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 μm [$PM_{2·5}$] or <10 μm [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 ($PM_{2·5}$ 2·12% per 10 μg/m³, 95% CI 1·42–2·82; PM_{10} 1·63% per 10 μg/m³, 95% CI 1·20–2·07). Strongest associations were seen on the day of exposure, with more persistent effects for $PM_{2·5}$. In the USA, we estimate that a mean reduction in $PM_{2·5}$ of 3·9 μg/m³ 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.

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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.

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 PM_{10}) 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 PM_{10}, 10 parts per billion for nitrogen dioxide (NO_2), sulphur dioxide (SO_2), and ozone (O_3), 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:

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

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:

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

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 Database[13] 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	1 142 928	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[25]	Taiwan	2007	1996–2004	Time-series	National Health Institute registry	All	13 475	HA
Peel et al[28]‡	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 NO_2, SO_2, and PM_{10} in Italian. These data were later published in 2012 in English but only reporting estimates for PM_{10}. We have therefore used the PM_{10} estimates from 2012 and NO_2 and SO_2 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 PM_{10} whereas Morris et al did not and the study was included in the PM_{10} 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 designs[67] 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 PM_{10} (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

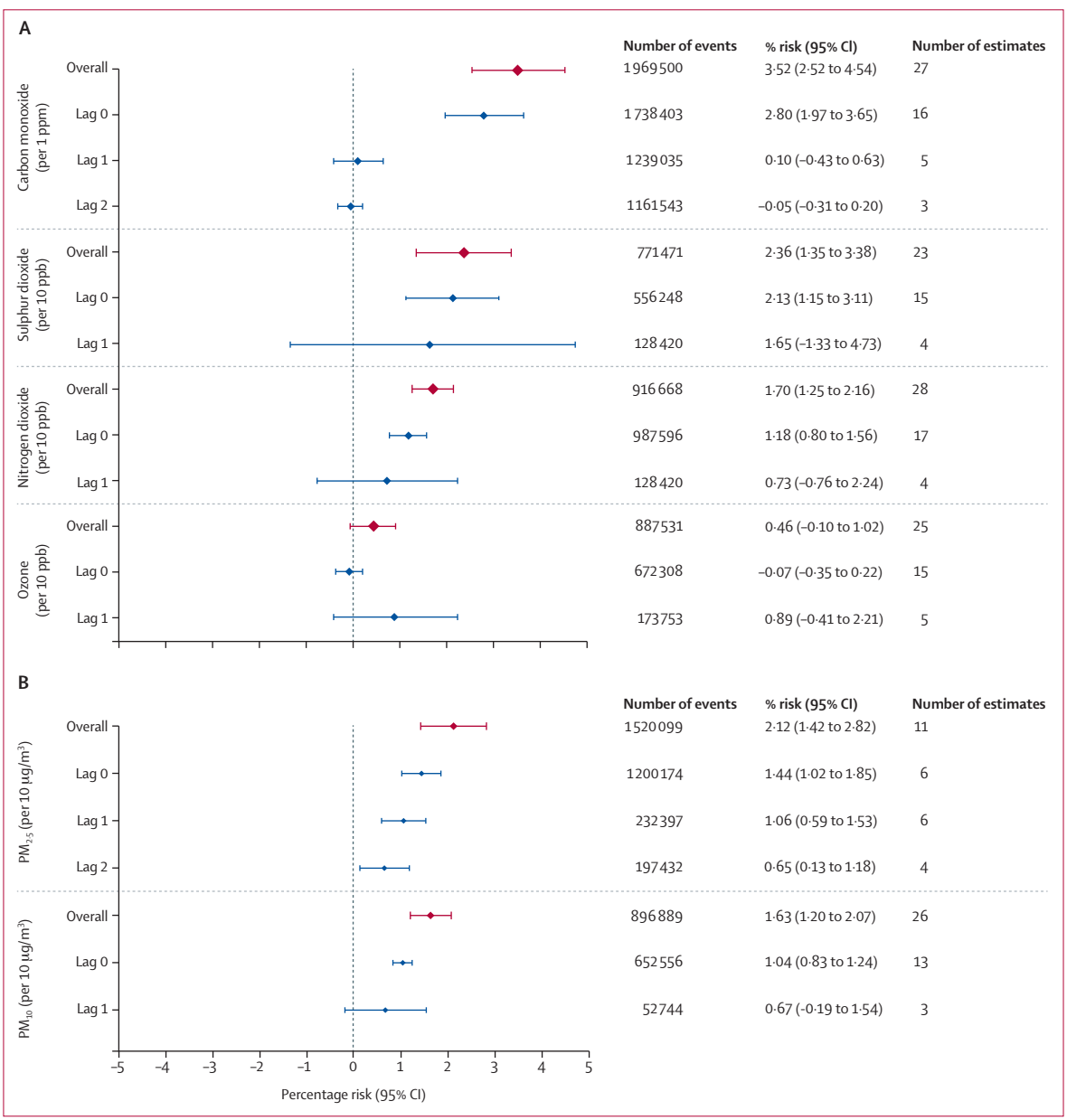

Figure 1: **Association between (A) gaseous and (B) particulate air pollutants and heart failure hospitalisation or heart failure mortality**
ppm=parts per million. ppb=parts per billion.

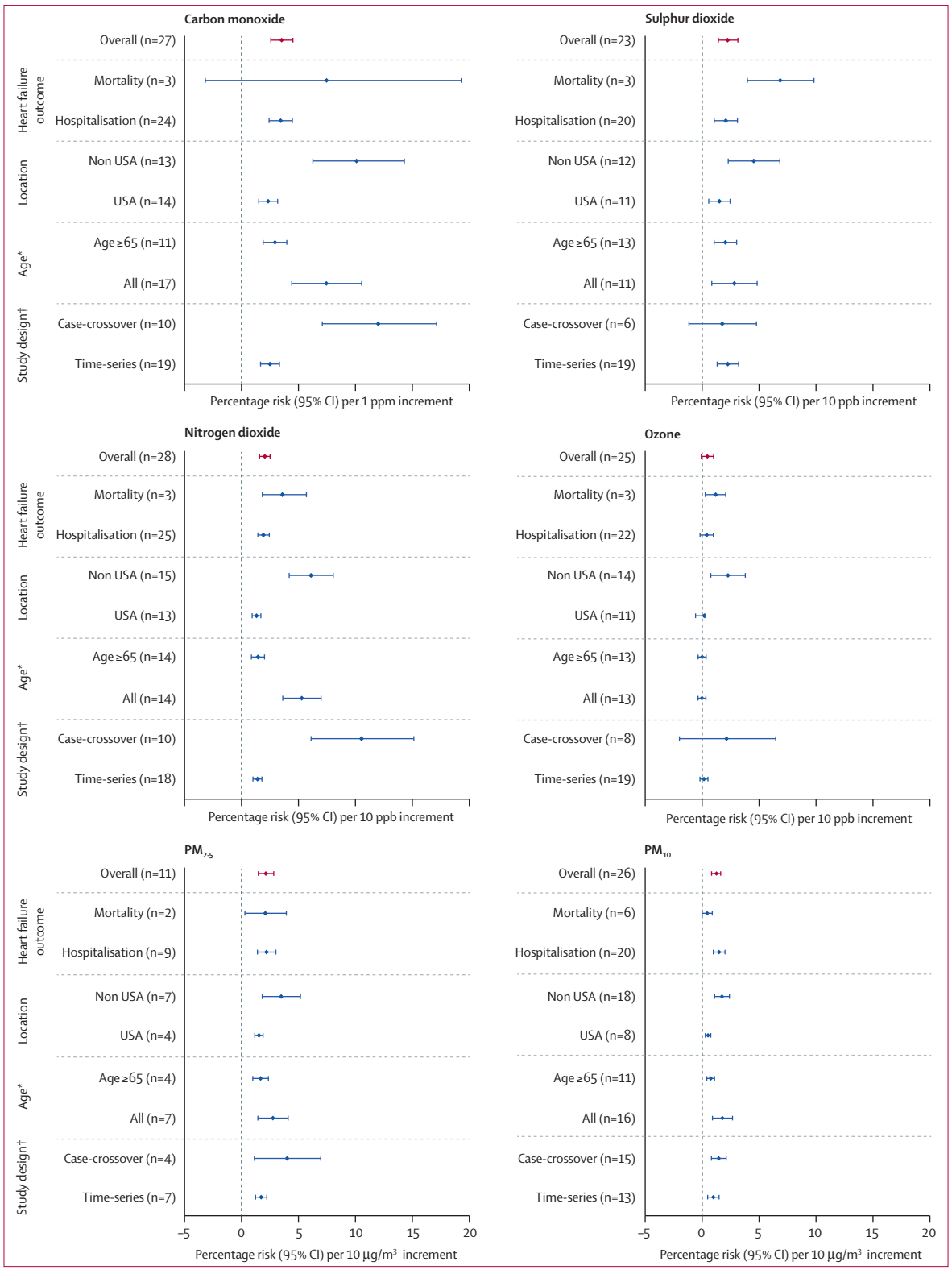

Figure 2: **Additional analysis across all gaseous and particulate air pollutants**

*Kwon et al[67] 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[27,28,67] 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/m³)	PM_{10} (μg/m³)
Increment	1 ppm	10 ppb	10 ppb	10 ppb	10 μg/m³	10 μg/m³
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**

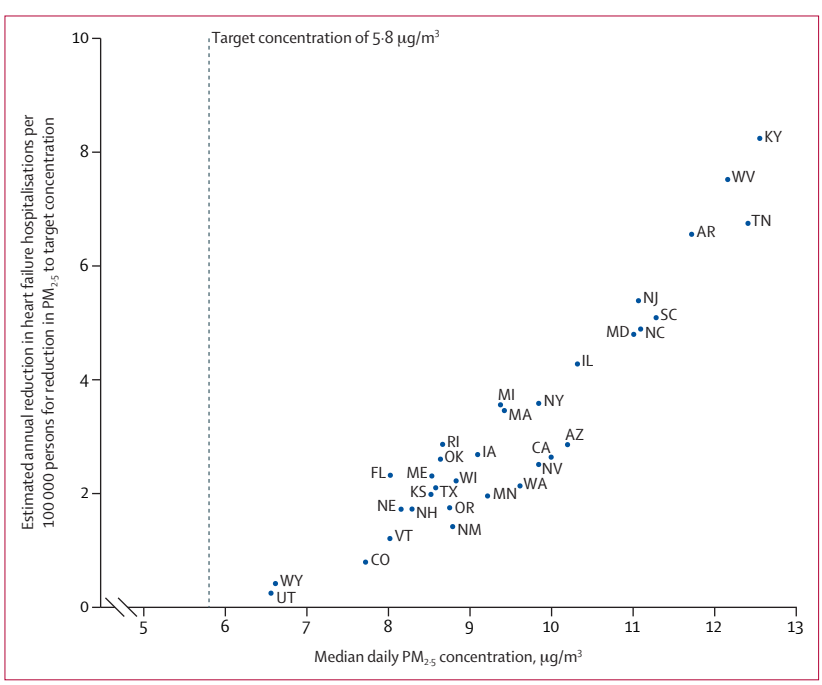

***Figure 3*: Median daily $PM_{2.5}$ concentrations and estimated impact of a reduction in $PM_{2.5}$ to a target concentration on heart failure hospitalisation per US state**

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 (I^2 of 91%) and least evident for $PM_{2.5}$ (I^2 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 healthcare 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.

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