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Citation for published version:

Shah, AS, Langrish, JP, Nair, H, McAllister, DA, Hunter, AL, Donaldson, K, Newby, DE & Mills, NL 2013, 'Global association of air pollution and heart failure: a systematic review and meta-analysis', *The Lancet*, vol. 382, no. 9897, pp. 1039-1048. [https://doi.org/10.1016/S0140-6736\(13\)60898-3](https://doi.org/10.1016/S0140-6736(13)60898-3)

Digital Object Identifier (DOI):

[10.1016/S0140-6736\(13\)60898-3](https://doi.org/10.1016/S0140-6736(13)60898-3)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

The Lancet

Publisher Rights Statement:

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Global association of air pollution and heart failure: a systematic review and meta-analysis



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Summary

Background Acute exposure to air pollution has been linked to myocardial infarction, but its effect on heart failure is uncertain. We did a systematic review and meta-analysis to assess the association between air pollution and acute decompensated heart failure including hospitalisation and heart failure mortality.

Methods Five databases were searched for studies investigating the association between daily increases in gaseous (carbon monoxide, sulphur dioxide, nitrogen dioxide, ozone) and particulate (diameter $<2.5 \mu\text{m}$ [$\text{PM}_{2.5}$] or $<10 \mu\text{m}$ [PM_{10}]) air pollutants, and heart failure hospitalisations or heart failure mortality. We used a random-effects model to derive overall risk estimates per pollutant.

Findings Of 1146 identified articles, 195 were reviewed in-depth with 35 satisfying inclusion criteria. Heart failure hospitalisation or death was associated with increases in carbon monoxide (3.52% per 1 part per million; 95% CI 2.52–4.54), sulphur dioxide (2.36% per 10 parts per billion; 1.35–3.38), and nitrogen dioxide (1.70% per 10 parts per billion; 1.25–2.16), but not ozone (0.46% per 10 parts per billion; -0.10 to 1.02) concentrations. Increases in particulate matter concentration were associated with heart failure hospitalisation or death ($\text{PM}_{2.5}$ 2.12% per $10 \mu\text{g}/\text{m}^3$, 95% CI 1.42–2.82; PM_{10} 1.63% per $10 \mu\text{g}/\text{m}^3$, 95% CI 1.20–2.07). Strongest associations were seen on the day of exposure, with more persistent effects for $\text{PM}_{2.5}$. In the USA, we estimate that a mean reduction in $\text{PM}_{2.5}$ of $3.9 \mu\text{g}/\text{m}^3$ would prevent 7978 heart failure hospitalisations and save a third of a billion US dollars a year.

Interpretation Air pollution has a close temporal association with heart failure hospitalisation and heart failure mortality. Although more studies from developing nations are required, air pollution is a pervasive public health issue with major cardiovascular and health economic consequences, and it should remain a key target for global health policy.

Funding British Heart Foundation.

Introduction

The adverse effects of air pollution on cardiovascular health have been established in a series of major epidemiological and observational studies.^{1–4} WHO estimates that air pollution is responsible for over a million premature deaths worldwide every year.⁵ Even brief exposures to air pollution have been associated with increases in cardiovascular mortality,^{6,7} particularly in susceptible populations.

Heart failure is an escalating public health issue that affects more than 23 million people worldwide,⁸ with an increasing prevalence in elderly people.^{9,10} It has an annual hospitalisation rate of 2% with subsequent 1-year mortality of 30%.¹¹ Heart failure ranks as the most frequent reason for hospitalisation and rehospitalisation in older people,^{12,13} accounting for 5% of all hospital discharge diagnoses. The triggers of acute cardiac decompensation especially in susceptible individuals are therefore a major public health concern.

Population and individual level exposures to air pollution are associated with acute cardiovascular events such as myocardial infarction.^{14,15} However, the effect of air pollution on other cardiovascular conditions, such as acute decompensated heart failure, has been less well described.¹⁶ This issue is important

because there are major differences in the mechanisms that trigger myocardial infarction compared with acute decompensated heart failure.^{17–19}

Several studies of short-term exposure to air pollution have included heart failure hospitalisation and mortality, although these endpoints have not been the primary focus in most analyses. We therefore systematically reviewed the evidence examining the association between air pollution and acute decompensated heart failure, including hospitalisation and heart failure mortality.

Methods

Databases

We searched Ovid Medline, Embase, Global Health, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science using the following keywords: “heart failure”, “congestive cardiac failure”, “air pollution”, “particulate matter”, “ozone”, “carbon monoxide”, “sulphur dioxide”, and “nitrogen dioxide”. The full search criteria are available in the appendix. Bibliographic reference lists of studies selected for inclusion in our meta-analysis and relevant review articles were manually searched (appendix). We limited our search to studies published between 1948 and July 15, 2012.

Published Online

July 10, 2013
[http://dx.doi.org/10.1016/S0140-6736\(13\)60898-3](http://dx.doi.org/10.1016/S0140-6736(13)60898-3)

See Online/Comment

[http://dx.doi.org/10.1016/S0140-6736\(13\)61167-8](http://dx.doi.org/10.1016/S0140-6736(13)61167-8)

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See Online for appendix

Selection of articles and extraction of data

Studies were included if they presented original data for gaseous (carbon monoxide, sulphur dioxide, nitrogen dioxide, ozone) or particulate (PM_{2.5} or PM₁₀) air pollutants and reported heart failure hospitalisation or heart failure mortality. We included all studies that reported associations between exposure and outcome up to and including lag (day) 7. There were no language restrictions and we included only peer-reviewed original articles.

Data were extracted independently by two investigators (ASVS and JPL) and conflicts were adjudicated by a third investigator (ALH). We contacted authors for additional data or clarification where needed.

Both case-crossover and time-series studies were included. The case-crossover design compares exposure in a case period when the event occurred with exposure in specified control periods.²⁰ This design can control for individual characteristics such as age, sex, and comorbidity, as well as secular trends and seasonal patterns using a time-stratified approach, but assumes time-varying risk factors are constant within reference periods.²¹ Time-series studies were used to assess the relation between exposure and outcome using regression analysis accounting for confounding factors, such as meteorological parameters, but are less effective at controlling for secular trends such as seasonality.²² The study design, study population, and adjustment undertaken for potential confounders have been summarised for each study in the appendix.

Data synthesis

Relative risks (RR) were pooled for a standardised increment in pollutant concentration as follows: 10 µg/m³ for PM_{2.5} and PM₁₀, 10 parts per billion for nitrogen dioxide (NO₂), sulphur dioxide (SO₂), and ozone (O₃), and 1 part per million for carbon monoxide (CO). Many studies used generalised linear models and therefore we assumed a linear relation between exposure and outcome. Standardised risk estimates were calculated for each study using the following formula:

$$RR_{(\text{standardised})} = RR_{(\text{original})}^{\text{Increment}(10)/\text{Increment}(\text{original})}$$

Four studies reported stratified risk estimates by age,²³ location,²⁴ and temperature^{25,26} rather than overall risk estimates, and the stratified estimates were included in our meta-analysis. Two studies reported results from the same population using both case-crossover and time-series analysis^{27,28} and estimates from the time-series analyses were included. Three studies^{29–31} subsequently revised their time series analyses and the revised estimates were included.^{32,33} Time-series analyses were mainly based on routine administrative datasets and did not adjust for individual characteristics such as age, sex, or socioeconomic status. For all studies, we pooled adjusted risk estimates controlling for meteorological, temporal, and seasonal parameters (appendix).

Many studies provided multiple estimates for single lags (for example lag 0 or lag 1) and were pooled separately. We only pooled estimates for single lags where more than three estimates were available. The shortest lag was used to assess overall risk estimates. A few studies only provided cumulative lags (for example lag 0–1 or 0–2), and were not suitable for pooling in the single lag analysis, but were used to determine overall risk estimates.

Additional analyses

We did additional analyses stratifying studies by study design (time-series *vs* case-crossover), geographical location (USA *vs* non-USA), age (all ages *vs* ≥65 years of age), and outcome (heart failure hospitalisation *vs* heart failure mortality). We assumed that the prevalence of air pollution exposure was 100% and therefore calculated population-attributable risks per pollutant using our overall risk estimates and the formula:

$$\text{Population-attributable risks} = \frac{(\text{RR} - 1)}{\text{RR}}$$

Funnel plots were constructed for assessment of publication bias (data not shown) and assessed for asymmetry using Egger's regression test.³⁴ Asymmetry was then corrected using the trim and fill method, with adjusted relative risks and number of studies adjusted presented per pollutant.³⁵

We used PM_{2.5} to illustrate the potential effect of reducing air pollution concentration on heart failure hospitalisations in the USA. For each state we obtained the number of heart failure hospitalisations and average cost per hospitalisation (amount charged for the hospital stay excluding professional fees) from the US Healthcare Cost and Utilization Project State Inpatient Database¹³ and the Chronic Condition and Data Warehouse (appendix). The median daily PM_{2.5} concentration was calculated for each state from the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research (WONDER) database. In each state, we estimated the population-attributable risks and annual reduction in heart failure hospitalisations per 100 000 people for a reduction in PM_{2.5} concentration to 5.8 µg/m³. This concentration represents a target threshold below which the adverse health effects of PM_{2.5} are uncertain.^{36,37}

Statistical analysis

We anticipated heterogeneity between studies due to different study designs, methods of analysis, different lag exposures, and geographical and population differences. We used a random-effects model to account for both within and between study heterogeneity. Heterogeneity was examined using the standard *I*² test. As this test has limited power when applied to a small number of studies, we considered the presence of heterogeneity at 10% level of significance and *I*² exceeding 30%. The analysis was

done using Comprehensive Meta-Analysis (version 2.0, 2005, Biostat Inc, NJ, USA) and Stata Software (Version 11.2 2011, StataCORP, TX, USA). Statistical significance was taken as two-sided $p < 0.05$.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or

writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The abstracts of 1146 articles were assessed and 195 studies underwent in-depth review, with 35 studies fulfilling the inclusion criteria. Ten studies used a case-crossover

	Location	Published	Period	Study design	Data source	Population	Number of events*	Outcome
Belleudi et al ³⁸	Italy	2010	2001–05	Case-crossover	Hospital discharge registry	≥65 years	17 561	HA
Bell et al ⁴⁷	USA	2009	1999–2005	Time-series	Medicare data	All	1142 928	HA
Haley et al ³⁹	USA	2009	2001–05	Case-crossover	NYSDOH registry	All	170 502	HA
Stieb et al ⁴⁹	Canada	2009	1999–2000	Time-series	Emergency department registry	All	32 313	HA
Ueda et al ⁵⁰	Japan	2009	2002–04	Time-series	Ministry of Health	≥65 years	17 548	Mortality
Zanobetti et al ⁵¹	USA	2009	2000–03	Time-series	Medicare data	All	238 587	HA
Colais et al ^{40,46†}	Italy	2009	2001–05	Case-crossover	Hospital discharge registry	≥65 years	55 339	HA
Forastiere et al ⁴¹	Italy	2008	1997–2004	Case-crossover	Regional registries of cause of death	All	9569	Mortality
Yang et al ²⁶	Taiwan	2008	1996–2004	Case-crossover	National Health Institute registry	All	24 240	HA
Lee et al ¹⁵	Taiwan	2007	1996–2004	Time-series	National Health Institute registry	All	13 475	HA
Peel et al ^{29‡}	USA	2007	1993–2000	Case-crossover	Billing records	>64 years	20 073	HA
Martins et al ⁵³	Brazil	2006	1996–2001	Time-series	Department of Data Analysis of the Unified Health System	≥65 years	24 476	HA
Dominici et al ⁵⁴	USA	2006	1999–2002	Time-series	Medicare data	≥65 years	986 392	HA
Wellenius et al ⁴³	USA	2006	1986–99	Case-crossover	Medicare and Medicaid data	All	292 918	HA
Barnett et al ²³	Australia and New Zealand	2006	1998–2001	Case-crossover	Government health departments (Australia) and Ministry of Health (NZ)	≥65 years	NR	HA
Wellenius et al ⁴²	USA	2005	1987–99	Case-crossover	Medicare and Medicaid data	≥65 years	55 019	HA
Bateson et al ⁴⁵	USA	2004	1988–91	Case-crossover	Medicare and Medicaid data	All	26 923	Mortality
Metzger et al ^{27‡}	USA	2004	1993–2000	Time-series	Billing data	All	20 073	HA
Goldberg et al ^{29,32§}	Canada	2003	1984–93	Time-series	Billing and prescription data	≥65 years	16 794	Mortality
Koken et al ⁵⁵	USA	2003	1993–97	Time-series	Agency for Healthcare Research and Quality	All	1860	HA
McGowan et al ⁵⁶	New Zealand	2002	1988–98	Time-series	Hospital data admission registry	All	5146	HA
Hoek et al ^{30,32§}	Netherlands	2001	1986–94	Time-series	Death certificates	All	45 333	Mortality
Kwon et al ⁶⁷	South Korea	2001	1994–98	Case-crossover and time-series	Mortality records	≥65 years	1807	Mortality
Ye et al ⁵⁷	Japan	2001	1980–95	Time-series	Ministry of Health	≥65 years	4469	HA
Lippmann et al ^{32,58§}	USA	2000	1992–94	Time-series	Medicare data	All	18 615	HA
Stieb et al ^{48¶}	Canada	2000	1992–94	Time-series	Emergency department registry	>30 years	1312	HA
Linn et al ⁵⁹	USA	2000	1992–95	Time-series	CA OSHPD	All	71 540	HA
Wong TW et al ⁶⁰	Hong Kong	1999	1994–95	Time-series	Hospital data admission registry	All	NR	HA
Burnett et al ⁶³	Canada	1999	1980–94	Time-series	Ontario Ministry of Health	All	49 311	HA
Wong CM et al ⁶¹	Hong Kong	1999	1995–97	Time-series	Hospital authority data	≥65 years	NR	HA
Morris et al ⁶⁴	USA	1998	1986–89	Time-series	Medicare data	≥65 years	49 640	HA
Burnett et al ⁶²	Canada	1997	1981–91	Time-series	Hospital discharge records	≥65 years	157 865	HA
Poloniecki et al ⁶⁶	UK	1997	1987–94	Time-series	Hospital episode records	≥65 years	62 853	HA
Morris et al ²⁴	USA	1995	1986–89	Time-series	Medicare data	≥65 years	227 985	HA
Schwartz et al ⁶⁵	USA	1995	1986–89	Time-series	Medicare data	≥65 years	38 862	HA

HA=Hospital admissions. NYSDOH=New York State Department of Health. NR=not reported. CA OSHPD=California Office of Statewide Health Planning and Development. *Number of events, when not stated in the paper, were estimated from mean daily values and the study period. †Colais et al initially published results in 2009 looking at NO₂, SO₂, and PM₁₀ in Italian. These data were later published in 2012 in English but only reporting estimates for PM₁₀. We have therefore used the PM₁₀ estimates from 2012 and NO₂ and SO₂ estimates from 2009. ‡Peel et al and Metzger et al reported results from the same study cohort but using case-crossover and time-series study designs, respectively. §Lippmann et al, Goldberg et al, and Hoek et al presented revised estimates of time-series analyses. ¶Stieb et al (2000) did not report numerical risk estimates and increment value for pollutants measured. This study was therefore excluded from the meta-analysis. ||Morris et al and Schwartz et al both reported data from Detroit across the same study period albeit with different lag structures. Morris et al measured associations across shorter lag structures and these estimates were chosen for the meta-analysis of gaseous pollutants. Schwartz et al additionally reported data for PM₁₀ whereas Morris et al did not and the study was included in the PM₁₀ meta-analysis.

Table 1: Contextual details of studies included in the meta-analysis by publication year

design,^{26,28,38–46} 24 used a times-series design,^{24,27,29,30,47–66} and one used both study designs⁶⁷ incorporating four million events across the world (table 1).

There was a positive association between heart failure hospitalisation or heart failure mortality, and all gaseous and particulate air pollutants except ozone (figure 1). The strongest associations were seen at lag 0, with this effect diminishing at longer lag times. Carbon monoxide was the most frequently studied gaseous pollutant, and showed a 3.52% (95% CI 2.52–4.54%) increase in heart failure hospitalisations or mortality per 1 part per million increment across nearly two million events. Both

PM_{2.5} (2.12%, 95% CI 1.42–2.82) and PM₁₀ (1.63%, 1.20–2.07) were positively associated with heart failure hospitalisation or mortality with a marked temporal relation and the strongest associations present at lag 0.

We did additional analyses by outcome, study design, age, and geographical location (figure 2). There was no change in effect direction across all pollutants in these analyses. Publication bias (Egger’s test for asymmetry, p<0.05) was noted for all pollutants except ozone (table 2). Adjusting for asymmetry using the trim and fill method did not alter the effect direction but, as expected, did attenuate the effect size. We observed heterogeneity

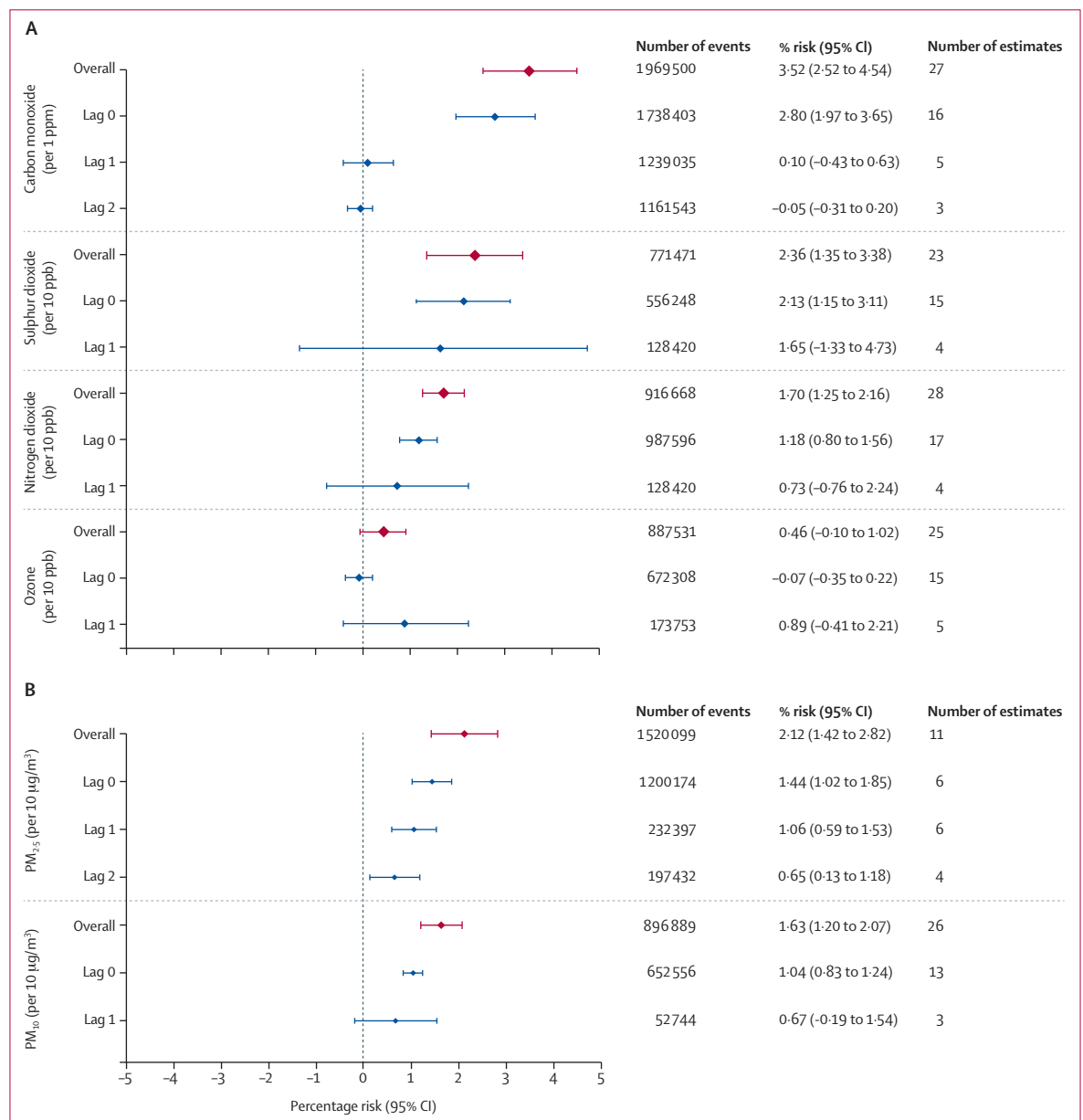


Figure 1: Association between (A) gaseous and (B) particulate air pollutants and heart failure hospitalisation or heart failure mortality ppm=parts per million. ppb=parts per billion.

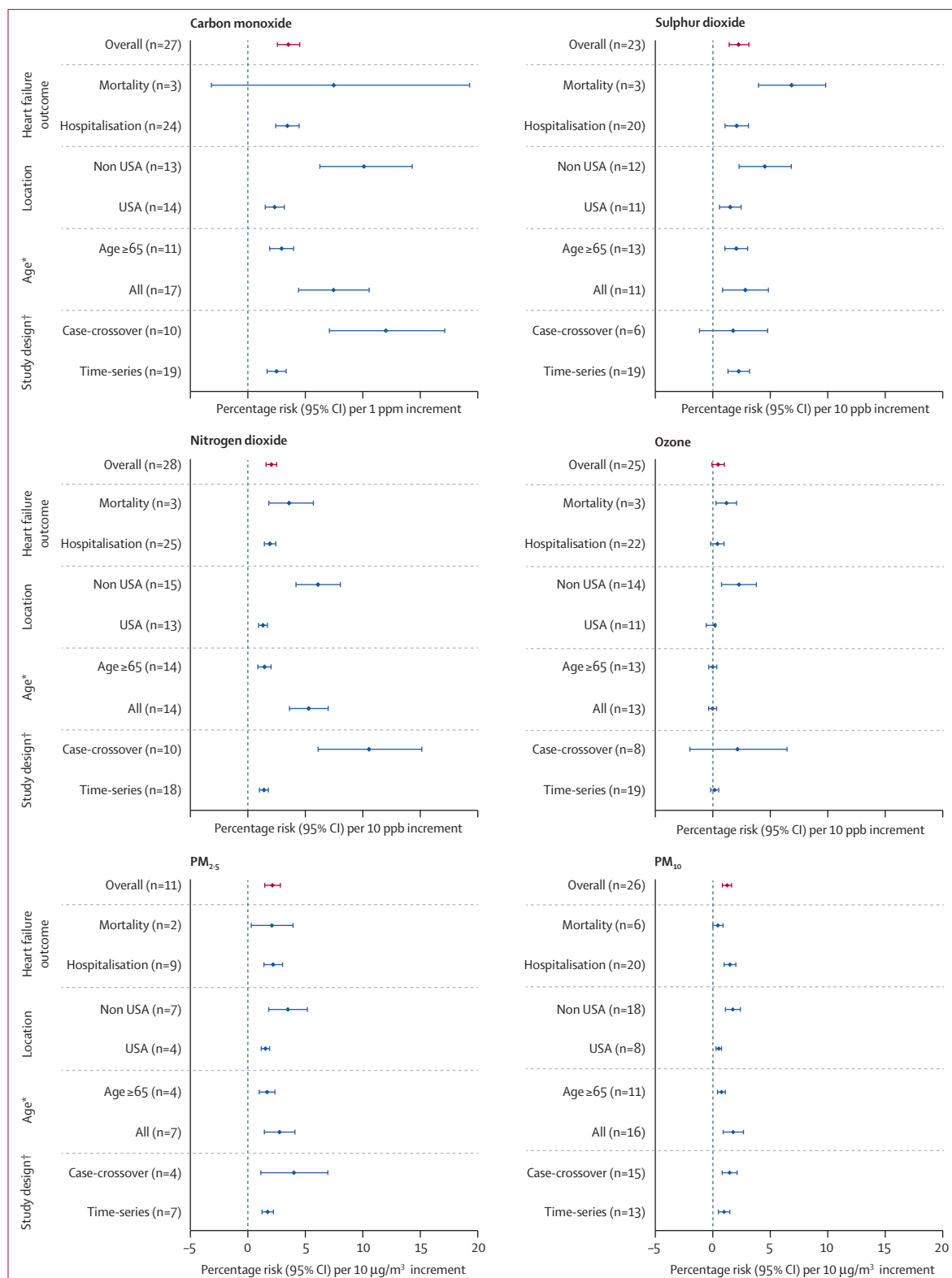


Figure 2: Additional analysis across all gaseous and particulate air pollutants

*Kwon et al⁹⁷ provided separate estimates for all age groups and for people older than 75 years. This study therefore appears twice in the additional analysis when stratified by age. For the overall analysis, we have used the estimates provided for all age groups. †Kwon and Peel et al^{97,28,67} provided separate estimates stratified by study design and therefore appear twice in the additional analysis. For the overall analysis, we have used the estimates provided for the time-series study design. ppm=parts per million. ppb=parts per billion.

	Gaseous pollutants				Particulate matter	
	Carbon monoxide (ppm)	Nitrogen dioxide (ppb)	Sulphur dioxide (ppb)	Ozone (ppb)	PM _{2.5} (µg/m ³)	PM ₁₀ (µg/m ³)
Increment	1 ppm	10 ppb	10 ppb	10 ppb	10 µg/m ³	10 µg/m ³
Median pollutant concentration (IQR)*	1.1 (0.9–1.6)	26.4 (22.5–30.1)	6.3 (4.7–11.9)	23.5 (17.6–32.0)	15.0 (10.8–17.6)	38.0 (27.0–45.5)
Range (min–max)†	0.6–5.6	16.0–77.0	3.0–32.0	12.3–75.0	4.5–20.5	19.0–75.3
Number of studies	18	18	14	18	10	22
Number of estimates	27	28	23	25	11	26
Heterogeneity, I ²	91%	91%	78%	87%	53%	75%
Population-attributable risk, % (95% CI)‡	3.41 (2.46–4.34)	1.67 (1.23–2.11)	2.31 (1.33–3.27)	N/A	2.06 (1.38–2.72)	1.60 (1.18–2.03)
Publication bias						
Egger regression test, p value	<0.001	0.028	0.009	0.304	0.003	0.007
Non-adjusted RR (95% CI)§	1.035 (1.025–1.045)	1.017 (1.012–1.022)	1.024 (1.014–1.034)	1.005 (0.999–1.011)	1.021 (1.014–1.028)	1.016 (1.012–1.021)
Adjusted RR (95% CI)¶	1.018 (1.007–1.029)	1.009 (1.004–1.014)	1.014 (1.003–1.026)	1.001 (0.995–1.007)	1.016 (1.008–1.023)	1.010 (1.005–1.016)
Number of studies adjusted	12	10	6	2	6	6

ppm=parts per million, ppb=parts per billion, PM=particulate matter, PAR=population-attributable risk, IQR=interquartile range. *Median pollutant concentration (IQR) derived from the average daily pollutant concentrations reported per study. †Range of the average pollutant concentrations across the studies from minimum to maximum. ‡PAR reported per ten-unit increment in air pollutant concentration, except for CO where per one-unit increment. Calculated as $PAR = X(RR - 1) / [X(RR - 1) + 1]$, where X indicates prevalence exposure (assumed to be 100% here). §Risk estimates derived from pooled analysis of studies. ¶Risk estimates after adjustment for publication bias using the trim and fill method.

Table 2: Heterogeneity, population-attributable risk, and assessment for publication bias stratified by gaseous and particulate air pollutants

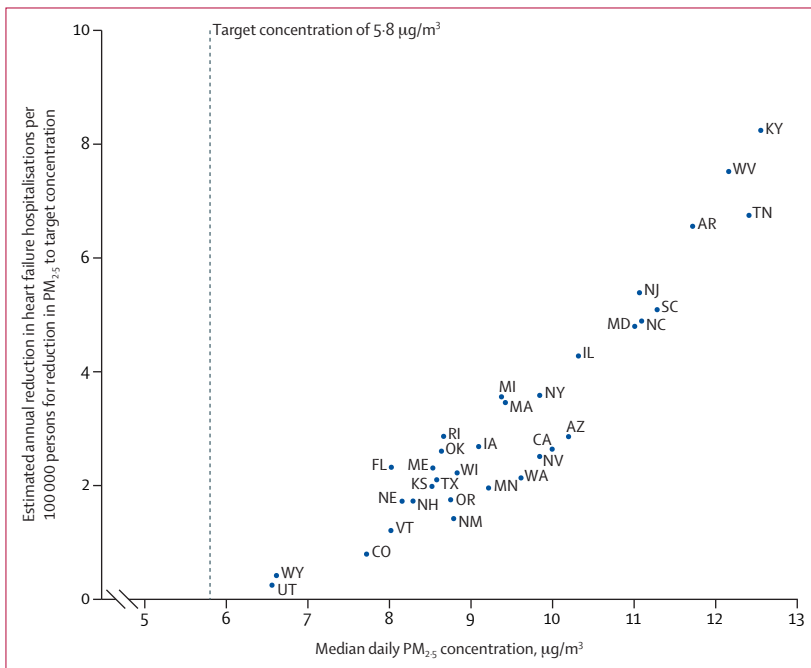


Figure 3: Median daily PM_{2.5} concentrations and estimated impact of a reduction in PM_{2.5} to a target concentration on heart failure hospitalisation per US state
Heart failure hospitalisation rates were not available for 15 states (appendix); data not shown for Mississippi (median daily PM_{2.5} 13.4 µg/m³; annual reduction in heart failure hospitalisations 15 per 100 000). US state abbreviations are defined in the appendix.

across all pollutants, which was most evident for nitrogen dioxide and carbon monoxide (I² of 91%) and least evident for PM_{2.5} (I² of 53%).

Median daily PM_{2.5} concentrations varied across states, with the highest population-attributable risks seen in Mississippi, Kentucky, and Tennessee and the lowest in Utah, Wyoming, and North Dakota (appendix). Reducing PM_{2.5} concentrations to 5.8 µg/m³ in each state would require a mean reduction in PM_{2.5} of 3.9 µg/m³ across the USA. The greatest effect on heart failure hospitalisations would be in those states with the highest median daily PM_{2.5} concentrations (figure 3). We estimate that this reduction would prevent 7978 heart failure hospitalisations and would be associated with savings of around US\$307 million per year (appendix).

Discussion

There were robust and clear temporal associations between exposure to air pollutants and heart failure hospitalisations and mortality. The magnitude and direction of our overall estimates persisted despite conservative modelling. All studies except one were done in developed countries where even modest improvements in air quality standards are projected to have major population health benefits and substantial health-care cost savings.

The effect of air pollution on heart failure hospitalisation and mortality might be underestimated. First, our estimates are based on acute events associated with short-term exposures and do not take into account the adverse effects of chronic exposure to air pollution.³ We

have not considered long-term studies of air pollution in the current meta-analysis and therefore are unable to quantify any additive temporal effects of air pollution. Second, although our meta-analysis estimates the effect of short-term increases in air pollution on the population, this effect is likely to be greater in patients with pre-existing heart failure. Unfortunately, we were unable to stratify our analysis on the presence, severity, or phenotype of pre-existing heart failure, since these data were not available. Third, regional monitoring sites are likely to underestimate personal exposure in individuals living near major roadways. This may be an important consideration in estimating individual risk given that traffic-related air pollutants are thought to be the primary mediators of the cardiovascular effects of air pollution.¹⁹

A recent assessment of the global burden of disease ranked PM_{2.5} air pollution as one of the leading causes of death and disability worldwide.³⁷ The American Thoracic Society recently advocated stricter standards for PM_{2.5} recommending a 10 µg/m³ reduction in daily maximum concentrations to 25 µg/m³.⁶⁸ Recent studies indicate the persistence of adverse health effects at concentrations below those recommended by WHO.⁶⁹ In our impact analysis, we estimate that reducing median daily PM_{2.5} concentrations by a mean of 3.9 µg/m³ would prevent roughly 8000 heart failure hospitalisations in the USA, with an associated saving of nearly a third of a billion dollars per annum. Smaller reductions in PM_{2.5} would prevent fewer hospitalisations, but could still confer significant public health benefits.

Urban cities in developing countries are likely to have PM_{2.5} concentrations up to 10-fold higher than the US National Ambient Air Quality Standards.^{70,71} So-called megacities, with populations well above 10 million people such as New Delhi in India and Beijing in China, have daily PM_{2.5} concentrations of 100–300 µg/m³ compared with a median PM_{2.5} concentration of 15 µg/m³ in the cities included in our meta-analysis.^{70,72} However, assessment of the effect of air pollution in developing countries is difficult because of a lack of cohesive air quality policies in combination with poor environmental monitoring and a paucity of disease surveillance data.⁷³

The lack of data from developing countries is concerning because these regions are likely to be affected most and have the greatest potential to improve health. The problem is highlighted in our meta-analysis where only one of the 35 studies was done in a developing country.⁵³ In areas with high levels of air pollution there are likely to be more frequent and more marked changes in air pollution exposure on a daily basis.⁷² Whether actual or relative increases in exposure would determine outcomes in these regions is uncertain.

In our additional analysis stratifying studies by location, we found risk estimates were almost twice as high in countries outside the USA where ambient concentrations are generally higher. As such, caution is necessary when extrapolating overall risk estimates

from our meta-analysis to regions with higher air pollution concentrations.

Most hospitalisations in patients with heart failure are due to acute decompensated heart failure and dysrhythmias,⁷⁴ with fewer patients hospitalised because of coexisting coronary heart disease and pulmonary disease.¹⁶ The biological mechanisms precipitating acute decompensation in patients with heart failure are likely to differ substantially from those involved in triggering acute myocardial infarction.¹⁹ Acute decompensated heart failure can be caused by increasing demand on the heart, such as increased heart rate, blood pressure, and filling pressures, or further impairment of cardiac performance, such as reduced contractility and increased myocardial injury. Exposure to particulate matter air pollution has been associated with increased systemic blood pressure and vasoconstriction.^{75–77} Both pulmonary and right ventricular diastolic filling pressures are increased by exposure to ambient particulate matter, suggesting a pulmonary vasoconstrictor effect of air pollution.⁷⁸ Together with arrhythmias,⁷⁹ these effects of air pollution will markedly increase the demands on the failing heart and thereby potentially precipitate acute decompensation. In addition to loss of contractile capacity through myocardial infarction,⁸⁰ inhalation of particulate matter is associated with adverse ventricular remodelling and a worsening of myocardial fibrosis.⁸¹ These factors could have synergistic detrimental effects on cardiac function.

Although particulate matter is considered to be responsible for most adverse cardiovascular outcomes,⁸² we cannot exclude an effect of non-particulate air pollutants either in isolation or combination. We noted an adverse relation between exposure to all gaseous pollutants except for ozone and heart failure outcomes. The acute effects of carbon monoxide exposure on cardiac function are well known,⁸³ but most of these studies have assessed the effects of exposure to more than 1000 parts per million of carbon monoxide as a model of cigarette smoking.^{84,85} Ambient carbon monoxide or nitrogen dioxide concentrations might simply reflect exposure to road traffic or combustion derived particles. Chamber studies also show that exposure to gaseous pollutants alone at high ambient concentrations does not cause acute cardiovascular dysfunction.^{86,87}

Several limitations of our study should be considered. First, we found significant heterogeneity across all pollutants, which could indicate differences in population demographics, sample size, patient characteristics, and exposure misclassification due to variation in the accuracy of regional air pollution monitoring. However, pooled risk estimates showed consistency across all pollutants and the effect direction was not changed in our additional analyses. Second, we report estimates for single pollutants, which do not take into consideration potential additive effects of multiple pollutants or adjustments for collinearity.⁸⁸ Third, meta-analysis of observational studies has limitations with inherent biases. We noticed

significant publication bias across all pollutants, except ozone. However, after adjustment for asymmetry, the overall effect direction remained unchanged. Fourth, most studies pooled in our meta-analysis used data from routine administrative sources. There was limited validation of outcomes, with coding error and misclassification potentially giving rise to non-differential bias. However, nine of the 35 studies in our meta-analysis, encompassing almost 2 million events, used Medicare's hospital claims database. Coding for heart failure has been validated by case note review and found to have 84% agreement with the principal diagnosis.⁸⁹ Finally, we did not have access to primary data and were unable to establish whether multiple hospitalisations might have occurred in the same patient. This point is important, since patients with recurrent hospitalisations could be more susceptible to the effects of air pollution.

Acute decompensated heart failure is a common, costly, and often fatal condition. Change in gaseous and particulate air pollutant concentrations have a marked and close temporal association with adverse outcomes in heart failure. More high-quality studies are urgently needed to establish the effect of air pollution on heart failure outcomes in middle-income and low-income countries. Although the causality and biological mechanisms need further exploration, air pollution is a pervasive public health issue with major cardiovascular and health-care economic consequences presenting a key target for national and international intervention.

Conflicts of interest

We declare that we have no conflicts of interest.

Contributors

ASVS conceived and designed the study. ASVS, JPL, and ALH acquired the data. ASVS, HN, DEN, and NLM analysed and interpreted the data. ASVS, DEN, and NLM drafted the initial manuscript. ASVS, JPL, HN, DAM, ALH, KD, DEN, and NLM made critical revisions of the manuscript for important intellectual content. All authors approved the final version of the report.

Acknowledgments

ASVS, DEN, and NLM are supported by a Clinical Research Fellowship (SS/CH/09/002), Chair (CH/09/002), and Intermediate Clinical Research Fellowship (FS/10/024/28266), respectively, from the British Heart Foundation. This research is supported by a British Heart Foundation Programme Grant (RG/10/9/28286). We thank Michelle Bell (Yale University), Mark Goldberg (McGill University), and William Linn (University of Southern California) for providing additional data for this meta-analysis.

References

- Dockery DW, Pope CA 3rd, Xu X, et al. An association between air pollution and mortality in six US cities. *N Engl J Med* 1993; **329**: 1753–59.
- Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet* 2002; **360**: 1203–09.
- Pope CA 3rd, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004; **109**: 71–77.
- Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007; **356**: 447–58.
- Global Health Observatory Data Repository. Urban outdoor air pollution: burden of disease by country. Geneva: World Health Organization, 2008. <http://apps.who.int/gho/data/node.main.285> (accessed Sept 1, 2012).
- Samet JM, Dominici F, Currier FC, Coursac I, Zeger SL. Fine particulate air pollution and mortality in 20 US cities, 1987–1994. *N Engl J Med* 2000; **343**: 1742–49.
- Peters A, Dockery DW, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. *Circulation* 2001; **103**: 2810–15.
- Berry C, Murdoch DR, McMurray JJ. Economics of chronic heart failure. *Eur J Heart Fail* 2001; **3**: 283–91.
- Davies M, Hobbs F, Davis R, et al. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet* 2001; **358**: 439–44.
- Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003; **289**: 194–202.
- Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998–2008. *JAMA* 2011; **306**: 1669–78.
- Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med* 2009; **360**: 1418–28.
- Healthcare Cost and Utilization Project. HCUP facts and figures: statistics on hospital-based care in the United States, 2008. http://www.hcup-us.ahrq.gov/reports/factsandfigures/2008/exhibit2_3.jsp (accessed Sept 1, 2012).
- Nawrot TS, Perez L, Kunzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet* 2011; **377**: 732–40.
- Mustafic H, Jabre P, Caussin C, et al. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. *JAMA* 2012; **307**: 713–21.
- Dunlay SM, Redfield MM, Weston SA, et al. Hospitalizations after heart failure diagnosis: a community perspective. *J Am Coll Cardiol* 2009; **54**: 1695–702.
- Mills NL, Tornqvist H, Gonzalez MC, et al. Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *N Engl J Med* 2007; **357**: 1075–82.
- Lucking AJ, Lundback M, Mills NL, et al. Diesel exhaust inhalation increases thrombus formation in man. *Eur Heart J* 2008; **29**: 3043–51.
- Mills NL, Donaldson K, Hadoke PW, et al. Adverse cardiovascular effects of air pollution. *Nat Clin Pract Cardiovasc Med* 2009; **6**: 36–44.
- Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991; **133**: 144–53.
- Lumley T, Levy D. Bias in the case-crossover design: implications for studies of air pollution. Washington DC: University of Washington, 1999.
- Fung KY, Krewski D, Chen Y, Burnett R, Cakmak S. Comparison of time series and case-crossover analyses of air pollution and hospital admission data. *Int J Epidemiol* 2003; **32**: 1064–70.
- Barnett AG, Williams GM, Schwartz J, et al. The effects of air pollution on hospitalizations for cardiovascular disease in elderly people in Australian and New Zealand cities. *Environ Health Perspect* 2006; **114**: 1018–23.
- Morris RD, Naumova EN, Munasinghe RL. Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. *Am J Public Health* 1995; **85**: 1361–65.
- Lee IM, Tsai SS, Ho CK, Chiu HF, Yang CY. Air pollution and hospital admissions for congestive heart failure in a tropical city: Kaohsiung, Taiwan. *Inhal Toxicol* 2007; **19**: 899–904.
- Yang CY. Air pollution and hospital admissions for congestive heart failure in a subtropical city: Taipei, Taiwan. *J Toxicol Environ Health A* 2008; **71**: 1085–90.
- Metzger KB, Tolbert PE, Klein M, et al. Ambient air pollution and cardiovascular emergency department visits. *Epidemiology* 2004; **15**: 46–56.

- 28 Peel JL, Metzger KB, Klein M, Flanders WD, Mulholland JA, Tolbert PE. Ambient air pollution and cardiovascular emergency department visits in potentially sensitive groups. *Am J Epidemiol* 2007; **165**: 625–33.
- 29 Goldberg MS, Burnett RT, Valois MF, et al. Associations between ambient air pollution and daily mortality among persons with congestive heart failure. *Environ Res* 2003; **91**: 8–20.
- 30 Hoek G, Brunekreef B, Fischer P, van Wijnen J. The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. *Epidemiology* 2001; **12**: 355–57.
- 31 Lippmann M, Ito K, Nádas A, Burnett RT. Association of particulate matter components with daily mortality and morbidity in urban populations. *Res Rep Health Eff Inst* 2000; **95**: 5–72.
- 32 Health Effects Institute. Revised analyses of time-series studies of air pollution and health. Special report. Boston: Health Effects Institute, 2003.
- 33 Dominici F, McDermott A, Zeger SL, Samet JM. On the use of generalized additive models in time-series studies of air pollution and health. *Am J Epidemiol* 2002; **156**: 193–203.
- 34 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–34.
- 35 Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56**: 455–63.
- 36 Evans J, van Donkelaar A, Martin RV, et al. Estimates of global mortality attributable to particulate air pollution using satellite imagery. *Environ Res* 2013; **120**: 33–42.
- 37 Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2224–60.
- 38 Belleudi V, Faustini A, Stafoggia M, et al. Impact of fine and ultrafine particles on emergency hospital admissions for cardiac and respiratory diseases. *Epidemiology* 2010; **21**: 414–23.
- 39 Haley VB, Talbot TO, Felton HD. Surveillance of the short-term impact of fine particle air pollution on cardiovascular disease hospitalizations in New York State. *Environ Health* 2009; **8**: 42.
- 40 Colais P, Serinelli M, Faustini A, et al. Air pollution and urgent hospital admissions in nine Italian cities. Results of the EpiAir Project. *Epidemiol Prev* 2009; **33** (6 suppl 1): 77–94 (in Italian).
- 41 Forastiere F, Stafoggia M, Berti G, et al. Particulate matter and daily mortality: a case-crossover analysis of individual effect modifiers. *Epidemiology* 2008; **19**: 571–80.
- 42 Wellenius GA, Bateson TF, Mittleman MA, Schwartz J. Particulate air pollution and the rate of hospitalization for congestive heart failure among medicare beneficiaries in Pittsburgh, Pennsylvania. *Am J Epidemiol* 2005; **161**: 1030–36.
- 43 Wellenius GA, Schwartz J, Mittleman MA. Particulate air pollution and hospital admissions for congestive heart failure in seven United States cities. *Am J Cardiol* 2006; **97**: 404–08.
- 44 Barnett AG, Williams GM, Schwartz J, et al. The effects of air pollution on hospitalizations for cardiovascular disease in elderly people in Australian and New Zealand cities. *Environ Health Perspect* 2006; **118**: 23–31.
- 45 Bateson TF, Schwartz J. Who is sensitive to the effects of particulate air pollution on mortality? A case-crossover analysis of effect modifiers. *Epidemiology* 2004; **15**: 143–49.
- 46 Colais P, Faustini A, Stafoggia M, et al. Particulate air pollution and hospital admissions for cardiac diseases in potentially sensitive subgroups. *Epidemiology* 2012; **23**: 473–81.
- 47 Bell ML, Peng RD, Dominici F, Samet JM. Emergency hospital admissions for cardiovascular diseases and ambient levels of carbon monoxide: results for 126 United States urban counties, 1999–2005. *Circulation* 2009; **120**: 949–55.
- 48 Stieb DM, Beveridge RC, Brook JR, et al. Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. *J Expo Anal Environ Epidemiol* 2000; **10**: 461–77.
- 49 Stieb DM, Szyszkowicz M, Rowe BH, Leech JA. Air pollution and emergency department visits for cardiac and respiratory conditions: a multi-city time-series analysis. *Environ Health* 2009; **8**: 25.
- 50 Ueda K, Nitta H, Ono M. Effects of fine particulate matter on daily mortality for specific heart diseases in Japan. *Circ J* 2009; **73**: 1248–54.
- 51 Zanobetti A, Franklin M, Koutrakis P, Schwartz J. Fine particulate air pollution and its components in association with cause-specific emergency admissions. *Environ Health* 2009; **8**: 58.
- 52 Lee I-M, Tsai S-S, Ho C-K, Chiu H-F, Yang CY. Air pollution and hospital admissions for congestive heart failure in a tropical city: Kaohsiung, Taiwan. *Inhal Toxicol* 2007; **19**: 899–904.
- 53 Martins LC, Pereira LA, Lin CA, et al. The effects of air pollution on cardiovascular diseases: lag structures. *Rev Saude Publica* 2006; **40**: 677–83.
- 54 Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 2006; **295**: 1127–34.
- 55 Koken PJ, Piver WT, Ye F, Elixhauser A, Olsen LM, Portier CJ. Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in Denver. *Environ Health Perspect* 2003; **111**: 1312–17.
- 56 McGowan JA, Hider RN, Chacko E, Town GI. Particulate air pollution and hospital admissions in Christchurch, New Zealand. *Aust N Z J Public Health* 2002; **26**: 23–29.
- 57 Ye F, Piver WT, Ando M, Portier CJ. Effects of temperature and air pollutants on cardiovascular and respiratory diseases for males and females older than 65 years of age in Tokyo, July and August 1980–1995. *Environ Health Perspect* 2001; **109**: 355–59.
- 58 Lippmann M, Ito K, Nádas A, Burnett RT. Association of particulate matter components with daily mortality and morbidity in urban populations. *Res Rep Health Eff Inst* 2000; **95**: 5–72.
- 59 Linn WS, Szlachcic Y, Gong H Jr, Kinney PL, Berhane KT. Air pollution and daily hospital admissions in metropolitan Los Angeles. *Environ Health Perspect* 2000; **108**: 427–34.
- 60 Wong TW, Lau TS, Yu TS, et al. Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. *Occup Environ Med* 1999; **56**: 679–83.
- 61 Wong CM, Ma S, Hedley AJ, Lam TH. Does ozone have any effect on daily hospital admissions for circulatory diseases? *J Epidemiol Community Health* 1999; **53**: 580–81.
- 62 Burnett RT, Dales RE, Brook JR, Raizenne ME, Krewski D. Association between ambient carbon monoxide levels and hospitalizations for congestive heart failure in the elderly in 10 Canadian cities. *Epidemiology* 1997; **8**: 162–67.
- 63 Burnett RT, Smith-Doiron M, Stieb D, Cakmak S, Brook JR. Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. *Arch Environ Health* 1999; **54**: 130–39.
- 64 Morris RD, Naumova EN. Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increased effect at low temperatures. *Environ Health Perspect* 1998; **106**: 649–53.
- 65 Schwartz J, Morris R. Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. *Am J Epidemiol* 1995; **142**: 23–35.
- 66 Poloniecki JD, Atkinson RW, de Leon AP, Anderson HR. Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. *Occup Environ Med* 1997; **54**: 535–40.
- 67 Kwon HJ, Cho SH, Nyberg F, Pershagen G. Effects of ambient air pollution on daily mortality in a cohort of patients with congestive heart failure. *Epidemiology* 2001; **12**: 413–19.
- 68 American Thoracic Society. ATS Testifies at EPA field hearing on particulate matter pollution. Washington: American Thoracic Society, 2012. <http://www.thoracic.org/advocacy/washington-letter/archive/2012/july-20-2012.php> (accessed Sept 1, 2012).
- 69 Wellenius GA, Burger MR, Coull BA, et al. Ambient air pollution and the risk of acute ischemic stroke. *Arch Intern Med* 2012; **172**: 229–34.
- 70 Langrish JP, Li X, Wang S, et al. Reducing personal exposure to particulate air pollution improves cardiovascular health in patients with coronary heart disease. *Environ Health Perspect* 2012; **120**: 367–72.
- 71 Molina MJ, Molina LT. Megacities and atmospheric pollution. *J Air Waste Manag Assoc* 2004; **54**: 644–80.
- 72 Guttikunda SK, Calori G. A GIS based emissions inventory at 1 km×1 km spatial resolution for air pollution analysis in Delhi, India. *Atmos Environ* 2013; **67**: 101–11.
- 73 Briggs D. Environmental pollution and the global burden of disease. *Br Med Bull* 2003; **68**: 1–24.

- 74 Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case-control study. *Am J Med* 2009; **122**: 1023–28.
- 75 Pieters N, Plusquin M, Cox B, Kicinski M, Vangronsveld J, Nawrot TS. An epidemiological appraisal of the association between heart rate variability and particulate air pollution: a meta-analysis. *Heart* 2012; **98**: 1127–35.
- 76 Brook RD, Brook JR, Urch B, Vincent R, Rajagopalan S, Silverman F. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. *Circulation* 2002; **105**: 1534–36.
- 77 Tsai DH, Riediker M, Wuerzner G, et al. Short-term increase in particulate matter blunts nocturnal blood pressure dipping and daytime urinary sodium excretion. *Hypertension* 2012; **60**: 1061–69.
- 78 Rich DQ, Freudenberger RS, Ohman-Strickland P, Cho Y, Kipen HM. Right heart pressure increases after acute increases in ambient particulate concentration. *Environ Health Perspect* 2008; **116**: 1167–71.
- 79 Peters A, Liu E, Verrier RL, et al. Air pollution and incidence of cardiac arrhythmia. *Epidemiology* 2000; **11**: 11–17.
- 80 Gomez AM, Guatimosim S, Dilly KW, Vassort G, Lederer WJ. Heart failure after myocardial infarction: altered excitation-contraction coupling. *Circulation* 2001; **104**: 688–93.
- 81 Wold LE, Ying Z, Hutchinson KR, et al. Cardiovascular remodeling in response to long-term exposure to fine particulate matter air pollution. *Circ Heart Fail* 2012; **5**: 452–61.
- 82 Brook RD, Rajagopalan S, Pope CA 3rd, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation* 2010; **121**: 2331–78.
- 83 Allred EN, Bleecker ER, Chaitman BR, et al. Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. *N Engl J Med* 1989; **321**: 1426–32.
- 84 Niedermaier ON, Smith ML, Beightol LA, Zukowska-Grojec Z, Goldstein DS, Eckberg DL. Influence of cigarette smoking on human autonomic function. *Circulation* 1993; **88**: 562–71.
- 85 Zevin S, Saunders S, Gourlay SG, Jacob P, Benowitz NL. Cardiovascular effects of carbon monoxide and cigarette smoking. *J Am Coll Cardiol* 2001; **38**: 1633–38.
- 86 Langrish JP, Lundback M, Barath S, et al. Exposure to nitrogen dioxide is not associated with vascular dysfunction in man. *Inhal Toxicol* 2010; **22**: 192–98.
- 87 Mills NL, Miller MR, Lucking AJ, et al. Combustion-derived nanoparticulate induces the adverse vascular effects of diesel exhaust inhalation. *Eur Heart J* 2011; **32**: 2660–71.
- 88 Dominici F, Peng RD, Barr CD, Bell ML. Protecting human health from air pollution: shifting from a single-pollutant to a multipollutant approach. *Epidemiology* 2010; **21**: 187–94.
- 89 Fisher ES, Whaley FS, Krushat WM, et al. The accuracy of Medicare's hospital claims data: progress has been made, but problems remain. *Am J Public Health* 1992; **82**: 243–48.