The effects of ambient temperature and the role of air pollution on the risk of myocardial infarction

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Declaration of authorship

I, Krishnan Bhaskaran, declare that this thesis is my own work, and that I have acknowledged all results and quotations from the published or unpublished work of other people.

Signed Date

_____ _____

Krishnan Bhaskaran

Use of published work

Three papers have been published based on work undertaken for this thesis (Appendix II). All research for these papers was carried out as part of the PhD and took place during the period of registration of the PhD. The papers were based on drafts of the PhD chapters which now appear as Chapters 2, 3 and 6 in this thesis and include some passages and tables/figures from these chapters. For all three papers, Krishnan Bhaskaran (KB) was the lead and corresponding author, carried out the reviews/analysis and prepared all drafts of the paper. The co-authors' contributions to the manuscripts were restricted to providing comments on the drafts prepared by KB.

Abstract

Background: High and low ambient temperature, and increased pollution levels have been associated with increases in both overall and cardiovascular mortality, but systematic reviews suggested that associations with myocardial infarction (MI) specifically are unclear.

Methods: Using data from the Myocardial Ischaemia National Audit Project (MINAP) registry, which aims to record all hospital admissions for acute coronary events in England and Wales, daily numbers of MI admissions in 15 large conurbations in England and Wales during 2003-6 were related first to daily mean temperature, and then daily mean levels of five pollutants (particulate matter with diameter < 10μm or PM_{10}, ozone, CO, NO_2 and SO_2). Poisson-based regression models were used, allowing for delayed effects and adjusted for a number of potential time-varying confounding factors. In a subsequent analysis the effects of each pollutant were investigated at an hourly temporal resolution, using a case crossover study design.

Results: 84010 MI events were recorded in the 15 conurbations during the study period. Ambient temperature was inversely associated with MI risk in a broadly linear relationship, with each 1°C decrease in temperature associated with a 2% (95% CI 1.1 to 2.9) increase in MI risk over the current and subsequent 28 days. Elderly individuals up to age 85 years and those with previous coronary heart disease appeared to be most vulnerable to the effect. No detrimental effect of higher temperatures was observed. There was little evidence that daily pollutant levels were associated with MI risk. In hourly analyses, 10μg/m^3 increases in PM_{10} and NO_2 levels were respectively associated with 1.0% (0.0 to 2.0) and 2.0% (0.8 to 3.3) increases in MI risk 1-6 hours later, but this was followed by a period of reduced risk at longer lags.

Conclusions: Lower temperatures appear to be associated with an increased risk of MI; adaptive measures and public health interventions may have a role in mitigating this effect. A transiently increased risk of MI a few hours after exposure to higher levels of PM_{10} and NO_2 appears to be followed by risk reductions at longer lags and may reflect events being triggered a few hours earlier than they would have otherwise occurred.

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List of abbreviations

ACS	acute coronary syndrome
AO	arctic oscillation
CABG	coronary artery bypass graft
CHD	coronary heart disease
CVD	cardiovascular disease
CK	creatine kinase
df	degrees of freedom
ECG	electrocardiograph
LL	log-likelihood
MI	Myocardial infarction
MINAP	Myocardial Ischaemia National Audit Project
OR	odds ratio
PCI	percutaneous coronary intervention
PM	particulate matter
ppb	parts per billion
ppm	parts per million
RH	relative humidity
RR	relative risk
STEMI	ST elevation myocardial infarction

1 Background

1.1 Introduction

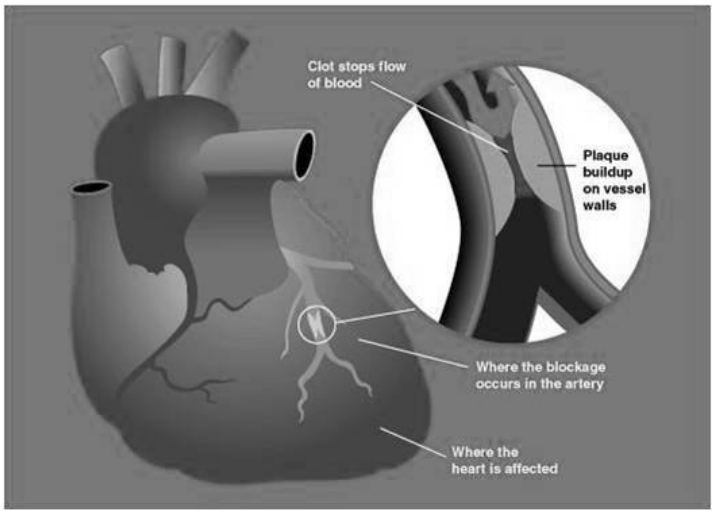
In this chapter, the definition and epidemiology of myocardial infarction are outlined, the environmental exposures relevant to this thesis are introduced, and the evidence for associations of these environmental exposures with broad health outcomes including overall and cardiovascular mortality is briefly reviewed. Finally, the aims and objectives of the thesis are described.

1.2 Myocardial infarction

1.2.1 Definition, diagnosis, and treatment

The term myocardial infarction (MI), commonly known as heart attack, refers to evidence of myocardial necrosis in the presence of myocardial ischaemia. In the majority of cases, this is caused by coronary artery occlusion, due to the rupture of built-up plaques from the vessel wall triggering platelet aggregation and clot formation (*Figure 1.1*).[1] Symptoms of MI typically include chest pain and shortness of breath, though other symptoms can occur, and a proportion of MIs have no symptoms at all.

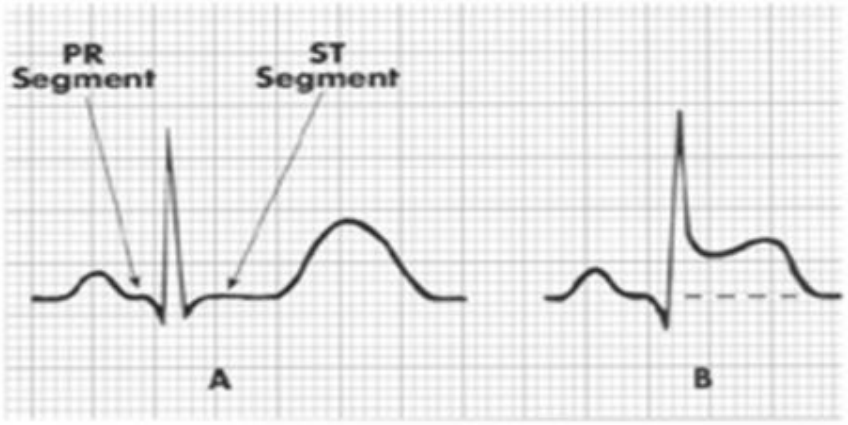
Figure 1.1: Illustration of myocardial infarction [reproduced from US Federal Government public domain illustration[2]]



In patients with suspected MI, standard investigations include examination of a 12-lead electrocardiograph (ECG) trace, and measurement of the levels of

biomarkers indicative of tissue death (specifically troponin and/or creatine kinase-MB (CK-MB)). Firm diagnosis in a clinical setting is usually based on a characteristic rise and fall in levels of one or both of these biomarkers, along with typical ECG changes, typical symptoms, or imaging evidence showing loss of myocardium.[3] MIs can be classified as ST-elevation MI (STEMI) and non-STEMI. ST-elevation refers to a characteristic of the ECG trace (*Figure 1.2*). In clinical terms, STEMI usually implies complete and persistent occlusion of the coronary artery with progressive death of heart tissue; non-STEMI implies incomplete or temporary occlusion, though some evidence of myocardial necrosis (e.g. raised biomarkers such as troponin or CK-MB) must still be present, to distinguish the event from an episode of unstable angina.

Figure 1.2: ECG trace without (A) and with (B) ST-elevation [reproduced from University of New Mexico EKG course learning resources[4]]



Various treatment options exist for MI. Rapid reperfusion using a thrombolytic drug delivered intravenously is an established standard treatment of choice for acute STEMI,[5] while non-STEMIs may be treated with anticoagulation and antiplatelet agents in the first instance.[1] Treatment of MI may also include coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI), also known as angioplasty, in which the obstructed artery is mechanically widened using a balloon and/or stents. Long-term drug therapy and lifestyle changes may be indicated for secondary prevention.

1.2.2 Epidemiology and risk factors

MI is a manifestation of ischaemic heart disease (IHD), which is the leading cause of mortality in both developed and developing countries, accounting for 7.2 million deaths worldwide each year according to the World Health Organization's 2004 Global Burden of Disease data.[6] In the UK an estimated 146000 myocardial infarctions occur annually, with 60% of diagnoses among men and incidence increasing with age.[7]

The INTERHEART study, which included over 15000 MI cases and a similar number of controls, examined potentially modifiable risk factors for MI in 52 countries and estimated that, within age groups, smoking, alcohol, physical activity, obesity, fruit and vegetable intake, diabetes, hypertension and abnormal lipids together accounted for 90% and 94% of the population attributable risk of MI in men and women respectively, in all regions.[8]

1.3 Health effects of environmental exposures

A number of environmental exposures have been linked with human health outcomes, and relevant to this thesis are the effects of ambient temperature, and a range of common pollutant exposures. The nature of these exposures and their effects on broad health outcomes are outlined below.

1.3.1 Ambient temperature

Ambient temperature in the context of this thesis refers to the air temperature to which individuals are exposed in their daily lives, and in practice most large-scale research studies take outdoor temperature, as measured by weather monitoring stations, as the best available proxy for this.

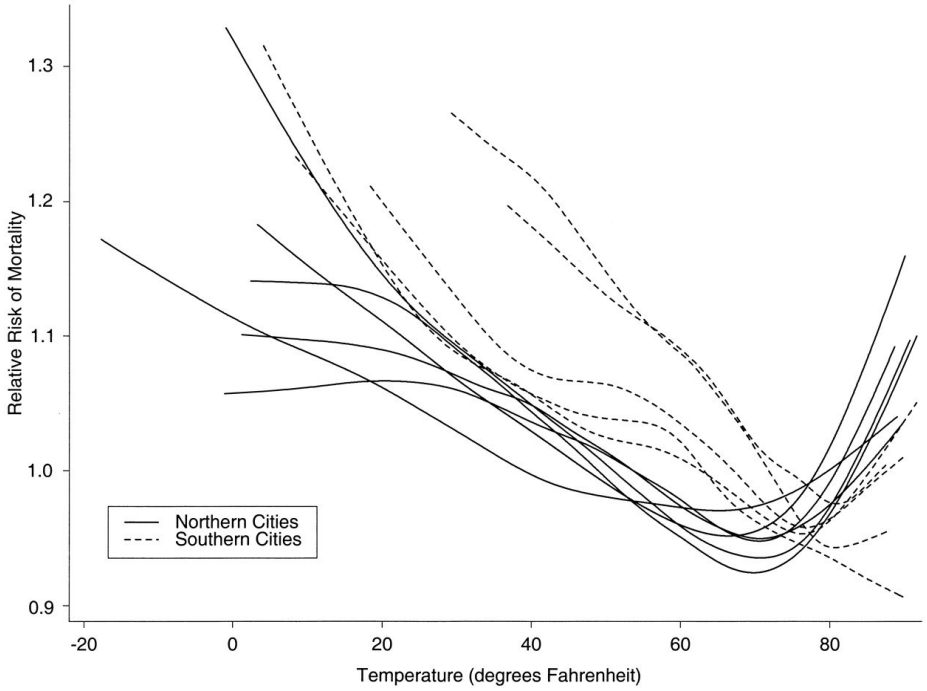
Ambient outdoor temperature has been shown in a number of studies to affect overall mortality rates in the short-term. A noteworthy study conducted in 11 US cities demonstrated a U-shaped relationship between temperature and all-cause mortality: mortality was observed to decrease as temperatures increased from the coldest days up to a certain threshold temperature, above which mortality increased with temperature (*Figure 1.3*).[9-10]

Other studies in Europe[11-12], the US[13-14], and a number of lower and middle-income countries[15] have similarly demonstrated increases in mortality at higher

and lower temperatures, and specific periods of extreme cold or heat, so-called "cold snaps" and "heat waves", have been associated with mortality peaks.[16] Ambient temperature may have a delayed, or "lagged", effect on mortality: while heat is commonly associated with immediate (same day or next day) increases in mortality, cold effects have been found to operate up to several weeks after the temperature reduction.[17]

Temperature-mortality relationships are unlikely to be explained purely by direct hypothermia/hyperthermia deaths. Indeed, as well as overall mortality, ambient outdoor temperature has also been linked to mortality from a number of specific causes, including cardiovascular diseases (CVDs); again U-shaped relationships have been described,[18] and studies have shown increases in CVD mortality associated both with cold[19-22] and hot[23-24] outdoor temperatures.

Figure 1.3: Relative risk of mortality by temperature in 11 US Cities [reproduced from Curriero et al[9]]



Note: non-parametric smoothing functions (splines) were used to summarise non-linear associations between temperature and mortality

Mortality studies suggest that there may be increased vulnerability to the effects of temperature among the elderly,[19, 25-27] US studies have also shown an increased vulnerability among individual living in lower socioeconomic conditions,[9, 28] though this may be partly explained by a greater prevalence of

air conditioning among those with higher incomes: in Europe, where home air conditioning is less common, there is less evidence of a socioeconomic gradient.[29] Existing medical problems including diabetes and chronic obstructive pulmonary disorder also appear to increase the likelihood of temperature-associated death.[13] In the US, the most pronounced cold effects were observed in southern cities, and the most pronounced heat effects in and northern cities (*Figure 1.3*),[9] suggesting that the temperature-mortality association may be affected by latitude. Correspondingly, in Europe, larger effects of cold have been observed in warmer southern regions.[12, 19] It has been suggested that populations familiar with local hot or cold extremes may have established adaptation measures, such as using appropriate clothing, installing heating/air conditioning, and reducing outdoor activity, and that this may at least partly explain the apparent latitude effect.[12]

The effects of temperature on morbidity and mortality from MI specifically have not been investigated as commonly as the effects on broader outcomes; the existing evidence on this specific question is examined in detail in Chapter 2.

1.3.2 Air pollution

1.3.2.1 Overview of specific pollutants and their sources

The term air pollution covers a wide range of exposures with potential health consequences, some of which are specific to certain locations (e.g. around industrial sources). This thesis concentrates on a smaller subset of pollutants which are common to most populated areas, are routinely measured, and have relatively well-established associations with various health outcomes; these are particulate matter (PM), ozone, carbon monoxide (CO), oxides of nitrogen including nitrogen dioxide (NO_2), and sulphur dioxide (SO_2).[30-31]

PM

PM consists of solid and liquid particles suspended in air. The composition is highly variable and depends on the source; carbon, nitrates, sulphates, organic compounds, biological material and various metals are commonly found in PM, though many other chemicals and materials have been detected.[31] Partly due to its compositional heterogeneity, PM is commonly classified not on composition

but size, and this is of relevance to its potential health effects: particulate matter with diameter less than approximately 10μm ("thoracic particles", known as PM_{10}) can settle in the bronchi and lungs, while particles with diameter less than approximately 2.5μm ("fine particles", $PM_{2.5}$) can reach the gas exchange regions of the lung. Yet smaller particles with diameter <0.1μg ("ultrafine particles", $PM_{0.1}$) may be able to pass rapidly into the systemic circulation.[32] PM_{10} is the most widely monitored class of particulate pollutants; widespread monitoring data on fine and ultrafine particles are lacking. Sources of PM are extremely wide-ranging, but motor vehicles are a major human source, particularly in urban areas.

Ozone

Ozone, sometimes known by its chemical formula O_3, is an allotrope of oxygen consisting of triatomic oxygen molecules. It occurs naturally in the upper atmosphere where it is formed by the action of sunlight on common diatomic oxygen (O_2). Ozone as a pollutant is usually formed indirectly from NO_2. Molecules of the latter, in the presence of sunlight, can split into NO plus an oxygen atom (O) which may then react with an oxygen molecule (O_2) to form ozone. The resulting NO and ozone are unstable and will under favourable conditions rapidly react to regenerate NO_2 and oxygen, but this reaction is impeded in the presence of various reactive organic compounds. Thus sources which emit both NO_2 and these reactive organic compounds are the most important cause of net ozone level increases. Motor vehicles and certain industrial processes are the common culprits. The immediate effects of exposure to high concentrations of ozone include irritation of the respiratory tract, as well as chest tightness, coughing and wheezing.

CO

CO, a colourless and odourless gas, is formed as a result of the incomplete combustion of fossil fuels; there are numerous sources, including some natural ones such as volcanoes. The main human sources of outdoor CO are petrol-powered motor vehicle emissions and some industrial processes. Tobacco smoking and cooking/heating appliances are important indoor sources. CO has a strong affinity for haemoglobin, which can result in impaired transport of

oxygen around the body; indoors, undetected CO emissions, for example from malfunctioning fuel-burning appliances, can quickly become lethal.

NO_2 and nitrogen oxides

There are a number of nitrogen oxides (NO_x) that have been studied as air pollutants: NO, NO_2, N_2O_4, and N_2O_5 but most studies concentrate on NO_2, a foul-smelling gas which is the most widely monitored and the most stable of the compounds. The most important source of outdoor NO_2 in urban areas is motor vehicle exhaust, though there are contributions from industry, in particular due to electricity generation from fossil fuels. There are also important indoor sources of NO_2, most notably gas cookers, fireplaces, and tobacco smoke. At high levels, NO_2 can exacerbate respiratory problems including asthma and bronchitis.[33]

SO_2

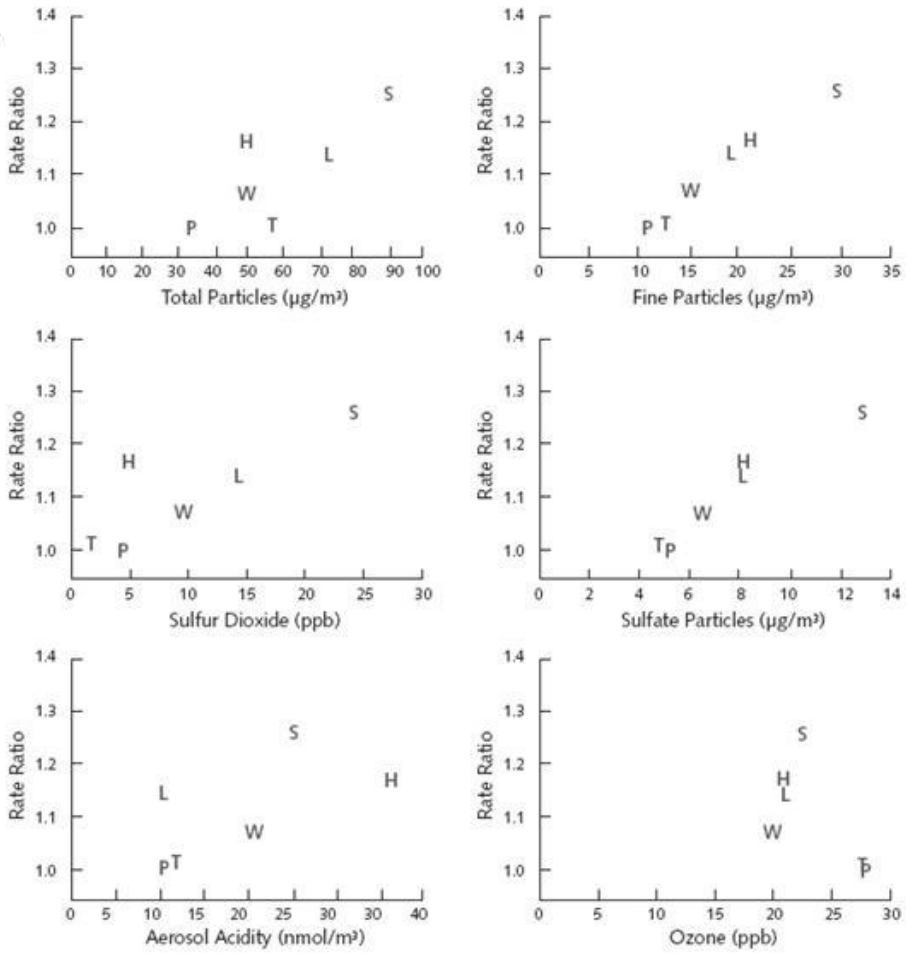
SO_2 is an invisible gas with a pungent odour. It reacts easily with water to form sulphurous acid and can form other harmful compounds. Breathing in high levels of SO_2 can thus cause immediate irritation, as well as coughing and shortness of breath. Almost all of the SO_2 in the air comes from human sources – the principal ones being industrial processes, such as electricity generation, that involve the burning of fossil fuels which contain sulphur, for example in coal-fired power stations. There are few significant indoor sources of SO_2; indoor levels of the gas are generally low except in industrial settings.

1.3.2.2 Health effects of air pollution

As described above, exposure to and inhalation of these chemicals at high concentrations results in various well-known immediate effects such as irritation and respiratory problems. However, of greater concern in terms of public health are the effects of exposure to the lower levels present in the air as a result of pollution. Such concern has existed over several decades: the infamous London smog of 1952, which caused thousands of deaths, led to the passing of the UK Clean Air Act in 1956 and similar legislation elsewhere, which has in turn led to huge reductions in ambient pollution levels in many developed countries. However, even at the relatively low pollutant levels seen more recently, effects

on broad health outcomes have been observed, not only in experimental "chamber" studies (which are not reviewed here), but also in population-based studies. Early time-series studies demonstrated an effect of short-term changes in the levels of pollutants, in particular PM, on overall mortality in both the USA[34] and Europe.[35] Two noteworthy prospective cohort studies also reported that mortality risk was increased by up to 26% for people living in cities with the highest mean pollution levels, after adjusting for individual risk factors such as smoking (*Figure 1.4*).[36-37]

Figure 1.4: Estimated adjusted mortality-rate ratios and pollution levels in the Six Cities study [reproduced from Dockery et al][36]

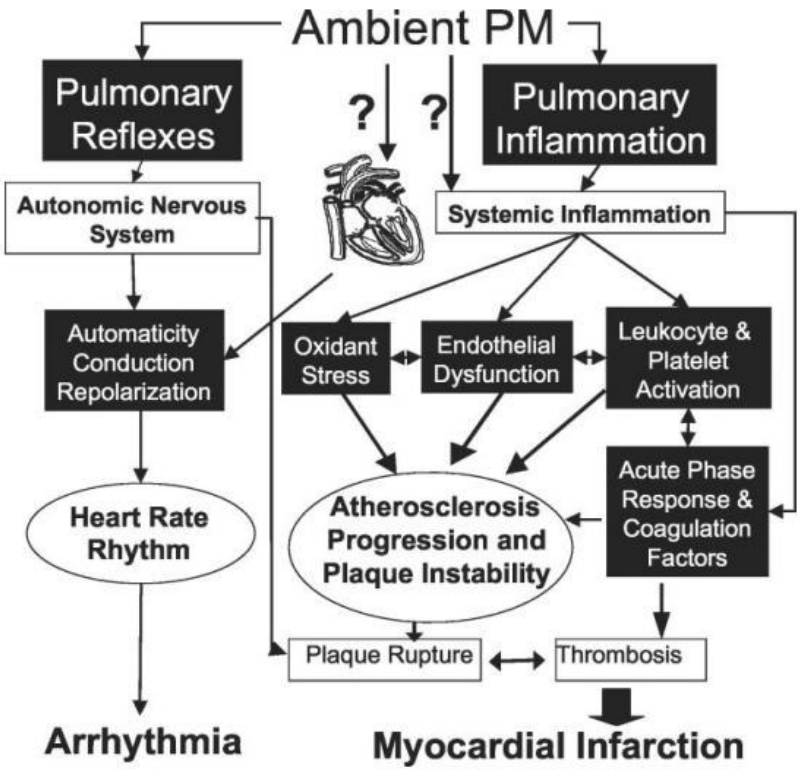


Mean values are shown for the measures of air pollution.
P= Portage, Wisconsin; T= Topeka, Kansas; W= Watertown, Massachusetts; L= St Louis, Missouri; H=Harriman, Tennessee; and S=Steubenville, Ohio.

More specific outcomes have also been investigated, and studies of cardiovascular mortality and morbidities have suggested that both day-to-day

changes in pollutant levels[38-39] and longer-term exposure[40-41] may affect risk. A major review of the epidemiological evidence on air pollution and cardiovascular disease conducted for the UK Department of Health stated that ‘‘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”.[42] A statement from the American Heart Association emphasised the effects of PM, concluding that short-term increases in PM levels led to corresponding increases in cardiovascular mortality, and in hospital admissions for several cardiovascular diseases;[31] the authors also reviewed possible mechanisms, with the two main theories being: (a) that a systemic inflammatory response to PM might lead, via various pathways, to accelerated plaque rupture or thrombosis; and (b) that an autonomic nervous system response might result in changes in heart rate and heart rate variability (Figure 1.5)

Figure 1.5: Possible mechanisms for an effect of PM on cardiovascular disease [reproduced from Brook et al[31]]



As with temperature, it has been suggested that older individuals and those with lower socioeconomic status may be more vulnerable to pollution effects.[36, 43-46] Pre-existing coronary heart disease may also increase individuals' vulnerability to the effects on cardiovascular mortality in particular;[47] indeed thrombotic and ischaemic effects have been directly observed among men with coronary heart disease exposed to diesel exhaust under controlled conditions.[48]

The majority of work on air pollution effects to date has made use of data on either overall mortality, or broadly categorised cause-specific mortality. Associations between pollutant levels and risk of MI specifically have been less commonly investigated. The existing evidence on this is examined in detail in Chapter 3.

1.4 Thesis rationale and aims

The observed effects of temperature and pollution on overall and cardiovascular mortality motivate more focused study regarding the effects on MI for two main reasons. First, mortality is likely to reflect only a small proportion of the total health impact of environmental exposure since many events do not directly result in death; if MI is susceptible to these environmental exposures, mortality studies are unlikely to fully capture the effects. Second, a clearer description of the effects on MI risk would reveal the extent to which these effects are drivers of the broader associations with mortality, and, given the specific pathophysiology of MI, may lead to a better understanding of potential triggering mechanisms at work.

1.4.1 Aims

The thesis has the following principal research aims:

1. To review and describe the literature to date regarding the effects of temperature and air pollution on the specific outcome of MI.
2. To characterise the short-term effects of temperature and air pollution on the risk of MI using new data from a UK setting, accounting for potential confounding factors.

In addition, further objectives of the thesis are:

- To gain an understanding of the main analysis methods used to investigate the health effects of environmental exposures in population-based studies, and the strengths and weaknesses of these methods.
- If strong effects of temperature and pollution effects are found, to perform exploratory analyses to consider which subgroups of individuals, if any, may be most vulnerable to these effects.

1.4.2 Organisation of the thesis

Chapters 2 and 3 describe systematic reviews that were conducted to ascertain the current state of knowledge regarding the effects of temperature and air pollution respectively on the specific outcome of MI. Chapter 4 describes the data sources used for original analyses in this thesis, and the overall methods for the research. Chapter 5 provides a descriptive analysis of the data. Chapters 6, 7 and 8 present the main new analyses performed for the thesis; in each of these chapters, the specific statistical methods are detailed, and the results presented and discussed. Chapter 6 describes the analysis investigating the short-term effects of ambient temperature on MI risk, while Chapters 7 and 8 present analyses investigating the short-term effects of pollutant levels at a daily and then hourly temporal resolution. Finally Chapter 9 summarises the main findings and discussion points from the body of the thesis.

1.5 Summary

- MI, commonly known as heart attack, describes the death of heart tissue following an interruption of blood supply to the heart.

- MI is one of the leading causes of mortality globally, and is more common among men and older individuals. There are a number of other known risk factors including smoking and abnormal lipids.

- Both ambient temperature and air pollution have been associated with adverse health outcomes including overall and cardiovascular mortality.

- This thesis will investigate the effects of temperature and pollution on the more specific outcome of MI, first through review of the existing evidence, and second through original analyses of new data.

2 Systematic review of the effects of ambient temperature on incidence of myocardial infarction

2.1 Introduction and aims

A substantial amount of research has been published on the effects of various aspects of weather on human health. The main objective of the systematic review presented below was to collate and present published evidence on one specific aspect of this wide topic, namely the effects of ambient temperature on the risk of myocardial infarction.

2.2 Methods

2.2.1 Search strategy

2.2.1.1 Databases and sources

Two large databases covering health and medical journals were searched: Medline (1950 to present) and EMBASE. Since meteorological exposures were being considered, the specialist database GEOBASE was also included. GEOBASE covers "development studies, the Earth sciences, ecology, geomechanics, human geography, and oceanography," and was included to capture any relevant studies that might have been published in the geographical/meteorological rather than the medical literature. Reference lists of all relevant studies were also scanned to identify any further studies, and if these revealed that search terms had been missed, extra terms were added to the main database searches. In order to capture important "grey literature" the websites of the following organisations were scanned for relevant reports: World Health Organisation; European Union; Health Effects Institute (USA); Environmental Protection Agency (USA); National Institutes of Health (USA); Department of Health (UK); and Department for Environment, Food, and Rural Affairs (UK). As well as searching for original research, the reference lists of any relevant reviews appearing in their reports were also examined.

2.2.1.2 Search keywords and terms

Medline is indexed according to MeSH terms. The following MeSH keywords were identified as relevant and combined as the primary search:

> [WEATHER or CLIMATE (plus all sub-terms in the MeSH tree)] and
>
> [MYOCARDIAL INFARCTION {subheadings: chemically induced, mortality, physiopathology, prevention and control, epidemiology, aetiology} (plus all sub-terms in the MeSH tree)] and HUMANS [not (ADOLESCENT or CHILD or INFANT not ADULT)]; limited to article types: JOURNAL ARTICLE or CLASSICAL ARTICLE or GOVERNMENT PUBLICATIONS or CLINICAL CONFERENCE or CLINICAL TRIAL or COMPARATIVE STUDY or META ANALYSIS; limited to language: ENGLISH

The EMBASE database has its own classification of headings. Appropriate terms were identified leading to the following search:

> [WEATHER or CLIMATE or AIR TEMPERATURE or ENVIRONMENTAL TEMPERATURE (plus relevant sub-terms in the classification tree)] and
>
> [HEART INFARCTION or ACUTE HEART INFARCTION or HEART VENTRICLE INFARCTION]; limited to language: ENGLISH

GEOBASE does not use a classification system, therefore a keyword search was used, with the following terms (* at the end of a term indicates that any ending is accepted):

> [WEATHER or CLIMAT* or TEMPERATURE or HEAT or COLD] and [MYCARDIAL INFARCT* or CORONARY EVENT or HEART ATTACK or Q WAVE INFARCT* or NON-Q WAVE INFARCT* or STEMI or MYOCARDIAL THROMBOSIS or CORONARY THROMBOSIS]

A secondary search of Medline was then run to identify any studies where myocardial infarction may have been included as part of a wider study of cardiovascular outcomes (such studies would likely be indexed under a broader term than “myocardial infarction”). Thus this secondary search used the MeSH heading CARDIOVASCULAR DISEASES (plus all sub-terms) in place of MYOCARDIAL INFARCTION. To further restrict the search output to a manageable size and focus on the most relevant studies, the following terms were required to be present in the title, abstract, or keywords (* at the end of a term indicates that any ending is accepted):

(MYOCARDIAL INFARCT* or CORONARY EVENT or HEART ATTACK or Q WAVE INFARCT* or NON-Q WAVE INFARCT* or STEMI or CORONARY INFARCT* or HEART INFARCT* or MYOCARDIAL THROMBOSIS or CORONARY THROMBOSIS)

2.2.1.3 Inclusion and exclusion criteria

In order to capture studies which investigated the effects of ambient temperature on the risk of myocardial infarction, specific inclusion and exclusion criteria were applied to select studies from the search results.

Inclusion criteria

The following study characteristics were required for inclusion:

1. Includes analysis of original data
2. Ambient temperature included as an exposure (or a composite measure which incorporates this)
3. Myocardial infarction included as a specific outcome
4. Manuscript available in English language
5. Study of adult humans

Exclusion criteria

Studies were excluded if they had:

1. No control for (or stratification by) any potential confounding factors
2. No measure of precision or p-value associated with main result(s) of interest

The purpose of these exclusion criteria was to systematically exclude studies with generally very basic methodology, whose results, even if positive, would not provide convincing evidence regarding the effect of temperature on risk of MI. Which specific confounding factors should be controlled for was not specified, since there is some variation in which factors authors consider potentially important, and the dependence of results on the choice of covariates included in models could itself be informative.

2.2.1.4 Procedure

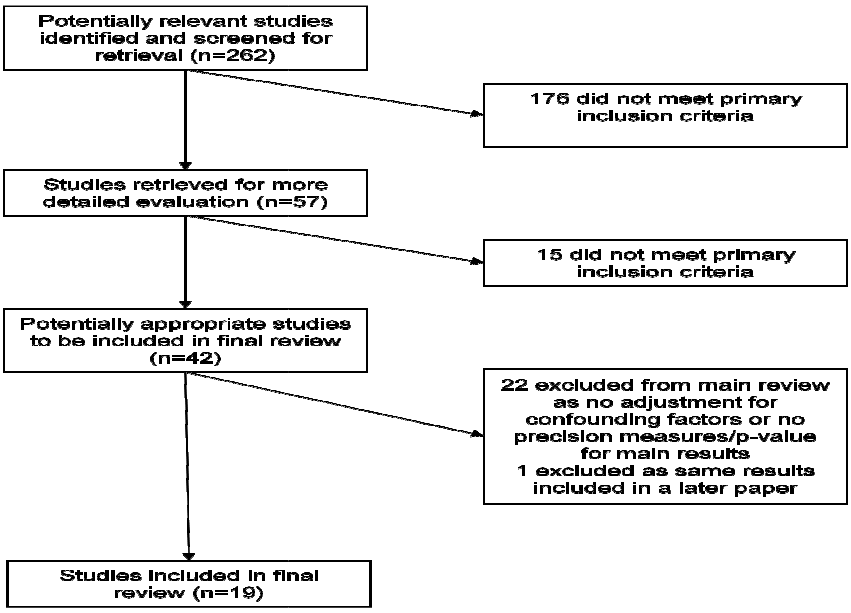
Titles and abstracts from the above searches were screened for relevance. Full text versions of potentially relevant papers were then obtained where possible and assessed with reference to the inclusion and exclusion criteria (see Section 2.2.1.3). For each study included, the following information was extracted: study population, event of interest, number included, age range included, location and setting, time period, exposure variables, ascertainment of MI, spatial resolution, temporal resolution, adjustment for air pollution and other potential confounders, lags considered. In addition, main results were recorded, in particular the effects of temperature on risk of myocardial infarction, including effect sizes and confidence intervals where possible. Where authors reported several relevant results (e.g. for different lag days, or for different subgroups), it was necessary to decide which result(s) to record; where a main or final model could be identified, this was chosen, otherwise results were recorded from the analysis on which the authors focused or that which best represented the overall conclusions of the study. Though this was a somewhat subjective process, in all cases, any important heterogeneity in the effect estimates between different analyses was noted. For context, the temperature range for the location studied was recorded where given. Finally, effects of other meteorological variables were also noted.

The search was initially conducted in July 2008. An additional search was undertaken in July 2010 to identify major studies published since the systematic review (see Section 2.5).

2.3 Results

After running the search strategy and screening abstracts for relevance, a total of 57 full text articles were obtained for further inspection. Of these, 42 met the primary inclusion criteria (*Figure 2.1*). 22 of these studies were excluded, four because they reported no direct effect estimates, and a further 18 because they did not control for any potential confounding factors. One further research paper was excluded because the same data were reported in a later paper, leaving a total of 19 studies in the main review.

Figure 2.1: Flow diagram for search strategy



The majority of studies selected for inclusion used a time series design to relate daily counts of MI events with daily measures of temperature. Analyses most commonly used Poisson regression modelling, a framework with the flexibility to allow adjustment for confounding factors; these studies may provide the best quality of evidence and are discussed in section 2.3.1. A small number of publications investigated longer-term effects of temperature, or weather-related exposures which were only indirectly related to temperature; these are covered in section 2.3.2. Finally, in section 2.3.3, the excluded studies (which were based on basic analyses with no control for confounding and/or reported no measures of precision or p-values for the results of interest) are discussed.

2.3.1 Short-term effects of temperature

The largest single group of studies were daily time series studies investigating the short-term (day-to-day) effects of temperature, analysed by Poisson regression (*Table 2.1*, *Table 2.2*, and *Table 2.3*). In such studies, the number of MI events each day is typically obtained retrospectively from sources such as death records, morbidity registers, or hospital databases, and then related via the regression model to some daily measure of temperature.

Table 2.1: Daily time series studies with temperature exposures and MI outcomes – description of studies

First author & Year of publication	Population/data source	Location & Time period	Number of MI events included (mean MIs/day)	Main temperature exposure variable(s)	Potential confounders included	MI ascertainment	Lags considered (days)
Studies of Fatal & non-fatal events							
Gerber 2006[49]	County medical care registers	Olmsted County, USA 1979-2002	2676 (0.3)	Maximum temperature	Annual population, calendar year, season, rain, snowfall	Diagnoses compatible with MI extracted and validated using cardiac pain, biomarker, and ECG criteria	None
Wang 2006[50]	Ambulance service centre data	Hiroshima, Japan 1993-2002	3755 (1.0)	Mean temperature, humidity-adjusted temperature	Atmospheric pressure	Diagnosis based on anamnestic, clinical, lab, and ECG criteria	None
Enquselassie 1993[51]	MONICA morbidity registry (covering ages <70 years)	Hunter Region, New South Wales, Australia 1985-1990	3889 (1.9)	Maximum temperature	Calendar month, rainfall	Non-fatal definite MI and fatal MI/sudden coronary death, based on MONICA ECG, symptom, and enzyme criteria[52]	None
Ohlson 1991[53]	Single clinic diagnosis register (ages <70)	Orebro, Sweden 1985-1987 (cold seasons only)	357 (0.6)	Windchill adjusted temperature (as measured at 7pm)	Day of week, snowfall, atmospheric pressure	Records with ICD8 code 410.10, 410.99, or ICD9 code 410A/B/W/X	None
Barnett 2005[54]	24 MONICA morbidity registries (covering ages 35-64 years)	Europe, China, USA, Australia 1980-1995	87410 (0.4 to 2.8 by location)	Mean temperature	Season & trend, day of week, humidity	Non-fatal definite MI and fatal definite/possible MI/unclassifiable event based on MONICA ECG, symptom, and enzyme criteria[42]	0 to 14 inclusive
Morabito 2005[55]	Hospitalisations database (Florentine area)	Florence, Italy 1998-2002	2683 (1.5)	Hours of severe discomfort (based on extremes of apparent and windchill temperature indices)	Stratified by season	Records with ICD9 =410-410.92	0 to 3 inclusive
Ebi 2004[56]	Hospitalisations data (covering all non-federal hospitals)	3 counties in California, USA 1993-1998	283031 (4.5 to 39.4 by location)	Minimum & maximum temperature	Season & trend	Records with ICD9 code 410	0, 7, 14, 30

Koken 2003[57]	Hospital admissions data (11 hospitals, covering ages 65+ years)	Denver county, USA 1993-1997 (July and August only)	Not reported	Maximum temperature, dewpoint temp	Season & trend, day of week, air pollution variables	Primary discharge diagnosis (ICD9=410.XX)	0 to 4 inclusive
Messner 2002[58]	Hospital and GP records, and death certificates data (ages 25-64)	Northern Sweden 1985-1992	3322 (approx 0.9**)	Temperature, change in temperature from previous day	Season, humidity, air pressure, change in humidity and air pressure from previous day	Suspected cases validated using symptom, ECG, and enzyme marker data	None
Danet 1999[59]	Lille-WHO MONICA morbidity registry (covering ages 25-64 years)	Nord district, France 1985-1994	3314 (approx 0.9**)	Mean temperature	Annual population, mean atmospheric pressure, calendar year	Non-fatal definite MIs and fatal definite/possible MIs, based on MONICA ECG, symptom, and enzyme criteria[52]	None
Fatal events only							
Dilaveris 2006[60]	Death certificate data	Athens territory 2001	3126 (8.6)	Daily mean/minimum/maximum temperature	Atmospheric pressure, relative humidity, season (based on calendar date)	Death certificates with ICD10 codes of I20.0-4, I21.9, I22.0, I22.1, I22.8, I22.9)	Mean of 0, 7
Sharovsky 2004[61]	Death registry data	Sao Paulo, Brazil 1996-1998	12007 (16.4)	Mean temperature	Season & trend, relative humidity, atmospheric pressure, day of week, holidays, influenza levels, air pollution variables	Death certificates with MI (ICD10 = I21) listed as primary cause	0, and moving average of up to previous 7 days
Rossi 1999[62]	Vital statistics department mortality data	Milan, Italy 1985-1989	Approx 1600* (0.9)	Mean temperature	Season & trend, relative humidity, day of week, holidays, respiratory infection epidemics, pollution variables	Deaths with ICD9 codes of 410	Different lags considered, exact strategy unclear

** derived from reported mean daily rate, and length of period under study*

*** derived from reported total number of events, and reported length of study*

Table 2.2: Daily time series studies with temperature exposures and MI outcomes – summary/interpretation

First author & Year	# MIs	Long-term local mean temp and annual range[+] (°C)	Detrimental effect of cold?	Detrimental effect of heat?	Adjusted for season and trend?	MI events: validation or specified criteria	Adjusted for humidity	Adjusted for Atmos. pressure	Adjusted for infectious disease levels	Adjusted for air pollution	Adjusted for day of week?	Allowance for non-linear temp effects?	Investigated lag effects?
Studies of Fatal & non-fatal events													
Gerber 2006[49]	2676	7 (-10.8 to 21.2)	No	No	✓	✓	×	×	×	×	×	✓	×
Wang 2006[50]	3755	16.7 (5.6 to 28.3)	Yes	No	×	✓	×	✓	×	×	×	✓	×
Enquselassie 1993[51]	3889	17.9 (11.9 to 23.7)	Yes (fatal MIs only)	No	×*	✓	×	×	×	×	×	✓	×
Ohlson 1991[53]	357	6.3 (-3.9 to 17.3)	No	N/A	×	×	×	✓	×	×	✓	✓	×
Barnett 2005[54]	87410	-	Yes	No	✓	×	✓	×	×	×	✓	×	✓
Morabito 2005[55]	2683	14.1 (5.8 to 23.5)	Yes	Yes (for increased hours of discomfort)	✓	×	×	×	×	×	×	×	✓
Ebi 2004[56]	283031	14.7 (10.1 to 18.6) to 19.3 (14.8 to 24.4)	Certain regions only (1/3 regions for night temp; 2/3 regions for day temp)	Certain regions only (2/3 regions for night temp;0/3 regions for day temp)	✓	×	×	×	×	×	×	×	✓
Koken 2003[57]	Not given	9.7 (-1.4 to 21.9)	N/A	Yes	✓	×	×	×	×	✓	✓	×	✓
Messner 2002[58]	3322	-1.4 (-15.6 to 13.5) to 4.6 (-5.5 to 16.5)	No	Yes (change from previous day, non-fatal MIs only)	×**	✓	✓	✓	×	×	×	×	×
Danet 1999[59]	3314	10.6 (2.0 to 19.1)	Yes	No	×***	✓	×	✓	×	×	×	×	×
Fatal events only													
Dilaveris 2006[60]	3126	18.0 (8.6 to 28.4)	Yes	Yes	×*	×	✓	✓	×	×	×	✓	✓
Sharovsky 2004[61]	12007	18.0 (13.9 to 21.8)	Yes	Yes	✓	×	✓	✓	✓	✓	✓	✓	✓
Rossi 1999[62]	Approx 1600	12.8 (3.8 to 22.9)	Not mentioned	Yes	✓	×	✓	×	✓	✓	✓	✓	✓

+: 10-year average of the monthly mean temperatures, and of the minimum and maximum monthly mean temperature in the study area, as recorded at the nearest available monitoring station included in the Goddard Institute for Space Studies (GISS) Surface Temperature Data[63], using data from the years 1991-2000 inclusive

*: authors adjusted for calendar month, which should have approximately captured any season effect

**: authors performed a basic adjustment for season in a sensitivity analysis which did not change the conclusions

***: authors adjusted for annual population and calendar year, which should have approximately captured any long-term trend

Table 2.3: Daily time series studies with temperature exposures and MI outcomes – study results

First author & Year	Temperature variable[$], range [if reported] (°C)	Relative risk or rate ratio for temperature (95% CI if reported)	(Change in temperature variable to which RR refers)	**Subgroup to which RR refers (if applicable)**	**Lag for temp effect (days)**	**Comment**
Studies of Fatal & non-fatal events						
Gerber 2006[49]	tmax -29 to 39	0.93 (0.73, 1.14) 1.00 (reference) 0.97 (0.89, 1.06) 1.03 (0.92, 1.14)	>30°C 18-30°C 0-17°C <0°C		0	-
Wang 2006[50]	tmean -0.9 to 32.7	1.00 (reference) 1.12 (0.99, 1.27) 1.17 (1.01, 1.35)	>20°C 10-20°C <10°C		0	-
Enquselassie 1993[51]	tmax <16 to >30	1.2 (0.9, 1.5)* 1.0 (reference) 1.4 (1.1, 1.8)* 1.2 (0.9, 1.4)* 1.0 (reference) 1.0 (0.8,1.3)*	>30°C 23-27°C ≤16°C >30°C 23-27°C ≤16°C	fatal MIs “ “ non-fatal MIs “ “	0	-
Ohlson 1991[53]	Twind <-20 to >0	1.00 (reference) 1.09 (0.82, 1.44) 1.10 (0.79, 1.52) 1.12 (0.67, 1.85)	≥0°C -10 to -1°C -20 to -11°C <-20°C		0	-
Barnett 2005[54]	tmean 1.5 to 23.0	1.008 (1.004, 1.012)	Per 1°C decrease		Av 0-3	Only a linear temperature effect appears to have been considered
Morabito 2005[55]	tmean, discomfort hours	1.03 (p<0.01) 1.06 (p<0.01)	Per extra 2 heat discomfort hrs Per extra 2 cold discomfort hrs	summer, males, <65y winter, females, ³65y	0	Only a linear effects of the exposure variables appear to have been considered. However, discomfort hours analysis was performed separately for winter and summer.

Ebi 2004[56]	tmin, tmax -1 to 37 [tmin]	1.072 (1.057, 1.086) 1.008 (1.004, 1.012) 1.223 (1.083, 1.381) 1.025 (1.000, 1.052) 1.066 (1.023, 1.111) 1.109 (1.051, 1.169)	Per 3°C decrease [tmin] Per 3°C increase [tmin] Per 3°C increase [tmin] Per 3°C increase [tmax] Per 3°C decrease [tmax] Per 3°C decrease [tmax]	males, 55-69y, LA+ males, 55-69y, SF+ males, 55-69y, Sa+ males, 55-69y, LA+ males, 55-69y, SF+ males, 55-69y, Sa+	7	Only linear temperature effects appears to have been considered. Effects for age ≥70y and for women were all in the same direction as those shown here.
Koken 2003[57]	tmax 16.7 to 30.8	1.175 (1.029, 1.343)	Per 5.9°C increase	≥65y	0	Analysis was for July/August only
Messner 2002[58]	temp, tchange -38 to 30 [temp]	1.001 (0.993, 1.008) 1.000 (0.997, 1.003) 1.003 (0.979, 1.028) 1.015 (1.003, 1.027)	Per 1°C decrease [temp] Per 1°C increase [temp] Per 1°C increase [tchange] Per 1°C increase [tchange]	fatal MIs non-fatal MIs| fatal MIs non-fatal MIs	0	Only linear temperature effects appears to have been considered
Danet 1999[59]	tmean -15 to 28	1.05 (1.02, 1.09)	Per 5°C decrease		0	Only linear temperature effects appears to have been considered
Fatal events only						
Dilaveris 2006[60]	tmean 1 to 39	1.13* 1.00 (reference) 1.40* (p<0.001)	30°C 23.3°C 10°C		Mean of last 7 days	Results are from fitted the regression line, which shows minimum event rate at 23.3°C, with the event rate increasing smoothly above and below this temperature (levelling off at mean temperatures below 10°C)
Sharovsky 2004[61]	tmean 11 to 27	1.11 (1.06, 1.16)* 1.00 (reference) 1.16 (1.05, 1.27)* 1.17 (1.07, 1.28)* 1.31 (1.19, 1.44) *	23.8-27.3°C 21.6-22.6°C 16.4-17.3°C 15.2-16.4°C 11.0-15.2°C		2-day average	-
Rossi 1999[62]	tmean -6 to 32	1.44 (1.10, 1.90) 1.00 (reference)	>27°C 14°C		1	Effect of colder temperatures is not described

£: note, % changes were converted to RR by dividing by 100 and adding one
$: key to abbreviations - tmax = daily maximum temperature, tmin = daily minimum temperature, tmean = daily mean temperature, discomfort = number of discomfort hours per day, temp = temperature (unspecified), tchange = temperature change from previous day, twind = windchill-adjusted temperature, tfelt = felt temperature
*: approximate RR, derived from graphical presentation of results
+: LA = Los Angeles region, SF = San Francisco region, Sa = Sacramento region

Only one study used a different design: Hirasawa et al[64] looked at the effectiveness of 10 meteorological parameters in discriminating between days with and without MI events in Hokkaido, Japan; however this small study identified no useful discriminating factors. The 13 daily time-series studies are now considered in more detail.

2.3.1.1 Methodological considerations

Variations in methodological aspects of the 13 daily time series studies occurred in three main areas: ascertainment and validation of MI outcome events; adjustment for potential confounding factors; and flexibility of the fitted temperature effect in terms of allowance for non-linear and delayed (or "lagged") effects.

MI data came from a variety of sources, the primary sources being hospital, clinic or medical care databases (n=6), morbidity registries (n=3), ambulance data (n=1), and death certificate/mortality data (n=3). Most studies, including all of those concentrating purely on mortality data, generally took the cause of death as coded in the source data. Such cause of death coding may be unreliable and this strategy is likely to have led to non-MI deaths being included to some degree. However five studies, with access to symptom, ECG, and biomarker records, validated potential MI events using specific diagnostic criteria (*Table 2.1*).

Adjustment for regular seasonal patterns within years, and for long-term trends over a number of years, was performed to varying degrees in a number of studies and may, where performed, lead to more reliable estimates of short term temperature effects. Without adjustment for season, estimated temperature effects are likely to be dominated by longer-term differences (e.g. between winter and summer), and other factors which vary seasonally (such as other meteorological parameters, and levels of infectious disease) could confound associations. Control for long-term trend may be similarly important; event rates may change over the long-term, for example, due to changes over time in MI ascertainment, recording practices, advances in prevention, or in underlying population size; if such changes happened concurrently with long

term changes in temperature (e.g. a sequence of increasingly warm years), a spurious effect could be estimated.

A few studies included more specific potential confounders. Potential confounders for the relationship between temperature and MI, since they must by definition be associated with temperature, are usually other time-varying external factors, such as other meteorological parameters, pollution levels such as ambient particulate matter and ozone, and levels of infectious diseases such as influenza. Of note, only 3 studies[57, 61-62] made any adjustment for daily pollution levels, which are likely to be associated with daily temperature, and which a number of studies have suggested may affect short-term risk of MI.

Finally, there was variation in the way temperature relationships were investigated. Six of the 13 studies appeared to investigate temperature only as a linear effect, meaning that U-shaped relationships similar to those reported in some mortality studies could not have been detected. In addition, only 7/13 studies investigated the possibility of the effects of temperature on MI being delayed ("lagged") by one or more days: this is a potentially important consideration if the effects of temperature on MI incidence extend beyond same-day effects; for example, an extreme cold day may lead to an increase in MI incidence over the next several days. Even among studies that considered this, the potential lagged effects investigated varied widely, ranging from 1 to 30 days.

2.3.1.2 Reported effects of temperature

The main results of the 13 time series studies investigating the short-term effects of temperature are shown in *Table 2.2* and Table 2.3. Overall, 8 of the 12 studies which included data from the winter season reported a statistically significant increased risk of MI at colder temperatures, either overall or for some subgroup, while statistically significant increases in MI risk with higher temperatures were reported in 7 out of the 13 studies. Four studies reported separate effects of both heat and cold. The studies can be divided into those including data on fatal MIs only, and those including non-fatal events.

Studies of fatal events

Three studies analysed the effects of temperature on death from MI. Sharovsky et al[61], using mortality data from Sao Paulo, Brazil where the lowest mean temperature was 11°C, found that both cold and heat increased the MI risk. There were 31% more MI deaths on days in the coldest mean temperature category of 11.0-15.2°C compared with 21.6-22.6°C (RR=1.31 [95% CI 1.19 to 1.44]). On the warmest days (23.8-27.3°C), the authors estimated an 11% higher risk of fatal MI with respect to the same reference group (RR=1.11 [1.06, 1.16]). The study adjusted for daily levels of air pollutants (sulphur dioxide, carbon monoxide, and particulate matter), as well as other meteorological variables, influenza levels, and day of the week. Dilaveris et al[60] also observed both cold and heat effects: in an analysis of data from Athens which were presented graphically, a minimum death rate was identified at 23.3°C, with the death rate increasing at both higher and lower temperatures compared to this optimum (daily MI deaths increased by approximately 13% at 30°C and by 40% at 10°C). The analysis adjusted for other meteorological factors (humidity and atmospheric pressure). Rossi et al[62] also performed an analysis including both temperature and air pollution variables, using data from Milan, Italy. Fatal MI was one of several outcomes in reported in the paper, and comprehensive results were not given for the MI outcome. However, the authors did report a detrimental effect of hotter daily mean temperature on the risk of fatal MI (RR=1.44 [1.10, 1.90] for >27°C vs. 14°C); no effect of cold was mentioned.

An important potential weakness of these three studies is that MIs were ascertained purely through cause of death data as recorded on death certificates or death registries, raising the possibility that cause of death coding errors could potentially have led to a substantial proportion of unrelated deaths being counted as MIs.

Studies including non-fatal events

The remaining 10 studies included data on non-fatal MI events. The only international study included was Barnett et al,[54] in which data from 24 populations with varying climates within the MONICA project were analysed. Significant effect of cold were observed on combined fatal and non-fatal

coronary events, with event counts falling as temperatures increased (RR = 0.993 [0.990, 0.996] per 1°C increase). These results refer to the mean temperature over the current and previous three days, which were found to fit the data better than other lag structures considered. Koken et al[57] analysed the effect of maximum temperature on hospital admissions in Denver County, USA, restricting to the summer months of July and August only. Air pollution and day of the week effects were taken into account. The authors reported that a 5.9°C increase in maximum temperature resulted in a 17.5% higher risk of MI on the same day (RR=1.175 [1.029, 1.343]). Ebi et al[56] analysed separately the effects of daily minimum and maximum temperatures in three regions of California. The two variables considered are likely to reflect night and day temperatures respectively. The results were rather inconsistent: for minimum temperature, there was an increase in events at higher temperatures in San Francisco and Sacramento, but a significant effect in the opposite direction in Los Angeles; for maximum temperature, there was an increase in events at higher temperatures for Los Angeles, but a significant effect in the opposite direction in San Francisco and Sacramento. These conflicting results may reflect the problem of modelling temperature as a purely linear term, which can only identify either a cold effect or a heat effect. If, in reality, there are increases in events at both extremes of the temperature scale, such an approach would be flawed. The authors speculate that other differences between the regions explain the discrepancies, for example warmer weather in Los Angeles, and a lower prevalence of home temperature control systems in San Francisco.

Morabito et al[55], analysing hospital data from Florence, Italy took the novel approach of looking at the effect of the number of “discomfort hours” in the day, based on indices incorporating a combination of weather variables. Hours above the 90th percentile of the Apparent Temperature Index, or below the 10th percentile of the New US/Canada Wind Chill Temperature Index were defined as discomfort hours for summer and winter respectively. Discomfort hours associated with summer heat appeared to predict an increased admissions rate in males aged <65 years (by 3% per 2 hours), but not for those aged ≥65 years. Conversely, discomfort hours associated with cold in winter appeared to predict increased admissions most strongly among females aged ≥65 years, and there

was no effect among males. The authors' approach is interesting, though the presentation of selected subgroups of age and sex may argue against a convincing effect.

Three studies[50-51, 59] found that only colder temperatures increased the risk of MI. All three mentioned the use of specific criteria (incorporating symptoms, and ECG/laboratory results) in the diagnosis of MI: Wang et al[50] analysed the effects of temperature on ambulance call-outs resulting in an MI diagnosis, adjusting for atmospheric pressure, finding a 17% increase in call-outs was reported at temperatures on <10°C compared with >20°C in the relatively warm climate of Hiroshima City, Japan (RR=1.17 [1.10, 1.35]); Enquselassie et al[51], in an unadjusted analysis of morbidity data from New South Wales, Australia, found an increase in fatal MIs at cold temperatures (RR = 1.4 [1.1, 1.8] for ≤16°C compared with 23-27°C) but there was no similar effect for non-fatal events; Danet[59], studying similar data from Nord District, France (where temperatures fell to as low as -15°C), investigated the effect of temperature using only a linear term, and found that the daily rate of fatal and non-fatal MIs decreased as temperature increased (RR=0.95 [0.92, 0.98] per 5°C increase, adjusted for atmospheric pressure). However, adjustments for season and long-term trend, as well as other potential confounding factors, were not comprehensive in any of the three studies.

Messner et al[58] investigated not only the effect of absolute temperature, but also of change from the previous day. This addresses the interesting hypothesis that sudden changes may be more harmful than absolute extremes of temperature arrived at in a smooth way. The study used data from Northern Sweden, where temperatures range from -38°C to +30°C. After adjusting for humidity and atmospheric pressure, absolute temperature did not have any effect on the daily number of MI cases (validated using common diagnostic criteria). However, increases in temperature from the previous day did increase the risk of non-fatal MIs (RR=1.015 [1.003, 1.027] per 1°C increase). There was no similar effect for fatal MIs.

Finally, Gerber et al[49] looked at the effect of maximum temperature in Olmsted County, USA, and found no effect across the broad range of temperature (the daily maximum ranged from -29 to +39°C over the period studied, while Ohlson

et al[53] similarly found no significant effect of cold or of heat in a small Swedish study. In both cases confidence intervals were wide so that fairly large effects in either direction could not be ruled out, and the latter study did show a non-significant trend that suggested an increase in the risk of MI at colder "wind chill-adjusted" temperatures (RR=1.12 [0.67, 1.85] for <-20°C compared with ≥0°C)

2.3.1.3 Potential modifiers of temperature-MI effects

Role of local climate

Barnett et al[54] considered heterogeneity in the temperature effect across the 24 populations (from 21 countries) included in their study. There was some variation in the estimated size of the risk increase associated with a drop in temperature (ranging from a 0 to 1.8% increase in risk per 1°C). Interestingly, 28% of this variation was explained by local mean temperature (rising to 54% when 2 outliers were excluded); in general, locations with higher mean temperatures were more vulnerable to cold days.

This was explored further in the remaining single-location studies by considering the 10-year mean temperature and the average annual range temperatures (*Table 2.2*). Studies in the six "warmest" regions all reported a detrimental effect of cold;[50-51, 55-56, 60-61] of note, these warmer regions also tended to have smaller average annual temperature ranges (<20°C in 5/6 cases). In contrast, considering studies in the six "coolest" regions, which tended to experience a greater range of temperatures across the year (average range >20°C in 4/6 cases), only 1 of 5 investigating cold effects reported a significant effect of cold[49, 53, 58-59, 62] (with one further study[57] using data from the summer months only).

No such pattern could be detected for heat effects; indeed, the studies based in the regions with the coolest and warmest mean temperatures (Northern Sweden and Sao Paulo, Brazil respectively) both reported detrimental effects of heat.

Vulnerability among subgroups

A few studies investigated vulnerability to temperature effects according to individual-level characteristics. Among those considering the effects of temperature separately for different age-groups, there were inconsistent results; 2 studies, both of which had found significant detrimental effects of cold, reported that analyses restricted to the oldest age group gave similar effect size estimates to those including all patients,[51, 59] though it should be noted that in the former study the oldest age group accounted for over half of the events, while in the latter the age structure of the study population was not reported. Morabito et al[55] on the other hand reported that correlations between "cold discomfort hours" and MI rates in winter were larger among those aged >65 years, while correlations between "heat discomfort hours" and MI rates in summer were larger among those aged <65 years. Age appeared to affect the magnitude of temperature effects in one study in California though the direction of the association was not consistent across the three regions studied.[56] In the same study, analyses were also presented stratified by sex: the estimated increase in risk of MI for a 3°C decrease in maximum temperature was greater among women in the Sacramento region (15.7% [4.9, 27.6] compared with 10.9% [5.1, 16.9] for men, among those aged 55-69 years), whereas the increase in MI risk following an equivalent temperature drop in San Francisco was larger among men (6.6% compared with 2.2% in women). Barnett et al[54] reported that the increase in event rates in cold periods was greater among women than men (OR 1.07 [1.03-1.11]), averaging over all 24 included populations. The same study found no difference between those with and without previous MI. Similarly, Enquselassie et al[51] reported that the effects of heat and cold among individuals with prior history of ischaemic heart disease were similar to effects among all study participants.

2.3.1.4 Effects of atmospheric pressure and relative humidity

This section briefly summarises the effects of the two other main weather variables covered by studies included in this section. Only a small proportion presented results for the effects of non-temperature weather variables on MI outcome.

Atmospheric pressure

Wang et al[50] included an interaction between atmospheric pressure and temperature. An increase in MI risk was seen at lower levels of atmospheric pressure, but only on days with temperatures <10°C (RR = 1.37 [1.00, 1.86] for pressure ≤1005hPa compared with 1005-1012hPa). Danet et al[50] reported a V-shaped relationship between atmospheric pressure and MI risk. At levels below 1016 mbar, lower atmospheric pressure was associated with an increased risk of MI (RR = 1.12 [1.05, 1.19] per 10mbar drop), whereas at levels above 1016 mbar the effect was in the opposite direction (RR = 1.11 [1.04, 1.18] per 10mbar increase). Only three other studies reported on atmospheric pressure as an explanatory variable, and all three found no effect on MI occurrence.[53, 58, 61]

Relative humidity

Sharovsky et al[61] found that low relative humidity (measured as the 2-day average) was associated with an increase in MI deaths (RR 1.11, 1.03-1.18) for the lowest vs highest quintile of relative humidity (58-68 vs. 86-96%). Dilaveris et al[60] reported the association between relative humidity and MI deaths on a monthly timescale only. There was a strong correlation between monthly humidity and monthly MI deaths (correlation coefficient = 0.76, p = 0.004), and the relationship appeared to be linear with an approximately 13% increase in MI deaths per 10% increase in relative humidity after adjusting for other factors. The only study that included non-fatal events and reported on the effect of relative humidity was Messner et al.[58] The authors of this study reported no significant effect of either humidity or change from previous day's humidity, though there was a suggestion of an effect of the latter variable on non-fatal events alone; a rise in humidity from the previous day was marginally associated with a fall in non-fatal MIs (RR = 0.995 [0.990, 1.000] per 1% increase, p = 0.06)

2.3.2 Other study designs and complex exposure variables

2.3.2.1 Long-term effects of temperature

Two studies investigated longer-term effects of temperature. Chang et al[65] included 369 hospitalisations for MI among women aged 20-44 years in 24 centres covering 4 continents between 1989 and1995; the cases arose from a WHO hospital-based case-control study. A time series design was used but importantly event counts and mean temperatures were related only on a monthly timescale (adjusting for relative humidity and rainfall). Temperature effects were investigated in a linear way, and monthly event counts appeared to decrease as temperature increased (RR = 0.88 [0.80, 0.97] per 5°C increase), suggesting a detrimental effect of cold on this broader timescale. A paper led by Gyllerup[66] reported results of a regional comparison study, in which MI mortality between 1975 and 1984 was compared between 284 municipalities in Sweden and related to the number of cold days (<-10°C, adjusted for wind chill) in each municipality over the same calendar years. MI mortality was ascertained using a national cause of death register. When the municipalities were divided in to deciles according to the number of cold days, a trend was evident with municipalities in the 3 coldest deciles reported to have standardised mortality ratios (SMRs) of >1 (SMR = 1.4 in the coldest decile), and municipalities in the 7 least cold deciles all having SMRs <1 (SMR = 0.9 for those in the least cold decile).

2.3.2.2 Studies investigating more complex meteorological variables

A few studies did not investigate the effects of air temperature directly, but used as exposures of interest more advanced meteorological variables which may reflect not only temperature but the overall characteristics of the daily weather.

Morabito et al[67] considered 808 hospitalisations in the winter months of December-February with a primary discharge diagnosis of MI in Tuscany, Italy. Daily weather was categorised into 5 categories of air mass by combining 7 weather variables (dry bulb temperature, cloud cover, saturation deficit, atmospheric pressure, wind speed, west-east component of wind, and north-south component of wind) using principal components analysis techniques. An

MI admission index was calculated for each day and represented the number of MI admissions relative to the winter average (fixed at 100). The MI admission index 1 day after an anticyclonic continental air mass, representing cold and clear weather, was 113 and was significantly higher than that 1 day after a mixed air mass (92, $p<0.05$), which represented mild, humid, cloudy weather. Particular 2-day sequences of air masses were also associated with large increases in the MI admission index, namely anticyclonic continental followed by polar continental which represents cold, then cold and blustery days, and sequences of days with rapid alternation of anticyclonic/cyclonic which are characterised by sudden changes in pressure, humidity and cloud cover. Although this more unusual method of classifying weather allowed more complete use of the various meteorological parameters, the validity and interpretation of these classifications are uncertain.

Messner,[68] in a study in Northern Sweden which included 7076 well-validated MIs identified through hospitals and GPs, considered the association between arctic oscillation (AO) index and MI incidence. AO is expressed as an index of normalised, time-averaged pressure differences between observation stations, and can capture various aspects of weather, with a low value bringing cold and dry weather, with storms in southern regions, and a high value corresponding to warmer, more humid, cloudier, and wetter weather. The results suggested that this latter set of conditions was associated with a higher incidence of MIs three days later (RR = 1.038 [1.015, 1.062] per unit increase in AO index, 3-day lag), though it was unclear whether the model used was flexible enough to allow a non-linear or non-monotonic effect of the AO index. Though the effect size peaked with a 3-day lag, the AO index was also reported to be significantly associated with MI incidence at lags of 0, 1, 2, 4, and 5 days ($p<0.01$ in each case).

Kveton[69] considered weather fronts as an explanatory variable in an analysis of daily MI counts in six hospitals in Czechoslovakia. Although the authors reported some effects of weather fronts, the results were difficult to interpret without specialist expertise in meteorology so are not considered further here.

2.3.3 Excluded studies

A total of 22 studies were excluded from the main review because they did not include any control for confounding factors, or did not present any measures of precision or p-values for the results of interest. These studies were of similar overall design to those covered in section 2.3.1, i.e. time series studies analysing daily counts of MI events and daily measures of one or more temperature/weather variable(s). Most were older studies analysed using only basic statistical methods without the flexibility to adjust for confounders.

18 of the excluded studies are summarised in *Table 2.4* and overall show remarkable consistency; a majority describe a monotonic effect of temperature, with event rates higher at colder temperatures, and lower at warmer temperatures. However it is possible that any effects described do not reflect just well-isolated short-term temperature effects, but rather broader seasonal differences in event rates, the potential causes of which could be numerous. A further four time series studies are omitted from *Table 2.4*: three [70-72] did not directly present any effect estimates or correlations, while in a fourth[18] the reference category was unclear, and so results could not be interpreted.

Table 2.4: Studies excluded due to lack of control for confounders or lack of precision/p-values for effect estimates

First author & Year of publication	Population/data source	Location & Time period	Number of events included	Temperature variable and range (if available)	MI ascertainment	Statistic	Result	Temperature variable/values to which result applies	**Subgroup (if applicable)**
Studies of Fatal & non-fatal events									
Schwartz 2004[73]	Medicare files (>65s only)	12 cities, USA 1986-1994	Not reported	Mean temperature <-13 to >30°C	Records with ICD9 code 410	Relative risk	1.04* 1.00 [ref] 0.94*	27°C -18°C -29°C	-
Fries 1998[74]	Consecutive MI admissions to intensive care units (8 hospitals)	South West Germany 1990-1992	693	Felt temperature based on thermophysical model <-6.7 to >26.6°C	Diagnosis based on 2 of : chest pain > 30mins, supporting ECG, raised CK	Relative incidence	0.95 1.00 [ref] 0.86 (p non-significant)	Class 12 (mean 34°C) Class 7 (mean 11°C) Class 1 (mean -7 °C)	-
Bull 1978[75]	Death registry data	New York, England & Wales 1965-1968 & 1970-1971 (respectively)	Not reported	Minimum temperature, mean temperature -10 to 20°C (EW[+])	Deaths with ICD7 codes of 420.1	Rate ratio	0.9884	Per 1°C increase	<60y, EW[++]
Sarna 1977[76]	Ischaemic heart disease registry database	Helsinki, Finland 1970	756	Mean temperature -19.7 to 21.2°C	Cases in the registry fulfilling minimum criteria for MI given by WHO	Rate ratio	1.00 [ref] 1.15* 0.94* 1.11* 0.96* 0.89* (p non-significant[+])	1st decile (<-7°C)* 2nd decile (-7 to -4°C)* 4th decile (-1 to 2°C)* 6th decile (5-8°C)* 8th decile (12-14°C)* 10th decile (>17°C)*	-
Marchant 1993[77-78]	Consecutive admissions to a coronary care unit	Newham, UK 1988-1991	633	Minimum temperature <3 to ≥15°C	Diagnoses confirmed by 2 of: supportive ECG, CK elevation, chest pain >30mins	O/E ratio	1.52 0.90 0.78 (p<0.001 for trend)	<3°C 6-8.9°C ≥15°C	-
Thakur 1987	Hospital admissions records (single hospital)	Panta, India 1979-1983	1217	Minimum temperature 3.9 to 44.6°C	As diagnosed (required chest pain plus ECG changes, or elevation of cardiac enzymes)	O/E ratio	1.27 1.11 0.93 (p<0.001[+])	≤8°C 8-16°C ≥16°C	-

Bull 1973[79]	Hospital admissions records (single medical unit)	Belfast, UK 1953-1966	2348	Maximum/minimum temperature <4.4 to >21.1°C	Details not given	O/E ratio	Non-significant ($p>0.05^{+}$) 1.19 1.02 0.72 ($p<0.001^{+}$) 1.15 0.97 0.91 ($p<0.05^{+}$)	[tmax] [tmax] <4.4°C 10-12.2°C ≥21.1°C [tmax] <4.4°C 10-12.2°C ≥21.1°C	<55y Male, ≥55y Male, ≥55y Male, ≥55y Female, ≥55y Female, ≥55y Fenale, ≥55y
Sotaniemi 1970[80]	Hospital admissions records (single medical department)	Oulu, Finland 1965-1968	771	Mean temperature <-30 to >20°C	As diagnosed (based on anamnestic, clinical, lab, and ECG criteria)	O/E ratio	1.36 1.11 1.01 (p<0.001 for ≥0 vs. <0°C)	<-30°C -9-0°C 20-30°C	-
Giroux 2000[81]	Exact source unclear; events among persons aged 35-64 living <25km from Toulouse	Toulouse, France 1985-1986	282	Temperature 0 to 27°C	Records meeting MONICA definition of MI[52]	Events/day	0.66 (sd 0.87) 0.85 (sd 0.83)	0-12.9°C 13-27°C	-
Ruscone 1985[82]	Coronary care unit records (6 units)	Milan, Italy 1979-1980	2830	Mean/minimum/maximum temperature -4.7 to 34.8°C [lowest minimum to highest maximum]	Potential cases examined for all of: typical pain >30mins with shock or syncope, ECG changes, and CK elevation	Correlation coefficient	-0.21 -0.22 -0.22 (p non-significant in each case for H_o: r = 0)	[tmean] [tmin] [tmax]	
Ruhenstroth-Bauer 1985[83]	MI admissions to four cardiology clinics	Munich, Germany 1981 Jan-Mar	162	Mean/minimum/maximum temperature	Details not given	Correlation coefficient	-0.16 -0.15 -0.16	[tmean] [tmin] [tmax]	-
Fatal events only									
Frost 1992[84]	New Zealand Department of Health death statistics	Auckland, New Zealand 1984-1985	Not reported	Minimum temperature 4 to 20°C	Deaths with ICD9 codes of 410	Event rate ($/10^6$)	 34* 30* 31* 21*	[tmin] 5°C 10°C 15°C 20°C	 >65y >65y >65y >65y

Auliciems 1989a[85]	Australian Bureau of Statistics data	Brisbane, Australia 1984-1985	Not given	Mean/minimum temperature 9 to 32°C [lowest minimum to highest maximum]	Deaths with ICD9 codes of 410	Event rate (/10^6)	35* 30* 25* 19*	[tmin] 5°C 10°C 15°C 20°C	>60y >60y >60y >60y
Auliciems 1989b[86]	Statistics Canada data	Montreal, Canada 1983-1984	Not given	Mean temperature	Deaths with ICD9 codes of 410	Events/day	7.26 6.62 5.37	[tmean] -10 to -5°C <5°C >15°C	-
Mannino 1989[87]	Death certificate data	Wisconsin, USA 1982-1987	926	Mean temperature <-18 to >16°C	As per death certificate (91% certified by medical examiner). Deaths in health care facilities excluded.	Events/day (age adjusted)	0.145* 0.110* 0.090* (p-trend <0.01)	≤17.8°C -0.6 to 7.2°C ≥16.1°C	-
Frost 1993[88]	Australian Bureau of Statistics, and Statistics Canada data	Brisbane, Australia (1984-1985) and Montreal, Canada (1983-1987)	Not given	Mean temperature 13-26°C (AU[&]) -15 to 25°C (CA[&])	Deaths with ICD9 codes of 410	Correlation coefficient[$]	0.55 to 0.77[$] -0.73 to -0.91[$] (p<0.01 in each case) 0.15 to 0.63[$] -0.40 to 0.31[$] (p≤0.01 except winter 1983)	-	Summer,AU[&] Winter, AU[&] Summer, CA[&] Winter, CA[&]
Baker-Blocker 1982[89]	National Center For Health Statistics mortality tapes	Minneapolis, USA 1973-1977 (winters only)	Not given	Departure of minimum temperature from long term average	Deaths with ICD8 codes of 410	Correlation coefficient	No effect in 4/5 winters studied (p>0.05) r=-0.28 for winter 1976-1977 (p<0.01)	-	-
Bull 1975[90]	Office of Polulation Censuses and Surveys Data	England and Wales 1970-1971	Not given	Minimum temperature	Deaths with ICD8 codes of 410	Correlation coefficient	-0.10*	-	At 1 day lag

+ p-value for heterogeneity across temperature categories
++: EW = England and Wales
** approximate figures, derived from graphical presentation of results*
$ correlations were presented for each individual year in the paper, range of values shown here
& AU = Australia, CA = Canada

2.4 Discussion

The systematic review presented here is the first to focus on the association between ambient temperature and the specific outcome of MI. The search strategy employed is likely to have identified most major studies focussing on this question. Steps were also taken to include papers in which MI was investigated as a sub-analysis within a broader study.

A total of 19 relevant studies were identified, with 14 investigating short-term (day-to-day) effects of temperature on MI risk. A number of large and relatively well-controlled studies have reported a statistically significant short-term effect of ambient temperature on MI risk. The vast majority of studies reported main effects on the same day or up to 3 days later, with no study reporting substantial effects lagged by more than one week. Over half of the daily time series regression studies reported detrimental effects of cold and over half reported detrimental effects of heat; indeed a few studies found a U-shaped relationship with MI risk increasing at both ends of the temperature scale.

The size of temperature effects varied. Three studies of MI mortality outcomes were among those estimating the largest temperature effects, estimating as much as a 31-44% increase in risk at the extremes of the local temperature scale compared with intermediate local temperatures. The larger size of these mortality effects might reflect an inherent lack of specificity in studies with mortality outcomes; some deaths are likely to have been coded as MI based on limited information leading to potential misclassification, and if such misclassified causes of death were more strongly associated with temperature, results may have been exaggerated. On the other hand studies based on hospital admissions may have underestimated the true temperature effects if difficulties in getting to hospital during temperature extremes led to more out-of-hospital MI deaths occurring which would not have been included. Although studies including non-fatal events generally estimated effects that were smaller in magnitude, detrimental effects of both heat and cold were still found in a number of these studies; considering the 5 studies in which MI outcomes were validated against diagnostic criteria, 1 and 3 studies found significant effects of heat and cold respectively.

Various mechanisms have been suggested through which cold exposure could act as a trigger for myocardial infarction, and it is possible that a number of parallel processes contribute to the effect. Experimental studies have found increased arterial pressure and blood viscosity during cold exposure,[91] as well as an increased need for oxygen and consequently an increase in the cardiac workload.[92] Furthermore, red cell counts, plasma cholesterol and fibrinogen concentrations, all of which may be thrombogenic, appear to be elevated on exposure to cold.[91, 93] Heat exposure has also been shown under controlled conditions to lead to increases in red blood cell counts, platelet counts, and blood viscosity, as well as increases in heart rate.[94] Finally, one study has suggested that the density distribution of blood platelet subpopulations may be affected, with an observed increase in less dense platelets that were more sensitive towards aggregation-inducing agents.[95] However there is a lack of more recent data regarding the effects of temperature on an updated range of clotting measures and more research is needed in this area.

The majority of studies included used data sources such as hospital databases and registries which would have had the potential to capture events across the local population, thus their findings should have good generalisability within the local settings. There could be a number of reasons for the heterogeneity in results between studies. One must consider that the studies included here cover a wide range of populations with differing demographic profiles, as well as a wide range of geographical locations. There were also many methodological differences across the studies included: MI events were identified from sources of various types; modelling strategies varied; different definitions of temperature were used as the main exposure (such as minimum, maximum, mean, wind-chill-adjusted); different allowances for non-linear temperature effects were made; and different lag days considered. There was also variation in the level of adjustment for potential confounding factors, and inadequate control for factors such as air pollution (which was only controlled for in a handful of studies) could have led to some spurious results.

In addition local climate may play a role in the vulnerability to temperature effects. One study which incorporated data from 21 countries found that local mean temperature explained much of the variation in the magnitude of the detrimental effect of cold on MI risk,[54] and it was correspondingly observed that,

among single-location studies, those conducted in areas with higher long-term mean temperatures tended to more frequently report detrimental effects of cold than those conducted in warmer areas, and indeed tended to report effect estimates with larger magnitude. No such pattern was observed for the effect of heat, despite the differing effects of heat that have been reported on overall mortality in different locations.[11] These findings must be interpreted with caution, since the studies included in the review differed in so many ways. Nevertheless, increases in systolic blood pressure in response to lower temperatures have been found to be larger in warmer countries,[96] and studies of all-cause mortality have similarly reported local climate to be a strong modifier of temperature effects.[9, 19] Such effect modification may simply reflect better established adaptive measures in colder countries; the Eurowinter Group found that, at the same outdoor temperatures, individuals in Finland were more likely to have bedroom heating, kept their indoor temperatures higher, and were more likely to wear hats, gloves, anoraks, and (among women) trousers, compared with individuals in Athens, Greece,[12] and the potential benefits of such adaptive measures are suggested by the observed improvements in blood pressure achieved following installation of home heating in a UK study.[97] Others have suggested that there may be some biological adaptation to cold,[98] and cold-adapted individuals have been shown to have reduced activity of the sympathetic nervous system in response to cold stress.[99]

Long-term effects of temperature were investigated by only two small studies, both of which reported increased MI risk associated with exposure to cold; firm conclusions cannot be drawn from such limited data. Approaches using more complex composite weather parameters were also used in only a handful of studies. Though such parameters may be attractive in principal (they seem intuitively better equipped to capture the overall weather experience), results from these studies proved difficult to interpret and compare in practice; furthermore, the practical usefulness of such parameters as part of any public health warning system would be dependent upon easily available forecasts.

This review inevitably has some limitations. First, the search strategy could have missed some studies. However, by searching a number of different databases, with different indexing systems, and furthermore checking reference lists and the websites of major organisations, it is likely that all major studies

with MI as the primary outcome should have been picked up. Steps were also taken to include studies of cardiovascular diseases more broadly, where an analysis of MI was also performed separately. The decision to include only papers analysing specific MI outcomes may also have led to some informative studies of related outcomes being excluded, though it was felt that this would be outweighed by the advantage in interpretability from the very specific focus on MI. Second, as with any review of the literature, there may have been publication bias: studies finding effects may have been more likely to be published. The extent of publication bias is difficult to assess in studies with such varied methodology and reporting. Though such concerns should always be borne in mind, the goal was not to produce a definitive numerical estimate of the effects of temperature on MI risk, but rather to give an overview of the evidence available. Finally, non-English-language citations were excluded due to resource limitations, though this is unlikely to have led to the omission of any major papers in the area.

There is some public health motivation for further clarifying the effects of temperature. Weather forecasting is reasonably accurate up to a few days in advance, and with a well understood relationship between temperature and MI, those most vulnerable could be warned when the risk of MI was likely to increase, and given advice to reduce their personal risk. The UK Met Office recently set up a similar targeted warning system for chronic obstructive pulmonary disease sufferers in which patients are alerted by an automated telephone call when the risk of disease exacerbation is elevated based on the ambient temperature; they are given advice on keeping warm, avoiding low temperatures, and watching for warning signs of their condition worsening. It is claimed that a 20.5 to 48% reduction in hospital admissions has been achieved among practices signing up to the scheme.[100] Health service providers could also be warned in advance where rates of MI were likely to increase, to aid the short-term allocation of resources.

A number of suggestions arise for future research. Though the majority of the studies included were of similar basic design (daily time series studies), there was wide variation in the methodology and reporting used. More consistent adjustment for potential confounders such as season, long-term trend, and air pollution; allowance for non-linear and delayed temperature effects; and more

consistent reporting standards would make future studies in this area easier to compare and interpret. More large studies with this kind of consistent methodology and reporting will be required in a number of geographical locations to characterise the short-term effects of temperature on MI risk, and the relationship of such effects to local climate. There is also a need for more studies which take account of potential effect modifiers such as air conditioning for heat-related MIs, and home heating and use of cold weather clothing for cold-related MIs. Though a few studies have presented stratified or age-restricted data, there is little direct evidence on how age, and other individual-level factors such as previous disease, affects an individual's vulnerability to temperature effects. In addition, individual-level studies collecting detailed information on factors as clothing and home heating, though expensive and difficult to design, would provide valuable data to assess the role of adaptive measures. Finally, though the role of more complex weather indicators, such as air mass type, remains unclear and difficult to interpret, the effects of such factors may be worthy of further investigation, since weather effects on human health may not be captured fully by investigating only specific parameters such as temperature and humidity; indeed interactions between the various aspects of weather may in part help to explain some of the variation in results across studies included in this review.

2.5 Update: studies published since this review

Two studies, published since this review was undertaken and fulfilling the original inclusion criteria, were identified by a literature search update performed in July 2010.

Wolf et al[101] analysed data on 9801 fatal and non-fatal MIs occurring in Augsburg, Germany between 1995 and 2004 using data from the Augsburg MI registry. Lower temperatures were associated with increased MI risk (RR = 1.10 per 10°C reduction, 95% CI 1.04-1.15). Linear and non-linear effects were examined but there was no evidence of non-linearity and no heat effect was observed. Effects lagged by up to 5 days were investigated; interestingly, the effects of temperature reductions appeared to be more delayed for non-fatal than fatal MIs, with the quickest effects being observed at two days lag for the non-fatal, but on the same day for fatal MIs. In a smaller study, Abrignani et

al[102] investigated admissions for acute MI to a single hospital in Sicily between 1987 and 1998. 3918 events were included and higher minimum daily temperature was associated with a reduction in MI risk, consistent with a detrimental cold effect, though the effect size was not clear from the study report and non-linear temperature effects were not considered.

Taken together, these two studies are in agreement with the majority of studies identified in the review in finding an association between lower temperatures and MI risk, but it was noteworthy that neither of the studies, conducted in Central and Southern Europe, observed a detrimental effect of higher temperatures.

2.6 Summary

A systematic review was undertaken focussing on the effects of ambient temperature on MI risk.

19 studies were identified, with 13 investigating the short-term (day-to-day) effects of temperature using daily time series data.

Over half of the daily time series regression studies reported detrimental effects of cold and over half reported detrimental effects of heat.

Overall, there was strong evidence, including from a few large and well controlled studies, that ambient temperature influences the risk of MI, but the exact nature of the relationship and strength of the effects were unclear.

3 Systematic review of the effects of air pollution on incidence of myocardial infarction

3.1 Introduction and aims

There has been considerable recent research into the effects of air pollution on health outcomes, which has been facilitated by an increase in air quality monitoring data in many countries. A wide array of outcomes and combinations of exposures has been considered, with consistent associations being observed between levels of certain pollutants and mortality in particular. Effects on more specific outcomes have been less commonly studied. The aim of the systematic review presented below was to collate and present published evidence on the effects of common air pollutants (including PM, ozone, CO, oxides of nitrogen (NO, NO_2, NO_x), and SO_2) on the risk of MI.

3.2 Methods

The methods of this review were similar to those of the earlier review into the effects of ambient temperature (see Chapter 2), and are therefore summarised more briefly here.

3.2.1 Search strategy

3.2.1.1 Databases and sources

Searches of the publication databases Medline (1950 to present), EMBASE, and GEOBASE were undertaken. Since the study of air pollution effects on health could be considered a form of toxicology, TOXNET, a bibliographic database specialising in this discipline, was also searched. Reference lists of all relevant studies were scanned to identify any further studies, and where appropriate, index terms from such studies were added to the main database search. The websites of key research organisations (World Health Organisation; European Union; Health Effects Institute (USA); Environmental Protection Agency (USA); National Institutes of Health (USA); Department of Health (UK);

and Department for Environment, Food, and Rural Affairs (UK)) were also searched for relevant reports.

3.2.1.2 Search keywords and terms

For Medline and TOXNET, which employ the MeSH classification system, the following MeSH terms were used for the primary search:

> [AIR POLLUTION or AIR POLLUTANTS or OZONE or CARBON MONOXIDE or SULFUR DIOXIDE or PARTICULATE MATTER or NITROGEN OXIDES or ENVIRONMENTAL EXPOSURE (plus all sub-terms in the MeSH tree)] and
>
> not TOBACCO SMOKE POLLUTION and
>
> [MYOCARDIAL INFARCTION {subheadings: chemically induced, mortality, physiopathology, prevention and control, epidemiology, aetiology} (plus all sub-terms in the MeSH tree)] and
>
> HUMANS [not (ADOLESCENT or CHILD or INFANT not ADULT)];
>
> limited to article types: JOURNAL ARTICLE or CLASSICAL ARTICLE or GOVERNMENT PUBLICATIONS or CLINICAL CONFERENCE or CLINICAL TRIAL or COMPARATIVE STUDY or META ANALYSIS;
>
> limited to language: ENGLISH

For EMBASE the following terms were used:

> [AIR POLLUTION or AIR POLLUTANT or AIR POLLUTION CONTROL or OZONE or CARBON MONOXIDE or NITROGEN DIOXIDE or NITROGEN OXIDE or SULFUR DIOXIDE or PARTICULATE MATTER] and
>
> [HEART INFARCTION or ACUTE HEART INFARCTION or HEART VENTRICLE INFARCTION]; limited to language: ENGLISH

For GEOBASE, a keyword search was used (* at the end or ? in the middle of a term indicate that any letters are accepted in the given position):

> [AIR POLLUT* OR OZONE OR CARBON MONOXIDE OR SUL?UR DIOXIDE OR PARTIC* OR NITROGEN DIOXIDE OR NITROGEN OXID* OR NITRIC ACID] and [MYCARDIAL INFARCT* or CORONARY EVENT or HEART ATTACK or Q WAVE INFARCT* or NON-Q WAVE INFARCT* or STEMI or MYOCARDIAL THROMBOSIS or CORONARY THROMBOSIS]

As in the previous systematic review (Chapter 2), a secondary search of Medline was then run to identify any studies where MI may have been included as part of a wider study of cardiovascular outcomes, using the MeSH heading CARDIOVASCULAR DISEASES (plus all sub-terms) in place of MYOCARDIAL INFARCTION, and restricting to studies where one of the following terms was present in the title, abstract, or keywords (* at the end of a term indicates that any ending is accepted):

(MYOCARDIAL INFARCT* or CORONARY EVENT or HEART ATTACK or Q WAVE INFARCT* or NON-Q WAVE INFARCT* or STEMI or CORONARY INFARCT* or HEART INFARCT* or MYOCARDIAL THROMBOSIS or CORONARY THROMBOSIS)

3.2.1.3 Inclusion and exclusion criteria

Inclusion criteria

The following study characteristics were required for inclusion:

1. Analysis of original data included
2. One or more of the following exposures investigated: particulate matter or black carbon/black smoke, ozone, carbon monoxide, any oxide of nitrogen, sulphur dioxide. Studies using reasonable proxies such as exposure to traffic were also included.
3. Myocardial infarction included as a specific outcome
4. Manuscript available in English language
5. Study of adult humans

Exclusion criteria

Studies were excluded if they had:

1. No control for (or stratification by) any potential confounding factors
2. No measure of precision or p-value associated with main result(s) of interest

3.2.1.4 Procedure

The procedure was similar to that described for the earlier review or weather effects (Chapter 2). Titles and abstracts were screened for relevance, and full

text versions obtained where appropriate for assessment with reference to the inclusion and exclusion criteria (see Section 3.2.1.3). For each study included, the following information was recorded: study population, event of interest, number included, age range included, location and setting, time period, exposure variables, ascertainment of MI, spatial resolution, temporal resolution, adjustment for weather variables and other potential confounders, lags considered.

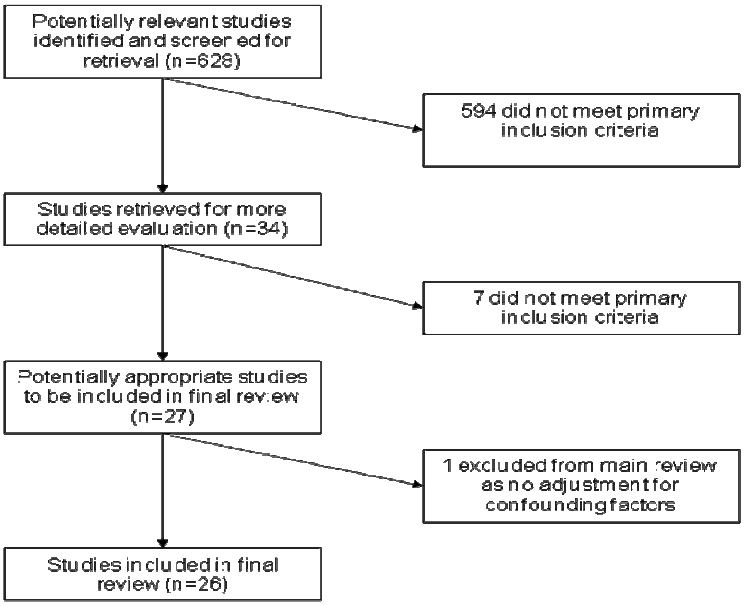
The main results of each study were also recorded, in particular the effects of each pollutant of interest on risk of myocardial infarction, including effect sizes and confidence intervals where possible. Where authors reported several relevant results (e.g. for different lag days, or for different subgroups), we chose results from the main or final model if such a model could be identified, or else from the analysis on which the authors focused or that which best represented the overall conclusions of the study, noting any important heterogeneity in the effect estimates between different analyses.

The search was initially conducted in July 2008. An additional search was undertaken in July 2010 to identify major studies published since the systematic review (see Section 3.5).

3.3 Results

A total of 27 studies met the inclusion criteria, however one[81] was excluded because only a basic analysis was performed with no consideration of potential confounding factors., leaving 26 in the final review (Figure 3.1). The majority of studies were concerned with identifying short-term associations between air pollution exposures and MI risk; these studies, generally based on population-based case-only designs, are considered in Section 3.3.1. A few papers considered longer-term effects of air pollution, including analyses of two prospective cohort studies, and three case-control studies; these are covered in Section 3.3.2.

Figure 3.1: Flow diagram for search strategy



3.3.1 Short-term effects of air pollution

19 studies investigated the short term associations between air pollution and MI risk (Table 3.1, Table 3.2, and Table 3.3). A number of specific pollutants were investigated, the most common being PM_{10} (10 studies), $PM_{2.5}$ (5 studies), ozone (12 studies), CO (13 studies), NO_2 (13 studies), and SO_2 (10 studies). The number of individual pollutants investigated by a single study ranged from 1 to 8. The studies fell into two categories in terms of design: 10 were analyses of daily time series data, while the remaining 9 used case-crossover designs.

3.3.1.1 Study designs and methodological considerations

Both time series and case crossover study designs are based solely on data from individuals who have experienced the event of interest (in this case, MI). The time series design was introduced in the review of temperature effects (Section 2.3.1.1); briefly, such studies typically take as their outcome the daily number of events in a defined region, and a regression analysis is performed to relate these daily counts to explanatory variables (in this case, pollutant levels) and potential confounders.

Table 3.1: Studies of short-term effects of air pollution on MI outcomes - description of studies

First author & Year of publication	Population/ data source	Location & Time period	No. of events included (mean/ per day)	Air pollution exposure variable(s)	Potential confounders included	MI ascertainment	Lags considered (days, except where noted)
Daily time series studies studies							
Fatal & non-fatal events							
Cendon 2006[103]	Hospital admissions data (112 hospitals: infirmaries and ICUs); age >64 only	Sao Paulo, Brazil	19272* (26.4)	PM_{10} (24hr av),	Season and trend, temperature (*non-linear, 2 day moving average*), humidity, day of week	Events with ICD-10 codes suggesting MI in the Public Health Data Analysis System Division	0 to 7 inclusive
Lanki 2006[104]	MI registers and hospital discharge registers	5 European cities (1992-2000 (3-7 yrs period per city)	26854 (between 0.9 to 8.4 per city)	PM10, O3 (8hr av, summer only), NO2, CO, modeled particle number conc. (proxy for PM <0.1ug/m3)	Season and trend, apparent temperature (*non-linear, same day and average of lag days 1-3*), barometric pressure, weekday indicator, holiday indicator	Records with ICD9 code 410 in hospital registers (2 cities); or records meeting MONICA definition of MI in MI registers (3 cities)[52]	0 to 3 inclusive
Koken 2003[57]	Hospital admissions data (11 hospitals, covering ages 65+)	Denver county, USA 1993-1997 (July/August only)	1576* (5.1)	PM_{10}, O_3, NO_2, SO_2, CO (all 24hr av)	Daily maximum temperature (*lag days 0-4*), dewpoint temperature, day of week, calendar year, population size	Primary discharge diagnosis (ICD9=410.XX)	0 to 4 inclusive
Mann 2002[38]	Records from a health maintenance organization	Southern California, USA 1988-1995	19690 (6.7*)	PM_{10} (24hr av), O_3 (8hr av), NO2, (24hr av) CO (8hr av)	Season and trend, temperature (*non-linear, same day*), relative humidity, calendar year, day of week, annual population size	Records with ICD9 code 410	0 to 5 days inclusive
Ye 2001[72]	Hospital emergency transports records (4 hospitals, age 65+)	Tokyo, Japan 1980-1995 (July and August only)	3200* (3.28)	PM_{10}, O_3, CO, NO_2, SO_2, (all daily av)	Annual trends, daily maximum temperature (*lag days 0-4*), population size.	As diagnosed by emergency physician, based on presenting symptoms	0 (adjusted for 1-4 inclusive)
Linn 2000[105]	Hospital admissions data	Los Angeles, USA 1992-1995	Not reported	PM_{10}, O_3, CO, NO_2 (all 24hr av)	Season and trend, day of week, holidays, mean temperature (*same day*), barometric pressure, indicators for hot days, cold days, rain days	Records with an All-Patient-Refined Diagnosis-Related Group code of 111, 115, or 121	Different lags considered, exact strategy unclear
Poloniecki 1997[106]	Hospital episode statistics	London, UK 1987-1994	68300* (26.7)	O_3 (8hr av); NO_2, SO_2, CO, black smoke (all 24hr av)	Season and trend, temperature (*lag day 1*), humidity, day of week, public holidays, 'flu epidemic indicator	Records with ICD9 code 410	1
Fatal events only							
Murakami 2006[107]	Vital statistics of Japan data (34 districts)	34 districts, Japan 1990-1994	14430 (7.9*)	Suspended particulate matter (hourly measurements)	Time of day, temperature (*non-linear, same day*), region	Records with ICD9 code 410	Exposure windows from 1 to 48 hrs
Sharovsky 2004[61]	Death registry data	Sao Paulo, Brazil 1996-1998	12007 (16.4)	PM_{10}, CO, SO_2 (daily av)	Season and trend, mean temperature (*non-linear, up to lag day 7*), relative humidity, atmospheric pressure, day of week, holidays, influenza levels	Death certificates with MI (ICD10 = I21) listed as primary cause	0, and moving average of up to previous 7 days

Rossi 1999[62]	Vital statistics department mortality data	Milan, Italy 1985-1989	1600* (0.9)	Total suspended particles	Season & trend, temperature (*non-linear, lag days unclear*), relative humidity, day of week, holidays, epidemics, pollution	Deaths with ICD9 codes of 410	Different lags considered, exact strategy unclear
Case –crossover studies (*fatal & non-fatal events)*							
Barnett 2006[108]	Hospital admissions data from 7 cities	Australia (5 cities) and New Zealand (2 cities) 1998-2001	28818*	$PM_{2.5}$ (24hr av), PM_{10} (24hr av), O_3 (8hr av), CO (8hr av), NO_2 (24hr av)	Temperature (*lag days 0-1*), change in temperature from previous day, humidity, hot and cold days, pressure, day of week, holiday, rainfall	Records with ICD9 code 410 or ICD10 code I21-22	Average of 0 to 1
Zanobetti 2006[109]	Hospital admissions from US Medicare programme (age 65+)	Boston metropolitan area, USA 1995-1999	15578	PM2.5, PM non-traffic (modeled), O3, CO, NO2, black carbon	Apparent temperature (*non-linear, lag day 1*); also matched for same day temperature), day of week	Records with ICD9 code of 410	0, 1, and mean of 0 and 1
Peters 2005[110]	Coronary event registry (cases surviving first 24 hours only)	Augsburg, Germany 1999-2001	851	$PM_{2.5}$, total number concentration (proxy for ultrafine particles), O_3, SO_2, CO, NO_2 (all 24hr av; 1hr av also considered for PM)	Temperature (*non-linear, same day*), day of week	Patients meeting MONICA definition of MI[52]	0 to 5 (also 0 to 6 hours for hourly analysis)
Ruidavets 2005[111]	MI registry	Toulouse, France 1997-1999	399	O_3 (highest 8 hr av of the day), SO_2 (24hr av) , NO_2 (24hr av0)	Day of week (matched), min and max temperature (*same day*), humidity, influenza levels	Clinical, ECG and enzyme data available to support diagnosis	0 to 3 days inclusive
Sullivan 2005[112]	Community database linking emergency service and hospital outcome data	Washington State, USA 1988-1994	5793	Increase in short-term average $PM_{2.5}$ (derived from fine PM), defined as 10ug/m3 increase in 1, 2, 4, 24 hr - averaged PM2.5). Similar for SO2 and CO.	Temperature (*non-linear, same day*), relative humidity,	Discharge diagnosis of MI confirmed by enzyme and ECG changes	0 to 2 days inclusive
Zanobetti 2005[113]	Hospital admissions from US Medicare programme (age 65+)	21 cities, USA 1986-1999	302453	PM_{10} (daily av)	Day of week (matched), apparent temperature (*non-linear, lag days 0-1*)	Medicare claims where primary diagnosis had ICD9 code 410	0 to 2 days inclusive
Peters 2004[114]	KORA MI registry	Augsburg, Germany 1999-2001	691	Exposure to traffic (from retrospective diary for the 4 days preceding event	None specified	Records meeting MONICA definition of MI[52]	0 to 6 days inclusive
D'Ippoliti 2003[115]	Regional hospital admissions data	Rome, Italy 1995-1997	6531	Total suspended particles, CO, SO_2, NO_2 (all 24hr av)	Day of week (matched), temperature (*non-linear, lag day 1*), humidity, air pressure	Records with ICD9 code of 410	0 to 4, and mean of 0-2 days
Peters 2001[116]	Coronary care unit admissions records	Greater Boston, USA 1995-1996	772	$PM_{2.5}$, PM_{10}, ozone, SO_2, NO_2, CO, black carbon	Season, day of week, minimum daily temperature (*non-linear, same day*), relative humidity	Patients had all of: ≥1 CK above upper limit of normal, positive MB isoenzymes, symptoms	0 to 5 inc, also 0 to 5 hrs for hourly analysis

** derived from reported mean daily rate, and length of period under study*

Table 3.2: Studies of short-term effects of air pollution on MI outomes - summary interpretation

First author & Year	Significant effect of exposure?								Adjusted for season and trend?	MI events: validation or specified criteria	Adjusted for temperature	Adjusted for infectious disease levels	Adjusted for day of week?	Investigated different lag effects?
	$PM_{2.5}$	PM_{10}	O_3	CO	NO_2	SO_2	Other particulate exposures	Other non-particle exposures						
Daily time series studies														
Fatal & non-fatal events														
Cendon 2006[103]	-	No	Yes	No	No	Yes	-	-	✓	×	✓	×	✓	✓
Lanki 2006[104]	-	No	No	Yes	No	-	No (PNC*)	-	✓	✓	✓	×	✓	✓
Koken 2003[57]	-	No	Protective effect	No	No	No	-	-	N/A+	×	✓	×	✓	✓
Mann 2002[38]	-	No	Protective effect	Yes	Yes	-	-	-	✓	×	✓	×	✓	✓
Ye 2001[72]	-	No	No	No	Yes	No	-	-	N/A+	×	✓	×	×	✓
Linn 2000[105]	-	Yes	No	Yes	Yes	-	-	-	✓	×	✓	×	✓	✓
Poloniecki 1997[106]	-	-	No	Yes	Yes	Yes	Yes (BS*)	-	✓	×	✓	✓	✓	×
Fatal events only														
Murakami 2006[107]	-	-	-	-	-	-	Yes (TSP*)	-	×	×	✓	×	×	✓
Sharovsky 2004[61]	-	No	-	No	-	Yes	-	-	✓	×	✓	✓	✓	✓
Rossi 1999[62]	-	-	-	-	-	-	Yes (TSP*)	-	✓	×	✓	✓	✓	✓
Case -crossover studies *(fatal and non-fatal events)*														
Barnet 2006[108]	Yes	No	No	Yes	Yes	-	-	-	N/A$	×	✓	×	✓	×
Zanobetti 2006[109]	Yes	-	No	No	Yes	-	Yes (BC*) No (PM non-traffic)	-	N/A$	×	✓	×	✓	✓
Peters 2005[110]	No	-	Protective effect	No	No	Yes	No (TNC*)	-	N/A$	✓	✓	×	✓	✓
Ruidavets 2005[111]	-	-	No	-	No	No	-	-	N/A$	✓	✓	✓	✓	✓
Sullivan 2005[112]	No	-	-	No	-	No	-	-	N/A$	✓	✓	×	×	✓
Zanobetti 2005[113]	-	Yes	-	-	-	-	-	-	N/A$	×	✓	×	✓	✓
Peters 2004[114]	-	-	-	-	-	-	-	Yes (traffic exposure)	N/A$	✓	×	×	×	✓
D'Ippoliti 2003[115]	-	-	-	Yes	No	No	Yes (TSP*)	-	N/A$	×	✓	×	✓	✓
Peters 2001[116]	Yes	Yes	No	No	No	No	No (coarse mass, BC)	-	N/A$	✓	✓	×	✓	✓

** PNC = particle number concentration; TSP = total suspended particulate; TNC = total number concentration; BS = black smoke; BC = black carbon*

+ Adjustment for season not applicable since study used data from summer months only

$ Case-crossover design allows for season and trend by design

Table 3.3: Studies of short-term effects of air pollution on MI outomes - detailed study results

First author & Year	Exposure variable	Relative risk or rate ratio (95% CI)	Exposure increase (or category) to which RR refers	Lag (days)	Comment
Daily time series studies (*Fatal & non-fatal events)*					
Cendon 2006[11]	PM_{10} O_3 CO NO_2 SO_2	1.032 (0.978, 1.086) 1.093 (1.011, 1.174) 0.998 (0.933, 1.066) 1.038 (0.962, 1.114) 1.129 (1.064, 1.194)	22.5 [units not given] 50.23 1.42 54.67 10	Sum of 0-7	For NO_2, cumulative effect estimate hides a significant effect at lag 0, but then reduced risk at lags 2-3. For other pollutants, effects appeared to be dominated by lag 0 effect. Effects shown are for ICU admissions, similar effects seen when infirmary admissions were considered; (for PM_{10} – effect reached significance)
Lanki 2006[12]	PM_{10} O_3 CO NO_2 PNC*	1.003 (0.995, 1.011) 0.994 (0.986, 1.002) 1.025 (1, 1.051) 0.995 (0.985, 1.006) 1.005 (0.996, 1.015)	10µg/m^3 10µg/m^3 1mg/m^3 10µg/m^3 10000 /cm^3	0	No statistically significant effects at lags 1, 2, 3 days for any pollutant. There was a suggestive effect of PNC, when restricting to the three cities using hospital discharge register data, which had higher power.
Koken 2003[13]	PM_{10} O_3 CO NO_2 SO_2	N.S. (detail not reported) 0.819 (0.726, 0.923) N.S. (detail not reported) N.S. (detail not reported) N.S. (detail not reported)	 10ppb	0	Only the lag value with the strongest effect was given; therefore the effect of ozone at 1-4 days lag was not reported.
Mann 2002[5]	PM_{10} O_3 CO NO_2	0.999 (0.987, 1.011) 0.993 (0.985, 0.997) 1.035 (1.024, 1.046) 1.02 (1.011, 1.03)	10µg/m^3 10ppb 1ppm 10ppb	Not reported	-
Ye 2001[14]	PM_{10} O_3 CO NO_2 SO_2	N.S. (detail not reported) N.S. (detail not reported) N.S. (detail not reported) 0.006 (0.003, 0.010) N.S. (detail not reported)	- - - Not reported -	Not reported	Model estimates do not directly indicate effect size. We can only conclude that there was some positive effect of NO2 on MI outcomes, and no significant effect of other pollutants
Linn 2000[15]	PM_{10} O_3 CO NO_2	1.01 (1, 1.01) 0.965 (0.899, 1.035) 1.041 (1.023, 1.059) 1.056 (1.005, 1.11)	10µg/m^3 10ppb 1ppm 10ppb	0	Part of a wider paper on CVD - the effects seen were not specific to MI alone: CO and NO_2 were also associated with congestive heart failure, asthma and COPD, suggesting just one manifestation of an effect on susceptible individuals
Poloniecki 1997[16]	O_3 CO NO_2 SO_2	0.993 (0.981, 1.006) 1.023 (1.007, 1.04) 1.009 (1.003, 1.016) 1.017 (1.007, 1.027)	10ppb 1ppm 10ppb 10ppb	1	Futher breakdown indicated that the effects found were only significant in the cool season (Oct-Mar). SO_2 was independently associated with MI in the cool season in all 2-pollutant model combinations. NO_2, CO, black smoke were not associated in 2-pollutant models, except in combination with O_3.
Daily time series studies *(Fatal events only)*					
Murukami 2006[17]	TSP* (categorized)	1.00 [reference category] 1.13 (1.07, 1.20) 1.18 (1.01, 1.37) 1.40 (1.00, 1.97)	0-99µg/m^3 100-149µg/m^3 200-249µg/m^3 ≥300µg/m^3	0-1 hours	The effects were similar when exposure windows of up to 6 hours were considered; but there was a less clear "dose-response" relationship when periods longer than 6 hours were used.

Sharovsky 2004[18]	PM_{10} CO SO_2	1.01 (0.91, 1.11) 1.014 (0.995, 1.03) 1.03 (1.005, 1.07)	10µg/m^3 1ppm 10µg/m^3	Av of 0-3	-
Rossi 1999[19]	TSP	1.10 (1.13, 1.18)	100µg/m^3	Av of 3-4	Av of 3-4 day lag best predictor; little effect of concurrent day's exposure
Case -crossover studies *(Fatal and non-fatal events)*					
Barnett 200620	$PM_{2.5}$ PM_{10} O_3 CO NO_2	1.073 (1.035, 1.114) N.S. (detail not reported) N.S. (detail not reported) 1.032 (1.009, 1.055) 1.088 (1.02, 1.163)	10µg/m^3 - - 1ppm 10ppb	Av of 0-1	Effect estimates shown are for ages 65+ years, effects were in the same direction for those aged <65 years, but none were statistically significant
Zanobetti 2006[21]	$PM_{2.5}$ PM non-traffic O_3 CO NO_2 Black carbon	1.052 (1.007, 1.092) 1.0439 (0.9688, 1.1170) 0.988 (0.957, 1.017) 1.124 (0.973, 1.284) 1.074 (1.034, 1.104) 1.0834 (1.0021, 1.1582)	10µg/m^3 10.28µg/m^3 10ppb 1ppm 10ppb 1.69µg/m^3	Av of 0-1	Results for same-day pollution levels only were in the same direction and of similar magnitude; the effect of black carbon was non-significant on the same day alone, whereas CO was significantly predictive of MI on the same day (though not for days 0 and 1 averaged)
Peters 2005[22]	$PM_{2.5}$ O_3 CO NO_2 SO_2 TNC*	1.105 (0.987, 1.226) 0.94 (0.895, 0.987) 1.32 (0.968, 1.801) 1.033 (0.966, 1.104) 1.475 (1.069, 2.005) 1.04 (0.90, 1.20)	10µg/m^3 10µg/m^3 1mg/m^3 10µg/m^3 10µg/m^3 6400/cm^3	2	Strong effect of PM2.5 among the subgroup of never-smokers (RR 1.20, 1.04-1.39 per 7.7µg/m3). Strongest pollution effects seen at 2 days lag as shown. There were no statistically significant effects of pollutants on any other lag days. In an hourly analysis, there was no effect of $PM_{2.5}$ or TNC at the hourly level at up to 6 hours lag.
Ruidavets 2005[23]	O_3 NO_2 SO_2	1.082 (0.98, 1.166) 0.922 (0.81, 1.04) 0.98 (0.723, 1.323)	10µg/m^3 10µg/m^3 10µg/m^3	0	There was an effect for O_3 at 1 day lag (p=0.02), but not longer lags. The O_3 effect only was statistically significant at 0 and 1-day lag when possible coronary deaths/sudden deaths/deaths with insufficient data included
Sullivan 2005[24]	$PM_{2.5}$ CO SO_2	1.01 (0.98, 1.05) 1.04 (0.99, 1.08) 0.97 (0.94, 1.01)	10µg/m^3 1ppm 10ppb	Av of 0-1 hours	The authors also found no effects when increasing the averaging time for the exposure variables from 1 to 24hours before the event.
Zanobetti 2005[25]	PM_{10}	1.007 (1.003, 1.01)	10µg/m^3	0	Dose-response relationship observed. Little effect at lag days 1 or 2.
Peters 2004[26]	Traffic	2.73 (2.06, 3.61)	Odds ratio for traffic exposure	1 hour	-
D'Ippoliti 2003[27]	TSP* CO NO_2 SO_2	1.028 (1.005, 1.052) 1.044 (1, 1.089) 1.293 (0.97, 1.741) N.S. (detail not reported)	10µg/m^3 1mg/m^3 10µg/m^3 -	Av of 0-2	For total suspended particulate and CO, the only effect was the same-day; for NO2, there was no same-day effect, but a significant effect with 2 days lag. Effects of TSP and CO were stronger in the warm season, and among those with heart conduction disorders
Peters 2001[28]	$PM_{2.5}$ PM_{10} O_3 CO NO_2 SO_2	1.17 (1.035, 1.325) 1.109 (1.015, 1.211) 1.062 (0.965, 1.17) 1.22 (0.89, 1.67) 1.019 (0.934, 1.112) 0.98 (0.911, 1.058)	10µg/m^3 10µg/m^3 10ppb 1ppm 10ppb 10ppb	2 hr, hourly analysis	Coarse mass and black carbon also investigated but were not significantly associated with MI risk There was also a significantly elevated risk of MI associated with 24 hr average levels lagged by one day (i.e. levels from 24-48 hrs before the event), for $PM_{2.5}$, PM_{10}; and non-significant increased risks for coarse mass, black carbon, and NO_2.

**PNC = particle number concentration; TSP = total suspended particulate; TNC = total number concentration; SPM = suspended particulate matter*

Note: estimates converted where possible to:– PM_{10}: per 10µg/m^3; $PM_{2.5}$: per 10µg/m^3; O_3: per 10ppb or 10µg/m^3; CO: per ppm or mg/m^3; NO_2: per 10ppb or 10µg/m^3; SO_2: per 10ppb or 1µg/m^3

A case-crossover study can be thought of as a kind of self-matched case-control study. For each individual, exposure data are collected for the "hazard" period (usually the period immediately before the MI) and for one or more "control" periods which were not associated with the event of interest. For example, consider an individual who has experienced an MI: the period immediately before the MI (say, the 24 hours leading up to the event) might be defined as the hazard period for that individual; a control period might be a similar 24-hour period 7 days before the event. Exposure data are then collected from the hazard period and the control period(s), analogous to collecting exposure data from a case and their matched control(s) in an ordinary matched case-control study. Analysis can be performed using conditional logistic regression models. It should be noted that in reality the choice of appropriate control periods in case-crossover studies requires rather more care than is implied in the simplified example above, since some control selection strategies can lead to biases arising.[117]

Air pollutant data originated from monitoring stations and were most commonly recorded as 24-hour averages, though 8-hour averages were also frequently used (Table 3.1). One study by Peters et al used traffic exposure as the exposure of interest and this was ascertained from diary data.[114] MI data came from more varied sources. Three studies looked exclusively at MI deaths, and used death registry and vital statistics data to identify cases: as discussed previously (Section 2.3.1.1), mortality studies relying purely on routine cause of death coding may be more likely to include a proportion of deaths in which MI was not the true cause. The remaining 16 studies included data on both fatal and non-fatal MI events. The majority identified MI cases through hospital admissions records (n=8 studies), while the remainder used data from other hospital records (n=3), MI registers (n=3), and other databases (n=2). Six studies, with access to symptom, ECG, and biomarker records, validated potential MI events using specific diagnostic criteria.

Key potential confounders and the possibility of delayed effects were dealt with fairly consistently across studies. In case-crossover studies, confounding by season, long-term trend, and factors which do not vary over the short-term, is dealt with by design. The majority of time series studies included also adjusted

for season and long-term trend, as well as temperature, which is a potential confounder since temperature may be associated with both pollution levels and MI risk. However the specific way in which authors adjusted for temperature was varied; while a few studies allowed for both non-linearity of the temperature effect and for delayed (lagged) temperature effects over a number of days, others performed only a more basic adjustment (Table 3.1), Lagged effects of air pollution itself were included in all studies; in most cases both immediate (same day) effects and a number of different lags were considered.

3.3.1.2 Results of time series studies

A total of 10 studies included in the review were analyses of time series data. The earliest study, by Poloniecki et al,[106] included over 68000 London hospital admissions for acute MI over a 7 year period, and assessed the effects of 1-day lagged pollutants (ozone, SO_2, NO_2, CO, and black smoke), finding significant detrimental effects of all pollutants except for ozone. Estimated effect sizes for each pollutant ranged from a 2.7% to a 3.3% increase for an increase in pollutant level from the 10^{th} to 90^{th} percentile. Further analyses suggested that these effects were limited to the cold season only (October to March). Interestingly, though the authors investigated a number of outcomes (including angina pectoris, cardiac arrhythmia, heart failure, cerebrovascular diseases, and other circulatory diseases), only acute MI was consistently associated with all pollutants except ozone. Only SO_2 retained a statistically significant effect in all 2 pollutant model combinations.

Three studies investigated a common set of pollutant exposures: PM_{10}, ozone, CO, NO_2, and SO_2. Cendon et al[103] included admissions to ICUs and infirmaries in Sao Paulo, Brazil. SO_2 and PM_{10} were significantly associated with both outcomes, with ozone associated with an increase in admissions to ICUs but not infirmaries, and no effect of CO or NO_2. The generally stronger effect of pollutants on ICU admissions (compared with infirmaries) may reflect a greater specificity of diagnoses in this setting, as well as more severe disease. The authors presented cumulative effects over lag days 0-7, though lag days 0 and 1 contributed the majority of the observed effects. Both Koken et al[57] and Ye et al[72] conducted studies restricted to over-65 year olds and to the months of July

and August, located in Denver (USA) and Tokyo (Japan) respectively. The former study found no detrimental effect of any pollutant, and actually reported a protective effect of ozone (17.5% [95% CI 7.5 to 26.7%] reduction in the same-day MI risk for a 9.7ppb increase in ozone levels), while the latter found that only NO_2 was associated with an increased risk of MI, though the authors did not present any directly interpretable effect sizes.

A further three studies investigated the effects of the four pollutants PM_{10}, ozone, CO and NO_2. Linn et al[105] looked at the effects of these pollutants on hospital admissions for MI over a 3 year period in Los Angeles, USA. Like Poloniecki et al,[106] the authors found that all pollutants with the exception of ozone were associated with an increase in MI risk. However in this paper, which looked at a number of cardiovascular outcomes, the effects seen were not specific to MI alone: CO and NO_2 were also associated with congestive heart failure, asthma and COPD, suggesting that the MI effect may have been just one manifestation of a more general effect on susceptible individuals. Mann et al[38] also studied hospital admissions in a region which included Los Angeles, USA. MI was not the primary outcome of this study, therefore only brief results were reported. Again CO and NO_2 were found to be associated with an increase in MI risk, though in this study, the authors found no effect of PM_{10}. Ozone was significantly protective for MI; a 10ppb increase in ozone levels was associated with a 0.7% reduction in MI risk (95% CI 0.3 to 1.5% risk reduction). Lanki et al[104] found little effect of any of the 4 pollutants in an analysis of 26854 first MI hospitalisations from 5 European cities, though ozone was considered in the summer only. The authors additionally looked at the effects of particle number concentration (PNC), a proxy for ultrafine particles (<0.1 μg), which was measured for a year in each city and modelled retrospectively to cover the full study period. There was no effect of PNC in the main analysis, though in an analysis restricted to the 3 cities using hospital discharge (as opposed to MI registry) data, there was a suggestion of a detrimental effect of PNC, particularly among fatal cases in the under-75s; it seems possible that this result, based on cause of death data in a non-specific discharge register, may have been influenced by misclassification of other non-MI events.

Three studies analysed MI mortality data only. Sharovsky et al[61] looked at the effects of PM_{10}, CO, and SO_2 on MI deaths in Sao Paulo, Brazil. 12007 MI deaths over a 3 year period were included. The study included adjustment for a number of potential confounders. There was no effect of PM_{10} or CO, though for the latter there was a suggestion of an increase in MI deaths during periods with higher CO levels. SO_2 was significantly associated with MI mortality: a 10μg/m^3 increase in SO_2 levels, averaged over lag days 0-3, was associated with a 3.0% increase in MI deaths (95% CI 0.5 to 7.0%). A further two studies looked specifically at the effect of total suspended particulate (TSP); Rossi et al[62] included 1600 MI deaths and controlled for a number of potential confounders. An effect of TSP (which the authors suggested was approximately equivalent to PM_{13}) was found at 3-4 days lag, with a 100μg/m^3 increase in TSP associated with an estimated 10% increase in MI mortality (95% CI 13 to 18). There was little effect of exposure on the same day. Murakami et al[107] considered the effect of a similar exposure at an hourly level, finding that MI rates increased in the hour following high TSP levels (and for up to 6 hours); there was an apparent dose response relationship with higher TSP threshold levels associated with greater increases in MI rates. It is worth reiterating that all of these mortality studies may inadvertently have included a higher proportion of non-MI events than studies of non-fatal MIs, and this could either dilute or exaggerate observed effects.

3.3.1.3 Results of case-crossover studies

9 further studies considered short-term air pollution effects on MI risk using a case-crossover study design, all of which included non-fatal MI events. The two largest studies were based on US hospital admissions data from the Medicare programme, which has data on those aged over 65 years only. Zanobetti and Schwartz[113] studied data from 302453 hospital admissions in 21 US cities, considering only PM_{10} as the exposure of interest, and finding a small but statistically significant association with same-day MI risk (0.65% increase in risk [95% CI 0.3 to 1.0%] per 10μg/m^3 increase in PM_{10} levels). There did not appear to be any lagged effect, at the lags of 1 and 2 days considered in the analysis. A second study by the same authors reports results from similar Medicare data in Boston (n=15578), this time on a wider range of exposures.[109]

An increase in $PM_{2.5}$ levels from the 10^{th} to 90^{th} percentile (averaged over 0 and 1 days' lag) was associated with a 8.6% increase in MI risk (95% CI 1.2 to 15.4). PM "not from traffic" (a modelled exposure) showed no effect and the only gaseous pollutant to be significantly associated with MI was NO_2, with no effect of ozone or CO.

D'Ippoliti et al[115] found that a 10μg/m^3 increase in TSP (averaged over 0-2 days lag) was associated with a 2.8% (95% CI 0.5 to 5.2%) increase in MI risk in Rome, Italy, though further analysis of different lags revealed that the effect was actually restricted to the same day. The authors also looked at the effects of gaseous pollutants CO, SO_2, and NO_2, with only CO appearing to be associated with MI (4.4% [0.0 to 8.9%] increase in risk per 1μg/m^3 increase in CO averaged over 0-2 days lag); again the real effect was restricted to the same day. A study by Barnett et al[108] in Australia and New Zealand made comprehensive adjustment for weather, with the authors including relative humidity, pressure, and rainfall in their models. Among older patients (aged ≥65 years), higher levels of $PM_{2.5}$, CO, and NO_2 were all associated with increased MI risk, though there was no effect of PM_{10} or ozone. Low power may have been an issue for Ruidavets et al,[111] who found no effect of ozone, SO_2, or NO_2 in a very small case crossover study (n=399) based in the Toulouse area of France. However a suggestion of a detrimental effect of ozone (lagged by one day) was strengthened when the authors loosened their definition of MI to include 76 "possible coronary deaths".

Three studies were able to look at the effects of pollutants at an hourly, rather than daily, temporal resolution. Peters et al[116] studied 772 coronary care admissions data from Greater Boston, USA finding an effect of hourly $PM_{2.5}$ concentration lagged by 1, and 2 hours. When daily $PM_{2.5}$ levels were considered, there was also a lagged effect at 1 and 2 days before onset. Results were similar for PM_{10}, but gaseous pollutants (O_3, CO, NO_2, and SO_2) did not show a significant effect on the risk of MI. Since the exact timing of MI was determined by patient interview a median of 4 days after the event, this may have been subject to some recall error. Furthermore, since only one monitoring station was used covering the whole Greater Boston area, the measured pollutant levels may not have reflected personal exposure accurately.

Nevertheless, the results do raise the possibility that other studies using 24 hour mean values and analyses with daily resolution may miss transient immediate increased risks associated with hourly pollutant levels. Sullivan et al[112] attempted to confirm these findings in a larger study of 5793 MI events, taken from a community database linking emergency service response data with hospital outcomes in Washington State, USA. The exact time of the emergency call was available, as well as the duration of pain at this point, hence time of symptom onset could be estimated. Interestingly, in this larger study, no effect of $PM_{2.5}$ was found, using exposure averaging periods ranging from 1 hour before the event, to 24 hours before the event. Even when the authors deliberately replicated the methods of Peters et al, no similar effect was found. The authors speculate that this may be due to different composition of particulate matter in the different regions, or due to differing susceptibilities of the populations of the two areas to air pollution effects. A later study by Peters et al[110] using data from Germany found no effect of $PM_{2.5}$ in an hourly analysis looking at up to 6 hours lag. However, analysis at a daily resolution suggested a possible effect of $PM_{2.5}$ delayed by 2 days, with a 7.7μg/m^3 increase associated with an 8% increase in MI risk 2 days later (95% CI -1 to 17%). In this study SO_2 was also associated with increased MI risk 2 days later, though ozone, CO, and NO_2 had no effect.

Finally, Peters et al[114] took a slightly different approach; instead of using directly measured pollutant levels, the study looked simply at the risks associated with exposure to traffic, as recorded in an interview-based diary completed retrospectively by the 691 participants, covering the 4 days before the MI. Exposure to traffic (defined as the patient using any means of transportation) was strongly associated with MI risk; there was a significant immediate effect, as well as an effect 1, 2 and 5 hours later (OR = 2.92 [2.22 to 3.83] for exposure to traffic 1 hour before the event). Cycling was more strongly associated with MI than travel by car or public transport. It should be noted that factors other than air pollution may have contributed to the effects found. Though the authors attempted to control for severe exertion, being outside, and getting up in the morning, there may still have been residual effects of physical exertion or stress that could be associated with both travel and MI risk. It is also possible that

recall bias could have operated in the data collection process; interviews were conducted a median of 9 days after the event and a bus ride or car journey a few hours before a subject had an MI may be more likely remembered than one on a less eventful day some time earlier.

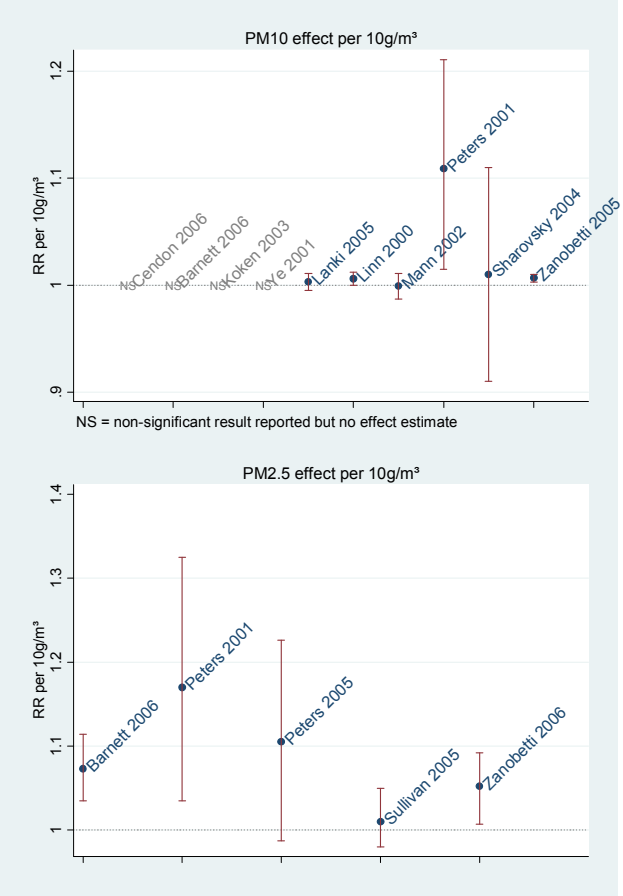
3.3.1.4 Summary of studies of short-term effects of air pollution

Having considered the particular features of individual studies, it is helpful to consider the overall evidence regarding each pollutant and its associations with MI risk. To aid comparison between studies, effect estimates in this section and in Figure 3.2 and Figure 3.3 are rescaled to refer to a standardised increase in pollutant levels where possible.

Particulate pollutants

Out of 10 studies investigating the effects of PM_{10} on MI risk, 7 found no effect at all (Table 3.2 and Figure 3.2). Zanobetti et al estimated a 0.65% (95% CI 0.3 to 1.0%) increase in MI admissions on the same day as a 10μg/m^3 increase in PM_{10} among those aged ≥65 years,[113] while Linn et al reported an effect of similar size for a study population with no age restriction.[105] However the Onset Study, which used admissions records from a Boston coronary care unit and analysed data at an hourly level, found a considerably larger effect, their estimate implying an 11% increase in risk for a 10μg/m^3 increase in PM_{10} one hour earlier.[116] This larger effect was not only observed at the hourly timescale; the same authors also found a large and statistically significant effect at a daily resolution, in contrast with the lack of effect found by most studies.

Figure 3.2: Estimated effects of particulate pollution on MI risk



RR = relative risk

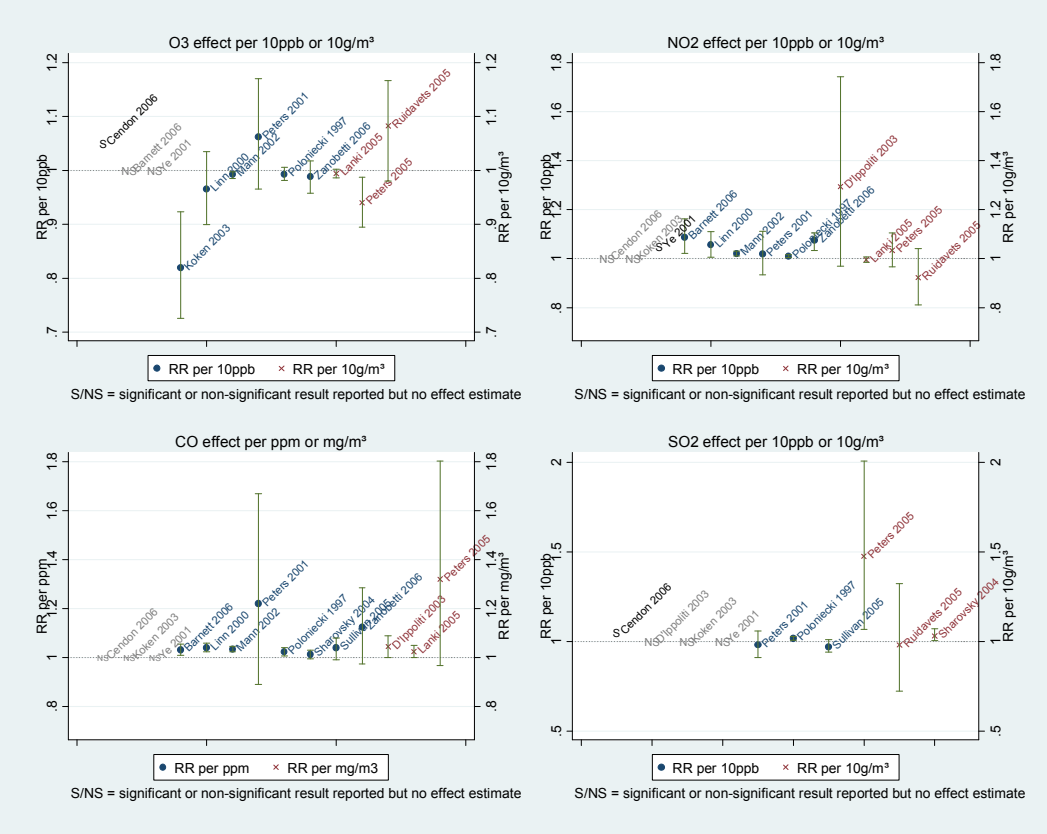
$PM_{2.5}$ was included as an exposure of interest in 5 studies, all of which were of a case-crossover design. 3 of the 5 studies reported that $PM_{2.5}$ significantly increased the risk of MI. Effect sizes of 5 to 7% per 10μg/m^3 increase were estimated in 2 studies using a daily timescale for analysis,[108-109] while a third found no effect overall.[110] These effects were observed between 0 and 2 days after a change in $PM_{2.5}$ levels. A few studies were able to analyse data at an hourly resolution, with 2 finding no effect of $PM_{2.5}$ on this timescale.[110, 112] As with PM_{10}, results from the Onset Study were contrasting: the authors estimated a 17% increase in risk 2 hours after a 10μg/m^3 increase in $PM_{2.5}$.[116]

Other particulate exposures were investigated in some studies. Of note, two studies looking at proxies for ultrafine particles found no effect on MI risk.[104, 110] On the other hand, total suspended particulate was included as an exposure in three studies, and all reported a significant association with MI, either on the same day,[107, 115] or with some delay.[62]

Gaseous pollutants

Ambient ozone was investigated as a risk factor for MI by 12 studies, only one of which reported a detrimental effect, with MI admissions to intensive care units increasing on days with higher ambient ozone.[103] More common were studies reporting a protective effect of ozone (Table 3.2 and Figure 3.3). Surprisingly, out of 10 studies reporting a numerical estimated odds ratio or relative risk for MI associated with an increase in ozone levels, the estimate was <1 in 7 studies, and this protective effect was statistically significant in 3 studies. However, effect sizes varied: while Koken et al[57] estimated an 18% reduction in MI risk for a 10 parts per billion (ppb) increase in ozone, Mann et al[38] estimated only a 0.7% risk reduction for an equivalent increase in ozone. It is worth recording that the relationship between ozone levels and the levels of other pollutants appeared to vary between studies. For example, considering the four studies reporting a significant effect of ozone in either direction, Cendon et al[103] (the only study finding a detrimental effect of ozone) recorded positive correlations between ozone and other measured pollutants, whereas the remaining studies reported correlations that were either negative[57, 110] or both negative and positive.[38]

Figure 3.3: Estimated effects of gaseous pollutants on MI risk



RR = relative risk

Evidence for an effect of ambient CO, NO_2, or SO_2 levels on MI risk was mixed, however for each of these pollutants, a proportion of studies (6/14, 6/13, and 4/10 respectively) found a significant detrimental effect, whereas no study found an effect in the opposite direction. Only four studies studying multiple pollutants found no effect of any of these gases;[57, 111-112, 116] one did not report the number of cases included but the other three were relatively small studies (n=5793, 772, and 399) which may have had limited power. Among studies which measured CO levels in parts per million (ppm, as used more commonly than $\mu g/m^3$ or mg/m^3), the four studies finding a significant effect presented effect sizes that were fairly consistent, each estimating a 2-4% increase in MI risk per 1ppm increase in CO.[38, 105-106, 108] For NO_2, effect sizes ranged from a 1% to a 9% increase in risk per 10ppb increase in NO_2 levels, though the largest effects appeared in study populations restricted to those aged over 65 years.[108-109] Comparison of effect sizes among the four studies reporting an SO_2 effect is more difficult since different pollutant measures were used between the studies.

Finally, it is worth noting that the effects of these gases, where reported, appeared to operate relatively quickly: in most cases either on the same or next day.

3.3.1.5 Vulnerability among subgroups

A number of the studies included in this review performed analyses stratified by various factors to assess the vulnerability of particular subgroups to any effects of air pollution on MI risk. In general, study reports did not state whether such subgroup analyses were pre-planned and their results should thus be interpreted cautiously. Most commonly investigated was the role of age.

Barnett et al,[108] who found detrimental effects of $PM_{2.5}$, CO, and NO_2 among those aged 65 years and over (Table 3.3), reported that effects for those aged <65 years were smaller and non-significant, though it should be noted that event rates were lower among this age group so that lack of power could have been responsible for the lack of a statistically significant effect. Lanki et al[104] correspondingly reported that the effects of CO and particle number concentration were larger among those aged ≥75 years, though only for non-fatal outcomes (for CO: RR per 0.2mg/m3 = 1.015, 95% CI 1.004-1.026 compared with 1.001, 0.995-1.008 for those aged <75 years); indeed the opposite effect was seen when fatal MIs were considered. The detrimental effects of ozone[111] and of traffic exposure[114] also appeared to increase for older subgroups. In contrast, Sullivan et al reported no modification by age of the effect of $PM_{2.5}$ on MI risk.[112]

Other potential effect modifiers were less commonly investigated. One study considered the effects or $PM_{2.5}$ by race, sex, and smoking status, and found no differences;[112] this was in contrast with a study suggesting that the effect of $PM_{2.5}$ may be larger among never-smokers than current- or ex-smokers (OR per IQR increase = 1.20, 95% CI 1.04-1.39 for never-smokers compared with 1.04, 0.90-1.21 for current smokers),[110] and that increased risk associated with traffic exposure may be larger among women compared with men (OR per IQR increase = 4.51, 2.55-8.00 for women compared with 2.59, 1.90-3.53 for men).[114] The detrimental effects of traffic exposure were also reported to be larger among those out of employment though confidence intervals were

overlapping (OR 4.20, 2.88-6.12 compared with 2.20, 1.47-3.28 for those currently employed).[114]

3.3.2 Long-term effect of air pollution exposures on MI risk

The studies reviewed in section 3.3.1 were designed to detect short term effects of air pollution, i.e. effects acting over a matter of a few hours or days. A few studies have looked at longer range effects (Table 3.4).

One such study in Rome, Italy, looking specifically at the effects of NO_2 as a marker of traffic-related pollution, related the mean annual NO_2 level to the incidence of MI, using Poisson regression.[118] 1061 fatal and 6513 non-fatal MIs were included, from regional cause of death and hospital discharge registers respectively. Though mean annual exposure to NO_2 appeared to be associated with MI risk in univariate analyses, there was no significant effect after adjusting for age, sex, and socioeconomic status. The authors separately analysed out-of-hospital deaths, in which they included all ischaemic heart disease; when this outcome was used, NO_2 did appear to be associated with incidence (RR = 1.04 [1.02 to 1.12] per 10μg/m^3 increase).

The remaining studies of long term effects fall into two main categories – prospective cohort studies, and case-control studies.

3.3.2.1 Prospective cohort studies

Three papers reported on prospective cohort studies. In such studies, data are collected on “healthy” individuals (in terms of the outcome of interest) who are then followed up to see if they develop disease. This approach can avoid certain biases associated with identifying cases retrospectively. However, for anything other than very common conditions, the design may be inefficient: many people must be followed up, and even then only a small number of cases may be observed. This can lead to low power to detect small effects.

Table 3.4: Studies of long-term effects of air pollution on MI outcomes

First author & Year of publication	Population/data source	Location & Time period	Number of MI events	Air pollution exposure variable(s)	MI ascertainment	Result		
Cohort studies								
Miller 2007[29]	Cohort of postmenopausal women aged 50-79 years	36 cities, USA 1994-1998	584 (cohort size =65893)	Average annual exposure to PM2.5*	From annual questionnaires and national death index; independently adjudicated by investigators.	$PM_{2.5}$:	[Hazard ratio] 1.06 (0.85, 1.34)	Per 10μg/m^3 increase
Abbey 1993[30]	Cohort of seventh-day Adventists	California, USA 1977-1982	62 (cohort size =6303)	Average and cumulative exposure to ambient NO_2 estimated for places of residence /work*	From hospital records; reviewed by a cardiologist on the study staff	NO_2:	"No association" (details not reported)	
Abbey 1991[31]	Cohort of seventh-day Adventists	California, USA 1977-1982	62 (cohort size =6303)	Cumulative exposure to total suspended particles (TSP), and O_3* over a 5 year period prior to follow-up	From hospital records; reviewed by a cardiologist on the study staff	TSP: O3:	[Hazard ratio] 0.93 (0.57, 1.51) 1.06 (0.69, 1.61)	≥1000 vs. <1000 hours exposure to 200μg/m3 ≥500 vs. <500 hours exposure to 10pphm
Case-control studies								
Tonne 2007[32]	Cases from community-based MI study; population controls	Worcester, Massachusetts, USA 1995-2003	5049 (controls =10277)	Cumulative traffic at place of residence (average daily traffic within 100m multiplied by total length of road)	MI reviewed and independently validated according to diagnostic criteria	Cum-ulative traffic:	[Odds ratio] 1.04 (1.02-1.07)	Per 794 vehicle-kms
Rosenlund 2006[33]	Cases (aged 45-70y) from coronary and intensive care unit discharge registers & death certificate data; population controls	Stockholm, Sweden 1992-1994 (exposure estimated over 30 years prior to events)	1397 (controls =1870)	30-year mean annual NO_2, CO, SO_2 modelled from source-specific emissions database. PM estimated in 2000 and assumed constant.	From coronary units, ICUs, hospital discharge register, death certificates using standard diagnostic criteria	 PM_{10}: CO: NO_2: SO_2:	[Odds ratios] 1.0 (0.79, 1.27) 1.04 (0.89, 1.21) 0.99 (0.76, 1.30) 1.03 (0.78, 1.36)	 Per 5μg/m3 increase Per 300μg/m3 increase Per 30μg/m3 increase Per 40μg/m3 increase
Grazuleviciene 2004[34]	Cases (aged 25-64y) from coronary and intensive care discharge registers; population controls	Kaunas, Lithuania 1997-2000	448 (controls =1777)	NO_2 exposure in district of residence (categorised into high/medium/low tertiles)	Records with ICD10 codes of I21 and consistent symptoms, ECG, marker levels	NO_2:	[Odds ratios] 1.00 [ref] 1.43 (1.04, 1.96) 1.43 (1.07, 1.35)	 Low (mean 13.1μg/m3) Medium (mean 18.7μg/m3) High (mean 24.7μg/m3)
Population based studies								
Rosenlund 2008[35]	Hospital discharge registry and regional cause of death registry	Rome, Italy 1998-2000	1056 (fatal) + 6513 (non-fatal)	Mean annual NO_2 exposure	Records with ICD9 codes of 410	NO_2:	[Relative risk] fatal: 1.05 (0.97, 1.15) non-fatal: 1.01 (0.97, 1.05)	 Per 10μg/m3 increase Per 10μg/m3 increase

**based on measured data from monitoring station*

One such study, described in two papers,[119-120] followed a cohort of 6303 seventh-day Adventists in California, USA, between 1977 and 1982. During this time 62 MIs occurred among study participants; cardiologists on the study staff reviewed enzymes and ECG readings to confirm these MIs. Cumulative exposure to total suspended particles and ozone over the five years prior to the study follow-up period were not found to be related to MI. However, with few events, confidence intervals were wide and did not rule out large effects in either direction, highlighting the potential difficulties of prospective cohort studies in this field. The later report,[119] which looked at the effect of NO_2 also reported no effect. In a more recent study[121] among 65893 postmenopausal women aged 50-79 in 36 US cities, 584 MI events were observed between 1994 and 1998; again MI events were independently verified by study staff. The authors concentrated on a particular pollutant, $PM_{2.5}$. Average annual exposure to this particulate matter was obtained for each woman, by collecting data from the nearest monitoring station to her home. However these $PM_{2.5}$ measures were not related to MI risk in multivariate Cox models.

3.3.2.2 Case control studies

Case-control studies have been used as an alternative design to prospective cohort studies for assessing long-term effects of air pollution. Since patients with MI are identified retrospectively, they have the advantage that many more cases can be included without the need for a vast study population. Such studies may therefore have greater power to detect effects.

Grazuleviciene et al[122] collected data on 448 cases of MI using coronary and intensive care unit registers in Kaunas, Lithuania. Cases were among 25-64 year-olds, and 1777 controls were drawn from the local population. Annual mean NO_2 levels, based on the participant's place of residence, were used as a marker of exposure to vehicle exhaust. Those in the highest tertile of NO_2 exposure (exposed to mean NO_2 concentrations of 24.7 $\mu g/m^3$) were at increased risk of MI (OR = 1.43 [1.07 to 1.35]) compared to those in the lowest tertile (with mean exposure 13.1$\mu g/m^3$). The authors found a yet stronger effect in the older individuals (age 55-64: OR = 2.07 (1.28, 3.35) for 3rd vs 1st tertile).

The authors adjusted for age, smoking, blood pressure, body mass index, psychological stress, marital status, and education. Nevertheless the principal concern about the conclusions is that residual confounding may have been present because of the classification of NO_2 exposure based on residential district, which may bring with it many other differences, e.g. in environmental factors, socioeconomic status, and occupation.

Rosenlund et al[123] looked at data on 1397 cases of MI, drawn from hospital-based registers and death certificate data; controls (n=1870) had no history of MI and were randomly selected from the study base, stratified by age, sex and hospital catchment area. Air pollution exposure came from a spatial model based on Swedish emission databases. Annual mean levels of NO_x, NO_2, CO, SO_2 were estimated at high spatial resolution, and mapped to the study population by their residential addresses to create an overall 30-year average exposure for each pollutant. PM_{10} and $PM_{2.5}$ exposure was calculated for the year 2000 only and assumed to be constant throughout the study period due to a lack of historical data. The authors found no effect of long term exposure to any pollutant on MI incidence, though there was some suggestion of an increase in the risk for out of hospital MI deaths for NO_2, CO, and PM_{10}.

Finally, Tonne et al[124] report on a case-control study with 5049 confirmed cases of MI and 10277 controls (matched on age, sex and region). The exposure measure was a proxy for exposure to traffic, and was based on the product of the total road length within 100m of the subject's home, and the average traffic levels in the same zone. It is difficult to judge how good this proxy is likely to be for personal exposure, and the measure does not account for possible behavioural differences for those near roads (e.g. staying indoors, closing windows), or for individuals moving in and out of the area. That said, the authors found a 4% (95% CI 2-7) increase in the odds of MI per IQR increase in this proxy for cumulative traffic.

3.4 Discussion

This review has identified a number of studies investigating both the short- and long-term associations between pollutant levels and the risk of MI,

concentrating principally on the effects of exposure to particulate matter and a range of common gaseous pollutants.

From a total of 19 studies looking at short-term pollution effects, fairly persuasive evidence emerges of some short-term effects on MI risk. Among particle exposures, though no effect of PM_{10} was found in most studies, increasing daily $PM_{2.5}$ levels were commonly associated with increasing MI risk between 0 and 2 days later. Increases in risk of 5-7% for a 10μg/m^3 increase in $PM_{2.5}$ levels were typically reported, though one study reported an effect over three times this size. The evidence concerning effects of gaseous pollutants was more mixed: increases in CO, NO_2, and SO_2 were all associated with increases in MI risk in a substantial proportion of studies, yet just over half of the studies that investigated each of these exposures reported no effects. Surprisingly, higher levels of ozone were in a number of studies associated with a reduction in MI risk. However, ozone levels may be reduced close to sources of nitric oxide (such as vehicular traffic), where the two gases react to produce NO_2. It has also been suggested that a negative correlation between ozone and methyl nitrate (a combustion product of some engine fuels) could be responsible for such paradoxical associations.[125] Thus higher ozone levels may be acting as a marker of reductions in other pollutants. We noted that among a limited number of studies that addressed the question of effect modifiers, there was some suggestion that older individuals may be more vulnerable to the detrimental effects of pollution.

Though the evidence concerning most commonly measured pollutants may appear to be varied and sometimes conflicting, it should be borne in mind that, as in the previous review of temperature effects (Chapter 2), the studies included here were conducted using varying methodologies, and in varying situations. Variation in estimated effects may have been caused by a number of factors: different locations may have had differing underlying pollutant levels, different populations may have had differing susceptibilities, and different methods of exposure measurement, event ascertainment, and statistical analysis may have led to differing results.

With the earliest study of short-term effects meeting our inclusion criteria published in 1997, the quality of methodology seen in these studies reflects recent standards, with widespread attempts to control for important potential confounders, such as season, trend, and ambient temperature, using statistical models. The majority of studies also included non-fatal MIs which may be less susceptible to misclassification than MI deaths; some further validated MI diagnoses by having ECG and enzyme data examined by study investigators. Nevertheless there are inherent limitations in observational studies of air pollution effects. A common concern is that pollution measured by outdoor monitors may not be a good measure of personal exposures,[126] though median correlations as high as 0.92 have been reported between personal and central station $PM_{2.5}$ in homes without environmental tobacco smoke.[127] In time series studies, by design, exposure must be averaged over the whole region being analysed. This is a potential weakness since in reality levels of pollutants may vary substantially over, say, a city. Although the case-crossover design allows for individualised exposure measures, in practice exposure must be approximated using the limited number of pollution monitors available, so the same problem arises. Only the study by Peters et al[114] in which the exposure of interest was exposure to traffic, used a truly individualised exposure, based on diary data. Finally, since commonly measured air pollutants are likely to be highly correlated in any given situation, and unmeasured pollutants may also confound associations, studies such as those included here are unlikely to provide reliable evidence concerning the separate the effects of individual pollutants.

A number of possible mechanisms have been suggested through which air pollution may affect cardiovascular function and trigger acute events. Increases in levels of C-reactive protein[128] and other inflammatory markers[129] at times of higher ambient pollution have been observed, suggesting a systemic inflammatory response associated with exposure. On the other hand, a number of experimental studies have reported no clear systemic inflammatory response on controlled exposure to SO_2, pure carbon particles,[130] fine and ultrafine particles,[131] dilute diesel exhaust,[48] or concentrated ambient particles.[132]

A second proposed pathway is that air pollutant exposure may cause altered autonomic control of the heart rate or heart rate variability. Observational studies have indeed linked higher levels of exposure to particulate air pollution with increases in heart rate[133] and decreases in heart rate variability;[128] furthermore, two studies in which incidence of arrhythmias could be measured using data from implanted cardioverter defibrillators found an increase in discharges of the defibrillators following increases in ambient exposure to fine particles, NO_2, CO, and black carbon,[134-135] while SO_2 has been found in a controlled study among healthy volunteers to reduce cardiac vagal control, which could increase susceptibility to arrhythmias.[130]

A third hypothesis is that pollution induces changes in blood viscosity and factors that may increase the propensity to clot or impair the dissolution of thrombi. Plasma viscosity increased among individuals exposed to a severe episode of air pollution in Germany in 1985.[136] Controlled exposure experimental studies have demonstrated concentrated environmental particles leading to an increase in plasma fibrinogen levels in healthy volunteers,[137] and dilute diesel exhaust leading to an increase in thrombus formation and platelet activation,[138] and an impairment of the acute release of tissue plasminogen activator, an enzyme involved in the breakdown of blood clots.[48] On the other hand one controlled study found that 2 hours of ambient particulate exposure had no effect on fibrinolytic function among either healthy middle-aged volunteers or patients with prior coronary heart disease, despite delivery at 3 to 5 times US EPA National Ambient Air Quality standards.[132]

A fourth possible pathway is suggested by a study in rats in which exposure to urban particulate matter led to an increase in endothelins, which act as vasoconstrictors.[139] Indeed, controlled exposure to a mixture of concentrated ambient particles and ozone in humans led to arterial vasoconstriction in one study.[140] Correspondingly, increased vascular resistance was measured in rabbits following 4 hours exposure to ozone,[141] and one observational study in humans reported an increase in blood pressure associated with increased $PM_{2.5}$ levels in cardiac rehabilitation patients.[142]

Finally, a few individual studies have reported observations suggesting other possible mechanisms: air pollution exposure has been associated with accelerated progression of atherosclerosis and decreased plaque stability,[143] decreased oxygen saturation and hypoxaemia,[144] and increased ischaemic burden.[48] With observational and experimental evidence seemingly supporting a number of potential pathways, it seems plausible that exposure to air pollution may affect the risk of acute cardiac events through multiple mechanisms.

The final part of this review considered studies looking at longer-term effects of air pollution. A small number of prospective cohort studies have observed only a small number of events and thus reported effect estimates with wide confidence intervals. Notably, two case-control studies which looked at long term exposure to traffic based on place of residence (one directly, and one using NO_2 exposure as a proxy) did show a detrimental effect, however these effects could be confounded by factors related to socioeconomic status and occupation. Thus, in contrast with short-term effects, the evidence base for long-term effects of air pollution exposures on MI risk is limited and few convincing conclusions can be drawn.

This review, like that described in the previous chapter, has its limitations. These include the possibility that some studies may have been missed, though it is likely that the search strategy, employing various sources, will have picked up all major studies with MI as the primary outcome. Perhaps of more concern is the potential for publication bias to have coloured the review findings: as well as the classic publication bias mechanism (i.e. a lack of interest from authors and/or journals in publishing negative studies), the field of air pollution epidemiology may be susceptible to a more subtle form of publication bias due to the numerous exposures investigated in most analyses. Authors often appeared to analyse large combinations of pollutants and lag periods, sometimes reporting the strongest effects in quite a post-hoc way, which may have led to a selective emphasis on positive effects. Assessing the extent of such biases is difficult given the variations in methodology and reporting, but such concerns should be borne in mind as a caveat to the findings of this review.

In conclusion, though this review seems to reveal compelling evidence for some effect of air pollution on MI risk, there is much room for further research. Observed pollution effects were not consistent between studies and more large population-based studies may help to clarify the true nature of these effects and the reasons for discrepancies between studies. The exact role of individual pollutants is unclear, and perhaps only further experimental studies under controlled conditions can address this issue. A large number of potential mechanisms have been suggested and though some have the support of limited data, no single mechanism has emerged as the most likely, indeed multiple mechanisms may be at work; further work may reveal the relative importance of each. Finally, future studies may investigate more fully factors that might make some individuals or indeed populations more susceptible than others to the detrimental effects of air pollution.

3.5 Update: studies published since this review

A literature search update performed in July 2010 identified seven studies published since this review was undertaken and fulfilling the original inclusion criteria.

Two new time series studies investigated the short-term effects of fine particulate matter ($PM_{2.5}$) on MI mortality in 112 US[145] and 9 Japanese[146] cities. The larger American study identified a significantly increased risk of MI associated with higher $PM_{2.5}$ levels (estimated increase in risk = 1.2% [0.48-1.89] per 10μg/m^3 increase in $PM_{2.5}$ over lag days 0-1); of note there was no effect of coarse particles (with diameter >2.5 and ≤10μm) in this study. In the Japanese study an effect of similar magnitude was estimated for $PM_{2.5}$ but a wider confidence interval implied that the evidence for an effect from this study was weak, possibly due to lower power (estimated increase in risk 1.8% [-1.17-4.77] per 10μg/m^3 increase in $PM_{2.5}$ over lag days 0-2).

Two case-crossover studies were carried out in Taiwan, one including 9349 hospital admissions for MI in the tropical city of Kaohsiung,[147] and the other 23420 admissions in the sub-tropical city of Taipei.[148] In both cases the effects of PM_{10}, ozone, CO, NO_2 and SO_2, averaged over lag days 0-2, were

investigated. In Taipei, all pollutants except SO_2 were positively associated with MI risk with effect sizes similar on both warm and cool days. In Kaohsiung there was more variation by temperature: on cool days (<25°C) all pollutants except ozone were positively associated with MI risk, while on warm days (≥25°C), though an effect of ozone emerged, all other pollution effect estimates were smaller, and in the case of PM_{10} and SO_2 the effects were no longer statistically significant.

Three studies looked at longer-term effects of exposure to pollution. Following up on their earlier case control study[124] (described in Section 3.3.2.2), which looked at the effects of residential proximity to traffic on MI risk in Massachusetts, USA, Tonne et al[149] considered the effects of long-term exposure to traffic particles, modelled at participants' place of residence based on measured $PM_{2.5}$ and NO_2 emissions. An IQR increase in estimated emission density was associated with an odds ratio for MI of 1.10 (95% CI 1.04-1.16). A second case control study in Sweden modelled 5-year average levels of the traffic-generated pollutants PM_{10}, CO and NO_2 at the home addresses of 24347 individuals who had recorded MI in a Stockholm registry, and 276926 controls.[150] An increase from the 5th to 95th percentile of each pollutant was associated with a significant increase in the odds of fatal MI (ORs ranged from 1.14 to 1.23 for the three pollutants investigated), but there was no effect on non-fatal MI (all ORs <1). Finally, a prospective cohort study in which 66250 female nurses in the north east of the USA were followed up looked at the effects of chronic exposure to PM_{10} using various averaging strategies to estimate exposure.[151] 854 MI events were observed but there was no effect of PM_{10}, regardless of the averaging strategy used.

Overall, the studies identified since the systematic review were in keeping with the earlier literature: in the short-term, MI risk appeared to be associated with daily $PM_{2.5}$ levels, while the evidence for an association with coarser particles and with gaseous pollutants was mixed. The studies of longer-term effects were suggestive of a link between chronic pollution exposure and MI risk but highlighted that observed associations may be dependent on how long-term pollution exposure is measured and defined.

3.6 Summary

- A systematic review was undertaken focussing on the effects of common pollutants on MI risk. 26 studies were identified: 19 investigating effects on a daily or hourly timescale, and 7 investigating longer-term effects.
- Fine particles ($PM_{2.5}$) appeared to be associated with MI risk in a few studies while most studies investigating PM_{10} found no effect.
- Just under half of the studies investigating short-term effects of CO, NO_2, and SO_2 reported positive associations with MI. Ozone levels were inversely associated with MI risk in a number of studies.
- Few informative data were available regarding the effects of long-term exposure to air pollution.
- Overall, there was some evidence that short-term fluctuations in air pollution affect the risk of MI, but further research is needed to clarify the relationship.

4 Data sources and study methods

4.1 Introduction

In this chapter, the main data sources and study methods are described. A brief outline of analytical methods is also given (detailed statistical methods are described in the relevant analysis chapters).

4.2 Data sources

4.2.1 The Myocardial Ischaemia National Audit Project (MINAP)

MINAP is a national register of MI and other acute coronary syndromes (ACS), with participation from all hospitals in England and Wales that admit patients with these conditions.[152] It was set up initially in 1998 to allow clinicians to assess the local management of myocardial infarction against national guidelines and targets.

MINAP aims to include data on all hospital admissions with an ACS diagnosis. The identification of such admissions is managed at the individual hospital level and is not trivial: though ACS or suspected ACS may represent a large proportion of medical admissions, these admissions are likely to be through a number of individual wards and units within each hospital. A set of guidelines exists recommending identifying eligible admissions through a combination of avenues including biochemistry records (specifically troponin measurements), admission notes, and discharge slips.

Each month MINAP accrues around 7000 MI events, recording 108 data fields covering basic demographic data, timing of onset of symptoms, ECG changes, markers of myocardial necrosis, final diagnosis and thrombolytic or other treatment received. Also recorded are pre-existing co-morbidities including hypertension, diabetes and previous cardiovascular events.

Data from participating hospitals are then collated centrally and held at the National Institute for Clinical Outcomes Research at the Heart Hospital, London.

These data have recently become available for researchers, subject to approval by the MINAP Academic Group.

The MINAP dataset in its raw form was delivered as a large SPSS file with a number of data items in string form, which was then transformed into a compact Stata dataset containing the key data items. Tabulations showing the distribution and missingness of a number of variables were examined. A descriptive analysis of the dataset is presented in Chapter 5.

4.2.1.1 Included events

MIs occurring among patients residing within one of 15 conurbations in England and Wales (Greater London, West Midlands, Greater Manchester, West Yorkshire, Tyneside, Liverpool, Nottingham, Sheffield, Bristol, Leicester, Potteries, Cardiff, Southampton, Kingston upon Hull, Norwich) during the period 2003-2006 were included. These conurbations and their boundaries were defined for previous projects[153] and were originally chosen as the largest fourteen conurbations in England and Wales in which regular pollution data were available, plus the largest conurbation in one otherwise unrepresented region (Norwich in the East). The total population of the 15 conurbations is estimated at just less than 18 million.

The discharge diagnosis as recorded in MINAP was used as the basis for defining MI events for inclusion in analyses. Discharge diagnosis in MINAP is grouped into nine categories, and for analyses in this thesis, all events with a discharge diagnosis classified as ST elevation MI, non ST elevation MI, or troponin positive acute coronary syndrome were included. The included diagnoses were defined within MINAP as follows:

ST elevation MI

- Cardiographic changes of ST elevation consistent with infarction of ≥2mm in contiguous chest leads and/or ST elevation of ≥1 mm in 2 or more standard leads, or left bundle branch block (LBBB). Typical changes may have been evident on the admission ECG or may have developed subsequently.

- Enzyme or troponin elevation. For CK, the peak value exceeds twice the upper limit of the reference range. For troponin, the locally accepted cut off value is used.
- History consistent with the diagnosis

non ST elevation MI

- Cardiographic changes consistent with the diagnosis. These may include new ST or T wave changes (except ST elevation).
- Cardiac enzyme or troponin elevation. For CK, the peak value exceeds twice the upper limit of the reference range. For troponin, locally accepted cut off value is used.
- History consistent with the diagnosis
- This group includes infarctions otherwise known as non Q wave, subendocardial and partial thickness infarction.

acute coronary syndrome (troponin positive)

- Symptoms consistent with cardiac ischaemia with release of troponin; the distinction between non ST elevation infarction and an acute coronary syndrome depends on locally applied definitions. The suggested use of this term is when troponin was elevated above the minimum detectable level but less than the locally accepted cut off for MI or when troponin was elevated with a CK value less than twice the upper limit of normal for the hospital.

The decision to include acute coronary syndromes with troponin release was made in order to produce a more consistent definition. Any troponin release indicates muscle death, i.e. infarction, and it was felt that the use of arbitrary and locally variable cut offs for troponin to distinguish between non ST elevation MI and acute coronary syndromes would lead to an inconsistent outcome.

Two versions of the discharge diagnosis were available in the MINAP dataset – the raw diagnosis as coded by the hospital, and an amended diagnosis that corrected inconsistencies with the recorded treatment-determining ECG

appearance as follows. Firstly, where an ECG appearance of ST elevation was recorded but the raw discharge diagnosis was not ST elevation MI, the discharge diagnosis was recoded to ST elevation MI in the amended version. Secondly, where a diagnosis of STEMI had been made but the ECG record did not show ST elevation or left bundle branch block, the diagnosis was recoded to non ST elevation MI in the amended version. After taking advice from the MINAP data management team, the decision was taken to use the amended version of the discharge diagnosis. In particular it was felt that the original coding may have been made by audit clerks with limited knowledge of cardiology, and that ECG appearances should be a major determinant of the final diagnosis.

4.2.1.2 Excluded events

In order to maximise the specificity of the outcome and minimise the possibility of finding spurious effects driven by misclassified outcome events, MINAP events with the following discharge diagnoses were excluded: threatened MI, acute coronary syndrome (troponin negative or troponin unspecified), chest pain of uncertain cause, myocardial infarction (unconfirmed), and other diagnosis. These excluded events were defined in MINAP as follows:

threatened MI

- Rapid resolution of existing ST elevation after early reperfusion treatment + CK rise less than twice the upper limit of normal or a small troponin release. (If only troponin was measured and was elevated; a local decision was made between 'definite infarction' and 'threatened infarction').

acute coronary syndrome (troponin negative)

- Symptoms consistent with cardiac ischaemia without troponin release + dynamic ECG changes consistent with fluctuating ischaemia.

acute coronary syndrome (troponin unspecified)

- Dynamic ECG changes consistent with fluctuating ischaemia, but without a troponin value being available.

chest pain of uncertain cause

- Chest pain not accompanied by significant cardiographic change or enzyme / troponin release, and with no other clear diagnosis. It is likely that at admission there was a high index of clinical suspicion that the pain was cardiac, but this remained unconfirmed.

myocardial infarction (unconfirmed)

- Death before enzyme release could occur or samples be taken, but where clinical judgement, preferably with additional evidence of a history of chest pain or cardiographic changes, suggests myocardial infarction. This definition can only apply to patients who died in hospital.

other diagnosis

- Confirmed diagnosis other than cardiac ischaemia.

4.2.1.3 Dating of MI events

Timing data in MINAP may be recorded at a number of points during the course of an event. For the purpose of these analyses, MIs were dated using the earliest recorded time relating to the event: in most cases the date and time of initial symptom onset as recorded in MINAP. However, this field was not 100% complete; to obtain a complete date field each MI event was dated using the first non-missing date from the following sequence of date fields in MINAP:

1. Symptom onset
2. First call for help
3. Arrival of first professional
4. Arrival of emergency services
5. Arrival at hospital

6. Reperfusion

7. Cardiac arrest

8. Referral for investigations

9. Angiography

10. First intervention

11. Discharge

4.2.1.4 Geographical data processing

Each MINAP event is defined geographically by the number of metres east (easting) and north (northing) of the patient's place of residence, relative to the origin of the British National Grid. For analysis, it was necessary to ascertain which events belong to one of the 15 conurbations specified, and to tie each event to its respective conurbation. The boundaries of the 15 conurbations have been defined for other work, and were available for import into the GIS software package ArcView. By importing the MINAP events themselves into the same software, it was possible to link events to conurbations using the easting and northing coordinates.

4.2.2 Meteorological data

MIDAS is the current climate database of the UK Met Office, and includes surface observations over land areas of the UK dating back to the late 19th century, and originating from monitoring stations of various types (including over 600 in England and Wales).

Climate stations are located at sites selected to be representative of the wider surrounding area, on level ground, and away from trees or large obstructions. Since the 1970s the majority of observations have been automatic.

Daily climate monitoring stations make a single observation at 9am each day, recording the minimum and maximum temperatures reached over the preceding 24 hours (as measured by electrical resistance thermometers), as well as other parameters. This was the primary source of temperature data for analyses in this thesis. In addition, a number of stations record climate observations hourly.

Raw weather data, in particular daily minimum and maximum temperature, and 9am and 3pm temperature and dewpoint temperature, were downloaded from the British Atmospheric Data Centre (BADC), listed by weather monitoring station and measurement date. Maximum temperature as recorded effectively applies to the previous day (since recordings are made at 9am and refer to the maximum over the previous 24 hours); these data were therefore shifted back one day for analysis. Daily mean temperature was then generated, approximated as the mean of the daily minimum and maximum temperature.

Relative humidity (RH) at 9am 3pm was derived from the 9am and 3pm measurements of dewpoint and temperature, and the mean of the 9am and 3pm RH values was then used as the daily measure.

The postcode of the weather monitoring station was included as part of the dataset. A list of the postcodes falling within each of the 15 conurbations of interest had been prepared for an earlier project and was obtained, allowing the weather stations located within each of the conurbations to be identified. In order to produce a final dataset for analysis, it was necessary to overcome the following issues: some conurbations contained no monitoring stations; some conurbations contained more than one monitoring station; and some conurbations contained monitoring stations with data missing on a percentage of days.

4.2.2.1 Conurbations with >1 monitoring station

Where data from >1 station were available in a conurbation, these were combined to one series using the AIRGENE algorithm.[154] Briefly, on days where all stations have non-missing readings, the output series simply takes the value of the mean of these readings. If a particular monitor (say, monitor A) has a missing value on a particular day (day δ), this would first be replaced with the mean value of monitor A over all days, plus a value derived from the mean of the readings over all other monitors in the conurbation on day δ (the exact value added is the mean of the standardised (Normal deviate) values of all monitors on day δ, multiplied by the standard deviation of monitor A readings for all

days). Finally the output series, on day δ, then takes the value of the mean of readings from all stations on day δ, including the newly imputed reading.

4.2.2.2 Conurbations with incomplete data, or with no monitoring stations

After combining data in conurbations with multiple stations as described above, 8 conurbations had some missing data or no data at all (see Section 5.3.1).

10 complete meteorological series were available at a broader "regional" level, for the whole of England and Wales, based on the following regions: North East, North West, Yorkshire and the Humber, East Midlands, West Midlands, East, London, South East, South West, and Wales. These regional series draw from all available monitoring data in the region to produce a representative series for the whole region. We used these series as a basis for imputing data for days with missing temperature at the narrower conurbation level.

Specifically, for each conurbation, a simple linear model was fitted over all days in the period 2003-2006, specified as follows:

$$(\text{conurbation temperature}) = \beta\ 0 + \beta 1(\text{regional temperature})$$

This model was estimated using days with non-missing conurbation temperature. The resulting model was then used to predict conurbation temperature on days when this was missing.

Since no conurbation-level data at all were available in 2003-2006 for Leicester or Southampton, pre-2003 conurbation-level data were used to estimate the model for these two conurbations, and the 2003-2006 data were then imputed in the same way.

A similar procedure was used for imputing relative humidity data that were missing at the conurbation level. Thus, a single and complete temperature and relative humidity series was produced for each of the conurbations under study.

4.2.3 Air pollution data

The UK Air Quality Data and Statistics Database contains tables of measured concentration data from monitoring networks operated on behalf of the Department for Environment, Food and Rural Affairs (DEFRA). Air quality is

monitored at over 1500 sites across the UK. Of interest for the present study is the Automatic Urban and Rural Netwok (AURN), which includes 103 automatic pollutant monitors in England and Wales, producing hourly pollutant concentrations. These monitors are located to measure either background pollution levels (n=85 monitors), or levels near particular sources (roads, airports, industries; n=18 monitors). The former were used for the present study.

Among the 85 background pollution monitoring stations, 53 measure PM_{10}, 68 measure ozone, 30 measure CO, 70 measure oxides of nitrogen, and 48 measure SO_2. $PM_{2.5}$ is not widely monitored: background $PM_{2.5}$ levels are measured at sites in Birmingham, Harwell, London North Kensington, Manchester Piccadilly, and Port Talbot, with hourly $PM_{2.5}$ data available in London Bloomsbury, Harwell, and Rochester.

The monitoring network uses a variety of methods to measure pollutant levels with high temporal resolution, including spectroscopic methods such as infra-red or ultra-violet absorption, ultra-violet fluorescence, and chemiluminescence. Particulates are typically measured using sophisticated filtration techniques.

Raw data for PM_{10}, ozone, CO, NO_2 and SO_2 were downloaded from the National Air Quality Archive, and processed in a similar way to the temperature data: raw data were linked to specific conurbations, and where a conurbation had multiple stations for a given pollutant, these data were combined into a single series using the AIRGENE algorithm (see section 4.2.2.1). No further imputation for missing values (e.g. using data from outside the conurbation) was performed since, due to the high spatial variation of pollutant levels, data originating from some distance away are likely to be poor markers of the levels of interest.

4.2.4 Influenza and respiratory syncytial virus

Circulating levels of infections, in particular influenza and respiratory syncytial virus (RSV, a virus that causes respiratory tract infections), may be associated with both weather and MI risk, and could thus act as confounders, particularly for temperature-MI associations. Levels of both infections tend to peak during the winter season, though not necessarily at the same time. To allow

adjustment for levels of these infections, daily counts of lab confirmed cases of influenza A and RSV were obtained from laboratory reports to the Communicable Diseases Surveillance Centre (CDSC) at the Health Protection Agency, UK. These data were available by UK region (London, South East, South West, West Midlands, East Midlands East, Yorkshire and Humber, North West, North East, Wales). To obtain conurbation-level data, data were simply drawn from the appropriate region.

4.3 Overview of analytical methods

Three main analyses were undertaken for this thesis, as reported in Chapters 6, 7 and 8. The following is a brief overview of the analyses performed; detailed statistical methods are described in the relevant analysis chapters.

Characterising the short-term effects of temperature on MI risk

First, a daily time series regression analysis was undertaken linking daily numbers of hospital admissions for MI (as defined in Section 4.2.1.1) with daily mean ambient temperature, adjusting for seasonality and long-term trend, relative humidity, particulate and ozone pollution, circulating influenza and respiratory syncytial virus, public holidays, and day of the week. The time series study design was introduced in Chapter 2. Initially, separate analyses were conducted for each of the 15 conurbations individually, but subsequently a single stratified analysis was performed (as described in Chapter 6).

Temperature effects lagged by up to 28 days were investigated using distributed lag models. Both non-linear and linear temperature-MI associations were considered in the modelling process.

Characterising the short-term effects of daily air pollution levels on MI risk

The final model from the analysis of temperature-MI associations was used as a base model for a second daily time series regression analysis focussing on air pollution effects. In place of short-lag terms for PM_{10} and ozone (used to control for pollution when temperature was the focus), single pollutants (PM_{10}, ozone, CO, NO_2, SO_2) were introduced into the model in turn as linear terms. Pollution

effects lagged by up to 7 days were allowed for, and as well as single-pollutant models, multi-pollutant models were also investigated.

Investigating air pollution effects at an hourly temporal resolution

Finally, air pollution effects were investigated at a finer temporal resolution, making use of the hourly data available from both MINAP and the pollution data sources. To accommodate the hourly data, a time-stratified case-crossover design with calendar month strata was used, and the effects of PM_{10}, ozone, CO, NO_2, and SO_2, lagged by 1-6, 7-12, 13-18., 19-24, and 25-72 hours were investigated in both single- and multi-pollutant models. The case-crossover design was introduced in Chapter 3. Models were again adjusted for ambient temperature, relative humidity, circulating influenza and RSV levels, day of the week, holidays, and residual seasonality within calendar months.

4.4 Summary

- Details of hospital admissions occurring in 2003-2006 among residents of 15 conurbations in England and Wales and with a discharge diagnosis of MI were obtained from the Myocardial Ischaemia National Audit Project (MINAP) database.

- Data on temperature and specific air pollutants (PM_{10}, ozone, CO, NO_2, SO_2) from monitoring stations were obtained from the UK Met Office and the UK Air Quality and Statistics Database respectively. Data on potential confounding factors were also collected.

- Daily time series regression analyses linking clinical and environmental data were used to characterise the short-term (day to day) effects of temperature and pollution on MI risk.

- A case-crossover design was then used to investigate effects of air pollution at an hourly temporal resolution.

5 Results – Descriptive Analysis

5.1 Introduction

In this chapter, some basic descriptive analyses of the main data sources used in this thesis are presented.

5.2 MINAP

5.2.1 Inclusion and exclusion

Between January 2003 and December 2006 a total of 352972 events had a discharge diagnosis recorded in MINAP, of which 284170 were MI (119696 ST elevation MI [STEMI] and 164474 non ST elevation MI). A total of 84010 events were attributed to patients living within one of the 15 conurbations of interest and a median of 57 IQR (50-64) events per day were recorded in the 15 conurbations combined (Table 5.1).

Table 5.1: Number of events by conurbation

	Total Events (%)	**Events per day [Median (IQR)]**
Within 15 conurbations	84010 (29.6)	57 (50, 64)
Bristol	2376 (0.8)	1 (0, 2)
Cardiff	1471 (0.5)	1 (0, 2)
G London	26607 (9.4)	18 (15, 21)
G Manchester	12434 (4.4)	8 (6, 11)
Kingston-upon-Hull	407 (0.1)	0 (0, 0)
Leicester	1768 (0.6)	1 (0, 2)
Liverpool	4358 (1.5)	3 (2, 4)
Newcastle	8017 (2.8)	5 (4, 7)
Norwich	874 (0.3)	0 (0, 1)
Nottingham	1488 (0.5)	1 (0, 2)
The Potteries	2205 (0.8)	1 (1, 2)
Sheffield	4903 (1.7)	3 (2, 5)
Southampton	1259 (0.4)	1 (0, 1)
W Midlands	9265 (3.3)	6 (4, 8)
W Yorks	6578 (2.3)	4 (3, 6)
Outside 15 conurbations	176519 (62.1)	121 (109, 133)
No geographical info	23641 (8.3)	11 (8, 23)
Total	284170 (100.0)	194 (181, 208)

Greater London had the largest number of events (n = 26607, median [IQR] 18 [15-21] per day), while Kingston-upon-Hull had the least with events recorded on only 23.5% of days (n = 407, median [IQR] 0 [0-0] per day).

5.2.2 Description of included events

5.2.2.1 Demographic characteristics

The remainder of this section describes the main "study population"; i.e. the 84010 events taking place within the 15 conurbations of interest. Both sex and age were well recorded (99.3% and 96.9% complete respectively, Table 5.2).

Table 5.2: Demographic characteristics recorded for included events

	Total MIs	Male (%)		Median age (IQR)
Bristol	2376	1519/2354	(64.5)	71 (60-80)
Cardiff	1471	857/1464	(58.5)	75 (63-83)
G London	26607	17863/26532	(67.3)	69 (57-79)
G Manchester	12434	7722/12424	(62.2)	71 (59-80)
Kingston-on-Hull	407	278/406	(68.5)	64 (56-73)
Leicester	1768	1239/1768	(70.1)	68 (56-77)
Liverpool	4358	2623/4355	(60.2)	72 (61-80)
Norwich	874	605/874	(69.2)	70 (60-77)
Nottingham	1488	974/1476	(66.0)	68 (57-77)
Potteries	2205	1437/2205	(65.2)	72 (60-80)
Sheffield	4903	2891/4878	(59.3)	72 (61-81)
Southampton	1259	875/1259	(69.5)	69 (58-78)
Tyneside	8017	4697/8010	(58.6)	72 (60-81)
W Midlands	9265	6258/9245	(67.7)	68 (57-77)
W Yorkshire	6578	3981/6174	(64.5)	69 (58-77)
Overall	84010	53819/83424	(64.5)	70 (58-79)

Note: sex was missing for 586 (=84010 – 83424) events in total

MI events were more commonly recorded among men (64.5% overall) though there was some variation across conurbations (X^2 p-value <0.001) from 58% of

events being among men in Cardiff, to 70% in Leicester. The overall median age was 70 years (IQR 58-79) though again there was some variation across conurbations (Kruskall-Wallis p-value <0.001): the median age in Kingston-upon-Hull was the lowest at 64 years while events recorded in Cardiff tended to be among older individuals (median age 75 years).

5.2.2.2 MI diagnosis and supporting evidence

Of 84010 MIs, 35664 (42.5%) were STEMI (Table 5.3). ST elevation (described in Section 1.2.1) was recorded as the ECG trace determining treatment for 93% of these STEMI events; for the remainder this ECG information was missing. Though there was some variation across conurbations, ST elevation was recorded for at least 86% of events in all individual conurbations. Non-STEMI diagnoses, by definition, could not have ST elevation recorded (see Section 4.2.1.1); however ECG information was unavailable for 21% of non-STEMIs overall and for up to 46% in individual conurbations.

For both STEMI and non-STEMI, elevated troponin or CK would be expected (see Section 1.2.1) and was indeed recorded for 76% and 82% of the respective diagnoses. 8% of both diagnoses were made despite “normal” markers being recorded, while data on markers were unavailable for 16% and 10% of STEMIs and non-STEMIs respectively, with higher proportions of missing markers data in some conurbations.

Finally there was evidence that reperfusion took place in 91% of STEMI events. Reperfusion is a treatment and thus cannot provide diagnostic information, however a recording of reperfusion does suggest that the event was genuinely believed to be STEMI by the treating clinician, and provides some evidence against recording or database errors for these diagnoses.

Table 5.3: MI diagnosis and supporting evidence

	ECG on which treatment was based				CK/Troponin marker levels			Evidence of	
	ST elevation	LBBB	Other/normal	Missing	Elevated	Normal	Missing	reperfusion	Total
	N %	N %	N %	N %	N %	N %	N %	N %	N
Bristol									
STEMI	910 (90)	22 (2)	0 (0)	75 (7)	862 (86)	55 (5)	90 (9)	925 (92)	1007
non-STEMI	0 (0)	61 (4)	727 (53)	581 (42)	1231 (90)	41 (3)	97 (7)	128 (9)	1369
Cardiff									
STEMI	490 (97)	12 (2)	0 (0)	5 (1)	435 (86)	23 (5)	49 (10)	462 (91)	507
non-STEMI	0 (0)	90 (9)	855 (89)	19 (2)	940 (98)	10 (1)	14 (1)	59 (6)	964
Greater London									
STEMI	11097 (92)	213 (2)	0 (0)	738 (6)	8755 (73)	1053 (9)	2240 (19)	11045 (92)	12048
non-STEMI	0 (0)	956 (7)	11389 (78)	2214 (15)	11852 (81)	1386 (10)	1321 (9)	1667 (11)	14559
Greater Manchester									
STEMI	4439 (86)	125 (2)	0 (0)	575 (11)	3199 (62)	340 (7)	1600 (31)	4515 (88)	5139
non-STEMI	0 (0)	376 (5)	3538 (48)	3381 (46)	5646 (77)	302 (4)	1347 (18)	533 (7)	7295
Kingston									
STEMI	359 (97)	7 (2)	0 (0)	3 (1)	292 (79)	19 (5)	58 (16)	366 (99)	369
non-STEMI	0 (0)	1 (3)	31 (82)	6 (16)	33 (87)	3 (8)	2 (5)	15 (39)	38
Leicester									
STEMI	936 (97)	20 (2)	0 (0)	13 (1)	803 (83)	132 (14)	34 (4)	746 (77)	969
non-STEMI	0 (0)	77 (10)	698 (87)	24 (3)	725 (91)	64 (8)	10 (1)	86 (11)	799
Liverpool									
STEMI	1605 (96)	60 (4)	0 (0)	9 (1)	1237 (74)	60 (4)	377 (23)	1591 (95)	1674
non-STEMI	0 (0)	209 (8)	2401 (89)	74 (3)	2106 (78)	7 (0)	571 (21)	84 (3)	2684
Norwich									
STEMI	335 (99)	3 (1)	0 (0)	1 (0)	328 (97)	8 (2)	3 (1)	329 (97)	339
non-STEMI	0 (0)	17 (3)	509 (95)	9 (2)	525 (98)	9 (2)	1 (0)	9 (2)	535
Nottingham									
STEMI	839 (93)	21 (2)	0 (0)	47 (5)	729 (80)	117 (13)	61 (7)	847 (93)	907
non-STEMI	0 (0)	34 (6)	401 (69)	146 (25)	476 (82)	80 (14)	25 (4)	97 (17)	581
Potteries									
STEMI	822 (96)	13 (2)	0 (0)	19 (2)	579 (68)	109 (13)	166 (19)	808 (95)	854
non-STEMI	0 (0)	90 (7)	1195 (88)	66 (5)	868 (64)	210 (16)	273 (20)	146 (11)	1351

	ECG on which treatment was based						CK/Troponin marker levels			Evidence of	
	ST elevation		LBBB		Other/normal		Missing		Elevated	Normal	Missing	reperfusion	Total
	N	%	N	%	N	%	N	%	N %	N %	N %	N %	N
Sheffield													
STEMI	1359	(94)	25	(2)	0	(0)	59	(4)	1273 (88)	54 (4)	116 (8)	1322 (92)	1443
non-STEMI	0	(0)	213	(6)	1673	(48)	1574	(45)	3108 (90)	84 (2)	268 (8)	220 (6)	3460
Southampton													
STEMI	497	(96)	8	(2)	0	(0)	12	(2)	485 (94)	14 (3)	18 (3)	487 (94)	517
non-STEMI	0	(0)	45	(6)	631	(85)	66	(9)	732 (99)	6 (1)	4 (1)	59 (8)	742
Tyneside													
STEMI	2280	(95)	61	(3)	0	(0)	68	(3)	1924 (80)	151 (6)	334 (14)	2102 (87)	2409
non-STEMI	0	(0)	414	(7)	4848	(86)	346	(6)	4320 (77)	787 (14)	501 (9)	687 (12)	5608
West Midlands													
STEMI	4508	(93)	82	(2)	0	(0)	237	(5)	4085 (85)	384 (8)	358 (7)	4566 (95)	4827
non-STEMI	0	(0)	224	(5)	2841	(64)	1373	(31)	3844 (87)	377 (8)	217 (5)	381 (9)	4438
West Yorkshire													
STEMI	2553	(96)	90	(3)	0	(0)	12	(0)	2180 (82)	290 (11)	185 (7)	2430 (92)	2655
non-STEMI	0	(0)	274	(7)	3511	(89)	138	(4)	3095 (79)	676 (17)	152 (4)	656 (17)	3923
Total													
STEMI	33029	(93)	762	(2)	0	(0)	1873	(5)	27166 (76)	2809 (8)	5689 (16)	32541 (91)	35664
non-STEMI	0	(0)	3081	(6)	35248	(73)	10017	(21)	39501 (82)	4042 (8)	4803 (10)	4827 (10)	48346

Note: LBBB = left bundle branch block (an ECG abnormality that can indicate acute MI)

Considering these factors together, Table 5.4 shows that for the total of 35664 STEMIs, 24176 (68%) had triple “supporting evidence”, 9059 (25%) had dual evidence, and 2090 (6%) had single evidence, with only 1% of STEMI diagnoses being unsupported by further data. For non-STEMIs, only elevated markers would be expected and this positively recorded in the case for 39501/48346 diagnoses (82%; for the remainder there was simply an absence of evidence of raised markers rather than specific evidence of non-raised markers). For both diagnoses together, 75901/84010 (90%) events had at least one piece of supportive evidence recorded, or 74025/84010 (88%) excluding thrombolysis alone.

Table 5.4: Level of supporting evidence for MI diagnoses

	STEMI	**non-STEMI**	**Total**
Evidence supporting diagnosis [n, (%)]			
None	339 (1)	7770 (16)	8109 (10)
Single	2090 (6)	36824 (76)	38914 (46)
ECG showing ST elevation	*793*	*0*	*793*
Elevated markers	*496*	*35749*	*36245*
Thrombolysis given	*801*	*1075*	*1876*
Dual	9059 (25)	3752 (8)	12811 (15)
ECG & Markers	*1495*	*0*	*1495*
ECG & Thrombolysis	*6565*	*0*	*6565*
Markers & Thrombolysis	*999*	*3752*	*4751*
Triple	24176 (68)	0 (0)	24176 (29)
ECG & Markers & Thrombolysis	*24176*	*0*	*24176*
Total	35664 (100)	48346 (100)	84010 (100)

5.2.2.3 Dating of MI events

Date of symptom onset was available for 59369 events (71%, Table 5.5). An algorithm was used to complete the dating of events (see Section 4.2.1.3), with the majority of missing information being filled in using the date of first call for help (8%) or the date of arrival at hospital (18%).

Table 5.5: Dating of MI events

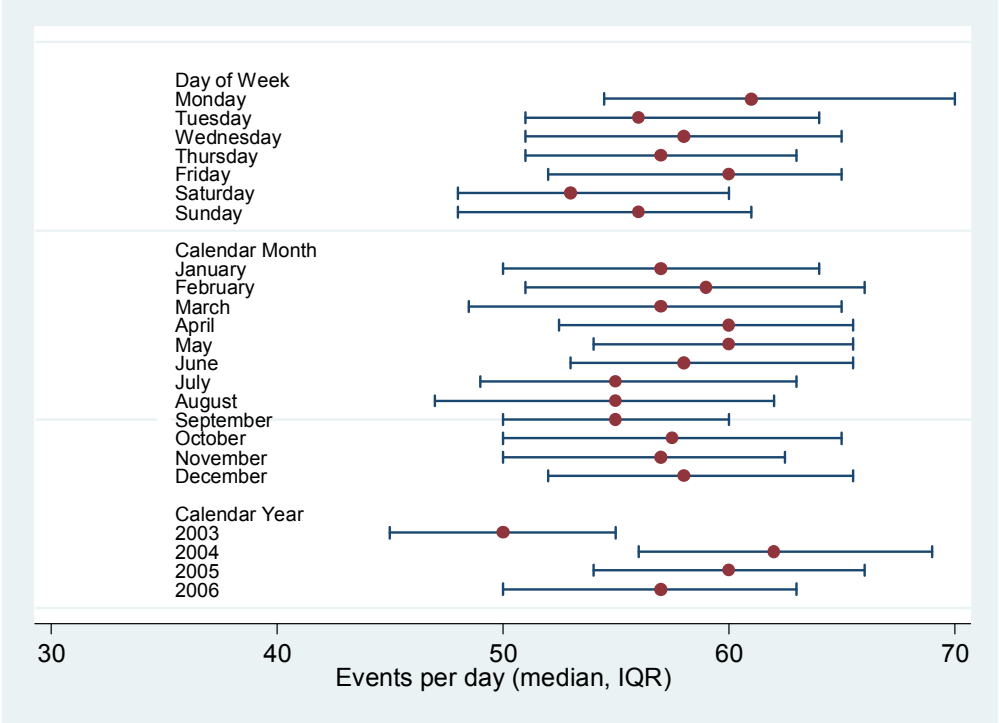
	Completeness of specific date variable (%)	Number of times used in composite date variable	Cumulative completeness of composite date variable (%)
Date of ...			
1. Symptom onset	70.7	59369	70.7
2. First call for help	8.3	6986	79
3. Arrival of first professional	0.2	146	79.2
4. Arrival of emergency servic	0.5	395	79.6
5. Arrival at hospital	17.9	15018	97.5
6. Reperfusion	0.1	73	97.6
7. Cardiac arrest	0.1	51	97.7
8. Referral for investigations	0.5	383	98.1
9. Angiography	0.2	157	98.3
10. First intervention	0	42	98.3
11. Discharge	1.7	1390	100
Total	-	84010	100

5.2.2.4 Temporal patterns

There appeared to be some temporal patterns in the data, with more events occurring on Mondays (median [IQR] 61 [54.5–70] events per day), and fewer on Saturdays (53 [48-60], Figure 5.1). By calendar month, event rates were at their lowest in July, August and September (median 55 events per day in each case). Finally, by calendar year, the median (IQR) events per day increased from 50 (45-55) in 2003 to 62 (56-69), 60 (54-60), and 57 (50-63) in 2004, 2005, and 2006 respectively. Data on temporal patterns in event rates, broken down by conurbation, are presented in Appendix I (Table 11.1, Table 11.2, Table 11.3). It is worth noting that the two largest conurbations (Greater London and Greater Manchester) similarly saw a notable increase in the median events

recorded per day after 2003 (Appendix I Table 11.3). The lower numbers of events in 2003 likely reflect incomplete data collection in the early years of MINAP, which had only achieved full recruitment of hospitals a few months earlier in mid-2002.[152]

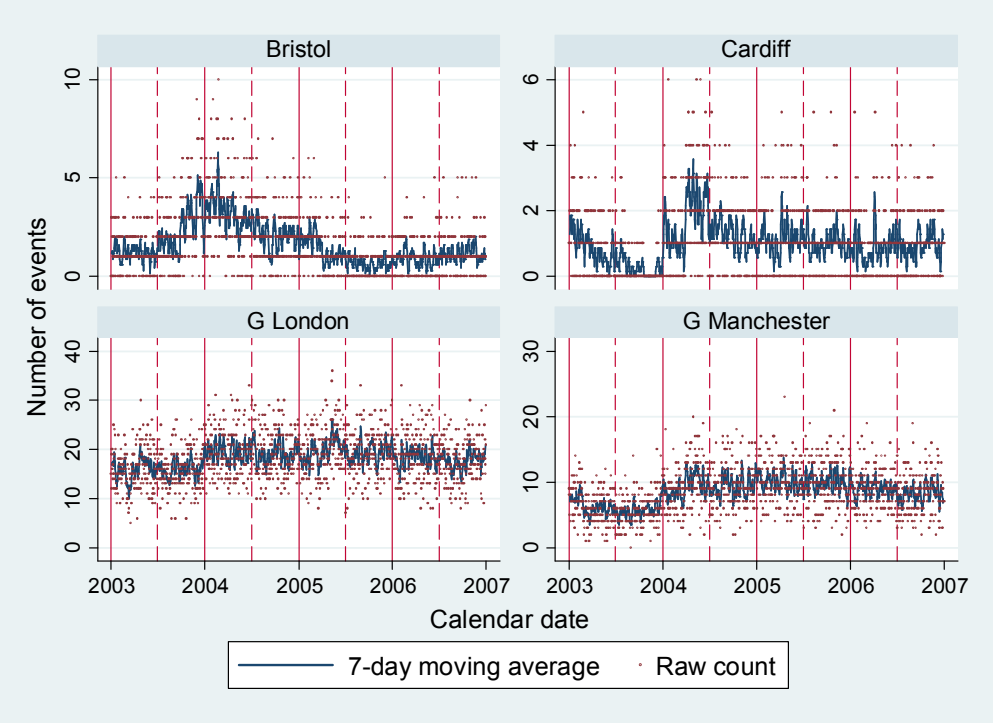
Figure 5.1:Temporal patterns in MI diagnoses



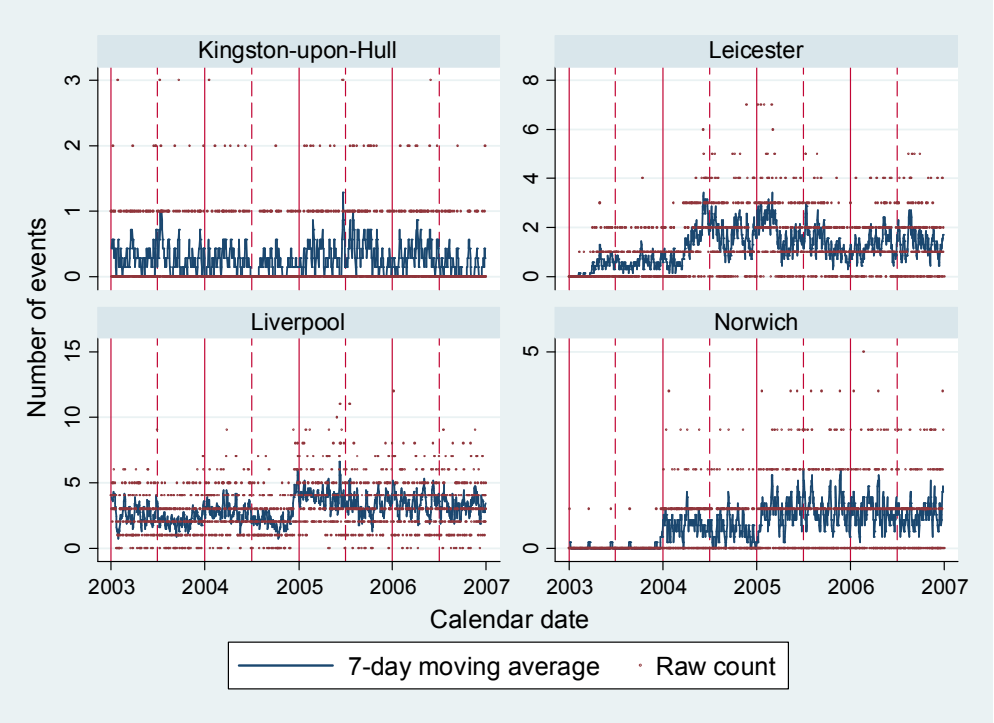
5.2.2.5 Event rates over time in individual conurbations

Figure 5.2, showing raw and 7-day average daily counts of MI by conurbation, also indicates increases in rates of recorded MIs in a number of conurbations at various time points, most notably Leicester (2004), Liverpool (2005), Norwich (2004), and Sheffield (mid-2003). Smoother changes in MI diagnoses are seen elsewhere though no clear pattern emerges.

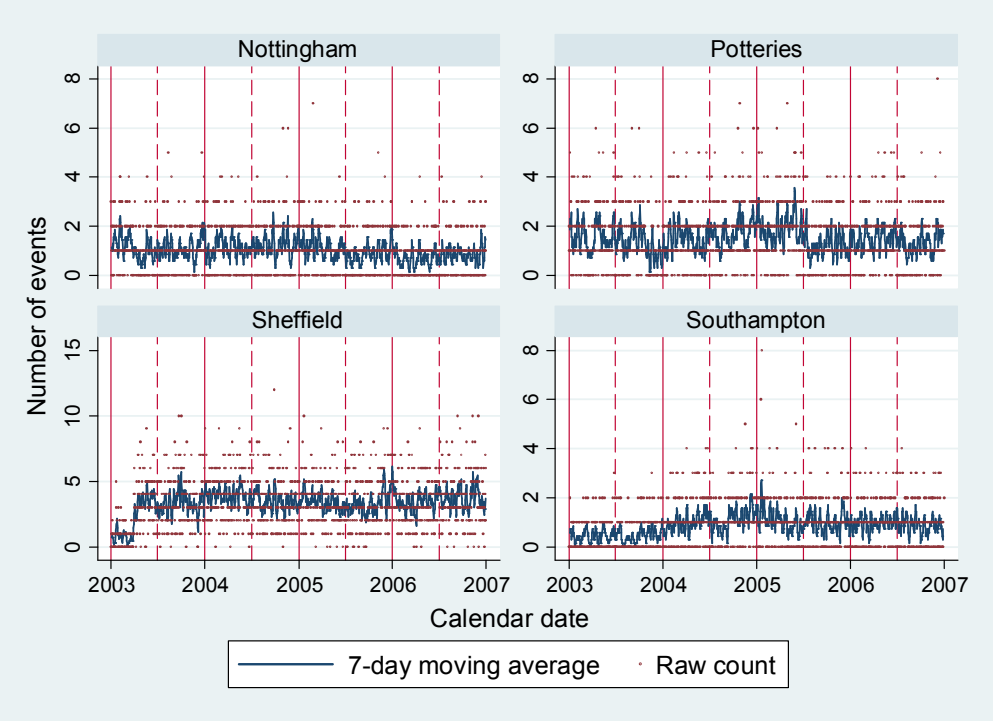
Figure 5.2: Raw daily counts and 7-day average of MI events over calendar time
a) Bristol, Cardiff, Greater London, Greater Manchester



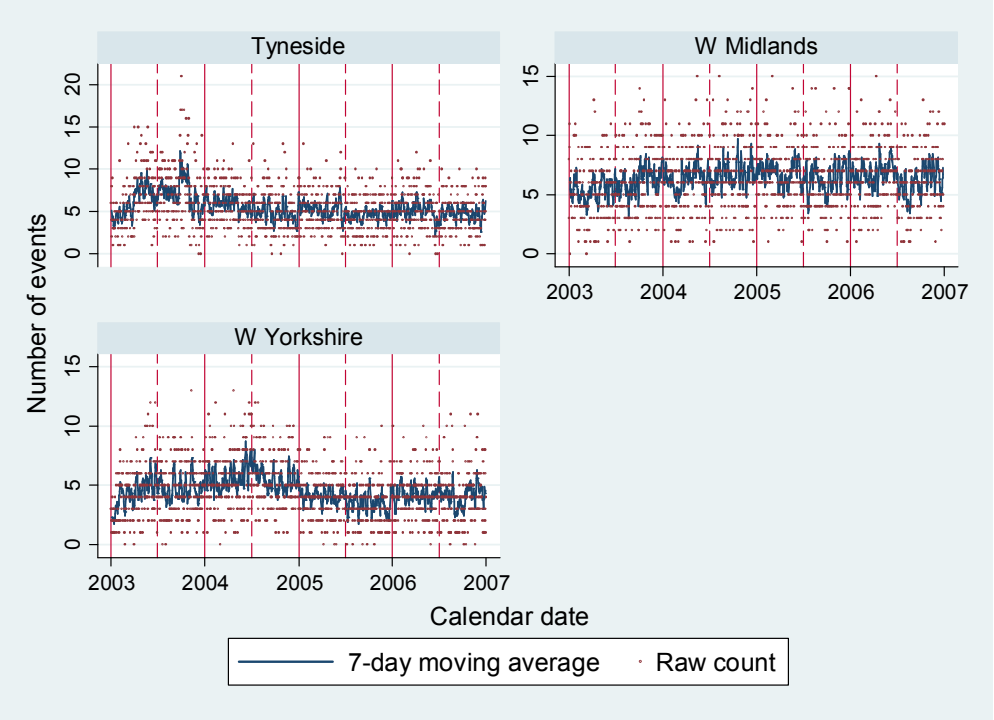
b) Kingston-upon-Hull, Leicester, Liverpool, Norwich



c) Nottingham, Potteries, Sheffield, Southampton



d) Tyneside, West Midlands, West Yorkshire



5.3 Meteorological and air pollution data

5.3.1 Conurbations with incomplete data/ no monitoring stations

The primary sources of temperature data were 8 monitoring stations within Greater London, 2 each within Cardiff, Greater Manchester, Nottingham, West Midlands, and West Yorkshire, and 1 station for each of the remaining conurbations with the exception of Southampton where no stations were available (Table 5.6) Within conurbations where >1 station was available, pairwise correlations of daily mean temperature series between stations were extremely high (≥0.98 in all cases). After combining data in conurbations with multiple stations as described in Section 4.2.2.1, 7 of 15 conurbations had a 100% complete daily temperature series for the period under study. The remaining 8 conurbations had some missing data or no data at all and these missing data were imputed using regional temperature data (see Section 4.2.2.2) to produce the final analysis data.

Table 5.6: Monitoring stations for temperature & relative humidity within the 15 conurbations

Conurbation	Temperature (daily min/max)		Relative humidity	
	Stations (n)	% Days non-missing	Stations (n)	% Days non-missing
Bristol	1	99%	1	92%
Cardiff	2	100%	1	86%
G London	8	100%	5	100%
G Manchester	2	99%	2	100%
Kingston on Hull	1	54%	0	0%
Leicester	1	2%	0	0%
Liverpool	1	100%	1	96%
Norwich	1	54%	0	0%
Nottingham	2	100%	1	95%
The Potteries	1	98%	1	13%
Sheffield	1	100%	1	77%
Southampton	0	0%	1	92%
Tyneside	1	69%	1	68%
West Midlands	2	100%	3	100%
West Yorkshire	2	100%	1	89%

For pollution data, multiple stations contributed to data for Greater London, Greater Manchester, Sheffield, West Midlands, and West Yorkshire (Table 5.7), while in the remaining conurbations, data for each pollutant came from a single monitoring station.

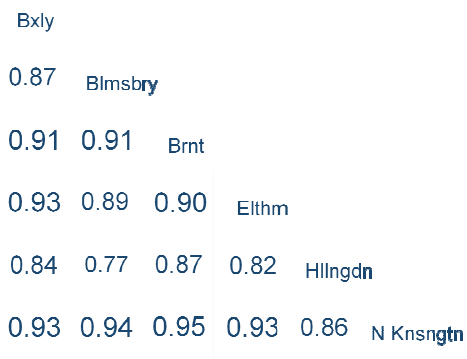
Table 5.7: Completeness of air pollutant data within the 15 conurbations

	Number of stations (% days non-missing in final dataset)				
	PM_{10}	Ozone	CO	NO_2	SO_2
Bristol	1 (65)	1 (64)	1 (63)	1 (65)	1 (64)
Cardiff	1 (83)	1 (84)	1 (85)	1 (85)	1 (85)
Greater London	6 (100)	13 (100)	9 (100)	13 (100)	10 (100)
Greater Manchester	3 (100)	3 (100)	4 (100)	5 (100)	4 (100)
Kingston-upon-Hull	1 (95)	1 (97)	1 (76)	1 (86)	1 (91)
Leicester	1 (95)	1 (98)	1 (90)	1 (94)	1 (97)
Liverpool	1 (84)	1 (86)	1 (85)	1 (85)	1 (83)
Norwich	1 (89)	1 (97)	1 (86)	1 (93)	1 (94)
Nottingham	1 (95)	1 (97)	1 (92)	1 (90)	1 (95)
The Potteries	1 (82)	1 (96)	1 (94)	1 (96)	1 (83)
Sheffield	1 (97)	2 (99)	1 (97)	2 (94)	2 (97)
Southampton	1 (92)	1 (92)	1 (80)	1 (94)	1 (89)
Tyneside	1 (96)	1 (94)	1 (90)	1 (85)	1 (94)
West Midlands	3 (100)	4 (100)	4 (100)	6 (100)	4 (100)
West Yorkshire	2 (99)	2 (100)	2 (98)	2 (99)	2 (99)

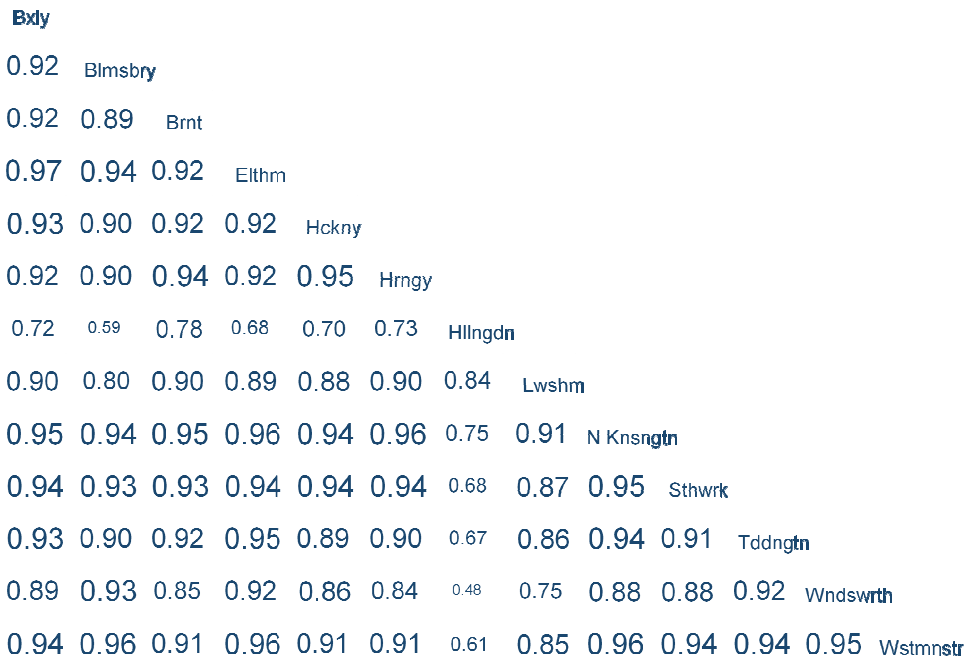
For conurbations with multiple stations, correlations of daily mean pollutant levels between stations for varied by pollutant (Figure 5.3 and Appendix I Table 11.4-Table 11.7). Within London, the majority of correlations between pairs of individual monitoring stations were at least 0.8 for PM_{10}, ozone, and NO_2, while for CO and SO_2 most pairwise correlations were lower, indicating a greater variability of the levels of these pollutants across the city.

Figure 5.3:Correlations of daily pollutant levels between monitoring stations within London

a) PM_{10}



b) Ozone



Note: station names abbreviated - Bxly = Bexley, Blmsbry = Bloomsbury, Brnt = Brent, Elthm = Eltham, Hckny = Hackney, Hllngdn = Hillingdon, Lwshm = Lewisham, N Knsngtn = North Kensington, Sthwrk = Southwark, Tddngtn = Teddington, Wndswrth = Wandsworth, Wstmnstr = Westminster, Wstlndn = West London
Font size proportional to magnitude of correlation

c) CO

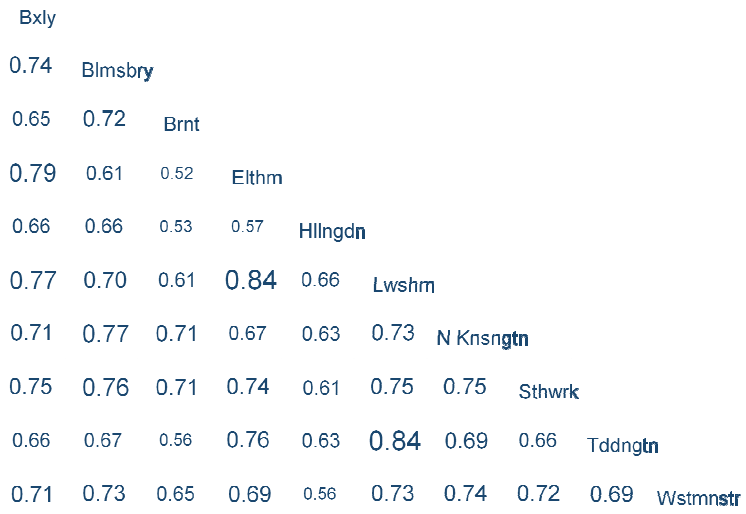
Bxly								
0.57	Blmsbry							
0.72	0.60	Brnt						
0.66	0.42	0.73	Hckny					
0.66	0.50	0.81	0.68	Hllngdn				
0.76	0.63	0.78	0.67	0.72	N Knsngtn			
0.71	0.52	0.74	0.66	0.62	0.70	Sthwrk		
0.72	0.76	0.73	0.66	0.64	0.78	0.73	Wstmnstr	
0.63	0.52	0.68	0.59	0.57	0.64	0.63	0.66	Wstlndn

d) NO_2

Bxly										
0.80	Blmsbry									
0.83	0.69	Brnt								
0.88	0.82	0.78	Elthm							
0.87	0.74	0.85	0.77	Hckny						
0.55	0.29	0.65	0.45	0.68	Hllngdn					
0.77	0.48	0.76	0.71	0.79	0.80	Lwshm				
0.89	0.80	0.89	0.88	0.88	0.60	0.78	N Knsngtn			
0.87	0.81	0.79	0.82	0.80	0.42	0.65	0.82	Sthwrk		
0.81	0.82	0.76	0.85	0.72	0.30	0.58	0.85	0.76	Tddngtn	
0.79	0.87	0.65	0.81	0.69	0.18	0.47	0.78	0.78	0.88	Wndswrth
0.80	0.85	0.67	0.82	0.71	0.29	0.59	0.80	0.75	0.81	0.83	Wstmnstr
0.90	0.87	0.82	0.89	0.86	0.52	0.74	0.93	0.84	0.89	0.87	0.87	Wstlndn

Note: station names abbreviated - Bxly = Bexley, Blmsbry = Bloomsbury, Brnt = Brent, Elthm = Eltham, Hckny = Hackney, Hllngdn = Hillingdon, Lwshm = Lewisham, N Knsngtn = North Kensington, Sthwrk = Southwark, Tddngtn = Teddington, Wndswrth = Wandsworth, Wstmnstr = Westminster, Wstlndn = West London
Font size proportional to magnitude of correlation

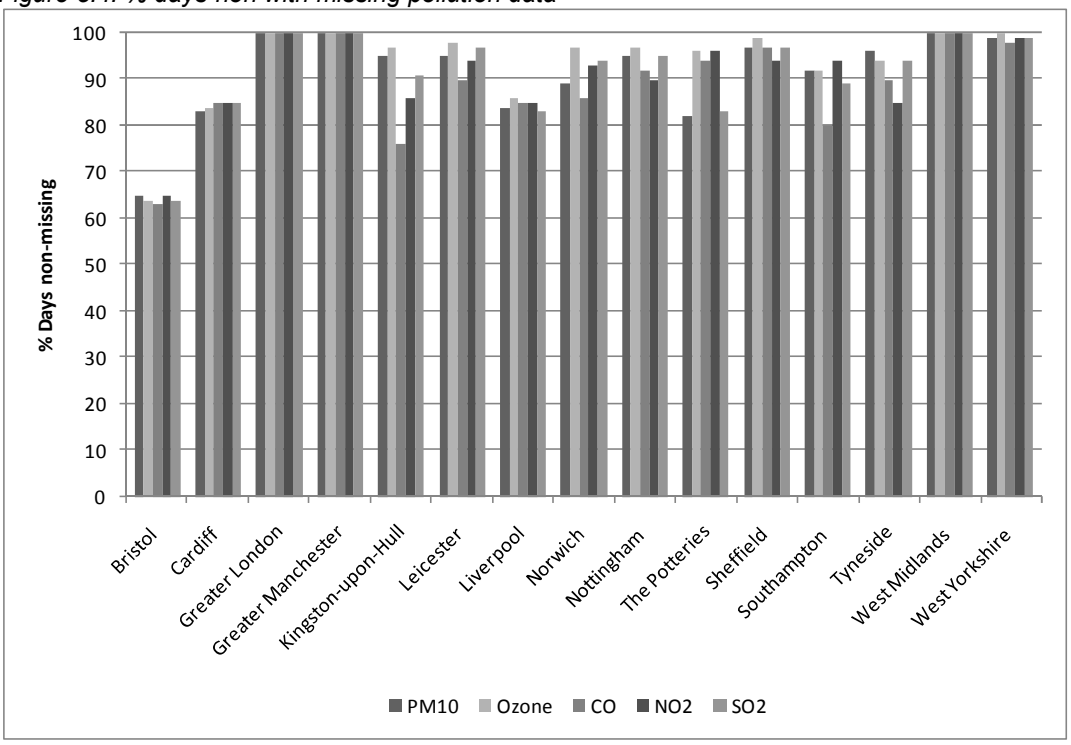
e) SO_2



Note: station names abbreviated - Bxly = Bexley, Blmsbry = Bloomsbury, Brnt = Brent, Elthm = Eltham, Hckny = Hackney, Hllngdn = Hillingdon, Lwshm = Lewisham, N Knsngtn = North Kensington, Sthwrk = Southwark, Tddngtn = Teddington, Wndswrth = Wandsworth, Wstmnstr = Westminster, Wstlndn = West London
Font size proportional to magnitude of correlation

Imputation of pollution data was not attempted, though in fact data completeness was relatively high: 7 conurbations had data for all pollutants on ≥90% of days, and for all other conurbations, all pollutant data were over 75% complete with the exception of Bristol where data were available for only 63-65% of days (Table 5.7 and Figure 5.4). Within conurbations, completeness of individual pollutants was broadly similar, though CO completeness was somewhat lower in Kingston-upon-Hull and Southampton, while PM_{10} and SO_2 data were less complete in the Potteries.

Figure 5.4: % days-non with missing pollution data



5.3.2 Summary data for main exposure variables

The daily mean temperature ranged from -3°C to 27°C across the 15 conurbations, with individual conurbations having a median value of between 9 and 12°C over the 2003-2006 calendar period of interest (Table 5.8). Pollution patterns varied by both conurbation and pollutant. Over all conurbations, the median levels of PM_{10}, ozone, CO, NO_2 and SO_2 were 22μg/m^3, 39μg/m^3, 0.3mg/m^3, 30μg/m^3, and 5μg/m^3 respectively and interquartile ranges in the same units were of width 12, 26, 0.2, 19 and 6 respectively.

Table 5.8: Median and range of the mean daily values of each exposure variable, for 2003-2006

	Temperature (°C)	PM_{10} (μg/m^3)	Ozone (μg/m3)	CO (mg/m3)	NO_2 (μg/m3)	SO_2 (μg/m3)
	Median [range]	Median [range]	Median [range]	Median [range]	Median [range]	Median [range]
Bristol	11 [-2, 26]	23 [5, 80]	42 [2, 101]	0.4 [0.1, 2.8]	33 [6, 93]	4 [0, 29]
Cardiff	12 [0, 25]	26 [9, 162]	42 [2, 124]	0.3 [0.1, 1.1]	31 [4, 80]	3 [0, 19]
G London	12 [-1, 27]	23 [6, 104]	36 [1, 119]	0.3 [0.2, 1.9]	42 [13, 107]	4 [1, 31]
G Manchester	11 [-3, 26]	20 [3, 67]	35 [-0, 106]	0.3 [0.1, 2.0]	31 [10, 88]	6 [0, 31]
Kingston-upon-Hull	11 [-2, 23]	22 [6, 81]	44 [2, 127]	0.2 [0.0, 1.5]	25 [3, 85]	5 [0, 28]
Leicester	10 [-2, 23]	21 [4, 126]	38 [0, 138]	0.3 [0.1, 1.5]	32 [7, 128]	3 [0, 31]
Liverpool	11 [-3, 24]	20 [3, 119]	48 [2, 129]	0.1 [0.0, 1.6]	21 [3, 91]	5 [0, 41]
Norwich	10 [-2, 25]	19 [4, 74]	43 [2, 126]	0.2 [0.1, 1.5]	21 [3, 82]	11 [0, 33]
Nottingham	10 [-2, 23]	21 [3, 84]	33 [2, 122]	0.3 [0.1, 2.1]	33 [9, 93]	12 [0, 47]
Potteries	10 [-3, 25]	22 [4, 78]	43 [5, 183]	0.4 [0.1, 2.1]	29 [6, 116]	8 [0, 41]
Sheffield	10 [-2, 24]	21 [4, 110]	33 [2, 96]	0.3 [0.1, 2.0]	34 [11, 120]	10 [1, 35]
Southampton	12 [0, 25]	24 [7, 93]	36 [2, 97]	0.3 [0.0, 2.1]	30 [7, 75]	4 [0, 41]
Tyneside	10 [-2, 23]	16 [3, 75]	43 [2, 112]	0.1 [0.0, 1.2]	27 [6, 79]	3 [0, 33]
W Midlands	10 [-3, 24]	21 [5, 77]	42 [1, 111]	0.3 [0.1, 1.8]	31 [7, 106]	3 [0, 29]
W Yorkshire	9 [-2, 22]	24 [4, 105]	36 [1, 96]	0.4 [0.1, 1.9]	32 [0, 100]	8 [0, 60]
Total	**11 [-3, 27]**	**22 [3, 162]**	**39 [0, 183]**	**0.3 [0.0, 2.8]**	**30 [0, 128]**	**5 [0, 60]**

There was an inverse relationship between ozone and other pollutants, highlighted by negative correlations between ozone and PM_{10}, CO, NO_2, and SO_2, however, when examined by season, these negative correlations were reduced or reversed in the summer (Table 5.9). For other pairs of pollutants (excluding ozone), positive correlations were seen with little variation by season, the largest being between PM_{10} and NO_2 (correlation coefficient (ρ) = 0.48), and between NO_2 and CO (ρ = 0.61). Daily mean temperature was positively associated with ozone (ρ = 0.38) and, outside of summer, negatively associated with CO and NO_2 (ρ = -0.23 and -0.22 respectively); correlations of temperature with PM_{10} and SO_2 were small in magnitude over the whole year, though there were moderate positive associations in the summer.

Table 5.9: Correlations for pairs of exposure variables

Key: overall
(summer/other seasons) *

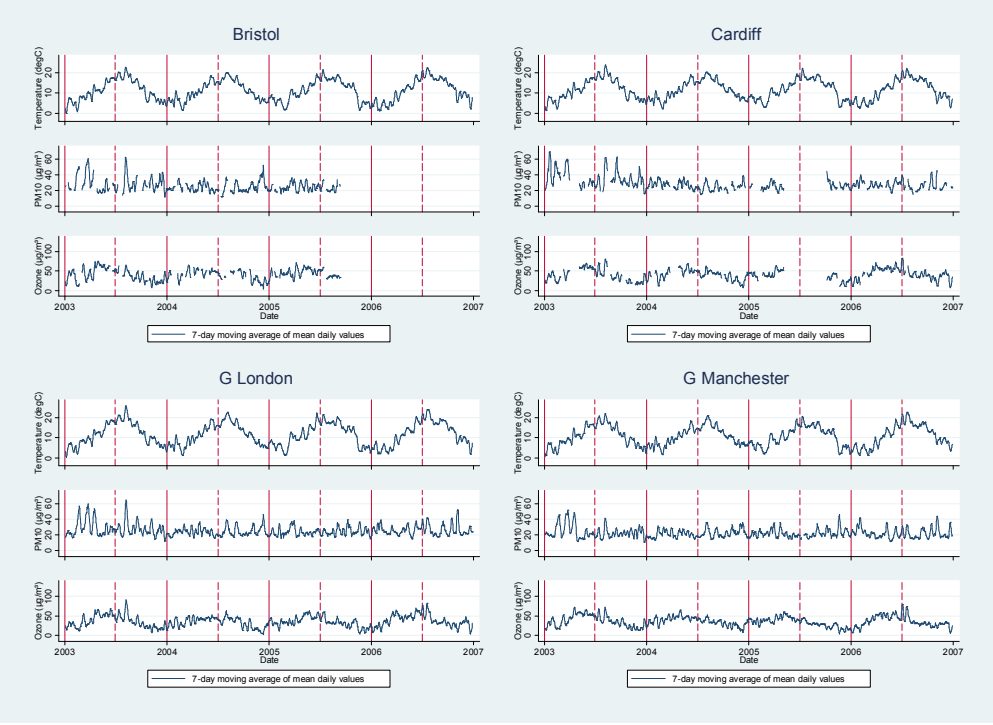
	Temp	**PM_{10}**	**Ozone**	**CO**	**NO_2**	**SO_2**
Temp	**1.00**					
PM_{10}	0.04 (0.37/ 0.02)	**1.00**				
Ozone	0.38 (0.56/ 0.31)	-0.15 (0.21/-0.26)	**1.00**			
CO	-0.24 (0.13/-0.23)	0.40 (0.23/ 0.44)	-0.37 (-0.06/-0.42)	**1.00**		
NO_2	-0.25 (0.17/-0.22)	0.48 (0.43/ 0.49)	-0.58 (-0.23/-0.66)	0.61 (0.45/ 0.62)	**1.00**	
SO_2	-0.03 (0.17/-0.04)	0.26 (0.21/ 0.28)	-0.14 (0.02/-0.18)	0.30 (0.23/ 0.31)	0.31 (0.27/ 0.32)	**1.00**

Temp = temperature
Note: Correlation coefficients were calculated based on the daily mean values of each exposure
Within-conurbation correlation coefficients estimated from regression models adjusted for conurbation[155]
**Summer defined as the months of June/July/August*

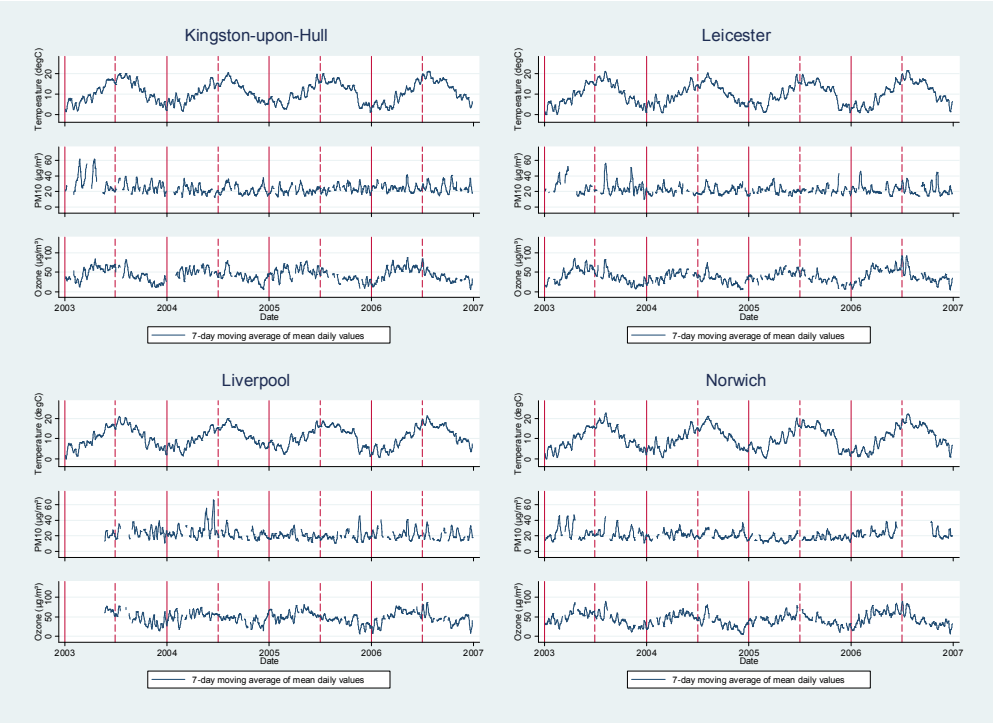
5.3.3 Exposure levels over calendar time

Considering 7-day moving averages for the daily mean values of exposure variables across calendar time, strong seasonality was observed, as expected, for temperature (Figure 5.5). Seasonality was also evident in most conurbations for ozone, with peaks in the summer and troughs in the winter. Such a pattern was not obvious for PM_{10}. Of note, there were extended gaps in the pollutant data for Bristol (2005 onward), Cardiff (2005), Liverpool (2003) and the Potteries (2003-4). Similar plots for CO, SO_2, and NO_2 are presented in Appendix I Figure 11.1-Figure 11.4.

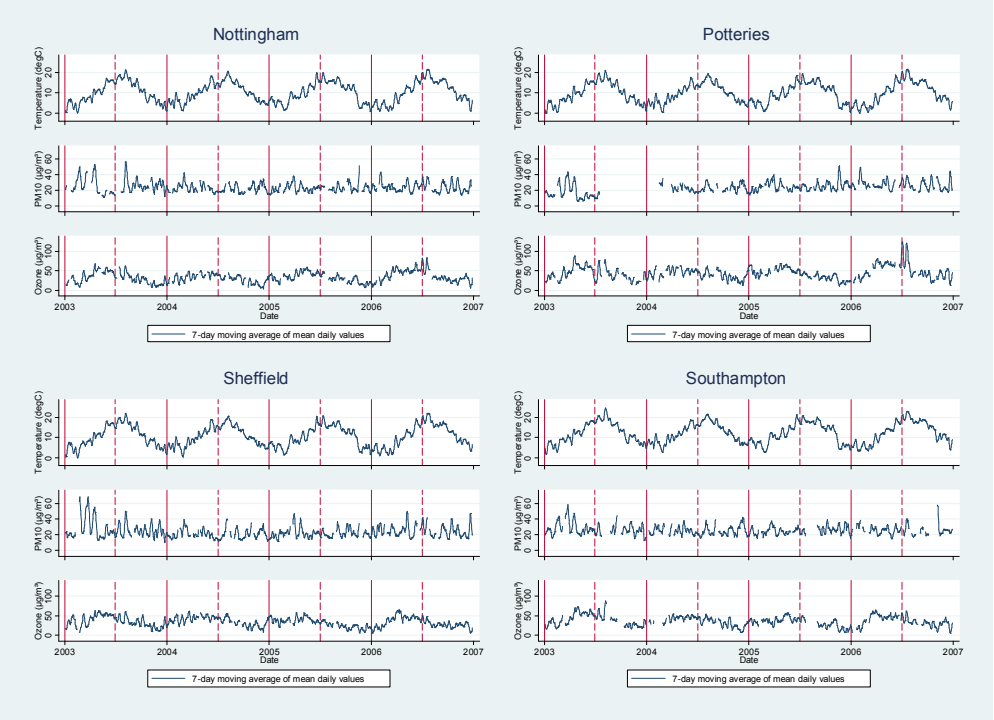
Figure 5.5: 7-day average of mean daily temperature, PM10 and ozone over calendar time a) Bristol, Cardiff, Greater London, Greater Manchester



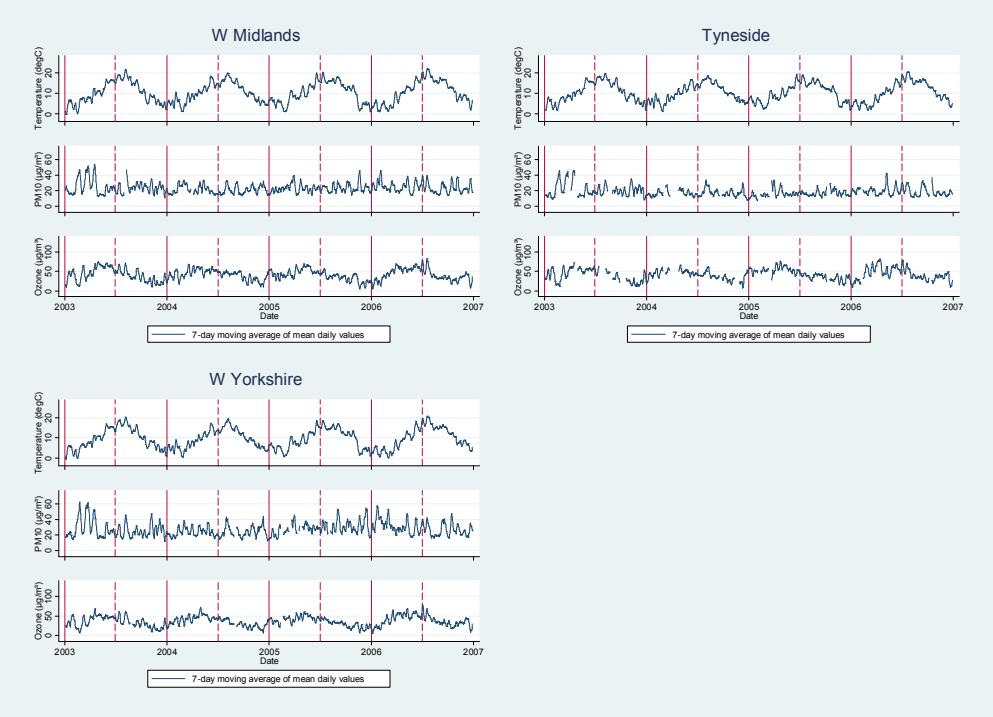
b) Kingston-upon-Hull, Leicester, Liverpool, Norwich



c) Nottingham, Potteries, Sheffield, Southampton



d) Tyneside, West Midlands, West Yorkshire



5.4 Summary

- 84010 MI events were recorded in MINAP in the 15 conurbations of interest between 2003-6, a median of 57 per day over all. Most were among men and older individuals.
- For 88% of MI events, there was a recorded ECG trace or laboratory marker levels consistent with the diagnosis.
- The daily mean temperature ranged from -3 to 27°C across the conurbations. Patterns in pollutant levels varied by conurbation.
- Ozone was negatively correlated with all other pollutants except in the summer season. Excluding ozone, other pollutant pairs had small to moderate positive correlations.

6 Characterising the short-term effects of temperature on MI risk

6.1 Introduction

This chapter describes a series of analyses aiming to assess and characterise the short-term effects of ambient temperature on the risk of MI.

6.2 Statistical methods

6.2.1 Pre-planned analysis

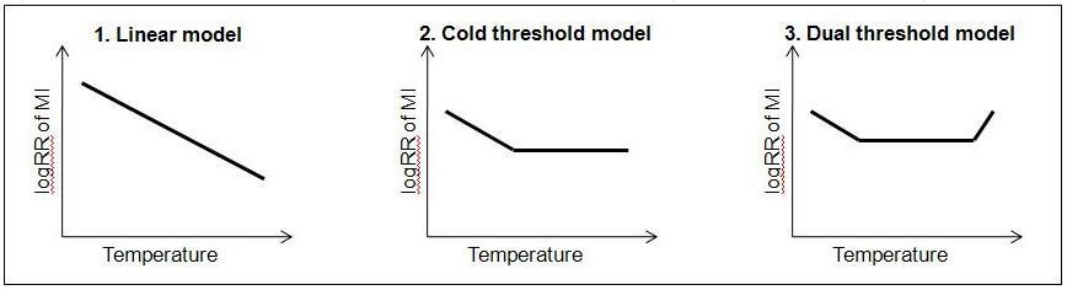
Initially, a time series model was set up to capture the main effect of mean daily temperature, adjusting for season, trend, and potential time-varying confounders. For each conurbation, the daily number of MI events in MINAP from the years 2003–2006 inclusive was used as the outcome series in a generalised linear model with Poisson error structure and with scale parameter set to the Pearson chi-squared statistic divided by the residual degrees of freedom to model overdispersion.[156-157]

To provide an initial description of the overall shape of the temperature and lagged temperature effects, a non-linear distributed lag model was used.[158] This is a recently developed class of models in which both the exposure-outcome association and the lag structure of that association has a flexible shape. The overall relationship is therefore effectively modelled by a 3-dimensional surface. In line with the use of this model in the analysis of mortality data,[158] a 5 degrees of freedom natural cubic spline was used for the temperature-MI relationship, and a 4 degrees of freedom natural cubic spline for the dependence of the effect on lag. Spline functions, defined by piecewise polynomials, have a flexible shape (the higher the number of “knots”, or degrees of freedom, the greater the flexibility) and are useful for modelling non-linear effects with unknown shape. A lag period of up to 28 days was considered since cold effects on mortality have been found to persist for over three weeks.[19]

Simplified models with more directly interpretable numerical coefficients were then considered. For each model a 28-day distributed lag structure was used for the temperature effect, meaning that separate terms were entered into the model to capture the temperature effect on each individual lag day from 0 to 28 inclusive. Three specifications for the shape of the temperature effect were considered (Figure 6.1):

1. A log-linear temperature model without threshold
2. cold threshold model in which a log-linear temperature effect operates only below a certain threshold temperature
3. A dual threshold model in which separate log-linear temperature effects operate both below a certain cold threshold (the “cold” effect) and above a certain heat threshold (the “heat effect”)

Figure 6.1: Illustration of linear and threshold models for temperature-MI relationship



Note: in the threshold models, thresholds were constrained to be the same for all lag days

All models included adjustment for:

- A cubic spline function of calendar time with 7 degrees of freedom per calendar year to capture season and trend, in keeping with previous studies as a compromise between providing adequate control for unmeasured confounders and leaving sufficient information from which to estimate temperature effects.[159-160]
- Day of the week (6 indicator variables).
- Holidays (indicator variables).
- Daily influenza and RSV levels (each in three categories representing 0, 1, or 2+ lab confirmed cases in the conurbation in question).

- Daily relative humidity (average of the current and previous 3 days), as a 4 degrees of freedom cubic spline to allow for potential non-linearity.

- PM_{10} and ozone (each modelled as linear effects at lag days 0 to 3 inclusive since there appears to be little evidence of pollution effects at longer lags, and little evidence of non-linearity (Chapter 3)).

6.2.1.1 Model Selection

Initially, the "best" model in each of categories 1 (log-linear temperature model), 2 (cold threshold model), and 3 (dual, or cold and heat, threshold model) was chosen for each conurbation. For (1), the model chosen was simply the model estimated by maximum likelihood. For (2), the best cold threshold model was chosen by considering every possible threshold in 1°C steps from the minimum to maximum of temperature. At each possible threshold, the maximum likelihood estimates were found for all other parameters, and the log-likelihood was recorded, resulting in an evaluation of the profile likelihood for the threshold parameter. The threshold with the highest profile likelihood was selected. For (3), a similar procedure was followed, except that every possible combination of cold *and* heat thresholds (T_C and T_H respectively) was considered, and the combination maximising the profile likelihood for (T_C, T_H) was selected.

Selection between the best log-linear, cold threshold, and dual threshold model was based on minimising the Akaike Information Criterion (AIC), defined as:

$$AIC = -2 \times (\text{model log likelihood} - \text{number of parameters in model})$$

Since models (2) and (3) involve indirectly estimating one and two extra parameters respectively (namely, the thresholds themselves), the AIC was penalised accordingly.

Finally, heterogeneity of the thresholds was assessed by comparing the combined log-likelihood across all conurbations from models with (a) individually optimised thresholds for each conurbation (as above); and (b) the best fitting single threshold fixed across all conurbations. The difference in (2 x combined log-likelihood) was formally compared to a chi-squared distribution.

6.2.2 Revised analysis strategy

The above analysis was pre-planned and a similar approach has been used in studies of mortality data. However, it was found that with the MI data available for the present study (with lower event rates than large mortality studies), estimated effects in individual conurbations were imprecise and difficult to interpret, and the estimation of thresholds for the temperature effects rather unstable.

A revised analysis strategy was therefore subsequently implemented, in which all conurbations were included in a single modelling framework (stratified by conurbation), and the lag structure for temperature in the models was simplified. This framework had the added advantage that heterogeneity of effects across conurbations could be tested directly by fitting interaction terms in the usual way.

As before, a cubic spline function based on calendar date with 7 degrees of freedom per calendar year was used to control for seasonality and long term trends. However in order to include all 15 conurbations in one stratified model, 15 copies of the spline basis variables were generated; the first set of spline bases was then multiplied by an indicator variable for the first conurbation (resulting in zero values elsewhere), the second by an indicator for the second conurbation, and so on, so that the basic model for seasonality and long term trend was as follows with a separate set of parameter estimates for each spline, and thus a separate smooth function of time for each conurbation:

$$\log(E(MI_d)) = \sum_{c=1}^{15}(\beta_{1c}(splinebasis_{1,d} \times i_c) + \beta_{2c}(splinebasis_{2,d} \times i_c) + ... + \beta_{k+2,c}(splinebasis_{k+2,d} \times i_c))$$

where $E(MI_d)$ = expected number of MIs on day d, i_c is an indicator variable for conurbation c and $splinebasis_1 .. splinebasis_{k+2}$ is the basis for a k-knot spline for calendar date.

A simplified lag structure was employed to capture temperature effects in the model. Instead of including every lagged temperature from day 0 to 28, 5 temperature lags periods were used: the average of lag days 0-1, 2-7, 8-14, 15-21, and 22-28. The 0-1-day short-lag period was chosen since mortality studies suggest that any heat impacts would likely operate with little delay.[161-162] Effects

of cold have been reported with longer delays and hence the remaining terms covered up to 28 days delay, with weekly groupings chosen to allow more precise estimation of effects, and since at longer lags any temperature effects would be unlikely to vary sharply from day to day. All 5 lag periods were included simultaneously in all models, so that individual lag effects were always controlled for all other lags.

As before, all models were adjusted for :

- Day of week (6 indicator variables).
- Holidays (indicator variables).
- Daily influenza and RSV levels (each in three categories representing 0, 1, or 2+ lab confirmed cases in the conurbation in question.)
- Daily relative humidity (average of the current and previous 3 days), as a 4 degrees of freedom cubic spline.
- PM_{10} and ozone (each modelled as linear effects at lag days 0-3 inclusive)

6.2.2.1 Initial modelling of temperature effect

The revised modelling framework allowed for an initial simplifying assumption that the effects of temperature and potential confounders would be the same for all conurbations, and this was the starting point of the revised modelling strategy. To obtain a visual estimate of the temperature effect, a natural 4-knot cubic spline (with interior knots equally spaced along the range of temperatures) was included for each of the 5 lagged temperature effects in a model adjusted for the above confounding factors, with each effect constrained to be common across conurbations. Since each spline basis was parameterised as a linear term plus a further 4 non-linear terms, it was possible to perform Wald tests to assess the statistical significance of both the overall temperature effect (testing all 5 terms), and its non-linearity (testing only the 4 non-linear terms).

As in the original modelling process, simplified temperature effects with more directly interpretable numerical coefficients were then considered, namely log-linear temperature models and log-linear models with threshold. For the latter

the model was fitted repeatedly with every possible threshold from the 5th to the 95th percentile of mean daily temperature in 1°C steps, and then with thresholds specified as percentiles of temperature within the conurbation (assessing the 5th, 10th, 15th, … , 95th percentiles). These models were compared and the final temperature effect specification was selected as the model with the lowest AIC.

The cumulative effect of temperature was estimated by summing (on the log scale) the regression coefficients of the 5 individual lagged effects. For a given day, this cumulative effect can be interpreted as the total effect of a difference in daily temperature over the current and following 28 days.[158]

6.2.2.2 Assessment of heterogeneity across conurbations

Interaction terms were then added to allow all effects to vary across conurbations. Heterogeneity of effects was assessed by examining the statistical significance of these interaction terms using Wald tests.

6.2.2.3 Effect modification by individual-level factors

An exploratory analysis was conducted to assess effect modification by age, sex, previous coronary heart disease, previous hypertension, and current aspirin use. Each potential effect modifier was investigated separately: the daily number of events was broken down by the factor under consideration, which was itself included in the model as an interaction with the daily temperature. For the purposes of this exploratory analysis, only a single temperature term (average of lag days 0 – 28) was included to allow the models to fit given the small numbers of events in some subgroups. The temperature effect from such a model is broadly comparable to the estimate of the cumulative effect over all lag days, as obtained by summing the 5 lag terms in our main model.

6.2.2.4 Diagnostics and sensitivity analyses

The deviance residuals for the final model were calculated and plotted against calendar date in each conurbation. Partial autocorrelation plots of these deviance residuals were also generated by conurbation.

A number of sensitivity analyses were performed; for each sensitivity analysis the final model was modified in one particular way and the resulting temperature effect examined:

1. The dataset was restricted to only MI events for which the validity of the diagnosis could be confirmed against ECG or laboratory marker data.
2. Minimum and then maximum daily temperature were used in place of mean daily temperature.
3. The analysis was repeated including only the 5 conurbations with the highest daily event rates (namely Greater London, Greater Manchester, West Midlands, Tyneside, West Yorkshire all of which had median daily events ≥4).
4. In order to include information from the 9.5% of observations with missing pollution levels (PM_{10} and/or ozone), a multiple imputation procedure with 5 imputations was used to handle the missing data. A multivariate normal model for PM_{10} and ozone containing all variables from the final temperature model was used for the imputation.
5. In case of residual autocorrelation in the final model, lagged deviance residuals were added to the model for each conurbation in which significant early residual autocorrelation was seen (as defined by absolute partial autocorrelations of the deviance residuals exceeding 0.05 at lag days 0-3).
6. Finally, to assess the impact of varying the level of seasonal control in the model, the number of degrees of freedom per year used to define the spline function of date was varied in single step increments from 1 to 14 (compared with the original value of 7).

6.3 Results

6.3.1 Study population

A total of 84010 MI events were recorded within the 15 conurbations of interest (see Chapter 5 Table 5.1). Due to a lack of data on MI before January 2004 in

Norwich, and extended spells with missing pollutant data in Kingston-upon-Hull up to April 2003, Liverpool up to June 2003 and Bristol from August 2005 (Chapter 5 Figure 5.2 and Figure 5.5) these time-periods were excluded in these conurbations to allow models to be estimated.

6.3.2 Original analysis strategy by conurbation

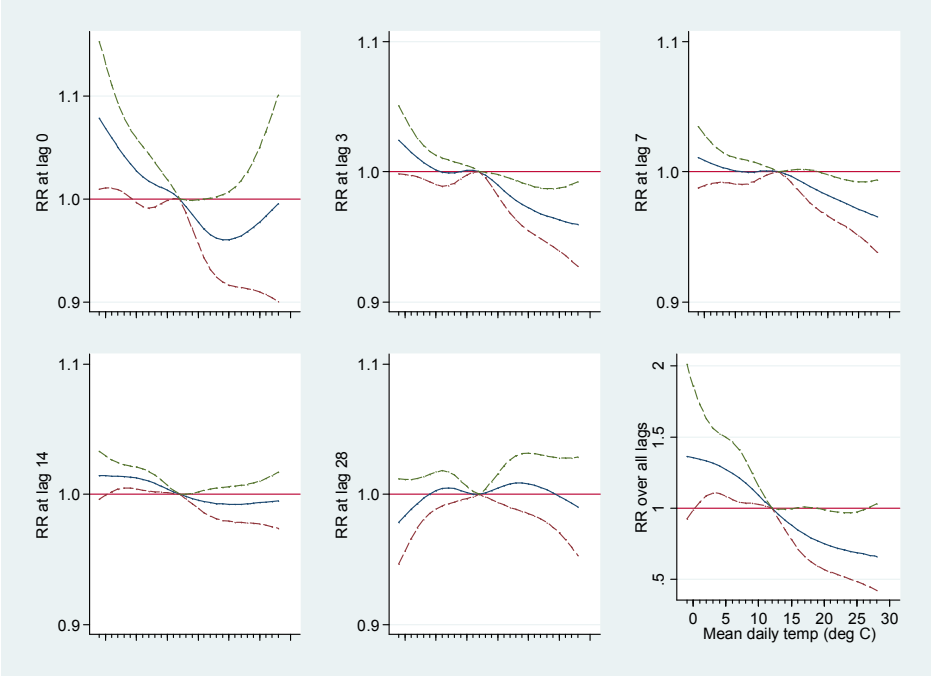
The results of the pre-planned analysis, in which a separate model was estimated for each conurbation, are now presented.

6.3.2.1 Non-linear distributed lag models for temperature effect

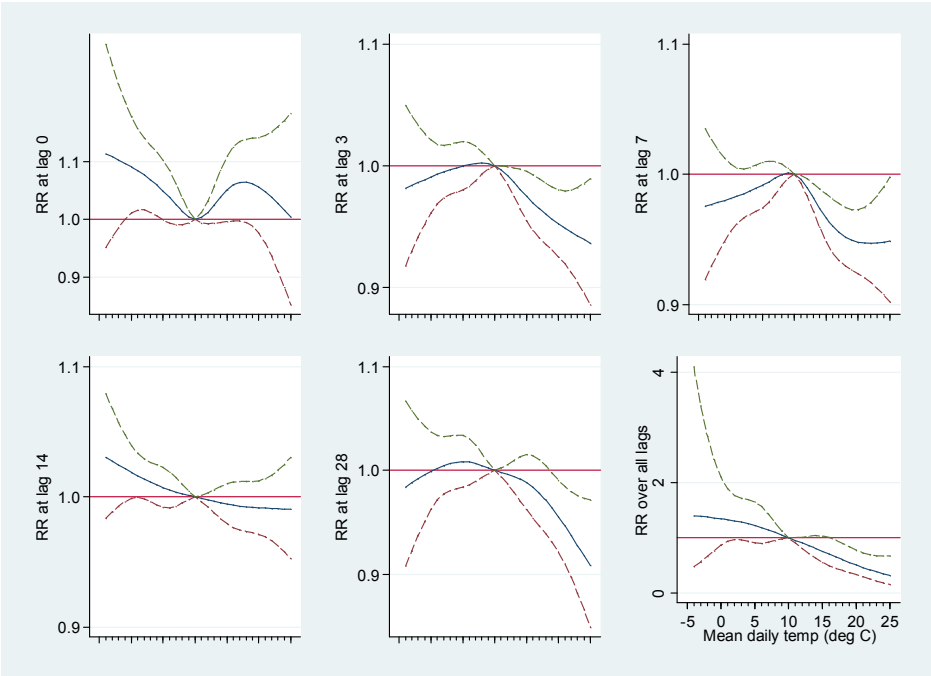
Estimates from a non-linear distributed lag model showed quite varied patterns of observed effects between conurbations (Figure 6.2 and Appendix I Figure 11.5). There were no clear same-day (lag 0) temperature effects: the confidence intervals for the relative risk of MI generally spanned 1 across the temperature range. In a number of conurbations there were suggestions of temperature effects acting with longer delays but the results were varied. In Greater London, the conurbation with the highest median daily event rates, there was an approximately linear cold effect operating at intermediate lag days which disappeared at lags of 14 days and more (Figure 6.2a); combined over all lag days there appeared to be a significant detrimental effect of lower temperatures. A similar pattern was seen in the West Midlands (Figure 6.2b), though the estimated temperature effects at individual lags appeared less “linear”. By contrast, Greater Manchester, which had the second highest median daily event rates, showed no temperature effect at any lag (Figure 6.2c), and nor did Kingston-upon-Hull (Figure 6.2d) though in the latter case the power to detect effects given very low event rates would likely have been inadequate. The remaining conurbations showed similarly mixed patterns (Appendix I Figure 11.5) though it is worth noting that in no case was a significant effect of heat or temperature increases observed.

Figure 6.2: Estimated relative risk of MI by temperature on specific lag days and overall

(a) Greater London

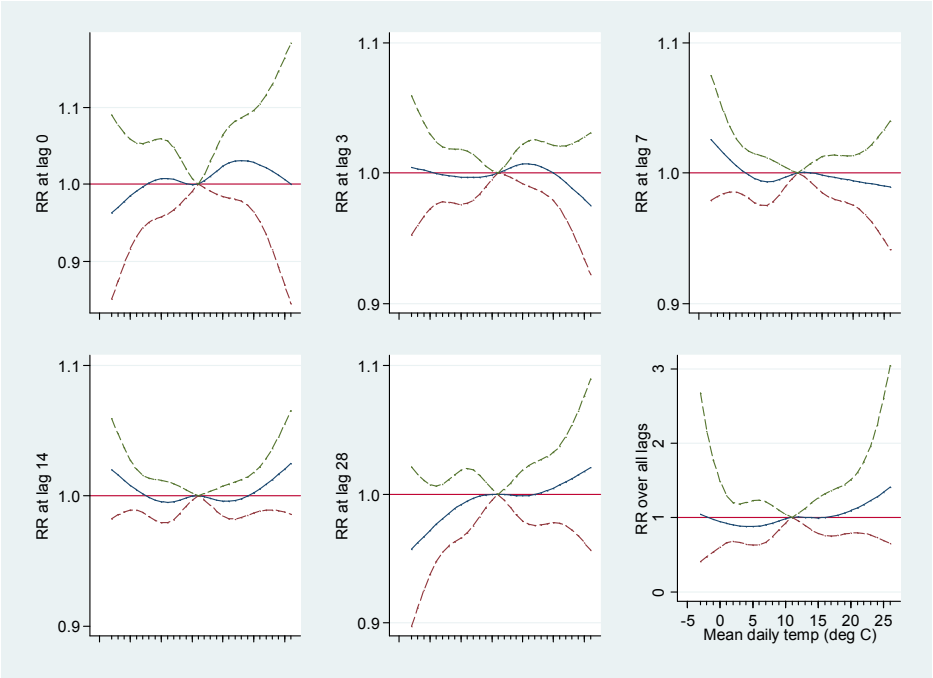


(b) West Midlands

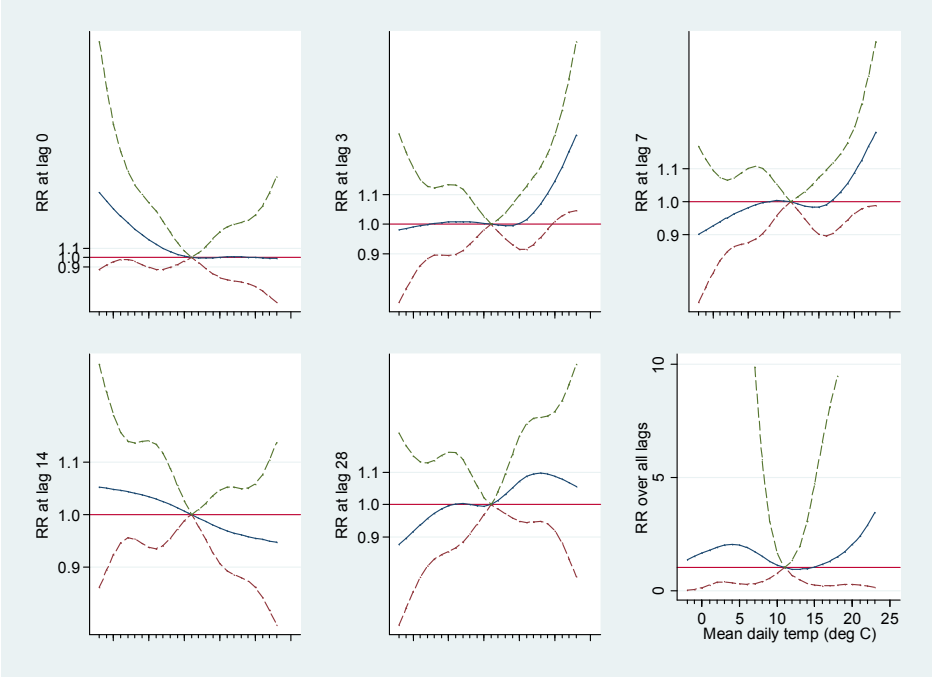


Estimates come from a non-linear distributed lag model adjusted for calendar time, relative humidity (av lags 0-3), day of week, holiday, influenza, RSV, pm10 (lags 0-3) and ozone (av lags 0-3)

(c) Greater Manchester



(d) Kingston-upon-Hull



Estimates come from a non-linear distributed lag model adjusted for calendar time, relative humidity (av lags 0-3), day of week, holiday, influenza, RSV, pm10 (lags 0-3) and ozone (av lags 0-3)

6.3.2.2 Effects of temperature in linear/threshold models

Simplified models were then considered using a selection process taking as candidates log-linear based models with and without temperature thresholds. In five conurbations (Cardiff, Nottingham, Southampton, West Midlands, West Yorkshire), a log-linear model without threshold was selected (Table 6.1) but only in the case of the West Midlands was a clear temperature effect seen, the estimate suggesting a detrimental effect of lower temperature (increase in risk per 1°C drop in temperature = 5.3% (2.3, 8.3) combined over all lag days).

Table 6.1: Measures of model fit and threshold/effect estimates for linear vs threshold temperature models in each of the 15 conurbations

	AIC			Best model by AIC	Estimated cold threshold and 95% CI*		Change in risk per 1°C drop in temp below threshold	
	Best linear model	Best cold threshold model	Best hot/cold threshold model	CT = cold threshold LIN = linear	(°C)		% change [95% CI]	
Bristol	2842	2840	2862	CT	17	[-, -]	-0.7	[-8.3, 7.4]
Cardiff	2793	2794	2814	LIN	N/A		-1.8	[-11.0, 8.3]
G London	8563	8563	8588	CT	18	[17, -]	3.6	[1.8, 5.4]
G Manchester	7356	7337	7366	CT	3	[-, 10]	-2.5	[-23.1, 23.6]
Kingston-upon-Hull	1787	1776	1800	CT	5	[5, 6]	-5.0	[-45.1, 64.4]
Leicester	3599	3596	3617	CT	2	[-, 4]	-24.3	[-68.2, 80.2]
Liverpool	4672	4661	4697	CT	9	[-, 11]	3.6	[-3.7, 11.6]
Norwich	2236	2227	2258	CT	13	[12, 14]	4.7	[-5.8, 16.3]
Nottingham	3563	3565	3588	LIN	N/A		1.5	[-5.5, 9.1]
Potteries	3600	3581	3601	CT	9	[9, 9]	3.8	[-5.8, 14.4]
Sheffield	5505	5499	5534	CT	13	[12, 15]	3.6	[-1.8, 9.3]
Southampton	2981	2984	3010	LIN	N/A		1.8	[-5.8, 10.1]
Tyneside	5875	5871	5891	CT	6	[4, 7]	5.7	[-3.8, 16.1]
W Midlands	6922	6926	6934	LIN	N/A		5.3	[2.3, 8.3]
W Yorkshire	6234	6237	6248	LIN	N/A		-1.5	[-4.9, 2.0]

Note: Lower AIC indicates a better model, based on balancing model fit and parsimony
Estimated temperature effects represent the total temperature effect combined over lag days 0-28 inclusive
All models adjusted for season & trend, relative humidity (av lags 0-3), day of week, holiday, influenza, RSV, pm10 (lags 0-3) and ozone (av lags 0-3)
**Incomplete 95% CIs indicated by a lower or upper limit of "-" means the lower or upper CI limit extended beyond the range of temperatures in that conurbation*

In the remaining ten conurbations, the modelling process selected a cold threshold model. However, the thresholds appeared to be poorly estimated. For example, in Greater Manchester, Kingston-on-Hull, Leicester, and Tyneside, the cold threshold value maximising the profile likelihood was at or very close to the lower extreme of the temperature range, resulting in very imprecisely estimated cold effects acting over a very small temperature range. In Leicester, the estimated temperature effect suggested a 24.3% decrease in risk per 1°C drop below 2°C with a confidence interval including a 68.2% decrease and an 80.2% increase in risk. On the other hand, in the cold threshold model for Greater London, the only one in which the effect was statistically significant, the threshold was estimated at 18°C; this was close to the upper extreme of the mean daily temperature range resulting in something close to a log-linear temperature model without threshold. A 3.6% (1.8, 5.4) increase in MI risk per 1°C reduction in temperature was estimated below this 18°C threshold.

In no conurbations did the modelling process lead to the selection of separate heat and cold thresholds, which would have implied a U- or V-shaped temperature relationship. This further suggested a lack of heat effects.

Finally, the heterogeneity of thresholds across conurbations was considered. Considering thresholds to be fixed across conurbations, the log-likelihood was maximised when a cold threshold at the 95^{th} %-ile of local temperature was applied, though it should be noted that this was not a statistically significant improvement over a linear temperature model for all conurbations (difference in -2log-likelihood = 1.24, over 1 degree of freedom, p=0.27). However a model with variable thresholds across conurbations was a comfortable improvement over the best fixed threshold model (difference in -2log-likelihood = 114.92, over 14 degrees of freedom, $p < 0.001$) suggesting significant heterogeneity across conurbations in the thresholds (Table 6.2).

Table 6.2: Model fit for fixed vs variable thresholds across conurbations

Model[+]	Combined log likelihood across all conurbations*
1.Best "fixed" threshold is at 18°C	-32819.82
2.Best "fixed" threshold as a %ile at 95th %ile	-32819.07
3.Linear effects only (no threshold)	-32819. 69
4.Variable thresholds (i.e. optimal threshold for each conurbation)	-32761.61

Note: Higher (less negative) log likelihood indicates better fit
+Models adjusted for separate effects of confounders in each conurbation: season and trend (27 knot spline for each conurbation), relative humidity (4 knot spline for lags 0-3), holiday, day of week, flu, RSV, pm10 (av of lag 0-3), ozone (av of lag 0-3)
**sum of individual conurbation log likelihoods*

6.3.3 Revised analysis strategy combining conurbations

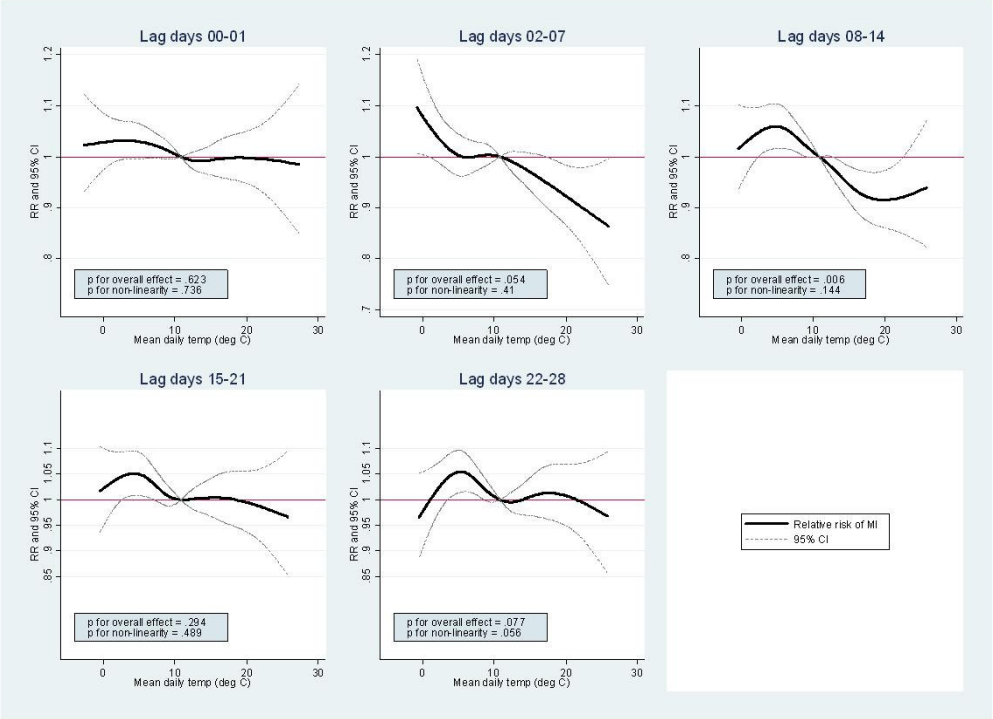
Given the apparently poor estimation of individual conurbation effects in both flexible models and simpler threshold models (Figure 6.2a-d and Table 6.1), the modelling process was revised as described in Section 6.2.2. Firstly, all conurbations were combined in one model, stratified by conurbation, and secondly, the lag structure of the models was simplified by using only five lag periods for temperature (average of lag days 0-1, 2-7, 8-14, 15-21, and 22-28).

6.3.3.1 Modelling temperature effects as flexible curves

With both temperature effects and confounders initially fixed across conurbations, and each lagged temperature effect entered into the model as a natural cubic spline, 5 estimated temperature effect curves representing the combined effect of temperature across all 15 conurbations were estimated (Figure 6.3). These curves suggested a broadly linear effect of temperature at short lags (days 0-1 and 2-7) with the risk of MI increasing at lower temperatures, though the temperature effect was not statistically significant at days 0-1 ($p = 0.62$). At days 8-14 there was strong evidence of a temperature effect ($p = 0.005$); again an increase in the risk of MI was seen at lower temperatures, and though the curve suggested a levelling off of the effect at both the lower and upper extremes of the temperature range, confidence intervals in these regions were wide reflecting the limited number of days on which these extremes of temperature occurred, and a formal test suggested

little evidence of non-linearity (p = 0.13). At lag days 15-21 and 22-28 there was little evidence of any continuing temperature effect though the estimated curves were broadly in the direction of a detrimental cold effect in both cases.

Figure 6.3: Estimated relative risk of myocardial infarction by temperature in the 15 conurbations combined



Estimated curves come from a combined model including all 5 lag periods for temperature (0-1, 2-7, 8-14, 15-21, 22-28 days), and adjusted for calendar time (stratified by conurbation), relative humidity (average of lags 0-3), day of week, holiday, influenza, RSV, pm10 (lags 0-3) and ozone (lags 0-3).
The reference value for relative risk estimates is the mean value of daily mean temperature across all days included.

6.3.3.2 Effects of temperature in linear/threshold models

Within the same modelling framework, simplified specifications of the temperature effect were considered, namely log-linear models with or without cold threshold; given that there were no suggestions of heat effects from the previous analyses, dual (heat and cold) threshold models were not formally assessed. Table 6.3 shows that the AIC was minimised by the most parsimonious “all-linear” model; in the optimal threshold model the cold threshold was at the 90th percentile of local temperature – it is worth noting that this in any case represents close to a simple log-linear temperature effect.

Table 6.3: Model fit and effect estimates for linear vs cold threshold models, in order of increasing model AIC

			RR (95% CI) per 1°C drop in temperature				
Cold threshold	**Log-likelihood**	**AIC**	**Lag 0-1**	**Lag 2-7**	**Lag 8-14**	**Lag 15-21**	**Lag 22-28**
LINEAR MODEL	-33326.98	67591.96	1.002 (0.998, 1.005)	1.006 (1.002, 1.011)	1.007 (1.003, 1.011)	1.003 (0.999, 1.007)	1.002 (0.998, 1.006)
90th %ile	-33326.32	67592.63	1.002 (0.999, 1.006)	1.006 (1.002, 1.011)	1.008 (1.003, 1.013)	1.003 (0.998, 1.007)	1.003 (0.998, 1.007)
95th %ile	-33326.66	67593.32	1.002 (0.998, 1.006)	1.006 (1.002, 1.011)	1.007 (1.003, 1.012)	1.003 (0.998, 1.007)	1.002 (0.998, 1.007)
85th %ile	-33327.02	67594.04	1.002 (0.999, 1.006)	1.006 (1.002, 1.011)	1.008 (1.003, 1.013)	1.003 (0.998, 1.007)	1.003 (0.998, 1.008)
19°C	-33327.33	67594.66	1.002 (0.999, 1.006)	1.006 (1.001, 1.011)	1.007 (1.003, 1.012)	1.003 (0.998, 1.007)	1.002 (0.997, 1.006)
18°C	-33327.7	67595.4	1.002 (0.999, 1.006)	1.006 (1.001, 1.010)	1.008 (1.003, 1.012)	1.003 (0.998, 1.007)	1.002 (0.997, 1.006)
17°C	-33328.34	67596.68	1.002 (0.999, 1.006)	1.006 (1.001, 1.011)	1.008 (1.003, 1.013)	1.003 (0.998, 1.007)	1.002 (0.998, 1.007)
80th %ile	-33328.75	67597.51	1.003 (0.999, 1.007)	1.006 (1.001, 1.011)	1.008 (1.003, 1.012)	1.003 (0.998, 1.008)	1.003 (0.998, 1.008)
16°C	-33329.43	67598.85	1.002 (0.999, 1.006)	1.006 (1.001, 1.010)	1.008 (1.003, 1.013)	1.003 (0.998, 1.008)	1.003 (0.998, 1.007)
75th %ile	-33329.72	67599.44	1.003 (0.999, 1.007)	1.006 (1.001, 1.011)	1.007 (1.002, 1.012)	1.003 (0.999, 1.008)	1.003 (0.998, 1.008)

Note: Higher (less negative) log likelihood indicates better model fit; lower AIC indicates better model based on balancing model fit and parsimony
All models adjusted for calendar time (stratified by conurbation), relative humidity (av lags 0-3), day of week, holiday, influenza, RSV, pm10 (lags 0-3) and ozone (av lags 0-3)

6.3.3.3 Description of effects in the final model

Estimates from the final model (log-linear temperature effects without threshold) showed significant effects of temperature, day of the week, and PM_{10} levels (Table 6.4). A 1°C drop in temperature on a given day was associated with a cumulative increase in MI risk of 2.0% [1.1 to 2.9] over the current and following 28 days, with the strongest effects being estimated at intermediate lags of 2-7 and 8-14 days.

As expected, there also appeared to be an increased risk of MIs being reported on weekdays compared with weekends: compared with Sunday, there was a 14% [11-17] increased risk of an MI being recorded on a Monday and a 4 to 8% increase for Tuesday-Friday. There was a suggestion that increases in PM_{10} levels by 10μg/m^3 were associated with a small increase in MI risk on the same day (0.8% [-0.2 to 1.7]) though at longer lags the risk was reduced; no effect of ozone was observed ($p = 0.18$).

Relative humidity did not appear to be associated with MI risk ($p = 0.29$) though there was a non-significant increase in risk at both low and high humidity values (RR = 1.03 [0.99-1.06] and 1.06 [0.99-1.13] at 55% and 95%, compared with 75%).

Finally, there was no evidence of an effect of holiday, influenza or RSV in the final model though effect estimates were in the direction expected in each case (i.e. a reduced risk of MIs being recorded on holidays, and an increased risk on days with lab confirmed influenza or RSV cases).

Table 6.4: Estimated effects of temperature and potential confounders in the final model

	Relative Risk [95% CI]	p-value
Temperature (per °C drop)		<0.001
Lag 0-1	1.002 [0.998 to 1.005]	
Lag 2-7	1.006 [1.002 to 1.011]	
Lag 8-14	1.007 [1.003 to 1.011]	
Lag 15-21	1.003 [0.999 to 1.007]	
Lag 22-28	1.002 [0.998 to 1.006]	
Cumulative effect over all lags	1.020 [1.011 to 1.029]	
Relative humidity		0.29
55%	1.03 [0.99 to 1.06]	
65%	1.01 [0.99 to 1.03]	
75%	1.00 (ref)	
85%	1.01 [0.98 to 1.04]	
95%	1.06 [0.99 to 1.13]	
Day of Week		<0.001
Sunday	1.00 (ref)	
Monday	1.14 [1.11 to 1.17]	
Tuesday	1.05 [1.02 to 1.08]	
Wednesday	1.07 [1.04 to 1.10]	
Thursday	1.04 [1.01 to 1.07]	
Friday	1.08 [1.05 to 1.11]	
Saturday	0.99 [0.96 to 1.02]	
Holiday		0.21
No	1.00 (ref)	
Yes	0.97 [0.92 to 1.02]	
Influenza A levels (lab confirmed cases)		0.58
0	1.00 (ref)	
1	1.02 [0.99 to 1.05]	
2+	1.01 [0.97 to 1.05]	
RSV levels (lab confirmed cases)		0.84
0	1.00 (ref)	
1	0.99 [0.96 to 1.02]	
2+	1.01 [0.95 to 1.06]	
PM10 (per 10 μg/m^3)		0.02
Lag 0	1.008 [0.998,1.017]	
Lag 1	0.992 [0.981,1.002]	
Lag 2	0.989 [0.979,1.000]	
Lag 3	1.003 [0.994,1.013]	
Ozone (per 10 μg/m^3)		0.19
Lag 0	1.000 [0.993,1.006]	
Lag 1	0.995 [0.988,1.002]	
Lag 2	1.001 [0.994,1.009]	
Lag 3	0.995 [0.989,1.001]	

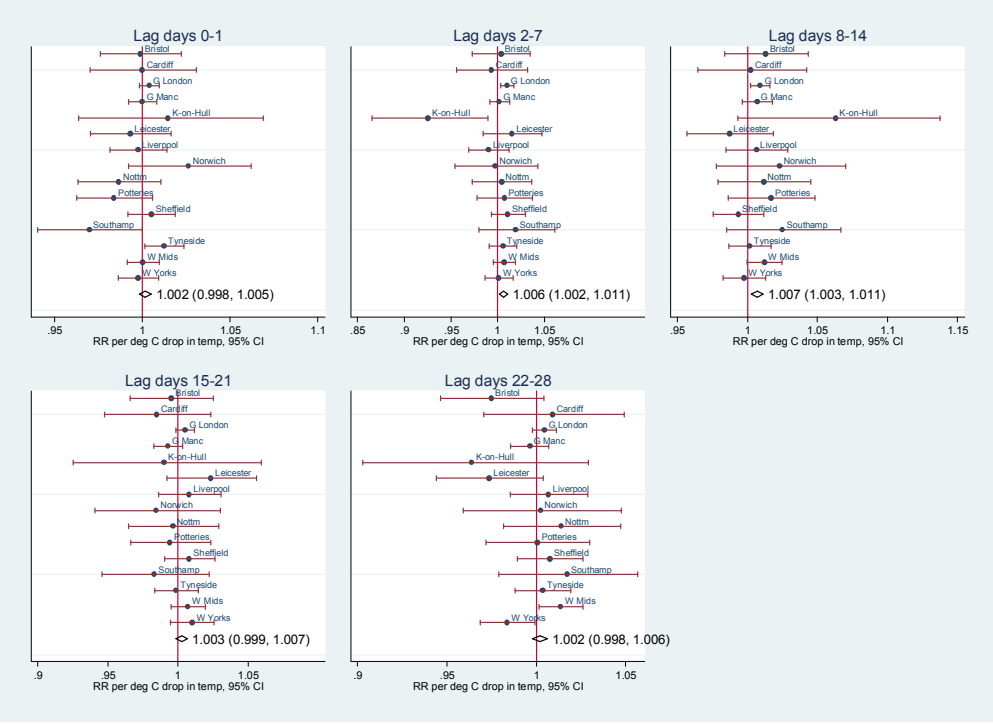
Model adjusted for season and trend using spline function of calendar date (7df/year)

6.3.3.4 Variation of effects across conurbations

Temperature interactions

The individual and combined effect estimates for temperature across conurbations are shown in Figure 6.4. There was no evidence of heterogeneity of the temperature effect across conurbations (p = 0.43). Of note at lag days 2-7 and 8-14, at which significant combined cold effects were estimated, effect estimates were in a direction suggesting cold effects for 11/15 and 12/15 individual conurbations respectively, however the only conurbation in which this effect was individually statistically significant was Greater London. Greater London had a median of 18 events per day compared with <8 in all other conurbations and therefore was much better powered to detect these effects.

Figure 6.4: Estimated relative risk of myocardial infarction per 1°C reduction in temperature - variation by conurbation



Estimates from a combined model including all 5 temperature terms (lag days 0-1, 2-7, 8-14, 15-21, 28), adjusted for calendar time (stratified by conurbation), and fixed effects across conurbations of relative humidity (average of lags 0-3), day of week, holiday, influenza, respiratory syncytial virus, pm10 (lags 0-3) and ozone (lags 0-3)

Other interactions

There was no evidence of variation in the effects of day of week (p = 0.14), holiday (p = 0.15), influenza (p = 0.97), respiratory syncytial virus (p = 0.25), PM_{10} levels (p = 0.91) or ozone levels (p = 0.50) across conurbations.

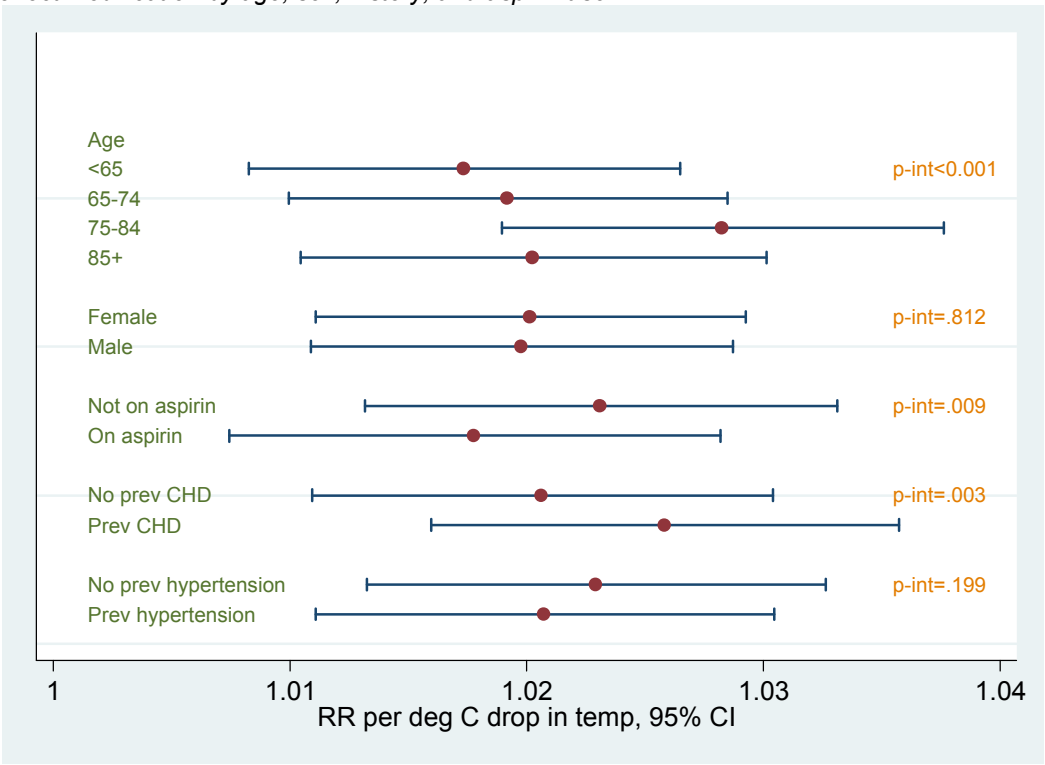
6.3.4 Effect modification by individual-level factors

In a simplified model with a single temperature term (the average of lag days 0 – 28), there was strong evidence of effect modification by age (p-interaction<0.001); notably, those aged 75-84 years appeared more vulnerable to the effects of cold than other age groups including the eldest (relative risk per 1°C reduction in temperature = 1.016 [1.007 to 1.025], 1.018 [1.009 to 1.027], 1.027 [1.018 to 1.036], and 1.019 [1.009 to 1.029] for those aged <65, 65-74, 75-84, and 85+ years respectively, Figure 6.5).

There was no evidence of a difference in the temperature effect between men and women (p=0.80). Data were available on previous coronary heart disease (MI or angina) for 82% of events, and those with previous disease appeared more vulnerable to the effects of temperature than those without (relative risks per 1°C reduction in temperature = 1.025 [1.015 to 1.034] and 1.019 [1.011 to 1.029] respectively, p-interaction=0.001). However there was little evidence of any effect modification by previous hypertension (p-interaction=0.16). Finally, considering the 86% of events where current aspirin usage data were available, those on aspirin appeared less vulnerable to temperature effects (relative risk per 1°C reduction in temperature = 1.016 [1.006 to 1.026] compared with 1.022 [1.012 to 1.031] for those not on aspirin, p-interaction=0.007).Effect modification by statin use was not assessed due to incomplete data.

It is worth noting that despite heterogeneity in the sizes of the temperature effect, temperature reductions were associated with a significant increase in MI risk for all subgroups considered.

Figure 6.5: Estimated relative risk of myocardial infarction per 1°C reduction in temperature – effect modification by age, sex, history, and aspirin use



Graph shows the estimated effect of temperature (average of lag days 0-28), adjusted for calendar time (stratified by conurbation), and fixed effects across conurbations of relative humidity (av lags 0-3), day of week, holiday, influenza, respiratory syncytial virus, pm10 (lags 0-3) and ozone (lags 0-3)

6.3.5 Diagnostics and sensitivity analyses for final model

6.3.5.1 Regression diagnostics

Plots of deviance residuals against calendar time were generated for each conurbation and no clear pattern was seen in the larger conurbations (Figure 6.6 and Appendix Figure 11.6). In the conurbations which tended to record low daily event rates, residual plots did tend to follow the overall fitted long term trend; however this is unsurprising since in these conurbations there was little information and therefore little variation in the predicted daily numbers of events. Partial autocorrelation plots of model deviances in most conurbations suggested little evidence of autocorrelation with most partial autocorrelations falling within the confidence bands. (Figure 6.7 and Appendix Figure 11.7). Nevertheless, the effect of including additional terms in the model allow for any residual autocorrelation was checked in a sensitivity analysis (section 6.3.5.2).

Figure 6.6: Individual conurbation plots of deviance residual vs calendar time

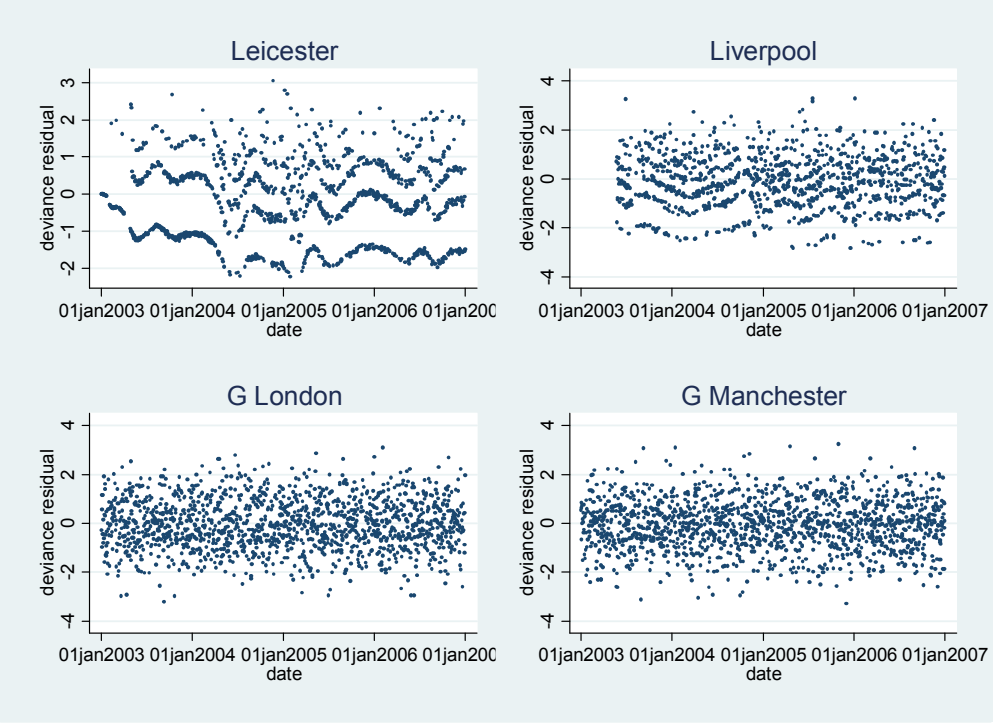
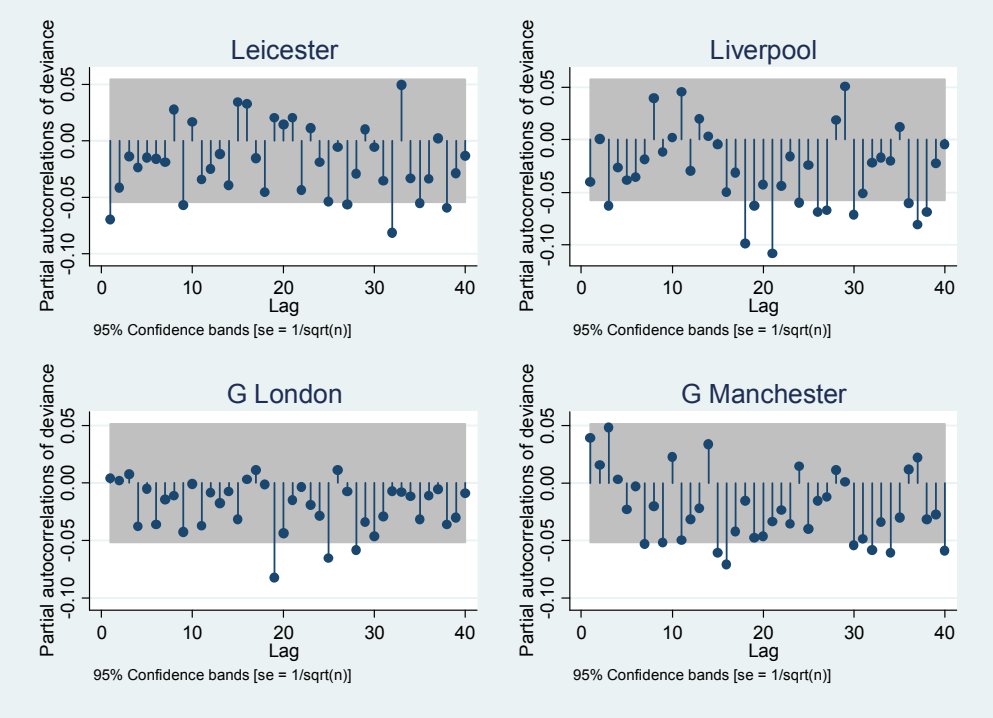


Figure 6.7: Partial autocorrelations of deviance residuals



6.3.5.2 Sensitivity analyses

Several modifications were made to the final model in order to test the robustness of effect estimates. The estimated overall temperature effect did not appear to be sensitive to restricting to only validated myocardial infarction events; using minimum and maximum daily temperature in place of mean temperature; restricting analyses to the five conurbations with the highest event rates; imputing pollution data to enable all observed data to be used; or including additional terms to allow for residual autocorrelation in the final model (Table 6.5). For all of these sensitivity analyses, the estimated cumulative effect of a 1°C reduction in temperature was between a 1.7 and 2.2% increase in risk, comparable to our final model estimate of a 2.0% increase in risk. Considering the temperature effect at specific lag periods, the effects of temperature at lag days 2-7 and 8-14 were estimated at 0.4-0.8% per 1°C reduction in temperature in all models, with no evidence of non-linearity in these effects. At shorter (0-1 day) and longer (15-21, 22-28 day) lag periods, the lack of evidence for a temperature effect was consistent across models.

Varying the level of seasonal control had only a small effect on the size and not direction of the estimated cumulative temperature effect: estimated effect sizes were 1.2-1.4% for a 3-6 degrees of freedom/year spline; 1.8-2.0% for 7-9 degrees of freedom/year, and 1.0-1.4 for 10-14 degrees of freedom/year (Table 6.6). Confidence intervals included the original estimate of a 2.0% increase in risk per 1°C reduction in temperature for all levels of seasonal control above 3 degrees of freedom/year.

Table 6.5: Sensitivity of estimated temperature effect to analysis strategies

Cell contents: *RR per 1 ℃ drop* *[95% CI]* *p-value*	Temperature effect						
	Lag 0-1	Lag 2-7	Lag 8-14	Lag 15-21	Lag 22-28	Combined effect over all lag days	Overall p for temp effect
Final model	1.002 [0.998,1.005] *0.30*	1.006 [1.002,1.011] *0.01*	1.007 [1.003,1.011] *0.00*	1.003 [0.999,1.007] *0.20*	1.002 [0.998,1.006] *0.36*	1.020 [1.011,1.029]	<0.001
Including only MI events validated by ECG/biomarkers	1.002 [0.999,1.005] *0.25*	1.005 [1.001,1.009] *0.03*	1.008 [1.003,1.012] *0.00*	1.002 [0.998,1.006] *0.44*	1.002 [0.999,1.007] *0.11*	1.019 [1.011,1.028]	<0.001
Minimum temperature instead of mean	1.002 [0.999,1.005] *0.25*	1.006 [1.002,1.010] *0.01*	1.006 [1.002,1.010] *0.00*	1.004 [1.000,1.008] *0.04*	1.002 [0.998,1.006] *0.31*	1.020 [1.011,1.029]	<0.001
Maximum temperature instead of mean	1.002 [0.999,1.005] *0.31*	1.006 [1.001,1.010] *0.01*	1.007 [1.003,1.011] *0.00*	1.001 [0.997,1.005] *0.52*	1.002 [0.998,1.005] *0.43*	1.017 [1.008,1.025]	<0.001
Restrict analysis to 5 largest conurbations	1.002 [0.998,1.006] *0.26*	1.006 [1.001,1.011] *0.01*	1.008 [1.003,1.012] *0.00*	1.003 [0.998,1.008] *0.21*	1.002 [0.997,1.007] *0.37*	1.022 [1.011,1.032]	<0.001
Multiple imputation of missing PM10 and ozone	1.001 [0.998,1.005] *0.44*	1.006 [1.002,1.011] *0.00*	1.006 [1.002,1.011] *0.00*	1.002 [0.998,1.006] *0.27*	1.001 [0.998,1.006] *0.41*	1.018 [1.009,1.027]	0.002
Inclusion of autocorrelation terms	1.002 [0.998,1.005] *0.30*	1.007 [1.002,1.011] *0.00*	1.007 [1.003,1.011] *0.00*	1.003 [0.999,1.007] *0.18*	1.002 [0.998,1.006] *0.32*	1.020 [1.011,1.030]	<0.001

Table 6.6: Sensitivity of estimated temperature effect to level of seasonal control

Degrees of freedom per calendar year for seasonal control	Combined temperature effect over lag days 0-28 (RR per 1°C reduction and 95% CI)
1	1.005 (1.003, 1.007)
2	1.006 (1.004, 1.008)
3	1.012 (1.006, 1.018)
4	1.013 (1.005, 1.021)
5	1.014 (1.006, 1.022)
6	1.013 (1.005, 1.022)
7	1.020 (1.011, 1.029)
8	1.018 (1.009, 1.028)
9	1.018 (1.008, 1.028)
10	1.013 (1.001, 1.025)
11	1.010 (.997, 1.022)
12	1.014 (.999, 1.029)
13	1.007 (.992, 1.022)
14	1.012 (.997, 1.027)

Each estimate from a model identical to the final model except for the level of seasonal control

6.4 Discussion

Across the 15 conurbations in England and Wales included in these analyses, there was a broadly linear temperature-MI relationship which was well characterised by log-linear models without temperature threshold. Each 1°C reduction in temperature was associated with a cumulative 2.0% (95% 1.1 to 2.9) increase in MI risk over the current and subsequent 28 days. Because MIs are common, and temperature changes are experienced by the whole population, even a small risk increase translates to substantial absolute numbers of extra MIs. For example, in the UK which sees an estimated 146000 MIs per year,[7] 11600 events would be expected on average in a 29-day period; our results suggest that each 1°C drop in temperature nationwide on a single day would be associated with an extra 232 MI events.

The temperature effect appeared to operate most strongly at 2 to 14 days after the reduction in temperature. The absence of a more immediate effect may be characteristic of the underlying mechanism at work, or might simply reflect

delays in MI patients being admitted to hospital. A similarly delayed cold effect has also been seen for overall mortality[162] though more immediate effects have also observed[9]. There was no indication of any detrimental heat effect.

In the systematic review of ambient temperature effects on MI risk (Chapter 2), 8 out of 12 and 7 out of 13 relevant studies identified cold and heat effects on MI risk respectively. The present analysis adds to the weight of evidence for a detrimental effect of lower temperatures but is not in agreement with the hypothesis raised in Chapter 2 that countries at more northern latitudes may be more likely to experience heat rather than cold effects. Some methodological questions hung over virtually all of the studies included in the systematic review and the effects reported were therefore sometimes questionable. Nevertheless one could argue that the cold effect was the more convincing to emerge from the review: considering the 5 studies in which the MI outcome was independently validated, 3 reported adverse effects only of cold, whereas only 1 based on data from a subarctic region found a detrimental effect of heat (Chapter 2 Table 2.2). This is in keeping with the present analysis which was based on an audit database in which 88% of MI events had an ECG trace, raised markers, or both to corroborate the MI diagnosis, and in which the findings were robust to exclusion of the remaining 12% of events. The analysis attempted to address the methodological weaknesses present in many previous studies; all models were adjusted for season and trend, relative humidity, air pollution, infectious disease levels, and day of the week, and both non-linear temperature-MI relationships, and delayed temperature effects were considered. The only study in the systematic review to address all of these issues was the study of MI mortality by Sharovsky et al[61] which found both heat and cold effects, however as discussed in Chapter 2 there may be reason for caution about the specificity of outcomes which rely only on mortality data.

There was evidence of effect modification by age, with those aged 75-84 years apparently more vulnerable to temperature effects than other age-groups. The age structure of patients recorded in MINAP allowed for those aged ≥65 years to be subdivided into three age groups and it was of interest that an increased vulnerability did not extend into the oldest group (≥85 years). Whilst this may reflect a lower number of events, and therefore lower power to detect an

increased temperature-associated risk in the oldest age group, another possible explanation is that individuals in this age group may spend less time outdoors, and may be more likely to live in residential or nursing homes with effective heating systems. An increased vulnerability to cold was also observed among those with previous CHD, though it should be noted that it was not possible to assess the three-way interaction between temperature, age group and previous CHD due to low numbers of daily events in the combined subgroups, therefore whether the vulnerabilities due to age and previous disease are independent remains an open question. Nevertheless, identifying subgroups that might be particularly vulnerable to cold effects is of interest since one potential application of these findings would be a to inform a targeted early warning system based on forecasted weather, as discussed in Section 2.4. The likely cost-effectiveness of any such scheme would need to be evaluated. It could be argued that since the results of this study imply an effect of temperature reductions across the temperature range, and even among individuals outside the most vulnerable groups, a more widespread health education message aimed at reducing the impact of lower temperatures may be of value.

Various proposed mechanisms to explain an effect of cold on MI risk were discussed in Section 2.4. A number of small experimental studies combine to suggest that a pathway for cold-induced thrombogenesis might involve a combination of factors including haemoconcentration, an inflammatory response, and a tendency for an increased state of hypercoagulability. Furthermore, the observation in the present study that aspirin seemed to be partially protective suggests that part of the effect may be mediated by changes in platelet function. However, there has been little recent research into mechanisms in this area and these hypotheses need to be tested in larger studies examining a range of updated measures.

There are a few possible explanations for the notable lack of an apparent effect of heat on MI risk in this study. First, temperature in the United Kingdom is rarely very high in global terms; although data from the unusually hot summer of 2003 were included, even the warmest periods are quite brief, which may have limited the power to detect a heat effect. On the other hand, such heat effects have been established in studies of overall mortality even in a UK setting.[161] A

second possibility is that any heat effects might have been too immediate to be detected by a daily time series study; this is further suggested by data at a finer temporal resolution which are examined as part of the analysis presented in Chapter 8 (Table 8.3 and Figure 8.7). Finally, these results might simply reflect a genuine absence of any heat effect on MI, indicating that other mechanisms are more important drivers of the heat-mortality relationship; this is also suggested by mortality data from London showing no increase in mortality from MI at higher temperatures despite clear heat-related increases in other cardiovascular deaths.[163]

Methodological problems were encountered with the initial modeling strategy attempted for this analysis. In retrospect, it may have been ambitious to attempt to estimate temperature effects in individual conurbations, when median daily event rates in over half of the 15 conurbations were ≤1. The strategy of choosing between linear and threshold temperature models proved particularly sensitive in this context, and thresholds were estimated quite erratically, likely due to the limited power in a number of conurbations. It was also felt that fitting 29 separate lag terms (lag days 0 to 28 inclusive) for temperature may have contributed to unstable models. Furthermore, delayed temperature effects would be unlikely to change in character from one day to the next, beyond the first few lag days, so including such a large number of terms was probably unnecessary. The revised model overcame these problems by utilizing all the information available from the 15 conurbations together in a single model to estimate the overall effect of temperature in each of the 5 lag periods; not surprisingly this model proved more stable and the analysis retained effective stratification by conurbation by including a separate spline function of calendar time for each conurbation to capture long term trends and seasonality.

Nevertheless, the revised analyses still has some limitations, reflecting the nature of the data. First, the MINAP database is restricted to patients admitted to hospital; MIs leading to death before hospital admission would therefore not have been included. The likelihood of a person suffering MI surviving to be admitted to hospital could conceivably be related to temperature if, for example, bad weather led to ambulance delays. However if such a mechanism were operating, it seems likely that the number of MIs would then be underestimated

on particularly cold days leading to an underestimation of the estimated adverse effects of cold. A second limitation of MINAP is suggested by the wide and disproportionate variation in the number of MIs recorded between conurbations, which implies some regional inconsistency in the recording of events. Though this may have led to some missed events and a consequent loss of power, it is unlikely to be related to day to day changes in temperature, so confounding should not have resulted from these apparent recording inconsistencies. A final limitation is that there may have been residual confounding in the final model, due both to imperfect adjustment for suspected confounders such as influenza (the marker of influenza activity was based on low numbers of laboratory confirmed flu cases and may not have been sufficiently sensitive to fully capture flu effects), and to the always-present possibility of unknown confounding factors having been omitted. However, it was reassuring that partial autocorrelations of residuals were not suggestive of substantial residual confounding.

Despite these limitations, this large study addresses many of the weaknesses of previous research in the area: MI diagnoses occurring in MINAP are likely to have high specificity and there is reason for confidence that the vast majority of outcome events included were indeed genuine MIs; indeed, most cases could be validated against ECG and/or laboratory marker data to confirm the diagnosis. Up to date methods based on smooth functions of time were used to control for seasonality and long term trends and models were adjusted for the most commonly suspected potential confounders relevant to analyses of temperature-MI relationships; non-linear and delayed temperature effects were also examined. A number of choices had to be made with regards to modeling strategies, however several sensitivity analyses suggested a robustness of the final estimated temperature effects to these decisions.

In conclusion, there appears to be a convincing short-term increase in MI risk associated with reductions in ambient temperature, predominantly operating in the two weeks following exposure. International studies with consistent methods will be required to clarify the dependence of these effects on local climate, while individual-level studies collecting demographic, clinical, and behavioural data may shed light on the role of adaptive measures such as clothing and home

heating, and further clarify which subgroups are likely to be the most vulnerable. Finally, studies of specific public health interventions aimed at reducing the impact of temperature-related increases in MI risk are needed.

6.5 Summary

- A daily time series regression was carried out, examining the short-term associations between daily mean temperature and MI risk
- Lower daily mean temperature was associated with increased risk of MI. The relationship was broadly linear, with each 1°C reduction in temperature associated with a cumulative 2% (95% 1.1 to 2.9) increase in MI risk over the current and subsequent 28 days
- Elderly individuals up to age 85 years and those with previous coronary heart disease appeared most vulnerable to the effects of temperature reductions; those taking prophylactic aspirin were less vulnerable
- No increase in the risk of MI at higher temperatures was detected

7 Characterising the short-term effects of daily air pollution levels on MI risk

7.1 Introduction

This chapter describes a series of analyses investigating and characterising the short-term effects of daily air pollution levels on the risk of MI.

7.2 Statistical methods

7.2.1 Main models for estimating the effects of pollutants on MI risk

To investigate the role of the 5 pollutants (PM_{10}, ozone, CO, NO_2 and SO_2) on MI risk, the final temperature model from Chapter 6 was modified. In place of the short-lag terms for PM_{10} and ozone used to control for pollution effects in the previous analysis, each of the 5 pollutants in turn was included as the main effect of interest. Based on the literature review (Chapter 3), which gave no suggestion of non-linear effects, or of any long-delayed effects, 8 linear terms (representing lag days 0 to 7 inclusive) were used for each pollutant in an unconstrained distributed lag model.

The effects of the 5 pollutants were initially investigated in separate models. As before, each model was a Poisson time series regression model combining data from the 15 conurbations. Daily numbers of MI events in MINAP from the years 2003–2006 inclusive formed the outcome series, and as well as adjusting for temperature using 5 terms (representing lag days 0-1, 2-7, 8-14, 15-21, 22-28) the models also included:

- A cubic spline function of calendar time with 7 degrees of freedom per calendar year to capture season and trend, estimated separately for each conurbation.
- Day of week (6 indicator variables).
- Holidays (indicator variables).

- Daily influenza and RSV levels (each in three categories representing 0, 1, or 2+ lab confirmed cases in the conurbation in question.
- Daily relative humidity (average of the current and previous 3 days), as a 4 degrees of freedom cubic spline.
- Scale parameter to account for overdispersion.

As a summary of the overall effect of each pollutant, the cumulative effect over lag days 0 to 7 combined (obtained by summing the regression coefficients of the 8 individual lagged effects on the log scale) was chosen as the primary outcome of interest. For a given day, this cumulative effect can be interpreted as the total effect of a change in pollutant levels over the current and subsequent 7 days. It should be noted that this choice of outcome places emphasis on the net effect of a pollution increase, rather than any short-term displacement of events (a hypothesised phenomenon also known as "harvesting" in which very frail individuals who were destined to have an MI within a few days anyway simply have their MI "brought forward" by the pollution exposure).

7.2.2 Heterogeneity of pollution effects across conurbations and by season

To assess heterogeneity of pollution-MI associations across conurbations, interactions between conurbation and pollution terms were then added to the model; heterogeneity of effects was assessed by examining the statistical significance of these interaction terms using Wald tests. Interaction terms with conurbation were not included for other confounder variables since there was no evidence of heterogeneity in previous analyses (see Section 6.2.2.2).

Since correlations between pollutants tended to differ in summer (Chapter 5 Table 5.9), pollution effects in summer (defined as June-August) vs other seasons were compared by fitting interaction terms in the main model for each pollutant. Heterogeneity of effects by season was again examined using Wald tests.

7.2.3 Role of temperature as a confounder

The majority of previous studies looking at pollution effects on MI either did not control for ambient temperature or included only very crude control for temperature effects (see Chapter 3). Understanding the impact of omitting temperature as a confounder would aid the interpretation of these previous studies. To this end, each pollution model was re-fitted both with and without control for temperature and the estimated pollution effects compared.

7.2.4 Further exploratory analyses

To explore the time course of pollution effects, i.e. the breakdown of the cumulative effect over the individual lag days 0-7, and any potential role of "harvesting", the relative risks associated with pollution increases for each individual lag day were estimated. The base confounder model was unchanged and as before, each pollutant was considered in a separate model. Individual lag day effects were estimated in two ways, firstly by adding each lag day univariately into the base model, and secondly by adding all 8 lag terms into the model together (the unconstrained distributed lag model). These two approaches have their advantages and disadvantages: the former technique avoids collinearity between adjacent lag terms, and therefore can produce more precise estimates, but it also effectively places a strong constraint on the model by restricting effects to one day, so that confounding by effects on other days may impact on estimates; on the other hand the latter approach, while avoiding such confounding, tends to produce imprecise effect estimates for individual lags due to neighbouring lag terms in the model being highly collinear, though overall effects summed over all lags are estimated adequately.

A more parsimonious distributed lag model was then fitted as a final descriptive model for each pollutant using 3 lag terms representing days 0, 1-2, and 3-7. This choice of lag day combinations was guided by the results of the initial explorations of individual lag effects. The model was intended to be a compromise avoiding both the residual confounding of the univariate lag models, and the imprecision of the unconstrained distributed lag model. Finally, using the same lag structure, all 5 pollutants were included in a single multi-pollutant model to explore the independence of individual pollutant effects.

7.2.5 Regression diagnostics

The deviance residuals for the final model for each pollutant were calculated and plotted against calendar date in each conurbation. Partial autocorrelation plots of these deviance residuals were also generated by conurbation. Finally, sensitivity of the main results to the level of seasonal control in the model was explored by varying the number of degrees of freedom per year defining the spline function used to control for seasonal confounding.

7.3 Results

7.3.1 Study population

The clinical and confounder data were the same as described and used in the previous chapter; 84010 MI events occurring within the 15 conurbations were included.

7.3.2 Cumulative effect of daily pollutant levels over 7 days

The results of the pre-planned analysis are now presented, in which the effects of each pollutant in turn were investigated by fitting 8 lag terms (lag days 0-7 days inclusive) in an unconstrained distributed lag model, with potential confounders modelled as in the final temperature model from Chapter 6.

7.3.2.1 Pollutant effects in all conurbations combined

Table 7.1 shows the cumulative effect of each pollutant on the risk of MI over lag days 0-7 inclusive. There was no evidence from this analysis of a detrimental effect of any of the five pollutants considered; indeed all estimated relative risks were in a direction implying a negative association with MI risk, although none were statistically significant.

Table 7.1: Cumulative effect of pollutants on the risk of MI over lag days 0-7 inclusive

Pollutant	RR (95% CI)	Increase in pollutant to which RR refers
PM_{10}	0.987 [0.974, 1.000]	$10\mu g/m^3$
Ozone	0.994 [0.983, 1.004]	$10\mu g/m^3$
CO	0.992 [0.982, 1.002]	$0.1mg/m^3$
NO_2	0.990 [0.979, 1.001]	$10\mu g/m^3$
SO_2	0.978 [0.935, 1.023]	$10\mu g/m^3$

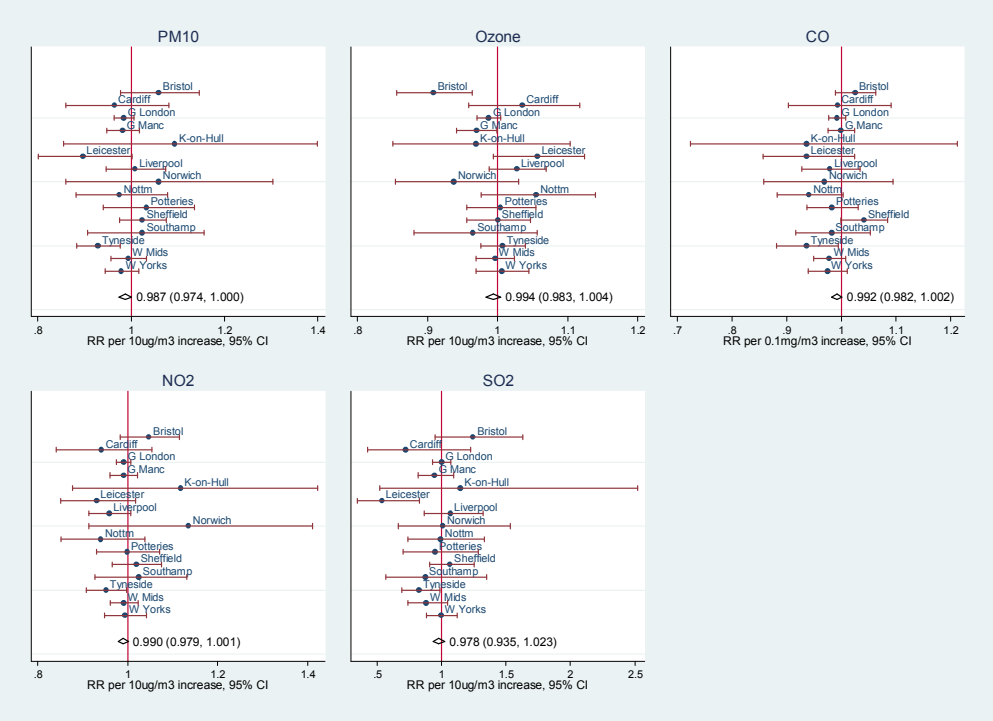
Note: Separate model for each pollutant; all models adjusted for calendar time (stratified by conurbation), temperature (5 terms spanning lag days 0-28), relative humidity (av lags 0-3), day of week, holiday, influenza, RSV.

7.3.2.2 Variation of pollutant effects across conurbations and by season

When interaction terms were added allowing the pollution effects to vary by conurbation, there was no evidence for heterogeneity of the pollution effects across conurbations (p=.60, .37, .40, .51, .49 for PM_{10}, ozone, CO, NO_2, SO_2 respectively, Figure 7.1). For PM_{10} and ozone, relative risk estimates in individual conurbations were quite evenly spread above and below 1. For the remaining pollutants, estimates were in a direction implying negative associations with MI risk for the majority of conurbations. Tyneside was the only individual conurbation in which a number of statistically significant pollution effects were estimated, with protective effects of PM_{10}, CO, NO_2 and SO_2 observed.

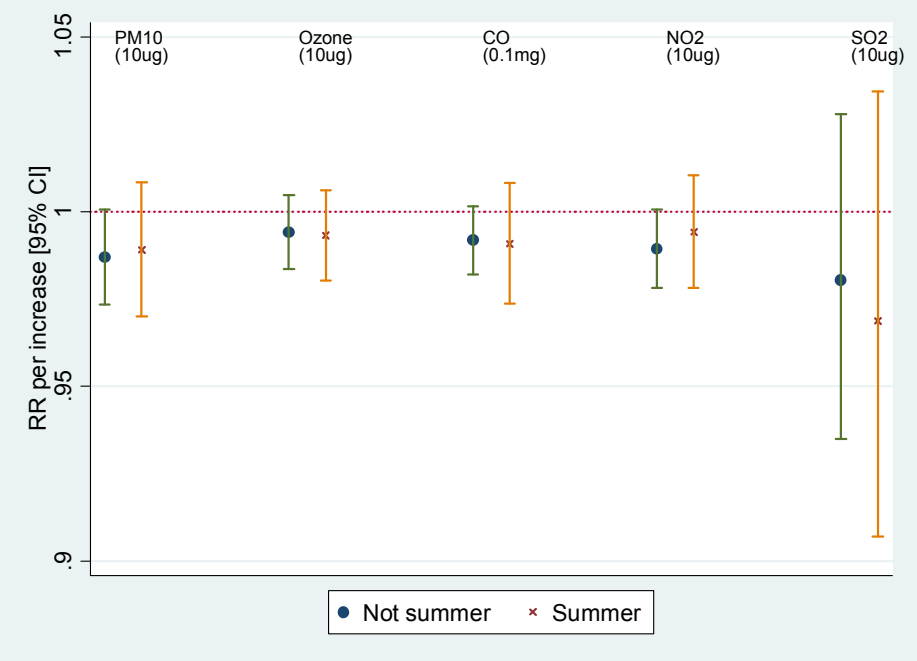
There was no evidence variation by season in the estimated pollution effects over lag days 0-7 combined (Figure 7.2, p-interaction>0.25 for all pollutants).

Figure 7.1: Effects of each pollutant by conurbation and combined across conurbations



Note: RRs are cumulative effects over lag days 0-7 inclusive
Separate model for each pollutant; all models adjusted for calendar time (stratified by conurbation), temperature (5 terms spanning lag days 0-28), relative humidity (av lags 0-3), day of week, holiday, influenza, RSV.

Figure 7.2: Relative risk of MI associated with pollution increases - variation by season

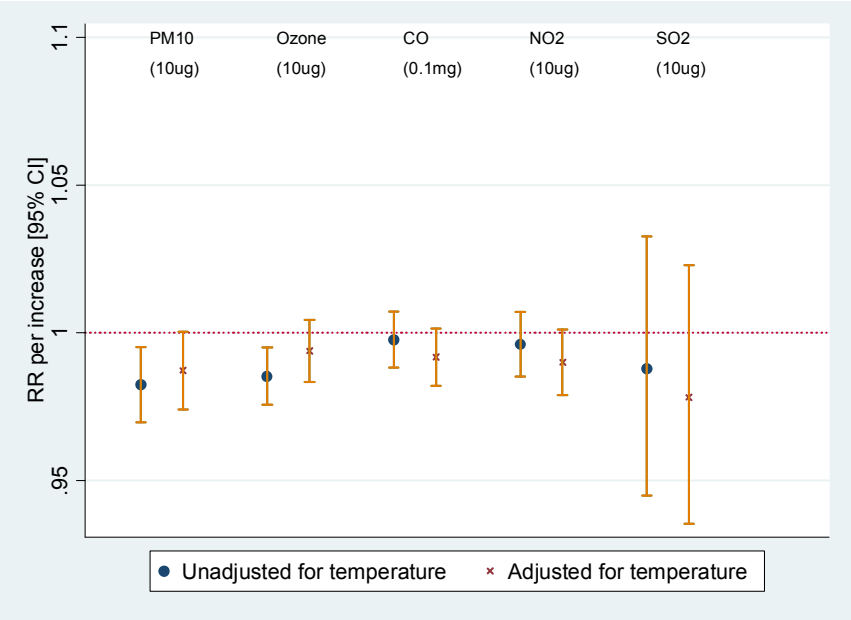


Note: RRs are cumulative effects over lag days 0-7 inclusive
Separate model for each pollutant; all models adjusted for calendar time (stratified by conurbation), temperature (5 terms spanning lag days 0-28), relative humidity (av lags 0-3), day of week, holiday, influenza, RSV.

7.3.2.3 Role of daily temperature as a confounder

Omitting temperature from models had some effect on estimated pollution effects, though the direction of the confounding varied across the five pollutants (Figure 7.3). Of note, omitting temperature from the ozone model led to a significant protective effect of ozone being estimated, as has been reported in the literature (see Chapter 3). A similar phenomenon was noted for PM_{10}, while for the remaining pollutants, omitting temperature from the model tended to move effect estimates towards the null.

Figure 7.3: Effect of omitting or including temperature on estimated pollution effects



Note: RRs are cumulative effects over lag days 0-7 inclusive
Separate model for each pollutant; all models adjusted for calendar time (stratified by conurbation), temperature (5 terms spanning lag days 0-28), relative humidity (av lags 0-3), day of week, holiday, influenza, RSV.

7.3.3 Exploration of the lag structure of pollutant effects

The breakdown of effects over individual lag days from 0 to 7 inclusive was examined to investigate the time course of the observed effects (Table 7.2).

7.3.3.1 Effects of pollutants at individual lag days

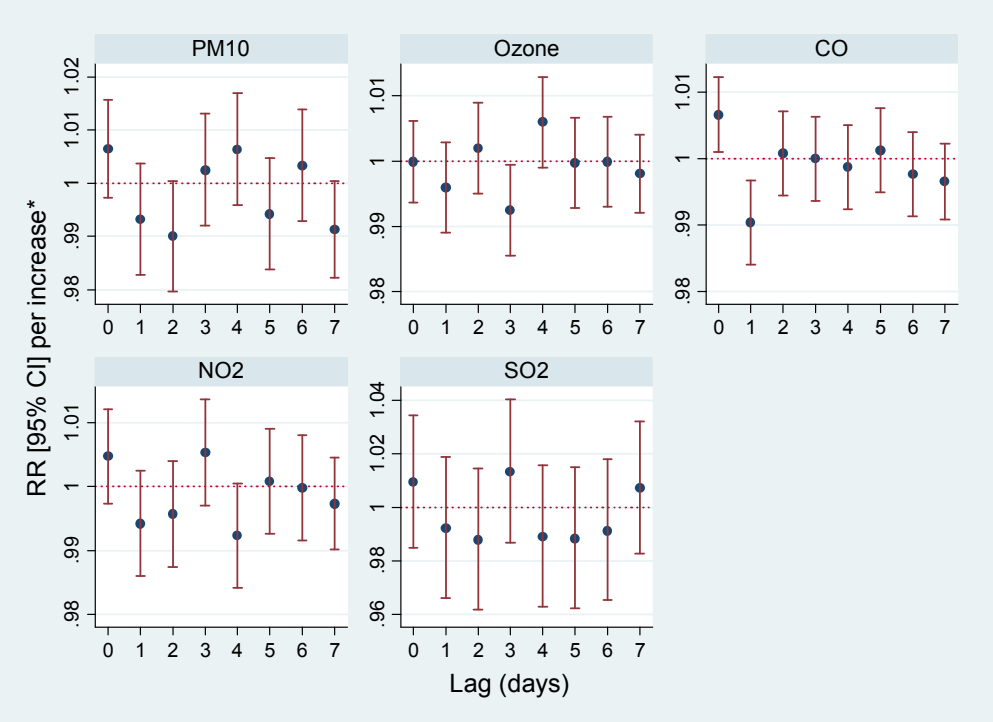
In single-lag models, i.e. with just one term to capture pollutant effects, the estimate for day 0 was in a direction associated with a detrimental effect of pollution for all pollutants except ozone, with the effect estimates on subsequent days mainly in the protective direction, a pattern consistent with a harvesting effect. However confidence intervals included the null in most cases. Estimates for individual lag days arising from distributed lag models (including all lag terms simultaneously) can suffer from imprecision due to the collinearity of neighbouring lag terms; nevertheless a similar pattern was observed in such models, and indeed the estimated detrimental effects of PM_{10}, CO and NO_2 at day 0 were larger (Table 7.2 and Figure 7.4). As before, with the exception of ozone, estimates suggested a positive pollution-MI association at day 0 followed by a negative association 1 to 2 days later, though statistically significant effects were seen only for CO (estimated RR per mg/m^3 CO increase 1.068 [1.010 – 1.130] at day 0 and 0.908 [0.852 -0.968] at lag day 1).

Table 7.2: Estimated effects of pollutants on MI risk over individual lag days 0 to 7

Pollutant and lag (days)		RR and 95% CI per increase*	
		Single lag model	**Distributed lag model**
PM_{10}	*Lag 0*	1.002 [0.995, 1.010]	1.006 [0.997, 1.016]
	1	0.993 [0.986, 1.001]	0.993 [0.983, 1.004]
	2	0.990 [0.983, 0.998]	0.990 [0.980, 1.000]
	3	0.997 [0.990, 1.005]	1.003 [0.992, 1.013]
	4	1.001 [0.993, 1.008]	1.006 [0.996, 1.017]
	5	0.996 [0.988, 1.003]	0.994 [0.984, 1.005]
	6	0.997 [0.989, 1.004]	1.003 [0.993, 1.014]
	7	0.992 [0.985, 1.000]	0.991 [0.982, 1.000]
Ozone	*Lag 0*	0.998 [0.992, 1.003]	1.000 [0.994, 1.006]
	1	0.996 [0.990, 1.001]	0.996 [0.989, 1.003]
	2	0.997 [0.992, 1.003]	1.002 [0.995, 1.009]
	3	0.995 [0.990, 1.001]	0.992 [0.986, 0.999]
	4	1.002 [0.996, 1.007]	1.006 [0.999, 1.013]
	5	1.001 [0.996, 1.006]	1.000 [0.993, 1.007]
	6	0.999 [0.994, 1.005]	1.000 [0.993, 1.007]
	7	0.999 [0.993, 1.004]	0.998 [0.992, 1.004]
CO	*Lag 0*	1.002 [0.997, 1.007]	1.007 [1.001, 1.012]
	1	0.995 [0.990, 1.000]	0.990 [0.984, 0.997]
	2	0.997 [0.992, 1.002]	1.001 [0.994, 1.007]
	3	0.998 [0.994, 1.003]	1.000 [0.994, 1.006]
	4	0.999 [0.994, 1.003]	0.999 [0.992, 1.005]
	5	0.999 [0.994, 1.004]	1.001 [0.995, 1.008]
	6	0.997 [0.992, 1.002]	0.998 [0.991, 1.004]
	7	0.996 [0.991, 1.000]	0.997 [0.991, 1.002]
NO_2	*Lag 0*	1.001 [0.995, 1.007]	1.005 [0.997, 1.012]
	1	0.995 [0.989, 1.001]	0.994 [0.986, 1.002]
	2	0.995 [0.989, 1.001]	0.996 [0.987, 1.004]
	3	0.998 [0.992, 1.004]	1.005 [0.997, 1.014]
	4	0.994 [0.988, 1.000]	0.992 [0.984, 1.000]
	5	0.996 [0.990, 1.002]	1.001 [0.993, 1.009]
	6	0.997 [0.991, 1.003]	1.000 [0.992, 1.008]
	7	0.996 [0.990, 1.002]	0.997 [0.990, 1.005]
SO_2	*Lag 0*	1.010 [0.988, 1.032]	1.009 [0.985, 1.034]
	1	0.997 [0.975, 1.019]	0.992 [0.966, 1.019]
	2	0.989 [0.968, 1.011]	0.988 [0.962, 1.015]
	3	1.002 [0.980, 1.024]	1.013 [0.987, 1.040]
	4	0.989 [0.968, 1.011]	0.989 [0.963, 1.016]
	5	0.981 [0.959, 1.002]	0.988 [0.962, 1.015]
	6	0.989 [0.968, 1.011]	0.991 [0.965, 1.018]
	7	0.997 [0.975, 1.019]	1.007 [0.983, 1.032]

** RRs are per 10μg/m^3 increase for all pollutants except CO, per 0.1mg/m^3 increase*
Note: Separate model for each pollutant; all models adjusted for calendar time (stratified by conurbation), temperature (5 terms spanning lag days 0-28), relative humidity (av lags 0-3), day of week, holiday, influenza, RSV.

Figure 7.4: Estimated effects of pollutants on MI risk over individual lag days 0 to 7 from a distributed lag model



** RRs are per 10μg/m^3 increase for all pollutants except CO, per 0.1mg/m^3 increase*
Note: Separate model for each pollutant; all models adjusted for calendar time (stratified by conurbation), temperature (5 terms spanning lag days 0-28), relative humidity (av lags 0-3), day of week, holiday, influenza, RSV.

7.3.3.2 Selection of final descriptive models describing lag structure

In order to estimate the lag structure of the apparent pollutant effects more precisely, a final set of descriptive models was fitted containing 3 lag terms: lag 0 days, average of lag 1-2 days, and average of lag 3-7 days. This was chosen as a compromise between avoiding the collinearity present in the 8-term unconstrained distributed lag models while retaining the key lag structure of pollutant effects, with the specific breakdown chosen based on the patterns observed in the unconstrained distributed lag model results. Table 7.3 shows the estimates from these models which confirm the previously observed patterns. In single pollutant models, a 10μg/m^3 increase in PM_{10} was associated with a 0.9% [0.0 to 1.7] increase in the risk of MI on the same day, and then a 1.4% [0.4 to 2.5] reduction in MI risk on the following 2 days. Similar patterns were seen for the remaining pollutants except ozone, with effect estimates

suggesting that a rise in pollution levels was associated with an increased risk of MI on the same day, followed by a reduced risk of MI which was strongest at lag days 1-2. However it should be noted that, with the exception of PM_{10} effects at lag days 0 and 1-2, and CO effects at lag days 1-2, 95% confidence intervals were wide enough to include no real effect.

In a multi-pollutant model containing all 5 pollutants, patterns were broadly similar though confidence intervals were wider. The lagged protective effects of ozone and NO_2 were larger after adjustment for other pollutants, while the apparent effects of CO were attenuated.

Table 7.3: 3-term single and multi-pollutant models describing lag structure of pollutant effects on MI risk

Pollutant and lag (days)		RR and 95% CI per increase* Single pollutant model	Multi-pollutant model
PM_{10}	*0*	1.009 [1.000, 1.017]	1.007 [0.995, 1.018]
	mean 1-2	0.986 [0.976, 0.996]	0.987 [0.973, 1.001]
	mean 3-7	0.996 [0.985, 1.007]	1.005 [0.988, 1.023]
Ozone	*0*	0.999 [0.993, 1.005]	0.998 [0.984, 1.013]
	mean 1-2	0.996 [0.989, 1.002]	0.979 [0.961, 0.998]
	mean 3-7	0.999 [0.991, 1.007]	0.965 [0.940, 0.991]
CO	*0*	1.004 [0.999, 1.010]	1.003 [0.992, 1.014]
	mean 1-2	0.993 [0.987, 1.000]	0.996 [0.986, 1.006]
	mean 3-7	0.995 [0.988, 1.003]	0.999 [0.987, 1.012]
NO_2	*0*	1.004 [0.997, 1.011]	1.000 [0.985, 1.016]
	mean 1-2	0.992 [0.985, 1.000]	0.989 [0.973, 1.005]
	mean 3-7	0.994 [0.985, 1.003]	0.980 [0.961, 1.000]
SO_2	*0*	1.012 [0.988, 1.035]	1.007 [0.978, 1.035]
	mean 1-2	0.988 [0.961, 1.017]	1.012 [0.977, 1.048]
	mean 3-7	0.983 [0.949, 1.019]	1.011 [0.963, 1.060]

** RRs are per 10μg/m^3 increase for all pollutants except CO, per 0.1mg/m^3 increase*
Note: Separate model for each pollutant; all models adjusted for calendar time (stratified by conurbation), temperature (5 terms spanning lag days 0-28), relative humidity (av lags 0-3), day of week, holiday, influenza, RSV.

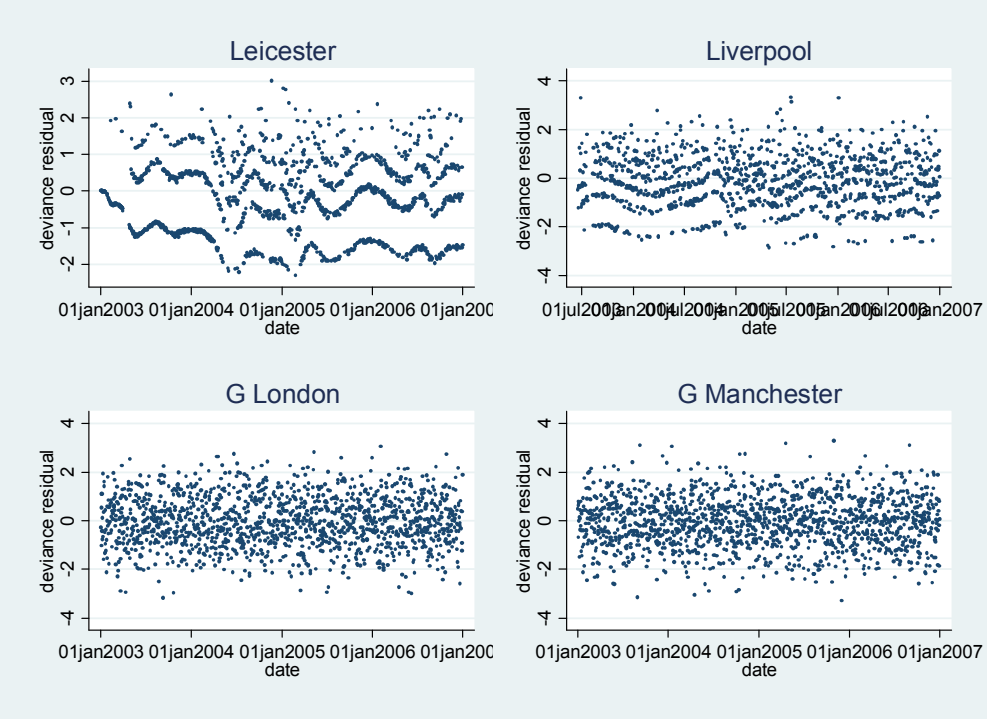
7.3.4 Diagnostics for the final descriptive models

7.3.4.1 Regression diagnostics

Plots of deviance residuals against calendar time were generated for each conurbation and, as for the final temperature model (Chapter 6) there was no

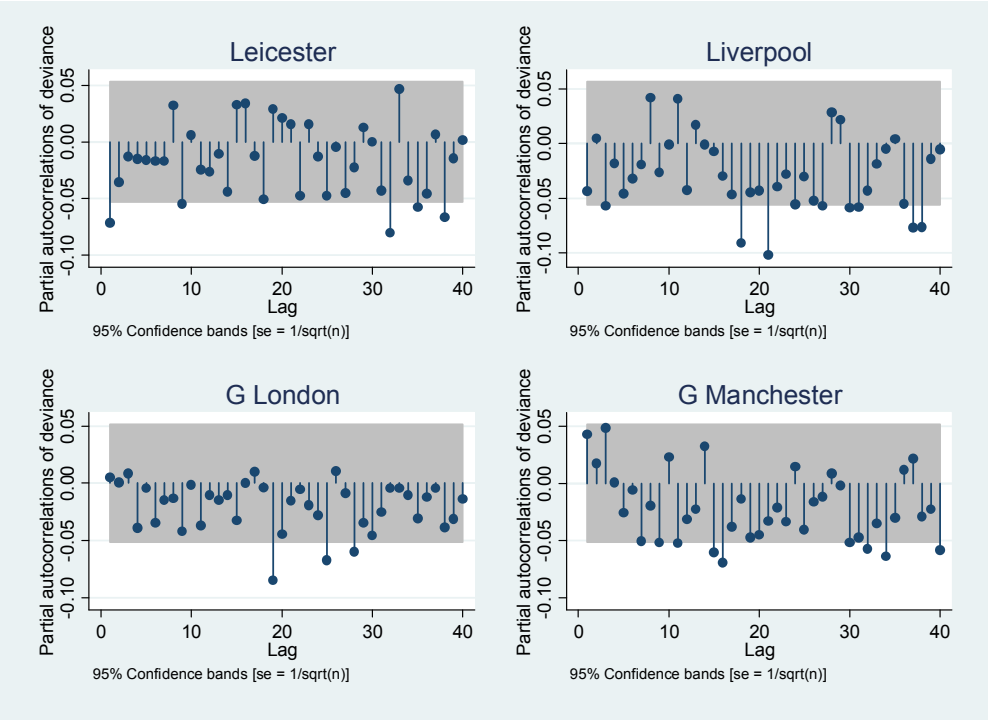
clear pattern in the larger conurbations (Figure 7.5 and Appendix Figure 11.8-Figure 11.12) In the conurbations which recorded low daily event rates, residual plots tended to follow the overall fitted long term trend as expected (see Section 6.3.5.1).

Figure 7.5: Individual conurbation plots of deviance residual vs. calendar time from the PM_{10} model



Partial autocorrelation plots of model deviances showed partial autocorrelations at almost all lags falling within the confidence bands suggesting little residual autocorrelation (Figure 7.6 and Appendix Figure 11.13-Figure 11.17).

Figure 7.6: Partial autocorrelations of deviance residuals from the PM_{10} model



However a majority of partial autocorrelations were in the negative direction, which may indicate an overfitted model.

To address this, a sensitivity analysis was carried out reducing the level of seasonal control (Table 7.4). With less seasonal control, the previously observed overall protective associations between pollutant levels and MI risk tended to be exaggerated; the exception was ozone, for which positive associations with MI risk emerged with low levels of seasonal control. The sum of the first 20 partial autocorrelation coefficients was balanced (i.e. equal to zero) with seasonal control of between 3 and 4 degrees of freedom per year.

Table 7.4: Sensitivity of pollutant effects to level of seasonal control

Pollutant	Degrees of freedom/year for season control	Relative risk per increase* (95% CI)	Sum of first 20 partial autocorrelations of deviance residuals
PM_{10}	1	0.973 [0.962, 0.985]	5.24
	2	0.974 [0.963, 0.986]	2.29
	3	0.981 [0.969, 0.993]	0.74
	4	0.981 [0.968, 0.993]	-0.95
	5	0.982 [0.969, 0.995]	-2.44
	6	0.987 [0.974, 1.000]	-4.54
	7	0.987 [0.974, 1.000]	-6.37
Ozone	1	1.014 [1.006, 1.022]	4.88
	2	1.016 [1.008, 1.024]	1.65
	3	1.006 [0.997, 1.016]	0.40
	4	1.001 [0.992, 1.011]	-1.28
	5	1.000 [0.990, 1.010]	-2.82
	6	0.996 [0.986, 1.007]	-4.72
	7	0.994 [0.983, 1.004]	-6.45
CO	1	0.984 [0.976, 0.992]	5.60
	2	0.986 [0.978, 0.994]	2.66
	3	0.990 [0.981, 0.998]	0.98
	4	0.990 [0.981, 0.999]	-0.94
	5	0.987 [0.978, 0.996]	-2.69
	6	0.991 [0.982, 1.001]	-4.56
	7	0.992 [0.982, 1.002]	-6.49
NO_2	1	0.979 [0.970, 0.989]	5.36
	2	0.980 [0.970, 0.990]	2.23
	3	0.985 [0.975, 0.996]	0.57
	4	0.985 [0.975, 0.995]	-1.24
	5	0.987 [0.976, 0.998]	-2.72
	6	0.989 [0.978, 1.000]	-4.63
	7	0.990 [0.979, 1.001]	-6.35
SO_2	1	0.969 [0.932, 1.006]	5.50
	2	0.960 [0.922, 0.998]	2.56
	3	0.968 [0.928, 1.008]	0.78
	4	0.970 [0.930, 1.011]	-1.00
	5	0.965 [0.924, 1.007]	-2.76
	6	0.985 [0.943, 1.029]	-4.56
	7	0.978 [0.935, 1.023]	-6.25

**RRs are per 10μg/m^3 increase for all pollutants except CO, per 0.1mg/m^3 increase*
Note: RRs are cumulative effects over lag days 0-7 inclusive
Separate model for each pollutant; all models adjusted for calendar time (stratified by conurbation), temperature (5 terms spanning lag days 0-28), relative humidity (av lags 0-3), day of week, holiday, influenza, RSV.

7.4 Discussion

In the main pre-planned analysis investigating the effects of mean daily levels of PM_{10}, ozone, CO, NO_2 and SO_2, there was no evidence of any net effect on MI risk for any pollutant over days 0 to 7 inclusive following exposure. In fact, though not statistically significant, surprisingly all estimates were in the protective direction, with 'standard' pollution increases of $10\mu g/m^3$ (or $0.1mg/m^3$ for CO) associated with estimated reductions in MI risk ranging from 0.6 to 2.2%. Further exploration of individual lag day effects suggested that these apparently protective cumulative effects were made up of detrimental effects on lag day 0, followed by broadly protective effects at longer lags, in particular on lag days 1-2; this pattern was consistent across the pollutants considered with the exception of ozone (for which no detrimental day 0 effect was observed). In the final descriptive model, a $10\mu g/m^3$ increase in PM_{10} was estimated to be associated with a 0.9% [95% CI 0.0 to 1.7] increase in MI risk on the same day, followed by a 1.4% [0.4 to 2.5] reduction in MI risk over the following 2 days, with little effect evident at lag days 3-7. Similar patterns were seen for CO, NO_2 and SO_2 though for these pollutants 95% confidence intervals included the null so the observed effects may have been due to chance.

The apparent lack of any overall detrimental pollution effects observed in these analyses is not inconsistent with the literature to date on the five pollutants considered. In the systematic review presented in Chapter 3, a clear majority of studies of PM_{10} and ozone, as well as over half the studies of CO, NO_2, and SO_2 similarly reported no evidence of positive associations between the levels of these pollutants and MI risk. In contrast with the present analysis, many previous studies of pollution-MI associations have reported effects based only on models using a single pollution term, often representing one specific lag day. For example, both reports in the literature of significant positive associations between daily PM_{10} levels and MI risk were based on models with only same-day (lag 0) pollution terms. The exploratory analysis presented in Section 7.3.3 similarly showed a significantly increased risk of MI associated with same-day PM_{10} increases, but overall, reductions in MI risk 1-2 days after a pollution level increase appeared to cancel out immediate detrimental effects. This highlights the sensitivity of pollution-MI models to the choice of lag terms included, and the

need for caution in interpreting studies with models that include only limited lag terms.

Only one other study[103] has reported cumulative pollution effects over lag days 0-7; no effects of PM_{10}, CO or NO_2 were found, though increases in SO_2 and, interestingly, ozone were reported to be associated with increased MI risk. Of note, the authors reported that the overall cumulative effect estimate for NO_2 suggesting no effect masked a same-day increase in risk followed by a reduced risk at lag days 2-3, a similar pattern to that observed in this analysis for PM_{10}, CO, NO_2 and SO_2.

There appeared to be little association between ozone and MI risk, either at individual lag days or cumulatively, in contrast with a few previous studies which have reported significantly protective effects of ozone.[38, 57, 110] However it is worth noting that such findings were based on models which included only limited control for temperature (only same-day temperature was controlled for in each case), while the analysis presented here included comprehensive control for temperature effects using five temperature terms covering lag days 0-28 inclusive. Furthermore, removing temperature from the models altered pollution effect estimates, with ozone in particular appearing significantly protective in an unadjusted model. Although reliably delineating the effects of ozone and temperature is problematic given their collinearity, it seems reasonable to hypothesise that residual confounding by temperature may have played a role in studies where protective ozone-MI associations have been observed: temperature and ozone were positively correlated in our data (see Chapter 5 Table 5.9) so in the model without adequate control for temperature, higher ozone levels may have been a acting as marker for higher temperatures, which, based on the analyses presented in Chapter 6, are in turn associated with decreased MI risk.

The observation of pollution increases being associated with a raised and then subsequently reduced MI risk, is consistent with the theory of pollution increases having a “harvesting” effect at a population level.[164] According to the theory, increased pollution levels are associated with the early triggering of MI events among individuals who would otherwise have had an MI one or more days later. In other words, this pollution-induced early triggering of MIs simply

causes a short-term temporal displacement of events that would have happened anyway, leading to an increased concentration of events on days of increased pollution, and a deficit of events on the days following pollution increases. One interesting observation was that lagged protective pollutant-MI associations appeared to more than cancel out the detrimental day 0 effects: cumulative effect estimates for lag days 0-7 were all in the direction of a protective overall association. This seems implausible and one possible explanation is that pollution effects on day 0 may have been too fast-acting to be adequately captured in an analysis using only daily mean pollution exposures. This is addressed in the next chapter in which pollution effects at an hourly timescale are investigated.

The fact that there was no evidence over an 8-day period of a net increase in the risk of MI suggests that the established effects of pollution on overall and cardiovascular mortality[42] are not due to increases in MI. Furthermore, since MI is a disease outcome with an unambiguously thrombotic pathogenesis, these findings indicate that thrombotic mechanisms may not be the real drivers of the observed effects on mortality.

Some of the strengths of this study and analysis have already been outlined in Chapter 6, and include the high specificity of MI outcomes, the use of up to date and flexible methods to control for seasonality and long-term trend, and the inclusion of the most commonly suspected potential confounders such as infectious disease levels, day of the week, and holiday effects. A key further advantage of this analysis over most previous studies of pollution-MI associations is the comprehensive adjustment for temperature. Control for temperature was based on the previous thorough analysis of temperature effects, and included 5 lag terms spanning lag days 0-28, in contrast with other studies which have typically included more crude adjustment for temperature with one or two terms at short lags.

Some limitations of the study must also be acknowledged. As with most population-based studies of air pollution health effects, background pollution levels as measured by outdoor monitors were used as the exposure of interest; in reality personal exposure may depend not only on ambient outdoor levels but also a number of factors including indoor exposure and time spent outdoors.

Furthermore since time series regression analysis methods use daily counts of events in each conurbation as the outcome, it was necessary to also summarise daily pollutant levels in each conurbation with one "aggregated" figure per day, even where several monitors were available. In reality pollution levels are likely to vary across a conurbation, as indicated by the variable correlations between pollutant levels measured by different monitors within the same conurbation (Chapter 4 Figure 5.3 and Appendix I Table 11.4-Table 11.7). The use of ambient pollution levels averaged over a conurbation, as a proxy for personal exposure, is therefore likely to have resulted in some degree of "measurement error." As long as the true personal exposures, averaged across the population, can be assumed to fluctuate in step with measured ambient levels, no bias would have been introduced, though some precision would have been lost. In reality this assumption may not hold perfectly, and measurement errors may therefore have resulted in bias towards the null for single pollutant models, or in either direction for multi-pollutant models.[165] Novel methods have been suggested to evaluate or remove the potential biases associated with measurement error using hierarchical models;[166-168] their applicability in the present analysis is limited by a lack of validation data,[166] and a relatively small number of individual locations with generally low event rates.[167-168] Nevertheless, exploration and development of these methods for use in the context of this work would be a potentially interesting area for future research.

Another limitation was that no data were available on $PM_{2.5}$ which may be a more important predictor of MI risk than larger particle exposures (Chapter 3). A final limitation is that the analysis was performed at a daily time resolution; the suggestion of positive same-day associations between pollution and MI risk raises the concern that pollutant effects may be too fast-acting to be adequately detected on this timescale. In the following chapter this limitation is addressed by the use of data at an hourly resolution.

7.5 Summary

- The analysis from the previous chapter was extended to look at the effects of day-to-day changes in PM_{10}, ozone, CO, NO_2 and SO_2 levels on MI risk.
- No associations were observed between pollutant levels and the net MI risk over the full 0-7 day lag period considered.
- For PM_{10}, CO, NO_2, and SO_2, estimates at individual lags were suggestive of positive pollution-MI associations on the day of exposure, cancelled out by negative associations at longer lags.
- There was little effect of ozone at any lag, though a significant negative association with MI risk emerged when control for temperature was omitted.

8 Investigating the role of same-day air pollution effects at an hourly temporal resolution

8.1 Introduction

Analyses presented in the previous chapter suggested that pollutant levels may have an effect on MI risk on the same day as exposure. Such an immediate effect would not necessarily be wholly captured by models based only on daily data. In this chapter a further analysis is presented which investigated air pollution effects on MI risk at a finer temporal resolution, using hourly data.

8.2 Statistical methods

8.2.1 Data on timing of MI events and pollutant exposure

To investigate the role of air pollution on MI risk at an hourly temporal resolution, the analyses was restricted to individuals for which the time of day of the MI event was recorded. The MINAP database records both date and time for a number of key points in the run-up and aftermath of an event, including symptom onset, first call for help, and arrival at hospital. To assign an event time, time of symptom onset was used where possible, and other timing variables where this was not recorded, following the same algorithm as that used to define event date in previous analyses (Section 4.2.1.3); where recorded, time of symptom onset was used as the time of the event; where this was not available one of the following time fields was used (in order of preference): first call for help, arrival of first professional, arrival of emergency services, arrival at hospital, reperfusion, cardiac arrest.

Hourly pollution data were available for all five pollutants under study (PM_{10}, ozone, CO, NO_2, SO_2) in all of the 15 conurbations. For each pollutant, a single hourly series was generated for each conurbation. Where monitor data from more than 1 station was available, these data were combined using the AIRGENE algorithm that has been described previously (Section 4.2.2.1).

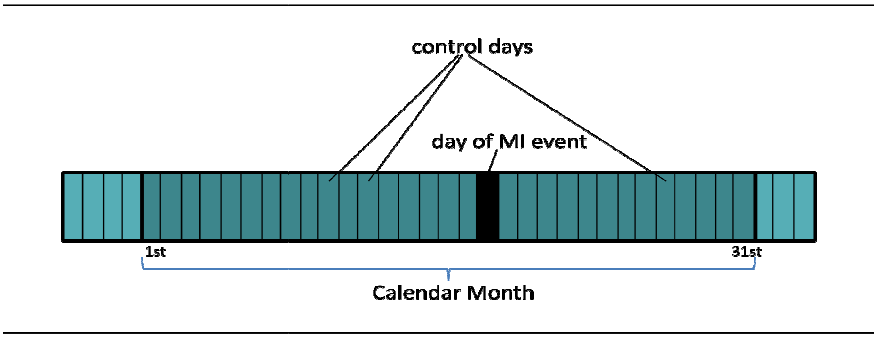
8.2.2 Case-crossover study design and model specifications

The Poisson time series regression methods that were used in the previous analyses do not lend themselves well to an analysis of hourly data: if there were a natural circadian pattern in MI risk this could act as a confounder for any short-term pollution-MI association, yet it would be difficult to separate the two using the usual modelling techniques due to the overlapping time-scales of effects. The case-crossover design[169] overcomes this problem since diurnal variations can be dealt with directly by matching.

Like the time series design, the case-crossover design (introduced in Chapter 3) is based purely on data from individuals experiencing an event; for each such individual, the "case" day is taken as the day of the event, and a set of "control" days (days on which the individual did not experience an event) are selected using a specified strategy. For each individual, exposure is then obtained for both case and control days, resulting in a design that is analogous to a matched case-control study.

There is some debate in the literature over the optimal strategy for selecting control days.[170-172] For this analysis, a time-stratified approach was chosen, to ensure the validity of standard analytical methods (conditional logistic regression) and avoid the biases to which unidirectional control selection strategies are vulnerable.[170] Calendar month time strata were used, so that for each case, the set of control days comprised all other days in the same calendar month and year (Figure 8.1). Since data were at an hourly resolution, case and control data were matched on hour of the day, so that if, for example, an individual had an MI at 1pm, then control data were taken from 1pm on every other day in the same calendar month, thus "matching out" time of day so that any confounding effects due to of natural circadian patterns in MI risk coinciding with natural diurnal variation in pollution levels would be removed.

Figure 8.1: Illustration of case and control days in the case-crossover calendar-month stratified design



Analyses in the previous chapter suggested pollution effects with up to 2 days delay, so to ensure coverage of this period, distributed lag terms covering a 72-hour lag period for each pollutant were used, specifically 1-6, 7-12, 13-18, 19-24, and 25-72 hours. These periods were chosen as a compromise between flexibility and model parsimony: four lag terms were chosen to cover the first 24-hour period since short-lived pollution effects might feasibly change rapidly over such a period; one further lag term covering 25-72 hours was intended to capture any longer-delayed effects such as those observed for lag days 1-2 in the previous chapter. The lagged pollutant terms were generated as the mean of pollutant levels at individual lags (e.g. the 1-6 hour term was generated as the mean of the pollutant levels at lags 1, 2, 3, 4, 5 and 6 hours). In some cases pollutant data at individual hours was missing. Where at least 2/3 of individual hourly measurements were available (i.e. 4 measurements for lag terms 1-6, 7-12, 13-18, 19-24 hours; 32 measurements for lag term 25-72 hours), the average lag term was generated as the mean of the remaining hours; where less than 2/3 of individual hourly measurements were available, the average lag term was set to missing and the associated observation excluded from models involving that pollutant.

The cumulative effect (over 72 hours) of a change in pollution was calculated by summing parameter estimates. Both single pollutant models and multi-pollutant models including all 5 pollutants were considered. Dual pollutant models for each pairing of pollutants were also examined in a supplementary analysis.

As in previous analyses, all models were adjusted for

- Day of week (6 indicator variables).
- Holidays (indicator variables).
- Daily influenza and RSV levels (each in three categories representing 0, 1, or 2+ lab confirmed cases in the conurbation in question.
- Daily relative humidity (average of the current and previous 3 days), as a 4 degrees of freedom cubic spline

By design, the case-crossover analysis assumes a constant background risk of MI within each time stratum (i.e. within each calendar month) which could lead to residual seasonal confounding.[117] To allow for any such residual seasonality, a single Fourier pair (a pair of cos/sin terms with annual periodicity) was included in the models. This choice was informed by a preliminary analysis in which the effect of daily temperature was modelled within the case-crossover framework (broadly reproducing the results of Chapter 6): with no additional control for residual seasonality, the temperature effect estimate did not match earlier analyses well and was highly sensitive to other model specifications such as the stratum length. Inclusion of a single Fourier pair resolved this (Appendix I Table 11.8).

8.2.3 Pollution effects by age and prior CHD

To explore how pollutant-MI associations might differ among subgroups within the population that might be more or less vulnerable to MI, terms were added to the multi-pollutant model to model interactions of first age group (categorised as before into <65, 65-74, 75-84, 85+ years), and then prior CHD, with each the five pollutant lag terms. Effects of pollutant level increases were then estimated in each subgroup by combining the estimated main and interaction effects.

8.2.4 The role of season and hourly temperature

Two further exploratory analyses were performed. First, since correlations between pollutants varied by season and followed a different pattern in summer (defined as July-September, Chapter 5 Table 5.9), interactions between season (summer vs. other seasons) and pollution effects were explored. Second, the

effect of controlling for ambient temperature at an hourly rather than daily resolution was investigated, in an analysis restricted to the 9/15 conurbations in which hourly temperature data were available (Bristol, Cardiff, Greater London, Greater Manchester, Liverpool, Nottingham, Sheffield, West Midlands, West Yorkshire). Hourly temperature was incorporated in the main multi-pollutant model with a similar lag structure to hourly pollution variables, namely as initially linear effects across 5 lag periods (1-6, 7-12, 13-18, 19-24, 25-72 hours). Daily temperature effects at longer lags (2-28 days) were retained in the model. To check the linearity assumption, a 4-knot natural cubic spline was then used so that the shape of any hourly temperature effect could be examined graphically.

8.2.5 Sensitivity analyses

Three sensitivity analyses were performed to check the robustness of the main findings to key aspects of study design and model specification. First, due to the importance of an accurate event time to these analyses, the study population was restricted to those with a recorded time of symptom onset, thus excluding the 28% of events for which the event time was drawn from other variables such as time of arrival of emergency services and time of arrival at hospital. Second, since control selection strategies can affect the results of case-crossover analyses, the data were re-analysed using different time strata to define case and control days: calendar month strata were replaced with strata of 14 days' length beginning at the start of the study period (1st January 2003), and for each case, 13 control days were selected by using all remaining days in the 14-day time stratum in which the case itself occurred. Third, returning to the calendar month-stratified design, an analysis was carried out using fewer control days and with case and control days matched on day of the week. For example if a case occurred on a particular Wednesday in February 2004, then the control days were defined as every other Wednesday in February 2004. This last sensitivity analysis effectively introduces a 7-day gap between case and control days addressing concerns that autocorrelation between exposure measures on the case day and immediately adjacent days might have an effect on results; the matching also provides an alternative way of controlling for day of the week rather than including this as a variable in the model.

8.3 Results

8.3.1 Study population and timing of MI events

Of the 84010 MI events recorded in MINAP within the 15 conurbations in 2003-6, the time of day of the MI was available for 81042 (96%). This time was most commonly based on the time of symptom onset (59369 events, 72%), time of call for help (6986 events, 9%) or time of arrival at hospital (15018 events, 18%).

Figure 8.2: Distribution of time of day of MI events

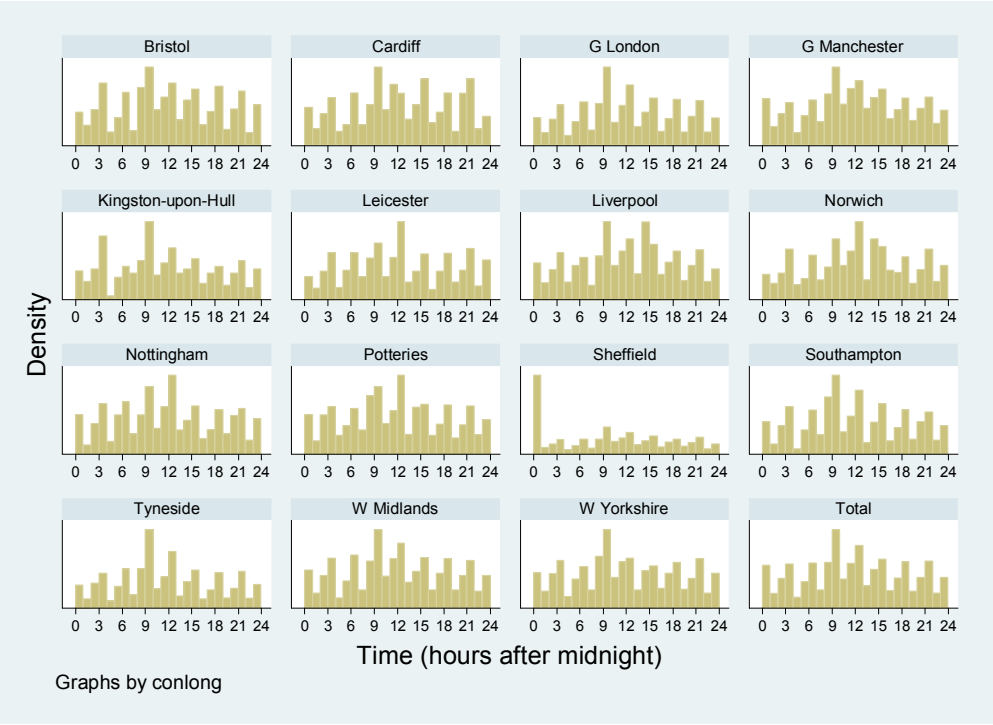


Figure 8.2 shows the distribution of MI events by time of day in each conurbation. In most conurbations, MIs appeared to peak at around 9-10am. On investigating the unusual feature of the distribution in Sheffield, namely the high peak of events reported to occur around midnight, it was noted that of 1754 cases in this conurbation that were assigned an event time using the date of time at arrival at hospital, 888 (51%) had the time recorded as midnight exactly suggesting that the recording of time of arrival at hospital was incomplete in this conurbation. These 1754 events were therefore excluded from further analysis, leaving 3149 events in Sheffield and 79288 overall.

Missing pollution data, which was handled as described in Section 8.2.2, resulted in a further 2107 (2.7%), 1952 (2.5%), 2447 (3.1%), 2216 (2.8%), and 2208 (2.8%) events being excluded from the single pollutant models for PM_{10}, ozone, CO, NO_2 and SO_2 respectively, and 4931 (6.2%) events being excluded from the multi-pollutant model.

8.3.2 Pollution effects modelled at an hourly resolution

In single-pollutant models, there was evidence at the shortest lag term of 1-6 hours of immediately raised risk of MI associated with higher PM_{10} and NO_2 levels, though longer lag term effect estimates were in the protective direction (Table 8.1). A similar pattern was observed for CO though confidence intervals in this case included no effect; there was little evidence of any effect of ozone or SO_2 in these single pollutant models.

The immediate effects of PM_{10} and NO_2 persisted in a multi-pollutant model containing all five pollutants (Table 8.1 and Figure 8.3). A 10μg/m^3 increase in PM_{10} was associated with a 1.0% (95% CI 0.0 to 2.0) increase in MI risk 1-6 hours later, but in subsequent lag periods the risk was reduced so that over 1-72 hours there was no overall risk increase (cumulative change in risk -0.2% [-1.7 to +1.3]). Similarly for NO_2, a 10μg/m^3 increase was associated with a 2.0% (0.8 to 3.3) increase in MI risk 1-6 hours later, but no net risk increase over 72 hours (cumulative change in risk -0.2% [-1.8 to +1.4]). The multi-pollutant model also confirmed the lack of evidence for any effect of SO_2 in any lag period.

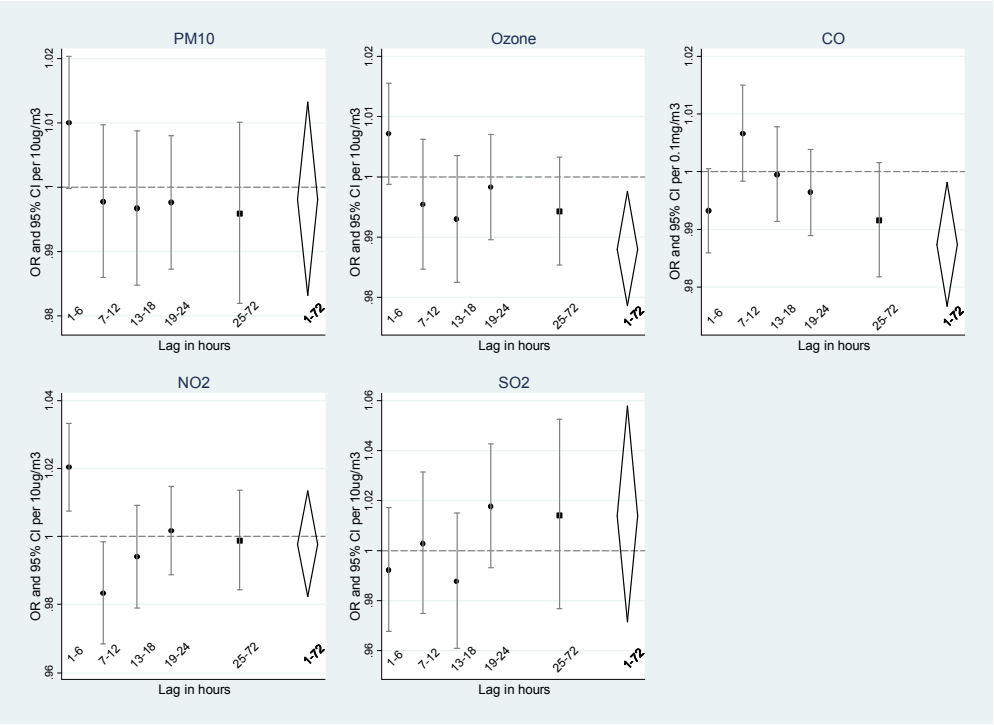
The apparent roles of ozone and CO were altered in the multi-pollutant model. A suggestion of a positive association was observed between ozone increases and MI onset at 1-6 hours lag, but over the longer-term (1-72 hours lag) there was a net protective association (-1.2% [-2.1 to -0.2] change in risk per 10μg/m^3 increase in ozone). For CO, both the shortest lag effect and the cumulative effect were in the protective direction (cumulative change in risk over 1-72 hours -1.3% [-2.3 to -0.2] per 0.1mg/m^3 increase). Of note, in two-pollutant models, both the detrimental effect of ozone at lag 1-6 hours and the apparently protective effect of CO at lag 1-6 hours appeared to be driven by adjustment for NO_2, with which both ozone and CO are strongly correlated in opposite directions (ρ = -0.58 and 0.61 respectively, Appendix Table 11.9).

Table 8.1: Pollution effects at 6-hourly temporal resolution, in single and multi-pollutant models

		OR and 95% CI per 10μg/m^3 increase (except CO: per 0.1mg/m^3 increase)	
Pollutant and lag		**Single pollutant model**	**Multi-pollutant model**
PM_{10}	*Lag 1-6*	1.012 [1.003, 1.021]	1.010 [1.000, 1.020]
	7-12	0.993 [0.983, 1.003]	0.998 [0.986, 1.010]
	13-18	0.997 [0.986, 1.007]	0.997 [0.985, 1.009]
	19-24	0.998 [0.989, 1.007]	0.998 [0.987, 1.008]
	25-72	0.992 [0.982, 1.002]	0.996 [0.982, 1.010]
	Σ(*1-72)*	*0.992 [0.982, 1.002]*	*0.998 [0.983, 1.013]*
Ozone	*Lag 1-6*	0.998 [0.992, 1.004]	1.007 [0.999, 1.016]
	7-12	1.004 [0.997, 1.012]	0.995 [0.985, 1.006]
	13-18	0.994 [0.987, 1.001]	0.993 [0.982, 1.004]
	19-24	0.999 [0.993, 1.005]	0.998 [0.990, 1.007]
	25-72	0.998 [0.991, 1.004]	0.994 [0.985, 1.003]
	Σ(*1-72)*	0.994 [0.987, 1.001]	0.988 [0.979, 0.998]
CO	*Lag 1-6*	1.002 [0.997, 1.007]	0.993 [0.986, 1.001]
	7-12	1.001 [0.994, 1.007]	1.007 [0.998, 1.015]
	13-18	0.997 [0.991, 1.003]	1.000 [0.991, 1.008]
	19-24	0.998 [0.993, 1.004]	0.996 [0.989, 1.004]
	25-72	0.994 [0.988, 1.001]	0.992 [0.982, 1.002]
	Σ(*1-72)*	0.992 [0.986, 0.999]	0.987 [0.977, 0.998]
NO_2	*Lag 1-6*	1.011 [1.003, 1.018]	1.020 [1.008, 1.033]
	7-12	0.991 [0.982, 0.999]	0.983 [0.968, 0.998]
	13-18	0.999 [0.990, 1.008]	0.994 [0.979, 1.009]
	19-24	1.000 [0.993, 1.008]	1.002 [0.989, 1.015]
	25-72	0.995 [0.987, 1.003]	0.999 [0.984, 1.014]
	Σ(*1-72)*	0.996 [0.988, 1.004]	0.998 [0.982, 1.014]
SO_2	*Lag 1-6*	1.000 [0.978, 1.023]	0.992 [0.968, 1.017]
	7-12	1.002 [0.977, 1.028]	1.003 [0.975, 1.032]
	13-18	0.985 [0.961, 1.010]	0.988 [0.961, 1.015]
	19-24	1.016 [0.994, 1.039]	1.018 [0.993, 1.043]
	25-72	0.992 [0.963, 1.023]	1.014 [0.977, 1.053]
	Σ(*1-72)*	0.996 [0.964, 1.029]	1.014 [0.972, 1.058]

Note: Models included the presented pollutant effects, and were adjusted for temperature (5 lag terms covering days 0-28 inclusive), relative humidity (average of lags 0-3 days), day of week, influenza, RSV, and residual seasonality within calendar month strata (single sin/cos pair per conurbation)
Σ(1-72) effect for each pollutant estimated by summing regression coefficients for the 5 lag terms

Figure 8.3: Lagged and cumulative pollutant effects on MI risk from a multi-pollutant model



Note: Model with 5 lag terms for each of the 5 pollutants, and was adjusted for temperature (5 lag terms covering days 0-28 inclusive), relative humidity (average of lags 0-3 days), day of week, influenza, RSV, and residual seasonality within calendar month strata (single sin/cos pair per conurbation)
Σ(1-72) effect for each pollutant estimated by summing regression coefficients for the 5 lag terms

The estimated effects of daily mean temperature, relative humidity, influenza/RSV levels, and day of week/holiday effects, were similar to those observed in previous analyses, with a significantly increased risk of MI observed on weekdays compared with weekends, and 2-14 days after a decrease in ambient temperatures (Table 8.2). As before, there was no evidence that relative humidity, influenza/RSV levels, or holidays were associated with MI risk.

Table 8.2: Other effect estimates in the multi-pollutant model for MI risk

	Odds Ratio [95% CI]
Temperature (per °C drop)	
Lag 0-1 (days)	1.002 [0.998, 1.005]
Lag 2-7	1.006 [1.001, 1.011]
Lag 8-14	1.006 [1.001, 1.011]
Lag 15-21	1.002 [0.997, 1.007]
Lag 22-28	1.000 [0.995, 1.005]
Relative humidity	
55%	1.03 [1.00,1.07]
65%	1.01 [0.99,1.03]
75%	1.00 [1.00,1.00]
85%	1.01 [0.98,1.04]
95%	1.05 [0.98,1.12]
Day of Week	
Sunday	1.00 (ref)
Monday	1.11 [1.07,1.14]
Tuesday	1.02 [0.99,1.05]
Wednesday	1.03 [1.00,1.06]
Thursday	1.01 [0.98,1.04]
Friday	1.04 [1.01,1.07]
Saturday	0.98 [0.95,1.01]
Holiday	
No	1.00 (ref)
Yes	0.98 [0.93,1.03]
Influenza A levels (lab confirmed cases)	
0	1.00 (ref)
1	1.01 [0.98,1.04]
2+	1.00 [0.96,1.05]
RSV levels (lab confirmed cases)	
0	1.00 (ref)
1	0.99 [0.96,1.02]
2+	1.00 [0.95,1.06]

Note: From a model with 5 lag terms for each of the 5 pollutants, adjusted for residual seasonality within calendar month strata (single sin/cos pair per conurbation)

8.3.3 Pollution effects by age and prior CHD

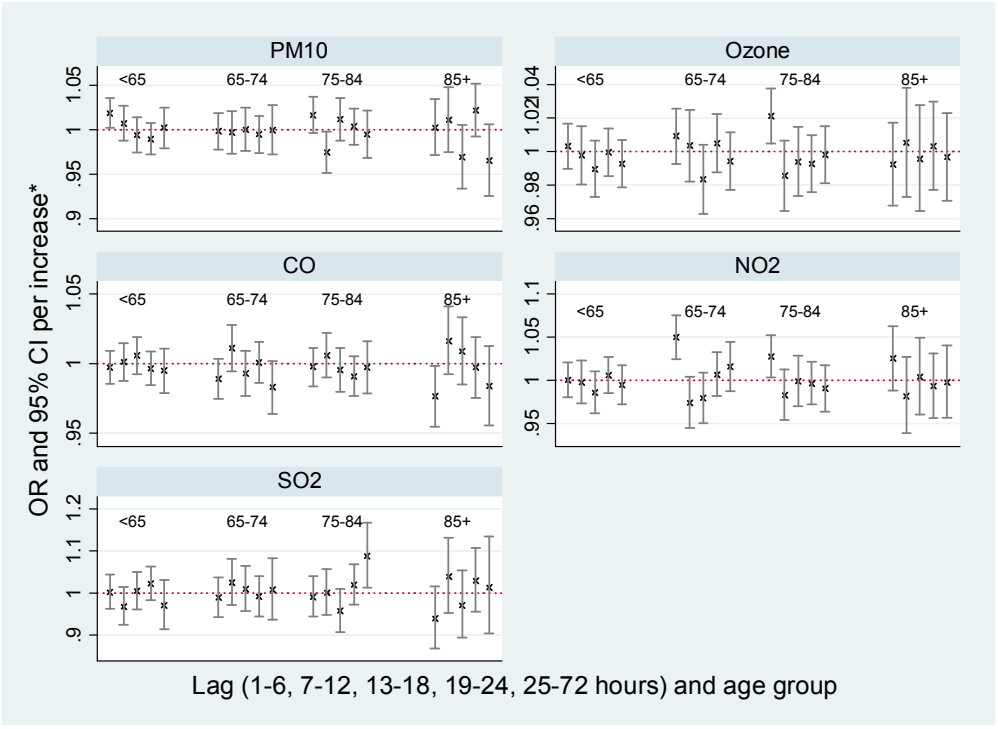
When examined by age group, the observed patterns of effects for ozone and NO_2 (namely an increased odds of MI 1-6 hours after a pollution increase, followed by a reduced odds at longer lags) were more pronounced among those aged 65-74 and 75-84 years than those aged <65 years; for PM_{10}, the pattern was similarly most prominent among those aged 75-84 years (Figure 8.4a). However, among those in the eldest age group (85+ years), there appeared to be little effect of PM_{10} or ozone, and only an attenuated effect of NO_2.

Patterns of effects also appeared to be stronger among those with prior CHD, with the exception of PM_{10}, for which the shortest-lag association with MI was strongest among those with no prior disease (Figure 8.4b).

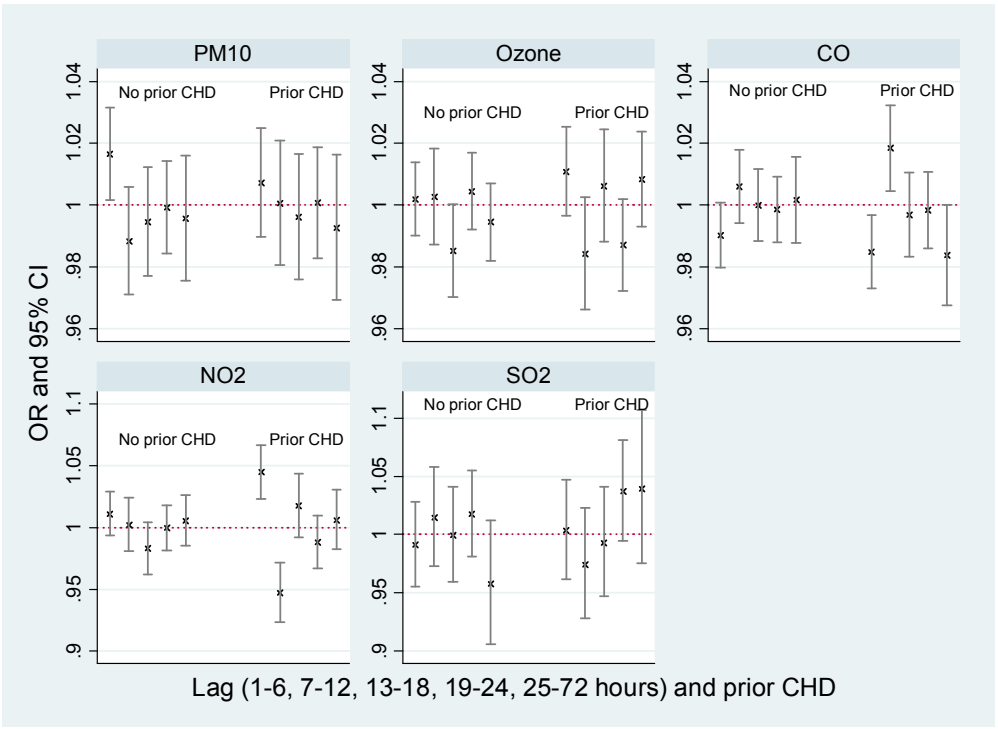
8.3.4 Pollution effects by season

On exploring interactions between pollution effects and season (summer vs. autumn/winter/spring) there was no statistical evidence of differing effects by season ($p>0.26$ for each pollutant). However, this analysis may have had limited power to formally detect such interactions and effect estimates did suggest some interesting patterns that may be worthy of future investigation (Figure 8.5). For ozone, which has higher overall levels but weaker correlations with other pollutants in summer (Chapter 5 Figure 5.5 and Table 5.9), the overall effects described earlier interestingly appeared to be more pronounced in the autumn/winter/spring periods compared with summer. The effects of NO_2 and CO also appeared to be largely restricted to autumn, winter and spring. For PM_{10}, the opposite pattern was observed, with estimated effects for each lag period larger in summer. These observations should include the caveat that due to fewer events, confidence intervals for summer effect estimates were in all cases wide enough to include the corresponding autumn/winter/spring effect estimate; this is consistent with the lack of statistical evidence for a formal interaction.

Figure 8.4: Odds ratio of MI associated with pollutant level increases
a) by age group

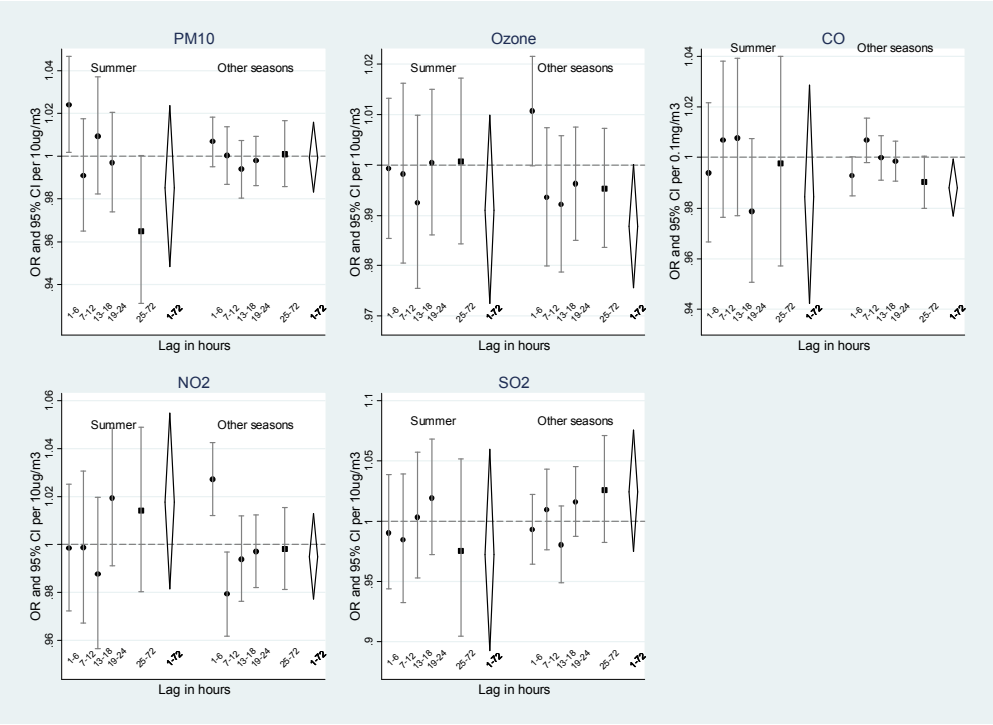


b) by prior CHD



**Effects are per 10μg/m^3 increase for PM_{10}, ozone, NO_2 and SO_2, and per 0.1mg/m^3 for CO*
Note: within age groups, estimates are the OR for MI for the following lag periods in hours: 1-6 (left most), 7-12, 13-18, 19-24, and 25-72 (right most)
From multi-pollutant models adjusted for temperature (5 lag terms covering days 0-28 inclusive), relative humidity (average of lags 0-3 days), day of week, influenza, RSV, and residual seasonality within calendar month strata (single sin/cos pair per conurbation)

Figure 8.5: Pollutant effects by season in a multipollutant model



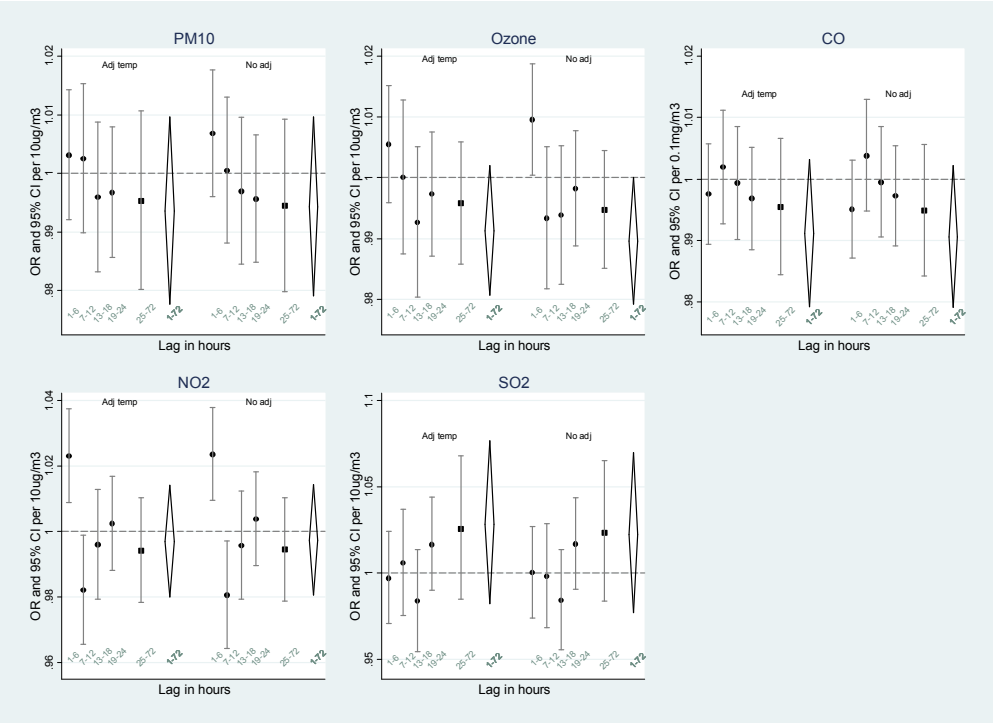
Note: Model adjusted for temperature (5 lag terms covering days 0-28 inclusive), relative humidity (average of lags 0-3 days), day of week, influenza, RSV, and residual seasonality within calendar month strata (single sin/cos pair per conurbation)

8.3.5 Role of hourly temperature

Hourly temperature data were available for 9/15 conurbations (Bristol, Cardiff, Greater London, Greater Manchester, Liverpool, Nottingham, Sheffield, West Midlands, West Yorkshire). The following analyses were restricted to these conurbations.

Patterns of pollution effects were broadly similar before and after adjusting for hourly temperature with up to 72 hours lag (five lag terms, matching the hourly lag breakdown for pollutant effects, Figure 8.6). However the estimated increase in risk of MI 1-6 hours after an increase in ozone was somewhat attenuated after adjusting for hourly temperature (RR = 1.010 [1.000 to 1.019] per 10μg/m^3 before adjustment, and 1.005 [0.996 to 1.015] after adjustment).

Figure 8.6: The impact of adjusting for hourly temperature on pollution effect estimates in the multipollutant model



Note: Adjustment for hourly temperature comprised 5 lag terms matching hourly pollution lags (1-6, 7-12, 13-18, 19-24, 25-72 hours). Model also adjusted for daily mean temperature (5 lag terms covering days 0-28 inclusive), relative humidity (average of lags 0-3 days), day of week, influenza, RSV, and residual seasonality within calendar month strata (single sin/cos pair per conurbation). Analysis was restricted to the 9 conurbations in which hourly temperature data were available

The estimated effect of ambient temperature itself at an hourly temporal resolution suggested a statistically significant detrimental effect of higher temperature at very short (1-6 hours) lag, followed by a risk reduction at 7-12 hours lag (Table 8.3). The cumulative effect estimate over 1-72 hours suggested no net temperature effect (OR = 0.999 [0.994 to 1.004]) at this timescale.

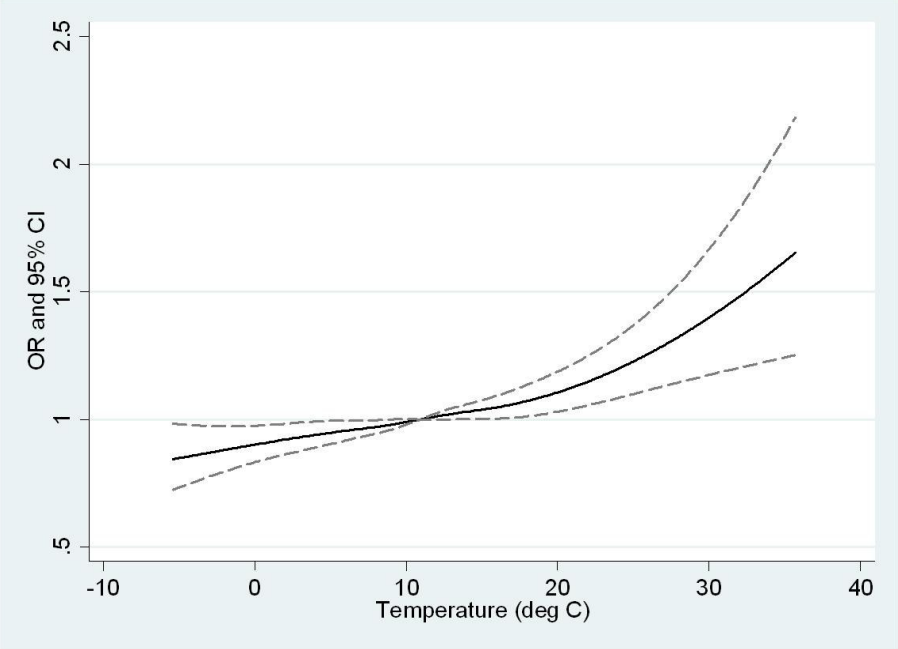
When non-linearity was allowed for by modelling temperature as a 4-knot cubic spline, the resulting plot still (for lag 1-6 hours) revealed a broadly linear effect (p for non-linearity = 0.45, Figure 8.7).

Table 8.3: Effect of hourly temperature on MI risk in a multipollutant model

		OR and 95% CI per 1°C increase in temperature
Lag (hours)	*1-6*	1.011 [1.004, 1.018]
	7-12	0.989 [0.979, 0.998]
	13-18	1.002 [0.992, 1.011]
	19-24	0.999 [0.992, 1.006]
	25-72	0.999 [0.993, 1.005]
	Σ(1-72)	*0.999 [0.994, 1.004]*

Note: Adjustment for hourly temperature comprised 5 lag terms matching hourly pollution lags (1-6, 7-12, 13-18, 19-24, 25-72 hours). From a multipollutant model with 5 lag terms for each of 5 pollutants, also adjusted for daily mean temperature (5 lag terms covering days 0-28 inclusive), relative humidity (average of lags 0-3 days), day of week, influenza, RSV, and residual seasonality within calendar month strata (single sin/cos pair per conurbation). Analysis restricted to the 9 conurbations in which hourly temperature data were available (excluding Kingston-upon-Hull, Leicester, Newcastle, Norwich, Potteries, Southampton)

Figure 8.7: Estimated effect of temperature at lag 1-6h allowing for non-linear effects



Note: From a multipollutant model with 5 lag terms for each of 5 pollutants, adjusted for temperature effects at lag 7-12, 13-18, 19-24, and 25-72 hours, and for daily mean temperature (5 lag terms covering days 0-28 inclusive), relative humidity (average of lags 0-3 days), day of week, influenza, RSV, and residual seasonality within calendar month strata (single sin/cos pair per conurbation)
Analysis restricted to the 9 conurbations in which hourly temperature data were available (excluding Kingston-upon-Hull, Leicester, Newcastle, Norwich, Potteries, Southampton)

8.3.6 Sensitivity of pollutant effects to key model specifications

Three sensitivity analyses were carried out in which (i) the study population was restricted to those with a recorded time of symptom onset, (ii) the calendar month strata for defining sets of case/control days were replaced with strata of 14 days' length , and (iii) control days were matched on day of the week. All suggested that the principal observations were robust to changes in these key analysis/modelling decisions (Table 8.4). For each sensitivity analysis, all confidence intervals comfortably included the original effect estimates. For some "statistically significant" effects from the original analysis, confidence intervals in one or more of the sensitivity analyses widened to span 1 indicating a loss of statistical significance, but this is not surprising; each of these analyses would have had reduced power compared to the original, due to fewer events being included (analysis i), and smaller case/control sets (analyses ii and iii). The estimated effect sizes were in all cases consistent with the original analysis.

Table 8.4: Sensitivity of pollutant effects to model specifications

Pollutant		RR and 95% CI from sensitivity analysis model		
		Symptom onset only*	14 day stratum length*	Matched on day of week*
PM_{10}	*Lag 1-6*	1.010 [0.998, 1.022]	1.007 [0.995, 1.018]	1.010 [0.998, 1.022]
	7-12	1.000 [0.986, 1.014]	1.000 [0.987, 1.013]	1.001 [0.987, 1.014]
	13-18	0.999 [0.986, 1.013]	0.997 [0.984, 1.010]	0.999 [0.985, 1.012]
	19-24	0.997 [0.985, 1.009]	0.996 [0.985, 1.007]	0.997 [0.985, 1.009]
	25-72	0.996 [0.980, 1.013]	0.992 [0.974, 1.009]	0.993 [0.978, 1.009]
	Σ(*1-72*)	*1.002 [0.985, 1.020]*	*0.991 [0.970, 1.013]*	*0.999 [0.983, 1.015]*
Ozone	*Lag 1-6*	1.007 [0.997, 1.017]	1.006 [0.996, 1.015]	1.010 [1.000, 1.019]
	7-12	0.995 [0.983, 1.008]	0.996 [0.984, 1.007]	0.992 [0.980, 1.004]
	13-18	0.990 [0.978, 1.003]	0.993 [0.981, 1.004]	0.996 [0.984, 1.008]
	19-24	1.000 [0.990, 1.011]	0.998 [0.989, 1.008]	0.996 [0.986, 1.006]
	25-72	0.995 [0.984, 1.005]	0.992 [0.981, 1.003]	0.995 [0.985, 1.005]
	Σ(*1-72*)	0.988 [0.977, 0.999]	0.984 [0.971, 0.997]	0.989 [0.979, 0.999]
CO	*Lag 1-6*	0.999 [0.991, 1.007]	0.996 [0.988, 1.004]	0.994 [0.985, 1.002]
	7-12	1.004 [0.995, 1.014]	1.006 [0.997, 1.015]	1.006 [0.997, 1.016]
	13-18	1.003 [0.993, 1.012]	1.000 [0.991, 1.009]	0.996 [0.987, 1.006]
	19-24	0.996 [0.988, 1.005]	0.994 [0.986, 1.002]	0.994 [0.986, 1.003]
	25-72	0.990 [0.979, 1.001]	0.997 [0.985, 1.009]	0.992 [0.981, 1.003]
	Σ(*1-72*)	0.992 [0.980, 1.004]	0.993 [0.978, 1.007]	0.982 [0.971, 0.994]
NO_2	*Lag 1-6*	1.013 [0.998, 1.028]	1.020 [1.006, 1.034]	1.019 [1.004, 1.034]
	7-12	0.984 [0.967, 1.002]	0.980 [0.964, 0.996]	0.986 [0.969, 1.004]
	13-18	0.991 [0.974, 1.009]	0.996 [0.980, 1.013]	1.000 [0.983, 1.018]
	19-24	0.998 [0.983, 1.013]	1.003 [0.989, 1.017]	0.999 [0.984, 1.014]
	25-72	1.007 [0.990, 1.024]	0.995 [0.978, 1.013]	0.998 [0.981, 1.014]
	Σ(*1-72*)	0.993 [0.975, 1.010]	0.994 [0.973, 1.016]	1.001 [0.985, 1.018]
SO_2	*Lag 1-6*	0.987 [0.958, 1.016]	0.993 [0.967, 1.020]	0.990 [0.963, 1.018]
	7-12	1.012 [0.980, 1.045]	1.005 [0.975, 1.037]	0.996 [0.964, 1.028]
	13-18	0.982 [0.951, 1.013]	0.984 [0.956, 1.014]	0.990 [0.960, 1.021]
	19-24	1.036 [1.007, 1.066]	1.022 [0.996, 1.049]	1.010 [0.982, 1.038]
	25-72	0.980 [0.939, 1.024]	1.026 [0.981, 1.073]	1.026 [0.984, 1.069]
	Σ(*1-72*)	0.995 [0.948, 1.045]	1.030 [0.974, 1.089]	1.011 [0.967, 1.058]

** -Symptom onset only analysis included only cases of MI where the time of event was determined by the time of symptom onset; 14-day stratum length analysis replaced calendar month strata with a 14-day stratum length in the case-crossover setup; matched on day of week model selected control days for each case as the remaining days of the calendar month with the same day of the week (with day of the week removed from the confounder model)*

Note: Estimates for each analysis are from a multi-pollutant model adjusted for temperature (5 lag terms covering days 0-28 inclusive), relative humidity (average of lags 0-3 days), day of week, influenza, RSV, and residual seasonality within calendar month strata (single sin/cos pair per conurbation)

8.4 Discussion

There were immediate increases in MI risk 1-6 hours after an increase in PM_{10} and NO_2 in both single- and multi-pollutant models (estimated increase in risk from the multi-pollutant model = 1.0% [0.0 to 2.0] and 2.0% [0.8 to 3.3] per 10μg/m^3 respectively), but these were followed by reductions in risk at longer lags. Over the full 72 hour period following exposure, there was no evidence of any net detrimental effects of any pollutant; interestingly for ozone and CO, net protective associations with MI risk were observed over 72 hours, despite in the case of ozone the suggestion of short-term detrimental effect in the first 1-6 hours following exposure. No effect of SO_2 in either direction was observed.

Only a handful of studies have looked at the effects of pollution on MI risk at an hourly temporal resolution, with still less investigating the specific pollutants included in this study. A study in Greater Boston[116] estimated an 11% (95% CI 1.5 to 21.1) increase in MI risk 1-3 hours after a 10μg/m^3 increase in PM_{10}, a larger effect than estimated here and indeed by some way the largest effect estimate for PM_{10} identified in the review of the published literature (Chapter 3 Table 3.3), though it should be noted that in this small (n=772) study the wide confidence interval would not rule out a more modest true effect. The authors found no convincing effects of ozone, CO, NO_2 or SO_2 at a similar 1-3 hour lag, though with the exception of SO_2, effect estimates were in the direction of a detrimental effect and confidence intervals were relatively wide. A larger American study found no effects of $PM_{2.5}$, CO or SO_2 using various "averaged" lag periods ranging from 0-1 hours to 0-24 hours;[112] PM_{10} and NO_2, for which the most consistent short-lag effects were observed in the present analysis, were not included in this study. Other studies have looked at various particulate exposures with varied results: total suspended particulate levels (thought to be equivalent to PM_{13}) have been associated with MI risk at lags up to 6 hours[107] which would be consistent with the findings of the present analysis, but longer lags were not included and it is not possible to say whether a subsequent reduction in risk over the longer term would have been observed in this study as in ours. A study in Germany looking at short-lag effects of $PM_{2.5}$ and "total number concentrate" (TNC) found no associations with MI risk at 1-hour lag.[110] On the other hand results from the same study did suggest a significantly

increased risk of MI associated with exposure to traffic 1 hour earlier;[114] again longer lags were not included so it is not possible to say whether there would have been a subsequent reduction in risk at longer lags.

The results observed here are consistent with the suggestion raised in the previous chapter that increasing pollution levels may be associated with short-term displacement of events, a "harvesting" phenomenon, rather than any net increase in risk. For PM_{10} and NO_2 in particular a clear pattern emerged in both single and multi-pollutant models of a positive association between pollutant level and immediate MI risk over 1-6 hours, but then an inverse association at longer lags, with no net association with MI risk over a 72-hour period. This short-term displacement pattern was generally more prominent among older individuals (up to age 85 years) and those with prior CHD, an observation that is consistent with harvesting since those with a higher baseline risk of MI would be expected to be more vulnerable to the phenomenon. This indicates that one of the pathways through which pollution affects cardiovascular diseases may involve the bringing forward (for example, by a few hours) of events that would have happened anyway. Since no net increase in MI risk was observed over a broader timescale, there may be limited potential for reducing the overall burden of MI through reductions in pollution alone, but this should not undermine calls for action on air pollution, which has well-established associations with broader health outcomes including overall, respiratory, and cardiovascular mortality.[42, 121, 173] Indeed, air pollution effects on mortality are unlikely to be explained purely by short-term displacement;[164, 174] the present findings might therefore suggest that other, perhaps non-thrombotic, mechanisms are more important drivers of the net mortality increases associated with higher pollution levels.

If pollution level increases are indeed associated with the bringing forward of MI events, this implies that some triggering mechanism may be at work, and observational and experimental studies suggest various possible mechanisms, discussed in more detail in Section 3.4. Immediate effects on ischaemic burden and fibrinolytic capacity during controlled exposure to diesel fumes have been observed among men with coronary heart disease.[48] Pollution exposure has also been associated with a systemic inflammatory response,[128] increased heart rate and/or decreased heart rate variability,[128, 133] blood viscosity and plasma

fibrinogen changes,[136-137] and increased blood pressure.[142] However, it cannot be safely assumed that PM_{10} and NO_2, which are particularly associated with traffic exhaust, are the real triggers. These pollutants and the others studied here are in most cases emitted as part of a complicated mixture (including for example hydrocarbons in the case of traffic emissions), and furthermore certain combinations of pollutants are likely to inter-react, so confounding by unmeasured pollutants is difficult to avoid, and individual causal pollutant effects difficult to infer outside of controlled exposure studies in a laboratory setting.

This point may also be pertinent to the observation of net protective effects of both ozone and CO on MI risk over 72 hours, which seems implausible as a causal relationship. Protective ozone effects have been observed in other studies[38, 57, 110] and one theory is that ozone is acting as a marker for some unmeasured pollutant with which it is inversely correlated and which has a positive association with MI risk. Since multi-pollutant models were used, confounding by the other pollutants is unlikely. But there were no data available on $PM_{2.5}$ which may be associated with MI risk and may have inverse correlations, in particular with ozone. It has also been suggested that inverse correlations between ozone and methyl nitrites may explain protective ozone effects.[125] Another possibility is that collinearities between the model covariates, perhaps complicated by measurement errors, have contributed to these unexpected effect estimates. It has been observed that in the presence of measurement error and highly correlated exposures, some of the effect of a more poorly measured variable can be transferred to a better measured variable.[165] In the present analysis, comparing the single pollutant to the multi-pollutant model, the detrimental effect of NO_2 at lag 1-6 hours almost doubled in magnitude, while the effect estimate for CO became protective. Two-pollutant models further suggested that adjustment for NO_2 was the main driver of observed protective CO effects at lag 1-6 hours. But importantly, the correlation between daily NO_2 and CO was 0.61, one of the highest correlations between pollutant pairs (Chapter 5 Table 5.9), which suggests that a degree of caution should be applied in interpreting the independent effect estimates.

Given that no heat effect was observed in the earlier analysis of temperature effects on a daily timescale (Chapter 6), it was of interest that a detrimental

effect of increased ambient temperature was observed at very short lags (1-6 hours). However, when longer lags were taken into account there was no net heat effect over a 72-hour period, consistent with the previous analysis. These results suggest that the effects of higher temperatures observed in this section may be restricted to short-term displacement; the bringing forward of events by a matter of hours. This is in contrast with the effects of temperature reductions observed in Chapter 6 which operated over a longer timescale and did not appear to be explained by short-term "harvesting" alone.

Some of the key limitations of the study have been set out in the previous chapter: there were no data on $PM_{2.5}$; pollution measures from outdoor monitors were used, which may not represent personal exposure perfectly and could therefore have led to a loss of precision or the introduction of biases in the analysis; pollution measures were also aggregated across each conurbation which ignores the local variability in pollutant levels that appeared to be particularly marked for CO and SO_2 (Chapter 5 Figure 5.3 and Appendix I Table 11.4-Table 11.7). It should also be noted that, given the limited prior evidence available at an hourly temporal resolution, this study did not test specific prior hypotheses, but rather explored a number of possible pollution-MI associations on this timescale. This raises the possibility that multiple statistical comparisons may have led to spurious associations being observed by chance; further studies aimed at replicating the findings reported here will be needed to discount this possibility. The study strengths outlined previously also apply to this analysis: ascertainment of MI cases from MINAP would likely have had high specificity, and key confounders were adjusted for. The significant additional strength of the analyses in this chapter is the availability of hourly data; only a handful of studies have looked at air pollution effects on MI at an hourly temporal resolution, and the largest of these had data on less than 6,000 cases, compared with over 80,000 in these analyses. Hourly air pollution monitoring data were available in every conurbation in the study, and because of the nature of MINAP, which was set up as an audit database, and which is used to monitor targets for reducing treatment delays for suspected coronary events, detailed timing data were available for clinical events, with the time of onset of the first symptoms recorded for the majority of MI events.

To conclude, for some pollutants, most prominently PM_{10} and NO_2, a transiently increased risk of MI was observed up to 6 hours after a pollution increase but reductions in risk at longer lags cancelled out the effect over a 72 hour period, consistent with a short-term displacement or harvesting effect. Thus, as in the previous chapter there was no evidence that higher levels of any of the 5 pollutants considered were associated with a net increase in MI risk. Net protective effects of ozone and CO on MI risk over a 72 hour lag period require explanation and may indicate an important role for one or more pollutants that were not included in these analyses.

8.5 Summary

- A case-crossover analysis was carried out to assess associations between pollution levels and MI risk at an hourly temporal resolution
- In a multi-pollutant model, higher PM_{10} and NO_2 levels were associated with a transiently increase risk of MI 1-6 hours later. However these effects were cancelled out by risk reductions at longer lags, consistent with a short-term displacement, or “harvesting” effect. There was a suggestion of a similar pattern for ozone.
- The harvesting pattern appeared to be more prominent in older individuals (up to age 85) and those with prior CHD
- Over the full 72-hour lag period considered, higher pollution levels were not associated with any net increase in MI risk

9 Summary and Conclusions

9.1 Introduction

In this chapter, the main findings and key discussion points that have been outlined in detail in the body of the thesis are summarised and drawn together. First, the results of the analyses undertaken for the thesis are summarised and compared with previous research identified by the systematic reviews described in Chapters 2-3. Second, the overall strengths and limitations of the work are outlined. Third, key public health and policy implications are summarised, and finally, suggestions are made for future research.

9.2 Summary of research undertaken

i. Two systematic reviews were carried out, bringing together studies in which MI was a specific outcome, and which investigated the effects of ambient temperature or one of the commonly measured pollutants on MI risk.

ii. A daily time series analysis using hospital admissions data from 15 conurbations taken from the MINAP database was performed to characterise the short-term effects of daily mean temperature on MI risk, adjusting for key potential confounders.

iii. Within the same framework, the analysis was then extended focussing on the effects of daily mean PM_{10}, ozone, CO, NO_2 and SO_2 on MI risk, adjusting for temperature.

iv. Finally, informed by the results of the daily analysis, and making use of data at an hourly resolution, a case-crossover analysis was carried out, and the effects of the same five pollutants were examined at shorter (<1 day) time scales.

9.3 Summary of findings and comparison with literature

9.3.1 Short-term effects of temperature on MI risk

v. In a daily time series analysis, MI risk was increased at lower ambient temperatures. The effect was well characterised by log-linear models without temperature threshold, and over the 28 days following exposure, a cumulative 2% (95% CI 1.1 to 2.9) increase in MI risk per 1°C lower temperature was estimated, with the effect mainly operating with at a lag of 2 days to 2 weeks. .

vi. In absolute terms, it was estimated that each 1°C reduction in temperature in the UK would be associated with an extra 232 MI events, based on the estimated overall incidence of 146000 MIs/year.

vii. Older people (up to age 85 years) and those with prior coronary heart disease appeared to be most vulnerable to lower temperature, though the effects were not restricted to these groups. Those taking aspirin appeared to be less vulnerable.

viii. The results did not suggest that the cold effect simply reflected short-term displacement (or “harvesting”) of events within the 28-day lag period studied, since risk increases were not followed by subsequent risk reductions at longer lags, as is typically seen with harvesting effects. Nevertheless displacement of events by >28 days cannot be ruled out.

ix. There was no observed increase in MI risk at higher temperatures in the main daily time series analysis of temperature effects: in analyses allowing for non-linear temperature effects, MI risk appeared to be inversely associated with temperature, even at the upper end of the temperature scale.

x. Interestingly, analyses at an hourly resolution, in which pollutant effects were the main focus, did indicate some transient heat effect: higher temperatures appeared to be associated with increased MI risk 1-6 hours later, but at longer lags the effect was cancelled out, so that over 1-72 hours there was no net increase in risk (Section 8.3.5).

9.3.2 Temperature effects in the context of previous research

xi. There was generally very varied methodology among studies investigating the effects of ambient temperature on MI risk, as well as differences in local climate and the demographic characteristics of participants between studies. Comparisons between study results must therefore be made cautiously.

xii. The observed effects of colder temperatures in the present study were in keeping with the detrimental cold effects identified by 8 of the 12 studies included in the systematic review which investigated cold effects on MI and indeed by 3 of the 5 studies included in the review that used a separately validated MI outcome.

xiii. In the systematic review, most studies reported effects on the same day or up to 3 days after exposure, with no effects lagged by more than 1 week, though few studies actually investigated effects beyond 7 days. In contrast, the present study investigated the effects of temperature with up to 4 weeks lag, and significant effects of lower temperature were observed at lags ranging from 2 days to 2 weeks.

xiv. There was a suggestion from studies identified in the systematic review that countries at more northern latitudes may be more likely to experience heat, rather than cold effects. This is consistent with the idea that people living in colder countries or regions may adapt less well to higher temperatures. However, the findings of the present study, based on data from England and Wales, which has a relatively cool climate, did not support this theory.

xv. A few small experimental studies combine to suggest that a pathway through which reduced temperatures might induce thrombogenesis could involve a combination of factors. Cold exposure has been associated with haemoconcentration, an inflammatory response, and a tendency for an increased state of hypercoagulability. The apparently protective effect of aspirin suggests that platelet function may also play a role.

xvi. In the published literature, 13 studies were identified that included analyses investigating the short-term effects of heat or increases in

temperature. Of these, 7 reported a significant heat effect, in contrast to the results of the daily time series analyses presented here, though 3 of these considered only MI mortality, which may have included some misclassified deaths, and only one of the 5 studies with a separately validated MI outcome reported a heat effect.

xvii. Temperatures in England and Wales are rarely very high in global terms and hot periods are typically short. This means that the heat effects observed in other settings may be difficult to detect in a UK setting, though heat effects on mortality outcomes have been observed in the UK.[161]

xviii. It is possible that observed heat effects in studies using less reliable MI diagnoses may in reality, due to misclassification of outcomes, represent effects on more broad cardiovascular health outcomes.

xix. No previous studies were identified that investigated the effects of temperature at an hourly, rather than daily, temporal resolution.

9.3.3 Short-term effects of air pollution on MI risk

xx. A daily time series analysis indicated no net detrimental effect on MI risk of PM_{10}, ozone, CO, NO_2, or SO_2 over lag days 0 to 7 combined. However, estimated effects of pollution increases at individual lag days were suggestive of increases in risk at day 0 followed by decreases in risk at days 1-2, for all pollutants except ozone.

xxi. Analyses using data at a finer (hourly) temporal resolution showed a transiently increased risk of MI 1-6 hours after increased levels of PM_{10} and NO_2 in a model including all five pollutants. A 10μg/m^3 increase was associated, 1-6 hours later, with a 1.0% (0.0 to 2.0) and 2.0% (0.8 to 3.3) increase in MI risk for PM_{10} and NO_2 respectively. There was a suggestion of a similar effect of ozone (0.7% [-0.1 to 1.6] increase in risk, 1-6 hours later).

xxii. Reductions in risk at longer lags cancelled out the 1-6 hour effects of PM_{10}, NO_2 and ozone such that no net detrimental effects of any pollutant were observed over a 72-hour period following exposure.

xxiii. The observed pattern of a positive association between pollutant levels and MI risk at short lags, followed by negative associations at longer lags is consistent with a short-term displacement ("harvesting") effect, where higher pollution levels are associated with events being brought forward in time by a few hours or days.

xxiv. Patterns of effect estimates consistent with harvesting were generally more pronounced in older individuals (up to age 85 years) and those with prior CHD.

xxv. Surprisingly, both CO and ozone appeared to have a net protective effect over 72 hours. This may indicate some confounding effect of unmeasured pollutants. However, high correlations of both pollutants with NO_2 were also noted, suggesting that independent effect estimates should be interpreted with some caution.

9.3.4 Pollution effects in the context of previous research

xxvi. Most studies to date have been based on data at a daily temporal resolution. These studies suggest little convincing evidence of PM_{10}, and mixed evidence on the effects of ozone, CO, NO_2 and SO_2. The lack of any net detrimental pollutant effects on MI risk in the present study is in this respect not inconsistent with the published literature.

xxvii. Only a few studies, with relatively small numbers of events, have investigated the effects on MI risk of hourly differences in pollutant levels. Significant effects of particulate exposures and exposure to traffic at a few hours lag have been described, consistent with the findings of the present analyses, but other studies have found no effects. Of note, previous studies looking at hourly effects of pollution did not examine lagged effects beyond a few hours, so it is not possible to say whether reductions in risk at longer lags would have been observed as in the present study.

xxviii. Observational and experimental studies suggest a few possible mechanisms through which pollution increases could trigger MI events: pollution exposure has been associated with a systemic inflammatory response, changes in heart rate and heart rate variability, changes in

blood viscosity, plasma fibrinogen, and fibrinolytic capacity, increased ischaemic burden, and changes in blood pressure.

xxix. Previous studies have had varied methods and have been conducted in varied settings. In addition, a number of studies only reported pollutant effects using a single lag term so are difficult to compare with estimates from the present analysis which appeared to show a pattern of changing effects over time.

xxx. Negative associations have previously been observed between ozone levels and MI risk. In both the daily and hourly analyses presented here, there was some suggestion that lack of adequate control for temperature can induce or exaggerate protective ozone-MI associations. This is likely due to the positive correlation between ozone and temperature, coupled with the increased risk of MI associated with lower temperatures.

xxxi. A few previous studies have investigated the effects $PM_{2.5}$, with the majority reporting significant positive associations with MI risk. For the present study, insufficient data on $PM_{2.5}$ were available to investigate the effects of this pollutant.

9.4 Strengths of the study

xxxii. The study was among the largest to date to investigate temperature and pollution effects on the specific outcome of MI.

xxxiii. Given the specialist nature of the database, MI events drawn from MINAP are likely to be highly specific, and furthermore could be validated against ECG and laboratory marker data which are also recorded in the database.

xxxiv. The availability of accurate timing data for MIs was also a major strength of the study, and allowed analyses at an hourly, as well as daily, temporal resolution.

xxxv. The study was able to make use of the UK's well-established networks of monitoring stations recording both weather and pollution parameters.

xxxvi. Air pollution analyses included comprehensive adjustment for temperature effects, and vice versa. Flexible spline-based methods were

used to model season and long-term trend effects (for daily time series analyses). In addition, all analyses were adjusted for other key confounders including day of the week and holidays, infectious disease levels, and relative humidity.

xxxvii. A number of sensitivity analyses were performed following both the temperature- and pollution-focussed analyses, and the main conclusions were robust to changes in various aspects of the model specifications, and to restricting to the most reliable data.

9.5 Limitations

xxxviii. A principle limitation of the MINAP database is that only events resulting in hospital admission were included. MI events resulting in death before admission to hospital will have been missed. Furthermore, the probability of surviving an MI long enough to be admitted to hospital could conceivably be related to environmental exposures, especially temperature, if extreme weather were to result in, for example, ambulance delays. If operating, such a mechanism would likely lead to an underestimation of temperature effects.

xxxix. MINAP theoretically records every hospital admission for MI, but disproportionate variations in the numbers of events recorded between conurbations suggest some regional inconsistency in the recording of events. However, this is unlikely to be related to exposure and is therefore likely to have led simply to a loss of study power rather than any confounding.

xl. Outdoor pollution levels from monitoring stations, particularly when averaged over a large area, may not be an ideal proxy for personal exposure. Such summary measures ignore both local variation in pollutant levels, and individual behavioural factors, such as time spent outdoors, and the resulting measurement error may have resulted in a loss of precision or the introduction of biases in the estimated pollution MI associations.

xli. Given the high correlations between many environmental exposures, there is an unavoidable potential for unmeasured confounding in population-based studies such as that presented here. Furthermore, the separation of specific pollutant effects, even among measured pollutants, is problematic due to collinearities between the pollutants.

xlii. Due to the limited previous evidence available, analyses of pollution-MI associations were exploratory in nature, rather than hypothesis testing. Multiple comparisons could have led to spurious associations being observed by chance; further studies aimed at testing the observed associations using different data sources will be needed to confirm the main findings.

xliii. There was a lack of available data on $PM_{2.5}$, which other studies have suggested may be an important predictor of MI risk.

9.6 Implications for public health and policy

xliv. Since lower ambient temperatures appeared to be associated with higher overall MI risk, and not simply the short-term displacement of events, there may be scope for reducing the overall public health burden of MI through cold avoidance and adaptive measures.

xlv. The relative risk associated with temperature reductions was largest among older age groups (up to age 85 years), and those with prior coronary heart disease. Schemes to mitigate the effects of temperature might be targeted at such groups. For example, automated phone calls, delivered when lower temperatures are forecast, might remind individuals to stay indoors and wrap up in adequate clothing. Schemes of this nature have had some success among chronic obstructive pulmonary disorder sufferers in the UK. Their efficacy and cost-effectiveness in the context of protecting those at highest risk of MI would need to be evaluated.

xlvi. Although the effects of lower temperatures were larger in certain subgroups, they were not restricted to these subgroups. Therefore, there may be a case for putting across a broader public health education

message promoting cold avoidance and/or the use of warmer clothing when lower temperatures are expected.

xlvii. The absence of any net detrimental effects of air pollution suggests that other, perhaps non-thrombotic, mechanisms are more important drivers of the net mortality increases associated with higher pollution levels. Identifying the specific conditions responsible for these mortality increases with a view to eventually identifying interventions that could protect the most vulnerable will be a continuing priority for research in this area.

xlviii. Although there appeared to be no net detrimental effects of air pollution over a 72-hour lag period, this should not undermine attempts to reduce pollution levels, since other health outcomes including overall, cardiovascular and respiratory mortality have established links to pollution levels that are unlikely to be explained purely by short-term displacement effects.

9.7 Future research

9.7.1 Temperature and MI

xlix. Drivers of the differences in temperature effects observed in different studies remain unclear, and in any case the varied methodology and reporting within the published literature makes direct comparisons difficult. To confirm the findings presented in this thesis, and explore whether they carry over to other settings, more large studies are needed in a number of geographical locations with consistent adjustment for potential confounders such as season, long-term trend and air pollution; allowance for non-linear and delayed temperature effects; and consistent reporting standards.

l. Few studies of temperature effects have investigated effect modifiers; more data are needed on the roles of age, sex, previous medical history and prophylactic drug use in modifying the effects of temperature on MI risk.

li. Future studies might investigate whether sudden temperature changes affect MI risk more than gradual changes in absolute temperature.

lii. Since analyses presented here at an hourly level suggested that there may be some very short-term transient effect of higher temperatures on MI risk, further data at an hourly resolution would be of value.

liii. Studies of temperature effects with individual-level data on factors such as clothing, home heating and air conditioning would be helpful in evaluating the role of adaptive measures.

liv. Further studies looking at the effects of more complex weather indicators (such as air mass type) on MI risk, and how easily such indicators can be forecast, might clarify the usefulness of such measures in this context.

lv. Mechanistic studies examining the effects of temperature on an up-to-date range of clotting measures are needed.

lvi. Potential interventions such as targeted warning systems, or more general public health education messages, aimed at changing behaviour to reduce the temperature-associated excess MI risk, could be evaluated in formal trials.

9.7.2 Pollution and MI

lvii. Outdoor pollution levels from monitoring stations, particularly when averaged over a large area, may not be an ideal proxy for personal exposure. Studies making use of personal exposure monitors might provide valuable data, though such studies would necessarily be smaller-scale and require the use of non-clinical outcomes. Biomarkers of exposure might also be developed for use in epidemiological studies to give more reliable estimates of individual exposure to air pollutants.

lviii. For larger, population-based studies, novel statistical methods aimed at quantifying or reducing biases due to measurement error might be utilized, and reliable spatial models allowing the interpolation of pollution levels between monitoring stations could enable personal exposures to be estimated more accurately without the need for individual-level measurements.

lix. Only controlled exposure studies in a laboratory setting are likely to delineate the effects of individual pollutants, since the collinearity of pollutants makes confounding outside of the laboratory impossible to avoid. Studies of this type might also be used to investigate the various mechanisms that have been suggested to explain air pollution effects on MI.

9.8 Conclusions

The work presented in this thesis has focussed on the short-term effects of two major classes of environmental exposure on MI risk: ambient temperature, and air pollution.

A convincing effect of temperature was observed, with lower temperatures associated with a higher risk of MI for up to 2 weeks following exposure. There was no evidence for an overall effect of higher temperatures. The elderly and those with prior coronary heart disease were most vulnerable to temperature effects and might benefit from targeted warning systems, linked to weather forecasts, and advising, for example, cold avoidance, wearing adequate clothing, or other adaptive measures. Since the effects of temperature persisted in all subgroups that were examined, a more general public health education message might also help to reduce the extra burden of MI associated with lower temperatures.

Higher levels of PM_{10} and NO_2 were associated with transiently increase risk of MI 1-6 hours after exposure, and there was a suggestion of a similar effect for ozone. However, reductions in risk at longer lags meant that there was no overall increase in MI risk over a 72-hour period. These findings suggest that other, perhaps non-thrombotic, mechanisms are more important drivers of the net mortality increases associated with higher pollution levels; identifying the specific conditions and mechanisms responsible for such mortality increases is a continuing research priority.

Many questions remain and there is a need for more research in a number of areas. Potential interventions aimed at reducing the burden of MIs associated with lower temperatures should be evaluated. Studies with individual-level data could also provide important information on the role of adaptive measures, and

there has been little recent work looking at potential mechanisms for temperature effects. The exact roles of individual pollutants may only be revealed by controlled exposure studies in a laboratory setting, which might also reveal potential mechanisms. However further large-scale population-based studies are also needed: the effects of fine and ultrafine particulate matter need to be clarified as monitoring data becomes available; and more data at a sub-daily temporal resolution are needed, since the results presented here suggest that pollution effects may operate faster than has been previously assumed, and may therefore have been missed by much of the research to date.

9.9 Summary

Table 9.1: Summary of findings

	What previous studies have shown	What this study found	Key unanswered questions
Short-term effects of temperature	1. Both hot and cold ambient temperatures increase overall mortality risk in the short-term. 2. Most studies looking specifically at MI outcomes observed detrimental cold effects. 3. About half of studies looking at MI outcomes have identified detrimental heat effects.	1. Lower daily mean temperature was associated with increased risk of MI. 2. Elderly individuals (≤85 years) and those with prior CHD were most vulnerable to the effects. 3. No increase in MI risk was detected at higher temperatures.	1. Through what mechanisms do temperatures affect MI risk? 2. Can adaptive measures and public health interventions mitigate the effects? 3. Why do only some studies find heat effects? Is local climate important?
Short-term effects of air pollution	1. Higher daily levels of some pollutants are associated with increased mortality. 2. There is mixed evidence on the effects of pollution on MI risk specifically. 3. A few studies with hourly data have found pollution effects just a few hours after exposure.	1. MI risk was transiently increased up to 6 hours after exposure to higher PM10, NO2. 2. Pollution effects were consistent with short-term displacement of events ("harvesting"). 3. Higher PM10, ozone, CO, NO_2, or SO_2 levels did not increase overall MI risk over 72 hours.	1. Is personal pollution exposure more predictive of MI risk than ambient levels? 2. How might pollution exposure bring impending MI events forward in time? 3. Can the roles of specific pollutants be delineated in a laboratory setting?

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11 Appendix I – Additional results tables and figures

11.1 Further descriptive analysis

Table 11.1: Median events per day, by conurbation and calendar month

	Median [IQR] number of events per day, by calendar month											
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Bristol	2 [1, 3]	2 [1, 3]	2 [1, 3]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	2 [1, 3]	1 [0, 3]
Cardiff	1 [0, 2]	1 [0, 2]	1 [0, 1]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 1]	1 [0, 1]	1 [0, 1]
G London	18 [15, 21]	18 [15, 22]	18 [14, 20]	18 [14, 22]	19 [16, 22]	19 [16, 21]	18 [15, 21]	17 [14, 21]	17 [14, 20]	18 [15, 22]	18 [15, 21]	18 [16, 21]
G Manch	9 [6, 10]	9 [7, 11]	8 [6, 10]	9 [6, 12]	9 [7, 11]	9 [7, 11]	7 [5, 9]	8 [5, 11]	8 [6, 11]	8 [6, 10]	9 [6, 11]	8 [7, 11]
Hull	0 [0, 0]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 0]	0 [0, 0]	0 [0, 1]	0 [0, 1]	0 [0, 0]	0 [0, 0]	0 [0, 0]	0 [0, 0]
Leicester	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 1]
Liverpool	3 [2, 4]	3 [2, 5]	3 [2, 4]	3 [2, 5]	3 [2, 4]	3 [2, 5]	2 [1, 4]	2 [1, 3]	2 [1, 4]	2 [1, 4]	3 [2, 4]	3 [2, 5]
Norwich	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]
Nottingham	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 1]	1 [0, 1]	1 [0, 2]	1 [0, 2]	1 [0, 1]	1 [0, 2]	1 [0, 1]	1 [0, 2]	1 [1, 2]
Potteries	1 [1, 2]	1 [1, 2]	1 [0, 2]	2 [1, 2]	1 [1, 2]	1 [1, 2]	1 [0, 2]	1 [0, 2]	1 [1, 2]	1 [1, 2]	1 [0, 2]	1 [1, 2]
Sheffield	3 [1, 5]	3 [2, 4]	3 [1, 4]	3 [2, 4]	4 [3, 5]	3 [2, 5]	3 [2, 5]	3 [2, 5]	3 [2, 5]	3 [2, 5]	4 [2, 5]	3 [2, 5]
Southamp	1 [0, 1]	1 [0, 1]	1 [0, 1]	1 [0, 1]	1 [0, 1]	1 [0, 2]	1 [0, 1]	1 [0, 1]	1 [0, 1]	1 [0, 1]	1 [0, 2]	1 [0, 2]
Tyneside	5 [4, 7]	5 [4, 7]	5 [4, 7]	6 [4, 8]	6 [4, 7]	5 [3, 7]	5 [4, 7]	5 [3, 7]	5 [3, 7]	5 [4, 7]	5 [3, 6]	5 [3, 6]
W Midlands	6 [5, 8]	6 [4, 8]	6 [4, 8]	6 [4, 8]	7 [5, 8]	6 [5, 8]	6 [4, 8]	6 [4, 8]	6 [4, 8]	6 [5, 9]	6 [5, 9]	7 [5, 9]
W Yorks	4 [3, 5]	4 [3, 6]	4 [3, 6]	4 [3, 6]	4 [3, 6]	5 [3, 7]	4 [3, 6]	4 [2, 6]	4 [3, 5]	4 [3, 6]	4 [3, 6]	4 [3, 6]

Table 11.2: Median events per day, by conurbation and day of week

	Median [IQR] number of events per day, by day of week						
	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Bristol	1 [0, 3]	1 [0, 3]	1 [0, 2]	1 [1, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]
Cardiff	1 [0, 2]	1 [0, 1]	1 [0, 1]	1 [0, 2]	1 [0, 2]	1 [0, 1]	1 [0, 1]
G London	20 [16, 23]	18 [15, 22]	18 [15, 21]	18 [14, 21]	18 [15, 22]	17 [14, 20]	17 [15, 20]
G Manch	9 [7, 12]	8 [7, 10]	8 [6, 11]	8 [6, 10]	8 [6, 11]	8 [6, 10]	8 [6, 10]
K-on-Hull	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 0]	0 [0, 0]	0 [0, 1]	0 [0, 0]
Leicester	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]
Liverpool	3 [2, 4]	3 [2, 4]	3 [2, 4]	3 [2, 4]	3 [2, 4]	3 [2, 4]	3 [1, 4]
Norwich	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 1]
Nottm	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]
Potteries	1 [1, 2]	1 [1, 2]	1 [1, 2]	1 [1, 2]	1 [1, 2]	1 [0, 2]	1 [1, 2]
Sheffield	4 [2, 5]	3 [2, 5]	3 [2, 5]	3 [2, 5]	4 [2, 5]	3 [2, 4]	3 [2, 4]
Southamp	1 [0, 1]	1 [0, 1]	1 [0, 1]	1 [0, 1]	1 [0, 1]	1 [0, 1]	1 [0, 1]
Tyneside	6 [4, 7]	5 [4, 7]	5 [4, 7]	5 [4, 7]	5 [4, 7]	5 [4, 6]	5 [3, 7]
W Mdlnds	6 [5, 9]	6 [4, 8]	6 [5, 9]	6 [5, 8]	7 [5, 8]	6 [4, 8]	6 [4, 7]
W Yorks	5 [3, 6]	4 [3, 6]	4 [3, 6]	4 [3, 6]	5 [3, 6]	4 [3, 5]	4 [3, 5]

Table 11.3: Median events per day, by conurbation and calendar year

	Median [IQR] events per day, by calendar year			
	2003	2004	2005	2006
Bristol	1 [1, 3]	2 [1, 4]	1 [0, 2]	1 [0, 1]
Cardiff	0 [0, 1]	1 [1, 2]	1 [0, 2]	1 [0, 1]
G London	15 [13, 19]	19 [16, 23]	19 [16, 23]	18 [15, 21]
G Manche	6 [4, 8]	9 [7, 11]	10 [8, 12]	9 [6, 11]
Kingston-	0 [0, 1]	0 [0, 0]	0 [0, 1]	0 [0, 0]
Leicester	0 [0, 1]	1 [0, 2]	1 [1, 2]	1 [0, 2]
Liverpool	2 [1, 3]	2 [1, 4]	3 [2, 5]	3 [2, 5]
Norwich	0 [0, 0]	0 [0, 1]	1 [0, 1]	1 [0, 1]
Nottingha	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 1]
Potteries	1 [0, 2]	1 [1, 2]	1 [1, 2]	1 [1, 2]
Sheffield	2 [1, 4]	4 [2, 5]	3 [2, 5]	3 [2, 5]
Southamp	0 [0, 1]	1 [0, 2]	1 [0, 2]	1 [0, 1]
Tyneside	6 [4, 9]	5 [4, 7]	5 [3, 6]	5 [3, 6]
W Midlan	6 [4, 8]	6 [5, 8]	6 [5, 8]	6 [5, 8]
W Yorksh	4 [3, 6]	5 [4, 7]	4 [2, 5]	4 [3, 5]

Table 11.4: Correlations of daily pollutant levels between monitoring stations within Manchester

a) PM10

	Bolton	Manchester Piccadilly	Stockport Shaw Heath
Bolton	1		
Manchester Piccadilly	0.8831	1	
Stockport Shaw Heath	0.7574	0.8006	1

b) Ozone

	Bolton	Manchester Piccadilly	Manchester Town Hall
Bolton	1		
Manchester Piccadilly	0.9058	1	
Manchester Town Hall	0.8488	0.8666	1

c) CO

	Bolton	Manchester Piccadilly	Manchester Town Hall	Stockport Shaw Heath
Bolton	1			
Manchester Piccadilly	0.6357	1		
Manchester Town Hall	0.5243	0.603	1	
Stockport Shaw Heath	0.5571	0.5883	0.5242	1

d) NO2

	Bolton	Manchester Piccadilly	Manchester South	Manchester Town Hall	Stockport Shaw Heath
Bolton	1				
Manchester Piccadilly	0.8212	1			
Manchester South	0.7471	0.7009	1		
Manchester Town Hall	0.8147	0.8162	0.8713	1	
Stockport Shaw Heath	0.5779	0.5922	0.7606	0.7603	1

e) SO2

	Bolton	Manchester Piccadilly	Manchester South	Stockport Shaw Heath
Bolton	1			
Manchester Piccadilly	0.4575	1		
Manchester South	0.4449	0.7495	1	
Stockport Shaw Heathport Shaw Heath	0.6109	0.4253	0.5256	1

Table 11.5: Correlations of daily pollutant levels between monitoring stations within the West Midlands

a) PM10

	Birmingham Centre	Birmingham Tyburn	Wolverhampton Centre
Birmingham Centre	1		
Birmingham Tyburn	0.8005	1	
Wolverhampton Centre	0.8165	0.697	1

b) Ozone

	Birmingham Centre	Birmingham Tyburn	Sandwell W Bromwich	Wolverhampton Centre
Birmingham Centre	1			
Birmingham Tyburn	0.8677	1		
Sandwell W Bromwich	0.9272	0.9378	1	
Wolverhampton Centre	0.9324	0.8532	0.9087	1

c) CO

	Birmingham Centre	Birmingham Tyburn	Sandwell W Bromwich	Wolverhampton Centre
Birmingham Centre	1			
Birmingham Tyburn	0.7001	1		
Sandwell W Bromwich	0.6657	0.6748	1	
Wolverhampton Centre	0.7108	0.7072	0.6025	1

d) NO2

	Birmingham Centre	Birmingham Tyburn	Sandwell W Bromwich	Walsall Alumwell	Walsall Willen Hall
Birmingham Centre	1				
Birmingham Tyburn	0.7142	1			
Sandwell W Bromwich	0.768	0.8454	1		
Walsall Alumwell	0.5883	0.8714	0.7563	1	
Walsall Willen Hall	0.8539	0.7187	0.8535	0.6261	1
Wolverhampton Centre	0.8226	0.6973	0.8295	0.5841	0.8557

e) SO2

	Birmingham Centre	Birmingham Tyburn	Sandwell W Bromwich	Wolverhampton Centre
Birmingham Centre	1			
Birmingham Tyburn	0.6389	1		
Sandwell W Bromwich	0.5366	0.23	1	
Wolverhampton Centre	0.5197	0.4855	0.4712	1

Table 11.6: Correlations of daily pollutant levels between monitoring stations within Sheffield

a) Ozone

	Rotherham Centre	Sheffield Centre
Rotherham Centre	1	
Sheffield Centre	0.8943	1

b) NO2

	Rotherham Centre	Sheffield Centre
Rotherham Centre	1	
Sheffield Centre	0.6884	1

c) SO2

	Rotherham Centre	Sheffield Centre
Rotherham Centre	1	

Table 11.7: Correlations of daily pollutant levels between monitoring stations within West Yorkshire

a) PM10

	Bradford Centre	Leeds Centre
Bradford Centre	1	
Leeds Centre	0.6259	1

b) Ozone

	Bradford Centre	Leeds Centre
Bradford Centre	1	
Leeds Centre	0.9111	1

c) CO

	Bradford Centre	Leeds Centre
Bradford Centre	1	
Leeds Centre	0.6572	1

d) NO2

	Bradford Centre	Leeds Centre
Bradford Centre	1	
Leeds Centre	0.7406	1

e) SO2

	Bradford Centre	Leeds Centre
Bradford Centre	1	
Leeds Centre	0.5393	1

Figure 11.1: 7-day moving averages of CO, SO2, NO2 over calendar time, by conurbation

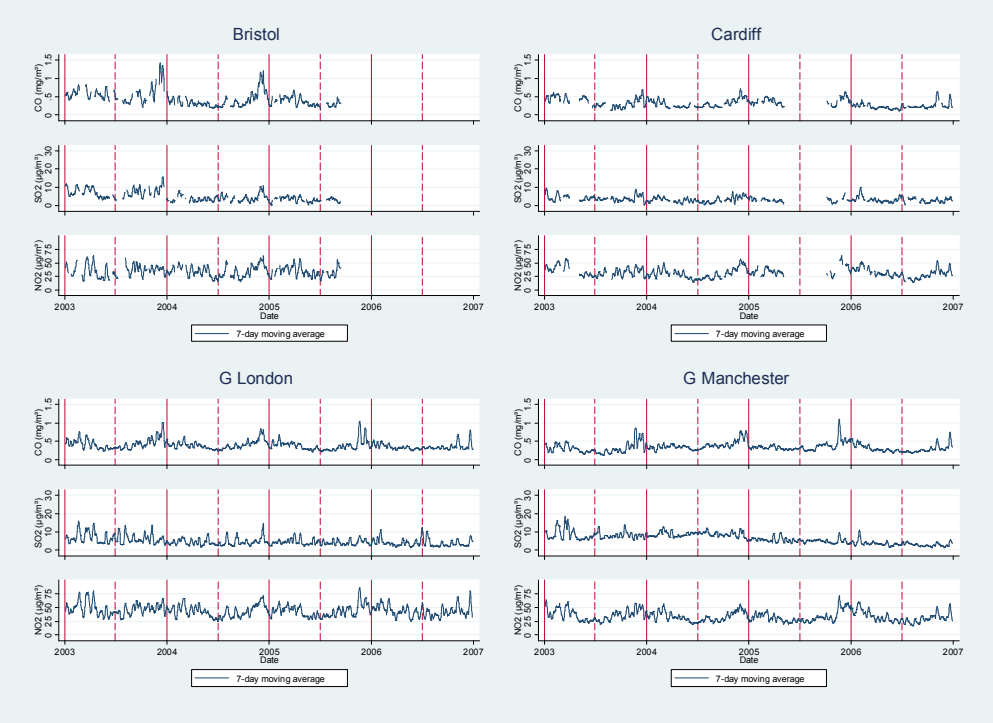


Figure 11.2: 7-day moving averages of CO, SO2, NO2 over calendar time, by conurbation

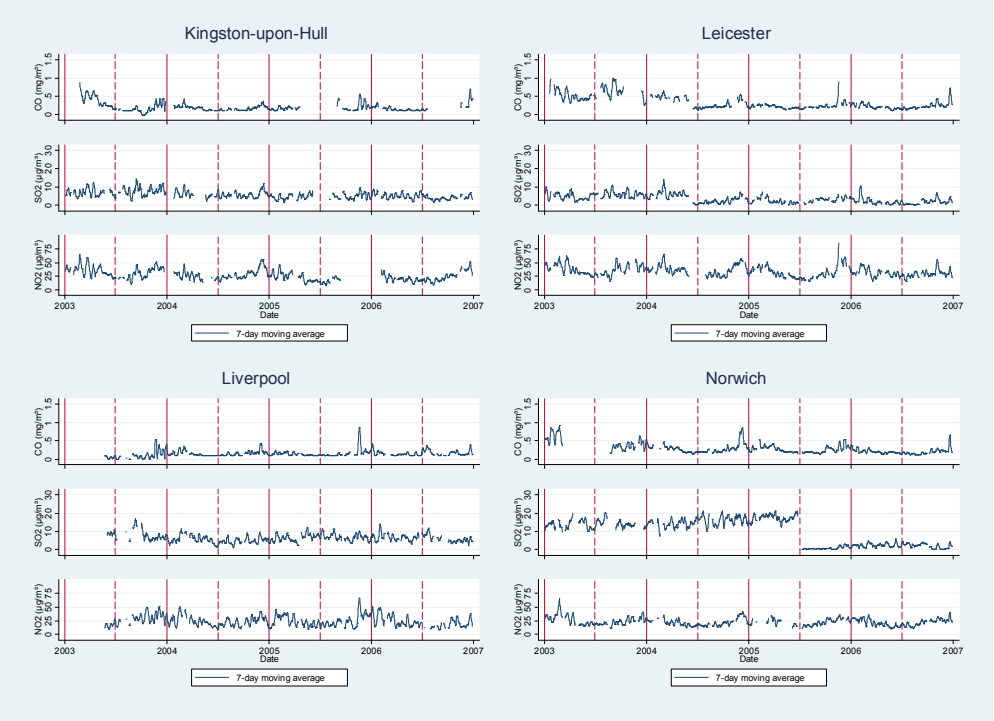


Figure 11.3: 7-day moving averages of CO, SO2, NO2 over calendar time, by conurbation

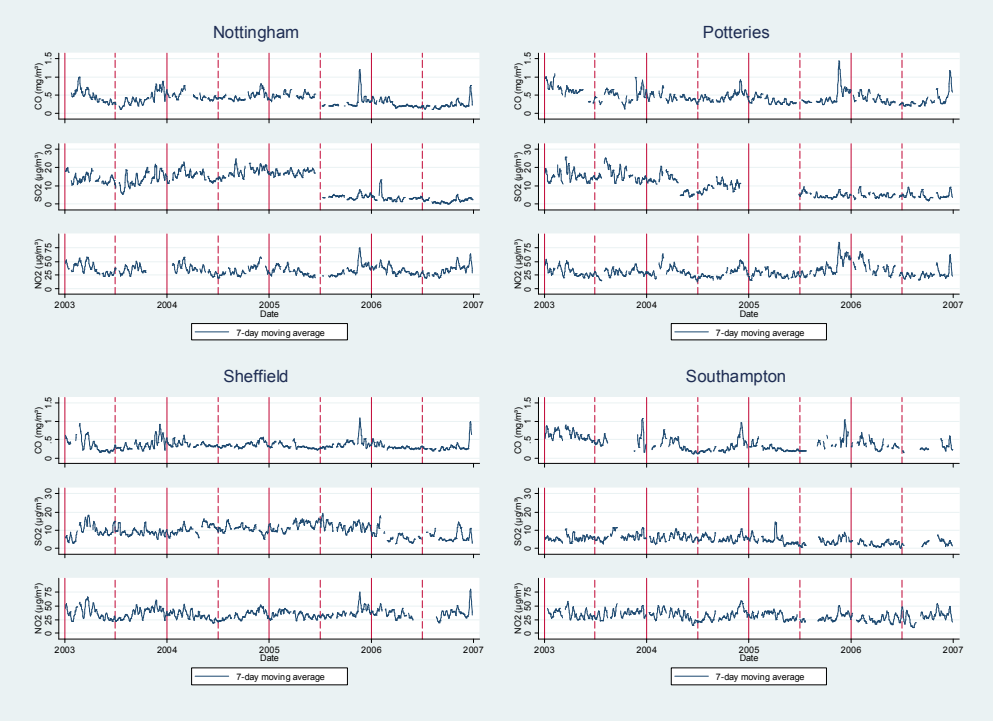
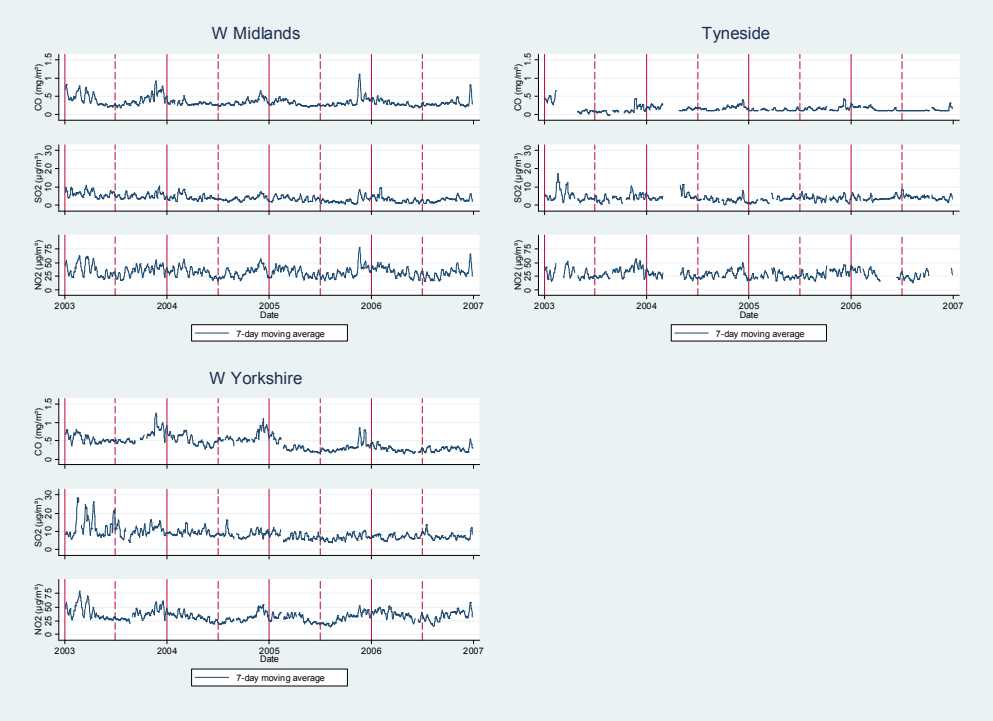
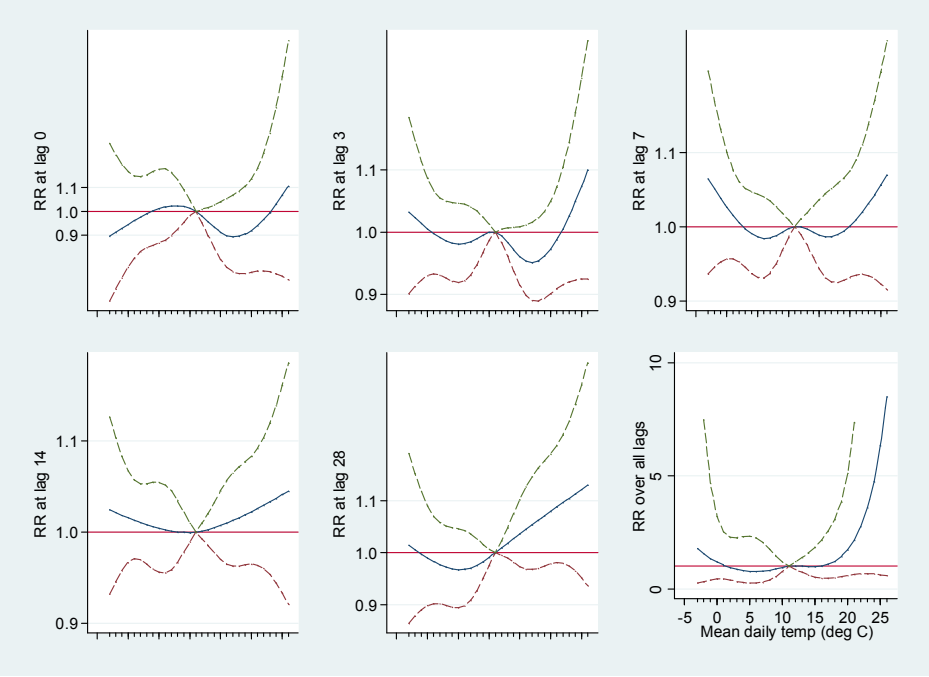


Figure 11.4: 7-day moving averages of CO, SO2, NO2 over calendar time, by conurbation

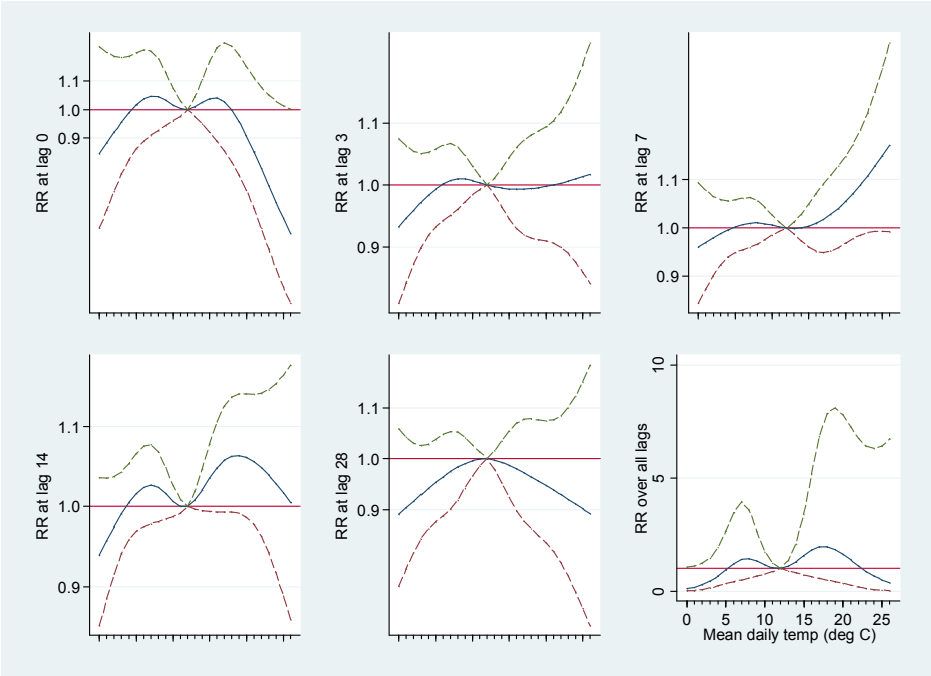


11.2 Short-term effects of temperature – additional output

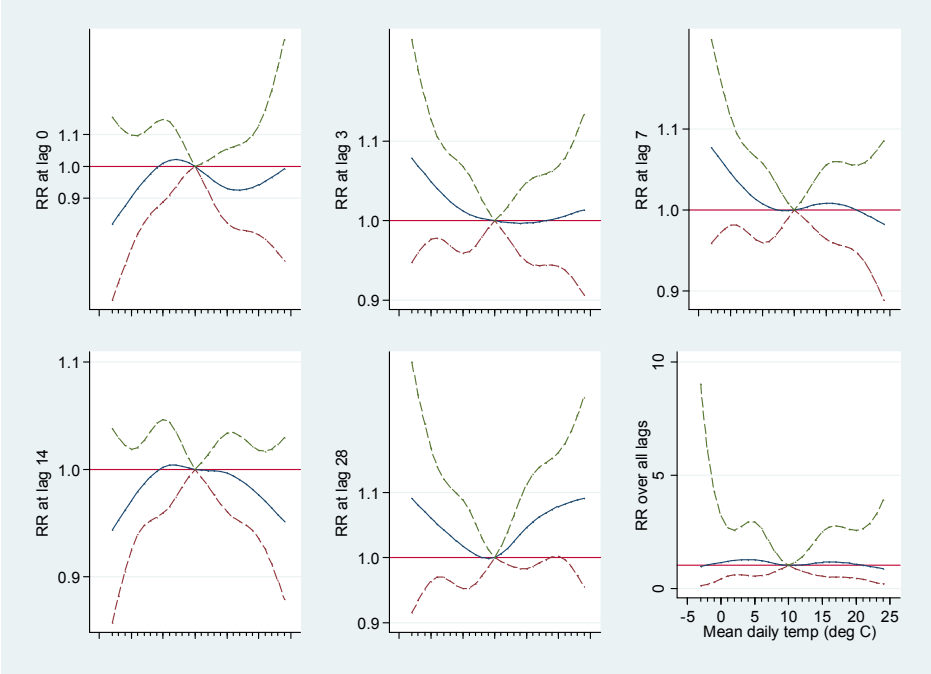
Figure 11.5: Temperature effects from non-linear distributed model
a) Bristol



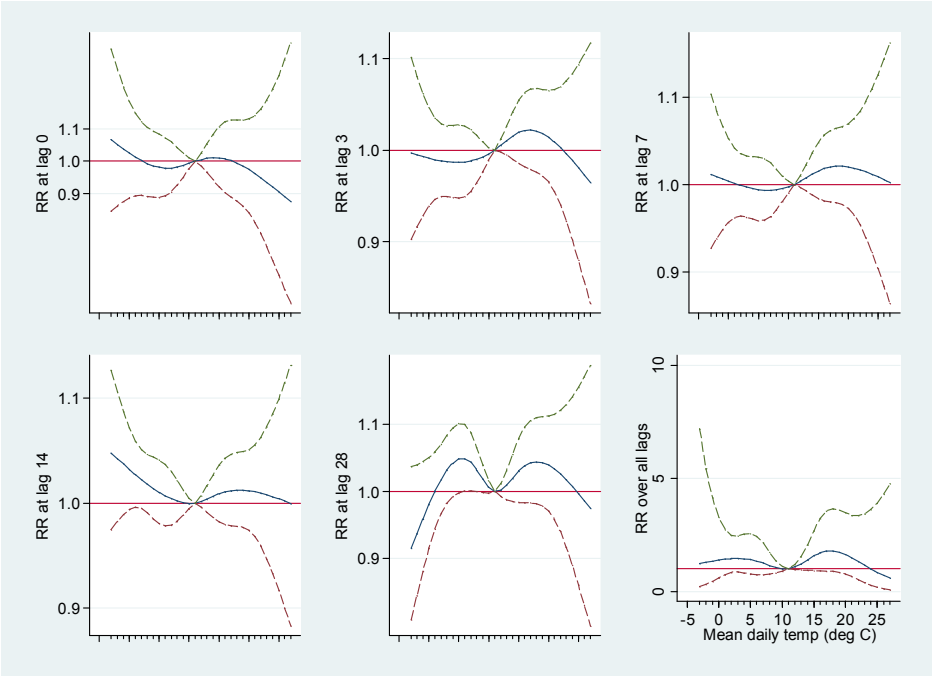
b) Cardiff



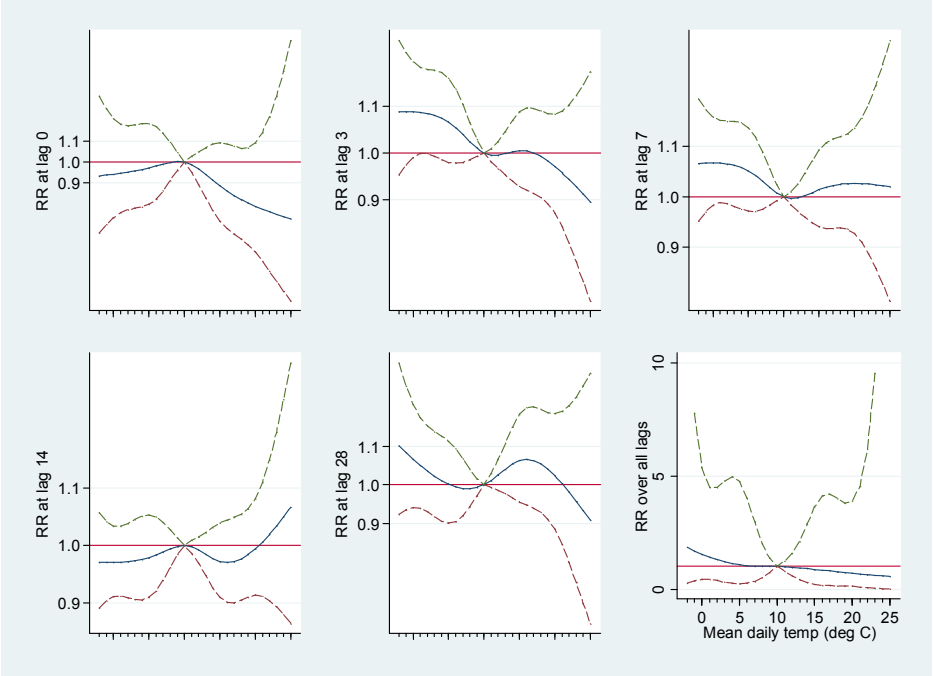
c) Leicester



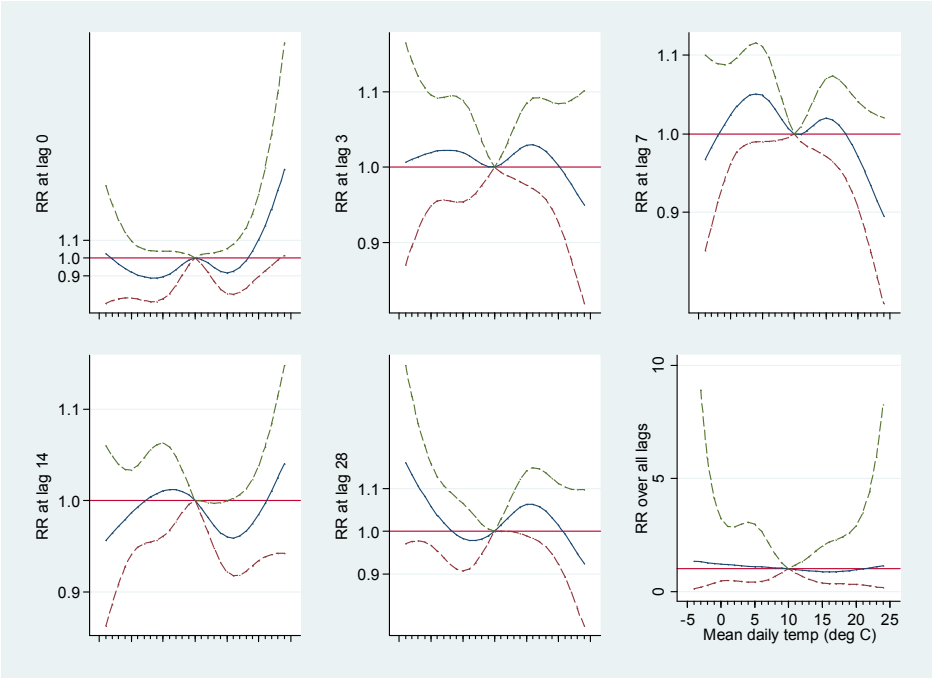
d) Liverpool



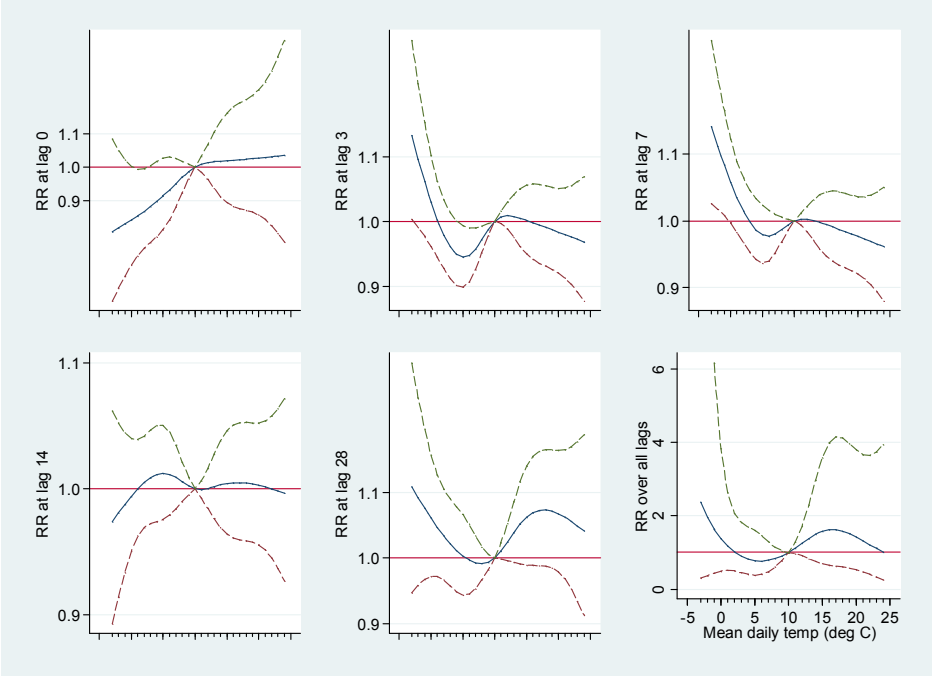
e) Norwich



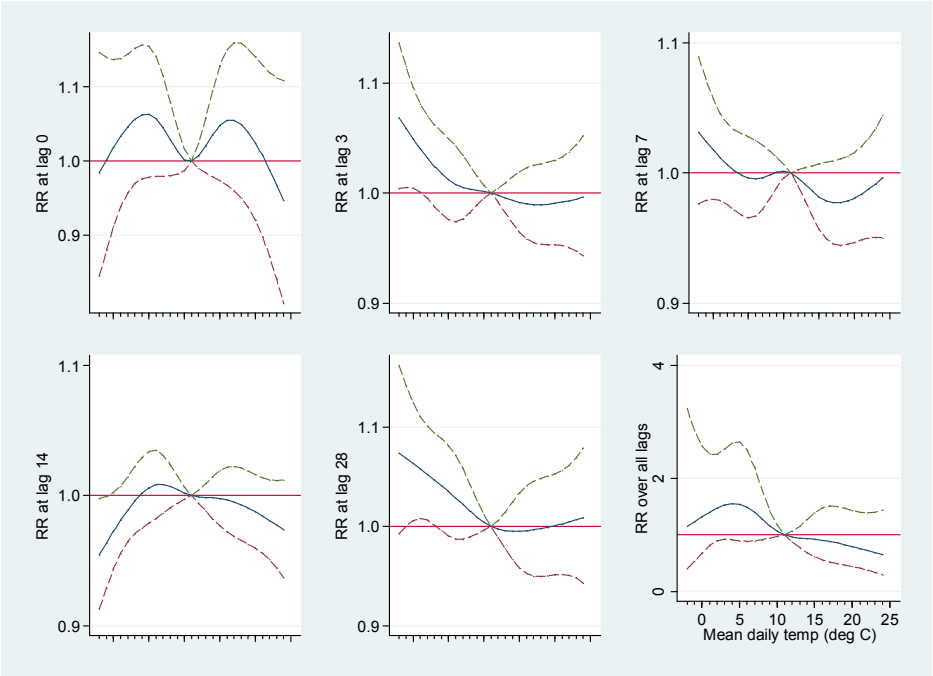
f) Nottingham



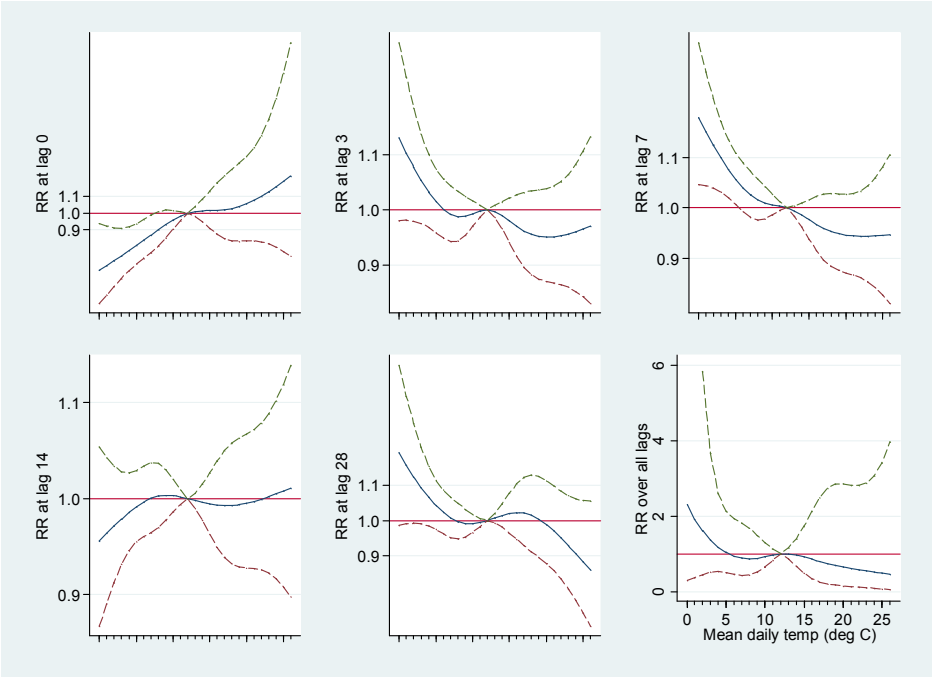
g) Potteries



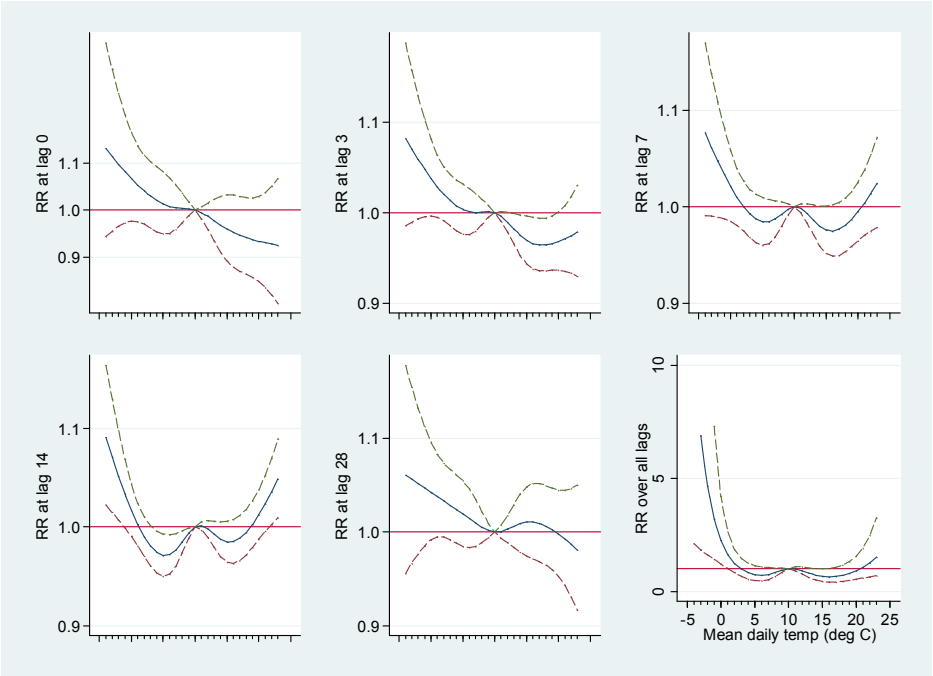
h) Sheffield



i) Southampton



j) Tyneside



k) West Yorkshire

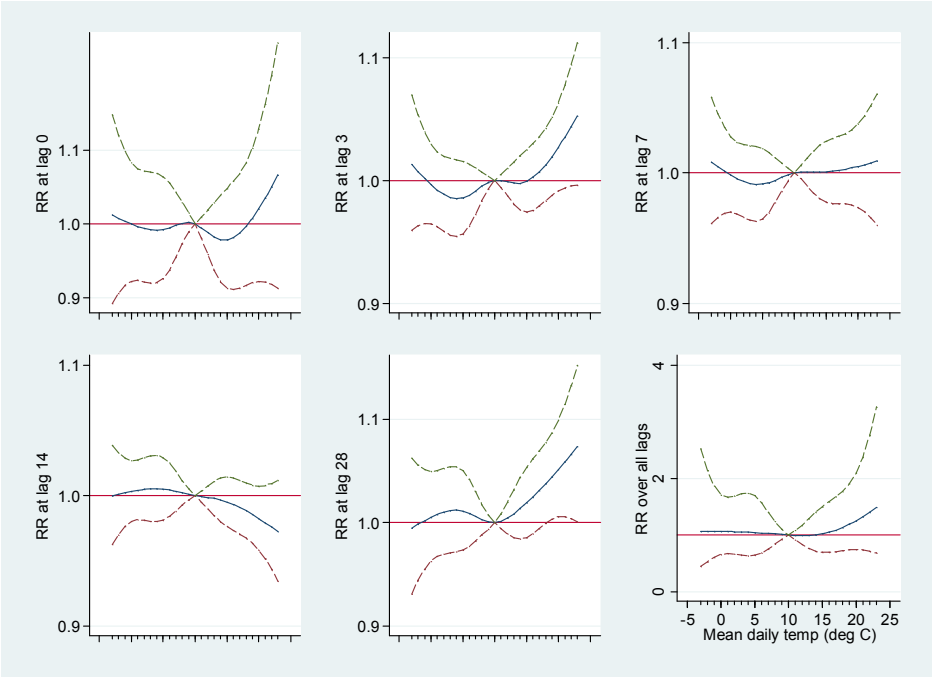
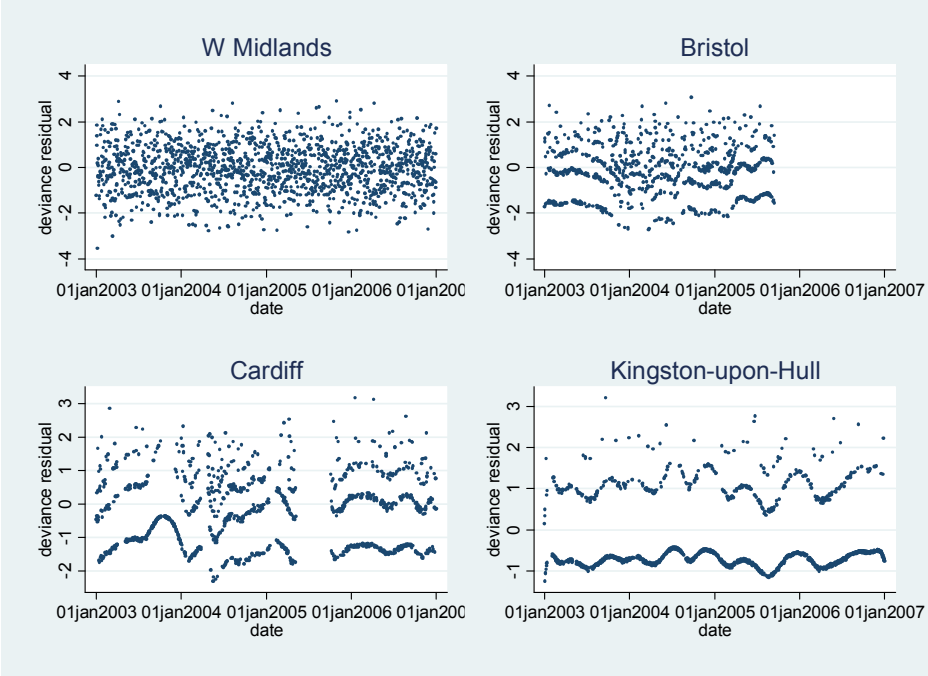
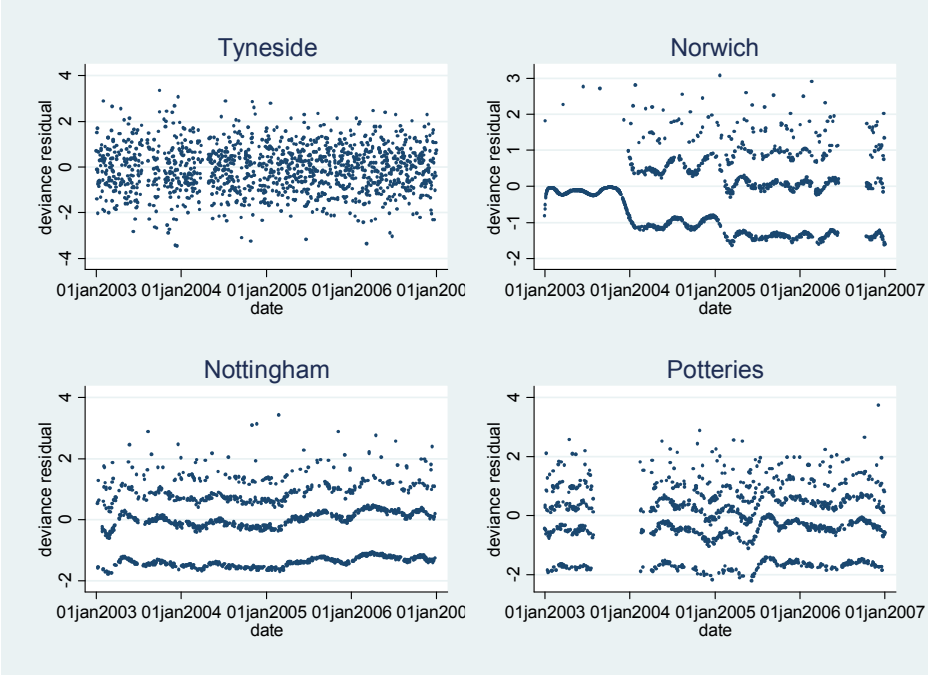


Figure 11.6: Individual conurbation plots of deviance residual vs. calendar time

a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



b) Tyneside, Norwich, Nottingham, Potteries



c) Sheffield, Southampton, West Yorkshire

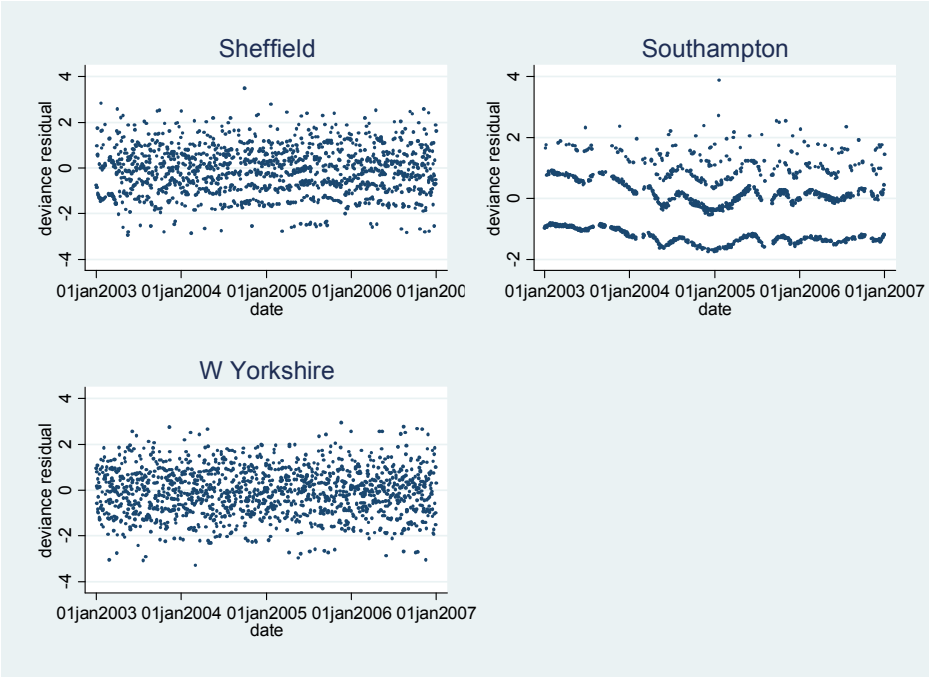
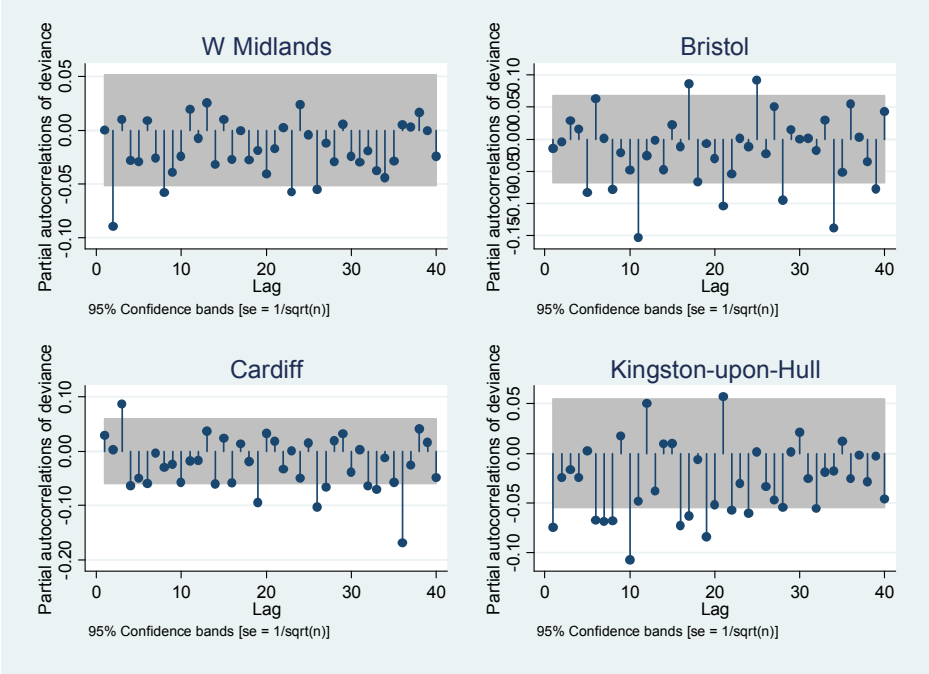
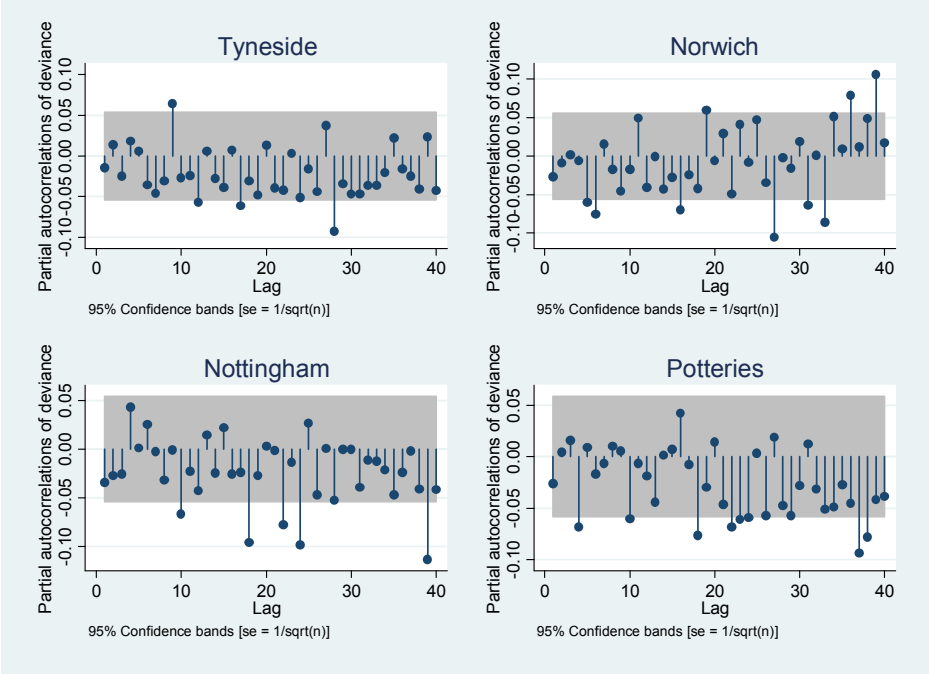


Figure 11.7: Partial autocorrelations of deviance residuals in individual conurbations
a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



b) Tyneside, Norwich, Nottingham, Potteries

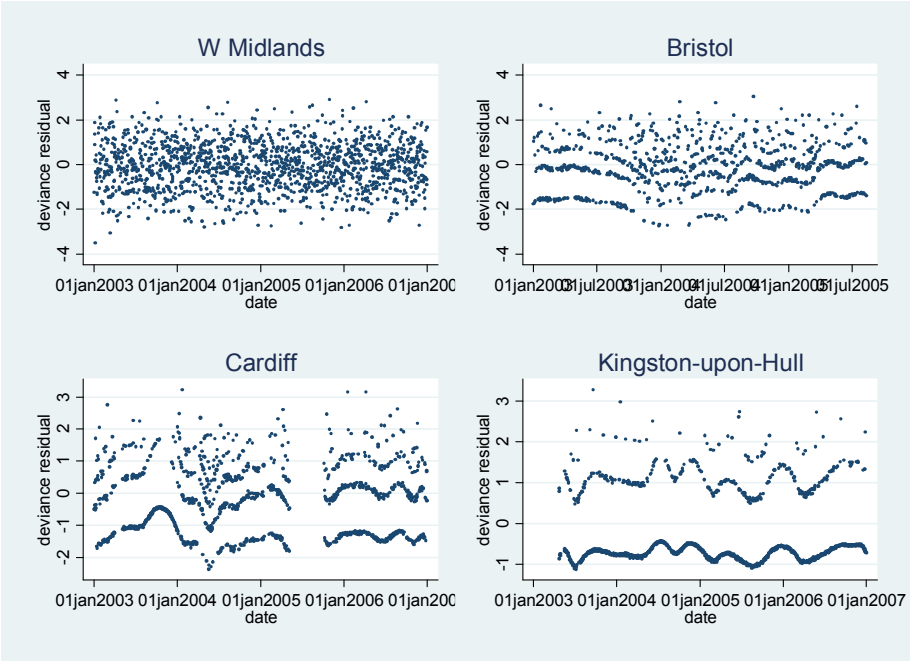


c) Sheffield, Southampton, West Yorkshire

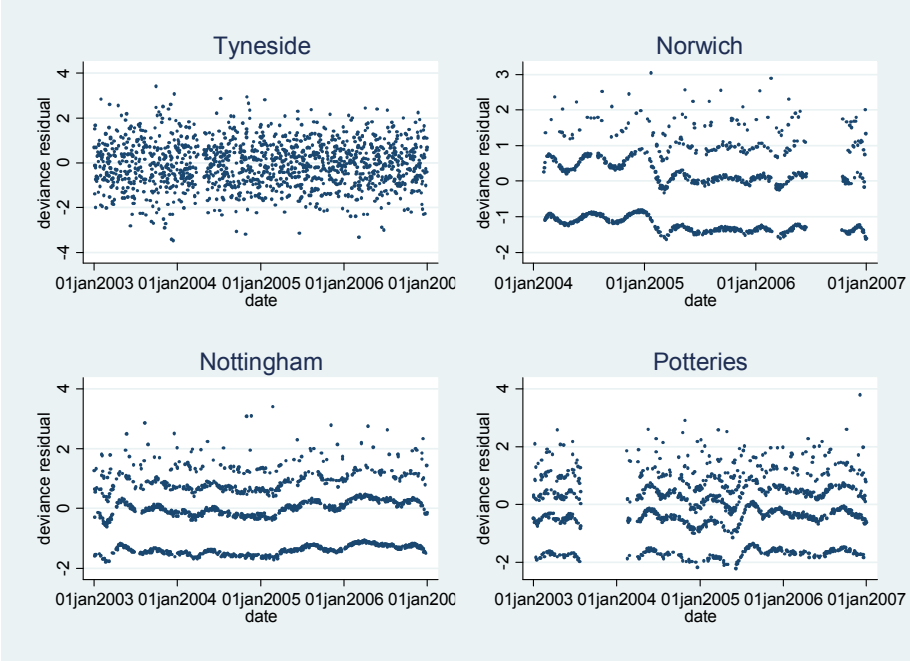
11.3 Effects of daily air pollution levels – additional output

Figure 11.8: Individual conurbation plots of deviance residual vs. calendar time from the PM10 model

a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



b) Tyneside, Norwich, Nottingham, Potteries



c) Sheffield, Southampton, West Yorkshire

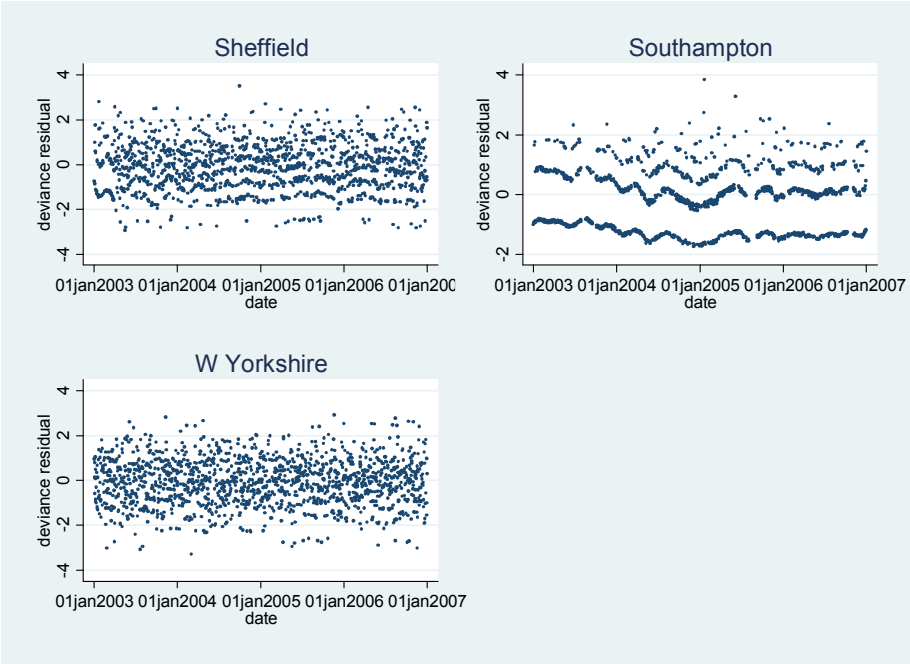
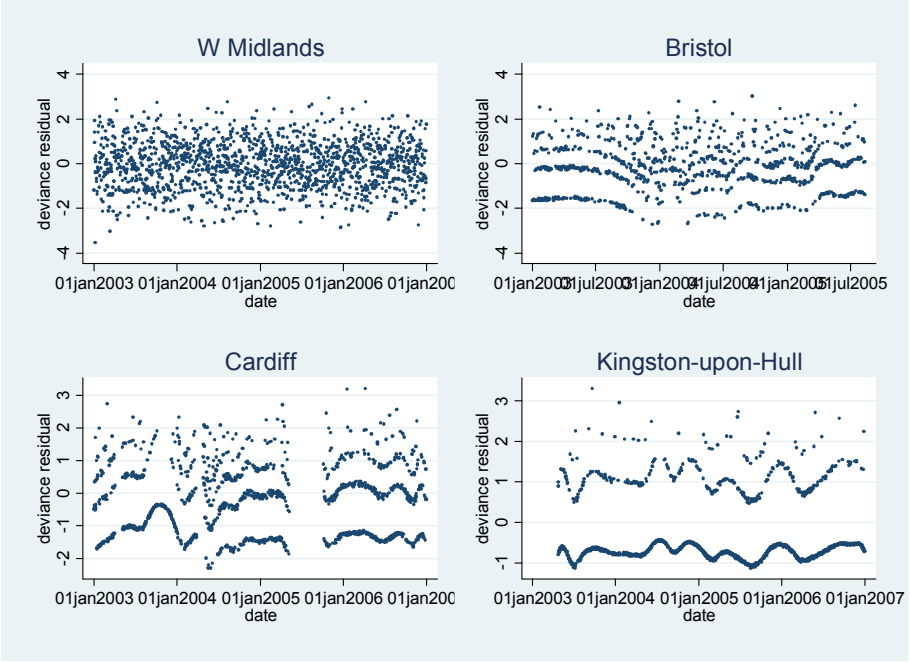
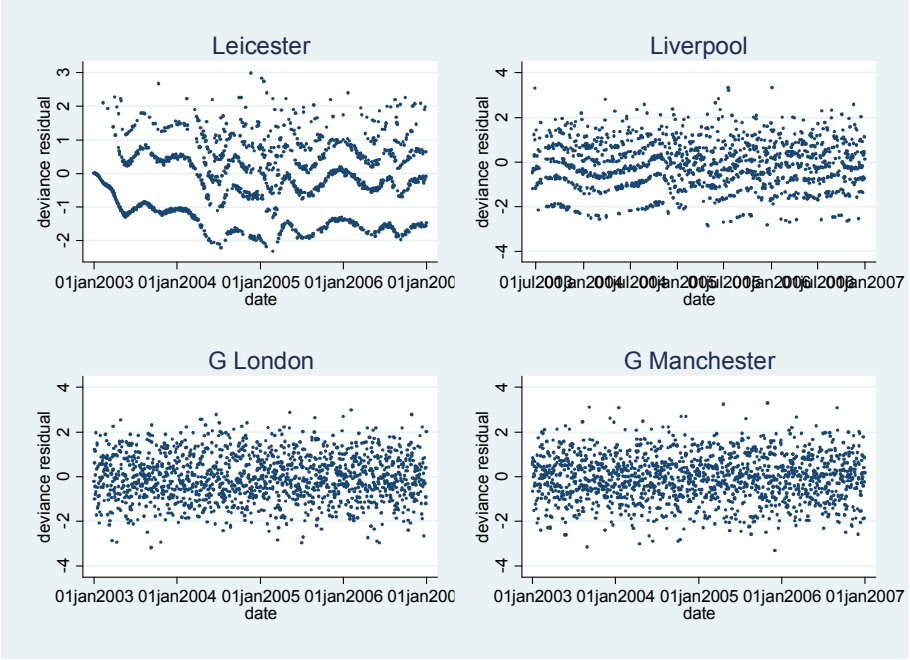


Figure 11.9: Individual conurbation plots of deviance residual vs. calendar time from the Ozone model

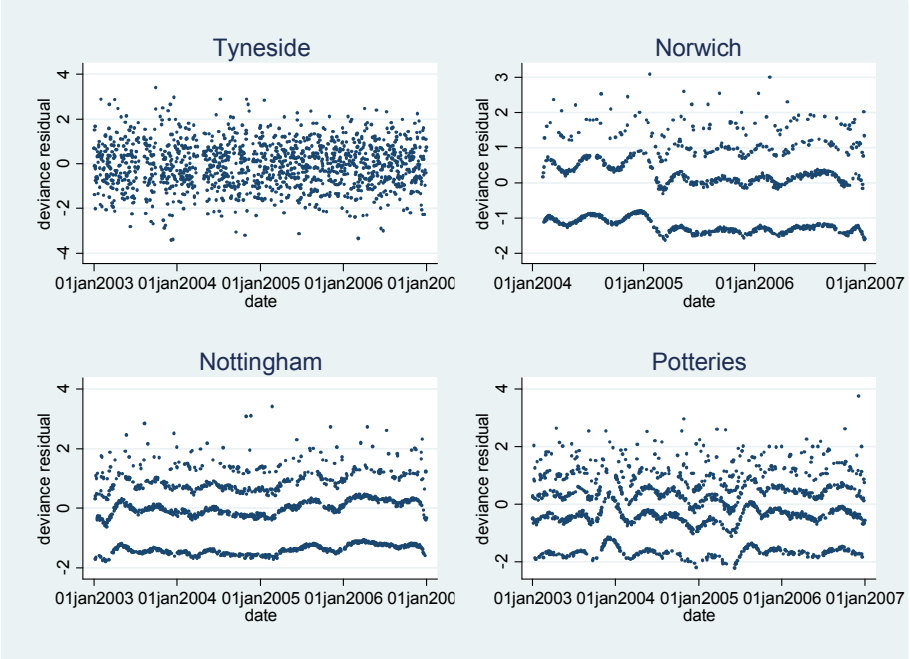
a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



b) Leicester, Liverpool, Greater London, Greater Manchester



c) Tyneside, Norwich, Nottingham, Potteries



d) Sheffield, Southampton, West Yorkshire

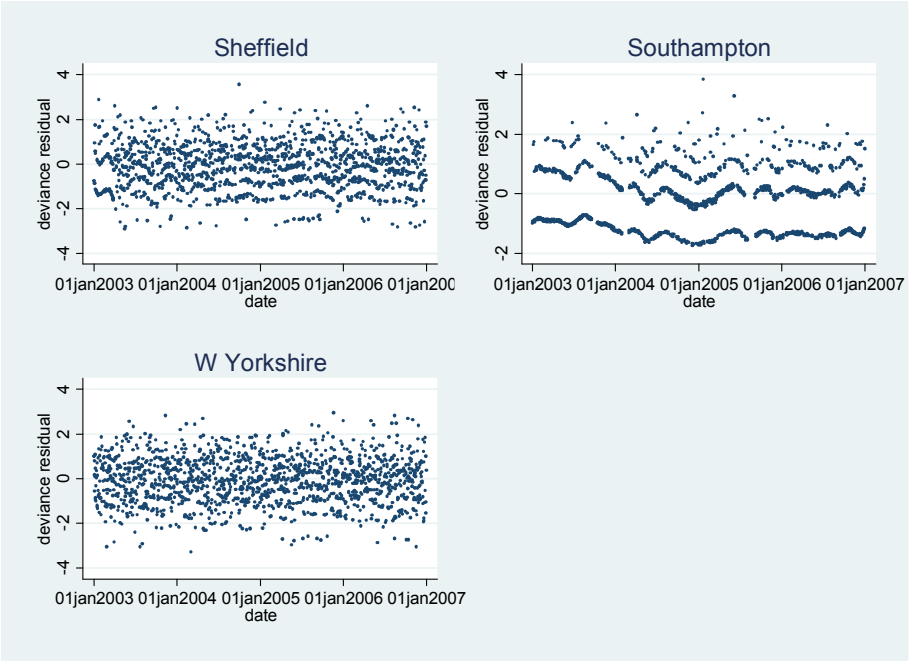
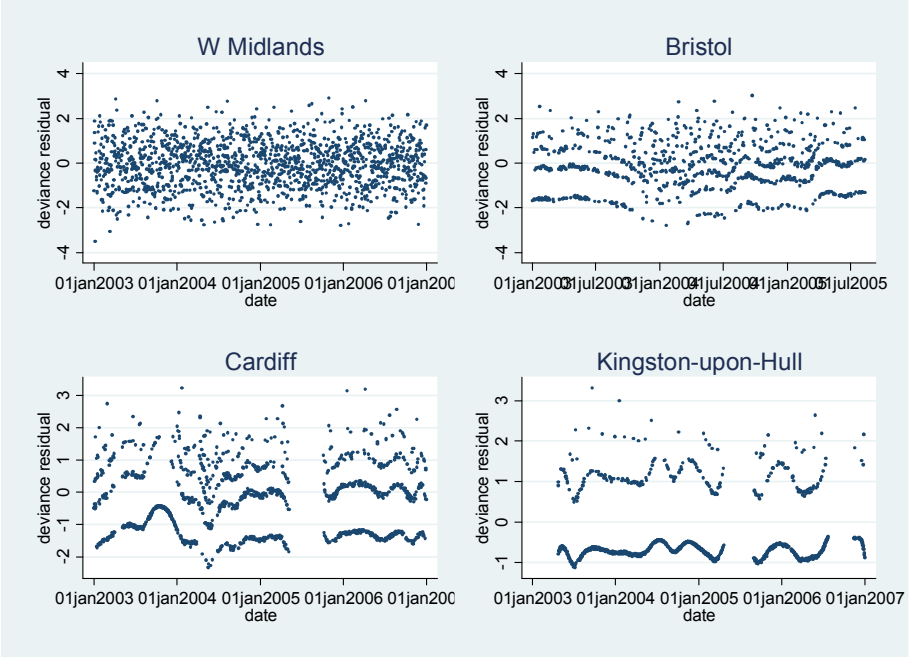
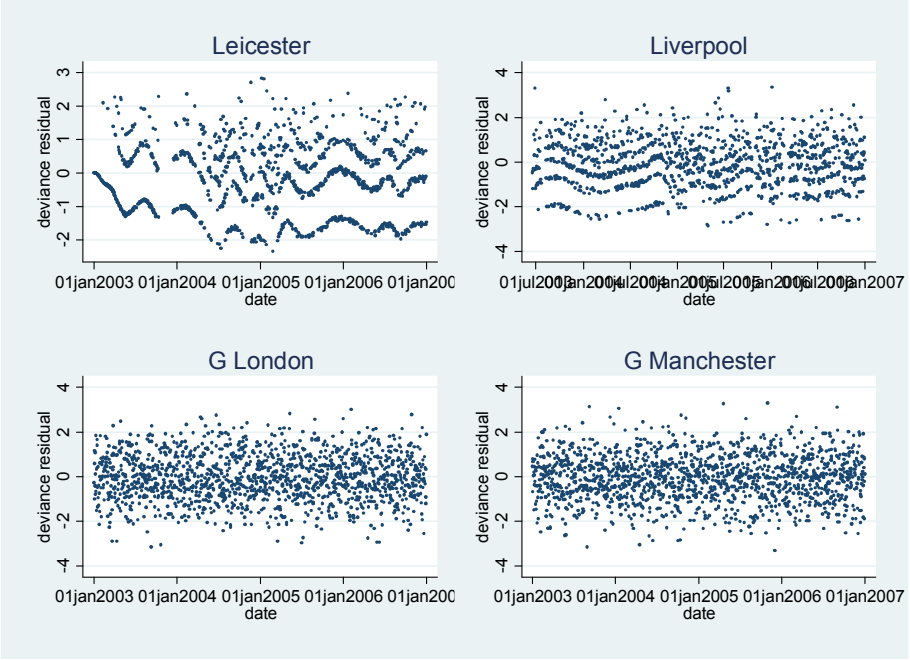


Figure 11.10: Individual conurbation plots of deviance residual vs. calendar time from the CO model

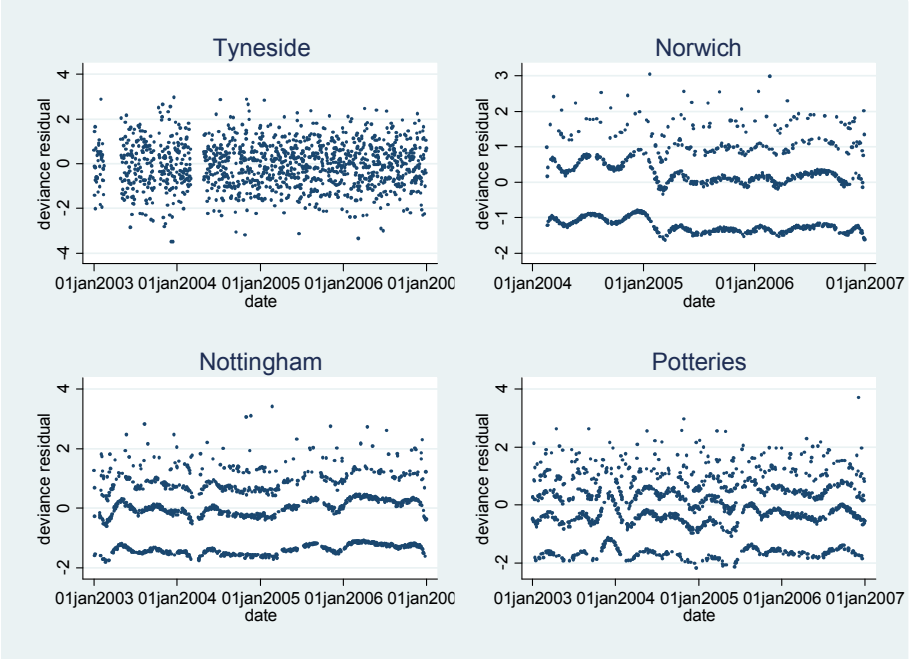
a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



b) Leicester, Liverpool, Greater London, Greater Manchester



c) Tyneside, Norwich, Nottingham, Potteries



d) Sheffield, Southampton, West Yorkshire

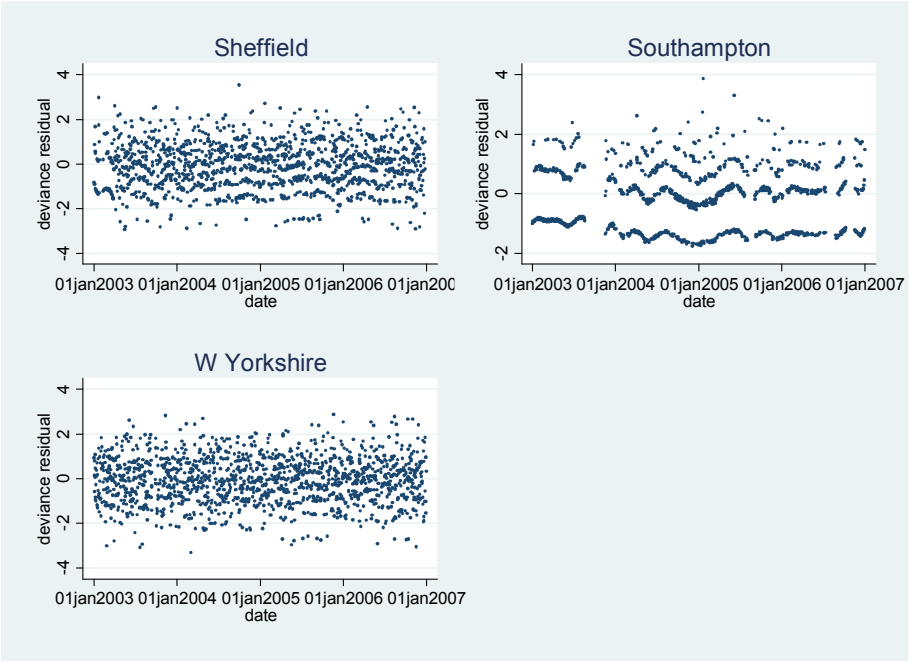
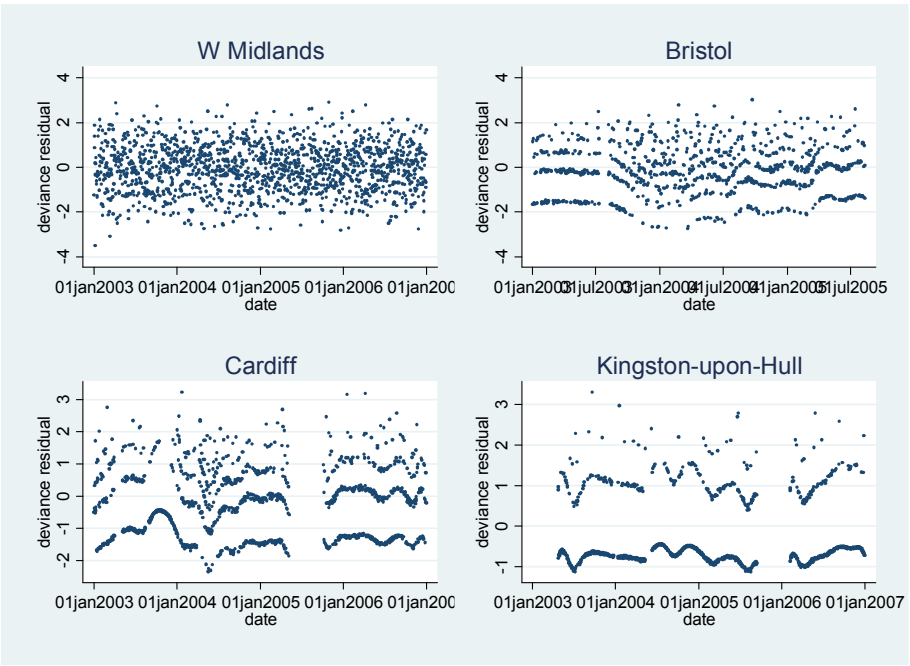
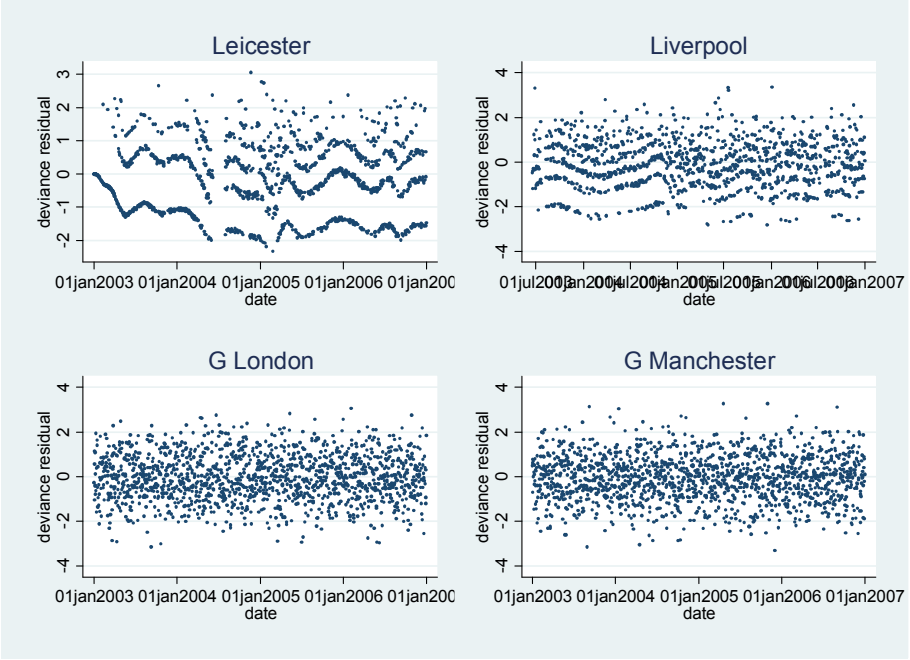


Figure 11.11: Individual conurbation plots of deviance residual vs. calendar time from the NO2 model

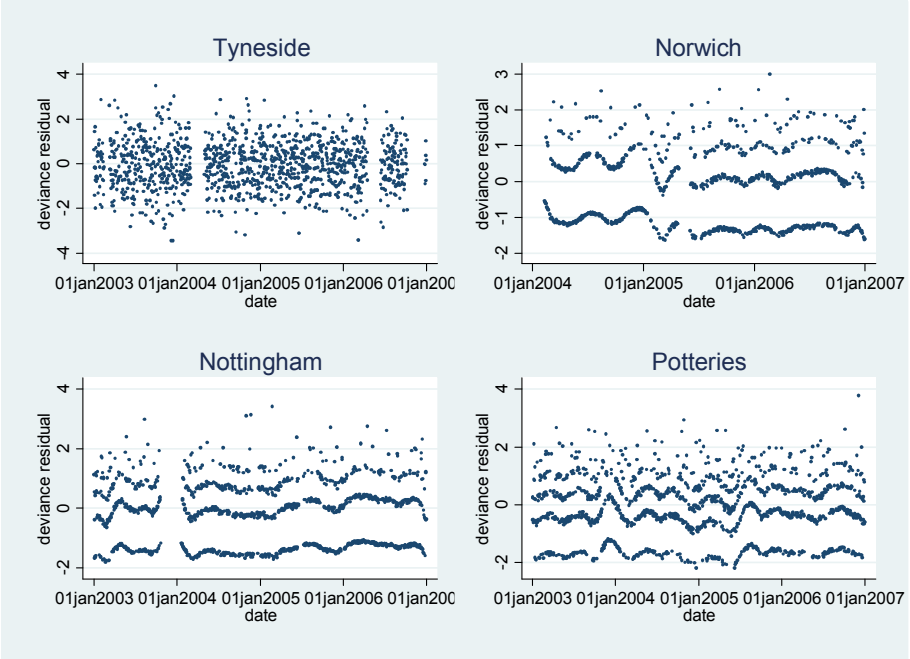
a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



b) Leicester, Liverpool, Greater London, Greater Manchester



c) Tyneside, Norwich, Nottingham, Potteries



d) Sheffield, Southampton, West Yorkshire

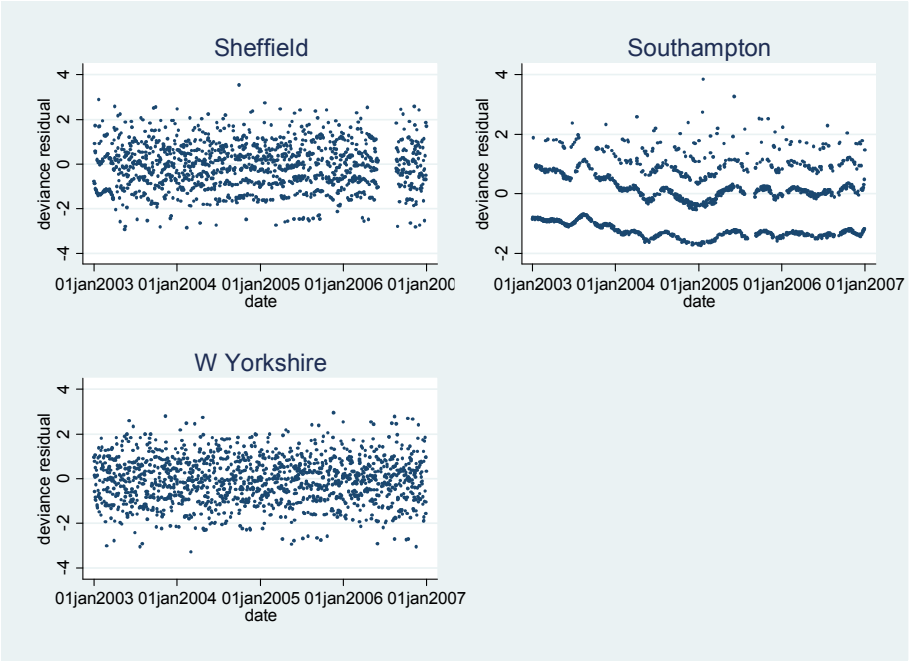
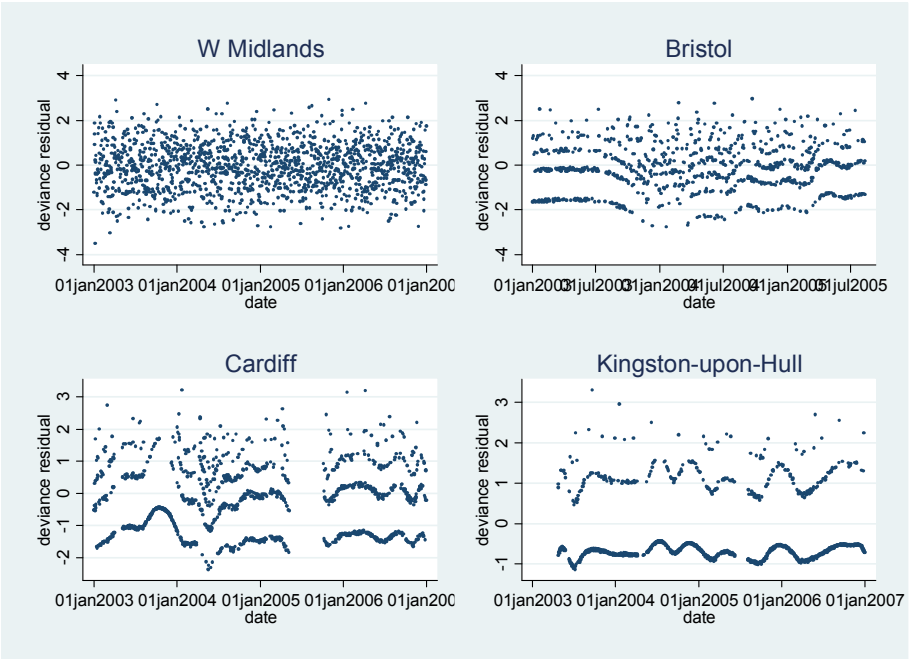
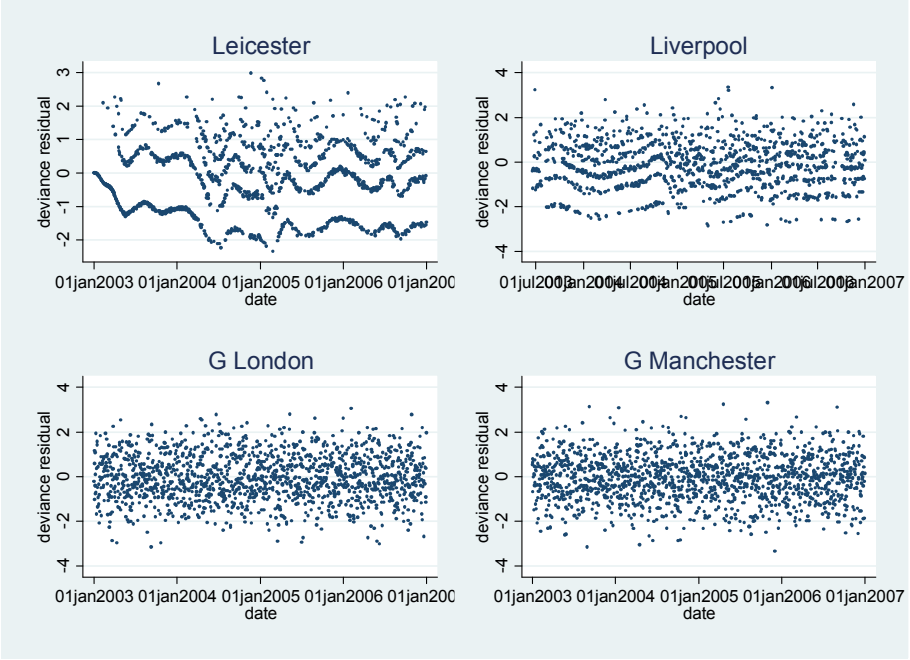


Figure 11.12: Individual conurbation plots of deviance residual vs. calendar time from the SO2 model

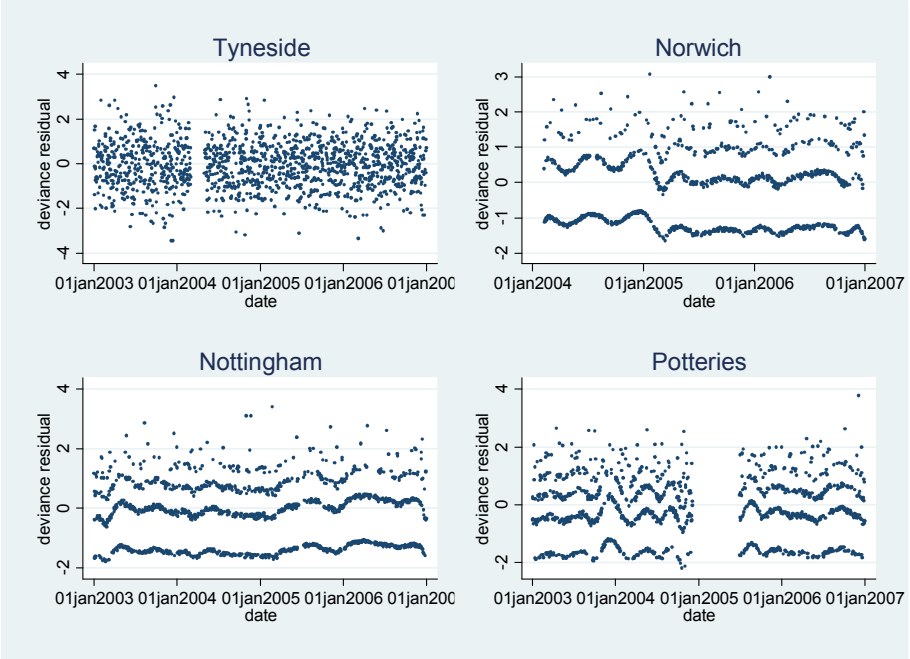
a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



b) Leicester, Liverpool, Greater London, Greater Manchester



c) Tyneside, Norwich, Nottingham, Potteries



d) Sheffield, Southampton, West Yorkshire

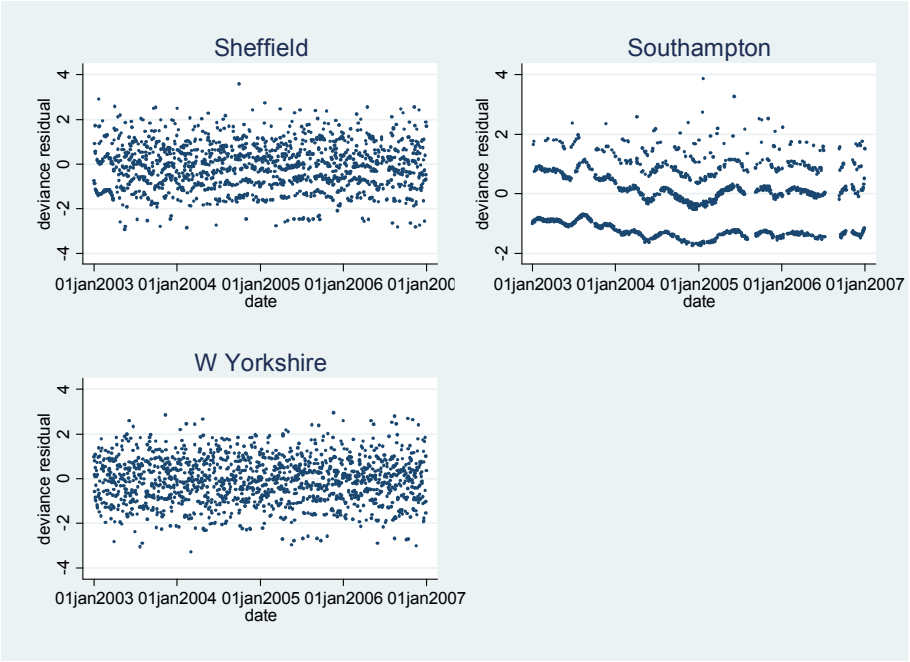
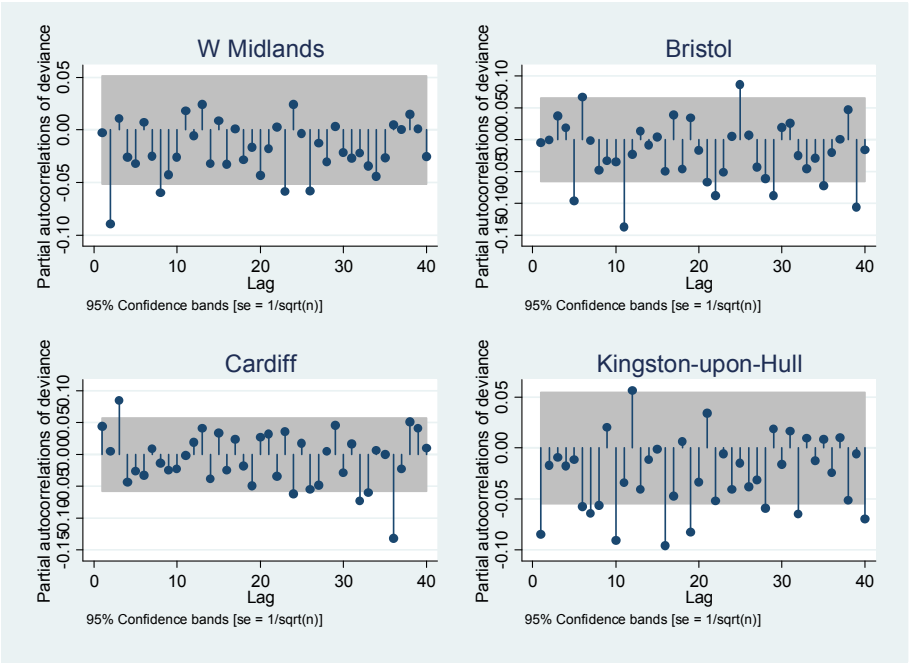
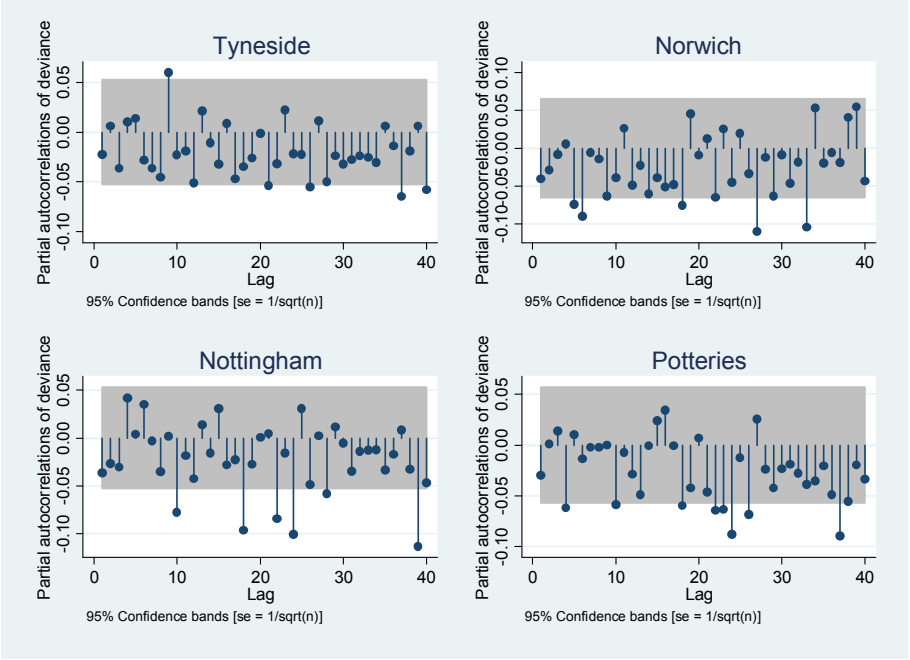


Figure 11.13: Partial autocorrelations of deviance residuals for the PM10 model
a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



b) Tyneside, Norwich, Nottingham, Potteries



c) Sheffield, Southampton, West Yorkshire

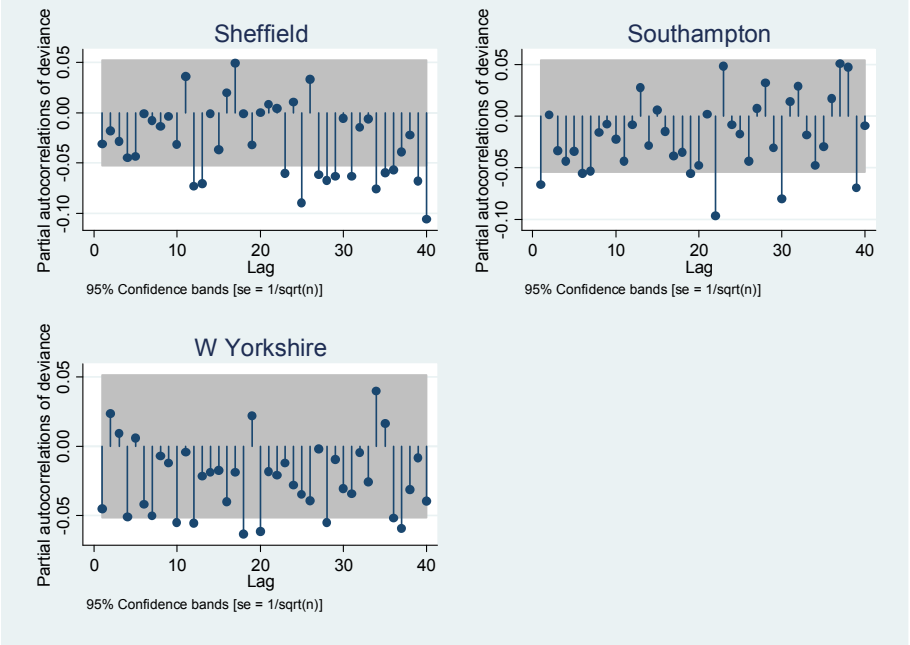
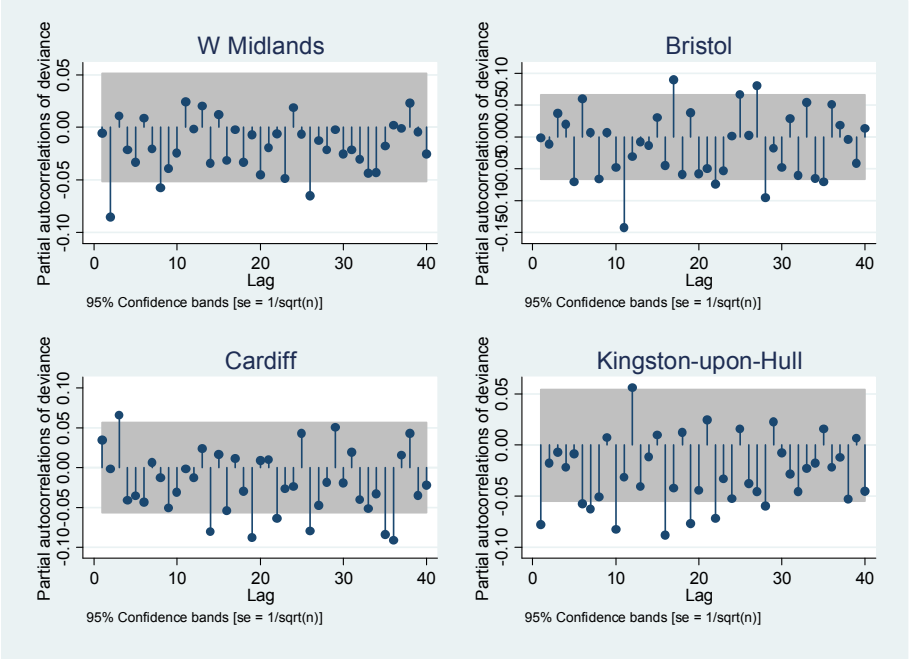
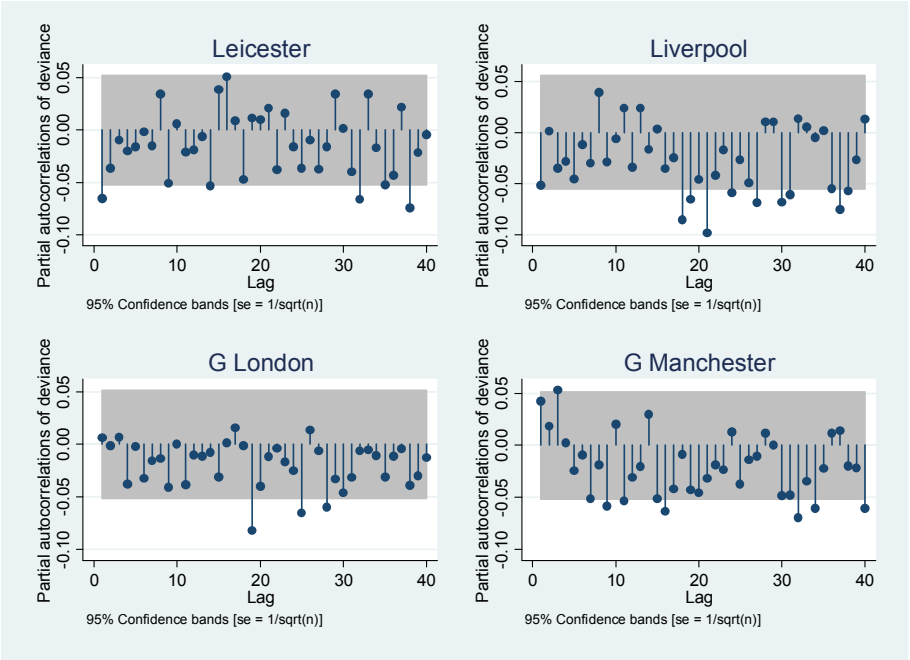


Figure 11.14: Partial autocorrelations of deviance residuals for the Ozone model

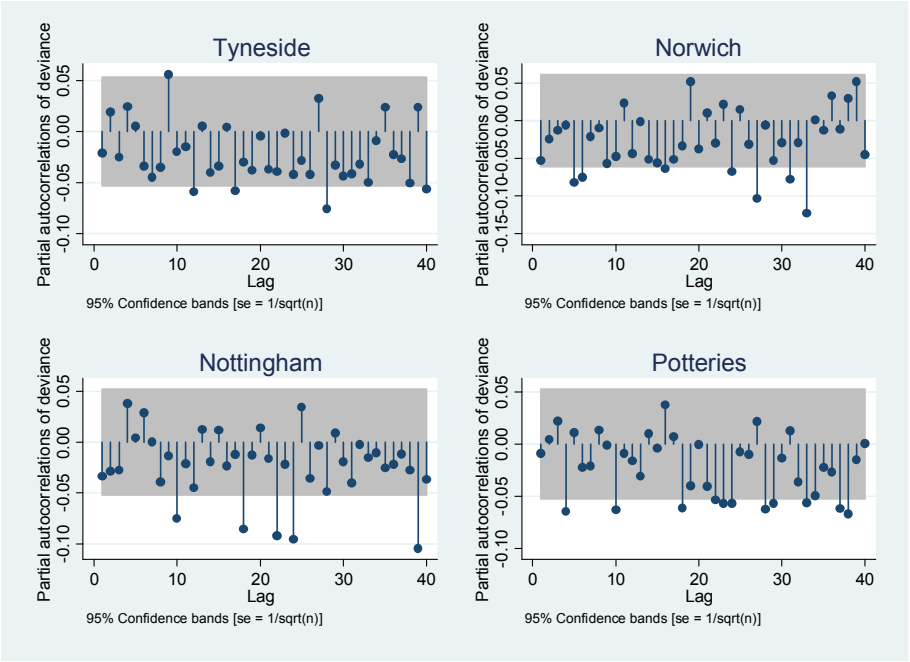
a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



b) Leicester, Liverpool, Greater London, Greater Manchester



c) Tyneside, Norwich, Nottingham, Potteries



d) Sheffield, Southampton, West Yorkshire

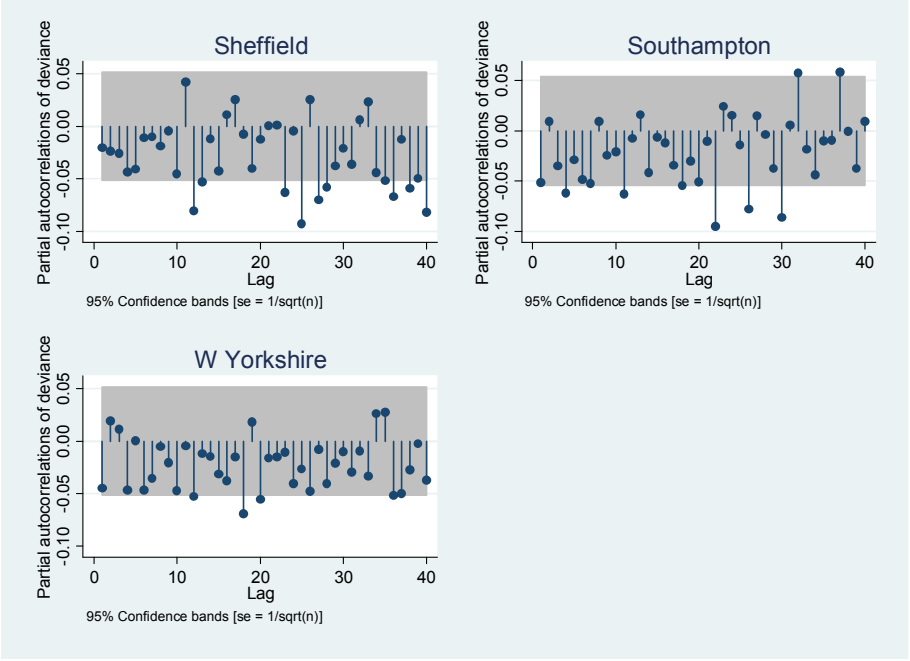
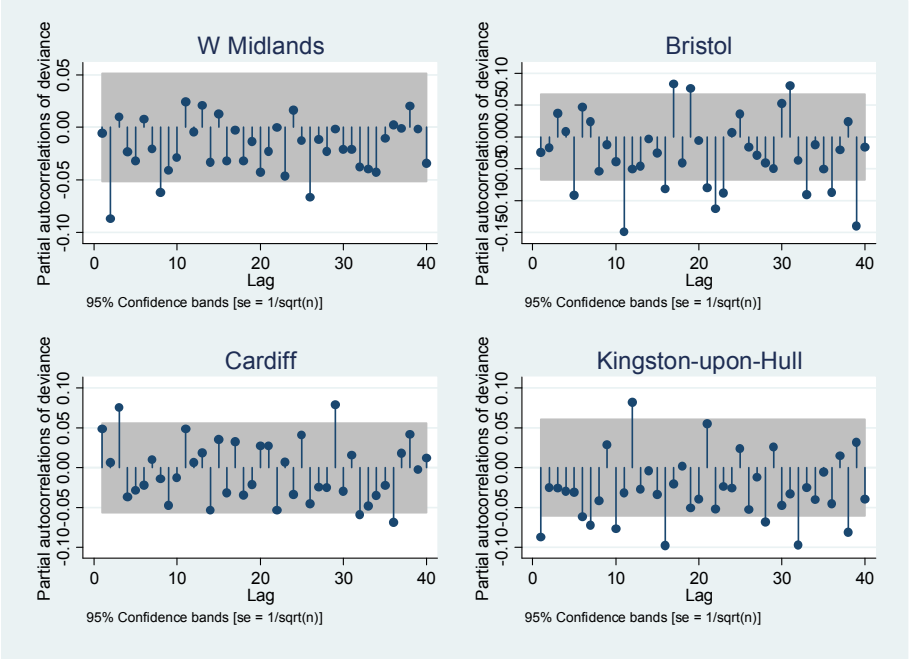
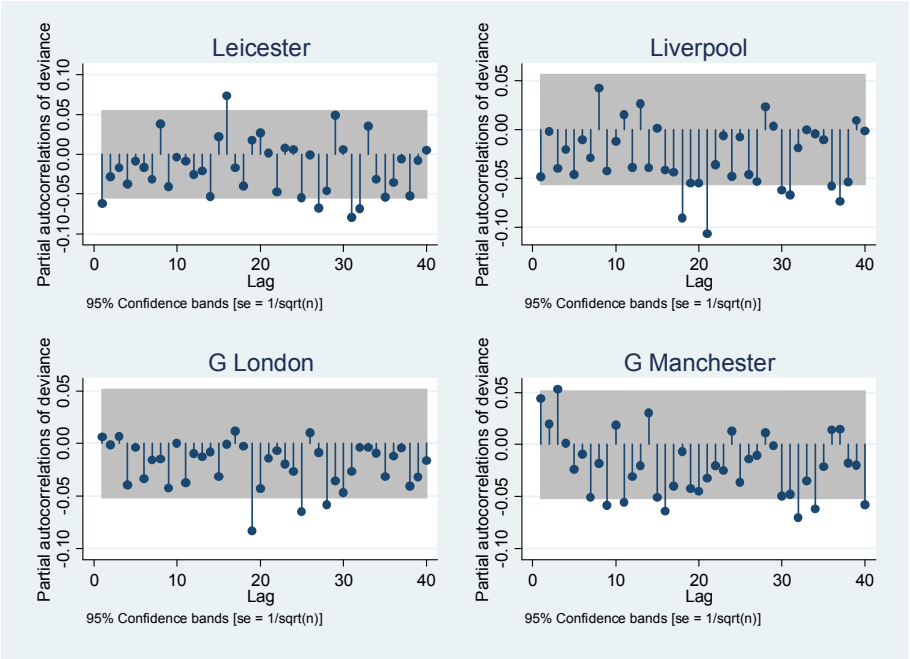


Figure 11.15: Partial autocorrelations of deviance residuals for the CO model

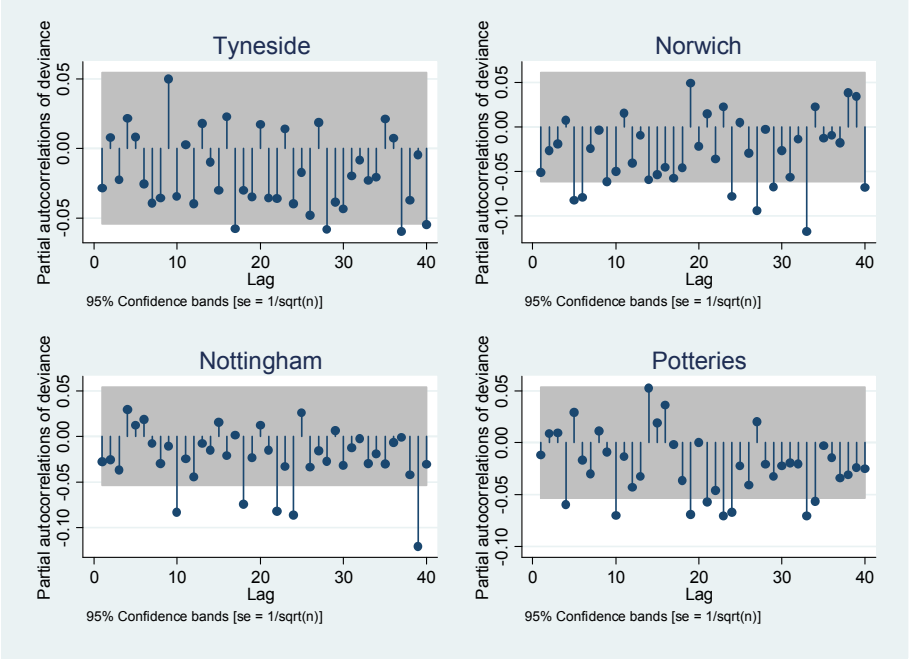
a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



b) Leicester, Liverpool, Greater London, Greater Manchester



c) Tyneside, Norwich, Nottingham, Potteries



d) Sheffield, Southampton, West Yorkshire

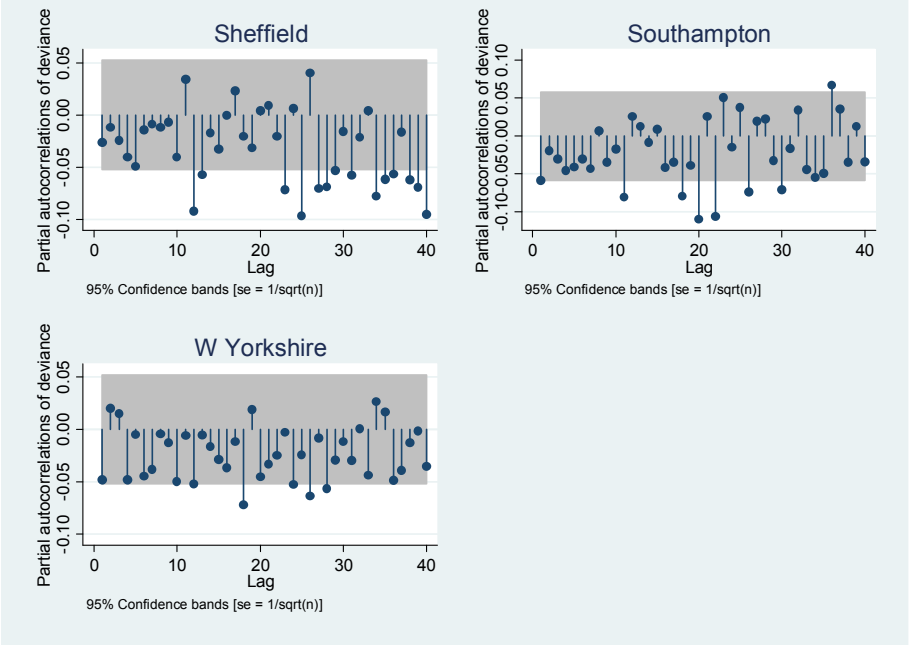
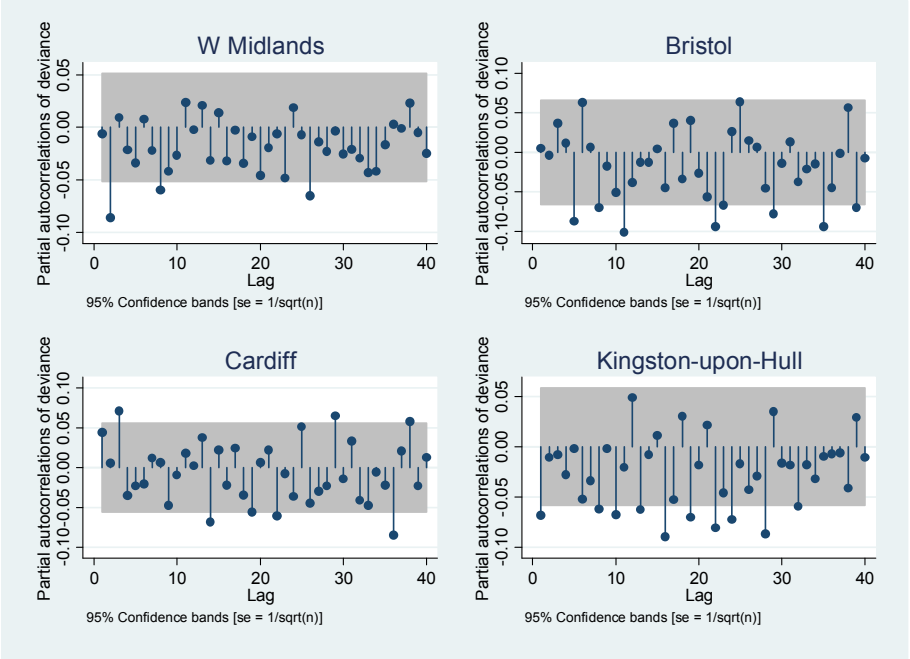
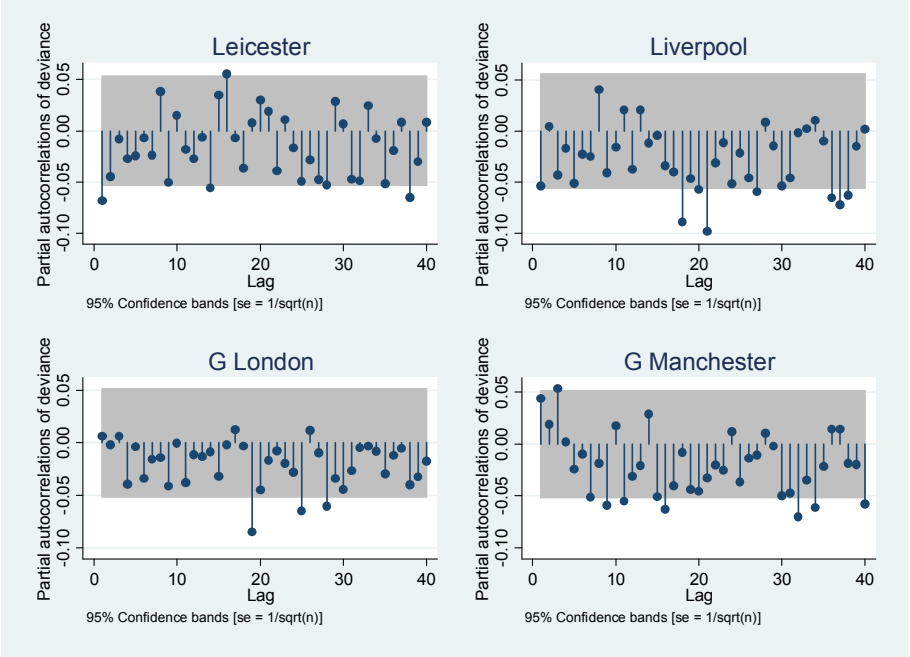


Figure 11.16: Partial autocorrelations of deviance residuals for the NO2 model

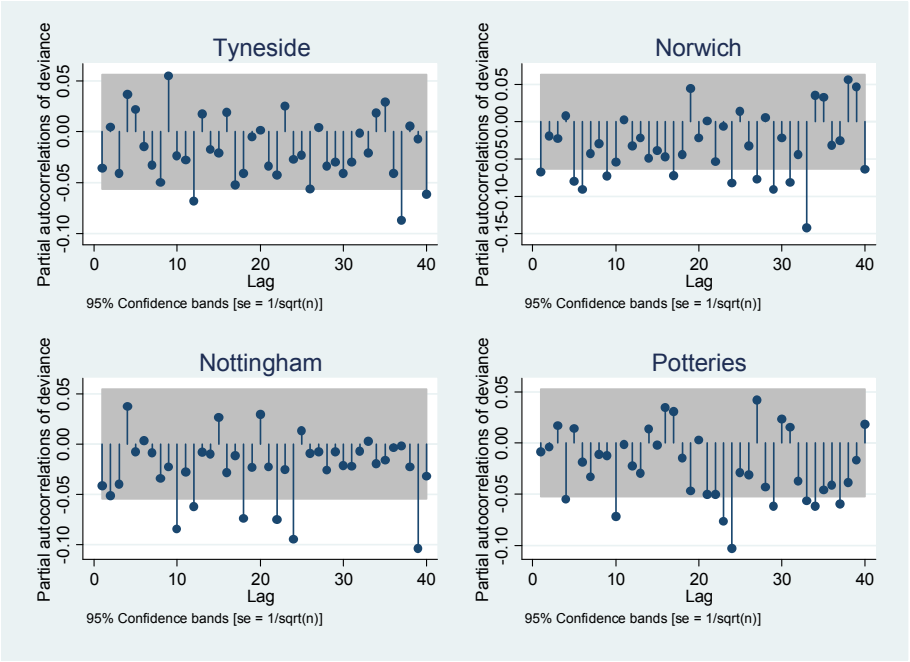
a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



b) Leicester, Liverpool, Greater London, Greater Manchester



c) Tyneside, Norwich, Nottingham, Potteries



d) Sheffield, Southampton, West Yorkshire

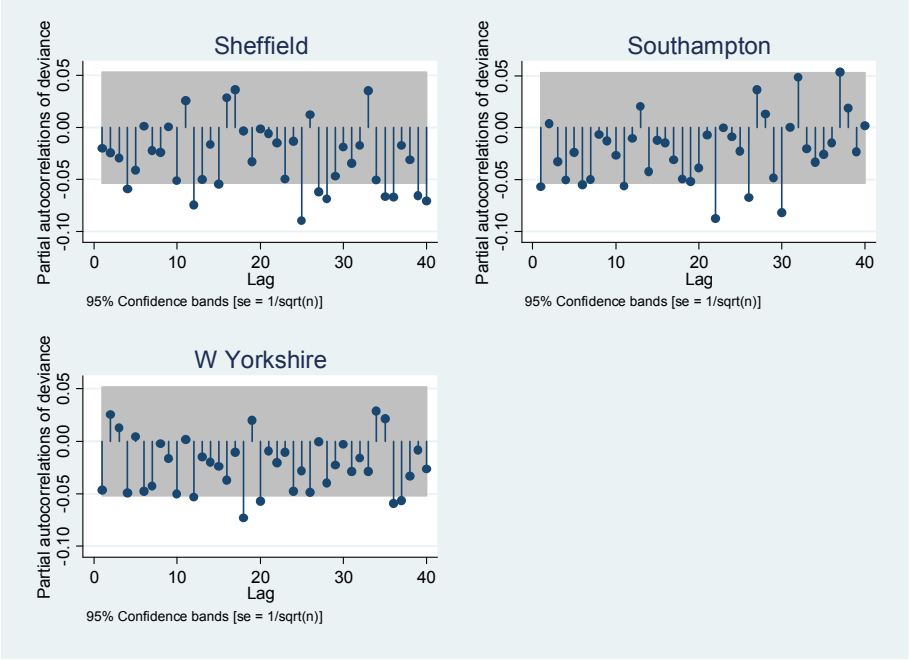
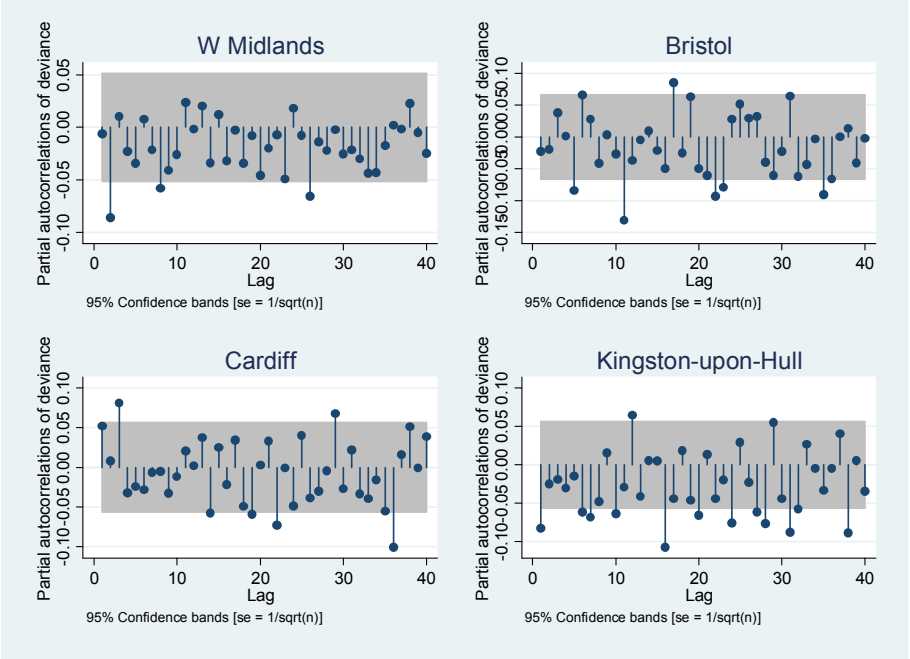
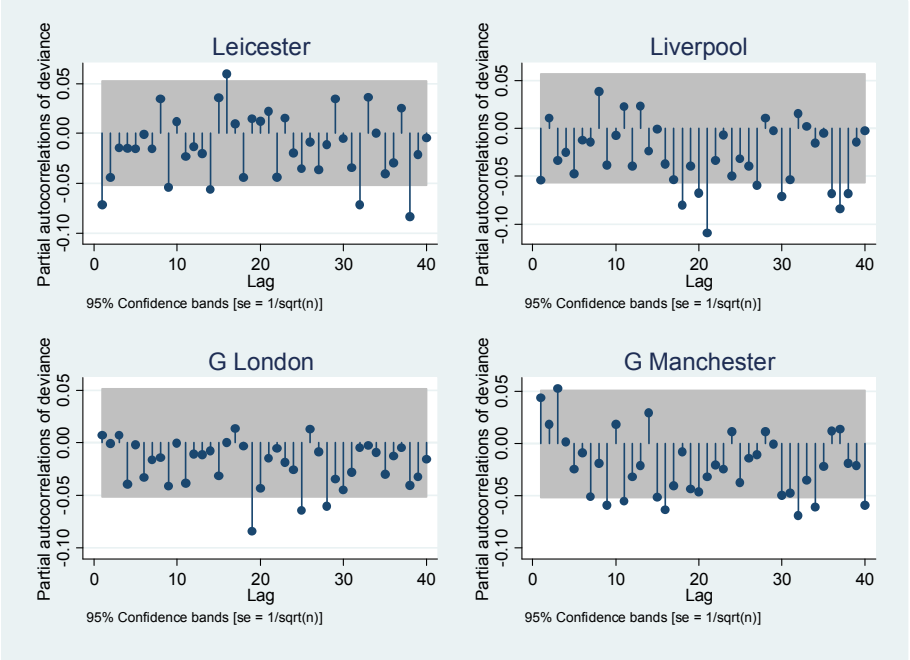


Figure 11.17: Partial autocorrelations of deviance residuals for the SO2 model

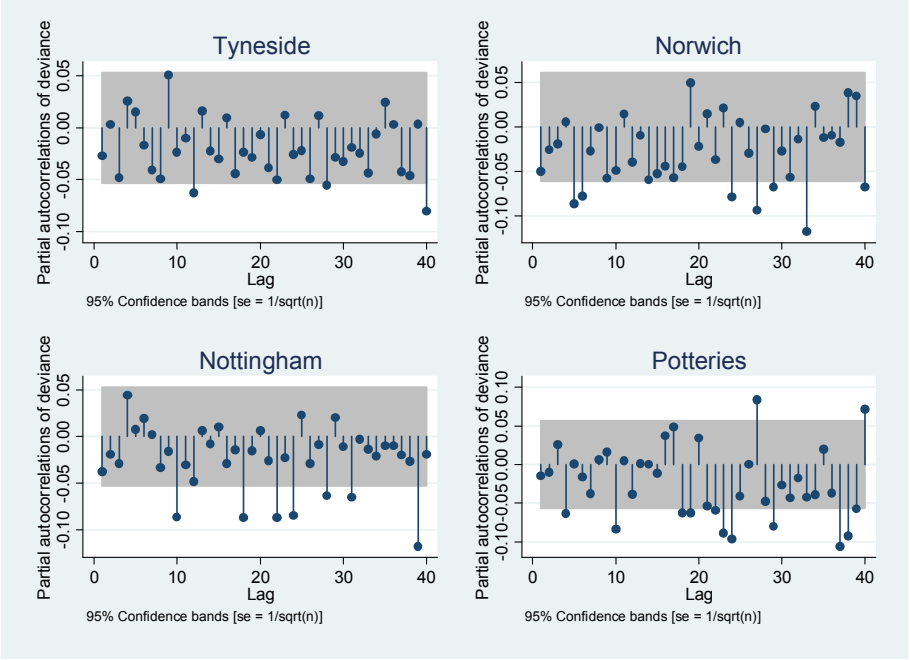
a) West Midlands, Bristol, Cardiff, Kingston-upon-Hull



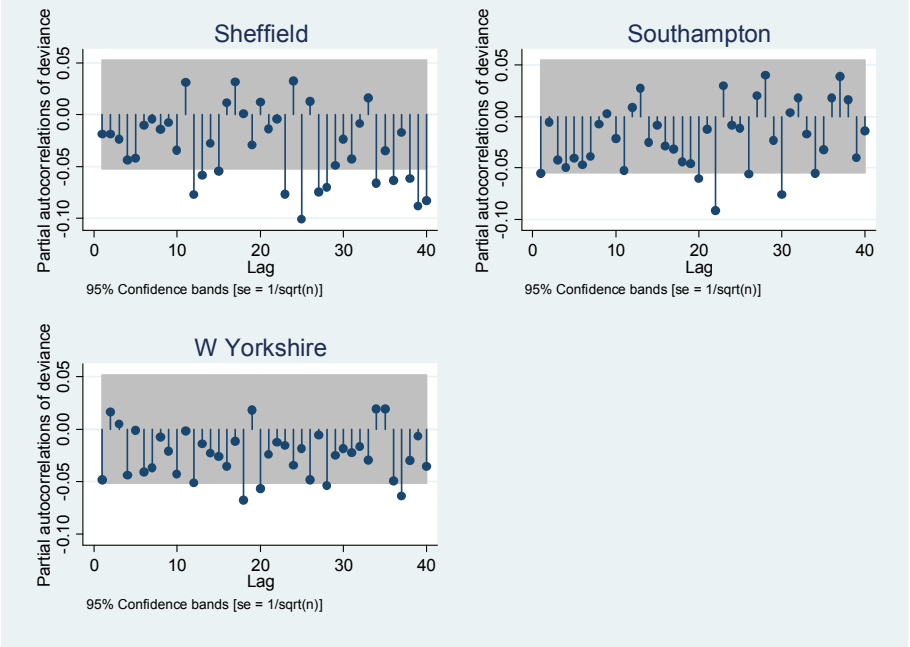
b) Leicester, Liverpool, Greater London, Greater Manchester



c) Tyneside, Norwich, Nottingham, Potteries



d) Sheffield, Southampton, West Yorkshire



11.4 Effects of hourly air pollution levels – additional output

Table 11.8: Effect on the estimated temperature effect of introducing extra seasonal control in a case-crossover model design

Stratum length	OR and 95% CI per 1°C drop in temperature over lag days 0-28	
	Without extra seasonal control	With extra seasonal control*
28	1.005 [0.997, 1.013]	1.022 [1.011, 1.034]
29	1.014 [1.006, 1.022]	1.021 [1.009, 1.032]
30	1.009 [1.002, 1.017]	1.017 [1.005, 1.028]
31	1.010 [1.003, 1.017]	1.019 [1.008, 1.030]
32	1.009 [1.002, 1.016]	1.021 [1.010, 1.032]

Note: stratum length refers to the length (in days) of calendar time strata used to define case and control days for each individual
**Seasonal control included as one sin/cos Fourier pair with annual period*

Table 11.9: Effects of pollutants on MI risk in 2-pollutant models

Pollutant and lag (hrs)		OR and 95% CI per 10μg/m^3 increase (except CO: per 0.1mg/m^3 increase)				
		2 pollutant model adjusted for…				
		PM_{10}	*Ozone*	*CO*	*NO_2*	*SO_2*
PM_{10}	*Lag 1-6*	-	1.013 [1.005, 1.022]	1.015 [1.005, 1.025]	1.009 [0.999, 1.019]	1.014 [1.005, 1.023]
	7-12	-	0.993 [0.982, 1.003]	0.990 [0.979, 1.002]	0.996 [0.984, 1.007]	0.992 [0.982, 1.003]
	13-18	-	0.995 [0.984, 1.005]	0.997 [0.985, 1.008]	0.997 [0.986, 1.008]	0.997 [0.987, 1.008]
	19-24	-	0.997 [0.988, 1.006]	0.999 [0.989, 1.008]	0.997 [0.987, 1.007]	0.997 [0.988, 1.006]
	25-72	-	0.991 [0.981, 1.001]	0.999 [0.987, 1.012]	0.994 [0.981, 1.006]	0.988 [0.977, 1.000]
	Σ(1-72)	-	*0.989 [0.979, 0.999]*	*1.000 [0.987, 1.012]*	*0.992 [0.979, 1.006]*	*0.988 [0.977, 1.000]*
Ozone	*Lag 1-6*	1.000 [0.994, 1.006]	-	1.000 [0.993, 1.006]	1.008 [1.000, 1.016]	0.998 [0.992, 1.004]
	7-12	1.003 [0.995, 1.011]	-	1.006 [0.998, 1.014]	0.998 [0.988, 1.008]	1.005 [0.998, 1.013]
	13-18	0.993 [0.985, 1.000]	-	0.992 [0.984, 1.000]	0.988 [0.978, 0.998]	0.993 [0.986, 1.001]
	19-24	0.999 [0.993, 1.006]	-	0.999 [0.992, 1.005]	1.000 [0.992, 1.008]	0.999 [0.993, 1.006]
	25-72	0.997 [0.990, 1.004]	-	0.994 [0.986, 1.001]	0.993 [0.985, 1.002]	0.997 [0.990, 1.004]
	Σ(1-72)	0.992 [0.984, 1.000]	-	0.989 [0.981, 0.998]	0.987 [0.978, 0.997]	0.993 [0.985, 1.001]
CO	*Lag 1-6*	0.999 [0.993, 1.005]	1.003 [0.997, 1.009]	-	0.996 [0.989, 1.002]	1.002 [0.997, 1.008]
	7-12	1.003 [0.996, 1.009]	1.002 [0.996, 1.008]	-	1.007 [0.999, 1.015]	1.000 [0.994, 1.006]
	13-18	0.998 [0.992, 1.005]	0.995 [0.988, 1.001]	-	0.998 [0.990, 1.005]	0.998 [0.992, 1.004]
	19-24	0.999 [0.993, 1.005]	0.997 [0.991, 1.003]	-	0.998 [0.991, 1.005]	0.998 [0.993, 1.004]
	25-72	0.994 [0.986, 1.002]	0.992 [0.985, 0.999]	-	0.993 [0.984, 1.002]	0.992 [0.986, 0.999]
	Σ(1-72)	0.992 [0.984, 1.001]	0.988 [0.981, 0.996]	-	0.991 [0.981, 1.001]	0.991 [0.983, 0.998]
NO_2	*Lag 1-6*	1.009 [1.001, 1.017]	1.019 [1.009, 1.028]	1.016 [1.007, 1.026]	-	1.013 [1.005, 1.020]
	7-12	0.992 [0.983, 1.001]	0.991 [0.980, 1.003]	0.985 [0.974, 0.996]	-	0.991 [0.982, 0.999]
	13-18	0.999 [0.990, 1.009]	0.987 [0.975, 0.998]	0.999 [0.989, 1.010]	-	0.999 [0.990, 1.008]
	19-24	1.001 [0.993, 1.010]	1.000 [0.990, 1.010]	1.001 [0.992, 1.011]	-	0.999 [0.991, 1.007]
	25-72	0.998 [0.988, 1.008]	0.992 [0.983, 1.002]	1.003 [0.992, 1.015]	-	0.994 [0.984, 1.003]
	Σ(1-72)	1.000 [0.989, 1.011]	0.989 [0.979, 0.999]	1.005 [0.993, 1.017]	-	0.995 [0.985, 1.004]
SO_2	*Lag 1-6*	0.993 [0.970, 1.016]	0.999 [0.977, 1.021]	1.003 [0.980, 1.026]	0.991 [0.968, 1.014]	-
	7-12	1.006 [0.980, 1.033]	1.002 [0.977, 1.028]	0.997 [0.971, 1.024]	1.008 [0.982, 1.035]	-
	13-18	0.986 [0.961, 1.011]	0.976 [0.952, 1.000]	0.988 [0.963, 1.013]	0.982 [0.957, 1.008]	-
	19-24	1.016 [0.993, 1.039]	1.013 [0.991, 1.036]	1.013 [0.990, 1.036]	1.017 [0.994, 1.041]	-
	25-72	1.014 [0.980, 1.050]	0.992 [0.962, 1.023]	1.010 [0.978, 1.043]	1.008 [0.973, 1.043]	-
	Σ(1-72)	1.014 [0.976, 1.054]	0.982 [0.949, 1.016]	1.010 [0.975, 1.047]	1.006 [0.968, 1.046]	-

12 Appendix II – Publications arising from this thesis

EDITOR'S CHOICE

Effects of ambient temperature on the incidence of myocardial infarction

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See Featured editorial, p 1721

► An additional table and references are published online only at http://heart.bmj.com/content/vol95/issue21

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ABSTRACT

Context: While the effects of weather and, in particular, ambient temperature on overall mortality are well documented, the strength of the evidence base for the effects on acute myocardial infarction (MI) are less clear.

Objective: To systematically review studies specifically focusing on the effects of temperature on MI.

Data sources: Medline, Embase, and GeoBase publication databases, as well as reference lists, and the websites of a number of relevant public organisations.

Study selection: Studies of original data in which ambient temperature was an exposure of interest and MI a specific outcome were selected.

Data extraction: The reported effects of ambient temperature on the risk of MI, including effect sizes and confidence intervals, where possible, were recorded. Methodological details were also extracted, including study population, location and setting, ascertainment of MI events, adjustment for potential confounders and consideration of lagged effects.

Results: 19 studies were identified, of which 14 considered the short-term effects of temperature on a daily timescale, the remainder looking at longer-term effects. Overall, 8 of the 12 studies which included relevant data from the winter season reported a statistically significant short-term increased risk of MI at lower temperatures, while increases in risk at higher temperatures were reported in 7 of the 13 studies with relevant data. A number of differences were identified between studies in the population included demographics, location, local climate, study design and statistical methodology.

Conclusion: A number of studies, including some that were large and relatively well controlled, suggested that both hot and cold weather had detrimental effects on the short-term risk of MI. However, further research with consistent methodology is needed to clarify the magnitude of these effects and to show which populations and individuals are vulnerable.

In the light of global climate change, there is increasing interest in the effects of meteorological factors on health outcomes. A number of studies have found that ambient outdoor temperatures have a short-term effect on overall mortality, with many describing a U- or V-shaped relationship; for example, a large study in 11 US cities described a decreasing mortality risk as the temperature increased from the coldest days to a certain threshold temperature, above which mortality risk increased with temperature.[1] A similar pattern has been seen in Europe,[2–5] and in a number of lower- and middle-income countries.[6] Periods of extreme cold or heat have also been associated with mortality peaks.[7]

Evidence suggests that cardiovascular effects of differences in ambient temperature may contribute to the increased mortality risk. Ambient outdoor temperature has been linked to mortality specifically from cardiovascular diseases (CVDs); similar U-shaped relationships have been described,[8] and studies have shown increases in CVD mortality associated both with cold[9 10] and hot[11] outdoor temperatures.

The effects of temperature on morbidity and mortality from myocardial infarction (MI) specifically have not been investigated as commonly as the effects on broader outcomes. We aimed to review the evidence for an effect of temperature on the risk of MI, hypothesising that MI risk would increase at both the upper and lower extremes of temperature. The motivation for a focused review on MI outcomes was twofold: first, mortality, though investigated frequently as an outcome, is likely to reflect only a small proportion of the total health impact of environmental exposure since many events do not directly result in death. Second, since MI is a specific outcome with a specific pathophysiology, a clearer description of the effects of temperature on MI may lead to a better understanding of the potential triggering mechanisms at work among those at high risk of an ischaemic event.

METHODS

Databases and sources

We searched two large databases covering health and medical literature: Medline (1950 to the present) and Embase. Since meteorological exposures were being considered, we also included the specialist database GeoBase to capture any relevant studies that might have been published in the geographical/meteorological rather than the medical literature. Reference lists of all relevant studies were scanned to identify any further studies, and if these showed that search terms had been missed, extra terms were added to the main database searches. The searches were performed by a statistician/epidemiologist (KB), initially in July 2008, with the main database searches updated in May 2009.

In order to capture important "grey literature" we searched the websites of the following organisations for relevant reports: World Health Organization; European Union; Health Effects Institute (USA); Environmental Protection Agency (USA); National Institutes of Health (USA); Department of Health (UK); and Department for Environment, Food, and Rural Affairs (UK). As well as searching for original research, we examined the reference lists of any

relevant reviews appearing in their reports. Conference abstracts and unpublished studies were not included in this review.

Search keywords and terms

Medline (accessed via OvidSP) is indexed according to MeSH terms. Our primary search used the following MeSH keywords: (''weather'' or ''climate'') and ''myocardial infarction'' and ''humans''. All subterms were also included, and we limited the search to studies of adult humans, published in English. We performed equivalent searches in Embase (using equivalent headings in the Embase indexing system) and GeoBase (using keywords).

To identify studies in which a temperature effect on MI was reported as a specific secondary outcome within a broader study, we performed a secondary Medline search, as above but using the broader MeSH term ''cardiovascular diseases'' in place of ''myocardial infarction''; we then limited the results to reports where ''myocardial infarction'' or an equivalent term was present in the title, abstract, or keywords (equivalent terms were defined as ''myocardial infarct*'', ''coronary event'', ''heart attack'', ''Q wave infarct*'', ''non-Q wave infarct*'', ''STEMI'', ''coronary infarct*'', ''heart infarct*'', ''myocardial thrombosis'', or ''coronary thrombosis'', where ''*'' indicates any word ending).

Inclusion and exclusion criteria

In order to examine the hypothesis that temperature is associated with MI risk, studies of any relevant design were included provided that they presented original data, and included at least one analysis where ambient temperature (or a composite measure incorporating this) was an exposure of interest, and MI was the specific outcome; we did not include studies looking only at broader CVD outcomes and not considering MI specifically. Studies were excluded if the authors did not control for (or stratify by) any potential confounding factors, or did not report measures of precision or p values for the analysis of interest.

Procedure

Titles and abstracts were screened for relevance, and full-text versions obtained where appropriate for assessment with reference to the inclusion and exclusion criteria; we were able to obtain full-text papers in all cases where required and it was not necessary to contact specific authors. For each study included, the following information was recorded based on prior beliefs about key aspects of study methodology and in order to summarise study quality: study population, event of interest, number included, age range included, location and setting, time period, exposure variables, ascertainment of MI, spatial resolution, temporal resolution, adjustment for air pollution and other potential confounders, lags considered. In addition, main results were recorded, in particular the effects of temperature on risk of MI, including effect sizes and confidence intervals where possible. Where authors reported several relevant results (eg, for different lag days or for different subgroups), it was necessary to decide which result(s) to record; where a main or final model could be identified, this was chosen, otherwise we recorded results from the analysis on which the authors focused or that which best represented the overall conclusions of the study. Though this was a somewhat subjective process, in all cases, we also noted any important differences in the effect estimates between different analyses. For context, the temperature range for the location studied was recorded where given. Finally, effects of other meteorological variables were also noted.

To explore the role of local climate, we considered the 10-year average of the mean annual temperature and temperature range, using data from the Goddard Institute for Space Studies (GISS) surface temperature data.[12] We obtained monthly mean temperatures over the period 1991–2000 from the nearest available monitoring station to each study location. The 10-year mean was calculated as the mean of the monthly temperatures, and we also calculated the 10-year mean of the minimum and maximum monthly temperatures to give an average annual temperature range. Multinational studies were excluded from this exploratory analysis.

RESULTS

After running the search strategy and screening abstracts for relevance, a total of 57 full text articles were obtained for further inspection, and 42 met the primary inclusion criteria. We then excluded 22 studies, four of which reported no direct effect estimates, and 18 that did not control for any potential confounding factors or did not report measures of precision or p values for the results of interest (online supplementary table A1); one further research paper was excluded because the same data were reported in a later paper, leaving a total of 19 in the review (fig 1). The majority looked at short-term effects of daily temperature levels (n = 14).[13–26] A further two studies investigated temperature effects over the longer term (ie, on a monthly or yearly timescale),[27 28] while three looked at more complex weather parameters designed to capture the effects of overall weather patterns not restricted to ambient temperature.[29–31]

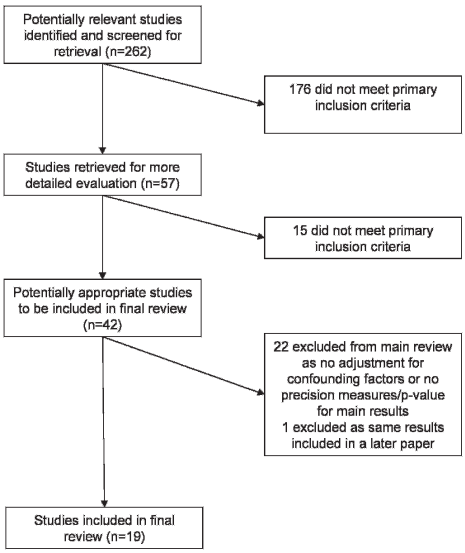

Figure 1 Flow diagram of search strategy.

Short-term effects of temperature

Thirteen studies used daily time-series data to investigate the short-term effect of temperature on MI risk (tables 1–3). Only one study used a different design: Hirasawa *et al*[15] looked at the effectiveness of 10 meteorological parameters in discriminating between days with and without MI events in Hokkaido, Japan; however this small study identified no useful discriminating factors. The 13 daily time-series studies are now considered in more detail.

Methodological considerations

Variations in methodological aspects of the 13 daily time-series studies occurred in three main areas: ascertainment and validation of MI outcome events; adjustment for potential confounding factors; and flexibility of the fitted temperature effect in terms of allowance for non-linear and delayed (or "lagged") effects.

MI data came from a variety of sources, the primary sources being hospital, clinic or medical care databases (n = 6), morbidity registries (n = 3), ambulance data (n = 1) and death certificate/mortality data (n = 3). Most studies, including all of those concentrating purely on mortality data, generally took the cause of death as coded in the source data. However, five studies, with access to symptom, ECG, and biomarker records, validated potential MI events using specific diagnostic criteria (table 1).

Adjustment for regular seasonal patterns within years, and for long-term trends over a number of years, was performed to varying degrees in a number of studies and may, where performed, lead to more reliable estimates of short-term temperature effects. Without such adjustment, estimated temperature effects are likely to include these seasonal and long-term changes in temperature and outcome, and any other factors which vary on these timescales could confound associations. A few studies included more specific potential confounders. Potential confounders for the relationship between temperature and MI, since they must by definition be associated with temperature, are usually other time-varying external factors, such as other meteorological parameters, pollution levels such as ambient particulate matter and ozone, and levels of infectious diseases such as influenza. Of note, only three studies[21 25 26] made any adjustment for daily pollution levels, which are likely to be associated with daily temperature, and which a number of studies have suggested may affect short-term risk of MI.

Finally, there was variation in the way temperature relationships were investigated. Six of the 13 studies appeared to investigate temperature only as a linear effect, meaning that U-shaped relationships similar to those reported in some mortality studies could not have been detected. In addition, only 7/13 studies investigated the possibility of the effects of temperature on MI being delayed ("lagged") by one or more days: this is a potentially important consideration if the effects of temperature on MI incidence extend beyond same-day effects; for example, an extremely cold day may lead to an increase in the incidence of MI over the next several days. Even among studies that considered this, the potential lagged effects investigated varied widely, ranging from 1 to 30 days.

Effects of lower temperatures

Overall, eight of the 12 studies which included data from the winter season reported a statistically significant increased risk of MI at colder temperatures, either overall or for some subgroup (tables 2–3), including three of the five studies in which MI outcomes were validated against specified diagnostic criteria, as well as the only multinational study included,[18] which estimated negative associations between temperature and MI risk for the majority of the 24 populations in Europe, China, the USA and Australia that were included (combined RR = 1.008 (95% CI 1.004 to 1.012) per 1°C drop in the temperature averaged over the current and previous 3 days). Estimated effect sizes varied between studies, however; for example, one study based in Sao Paulo, Brazil[25] estimated a relative risk for MI mortality of 1.31 (1.19 to 1.44) for temperature in the lowest decile (11–15°C) compared with the nadir mortality at 22–23°C; this was consistent with two other studies which reported large effects on fatal MI outcomes.[16 24]

Effects of higher temperatures

Statistically significant increases in MI risk with higher temperatures were reported in seven out of the 13 studies (tables 2 and 3), including all three with MI mortality outcomes, though of note, only one of the five studies in which the MI outcomes were validated against diagnostic criteria found a heat effect. Four studies reported separate effects of both heat and cold, including the earlier-mentioned Brazilian study by Sharovsky *et al*[25] (RR = 1.11 (95% CI 1.06 to 1.16) for 2-day average temperature 24–27°C compared with 22–23°C). As with cold effects, there were differences in the way in which effects were reported, and in their sizes. Of interest, a study in northern Sweden[22] found no effect of absolute temperature, but reported an increase in the risk of non-fatal MI when the temperature was higher than the previous day (RR = 1.015 (1.003 to 1.027) per 1°C increase). Morabito *et al*[19] found a 3% increase in MI risk associated with an extra 2 hours of "heat discomfort" in Florence, Italy (heat discomfort hours were defined as those above the 90th centile on an apparent temperature index incorporating temperature, humidity and wind velocity). It should be noted that the largest study to find no effect of heat[18] was one of those investigating temperature only as a linear effect; since the authors found a cold effect, by design they could not have also reported a separate effect of heat on the same lag days.

Role of local climate

Barnett *et al*[18] considered heterogeneity in the temperature effect across the 24 populations (from 21 countries) included in their study. There was some variation in the estimated size of the risk increase associated with a drop in temperature (ranging from a 0 to 1.8% increase in risk per 1°C). Interestingly, 28% of this variation was explained by local mean temperature (rising to 54% when two outliers were excluded); in general, locations with higher mean temperatures were more vulnerable to cold days.

We explored this further in the remaining single-location studies by considering the 10-year mean temperature and the average annual range of temperatures (table 2). Studies in the six "warmest" regions all reported a detrimental effect of cold[15 16 19 20 24 25]; of note, these warmer regions also tended to have smaller average annual temperature ranges (<20°C in five of six cases). In contrast, considering studies in the six "coolest" regions, which tended to experience a greater range of temperatures across the year (average range >20°C in four of six cases), only one of five investigating cold effects reported a significant effect of cold[14 17 22 23 26] (with one further study[21] using data from the summer months only).

Table 1 Daily time-series studies with temperature exposures and myocardial infarction (MI) outcomes: description of studies

First author and year of publication	Population/data source	Location and time period	Number of MI events included (mean MIs/day)	Main temperature exposure variable(s)	Potential confounders included	MI ascertainment	Lags considered (days)
Studies of fatal and non-fatal events							
Gerber 2006[14]	County medical care registers	Olmsted County, USA 1979–2002	2676 (0.3)	Maximum temperature	Annual population, calendar year, season, rain, snowfall	Diagnoses compatible with MI extracted and validated using cardiac pain, biomarker, and ECG criteria	None
Wang 2006[15]	Ambulance service centre data	Hiroshima, Japan 1993–2002	3755 (1.0)	Mean temperature, humidity-adjusted temperature	Atmospheric pressure	Diagnosis based on anamnestic, clinical, laboratory and ECG criteria	None
Enquselassie 1993[16]	MONICA morbidity registry (covering ages <70 years)	Hunter region, New South Wales, Australia 1985–90	3889 (1.9)	Maximum temperature	Calendar month, rainfall	Non-fatal definite MI and fatal MI/sudden coronary death, based on MONICA ECG, symptom and enzyme criteria[42]	None
Ohlson 1991[17]	Single clinic diagnosis register (ages <70)	Orebro, Sweden 1985–7 (cold seasons only)	357 (0.6)	Windchill-adjusted temperature (as measured at 7 pm)	Day of week, snowfall, atmospheric pressure	Records with ICD8 code 410.10, 410.99, or ICD9 code 410A/B/W/X	None
Barnett 2005[18]	24 MONICA morbidity registries (covering ages 35–64 years)	Europe, China, USA, Australia 1980–95	87 410 (0.4–2.8 by location)	Mean temperature	Season and trend, day of week, humidity	Non-fatal definite MI and fatal definite/possible MI/unclassifiable event based on MONICA ECG, symptom and enzyme criteria[42]	0–14 inclusive
Morabito 2005[19]	Hospitalisations database (Florentine area)	Florence, Italy 1998–2002	2683 (1.5)	Hours of severe discomfort (based on extremes of apparent and windchill temperature indices)	Stratified by season	Records with ICD9 = 410–410.92	0–3 inclusive
Ebi 2004[20]	Hospitalisations data (covering all non-federal hospitals)	Three counties in California, USA 1993–8	283 031 (4.5–39.4 by location)	Minimum and maximum temperature	Season and trend	Records with ICD9 code 410	0, 7, 14, 30
Koken 2003[21]	Hospital admissions data (11 hospitals, covering ages 65+ years)	Denver county, USA 1993–7 (July and August only)	Not reported	Maximum temperature, dew point temperature	Season and trend, day of week, air pollution variables	Primary discharge diagnosis (ICD9 = 410.XX)	0–4 inclusive
Messner 2002[22]	Hospital and GP records, and death certificates data (ages 25–64)	Northern Sweden 1985–92	3322 (approx 0.9†)	Temperature, change in temperature from previous day	Season, humidity, air pressure, change in humidity and air pressure from previous day	Suspected cases validated using symptom, ECG, and enzyme marker data	None
Danet 1999[23]	Lille-WHO MONICA morbidity registry (covering ages 25–64 years)	Nord district, France 1985–94	3314 (approx 0.9†)	Mean temperature	Annual population, mean atmospheric pressure, calendar year	Non-fatal definite MIs and fatal definite/possible MIs, based on MONICA ECG, symptom and enzyme criteria[42]	None
Fatal events only							
Dilaveris 2006[24]	Death certificate data	Athens territory, Greece 2001	3126 (8.6)	Daily mean/minimum/maximum temperature	Atmospheric pressure, relative humidity, season (based on calendar date)	Death certificates with ICD10 codes of I20.0–4, I21.9, I22.0, I22.1, I22.8, I22.9	Mean of 0, 7

Continued

Table 1 Continued

First author and year of publication	Population/data source	Location and time period	Number of MI events included (mean MIs/day)	Main temperature exposure variable(s)	Potential confounders included	MI ascertainment	Lags considered (days)
Sharovsky 2004[25]	Death registry data	Sao Paulo, Brazil 1996–8	12 007 (16.4)	Mean temperature	Season and trend, relative humidity, atmospheric pressure, day of week, holidays, influenza levels, air pollution variables	Death certificates with MI (ICD10 = I21) listed as primary cause	0, and moving average of up to previous 7 days
Rossi 1999[26]	Vital statistics department mortality data	Milan, Italy 1985–9	Approx 1600* (0.9)	Mean temperature	Season and trend, relative humidity, day of week, holidays, respiratory infection epidemics, pollution variables	Deaths with ICD9 codes of 410	Different lags considered, exact strategy unclear

*Derived from reported mean daily rate, and length of period under study; †derived from reported total number of events, and reported length of study.

No such pattern could be detected for heat effects; indeed, the studies based in the regions with the coolest and warmest mean temperatures (northern Sweden and Sao Paulo, Brazil, respectively) both reported detrimental effects of heat.

Vulnerability among subgroups

A few studies investigated vulnerability to temperature effects according to individual-level characteristics. Among those considering the effects of temperature separately for different age groups, there were inconsistent results; two studies, both of which had found significant detrimental effects of cold, reported that analyses restricted to the oldest age group gave similar effect size estimates to those including all patients,[16 23] though it should be noted that in the former study the oldest age group accounted for over half of the events, while in the latter the age structure of the study population was not reported. Morabito *et al*,[19] on the other hand, reported that correlations between "cold discomfort hours" and MI rates in winter were larger among those aged >65 years, while correlations between "heat discomfort hours" and MI rates in summer were larger among those aged <65 years. Age appeared to affect the magnitude of temperature effects in one study in California though the direction of the association was not consistent across the three regions studied.[20] In the same study, analyses were also presented stratified by sex: the estimated increase in risk of MI for a 3°C decrease in maximum temperature was greater among women in the Sacramento region (15.7% (4.9% to 27.6%) compared with 10.9% (5.1% to 16.9%) for men, among those aged 55–69 years), whereas the increase in MI risk following an equivalent temperature drop in San Francisco was larger among men (6.6% compared with 2.2% in women). Barnett *et al*[18] reported that the increase in event rates in cold periods was greater among women than men (OR = 1.07 (1.03 to 1.11)), averaging over all 24 included populations. The same study found no difference between those with and without previous MI. Similarly, Enquselassie *et al*[16] reported that the effects of heat and cold among subjects with a prior history of ischaemic heart disease were similar to the effects among all study participants.

Long-term effects of temperature

Two studies considered the effect of temperature on MI risk over timescales of >1 month. Results from a monthly time-series study among 369 women aged 20–44 years, hospitalised for MI in 24 centres covering four continents, appeared to show an detrimental effect of cold on a monthly timescale (RR = 1.14 (1.03 to 1.25) per 5°C temperature decrease).[27] A long-term effect of cold was also reported by Gyllerup, who compared MI mortality across 284 municipalities in Sweden, each of which was assigned a cold index based on the number of times the windchill-adjusted temperature in the municipality fell below −10°C in a 10-year period.[28] Municipalities in the three coldest deciles (based on this cold index) were reported to have standardised mortality ratios (SMRs) of >1 (SMR = 1.4 in the coldest decile), while those in the seven least cold deciles all had SMRs <1 (SMR = 0.9 for those in the least cold decile), with the effect persisting after adjustment for socioeconomic factors.

Effects of composite weather parameters

Three studies considered the effects of composite weather parameters: air mass type,[29] arctic oscillation index[30] and weather fronts[31] were all associated with short-term risk of MI. Results of such analyses can be difficult to interpret and compare; indeed two of these studies present two contrasting effects: Morabito *et al*, using hospitalisation data from Italy, found that an anticyclonic continental air mass, representing cold and clear weather, significantly increased the risk of MI compared with a mixed air mass representing mild, humid, cloudy weather (RR = 1.23, p<0.05, 1-day lagged effect), while Messner *et al*, in a study based in northern Sweden, found that MI risk increased with increasing arctic oscillation index, which corresponds to higher levels of temperature, humidity, and cloudiness (RR = 1.038 (1.015 to 1.062) per unit increase in arctic oscillation index, lagged by 3 days), though this apparent contradiction could simply represent the broadly U-shaped relationship between weather and MI that has been reported by other studies investigating temperature effects directly.

DISCUSSION

To our knowledge, this study is the first systematic review to specifically focus on the effects of ambient temperature on MI. Our search strategy is likely to have identified the majority of major studies focusing on this question, and we have also taken steps to include studies in which our specific outcome of interest was investigated as a subanalysis within a broader study.

Table 2 Daily time-series studies with temperature exposures and myocardial infarction (MI) outcomes: summary/interpretation

First author and year	MIs (n)	Long-term local mean temperature and annual range* (°C)	Detrimental effect of cold?	Detrimental effect of heat?	Adjusted for season and trend?	MI events: validation or specified criteria	Adjusted for humidity	Adjusted for atmospheric pressure	Adjusted for infectious disease levels	Adjusted for air pollution	Adjusted for day of week?	Allowance for non-linear temperature effects?	Investigated lag effects?
Studies of fatal and non-fatal events													
Gerber 2006[14]	2676	7 (−10.8 to 21.2)	No	No	✓	✓	✗	✗	✗	✗	✗	✓	✗
Wang 2006[15]	3755	16.7 (5.6 to 28.3)	*Yes*	No	✗	✓	✗	✓	✗	✗	✗	✓	✗
Enquselassie 1993[16]	3889	17.9 (11.9 to 23.7)	*Yes* (fatal MIs only)	No	✗†	✓	✗	✗	✗	✗	✗	✓	✗
Ohlson 1991[17]	357	6.3 (−3.9 to 17.3)	No	N/A	✗	✗	✗	✓	✗	✗	✓	✓	✗
Barnett 2005[18]	87 410	–	*Yes*	No	✓	✗	✓	✗	✗	✗	✓	✗	✓
Morabito 2005[19]	2683	14.1 (5.8 to 23.5)	*Yes*	*Yes* (for increased hours of discomfort)	✓	✗	✗	✗	✗	✗	✗	✗	✓
Ebi 2004[20]	283 031	14.7 (10.1 to 18.6) to 19.3 (14.8 to 24.4)	*Certain regions only* (1/3 regions for night temperature; 2/3 regions for day temperature)	*Certain regions only* (2/3 regions for night temperature;0/3 regions for day temperature)	✓	✗	✗	✗	✗	✗	✗	✗	✓
Koken 2003[21]	Not reported	9.7 (−1.4 to 21.9)	N/A	*Yes*	✓	✗	✗	✗	✗	✓	✓	✗	✓
Messner 2002[22]	3322	−1.4 (−15.6 to 13.5) to 4.6 (−5.5 to 16.5)	No	*Yes* (change from previous day, non-fatal MIs only)	✗‡	✓	✓	✓	✗	✗	✗	✗	✗
Danet 1999[23]	3314	10.6 (2.0 to 19.1)	*Yes*	No	✗§	✓	✗	✓	✗	✗	✗	✗	✗
Fatal events only													
Dilaveris 2006[24]	3126	18.0 (8.6 to 28.4)	*Yes*	*Yes*	✗†	✗	✓	✓	✗	✗	✗	✓	✓
Sharovsky 2004[25]	12 007	18.0 (13.9 to 21.8)	*Yes*	*Yes*	✓	✗	✓	✓	✓	✓	✓	✓	✓
Rossi 1999[26]	Approx 1600	12.8 (3.8 to 22.9)	Not mentioned	*Yes*	✓	✗	✓	✗	✓	✓	✓	✓	✓

*10-Year average of the monthly mean temperatures, and of the minimum and maximum monthly mean temperature in the study area, as recorded at the nearest available monitoring station included in the Goddard Institute for Space Studies (GISS) surface temperature data,[12] using data from the years 1991–2000 inclusive; †authors adjusted for calendar month, which should have approximately captured any seasonal effect; ‡authors performed a basic adjustment for season in a sensitivity analysis, which did not change the conclusions; §authors adjusted for annual population and calendar year, which should have approximately captured any long-term trend.

Table 3 Daily time-series studies with temperature exposures and myocardial infarction (MI) outcomes: study results

First author and year	Temperature variable*, range (if reported) (°C)	Relative risk (RR) or rate ratio for temperature (95% CI if reported)	(Change in temperature variable to which RR refers)	Subgroup to which RR refers (if applicable)	Lag for temp effect (days)	Comment
Studies of fatal and non-fatal events						
Gerber 2006[14]	tmax −29 to 39	0.93 (0.73 to 1.14)	>30°C		0	–
		1.00 (reference)	18–30°C			
		0.97 (0.89 to 1.06)	0–17°C			
		1.03 (0.92 to 1.14)	<0°C			
Wang 2006[15]	tmean −0.9 to 32.7	1.00 (reference)	>20°C		0	–
		1.12 (0.99 to 1.27)	10–20°C			
		1.17 (1.01 to 1.35)	<10°C			
Enquselassie 1993[16]	tmax <16 to >30	1.2 (0.9 to 1.5)*	>30°C	Fatal MIs	0	–
		1.0 (reference)	23–27°C	Fatal MIs		
		1.4 (1.1 to 1.8)*	⩽16°C	Fatal MIs		
		1.2 (0.9 to 1.4)*	>30°C	Non-fatal MIs		
		1.0 (reference)	23–27°C	Non-fatal MIs		
		1.0 (0.8 to1.3)*	⩽16°C	Non-fatal MIs		
Ohlson 1991[17]	twind <−20 to >0	1.00 (reference)	⩾0°C		0	–
		1.09 (0.82 to 1.44)	−10 to −1°C			
		1.10 (0.79 to 1.52)	−20 to −11°C			
		1.12 (0.67 to 1.85)	<−20°C			
Barnett 2005[18]	tmean 1.5 to 23.0	1.008 (1.004 to 1.012)	Per 1°C decrease		Average 0–3	Only a linear temperature effect appears to have been considered
Morabito 2005[19]	tmean, discomfort hours	1.03 (p<0.01)	Per extra two heat discomfort hours	Summer, men, <65 years	0	Only linear effects of the exposure variables appear to have been considered. However, discomfort hours analysis was performed separately for winter and summer
		1.06 (p<0.01)	Per extra two cold discomfort hours	Winter, women, <65 years		
Ebi 2004[20]	tmin, tmax −1 to 37 (tmin)	1.072 (1.057 to 1.086)	Per 3°C decrease (tmin)	Men, 55–69 years, LA	7	Only linear temperature effects appears to have been considered. Effects for age ⩾70 years and for women were all in the same direction as those shown here
		1.008 (1.004 to 1.012)	Per 3°C increase (tmin)	Men, 55–69 years, SF		
		1.223 (1.083 to 1.381)	Per 3°C increase (tmin)	Men, 55–69 years, Sa		
		1.025 (1.000 to 1.052)	Per 3°C increase (tmax)	Men, 55–69 years, LA		
		1.066 (1.023 to 1.111)	Per 3°C decrease (tmax)	Men, 55–69 years, SF		
		1.109 (1.051 to 1.169)	Per 3°C decrease (tmax)	Men, 55–69 years, Sa		
Koken 2003[21]	tmax 16.7 to 30.8	1.175 (1.029 to 1.343)	Per 5.9°C increase	⩾65 years	0	Analysis was for July/August only
Messner 2002[22]	temp, tchange −38 to 30 (temp)	1.001 (0.993 to 1.008)	Per 1°C decrease (temp)	Fatal MIs	0	Only linear temperature effects appears to have been considered
		1.000 (0.997 to 1.003)	Per 1°C increase (temp)	Non-fatal MIs		
		1.003 (0.979 to 1.028)	Per 1°C increase (tchange)	Fatal MIs		
		1.015 (1.003 to 1.027)	Per 1°C increase (tchange)	Non-fatal MIs		
Danet 1999[23]	tmean −15 to 28	1.05 (1.02 to 1.09)	Per 5°C decrease		0	Only linear temperature effects appears to have been considered
Fatal events only						
Dilaveris 2006[24]	tmean 1 to 39	1.13†	30°C		Mean of last 7 days	Results are from the regression line, which shows minimum event rate at 23.3°C, with the event rate increasing smoothly above and below this temperature (levelling off at mean temperatures below 10°C)
		1.00 (reference)	23.3°C			
		1.40† (p<0.001)	10°C			
Sharovsky 2004[25]	tmean 11 to 27	1.11 (1.06 to 1.16)†	23.8–27.3°C		2-Day average	–
		1.00 (reference)	21.6–22.6°C			
		1.16 (1.05 to 1.27)†	16.4–17.3°C			

Continued

Table 3 Continued

First author and year	Temperature variable*, range (if reported) (°C)	Relative risk (RR) or rate ratio for temperature (95% CI if reported)	(Change in temperature variable to which RR refers)	Subgroup to which RR refers (if applicable)	Lag for temp effect (days)	Comment
		1.17 (1.07 to 1.28)† 1.31 (1.19 to 1.44)†	15.2–16.4°C 11.0–15.2°C			
Rossi 1999[28]	tmean −6 to 32	1.44 (1.10 to 1.90) 1.00 (reference)	>27°C 14°C		1	Effect of colder temperatures is not described

Percentage changes were converted to relative risk by dividing by 100 and adding one.
*tmax, daily maximum temperature; tmin, daily minimum temperature; tmean, daily mean temperature; temp, temperature (unspecified); discomfort, number of discomfort hours per day; tchange, temperature change from previous day; twind, windchill-adjusted temperature; †approximate RR, derived from graphical presentation of results.
LA, Los Angeles region; Sa, Sacramento region; SF, San Francisco region.

We identified 19 relevant studies, with a total of 14 investigating short-term (day-to-day) effects of temperature on MI risk. A number of large and relatively well-controlled studies have reported a statistically significant effect of ambient temperature on MI risk. The vast majority of studies reported main effects on the same day or up to 3 days later, with no study reporting substantial effects lagging by more than 1 week. Over half of the time-series regression studies reported detrimental effects of cold and over half reported detrimental effects of heat; indeed a few studies found a U-shaped relationship, with MI risk increasing at both ends of the temperature scale. The size of temperature effects varied. Three studies of MI mortality outcomes were among those estimating the largest temperature effects—as much as a 31–44% increase in risk at the extremes of the local temperature scale compared with intermediate local temperatures. The larger size of these mortality effects might reflect an inherent lack of specificity in studies with mortality outcomes; some deaths are likely to have been coded as MI based on limited information, leading to potential misclassification, and if such misclassified causes of death were more strongly associated with temperature, results may have been exaggerated. On the other hand, studies based on hospital admissions may have underestimated the true temperature effects if difficulties in getting to hospital during temperature extremes led to more out-of-hospital MI deaths occurring which would not have been included. Although studies including non-fatal events generally estimated effects that were smaller in magnitude, detrimental effects of both heat and cold were still found in a number of these studies; considering the five studies in which MI outcomes were validated against diagnostic criteria, one and three studies found significant effects of heat and cold, respectively.

Various mechanisms have been suggested through which cold exposure might act as a trigger for MI, and it is possible that a number of parallel processes contribute to the effect. Experimental studies have found increased arterial pressure and blood viscosity during cold exposure,[32] as well as an increased need for oxygen and consequently an increase in the cardiac workload.[33] Furthermore, red cell counts, plasma cholesterol and fibrinogen concentrations, all of which may be thrombogenic, appear to be raised on exposure to cold.[32 34] Heat exposure has also been shown under controlled conditions to lead to increases in red blood cell counts, platelet counts, and blood viscosity, as well as increases in heart rate.[35] However, there is a lack of more recent data about the effects of temperature on an updated range of clotting measures and more research is needed in this area.

The majority of studies included used data sources such as hospital databases and registries, which would have had the potential to capture events across the local population, thus their findings should have good generalisability within the local settings. There might be a number of reasons for the heterogeneity in results between studies. One must consider that the studies included here cover a wide range of populations with differing demographic profiles, as well as a wide range of geographical locations. In each location, it is likely that various factors such as quality of housing, prevalence of air conditioning, central heating and insulation could have all influenced the strength and direction of the observed association between outdoor temperature and health outcomes at the population level. There were also many methodological differences across the studies included: MI events were identified from sources of various types; modelling strategies varied; different definitions of temperature were used as the main exposure (such as minimum, maximum, mean, windchill-adjusted); different allowances for non-linear temperature effects were made; and different lag days considered. There was also variation in the level of adjustment for potential confounding factors such as air pollution (which was only controlled for in a handful of studies).

In addition, local climate may have a role in the vulnerability to temperature effects. One study which incorporated data from 21 countries found that local mean temperature explained much of the variation in the magnitude of the detrimental effect of cold on MI risk,[18] and we correspondingly found that, among single-location studies, those conducted in areas with higher long-term mean temperatures tended more frequently to report detrimental effects of cold than those conducted in warmer areas, and indeed tended to report effect estimates with larger magnitude. We did not observe such a pattern for the effect of heat, despite the differing effects of heat that have been reported on overall mortality in different locations.[2] These findings must be interpreted with caution, since the studies included in our review differed in so many ways. Nevertheless, increases in systolic blood pressure in response to lower temperatures have been found to be larger in warmer countries,[36] and studies of all-cause mortality have similarly reported local climate to be a strong modifier of temperature effects.[1 9] Such effect modification may simply reflect better established adaptive measures in colder countries; the Eurowinter Group found that, at the same outdoor temperatures, people in Finland were more likely to have bedroom heating, keep their indoor temperatures higher, and were more likely to wear hats, gloves, anoraks, and (among women) trousers, than people in Athens, Greece[37]; the potential benefits of such adaptive measures are suggested by the improvements in blood pressure achieved on installing home heating in a UK study.[38] Others have suggested that there may be some

biological adaptation to cold,[39] and cold-adapted subjects have been shown to have reduced activity of the sympathetic nervous system in response to cold stress.[40]

Our review inevitably has some limitations. First, our search strategy might have missed some studies. However, by searching a number of different databases, with different indexing systems, and, furthermore, checking reference lists and the websites of major organisations, we believe that all major studies with MI as the primary outcome should have been picked up. We also took steps to include studies of CVDs more broadly, where an analysis of MI was also performed separately. Our decision to include only papers analysing specific MI outcomes might also have led to some informative studies of related outcomes being excluded, though we believe that this is outweighed by the advantage in interpretability from the very specific focus on MI. Second, as with any review of the literature, there might have been publication bias: studies finding effects may have been more likely to be published. The extent of publication bias is difficult to assess in studies with such varied methodology and reporting. Though such concerns should always be borne in mind, our goal was not to produce a definitive numerical estimate of the effects of temperature on MI risk, but rather to give an overview of the evidence available. Finally, we did not include non-English-language citations owing to resource limitations, but we believe that this is unlikely to have led to the omission of any major papers in the area.

There is some public health motivation for further clarifying the effects of temperature. Weather forecasting is reasonably accurate up to a few days in advance, and with a well-understood relationship between temperature and MI, those most vulnerable could be warned when the risk of MI was likely to increase, and given advice to reduce their personal risk. The UK Met Office recently set up a similar targeted warning system for people with chronic obstructive pulmonary disease, in which patients are alerted by an automated telephone call when the risk of disease exacerbation is elevated based on the ambient temperature; they are given advice on keeping warm, avoiding low temperatures and watching for warning signs of their condition worsening. It is claimed that a 20.5–48% reduction in hospital admissions has been achieved among practices signing up to the scheme.[41] Health service providers could also be warned in advance where rates of MI were likely to increase, to aid the short-term allocation of resources.

A number of suggestions arise for future research. Though the majority of the studies included were of similar basic design (daily time-series studies), there was wide variation in the methodology and reporting used. More consistent adjustment for potential confounders such as season, long-term trend and air pollution; allowance for non-linear and delayed temperature effects; and more consistent reporting standards would make future studies in this area easier to compare and interpret. More large studies with this kind of consistent methodology and reporting will be required in a number of geographical locations to characterise the short-term effects of temperature on MI risk, and the relationship of such effects to local climate. There is also a need for more studies which take account of potential effect modifiers: though a few studies have presented stratified or age-restricted data, there is little direct evidence on how age, and other individual-level factors such as previous disease, affect a person's vulnerability to temperature effects. In addition, individual-level studies collecting detailed information on such factors as clothing, air conditioning and home heating, though expensive and difficult to design, would provide valuable data to assess the role of adaptive measures. Finally, though the role of more complex weather indicators, such as air mass type, remains unclear and difficult to interpret, the effects of such factors are worthy of further investigation, since weather effects on human health may not be captured fully by investigating only specific parameters such as temperature and humidity; indeed interactions between the various aspects of weather may, in part, help to explain some of the variation in results across studies included in this review.

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Systematic review

EDITOR'S CHOICE

Effects of air pollution on the incidence of myocardial infarction

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ABSTRACT

Context: Short-term fluctuations in air pollution have been associated with changes in both overall and cardiovascular mortality.

Objective: To consider the effects of air pollution on myocardial infarction (MI) risk by systematically reviewing studies looking at this specific outcome.

Data sources: Medline, Embase and TOXNET publication databases, as well as reference lists and the websites of relevant public organisations.

Study selection: Studies presenting original data with MI as a specific outcome and one or more of the following as an exposure of interest were included: particulate matter (PM), black carbon/black smoke, ozone, carbon monoxide, nitrogen oxides, sulphur dioxide and traffic exposure.

Data extraction: The effects of each pollutant on risk of MI, including effect sizes and confidence intervals, were recorded where possible. Methodological details were also extracted including study population, location and setting, ascertainment of MI events, adjustment for potential confounders and consideration of lagged effects.

Results: 26 studies were identified: 19 looked at the short-term effects of pollution on a daily timescale; the remaining 7 at longer-term effects. A proportion of studies reported statistically significant detrimental effects of PM with diameter <2.5 μm (3/5 studies, risk increase estimates ranging from 5 to 17% per 10 μg/m^3 increase), PM <10 μm (3/10, 0.7–11% per 10 μg/m^3), CO (6/14, 2–4% per ppm), SO_2 (6/13, effect estimates on varied scales) and NO_2 (6/13, 1–9% per 10 ppb). Increasing ozone levels were associated with a reduction in MI risk in 3/12 studies. A number of differences in location, population and demographics and study methodology between studies were identified that might have affected results.

Conclusion: There is some evidence that short-term fluctuations in air pollution affect the risk of MI. However, further studies are needed to clarify the nature of these effects and identify vulnerable populations and individuals.

There has been considerable interest in recent years in the health effects of exposure to both short-term fluctuations and long-term levels of air pollution, in particular common environmental pollutants including particulate matter (PM), ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2) and sulphur dioxide (SO_2). Early time-series studies demonstrated an effect of short-term changes in the levels of pollutants, in particular PM, on overall mortality in both the USA[1] and Europe.[2] Two noteworthy prospective cohort studies also reported that mortality risk was increased by up to 26% for people living in cities with the highest mean pollution levels, after adjusting for individual risk factors such as smoking.[3 4]

More specific outcomes have also been investigated, and studies of cardiovascular mortality and morbidities, including ischaemic heart disease, have suggested that both day-to-day changes in pollutant levels[5 6] and longer-term exposure[7 8] may affect risk. A statement from the American Heart Association concluded that short-term increases in PM levels led to corresponding increases in cardiovascular mortality, and in hospital admissions for several cardiovascular diseases.[9] A major review of the epidemiological evidence on air pollution and cardiovascular disease conducted for the UK Department of Health went further, stating in particular that "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".[10] While an effect of air pollution on cardiovascular mortality and hospital admissions is to some extent established, the association between exposure to air pollution and risk of myocardial infarction (MI) is less clear.

The aim of this study was to systematically review the evidence concerning air pollution effects on the risk of MI. We hypothesised that increases in PM, O_3, CO, NO_2 and SO_2 levels would be associated with both short- and long-term increases in MI risk. To our knowledge no systematic review to date has focused on this specific outcome. Clarifying the effects of air pollution on MI is of particular interest, not only to aid the assessment of the likely burden to acute care facilities associated with changes in pollution levels but also to clarify whether MI is a major contributor to the increases in broader cardiovascular outcomes that have been associated with pollution, and thus to further our understanding of pathways and pathological mechanisms by which air pollution impacts on health.

METHODS

Databases and sources

We searched Medline (1950 to present) and Embase, as well as TOXNET, a bibliographic database specialising in toxicology literature. Reference lists of all relevant studies were scanned to identify any further studies, and if these revealed that search terms had been missed, extra terms were added to the main database searches. The searches were performed by a statistician/epidemiologist (KB), initially in July 2008, with the main database searches updated in May 2009. We also searched the websites of the following

organisations for relevant reports and reviews: World Health Organization; European Union; Health Effects Institute (USA); Environmental Protection Agency (USA); National Institutes of Health (USA); Department of Health (UK); Department for Environment, Food and Rural Affairs (UK). Conference abstracts and unpublished studies were not included in this review.

Search keywords and terms

Our search of Medline (via OvidSP) and TOXNET used the following MeSH keywords: (''air pollution'' or ''air pollutants'' or ''ozone'' or ''carbon monoxide'' or ''sulfur dioxide'' or ''particulate matter'' or ''nitrogen oxides'' or ''environmental exposure'') and ''myocardial infarction'' and ''humans'' not (''tobacco smoke pollution''). All subterms were also included and we limited the search to studies of adult humans, published in English. For Embase, which does not use the MeSH classification system, we used the nearest equivalent search terms from the Embase indexing system.

In order to identify studies in which air pollution effects on MI were reported as specific secondary outcomes within a broader study, we performed a secondary Medline search, as above but using the broader MeSH term ''cardiovascular diseases'' in place of ''myocardial infarction''; we then limited the results to reports where ''myocardial infarction'' or an equivalent term was present in the title, abstract, or keywords (equivalent terms were defined as ''myocardial infarct*'', ''coronary event'', ''heart attack'', ''Q wave infarct*'', ''Non-Q wave infarct*'', ''STEMI'', ''coronary infarct*'', ''heart infarct*'', ''myocardial thrombosis'', or ''coronary thrombosis'', where ''*'' indicates any word ending).

Inclusion and exclusion criteria

To examine the hypothesis that ambient air pollutant exposure would be associated with MI risk, studies of any relevant design were included if they presented original data, and included at least one analysis where MI was the specific outcome, and one or more of the following exposures were investigated: PM or black carbon/black smoke, ozone, carbon monoxide, any oxide of nitrogen, or sulphur dioxide. Studies using exposure to traffic as a proxy were also included. We excluded studies in which the authors did not control for (or stratify by) any potential confounding factors, or did not report measures of precision or p values for the analysis of interest

Procedure

Titles and abstracts were screened for relevance, and full-text versions obtained where appropriate for assessment with reference to the inclusion and exclusion criteria; we were able to obtain full-text papers in all cases where required and it was not necessary to contact specific authors. For each study included, the following information was recorded based on prior beliefs about key aspects of study methodology and in order to summarise study quality: study population, event of interest, number included, age range included, location and setting, time period, exposure variables, ascertainment of MI, spatial resolution, temporal resolution, adjustment for weather variables and other potential confounders, lags considered. The main results of each study were also recorded—in particular, the effects of each pollutant of interest on risk of MI, including effect sizes and confidence intervals where possible. Where authors reported several relevant results (eg, for different lag days, or for different subgroups), we chose results from the main or final model if such a model could be identified, or else from the analysis on which the authors focused or that which best represented the overall conclusions of the study, noting any important differences in the effect estimates between different analyses. Finally, effect estimates and their confidence intervals were standardised, where possible, to aid comparison; effect estimates for PM_{10} and $PM_{2.5}$ were converted to ''per 10 μg/m^3'', estimates for O_3, NO_2 and SO_2 were converted to ''per 10 ppb'' or ''per 10 μg/m^3'', and estimates for CO were converted to ''per ppm'', or ''per mg/m^3''

RESULTS

A total of 27 studies met the inclusion criteria; however, one was excluded because only a basic analysis was performed with no consideration of potential confounding factors, leaving 26 in the final review (fig 1).

The majority of studies (n = 19) were concerned with identifying short-term associations between air pollution exposures and MI risk (tables 1–3).[5 11–28] A further seven studies looked at the longer-term effects of air pollution on MI risk (table 4).[29–35]

Short-term effects of air pollution

Among the 19 studies that we identified which looked at the short-term effects of air pollution on MI risk, a number of specific pollutants were investigated, the most common being particles with diameter <10 μm (PM_{10}, 10 studies), particles with diameter <2.5 μm ($PM_{2.5}$, 5 studies), O_3 (12 studies), CO (14 studies), NO_2 (13 studies) and SO_2 (10 studies). The number of individual pollutants investigated by a single study ranged from 1 to 8. The design of the studies fell into two categories: 10 were analyses of daily time-series data, while the remaining nine used case-crossover designs.

Study designs and methodological considerations

Both time-series and case-crossover study designs are based solely on data from subjects who have experienced the event of

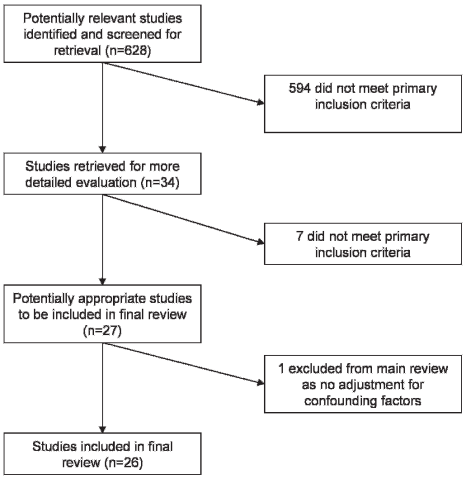

Figure 1 Flow diagram of search strategy.

Table 1 Daily time-series studies with air pollution exposures and myocardial infarction (MI) outcomes: description of studies

First author and year of publication	Population/data source	Location and time period	Number of events included (mean per day for time-series studies)	Air pollution exposure variable(s)	Potential confounders included	MI ascertainment	Lags considered (days, except where noted)
Daily time-series studies							
Fatal and non-fatal events							
Cendon 2006[11]	Hospital admissions data (112 hospitals: infirmaries and ICUs); age >64 only	Sao Paulo, Brazil 1998–9	19272* (26.4)	PM_{10} (24 h average)	Season and trend, temperature (*non-linear, 2-day moving average*), humidity, day of week	Events with ICD-10 codes suggesting MI in the Public Health Data Analysis System Division	0–7 inclusive
Lanki 2006[12]	AMI registers and hospital discharge registers	5 European cities (Augsburg, Barcelona, Helsinki, Rome, Stockholm) 1992–2000 (3–7 year period per city)	26 854 (between 0.9 and 8.4 per city)	PM_{10}, O_3 (8 h average, summer only), NO_2, CO, modelled particle number conc. (proxy for PM <0.1 μg/m³)	Season and trend, apparent temperature (*non-linear, same day and average of lag days 1–3*), barometric pressure, weekday indicator, holiday indicator	Records with ICD9 code 410 in hospital registers (two cities); or records meeting MONICA definition of MI in AMI registers (three cities)[58]	0–3 inclusive
Koken 2003[13]	Hospital admissions data (11 hospitals, covering ages 65+ years)	Denver county, USA 1993–7 (July and August only)	1576* (5.1)	PM_{10}, O_3, NO_2, SO_2, CO (all 24 h average)	Daily maximum temperature (*lag days 0–4*), dew point temperature, day of week, calendar year, population size	Primary discharge diagnosis (ICD9 = 410.XX)	0–4 inclusive
Mann 2002[5]	Records from a health maintenance organisation	Southern California, USA 1988–95	19 690 (6.7*)	PM_{10} (24 h average), O_3 (8 h average), NO_2, (24 h average) CO (8 h average)	Season and trend, temperature (*non-linear, same day*), relative humidity, calendar year, day of week, annual population size	Records with ICD9 code 410	0–5 days inclusive
Ye 2001[14]	Hospital emergency transports records (four hospitals, ages 65+ years)	Tokyo, Japan 1980–95 (July and August only)	3200* (3.28)	PM_{10}, O_3, CO, NO_2, SO_2, (all daily average)	Annual trends, daily maximum temperature (*lag days 0–4*), population size	As diagnosed by emergency doctor, based on presenting symptoms	0 (adjusted for 1–4 inclusive)
Linn 2000[15]	Hospital admissions data	Los Angeles, USA 1992–5	Not reported	PM_{10}, O_3, CO, NO_2 (all 24 h average)	Season and trend, day of week, holidays, mean temperature (*same day*), barometric pressure, indicators for hot days, cold days, rainy days	Records with an all-patient-refined diagnosis-related group code of 111, 115, or 121	Different lags considered, exact strategy unclear
Poloniecki 1997[16]	Hospital episode statistics	London, UK 1987–94	68 300* (26.7)	O_3 (8 h average); NO_2, SO_2, CO, black smoke (all 24 h average)	Season and trend, temperature (*lag day 1*), humidity, day of week, public holidays, influenza epidemic indicator	Records with ICD9 code 410	1
Fatal events only							
Murakami 2006[17]	Vital statistics of Japan data (34 districts)	34 districts, Japan 1990–4	14 430 (7.9*)	Suspended particulate matter (hourly measurements)	Time of day, temperature (*non-linear, same day*), region	Records with ICD9 code 410	Exposure windows from 1 to 48 h
Sharovsky 2004[18]	Death registry data	Sao Paulo, Brazil 1996–8	12 007 (16.4)	PM_{10}, CO, SO_2 (daily average)	Season and trend, mean temperature (*non-linear, up to lag day 7*), relative humidity, atmospheric pressure, day of week, holidays, influenza levels	Death certificates with MI (ICD10 = I21) listed as primary cause	0, and moving average of up to previous 7 days

Continued

Table 1 Continued

First author and year of publication	Population/data source	Location and time period	Number of events included (mean per day for time-series studies)	Air pollution exposure variable(s)	Potential confounders included	MI ascertainment	Lags considered (days, except where noted)
Rossi 1999[19]	Vital statistics department mortality data	Milan, Italy 1985–9	1600* (0.9)	Total suspended particles	Season and trend, temperature (*non-linear, lag days unclear*), relative humidity, day of week, holidays, epidemics, pollution	Deaths with ICD9 codes of 410	Different lags considered, exact strategy unclear
Case–crossover studies							
Fatal and non-fatal events							
Barnett 2006[20]	Hospital admissions data from seven cities	Australia (five cities) and New Zealand (two cities) 1998–2001	28 818*	$PM_{2.5}$ (24 h average), PM_{10} (24 h average), O_3 (8 h average), CO (8 h average), NO_2 (24 h average)	Temperature (*lag days 0–1*), change in temperature from previous day, humidity, hot and cold days, pressure, day of week, holiday, rainfall	Records with ICD9 code 410 or ICD10 code I21-22	Average of 0–1
Zanobetti 2006[21]	Hospital admissions data from the US Medicare programme (ages 65+ years)	Boston metropolitan area, USA 1995–9	15 578	$PM_{2.5}$, PM non-traffic (modelled), O_3, CO, NO_2, black carbon	Apparent temperature (*non-linear, lag day 1*); also matched for same day temperature), day of week	Records with ICD9 code 410	0, 1, and mean of 0 and 1
Peters 2005[22]	Coronary event registry (cases surviving first 24 h only)	Augsburg, Germany 1999–2001	851	$PM_{2.5}$, total number concentration (proxy for ultrafine particles), O_3, SO_2, CO, NO_2 (all 24 h average; 1 h average also considered for PM)	Temperature (*non-linear, same day*), day of week	Patients meeting MONICA definition of MI[58]	0–5 (also 0–6 h for hourly analysis)
Ruidavets 2005[23]	AMI registry	Toulouse, France 1997–9	399	O_3 (highest 8 h average of the day), SO_2 (24 h average), NO_2 (24 h average)	Day of week (matched), min and max temperature (*same day*), humidity, influenza levels	Clinical, ECG and enzyme data available to support diagnosis	0–3 days inclusive
Sullivan 2005[24]	Community database linking emergency service and hospital outcome data	Washington State, USA 1988–94	5793	Increase in short-term average $PM_{2.5}$ (derived from fine PM), defined as 10 $\mu g/m^3$ increase in 1, 2, 4, 24 h averaged $PM_{2.5}$). Similar for SO_2 and CO	Temperature (*non-linear, same day*), relative humidity	Discharge diagnosis of AMI confirmed by enzyme and ECG changes	0–2 days inclusive
Zanobetti 2005[25]	Hospital admissions data from the US Medicare programme (ages 65+ years)	21 Cities, USA 1986–99	302 453	PM_{10} (daily average)	Day of week (matched), apparent temperature (*non-linear, lag days 0–1*)	Medicare claims where primary diagnosis had ICD9 code 410	0–2 days inclusive
Peters 2004[26]	KORA MI registry	Augsburg, Germany 1999–2001	691	Exposure to traffic as measured by retrospective diary for the 4 days preceding event	None specified	Records meeting MONICA definition of MI[58]	0–6 days inclusive
D'Ippoliti 2003[27]	Regional hospital admissions data	Rome, Italy 1995–7	6531	Total suspended particles, CO, SO_2, NO_2 (all 24 h average)	Day of week (matched), temperature (*non-linear, lag day 1*), humidity, air pressure	Records with ICD9 code of 410	0–4, and mean of 0–2 days
Peters 2001[28]	Coronary care unit admissions records	Greater Boston, USA 1995–6	772	$PM_{2.5}$, PM_{10}, ozone, SO_2, NO_2, CO, black carbon	Season, day of week, minimum daily temperature (*non-linear, same day*), relative humidity	Patients had all of: ⩾1 CK above upper limit of normal, positive MB isoenzymes, symptoms	0–5 inclusive (also 0–5 h for hourly analysis)

*Derived from reported mean daily rate, and length of period under study.
AMI, acute myocardial infarction; ICI, intensive care unit; PM, particulate matter.

Table 2 Daily time-series studies with air pollution exposures and myocardial infarction (MI) outcomes: summary interpretation

	Significant effect of exposure?													
First author and year	$PM_{2.5}$	PM_{10}	O_3	CO	NO_2	SO_2	Other particulate exposures	Other non-particle exposures	Adjusted for season and trend?	MI events: validation or specified criteria	Adjusted for temperature	Adjusted for infectious disease levels	Adjusted for day of week?	Investigated different lag effects?
Daily time-series studies														
Fatal and non-fatal events														
Cendon 2006[11]	–	No	*Yes*	No	No	*Yes*	–	–	✓	✗	✓	✗	✓	✓
Lanki 2006[12]	–	No	No	*Yes*	No	–	No (PNC)	–	✓	✓	✓	✗	✓	✓
Koken 2003[13]	–	No	*Protective effect*	No	No	No	–	–	N/A*	✗	✓	✗	✓	✓
Mann 2002[5]	–	No	*Protective effect*	*Yes*	*Yes*	–	–	–	✓	✗	✓	✗	✓	✓
Ye 2001[14]	–	No	No	No	*Yes*	No	–	–	N/A*	✗	✓	✗	✗	✓
Lim 2000[15]	–	*Yes*	No	*Yes*	*Yes*	–	–	–	✓	✗	✓	✗	✓	✓
Poloniecki 1997[16]	–	–	No	*Yes*	*Yes*	*Yes*	*Yes* (BS)	–	✓	✗	✓	✓	✓	✗
Fatal events only														
Murakami 2006[17]	–	–	–	–	–	–	Yes (TSP)	–	✗	✗	✓	✗	✗	✓
Sharovsky 2004[18]	–	No	–	No	–	*Yes*	–	–	✓	✗	✓	✓	✓	✓
Rossi 1999[9]	–	–	–	–	–	–	*Yes* (TSP)	–	✓	✗	✓	✓	✓	✓
Case-crossover studies														
Fatal and non-fatal events														
Barnett 2006[20]	*Yes*	No	No	*Yes*	*Yes*	–	–	–	N/A†	✗	✓	✗	✓	✗
Zanobetti 2006[21]	*Yes*	–	No	No	*Yes*	–	Yes (BC)	–	N/A†	✗	✓	✗	✓	✓
							No (PM non-traffic)							
Peters 2005[22]	No	–	*Protective effect*	No	No	*Yes*	No (TNC)	–	N/A†	✓	✓	✗	✓	✓
Ruidavets 2005[23]	–	–	No	–	No	No	–	–	N/A†	✓	✓	✓	✓	✓
Sullivan 2005[24]	No	–	–	No	–	No	–	–	N/A†	✓	✓	✗	✗	✓
Zanobetti 2005[25]	–	*Yes*	–	–	–	–	–	–	N/A†	✗	✓	✗	✓	✓
Peters 2004[26]	–	–	–	–	–	–	–	*Yes* (exposure to traffic)	N/A†	✓	✗	✗	✗	✓
D'Ippoliti 2003[27]	–	–	–	*Yes*	No	No	*Yes* (TSP)	–	N/A†	✗	✓	✗	✓	✓
Peters 2001[28]	*Yes*	*Yes*	No	No	No	No	No (coarse mass, BC)	–	N/A†	✓	✓	✗	✓	✓

*Adjustment for season not applicable since study used data from summer months only; †case-crossover design allows for season and trend by design.
BC, black carbon; BS, black smoke; PNC, particle number concentration; TNC, total number concentration; TSP, total suspended particulate.

Table 3 Daily time-series studies with air pollution exposures and myocardial (MI) outcomes: study results details

First author and year	Exposure variable	Relative risk or rate ratio (95% CI if reported)	Exposure increase (or category) to which rate ratio refers	Lag for estimated effect (days unless specified)	Comment
Daily time-series studies					
Fatal and non-fatal events					
Cendon 2006[11]		(for ICU admissions)	(units not given)		NO_2: cumulative effect estimate hides a significant effect at lag 0, but then reduced risk at lags 2–3
	PM_{10}	1.032 (0.978 to 1.086)	22.5	Sum of 0–7	Other pollutants: effects appeared to be dominated by lag 0 effect
	O_3	1.093 (1.011 to 1.174)	50.23		Effects overall similar when infirmary admissions were considered (as opposed to ICU)
	CO	0.998 (0.933 to 1.066)	1.42		PM_{10}: effect similar for infirmaries but reached significance
	NO_2	1.038 (0.962 to 1.114)	54.67		
	SO_2	1.129 (1.064 to 1.194)	10		
Lanki 2006[12]	PM_{10}	1.003 (0.995 to 1.011)	10 μg/m^3	0	No statistically significant effects at lags 1, 2, 3 days for any pollutant
	O_3	0.994 (0.986 to 1.002)	10 μg/m^3		There was a suggestive effect of PNC, when restricting to the three cities using hospital discharge register data, which had higher power
	CO	1.025 (1 to 1.051)	1 mg/m^3		
	NO_2	0.995 (0.985 to 1.006)	10 μg/m^3		
	PNC	1.005 (0.996 to 1.015)	10 000/cm^3		
Koken 2003[13]	PM_{10}	NS (detail not reported)		0	Only the lag value with the strongest effect was given; therefore the effect of ozone at 1–4 days lag was not reported
	O_3	0.819 (0.726 to 0.923)	10 ppb		
	CO	NS (detail not reported)			
	NO_2	NS (detail not reported)			
	SO_2	NS (detail not reported)			
Mann 2002[5]	PM_{10}	0.999 (0.987 to 1.011)	10 μg/m^3	Not reported	–
	O_3	0.993 (0.985 to 0.997)	10 ppb		
	CO	1.035 (1.024 to 1.046)	1 ppm		
	NO_2	1.02 (1.011 to 1.03)	10 ppb		
Ye 2001[14]	PM_{10}	NS (detail not reported)	–	Not reported	Model estimates do not directly indicate effect size. We can only conclude that there was some positive effect of NO_2 on MI outcomes, and no significant effect of other pollutants
	O_3	NS (detail not reported)	–		
	CO	NS (detail not reported)	–		
	NO_2	0.006 (0.003, 0.010)	Not reported		
	SO_2	NS (detail not reported)	–		
Linn 2000[15]	PM_{10}	1.01 (1 to 1.01)	10 μg/m^3	0	Part of a wider paper on CVD—the effects seen were not specific to MI alone: CO and NO_2 were also associated with congestive heart failure, asthma and COPD, suggesting just one manifestation of an effect on susceptible subjects
	O_3	0.965 (0.899 to 1.035)	10 ppb		
	CO	1.041 (1.023 to 1.059)	1 ppm		
	NO_2	1.056 (1.005 to 1.11)	10 ppb		
Poloniecki 1997[16]	O_3	0.993 (0.981 to 1.006)	10 ppb	1	Further breakdown indicated that the effects found were only significant in the cool season (Oct–Mar)
	CO	1.023 (1.007 to 1.04)	1 ppm		SO_2 was independently associated with MI in the cool season in all two-pollutant model combinations
	NO_2	1.009 (1.003 to 1.016)	10 ppb		NO_2, CO, black smoke were not associated in two-pollutant models, except in combination with O_3
	SO_2	1.017 (1.007 to 1.027)	10 ppb		
	Black smoke	1.0303 (1.0092 to 1.0528)	15 μg/m^3		
Fatal events only					
Murakami 2006[17]	TSP (categorised)	1.00 (reference category)	0–99 μg/m^3	0–1 h	The effects were similar when exposure windows of up to 6 h were considered; but there was a less clear "dose–response" relationship when periods longer than 6 h were used
		1.13 (1.07 to 1.20)	100–149 μg/m^3		
		1.18 (1.01 to 1.37)	200–249 μg/m^3		
		1.40 (1.00 to 1.97)	⩾300 μg/m^3		
Sharovsky 2004[18]	PM_{10}	1.01 (0.91 to 1.11)	10 μg/m^3	Average of 0–3	–
	CO	1.014 (0.995 to 1.03)	1 ppm		
	SO_2	1.03 (1.005 to 1.07)	10 μg/m^3		
Rossi 1999[19]	TSP	1.10 (1.13 to 1.18)	100 μg/m^3	Average of 3–4	Average of 3–4 day lag best predictor; little effect of concurrent day's exposure

Continued

Table 3 Continued

First author and year	Exposure variable	Relative risk or rate ratio (95% CI if reported)	Exposure increase (or category) to which rate ratio refers	Lag for estimated effect (days unless specified)	Comment
Case-crossover studies					
Fatal and non-fatal events					
Barnett 2006[20]		(For ages ⩾65 years)			Effect estimates were in the same direction for those aged <65 years, but none were statistically significant
	$PM_{2.5}$	1.073 (1.035 to 1.114)	10 μg/m³	Average of 0–1	
	PM_{10}	NS (detail not reported)	–		
	O_3	NS (detail not reported)	–		
	CO	1.032 (1.009 to 1.055)	1 ppm		
	NO_2	1.088 (1.02 to 1.163)	10 ppb		
Zanobetti 2006[21]	$PM_{2.5}$	1.052 (1.007 to 1.092)	10 μg/m³	Av of 0–1	Results for same-day pollution levels only were in the same direction and of similar magnitude The effect of black carbon was non-significant on the same day alone, whereas CO was significantly predictive of MI on the same day (though not for days 0 and 1 averaged)
	PM non-traffic	1.0439 (0.9688 to 1.1170)	10.28 μg/m³		
	O_3	0.988 (0.957 to 1.017)	10 ppb		
	CO	1.124 (0.973 to 1.284)	1 ppm		
	NO_2	1.074 (1.034 to 1.104)	10 ppb		
	Black carbon	1.0834 (1.0021 to 1.1582)	1.69 μg/m³		
Peters 2005[22]	$PM_{2.5}$	1.105 (0.987 to 1.226)	10 μg/m³	2 days	Strong effect of $PM_{2.5}$ among the subgroup of never-smokers (RR = 1.20, 1.04 to 1.39 per 7.7 μg/m³) Strongest pollution effects seen at 2 days' lag as shown There were no statistically significant effects of pollutants on any other lag days In an hourly analysis, there was no effect of $PM_{2.5}$ or TNC at the hourly level at up to 6 h lag
	O_3	0.94 (0.895 to 0.987)	10 μg/m³		
	CO	1.32 (0.968 to 1.801)	1 mg/m³		
	NO_2	1.033 (0.966 to 1.104)	10 μg/m³		
	SO_2	1.475 (1.069 to 2.005)	10 μg/m³		
	TNC	1.04 (0.90 to 1.20)	6400/cm³		
Ruidavets 2005[23]	O_3	1.082 (0.98 to 1.166)	10 μg/m³	0	There was an effect for ozone at 1 day lag (p = 0.02), but not longer lags The ozone effect only was statistically significant at 0 and 1-day lag when possible coronary deaths, sudden deaths and deaths with insufficient data added to the outcome
	NO_2	0.922 (0.81 to 1.04)	10 μg/m³		
	SO_2	0.98 (0.723 to 1.323)	10 μg/m³		
Sullivan 2005[24]	$PM_{2.5}$	1.01 (0.98 to 1.05)	10 μg/m³	Average of 0–1 h	The authors also found no effects when increasing the averaging time for the exposure variables from 1 to 24 h before the event
	CO	1.04 (0.99 to 1.08)	1 ppm		
	SO_2	0.97 (0.94 to 1.01)	10 ppb		
Zanobetti 2005[25]	PM_{10}	1.007 (1.003 to 1.01)	10 μg/m³	0	Little effect at lag days 1 or 2 For same-day effect, a dose–response relationship was seen with steeper slope at PM_{10} <50 μg/m³
Peters 2004[26]	Traffic exposure	2.73 (2.06 to 3.61)	Odds ratio for traffic exposure	Exposure 1 h before the event	–
D'Ippoliti 2003[27]	TSP	1.028 (1.005 to 1.052)	10 μg/m³	Av of 0–2	For total suspended particulate and CO, the only effect was the same day; for NO_2, there was no same-day effect, but a significant effect with 2 days' lag Effects of TSP and CO were stronger in the warm season, and among those with heart conduction disorders
	CO	1.044 (1 to 1.089)	1 mg/m³		
	NO_2	1.293 (0.97 to 1.741)	10 μg/m³		
	SO_2	NS (detail not reported)	–		
Peters 2001[28]	$PM_{2.5}$	1.17 (1.035 to 1.325)	10 μg/m³	2 h, hourly analysis	There was also a significantly elevated risk of MI associated with 24 h average levels lagged by 1 day (ie, levels from 24 to 48 h before the event), for $PM_{2.5}$, PM_{10}; and non-significant increased risks for coarse mass, black carbon, and NO_2
	PM_{10}	1.109 (1.015 to 1.211)	10 μg/m³		
	Coarse mass	1.16 (0.89 to 1.51)	15 μg/m³		
	O_3	1.062 (0.965 to 1.17)	10 ppb		
	CO	1.22 (0.89 to 1.67)	1 ppm		
	NO_2	1.019 (0.934 to 1.112)	10 ppb		
	SO_2	0.98 (0.911 to 1.058)	10 ppb		
	Black carbon	1.27 (0.97 to 1.68)	3 μg/m³		

Estimates converted where possible to: PM_{10}: per 10 μg/m³; $PM_{2.5}$: per 10 μg/m³; O_3: per 10 ppb or 10 μg/m³; CO: per ppm or mg/m³; NO_2: per 10 ppb or 10 μg/m³; SO_2: per 10 ppb or 10 μg/m³.
COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; PNC, particle number concentration; RR, relative risk; TNC, total number concentration; TSP, total suspended particulate; SPM, suspended particulate matter.

Table 4 Studies of long-term effects of air pollution on myocardial infarction (MI) outcomes

First author and year of publication	Population/data source	Location and time period	Number of MI events	Air pollution exposure variable(s)	MI ascertainment	Result		
Cohort studies								
Miller 2007[29]	Cohort of postmenopausal women aged 50–79 years	36 cities, USA 1994–8	584 (cohort size = 65 893)	Average annual exposure to $PM_{2.5}$*	From annual questionnaires and national death index; independently adjudicated by investigator	$PM_{2.5}$	(Hazard ratio) 1.06 (0.85 to 1.34)	Per 10 μg/m^3 increase
Abbey 1993[30]	Cohort of seventh-day Adventists	California, USA 1977–82	62 (cohort size = 6303)	Average and cumulative exposure to ambient NO_2 estimated for places of residence/work*	From hospital records; reviewed by a cardiologist on the study staff	NO_2	"No association" (details not reported)	
Abbey 1991[31]	Cohort of seventh-day Adventists	California, USA 1977–82	62 (cohort size = 6303)	Cumulative exposure to total suspended particles (TSP), and O_3* over a 5-year period before follow-up	From hospital records; reviewed by a cardiologist on the study staff	TSP	(Hazard ratio) 0.93 (0.57 to 1.51)	⩾1000 vs <1000 h exposure to 200 μg/m^3
						O_3	1.06 (0.69 to 1.61)	⩾500 vs <500 h exposure to 10 pphm
Case–control studies								
Tonne 2007[32]	Cases from community-based MI study; population controls	Worcester, Massachusetts, USA 1995–2003	5049 (controls = 10 277)	Cumulative traffic at place of residence (average daily traffic within 100 m multiplied by total length of road)	AMI reviewed and independently validated according to diagnostic criteria	Cumulative traffic	(Odds ratio) 1.04 (1.02 to1.07)	Per 794 vehicle-km
Rosenlund 2006[33]	Cases (aged 45–70 years) from coronary and intensive care unit discharge registers and death certificate data; population controls	Stockholm, Sweden 1992–4 (exposure estimated over 30 years before events)	1397 (controls = 1870)	30-Year mean annual NO_2, CO, SO_2 modelled from source-specific emissions database PM estimated in 2000 and assumed constant	From coronary units, ICUs, hospital discharge register, death certificates using standard diagnostic criteria	PM_{10}	(Odds ratios) 1.0 (0.79 to 1.27)	Per 5 μg/m^3 increase
						CO	1.04 (0.89 to 1.21)	Per 300 μg/m^3 increase
						NO_2	0.99 (0.76 to 1.30)	Per 30 μg/m^3 increase
						SO_2	1.03 (0.78 to 1.36)	Per 40 μg/m^3 increase
Grazuleviciene 2004[34]	Cases (aged 25–64 years) from coronary and intensive care discharge registers; population controls	Kaunas, Lithuania 1997–2000	448 (controls = 1777)	NO_2 exposure in district of residence (categorised into high/medium/low tertiles)	Records with ICD10 codes of I21 and consistent symptoms, ECG, marker levels	NO_2	(Odds ratios) 1.00 (ref)	Low (mean 13.1 μg/m^3)
							1.43 (1.04 to 1.96)	Medium (mean 18.7 μg/m^3)
							1.43 (1.07 to 1.35)	High (mean 24.7 μg/m^3)
Population-based studies								
Rosenlund 2008[35]	Hospital discharge registry and regional cause of death registry	Rome, Italy 1998–2000	1056 (fatal) + 6513 (non-fatal)	Mean annual NO_2 exposure	Records with ICD9 codes of 410	NO_2	(Relative risk) 1.05 (0.97 to 1.15) fatal	Per 10 μg/m^3 increase
							1.01 (0.97 to 1.05) non-fatal	Per 10 μg/m^3 increase

*Based on measured data from monitoring stations.
AMI, acute myocardial infarction; ICU, intensive care unit.

interest (in this case, MI). Briefly, time-series studies typically take as their outcome the daily number of events in a defined region, and a regression analysis is performed to relate these daily counts to explanatory variables (in this case, daily pollutant levels) and potential confounders. A case-crossover study can be thought of as a kind of self-matched case–control study. For each individual, exposure data are collected for the "hazard" period (usually the period immediately before the MI) and for a "control" period which was not associated with the event of interest.

Air pollutant data originated from monitoring stations and were most commonly recorded as 24 h averages, though 8 h averages were also frequently used (table 1). One study by Peters *et al* used traffic exposure as the exposure of interest and

this was ascertained from diary data.[26] MI data came from more varied sources. Three studies looked exclusively at MI deaths, and used death registry and vital statistics data to identify cases. The rest included data on both fatal and non-fatal MI events. The majority identified MI cases through hospital admissions records (eight studies), while the remainder used data from other hospital records (three), MI registers (three) and other databases (two). Six studies, with access to symptom, ECG and biomarker records, validated potential MI events using specific diagnostic criteria.

Key potential confounders and the possibility of delayed effects were dealt with fairly consistently across studies. In case-crossover studies, confounding by season, long-term trend, and factors which do not vary over the short term, is dealt with by design. The majority of time-series studies included also adjusted for season and long-term trend, as well as temperature, which is a potential confounder since temperature may be associated with both pollution levels and MI risk. However, the specific way in which authors adjusted for temperature varied; while a few studies allowed for both non-linearity of the temperature effect and for delayed (lagged) temperature effects over a number of days, others performed only a more basic adjustment (table 1). Lagged effects of air pollution itself were included in all studies; in most cases both immediate (same day) effects and a number of different lags were considered.

Effects of particulate pollutants

Of 10 studies investigating the effects of PM_{10} on MI risk, seven found no effect at all (tables 2–3, fig 2). The authors of a US study in a population aged ⩾65 years estimated a 0.65% increase in MI admissions on the same day as a 10 μg/m^3 increase in PM_{10} (95% CI 0.3% to 1.0%).[25] A second study reported an effect of similar size for a study population with no age restriction.[15] However, the Onset Study, which used admissions records from a Boston coronary care unit and analysed data hourly, found a considerably larger effect: their estimate implied an 11% increase in risk for a 10 μg/m^3 increase in PM_{10} 1 h earlier.[28] This larger effect was not only observed at the hourly timescale; the same authors also found a large and statistically significant effect at a daily resolution, in contrast with the lack of effect found by most studies.

$PM_{2.5}$ was included as an exposure of interest in five studies, all of which were of a case-crossover design. Three of the five studies reported that $PM_{2.5}$ significantly increased the risk of MI. Effect sizes of 5–7% per 10 μg/m^3 increase were estimated in two studies using a daily timescale for analysis,[20 21] a third found no effect overall.[22] These effects were observed between 0 and 2 days after a change in $PM_{2.5}$ levels. A few studies were able to analyse data at an hourly resolution, with two finding no effect of $PM_{2.5}$ on this timescale.[22 24] As with PM_{10}, results from the Onset Study were contrasting: the authors estimated a 17% increase in risk 2 h after a 10 μg/m^3 increase in $PM_{2.5}$.[28]

Other particulate exposures were investigated in some studies. Of note, two studies looking at proxies for ultrafine particles found no effect on MI risk.[12 22] On the other hand, total suspended particulate was included as an exposure in three studies, and all reported a significant association with MI, either on the same day,[17 27] or with some delay.[19]

Effects of gaseous pollutants

Ambient ozone was investigated as a risk factor for MI by 12 studies, only one of which reported a detrimental effect, with MI admissions to intensive care units increasing on days with higher ambient ozone.[11] More common were studies reporting a protective effect of ozone (tables 2–3, fig 3). Surprisingly, of 10 studies reporting a numerical estimated odds ratio or relative risk for MI associated with an increase in ozone levels, the estimate was <1 in seven studies, and this protective effect was statistically significant in three studies. However, effect sizes varied from as little as a 0.7% reduction[13] to as much as an 18% reduction in MI risk for a 10 parts per billion (ppb) increase in ozone.[5] It is worth recording that the relationship between ozone levels and the levels of other pollutants appeared to vary between studies. For example, considering the four studies reporting a significant effect of ozone in either direction, Cendon *et al*[11] (the only study finding a detrimental effect of ozone) recorded positive correlations between ozone and other measured pollutants, whereas the remaining studies reported correlations that were either negative[13 22] or both negative and positive.[5]

Evidence for an effect of ambient CO, NO_2, or SO_2 levels on MI risk was mixed. However, for each of these pollutants, a proportion of studies (6/14, 6/13 and 4/10, respectively) found a significant detrimental effect, whereas no study found an effect in the opposite direction. Only four studies looking at multiple pollutants found no effect of any of these gases[13 25 24 28]; one did not report the number of cases included while the other three

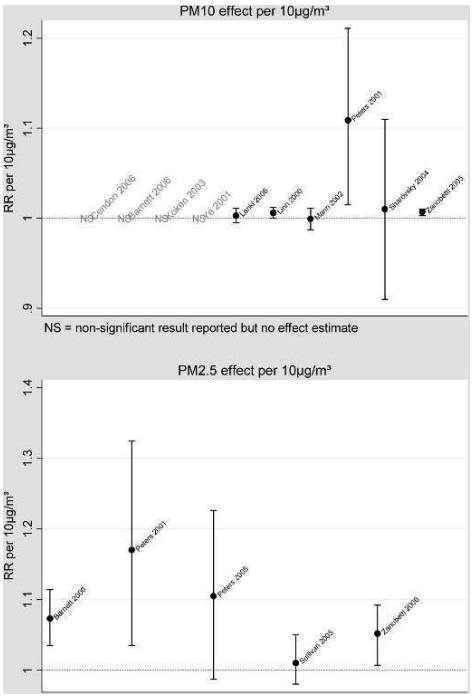

Figure 2 Estimate effects of particulate pollution on myocardial infarction risk. PM, particulate matter; RR, relative risk.

were relatively small studies (n = 5793, 772 and 399) which may have had limited power. Among studies which measured CO levels in parts per million (ppm, as used more commonly than $\mu g/m^3$ or mg/m^3), the four studies finding a significant effect presented effect sizes that were fairly consistent, each estimating a 2–4% increase in MI risk per 1 ppm increase in CO.[5 15 16 20] For NO_2, effect sizes ranged from a 1% to a 9% increase in risk per 10 ppb increase in NO_2 levels, though the largest effects appeared in study populations restricted to those aged >65 years.[20 21] Comparison of effect sizes among the four studies reporting an SO_2 effect is more difficult since different pollutant measures were used between the studies. Finally, it is worth noting that the effects of these gases, where reported, appeared to operate relatively quickly: in most cases either on the same or next day.

Vulnerability among subgroups

A number of the studies described in this review included analyses stratified by various factors to assess the vulnerability of particular subgroups to any effects of air pollution on MI risk. In general, study reports did not state whether such subgroup analyses were preplanned and their results should thus be interpreted cautiously. Most commonly investigated was the role of age.

Barnett *et al*,[20] who found detrimental effects of $PM_{2.5}$, CO and NO_2 among those aged ⩾65 years (table 3), reported that effects for those aged <65 years, though in the same direction, were smaller and non-significant, though it should be noted that event rates were lower among this age group so that lack of power might have been responsible for the lack of a statistically significant effect. Lanki *et al*[12] correspondingly reported that the effects of CO and particle number concentration were larger among those aged ⩾75 years, though only for non-fatal outcomes (for CO: relative risk (RR) per 0.2 mg/m^3 = 1.015, 95% CI 1.004 to 1.026 compared with 1.001, 0.995 to 1.008 for those aged <75 years); indeed the opposite effect was seen when fatal MIs were considered. The detrimental effects of ozone[23] and of traffic exposure[26] also appeared to increase for older subgroups. In contrast, Sullivan reported no modification by age of the effect of $PM_{2.5}$ on MI risk.[24]

Other potential effect modifiers were less commonly investigated. One study considered the effects or $PM_{2.5}$ by race, sex and smoking status, and found no differences[24]; this was in contrast with a study suggesting that the effect of $PM_{2.5}$ may be

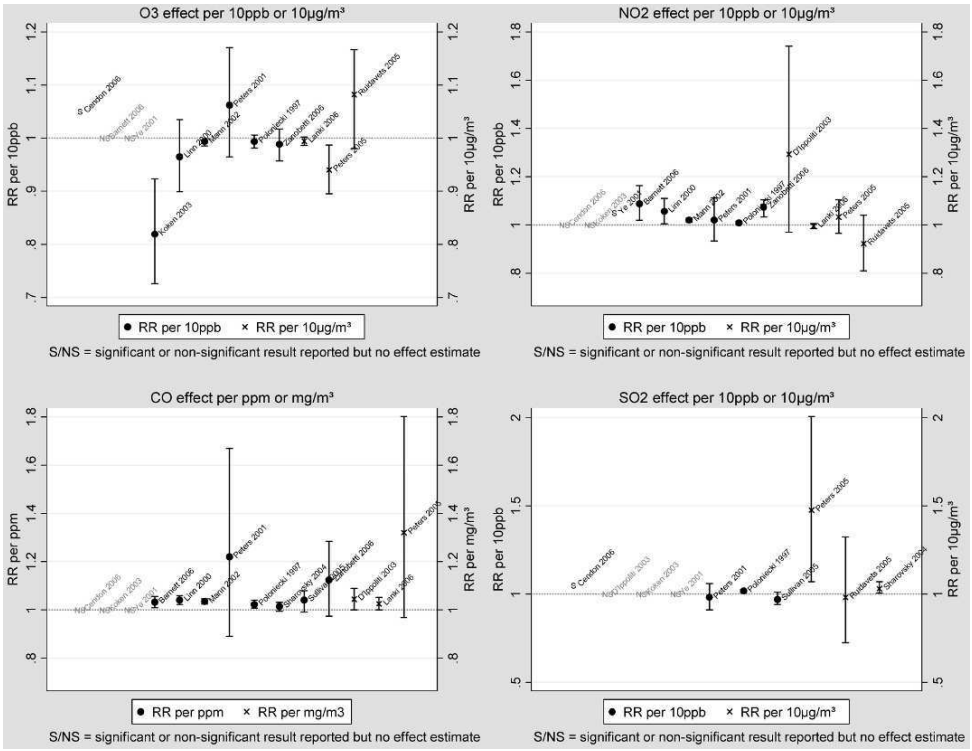

Figure 3 Estimated effects of gaseous pollutants on myocardial infarction risk. RR, relative risk.

larger among never-smokers than current- or ex-smokers (OR per IQR increase = 1.20, 95% CI 1.04 to 1.39 for never-smokers compared with 1.04, 0.90 to 1.21 for current smokers),[22] and that increased risk associated with traffic exposure may be larger among women than among men (OR per IQR increase = 4.51, 2.55 to 8.00 for women compared with 2.59, 1.90 to 3.53 for men).[26] The detrimental effects of traffic exposure were also reported to be larger among those out of employment, though confidence intervals were overlapping (OR = 4.20, 95% CI 2.88 to 6.12 compared with 2.20, 1.47 to 3.28 for those currently employed).[26]

Long-term effects of air pollution

Seven studies attempted to look at the long-term effects of cumulative exposure to air pollution on MI risk (table 4). Among these were three cohort studies in which "healthy" subjects were followed up for a number of years, and MI events accrued prospectively. Naturally, this approach can lead to relatively few events being included; indeed in the seventh-day Adventists cohort of 6303 subjects, only 62 MIs were observed[30 31] and, though no effects of NO_2, ozone or total suspended particles were found, large confidence intervals meant that important effects in either direction could not be ruled out. A more recent study included 584 MIs in a very large cohort of postmenopausal women (n = 65 893); no significant effect of $PM_{2.5}$ was found (HR = 1.06 per 10 μg/m^3 increase, 95% CI 0.85 to 1.34).

Two case–control studies found detrimental effects of long-term exposure to traffic, both for a directly estimated traffic exposure based on (road length × traffic density) as measured near the place of residence (OR = 1.04, 1.02 to 1.07 per 794 vehicle-km),[32] and for NO_2 exposure classified by residential district (OR = 1.43, 1.07 to 1.35 for regions with "high" versus "low" NO_2 levels).[34] The latter effect was reported to be stronger in older people (OR = 2.07, 1.28 to 3.35 for those aged 55–64 years). However, two further studies reported no effect of long-term exposure to NO_2,[33 35] or to PM_{10}, CO, or SO_2.[33]

DISCUSSION

This review has concentrated principally on the effects of specific pollutants on the risk of MI. To our knowledge this is the first time the evidence base for pollution effects on this specific outcome has been systematically reviewed. Our search strategy is likely to have identified the majority of major studies focusing on this question, and we have taken steps to include studies where our specific outcome of interest was investigated as a subanalysis within a broader study.

From a total of 19 studies looking at short-term pollution effects, fairly persuasive evidence emerges of some short-term effect on MI risk. Among particle exposures, though no effect of PM_{10} was found in most studies, increasing daily $PM_{2.5}$ levels were commonly associated with increasing MI risk between 0 and 2 days later. Increases in risk of 5–7% for a 10 μg/m^3 increase in $PM_{2.5}$ levels were typically reported, though one study reported an effect over three times this size. The evidence concerning effects of gaseous pollutants was more mixed: increases in CO, NO_2, and SO_2 were all associated with increases in MI risk in a substantial proportion of studies, yet just over half of the studies that investigated each of these exposures reported no effects. Surprisingly, higher levels of ozone were in a number of studies associated with a reduction in MI risk. However, ozone levels may be reduced close to sources of nitric oxide (such as vehicular traffic), where the two gases react to produce NO_2. It has also been suggested that a negative correlation between ozone and methyl nitrate (a combustion product of some engine fuels) might be responsible for such paradoxical associations.[36] Thus higher ozone levels may be acting as a marker of reductions in other pollutants. Of note, none of the studies finding significant protective effects of ozone looked at the effect in multipollutant models. An alternative explanation for the inconsistent effects observed for ozone is that since this gas may react with indoor surfaces, exposure measures based on outdoor monitors may be an inadequate marker of personal exposure among people spending a substantial proportion of their time indoors. We noted that among a limited number of studies that examined the question of effect modifiers, there was some suggestion that older people might be more vulnerable to the detrimental effects of pollution.

Though the evidence concerning most commonly measured pollutants may appear to be varied and sometimes conflicting, it should be borne in mind that the studies included were conducted using varying methodologies, and in varying situations. Variation in estimated effects may have been caused by a number of factors: different locations may have had differing underlying pollutant levels, different populations may have had differing susceptibilities, and different methods of exposure measurement, event ascertainment and statistical analysis may have led to differing results. With the earliest study of short-term effects meeting our inclusion criteria published in 1997, the quality of methodology seen in these studies reflects recent standards, with widespread attempts to control for important potential confounders, such as season, trend and ambient temperature, using statistical models. The majority of studies also included non-fatal MIs, which may be less susceptible to misclassification than MI deaths; some further validated MI diagnoses by having ECG and enzyme data examined by study investigators. Nevertheless, two important possibilities are that residual confounding by ambient temperature among studies performing only basic adjustments for temperature, and inclusion of misclassified events, may both have led to spurious results. The number of variations in study methodology, populations and settings make the extent of this problem difficult to ascertain. We did note that among the studies finding a relatively low proportion of significant pollutant effects were the few which had adjusted for lagged effects of temperature beyond the previous day,[12–14 18] and a number of the studies in which MIs were separately validated against diagnostic criteria.[12 22–24] However, this is at best suggestive and such differences in results might have a number of other explanations.

More generally, there are some inherent limitations in observational studies of air pollution effects. A common concern is that pollution measured by outdoor monitors may not be a good measure of overall personal exposure[37] since indoor pollution sources are ignored, although median correlations as high as 0.92 have been reported between personal $PM_{2.5}$ exposure in homes without environmental tobacco smoke[38] and levels as measured by a central outdoor monitoring station. Correlations may nevertheless be substantially lower depending on indoor pollution sources in individual homes (notably from smoking, heating and cooking). For example, it has been suggested that personal exposure to ozone[39] and nitrogen dioxide may be inadequately captured by ambient outdoor levels; indeed for the latter, indoor exposure, particularly for those with gas cookers, is likely to exceed exposure outside the home.[40] More generally, ambient PM may be a better proxy

than ambient gases for corresponding personal exposures.[41] In time-series studies, by design, exposure must be averaged over the whole region being analysed. This leads to a second potential weakness since in reality levels of pollutants may vary substantially over, say, a city. Although the case-crossover design allows for individualised exposure measures, in practice exposure must be approximated using the limited number of pollution monitors available, so the same problem arises. Only the study by Peters *et al*,[26] in which the exposure of interest was exposure to traffic, used a truly individualised exposure, based on diary data. Finally, since commonly measured air pollutants are likely to be highly correlated in any given situation, and unmeasured pollutants may also confound associations, studies such as those included here are unlikely to provide reliable evidence about the separate effects of individual pollutants.

A number of possible mechanisms have been suggested through which air pollution may affect cardiovascular function and trigger acute events. First, increases in levels of inflammatory markers such as C-reactive protein[42] at times of higher ambient pollution have been observed, suggesting a systemic inflammatory response associated with exposure, though a number of experimental studies have reported no clear systemic inflammatory response to pollutants.[43 44] Second, observational studies have linked higher levels of exposure to particulate air pollution with increases in heart rate[45] and decreases in heart rate variability[42]; furthermore, an increase in discharges of implanted cardioverter-defibrillators has been reported following increases in ambient exposure to fine particles, NO_2, CO and black carbon.[46] Third, air pollution may induce changes in blood viscosity and factors that may increase the propensity to clot or impair the dissolution of thrombi: plasma viscosity increased among people exposed to a severe episode of air pollution in Germany in 1985.[47] Controlled exposure experimental studies have demonstrated concentrated environmental particles leading to an increase in plasma fibrinogen levels in healthy volunteers,[48] and dilute diesel exhaust leading to an increase in thrombus formation (measured using an ex vivo perfusion chamber) and platelet activation,[49] and an impairment of the acute release of tissue plasminogen activator, an enzyme involved in the breakdown of blood clots.[44] A fourth possible pathway is suggested by a study in rats in which exposure to urban particulate matter led to an increase in endothelins, which act as vasoconstrictors.[50] Indeed, controlled exposure to a mixture of concentrated ambient particles and ozone in humans led to arterial vasoconstriction in one study,[51] whereas an observational study reported an increase in blood pressure associated with increased $PM_{2.5}$ levels in patients undergoing cardiac rehabilitation.[52]

Finally, a few individual studies have reported observations suggesting other possible mechanisms: air pollution exposure has been associated with accelerated progression of atherosclerosis and decreased plaque stability,[53] decreased oxygen saturation and hypoxaemia,[54] and increased ischaemic burden.[44] With observational and experimental evidence seemingly supporting a number of potential pathways, it seems plausible that exposure to air pollution may affect the risk of acute cardiac events through multiple mechanisms. The exact compounds responsible are difficult to disentangle on current levels of evidence: in observational studies, ambient levels of any given pollutant are likely to be highly correlated with other pollutants, and experimental studies to date have tended to deliver composite exposures comparable with "real-world" exposures.

The final part of this review considered studies looking at longer-term effects of air pollution. A small number of prospective cohort studies have observed only a small number of events and thus reported effect estimates with wide confidence intervals. Notably, two case–control which looked at long-term exposure to traffic based on place of residence (one directly, and one using NO_2 exposure as a proxy) did show a detrimental effect; however, these effects might be confounded by factors related to socioeconomic status and occupation. Thus, in contrast with short-term effects, the evidence base for long-term effects of air pollution exposures on MI risk is limited and few convincing conclusions can be drawn.

Air pollution guidelines[55] and legal limits[56 57] have generally not been based on cardiovascular outcomes. For example WHO recommend that average levels of PM_{10} (24 h average), ozone (8 h average), SO_2 (24 h average) and NO_2 (1 h average) should not exceed 50, 100, 20 and 200 $\mu g/m^3$, respectively, but these limits were derived principally from data on mortality (for PM_{10} and ozone) and respiratory outcomes among vulnerable individuals (for SO_2 and NO_2).[55] However, a notable implication of the linear pollution effects on MI risk estimated by most studies in this review is that if real, these effects would have an impact even below any threshold pollutant levels set by governments.

Our review has its limitations. First, our search strategy might have missed some studies. However, by searching a number of different databases, with different indexing systems, and furthermore, checking reference lists and the websites of major organisations, we believe that all major studies with MI as the primary outcome should have been picked up. We also took steps to include studies of cardiovascular diseases more broadly, where an analysis of MI was also performed separately. Our decision to include only papers analysing specific MI outcomes may also have led to some informative studies of related outcomes being excluded, though we believe that this is outweighed by the advantage in interpretability from the very specific focus on MI. Second, as with any review of the literature, there may have been publication bias: studies finding effects may have been more likely to be published. The extent of publication bias is difficult to assess in studies with such varied methodology and reporting. Though such concerns should always be borne in mind, our goal was not to produce a definitive numerical estimate of the effects of pollution effects on MI risk, but rather to give an overview of the evidence available. Finally, we did not include non-English-language citations owing to resource limitations, but we believe that this is unlikely to have led to the omission of any major papers in the area.

In conclusion, although the available literature is variable and sometimes conflicting, our review does seem to reveal compelling evidence for some effect of air pollution on MI risk based on studies in a variety of settings. There is much room for further research. The exact role of individual pollutants is unclear, and perhaps only further experimental studies under controlled conditions can deal with this topic. A large number of potential mechanisms have been suggested and though some have the support of limited data, no single mechanism has emerged as the most likely; indeed, multiple mechanisms may be at work, and further work may disclose the relative importance of each. There is also a need for biomarkers of exposure which can be used in epidemiological studies to give more reliable estimates of individual exposure to air pollutants. Finally, future studies may investigate factors that may make some people or indeed

populations more susceptible than others to the detrimental effects of air pollution.

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BMJ

RESEARCH

Short term effects of temperature on risk of myocardial infarction in England and Wales: time series regression analysis of the Myocardial Ischaemia National Audit Project (MINAP) registry

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ABSTRACT

Objective To examine the short term relation between ambient temperature and risk of myocardial infarction.

Design Daily time series regression analysis.

Setting 15 conurbations in England and Wales.

Participants 84 010 hospital admissions for myocardial infarction recorded in the Myocardial Ischaemia National Audit Project during 2003-6 (median 57 events a day).

Main outcome measures Change in risk of myocardial infarction associated with a 1°C difference in temperature, including effects delayed by up to 28 days.

Results Smoothed graphs revealed a broadly linear relation between temperature and myocardial infarction, which was well characterised by log-linear models without a temperature threshold: each 1°C reduction in daily mean temperature was associated with a 2.0% (95% confidence interval 1.1% to 2.9%) cumulative increase in risk of myocardial infarction over the current and following 28 days, the strongest effects being estimated at intermediate lags of 2-7 and 8-14 days: increase per 1°C reduction 0.6% (95% confidence interval 0.2% to 1.1%) and 0.7% (0.3% to 1.1%), respectively. Heat had no detrimental effect. Adults aged 75-84 and those with previous coronary heart disease seemed more vulnerable to the effects of cold than other age groups (P for interaction 0.001 or less in each case), whereas those taking aspirin were less vulnerable (P for interaction 0.007).

Conclusions Increases in risk of myocardial infarction at colder ambient temperatures may be one driver of cold related increases in overall mortality, but an increased risk of myocardial infarction at higher temperatures was not detected. The risk of myocardial infarction in vulnerable people might be reduced by the provision of targeted advice or other interventions, triggered by forecasts of lower temperature.

INTRODUCTION

In the light of global climate change the relations between weather and health are of increasing interest. In several studies ambient outdoor temperature was shown to affect mortality rates in the short term. A study in 11 US cities found a U-shaped relation between temperature and all cause mortality, with mortality decreasing as temperatures increased from the coldest days up to a certain threshold temperature, above which mortality increased with temperature.[1] A similar pattern has been observed in Europe[2] and in several lower and middle income countries.[3] Detrimental effects of both hot and cold days have also been associated with cardiovascular mortality.[4-6]

Less commonly investigated has been the short term effect of ambient temperature on risk of myocardial infarction. A recent systematic review suggested compelling evidence of some temperature effect but was inconclusive on the size or direction of the effect: eight of the 12 studies with data from the winter season found a statistically significant increased risk of myocardial infarction at colder temperatures, whereas seven of 13 studies found a statistically significant detrimental effect of heat, with effect estimates ranging from a 7% to 40% increase in rates of myocardial infarction on days with the most extreme temperatures.[7] Only a few studies have controlled for potentially important confounding variables such as air pollution and circulating influenza levels, which could be associated with both temperature and risk of myocardial infarction. Furthermore, concerns were expressed about the specificity of the outcome in some studies owing to the lack of separate validation, with the potential for inclusion of events not related to myocardial infarction.

We examined the short term effects of temperature in 15 conurbations in England and Wales, controlling for important confounders and making use of a large audit database of myocardial infarction events within which the validity of events could be confirmed against marker data from electrocardiographs and laboratories.

METHODS

The Myocardial Ischaemia National Audit Project (MINAP) is a national register of all hospital admissions for myocardial infarction and other acute coronary syndromes, with participation of all hospitals in England and Wales that admit patients with these conditions. The identification of admissions is managed at individual hospital level; guidelines recommend a combination of approaches to identify eligible admissions, including biochemistry records (specifically measurements of troponin), admission notes, and discharge slips. The database includes 123 fields covering basic demographic data, timing of onset of symptoms, changes on electrocardiographs, markers of myocardial necrosis, final diagnosis, thrombolytic or other treatment received, and the geographical coordinates of the super output area (an area with a mean population of 1500) containing the patient's place of residence. Also recorded are pre-existing comorbidities, including hypertension, diabetes, and previous cardiovascular events. We included all events with a discharge diagnosis classified as ST elevation myocardial infarction, non-ST elevation myocardial infarction, or troponin positive acute coronary syndrome, occurring among patients residing within one of 15 conurbations in England and Wales (Greater London, West Midlands, Greater Manchester, West Yorkshire, Tyneside, Liverpool, Nottingham, Sheffield, Bristol, Leicester, Potteries, Cardiff, Southampton, Kingston upon Hull, Norwich) during 2003-6. Conurbation boundaries were predefined to match earlier work.[8] In a separate sensitivity analysis we reran our final model including only those events that could be validated within the Myocardial Ischaemia National Audit Project database against the presence of recorded raised markers (troponin or creatine kinase) or an electrocardiograph trace showing ST elevation or left bundle branch block.

Meteorological data

We downloaded data on weather, in particular daily minimum and maximum temperature, temperature at 9 am and 3 pm, and dewpoint temperature, from the British Atmospheric Data Centre, listed by weather monitoring station and date of measurement. Daily mean temperature was then generated, approximated as the mean of the daily minimum and maximum temperature. We derived daily relative humidity from the measurements of dewpoint and temperature at 9 am and 3 pm. When data from more than one station were available in a conurbation, we combined these to one series using the AIRGENE (air pollution and inflammatory response in myocardial infarction survivors: gene-environment interaction in a high risk group) algorithm.[9] After combining data in conurbations with multiple stations, eight conurbations had missing data. However, 10 complete temperature series were available at a broader level, based on the following regions: North East, North West, Yorkshire and the Humber, East Midlands, West Midlands, East, London, South East, South West, and Wales. All available monitoring data are drawn from the area to produce a representative series for the whole region. We used these series as a basis for imputing data for days with missing temperature at the narrower level of conurbation. Specifically, for each conurbation we fitted a simple linear regression model over all days in 2003-6, relating daily conurbation temperature to daily regional temperature; this model was estimated using days with no missing data on conurbation temperature and then used to predict conurbation temperature on days with missing data.

Data on pollution and infectious disease levels

We downloaded data on daily mean levels of particulate matter with diameters less than 10 μm (abbreviated to PM10 and measured as mass in μg per m^3 of air) and ozone, from the UK air quality data and statistics database. To generate a pollution series for each conurbation for inclusion in our models, we used data from background pollution monitors only, located within one of the 15 conurbations (one to 13 monitors per conurbation). Again we used the AIRGENE algorithm to combine data from multiple stations within a conurbation.

As a measure of level of circulating viral infections, we obtained daily counts of laboratory confirmed cases of influenza A and respiratory syncytial virus for each of 10 UK regions, from the UK Communicable Diseases Surveillance Centre at the Health Protection Agency.

Statistical analysis

We carried out an ecological time series regression analysis: the daily number of myocardial infarction events was the outcome in a generalised linear model with Poisson error structure, and with scale variables set to the Pearson χ^2 statistic divided by the residual degrees of freedom to model overdispersion.[10,11] The main exposure of interest was daily mean temperature. To control for seasonality and long term trend we also included in the model a smooth function of calendar date based on splines, estimated separately for each conurbation. A spline function, defined by piecewise polynomials, has a flexible shape that is useful for modelling unknown and potentially variable seasonal and long term patterns. The smoothness of a spline is a function of the number of degrees of freedom; we chose seven degrees of freedom per calendar year in keeping with previous studies, as a compromise between providing adequate control for unmeasured confounders and leaving sufficient information from which to estimate temperature effects.[12,13] We adjusted the model for day of the week and public holidays, levels of influenza and respiratory syncytial viruses (three categories representing 0, 1, or ≥2 laboratory confirmed cases in the particular conurbation), and PM10 and ozone levels (each modelled at lag days 0-3 inclusive as there seems to be little evidence of pollution effects at longer lags[14]). We also controlled for

daily relative humidity (average of the current and previous three days) using a four knot natural cubic spline to allow for non-linearity.

To model the effects of mean temperature we used five lag periods: the average of lag days 0-1, 2-7, 8-14, 15-21, and 22-28. We chose the 0-1 day short lag period because mortality studies suggest that any effects from heat would probably operate with little delay.[15 16] Effects of cold have been reported with longer delays and hence the remaining terms covered delays of up to 28 days, with weekly groupings chosen to allow more precise estimation of effects, and because at longer lags any temperature effects would be unlikely to vary sharply from day to day. To obtain an initial visual estimate of the temperature effect, we included a natural four knot cubic spline for each of the five lagged temperature effects and we used Wald tests to assess the statistical significance of the overall temperature effect (testing all five spline terms) and its non-linearity (testing only the four non-linear terms). We then considered simplified temperature effects with more directly interpretable numerical coefficients—namely, linear and linear threshold temperature models. In the linear threshold temperature models a linear temperature effect only operates below a certain "threshold" temperature, and we fitted the model repeatedly with every possible threshold from the fifth to the 95th centile of mean daily temperature in 1°C steps. We also allowed the thresholds to be specified centiles of temperature within the conurbation, assessing the fifth, 10th, 15th . . . 95th centiles. These models were compared and we selected the final temperature effect specification by choosing the model with the lowest Akaike information criterion.

We estimated the cumulative effect of temperature by summing (on the log scale) the regression coefficients of the five individual lagged effects. For a given day, this cumulative effect can be interpreted as the total effect of a difference in daily temperature over the current and following 28 days.[17] We assessed the heterogeneity of the estimated effects of temperature and potential confounders by including interaction terms and using Wald tests to assess their statistical significance.

Finally, we did an exploratory analysis to assess effect modification by age, sex, previous coronary heart disease, previous hypertension, and current aspirin use. We investigated each potential effect modifier separately: the daily number of events was broken down by the factor under consideration, which was itself included in the model as an interaction with the daily temperature. For the purposes of this exploratory analysis, we included only a single temperature term (average of lag days 0-28) to allow the models to fit, given the small numbers of events in some subgroups. The temperature effect from such a model is comparable to the estimate of the cumulative effect over all lag days, as obtained by summing the five lag terms in our main model.

As well as rerunning our final model including only validated myocardial infarction events, we carried out several other sensitivity analyses, modifying the final model. Firstly, we used minimum and then maximum daily temperature in place of mean daily temperature. Secondly, we varied the number of degrees of freedom per year used to define the spline function of date, used to adjust for season and long term trends. Thirdly, we excluded all but the five conurbations with the highest daily event rates—Greater London, Greater Manchester, West Midlands, Tyneside, and West Yorkshire, all of which had median daily events of at least four). Fourthly, to include information from the 9.5% of observations with missing pollution levels (PM10 or ozone, or both), we used a multiple imputation procedure with five imputations to handle the missing data. For the imputation we used a multivariate normal model for PM10 and ozone levels containing all variables from the final temperature model. Finally, in case of residual autocorrelation in the final model, we added lagged deviance residuals to the model for each conurbation in which significant early residual autocorrelation was seen (as defined by absolute partial autocorrelations of the deviance residuals exceeding 0.05 at lag days 0-3).[18] For each sensitivity analysis we estimated the temperature effect at each lag, as well as the cumulative temperature effect.

RESULTS

Between January 2003 and December 2006, 84 010 events (median 57 per day, interquartile range 50-64 per day) were recorded within the 15 conurbations of interest (table 1). Greater London had the largest number of events (26 607, median 18, interquartile range 15-21, range 5-36 per day) and Kingston upon Hull the least, with events recorded on only 23.5% of days (407, median 0, interquartile range 0-0, range 0-3 per day). Overall, 35 664/84 010 (42%) of myocardial infarction diagnoses were ST elevation myocardial infarction and 74 185 (88%) were confirmed by at least one recorded corroborative electrocardiograph trace (for ST elevation myocardial infarction) or raised troponin or creatine kinase levels, or both.

Myocardial infarction events were recorded at a median age of 70 years (interquartile range 58-79 years) and 64.5% (53 819/83 424) of patients whose sex was recorded were men. The daily mean temperature ranged from −3°C to 27°C across the 15 conurbations, with individual conurbations having a median value of between 9°C and 12°C during 2003-6 (table 1).

Modelling temperature effects as flexible curves

Flexible curves representing the combined effect of temperature across all 15 conurbations, adjusted for potential confounders, were compatible with a broadly linear effect of temperature at short lags (days 0-1 and 2-7), with the risk of myocardial infarction increasing at lower temperatures, although the temperature effect was not significant at days 0-1 (P=0.62, fig 1). At days 8-14 evidence of a temperature effect was strong (P=0.006); again an increase in the risk of myocardial infarction was seen at lower temperatures, and

Table 1 | Temperature and characteristics of myocardial infarction events in 15 conurbations and overall

Conurbation	Median (range) of daily mean temperature (°C)	Total No of MIs	STEMI (%)	Median (interquartile range) MIs per day	Men (%)	Median (interquartile range) age*	Evidence supporting diagnosis† (%)
Bristol	11 (−2-26)	2376	1007 (42)	1 (0-2)	1519/2354 (64.5)	71 (60-80)	2224 (94)
Cardiff	12 (0-25)	1471	507 (34)	1 (0-2)	857/1464 (58.5)	75 (63-83)	1446 (98)
Greater London	12 (−1-27)	26 607	12 048 (45)	18 (15-21)	17 863/26 532 (67.3)	69 (57-79)	23 319 (88)
Greater Manchester	11 (−3-26)	12 434	5139 (41)	8 (6-11)	7722/12 424 (62.2)	71 (59-80)	10 492 (84)
Kingston upon Hull	11 (−2-23)	407	369 (91)	0 (0-0)	278/406 (68.5)	64 (56-73)	400 (98)
Leicester	10 (−2-23)	1768	969 (55)	1 (0-2)	1239/1768 (70.1)	68 (56-77)	1685 (95)
Liverpool	11 (−3-24)	4358	1674 (38)	3 (2-4)	2623/4355 (60.2)	72 (61-80)	3775 (87)
Norwich	10 (−2-25)	874	339 (39)	0 (0-1)	605/874 (69.2)	70 (60-77)	863 (99)
Nottingham	10 (−2-23)	1488	907 (61)	1 (0-2)	974/1476 (66.0)	68 (57-77)	1374 (92)
Potteries	10 (−3-25)	2205	854 (39)	1 (1-2)	1437/2205 (65.2)	72 (60-80)	1713 (78)
Sheffield	10 (−2-24)	4903	1443 (29)	3 (2-5)	2891/4878 (59.3)	72 (61-81)	4536 (93)
Southampton	12 (0-25)	1259	517 (41)	1 (0-1)	875/1259 (69.5)	69 (58-78)	1248 (99)
Tyneside	10 (−2-23)	8017	2409 (30)	5 (4-7)	4697/8010 (58.6)	72 (60-81)	6717 (84)
West Midlands	10 (−3-24)	9265	4827 (52)	6 (4-8)	6258/9245 (67.7)	68 (57-77)	8646 (93)
West Yorkshire	9 (−2-22)	6578	2655 (40)	4 (3-6)	3981/6174 (64.5)	69 (58-77)	5747 (87)
Overall	11 (−3-27)	84 010	35 664 (42)	57 (50-64)	53 819/83 424 (64.5)	70 (58-79)	74 185 (88)

MIs=myocardial infarctions; STEMI=ST elevation myocardial infarction.
*Data on age available for 81 441/84 010 (97%) of diagnoses, and sex for 83 424/84 010 (99%) of diagnoses.
†Evidence for STEMI diagnoses was defined as either an electrocardiograph trace indicating ST elevation or left bundle branch block, or raised markers (troponin or creatine kinase); evidence on diagnoses for non-ST elevation myocardial infarction was defined as raised markers (troponin or creatine kinase) only.

although the curve suggested a levelling off of the effect at both the lower and the upper extremes of the temperature range, confidence intervals in these regions were wide, reflecting the limited number of days on which these extremes of temperature occurred. At lag days 15-21 and 22-28 we found little evidence of any continuing temperature effect, although in both cases the estimated curves were broadly in the direction of a detrimental effect of cold.

Selection of linear or threshold temperature models

Simplified specifications of the temperature effect using linear and cold threshold models were considered within the same modelling framework. The Akaike information criterion was minimised by the most parsimonious "all-linear" model (that is, without threshold, Akaike information criterion 67 414.1); in the optimal threshold model the cold threshold was at the 90th centile of temperature (Akaike information criterion 67 414.9). This in any case represents close to a linear temperature effect.

Description of effects in final model

It was estimated that a 1°C reduction in temperature on a given day would cumulatively increase the risk of myocardial infarction by 2.0% (95% confidence interval 1.1% to 2.9%) over the current and following 28 days, with the strongest effects being estimated at intermediate lags of 2-7 and 8-14 days (relative risk 1.006 (95% confidence interval 1.002 to 1.011) and 1.007 (1.003 to 1.011), respectively, table 2).

Estimates from the final model also showed evidence of effects of day of the week and PM10 levels. As expected, the risk of myocardial infarctions being reported on weekdays compared with weekends was estimated to increase: compared with Sunday, the risk of a myocardial infarction being recorded on a Monday was increased by 14%[11-17] and on Tuesday to Friday by 4-8%. Increases in PM10 levels were associated with a small increase in risk of myocardial infarction on the same day (relative risk 1.001, 95% confidence interval 1.000 to 1.002), although no effect of ozone level was observed (P=0.19).

Relative humidity did not seem to be associated with risk of myocardial infarction (P=0.29), although there was a non-significant increase in risk at both low and high humidity values: relative risk 1.03 (95% confidence interval 0.99 to 1.06) and 1.06 (0.99 to 1.13) at 55% and 95% compared with 75%).

Finally no evidence was found of effects of public holiday or of influenza or respiratory syncytial virus in the final model although effect estimates were in the direction expected in each case—that is, a reduced risk of myocardial infarctions being recorded on public holidays and an increased risk on days with several laboratory confirmed cases of influenza or respiratory syncytial virus infection.

Variation across conurbations

The temperature effect across conurbations was not heterogeneous (P for interaction 0.43). At lag days 2-7 and 8-14, at which significant combined cold effects were estimated, effect estimates were in a direction suggesting cold effects for 11 and 12 conurbations, respectively; however, the only conurbation in which these effects were individually statistically significant was Greater London (fig 2). Greater London had a median of 18 events a day compared with fewer than eight in all other conurbations and therefore was much better powered to detect these effects.

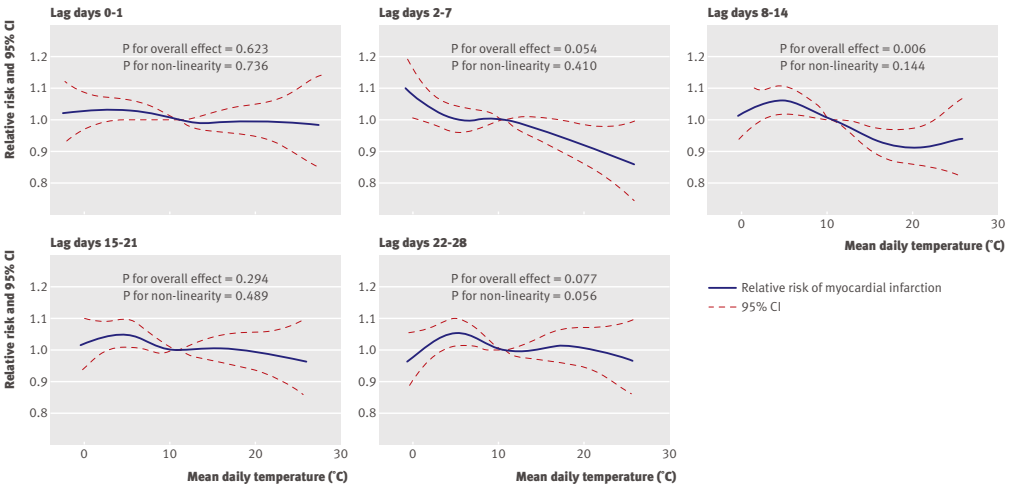

Fig 1 | Estimated relative risk of myocardial infarction by temperature in 15 conurbations combined, from a model including all five lag periods for temperature (0-1, 2-7, 8-14, 15-21, and 22-28 days) and adjusted for calendar time (stratified by conurbation), relative humidity (average of lags 0-3), day of week, public holiday, influenza, respiratory syncytial virus, PM10 level (lags 0-3), and ozone level (lags 0-3). Reference value for relative risk estimates is mean value of daily mean temperature across all days included

The effects of day of week (P=0.13), holiday (P=0.16), influenza (P=0.96), respiratory syncytial virus (P=0.23), PM10 levels (P=0.91), and ozone levels (P=0.56) did not vary across conurbations.

Effect modification by individual level factors

In a simplified model with a single temperature term (the average of lag days 0-28) evidence of effect modification by age was strong (P for interaction <0.001); notably, adults aged 75-84 seemed more vulnerable to the effects of cold than other age groups including the eldest (≥85): relative risk per 1°C reduction in temperature was 1.016 (95% confidence interval 1.007 to 1.025) for those aged less than 65, 1.018 (1.009 to 1.027) for those aged 65-74, 1.027 (1.018 to 1.036) for those aged 75-84, and 1.019 (1.009 to 1.029) for those aged 85 or more (fig 3). The temperature effect did not differ between men and women (P=0.80). Data were available on previous coronary heart disease (myocardial infarction or angina) for 82% of events, and those patients with previous disease seemed more vulnerable to the effects of temperature than those with no history of disease: relative risks per 1°C reduction in temperature 1.025 (1.015 to 1.034) and 1.019 (1.011 to 1.029); P for interaction 0.001. However, there was little evidence of any effect modification by previous hypertension (P for interaction 0.16). Finally, considering the 86% of events when data on current use of aspirin were available, those taking aspirin seemed less vulnerable to the effects of temperature than those not taking aspirin: relative risk per 1°C reduction in temperature 1.016 (1.006 to 1.026) compared with 1.022 (1.012 to 1.031); P for interaction 0.007. Effect modification by statin use was not assessed because of incomplete data.

Sensitivity analyses

To test the robustness of the effect estimates several modifications were made to the final model. The estimated overall temperature effect did not seem to be sensitive to restricting to only validated myocardial infarction events, using minimum and maximum daily temperature in place of mean temperature, restricting analyses to the five conurbations with the highest event rates, imputing pollution data to enable all observed data to be used, or including additional terms to allow for residual autocorrelation in the final model. For all of these sensitivity analyses the estimated cumulative effect of a 1°C reduction in temperature was between a 1.7% and 2.2% increase in risk of myocardial infarction, comparable to our final model estimate of a 2.0% increase in risk. Considering the temperature effect at specific lag periods, the effects of temperature at lag days 2-7 and 8-14 were estimated at 0.4-0.8% per 1°C reduction in temperature in all models, with no evidence of non-linearity in these effects. At shorter (0-1 day) and longer (15-21, 22-28 day) lag periods, the lack of evidence for a temperature effect was consistent across models.

Varying the level of seasonal control had only a small effect on the size and not direction of the estimated cumulative temperature effect: estimated effect

Table 2 | Estimated effects of temperature and potential confounders in final model

Potential confounders	Relative risk (95% CI)	Pvalue
Temperature (per °C drop):		
Lag 0-1	1.002 (0.998 to 1.005)	
Lag 2-7	1.006 (1.002 to 1.011)	
Lag 8-14	1.007 (1.003 to 1.011)	<0.001
Lag 15-21	1.003 (0.999 to 1.007)	
Lag 22-28	1.002 (0.998 to 1.006)	
Cumulative effect over all lags	1.020 (1.011 to 1.029)	
Relative humidity (%):		
55	1.03 (0.99 to 1.06)	
65	1.01 (0.99 to 1.03)	
75	1.00 (reference)	0.29
85	1.01 (0.98 to 1.04)	
95	1.06 (0.99 to 1.13)	
Day of week:		
Sunday	1.00 (reference)	
Monday	1.14 (1.11 to 1.17)	
Tuesday	1.05 (1.02 to 1.08)	
Wednesday	1.07 (1.04 to 1.10)	<0.001
Thursday	1.04 (1.01 to 1.07)	
Friday	1.08 (1.05 to 1.11)	
Saturday	0.99 (0.96 to 1.02)	
Public holiday:		
No	1.00 (reference)	0.21
Yes	0.97 (0.92 to 1.02)	
Confirmed cases of influenza A*:		
0	1.00 (reference)	
1	1.02 (0.99 to 1.05)	0.58
≥2	1.01 (0.97 to 1.05)	
Confirmed cases of respiratory syncytial virus*:		
0	1.00 (reference)	
1	0.99 (0.96 to 1.02)	0.84
≥2	1.01 (0.95 to 1.06)	
PM10 (per μg/m^3)†:		
Lag 0	1.001 (1.000 to 1.002)	
Lag 1	0.999 (0.998 to 1.000)	0.02
Lag 2	0.999 (0.998 to 1.000)	
Lag 3	1.000 (0.999 to 1.001)	
Ozone (per μg/m^3)		
Lag 0	1.000 (0.999 to 1.001)	
Lag 1	0.999 (0.999 to 1.000)	0.19
Lag 2	1.000 (0.999 to 1.001)	
Lag 3	1.000 (0.999 to 1.000)	

Model adjusted for season and trend using spline function of calendar date, with 7 knots per calendar year.
*Laboratory confirmed cases.
†Particulate matter with diameters less than 10 μm.

sizes were 1.2-1.4% for a 3-6 degrees of freedom per year spline; 1.8-2.0% for 7-9 degrees of freedom per year, and 1.0-1.4 for 10-14 degrees of freedom per year. Confidence intervals included our original estimate of a 2.0% increase in risk per 1°C reduction in temperature for all levels of seasonal control above 3 degrees of freedom per year.

DISCUSSION

Across the 15 conurbations in England and Wales included in our analyses we found a broadly linear association between daily mean ambient temperature and risk of myocardial infarction, with a 1°C reduction in temperature associated with a cumulative 2% (95% confidence interval 1.1% to 2.9%) increase in risk of myocardial infarction over the current and subsequent 28 days. Because myocardial infarctions are common, and ambient temperature is experienced by the whole population, even a small increase in risk translates to substantial absolute numbers of extra myocardial infarctions. For example, in the United Kingdom, which has an estimated 146 000 myocardial infarctions per year,[19] 11 600 events would be expected on average in a 29 day period; our results suggest that each 1°C reduction in temperature nationwide on a single day would be associated with around 200 extra myocardial infarction events. We found no evidence of any detrimental heat effect.

Comparison with other studies

The effects of lower temperatures seemed to operate most strongly at two to 14 days after the reduction in temperature. The absence of a more immediate effect may be characteristic of the underlying mechanism at work, or might simply reflect delays in patients with myocardial infarction being admitted to hospital. A similarly delayed cold effect has also been seen for overall mortality[16] although more immediate effects have also observed.[1]

In a recent systematic review of ambient temperature effects in studies with myocardial infarction outcomes, increases in risk of myocardial infarction at both higher and lower temperatures were reported by different studies, with four studies reporting both effects.[1] However, a key finding of the review was the highly variable methodology among studies in this area to date; only a few controlled for air pollution and levels of infectious diseases such as influenza, or investigated lagged temperature effects beyond a few days; control for season and long term trend has also been inconsistent. Two studies that did address all of these methodological concerns were those of data on myocardial infarction related mortality, which found a detrimental effect of heat[20] or of both heat and cold.[21] Such data may, however, have poor specificity because in a proportion of cases the myocardial infarction diagnosis is likely to be assumed; therefore these findings in reality may reflect temperature effects on more broad health outcomes. In contrast, of five studies that analysed validated myocardial infarction outcomes separately, only one based in a subarctic area reported a detrimental heat effect,[22] most reporting an adverse effect only of cold.[23-25] This is in keeping with the present analysis, which was based on an audit database in which 88% of myocardial infarction events were corroborated by an electrocardiograph trace, raised markers, or both, and in which our findings were robust to exclusion of the remaining 12% of events.

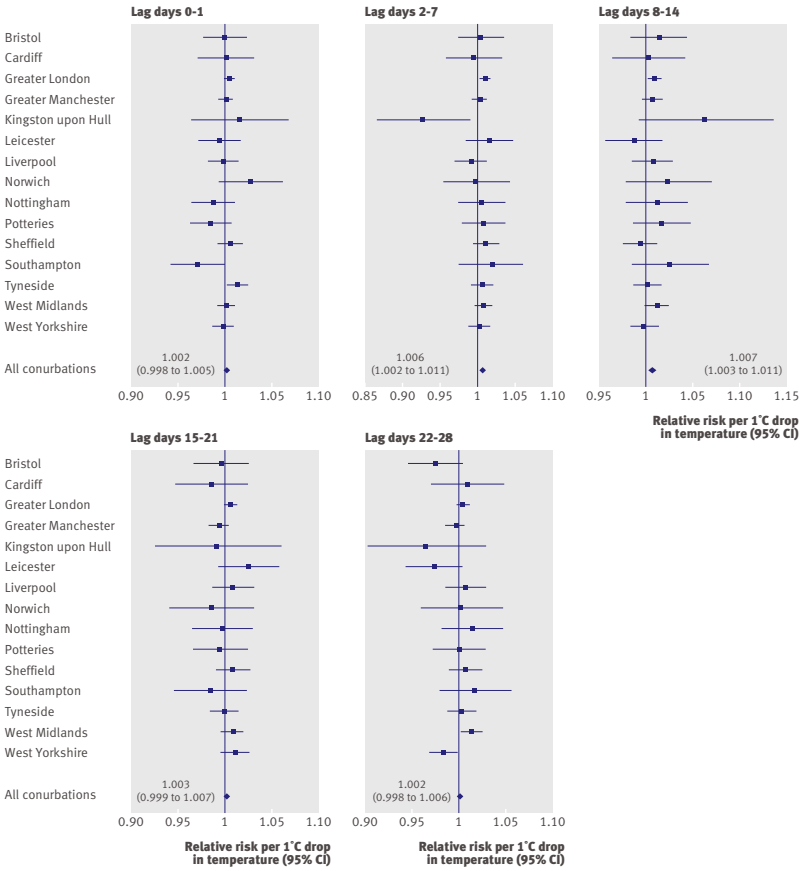

Fig 2 | **Estimated relative risk of myocardial infarction per 1°C reduction in temperature by conurbation. Estimates from a combined model including five temperature terms (lag days 0-1, 2-7, 8-14, 15-21, and 28), adjusted for calendar time (stratified by conurbation), and fixed effects across conurbations of relative humidity (average of lags 0-3), day of week, public holiday, influenza, respiratory syncytial virus, PM10 level (lags 0-3), and ozone level (lags 0-3)**

We observed evidence of effect modification by age, with those aged 75-84 apparently more vulnerable to temperature effects than other age groups. Only a few studies have investigated the effects of temperature on risk of myocardial infarction by age group; one reporting an increased cold effect among those aged more than 65[26] and a further two found no difference in effects when restricting their analyses only to older age groups.[23,24] The age structure of patients recorded in MINAP allowed us to subdivide those aged 65 or more into three age groups and it was of interest that an increased vulnerability did not extend into the oldest group (85 or more). A possible explanation is that people in this age group may spend less time outdoors and may be more likely to live in residential or nursing homes with effective heating systems. We also observed an increased vulnerability to cold among those with previous coronary heart disease, although we were not able to assess the three way interaction between temperature, age group, and previous coronary heart disease owing to low numbers of daily events in the combined subgroups; therefore whether the vulnerabilities owing to age and previous disease are independent remains an open question. People not taking aspirin also seemed to be more vulnerable to temperature effects.

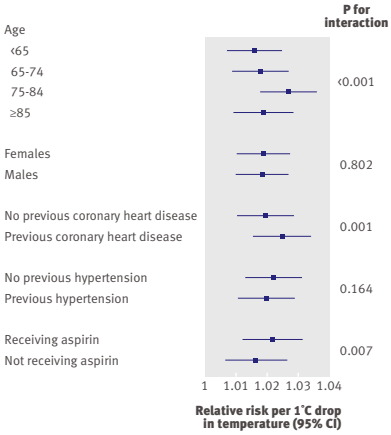

Fig 3 | **Estimated relative risk of myocardial infarction per 1°C reduction in temperature: effect modification by age, sex, history, and aspirin use. Graph shows estimated effect of temperature (average of lag days 0-28), adjusted for calendar time (stratified by conurbation), and fixed effects across conurbations of relative humidity (average lags 0-3), day of week, public holiday, influenza, respiratory syncytial virus, PM10 levels (lags 0-3), and ozone levels (lags 0-3)**

Policy implications and possible mechanisms

Identifying subgroups that might be particularly vulnerable to cold effects is of interest since one potential application of our findings would be to inform a targeted early warning system based on forecasted weather, similar to that recently set up by the UK Meteorological Office for people with chronic obstructive pulmonary disease: when the risk of exacerbation of this disorder is increased because of low ambient temperature, people who are at risk are given advice through automated telephone calls, such as to keep warm, stay indoors, and watch for warning signs of their condition worsening; reductions in hospital admissions of between 15% and 76% have been reported among practices in the scheme.[27] Our results suggest that for risk of myocardial infarction at colder temperatures, older people, those with coronary heart disease, and people who do not take aspirin could benefit from a similar targeted approach. However, since our findings imply an effect of temperature across the temperature range, and even among people outside the most vulnerable groups, a more widespread health education message aimed at reducing the impact of lower temperatures may be of value; such approaches should be evaluated.

Several mechanisms have been proposed to explain an effect of temperature reductions on risk of myocardial infarction. Exposure to cold under controlled conditions has been associated with increases in arterial pressure, blood viscosity, and cardiac workload.[28,29] A mobilisation of granulocytes has been observed,[30] and red cell counts and plasma cholesterol and fibrinogen concentrations, all of which may be thrombogenic, seem to be raised after exposure to cold.[28,31] Finally, one study has suggested that the density distribution of blood platelet subpopulations may be affected, with an observed increase in less dense platelets that were more sensitive towards agents that induce aggregation.[32] These small experimental studies combine to suggest that a pathway for cold induced thrombogenesis might involve a combination of factors, including haemoconcentration, an inflammatory response, and a tendency for an increased state of hypercoagulability. Furthermore, our observation that aspirin seemed to be partially protective suggests that part of the effect may be mediated by changes in platelet function. However, more recent data have been lacking and these hypothesised mechanisms need to be tested in larger studies examining a range of updated measures. Finally, it is possible that the observed effect of temperature reductions is not explained purely by direct biological pathways, but wholly or partly by other behaviour associated with lower temperatures—for example, increased snow shovelling activity might explain increases in risk of myocardial infarction at the lower extremes of temperature,[33] although this would not explain the observed effect across the temperature range.

Interestingly, we did not detect any detrimental effect of temperature increases on risk of myocardial infarction. There are a few possible explanations for this. Firstly, temperature in the United Kingdom is rarely very high in global terms; although we included data from the unusually hot summer of 2003, even the warmest periods are brief, which may have limited our ability to detect a heat effect. Such heat effects, however, have been established in studies of overall mortality even in a UK setting.[15] A second possibility is that any heat effects might have been too immediate to be detected by a daily time series study; data at a finer temporal resolution would be of interest. Finally, our results might simply reflect a genuine absence of any heat effect on myocardial infarction, indicating that other mechanisms are more important drivers of the heat-mortality relation; this is also indicated by mortality data from London that showed no increase in mortality from myocardial infarction at higher temperatures despite clear heat related increases in other cardiovascular deaths.[34]

Strengths and limitations of the study

Our study has some limitations. Firstly, the MINAP database is restricted to patients admitted to hospital; we therefore would not have included myocardial infarctions leading to death before hospital admission. The likelihood of a patient with myocardial infarction surviving to be admitted to hospital could conceivably be related to temperature if, for example, bad weather led to a delay in the ambulance. If such a mechanism were operating, however, it seems likely that the number of myocardial infarctions would then be

WHAT IS ALREADY KNOWN ON THIS TOPIC

Ambient outdoor temperature has been shown to affect mortality risk in the short term, with both hot and cold days associated with increased mortality

The effect of ambient temperature on the risk of myocardial infarction is unclear

WHAT THIS STUDY ADDS

In urban settings in England and Wales, a lower daily mean temperature was associated with an increased risk of myocardial infarction; no increased risk was detected at higher temperatures

Each 1°C reduction in temperature in the United Kingdom on a single day would be associated with around 200 extra myocardial infarction events

Older people (<85) and those with previous coronary heart disease seemed most vulnerable to the effects of temperature reductions; those taking prophylactic aspirin were less vulnerable

underestimated on particularly cold days, leading to an underestimation of the estimated adverse effects of cold. Secondly, owing to low numbers of events in some conurbations, the power to detect geographical heterogeneity of temperature effects was limited, and furthermore since our data were restricted to England and Wales we were unable to assess the hypothesis that temperature effects may vary with latitude and local climate.[7] Finally, data were not widely available on levels of particulates with a diameter less than 2.5 μm (PM2.5), which may be a more important predictor of risk of myocardial infarction than PM10,[14] therefore we cannot exclude residual confounding, although in the one monitoring station where both measures were recorded the correlation was high (0.92), so we believe that including PM10 in our models should have accounted for any major confounding effects of finer particulates.

Despite these limitations, to our knowledge this is the first large study to investigate the short term effects of ambient temperature on risk of myocardial infarction in which key potential confounders (air pollution, influenza activity, seasonality, and long term trend) were controlled for, non-linear effects were investigated, and in which most cases of myocardial infarction could be validated against electrocardiographic or marker criteria to confirm the diagnosis. In addition a range of sensitivity analyses confirmed that our main conclusions were robust to changes in aspects of the model specification, and to restricting to only the most "reliable" data.

Conclusions

In conclusion, our study shows a convincing short term increase in risk of myocardial infarction associated with lower ambient temperature, predominantly operating in the two weeks after exposure. International studies with consistent methods will be required to clarify the dependence of these effects on local climate, whereas individual level studies collecting demographic, clinical, and behavioural data may shed light on the role of adaptive measures such as clothing and home heating, and further clarify which subgroups are likely to be the most vulnerable. Finally, studies of specific public health interventions aimed at reducing the impact of temperature related increases in risk of myocardial infarction are needed.

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Competing interests: All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and all authors want to declare: (1) financial support for the submitted work from the British Heart Foundation, the Garfield Weston Trust, and the Wellcome Trust; (2) no financial relationships with commercial entities that might have an interest in the submitted work; (3) no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; and (4) no non-financial interests that may be relevant to the submitted work.
Ethical approval: This study was approved by the London School of Hygiene and Tropical Medicine ethics committee.
Data sharing: No additional data available.

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