Main Air Pollutants and Myocardial Infarction
A Systematic Review and Meta-analysis

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Context Short-term exposure to high levels of air pollution may trigger myocardial infarction (MI), but this association remains unclear.

Objective To assess and quantify the association between short-term exposure to major air pollutants (ozone, carbon monoxide, nitrogen dioxide, sulfur dioxide, and particulate matter ≤10 μm [PM_{10}] and ≤2.5 μm [$PM_{2.5}$] in diameter) on MI risk.

Data Sources EMBASE, Ovid MEDLINE in-process and other nonindexed citations, and Ovid MEDLINE (between 1948 and November 28, 2011), and EBM Reviews–Cochrane Central Register of Controlled Trials and EBM Reviews–Cochrane Database of Systematic Reviews (between 2005 and November 28, 2011) were searched for a combination of keywords related to the type of exposure (air pollution, ozone, carbon monoxide, nitrogen dioxide, sulfur dioxide, PM_{10}, and $PM_{2.5}$) and to the type of outcome (MI, heart attack, acute coronary syndrome).

Study Selection Two independent reviewers selected studies of any study design and in any language, using original data and investigating the association between short-term exposure (for up to 7 days) to 1 or more air pollutants and subsequent MI risk. Selection was performed from abstracts and titles and pursued by reviewing the full text of potentially eligible studies.

Data Extraction Descriptive and quantitative information was extracted from each selected study. Using a random effects model, relative risks (RRs) and 95% CIs were calculated for each increment of 10 μg/m³ in pollutant concentration, with the exception of carbon monoxide, for which an increase of 1 mg/m³ was considered.

Data Synthesis After a detailed screening of 117 studies, 34 studies were identified. All the main air pollutants, with the exception of ozone, were significantly associated with an increase in MI risk (carbon monoxide: 1.048; 95% CI, 1.026-1.070; nitrogen dioxide: 1.011; 95% CI, 1.006-1.016; sulfur dioxide: 1.010; 95% CI, 1.003-1.017; PM_{10}: 1.006; 95% CI, 1.002-1.009; and $PM_{2.5}$: 1.025; 95% CI, 1.015-1.036). For ozone, the RR was 1.003 (95% CI, 0.997-1.010; $P=.36$). Subgroup analyses provided results comparable with those of the overall analyses. Population attributable fractions ranged between 0.6% and 4.5%, depending on the air pollutant.

Conclusion All the main air pollutants, with the exception of ozone, were significantly associated with a near-term increase in MI risk.

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THE POTENTIALLY DELETERIOUS effect of episodes of high air pollution on health has been suspected for more than 50 years.[1] In industrialized countries, cardiovascular disease is the leading cause of mortality and is associated with significant morbidity.[2,3] These countries have high pollution levels. Since the 1990s, many epidemiological studies have demonstrated associations between air pollution levels and human health in terms of hospital admissions[4,5] and overall mortality, including respiratory[6] or cardiovascular mortality.[3] However, the association between air pollution and near-term risk of myocardial infarction (MI) remains controversial. Some studies have shown an association,[7,8] while other studies have found either no association[9,10] or association only for selected pollutants.[11,12]

Air pollution is due to a heterogeneous group of gaseous and particulate components. The main gaseous pollutants are ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide. The main particulate matter (PM) pollutants are defined according to their aerodynamic diameter (those ≤10 μm referred to as PM_{10} and those ≤2.5 μm

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referred to as $PM_{2.5}$). An association between PM and MI risk has been recently reported.[13] However, to the extent that PM represents a limited fraction of overall air pollution, one cannot necessarily extrapolate this preceding finding to the other air pollutants. Indeed, in the available literature, the toxicity by pollutant does not seem to be homogeneous.[3] To our knowledge, a comprehensive and systematic meta-analysis of studies published in any language investigating the association of short-term exposure to main air pollutants with MI risk has not been performed. Our study goal was to systematically review associations between air pollutants and risk of MI and to quantify these associations. Our hypothesis was that increases in ozone, carbon monoxide, nitrogen dioxide, sulfur dioxide, PM_{10}, and $PM_{2.5}$ levels would be associated with an increase in MI risk.

METHODS

Eligibility Criteria and Literature Search

We performed a search to identify studies analyzing the associations of short-term exposure, defined as an exposure of up to 7 days, to 1 or more of the main air pollutants with MI risk. The studies involved adults and could be of any study design and in any language. We excluded animal studies, ex vivo and toxicological studies, duplicates, summaries, commentaries and editorials, case reports, case series, studies that evaluated the association between long-term exposure to air pollution, and studies with no original data. For studies without enough quantitative data, the correspondent author was contacted and if no answer was obtained, the study was excluded.

A comprehensive search of several electronic databases (between 1948 and November 28, 2011) was conducted in EMBASE between 1988 and November 28, 2011; Ovid MEDLINE in-process and other nonindexed citations and Ovid MEDLINE between 1948 and November 28, 2011; and EBM Reviews–Cochrane Central Register of Controlled Trials and EBM Reviews–Cochrane Database of Systematic Reviews between 2005 and November 28, 2011. In addition, we searched the reference lists of eligible studies and relevant reviews for additional published and unpublished data, searched by contacting several experts, and used the web search engine "Google" for abstracts, conference proceedings, and unpublished studies. We used a combination of keywords related to the type of exposure (air pollution, ozone, carbon monoxide, nitrogen dioxide, sulfur dioxide, PM_{10}, and $PM_{2.5}$) and to the type of outcome (MI, heart attack, acute coronary syndrome). Details of the search strategy are provided in the eAppendix (available at http://www.jama.com).

Study Selection

Two independent reviewers (C.C. and H.M.) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then screened to determine the eligibility of the study for the review and meta-analysis. Disagreements regarding eligibility were resolved by consensus with the help of a third reviewer (P.J.).

Validity Assessment

This meta-analysis complies with the preferred reporting items of PRISMA for systematic reviews and meta-analyses.[14] Recommendations have been suggested to report quality assessment for time-series studies and case-crossover studies,[15,16] but to our knowledge there are no validated scales to evaluate methodological quality. We therefore adapted a quality scale from validated scales for other types of epidemiological studies and especially selected several items from the New Castle Ottawa[17] and the Cochrane risk of bias tool.[18] We evaluated 3 components (the validation of MI occurrence [0 to 1 point], the quality of air pollutant measurements [0 to 1 point], and the extent of adjustment for confounders [0 to 3 points]). Concerning the validation of MI occurrence, we considered the diagnosis to be validated if it was coded according to the *International Classification of Diseases* or based on the triad of clinical and laboratory and electrocardiographic criteria or based on angiographic criteria (0 was given in the absence of valid criteria).

For cases reported in myocardial registries, we considered the diagnosis as validated. The quality of air pollutant measurements was judged on the basis of the measurement frequency and the presence of missing data (0 was given if measurements were not performed at least daily or with >25% missing data, 1 was given if measurements were performed at least daily without >25% missing data). For the quality of the adjustment for confounders, 0 was given if no adjustment has been made for long-term trends, seasonality, and temperature. One point was given if only these 3 adjustments had been made. If an additional adjustment was made, either for humidity or day of week, a score of 2 was given. A score of 3 was given if an adjustment had been made for influenza epidemics and holidays in addition to the adjustments corresponding with a score of 2. In addition, if the maximum score was achieved for the 3 components, the study was deemed to be of good quality. If 1 component from the 3 components obtained the minimum score (ie, zero), the study was automatically considered to be of low quality. All other studies were judged to be of intermediate quality.

Data Extraction

Data extraction using a standardized form included a full description of the study characteristics (author, title, journal, year of publication, location and period, type of study, age and sex of the population studied, nature of the outcome [MI occurrence or mortality resulting from MI], validation of MI, pollutants studied, their concentration [peak or mean], quality of measurement methods, effect measurement, and adjustments performed [long-term trend, seasonality, temperature, humidity, pressure, day of the week, holidays, and influenza epidemics]). The authors were contacted in case of uncertainty about the data. Data extrac-

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tion was performed in duplicate by 2 reviewers (C.C. and H.M.) and then compared. In case of discordance, a third reviewer (P.J.) was asked to give her opinion for obtaining a consensus.

Quantitative Data Synthesis

All pollutant concentrations were converted, if necessary, to μg/m^3, with the exception of carbon monoxide, which was converted to mg/m^3. We used relative risk (RR) as a measure of effect size because it is an intuitive and commonly used measure in the medical and public health literature. Relative risks were expressed for a standardized increase in pollutant concentration of 10 μg/m^3 and 1 mg/m^3 for carbon monoxide. These levels are indeed the ones that are used most frequently.

To evaluate immediate and delayed associations, several studies analyzed the associations between pollutant exposure and MI occurrence while taking into account different lag patterns, using either single-day lags[8,10,12,19-29] from lag_0 (current day concentration) to lag_7 (7 days before the event day) or cumulative lags[9,30-34] (ie, mean between the same day and the previous n days, $lag_{0\text{-}n}$ [with n: $1 < n < 7$]). Other studies have used both lag patterns.[7,11,35-46] Nevertheless, the most frequent lag pattern used is a single-day lag. Thus, if several lag estimates were reported in the same article, we chose the most frequently used in all the selected studies for the pollutant under consideration. Most studies have verified the linearity assumption concerning the association between air pollutants increases and MI risk.

We estimated RRs and 95% CIs using a random-effects model. This model was chosen because of anticipated significant heterogeneity between studies in terms of population and methods. The random-effects model is the most conservative approach in this setting because it incorporates within and between-study heterogeneity in the CI. To assess the heterogeneity and to confirm the robustness of our results, subgroup analyses were performed.

The population attributable fractions (PAFs) were calculated from RRs in the overall analyses. We considered that in urban areas of industrialized countries, the prevalence of air pollution exposure was 100% (our first assumption). In addition, we issued an alternative assumption that in industrialized countries (in urban and nonurban areas), this prevalence was 80% vs 20% in nonindustrialized countries with low air pollution levels. With a prevalence of exposure of 100%, the PAF was calculated by [PAF = (RR–1)/RR] (TABLE). For a prevalence of ex-

Table. Overall Analyses and Subgroup Analyses Results

Characteristics	Air Pollutant (Incremental Unit)					
	Ozone (10 μg/m^3)	Carbon Monoxide (1 mg/m^3)	Nitrogen Dioxide (10 μg/m^3)	Sulfur Dioxide (10 μg/m^3)	PM_{10} (10 μg/m^3)	$PM_{2.5}$ (10 μg/m^3)
Overall Analyses						
No. of studies	19	20	21	14	17	13
I^2, %	83	93	71	65	57	51
RR (95% CI)	1.003 (0.997-1.010)	1.048 (1.026-1.070)	1.011 (1.006-1.016)	1.010 (1.003-1.017)	1.006 (1.002-1.009)	1.025 (1.015-1.036)
P value	.36	<.001	<.001	.007	.002	<.001
Egger regression test, *P* value	.56	.03	.08	.03	.61	.004
PAF, % (95% CI)[a]						
k=100%	NA	4.5 (2.5-6.5)	1.1 (0.6-1.6)	1.0 (0.3-1.7)	0.6 (0.2-0.9)	2.5 (1.5-3.5)
k=80%	NA	3.6 (2.0-5.2)	0.9 (0.5-1.3)	0.8 (0.2-1.4)	0.5 (0.2-0.7)	2.0 (1.2-2.8)
k=20%	NA	0.9 (0.5-1.3)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.1 (0.0-0.1)	0.5 (0.3-0.7)
Study Quality Subgroup Analyses						
No. of studies	10	13	11	6	9	8
I^2, %	61	78	61	10	35	51
RR (95% CI)	0.998 (0.994-1.002)	1.022 (1.009-1.034)	1.007 (1.002-1.012)	1.004 (1.001-1.007)	1.005 (1.002-1.007)	1.025 (1.014-1.036)
P value	.22	.001	.007	.004	<.001	<.001
Egger regression test, *P* value	.88	.053	.38	.68	.27	.054
Lag Exposure Subgroup Analyses						
No. of studies	6	7	7	3	8	3
Lag exposure, d	0	0	1	1	0	1
I^2, %	68	0	16	0	22	0
RR (95% CI)	0.992 (0.982-1.002)	1.030 (1.023-1.073)	1.007 (1.003-1.011)	1.005 (1.002-1.008)	1.007 (1.004-1.009)	1.017 (1.002-1.033)
P value	.12	<.001	.001	.001	<.001	.03
Egger regression test, *P* value	.52	.71	.51	.13	.43	.69

Abbreviations: PAF, population attributable fraction; PM_{10}, particulate matter of ≤10 μm; $PM_{2.5}$, particulate matter of ≤2.5 μm; RR, relative risk.
[a]The PAF was calculated by {PAF = k×[(RR–1)/k×(RR–1)+1]}, where k indicates exposure prevalence.

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posure different from 100%, the PAF was calculated by {PAF=k×[(RR-1)/k×(RR-1)+1]}, where k indicates exposure prevalence (Table). Statistical heterogeneity across the studies was calculated by the I^2 statistic to quantify inconsistencies between studies. I^2 values of 25% or less, 50%, and 75% or more represent low, moderate, and high inconsistency, respectively. This method is sometimes considered underpowered but it remains recommended by the Cochrane collaboration (http://www.cochrane.org).

To assess the potential for publication bias, we visually inspected funnel plots. However, because this method has limitations,[47] we also added the Egger regression test *P* value for funnel symmetry.

All tests were 2-sided and statistical significance was defined as $P<.05$, with the exception of the heterogeneity assessment, which was considered statistically significant at $P<.10$. Analyses were conducted with Comprehensive Meta-analysis Software version 2.0 (Biostat).

Subgroup Analyses

To determine the robustness of the results, we performed 2 subgroup analyses. The first analysis was based on study quality using only studies of good and intermediate quality, and the second analysis was based on studies that have used the same lag pattern for each analyzed pollutant.

RESULTS

Our initial search identified 1667 citations. After screening titles, abstracts, bibliographic references, and commentaries and editorials of articles, 117 citations were considered potentially eligible and the full-text article was retrieved. Of those, 83 citations were excluded (eFigure), resulting in 34 eligible studies.[7-12,19-46] Interrater agreement for study selection was high (κ=0.90; 95% CI, 0.87-0.93). The 34 eligible studies[7-12,19-46] included 17 time-series studies and 17 case-crossover studies. Time-series and case-crossover methods are often viewed as competing methods but when there is a common exposure such as in air pollution studies, these methods are equivalent and it is legitimate to analyze them together.[48]

The characteristics of eligible studies are shown in eTable 1. The number of patients or cases per study ranged between 399 and 302 153. The number of pollutants considered by study ranged between 1 and 6. The databases were drawn mainly from hospital admissions statistics, MI, or mortality registries. Several sites were investigated on every continent except Africa. The study population was predominantly the general population, with the exception of a few studies that focused on elderly individuals.[8,11,19,31,45] Lag expression varied from a specific day preceding the onset of MI to an average of 7 days before this event, while the number of lags ranged between 1 and 6 per pollutant and per study.

Overall Analyses

The associations between all analyzed air pollutants and MI risk, with the exception of ozone, reached statistical significance (carbon monoxide [20 studies*]: RR, 1.048; 95% CI, 1.026-1.070; $P<.001$; I^2=93%; PAF, 4.5%; 95% CI, 2.5%-6.5%; nitrogen dioxide [21 studies†]: RR, 1.011; 95% CI, 1.006-1.016; $P<.001$; I^2=71%; PAF, 1.1%; 95% CI, 0.6%-1.6%; sulfur dioxide [14 studies‡]: RR, 1.010; 95% CI, 1.003-1.017; P=.007; I^2=65%; PAF, 1.0%; 95% CI, 0.3%-1.7%; PM_{10} [17 studies§]: RR, 1.006; 95% CI, 1.002-1.009; P=.002; I^2=57%; PAF, 0.6%; 95% CI, 0.2%-0.9%; $PM_{2.5}$ [13 studies‖]: RR, 1.025; 95% CI, 1.015-1.036; $P<.001$; I^2=51%; PAF, 2.5%; 95% CI, 1.5%-3.5%; and ozone [19 studies¶]: RR, 1.003; 95% CI, 0.997-1.010; P=.36; I^2=83%) (FIGURE 1, FIGURE 2, and FIGURE 3).

Publication bias was observed in analyses evaluating carbon monoxide (P=.03), sulfur dioxide (P=.03), and $PM_{2.5}$ (P=.004), but not in analyses evaluating ozone (P=.56), nitrogen dioxide (P=.08), and PM_{10} (P=.61). PAFs with a prevalence of exposure of 80% and 20% are shown in the Table.

Subgroup Analyses

Study Quality. The subgroup analysis based on study quality included 24 studies (13 studies of good quality and 11 of intermediate quality) (Table and eTable 1). Significant associations were found with carbon monoxide, nitrogen dioxide, sulfur dioxide, PM_{10}, and $PM_{2.5}$, but not with ozone (carbon monoxide [13 studies#]: RR, 1.022; 95% CI, 1.009-1.034; P=.001; I^2=78%; Egger regression test, P=.053; nitrogen dioxide [11 studies**]: RR, 1.007; 95% CI, 1.002-1.012; P=.007; I^2=61%; Egger regression test, P=.38; sulfur dioxide [6 studies[22,23,27,40,44,46]]: RR, 1.004; 95% CI, 1.001-1.007; P=.004; I^2=10%; Egger regression test, P=.68; PM_{10} [9 studies[7,10,12,24,39-41,45,46]]: RR, 1.005; 95% CI, 1.002-1.007; $P<.001$; I^2=35%; Egger regression test, P=.27; $PM_{2.5}$ [8 studies[9,21,22,25,30,31,35,41]]: RR, 1.025; 95% CI, 1.014-1.036; $P<.001$; I^2=51%; Egger regression test, P=.054; and ozone [10 studies††]: RR, 0.998; 95% CI, 0.994-1.002; P=.22; I^2=61%; Egger regression test, P=.88) (Table).

Lag Exposure. The subgroup analysis based on the lag exposure included 16 articles (Table). The lag exposure was 0 days for ozone, carbon monoxide, and PM_{10}; and 1 day for nitrogen dioxide, sulfur dioxide, and $PM_{2.5}$. Similar to the overall analysis, the associations between all main air pollutants and MI risk, with the exception of ozone, reached statistical significance (carbon monoxide [7 studies[12,22-24,28,39,42]]: RR, 1.030; 95%

*References 9-12, 20, 22-24, 27, 28, 32-34, 36, 39, 40, 42, 43, 45, 46.
†References 9-12, 19, 20, 23, 24, 26-28, 32-34, 36, 39, 42-46.
‡References 11, 20, 22, 23, 26-28, 32-34, 40, 43, 44, 46.
§References 7, 10-12, 20, 24, 26, 28, 32-34, 39-42, 45, 46.
‖References 9, 20-22, 25, 28, 30, 31, 35, 38, 41, 43, 45.
¶References 8, 10-12, 20, 23, 24, 26-28, 32-34, 37, 39, 43-46.

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**References 9, 10, 12, 23, 24, 27, 36, 39, 44-46.
††References 10, 12, 23, 24, 27, 37, 39, 44-46.

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CI, 1.023-1.073; $P<.001$; $I^2=0\%$; Egger regression test, $P=.71$; nitrogen dioxide [7 studies[10,20,27,36,39,42,43]]: RR, 1.007; 95% CI, 1.003-1.011; $P=.001$; $I^2=16\%$; Egger regression test, $P=.51$; sulfur dioxide [3 studies[20,22,27]]: RR, 1.005; 95% CI, 1.002-1.008; $P=.001$; $I^2=0\%$; Egger regression test, $P=.13$; PM_{10} [8 studies[7,12,20,24,28,41,42,45]]: RR, 1.007; 95% CI, 1.004-1.009; $P<.001$; $I^2=22\%$; Egger regression test, $P=.43$; $PM_{2.5}$ [3 studies[21,22,41]]: RR, 1.017; 95% CI, 1.002-1.033; $P=.03$; $I^2=0\%$; Egger regression test, $P=.69$; and ozone [6 studies[8,12,23,24,28,39]]: RR, 0.992; 95% CI, 0.982-1.002; $P=.12$; $I^2=68\%$; Egger regression test, $P=.52$).

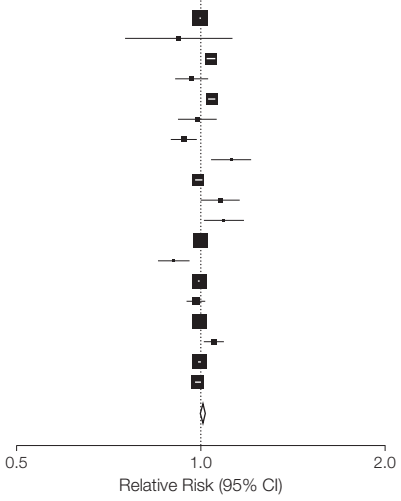
COMMENT

This meta-analysis is the first to our knowledge to assess the quality and magnitude of the associations between short-term exposure to major air pollutants and MI risk. We demonstrated a significant association between all analyzed pollutants, with the exception of ozone, and MI risk.

Figure 1. Overall Ozone and Carbon Monoxide Analyses

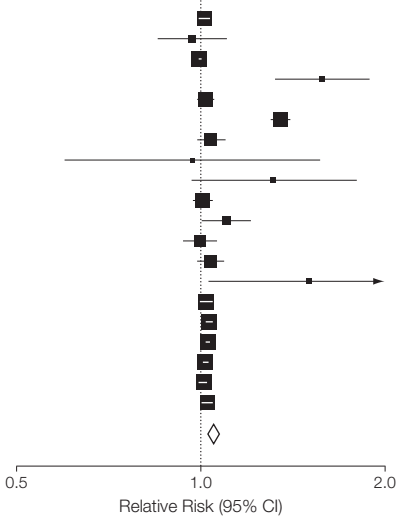
A Ozone analysis

Source	Study Design	Relative Study Weight, %	Relative Risk (95% CI)	*P* Value
Bhaskaran et al,[46] 2011	Case-crossover	11.44	0.999 (0.993-1.005)	.74
Berglind et al,[10] 2010	Case-crossover	0.10	0.920 (0.750-1.129)	.42
Cheng et al,[33] 2009	Case-crossover	6.84	1.042 (1.025-1.060)	<.001
Henrotin et al,[37] 2010	Case-crossover	0.97	0.967 (0.908-1.030)	.30
Hsieh et al,[34] 2010	Case-crossover	7.41	1.044 (1.028-1.060)	<.001
Peters et al,[20] 2001	Case-crossover	0.69	0.989 (0.917-1.067)	.78
Peters et al,[43] 2005	Case-crossover	1.54	0.940 (0.895-0.987)	.01
Ruidavets et al,[44] 2005	Case-crossover	0.66	1.123 (1.039-1.214)	.003
Zanobetti and Schwartz,[45] 2006	Case-crossover	7.50	0.993 (0.978-1.008)	.36
Eilstein et al,[23] 2001	Time-series	0.74	1.078 (1.002-1.159)	.04
Cendon et al,[11] 2006	Time-series	0.70	1.093 (1.014-1.178)	.02
Hoek et al,[32] 2000	Time-series	12.54	1.001 (0.999-1.003)	.33
Koken et al,[8] 2003	Time-series	1.06	0.904 (0.851-0.960)	.001
Lanki et al,[24] 2006	Time-series	10.61	0.994 (0.986-1.002)	.14
Linn et al,[12] 2000	Time-series	2.68	0.982 (0.948-1.017)	.31
Mann et al,[39] 2002	Time-series	12.35	0.996 (0.993-0.999)	.009
Medina et al,[26] 1997	Time-series	2.17	1.050 (1.009-1.093)	.02
Poloniecki et al,[27] 1997	Time-series	11.43	0.996 (0.990-1.002)	.19
Stieb et al,[28] 2009	Time-series	8.56	0.990 (0.978-1.003)	.12
Combined ($I^2=83\%$, Egger regression test, $P=.56$)			1.003 (0.997-1.010)	.36



B Carbon monoxide analysis

Source	Study Design	Relative Study Weight, %	Relative Risk (95% CI)	*P* Value
Barnett et al,[9] 2006	Case-crossover	7.10	1.016 (0.992-1.040)	.19
Berglind et al,[10] 2010	Case-crossover	1.91	0.970 (0.849-1.108)	.65
Bhaskaran et al,[46] 2011	Case-crossover	7.74	0.998 (0.993-1.004)	.48
Cheng et al,[33] 2009	Case-crossover	1.20	1.581 (1.323-1.890)	<.001
D'Ippoliti et al,[36] 2003	Case-crossover	6.59	1.021 (0.989-1.055)	.21
Hsieh et al,[34] 2010	Case-crossover	6.15	1.352 (1.300-1.406)	<.001
Nuvolone et al,[42] 2011	Case-crossover	5.15	1.040 (0.985-1.098)	.16
Peters et al,[20] 2001	Case-crossover	0.19	0.971 (0.600-1.571)	.91
Peters et al,[43] 2005	Case-crossover	0.44	1.320 (0.968-1.800)	.08
Sullivan et al,[22] 2005	Case-crossover	6.16	1.012 (0.973-1.052)	.55
Zanobetti and Schwartz,[45] 2006	Case-crossover	3.06	1.105 (1.005-1.214)	.04
Cendon et al,[11] 2006	Time-series	4.40	0.998 (0.934-1.067)	.95
Eilstein et al,[23] 2001	Time-series	5.43	1.039 (0.998-1.092)	.13
Hoek et al,[32] 2000	Time-series	0.31	1.501 (1.033-2.181)	.03
Lanki et al,[24] 2006	Time-series	7.03	1.025 (1.000-1.051)	.05
Linn et al,[12] 2000	Time-series	7.49	1.035 (1.020-1.051)	<.001
Mann et al,[39] 2002	Time-series	7.68	1.030 (1.021-1.039)	<.001
Poloniecki et al,[27] 1997	Time-series	7.54	1.020 (1.006-1.034)	.005
Sharovsky et al,[40] 2004	Time-series	7.42	1.012 (0.995-1.029)	.16
Stieb et al,[28] 2009	Time-series	7.00	1.026 (1.000-1.052)	.05
Combined ($I^2=93\%$, Egger regression test, $P=.03$)			1.048 (1.026-1.070)	<.001



For ozone analysis, 19 studies were used with incremental unit of 10 μg/m³ and lag exposure of 0 days. For carbon monoxide analysis, 20 studies were used with incremental unit of 1 mg/m³ and lag exposure of 0 days. The size of the relative risk data markers is relative to each study weight.

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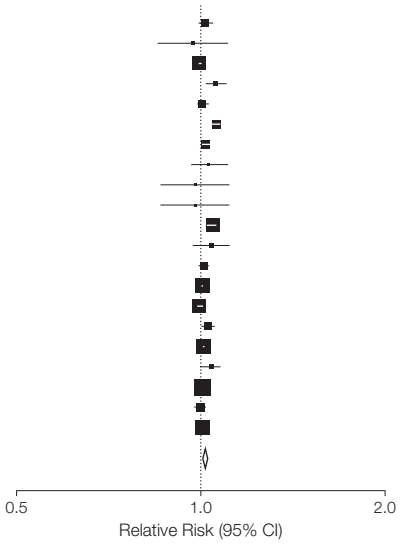
The subgroup analyses were associated with lower heterogeneity and no significant publication bias, while yielding results comparable with those from the overall analysis. Thus, the findings are robust. We cannot rule out, however, that the absence of publication bias in the subgroup analyses is due to the reduced sample size. The significant associations observed in our study were consistent with evidence from experimental cellular, histological, animal, and healthy volunteer studies.

A number of possible mechanisms for the associations reported herein have been suggested. The first potential mechanism is inflammation.[2,49] Studies have shown that levels of inflammatory markers such as C-reactive protein[50] are higher as a result of exposure to air pollution. The second potential mechanism is abnormal regulation of the cardiac autonomic system.[2] Several observational studies having linked high levels of air pollution with increased heart rate[51] and decreased heart rate variability.[49] The third possible mechanism is an increase in blood viscosity as a result of air pollution.[52] This association can promote thrombus formation,[53] accelerate the progression of atherosclerosis, and weaken the stability of atherosclerotic plaques. A fourth potential mechanism is that air pollutants may increase vasoconstrictors such

Figure 2. Overall Nitrogen Dioxide and Sulfur Dioxide Analyses

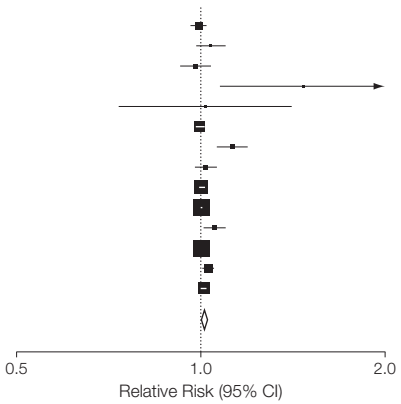
A Nitrogen dioxide analysis

Source	Study Design	Relative Study Weight, %	Relative Risk (95% CI)	*P* Value
Barnett et al,[9] 2006	Case-crossover	2.54	1.017 (0.998-1.046)	.25
Berglind et al,[10] 2010	Case-crossover	0.14	0.970 (0.849-1.108)	.65
Bhaskaran et al,[46] 2011	Case-crossover	9.78	0.995 (0.987-1.003)	.22
Cheng et al,[33] 2009	Case-crossover	1.39	1.057 (1.015-1.101)	.008
D'Ippoliti et al,[36] 2003	Case-crossover	3.45	1.006 (0.983-1.030)	.62
Hsieh et al,[34] 2010	Case-crossover	4.63	1.059 (1.039-1.079)	<.001
Nuvolone et al,[42] 2011	Case-crossover	4.71	1.020 (1.001-1.039)	.04
Peters et al,[20] 2001	Case-crossover	0.51	1.031 (0.962-1.105)	.39
Peters et al,[43] 2005	Case-crossover	0.15	0.980 (0.860-1.117)	.76
Ruidavets et al,[44] 2005	Case-crossover	0.15	0.980 (0.860-1.117)	.76
Zanobetti and Schwartz,[45] 2006	Case-crossover	4.51	1.038 (1.018-1.058)	<.001
Cendon et al,[11] 2006	Time-series	0.46	1.038 (0.965-1.117)	.32
Eilstein et al,[23] 2001	Time-series	3.95	1.011 (0.990-1.033)	.31
Hoek et al,[32] 2000	Time-series	11.00	1.005 (0.999-1.011)	.10
Lanki et al,[24] 2006	Time-series	8.31	0.995 (0.985-1.006)	.35
Linn et al,[12] 2000	Time-series	2.90	1.029 (1.002-1.056)	.03
Mann et al,[39] 2002	Time-series	11.55	1.010 (1.005-1.015)	<.001
Medina et al,[26] 1997	Time-series	1.40	1.037 (0.996-1.080)	.08
Poloniecki et al,[27] 1997	Time-series	12.42	1.004 (1.001-1.007)	.009
Stieb et al,[28] 2009	Time-series	3.63	0.997 (0.975-1.020)	.79
Ye et al,[19] 2001	Time-series	12.42	1.006 (1.003-1.009)	<.001
Combined (I^2 = 71%, Egger regression test, *P* = .08)			1.011 (1.006-1.016)	<.001



B Sulfur dioxide analysis

Source	Study Design	Relative Study Weight, %	Relative Risk (95% CI)	*P* Value
Bhaskaran et al,[46] 2011	Case-crossover	4.53	0.992 (0.962-1.022)	.60
Hsieh et al,[34] 2010	Case-crossover	1.57	1.042 (0.986-1.101)	.14
Peters et al,[20] 2001	Case-crossover	1.43	0.982 (0.927-1.041)	.54
Peters et al,[43] 2005	Case-crossover	0.05	1.475 (1.077-2.020)	.02
Ruidavetset al,[44] 2005	Case-crossover	0.05	1.020 (0.735-1.416)	.91
Sullivan et al,[22] 2005	Case-crossover	7.77	1.000 (0.979-1.021)	>.99
Cendon et al,[11] 2006	Time-series	1.45	1.129 (1.066-1.196)	<.001
Cheng et al,[33] 2009	Time-series	2.38	1.022 (0.978-1.068)	.33
Eilstein et al,[23] 2001	Time-series	15.17	1.007 (0.996-1.018)	.21
Hoek et al,[32] 2000	Time-series	21.85	1.002 (0.998-1.006)	.33
Medina et al,[26] 1997	Time-series	2.38	1.056 (1.011-1.104)	.02
Poloniecki et al,[27] 1997	Time-series	22.52	1.005 (1.002-1.008)	.001
Sharovsky et al,[40] 2004	Time-series	6.35	1.030 (1.005-1.055)	.02
Stieb et al,[28] 2009	Time-series	12.50	1.012 (0.998-1.026)	.09
Combined (I^2 = 65%, Egger regression test, *P* = .03)			1.010 (1.003-1.017)	.007



For nitrogen dioxide, 21 studies were used with incremental unit of 10 μg/m³ and lag exposure of 1 day. For sulfur dioxide, 14 studies were used with incremental unit of 10 μg/m³ and lag exposure of 1 day. The size of the relative risk data markers is relative to each study weight.

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as endothelins.[54] In addition, mechanisms including direct induction of cardiac ischemia by vasospasm[55] or direct arrhythmogenesis[56] have been evoked, although these were suggested from studies including women only. All these data from experimental studies strengthen the biological plausibility that exposure to air pollution may affect the risk of MI occurrence via multiple mechanisms.

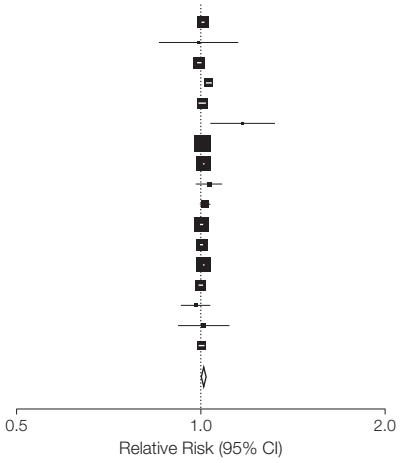
Our findings regarding ozone differed compared with findings for other air pollutants. However, associations of ozone with health are difficult to estimate. Ozone is only one of several air components of the "photochemical cocktail" and the mechanisms of its formation and destruction are complex and varied.[57] It is well established that MI is less prevalent in the summer when temperature and ozone concentrations tend to be the highest.[58] Therefore, an adjustment for temperature is necessary. However, there was also a wide variability of approaches of adjustment for temperature, which led to variability in the RR estimates between exposure to ozone and MI risk (eTable 2). The idea advanced in some studies would be to limit the analysis to summer periods but the downfall of this approach is the dramatic reduction of the exposure period.[23,57] Moreover, adjustment for temperature does not suffice because the mechanism of ozone formation is more closely dependent on solar radiation and brightness[57] and no study to our knowledge has ever adjusted for brightness.

We acknowledge that the magnitude of association is relatively small compared with those of classic MI risk factors, such as smoking, hypertension, or diabetes, which range from 2 to 3.[59] Nevertheless, the PAF of each pollutant is not negligible because the majority of the population, including

Figure 3. Overall PM_{10} and $PM_{2.5}$ Analyses

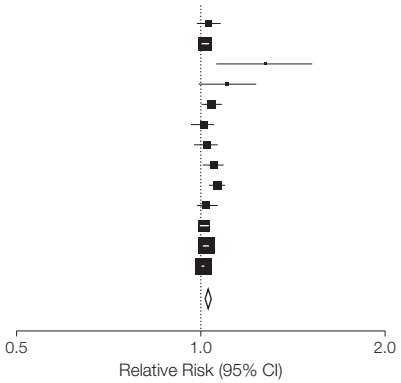
A PM_{10} analysis

Source	Study Design	Relative Study Weight, %	Relative Risk (95% CI)	*P* Value
Belleudi et al,[41] 2010	Case-crossover	8.80	1.007 (0.999-1.015)	.09
Berglind et al,[10] 2010	Case-crossover	0.06	0.990 (0.851-1.152)	.90
Bhaskaran et al,[46] 2011	Case-crossover	6.95	0.992 (0.982-1.002)	.12
Hsieh et al,[34] 2010	Case-crossover	4.78	1.031 (1.017-1.045)	<.001
Nuvolone et al,[42] 2011	Case-crossover	5.10	1.004 (0.991-1.017)	.55
Peters et al,[20] 2001	Case-crossover	0.08	1.169 (1.034-1.322)	.01
Zanobetti and Schwartz,[45] 2006	Case-crossover	14.10	1.006 (1.003-1.009)	<.001
Braga et al,[7] 2001	Time-series	13.10	1.007 (1.003-1.011)	.001
Cendon et al,[11] 2006	Time-series	0.45	1.032 (0.979-1.087)	.24
Cheng et al,[33] 2009	Time-series	2.82	1.015 (0.996-1.035)	.13
Hoek et al,[32] 2000	Time-series	11.97	1.001 (0.996-1.006)	.70
Lanki et al,[24] 2006	Time-series	8.77	1.003 (0.995-1.011)	.46
Linn et al,[12] 2000	Time-series	12.02	1.010 (1.005-1.015)	<.001
Mann et al,[39] 2002	Time-series	5.63	0.999 (0.987-1.011)	.87
Medina et al,[26] 1997	Time-series	0.41	0.979 (0.927-1.034)	.45
Sharovsky et al,[40] 2004	Time-series	0.13	1.010 (0.914-1.116)	.84
Stieb et al,[28] 2009	Time-series	4.84	1.002 (0.989-1.016)	.77
Combined (I^2 = 57%, Egger regression test, *P* = .61)			1.006 (1.002-1.009)	.002



B $PM_{2.5}$ analysis

Source	Study Design	Relative Study Weight, %	Relative Risk (95% CI)	*P* Value
Barnett et al,[9] 2006	Case-crossover	3.93	1.031 (0.983-1.082)	.21
Belleudi et al,[41] 2010	Case-crossover	13.82	1.018 (1.001-1.036)	.04
Peters et al,[20] 2001	Case-crossover	0.33	1.272 (1.061-1.525)	.009
Peters et al,[43] 2005	Case-crossover	0.89	1.105 (0.991-1.232)	.07
Pope et al,[35] 2006	Case-crossover	5.58	1.042 (1.003-1.083)	.04
Rich et al,[21] 2010	Case-crossover	4.43	1.010 (0.966-1.056)	.66
Sullivan et al,[22] 2005	Case-crossover	4.50	1.020 (0.976-1.066)	.38
Zanobetti and Schwartz,[45] 2006	Case-crossover	5.25	1.051 (1.010-1.094)	.02
Maté et al,[25] 2010	Time-series	7.26	1.066 (1.033-1.101)	<.001
Stieb et al,[28] 2009	Time-series	5.14	1.024 (0.983-1.066)	.25
Ueda et al,[38] 2009	Time-series	11.31	1.013 (0.991-1.035)	.24
Zanobetti et al,[30] 2009	Time-series	17.53	1.022 (1.011-1.034)	<.001
Zanobetti and Schwartz,[31] 2009	Time-series	20.03	1.011 (1.004-1.018)	.002
Combined (I^2 = 51%, Egger regression test, *P* = .004)			1.025 (1.015-1.036)	<.001



For PM_{10} (particulate matter of ≤10 μm), 17 studies were used with incremental unit of 10 μg/m³ and lag exposure of 0 days. For $PM_{2.5}$ (particulate matter of ≤2.5 μm), 13 studies were used with incremental unit of 10 μg/m³ and lag exposure of 1 day. The size of the relative risk data markers is relative to each study weight.

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young and disabled patients, is exposed to air pollution, particularly in urban settings, and thus an improvement in air quality could have a significant effect on public health.

Potential limitations of our study need to be considered. First, most studies have used a "single-pollutant" model in spite of possible interactions between pollutants. Few "multipollutant" models[9,37,42,46] have been used because they are difficult to implement and have not been validated. In addition, the application of an additive or multiplicative model requires a clear understanding of the nature of the relationship between exposure and disease, which is currently lacking.[3] Thus, we have independently analyzed the association of each pollutant on the risk of MI without being able to evaluate the interactions between these pollutants.

In addition, heterogeneity in exposure ascertainment across studies exists. Some studies have considered the mean of concentration,‡‡ other studies have used either peak or mean of concentration depending of the pollutant,[7,11,12,26,32,39,42,44] and the remaining studies have analyzed peak and mean of concentrations.[23,37] To the extent that the pathophysiological mechanisms are multiple, the dimension that is most likely to be involved in the risk of MI, between peak or mean of concentrations in pollutant, remains unclear. Additional limitations to inferences shown in our study relate to the observed statistical heterogeneity, publication bias, and the lack of validated quality scales for studies with time-series and case-crossover designs.

One strength of our study is the comprehensive nature of our search that spanned multiple databases and was not restricted to a particular publication language or a single pollutant. In addition, subgroup analyses confirmed the robustness of the original results.

In conclusion, our meta-analysis is the first to our knowledge to evaluate the quality and magnitude of associations between short-term exposure to major air pollutants and the risk of MI. We demonstrated an increase in near-term risk of MI associated with short-term exposure to all major air pollutants, with the exception of ozone. Although the RRs were relatively low, the PAFs were not negligible because the majority of the population is exposed to air pollution in industrialized countries. Further research is needed to determine whether effective interventions that improve air quality are associated with a decreased incidence of MI.

‡‡References 9, 10, 19-22, 24, 25, 27-31, 33, 34, 36, 38, 41, 43, 45, 46.

Author Contributions: Dr Mustafić had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Mustafić, Jabre, Murad, Escolano, Jouven.
Acquisition of data: Mustafić, Jabre, Caussin, Escolano, Tafflet, Périer, Vernerey.
Analysis and interpretation of data: Mustafić, Jabre, Murad, Escolano, Marijon, Empana, Jouven.
Drafting of the manuscript: Mustafić, Murad, Jouven.
Critical revision of the manuscript for important intellectual content: Mustafić, Jabre, Caussin, Murad, Escolano, Tafflet, Périer, Marijon, Vernerey, Empana, Jouven.
Statistical analysis: Mustafić, Jabre, Murad, Escolano, Jouven.
Administrative, technical, or material support: Mustafić, Jabre, Jouven.
Study supervision: Jouven.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Caussin reported receiving consultancy fees from Boston Scientific; payment for lectures including service on speakers bureaus from Daichii Sankyo and Novartis; and travel/meeting expenses from Medtronic, Edwards LifeScience, and Abbott. Dr Jouven reported receiving a grant from INSERM (National Research Institute). No other authors reported any financial disclosures.
Online-Only Material: The eAppendix, eFigure, and 2 eTables are available at http://www.jama/com.

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