et al*, 2001). This could provide a pathway for autonomically mediated effects on the heart, at least in the presence of chronic airway inflammation. In addition, an

established mechanism for producing airway inflammation – neurogenic inflammation – is linked with autonomic peptidergic or neural pathways, again providing a potential mechanistic link (Groneberg *et al*, 2004).

3.81 Although this review has focused on particles, experimental laboratory exposure to SO$_2$ in humans has also been shown to exert significant adverse effects on HRV (Tunnicliffe *et al*, 2001). Normal and asthmatic subjects exposed to 200 ppb of sulphur dioxide at rest for one hour showed opposing changes in HRV with a potentially cardio-protective increase in HF power in normal subjects but a decrease in those with asthma. While this may be identifying more a specific difference between asthmatic and normal subjects in autonomic responsiveness, the findings also cohere with epidemiological effects seen in older subjects.

3.82 Ozone, a gaseous pollutant that also has its effects through oxidative stress mechanisms has been reported to have adverse effects on the cardiovascular system. Rats exposed to ozone at 0.5-2.0 ppm showed consistent decreases in heart rate ranging from 50 to 100 beats per minute and also decreases in core temperature, typically falling from 1.5 to 2.5°C (Watkinson *et al*, 2001). However these effects appear to be adapted with ongoing exposure over 3 – 4 days (Iwasaki *et al*, 1998).

3.83 Rats chronically implanted with electrodes for EEG*, EMG* and ECG* were exposed to ozone or clean air for 5 consecutive days. Compared with control rats, heart rates of the ozone-exposed rats decreased and the number of bradyarrhythmic episodes increased with increasing ozone levels from 0.1 to 0.2 ppm. These responses were reversed with atropine, indicating involvement of the para-sympathetic nervous system (Arito *et al*, 1990; Arito *et al*, 1992). Electrocardiogram and arterial blood pressure of elastase-treated emphysematous rats and saline-treated control rats were recorded during exposure to ozone (0.2 to 1 ppm). The heart rates of both groups decreased to about half of the initial levels while arterial blood pressures decreased by about a quarter; there was no difference between emphysematous and control rats in the extent of these responses (Uchiyama and Yokoyama, 1989). Similar bradycardia and arrhythmias, reversible with atropine, were found in rats exposed to 20 ppm NO$_2$ for 3 hours (Tsubone *et al*, 1982).

3.84 In one study, catecholamine activity and tyrosine hydroxylase activity[25] was assessed in heart, brain and spinal cord following ozone exposure. Ozone inhibited noradrenaline turnover in heart and inhibited tyrosine hydroxylase activity in brain (Cottet-Emard *et al*, 1997). This result is difficult to interpret in terms of effects which may occur in man. Atrial natriuretic peptides (ANP) are potent vasodilating peptides that may contribute to inflammation and oedema. Ozone exposure increased ANP levels in

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* See glossary

25   an enzyme involved in catecholine synthesis

heart, lung and circulation 8 hours after cessation of exposure (Vesely *et al*, 1994). Evidence of systemic effects of ozone-mediated oxidative stress is shown by the fact that exposure of rats to ozone for 5 days resulted in an increased concentration of thiobarbituric acid-reactive material, catalase and glutathione peroxidase in heart and brain (Rahman *et al*, 1992).

Potential mechanisms for the effect of pollutants on the cardiac autonomic nervous system

3.85 How inhalation of pollutants and in particular fine particles might exert adverse effects on the autonomic control of cardiac function remains to be fully elucidated. In-keeping with the inflammation hypothesis, inhaled particles may indirectly promote an autonomic stress-response as a result of cytokine release. Alternatively, a direct neural effect might be attributable to stimulation of naso-pharyngeal, upper or lower airway receptors.

3.86 A brief introduction to the physiology of such receptors was provided above, a more detailed account which develops some of the points made earlier is provided below.

3.87 Animal work has demonstrated that stimulation of irritant or 'rapidly acting receptors' (RARs) can mediate powerful neural influences on the cardiovascular system (Yeates and Mauderly, 2001; Widdicombe, 2001; Nishino *et al*, 1996). RARs occur throughout the respiratory tract from the nose to the bronchi and are characterised by a rapid adaptation to a mechanical stimulus. They also respond, in a more prolonged manner, to a variety of chemical stimuli or irritants, including sulphur dioxide, smoke, dusts and inflammatory mediators (Yeates and Mauderly, 2001). The response to inhaled substances differs according to the location of the receptor (Widdicombe, 2001) and between individuals and may also depend on the amount of mucus being secreted (Nishino *et al*, 1996). Respiratory reflexes, such as cough and bronchoconstriction, arising from afferent receptors in the larynx and upper airways, will in turn influence arterial blood pressure and heart rate. Impulses from irritant receptors in the airways are transmitted via the vagal nerves and centrally processed in the medulla. It seems likely that cardiovascular reflex responses to RARs may occur, but to date the subject has not been thoroughly studied (Sant'Ambrogio and Widdicombe, 2001). While airway C-fibre receptors cause hypotension and bradycardia presumably via vagal activation, the cardiovascular consequences of airway RAR stimulation are unknown. Widdecombe and Lee, (2001) have described hypertension and tachycardia in response to tracheal stimulation and it has been speculated that this is a RAR mediated response. RARs are also present in the lung but again, no cardiovascular reflexes from these receptors are known. This subject has not been investigated; in their review on RARs Sant'Ambrogio and Widdicombe (2001) observed that "perhaps the definitive experiments have not been performed".

Two other mechanisms have been suggested. An effect of pollutants on olfactory afferents, perhaps involving olfactory or peptidergic nerve endings, is possible. The olfactory system is critically important in alerting most animals to danger, and it would be surprising if it were not able to elicit a residual "fight and flight" reaction in humans through its connections with the amygdaloid nuclei and thalamus. No evidence to support this hypothesis is currently available. Inhaled particles have been shown to enter the systemic circulation and direct effects on the sinus node or other cardiac structures is at least a theoretical possibility.

3.88 Thus inhalation of an irritant to the upper respiratory tract can result in the triggering of a neural reflex, the efferent component of which (and or the resulting change in respiratory pattern) would exert an influence on both sympathetic and vagal cardiac control.

Air pollution and coronary vasoconstriction

3.89 Another pathophysiological mechanism which might explain the epidemiological findings has recently been suggested (Brook *et al*, 2002). Using controlled exposures to concentrated ambient particles and ozone in combination, Brook and colleagues demonstrated that short-term inhalation of pollutants altered vascular function in a manner that might result in adverse cardiac events. Inhalation of particles and ozone for 2 hours caused acute significant brachial artery vasoconstriction but no change in endothelial dependent or independent function when compared to filtered air. Coronary and brachial artery endothelial function are strongly correlated (Takase *et al*, 1998) and the authors speculated that their response to air pollutants might also be similar. Thus, such changes could promote ischaemia in individuals with underlying coronary artery disease.

3.90 Observational evidence has, in addition, recently linked ambient pollutant exposure to increased risk of ECG ST segment depression suggestive of myocardial ischaemia. In 45 individuals with coronary artery disease, undergoing bi-weekly exercise testing, the likelihood of a positive test was associated with higher levels of $PM_{2.5}$ (Pekkanen *et al*, 2002). Potential biological mechanisms for pollutant-induced coronary vasoconstriction include reflex increases in sympathetic nervous system activity as a result of stimulation of airway receptors, or an acute increase in vascular endothelin release as a result of systemic inflammation and cytokine release.

3.91 Statistically significant associations between ambient concentrations of carbon monoxide and admissions to hospital for treatment of cardiac disease were noted in Chapter 2: see table 2.16. The recent emphasis on the possible role of fine particles has caused these findings to be rather ignored, despite evidence from chamber studies that shows that exposure to low concentrations of carbon monoxide can exacerbate

myocardial ischaemia in those with impaired coronary arterial blood flow. A detailed discussion of these studies has been provided by Maynard and Waller (Maynard and Waller, 1999). It was concluded that though a case could be made for acute exposure to ambient concentrations of carbon monoxide having an effect, there was little evidence to suggest that long-term exposure to ambient levels contributed to the development of cardiovascular disease, although it is noted that carbon monoxide has been discussed in the context of active smoking.

3.92 It is noted that ambient concentrations of carbon monoxide can act as a surrogate for exposure to traffic-generated pollution and that distinguishing between the possible effects of the closely correlated components of this complex mixture is difficult. Having said this, it is accepted that the possible effects of exposure to ambient levels of carbon monoxide requires further study.

Summary

3.93 The mechanistic hypotheses as outlined: inflammation, thrombosis, autonomic effects and arterial reactivity, might each independently, or perhaps more likely in combination, explain the observed association between air pollution and both cardiovascular morbidity and mortality, including arrhythmia (figure 3.2). For example, in a susceptible individual with coronary artery disease, exposure to pollution might cause systemic inflammation, increasing the likelihood of plaque rupture and an increased concentration of clotting factors in the blood might increase the likelihood of a clot forming on the damaged surface of the plaque, blocking the affected vessel. An adverse influence on cardiac autonomic control, particularly in an individual in whom autonomic control is already abnormal, might increase the vulnerability of the acutely ischaemic or failing myocardium to lethal ventricular arrhythmia.

3.94 Although both the autonomic and inflammatory hypotheses are plausible, with some supporting evidence, it should be noted that they remain hypotheses only and that a crucial piece of evidence for both of these possible mechanisms is missing. The evidence relating impaired cardiac autonomic control and raised inflammatory markers to prognosis, rests upon assessments of these values taken at a baseline time and related to medium and long-term outcomes, usually over a period of years. The theory that short term, day to day, fluctuations in autonomic control or levels of inflammation in response to environmental factors such as air pollution might be responsible for the occurrence of adverse cardiac events including sudden death, is attractive, but is unproven. Unless it can be shown that changes in these markers precede adverse events within an appropriate time scale, the significance of reports of changes in response to fluctuations in pollutant levels must remain in doubt.

3.95 On biological grounds however, both mechanisms appear plausible. An inflammatory cytokine response resulting in a rise in CRP occurs within hours in response to infection, inflammation and tissue damage, events which occur frequently throughout life. Similarly, sympathetic and cardiac vagal activities vary constantly in response to reflex stimuli, emotion, exertion and of course inflammation and infection. Notable papers were published following the San Francisco earthquake of 1994 and the Iraqi missile crisis in Israel in 1991, showing that the incidence of sudden cardiac death increased dramatically following these events (Leor *et al*, 1996; Meisel *et al*, 1991). Thus, intense emotional stress does appear to increase adverse cardiac events and the autonomic nervous system response to this stress is likely to account for at least part of this effect. Support for the inflammatory concept comes from two recent reports. Contrary to previous data suggesting that CRP is a very stable marker and therefore a useful indicator of long-term risk, it appears that in patients with coronary artery disease, CRP varies over time sufficiently to change the risk category even if infective episodes are excluded (Bogaty *et al*, 2005). Secondly, an important paper published in 2004 examined records from a large UK general practice database and showed that acute respiratory and urinary tract infections are associated with a transient 3 to 5-fold increase in the risk of a stroke and myocardial infarction. This risk was highest in the first 3 days after the onset of the illness and then fell gradually (Smeeth *et al*, 2004). Thus, the concept that an environmental stimulus causing an inflammatory response can result in a short term increase in acute cardiac events such as myocardial infarction and sudden death, within days, appears sound.

3.96 Attempts to determine whether or not autonomic control is abnormal immediately before the occurrence of arrhythmias (i.e. within minutes), have failed to provide consistent results. While a number of studies have found that HRV in the time and or frequency domain (or assessed using non-linear analysis) falls, prior to VT or VF in a manner suggesting vagal withdrawal and/or sympathetic activation, almost as many have found no change compared to control periods (Lombardi *et al*, 2000; Nemec *et al*, 1999; Tsuji *et al*, 1996; Vybiral *et al*, 1993). By their very nature however, such studies are difficult to do and current data are inadequate to allow safe conclusions to be drawn. A recent small prospective study of 40 patients with chronic heart failure undergoing monthly monitoring, may point the way to the design of future larger studies. Shehab and colleagues showed that intra-individual changes in markers of inflammation such as CRP and neutrophil count as well as falls in HRV, preceded cases of sudden death (Shehab *et al*, 2004). The time-scale was however, over months rather than days. This sort of work is labour intensive but by even more frequent measurement of biomarkers such as HRV and CRP in a panel of at risk subjects, the temporal relationship of environmental factors such as air pollution to these markers could be determined. This sort of design also offers the possibility of relating changes

in these markers to adverse cardiac events, although the numbers required for such an outcome study would be large.

References – Clotting Hypothesis

Barberà, J., Roger, N., Roca, K., Rovira, I., Higenbottam, T.W. and Rodriguez-Roison, R. (1996) Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. *Lancet* **347**, 436-440.

Bailey, M.R., Kreyling, W.G., Andre, S., Batechelor, A., Black, A., Collier, C.G., Drosselmeyer, E., Ferron, G.A., Foster, P., Haider, B., Hodgson, A., Metivier, H., Moores, S.R., Morgan, A., Muller, H.L., Patrick, G., Pickering, S., Ramsden, D., Stirling, C. and Talbot, R.J. (1988) An interspecies comparison of the translocation of material from lung to blood. *Ann.Occup.Hyg.* **32(Suppl 1)**, 975-985.

Batalha, J.R., Saldiva, P.H., Clarke, R.W., Coull, B.A., Sterns, R.C., Lawrence, J., Murthy, G.G., Koutrakis, P. and Godleski, J.J. (2002) Concentrated ambient air particles induce vasoconstriction of small pulmonary arteries in rats. *Environ.Health Perspect.* **110**, 1191-1197.

Becker, R.C. (2002) Antithrombotic therapy after myocardial infarction. *N.Engl.J.Med.* **347**, 1019-1022.

Bench, G. (1991) Scanning transmission ion microscopy. PhD Thesis. Melbourne, Australia: University of Melbourne.

Brommer, E.J. (1985) Delayed fibrinolysis: a cause of thrombosis? *Haemostasis* **15**, 247-253.

Brook, R.D., Brook, J.R. and Rajagopalan, S. (2003) Air pollution: the "heart" of the problem. *Curr.Hypertens.Rep.* **5**, 32-39.

Calderon-Garciduenas, L., Gambling, T.M., Acuna, H., Garcia, R., Osnaya, N., Monroy, S., Villarreal-Calderon, A., Carson, J., Koren, H.S. and Devlin, R.B. (2001) Canines as sentinel species for assessing chronic exposures to air pollutants: part 2. Cardiac pathology. *Toxicol.Sci.* **61**, 356-367.

Campen, M.J., Nolan, J.P., Schladweiler, M.C., Kodavanti, U.P., Evansky, P.A., Costa, D.L. and Watkinson, W.P. (2001) Cardiovascular and thermoregulatory effects of inhaled PM-associated transition metals: a potential interaction between nickel and vanadium sulphate. *Toxicol.Sci.* **64**, 243-252.

Chapman, R.S., Watkinson, W.P., Dreher, K.L. and Costa, D.L. (1997) Ambient particulate matter and respiratory and cardiovascular illness in adults: particle-borne transition metals and the heart-lung axis. *Environ.Toxicol.Pharmacol.* **4**, 331-338.

Comroe, J.F., Forster, R.E., Dubois, A.B., Briscoe, W.A. and Carlsen, E. (1962) *The Lung: Clinical Physiology and Pulmonary Function Tests.* 2nd Edition. Chicago, London: Year Book Medical Publishers, Inc.

Cook, N.S. and Ubben, D. (1990) Fibrinogen as a major risk factor in cardiovascular disease. *TIPS Rev.* **11**, 444-451.

Cooper, J. and Douglas, A.S. (1991) Fibrinogen level as a predictor of mortality in survivors of myocardial infarction. *Fibrinolysis* **5**, 105-108.

Costa, D.L. and Dreher, K.L. (1997) Bioavailable transition metals in particulate matter mediate cardiopulmonary injury in healthy and compromised animal models. *Environ.Health Perspect.* **105(Suppl 5)**, 1053-1067.

Crawford, T. (1977) Blood and lymphatic vessels. In: Anderson, A.D. and Kissare, J.M. *Pathology.* St Louis: the CV Mosby Company.

Danesh, J., Wheeler, J.G., Hirschfield, G.M., Eda, S., Eiriksdottir, G., Rumley, A., Lowe, G.D.O., Pepys, M.B. and Gudnason, V. (2004) C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N.Engl.J.Med.* **350**, 1387-1397.

Davies, M.J. (1995) Acute coronary thrombosis – the role of plaque disruption and its initiation and prevention. *Eur.Heart J.* **16(Suppl L)**, 3-7.

Davies, M.J., Woolf, N., Rowles, P. and Richardson, P.D. (1994) Lipid and cellular constituents of unstable human aortic plaques. *Basic Res. Cardiol.* **89(Suppl 1)**, 33-39.

Divine, K.K., Grant, P.G., Lewis, J.L. and Bench, G. (1999) Quantitative particle-induced x-ray emission imaging of rat olfactory epithelium applied to the permeability of rat epithelium to inhaled aluminum. *Chem.Res.Toxicol.* **12**, 575-581.

Donaldson, G.C. and Keatinge, W.R. (1997) Early increases in ischaemic heart disease mortality dissociated from and later changes associated with respiratory mortality after cold weather in south east England. *J.Epidemiol.Community Health* **51**, 643-648.

Falk, E., Shah, P.K. and Fuster, V. (1995) Coronary plaque disruption. *Circulation* **92**, 657-671.

Felton, C.V, Crook, D., Davies, M.J. and Oliver, M.F. (1997) Relation of plaque lipid composition and morphology to the stability of human aortic plaques. *Arterioscler. Thromb.Vasc.Biol.* **17**, 1337-1345.

Ferin, J., Oberdörster, G. and Penney, D.P. (1992) Pulmonary retention of ultrafine and fine particles in rats. *Am.J.Respir.Cell Mol.Biol.* **6**, 535-542.

Fernández-Ortiz, A., Badimon, J.J., Falk, E., Fuster, V., Meyer, B., Mailhac, A., Weng, D., Shah, P.K. and Badimon, L. (1994) Characterization of the relative thrombogenicity of atherosclerotic plaque components: implications for consequences of plaque rupture. *J.Am.Coll.Cardiol.* **23**, 1562-1569.

Gardner, S.Y., Lehmann, J.R. and Costa, D.L. (2000) Oil fly ash-induced elevation of plasma fibrinogen levels in rats. *Toxicol.Sci.* **56**, 175-180.

Ghio, A.J., Kim, C. and Devlin, R.B. (2000) Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. *Am.J.Respir.Crit.Care Med.* **162**, 981-988.

Gianutsos, G., Morrow, G.R. and Morris, J.B. (1997) Accumulation of manganese in rat brain following intranasal administration. *Fundam.Appl.Toxicol.* **37**, 102-105.

Glantz, S.A. (2002) Air pollution as a cause of heart disease. Time for action. [Editorial comment]. *J.Am.Coll.Cardiol.* **39**, 943-945.

Glantz, S.A. and Parmley, W.W. (1995) Passive smoking and heart disease. Mechanisms and risk. *J.Am.Med.Assoc.* **273**, 1047-1053.

Godleski, J.J., Verrier, R.L., Koutrakis, P., Catalano, P., Coull, B., Reinisch, U., Lovett, E.G., Lawrence, J., Murthy, G.G., Wolfson, J.M., Clarke, R.W., Nearing, B.D. and Killingsworth, C. (2000) Mechanisms of morbidity and mortality from exposure to ambient air particles. *Res.Rep.Health Eff.Inst.* **91**, 5-88.

Goel, M.S. and Diamond, S.L. (2001) Neutrophil enhancement of fibrin deposition under flow through platelet-dependent and –independent mechanisms. *Arterioscler.Thromb.Vasc.Biol.* **12**, 2093-2098.

Gordon, T., Nadziejko, C., Schlesinger, R. and Chen, L.C. (1998) Pulmonary and cardiovascular effects of acute exposure to concentrated ambient particulate matter in rats. *Toxicol.Lett.* **96-97**, 285-288.

Green, F. and Humphries, S. (1989) Control of plasma fibrinogen levels. *Balliere's Clin.Haematol.* **2**, 945-959.

Gurgeria, S.A., Lawrence, J., Coull, B., Murthy, K.G.G. and Gonzalez-Flecha, B. (2002) Rapid increases in the steady state concentration of reactive oxygen species in the lungs and heart after particulate pollution inhalation. *Environ.Health Perspect.* **110**, 749-755.

Hamsten, A., de Faire, U., Walldius, G., Dahlén, G., Szamosi, A., Landou, C., Blombäck, M. and Wiman, B. (1987) Plasminogen activator inhibitor in plasma: risk factor for recurrent myocardial infarction. *Lancet* **ii**, 3-9.

Harker, L.A. and Ritchie, J.L. (1980) The role of platelets in acute vascular events. *Circulation* **62(6 Part 2)**, 13-18.

Henriksson, J., Tallkvist, J. and Tjälve, H. (1997) Uptake of nickel into the brain via olfactory neurons in rats. *Toxicol.Lett.* **91**, 153-162.

Jimenez, L.A., Thompson, J., Brown, D.A., Rahman, I., Antonicelli, F., Duffin, R., Drost, E.M., Hay, R.T., Donaldson, K. and MacNee, W. (2000) Activation of NF-$\varkappa$B by PM_{10} occurs via an iron-mediated mechanism in the absence of I$\varkappa$B degradation. *Toxicol.Appl.Pharmacol.* **166**, 101-110.

Keatinge, W.R., Coleshaw, S.R.K., Cotter, F., Mattock, M., Murphy, M. and Chelliah, R. (1984) Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: factors in mortality from coronary and cerebral thrombosis in winter. *Br.Med.J.* **289**, 1405-1408.

Keatinge, W.R., Coleshaw, S.R.K., Easton, J.C., Cotter, F., Mattock, M.B. and Chelliah, R. (1986) Increased platelet and red cell counts, blood viscosity, and plasma cholesterol levels during heat stress and mortality from coronary and cerebral thrombosis. *Am.J.Med.* **81**, 795-800.

Kodavanti, U.P., Schladweiler, M.C., Ledbetter, A.D., Watkinson, W.P., Campen, M.J., Winsett, D.W., Richards, J.R., Crissman, K.M., Hatch, G.E. and Costa, D.L. (2000) The spontaneously hypertensive rat as a model of human cardiovascular disease: evidence of exacerbated cardiopulmonary injury and oxidative stress from inhaled emission particulate matter. *Toxico.Appl.Pharmacol.* **164**, 250-263.

Kullo, I.J., Gau, G.T. and Tajik, A.J. (2000) Novel risk factors for atherosclerosis. *Mayo Clin.Proc.* **75**, 369-380.

Lendon, C.L., Davies, M.J., Born, G.V. and Richardson, P.D. (1991) Atherosclerotic plaque caps are locally weakened when macrophages density is increased. *Atherosclerosis* **87(1)**, 87-90.

Lendon, C.L., Born, G.V., Davies, M.J. and Richardson, P.D. (1992) Plaque fissure: the link between atherosclerosis and thrombosis. *Nouv. Rev. Fr. Hematol.* **34(1)**, 27-29.

Lewis, J., Bench, G., Myers, O., Tinner, B., Staines, W., Barr, E., Divine, K.K., Barrington, W. and Karlsson, J. (2005) Trigeminal uptake and clearance of inhaled manganese chloride in rats and mice. *Neurotoxicology* **26**, 113-123.

Libby, P., Geng, Y.J., Aikawa, M., Schoenbeck, U., Mach, F., Clinton, S.K., Sukhova, G.K. and Lee, R.T. (1996) Macrophages and atherosclerotic plaque stability. *Curr.Opinion Lipidiology* **7**, 330-335.

Mann, J. and Davies, M.J. (1996) Vulnerable plaque. *Circulation* **94**, 928-931.

Mann, J. and Davies, M.J. (1999) Mechanisms of progression in native coronary artery disease: role of healed plaque disruption. *Heart* **82**, 265-268.

Meade, T.W., Mellows, S., Brozovic, M., Miller, G.J., Chakrabarti, R.R., North, W.R.S., Haines, A.P., Stirling, Y., Imeson, J.D. and Thompson, S.G. (1986) Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet* **ii**, 533-537.

Miller, G.J., Wilkes, H.C., Meade, T.W., Bauer, K.A., Barzegar, S. and Rosenberg, R.D. (1991) Haemostatic changes that constitute the hypercoagulable state. *Lancet* **338**, 1079.

Mills, N.L., Törnqvist, H., Robinson, S.D., Gonzales, M., Darnley, K., MacNee, W., Boon, N.A., Donaldson, K., Blomberg, A., Sandstrom, T. and Newby, D.E. (2005) Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis: an explanation for the increased cardiovascular mortality associated with air pollution. *Circulation* **112**, 3930-3936.

Ministry of Health. (1954) *Mortality and Morbidity during the London Fog of December 1952. Reports on Public Health and Medical Subjects No 95.* London; HMSO.

Moreno, P.R., Purushothaman, R., Fuster, V., Echeverri, D., Truszczynska, H., Sharma, S.K., Badimon, J.J. and O'Connor, W.N. (2004) Plaque neovascularization is increased in ruptured atherosclerotic lesions of human aorta. Implications for plaque vulnerability. *Circulation* **110**, 2032-2038.

Muller, J.E., Abela, G.S., Nesto, R.W. and Tofler, G.H. (1994) Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. *J.Am.Coll.Cardiol.* **23**, 809-813.

Neild, P.J., Syndercombe-Court, D., Keatinge, W.R., Donaldson, G.C., Mattock, M. and Caunce, M. (1994) Cold-induced increases in erythrocyte count, plasma cholesterol and plasma fibrinogen of elderly people without a comparable rise in Protein C or Factor X. *Clin.Sci.* **86**, 43-48.

Nemmar, A., Vanbilloen, H., Hoylaerts, M.F., Hoet, P.H.M., Verbruggen, A. and Nemery, B. (2001) Passage of intratracheally instilled ultrafine particles from the lung into the systemic circulation in hamster. *Am.J.Respir.Crit.Care Med.* **164**, 1665-1668.

Nemmar, A., Hoet, P.H.M., Vanquickenborne, B., Dinsdale, D., Thomeer, M., Hoylaerts, M.F., Vanbilloen, H., Mortelmans, L, and Nemery, B. (2002) Passage of inhaled particles into the blood circulation in humans. *Circulation* **105**, 411-414.

Nemmar, A., Hoylaerts, M.F., Hoet, P.H.M., Dinsdale, D., Smith, T., Xu, H., Vermylen, J. and Nemery, B. (2002) Ultrafine particles affect experimental thrombosis in an *in vivo* hamster model. *Am.J.Respir.Crit.Care Med.* **166**, 998-1004.

Nemmar, A., Hoylaerts, M.F., Hoet, P.H., Vermylen, J. and Nemery, B. (2003a) Size effect of intratracheally instilled particles on pulmonary inflammation and vascular thrombosis. *Toxicol.Appl.Pharmacol.* **186**, 38-45.

Nemmar, A., Hoet, P.H., Dinsdale, D., Vermylen, J., Hoylaerts, M.F. and Nemery, B. (2003b) Diesel exhaust particles in lung acutely enhance experimental peripheral thrombosis. *Circulation* **107**, 1202-1208.

Newby, D.E., Wright, R.A., Labinjoh, C., Ludlam, C.A., Fox, K.A., Boon, N.A. and Webb, D.J. (1999) Endothelial dysfunction, impaired endogenous fibrinolysis, and cigarette smoking: a mechanism for arterial thrombosis and myocardial infarction. *Circulation* **99**, 1411-1415.

Newby, D.E., McLeod, A.L., Uren, N.G., Flint, L., Ludlam, C.A., Webb, D.J., Fox, K.A. and Boon, N.A. (2001) Impaired coronary tissue plasminogen activator release is associated with coronary atherosclerosis and cigarette smoking: direct link between endothelial dysfunction and atherothrombosis. *Circulation* **103**, 1936-1941.

Normandin, L., Panisset, M. and Zayed, J. (2002) Manganese neurotoxicity: behavioral, pathological, and biochemical effects following various routes of exposure. *Rev.Environ.Health* **17**, 189-217.

Nunn, J.F. (1993) *Nunn's Applied Respiratory Physiology*. 4th Edition. Oxford: Butterworth Heineman Ltd.

Oberdörster, G., Ferin, J., Finkelstein, G., Wade, P, and Corson, N. (1990) Increased pulmonary toxicity of ultrafine particles? II. Lung lavage studies. *J.Aerosol Sci.* **21**, 384-391.

Oberdörster, G., Ferin, J., Gelein, R., Soderholm, S.C. and Finkelstein, J. (1992) Role of the alveolar macrophage in lung injury: studies with ultrafine particles. *Environ.Health Perspect.* **97**, 193-199.

Oliver, J.J., Webb, D.J. and Newby, D.E. (2005) Stimulated tissue plasminogen activator release as a marker of endothelial function in humans. *Arterioscler.Thromb.Vasc.Biol.* **25**, 2470-2479.

Pearson, T.A., LaCava, J. and Weil, H.F.C. (1997) Epidemiology of thrombotic-hemostatic factors and their associations with cardiovascular disease. *Am.J.Clin.Nutr.* **65(Suppl)**, 1674S-1682S.

Pekkenan, J., Brunner, E.J., Anderson, H.R., Tiitanen, P. and Atkinson, R.W. (2000) Daily concentrations of air pollution and plasma fibrinogen in London. *Occup.Environ.Med.* **57**, 818-822.

Penn, A., Chen, L.C. and Snyder, C.A. (1994) Inhalation of steady-state sidestream smoke from one cigarette promotes arteriosclerotic plaque development. *Circulation* **90**, 1363-1367.

Pepys, M.B. (1981) C-reactive protein fifty years on. *Lancet* **i**, 653-657.

Peters, A., Doring, A., Wichmann, H.-E. and Koenig, W. (1997) Increased plasma viscosity during an air pollution episode: a link to mortality? *Lancet* **349**, 1582-1587.

Peters, A., Dockery, D., Muller, J.E. and Mittleman, M.A. (2001) Increased particulate air pollution and the triggering of myocardial infarction. *Circulation* **103**, 2810-2815.

Peters, A., von Klot, S., Heier, M., Trentinaglia, B.S., Hörmann, A. and Wichmann, E. (2004) Exposure to traffic and the onset of myocardial infarction *N.Engl.J.Med.* **387**, 1721-1730.

Pope, C.A., Eatough, D.J., Gold, D.R., Pang, Y., Nielsen, K.R., Nath, P., Verrier, R.L. and Kanner, R.E. (2001) Acute exposure to environmental tobacco smoke and heart rate variability. *Environ.Health Perspect.* **109**, 711-716.

Riley, R.L. and Cournand, A. (1949) Ideal alveolar air and the analysis of ventilation-perfusion relationship in the lung. *J.Appl.Physiol.* **158**, 21-30.

Rollins, B.J., Yoshimura, T., Leonard, E.J. and Pober, J.S. (1990) Cytokine-activated human endothelial cells synthesize and secrete a monocyte chemoattractant, MCP-1/JE. *Am.J.Pathol.* **36**, 1229-1233.

Rosenfeld, M.E., Tsukada, T., Gown, A.M. and Ross, R. (1987) Fatty streak initiation in Watanabe heritable hyperlipemic and comparably hypercholesterolemic fat-fed rabbits. *Arteriosclerosis* **7**, 9-23.

Rothwell, P.M., Villagra, R., Gibson, R., Donders, R.C.J.M. and Warlow, C.P. (2000) Evidence of a chronic systemic cause of instability of atherosclerotic plaques. *Lancet* **355**, 19-24.

Saldiva, P.H., Clarke, R.W., Coull, B.A., Stearns, R.C., Lawrence, J., Murthy, G.G., Diaz, E., Koutrakis, P., Suh, H., Tsuda, A. and Godleski, J.J. (2002) Lung inflammation induced by concentrated ambient air particles is related to particle composition. *Am.J.Respir.Crit.Care Med.* **165**, 1610-1617.

Salvi, S., Blomberg, A., Rudell, B., Kelly, F., Sandstrom, T., Holgate, S.T. and Frew, A. (1999) Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. *Am.J.Respir.Crit.Care Med.* **159**, 702-709.

Schwartz, J. (2001) Air pollution and blood markers of cardiovascular risk. *Environ.Health Perspect.* **109(Suppl 3)**, 405-409.

Seaton, A. and Dennekamp, M. (2003) Ill-health associated with low concentrations of nitrogen dioxide: an effect of ultrafine particles? *Thorax* **58**, 1012-1015.

Seaton, A., MacNee, W., Donaldson, K. and Godden, D. (1995) Particulate air pollution and acute health effects. *Lancet* **345**, 176-178.

Seaton, A., Soutar, C.A., Crawford, V., Elton, R., McNerlan, S., Cherrie, J., Watt, M., Agius, R. and Stout, R. (1999) Particulate air pollution and the blood. *Thorax* **54**, 1027-1032.

Selkurt, E.E. (1976) *Physiology*. 4th Edition. Boston, MA: Little, Brown and Co.

Shanahan, C.M., Cary, N.R.B., Metcalfe, J.C. and Weissberg, P.L. (1994) High expression of genes for calcification-regulating proteins in human atherosclerotic plaques. *J.Clin.Invest.* **93**, 2392-2402.

Schwartz, J. (2001) Air pollution and blood markers of cardiovascular risk. *Environ.Health Perspect.* **109(Suppl 3)**, 405-409.

Shiomi, M., Ito, T., Hirouchi, Y. and Enomoto, M. (2001) Fibromuscular cap composition is important for the stability of established atherosclerotic plaques in mature WHHL rabbits treated with statins. *Atherosclerosis* **157**, 75-84.

Shiomi, M., Ito, T., Yamada, S., Kawashima, S. and Fan, J. (2003) Development of an animal model for spontaneous myocardial infarction (WHHLMI rabbit). *Arterioscler.Thromb.Vasc.Biol.* **23**, 1239-1244.

Squadrito, G.L., Cueto, R., Dellinger, B. and Pryor, W.A. (2001) Quinoid redox cycling as a mechanism for sustained free radical generation by inhaled airborne particulate matter. *Free Radic.Biol.Med.* **31**, 1132-1138.

Stary, H.C., Chandler, A.B., Glagov, W., Guyton, J.R., Insull, W., Rosenfeld, M.E., Schaffer, S.A., Schwartz, C.J., Wagner, W.D. and Wissler, R.W. (1994) A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation* **89**, 2462-2478.

Suwa, T., Hogg, J.C., Quinlan, K.B., Ohgami, A., Vincent, R. and van Eeden, S.F. (2002) Particulate air pollution induces progression of atherosclerosis. *J.Am.Coll.Cardiol.* **39**, 935-942.

Thompson, S.G., Kienast, J., Pyke, S.D.M., Haverkate, F. and Van de Loo, J.C.W. (1995) Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *N.Engl.J.Med.* **332**, 635-641.

Tjälve, H., Henriksson, J., Tallkvist, J., Larsson, B.S. and Lindquist, N.J. (1996) Uptake of manganese and cadmium from the nasal mucosa into the central nervous system via olfactory pathways in rats. *Pharmacol.Toxicol.* **79**, 347-356.

Van de Wouwer, M., Collen, D. and Conway, E.M. (2004) Thrombomodulin-protein C-EPCR system: integrated to regulate coagulation and inflammation. *Arterioscler.Thromb.Vasc.Biol.* **24**, 1374-1383.

van den Eijden-Schrauwen, Y., Kooistra, T., de Vries, R.E. and Emeis, J.J. (1995) Studies on the acute release of tissue-type plasminogen activator from human endothelial cells *in vitro* and in rats *in vivo*: evidence for a dynamic storage pool. *Blood* **85**, 3510-3517.

van Eeden, S.F. and Hogg, J.C. (2002) Systemic inflammatory response induced by particulate matter air pollution: the importance of bone marrow stimulation. *J.Toxicol.Environ.Health A* **65**, 1597-1613.

Vincent, R., Kumarathasan, P., Geogan, P., Bjarnason, S.G., Guenette, J., Berube, D., Adamson, I.Y., Desjardins, S., Burnett, R.T., Miller, F.J. and Battistini, B. (2001) Inhalation toxicology of urban ambient particulate matter: acute cardiovascular effects in rats. *Res.Rep.Health Eff.Inst.* **104**, 5-54.

Watanabe, Y., Ito, T. and Shiomi, M. (1985) The effect of selective breeding on the development of coronary atherosclerosis in WHHL rabbits. An animal model for familial hypercholesterolemia. *Atherosclerosis* **56**, 71-79.

Weinberger, B., Laskin, D., Heck, D. and Lasking, J. (2001) The toxicology of inhaled nitric oxide. *Toxicol.Sci.* **59**, 5-16.

Woodhouse, P.R., Khaw, K.T., Plummer, M., Foley, A. and Meade, T.W. (1994) Seasonal variation of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. *Lancet* **343**, 435-439.

Yarnell, W.G., Baker, I.A., Sweetnam, P.M., Bainton, D. and O'Brien, J.R. (1991) Fibrinogen viscosity, and white blood cell count are major risk factors for ischemic heart disease. The Caerphilly and Speedwell Collaborative Heart Disease Studies. *Circulation* **83**, 836-844.

Zhu, B.Q. and Parmley, W.W. (1995) Hemodynamic and vascular effects of active and passive smoking. *Am.Heart J.* **130**, 1270-1275.

References – Neural hypothesis

Anrep, G.V., Pascual, W. and Rossler, R. (1936a) Respiratory variations of the heart rate. The reflex mechanism of respiratory arrhythmia. *Proc.R.Soc.B.* **119**, 191-217.

Anrep, G.V., Pascual, W. and Rossler, R. (1936b) The central mechanism of respiratory arrhythmia and interrelations between central and reflex mechanisms. *Proc.R.Soc.B.* **119**, 218-230.

Arito, H., Uchiyama, I., Arakawa, H. and Yokayama E. (1990) Ozone-induced bradycardia and arrhythmia and their relation to sleep-wakefulness in rats. *Toxicol.Lett.* **52**, 169-178.

Arito, H., Uchiyama, I. and Yokayama E. (1992) Acute effects of ozone on EEG activity, sleep-wakefulness and heart rate in rats. *Ind.Health* **30**, 23-34.

Barnes, P.J. (1986) Asthma as an axon reflex. *Lancet* **i**, 242-245.

Barnes, P.J. and Lundberg, J.M. (1991) Airway neuropeptides and asthma. In: Kaliner, M.A., Barnes, P.J. and Persson, C.G.A., editors. *Asthma: its Pathology and Treatment.* New York: Marcel Dekker; pp385-407.

Bogaty, P., Brophy, J.M., Boyer, L., Simard, S., Joseph, L., Bertrand, F. and Dagenais, G.S. (2005) Fluctuating inflammatory markers in patients with stable ischemic heart disease. *Arch.Intern.Med.* **165**, 221-226.

Brook, R.D., Brook, J.R., Urch, B., Vincent, R., Rajagopalan, S. and Silverman, F. (2002) Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. *Circulation* **105**, 1534-1536.

Chan, C.C., Chuang, K.J., Shiao, G.M. and Lin, L.Y. (2004) Personal exposure to submicrometer particles and heart rate variability in human subjects. *Environ.Health Perspect.* **112**, 1063-1067.

Chen, C.Y., Bonham, A.C., Schelegle, E.S., Gershwin, L.J., Plopper, C.G. and Joad, J.P. (2001) Extended allergen exposure in asthmatic monkeys induces neuroplasticity in nucleus tractus solitarius. *Allergy Clin.Immunol.* **108(4)**,557-562.

Cheng, T.J., Hwang, J.S., Wang, P.Y., Tsai, C.F., Chen, C.Y., Lin, S.H., and Chan, C.C. (2003) Effects of concentrated ambient particles on heart rate and blood pressure in pulmonary hypertensive rats. *Environ.Health Perspect.* **111**, 147-150.

Cottet-Emard, J.M., Dalmaz, Y., Pequignot, J., Peyrin, L. and Pequignot, J.M. (1997) Long-term exposure to ozone alters peripheral and central catecholamine activity in rats. *Pflugers Arch.* **433**, 744-749.

Crystal, R.G., West, J.B., Weibel, E.R. and Barnes, P.J., editors. (1997) *The Lung: Scientific Foundations.* Philadelphia, PA: Lippencroft-Raven Inc.

Devlin, R.B., Ghio, A.J., Kehrl, H., Sanders, G. and Cascio, W. (2003) Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability. *Eur.Respir.J.* **21(Suppl 40)**, 76s-80s.

Dyer, A.R., Persky, V., Stamler, J., Paul, O., Shekelle, R.B., Berkson, D.M., Lepper, M., Schoenberger, J.A. and Lindberg, H.A. (1980) Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. *Am.J.Epidemiol.* **112,** 736-749.

Godleski, J.J., Verrier, R.L., Koutrakis, P., Catalano, P., Coull, B., Reinisch, U., Lovett, E.G., Lawrence, J., Murthy, G.G., Wolfson, J.M., Clarke, R.W., Nearing, B.D. and Killingsworth, C. (2000) Mechanisms of morbidity and mortality from exposure to ambient air particles. [Review]. *Res.Rep.Health Eff.Inst.* **91**, 5-103.

Gold, D.R., Litonjua, A., Schwartz, J., Lovett, E., Larson, A., Nearing, B., Allen, G., Verrier, M., Cherry, R. and Verrier, R. (2000) Ambient pollution and heart rate variability. *Circulation* **101**, 1267-1273.

Groneberg, D.A., Quarcoo, D., Frossard, N. and Fischer, A. (2004) Neurogenic mechanisms in bronchial inflammatory diseases. *Allergy* **59**, 1139-1152.

Hjalmarson, A.G., Kjekshus, J., Schieman, G., Nicod, P., Henning, H. and Ross, J. (1990) Influence of heart rate on mortality after acute myocardial infarction. *Am.J.Cardiol.* **65,** 547-553.

Holguin, F., Tellez-Rojo, M.T., Hernandez, M., Cortez, M., Chow, J.C., Watson, J.G., Mannino, D. and Romieu, I. (2003) Air pollution and heart rate variability among the elderly in Mexico City. *Epidemiology* **14**, 521-527.

Iwasaki, T., Takahashi, M., Saito, H. and Arito, H. (1998) Adaptation of extrapulmonary responses to ozone exposure in conscious rats. *Ind.Health* **36**, 57-60.

Katona, P.G., McLean, M., Dighton, D.H. and Guz, A. (1982) Sympathetic and parasympathetic cardiac control in athletes and nonathletes at rest. *J.Appl.Physiol.* **52,** 1652-1657.

Kikuya, M., Hozawa, A., Ohokubo, T., Tsuji, I., Michimata, M., Matsubara, M., Ota, M., Nagai, K., Araki, T., Satoh, H., Ito, S., Hisamichi, S. and Imai, Y. (2000) Prognostic significance of blood pressure and heart rate variabilities: the Ohasama study. *Hypertension* **36**, 901-906.

Krahl, V.E. (1964) In: *Handbook of Physiology, Section 3, 1, 213.* American Physiological Society.

La Rovere, M.T., Pinna, G.D., Hohnloser, S.H., Marcus, F.I., Mortara, A., Nohara, R., Bigger, J.T., Camm, A.J. and Schwartz, P.J. (2001) Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. *Circulation* **103**, 2072-2077.

Leor, J., Poole, K. and Kloner, R.A. (1996) Sudden cardiac death triggered by an earthquake. *N.Engl.J.Med.* **334**, 413-419.

Liao, D., Creason, J., Shy, C., Williams, R., Watts, R. and Zweidinger, R. (1999) Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. *Environ.Health Perspect.* **107**, 521-525.

Liao, D., Duan, Y., Whitsel, E.A., Zheng, Z.J., Heiss, G., Chinchili, V.M. and Lin, H.M. (2004) Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population based study. *Am.J.Epidemiol.* **159**, 768-777.

Lombardi, F., Porta, A., Marzegalli, M., Santini, M., Vincenti, A. and De Rosa, A. (2000) Heart rate variability patterns before ventricular tachycardia onset in patients with an implantable cardioverter defibrillator. *Am.J.Cardiol.* **86**, 959–963.

Lown, B. and Verrier, R.L. (1976) Neural activity and ventricular fibrillation. *N.Engl.J.Med.* **294**, 1165-1170.

Magari, S.R., Hauser, R., Schwartz, J., Williams, P.L., Smith, T.J. and Christiani, D.C. (2001) Association of heart rate variability with occupational and environmental exposure to particulate air pollution. *Circulation* **104**, 986-991.

Meisel, S.R., Kutz, I., Dayan, K.I., Pauzner, H., Chetboun, I., Arbel, Y. and David, D. (1991) Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. *Lancet* **338**, 660-661.

Mortara, A. and Schwartz, P.J. (1998) Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* **351**, 478-484.

Maynard, R. L. and Waller, R. (1999) Carbon Monoxide. In: Holgate, S.T., Samet, J.M., Koren, H.S. and Maynard, R.L., editors. *Air Pollution and Health.* London, Academic Press.

Nemec, J., Hammill, S.C. and Shen, W.K. (1999) Increase in heart rate precedes episodes of ventricular tachycardia and ventricular fibrillation in patients with implantable cardioverter defibrillators. *Pacing Clin. Electrophysiol.* **12**, 1729-1738.

Nishino, T., Tagaito, Y. and Isono, S. (1996) Cough and other reflexes on irritation of airway mucosa in man. *Pulmon.Pharmacol.* **9**, 285-292.

Nolan, J., Batin, P.D., Andrews, R., Lindsay, S.J., Brooksby, P., Mullen, M., Baig, W., Flapan, A.D., Cowley, A., Prescott, R.J., Neilson, J.M. and Fox, K.A. (1998) Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation* **98**, 1510-1516.

Paintal, A.S. (1983) Lung and airway receptors. In: Pallot, D.G. editor. *Control of Respiration.* London: Croom Helm.

Pekkanen, J., Peters, A., Hoek, G., Tiittanen, P., Brunekreef, B., de Hartog, J., Heinrich, J., Ibaldi-Mulli, A., Kreyling, W.G., Lanki, T., Timonen, K.L. and Vanninen, E. (2002) Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. *Circulation* **106**, 933-938.

Persson, C.G.A. (1991) Tracheobronchial microcirculation in asthma. In: Kaliner, M.A., Barnes, P.J. and Persson, C.G.A., editors. *Asthma: its Pathology and Treatment.* New York: Marcel Dekker; pp209-230.

Peters, A., Liu, E., Verrier, R.L., Schwartz, J., Gold, D.R., Mittleman, M., Baliff, J., Oh, J.A., Allen, G., Monahan, K. and Dockery, D.W. (2000) Air pollution and incidence of cardiac arrhythmia. *Epidemiology* **11**, 11-17.

Peters, A., Perz, S., Doring, A., Stieber, J., Koenig, W. and Wichmann, H.E. (1999) Increases in heart rate during an air pollution episode. *Am.J.Epidemiol.* **150,** 1094-1098.

Pope, C.A., Dockery, D.W., Kanner, R.E., Villegas, G.M. and Schwartz, J. (1999a) Oxygen saturation, pulse rate, and particulate air pollution: A daily time-series panel study. *Am.J. Respir.Crit.Care Med.* **159**, 365-372.

Pope, C.A., Hansen, M.L, Long, R.W., Nielsen, K.R., Eatough, N.L., Wilson, W.E. and Eatough, D.J. (2004) Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. *Environ.Health Perspect.* **112**, 339-345.

Pope, C.A., Verrier, R.L., Lovett, E.G., Larson, A.C., Raizenne, M.E., Kanner, R.E., Schwartz, J., Villegas, G.M., Gold, D.R. and Dockery, D.W. (1999b) Heart rate variability associated with particulate air pollution. *Am.Heart J.* **138**, 890-899.

Rahman, I., Massaro, G.D. and Massaro, D. (1992) Exposure of rats to ozone: evidence of damage to heart and brain. *Free Radic.Biol.Med.* **12**, 323-326.

Sant'Ambrogio, G. and Widdicombe, J. (2001) Reflexes from rapidly adapting receptors. *Respir.Physiol.* **125**, 33-45.

Schwartz, P., La Rovere, M.T. and Vanoli, E. (1992) Autonomic nervous system and sudden cardiac death. *Circulation* **85(Suppl 1)**, I-77-I-91.

Schwartz, P., Vanoli, E., Stramba-Badiale, M., De, F.G.M., Billman, G.E. and Foreman, R.D. (1988) Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation* **78**, 969-979.

Shehab, A.M., MacFadyen, R.J., McLaren, M., Tavendale, R., Belch, J.J. and Struthers, A.D. (2004) Sudden unexpected death in heart failure may be preceded by short term, intraindividual increases in inflammation and in autonomic dysfunction: a pilot study. *Heart* **90**, 1263-1268.

Sleight, P., La Rovere, M.T., Mortara, A., Pinna, G., Maestri, R., Bianchini, B., Tavazzi, L. and Bernardi, L. (1995) Physiology and pathophysiology of heart rate and blood pressure variability in humans: is power spectral analysis largely an index of baroreflex gain? *Clin. Sci.* **88**, 103-109.

Smeeth, L., Thomas, S.L., Hall, A.J., Hubbard, R., Farrington, P. and Vallance, P. (2004) Risk of myocardial infarction and stroke after acute infection or vaccination. *N.Engl.J.Med.* **351**, 2611-2618.

Takase, B., Uehata, A., Akima, T., Nagai, T., Nishioka, T., Hamabe, A., Satomura, K. and Ohsuzu, F. (1998) Endothelium-dependent flow-mediated vasodilation in coronary and brachial arteries in suspected coronary artery disease. *Am.J.Cardiol.* **82**, 1535–1539.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* **93**, 1043-1065.

Tsuji, H., Venditti, F.J., Manders, E.S., Evans, J.C., Larson, M.G., Feldman, C.L. and Levy, D. (1994) Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Study. *Circulation* **90**,878-883.

Tsuji, H., Larson, M.G., Venditti, F.J., Manders, E.S., Evans, J.C., Feldman, C.L. and Levy, D. (1996) Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation* **94**, 2850-2858.

Tsubone, H., Oda, H., Suzuki, A.K. and Kubota K. (1982) Electrocardiographic abnormalities in rats by acute exposure to nitrogen dioxide. *Toxicol.Lett.* **12**, 125-129.

Tunnicliffe, W.S., Hilton, M.F., Harrison, R.M. and Ayres, J.G. (2001) The effect of sulphur dioxide exposure on indices of heart rate variability in normal and asthmatic adults. *Eur.Respir.J.* **17**, 604-608.

Uchiyama, I. and Yokoyama, E. (1989) Effects of short and long-term exposure to ozone on heart rate and blood pressure of emphysematous rats. *Environ.Res.* **48**, 76-86.

Vesely, D.L., Giordano, A.T., Raska-Emery, P. and Montgomery, M.R. (1994) Ozone increases amino- and carboxy-terminal atrial natriuretic factor prohormone peptides in lung, heart and circulation. *J.Biochem.Toxicol.* **9**, 107-112.

Vybiral, T., Glaeser, D.H., Goldberger, A.L., Rigney, D.R., Hess, K.R., Mietus, J., Skinner, J.E., Francis, M. and Pratt, C.M. (1993) Conventional heart rate variability analysis of ambulatory electrocardiographic recordings fails to predict imminent ventricular fibrillation. *J.Am.Coll.Cardiol.* **22**, 557-565.

Watkinson, W.P., Campen, M.J. and Costa, D.L. (1998) Cardiac arrhythmia induction after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. *Toxicol.Sci.* **41**, 209-216.

Watkinson, W.P., Campen, N.J., Nolan, J.P. and Costa, D.L. (2001) Cardiovascular and systemic responses to inhaled pollutants in rodents: effects of ozone and particulate matter. *Environ.Health Perspect.* **109(Suppl 4)**, 539-546.

Wharton, J.M., Coleman, R.E. and Strauss, H.C. (1992) The role of the autonomic nervous system in sudden cardiac death. *Trends Cardiovasc.Med.* **2**: 65-71.

Wichmann, H.E., Mueller, W., Allhoff, P., Beckmann, M., Bocter, N., Csicsaky, M.J., Jung, M., Molik, B. and Schoeneberg, G. (1989) Health effects during a smog episode in West Germany in 1985. *Environ.Health Perspect.* **79**, 89-99.

Widdicombe, J. (2001) Airway receptors. *Respir.Physiol.* **125**, 3-15.

Widdicombe, J.G. (1992) Mechanism of sulphur dioxide-induced airway obstruction. In: *Sulphur Dioxide, Acid Aerosols and Particulates.* Second Report of the Department of Health Advisory Group on the Medical Aspects of Air Pollution Episodes. London: HMSO; 59-66.

Widdicombe, J. and Lee, L.-Y. (2001) Airway reflexes, autonomic function and cardiovascular responses. *Environ.Health Perspect.* **109(Suppl 4)**, 579-584.

Yeates, D.B. and Mauderly, J.L. (2001) Inhaled environmental/occupational irritants and allergens: mechanisms of cardiovascular and systemic responses. Introduction. *Environ.Health Perspect.* **109(Suppl 4)**, 479-481.

Chapter 4
Discussion, conclusions and recommendations

4.1 Summaries of the evidence presented in Chapters 2 and 3 have been provided already, it is not necessary to reproduce these here. Instead, some broad conclusions are given followed by responses to a number of important questions.

4.2 Cardiovascular disease is an important, probably the most important cause of death and disability in the UK. Amongst the many diseases of the cardiovascular system, Coronary Heart Disease (CHD) – caused by impaired blood supply to the heart muscle, is a leading cause of death and of admission to hospital and many people suffer restrictions to their daily lives due to symptoms caused by the same mechanism.

4.3 There is increasing and persuasive evidence that air pollution is associated with CHD, even at the generally low concentrations found today in the UK. Such concentrations are much lower than those recorded in ambient air years ago. This evidence is reviewed in Chapter 2.

4.4 In considering such associations as have been described, it is always important to ask whether they are likely to be causal in nature. We address this point below.

4.5 Two mechanistic hypotheses have been advanced to explain the associations observed in the epidemiological studies. The clotting hypothesis suggests that small particles reaching the airways and interstitial tissues initiate an inflammatory reaction leading to the production and release of humoral mediators by various cell types including the endothelium. These factors stimulate alterations in the concentrations of other factors that are associated with the clotting process and hence an increased potential to generate a clot is produced. Furthermore, the local and systemic inflammation induced by particle inhalation may result in destabilisation of atherosclerotic plaques, whose development and rupture are driven by inflammatory processes. Atherosclerotic plaque rupture increases the likelihood of thrombogenesis in a coronary blood vessel which may lead to decreased blood flow to the heart muscle resulting in acute myocardial infarction. The infarcted area does not conduct electrical activity well and this may lead to a change in the electrical rhythm of the heart that will contribute to the heart failure or to a fatal arrhythmia.

4.6 The neural hypothesis suggests that inhaled pollutants may act directly, or perhaps as a result of a local inflammatory response, on nerve endings in the walls of the airways. It is suggested that such effects could occur throughout the respiratory system from

the upper airways of the nose, pharynx and larynx to the deeper airways of the lung. Activation of such receptors is suggested to lead to changes in the autonomic control of the heart and thus to changes in the heart's rhythm. Such changes might, if sufficiently marked, lead to changes in the output of the heart or to more serious and possibly fatal arrhythmias.

4.7 It will be noted that both hypotheses are based on the suggestion that inhaled pollutants cause a local inflammatory response. That both hypotheses may be linked in this way is plausible. It is important to realise that the hypotheses are not mutually exclusive: it is possible that both may be playing a part. Evidence in favour of both hypotheses – and some against – has been presented above.

4.8 It is fair to say that neither hypothesis has attracted such evidence as to be now regarded as unquestionably true. It is also fair to say that neither hypothesis has been falsified or disproven. Each remains "in play" and in need of further study. It should also be noted that the possibility of other mechanisms, as yet unrecognised as playing a part, should not be excluded.

4.9 As noted earlier (para 2.107), it is our broad conclusion that many of the associations reported in Chapter 2 are convincing and important (i.e. if causal, they imply a non-trivial public health impact of air pollution).

4.10 It will be noted that the above conclusion is qualified by the phrase "many of the associations". By this it is implied that not all the associations are equally convincing. A number of questions need to be addressed.

Is there an association between daily concentrations of air pollutants and daily health outcomes (acute effects) relating to the cardiovascular system?

4.11 Given that there are many pollutants and many outcomes, it is not easy to provide a simple yet accurate answer to this question. Table 4.1 summarises our views. In the table, a '+' indicates a convincing and statistically significant positive association between an air pollutant and the outcome measure listed in the second column. It should be noted that each "result" recorded in this table is the result of a formal meta-analysis of original studies. We think that the evidence presented in this table is impressive; there is clearly a positive and statistically significant association between many classical air pollutants and acute effects on a wide range of cardiovascular outcomes.

Table 4.1 Summary table based on meta-analysis of time-series studies

The co-efficient shown in the right hand column is the percentage increase in the outcome measure per 10 µg/m³ change* in the concentration of the pollutant shown in the left hand column.

Pollutant (24 hr average)	N	Outcome measure	Assessment	Random effects (95% CI) (% Change per 10 µg/m³)*
PM_{10}	40	CV mortality	+	0.9 (0.7, 1.2)
PM_{10}	6	CV admissions		0.3 (-0.4, 0.9)
PM_{10}	51	Cardiac admissions	+	0.9 (0.7, 1.0)
PM_{10}	19	IHD admissions	+	0.8 (0.6, 1.1)
PM_{10}	7	Dysrhythmias	+	0.8 (0.1, 1.4)
PM_{10}	7	Heart failure	+	1.4 (0.5, 2.4)
PM_{10}	9	Cerebrovascular admissions	+	0.4 (0.0, 0.8)
$PM_{2.5}$	9	CV mortality	+	1.4 (0.7, 2.2)
TSP	21	CV mortality	+	0.5 (0.3, 0.8)
BS	29	CV mortality	+	0.6 (0.4, 0.7)
BS	5	CV admissions	+	1.0 (0.4, 1.5)
BS	6	Cardiac admissions	+	0.8 (0.2, 1.4)
BS	8	IHD admissions	+	1.1 (0.4, 1.7)
NO_2	44	CV mortality	+	1.0 (0.8, 1.3)
NO_2	17	Cardiac admissions	+	1.3 (1.0, 1.7)
NO_2	9	IHD admissions		0.6 (-0.1, 1.4)
NO_2	6	Heart failure admissions	+	1.3 (0.4, 2.3)
NO_2	8	Cerebrovascular admissions	+	0.4 (0.0, 0.8)
O_3 8-hr average	26	CV mortality	+	0.4 (0.3, 0.5)
O_3 8-hr average	8	CV admissions		0.1 (-0.5, 0.4)
O_3 8-hr average	6	IHD admissions		-0.1 (-0.7, 0.4)
SO_2	67	CV mortality	+	0.8 (0.6, 1.0)
SO_2	7	CV admissions	+	0.6 (0.1, 1.2)
SO_2	18	Cardiac admissions	+	2.4 (1.6, 3.3)
SO_2	10	IHD admissions	+	1.2 (0.5, 1.9)
SO_2	5	Heart failure admissions		0.9 (-0.1, 1.8)
SO_2	7	Cerebrovascular admissions		0.3 (-0.5, 1.1)
CO	12	CV mortality	+	1.1 (0.2, 2.1)
CO	8	Cardiac admissions	+	2.5 (1.8, 3.3)
CO	7	IHD admissions	+	2.4 (0.2, 4.6)
CO	5	Cerebrovascular admissions		0.8 (-0.1, 1.8)

PM_{10}: Mass (µg) per m³ of particles generally less than 10 µm aerodynamic diameter
$PM_{2.5}$: Mass (µg) per m³ of particles generally less than 2.5 µm aerodynamic diameter
TSP: Mass (µg) per m³ of all suspended particles
BS: Black Smoke (see glossary)
NO_2: Nitrogen dioxide
O_3: Ozone
SO_2: Sulphur dioxide
CO: Carbon monoxide
N: Number of studies included in meta-analysis

* In the case of CO, % change per 1 mg/m3

Is there an association between long-term exposure to air pollutants and the risk of death from cardiovascular disease?

4.12 The studies discussed in Chapter 2 provide evidence that long-term exposure to fine particles and to the fraction of the fine particulate aerosol represented by sulphate particles in cities in the United States, is associated with an increased risk of death from cardiovascular disease. It is noted that in comparison with the studies discussed above (Table 4.1), this evidence is limited and, in particular, no studies similar to those reported from the United States have been undertaken in the UK. It is also noted that there are inconsistencies in the evidence regarding the effects of long-term exposure to air pollutants. The studies of the natural experiments that occurred in Dublin and Hong Kong reported effects on both respiratory and cardiovascular deaths; no effect on respiratory deaths was found in the US cohort studies. Studies of the effects of occupational exposure to the major air pollutants have not produced unequivocal evidence of effects on the cardiovascular system though they point in that direction. The Seventh Day Adventist cohort study does not support the findings from the major (Six Cities and ACS cohort) US cohort studies. All this leads us to think that there is an association between long-term exposure to some air pollutants and the risk of death from cardiovascular disease. We are less convinced regarding the possible association between long-term exposure to the major gaseous air pollutants and the risks of death from cardiovascular disease. This is discussed in more detail below.

How large are the associations?

4.13 The coefficients from time-series studies shown in table 4.1 and in Chapter 2, generally refer to the effects of a 10 μg/m³ change in pollutant concentrations. Thus, a coefficient of 1.4% for $PM_{2.5}$ and cardiovascular mortality indicates that a 10 μg/m³ increase in pollutant concentration (e.g. $PM_{2.5}$) is associated with a 1.4% increase in the relevant health outcome. Thus, if 70 people die each day from, say, all cardiovascular causes, a 10 μg/m³ increase in $PM_{2.5}$ will increase the daily deaths by about one, to 71. This is a small effect – as are all the effects of the air pollutants considered here when expressed on a per 10 μg/m³ basis. Of course in a major air pollution episode, such as that of the London smog of 1952 where the particle concentration (measured as Black Smoke) rose to in excess of 1mg/m³, the potential impact on health would be expected to be, and was, large. The long-term studies suggest much larger associations. Though the associations are weak (i.e. numerically small) it must be recalled that all the population is exposed to air pollutants and thus the impact, in public health terms, is large.

Are the associations causal?

4.14 Whenever weak (i.e. numerically small) associations are discussed the question of whether they are in fact causal associations is, rightly, raised. In the introductory chapter of this report, Bradford Hill's list of typical characteristics of causal associations was mentioned. Bradford Hill listed strength of association as first in his list: this has been discussed above and it has been noted that the associations between air pollutants discussed in this report and indices of cardiovascular disease are weak in the sense that the coefficients linking, for example a 10 µg/m³ increment in $PM_{2.5}$ and deaths from cardiovascular disease are small. Large associations are more likely to be causal because residual confounding is unlikely to explain the reported effects. We point out with regard to this, the very detailed considerations of individual level confounding factors which is, particularly, a characteristic of the studies of the effects of long-term exposure to air pollutants. We now consider the other features of causal associations from Bradford Hill's list.

Consistency

4.15 Table 4.1 shows that consistency is a prominent feature of time-series studies of the associations between air pollutants and effects on the cardiovascular system. Figure 2.5b shows that nearly all of the studies which looked at the association between mortality from all cardiovascular causes and PM_{10} yielded a positive coefficient and that this varies from a very small percentage to about 4%. More interesting than the general consistency is the variation from location to location. If the list of studies is examined the reader will see that there is no very obvious geographical reason for this variation: for example, not all the studies yielding large coefficients come from America, or from Europe, or from hot countries, or from colder countries. Much work is currently underway to try to examine this variation from study to study. It seems that the variation may be in part explained by "effect modification"; the impact of one pollutant, for example PM_{10}, being affected by other pollutants (eg, nitrogen dioxide) or, perhaps, by temperature. This has been explored in depth in the recent APHEA 2 studies: the original papers should be consulted for details (Sunyer *et al*, 2003; Atkinson *et al*, 2001; Rossi *et al* 2001; Katsouyanni *et al*, 2001). We will not consider the phenomenon of effect modification any further here, but it is stressed that effect modification (i.e. variation in the strength of effect of one risk factor according to the levels of a second risk factor) should not be confused with confounding (i.e. where one risk factor appears to have an effect which in fact is attributable to its correlation with another risk factor which is also correlated with the outcome and which had been omitted from the analysis). Confounding is carefully taken into account in the design of time-series studies. The comparatively small number of cohort studies makes a discussion of consistency less relevant than in the case of the time-series studies.

Specificity

4.16   Specificity is often taken to mean that a putative cause (causal factor) is always associated with one specific effect. For example, some carcinogens are associated with only one sort of tumour. In the air pollution field it has been accepted that pollutants such as particles or ozone are associated with a range of effects including some on the respiratory system and some on the cardiovascular system. This has been seen by some as evidence of a lack of specificity and thus as a reason to doubt causality. But it may well be that air pollutants act by a limited range of mechanisms but that these can lead to a range of clinical effects. Consider, for example, an effect on blood clotting. This could well lead to a range of effects including myocardial infarction, heart failure, stroke and angina. Specificity as applied to mechanism seems to us important. It is not yet possible to be sure about mechanistic specificity, but work on the two leading mechanistic hypotheses, effects on clotting and effects on neural regulation of the heart, is encouraging.

Temporal plausibility (temporality)

4.17   This is widely regarded as a necessary feature of causal associations: the putative cause must precede the observed effect. The temporal plausibility of the results discussed in this report is widely accepted and is not controversial. Time-series studies generally relate health effects to daily variations in pollution in the immediately preceding days. Some however, relate daily health effects to same-day air pollution. Cohort studies of long-term exposure also use pollution measures that are contemporaneous with the mortality changes being studied. Strictly, these latter studies do not show that the health effect is preceded by exposure to pollution. This is generally seen as unimportant, because it is not seriously suggested that changes in health are a cause of air pollution changes. In conclusion, there is a strong body of evidence showing temporal plausibility.

Biological gradient (the concentration/exposure-response relationship)

4.18   Biological gradient means that as the putative cause increases in magnitude the observed outcome also increases (or, at least, does not decrease) in frequency and/or severity. Overall, among the studies considered in detail in this report (the time-series studies which have been included in the meta-analyses) and the cohort studies, modelling the responses has produced clear evidence of biological gradients of effect for those combinations of pollutant and endpoint where associations have been shown convincingly. In these studies, models which presuppose a biological gradient are generally found to fit the data well. More detailed analyses use non-parametric methods which do not impose any prior shape on the relationship between pollution and health. As would be expected, these have yielded relationships that are more variable in shape (e.g. some suggest thresholds of effect; others do not) but overall also

strongly support a biological gradient. Interestingly, the non-parametric models tend towards straight line relationships as the concentrations of pollutants rise. We have not examined these various models in detail.

Biological plausibility

4.19 Bradford Hill argued that not too much weight should be placed on this feature in reaching a view on the likelihood of causality. This was in opposition to a view, still sometimes encountered, that a relationship should not be accepted as causal unless it is biologically plausible. He noted that biological plausibility depended on the state of biological knowledge at the time when the view was taken: what may seem implausible today might well seem entirely plausible a few years hence. The appearance of plausible hypotheses increases our confidence in the biological plausibility of the associations discussed in this report. We stress, however, that plausible hypotheses alone do not represent firm evidence of biological mechanisms. Much more important are the results of studies designed to test these hypotheses: such studies are discussed in detail in Chapters 3 and 4. Some of the results obtained support the hypotheses, but others do not. In interpreting the results of studies in animal models we note the need to consider the effects of species differences. This is particularly important when considering reflexes affecting the cardiovascular system: important species differences have long been known to occur in this area of physiology. We conclude that:

(i) the appearance of plausible hypotheses strengthens our confidence in causality;

(ii) experimental work has provided some support for the hypotheses;

(iii) experimental work has not led to falsification and abandoning of either the inflammatory/clotting or the neural reflex hypothesis.

Coherence

4.20 Coherence means that a series of effects on different health outcomes fit together in a logically satisfying way. For example, if an increase in the concentration of some pollutant is associated with an increase in cardiac deaths it *should* also be associated with an increase in admissions to hospital for treatment of cardiac diseases and with an increase in reports, perhaps to General Practitioners, of complaints of symptoms associated with heart disease. A "coherent picture" of effects should emerge. This was stressed some years ago by Bates (1992). If the tables shown in Chapter 2 are examined it will be seen that there is distinct and impressive coherence across the studies of different health outcomes. But, in the case of ozone, cardiovascular deaths are associated with this pollutant but hospital admissions for treatment of cardiovascular diseases are not. This weakens our confidence in the causality of the association between ozone and cardiovascular deaths though we accept that it is

possible that different mechanisms may be involved in the process leading to cardiovascular deaths and cardiovascular admissions.

Support from experiment

4.21 "Experiment" is not taken, here, to mean laboratory experiments (such as those described above), but so-called natural experiments that feature some reduction or increase in pollutants that is associated with a change in health that fits with the causal explanation of the association. In a way, all time-series studies are studies of natural experiments: pollutant concentrations vary from day-to-day and this variation provides the data upon which the studies are based. Less often, some significant long-term change in pollution levels occurs and allows a special opportunity for study of its effects. The ban on the use of coal for domestic heating in Dublin (Clancy *et al*, 2002) provides a classic example of this type of natural experiment, as does the Hong Kong study (Hedley *et al*, 2002). The effect on deaths from cardiovascular diseases was marked and obvious. This greatly strengthens our confidence in the assertion that the association between particle concentrations and/or sulphur dioxide and deaths from cardiovascular diseases is causal.

Support from analogy

4.22 Though there are many occupational settings in which people are exposed to the same substances that occur in polluted ambient air, the age and health status of those exposed differ from those of the general population as do the patterns of exposure. This limits the use of data from such studies in assessing the cardiovascular effects of ambient pollutants although at higher exposures effects can be seen in certain workforces. Exposure to environmental tobacco smoke (ETS), however, provides an important analogy to exposure to ambient air pollution, at least as far as exposure to particles is concerned. This is discussed in Appendix 1. It was found that long-term exposure to ETS had effects on the cardiovascular system not very different from those associated with long-term exposure to ambient air pollutants. This is by no means proof that the associations with exposure to air pollutants are causal – it could be that different mechanisms are in play – but it does strengthen our confidence in the likely causality of the air pollution associations. The discussion of the effects of ETS in Appendix 1 is intentionally limited to effects on the cardiovascular system but we note that a range of other effects have also been reported. It is very suggestive that effects on the fetus, on infants, on children and on adults, overlap so largely with effects reported in studies of air pollution. That such an overlap could occur by chance is possible, but we think this unlikely. It is much more likely that two sources of exposure to a mixture of pollutants with many components in common are having similar effects on health.

4.23 Consideration of Bradford Hill's list of features of causal associations has persuaded us that at least some of the associations between concentrations of ambient air pollutants and effects on the cardiovascular system are likely to be causal. On balance, no more plausible explanation than that suggesting air pollution has an effect, has appeared. We point out that our confidence in this statement is greater with regard to the effects of short term changes in concentrations than with regard to those relating to long-term exposure. The relative weights of evidence at present, lead us to this cautious conclusion.

Which pollutants are most important?

4.24 Dissecting out the effects of individual air pollutants in the ambient mixture is extremely difficult. Several pollutants, for example fine particles (monitored as $PM_{2.5}$), nitrogen dioxide and carbon monoxide are all produced in urban areas largely by motor vehicles and thus their concentrations are closely correlated. In a study that relates only one component of this mixture to health outcomes it is not possible to be sure whether the pollutant monitored is acting *per se* or, rather, as an indicator or surrogate for another component of the mixture. Such complexity can be explored by use of two-pollutant and multi-pollutant models but such techniques have limitations. In the case of two perfectly correlated pollutants, such methods cannot provide any information on which pollutant is associated with the outcome. Where the two pollutants are highly correlated, ability to discriminate between the two is limited. Another approach to distinguishing effects of individual pollutants is by comparing the slopes of pollution variables entered individually (single-pollutant models) across cities (Schwartz *et al*, 2003). For example, if the CVD mortality slope for nitrogen dioxide was higher in cities with high levels of $PM_{2.5}$, and in all cities correlation of NO_2 with $PM_{2.5}$ was equally high, then this would suggest that $PM_{2.5}$ was contributing to the health impact independently of NO_2. Other sources of evidence, for example toxicological studies, are needed to achieve differentiation of the roles of the active and inactive components. We realise that there are many important questions that we cannot answer reliably; there are some which we cannot answer at all. We have, however, reached some conclusions.

(i) Particles are likely to be playing an important part in causing the health outcomes described in this report. The consistency of results and the coherence between associations with various health outcomes revealed by the time series studies, the cohort studies, the availability of plausible hypotheses, the availability of some experimental support for these hypotheses, the evidence from the natural experiments in Dublin and Hong Kong and the analogy with the effects of exposure to ETS, all lead us to think that the associations between concentrations of particles and effects on the cardiovascular system are causal.

(ii)   We find it much less easy to know which metric of the ambient aerosol (PM_{10}, $PM_{2.5}$, BS, sulphate and nitrate) most closely represents those particles having an effect. The associations between nitrogen dioxide and/or carbon monoxide revealed by the time-series studies lead us to think that primary, vehicle-generated, particles might be playing an important part and thus $PM_{2.5}$ has attractions as the surrogate best representing the active components of the ambient aerosol. The studies of the associations between long-term exposure to air pollutants and deaths from cardiovascular disease strongly suggest that fine particles ($PM_{2.5}$) rather than the more inclusive measure PM_{10}, represent the active fraction of the ambient aerosol. The possibility that sulphate particles (a component of the fine particle fraction of the ambient aerosol) may be important is acknowledged. In addition, the plausibility of the mechanistic hypotheses and the results from animal experiments lead us to think that particles capable of penetrating deep into the lung and, perhaps, of crossing the air-blood barrier, are more likely to play an important rôle than larger particles.

(iii)   We note that much less laboratory work on the effects of low concentrations of the vehicle-generated gaseous pollutants nitrogen dioxide, nitric oxide and carbon monoxide has been done than on those of particles. This is summarised in Table 4.2 which summarises the evidence on different pollutants across different research areas. It is also true that hypotheses explaining the possible effects of low concentrations of either oxides of nitrogen or carbon monoxide have not been put forward. As discussed in Chapter 3, theories regarding oxides of nitrogen could be developed, though whether nitrogen dioxide at low concentrations should be seen as a toxicologically active pollutant or as a surrogate for fine, perhaps ultrafine particles, remains uncertain. Based on the above, our tentative conclusion is that neither nitrogen oxides nor carbon monoxide, at ambient concentrations, are as likely to be as causally linked with cardiovascular disease as are fine particles.

(iv)   We are unable to come to firm conclusions regarding the importance of the associations between ozone and cardiovascular disease. This should *not* be taken to mean that we are convinced that the associations are *not* causal but, rather, that we are *not* convinced that they *are* causal. Much of our difficulty stems from a lack of evidence and we are anxious not to confuse a lack of evidence for a causal association with evidence of a lack of a causal association. The cohort studies were not designed to examine the long-term effects of ozone: for example, the difference in long-term ozone concentration between the cities in the Six Cities study was small. But other work, not discussed in this report, has shown that long-term exposure to raised concentrations of ozone can affect development of the lung in children. It is simply too early to be sure that such exposures have no effect on the cardiovascular system.

Table 4.2 Relative strength of evidence across different pollutants and different research areas

Pollutant	Short term associations (mortality)	Short term associations (admissions)	Long-term associations (mortality)	Mechanistic evidence (clotting/inflammation)[a]		Mechanistic evidence (reduced HRV)	
				Human	Animal	Human	Animal
PM_{10}	✓✓✓✓	✓✓✓✓	✓✓[c]	✓✓	✓✓[i]	✓✓	(✓)[kl]
$PM_{2.5}$	✓✓✓	✓✓[b]	✓✓	✓✓	✓✓[i]	✓✓	(✓)[kl]
sulphate	??	??	✓✓	–	–	–	–
BS	✓✓✓	✓✓✓	✓	–[f]	✓✓[f]	–	–
NO_2	✓✓✓	✓✓✓	X(✓)[d]	(✓)	–	(✓)	(✓)[l]
O_3	✓✓✓	XXX	X(✓)[e]	?[g]	–	✓	(✓)[l]
SO_2	✓✓✓	✓✓✓	✓✓	(✓)[h]	–	✓(✓)[j]	–
CO	✓✓	✓✓✓	X	–	–	(✓)	–

✓✓✓✓ Many studies, predominantly positive associations
✓✓✓ Reasonable no. of studies, predominantly positive associations
✓✓ Few studies, predominantly positive associations or mechanistic evidence
✓ One or very few studies, positive associations or mechanistic evidence
(✓) One or very few studies, mixed or uncertain results (see notes)
✓(✓) Few studies, some positive associations limited to certain circumstances (see notes)
XXX Reasonable number of studies, predominantly negative associations
X Single study, negative association
X(✓) Few studies, mixed results
– Not extensively studied as far as we are aware so not reviewed in detail
?? Few studies, inconclusive, some studies no confidence intervals
? Single study, no significant association

a Refers to systemic inflammation
b Few studies in each admissions category
c Weaker association than for $PM_{2.5}$
d Positive association when correlated with particles
e Positive association in summer and in regional adjustment model
f Studies with diesel exhaust particles
g Non-significant positive association
h Not maintained after control for particles
i Some studies at high concentrations or with unusual particles
j One study found reduced HRV in asthmatics only
k Some animal studies found conflicting results
l Reduces heart rate in animals (unexpected direction but vagus involved)

NB There are no columns for chamber studies or short-term associations with cardiovascular symptoms or for long term associations with cardiovascular morbidity endpoints due to lack of data. Only two possible mechanisms are shown – there is other mechanistic evidence e.g. human brachial artery vasoconstriction (Ozone with CAPs), increased lipid hydroperoxidation, decreased noradrenaline turnover and increased atrial natriuretic factor prohormone in the heart (all ozone), exercise induced ischaemia (CO, $PM_{2.5}$), speculative mechanism of rebound vasoconstriction (NO), translocation of particles to blood and nerves, particles and general oxidative stress, particles and ST segment depression.

The fact that pollutants may be closely correlated with each other needs to be borne in mind when interpreting this table. For example, BS, NO_2 and CO are all good markers for traffic pollution and ozone (which is higher in summer) may be negatively correlated with PM_{10} (which is often higher in winter).

(v)   As regards sulphur dioxide, evidence from both short term and long-term studies suggests an association with cardiovascular disease. The consistent findings of the long-term studies is especially difficult to dismiss (Hedley *et al*, 2002). However, no persuasive hypothesis to explain such associations has been put forward and the concentrations of sulphur dioxide reported in the long-term studies are well below those shown to be capable of causing even minor effects on the respiratory system in volunteers (Department of Health, 1992). It may be that sulphur dioxide is acting as a surrogate for sulphate particles though this leads us to the equally difficult question of how sulphate particles, which are likely to be soluble and thus not to cross the lung's air-blood barrier intact, could be having an effect. We regard the question of the possible role of sulphur dioxide as remaining open.

Are there particular susceptible groups?

4.25   We conclude from the evidence presented in this report that those with coronary artery disease are at greater risk of being affected by day-to-day variations in concentrations of air pollutants, especially particles, than individuals without such disease. We recognise that coronary artery disease is common and often not detected prior to an acute episode of illness, for example, a heart attack. This makes it difficult to estimate the size of the population at significantly increased risk and we have not attempted this. It is, however, known that coronary artery disease is more common in the elderly than in the young and thus we conclude that the elderly are at greater absolute/relative risk of an acute episode of cardiovascular disease as a result of exposure to air pollutants. Further and more detailed analyses of the results of time-series studies in specific age groups will be needed to take this conclusion further. However, in active cigarette smokers a strong association between smoking and myocardial infarction has been found in younger subjects: indeed the association is most demonstrable in younger individuals rather than in the elderly. If a parallel between the effects of exposure to ambient particles and active cigarette smoking is true, it would be unwise to identify the elderly rather than the young as an especially at risk group. As regards the effects of long-term exposure to air pollutants we cannot deduce from the data that any particular age group is at specially increased risk. Indeed the HEI re-analysis of the cohort studies did not suggest that the effects of exposure were age related and this is seen as implying that lengthy exposure is not needed to produce the increased risk.

What is the impact on public health?

4.26   We appreciate that it would be helpful to estimate the impact of air pollutants on cardiovascular disease in the UK in terms of the likely extent of advancement of death or loss of life expectancy. We think that these estimates can be made but we have not

made them here. The Committee will soon be revising its earlier reports on the size of the effects of air pollutants on health and during this work quantitative estimates of the effects on cardiovascular disease will, as far as possible, be made. An estimate of the impacts of long-term exposure to fine particles ($PM_{2.5}$) was included in our previous report (Department of Health, 2001) and an extract from this is reproduced below:

'18 µg/m³ $PM_{2.5}$ could be responsible for an average loss of life expectancy from birth of about 2-20 months. This compares with an estimate of around 7 years if all the population were smokers (using the relative risk of 2.07 for smokers from the HEI reanalysis and the same methodology). Thus, as would be expected, the impact is considerably smaller than for active smoking.'

Annual average concentrations of $PM_{2.5}$ are of the order of 7-10 µg/m³ in the UK generally and 18 µg/m³ in London today. Our current thinking is that the great majority of the effect described in the above extract is attributable to effects on the cardiovascular system.

What advice should be given to patients?

4.27 Doctors may wish to provide patients with advice on the effects of air pollutants on cardiovascular disease. Patients may ask what they can do to avoid such effects. These questions have been considered before and are easier to answer with regard to acute effects on the respiratory system than with regard to effects on the cardiovascular system. We conclude that in giving advice the following points might be made.

(i) Air pollution plays a part in causing and worsening cardiovascular disease.

(ii) It is likely that compared with factors affecting individuals such as active smoking, diet and lack of exercise, a more minor rôle is played by air pollution though this may well be similar to that played by passive smoking.

(iii) Patients should not avoid sensible exercise on the grounds that this will reduce their exposure to air pollutants: the value of exercise in preventing heart disease is likely to be more important.

(iv) Patients with cardiovascular disease who wish to adopt a precautionary approach could consider avoiding locations characterised by high concentrations of particles. These include cities with high traffic densities, especially in countries where pollution generated by industry adds to that generated by traffic.

(v) Patients should *not* adjust any therapies they are taking for the treatment of cardiovascular diseases on the basis that they may need more medicine on days when concentrations of air pollutants are raised.

What further research is needed?

4.28   It should be obvious that though we think that there is a causal association between exposure to air pollutants and both the causation and worsening of cardiovascular disease, a great deal remains to be learnt about these effects. We therefore make the following research recommendations.

Epidemiological studies

4.29   Further time-series studies designed to look at associations between different indices of the ambient aerosol and effects on the cardiovascular system are needed. We draw attention to the need to include indices of fine and ultrafine particles and suggest that $PM_{2.5}$, $PM_{1.0}$ and number concentration should be studied. Collaborative studies between groups working in different countries to allow examination of the comparative effects of aerosols of differing composition are recommended.

4.30   As has already been mentioned, heterogeneity between results obtained in differing geographical locations should be pursued. It is strongly recommended that studies designed to separate the effects of different components of traffic-generated pollution should be undertaken. These could include studies in areas where there are significant contributions from sources other than vehicles.

4.31   Confusion regarding the roles of nitrogen oxides and particles remains and this should be resolved. Work on multi-pollutant models may be a useful approach to this problem and we recommend that such work should be undertaken: we note with some concern the preponderance of single-pollutant models in the work we have reviewed. Work using NOx as a better marker for traffic-generated pollutants than NO_2 is recommended.

4.32   There is a need for research which considers the different components of particles with relation to toxicity.

4.33   There is a need for research using better exposure assessment, particularly for work examining associations between personal exposure and acute effects on health.

4.34   In addition to time-series studies, further work on the effects of long-term exposure to air pollutants with respect to possible effects on the cardiovascular system is needed in the UK. It is appreciated that such studies are inevitably costly and do not yield rapid results but the importance of such work cannot be over-emphasised. A European study would be a very powerful study as it would accommodate variations in air pollutant exposures both qualitatively and quantitatively. Work looking at historical

data on air pollution and the effect of smoke control policies on heart disease rates is also needed.

4.35   Epidemiological studies designed to test current and new mechanistic hypotheses are needed. We have noted inconsistencies in the findings of such studies as have been undertaken and see this as a strong reason for further work. We note that the number of epidemiological studies designed to relate measures of ultrafine particles (e.g. number and surface area concentrations) to physiological variables recorded at an individual level remains remarkably small. Liaison with research workers in the general fields of cardiovascular physiology and medicine is recommended: this is likely to be especially valuable in understanding the importance of changes in such physiological variables as heart rate variability.

4.36   Additionally, work on potentially susceptible subgroups in the population is needed. A focus on gene-environmental interactions would be helpful here.

4.37   Perhaps, most importantly, it needs to be shown whether or not short term fluctuations in 'inflammation' and in autonomic control in humans with Coronary Artery Disease (CAD) can result in adverse coronary events/sudden death/arrhythmia. A large prospective cohort study examining markers of inflammation and of autonomic control and possibly arterial stiffness/endothelial function on a regular basis, perhaps even every week, is needed. Over a longer period of time this would tell us:

a.   whether or not the variation in these markers is associated with rises and falls in pollutant levels or whether other factors 'drown' this effect;

b.   whether or not acute events – death/MI – are preceded by changes in the markers and with what time lag.

It is appreciated that this would be a large and expensive study.

Laboratory based studies

4.38   Work is needed both in animal models and in human volunteer subjects. Much work is underway in these fields in the United States and we recommend that a detailed appraisal of current research programmes be undertaken before launching studies in the UK. It is suggested that the Department of Health might commission such an appraisal. We note that more work has been done on particles than on gaseous pollutants with regard to the mechanistic hypotheses discussed in this report. This we see as in need of correction and work on nitrogen dioxide and on nitric oxide, a known vasoactive compound, is recommended. Work on the possible effects of

sulphur dioxide and carbon monoxide is also needed in view of the associations reported in epidemiological studies.

4.39 Further whole animal work examining the nature of any inflammatory response to inhaled pollutants is needed. This should be in two parts. The first, a detailed examination of the response to 'whole' pollutants such as diesel exhaust and CAPs at a range of concentrations. The nature of any pulmonary and systemic inflammatory response needs to be described more precisely in terms of the cytokine profile, time of onset and duration, etc. With this information one could re-look at the observational studies and concentrate on appropriate lag times. The second, an examination of the effects of administering pollutants via non-pulmonary routes, would give insight into whether the pulmonary inflammatory response is the initiator of a systemic reaction or whether the lungs are simply the portal of entry and the response is initiated in the circulation. It would be helpful if mechanistic studies used a range of pollutants within the same experimental system to aid consideration of the relative plausibility of the associations found for the different pollutants in the epidemiological studies.

4.40 Further work designed to discover which components are active in the pollutant mix is needed. This is easier for gases than for particles, although again, the nature and duration of any response needs to be detailed. For particles, the responses to components such as metals, salts, even bacterial cell wall components in a range of particle sizes/solubilities needs to be defined.

4.41 More whole animal work is required on the autonomic response to inhaled pollutants. Work to identify whether this is receptor mediated and if so, to define the identity and location of the receptors is needed.

4.42 Further studies of the development of atherosclerotic plaques and the effect upon them of oxidative stress is needed.

4.43 As far as possible this work requires duplication in human subjects. The animal work should point the way so that needless experimentation in humans is avoided. Similar information is needed about the inflammatory/autonomic responses and also whether or not the response to pollutants varies with the presence of atherosclerosis and/or chronic lung disease.

References

Atkinson, R.W., Anderson, H.R., Sunyer, J., Ayres, J., Baccini, M., Vonk, J.M., Boumghar, A., Forastiere, F., Forsberg, B., Touloumi, G., Schwartz, J. and Katsouyanni, K. (2001) Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air Pollution and Health: a European Approach. *Am.J.Respir.Crit.Care Med.* **164(10 Pt 1)**,1860-1866.

Bates, D.V. (1992) Health indices of the adverse effects of air pollution: the question of coherence. *Environ.Res.* **59**, 336-349.

Clancy, L., Goodman, P., Sinclair, H. and Dockery, D.W. (2002) Effect of air pollution control on death rates in Dublin, Ireland: an intervention study. *Lancet* **360**,1210-1214.

Department of Health, (1992) Advisory Group on the Medical Aspects of Air Pollution Episodes. *Sulphur Dioxide*. London: HMSO.

Department of Health. (2001) Committee on the Medical Effects of Air Pollutants. *Statement and report on long-term effects of particles on mortality*. London: The Stationery Office.
http://www.advisorybodies.doh.gov.uk/comeap/statementsreports/longtermeffects.pdf

Hedley, A.J., Wong, C.-M., Thach, T.Q., Ma, S., Lam, T.-H. and Anderson, H.R. (2002) Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. *Lancet* **360**, 1646-1652.

Katsouyanni, K., Touloumi, G., Samoli, E., Gryparis, A., Le Tertre, A., Monopolis, Y., Rossi, G., Zmirou, D., Ballester, F., Boumghar, A., Anderson, H.R., Wojtyniak, B., Paldy, A., Braunstein, R., Pekkanen, J., Schindler, C. and Schwartz, J. (2001) Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. *Epidemiology* **12**, 521-531.

Rossi, G., Sunyer, J., Bacharova, L., Anderson, H.R. and Katsouyanni, K. (2001) Investigating regional differences in short-term effects of air pollution on daily mortality in the APHEA project: a sensitivity analysis for controlling long-term trends and seasonality. *Environ.Health Perspect.* **109**, 349-353.

Schwartz, J., Zanobetti, A. and Bateson, T. (2003) Morbidity and mortality among elderly residents of cities with daily PM measurements. In: *Revised Analyses of the National Morbidity, Mortality and Air Pollution Study, Part II*. Boston, MA: Health Effects Institute; pp25-58.

Sunyer, J., Atkinson, R., Ballester, F., Le Tertre, A., Ayres, J.G., Forastiere, F., Forsberg, B., Vonk, J.M., Bisanti, L., Anderson, H.R., Schwartz, J. and Katsouyanni, K. (2003) Respiratory effects of sulphur dioxide: a hierarchical multicity analysis in the APHEA 2 study. *Occup.Environ Med.* **60**, e2.

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