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

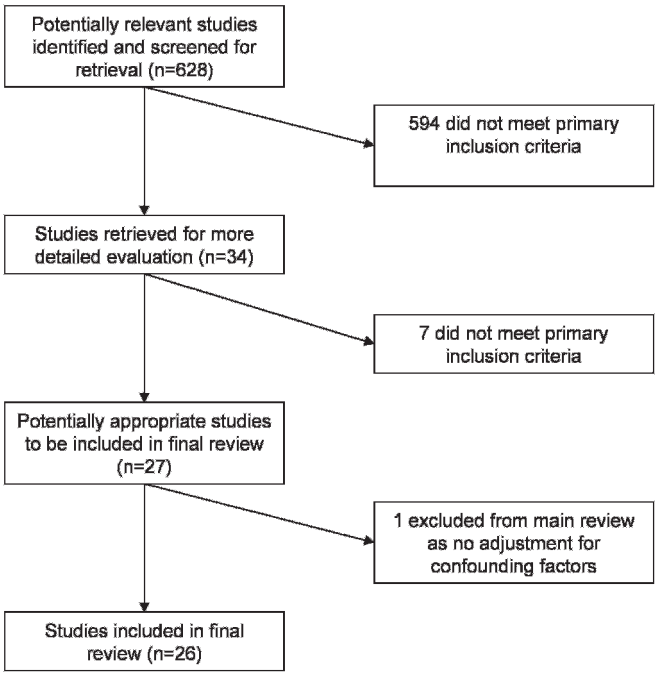

Figure 1 Flow diagram of search strategy.

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 $\mu g/m^3$)	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: $\geq$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

First author and 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 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*	✗	✓	✗	✗	✓
Linn 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[19]	–	–	–	–	–	–	*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) No (PM non-traffic)	–	N/A†	✗	✓	✗	✓	✓
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 Other pollutants: effects appeared to be dominated by lag 0 effect Effects overall similar when infirmary admissions were considered (as opposed to ICU) PM_{10}: effect similar for infirmaries but reached significance
	PM_{10}	1.032 (0.978 to 1.086)	22.5	Sum of 0–7	
	O_3	1.093 (1.011 to 1.174)	50.23		
	CO	0.998 (0.933 to 1.066)	1.42		
	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 There was a suggestive effect of PNC, when restricting to the three cities using hospital discharge register data, which had higher power
	O_3	0.994 (0.986 to 1.002)	10 μg/m^3		
	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) SO_2 was independently associated with MI in the cool season in all two-pollutant model combinations NO_2, CO, black smoke were not associated in two-pollutant models, except in combination with O_3
	CO	1.023 (1.007 to 1.04)	1 ppm		
	NO_2	1.009 (1.003 to 1.016)	10 ppb		
	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 23 24 28]; one did not report the number of cases included while the other three

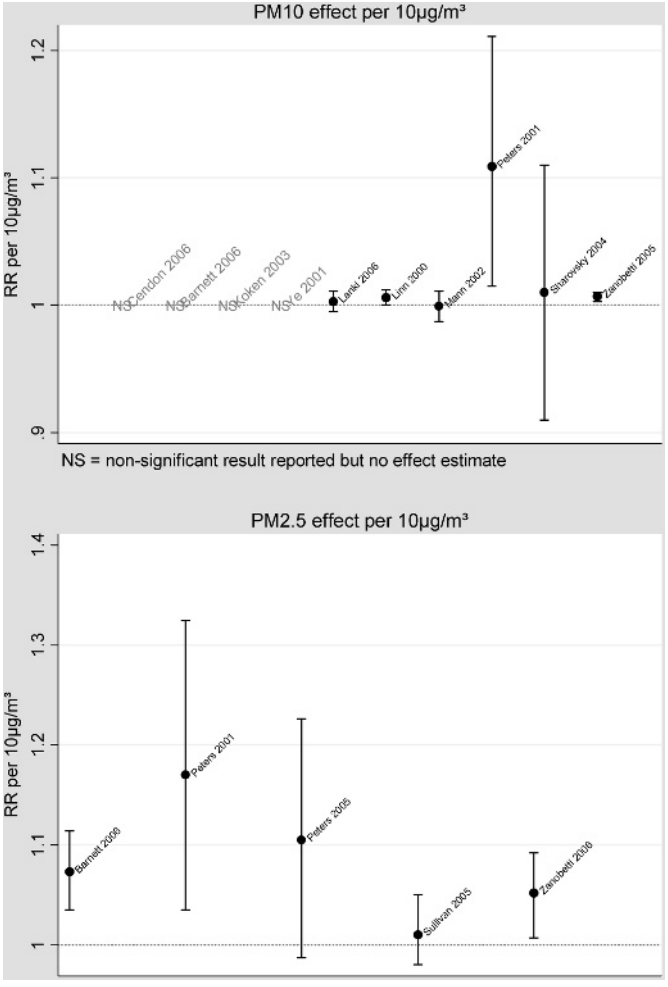

Figure 2 Estimate effects of particulate pollution on myocardial infarction risk. PM, particulate matter; RR, relative risk.

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 μg/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

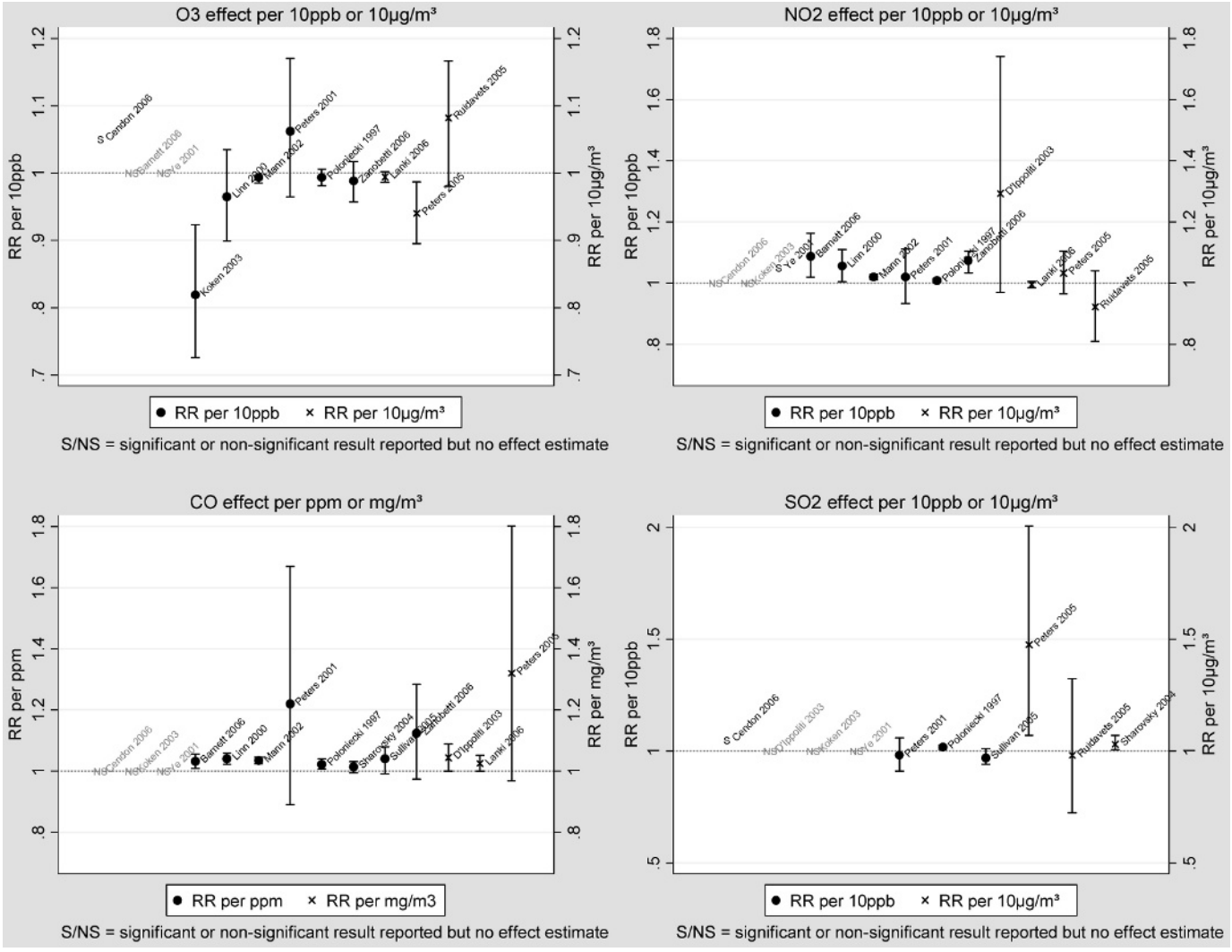

Figure 3 Estimated effects of gaseous pollutants on myocardial infarction risk. RR, relative risk.

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 $\mu g/m^3$ 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 $\mu g/m^3$ 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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