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Complete List of Authors:	Mills, Inga; Public Health England, Centre for Radiation, Chemical and Environmental Hazards Atkinson, Richard; St George's University, Population Health Research Institute Anderson, H; St Georges, University of London, Population Health Research Institute Maynard, Robert; University of Birmingham Strachan, David; St George's University, 6. Division of Community Health Sciences
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Distinguishing the associations between daily mortality and hospital admissions and nitrogen dioxide from those of particulate matter: a systematic review and meta-analysis.

IC Mills[1], RW Atkinson[2], HR Anderson[2,3], RL Maynard, DP Strachan[2].

1 - Public Health England, Centre for Radiation, Chemical and Environmental Hazards, UK
2 - Population Health Research Institute and MRC-PHE Centre for Environment and Health, St George's, University of London, London, UK
3 - MRC-PHE Centre for Environment and Health, King's College London, UK

Corresponding author:
I C Mills
Public Health England
Centre for Radiation Chemicals and Environmental Hazards (CRCE)
Environmental Change Department
Air Pollution and Climate Change Group
Chilton
Oxfordshire, OX11 0RQ
United Kingdom
Tel: +44 (0)1235 825146
Fax: +44 (0) 1235 833891
Email: inga.mills@phe.gov.uk

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Abstract

Objectives

To quantitatively assess time-series studies of daily nitrogen dioxide (NO_2) and mortality and hospital admissions which also controlled for particulate matter (PM) to determine whether or to what extent the NO_2-associations are independent of PM.

Design

A systematic review and meta-analysis

Methods

Time-series studies published in peer-review journals worldwide up to May 2011 which reported both single- and two-pollutant model estimates for NO_2 and PM were ascertained from bibliographic databases (PubMed, EMBASE, and Web of Science) and reviews. Random-effects summary estimates were calculated globally and stratified by different geographical regions, and effect modification was investigated.

Outcome measures

Mortality and hospital admissions for various cardiovascular or respiratory diseases in different age groups in the general population.

Results

Sixty eligible studies were identified, and meta-analysis was done on 23 outcomes. Two-pollutant model study estimates generally showed that the NO_2-associations were independent of PM mass. For all-cause mortality, a 10 $\mu g/m^3$ increase in 24 hour NO_2 was associated with a 0.78% (95% CI: 0.47, 1.09) increase in the risk of death, which reduced to 0.60% (0.33, 0.87) after control for PM. Heterogeneity between geographical region-specific estimates was removed by control for PM (I^2 from 66.9% to 0%). Estimates of PM and daily mortality assembled from the same studies were greatly attenuated after control for NO_2: from 0.51% (0.29, 0.74) to 0.18% (-0.11, 0.47) per 10 $\mu g/m^3$ PM_{10} and 0.74% (0.34, 1.14) to 0.54% (-0.25, 1.34) for $PM_{2.5}$.

Conclusions

The association between short-term exposure to NO_2 and adverse health outcomes is largely independent of PM mass. Further studies should attempt to investigate whether this is a generic PM-effect or modified by the source and physicochemical characteristic of PM. This finding strengthens the argument for NO_2 having a causal role in health effects.

Strengths and limitations of this study

- This is, to date, the most comprehensive, quantitative systematic review of the time-series literature on NO_2 published worldwide to evaluate the two-pollutant model estimates of mortality or hospital admissions and short-term exposure to NO_2 adjusted for particulate air pollution.
- It reports meta-analytical estimates both globally and for different geographical regions, as well as an assessment of heterogeneity between the region-specific estimates.
- The protocol-led approach to the identification of studies and estimates for use in meta-analysis minimised selection bias at each stage of the review.
- Meta-analysis was limited to studies which provided effect estimates in numerical, rather than graphical, form along with sufficient quantitative data to enable standardisation of estimates.
- Further work is needed to understand reasons for the heterogeneity observed and to quantitatively assess the extent to which PM may be associated with health independently of NO_2.

INTRODUCTION

Outdoor air pollution has long been established as a hazard to human health, with particulate matter (PM) regarded as the most plausible toxicant in the mixture of ambient air pollutants.[1-5] The epidemiological evidence has consistently shown adverse associations between chronic and short-term exposure to PM and mortality and morbidity from cardiovascular and respiratory disease, and this is supported by experimental evidence.[6] Whilst the epidemiological evidence also shows relationships between nitrogen dioxide (NO_2) and adverse health effects, concerns have been expressed repeatedly about the causal nature of these associations.[7-11] It has been asserted that the NO_2-associations do not reflect adverse effects of NO_2 itself, but rather the health effects of other air pollutants, mainly PM or other components of the complex mixture of traffic-related air pollutants. Primarily, this is due to the strong correlations between NO_2 and other combustion derived air pollutants, especially PM. The extent of these correlations varies from city-to-city and over time, due to variations in emission sources. Scepticism also exists because of limited experimental evidence (controlled human exposure and animal toxicology studies) for NO_2, which, to date, has focused largely on respiratory endpoints and have generally employed concentrations of NO_2 well above current ambient levels.[7-9] In light of the uncertainties regarding NO_2 and the stronger evidence for associations between PM and health, many researchers and policymakers adopted a view that the epidemiological associations of NO_2 reflect adverse health effects of PM.

In an earlier paper we reviewed the time-series evidence associating daily concentrations of NO_2 with daily mortality and emergency hospital admissions.[12] In this study we assess the subset of time-series studies, reporting all-year estimates of NO_2 from both single- and two-pollutant models adjusted for PM to determine whether the NO_2-associations are attenuated after adjustment for PM.

METHODS

The full method and a priori protocols governing the identification of studies and effect estimates for the systematic review have been described previously,[12-14] but a synopsis, along with aspects unique to this review, is provided below.

Identification of studies for review

Three bibliographic databases were searched to identify peer-reviewed time-series studies of NO_2 and daily mortality or hospital admissions indexed up to May 2011. No restriction on language was applied. The literature search strategy is described in the online supplementary material, and the following inclusion criteria were used: papers must (i) have had a minimum of one year of data; (ii) been based on the general population; (iii) have controlled for important confounding factors, including season and meteorological factors; (iv) have reported sufficient quantitative information, in numeric format, to enable the calculation of standardised effect estimates and standard errors for use in quantitative analysis.

Data extraction and coding

Data from each relevant study were entered into a Microsoft Access database (Microsoft Office 2010, Microsoft Corporation). These included:

a) citation details of each paper
b) all-year single- and two-pollutant model estimates of NO_2 adjusted for PM.
c) single- and two-pollutant model estimates of PM adjusted for NO_2 reported in studies providing data for NO_2.
d) season-specific estimates of NO_2, including those adjusted for PM, from studies reporting all-year estimates.
e) descriptive (outcome, diagnosis (International Classification of Diseases codes), age etc.) and quantitative data (pollution increment and averaging time etc.) associated with each estimate, and needed for calculating standardised estimates expressed as the percentage change (and 95% confidence interval (CI)) in the mean number of daily events associated with a 10 $\mu g/m^3$ increase in NO_2 (or PM).
f) correlations between concentrations of NO_2 and PM.
g) effect modifiers for investigating of sources of heterogeneity in all-year estimates

Time-series studies often report results for different time lags (in days) between exposure and health events, and they vary in the lag for the reported results. We identified for each outcome/disease/age/averaging time combination from each study a pair of estimates of NO_2, that is from a single-pollutant model and a corresponding estimate adjusted for PM, for the same lag to enable comparison of the NO_2-association before and after adjustment for PM. To avoid selection bias we developed an a priori protocol for identifying the principal lag for each outcome/disease/age/averaging time combination for use in our review: see the online supplementary material.

Processing of data also included classifying each study into the geographical region, as the WHO region, in which the study was conducted, as well as categorising, by size, the various metrics of PM controlled for in two-pollutant models: see supplementary material for details.

Statistical analyses

A similar procedure to that outlined in our earlier paper was used for meta-analysis,[12] but with some modifications in order to identify from each study a pair of estimates of NO_2 for each pollutant/outcome combination. We applied an a priori protocol to select estimates for meta-analysis to avoid selection bias and duplication of studies from the same population: see supplementary material.

Meta-analysis was conducted when ≥4 estimates were available for an outcome/disease/age/averaging time combination - including where a multi-city estimate was available - and summary estimates were calculated using a random-effects model.[15] We used a staged approach to meta-analysis, with single-city estimates pooled within WHO region prior to

the pooled single-city and selected multi-city estimates being pooled to produce a global estimate and WHO region-specific summary estimates. Heterogeneity between WHO region summary estimates was assessed using the I^2 statistic[16], with I^2 statistics >50% regarded as being evidence of high heterogeneity.[17]

Meta-analysis was undertaken for:

a) single-pollutant NO_2 estimates relating to two-pollutant models
b) corresponding NO_2 estimates adjusted for any PM metric:
    i) if within a study, several estimates of NO_2 adjusted for different individual PM metrics were available, a NO_2 estimate was selected according to the following order of priority of PM metric used in adjustment: PM_{10}, $PM_{2.5}$, Black Smoke, $PM_{10-2.5}$.
    ii) if having applied the protocol, a NO_2 estimate was not selected for a city because several were available due to different PM metrics used to adjust the NO_2 effect in different studies, the NO_2 estimate was chosen in the order of priority of the PM metrics listed above.
c) We conducted additional meta-analyses for NO_2 adjusted for specific metrics of particles, for example NO_2 adjusted for PM_{10}, and separately for $PM_{2.5}$, and so on, to determine whether the NO_2-associations show different sensitivity to control for different PM metrics.

All analyses were conducted in STATA (STATA/SE 11. StataCorp Texas).

RESULTS

Sixty studies provided estimates of both (i) NO_2, single-pollutant and (ii) NO_2 adjusted for PM: a list of references is provided in the supplementary material. Table 1 presents a summary of these 60 time-series studies stratified by the PM metric controlled for in regression models, broad disease categories, WHO regions in which the studies were conducted, single- and multi-city study designs, and by averaging time (24 hour and 1 hour).

There were 36 and 24 studies of daily mortality or hospital admissions, respectively, and 13 studies used a multi-city design. The majority of the studies were conducted in the WHO regions European A and Western Pacific region B and most used 24 hour NO_2. Forty of the 60 studies controlled for the effects of daily PM_{10} in the regression models for NO_2, and a much smaller number of studies used other particle size fractions or constituents of PM. Eight studies of mortality and two of hospital admissions reported estimates of NO_2, each adjusted for a different PM metric. None of the studies investigated the influence of carbon on the NO_2-associations, and four studies controlled for the effects of ultrafine particles.

Table 1: Summary of time-series studies of daily mortality or hospital admissions and NO_2 adjusted for particulate matter (PM)

Outcome		Total		Multi-city study		Single-city study	
		Mortality	Hospital admissions	Mortality	Hospital admissions	Mortality	Hospital admissions
Total		36	24	9	4	27	20
	PM_{10}	23	17	6	2	17	15
	$PM_{2.5}$	7	1	3	1	4	0
	$PM_{10-2.5}$	4	0	3	0	1	0
	BS	5	4	3	2	2	2
NO_2 + PM[a]	PNC	3	1	0	0	3	1
	Carbon	0	0	0	0	0	0
	TSP	4	2	0	1	4	1
	Visibility	2	1	2	1	0	0
	>1 PM metric	0	1	0	0	0	1
	All-cause	27	1	7	0	20	1
Disease[b]	Cardiovascular	17	11	4	2	13	9
	Respiratory	7	17	3	3	4	14
	American A	8	4	3	0	5	4
	European A	9	12	3	2	6	10
WHO Region[c]	Western Pacific B	14	5	2	0	12	5
	American B	4	2	0	0	4	2
	Western Pacific A	1	2	1	2	0	0
	South East Asia B	2	0	2	0	0	0
Averaging time	24 hours	29	21	6	3	23	18
	Maximum 1 hour	7	5	3	2	4	3

a - The eight categories of PM metrics listed in the table above have been generated by grouping different measures of particles. PM_{10} and $PM_{2.5}$ refer to the mass per cubic metre of particles of generally less than 10 μm, 2.5 μm diameter, respectively, in the ambient air. BS: Black Smoke; PNC: Particle Number Concentration; TSP: Total Suspended Particles.

b - Respiratory includes all-respiratory diseases, asthma, COPD, COPD (including asthma), lower respiratory infections, and upper respiratory diseases; Cardiovascular includes all-cardiovascular diseases, cardiac disease, heart failure, ischaemic heart disease, dysrhythmia, and stroke.

c - WHO regions: A: very low child and adult mortality; B: low child mortality and low adult mortality; C: low child mortality and high adult mortality; D: high child mortality and high adult mortality.

NO_2 and all-cause mortality

Figure 1 shows all available (32 pairs) single- and two-pollutant estimates for 24 hour NO_2 and daily all-cause mortality in all ages. In the majority of studies daily NO_2 was positively and significantly associated with increases in the risk of death including after controlling for daily PM. In many of the studies the NO_2 estimates were not greatly reduced in size, changed direction, or lose statistical significance after adjustment for PM. In general, the NO_2 estimates appeared robust to adjustment for PM at both high and low correlations between concentrations of NO_2 and PM.

Fifteen (of 32) pairs of estimates for 24 hour NO_2 and all-cause mortality, which represented 26 cities from five WHO regions, were selected for meta-analysis (Figure S1). The random-effects single-pollutant summary estimate for all-cause mortality was 0.78% (95% CI: 0.47, 1.09) per 10 μg/m^3 increase in NO_2.There was evidence of high heterogeneity (I^2=66.9%) between the WHO region-specific estimates which ranged from 0.48% for WHO region America A to 1.41% for South East Asia B (Table S1). The overall estimate was comparable to the single-pollutant summary estimate of 0.71% (95% CI: 0.43, 1.00) calculated from the larger body of time-series evidence analysed in our previous paper.[12] After adjustment for daily PM, all-cause mortality remained positively and significantly associated with 24 hour NO_2: 0.60% (95 CI%: 0.33, 0.87)

per 10 μg/m^3 increase in NO_2, and there was no evidence of heterogeneity (I^2=0%) between the region-specific estimates.

Control for specific PM metrics did not greatly alter the relationship of 24 hour NO_2 with all-cause mortality (Table 2). With the exception of NO_2 adjusted for PM_{10}, and to a lesser extent $PM_{2.5}$, meta-analyses for NO_2 adjusted for the remaining PM metrics were limited to findings from the multi-city Canadian study by Burnett et al[18] – see Figure 1.

Six pairs of estimates were available for meta-analysis for all-cause mortality and 1 hour NO_2 adjusted for PM (Figure S2). Thirty of the 36 cities represented by these estimates were from Europe. Meta-analysis of 4 pairs of estimates resulted in an overall estimate of 0.32% (95% CI: -0.02, 0.66) for a 10 μg/m^3 increment in 1 hour NO_2 and 0.20% (95% CI: -0.24, 0.65) following adjustment for PM (Table S2). High heterogeneity was observed between the WHO region-specific estimates. In contrast with findings for 24 hour measures, the summary estimate for 1 hour NO_2 for WHO region European A was little affected by adjustment for PM_{10} (or Black Smoke) –Table S2. Table 3 provides meta-analysis results for all-cause mortality and 1 hour NO_2 adjusted for different PM metrics. Control for PM_{10} led to attenuation of the estimate and loss of statistical significance, whilst the association was robust to control for Black Smoke and visibility (measured as black suspended particles, bsp).

Table 2: Random-effects summary estimates (as percentage change (95% confidence intervals)) for mortality or hospital admissions associated with a 10 μg/m^3 increase 24 hour average pollution

	All SC/MC[a]	Selected SC/MC (cities)[b]	24 hour NO_2		24 hour PM	
			Single-pollutant	Adjusted for PM	Single-pollutant	Adjusted for NO_2
All-cause mortality, all ages						
PM_{10}	13/3	4/1 (21)	0.92 (0.58, 1. 72)	0.85 (0.52, 1.18)	0.51 (0.29, 0.74)	0.18 (-0.11, 0.47)
$PM_{2.5}$	2/3	2/1 (14)	0.53 (0.42, 0.64)	0.57 (0.24, 0.89)	0.74 (0.34, 1.14)	0.54 (-0.25, 1.34)
$PM_{10-2.5}$	0/3	0/1 (12)	0.62 (0.19, 1.06)	0.73 (0.28, 1.18)	0.65 (-0.10, 1.42)	0.31 (-0.49, 1.11)
Visibility	0/1	0/1 (12)	0.60 (0.34, 087)	0.66 (0.33, 1.00)	40.93 (23.39, 60.97)*	12.42 (-4.47, 32.29)*
All cardiovascular mortality, all ages						
PM_{10}	10/0	4/0 (8)	0.99 (0.49, 1.49)	0.87 (0.28, 1.46)	0.48 (0.18, 0.78)	0.19 (-0.21, 0.59)
All respiratory mortality, all ages						
PM_{10}	7/0	2/0 (5)	1.44 (0.63, 2.27)	1.15 (0.47, 1.84)	0.58 (0.22, 0.93)	0.13 (-0.18, 0.44)
All respiratory hospital admissions, children (5-14 years)						
PM_{10}	0/1	0/1 (5)	5.95 (1.74, 1.033)	6.56 (3.08, 10.17)	-	-
Cardiac hospital admissions, all ages						
PM_{10}	2/1	2/1 (7)	0.93 (0.46, 1.40)	0.75 (-0.13, 1.64)	-	-
BS	0/1	0/1 (4)	0.68 (0.17, 1.20)	0.36 (-0.65, 1.38)	-	-
TSP	0/1	0/1 (6)	1.03 (0.45, 1.61)	1.08 (0.43, 1.72)	-	-

a -Numbers of available pairs of single-city (SC) / multi-city (MC) estimates from all studies
b -Numbers of pairs of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions. Estimates were selected for meta-analysis from all available. The number of cities represented by the summary estimates is given in brackets.
* The results for visibility (measured as Coefficient of Haze (COH units)) are not comparable to other PM results.

Table 3: Random-effects summary estimates (as percentage change (95% confidence intervals)) for mortality or hospital admissions associated with a 10 μg/m³ increase in air pollution

	All SC/MC[a]	Selected SC/MC (cities)[b]	1 hour NO_2		24 hour PM	
			Single-pollutant	Adjusted for PM	Single-pollutant	Adjusted for NO_2
All-cause mortality, all ages						
PM_{10}	2/1	2/1 (32)	0.22 (-0.15, 0.60)	0.10 (-0.40, 0.61)	0.52 (0.29, 0.75)	0.48 (0.31, 0.66)
BS	0/2	0/1 (30)	0.30 (0.22, 0.38)	0.33 (0.23, 0.43)	0.60 (0.30, 0.90)	0.26 (0.00, 0.52)
Visibility	0/1	0/1 (4)	0.63 (0.21, 1.05)	0.52 (0.05, 1.00)	35.70 (3.97, 77.12)*	10.24 (-20.03, 51.97)*
All cardiovascular mortality, all ages						
PM_{10}	1/1	0/1 (29)	0.40 (0.29, 0.51)	0.35 (0.21, 0.49)	0.76 (0.47, 1.05)	0.17 (-0.10, 0.44)
BS	0/1	0/1 (29)	0.40 (0.29, 0.51)	0.44 (0.31, 0.57)	0.62 (0.35, 0.90)	0.32 (0.05, 0.59)
All respiratory mortality, all ages						
PM_{10}	0/1	0/1 (29)	0.38 (0.17, 0.59)	0.37 (0.08, 0.66)	0.71 (0.22, 1.20)	0.20 (-0.29, 0.69)
BS	0/1	0/1 (29)	0.38 (0.17, 0.59)	0.26 (-0.12, 0.64)	0.84 (0.11, 1.58)	0.57 (-0.34, 1.48)
All respiratory hospital admissions, children (< 5 years)						
PM_{10}	1/1	1/1 (6)	0.77 (-0.59, 2.15)	0.13 (-0.09, 0.35)	-	-
$PM_{2.5}$	0/1	0/1 (4)	1.62 (0.41, 2.84)	4.85 (0.41, 9.50)	-	-
All respiratory hospital admissions, elderly (65 + years)						
Visibility	0/1	0/1 (4)	1.42 (0.79, 2.06)	1.21 (0.47, 1.95)	-	-
Cardiac hospital admissions, elderly						
Visibility	0/1	0/1 (4)	1.21 (0.84, 1.58)	0.73 (0.31, 1.16)	-	-

See Table 2 for footnotes

* The results for visibility (measured as black suspended particles ($10^{-4}.m^{-1}$)) are not comparable to other PM results.

NO_2 and mortality from specific causes

NO_2 estimates adjusted for PM were available for several specific causes of death in all ages: all cardiovascular (Figures S3 and S4), all respiratory (Figure S5), stroke (Figure S6), cardiac (Figure S7), ischaemic heart disease, dysrhythmia, chronic obstructive pulmonary disease including asthma, and lower respiratory infections (Figure S8). Sufficient numbers of estimates for meta-analysis were available for all cardiovascular (Table S3), all respiratory (Table S4), and stroke (Table S5) mortality.

Eight studies providing 14 pairs of estimates showed positive associations between all cardiovascular deaths and 24 hour NO_2 including after adjustment mainly for PM_{10} (Figure S3). However, attenuation of estimates and loss of statistical significance was observed in the few studies with control for $PM_{2.5}$ or Black Smoke. Meta-analysis of 10 pairs of estimates found a 1.07% (95% CI: 0.43, 1.72) increase in the risk of death from all cardiovascular diseases per 10 μg/m³ increase in 24 hour NO_2 (Table S3 and Figure S9). This was attenuated (0.82% (95% CI 0.22, 1.42)) Table S3) following adjustment for PM, but comparable to our earlier result (0.88% (95% CI: 0.63, 1.13)).[12] Control of the NO_2-association with all cardiovascular mortality for specific PM metrics showed an association which was robust to adjustment for PM_{10} (Table 2). There were too few estimates to permit meta-analysis for other PM metrics controlled for in the studies. The available data for 1 hour NO_2 and all cardiovascular mortality was sparse and

limited to two studies representing 29 European cities which showed positive NO_2-associations that were robust to adjustment for both PM_{10} and Black Smoke (Table 3 and Figure S4).

Evidence for all respiratory mortality and 24 hour NO_2 adjusted for PM came from six cities (Figure S5). Meta-analysis produced a 1.42% (95% CI: 0.64, 2.21) increased risk of all respiratory deaths per 10 μg/m^3 increase in 24 hour NO_2 (Table S4 and Figure S10). The corresponding estimate adjusted for particles was attenuated (1.13% (95% CI: 0.46, 1.81)) but was comparable with the single-pollutant estimate (1.09% (95% CI: 0.75, 1.42)) derived from the larger body of time-series evidence examined in our previous paper.[12] There was no evidence of heterogeneity (I^2=0%) between the geographic specific estimates either before or after adjustment for PM (Table S4). Evidence for associations between all respiratory mortality and 1 hour NO_2 came solely from the multi-city APHEA II study of 29 European cities,[19] which showed a positive association that was robust to adjustment for PM_{10} but not Black Smoke (Table 3).

PM and mortality

Meta-analyses were undertaken separately for PM adjusted for the different averaging times of NO_2 to allow comparison with the relevant meta-analyses for NO_2 using data from the same studies, cities and time periods. Figure 2 shows positive, single-pollutant associations between various mass metrics of PM and all-cause mortality. In the majority of studies, attenuation of estimates was observed following control for 24 hour NO_2. Estimates for ultrafine particles and all-cause mortality were robust to adjustment for 24 hour NO_2 (Figure S11), but the data came from three studies conducted in the same city, Erfurt, Germany. Results of meta-analysis for all-cause mortality and PM metrics are shown in Tables 2 and 3 for adjustment for 24 hour and 1 hour NO_2, respectively. In contrast to the results for NO_2, the summary estimates for PM were attenuated, in most cases by more than half and confidence intervals overlapped zero. Evidence of high heterogeneity between region-specific summary estimates for PM_{10} and all-cause mortality was identified (Table S6). Summary estimates for deaths from all cardiovascular or all respiratory diseases and PM were also sensitive to control for NO_2 (Tables 2 and 3; study estimates in Figures S12-S13).

NO_2 and hospital admissions

Few cause- and age-specific combinations of hospital admissions for 24 hour or 1 hour NO_2 with control for PM had sufficient numbers of estimates for meta-analysis - all respiratory diseases in children and the elderly, asthma in children, and cardiac disease in all ages and the elderly - and half were based solely on a multi-city estimate from a single study.

Positive associations were identified between all respiratory hospital admissions in different age groups and 24 hour or 1 hour NO_2, which remained after control for PM (Tables 2 and 3; Figures S14-S15 for available study estimates).

Evidence for the association between hospitalisation for asthma in different ages and daily NO_2 adjusted for PM came from seven studies (Figures S16-S17), six of which were conducted in Europe. Sufficient estimates for meta-analysis were only available for asthma admissions in children and 24 hour NO_2 adjusted for any particles (measured as Black Smoke, PM_{10} and PNC): a 2.81% (95% CI: -1.28, 7.06) increase in risk per 10 $\mu g/m^3$ 24 hour NO_2 was attenuated following adjustment for particles (2.24% (95% CI: -1.12, 5.71)).

Five studies provided evidence for the relationship between 24 hour NO_2 adjusted for PM and hospitalisation for cardiac disease in all ages (Figure S18) and the elderly (Figure S19). Meta-analysis for the all age category (Table 2) identified positive estimates which were attenuated and confidence intervals overlapped zero after control for PM_{10} and Black Smoke. One multi-city study of four Australian cities provided evidence for the relationship between 1 hour NO_2 and cardiac admissions in the elderly. The association (1.21% (95% CI: 0.84, 1.58)) was weakened by control for BSP (an indicator of fine particles), but remained statistically significant (0.73% (95% CI: 0.31, 1.16)).

Sources of variation in NO_2 estimates

We examined season-specific NO_2 estimates of mortality from studies which reported all-year estimates to explore possible effect modification by season. Some studies, mainly from Western Europe, Canada and the USA, reported stronger associations between daily mortality and NO_2 in the summer months (Figure S20-S22). The extent of the correlations between concentrations of NO_2 and PM in the different seasons is unclear because very few studies reported these data, and only one study reported season-specific estimates adjusted for PM. Similarly, limited evidence is available on which to base an assessment of seasonal variation of associations between hospitalisation for cardiovascular and respiratory diseases and 24 hour NO_2 (Figure S23).

We explored reasons for the observed high heterogeneity by ranking study estimates for all-cause mortality and 24 hour NO_2 (from the full dataset)[12] by different potential effect modifiers (Figures S24-S27). None of the variables used to represent the pollution and meteorological environments in the cities examined accounted for the observed between-study variability.

DISCUSSION

Sixty time-series studies of NO_2 were used to determine whether NO_2 is associated with daily mortality or hospital admissions independently of daily PM. In general, our results demonstrate that after controlling for PM, daily NO_2 remained significantly associated with increases in the risk of adverse health outcomes. The evidence appears clearest for daily deaths from all-causes and from all cardiovascular and all respiratory diseases, and for all respiratory hospital admissions, outcomes for which more co-pollutant estimates were available. Robustness of the NO_2-associations to control for PM was observed at both high and low correlations between NO_2 and PM, and no clear relationship could be discerned between the correlations and changes in the size of the adjusted NO_2 estimates. In contrast to the results for NO_2, the associations

between daily PM and the main mortality outcomes (all-cause, all cardiovascular, all respiratory) were very sensitive to the inclusion of NO_2 in two-pollutant models.

Two/multi-pollutant models are increasingly being used to draw conclusions about whether or not NO_2 is independently associated with adverse health outcomes. This comprehensive review provides systematic evaluation and formal meta-analysis of the full body of two-pollutant estimates of NO_2 adjusted for PM, across several cause- and age-specific health outcomes, both globally and by different geographical regions. Whilst earlier reviews[7-8, 13, 20-23] included some assessment of these data, they were either limited in scope to specific health outcomes and/or examined together two- and multi-pollutant model NO_2 estimates, or did not undertake meta-analysis whatsoever. Another key strength of this review is the protocol-led approach to identifying and assembling studies and estimates, which aimed to minimise selection bias in the different stages of the review.

The subset of studies of NO_2 analysed in this paper were generally comparable to the studies examined in our earlier paper in terms of the magnitudes of summary estimates and overlap in confidence intervals.[12] For example, the single-pollutant summary estimates for all-cause mortality, the outcome with the most data, were similar across both datasets, suggesting that the studies reporting two-pollutant model estimates were typical of the wider body of time-series evidence of NO_2.

Whilst evidence of NO_2-associations which are robust to control for PM mass have been identified, it is possible that there may be some residual confounding by PM. The components of PM - primary combustion particles, for example ultrafine particles or Black Carbon - which have been proposed as the real causal agents of the NO_2-associations were not included in co-pollutant models of NO_2 because concentration data for these pollutants were either unavailable or sparse, reflecting the fact that these PM metrics are not routinely measured. PM_{10} was by far the most used metric - in 67% of the studies. Summary estimates of NO_2 were generally robust to adjustment for PM_{10}. However, PM_{10} may not adequately reflect the toxic component of PM because it reflects a number of sources, which do not include combustion / traffic, that are not shared with NO_2. Where the data permitted meta-analysis, robustness of the NO_2 associations to adjustment for $PM_{2.5}$ and Black Smoke was observed. Few data were available to permit an assessment of the extent to which the NO_2-associations are sensitive to control for combustion derived particles such as Black Carbon or ultrafine particles. This has also been noted by others.[7-8,24]

Given that the sources and composition of PM vary by location, and hence its toxicity, it cannot be assumed that PM represents the same thing in each study (city/country). In view of the differential toxicity of PM, it is preferable to examine individual studies that used more than one particle metric to investigate possible confounding of the NO_2 associations by PM when answering the research question, because they 'tested' the robustness of the NO_2-associations to

different fractions / components of the ambient aerosol in the same location. Unfortunately, such studies were few in number (8), but their findings support the view that the associations of NO_2 with major health outcomes are robust to adjustment for PM measured in different ways.

We observed confounding of the associations between daily PM and mortality outcomes by NO_2. This suggests that NO_2, rather than the PM metrics examined, is a better predictor of the observed mortality effects in the cities examined. An alternative interpretation may be that daily variation in NO_2 in the cities better represents the mortality effects of daily variations in the complex urban air pollution mixture or an unknown toxic entity than the metrics of PM used in the analyses. Some caution is however needed in drawing conclusions about the analysis of PM estimates because it only reflects a subset of the available studies on PM. Whether the results are a feature of the subset of studies examined is unclear, and formal meta-analysis of the full body of PM estimates, similar to the current review, is warranted. This may provide further insights into whether the different fractions/component of PM might show different sensitivity to adjustment for NO_2.

Our results for PM are in contrast to the predominant views in the literature: although confounding of the PM-mortality associations by NO_2 has been observed in some time-series studies[19, 25-26] and noted in reviews[6], the general consensus is that the PM-mortality estimates are robust to adjustment for co-pollutants[6]. The associations have been regarded as reflecting a causal relationship, and experimental evidence has been used to support this. There is a lack of experimental evidence for NO_2 at current ambient concentrations and for cardiovascular endpoints, and this has contributed to uncertainty regarding whether NO_2 is causally related to health.

We also found evidence of high heterogeneity between the geographic specific summary estimates of NO_2, which suggests that it cannot be assumed that the results for one city (region) represent the results for all cities (regions). For all-cause mortality and 24 hour NO_2, the high heterogeneity between WHO region-specific estimates was completely removed after control for PM (I^2 from 66.9% to 0%), suggesting that some study estimates were a bit extreme in comparison with others in the meta-analysis, but were less so after adjustment for PM. Geographical variation in effect estimates may be due to variations in population characteristics and in pollution sources, mixtures, and ambient concentrations. However, none of the variables used to represent the pollution and meteorological environments in the cities examined accounted for the high between-study variability we observed. Further work is therefore required to investigate potential explanations for the heterogeneity.

Our review supports the conclusions of recent narrative reviews,[7-8] but also provides meta-analytical estimates based on two-pollutant model estimates of NO_2 from the worldwide data. Taken together with the recent quantitative reviews of cohort studies on long-term exposure to NO_2 and mortality[27-28] and of short-term exposure to NO_2 and respiratory symptoms in children

with asthma from panel studies,[8, 29] the evidence suggests a need for re-evaluation of the approach to health risk assessment (hazard identification and health impact assessment) for air pollution, an activity which has long been dominated by PM.[30] The current review suggests that the relationship between temporal variations in PM and mortality may not be as robust to control for NO_2 as previously thought. We note also that attenuation of PM-mortality estimates following control for NO_2 has been observed in long-term exposure studies.[31-32] These findings could have implications for the calculation of health impacts attributable to these pollutants and for possible double counting of effects.

In summary, we identified evidence of associations between NO_2 and adverse health outcomes that are independent of PM mass. However, there was limited evidence on adjustment of the NO_2-associations for primary combustion particles which are thought to be responsible for the NO_2-associations. Therefore, some uncertainty remains regarding possible confounding and health impact assessments should reflect this.

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CONTRIBUTORS: All authors contributed to the design of the study, to the drafting of the paper and have seen and approved the final version.
I Mills read all papers, checked data prior to meta-analysis, and carried out all analyses.
R Atkinson produced the statistical code in STATA used by I Mills in the analyses.
I Mills is responsible for the overall content as lead author of the paper.

DATA SHARING STATEMENT: No additional data are available.

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Legend (and footnotes) to Figures

Figure 1: All available studies providing two-pollutant model estimates for meta-analysis for all-cause mortality, all ages, 24 hour NO_2

Footnotes to Figure 1

1000xln(RR) approximates to a percentage change per 10 μg/m^3
* Single-pollutant model estimate for days with both NO_2 and visibility (Coefficient of Haze, COH) data in Burnett et al, 2004 [RMID 3000].

Figure 2: All studies providing two-pollutant model estimates for all-cause mortality, all ages, PM adjusted for 24 hour NO_2

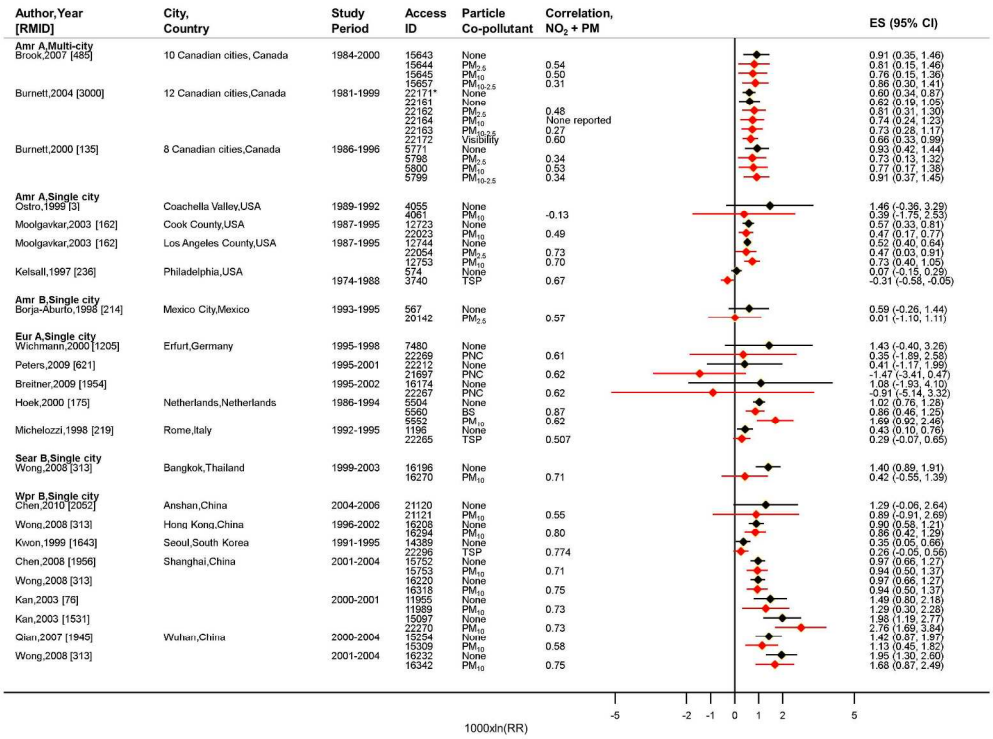


Figure 1: All available studies providing two-pollutant model estimates for meta-analysis for all-cause mortality, all ages, 24 hour NO2
485x359mm (300 x 300 DPI)

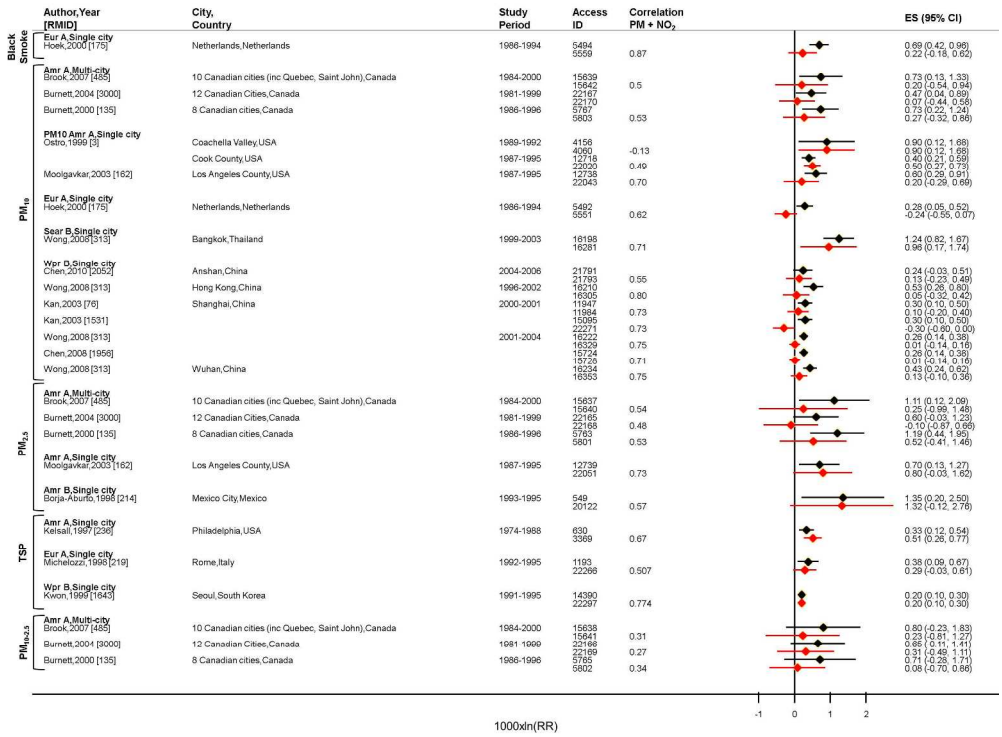


Figure 2: All studies providing two-pollutant model estimates for all-cause mortality, all ages, PM adjusted for 24 hour NO2
483x367mm (300 x 300 DPI)

Distinguishing the associations of short-term exposure to outdoor nitrogen dioxide with mortality and hospital admissions from those of particulate matter

IC Mills, RW Atkinson, HR Anderson, RL Maynard, DP Strachan

Online Supplementary Material

Contents list

5. List of figures

6. List of references included in the review

Literature search criteria

Bibliographic databases were searched to identify peer-reviewed time-series (and case crossover) studies of the relationship between daily concentrations of NO_2 and daily mortality or hospital admissions.

Bibliographic databases searched: PubMed, EMBASE or Web of Science (which includes the Science Citation Index).

The search terms used are shown below and minor refinements were made for use in each bibliographic database.

> (air pollution OR pollution OR nitric oxide* OR nitrogen dioxide?) AND (timeseries OR time series OR time-series OR daily OR case-crossover) AND (mortality OR death* OR dying OR hospital admission* OR admission* OR emergency room OR visit* OR attendance* OR 'a&e' OR 'a and e' OR accident and emergency OR general pract* OR physician* OR consultation* OR emergency department*)

No restriction on language was applied. The bibliographic databases were searched by St George's for peer-reviewed papers published up to May 2011.

Lag selection protocol

Time-series studies often report results for several different time lags (in days) between exposure and health events and vary in the lag for the reported headline results for outcome/disease/age combinations. To facilitate meta-analysis we developed a protocol for identifying the principal lag for our review for each outcome/disease/age combination from each paper. This was the lag highlighted by the author or stated a priori, and if this was not clear, because several lagged model estimates were reported, we chose (i) the lag with the highest statistical significance, regardless of the estimate being positive or negative, or (ii) the lag with the largest estimate, again, irrespective of its direction. If only results from cumulative or distributed lag models, i.e. lags averaged over several days, were reported in a study, this was used. In some instances, a different lag was investigated in two-pollutant models. In such cases, the lagged estimate from the two-pollutant model was coded according to the same algorithm, and the (additional) corresponding single-pollutant estimate for the same lag was coded in our database.

Protocol for selecting estimates for meta-analysis

We applied an a priori protocol for the selection of estimates for meta-analysis to avoid selection bias and duplication of studies from the same population. We gave priority to estimates from multi-city studies over estimates from single-city studies and the results from

any one city appeared only once in a meta-analysis. If results from more than one multi-city study within a WHO region were available we selected, in order of priority, the multi-city estimate from the study:

(i) with the most cities/greatest geographical coverage
(ii) the most recently published
(iii) the most recent study time period.

If a multi-city study did not report a summary estimate across the cities examined, for analysis, we treated estimates from these studies in the same manner as estimates from single-city studies. We selected estimates from single-city studies only if they did not appear in multi-city studies. For cities not included in a multi-city study summary result, we selected, in order of priority:

(i) the most recently published
(ii) the most recent study time period.

List of countries by WHO Region and mortality strata

Reproduced from The World Health Report 2002 (http://www.who.int/whr/2002/en/, accessed 7th February 2015)

African Region

Algeria — AFR-D
Angola – AFR-D
Benin – AFR-D
Botswana – AFR-E
Burkina Faso – AFR-D
Burundi – AFR-E
Cameroon – AFR-D
Cape Verde – AFR-D
Central African Republic – AFR-E
Chad – AFR-D
Comoros – AFR-D
Congo – AFR-E
Côte d'Ivoire – AFR-E
Democratic Republic of the Congo – AFR-E
Equatorial Guinea – AFR-D
Eritrea – AFR-E
Ethiopia – AFR-E
Gabon – AFR-D
Gambia – AFR-D
Ghana – AFR-D
Guinea – AFR-D
Guinea-Bissau – AFR-D
Kenya – AFR-E
Lesotho – AFR-E
Liberia – AFR-D
Madagascar – AFR-D
Malawi – AFR-E
Mali – AFR-D
Mauritania – AFR-D
Mauritius – AFR-D
Mozambique – AFR-E
Namibia – AFR-E
Niger – AFR-D
Nigeria – AFR-D
Rwanda – AFR-E
Sao Tome and Principe – AFR-D
Senegal – AFR-D
Seychelles – AFR-D
Sierra Leone – AFR-D
South Africa – AFR-E
Swaziland – AFR-E
Togo – AFR-D
Uganda – AFR-E
United Republic of Tanzania – AFR-E
Zambia – AFR-E
Zimbabwe – AFR-E

Region of the Americas

Antigua and Barbuda – AMR-B
Argentina – AMR-B
Bahamas – AMR-B
Barbados – AMR-B
Belize – AMR-B
Bolivia – AMR-D
Brazil – AMR-B
Canada – AMR-A
Chile – AMR-B
Colombia – AMR-B
Costa Rica – AMR-B
Cuba – AMR-A
Dominica – AMR-B
Dominican Republic – AMR-B
Ecuador – AMR-D
El Salvador – AMR-B
Grenada – AMR-B
Guatemala – AMR-D
Guyana – AMR-B
Haiti – AMR-D
Honduras – AMR-B
Jamaica – AMR-B
Mexico – AMR-B
Nicaragua – AMR-D
Panama – AMR-B
Paraguay – AMR-B
Peru – AMR-D
Saint Kitts and Nevis – AMR-B
Saint Lucia – AMR-B
Saint Vincent and the Grenadines – AMR-B
Suriname – AMR-B
Trinidad and Tobago – AMR-B
United States of America – AMR-A
Uruguay – AMR-B
Venezuela, Bolivarian Republic of – AMR-B

Eastern Mediterranean Region

Afghanistan – EMR-D
Bahrain – EMR-B
Cyprus – EMR-B
Djibouti – EMR-D
Egypt – EMR-D
Iran, Islamic Republic of – EMR-B
Iraq – EMR-D
Jordan – EMR-B
Kuwait – EMR-B
Lebanon – EMR-B
Libyan Arab Jamahiriya – EMR-B
Morocco – EMR-D
Oman – EMR-B
Pakistan – EMR-D
Qatar – EMR-B
Saudi Arabia – EMR-B
Somalia – EMR-D
Sudan – EMR-D
Syrian Arab Republic – EMR-B
Tunisia – EMR-B
United Arab Emirates – EMR-B
Yemen – EMR-D

Mortality strata
A. Very low child, very low adult
B. Low child, low adult
C. Low child, high adult
D. High child, high adult
E. High child, very high adult

European Region

Albania – EUR-B
Andorra – EUR-A
Armenia – EUR-B
Austria – EUR-A
Azerbaijan – EUR-B
Belarus – EUR-C
Belgium – EUR-A
Bosnia and Herzegovina – EUR-B
Bulgaria – EUR-B
Croatia – EUR-A
Czech Republic – EUR-A
Denmark – EUR-A
Estonia – EUR-C
Finland – EUR-A
France – EUR-A
Georgia – EUR-B
Germany – EUR-A
Greece – EUR-A
Hungary – EUR-C
Iceland – EUR-A
Ireland – EUR-A
Israel – EUR-A
Italy – EUR-A
Kazakhstan – EUR-C
Kyrgyzstan – EUR-B
Latvia – EUR-C
Lithuania – EUR-C
Luxembourg – EUR-A
Malta – EUR-A
Monaco – EUR-A
Netherlands – EUR-A
Norway – EUR-A
Poland – EUR-B
Portugal – EUR-A
Republic of Moldova – EUR-C
Romania – EUR-B
Russian Federation – EUR-C
San Marino – EUR-A
Slovakia – EUR-B
Slovenia – EUR-A
Spain – EUR-A
Sweden – EUR-A
Switzerland – EUR-A
Tajikistan – EUR-B
The former Yugoslav Republic of Macedonia – EUR-B
Turkey – EUR-B
Turkmenistan – EUR-B
Ukraine – EUR-C
United Kingdom – EUR-A
Uzbekistan – EUR-B
Yugoslavia – EUR-B

South-East Asia Region

Bangladesh – SEAR-D
Bhutan – SEAR-D
Democratic People's Republic of Korea – SEAR-D
India – SEAR-D
Indonesia – SEAR-B
Maldives – SEAR-D
Myanmar – SEAR-D
Nepal – SEAR-D
Sri Lanka – SEAR-B
Thailand – SEAR-B

Western Pacific Region

Australia – WPR-A
Brunei Darussalam – WPR-A
Cambodia – WPR-B
China – WPR-B
Cook Islands – WPR-B
Fiji – WPR-B
Japan – WPR-A
Kiribati – WPR-B
Lao People's Democratic Republic – WPR-B
Malaysia – WPR-B
Marshall Islands – WPR-B
Micronesia, Federated States of – WPR-B
Mongolia – WPR-B
Nauru – WPR-B
New Zealand – WPR-A
Niue – WPR-B
Palau – WPR-B
Papua New Guinea – WPR-B
Philippines – WPR-B
Republic of Korea – WPR-B
Samoa – WPR-B
Singapore – WPR-A
Solomon Islands – WPR-B
Tonga – WPR-B
Tuvalu – WPR-B
Vanuatu – WPR-B
Viet Nam – WPR-B

Metrics of particulate matter (PM) used in two-pollutant model analyses

Category of PM metric	Particulate pollutants which map to category
PM_{10}	PM_7; PM_{10}; PM_{13}; ln(PM_7); ln (PM_{13}); $\sqrt{}$(PM_{10}); ln(PM_{14});
$PM_{2.5}$	$PM_{2.5}$; PM<1; $PM_{0.5}$; Re-suspended Particulate Matter (RSPM); $PM_{2.5-1}$
$PM_{10-2.5}$	$PM_{10-2.5}$
Black Smoke	Black Smoke; ln(BS); sqrt(BS)
Particle Number Concentration (PNC)	10-100nm; PNC; <100nm; Nucleation <30nm; Aitken 30-100nm; Accumulation 100-290nm; NC 0.03-0.05; NC 0.05-0.1; NC 0.01-0.03; NC 0.01-0.1; $PM_{2.5}$ NC; $PM_{2.5-10}$ NC; PM_{10} NC; PNC size mode 12nm; PNC size mode 23nm; PNC size mode 57nm; PNC size mode 212nm; PNC size mode to 100nm; NC128; NC346; NC total; NC31; 10-100nm surface area
Carbon	Black Carbon (BC); Elemental Carbon (EC); Organic Carbon (OC); $PM_{2.5}$ OC; $PM_{2.5}$ EC; $PM_{2.5}$ OM; Total Carbon;
Total Suspended Particles (TSP)	TSP; ln(TSP); TSP-PM_{10}; PM_{20}; SPM; sqrt(TSP); blackness of TSP filters
Visibility	Coefficient of haze (COH); light scattering ($PM_{2.5}$ indicator = nephelometry measure instead of gravimetric); dry light scattering (PM<1 indicator); bsp ($PM_{2.5}$ indicator = an indicator for particles 01-2 um (nephelometry measure instead of gravimetric)); visibility ($PM_{2.5}$ indicator = digital photography visibility); $PM_{2.5}$ nephelpmetry ($PM_{2.5}$ indicator=(nephelometry measure*100,000-.01)/0.28.)

Table S1: Meta-analysis results for all-cause mortality in all-ages associated with a 10 µg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**29/3**	**5/1 (26)**	**0.78 (0.47, 1.09)**		**0.60 (0.33, 0.87)**	
AMR A	12/3	4/1 (16)	0.48 (0.24, 0.72)		0.55 (0.12, 0.99)	
AMR B	1/0	1/0 (1)	0.59 (-0.26, 1.45)	66.9	0.01 (-1.10, 1.12)	0
EUR A	6/0	3/0 (3)	0.71 (0.20, 1.22)		0.43 (-0.86, 1.73)	
SEAR B	1/0	1/0 (1)	1.41 (0.89, 1.93)		0.42 (-0.55, 1.40)	
WPR B	9/0	5/0 (5)	1.00 (0.54, 1.46)		0.85 (0.37, 1.33)	
NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	13/3	4/1 (21)	0.92 (0.58, 1. 72)	88.7	0.85 (0.52, 1.18)	72
NO_2 + $PM_{2.5}$	2/3	2/1 (14)	0.53 (0.42, 0.64)	0	0.57 (0.24, 0.89)	6.9
NO_2 + $PM_{10-2.5}$	0/3	0/1 (12)	0.62 (0.19, 1.06)	-	0.73 (0.28, 1.18)	-
NO_2 + Visibility	0/1	0/1 (12)	0.60 (0.34, 0.87)	-	0.66 (0.33, 1.00)	-
NO_2 + BS	1/0	-				
NO_2 + TSP	3/0	-	Insufficient estimates for meta-analysis			
NO_2 + PNC	3/0	-				

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S2: Meta-analysis results for all-cause mortality in all-ages associated with a 10 µg/m³ increase in 1 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2 single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI) [c]	I^2 (%)[d]	Random Effects (95% CI) [c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**2/4**	**2/2 (36)**	**0.32 (-0.02, 0.66)**		**0.20 (-0.24, 0.65)**	
AMR A	1/0	1/0 (1)	1.19 (0.20, 2.19)	93.8	0.78 (-0.35, 1.92)	95.2
AMR B	1/0	1/0 (1)	-0.09 (-0.19, 0.00)		-0.28 (-0.38, -0.19)	
EUR A	0/3	0/1 (30)	0.30 (0.22, 0.38)		0.27 (0.16, 0.38)	
WPR A	0/1	0/1 (4)	0.63 (0.21, 1.05)		0.52 (0.05, 1.00)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	2/1	2/1 (32)	0.22 (-0.15, 0.60)	95.4	0.10 (-0.40, 0.61)	96.5
NO_2 + BS	0/2	0/1 (30)	0.30 (0.22, 0.38)	-	0.33 (0.23, 0.43)	-
NO_2 + Visibility	0/1	0/1 (4)	0.63 (0.21, 1.05)	-	0.52 (0.05, 1.00)	-

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S3: Meta-analysis results for all cardiovascular mortality in all-ages associated with a 10 µg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI) [c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**13/0**	**5/0 (10)**	**1.07 (0.43, 1.72)**		**0.82 (0.22, 1.42)**	
AMR A	2/0	2/0 (2)	0.52 (0.37, 0.68)		0.47 (0.06, 0.88)	
AMR B	1/0	1/0 (1)	0.73 (-0.87, 2.36)	72	-0.36 (-2.47, 1.81)	58.8
EUR A	3/0	2/0 (2)	1.97 (-0.66, 4.66)		1.81 (0.67, 2.97)	
SEAR B	1/0	1/0 (1)	1.78 (0.47, 3.11)		-0.51 (-2.88, 1.92)	
WPR B	6/0	4/0 (4)	1.37 (0.87, 1.87)		1.13 (0.67, 1.58)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	10/0	4/0 (8)	0.99 (0.49, 1.49)	80.1	0.87 (0.28, 1.46)	61
NO_2 + $PM_{2.5}$	2/0	2/0 (2)	Insufficient estimates for meta-analysis			
NO_2 + BS	2/0	2/0 (2)	Insufficient estimates for meta-analysis			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S4: Meta-analysis results for all respiratory mortality in all-ages associated with a 10 µg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**8/0**	**3/0 (6)**	**1.42 (0.64, 2.21)**		**1.13 (0.46, 1.81)**	
AMR B	1/0	1/0 (1)	1.21 (-1.43, 3.91)	0	0.61 (-2.83, 4.17)	0
SEAR B	1/0	1/0 (1)	1.05 (-0.60, 2.73)		0.32 (-2.66, 3.39)	
WPR B	6/0	4/0 (4)	1.57 (0.63, 2.51)		1.20 (0.50, 1.90)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	7/0	2/0 (5)	1.44 (0.63, 2.27)	0	1.15 (0.47, 1.84)	0
NO_2 + $PM_{2.5}$	1/0	1/0 (1)	Insufficient estimates for meta-analysis			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S5: Meta-analysis results for stroke mortality in all-ages associated with a 10 µg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**8/0**	**2/0 (5)**	**1.76 (0.68, 2.85)**	25.6	**1.12 (0.50, 1.74)**	0
SEAR B	1/0	1/0 (1)	2.80 (0.70, 4.94)		1.60 (-2.20, 5.55)	
WPR B	7/0	4/0 (4)	1.47 (0.67, 2.27)		1.11 (0.48, 1.74)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	7/0	2/0 (4)	1.83 (0.76, 2.92)	9.3	1.04 (0.36, 1.73)	0
NO_2 + TSP	1/0	1/0 (1)	Insufficient estimates for meta-analysis			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S6: Meta-analysis results for all-cause mortality in all-ages associated with a 10 µg/m³ increase in metrics of Particulate Matter (PM) - estimates adjusted for 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	PM, single-pollutant		PM adjusted for 24 hour NO_2	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
PM_{10}						
Overall[e]	**12/3**	**4/1 (21)**	**0.51 (0.29, 0.74)**	**82.9**	**0.18 (-0.11, 0.47)**	**71.9**
AMR A	3/3	3/1 (15)	0.49 (0.31, 0.66)		0.33 (-0.04, 0.71)	
EUR A	1/0	1/0 (1)	0.28 (0.05, 0.52)		-0.24 (-0.55, 0.07)	
SEAR B	1/0	1/0 (1)	1.25 (0.82, 1.68)		0.96 (0.17, 1.76)	
WPR B	7/0	4/0 (4)	0.35 (0.22, 0.47)		0.05 (-0.06, 0.17)	
$PM_{2.5}$						
Overall[e]	**2/3**	**2/1 (14)**	**0.74 (0.34, 1.14)**	**19.6**	**0.54 (-0.25, 1.34)**	**23.9**
AMR A	1/3	1/1 (13)	0.66 (0.23, 1.08)		0.33 (-0.54, 1.22)	
AMR B	1/0	1/0 (1)	1.36 (0.20, 2.53)		1.33 (-0.12, 2.80)	
$PM_{10-2.5}$	**0/3**	**0/1 (12)**	**0.65 (-0.10, 1.42)**	**-**	**0.31 (-0.49, 1.11)**	**-**
Visibility	**0/1**	**0/1 (12)**	**40.93 (23.39, 60.97)**	**-**	**12.42 (-4.47, 32.29)**	**-**
Black Smoke	**1/0**	**-**	**Insufficient estimates for meta-analysis**			
PNC	**3/0**	**-**				
TSP	**3/0**	**-**				

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the selected estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ increase in 24 hour measures of PM. Estimates presented for 'Overall' and by WHO Region.
d -I^2 statistic for heterogeneity between WHO region-specific effect estimates
e -Estimate numbers for 'Overall' refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
AMR, region of the Americas; Eur, European region; WPR, Western Pacific region; SEAP, South East Asian region.

Table S7: Meta-analysis results for all cardiovascular mortality in all-ages associated with a 10 µg/m³ increase in metrics of Particulate Matter (PM) - estimates adjusted for 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	PM, single-pollutant		PM adjusted for 24 hour NO_2	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
PM_{10}						
Overall[e]	**9/0**	**4/0 (8)**	**0.48 (0.18, 0.78)**	**66.5**	**0.19 (-0.21, 0.59)**	**67.1**
AMR A	2/0	2/0 (2)	0.43 (0.17, 0.70)		0.33 (0.03, 0.62)	
EUR A	1/0	1/0 (1)	0.19 (-0.16, 0.54)		-0.32 (-0.80, 0.17)	
SEAR B	1/0	1/0 (1)	1.90 (0.80, 3.01)		2.27 (0.24, 4.34)	
WPR B	5/0	4/0 (4)	0.48 (0.26, 0.70)		0.22 (-0.09, 0.54)	
$PM_{2.5}$	**2/0**	**-**	**Insufficient estimates for meta-analysis**			
Black Smoke	**1/0**	**-**				

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the selected estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage increase (95% confidence interval) in the risk of death per 10 µg/m³ increase in 24 hour measures of PM. Estimates presented for 'Overall' and by WHO Region.
d -I^2 statistic for heterogeneity between WHO region-specific effect estimates
e -Estimate numbers for 'Overall' refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO Regions.
AMR, region of the Americas; Eur, European region; WPR, Western Pacific region; SEAP, South East Asian region.

Table S8: Meta-analysis results for all respiratory mortality in all-ages associated with a 10 µg/m³ increase in metrics of Particulate Matter (PM) - estimates adjusted for 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	PM, single-pollutant		PM adjusted for 24 hour NO_2	
			Random Effects (95% CI) [c]	I^2 (%)[d]	Random Effects (95% CI) [c]	I^2 (%)[d]
PM_{10}						
Overall[e]	**6/0**	**2/0 (6)**	**0.58 (0.22, 0.93)**	**0**	**0.13 (-0.18, 0.44)**	**0**
SEAR B	1/0	1/0 (1)	1.01 (-0.36, 2.40)		0.79 (-1.70, 3.34)	
WPR B	5/0	4/0 (4)	0.54 (0.17, 0.92)		0.12 (-0.19, 0.43)	
$PM_{2.5}$	**1/0**	**-**	**Insufficient estimates for meta-analysis**			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the selected estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage increase (95% confidence interval) in the risk of death per 10 µg/m³ increase in 24 hour measures of PM. Estimates presented for 'Overall' and by WHO Region.
d -I^2 statistic for heterogeneity between WHO region-specific effect estimates
e -Estimate numbers for 'Overall' refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO Regions.
WPR, Western Pacific region; SEAR, South East Asian region.

Figure S1: Studies and two-pollutant model estimates selected for meta-analysis for all-cause mortality, all ages, 24 hour NO_2

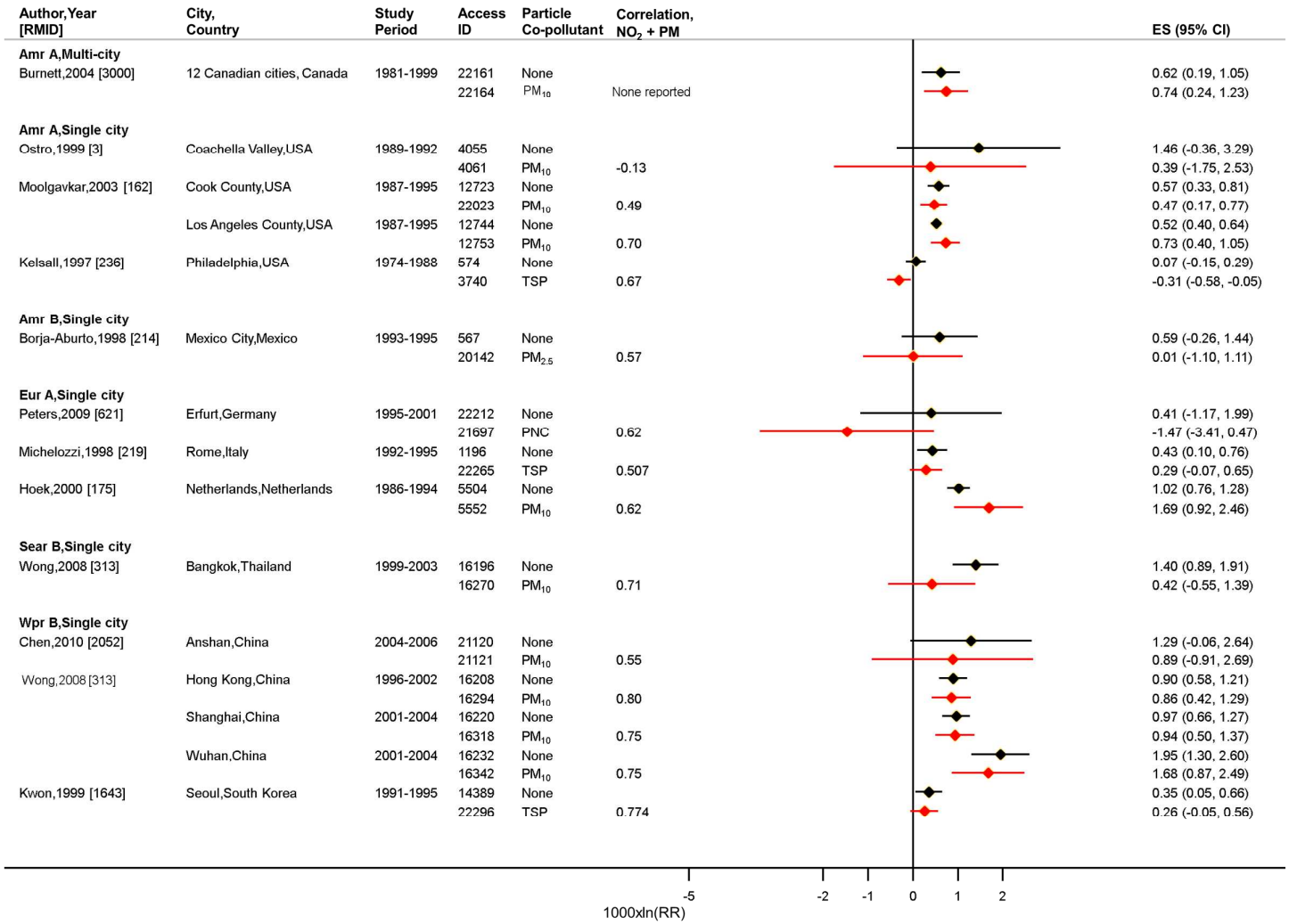


Figure S2: All available studies providing two-pollutant model estimates for meta-analysis for all-cause mortality, all ages, 1 hour NO_2

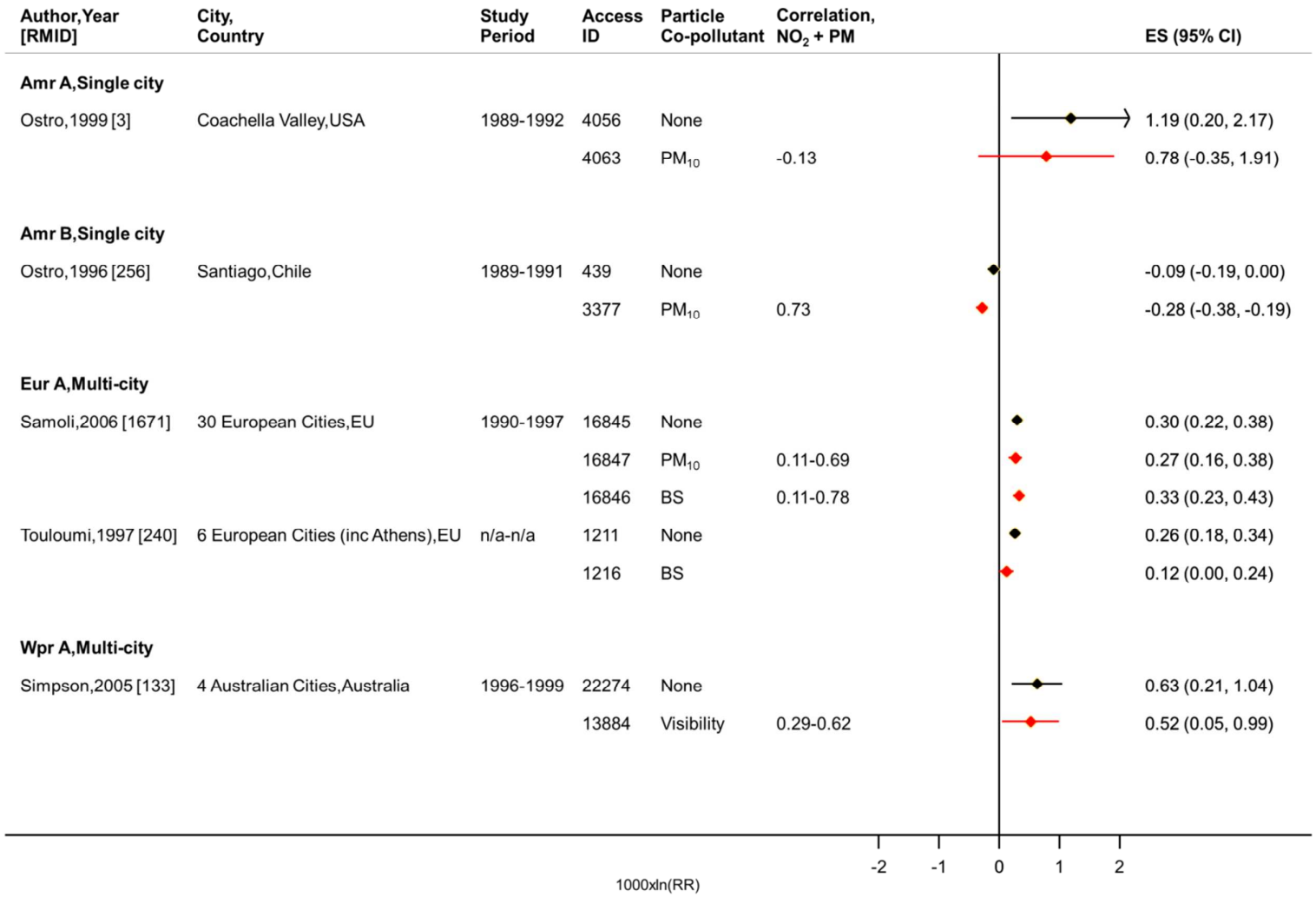


Figure S3: All available studies providing two-pollutant model estimates for meta-analysis for all cardiovascular mortality, all ages, 24 hour NO_2

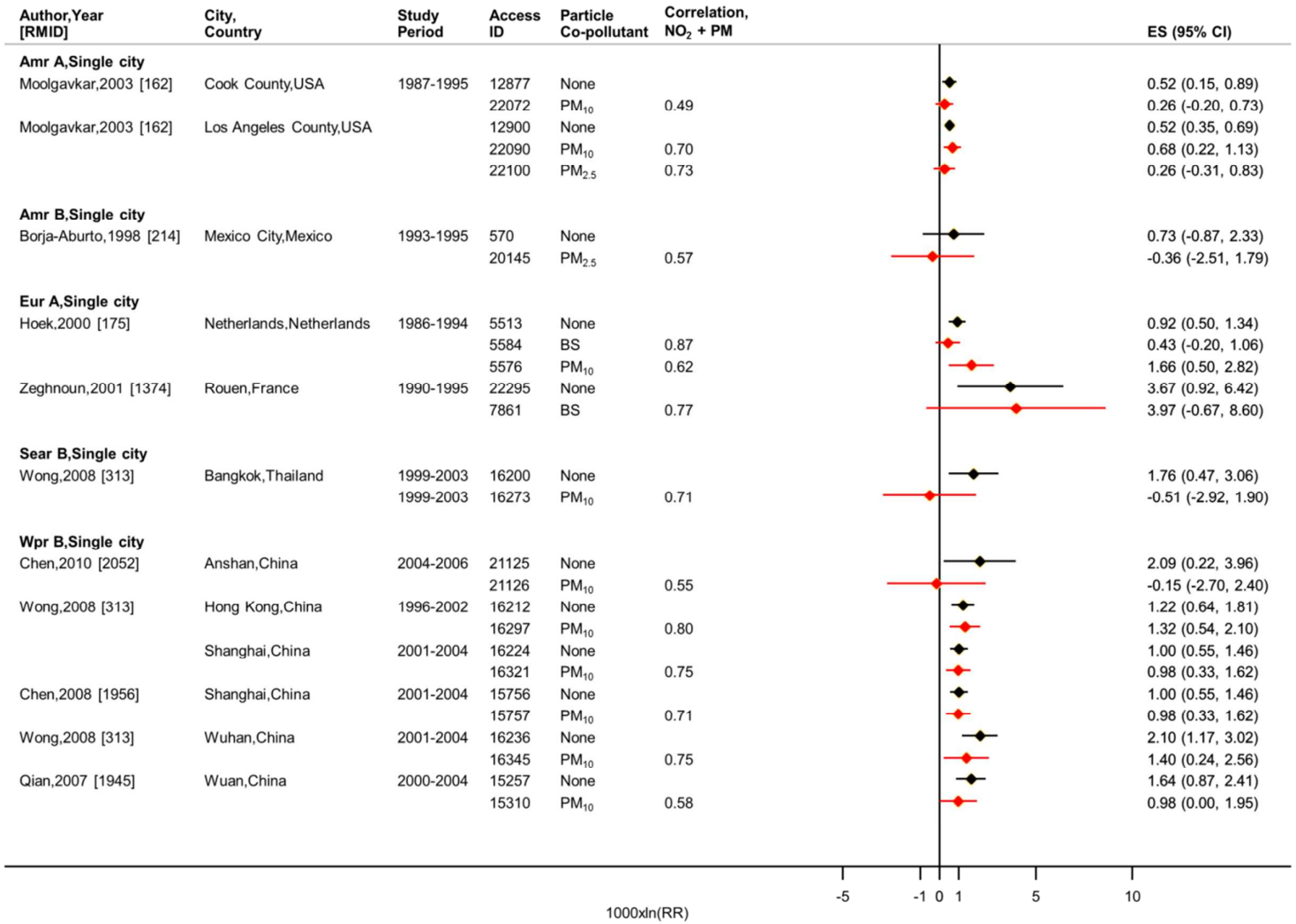


Figure S4: All available studies providing two-pollutant model estimates for meta-analysis for all cardiovascular mortality, all ages, 1 hour NO_2

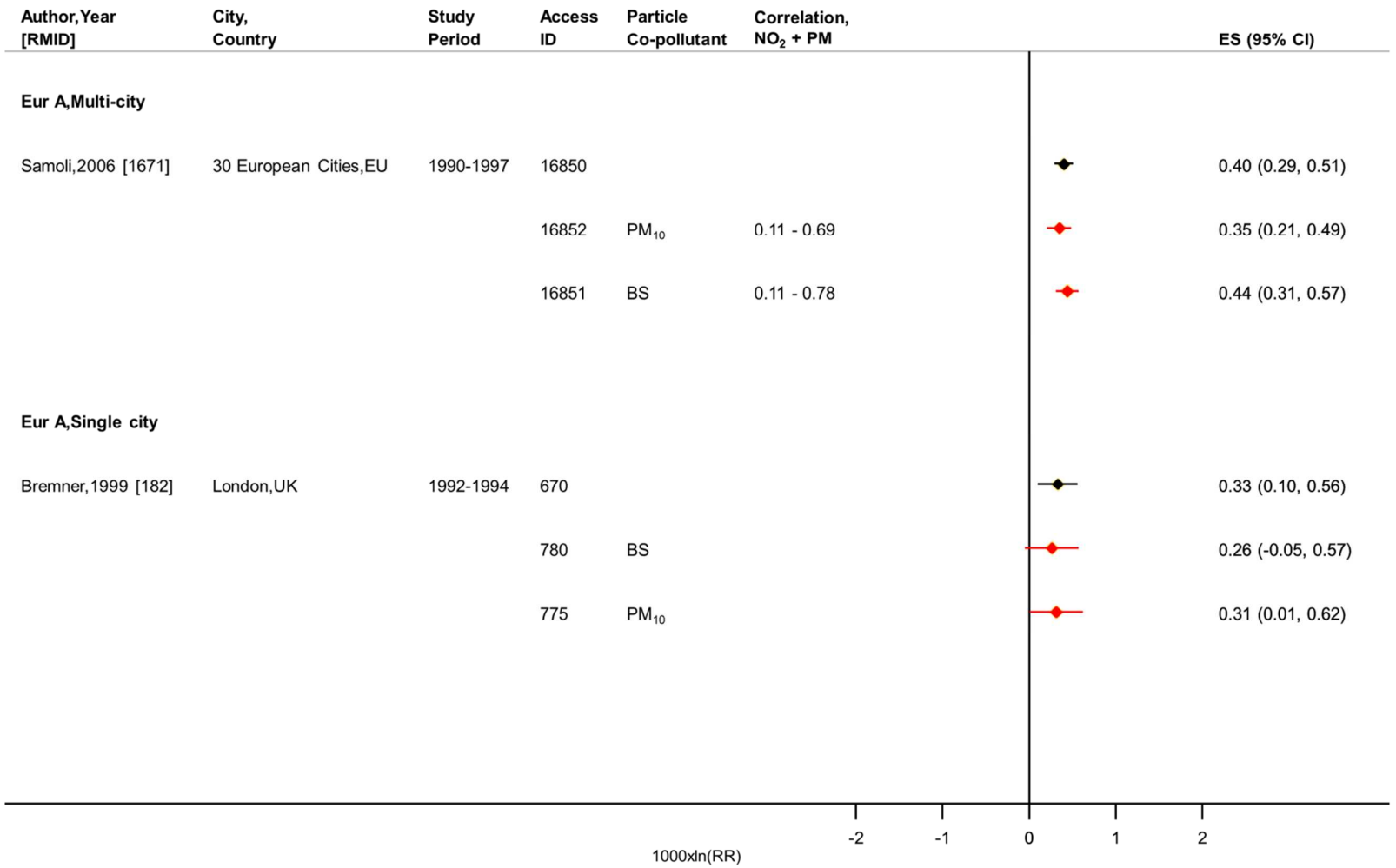


Figure S5: All available studies providing two-pollutant model estimates for meta-analysis for all respiratory mortality, all ages, 24 hour NO_2

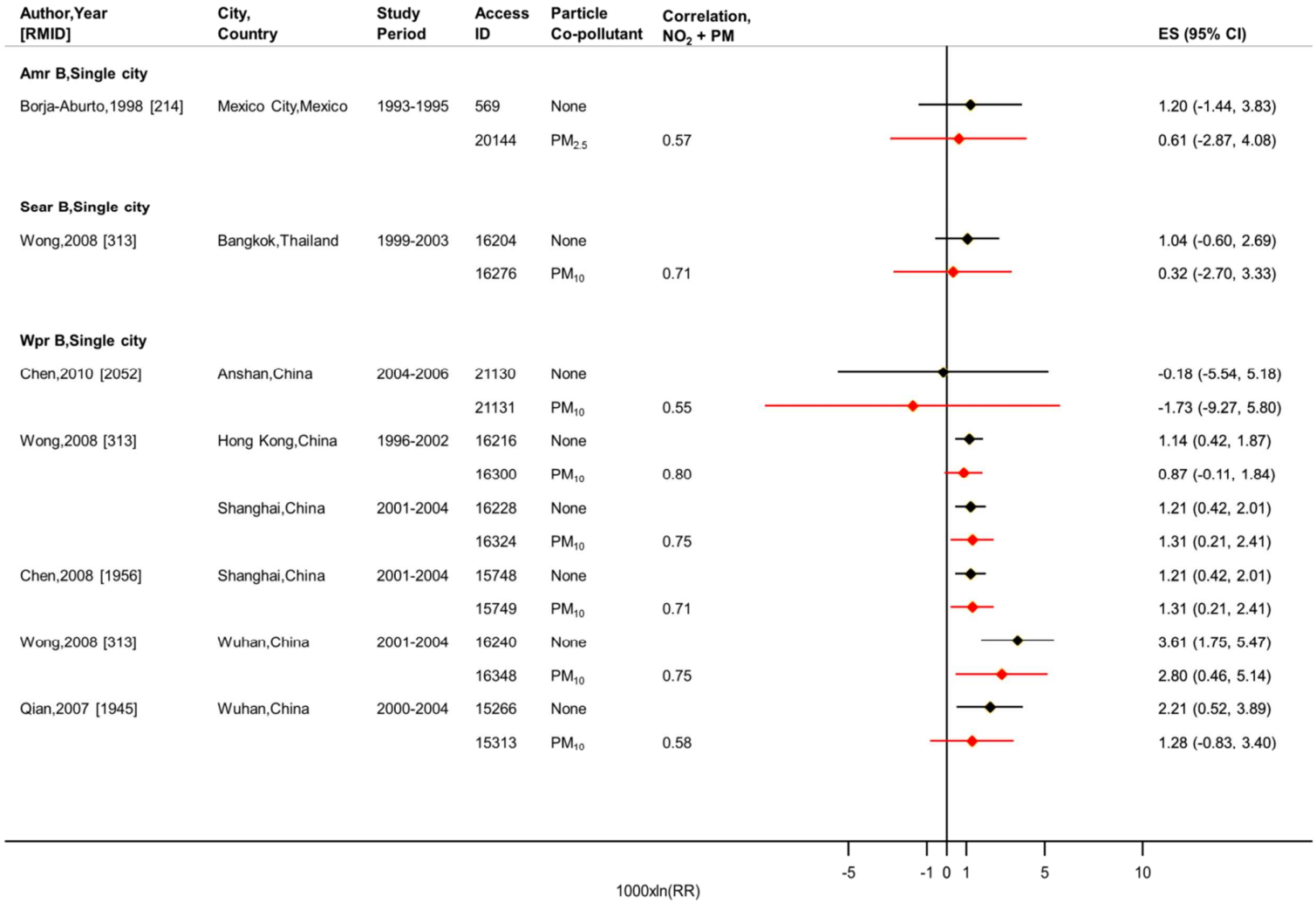


Figure S6: All available studies providing two-pollutant model estimates for meta-analysis for stroke mortality, all ages, 24 hour NO_2

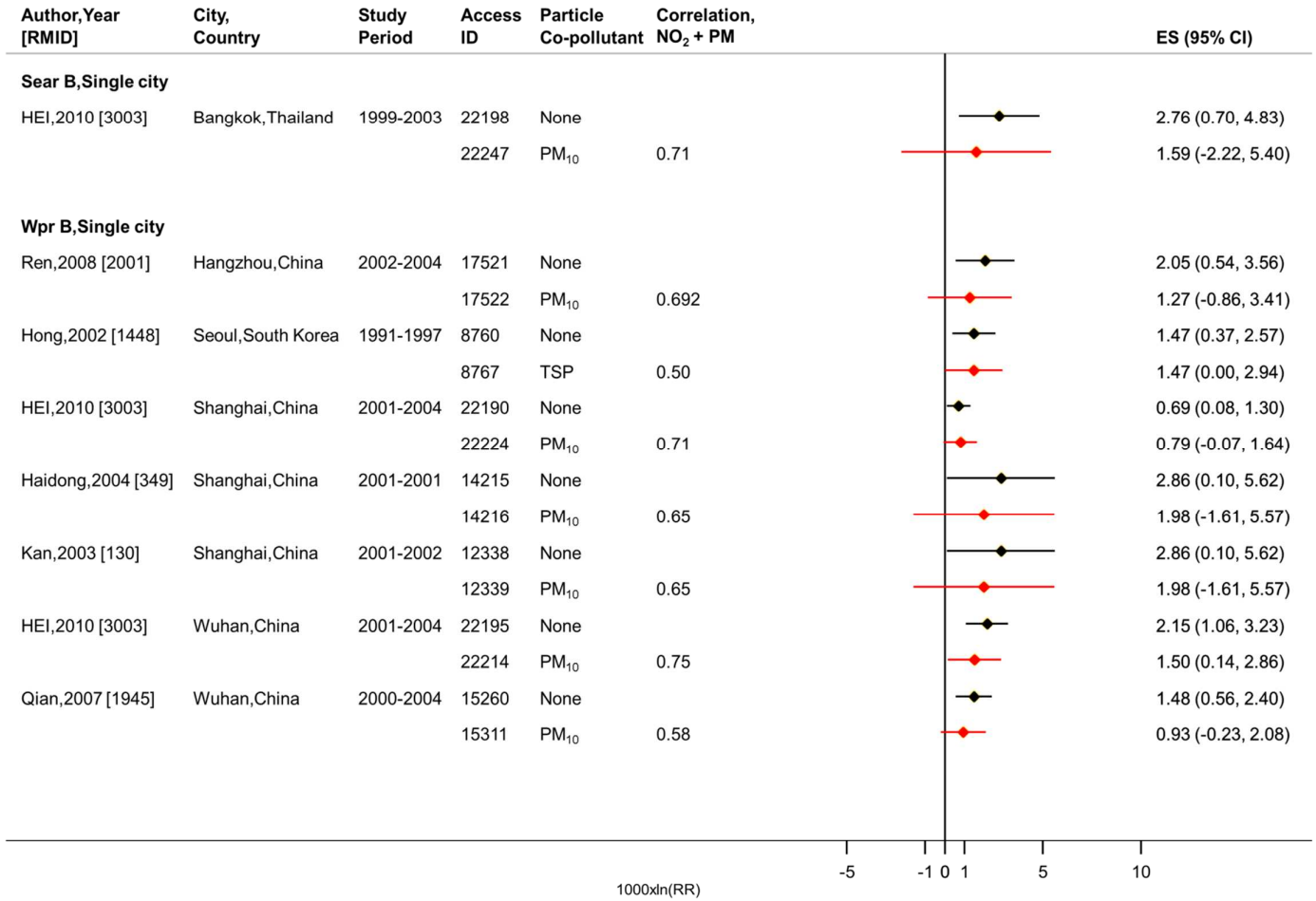


Figure S7: All available studies providing two-pollutant model estimates for meta-analysis for cardiac mortality, all ages, 24 hour NO_2

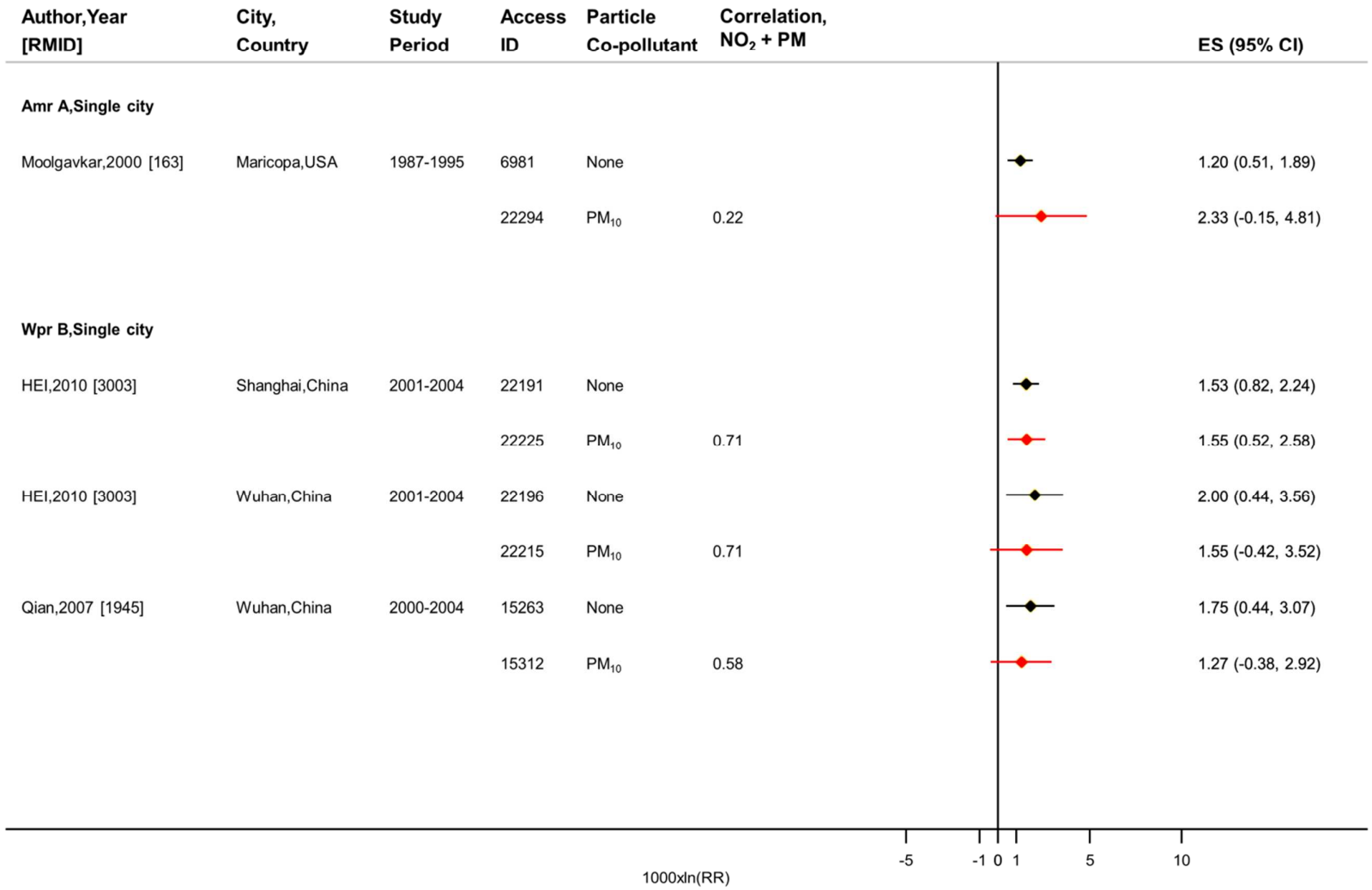


Figure S8: All available studies providing two-pollutant model estimates for meta-analysis for COPD (including asthma), Lower Respiratory Infections (LRI), ischaemic heart disease (IHD), dysrhythmia (DYS) mortality, all ages, 24 hour NO_2

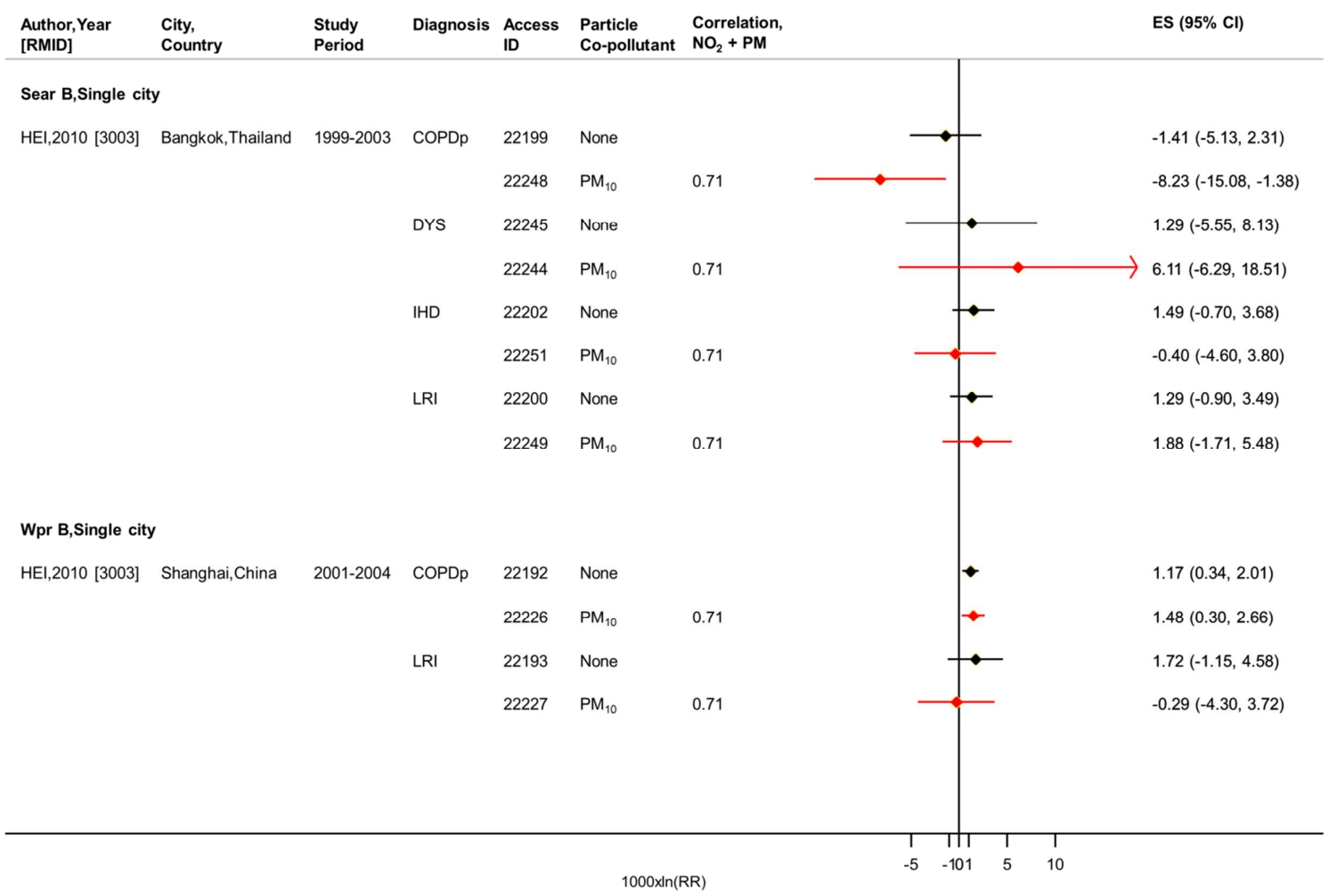


Figure S9: Studies and two-pollutant model estimates selected for meta-analysis for all cardiovascular mortality, all ages, 24 hour NO_2

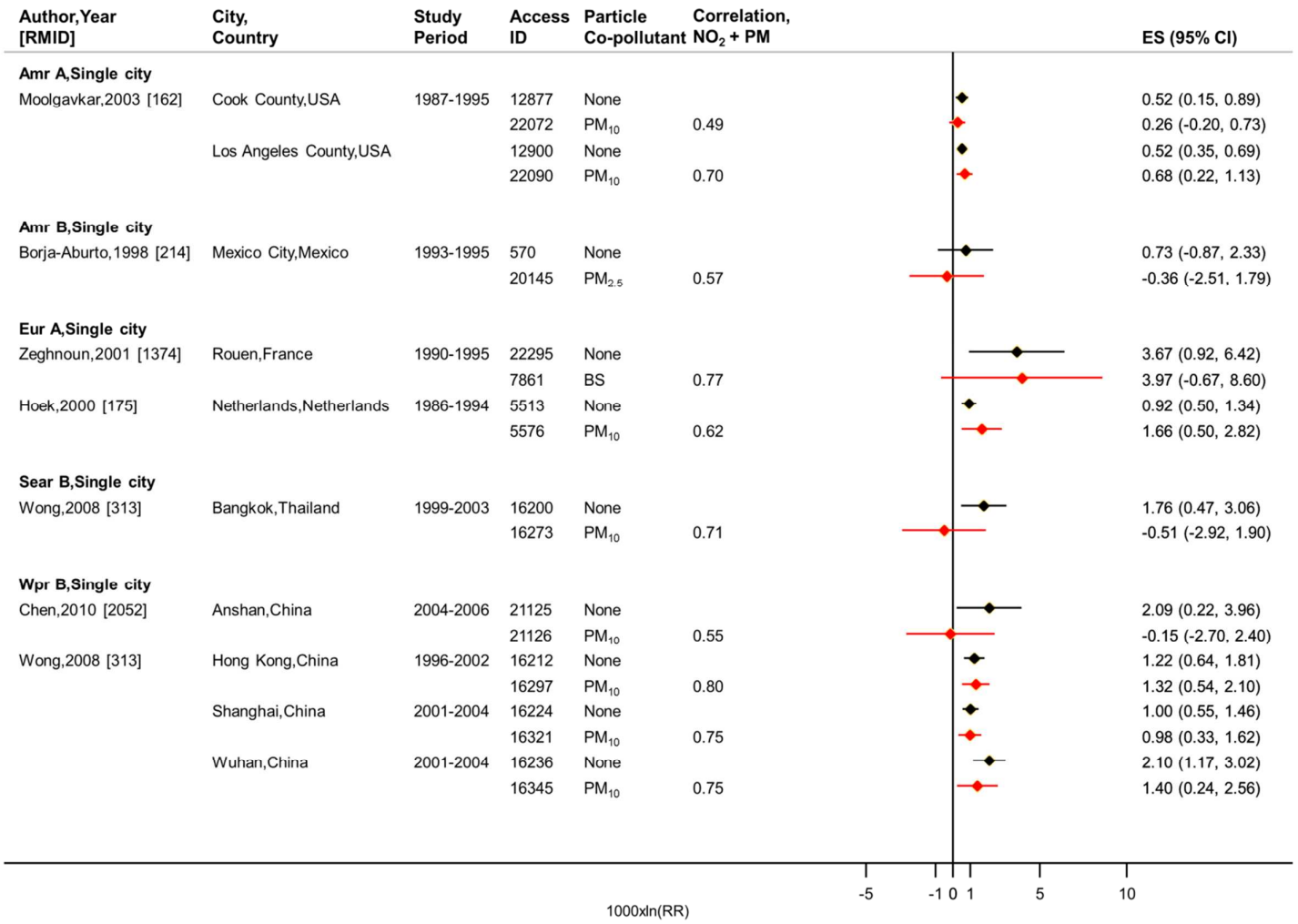


Figure S10: Studies and two-pollutant model estimates selected for meta-analysis for all respiratory mortality, all ages, 24 hour NO_2

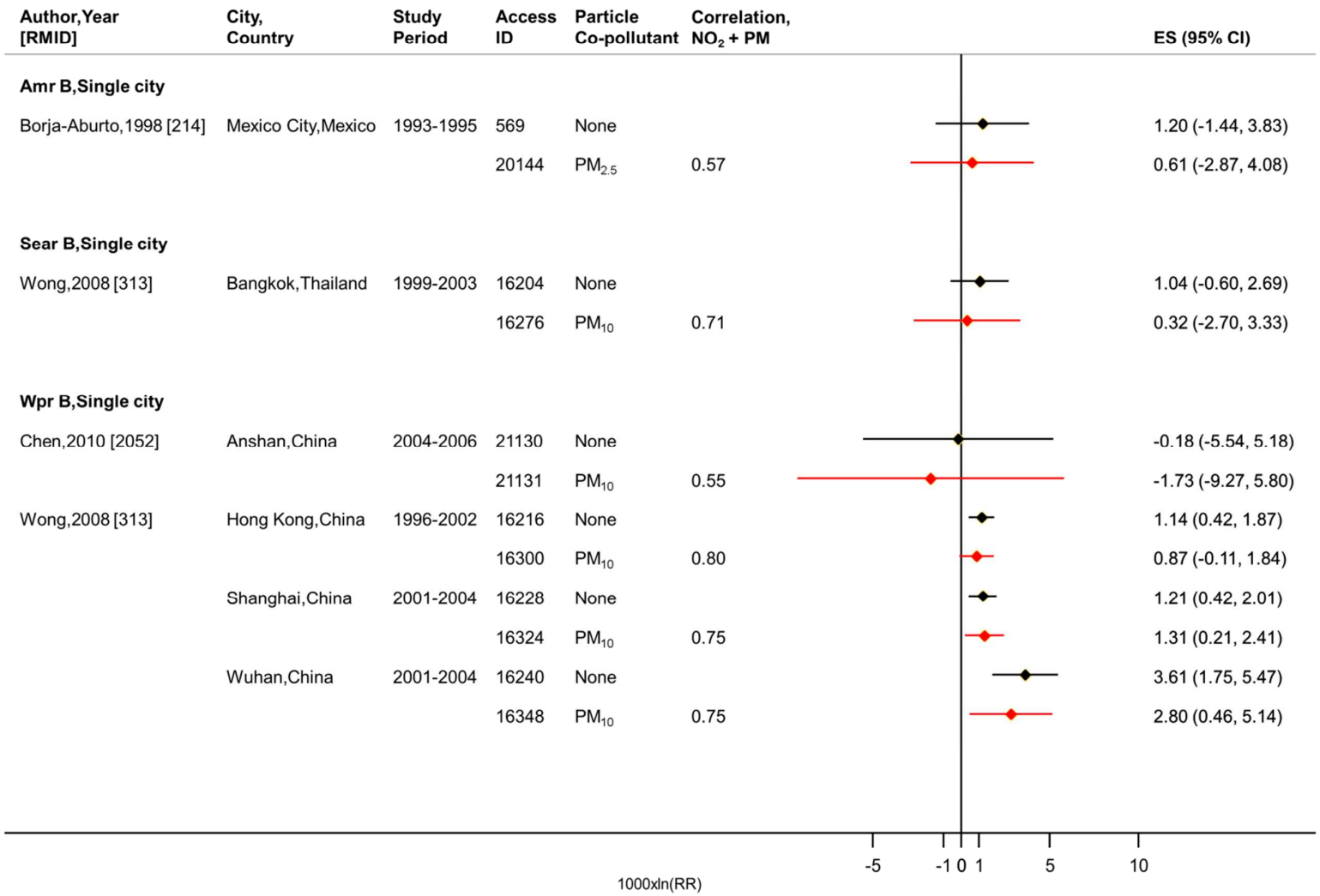


Figure S11: All studies providing two-pollutant model estimates for all-cause mortality, all-ages, ultrafine particles (UFP) adjusted for 24 hour NO_2

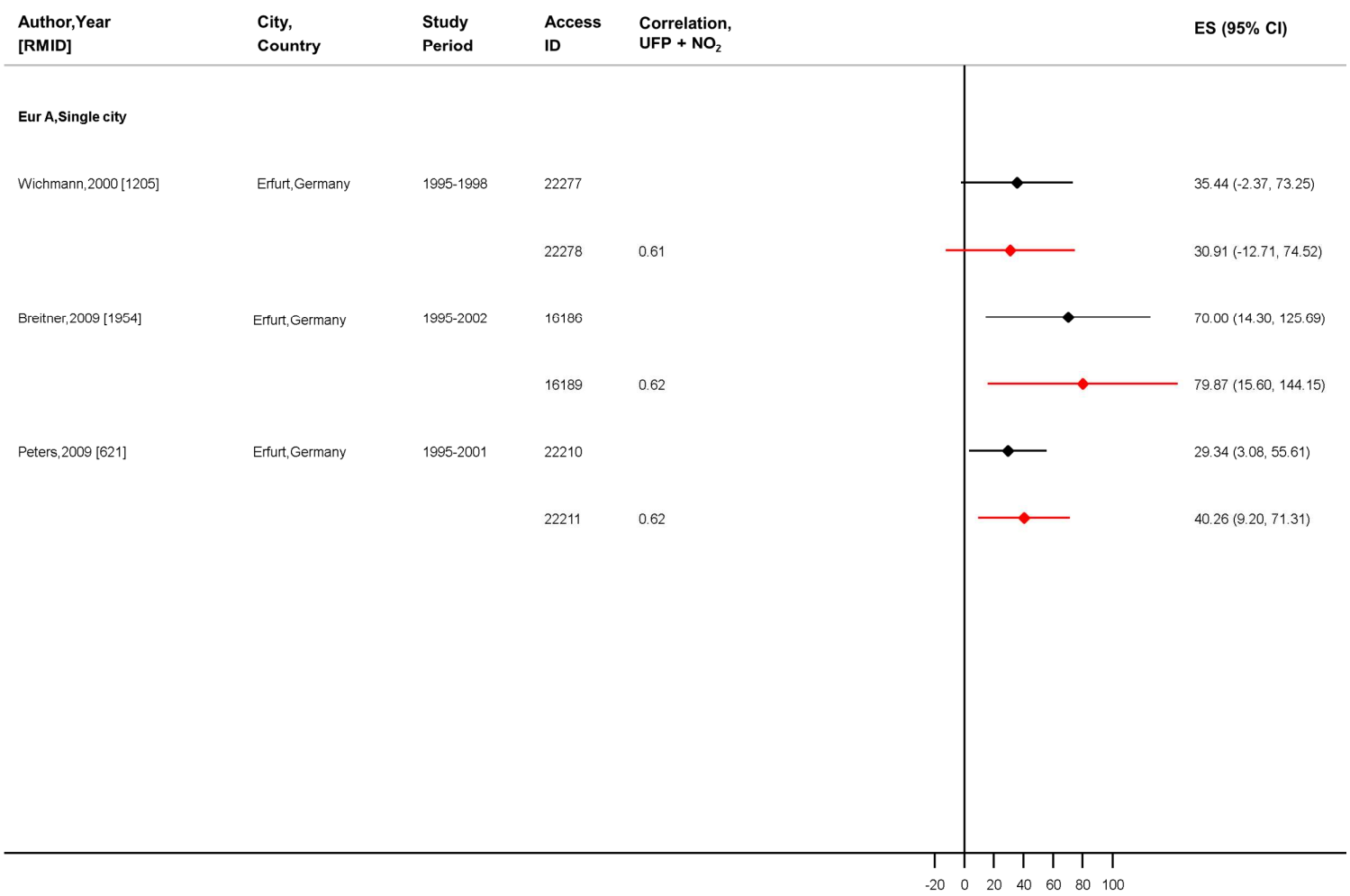


Figure S12: All studies providing two-pollutant model estimates for all cardiovascular mortality, all-ages, PM adjusted for 24 hour NO_2

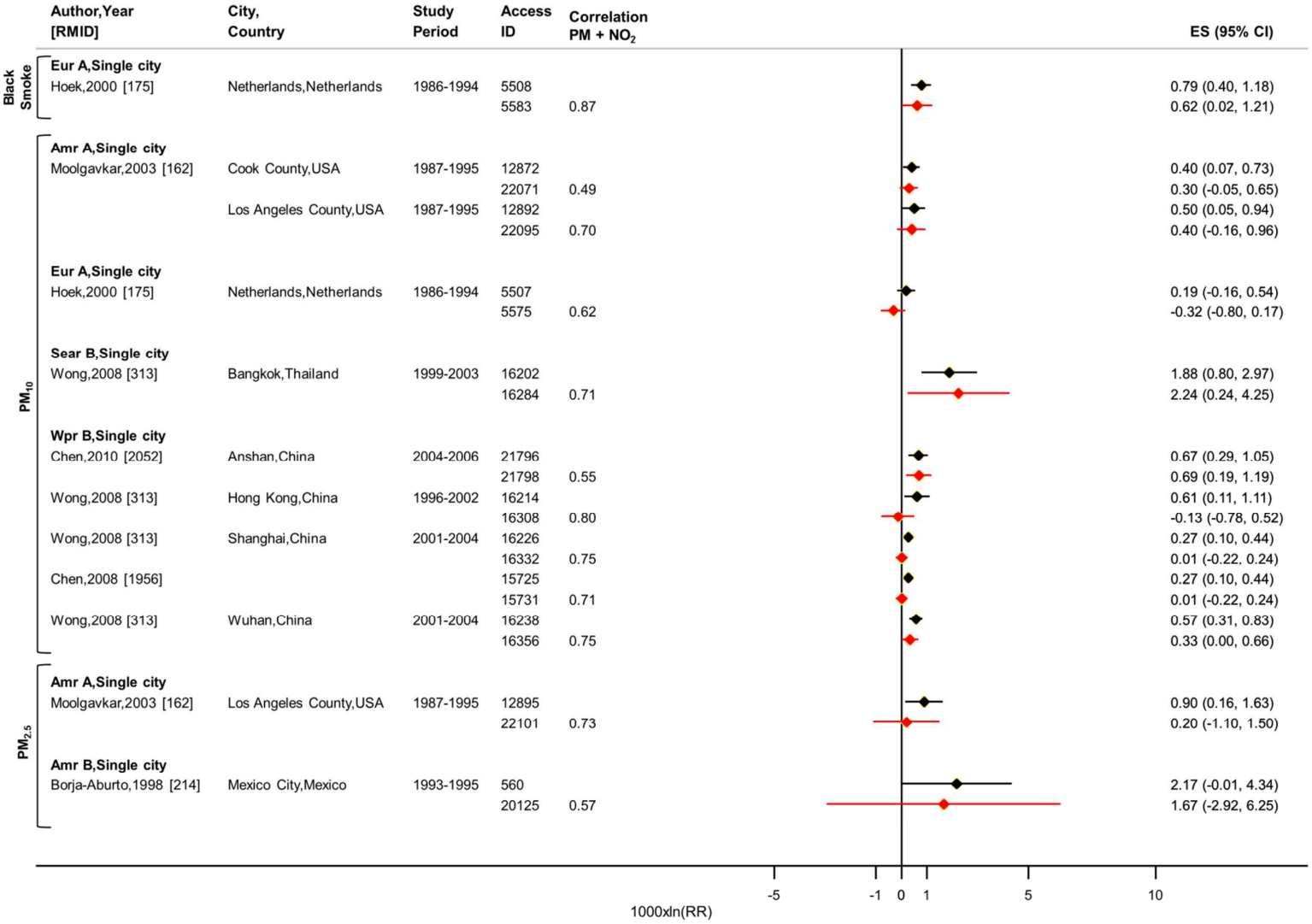


Figure S13: All studies providing two-pollutant model estimates for all respiratory mortality, all-ages, PM adjusted for 24 hour NO_2

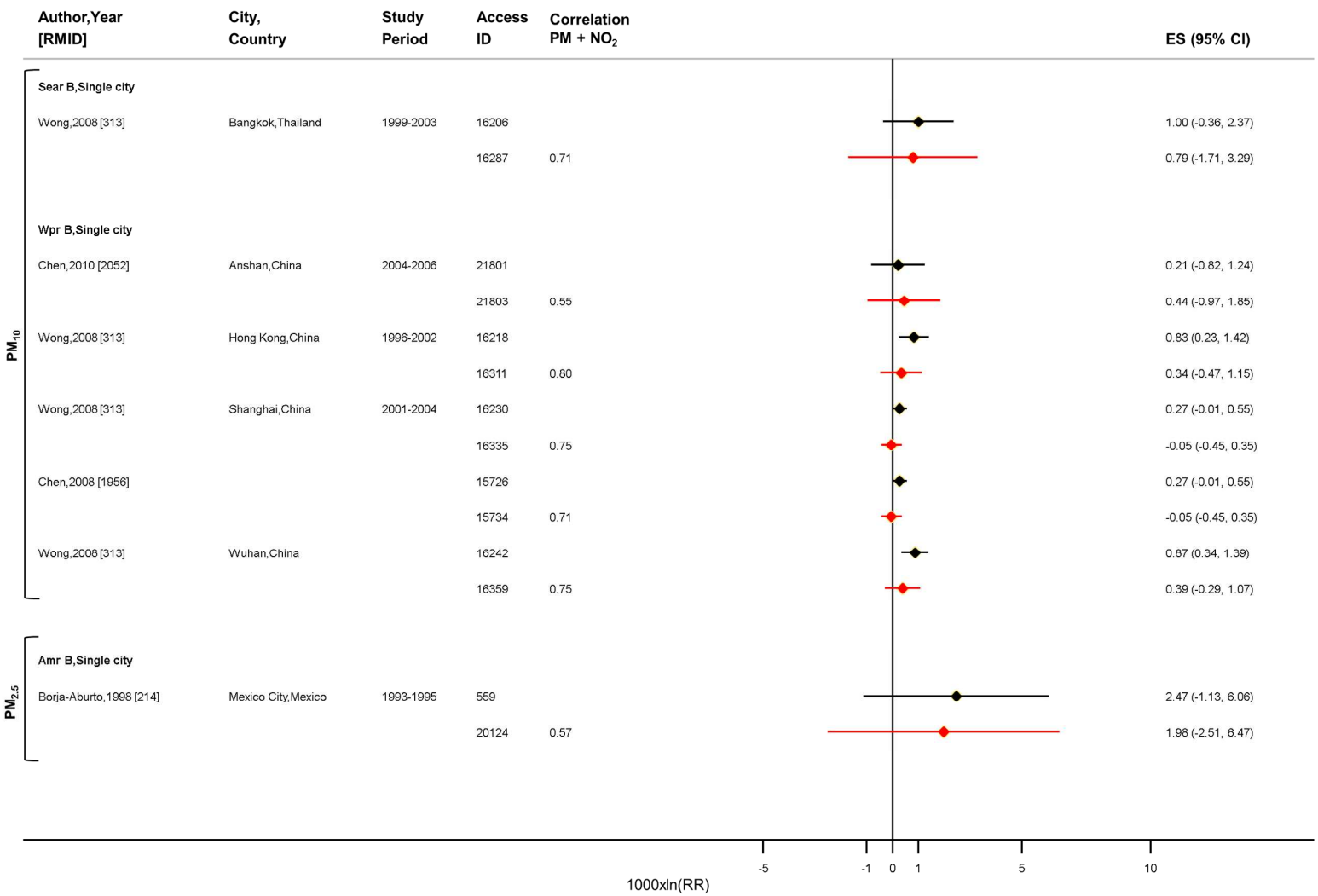
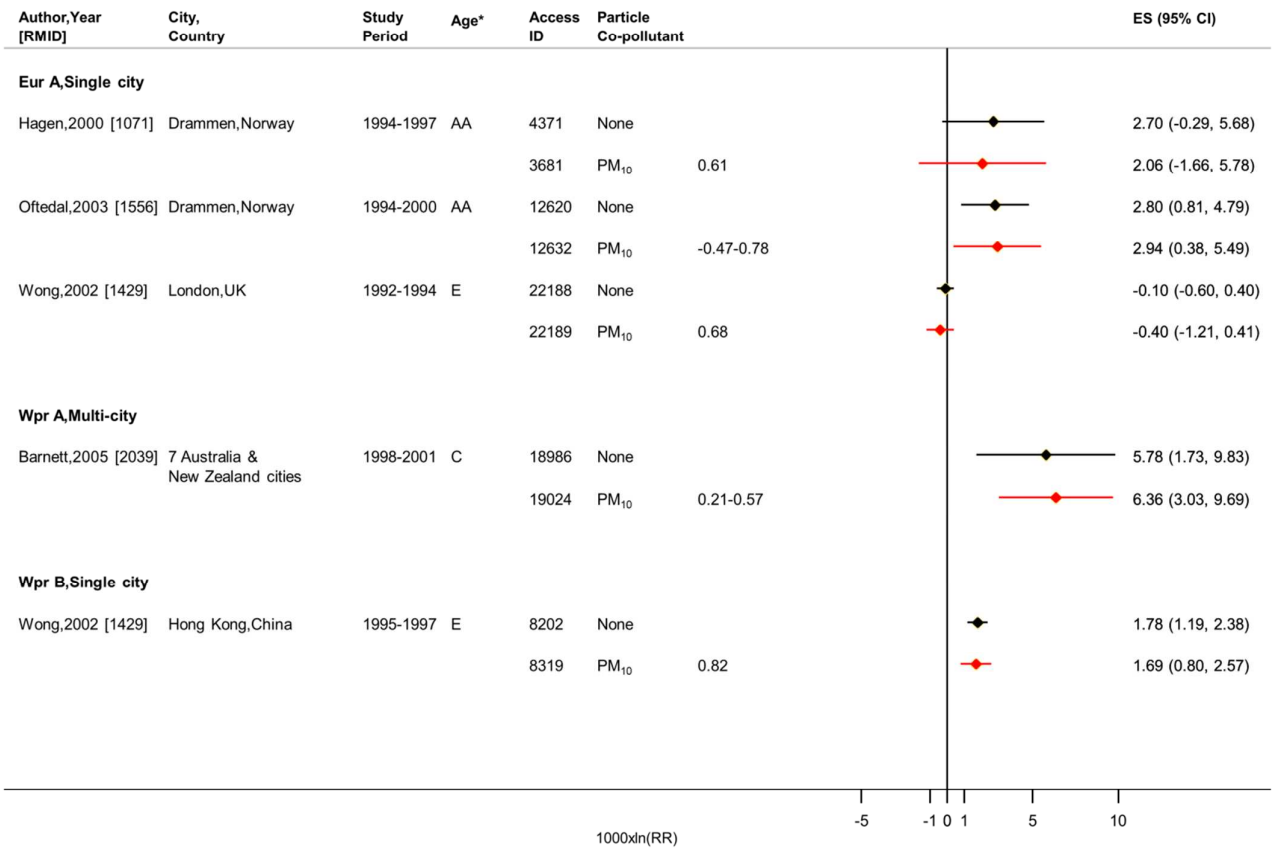
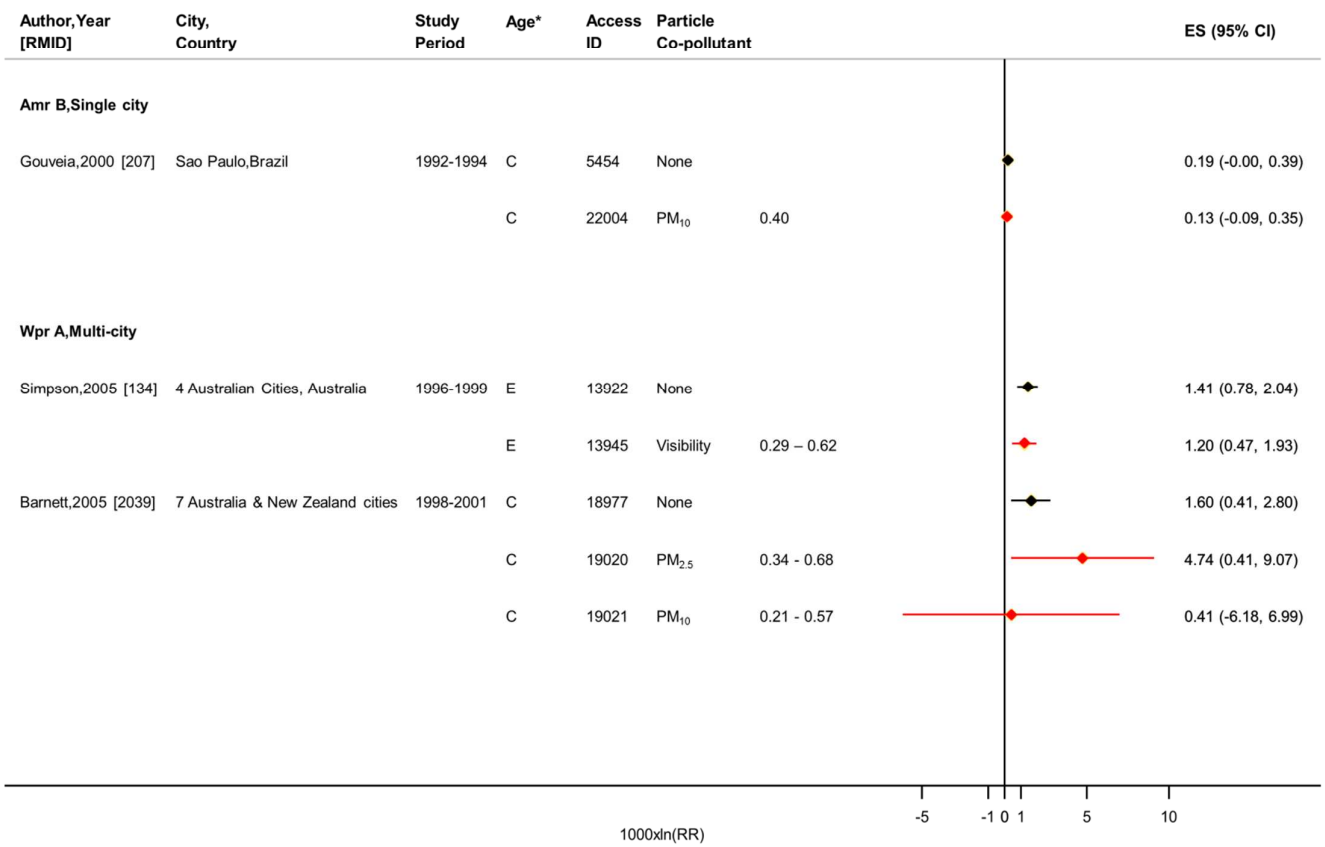


Figure S14: Studies providing two-pollutant model estimates for meta-analysis for all respiratory hospital admissions, various age groups, 24 hour NO_2



* Age: AA = all ages; E = Elderly; C = Children

Figure S15: Studies providing two-pollutant model estimates for meta-analysis for all respiratory hospital admissions, various age groups, 1 hour NO_2



* Age: C = Children; E = Elderly

Figure S16: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for asthma, children, 24 hour NO_2

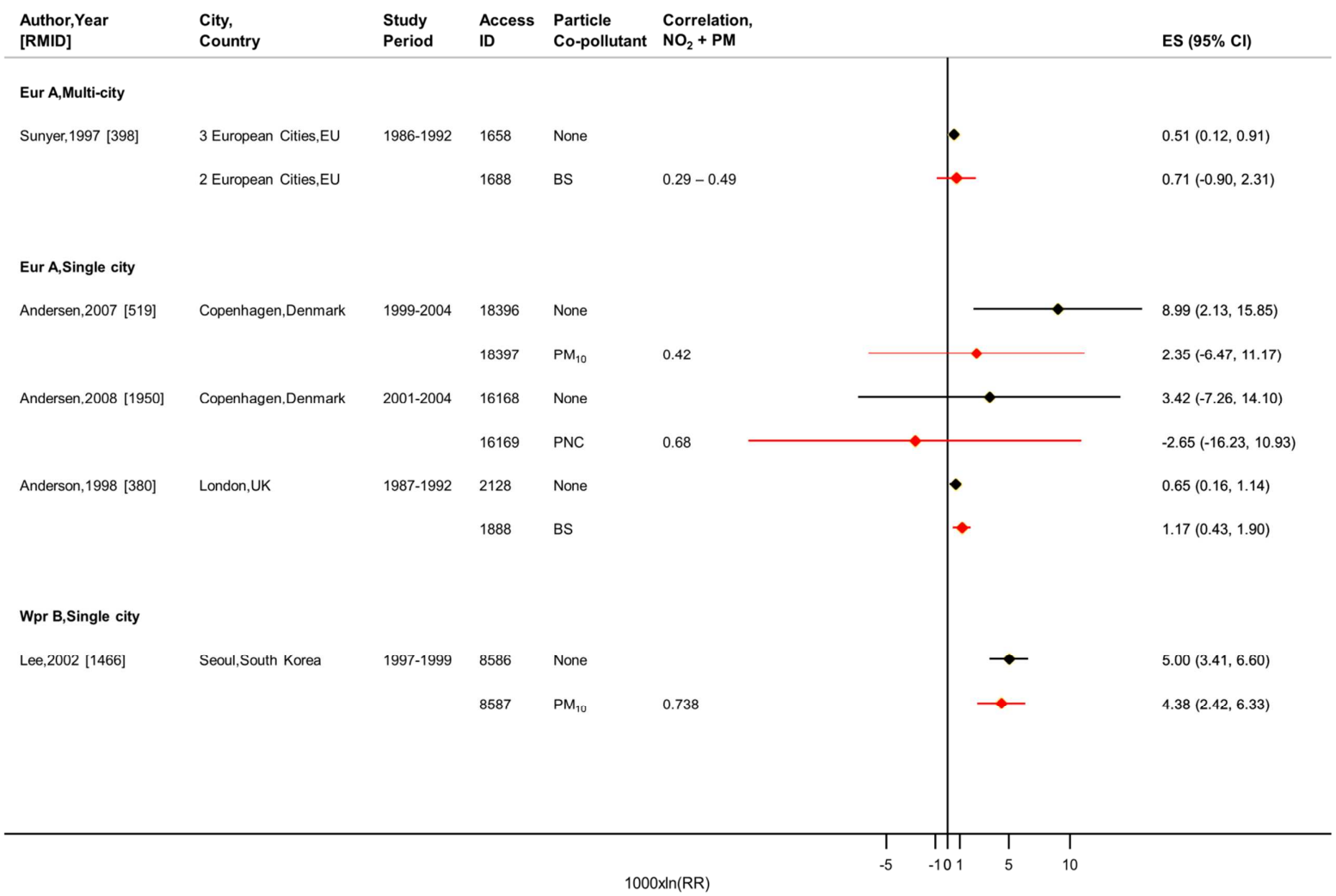
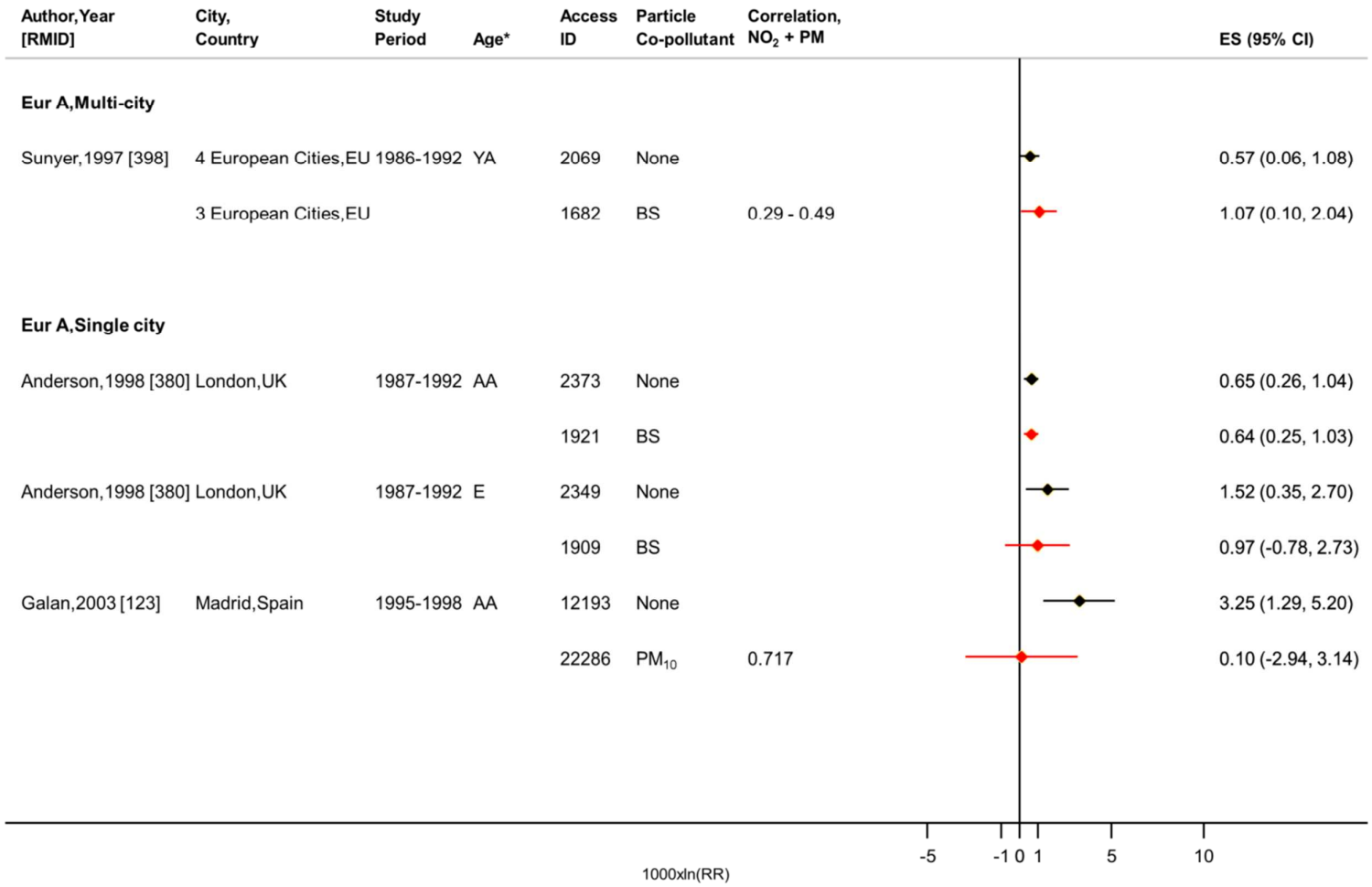


Figure S17: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for asthma, various age groups, 24 hour NO_2



* Age: AA = All-ages; E = Elderly; YA = Young adults

Figure S18: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for cardiac disease, all-ages, 24 hour NO_2

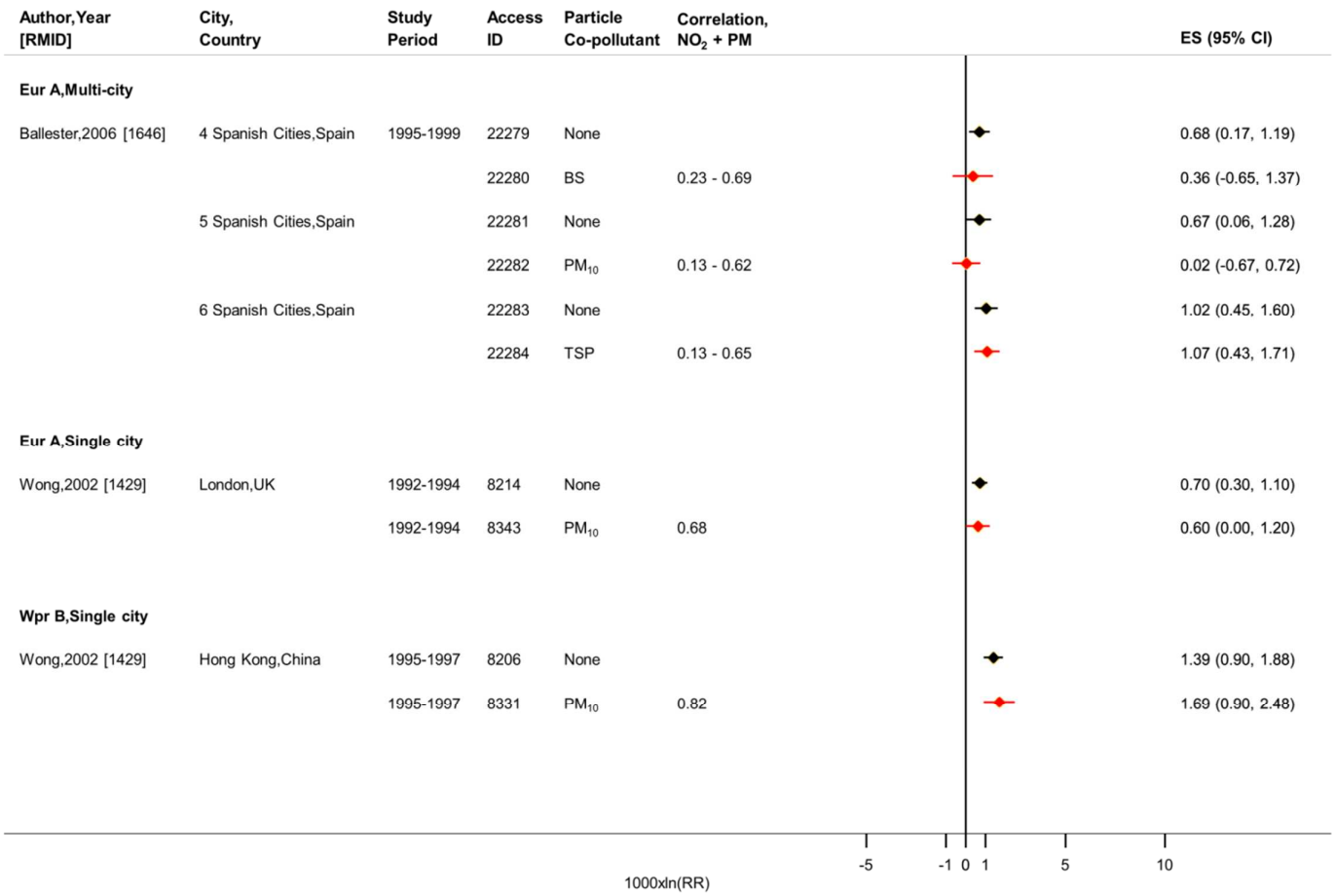


Figure S19: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for cardiac disease, elderly, 24 hour NO_2

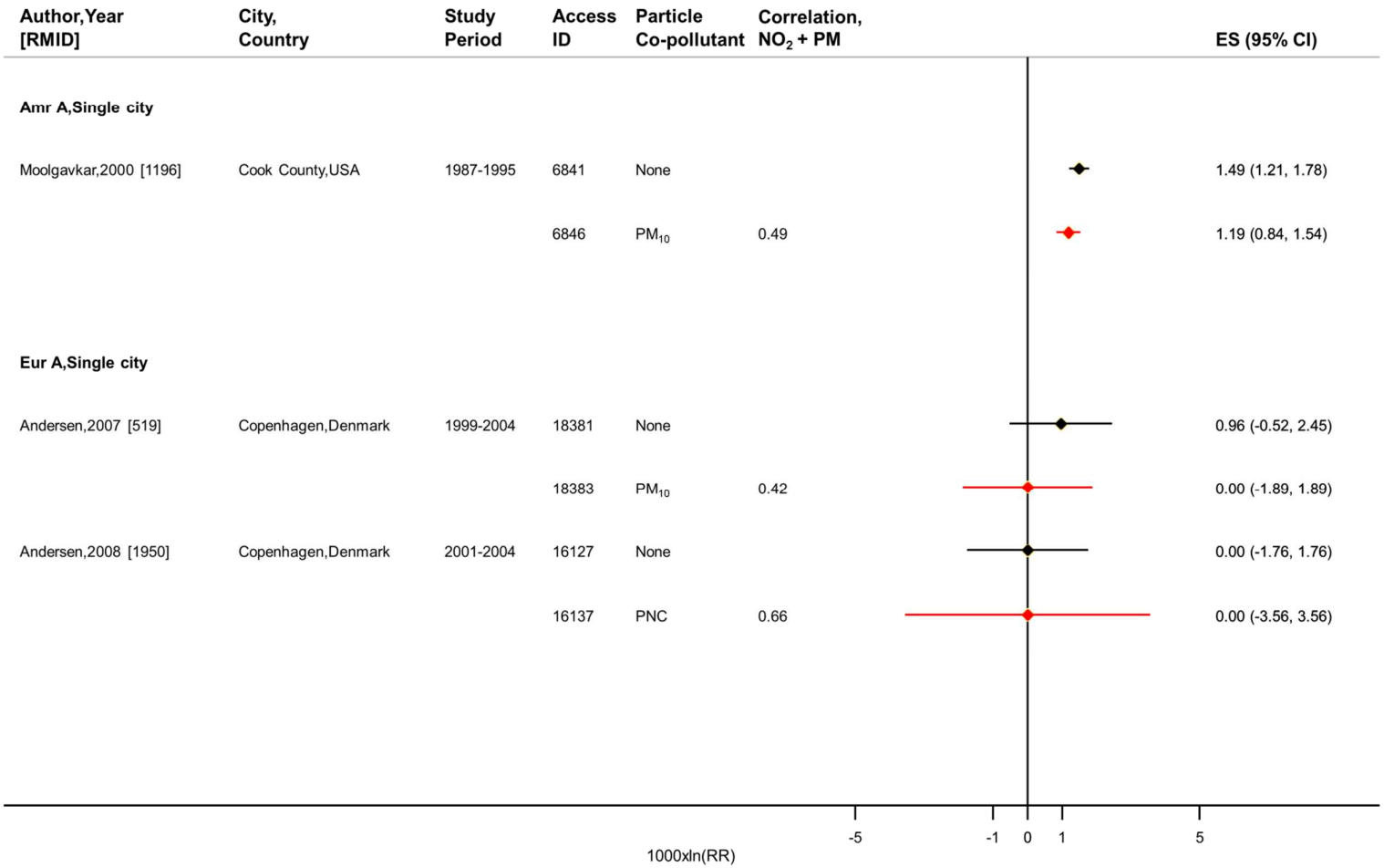


Figure S20: All available studies providing estimates from both single-pollutant and season-specific models for 24 hour NO_2 and all-cause mortality in all-ages

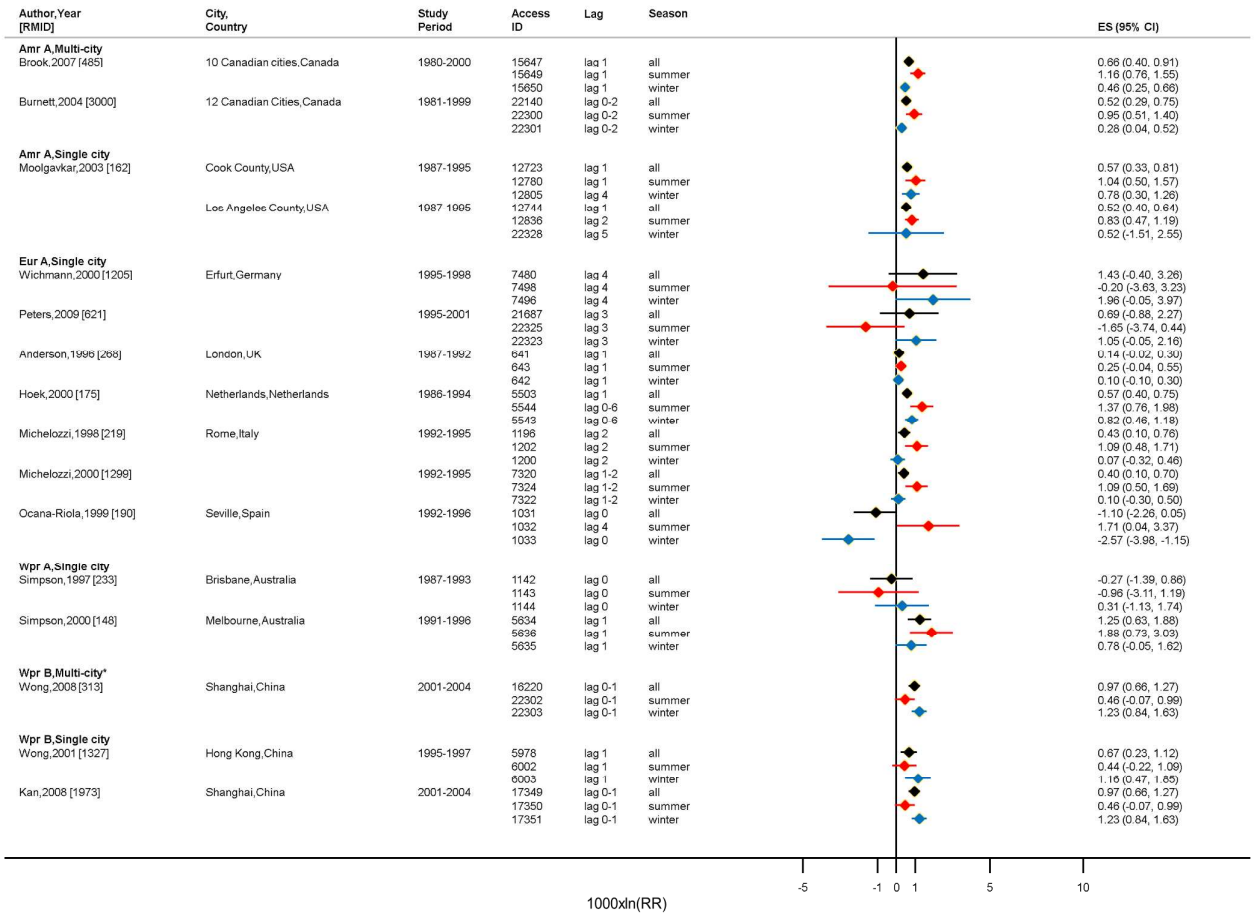


Figure S21: All available studies providing estimates from both single and season-specific models for 24 hour NO_2 and all cardiovascular mortality in all ages

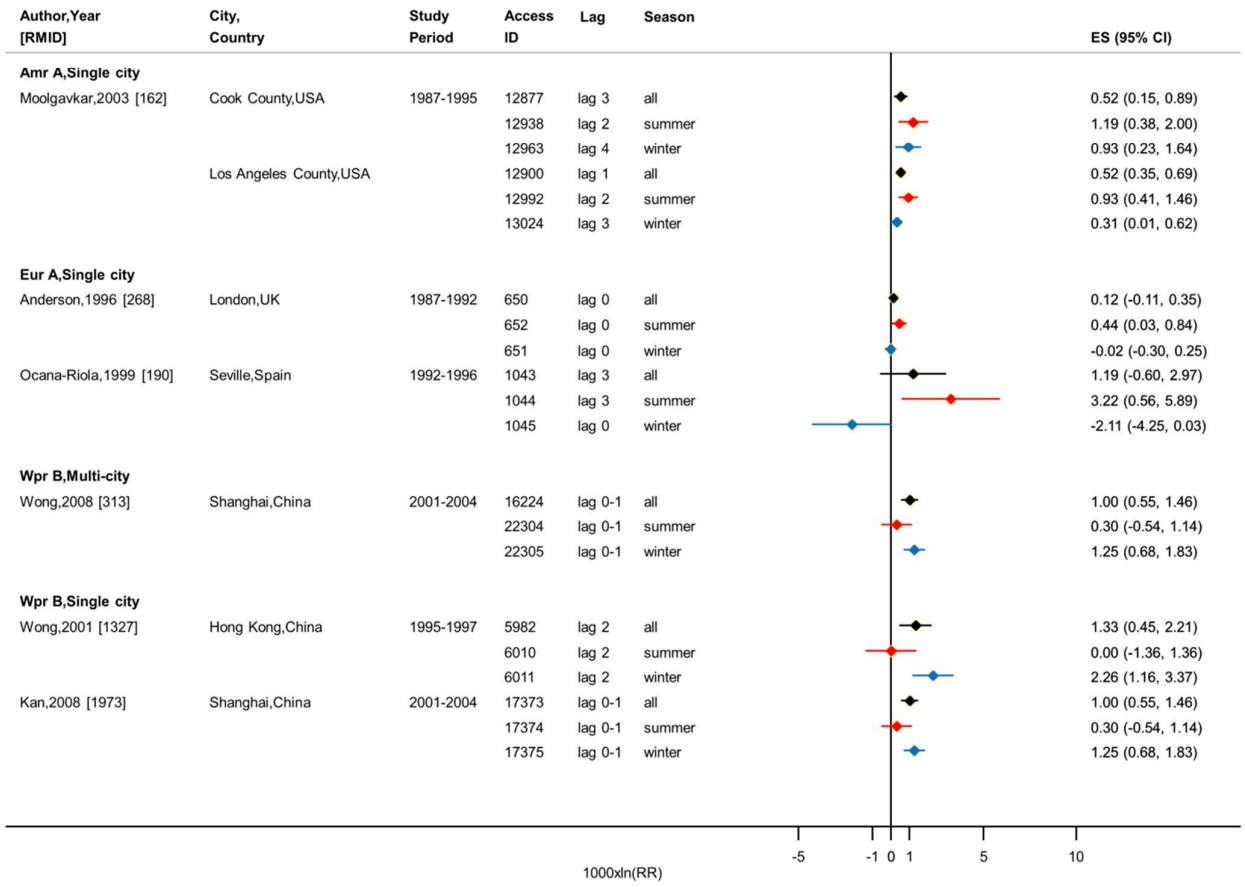


Figure S22: All available studies providing estimates from both single-pollutant and season-specific models for 24 hour NO_2 and all respiratory mortality in all-ages

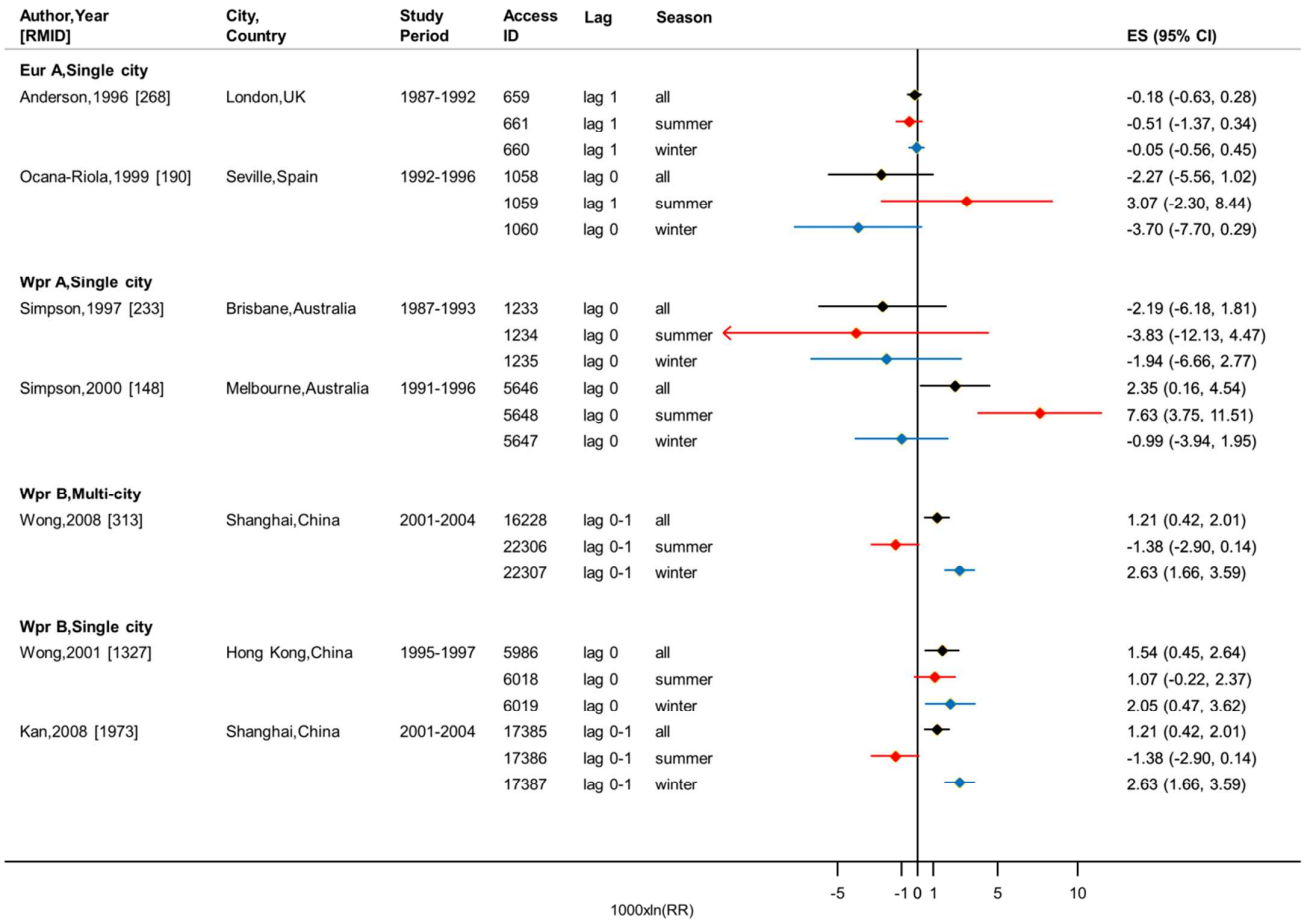


Figure S23: All available studies providing estimates from both single-pollutant and season-specific models for 24 hour NO_2 and all respiratory and all cardiovascular hospital admissions in all-ages

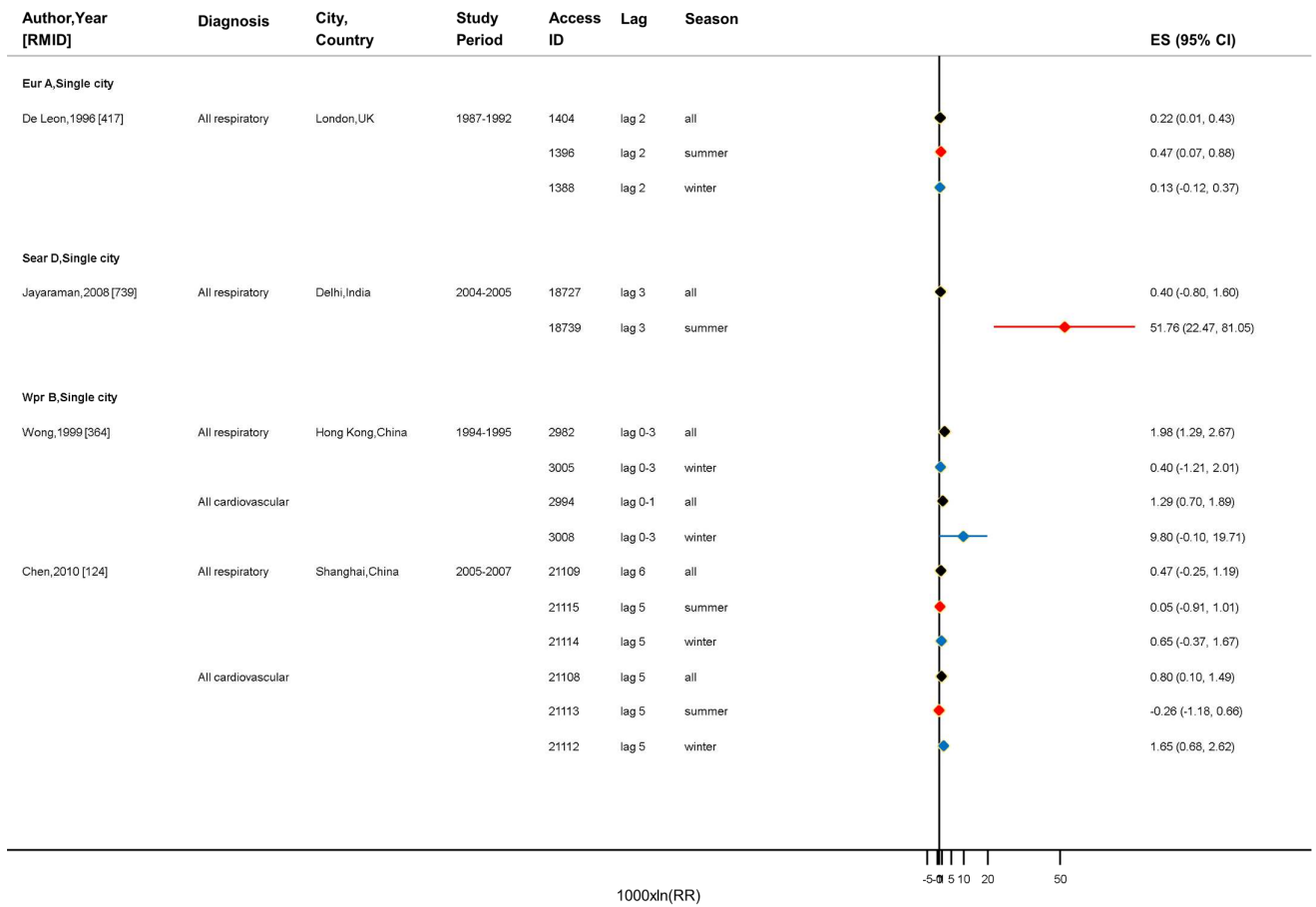


Figure S24: Ranking of NO_2 estimates for all-cause mortality in all-ages by mean levels of 24 hour NO_2 (multi-city studies shown using black bars)

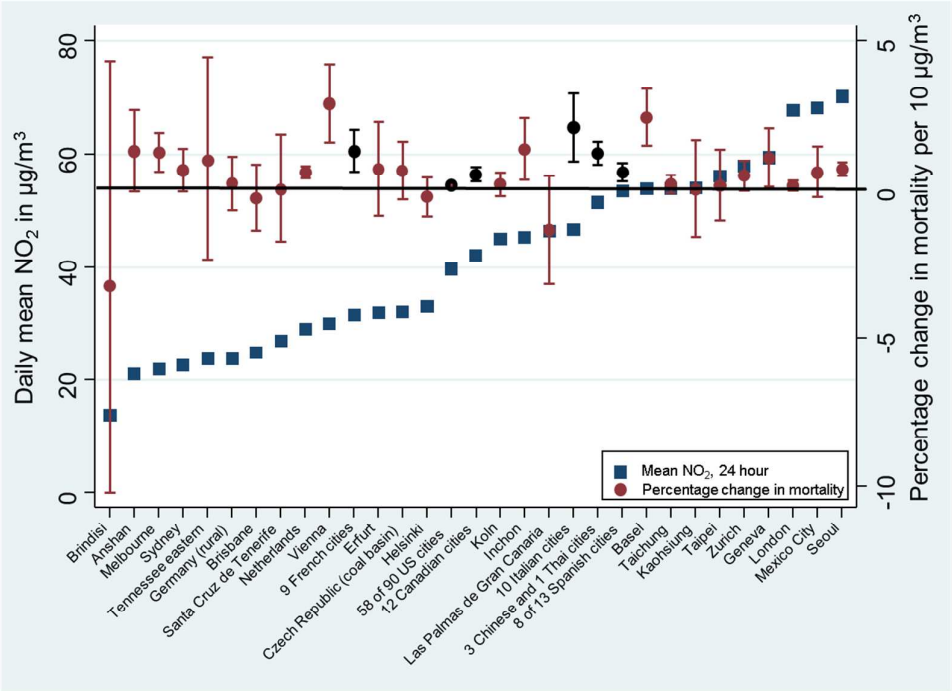


Figure S25: Ranking of NO_2 estimates for all-cause mortality in all-ages by mean levels of PM_{10} (multi-city studies shown using black bars)

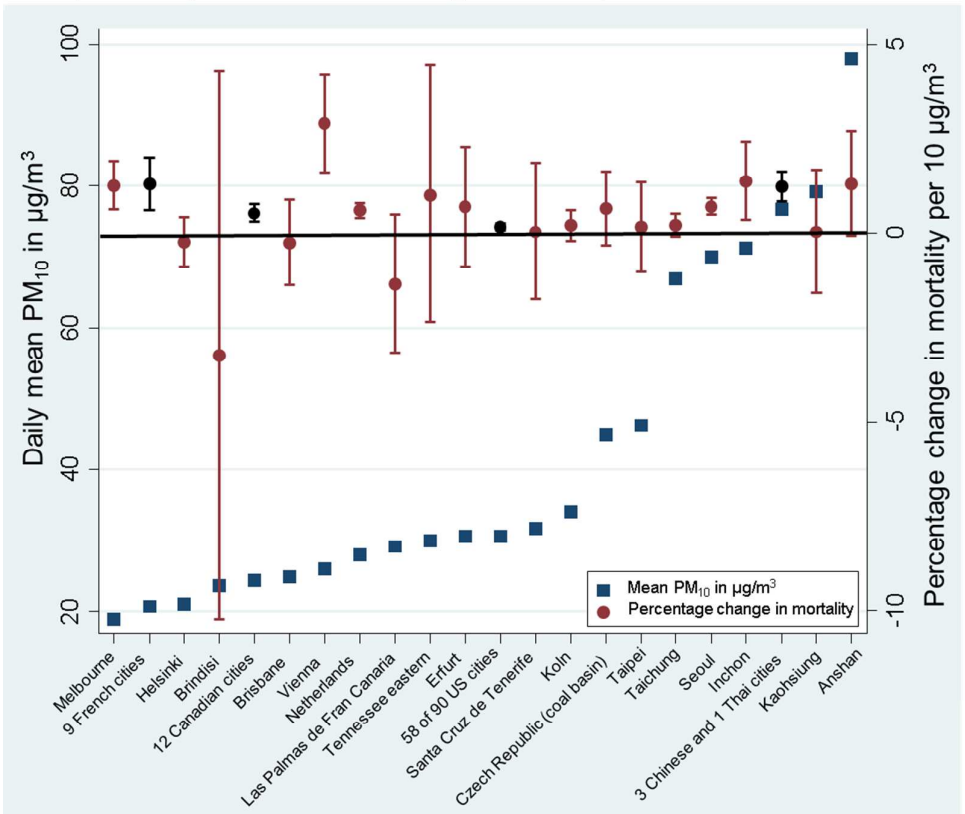


Figure S26: Ranking of NO_2 estimates for all-cause mortality in all-ages by the NO_2/PM_{10} concentration ratio (multi-city studies shown using black bars)

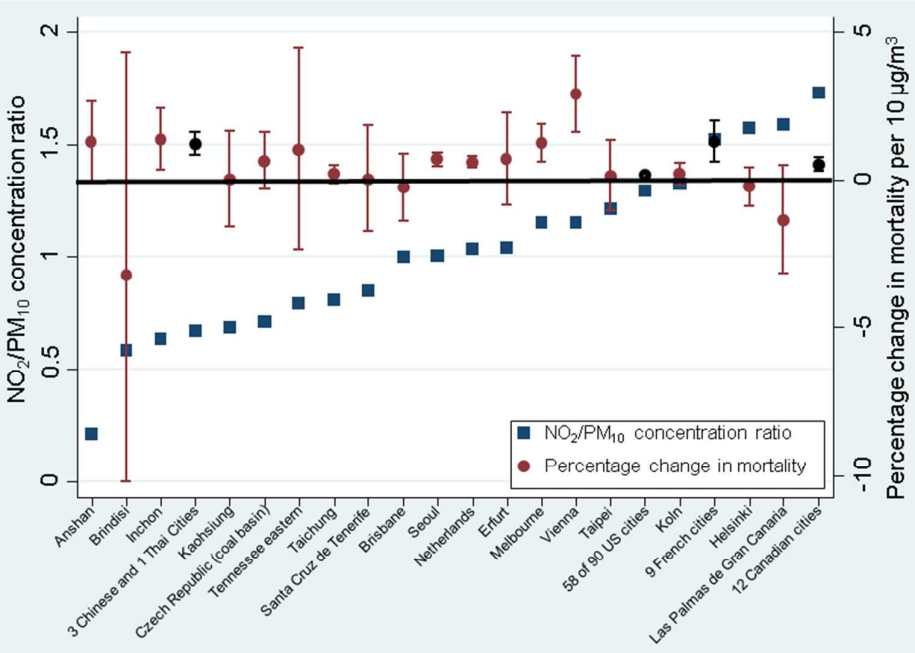
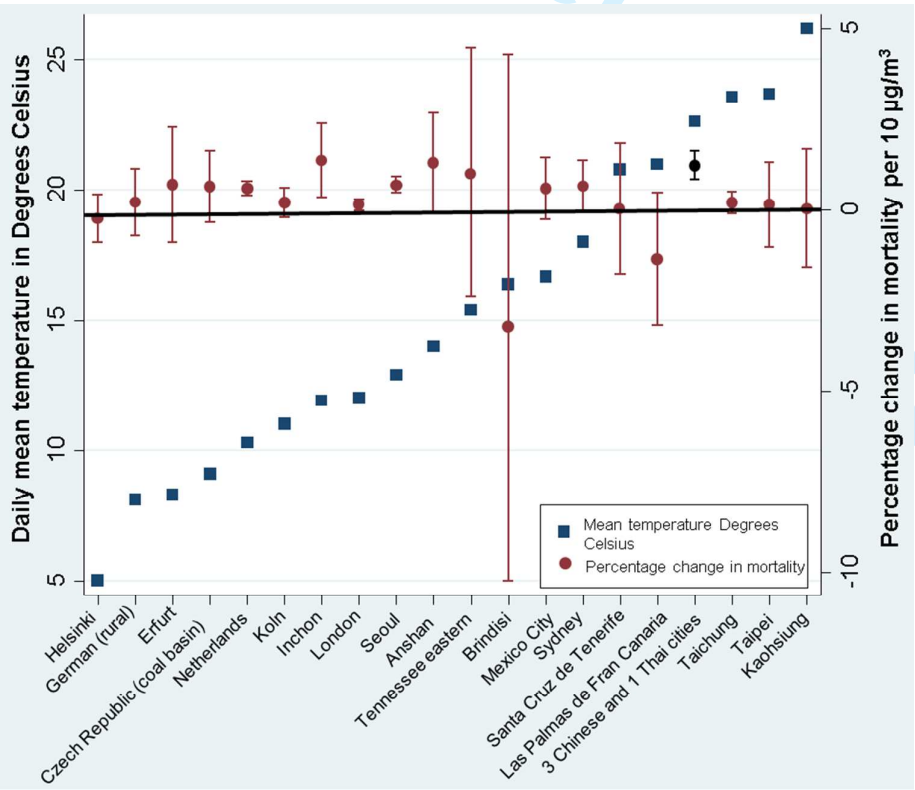


Figure S27: Ranking of NO_2 estimates for all-cause mortality in all-ages by daily mean temperature (multi-city studies shown using black bars)



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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4 and Supplementary Material
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4 and Supplementary Material
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4 and Supplementary Material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4 and Supplementary Material
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 and Supplementary Material
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 and Supplementary

PRISMA 2009 Checklist

			Material
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6 and Supplementary Material

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-7 and Supplementary Material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-11 and Supplementary Material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-11 and Supplementary Material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-11 and Supplementary Material
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	See previous related paper – reference 12 in

PRISMA 2009 Checklist

			manuscript for publication bias in full dataset. Data from the subset of studies examined in current manuscript were insufficient to permit assessment of publication bias.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Distinguishing the associations between daily mortality and hospital admissions and nitrogen dioxide from those of particulate matter: a systematic review and meta-analysis.

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine, Epidemiology, Public health
Keywords:	nitrogen dioxide, time series, mortality, hospital admissions, systematic review, meta-analysis

Type of manuscript: original article (systematic review and meta-analysis)

Distinguishing the associations between daily mortality and hospital admissions and nitrogen dioxide from those of particulate matter: a systematic review and meta-analysis.

IC Mills[1], RW Atkinson[2], HR Anderson[2,3], RL Maynard, DP Strachan[2].

1 - Public Health England, Centre for Radiation, Chemical and Environmental Hazards, UK
2 - Population Health Research Institute and MRC-PHE Centre for Environment and Health, St George's, University of London, London, UK
3 - MRC-PHE Centre for Environment and Health, King's College London, UK

Corresponding author:
I C Mills
Public Health England
Centre for Radiation Chemicals and Environmental Hazards (CRCE)
Environmental Change Department
Air Pollution and Climate Change Group
Chilton
Oxfordshire, OX11 0RQ
United Kingdom
Tel: +44 (0)1235 825146
Fax: +44 (0) 1235 833891
Email: inga.mills@phe.gov.uk

Keywords: nitrogen dioxide, mortality, hospital admissions, systematic review, meta-analysis
Word count: 4529~~040~~

Abstract

Objectives

To quantitatively assess time-series studies of daily nitrogen dioxide (NO_2) and mortality and hospital admissions which also controlled for particulate matter (PM) to determine whether or to what extent the NO_2-associations are independent of PM.

Design

A systematic review and meta-analysis

Methods

Time-series studies published in peer-review journals worldwide up to May 2011 which reported both single- and two-pollutant model estimates for NO_2 and PM were ascertained from bibliographic databases (PubMed, EMBASE, and Web of Science) and reviews. Random-effects summary estimates were calculated globally and stratified by different geographical regions, and effect modification was investigated.

Outcome measures

Mortality and hospital admissions for various cardiovascular or respiratory diseases in different age groups in the general population.

Results

Sixty eligible studies were identified, and meta-analysis was done on 23 outcomes. Two-pollutant model study estimates generally showed that the NO_2-associations were independent of PM mass. For all-cause mortality, a 10 $\mu g/m^3$ increase in 24 hour NO_2 was associated with a 0.78% (95% CI: 0.47, 1.09) increase in the risk of death, which reduced to 0.60% (0.33, 0.87) after control for PM. Heterogeneity between geographical region-specific estimates was removed by control for PM (I^2 from 66.9% to 0%). Estimates of PM and daily mortality assembled from the same studies were greatly attenuated after control for NO_2: from 0.51% (0.29, 0.74) to 0.18% (-0.11, 0.47) per 10 $\mu g/m^3$ PM_{10} and 0.74% (0.34, 1.14) to 0.54% (-0.25, 1.34) for $PM_{2.5}$.

Conclusions

The association between short-term exposure to NO_2 and adverse health outcomes is largely independent of PM mass. Further studies should attempt to investigate whether this is a generic PM-effect or modified by the source and physicochemical characteristic of PM. This finding strengthens the argument for NO_2 having a causal role in health effects.

Strengths and limitations of this study

- This is, to date, the most comprehensive, quantitative systematic review of the time-series literature on NO_2 published worldwide to evaluate the two-pollutant model estimates of mortality or hospital admissions and short-term exposure to NO_2 adjusted for particulate air pollution.
- It reports meta-analytical estimates both globally and for different geographical regions, as well as an assessment of heterogeneity between the region-specific estimates.
- The protocol-led approach to the identification of studies and estimates for use in meta-analysis minimised selection bias at each stage of the review.
- Meta-analysis was limited to studies which provided effect estimates in numerical, rather than graphical, form along with sufficient quantitative data to enable standardisation of estimates.
- Further work is needed to understand reasons for the heterogeneity observed and to quantitatively assess the extent to which PM may be associated with health independently of NO_2.

INTRODUCTION

Outdoor air pollution has long been established as a hazard to human health, with particulate matter (PM) regarded as the most plausible toxicant in the mixture of ambient air pollutants.[1-5] The epidemiological evidence has consistently shown adverse associations between chronic and short-term exposure to PM and mortality and morbidity from cardiovascular and respiratory disease, and this is supported by experimental evidence.[6] Whilst the epidemiological evidence also shows relationships between nitrogen dioxide (NO_2) and adverse health effects, concerns have been expressed repeatedly about the causal nature of these associations.[7-11] It has been asserted that the NO_2-associations do not reflect adverse effects of NO_2 itself, but rather the health effects of other air pollutants, mainly PM or other components of the complex mixture of traffic-related air pollutants. Primarily, this is due to the strong correlations between NO_2 and other combustion derived air pollutants, especially PM. The extent of these correlations varies from city-to-city and over time, due to variations in emission sources. Scepticism also exists because of limited experimental evidence (controlled human exposure and animal toxicology studies) for NO_2, which, to date, has focused largely on respiratory endpoints and have generally employed concentrations of NO_2 well above current ambient levels.[7-9] In light of the uncertainties regarding NO_2 and the stronger evidence for associations between PM and health, many researchers and policymakers adopted a view that the epidemiological associations of NO_2 reflect adverse health effects of PM.

In an earlier paper we reviewed the time-series evidence associating daily concentrations of NO_2 with daily mortality and emergency hospital admissions.[12] In this study we assess the subset of time-series studies, reporting all-year estimates of NO_2 from both single- and two-pollutant models adjusted for PM to determine whether the NO_2-associations are attenuated after adjustment for PM.

METHODS

The full method and a priori protocols governing the identification of studies and effect estimates for the systematic review have been described previously,[12-14] but a synopsis, along with aspects unique to this review, is provided below.

Identification of studies for review

Three bibliographic databases were searched to identify peer-reviewed time-series studies of NO_2 and daily mortality or hospital admissions indexed up to May 2011. No restriction on language was applied. The literature search strategy is described in the online supplementary material, and the following inclusion criteria were used: papers must (i) have had a minimum of one year of data; (ii) been based on the general population; (iii) have controlled for important confounding factors, including season and meteorological factors; (iv) have reported sufficient quantitative information, in numeric format, to enable the calculation of standardised effect estimates and standard errors for use in quantitative analysis. Two authors of the review – ICM and RWA – undertook the literature search.

Data extraction and coding

Data from each relevant study were entered into a Microsoft Access database (Microsoft Office 2010, Microsoft Corporation). These included:

a) citation details of each paper
b) all-year single- and two-pollutant model estimates of NO_2 adjusted for PM.
c) single- and two-pollutant model estimates of PM adjusted for NO_2 reported in studies providing data for NO_2.
d) season-specific estimates of NO_2, including those adjusted for PM, from studies reporting all-year estimates.
e) descriptive (outcome, diagnosis (International Classification of Diseases codes), age etc.) and quantitative data (pollution increment and averaging time etc.) associated with each estimate, and needed for calculating standardised estimates expressed as the percentage change (and 95% confidence interval (CI)) in the mean number of daily events associated with a 10 $\mu g/m^3$ increase in NO_2 (or PM).
f) correlations between concentrations of NO_2 and PM.
g) effect modifiers for investigating of sources of heterogeneity in all-year estimates

Time-series studies often report results for different time lags (in days) between exposure and health events, and they vary in the lag for the reported results. We identified for each outcome/disease/age/averaging time combination from each study a pair of estimates of NO_2, that is from a single-pollutant model and a corresponding estimate adjusted for PM, for the same lag to enable comparison of the NO_2-association before and after adjustment for PM. To avoid selection bias we developed an a priori protocol for identifying the principal lag for each outcome/disease/age/averaging time combination for use in our review. This was the lag highlighted by the author or stated a priori, and if this was not clear, because several lagged model estimates were reported, we chose (i) the lag with the highest statistical significance, regardless of the estimate being positive or negative, or (ii) the lag with the largest estimate, again, irrespective of its direction. If only results from cumulative or distributed lag models, i.e. lags averaged over several days, were reported in a study, this was used. In some instances, a different lag was investigated in two-pollutant models. In such cases, the lagged estimate from the two-pollutant model was coded according to the same algorithm, and the (additional) corresponding single-pollutant estimate for the same lag was coded in our database.

Processing of data also included classifying each study into the geographical region, as the WHO region, in which the study was conducted, as well as categorising, by size, the various metrics of PM controlled for in two-pollutant models: see supplementary material for details.

Statistical analyses

A similar procedure to that outlined in our earlier paper was used for meta-analysis,[12] but with some modifications in order to identify from each study a pair of estimates of NO_2 for each pollutant/outcome combination. We applied an a priori protocol to select estimates for meta-

analysis to avoid selection bias and duplication of studies from the same population. We gave priority to estimates from multi-city studies over estimates from single-city studies and the results from any one city appeared only once in a meta-analysis. If results from more than one multi-city study within a WHO region were available we selected, in order of priority, the multi-city estimate from the study: (i) with the most cities/greatest geographical coverage; (ii) the most recently published; (iii) the most recent study time period. If a multi-city study did not report a summary estimate across the cities examined, for analysis, we treated estimates from these studies in the same manner as estimates from single-city studies. We selected estimates from single-city studies only if they did not appear in multi-city studies. For cities not included in a multi-city study summary result, we selected, in order of priority: (i) the most recently published, and (ii) the most recent study time period.

Meta-analysis was conducted when ≥4 estimates were available for an outcome/disease/age/averaging time combination - including where a multi-city estimate was available - and summary estimates were calculated using a random-effects model.[15] We used a staged approach to meta-analysis, with single-city estimates pooled within WHO region prior to the pooled single-city and selected multi-city estimates being pooled to produce a global estimate and WHO region-specific summary estimates. Heterogeneity between WHO region summary estimates was assessed using the I^2 statistic[16], with I^2 statistics >50% regarded as being evidence of high heterogeneity.[17]

Meta-analysis was undertaken for:

a) single-pollutant NO_2 estimates relating to two-pollutant models
b) corresponding NO_2 estimates adjusted for <u>any</u> PM metric:
    i) if within a study, several estimates of NO_2 adjusted for different individual PM metrics were available, a NO_2 estimate was selected according to the following order of priority of PM metric used in adjustment: PM_{10}, $PM_{2.5}$, Black Smoke, $PM_{10-2.5}$.
    ii) if having applied the protocol, a NO_2 estimate was not selected for a city because several were available due to different PM metrics used to adjust the NO_2 effect in different studies, the NO_2 estimate was chosen in the order of priority of the PM metrics listed above.
c) We conducted additional meta-analyses for NO_2 adjusted for specific metrics of particles, for example NO_2 adjusted for PM_{10}, and separately for $PM_{2.5}$, and so on, to determine whether the NO_2-associations show different sensitivity to control for different PM metrics.

All analyses were conducted in STATA (STATA/SE 11. StataCorp Texas).

RESULTS

Sixty studies provided estimates of both (i) NO_2, single-pollutant and (ii) NO_2 adjusted for PM: a list of references is provided in the supplementary material. Table 1 presents a summary of these 60 time-series studies stratified by the PM metric controlled for in regression models, broad disease categories, WHO regions in which the studies were conducted, single- and multi-city study designs, and by averaging time (24 hour and 1 hour).

There were 36 and 24 studies of daily mortality or hospital admissions, respectively, and 13 studies used a multi-city design. The majority of the studies were conducted in the WHO regions European A and Western Pacific region B and most used 24 hour NO_2. Forty of the 60 studies controlled for the effects of daily PM_{10} in the regression models for NO_2, and a much smaller number of studies used other particle size fractions or constituents of PM. Eight studies of mortality and two of hospital admissions reported estimates of NO_2, each adjusted for a different PM metric. None of the studies investigated the influence of carbon on the NO_2-associations, and four studies controlled for the effects of ultrafine particles.

Table 1: Summary of time-series studies of daily mortality or hospital admissions and NO_2 adjusted for particulate matter (PM)

Outcome		Total		Multi-city study		Single-city study	
		Mortality	Hospital admissions	Mortality	Hospital admissions	Mortality	Hospital admissions
Total		36	24	9	4	27	20
NO_2 + PM[a]	PM_{10}	23	17	6	2	17	15
	$PM_{2.5}$	7	1	3	1	4	0
	$PM_{10-2.5}$	4	0	3	0	1	0
	BS	5	4	3	2	2	2
	PNC	3	1	0	0	3	1
	Carbon	0	0	0	0	0	0
	TSP	4	2	0	1	4	1
	Visibility	2	1	2	1	0	0
	>1 PM metric	0	1	0	0	0	1
Disease[b]	All-cause	27	1	7	0	20	1
	Cardiovascular	17	11	4	2	13	9
	Respiratory	7	17	3	3	4	14
WHO Region[c]	American A	8	4	3	0	5	4
	European A	9	12	3	2	6	10
	Western Pacific B	14	5	2	0	12	5
	American B	4	2	0	0	4	2
	Western Pacific A	1	2	1	2	0	0
	South East Asia B	2	0	2	0	0	0
Averaging time	24 hours	29	21	6	3	23	18
	Maximum 1 hour	7	5	3	2	4	3

a - The eight categories of PM metrics listed in the table above have been generated by grouping different measures of particles. PM_{10} and $PM_{2.5}$ refer to the mass per cubic metre of particles of generally less than 10 μm, 2.5 μm diameter, respectively, in the ambient air. BS: Black Smoke; PNC: Particle Number Concentration; TSP: Total Suspended Particles.

b - Respiratory includes all-respiratory diseases, asthma, COPD, COPD (including asthma), lower respiratory infections, and upper respiratory diseases; Cardiovascular includes all-cardiovascular diseases, cardiac disease, heart failure, ischaemic heart disease, dysrhythmia, and stroke.

c - WHO regions: A: very low child and adult mortality; B: low child mortality and low adult mortality; C: low child mortality and high adult mortality; D: high child mortality and high adult mortality.

NO_2 and all-cause mortality

Figure 1 shows all available (32 pairs) single- and two-pollutant estimates for 24 hour NO_2 and daily all-cause mortality in all ages. In the majority of studies daily NO_2 was positively and significantly associated with increases in the risk of death including after controlling for daily PM. In many of the studies the NO_2 estimates were not greatly reduced in size, changed direction, or lose statistical significance after adjustment for PM. In general, the NO_2 estimates appeared robust to adjustment for PM at both high and low correlations between concentrations of NO_2 and PM.

Fifteen (of 32) pairs of estimates for 24 hour NO_2 and all-cause mortality, which represented 26 cities from five WHO regions, were selected for meta-analysis (Figure S1). The random-effects single-pollutant summary estimate for all-cause mortality was 0.78% (95% CI: 0.47, 1.09) per 10 μg/m^3 increase in NO_2.There was evidence of high heterogeneity (I^2=66.9%) between the WHO region-specific estimates which ranged from 0.48% for WHO region America A to 1.41% for South East Asia B (Table S1). The overall estimate was comparable to the single-pollutant summary estimate of 0.71% (95% CI: 0.43, 1.00) calculated from the larger body of time-series evidence analysed in our previous paper.[12] After adjustment for daily PM, all-cause mortality remained positively and significantly associated with 24 hour NO_2: 0.60% (95 CI%: 0.33, 0.87) per 10 μg/m^3 increase in NO_2, and there was no evidence of heterogeneity (I^2=0%) between the region-specific estimates.

Control for specific PM metrics did not greatly alter the relationship of 24 hour NO_2 with all-cause mortality (Table 2). With the exception of NO_2 adjusted for PM_{10}, and to a lesser extent $PM_{2.5}$, meta-analyses for NO_2 adjusted for the remaining PM metrics were limited to findings from the multi-city Canadian study by Burnett et al[18] – see Figure 1.

Six pairs of estimates were available for meta-analysis for all-cause mortality and 1 hour NO_2 adjusted for PM (Figure S2). Thirty of the 36 cities represented by these estimates were from Europe. Meta-analysis of 4 pairs of estimates resulted in an overall estimate of 0.32% (95% CI: -0.02, 0.66) for a 10 μg/m^3 increment in 1 hour NO_2 and 0.20% (95% CI: -0.24, 0.65) following adjustment for PM (Table S2). High heterogeneity was observed between the WHO region-specific estimates. In contrast with findings for 24 hour measures, the summary estimate for 1 hour NO_2 for WHO region European A was little affected by adjustment for PM_{10} (or Black Smoke) –Table S2. Table 3 provides meta-analysis results for all-cause mortality and 1 hour NO_2 adjusted for different PM metrics. Control for PM_{10} led to attenuation of the estimate and loss of statistical significance, whilst the association was robust to control for Black Smoke and visibility (measured as black suspended particles, bsp).

Table 2: Random-effects summary estimates (as percentage change (95% confidence intervals)) for mortality or hospital admissions associated with a 10 μg/m³ increase 24 hour average pollution

	All SC/MC[a]	Selected SC/MC (cities)[b]	24 hour NO_2		24 hour PM	
			Single-pollutant	Adjusted for PM	Single-pollutant	Adjusted for NO_2
All-cause mortality, all ages						
PM_{10}	13/3	4/1 (21)	0.92 (0.58, 1. 72)	0.85 (0.52, 1.18)	0.51 (0.29, 0.74)	0.18 (-0.11, 0.47)
$PM_{2.5}$	2/3	2/1 (14)	0.53 (0.42, 0.64)	0.57 (0.24, 0.89)	0.74 (0.34, 1.14)	0.54 (-0.25, 1.34)
$PM_{10-2.5}$	0/3	0/1 (12)	0.62 (0.19, 1.06)	0.73 (0.28, 1.18)	0.65 (-0.10, 1.42)	0.31 (-0.49, 1.11)
Visibility	0/1	0/1 (12)	0.60 (0.34, 0.87)	0.66 (0.33, 1.00)	40.93 (23.39, 60.97)*	12.42 (-4.47, 32.29)*
All cardiovascular mortality, all ages						
PM_{10}	10/0	4/0 (8)	0.99 (0.49, 1.49)	0.87 (0.28, 1.46)	0.48 (0.18, 0.78)	0.19 (-0.21, 0.59)
All respiratory mortality, all ages						
PM_{10}	7/0	2/0 (5)	1.44 (0.63, 2.27)	1.15 (0.47, 1.84)	0.58 (0.22, 0.93)	0.13 (-0.18, 0.44)
All respiratory hospital admissions, children (5-14 years)						
PM_{10}	0/1	0/1 (5)	5.95 (1.74, 10.33)	6.56 (3.08, 10.17)	-	-
Cardiac hospital admissions, all ages						
PM_{10}	2/1	2/1 (7)	0.93 (0.46, 1.40)	0.75 (-0.13, 1.64)	-	-
BS	0/1	0/1 (4)	0.68 (0.17, 1.20)	0.36 (-0.65, 1.38)	-	-
TSP	0/1	0/1 (6)	1.03 (0.45, 1.61)	1.08 (0.43, 1.72)	-	-

a -Numbers of available pairs of single-city (SC) / multi-city (MC) estimates from all studies
b -Numbers of pairs of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions. Estimates were selected for meta-analysis from all available. The number of cities represented by the summary estimates is given in brackets.
* The results for visibility (measured as Coefficient of Haze (COH units)) are not comparable to other PM results.

Table 3: Random-effects summary estimates (as percentage change (95% confidence intervals)) for mortality or hospital admissions associated with a 10 μg/m³ increase in air pollution

	All SC/MC[a]	Selected SC/MC (cities)[b]	1 hour NO_2		24 hour PM	
			Single-pollutant	Adjusted for PM	Single-pollutant	Adjusted for NO_2
All-cause mortality, all ages						
PM_{10}	2/1	2/1 (32)	0.22 (-0.15, 0.60)	0.10 (-0.40, 0.61)	0.52 (0.29, 0.75)	0.48 (0.31, 0.66)
BS	0/2	0/1 (30)	0.30 (0.22, 0.38)	0.33 (0.23, 0.43)	0.60 (0.30, 0.90)	0.26 (0.00, 0.52)
Visibility	0/1	0/1 (4)	0.63 (0.21, 1.05)	0.52 (0.05, 1.00)	35.70 (3.97, 77.12)*	10.24 (-20.03, 51.97)*
All cardiovascular mortality, all ages						
PM_{10}	1/1	0/1 (29)	0.40 (0.29, 0.51)	0.35 (0.21, 0.49)	0.76 (0.47, 1.05)	0.17 (-0.10, 0.44)
BS	1/1	0/1 (29)	0.40 (0.29, 0.51)	0.44 (0.31, 0.57)	0.62 (0.35, 0.90)	0.32 (0.05, 0.59)
All respiratory mortality, all ages						
PM_{10}	0/1	0/1 (29)	0.38 (0.17, 0.59)	0.37 (0.08, 0.66)	0.71 (0.22, 1.20)	0.20 (-0.29, 0.69)
BS	0/1	0/1 (29)	0.38 (0.17, 0.59)	0.26 (-0.12, 0.64)	0.84 (0.11, 1.58)	0.57 (-0.34, 1.48)
All respiratory hospital admissions, children (< 5 years)						
PM_{10}	1/1	1/1 (6)	0.77 (-0.59, 2.15)	0.13 (-0.09, 0.35)	-	-
$PM_{2.5}$	0/1	0/1 (4)	1.62 (0.41, 2.84)	4.85 (0.41, 9.50)	-	-
All respiratory hospital admissions, elderly (65 + years)						
Visibility	0/1	0/1 (4)	1.42 (0.79, 2.06)	1.21 (0.47, 1.95)	-	-
Cardiac hospital admissions, elderly						
Visibility	0/1	0/1 (4)	1.21 (0.84, 1.58)	0.73 (0.31, 1.16)	-	-

See Table 2 for footnotes
* The results for visibility (measured as black suspended particles ($10^{-4}.m^{-1}$)) are not comparable to other PM results.

NO_2 and mortality from specific causes

NO_2 estimates adjusted for PM were available for several specific causes of death in all ages: all cardiovascular (Figures S3 and S4), all respiratory (Figure S5), stroke (Figure S6), cardiac (Figure S7), ischaemic heart disease, dysrhythmia, chronic obstructive pulmonary disease including asthma, and lower respiratory infections (Figure S8). Sufficient numbers of estimates for meta-analysis were available for all cardiovascular (Table S3), all respiratory (Table S4), and stroke (Table S5) mortality.

Eight studies providing 14 pairs of estimates showed positive associations between all cardiovascular deaths and 24 hour NO_2 including after adjustment mainly for PM_{10} (Figure S3). However, attenuation of estimates and loss of statistical significance was observed in the few studies with control for $PM_{2.5}$ or Black Smoke. Meta-analysis of 10 pairs of estimates found a 1.07% (95% CI: 0.43, 1.72) increase in the risk of death from all cardiovascular diseases per 10 $\mu g/m^3$ increase in 24 hour NO_2 (Table S3 and Figure S9). This was attenuated (0.82% (95% CI 0.22, 1.42)) Table S3) following adjustment for PM, but comparable to our earlier result (0.88% (95% CI: 0.63, 1.13)).[12] Control of the NO_2-association with all cardiovascular mortality for specific PM metrics showed an association which was robust to adjustment for PM_{10} (Table 2). There were too few estimates to permit meta-analysis for other PM metrics controlled for in the studies. The available data for 1 hour NO_2 and all cardiovascular mortality was sparse and limited to two studies representing 29 European cities which showed positive NO_2-associations that were robust to adjustment for both PM_{10} and Black Smoke (Table 3 and Figure S4).

Evidence for all respiratory mortality and 24 hour NO_2 adjusted for PM came from six cities (Figure S5). Meta-analysis produced a 1.42% (95% CI: 0.64, 2.21) increased risk of all respiratory deaths per 10 $\mu g/m^3$ increase in 24 hour NO_2 (Table S4 and Figure S10). The corresponding estimate adjusted for particles was attenuated (1.13% (95% CI: 0.46, 1.81)) but was comparable with the single-pollutant estimate (1.09% (95% CI: 0.75, 1.42)) derived from the larger body of time-series evidence examined in our previous paper.[12] There was no evidence of heterogeneity (I^2=0%) between the geographic specific estimates either before or after adjustment for PM (Table S4). Evidence for associations between all respiratory mortality and 1 hour NO_2 came solely from the multi-city APHEA II study of 29 European cities,[19] which showed a positive association that was robust to adjustment for PM_{10} but not Black Smoke (Table 3).

PM and mortality

Meta-analyses were undertaken separately for PM adjusted for the different averaging times of NO_2 to allow comparison with the relevant meta-analyses for NO_2 using data from the same studies, cities and time periods. Figure 2 shows positive, single-pollutant associations between various mass metrics of PM and all-cause mortality. In the majority of studies, attenuation of estimates was observed following control for 24 hour NO_2. Estimates for ultrafine particles and all-cause mortality were robust to adjustment for 24 hour NO_2 (Figure S11), but the data came

from three studies conducted in the same city, Erfurt, Germany. Results of meta-analysis for all-cause mortality and PM metrics are shown in Tables 2 and 3 for adjustment for 24 hour and 1 hour NO_2, respectively. In contrast to the results for NO_2, the summary estimates for PM were attenuated, in most cases by more than half and confidence intervals overlapped zero. Evidence of high heterogeneity between region-specific summary estimates for PM_{10} and all-cause mortality was identified (Table S6). Summary estimates for deaths from all cardiovascular or all respiratory diseases and PM were also sensitive to control for NO_2 (Tables 2 and 3; study estimates in Figures S12-S13; Tables S7 and S8 for region-specific results).

NO_2 and hospital admissions

Few cause- and age-specific combinations of hospital admissions for 24 hour or 1 hour NO_2 with control for PM had sufficient numbers of estimates for meta-analysis - all respiratory diseases in children and the elderly, asthma in children, and cardiac disease in all ages and the elderly - and half were based solely on a multi-city estimate from a single study.

Positive associations were identified between all respiratory hospital admissions in different age groups and 24 hour or 1 hour NO_2, which remained after control for PM (Tables 2 and 3; Figures S14-S15 for available study estimates).

Evidence for the association between hospitalisation for asthma in different ages and daily NO_2 adjusted for PM came from seven studies (Figures S16-S17), six of which were conducted in Europe. Sufficient estimates for meta-analysis were only available for asthma admissions in children and 24 hour NO_2 adjusted for any particles (measured as Black Smoke, PM_{10} and PNC): a 2.81% (95% CI: -1.28, 7.06) increase in risk per 10 $\mu g/m^3$ 24 hour NO_2 was attenuated following adjustment for particles (2.24% (95% CI: -1.12, 5.71)).

Five studies provided evidence for the relationship between 24 hour NO_2 adjusted for PM and hospitalisation for cardiac disease in all ages (Figure S18) and the elderly (Figure S19). Meta-analysis for the all age category (Table 2) identified positive estimates which were attenuated and confidence intervals overlapped zero after control for PM_{10} and Black Smoke. One multi-city study of four Australian cities provided evidence for the relationship between 1 hour NO_2 and cardiac admissions in the elderly. The association (1.21% (95% CI: 0.84, 1.58)) was weakened by control for BSP (an indicator of fine particles), but remained statistically significant (0.73% (95% CI: 0.31, 1.16)).

Sources of variation in NO_2 estimates

We examined season-specific NO_2 estimates of mortality from studies which reported all-year estimates to explore possible effect modification by season. Some studies, mainly from Western Europe, Canada and the USA, reported stronger associations between daily mortality and NO_2 in the summer months (Figure S20-S22). The extent of the correlations between concentrations of NO_2 and PM in the different seasons is unclear because very few studies reported these data,

and only one study reported season-specific estimates adjusted for PM. Similarly, limited evidence is available on which to base an assessment of seasonal variation of associations between hospitalisation for cardiovascular and respiratory diseases and 24 hour NO_2 (Figure S23).

We explored reasons for the observed high heterogeneity by ranking study estimates for all-cause mortality and 24 hour NO_2 (from the full dataset)[12] by different potential effect modifiers (Figures S24-S27). None of the variables used to represent the pollution and meteorological environments in the cities examined accounted for the observed between-study variability.

DISCUSSION

Sixty time-series studies of NO_2 were used to determine whether NO_2 is associated with daily mortality or hospital admissions independently of daily PM. In general, our results demonstrate that after controlling for PM, daily NO_2 remained significantly associated with increases in the risk of adverse health outcomes. The evidence appears clearest for daily deaths from all-causes and from all cardiovascular and all respiratory diseases, and for all respiratory hospital admissions, outcomes for which more co-pollutant estimates were available. Robustness of the NO_2-associations to control for PM was observed at both high and low correlations between NO_2 and PM, and no clear relationship could be discerned between the correlations and changes in the size of the adjusted NO_2 estimates. In contrast to the results for NO_2, the associations between daily PM and the main mortality outcomes (all-cause, all cardiovascular, all respiratory) were very sensitive to the inclusion of NO_2 in two-pollutant models.

Two/multi-pollutant models are increasingly being used to draw conclusions about whether or not NO_2 is independently associated with adverse health outcomes. This comprehensive review provides systematic evaluation and formal meta-analysis of the full body of two-pollutant estimates of NO_2 adjusted for PM, across several cause- and age-specific health outcomes, both globally and by different geographical regions. Whilst earlier reviews[7-8, 13, 20-23] included some assessment of these data, they were either limited in scope to specific health outcomes and/or examined together two- and multi-pollutant model NO_2 estimates, or did not undertake meta-analysis whatsoever. Another key strength of this review is the protocol-led approach to identifying and assembling studies and estimates, which aimed to minimise selection bias in the different stages of the review.

The subset of studies of NO_2 analysed in this paper were generally comparable to the studies examined in our earlier paper in terms of the magnitudes of summary estimates and overlap in confidence intervals.[12] For example, the single-pollutant summary estimates for all-cause mortality, the outcome with the most data, were similar across both datasets, suggesting that the studies reporting two-pollutant model estimates were typical of the wider body of time-series evidence of NO_2.

Whilst evidence of NO_2-associations which are robust to control for PM mass have been identified, it is possible that there may be some residual confounding by PM. The components of PM - primary combustion particles, for example ultrafine particles or Black Carbon - which have been proposed as the real causal agents of the NO_2-associations were not included in co-pollutant models of NO_2 because concentration data for these pollutants were either unavailable or sparse, reflecting the fact that these PM metrics are not routinely measured. PM_{10} was by far the most used metric - in 67% of the studies. Summary estimates of NO_2 were generally robust to adjustment for PM_{10}. However, PM_{10} may not adequately reflect the toxic component of PM because it reflects a number of sources, which do not include combustion / traffic, that are not shared with NO_2. Where the data permitted meta-analysis, robustness of the NO_2 associations to adjustment for $PM_{2.5}$ and Black Smoke was observed. Few data were available to permit an assessment of the extent to which the NO_2-associations are sensitive to control for combustion derived particles such as Black Carbon or ultrafine particles. This has also been noted by others.[7-8,24]

Given that the sources and composition of PM vary by location, and hence its toxicity, it cannot be assumed that PM represents the same thing in each study (city/country). In view of the differential toxicity of PM, it is preferable to examine individual studies that used more than one particle metric to investigate possible confounding of the NO_2 associations by PM when answering the research question, because they 'tested' the robustness of the NO_2-associations to different fractions / components of the ambient aerosol in the same location. Unfortunately, such studies were few in number (8), but their findings support the view that the associations of NO_2 with major health outcomes are robust to adjustment for PM measured in different ways.

We observed confounding of the associations between daily PM and mortality outcomes by NO_2. This suggests that NO_2, rather than the PM metrics examined, is a better predictor of the observed mortality effects in the cities examined. An alternative interpretation may be that daily variation in NO_2 in the cities better represents the mortality effects of daily variations in the complex urban air pollution mixture or an unknown toxic entity than the metrics of PM used in the analyses. Some caution is however needed in drawing conclusions about the analysis of PM estimates because it only reflects a subset of the available studies on PM. Whether the results are a feature of the subset of studies examined is unclear, and formal meta-analysis of the full body of PM estimates, similar to the current review, is warranted. This may provide further insights into whether the different fractions/component of PM might show different sensitivity to adjustment for NO_2.

Our results for PM are in contrast to the predominant views in the literature: although confounding of the PM-mortality associations by NO_2 has been observed in some time-series studies[19, 25-26] and noted in reviews[6], the general consensus is that the PM-mortality estimates are robust to adjustment for co-pollutants[6]. The associations have been regarded as reflecting a causal relationship, and experimental evidence has been used to support this. There is a lack of

experimental evidence for NO_2 at current ambient concentrations and for cardiovascular endpoints, and this has contributed to uncertainty regarding whether NO_2 is causally related to health.

We also found evidence of high heterogeneity between the geographic specific summary estimates of NO_2, which suggests that it cannot be assumed that the results for one city (region) represent the results for all cities (regions). For all-cause mortality and 24 hour NO_2, the high heterogeneity between WHO region-specific estimates was completely removed after control for PM (I^2 from 66.9% to 0%), suggesting that some study estimates were a bit extreme in comparison with others in the meta-analysis, but were less so after adjustment for PM. Geographical variation in effect estimates may be due to variations in population characteristics and in pollution sources, mixtures, and ambient concentrations. However, none of the variables used to represent the pollution and meteorological environments in the cities examined accounted for the high between-study variability we observed. Further work is therefore required to investigate potential explanations for the heterogeneity.

In addition to the issue of confounding, studies have examined the potential for factors (for example, season, socio-economic status, age, etc.) to modify the relationship between daily NO_2 and mortality or hospital admissions. Few studies have however examined modification of the associations of NO_2 with health by particulate air pollution. The available evidence suggests that the size of an NO_2 association may be dependent on concentrations of PM_{10}.[19] However, studies have also observed the potential for daily NO_2 to modify the relationship between PM and mortality.[33] The few available data on this issue come largely from the US and Europe, but interaction between NO_2 and PM (on cardiac hospitalisation) has also been observed in Hong Kong.[34] Further research on this aspect of the NO_2-PM issue is needed.

Our review supports the conclusions of recent narrative reviews,[7-8] but also provides meta-analytical estimates based on two-pollutant model estimates of NO_2 from the worldwide data. Taken together with the recent quantitative reviews of cohort studies on long-term exposure to NO_2 and mortality[27-28] and of short-term exposure to NO_2 and respiratory symptoms in children with asthma from panel studies,[8, 29] the evidence suggests a need for re-evaluation of the approach to health risk assessment (hazard identification and health impact assessment) for air pollution, an activity which has long been dominated by PM.[30] The current review suggests that the relationship between temporal variations in PM and mortality may not be as robust to control for NO_2 as previously thought. We note also that attenuation of PM-mortality estimates following control for NO_2 has been observed in long-term exposure studies.[31-32] These findings could have implications for the calculation of health impacts attributable to these pollutants and for possible double counting of effects.

In summary, we identified evidence of associations between NO_2 and adverse health outcomes that are independent of PM mass. However, there was limited evidence on adjustment of the

NO_2-associations for primary combustion particles which are thought to be responsible for the NO_2-associations. Therefore, some uncertainty remains regarding possible confounding and health impact assessments should reflect this.

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CONTRIBUTORS: All authors (ICM, RWA, HRA, RM, DS) contributed to the design of the study, to the drafting of the paper and have seen and approved the final version.
Two authors of the review – ICM and RWA – undertook the literature search.
ICM read all papers, checked data prior to meta-analysis, and carried out all analyses.
RWA produced the statistical code in STATA used by ICM in the analyses.
ICM is responsible for the overall content as lead author of the paper.

DATA SHARING STATEMENT: No additional data are available.

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Legend (and footnotes) to Figures

Figure 1: All available studies providing two-pollutant model estimates for meta-analysis for all-cause mortality, all ages, 24 hour NO_2

Footnotes to Figure 1

1000xln(RR) approximates to a percentage change per 10 μg/m^3
* Single-pollutant model estimate for days with both NO_2 and visibility (Coefficient of Haze, COH) data in Burnett et al, 2004 [RMID 3000].

Figure 2: All studies providing two-pollutant model estimates for all-cause mortality, all ages, PM adjusted for 24 hour NO_2

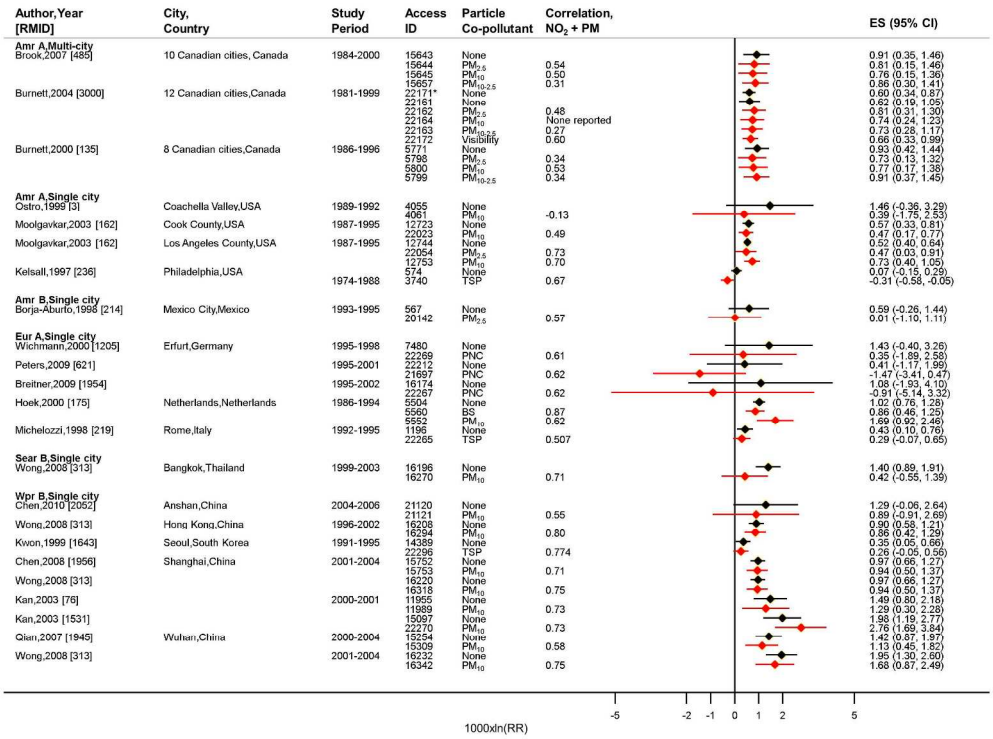


Figure 1: All available studies providing two-pollutant model estimates for meta-analysis for all-cause mortality, all ages, 24 hour NO2
485x359mm (300 x 300 DPI)

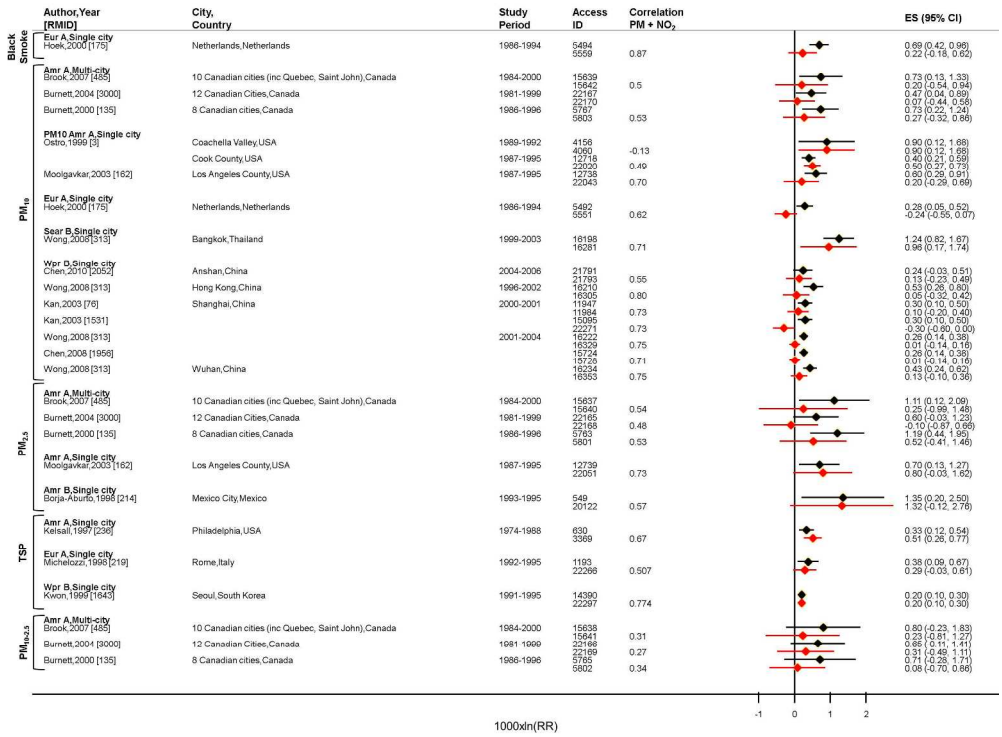


Figure 2: All studies providing two-pollutant model estimates for all-cause mortality, all ages, PM adjusted for 24 hour NO2
483x367mm (300 x 300 DPI)

Distinguishing the associations of short-term exposure to outdoor nitrogen dioxide with mortality and hospital admissions from those of particulate matter

IC Mills, RW Atkinson, HR Anderson, RL Maynard, DP Strachan

Online Supplementary Material

Contents list

5. List of figures

6. List of references included in the review

Literature search criteria

Bibliographic databases were searched to identify peer-reviewed time-series (and case-crossover) studies of the relationship between daily concentrations of NO_2 and daily mortality or hospital admissions.

Bibliographic databases searched: PubMed, EMBASE or Web of Science (which includes the Science Citation Index).

The search terms used are shown below and minor refinements were made for use in each bibliographic database.

> (air pollution OR pollution OR nitric oxide* OR nitrogen dioxide?) AND (timeseries OR time series OR time-series OR daily OR case-crossover) AND (mortality OR death* OR dying OR hospital admission* OR admission* OR emergency room OR visit* OR attendance* OR 'a&e' OR 'a and e' OR accident and emergency OR general pract* OR physician* OR consultation* OR emergency department*)

No restriction on language was applied. The bibliographic databases were searched for peer-reviewed papers published up to May 2011.

List of countries by WHO Region and mortality strata

Reproduced from The World Health Report 2002 (http://www.who.int/whr/2002/en/, accessed 7th February 2015)

African Region

Algeria — AFR-D
Angola – AFR-D
Benin – AFR-D
Botswana – AFR-E
Burkina Faso – AFR-D
Burundi – AFR-E
Cameroon – AFR-D
Cape Verde – AFR-D
Central African Republic – AFR-E
Chad – AFR-D
Comoros – AFR-D
Congo – AFR-E
Côte d'Ivoire – AFR-E
Democratic Republic of the Congo – AFR-E
Equatorial Guinea – AFR-D
Eritrea – AFR-E
Ethiopia – AFR-E
Gabon – AFR-D
Gambia – AFR-D
Ghana – AFR-D
Guinea – AFR-D
Guinea-Bissau – AFR-D
Kenya – AFR-E
Lesotho – AFR-E
Liberia – AFR-D
Madagascar – AFR-D
Malawi – AFR-E
Mali – AFR-D
Mauritania – AFR-D
Mauritius – AFR-D
Mozambique – AFR-E
Namibia – AFR-E
Niger – AFR-D
Nigeria – AFR-D
Rwanda – AFR-E
Sao Tome and Principe – AFR-D
Senegal – AFR-D
Seychelles – AFR-D
Sierra Leone – AFR-D
South Africa – AFR-E
Swaziland – AFR-E
Togo – AFR-D
Uganda – AFR-E
United Republic of Tanzania – AFR-E
Zambia – AFR-E
Zimbabwe – AFR-E

Region of the Americas

Antigua and Barbuda – AMR-B
Argentina – AMR-B
Bahamas – AMR-B
Barbados – AMR-B
Belize – AMR-B
Bolivia – AMR-D
Brazil – AMR-B
Canada – AMR-A
Chile – AMR-B
Colombia – AMR-B
Costa Rica – AMR-B
Cuba – AMR-A
Dominica – AMR-B
Dominican Republic – AMR-B
Ecuador – AMR-D
El Salvador – AMR-B
Grenada – AMR-B
Guatemala – AMR-D
Guyana – AMR-B
Haiti – AMR-D
Honduras – AMR-B
Jamaica – AMR-B
Mexico – AMR-B
Nicaragua – AMR-D
Panama – AMR-B
Paraguay – AMR-B
Peru – AMR-D
Saint Kitts and Nevis – AMR-B
Saint Lucia – AMR-B
Saint Vincent and the Grenadines – AMR-B
Suriname – AMR-B
Trinidad and Tobago – AMR-B
United States of America – AMR-A
Uruguay – AMR-B
Venezuela, Bolivarian Republic of – AMR-B

Eastern Mediterranean Region

Afghanistan – EMR-D
Bahrain – EMR-B
Cyprus – EMR-B
Djibouti – EMR-D
Egypt – EMR-D
Iran, Islamic Republic of – EMR-B
Iraq – EMR-D
Jordan – EMR-B
Kuwait – EMR-B
Lebanon – EMR-B
Libyan Arab Jamahiriya – EMR-B
Morocco – EMR-D
Oman – EMR-B
Pakistan – EMR-D
Qatar – EMR-B
Saudi Arabia – EMR-B
Somalia – EMR-D
Sudan – EMR-D
Syrian Arab Republic – EMR-B
Tunisia – EMR-B
United Arab Emirates – EMR-B
Yemen – EMR-D

Mortality strata
A. Very low child, very low adult
B. Low child, low adult
C. Low child, high adult
D. High child, high adult
E. High child, very high adult

European Region

Albania – EUR-B
Andorra – EUR-A
Armenia – EUR-B
Austria – EUR-A
Azerbaijan – EUR-B
Belarus – EUR-C
Belgium – EUR-A
Bosnia and Herzegovina – EUR-B
Bulgaria – EUR-B
Croatia – EUR-A
Czech Republic – EUR-A
Denmark – EUR-A
Estonia – EUR-C
Finland – EUR-A
France – EUR-A
Georgia – EUR-B
Germany – EUR-A
Greece – EUR-A
Hungary – EUR-C
Iceland – EUR-A
Ireland – EUR-A
Israel – EUR-A
Italy – EUR-A
Kazakhstan – EUR-C
Kyrgyzstan – EUR-B
Latvia – EUR-C
Lithuania – EUR-C
Luxembourg – EUR-A
Malta – EUR-A
Monaco – EUR-A
Netherlands – EUR-A
Norway – EUR-A
Poland – EUR-B
Portugal – EUR-A
Republic of Moldova – EUR-C
Romania – EUR-B
Russian Federation – EUR-C
San Marino – EUR-A
Slovakia – EUR-B
Slovenia – EUR-A
Spain – EUR-A
Sweden – EUR-A
Switzerland – EUR-A
Tajikistan – EUR-B
The former Yugoslav Republic of Macedonia – EUR-B
Turkey – EUR-B
Turkmenistan – EUR-B
Ukraine – EUR-C
United Kingdom – EUR-A
Uzbekistan – EUR-B
Yugoslavia – EUR-B

South-East Asia Region

Bangladesh – SEAR-D
Bhutan – SEAR-D
Democratic People's Republic of Korea – SEAR-D
India – SEAR-D
Indonesia – SEAR-B
Maldives – SEAR-D
Myanmar – SEAR-D
Nepal – SEAR-D
Sri Lanka – SEAR-B
Thailand – SEAR-B

Western Pacific Region

Australia – WPR-A
Brunei Darussalam – WPR-A
Cambodia – WPR-B
China – WPR-B
Cook Islands – WPR-B
Fiji – WPR-B
Japan – WPR-A
Kiribati – WPR-B
Lao People's Democratic Republic – WPR-B
Malaysia – WPR-B
Marshall Islands – WPR-B
Micronesia, Federated States of – WPR-B
Mongolia – WPR-B
Nauru – WPR-B
New Zealand – WPR-A
Niue – WPR-B
Palau – WPR-B
Papua New Guinea – WPR-B
Philippines – WPR-B
Republic of Korea – WPR-B
Samoa – WPR-B
Singapore – WPR-A
Solomon Islands – WPR-B
Tonga – WPR-B
Tuvalu – WPR-B
Vanuatu – WPR-B
Viet Nam – WPR-B

Metrics of particulate matter (PM) used in two-pollutant model analyses

Category of PM metric	Particulate pollutants which map to category
PM_{10}	PM_7; PM_{10}; PM_{13}; ln(PM_7); ln (PM_{13}); $\sqrt{}$(PM_{10}); ln(PM_{14});
$PM_{2.5}$	$PM_{2.5}$; PM<1; $PM_{0.5}$; Re-suspended Particulate Matter (RSPM); $PM_{2.5\text{-}1}$
$PM_{10\text{-}2.5}$	$PM_{10\text{-}2.5}$
Black Smoke	Black Smoke; ln(BS); sqrt(BS)
Particle Number Concentration (PNC)	10-100nm; PNC; <100nm; Nucleation <30nm; Aitken 30-100nm; Accumulation 100-290nm; NC 0.03-0.05; NC 0.05-0.1; NC 0.01-0.03; NC 0.01-0.1; $PM_{2.5}$ NC; $PM_{2.5\text{-}10}$ NC; PM_{10} NC; PNC size mode 12nm; PNC size mode 23nm; PNC size mode 57nm; PNC size mode 212nm; PNC size mode to 100nm; NC128; NC346; NC total; NC31; 10-100nm surface area
Carbon	Black Carbon (BC); Elemental Carbon (EC); Organic Carbon (OC); $PM_{2.5}$ OC; $PM_{2.5}$ EC; $PM_{2.5}$ OM; Total Carbon;
Total Suspended Particles (TSP)	TSP; ln(TSP); TSP-PM_{10}; PM_{20}; SPM; sqrt(TSP); blackness of TSP filters
Visibility	Coefficient of haze (COH); light scattering ($PM_{2.5}$ indicator = nephelometry measure instead of gravimetric); dry light scattering (PM<1 indicator); bsp ($PM_{2.5}$ indicator = an indicator for particles 01-2 um (nephelometry measure instead of gravimetric)); visibility ($PM_{2.5}$ indicator = digital photography visibility); $PM_{2.5}$ nephelpmetry ($PM_{2.5}$ indicator=(nephelometry measure*100,000-.01)/0.28.)

Table S1: Meta-analysis results for all-cause mortality in all-ages associated with a 10 µg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**29/3**	**5/1 (26)**	**0.78 (0.47, 1.09)**		**0.60 (0.33, 0.87)**	
AMR A	12/3	4/1 (16)	0.48 (0.24, 0.72)		0.55 (0.12, 0.99)	
AMR B	1/0	1/0 (1)	0.59 (-0.26, 1.45)	66.9	0.01 (-1.10, 1.12)	0
EUR A	6/0	3/0 (3)	0.71 (0.20, 1.22)		0.43 (-0.86, 1.73)	
SEAR B	1/0	1/0 (1)	1.41 (0.89, 1.93)		0.42 (-0.55, 1.40)	
WPR B	9/0	5/0 (5)	1.00 (0.54, 1.46)		0.85 (0.37, 1.33)	
NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	13/3	4/1 (21)	0.92 (0.58, 1. 72)	88.7	0.85 (0.52, 1.18)	72
NO_2 + $PM_{2.5}$	2/3	2/1 (14)	0.53 (0.42, 0.64)	0	0.57 (0.24, 0.89)	6.9
NO_2 + $PM_{10-2.5}$	0/3	0/1 (12)	0.62 (0.19, 1.06)	-	0.73 (0.28, 1.18)	-
NO_2 + Visibility	0/1	0/1 (12)	0.60 (0.34, 0.87)	-	0.66 (0.33, 1.00)	-
NO_2 + BS	1/0	-				
NO_2 + TSP	3/0	-	Insufficient estimates for meta-analysis			
NO_2 + PNC	3/0	-				

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S2: Meta-analysis results for all-cause mortality in all-ages associated with a 10 µg/m³ increase in 1 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2 single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI) [c]	I^2 (%)[d]	Random Effects (95% CI) [c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**2/4**	**2/2 (36)**	**0.32 (-0.02, 0.66)**		**0.20 (-0.24, 0.65)**	
AMR A	1/0	1/0 (1)	1.19 (0.20, 2.19)	93.8	0.78 (-0.35, 1.92)	95.2
AMR B	1/0	1/0 (1)	-0.09 (-0.19, 0.00)		-0.28 (-0.38, -0.19)	
EUR A	0/3	0/1 (30)	0.30 (0.22, 0.38)		0.27 (0.16, 0.38)	
WPR A	0/1	0/1 (4)	0.63 (0.21, 1.05)		0.52 (0.05, 1.00)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	2/1	2/1 (32)	0.22 (-0.15, 0.60)	95.4	0.10 (-0.40, 0.61)	96.5
NO_2 + BS	0/2	0/1 (30)	0.30 (0.22, 0.38)	-	0.33 (0.23, 0.43)	-
NO_2 + Visibility	0/1	0/1 (4)	0.63 (0.21, 1.05)	-	0.52 (0.05, 1.00)	-

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S3: Meta-analysis results for all cardiovascular mortality in all-ages associated with a 10 μg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI) [c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**13/0**	**5/0 (10)**	**1.07 (0.43, 1.72)**		**0.82 (0.22, 1.42)**	
AMR A	2/0	2/0 (2)	0.52 (0.37, 0.68)		0.47 (0.06, 0.88)	
AMR B	1/0	1/0 (1)	0.73 (-0.87, 2.36)	72	-0.36 (-2.47, 1.81)	58.8
EUR A	3/0	2/0 (2)	1.97 (-0.66, 4.66)		1.81 (0.67, 2.97)	
SEAR B	1/0	1/0 (1)	1.78 (0.47, 3.11)		-0.51 (-2.88, 1.92)	
WPR B	6/0	4/0 (4)	1.37 (0.87, 1.87)		1.13 (0.67, 1.58)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	10/0	4/0 (8)	0.99 (0.49, 1.49)	80.1	0.87 (0.28, 1.46)	61
NO_2 + $PM_{2.5}$	2/0	2/0 (2)	Insufficient estimates for meta-analysis			
NO_2 + BS	2/0	2/0 (2)	Insufficient estimates for meta-analysis			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 μg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S4: Meta-analysis results for all respiratory mortality in all-ages associated with a 10 µg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**8/0**	**3/0 (6)**	**1.42 (0.64, 2.21)**		**1.13 (0.46, 1.81)**	
AMR B	1/0	1/0 (1)	1.21 (-1.43, 3.91)	0	0.61 (-2.83, 4.17)	0
SEAR B	1/0	1/0 (1)	1.05 (-0.60, 2.73)		0.32 (-2.66, 3.39)	
WPR B	6/0	4/0 (4)	1.57 (0.63, 2.51)		1.20 (0.50, 1.90)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	7/0	2/0 (5)	1.44 (0.63, 2.27)	0	1.15 (0.47, 1.84)	0
NO_2 + $PM_{2.5}$	1/0	1/0 (1)	Insufficient estimates for meta-analysis			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S5: Meta-analysis results for stroke mortality in all-ages associated with a 10 µg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**8/0**	**2/0 (5)**	**1.76 (0.68, 2.85)**	25.6	**1.12 (0.50, 1.74)**	0
SEAR B	1/0	1/0 (1)	2.80 (0.70, 4.94)		1.60 (-2.20, 5.55)	
WPR B	7/0	4/0 (4)	1.47 (0.67, 2.27)		1.11 (0.48, 1.74)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	7/0	2/0 (4)	1.83 (0.76, 2.92)	9.3	1.04 (0.36, 1.73)	0
NO_2 + TSP	1/0	1/0 (1)	Insufficient estimates for meta-analysis			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S6: Meta-analysis results for all-cause mortality in all-ages associated with a 10 µg/m³ increase in metrics of Particulate Matter (PM) - estimates adjusted for 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	PM, single-pollutant		PM adjusted for 24 hour NO_2	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
PM_{10}						
Overall[e]	**12/3**	**4/1 (21)**	**0.51 (0.29, 0.74)**	**82.9**	**0.18 (-0.11, 0.47)**	**71.9**
AMR A	3/3	3/1 (15)	0.49 (0.31, 0.66)		0.33 (-0.04, 0.71)	
EUR A	1/0	1/0 (1)	0.28 (0.05, 0.52)		-0.24 (-0.55, 0.07)	
SEAR B	1/0	1/0 (1)	1.25 (0.82, 1.68)		0.96 (0.17, 1.76)	
WPR B	7/0	4/0 (4)	0.35 (0.22, 0.47)		0.05 (-0.06, 0.17)	
$PM_{2.5}$						
Overall[e]	**2/3**	**2/1 (14)**	**0.74 (0.34, 1.14)**	**19.6**	**0.54 (-0.25, 1.34)**	**23.9**
AMR A	1/3	1/1 (13)	0.66 (0.23, 1.08)		0.33 (-0.54, 1.22)	
AMR B	1/0	1/0 (1)	1.36 (0.20, 2.53)		1.33 (-0.12, 2.80)	
$PM_{10-2.5}$	**0/3**	**0/1 (12)**	**0.65 (-0.10, 1.42)**	**-**	**0.31 (-0.49, 1.11)**	**-**
Visibility	**0/1**	**0/1 (12)**	**40.93 (23.39, 60.97)**	**-**	**12.42 (-4.47, 32.29)**	**-**
Black Smoke	**1/0**	**-**	**Insufficient estimates for meta-analysis**			
PNC	**3/0**	**-**				
TSP	**3/0**	**-**				

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the selected estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ increase in 24 hour measures of PM. Estimates presented for 'Overall' and by WHO Region.
d -I^2 statistic for heterogeneity between WHO region-specific effect estimates
e -Estimate numbers for 'Overall' refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
AMR, region of the Americas; Eur, European region; WPR, Western Pacific region; SEAP, South East Asian region.

Table S7: Meta-analysis results for all cardiovascular mortality in all-ages associated with a 10 μg/m³ increase in metrics of Particulate Matter (PM) - estimates adjusted for 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	PM, single-pollutant		PM adjusted for 24 hour NO_2	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
PM_{10}						
Overall[e]	**9/0**	**4/0 (8)**	**0.48 (0.18, 0.78)**	**66.5**	**0.19 (-0.21, 0.59)**	**67.1**
AMR A	2/0	2/0 (2)	0.43 (0.17, 0.70)		0.33 (0.03, 0.62)	
EUR A	1/0	1/0 (1)	0.19 (-0.16, 0.54)		-0.32 (-0.80, 0.17)	
SEAR B	1/0	1/0 (1)	1.90 (0.80, 3.01)		2.27 (0.24, 4.34)	
WPR B	5/0	4/0 (4)	0.48 (0.26, 0.70)		0.22 (-0.09, 0.54)	
$PM_{2.5}$	**2/0**	**-**	**Insufficient estimates for meta-analysis**			
Black Smoke	**1/0**	**-**				

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the selected estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage increase (95% confidence interval) in the risk of death per 10 μg/m³ increase in 24 hour measures of PM. Estimates presented for 'Overall' and by WHO Region.
d -I^2 statistic for heterogeneity between WHO region-specific effect estimates
e -Estimate numbers for 'Overall' refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO Regions.
AMR, region of the Americas; Eur, European region; WPR, Western Pacific region; SEAP, South East Asian region.

Table S8: Meta-analysis results for all respiratory mortality in all-ages associated with a 10 µg/m³ increase in metrics of Particulate Matter (PM) - estimates adjusted for 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	PM, single-pollutant		PM adjusted for 24 hour NO_2	
			Random Effects (95% CI) [c]	I^2 (%)[d]	Random Effects (95% CI) [c]	I^2 (%)[d]
PM_{10}						
Overall[e]	**6/0**	**2/0 (6)**	**0.58 (0.22, 0.93)**	**0**	**0.13 (-0.18, 0.44)**	**0**
SEAR B	1/0	1/0 (1)	1.01 (-0.36, 2.40)		0.79 (-1.70, 3.34)	
WPR B	5/0	4/0 (4)	0.54 (0.17, 0.92)		0.12 (-0.19, 0.43)	
$PM_{2.5}$	**1/0**	**-**	**Insufficient estimates for meta-analysis**			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the selected estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage increase (95% confidence interval) in the risk of death per 10 µg/m³ increase in 24 hour measures of PM. Estimates presented for 'Overall' and by WHO Region.
d -I^2 statistic for heterogeneity between WHO region-specific effect estimates
e -Estimate numbers for 'Overall' refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO Regions.
WPR, Western Pacific region; SEAR, South East Asian region.

Figure S1: Studies and two-pollutant model estimates selected for meta-analysis for all-cause mortality, all ages, 24 hour NO_2

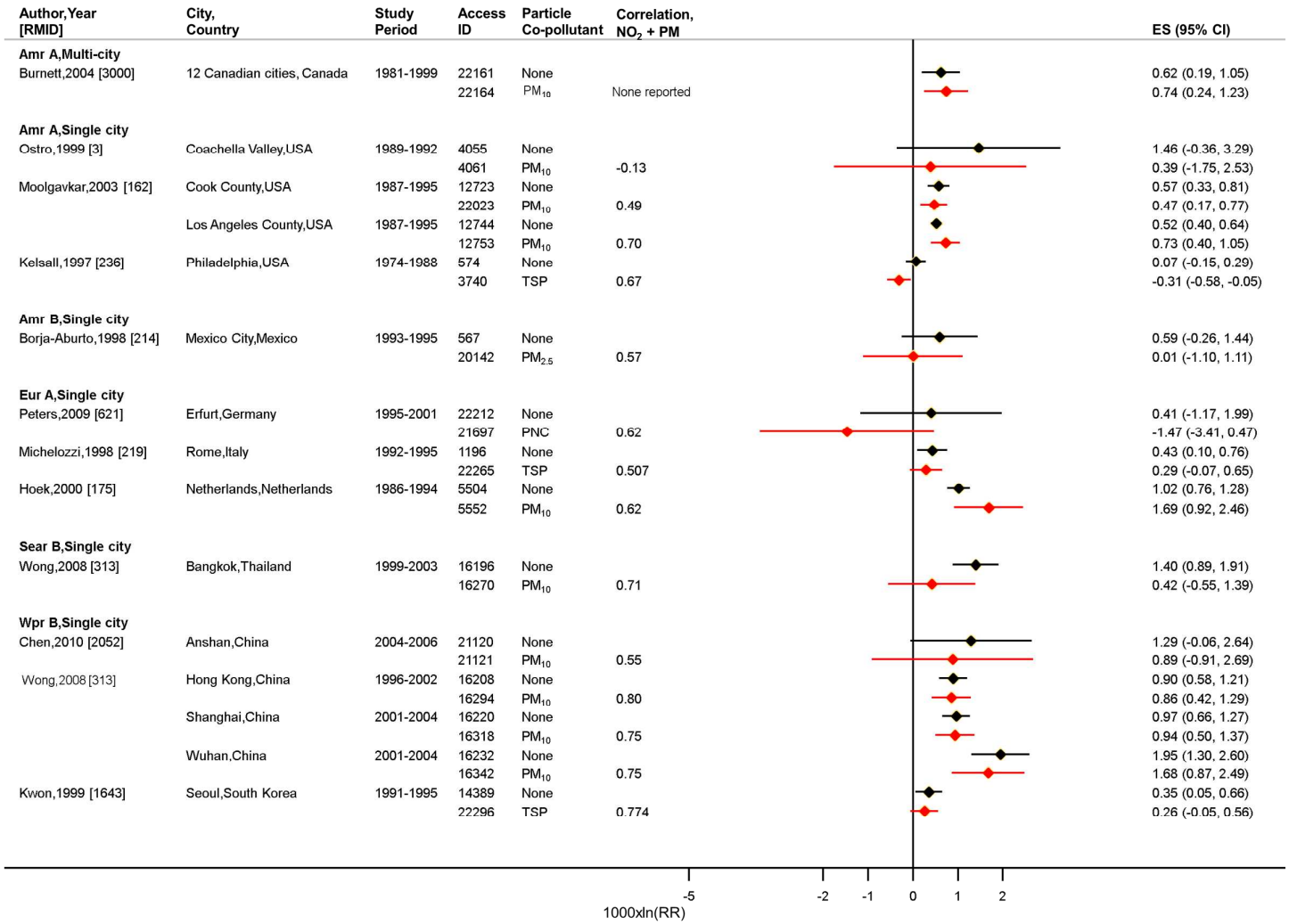


Figure S2: All available studies providing two-pollutant model estimates for meta-analysis for all-cause mortality, all ages, 1 hour NO_2

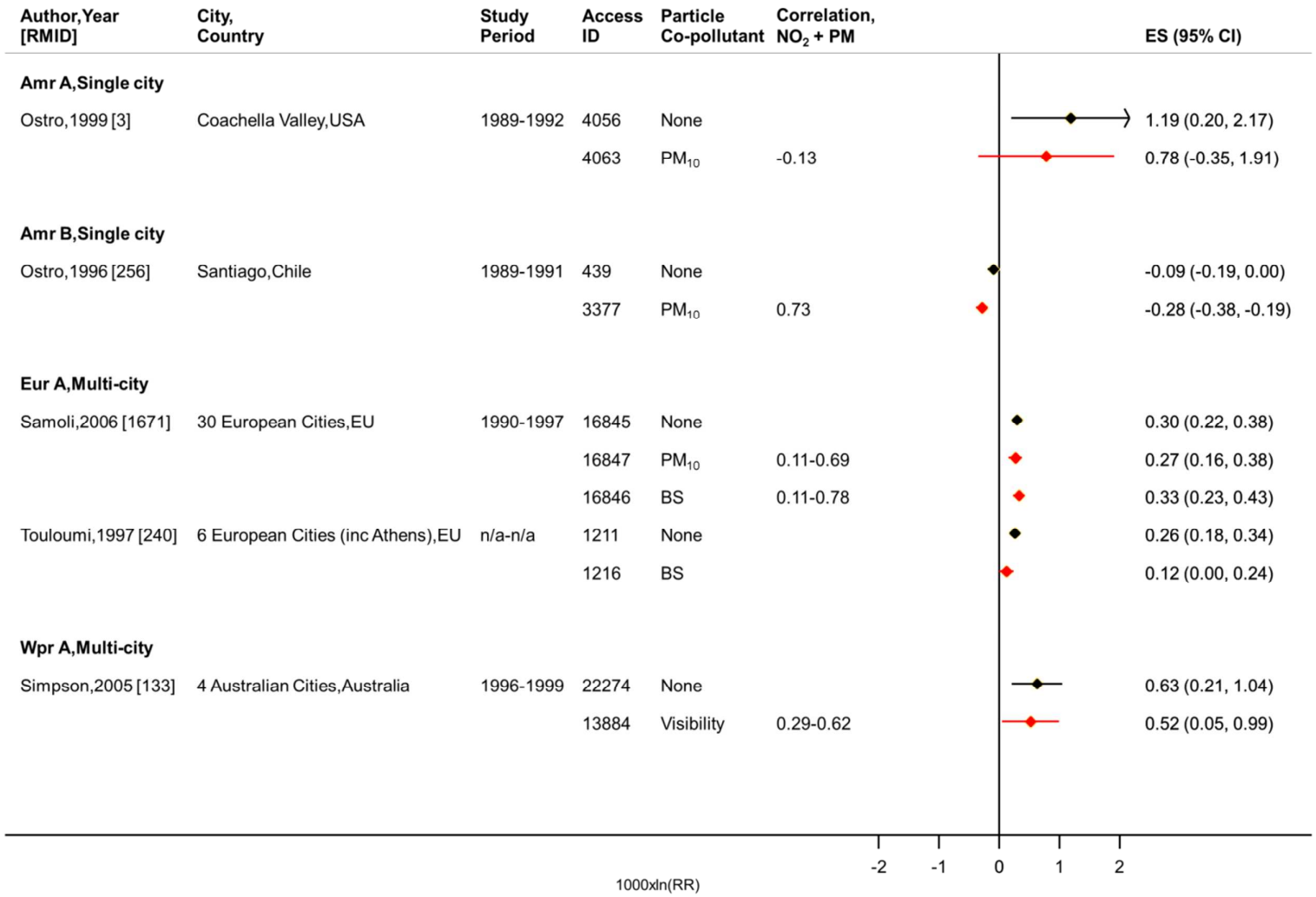


Figure S3: All available studies providing two-pollutant model estimates for meta-analysis for all cardiovascular mortality, all ages, 24 hour NO_2

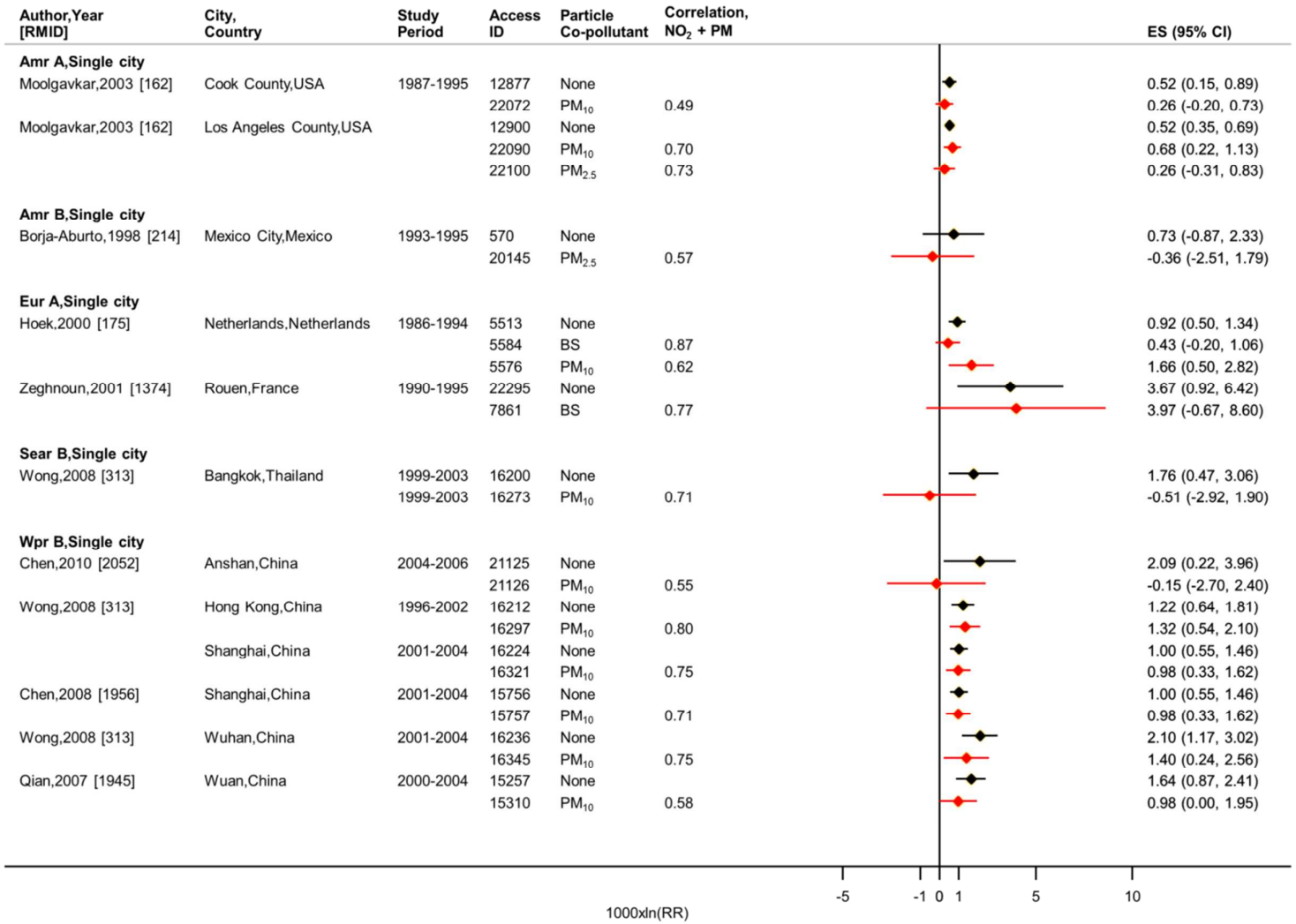


Figure S4: All available studies providing two-pollutant model estimates for meta-analysis for all cardiovascular mortality, all ages, 1 hour NO_2

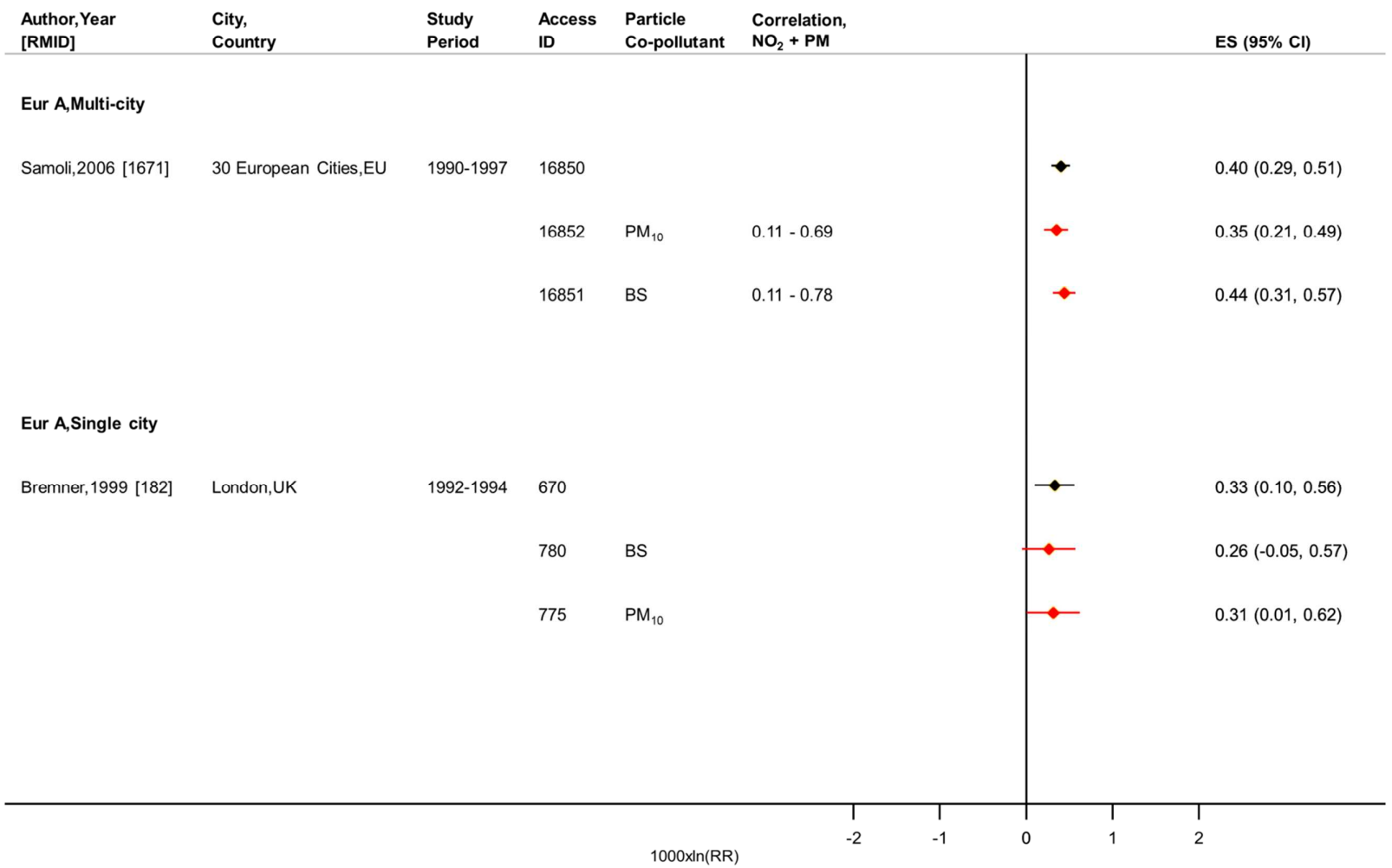


Figure S5: All available studies providing two-pollutant model estimates for meta-analysis for all respiratory mortality, all ages, 24 hour NO_2

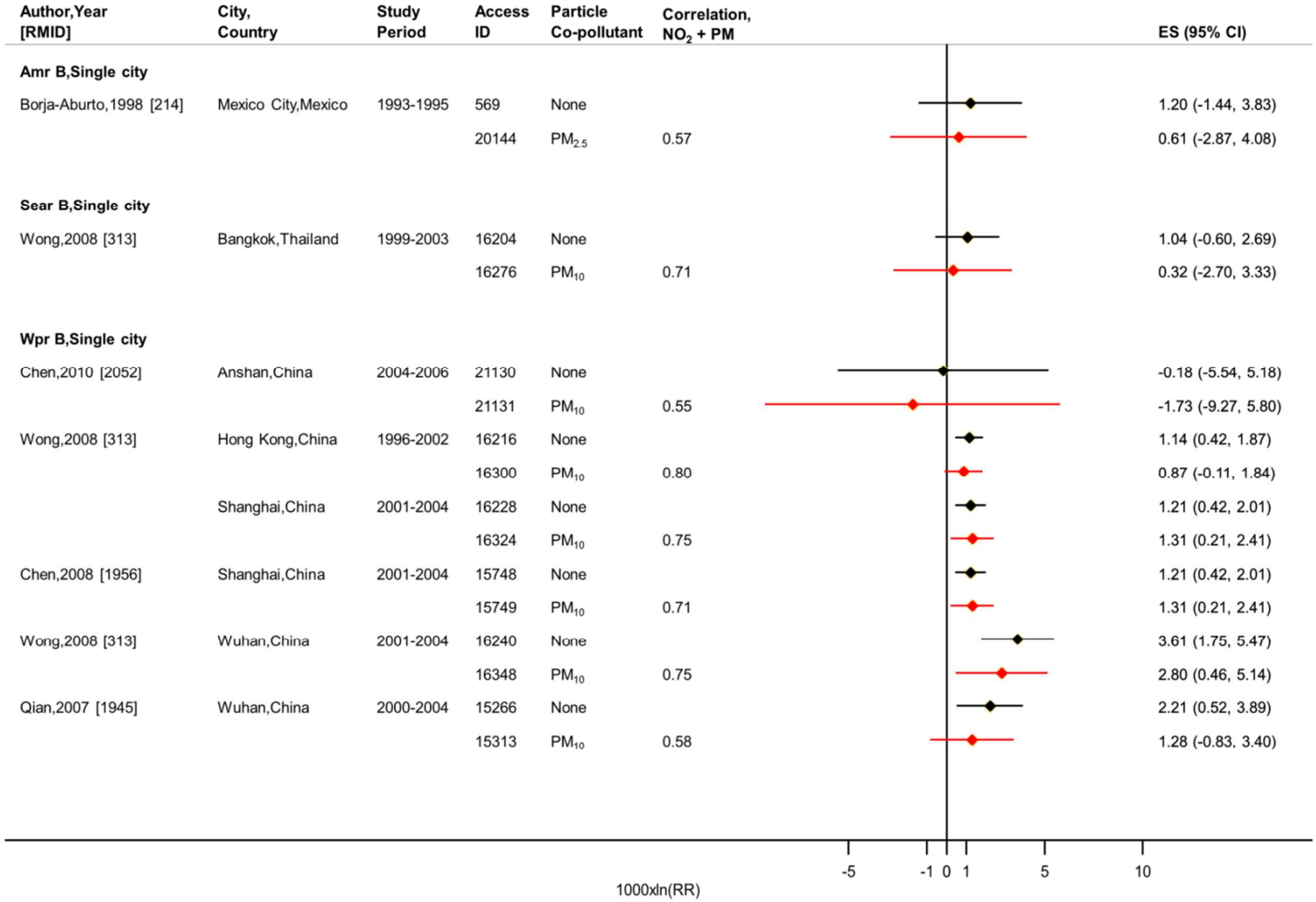


Figure S6: All available studies providing two-pollutant model estimates for meta-analysis for stroke mortality, all ages, 24 hour NO_2

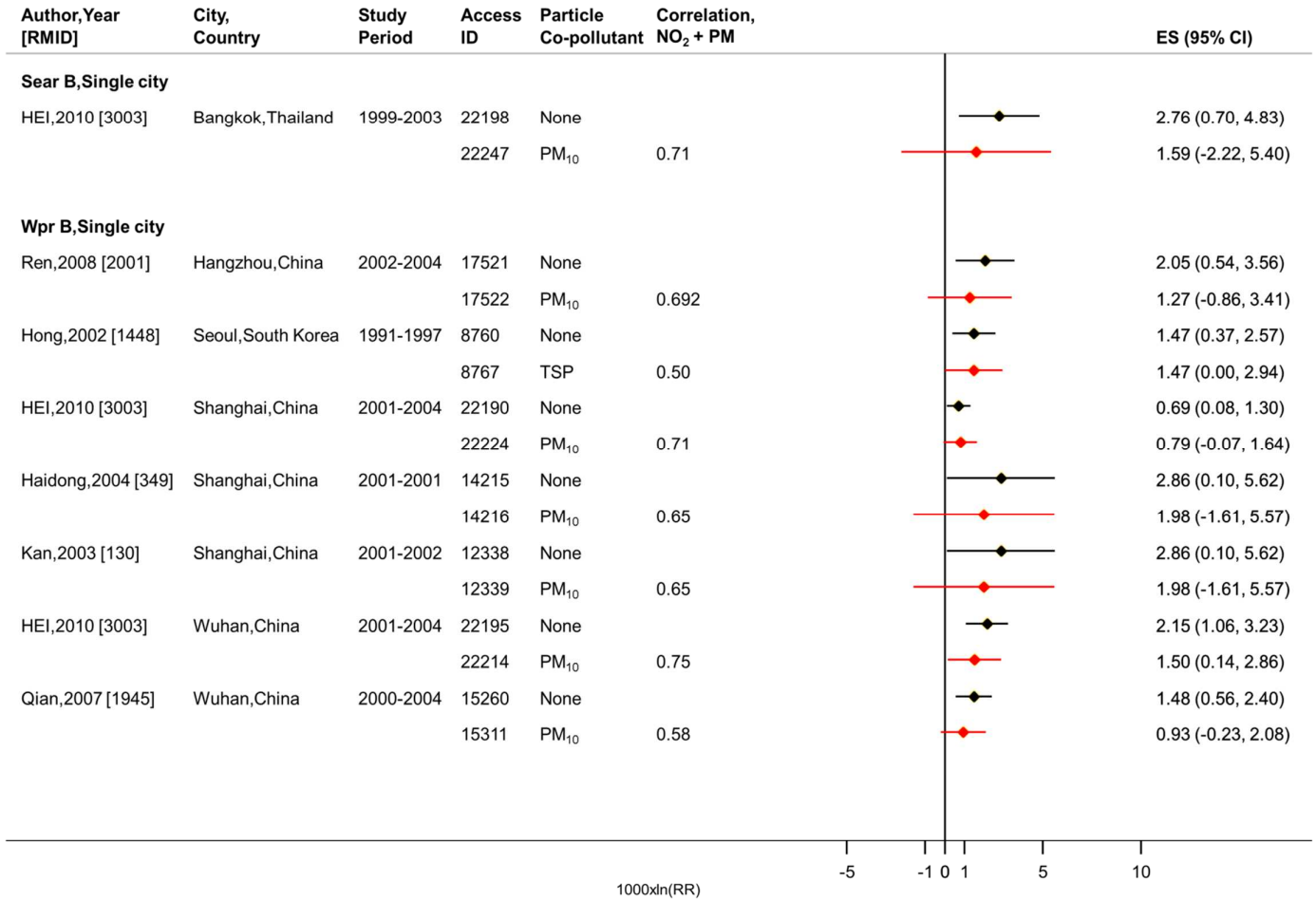


Figure S7: All available studies providing two-pollutant model estimates for meta-analysis for cardiac mortality, all ages, 24 hour NO_2

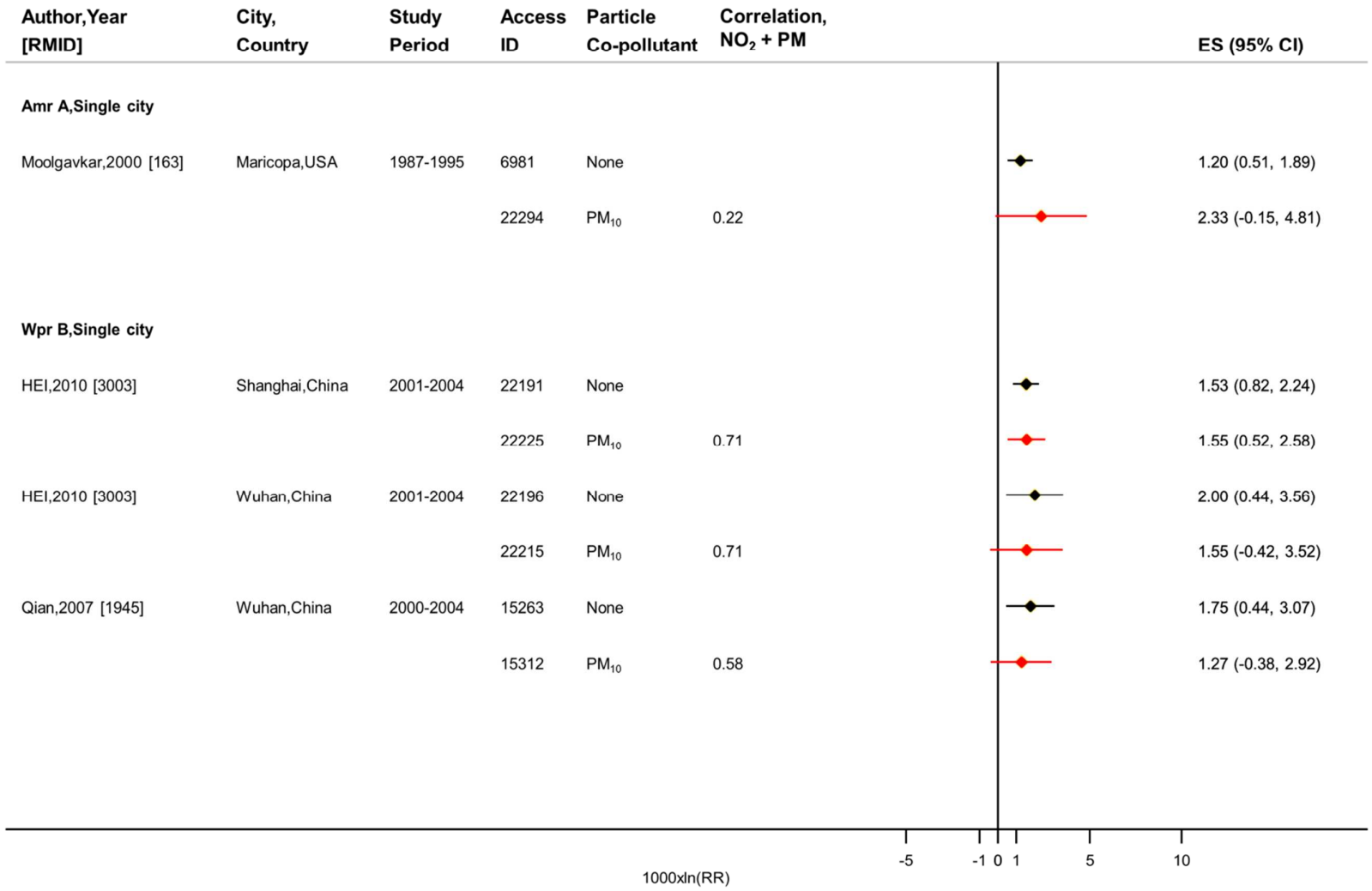


Figure S8: All available studies providing two-pollutant model estimates for meta-analysis for COPD (including asthma), Lower Respiratory Infections (LRI), ischaemic heart disease (IHD), dysrhythmia (DYS) mortality, all ages, 24 hour NO_2

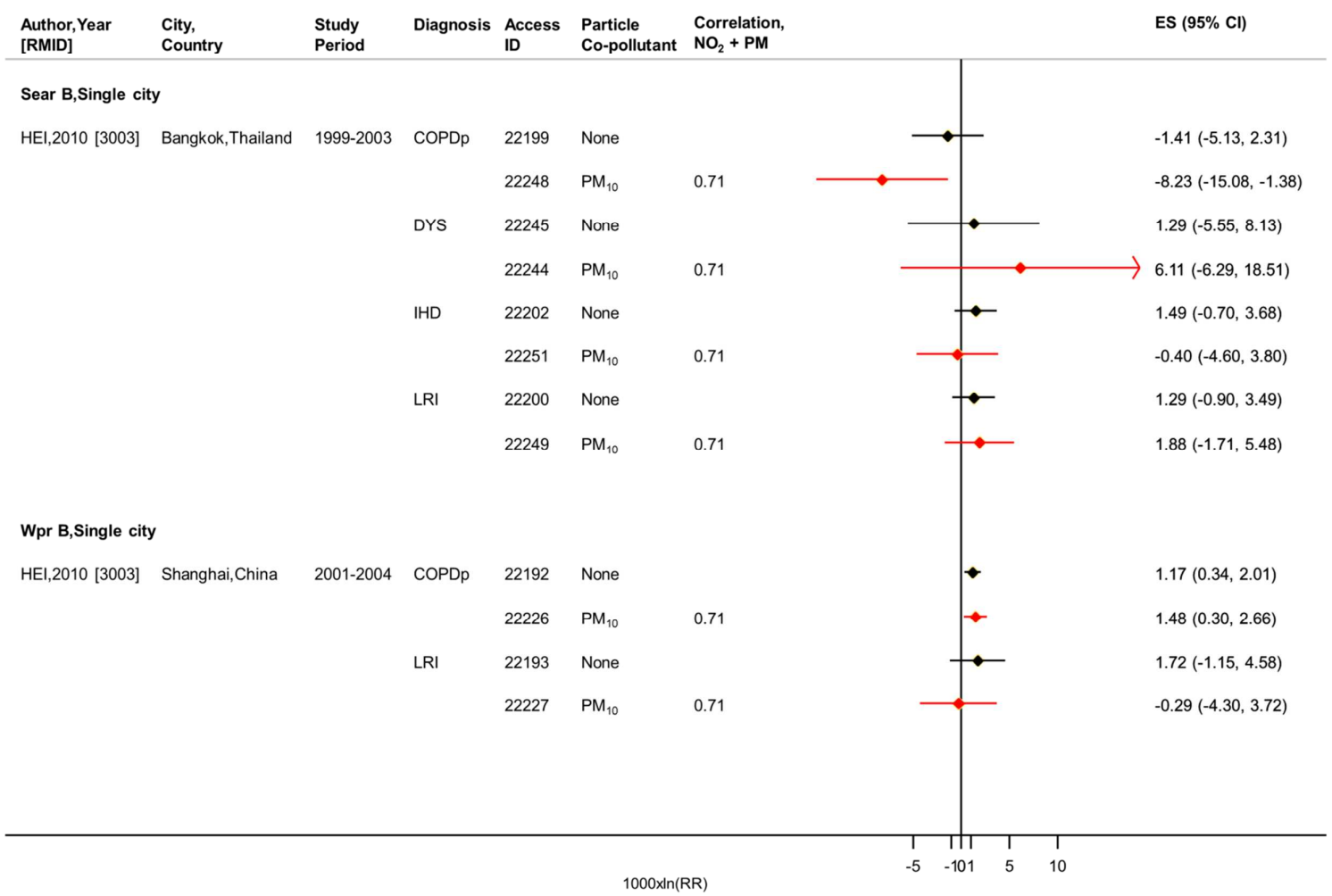


Figure S9: Studies and two-pollutant model estimates selected for meta-analysis for all cardiovascular mortality, all ages, 24 hour NO_2

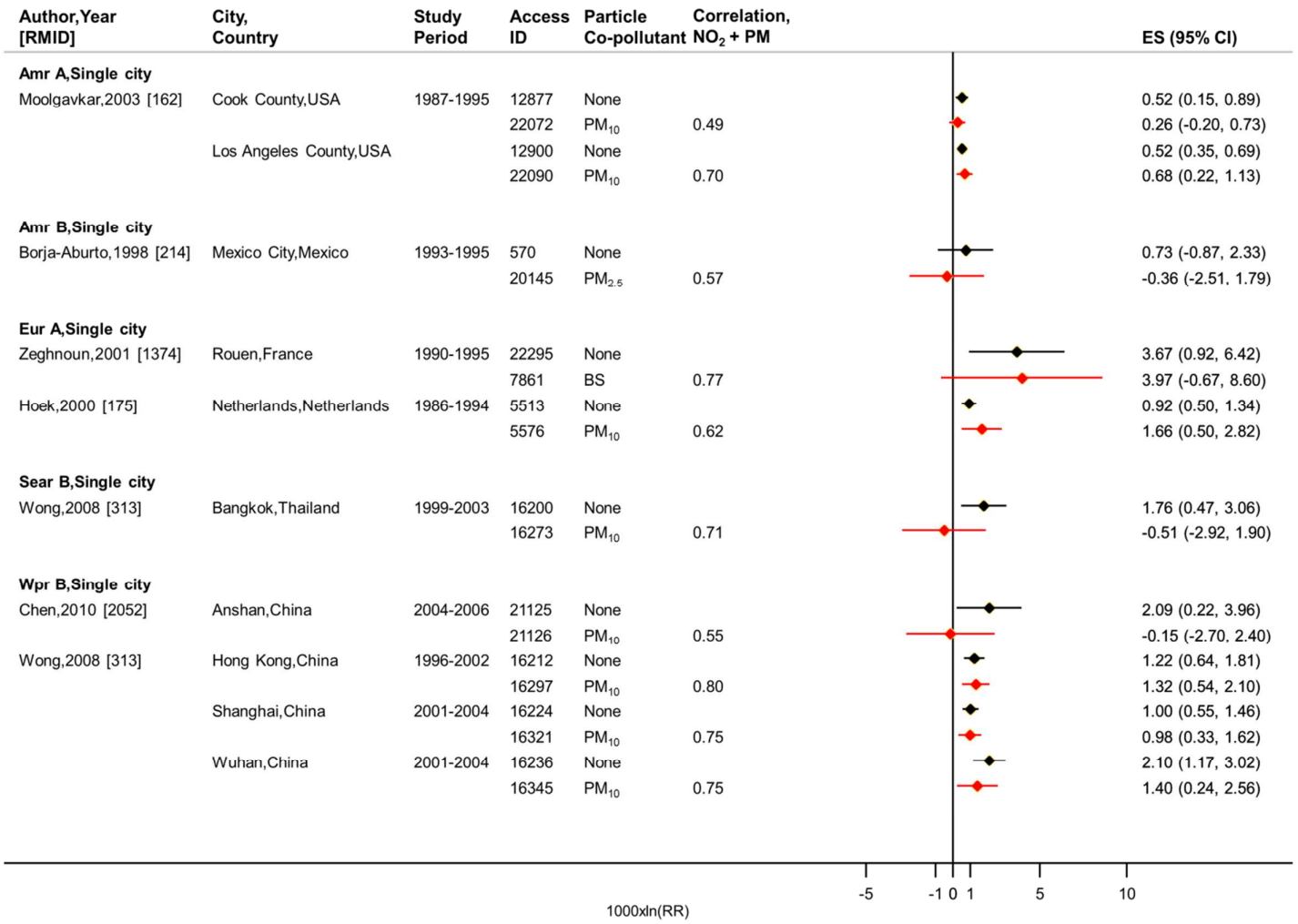


Figure S10: Studies and two-pollutant model estimates selected for meta-analysis for all respiratory mortality, all ages, 24 hour NO_2

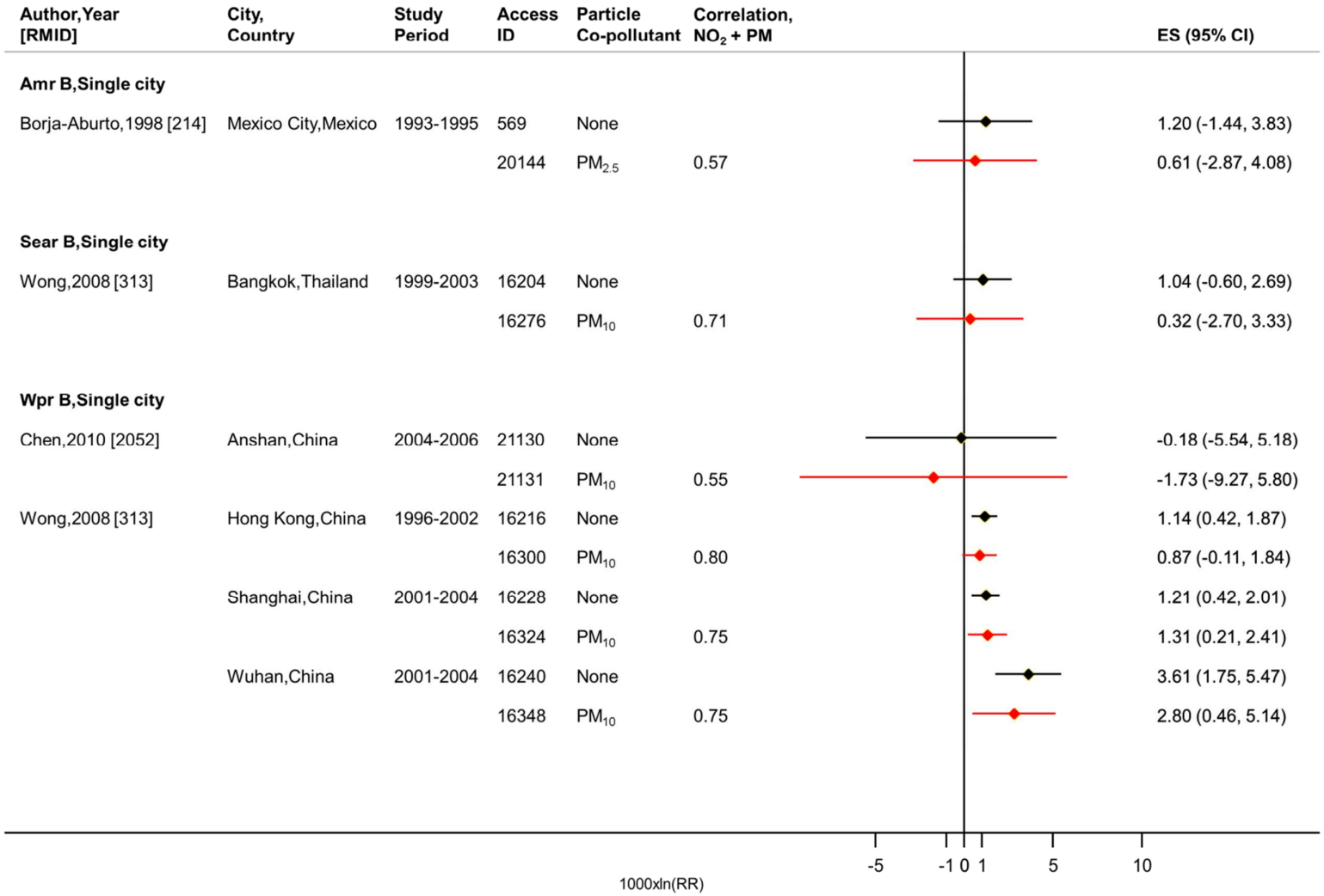


Figure S11: All studies providing two-pollutant model estimates for all-cause mortality, all-ages, ultrafine particles (UFP) adjusted for 24 hour NO_2

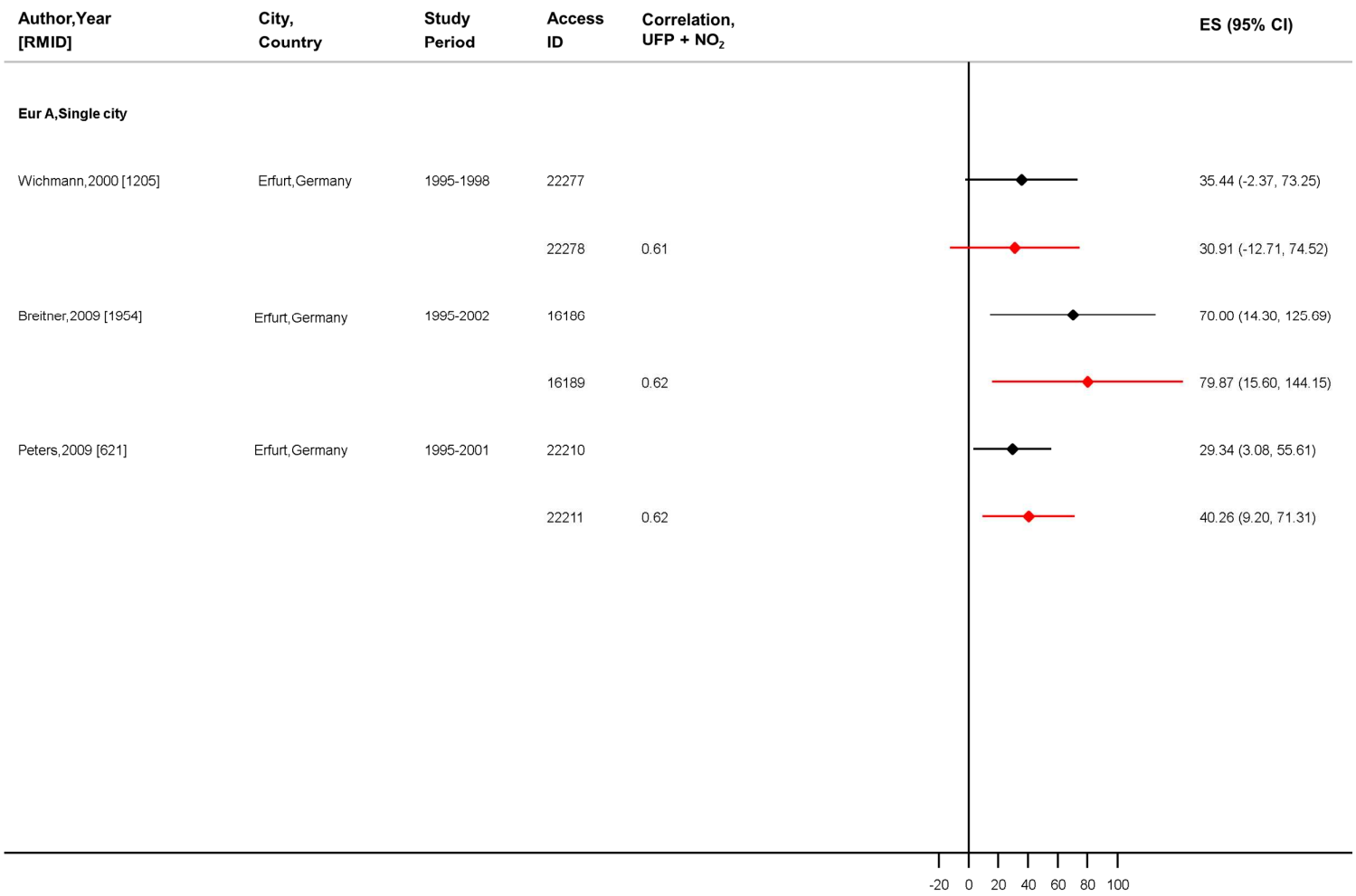


Figure S12: All studies providing two-pollutant model estimates for all cardiovascular mortality, all-ages, PM adjusted for 24 hour NO_2

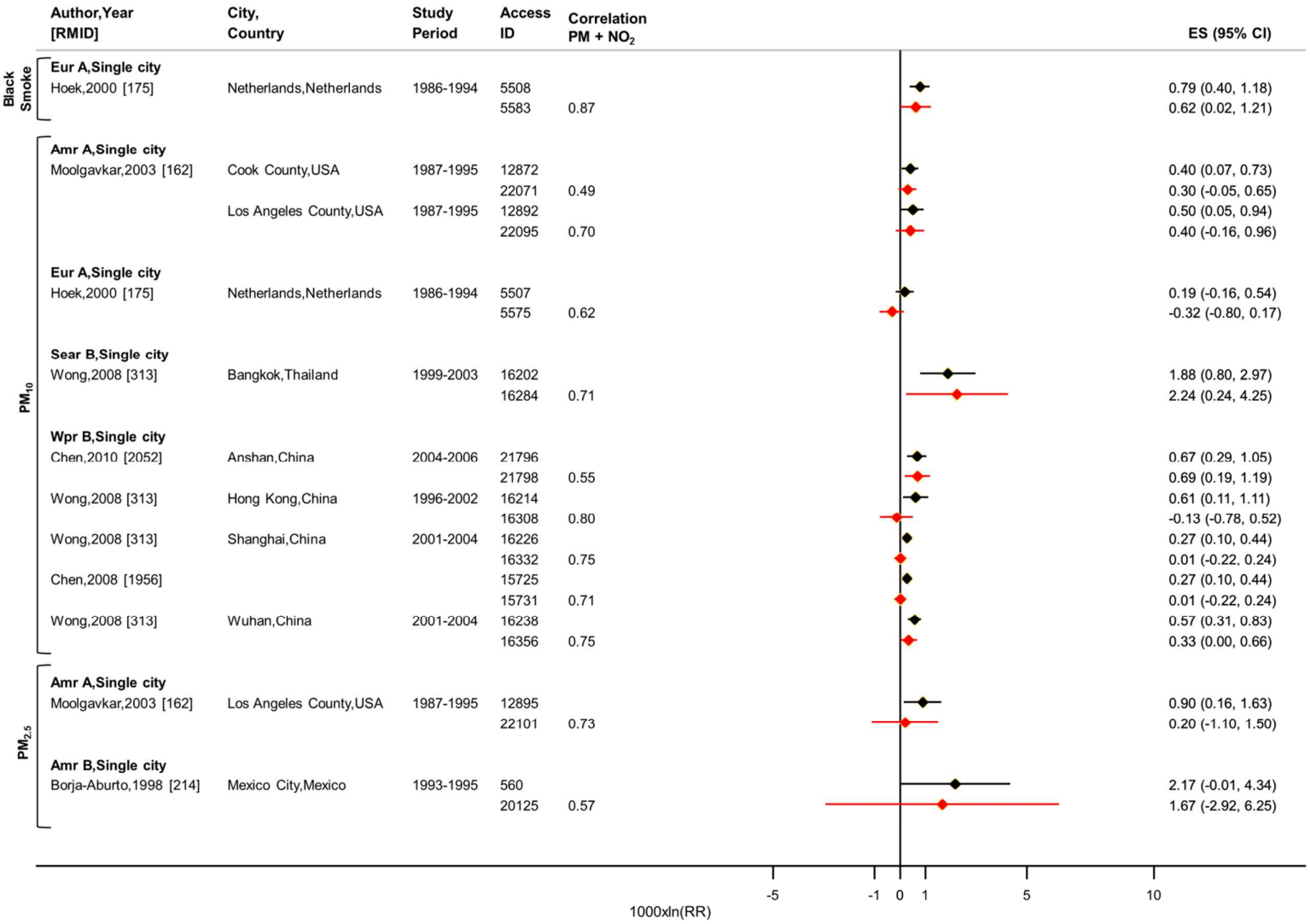


Figure S13: All studies providing two-pollutant model estimates for all respiratory mortality, all-ages, PM adjusted for 24 hour NO_2

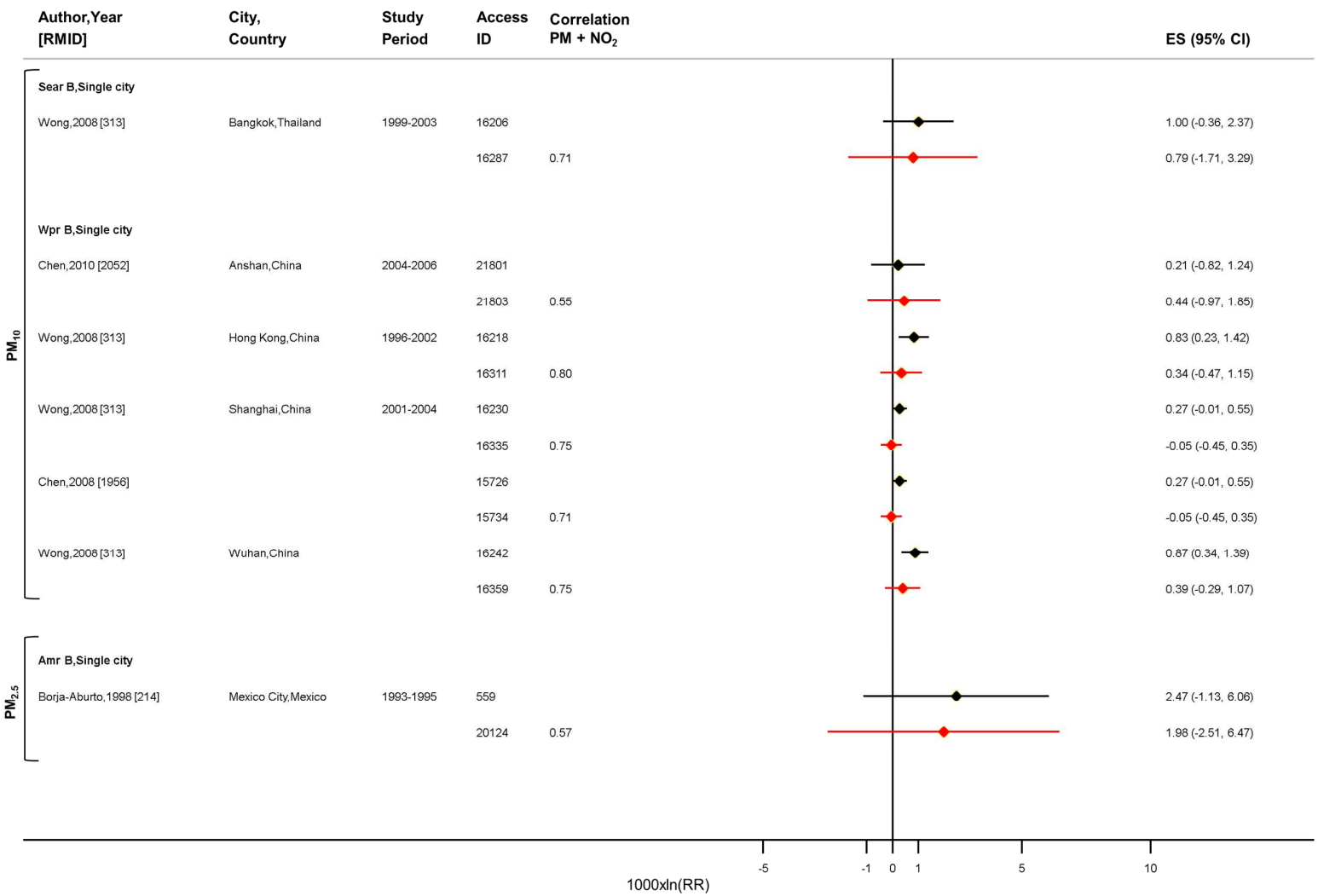
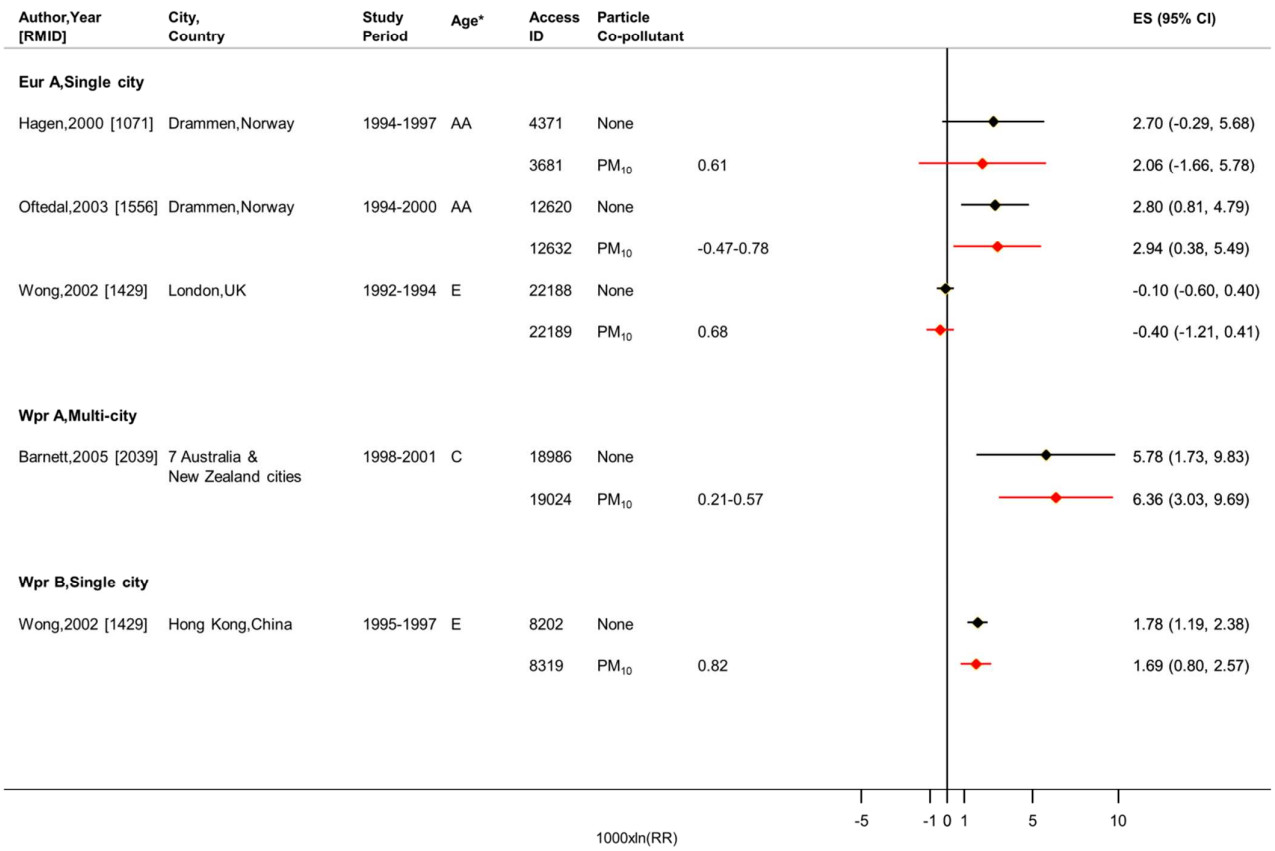
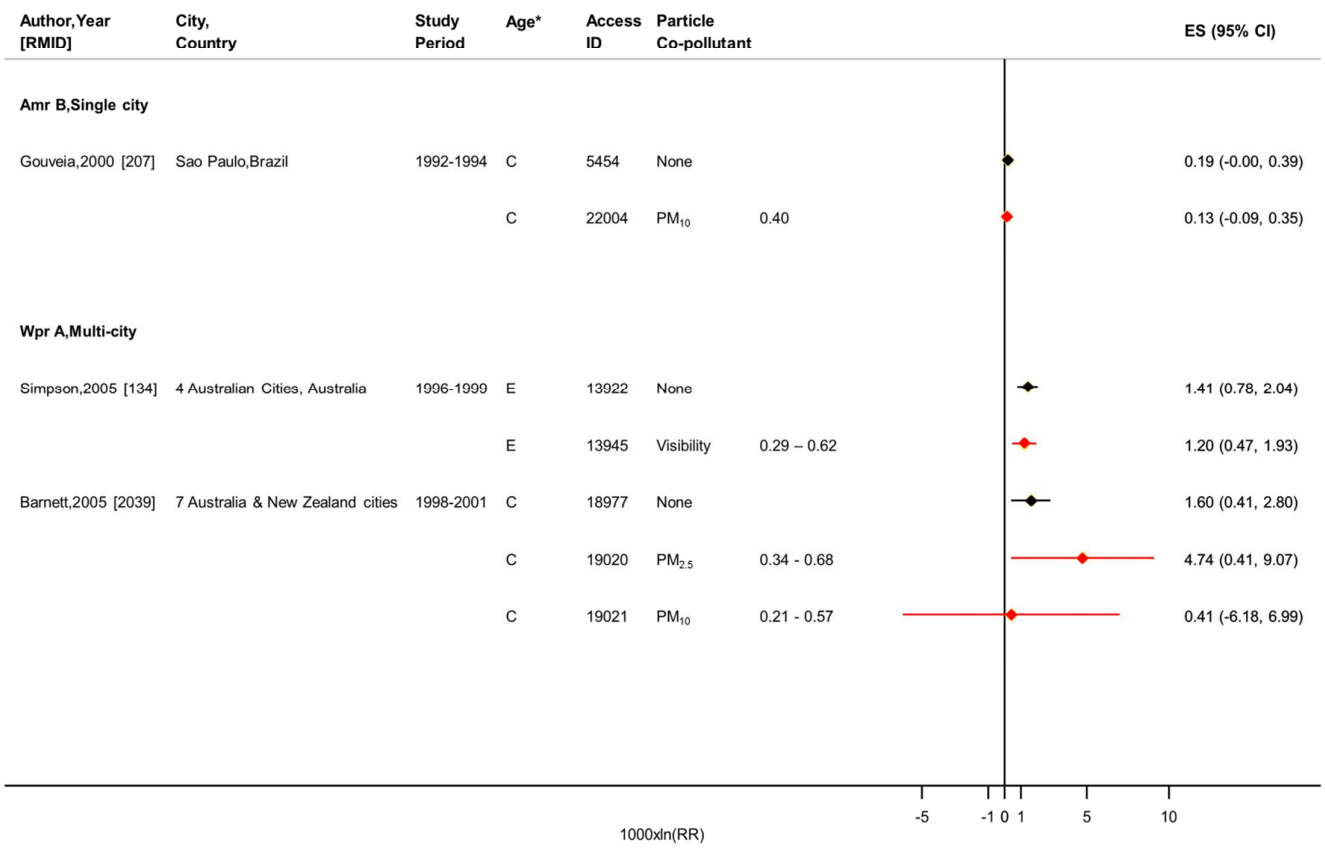


Figure S14: Studies providing two-pollutant model estimates for meta-analysis for all respiratory hospital admissions, various age groups, 24 hour NO_2



* Age: AA = all ages; E = Elderly; C = Children

Figure S15: Studies providing two-pollutant model estimates for meta-analysis for all respiratory hospital admissions, various age groups, 1 hour NO_2



* Age: C = Children; E = Elderly

Figure S16: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for asthma, children, 24 hour NO_2

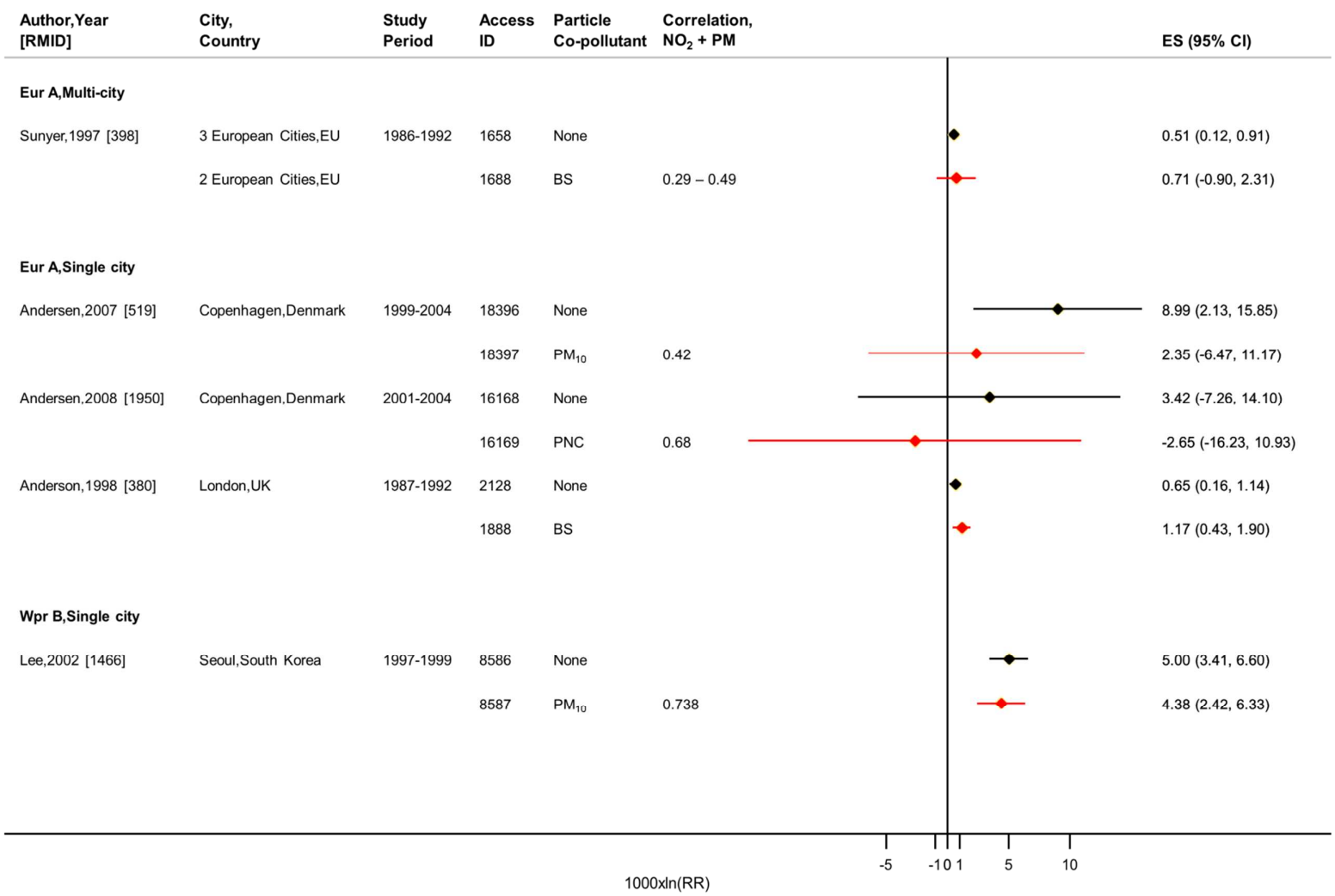
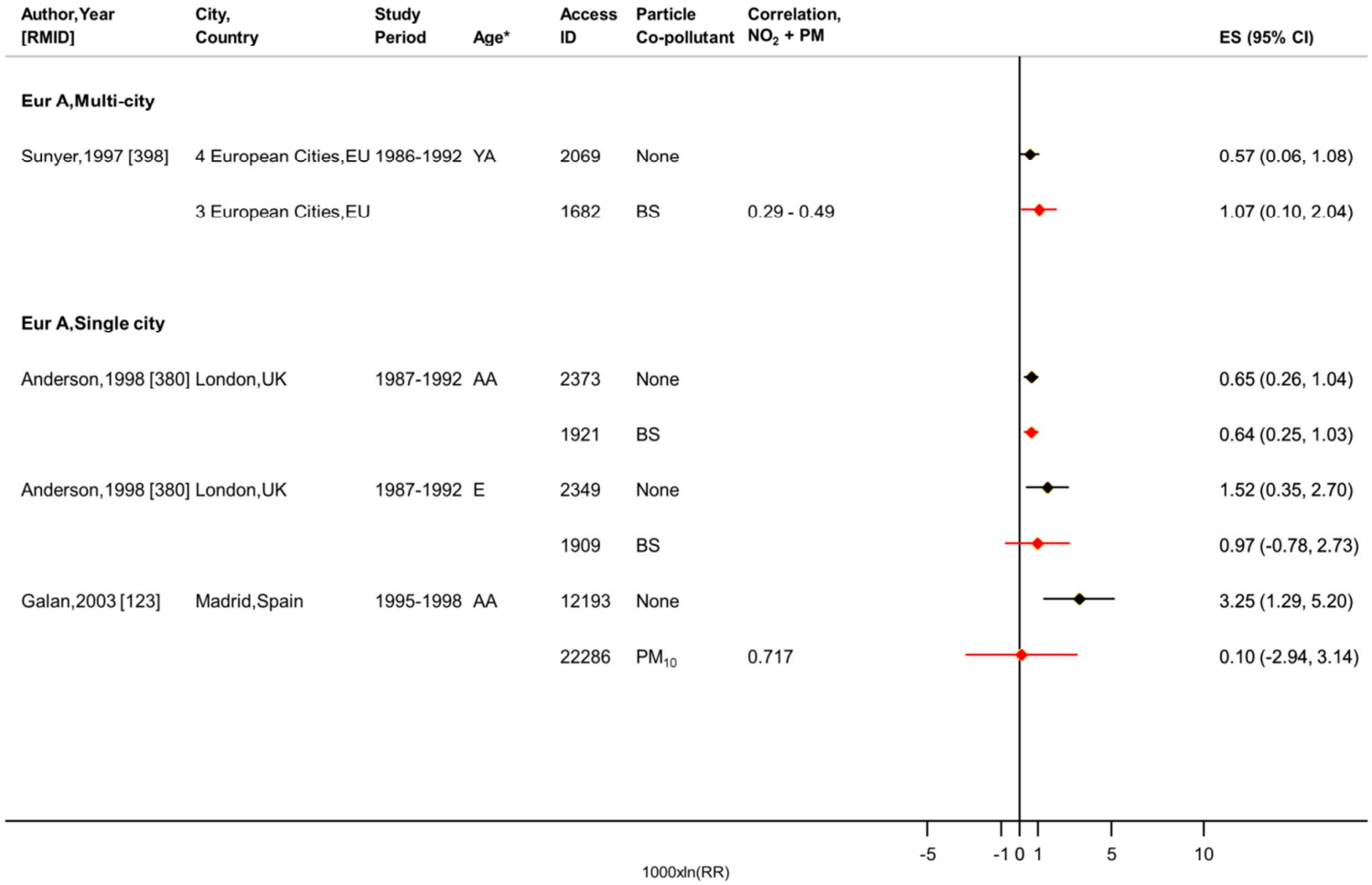


Figure S17: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for asthma, various age groups, 24 hour NO_2



* Age: AA = All-ages; E = Elderly; YA = Young adults

Figure S18: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for cardiac disease, all-ages, 24 hour NO_2

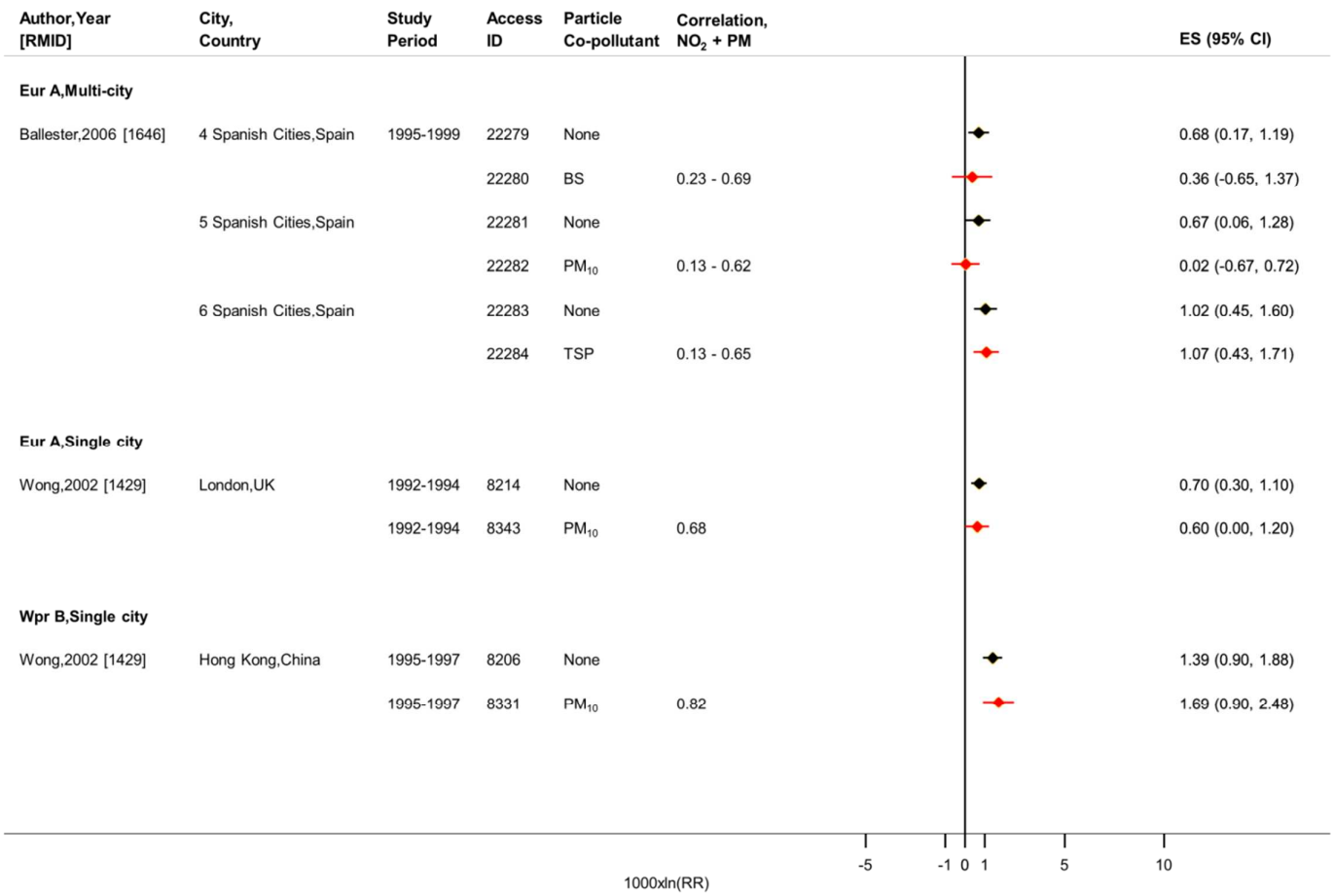


Figure S19: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for cardiac disease, elderly, 24 hour NO_2

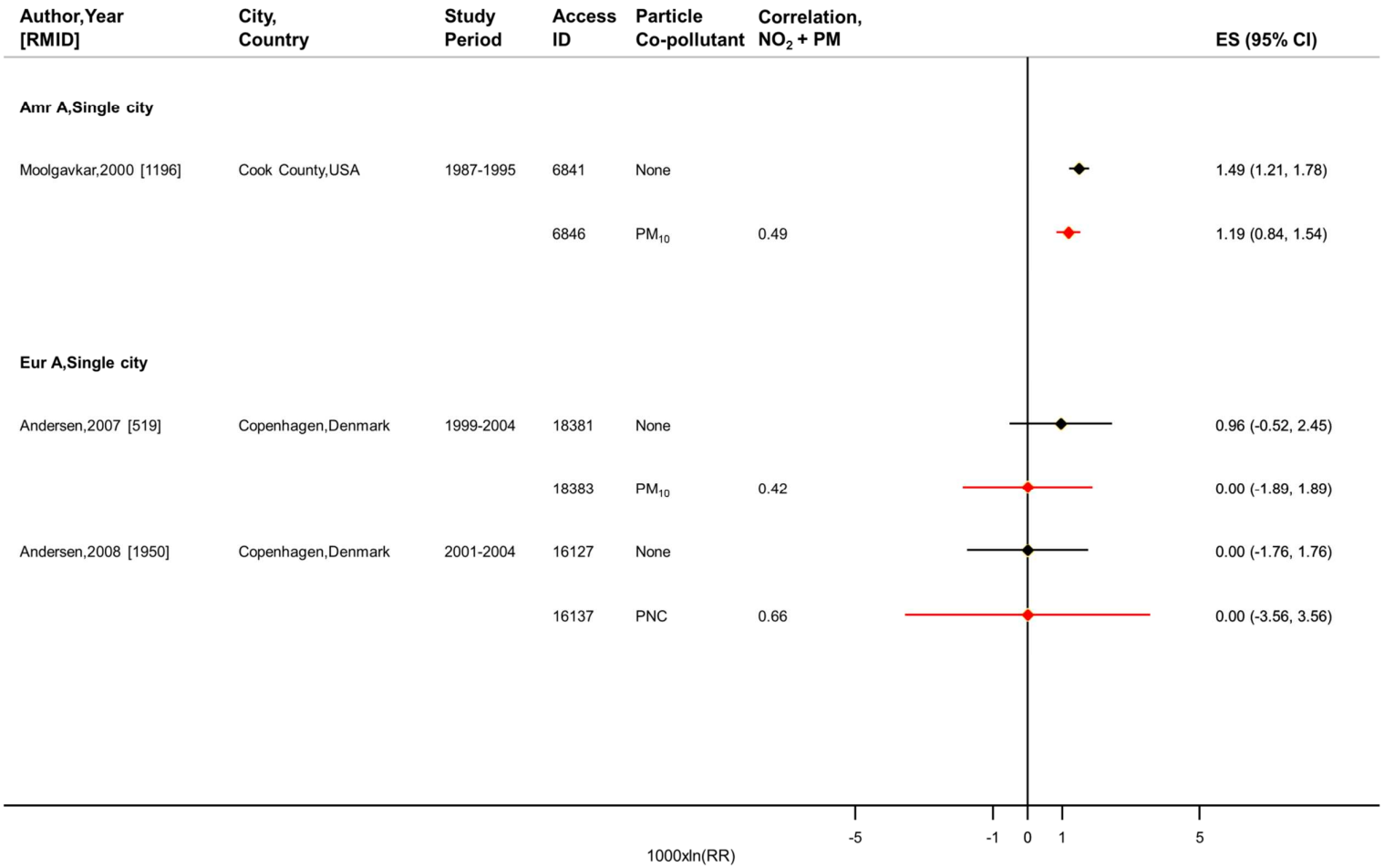


Figure S20: All available studies providing estimates from both single-pollutant and season-specific models for 24 hour NO_2 and all-cause mortality in all-ages

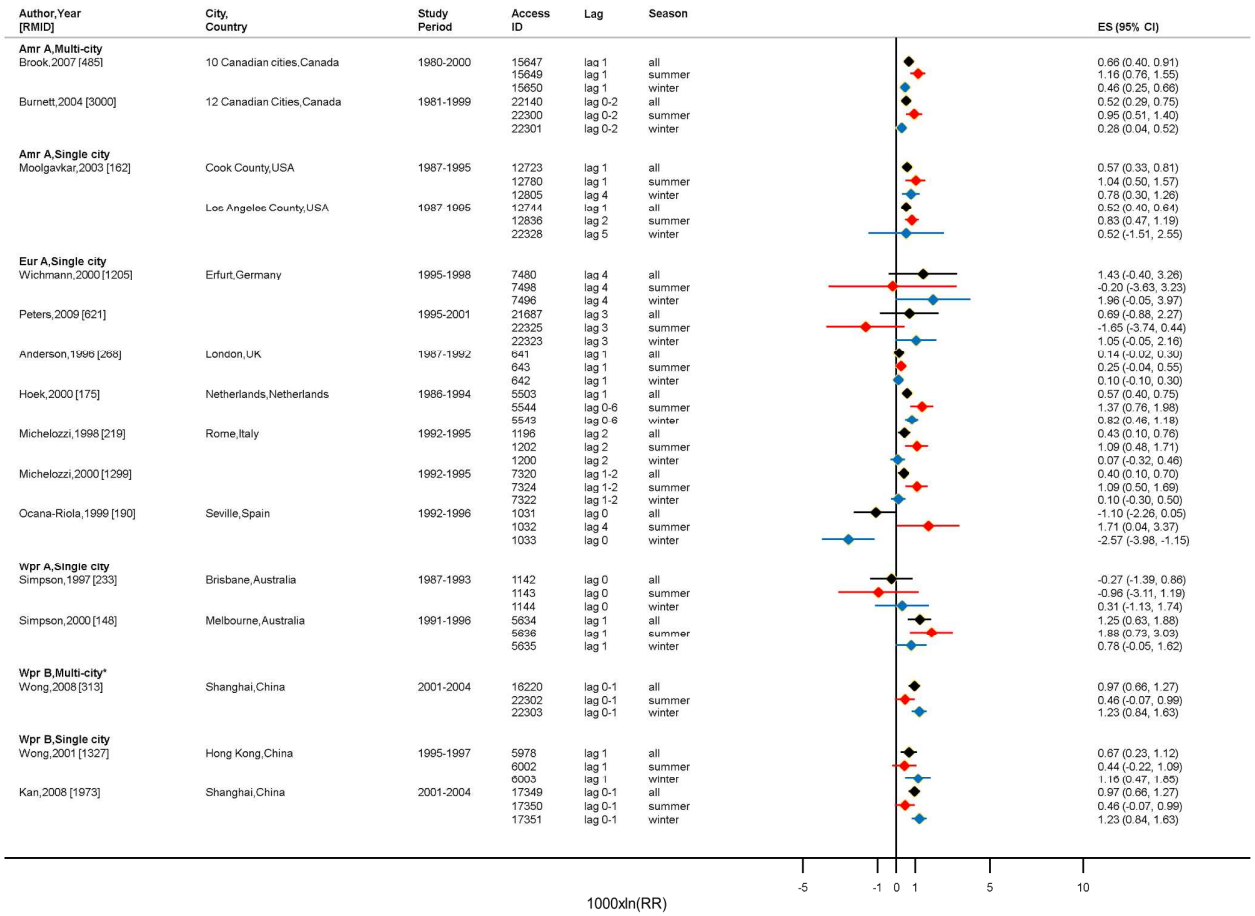


Figure S21: All available studies providing estimates from both single and season-specific models for 24 hour NO_2 and all cardiovascular mortality in all ages

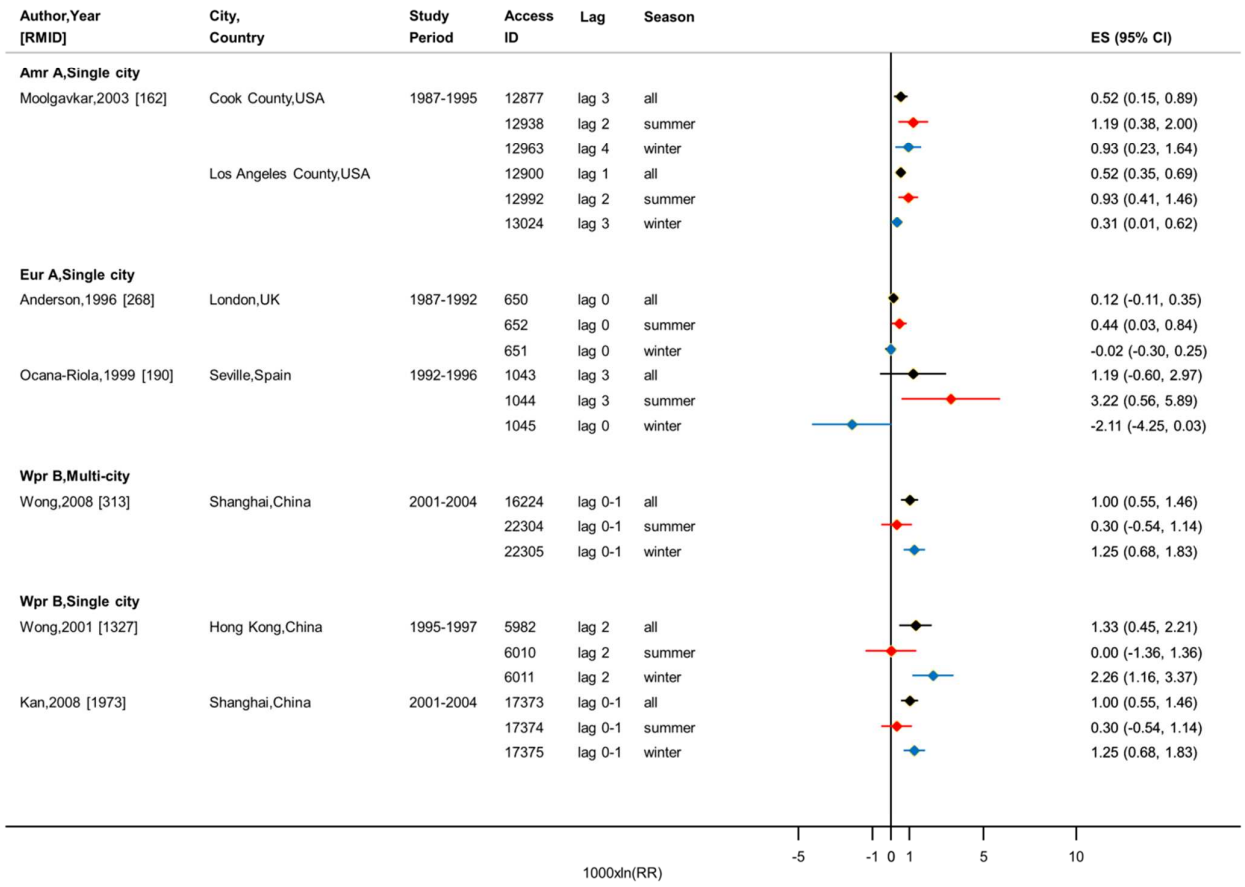


Figure S22: All available studies providing estimates from both single-pollutant and season-specific models for 24 hour NO_2 and all respiratory mortality in all-ages

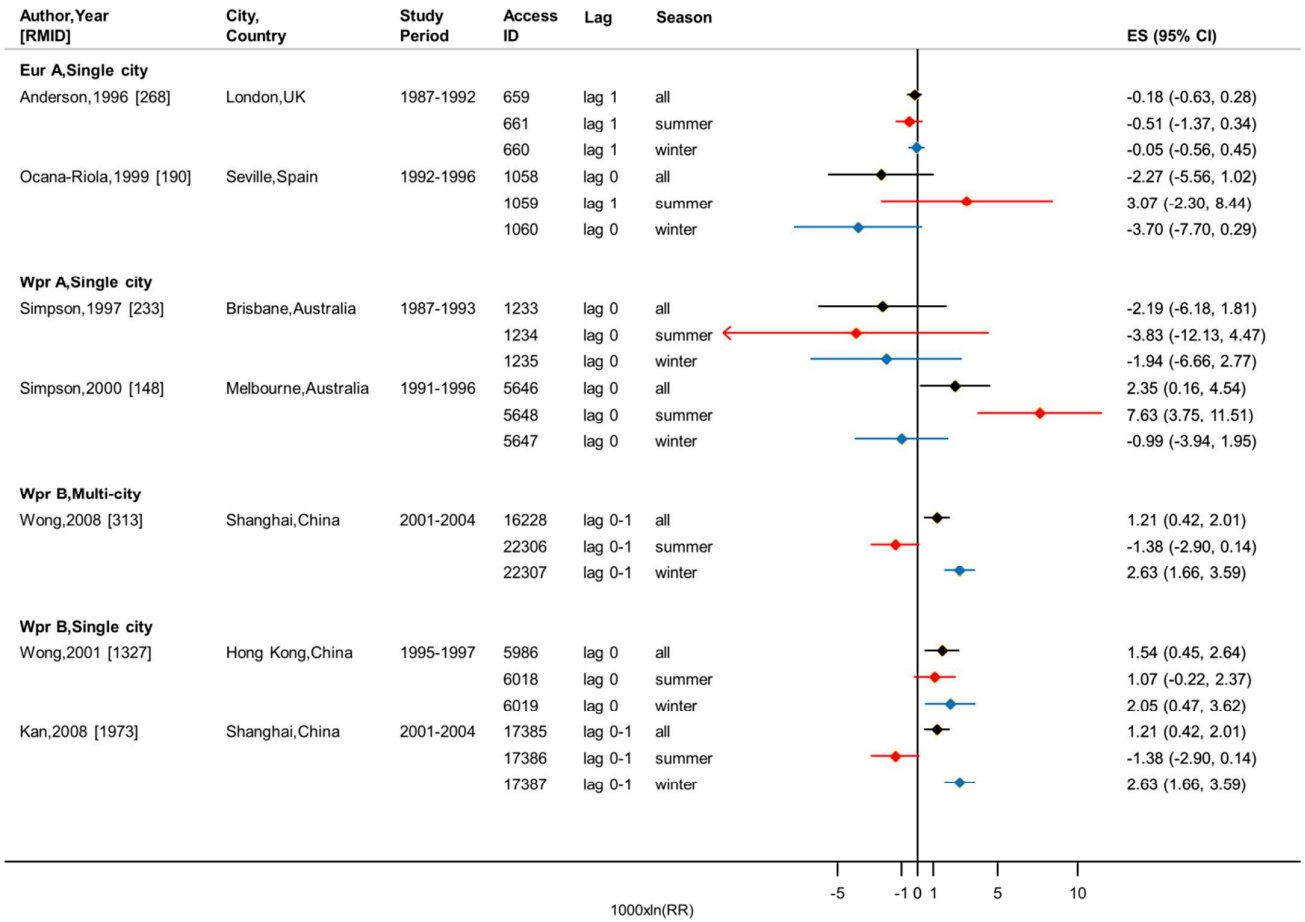


Figure S23: All available studies providing estimates from both single-pollutant and season-specific models for 24 hour NO_2 and all respiratory and all cardiovascular hospital admissions in all-ages

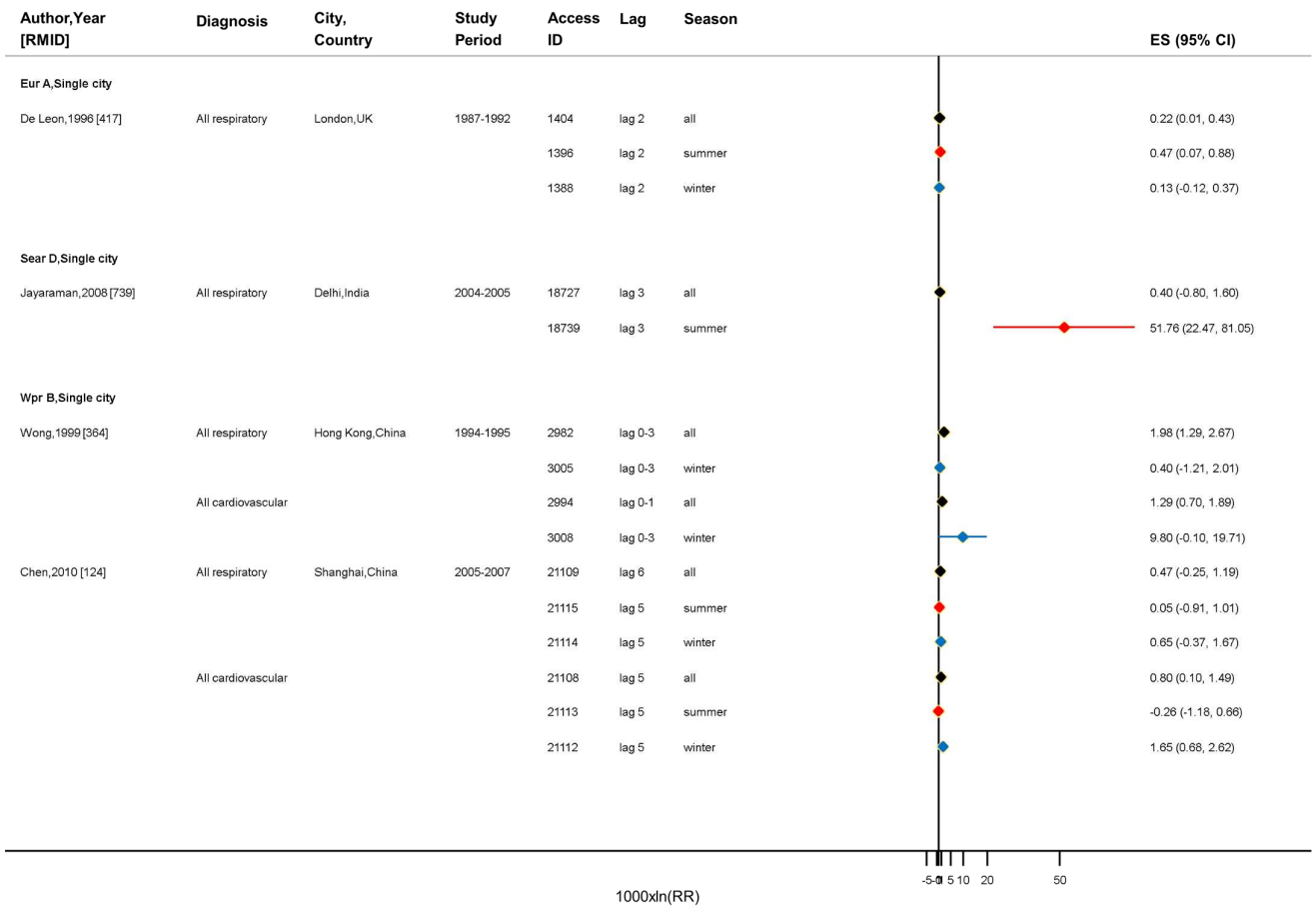


Figure S24: Ranking of NO_2 estimates for all-cause mortality in all-ages by mean levels of 24 hour NO_2 (multi-city studies shown using black bars)

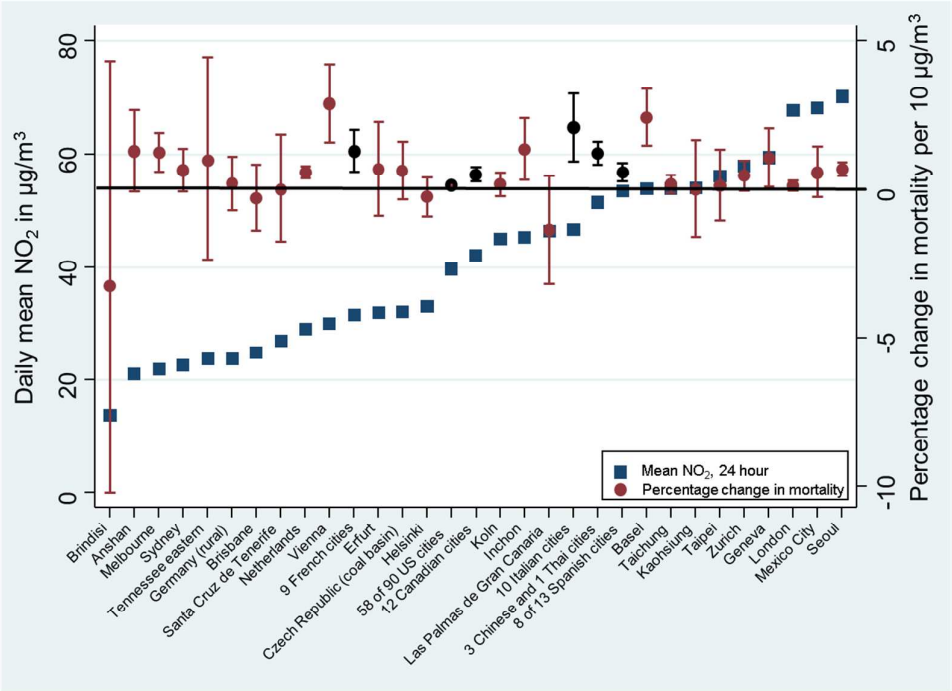


Figure S25: Ranking of NO_2 estimates for all-cause mortality in all-ages by mean levels of PM_{10} (multi-city studies shown using black bars)

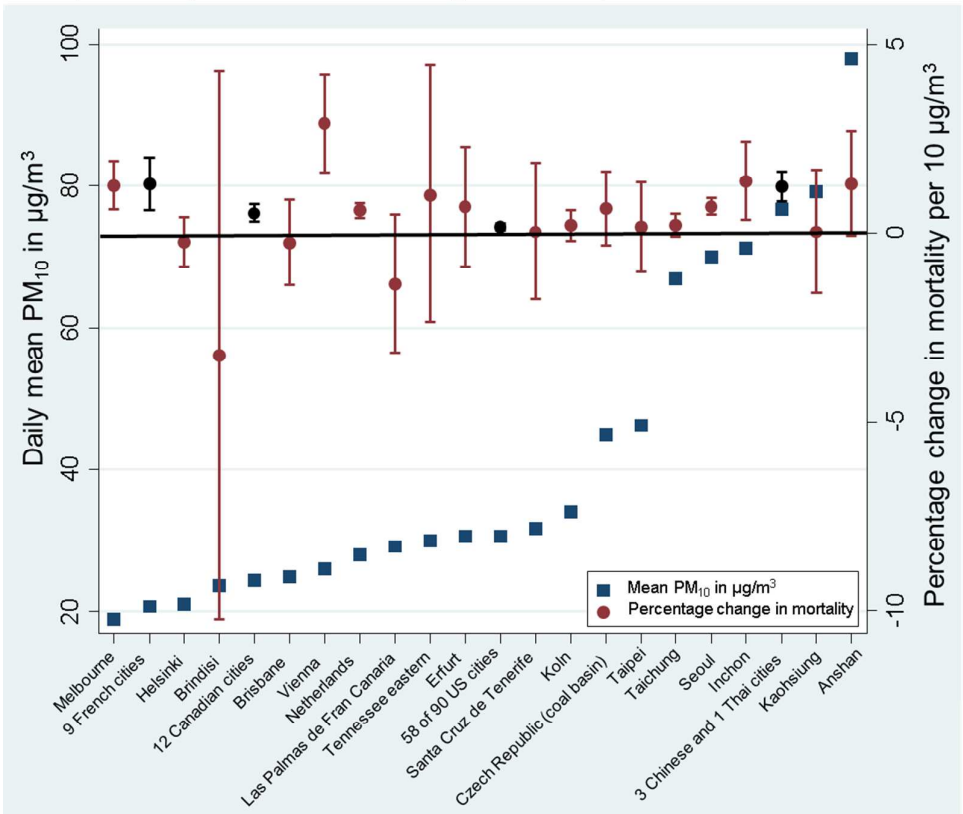


Figure S26: Ranking of NO_2 estimates for all-cause mortality in all-ages by the NO_2/PM_{10} concentration ratio (multi-city studies shown using black bars)

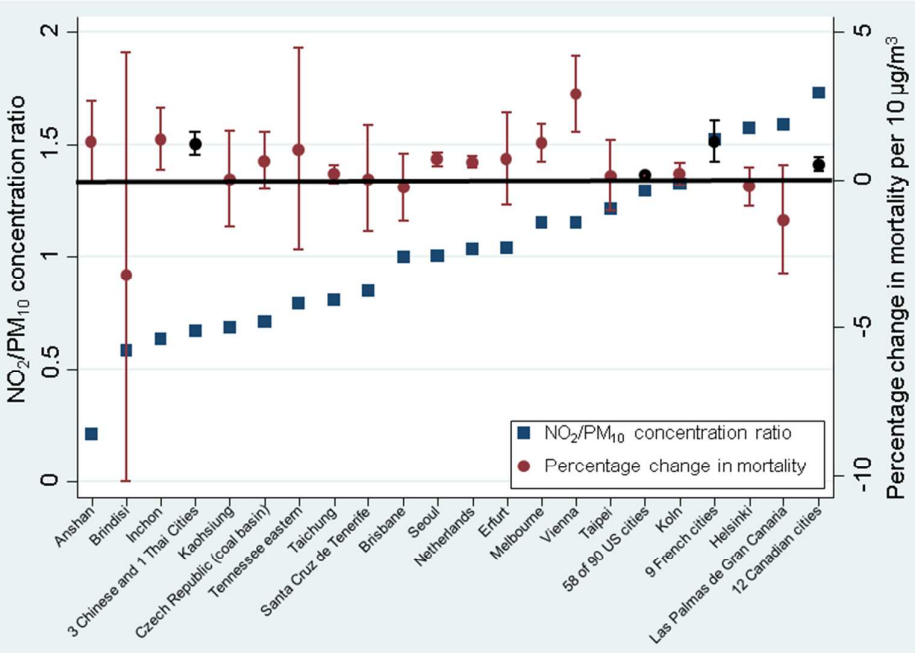
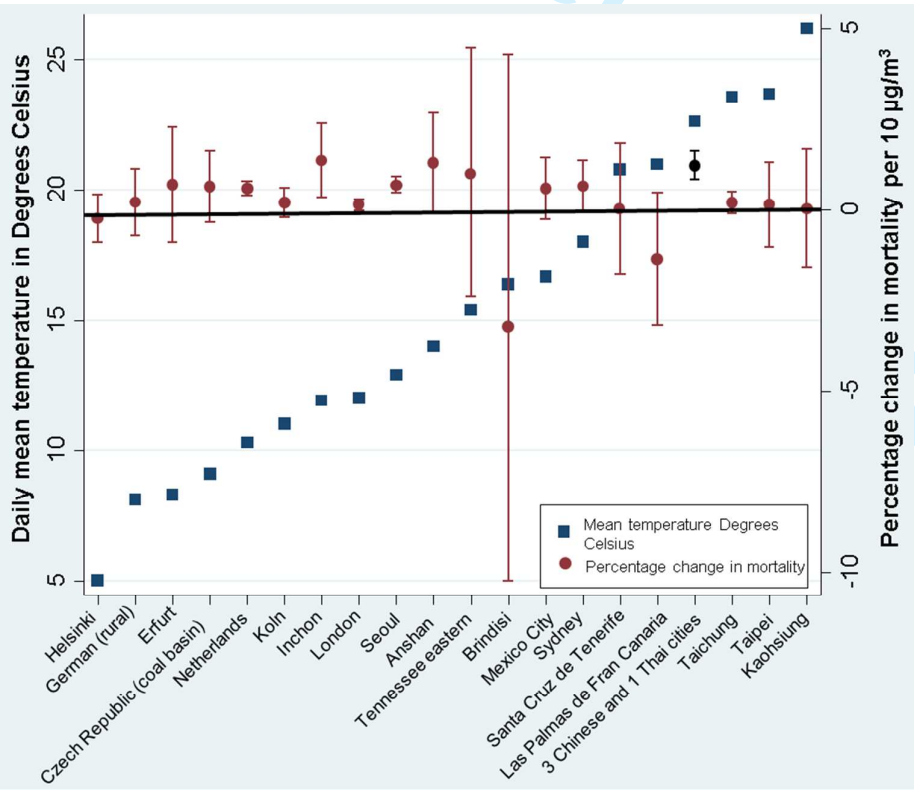


Figure S27: Ranking of NO_2 estimates for all-cause mortality in all-ages by daily mean temperature (multi-city studies shown using black bars)



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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4 and Supplementary Material
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4 and Supplementary Material
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4 and Supplementary Material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4 and Supplementary Material
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 and Supplementary Material
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 and Supplementary

PRISMA 2009 Checklist

			Material
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6 and Supplementary Material

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-7 and Supplementary Material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-11 and Supplementary Material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-11 and Supplementary Material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-11 and Supplementary Material
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	See previous related paper – reference 12 in

PRISMA 2009 Checklist

			manuscript for publication bias in full dataset. Data from the subset of studies examined in current manuscript were insufficient to permit assessment of publication bias.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

BMJ Open

Distinguishing the associations between daily mortality and hospital admissions and nitrogen dioxide from those of particulate matter: a systematic review and meta-analysis.

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine, Epidemiology, Public health
Keywords:	nitrogen dioxide, time series, mortality, hospital admissions, systematic review, meta-analysis

Type of manuscript: original article (systematic review and meta-analysis)

Distinguishing the associations between daily mortality and hospital admissions and nitrogen dioxide from those of particulate matter: a systematic review and meta-analysis.

IC Mills[1], RW Atkinson[2], HR Anderson[2,3], RL Maynard, DP Strachan[2].

1 - Public Health England, Centre for Radiation, Chemical and Environmental Hazards, UK
2 - Population Health Research Institute and MRC-PHE Centre for Environment and Health, St George's, University of London, London, UK
3 - MRC-PHE Centre for Environment and Health, King's College London, UK

Corresponding author:
I C Mills
Public Health England
Centre for Radiation Chemicals and Environmental Hazards (CRCE)
Environmental Change Department
Air Pollution and Climate Change Group
Chilton
Oxfordshire, OX11 0RQ
United Kingdom
Tel: +44 (0)1235 825146
Fax: +44 (0) 1235 833891
Email: inga.mills@phe.gov.uk

Keywords: nitrogen dioxide, mortality, hospital admissions, systematic review, meta-analysis
Word count: 4577

Abstract

Objectives

To quantitatively assess time-series studies of daily nitrogen dioxide (NO_2) and mortality and hospital admissions which also controlled for particulate matter (PM) to determine whether or to what extent the NO_2-associations are independent of PM.

Design

A systematic review and meta-analysis

Methods

Time-series studies published in peer-review journals worldwide up to May 2011 which reported both single- and two-pollutant model estimates for NO_2 and PM were ascertained from bibliographic databases (PubMed, EMBASE, and Web of Science) and reviews. Random-effects summary estimates were calculated globally and stratified by different geographical regions, and effect modification was investigated.

Outcome measures

Mortality and hospital admissions for various cardiovascular or respiratory diseases in different age groups in the general population.

Results

Sixty eligible studies were identified, and meta-analysis was done on 23 outcomes. Two-pollutant model study estimates generally showed that the NO_2-associations were independent of PM mass. For all-cause mortality, a 10 $\mu g/m^3$ increase in 24 hour NO_2 was associated with a 0.78% (95% CI: 0.47, 1.09) increase in the risk of death, which reduced to 0.60% (0.33, 0.87) after control for PM. Heterogeneity between geographical region-specific estimates was removed by control for PM (I^2 from 66.9% to 0%). Estimates of PM and daily mortality assembled from the same studies were greatly attenuated after control for NO_2: from 0.51% (0.29, 0.74) to 0.18% (-0.11, 0.47) per 10 $\mu g/m^3$ PM_{10} and 0.74% (0.34, 1.14) to 0.54% (-0.25, 1.34) for $PM_{2.5}$.

Conclusions

The association between short-term exposure to NO_2 and adverse health outcomes is largely independent of PM mass. Further studies should attempt to investigate whether this is a generic PM-effect or modified by the source and physicochemical characteristic of PM. This finding strengthens the argument for NO_2 having a causal role in health effects.

Strengths and limitations of this study

- This is, to date, the most comprehensive, quantitative systematic review of the time-series literature on NO_2 published worldwide to evaluate the two-pollutant model estimates of mortality or hospital admissions and short-term exposure to NO_2 adjusted for particulate air pollution.
- It reports meta-analytical estimates both globally and for different geographical regions, as well as an assessment of heterogeneity between the region-specific estimates.
- The protocol-led approach to the identification of studies and estimates for use in meta-analysis minimised selection bias at each stage of the review.
- Meta-analysis was limited to studies which provided effect estimates in numerical, rather than graphical, form along with sufficient quantitative data to enable standardisation of estimates.
- Further work is needed to understand reasons for the heterogeneity observed and to quantitatively assess the extent to which PM may be associated with health independently of NO_2.

INTRODUCTION

Outdoor air pollution has long been established as a hazard to human health, with particulate matter (PM) regarded as the most plausible toxicant in the mixture of ambient air pollutants.[1-5] The epidemiological evidence has consistently shown adverse associations between chronic and short-term exposure to PM and mortality and morbidity from cardiovascular and respiratory disease, and this is supported by experimental evidence.[6] Whilst the epidemiological evidence also shows relationships between nitrogen dioxide (NO_2) and adverse health effects, concerns have been expressed repeatedly about the causal nature of these associations.[7-11] It has been asserted that the NO_2-associations do not reflect adverse effects of NO_2 itself, but rather the health effects of other air pollutants, mainly PM or other components of the complex mixture of traffic-related air pollutants. Primarily, this is due to the strong correlations between NO_2 and other combustion derived air pollutants, especially PM. The extent of these correlations varies from city-to-city and over time, due to variations in emission sources. Scepticism also exists because of limited experimental evidence (controlled human exposure and animal toxicology studies) for NO_2, which, to date, has focused largely on respiratory endpoints and have generally employed concentrations of NO_2 well above current ambient levels.[7-9] In light of the uncertainties regarding NO_2 and the stronger evidence for associations between PM and health, many researchers and policymakers adopted a view that the epidemiological associations of NO_2 reflect adverse health effects of PM.

In an earlier paper we reviewed the time-series evidence associating daily concentrations of NO_2 with daily mortality and emergency hospital admissions.[12] In this study we assess the subset of time-series studies, reporting all-year estimates of NO_2 from both single- and two-pollutant models adjusted for PM to determine whether the NO_2-associations are attenuated after adjustment for PM.

METHODS

The full method and a priori protocols governing the identification of studies and effect estimates for the systematic review have been described previously,[12-14] but a synopsis, along with aspects unique to this review, is provided below.

Identification of studies for review

Three bibliographic databases were searched to identify peer-reviewed time-series studies of NO_2 and daily mortality or hospital admissions indexed up to May 2011. No restriction on language was applied. The literature search strategy is described in the online supplementary material, and the following inclusion criteria were used: papers must (i) have had a minimum of one year of data; (ii) been based on the general population; (iii) have controlled for important confounding factors, including season and meteorological factors; (iv) have reported sufficient quantitative information, in numeric format, to enable the calculation of standardised effect estimates and standard errors for use in quantitative analysis. Two authors of the review – ICM and RWA – undertook the literature search.

Data extraction and coding

Data from each relevant study were entered into a Microsoft Access database (Microsoft Office 2010, Microsoft Corporation). These included:

a) citation details of each paper
b) all-year single- and two-pollutant model estimates of NO_2 adjusted for PM.
c) single- and two-pollutant model estimates of PM adjusted for NO_2 reported in studies providing data for NO_2.
d) season-specific estimates of NO_2, including those adjusted for PM, from studies reporting all-year estimates.
e) descriptive (outcome, diagnosis (International Classification of Diseases codes), age etc.) and quantitative data (pollution increment and averaging time etc.) associated with each estimate, and needed for calculating standardised estimates expressed as the percentage change (and 95% confidence interval (CI)) in the mean number of daily events associated with a 10 $\mu g/m^3$ increase in NO_2 (or PM).
f) correlations between concentrations of NO_2 and PM.
g) effect modifiers for investigating of sources of heterogeneity in all-year estimates

Time-series studies often report results for different time lags (in days) between exposure and health events, and they vary in the lag for the reported results. We identified for each outcome/disease/age/averaging time combination from each study a pair of estimates of NO_2, that is from a single-pollutant model and a corresponding estimate adjusted for PM, for the same lag to enable comparison of the NO_2-association before and after adjustment for PM. To avoid selection bias we developed an a priori protocol for identifying the principal lag for each outcome/disease/age/averaging time combination for use in our review. This was the lag highlighted by the author or stated a priori, and if this was not clear, because several lagged model estimates were reported, we chose (i) the lag with the highest statistical significance, regardless of the estimate being positive or negative, or (ii) the lag with the largest estimate, again, irrespective of its direction. If only results from cumulative or distributed lag models, i.e. lags averaged over several days, were reported in a study, this was used. In some instances, a different lag was investigated in two-pollutant models. In such cases, the lagged estimate from the two-pollutant model was coded according to the same algorithm, and the (additional) corresponding single-pollutant estimate for the same lag was coded in our database.

Processing of data also included classifying each study into the geographical region, as the WHO region, in which the study was conducted, as well as categorising, by size, the various metrics of PM controlled for in two-pollutant models: see supplementary material for details.

Statistical analyses

A similar procedure to that outlined in our earlier paper was used for meta-analysis,[12] but with some modifications in order to identify from each study a pair of estimates of NO_2 for each pollutant/outcome combination. We applied an a priori protocol to select estimates for meta-

analysis to avoid selection bias and duplication of studies from the same population. We gave priority to estimates from multi-city studies over estimates from single-city studies and the results from any one city appeared only once in a meta-analysis. If results from more than one multi-city study within a WHO region were available we selected, in order of priority, the multi-city estimate from the study: (i) with the most cities/greatest geographical coverage; (ii) the most recently published; (iii) the most recent study time period. If a multi-city study did not report a summary estimate across the cities examined, for analysis, we treated estimates from these studies in the same manner as estimates from single-city studies. We selected estimates from single-city studies only if they did not appear in multi-city studies. For cities not included in a multi-city study summary result, we selected, in order of priority: (i) the most recently published, and (ii) the most recent study time period.

Meta-analysis was conducted when ≥4 estimates were available for an outcome/disease/age/averaging time combination - including where a multi-city estimate was available - and summary estimates were calculated using a random-effects model.[15] We used a staged approach to meta-analysis, with single-city estimates pooled within WHO region prior to the pooled single-city and selected multi-city estimates being pooled to produce a global estimate and WHO region-specific summary estimates. Heterogeneity between WHO region summary estimates was assessed using the I^2 statistic[16], with I^2 statistics >50% regarded as being evidence of high heterogeneity.[17]

Meta-analysis was undertaken for:

a) single-pollutant NO_2 estimates relating to two-pollutant models
b) corresponding NO_2 estimates adjusted for <u>any</u> PM metric:
    i) if within a study, several estimates of NO_2 adjusted for different individual PM metrics were available, a NO_2 estimate was selected according to the following order of priority of PM metric used in adjustment: PM_{10}, $PM_{2.5}$, Black Smoke, $PM_{10-2.5}$.
    ii) if having applied the protocol, a NO_2 estimate was not selected for a city because several were available due to different PM metrics used to adjust the NO_2 effect in different studies, the NO_2 estimate was chosen in the order of priority of the PM metrics listed above.
c) We conducted additional meta-analyses for NO_2 adjusted for specific metrics of particles, for example NO_2 adjusted for PM_{10}, and separately for $PM_{2.5}$, and so on, to determine whether the NO_2-associations show different sensitivity to control for different PM metrics.

All analyses were conducted in STATA (STATA/SE 11. StataCorp Texas).

RESULTS

Sixty studies provided estimates of both (i) NO_2, single-pollutant and (ii) NO_2 adjusted for PM: a list of references is provided in the supplementary material. Table 1 presents a summary of these 60 time-series studies stratified by the PM metric controlled for in regression models, broad disease categories, WHO regions in which the studies were conducted, single- and multi-city study designs, and by averaging time (24 hour and 1 hour).

There were 36 and 24 studies of daily mortality or hospital admissions, respectively, and 13 studies used a multi-city design. The majority of the studies were conducted in the WHO regions European A and Western Pacific region B and most used 24 hour NO_2. Forty of the 60 studies controlled for the effects of daily PM_{10} in the regression models for NO_2, and a much smaller number of studies used other particle size fractions or constituents of PM. Eight studies of mortality and two of hospital admissions reported estimates of NO_2, each adjusted for a different PM metric. None of the studies investigated the influence of carbon on the NO_2-associations, and four studies controlled for the effects of ultrafine particles.

Table 1: Summary of time-series studies of daily mortality or hospital admissions and NO_2 adjusted for particulate matter (PM)

Outcome		Total		Multi-city study		Single-city study	
		Mortality	Hospital admissions	Mortality	Hospital admissions	Mortality	Hospital admissions
Total		36	24	9	4	27	20
NO_2 + PM[a]	PM_{10}	23	17	6	2	17	15
	$PM_{2.5}$	7	1	3	1	4	0
	$PM_{10-2.5}$	4	0	3	0	1	0
	BS	5	4	3	2	2	2
	PNC	3	1	0	0	3	1
	Carbon	0	0	0	0	0	0
	TSP	4	2	0	1	4	1
	Visibility	2	1	2	1	0	0
	>1 PM metric	0	1	0	0	0	1
Disease[b]	All-cause	27	1	7	0	20	1
	Cardiovascular	17	11	4	2	13	9
	Respiratory	7	17	3	3	4	14
WHO Region[c]	American A	8	4	3	0	5	4
	European A	9	12	3	2	6	10
	Western Pacific B	14	5	2	0	12	5
	American B	4	2	0	0	4	2
	Western Pacific A	1	2	1	2	0	0
	South East Asia B	2	0	2	0	0	0
Averaging time	24 hours	29	21	6	3	23	18
	Maximum 1 hour	7	5	3	2	4	3

a - The eight categories of PM metrics listed in the table above have been generated by grouping different measures of particles. PM_{10} and $PM_{2.5}$ refer to the mass per cubic metre of particles of generally less than 10 μm, 2.5 μm diameter, respectively, in the ambient air. BS: Black Smoke; PNC: Particle Number Concentration; TSP: Total Suspended Particles.

b - Respiratory includes all-respiratory diseases, asthma, COPD, COPD (including asthma), lower respiratory infections, and upper respiratory diseases; Cardiovascular includes all-cardiovascular diseases, cardiac disease, heart failure, ischaemic heart disease, dysrhythmia, and stroke.

c - WHO regions: A: very low child and adult mortality; B: low child mortality and low adult mortality; C: low child mortality and high adult mortality; D: high child mortality and high adult mortality.

NO_2 and all-cause mortality

Figure 1 shows all available (32 pairs) single- and two-pollutant estimates for 24 hour NO_2 and daily all-cause mortality in all ages. In the majority of studies daily NO_2 was positively and significantly associated with increases in the risk of death including after controlling for daily PM. In many of the studies the NO_2 estimates were not greatly reduced in size, changed direction, or lose statistical significance after adjustment for PM. In general, the NO_2 estimates appeared robust to adjustment for PM at both high and low correlations between concentrations of NO_2 and PM.

Fifteen (of 32) pairs of estimates for 24 hour NO_2 and all-cause mortality, which represented 26 cities from five WHO regions, were selected for meta-analysis (Figure S1). The random-effects single-pollutant summary estimate for all-cause mortality was 0.78% (95% CI: 0.47, 1.09) per 10 μg/m^3 increase in NO_2.There was evidence of high heterogeneity (I^2=66.9%) between the WHO region-specific estimates which ranged from 0.48% for WHO region America A to 1.41% for South East Asia B (Table S1). The overall estimate was comparable to the single-pollutant summary estimate of 0.71% (95% CI: 0.43, 1.00) calculated from the larger body of time-series evidence analysed in our previous paper.[12] After adjustment for daily PM, all-cause mortality remained positively and significantly associated with 24 hour NO_2: 0.60% (95 CI%: 0.33, 0.87) per 10 μg/m^3 increase in NO_2, and there was no evidence of heterogeneity (I^2=0%) between the region-specific estimates.

Control for specific PM metrics did not greatly alter the relationship of 24 hour NO_2 with all-cause mortality (Table 2). With the exception of NO_2 adjusted for PM_{10}, and to a lesser extent $PM_{2.5}$, meta-analyses for NO_2 adjusted for the remaining PM metrics were limited to findings from the multi-city Canadian study by Burnett et al[18] – see Figure 1.

Six pairs of estimates were available for meta-analysis for all-cause mortality and 1 hour NO_2 adjusted for PM (Figure S2). Thirty of the 36 cities represented by these estimates were from Europe. Meta-analysis of 4 pairs of estimates resulted in an overall estimate of 0.32% (95% CI: -0.02, 0.66) for a 10 μg/m^3 increment in 1 hour NO_2 and 0.20% (95% CI: -0.24, 0.65) following adjustment for PM (Table S2). High heterogeneity was observed between the WHO region-specific estimates. In contrast with findings for 24 hour measures, the summary estimate for 1 hour NO_2 for WHO region European A was little affected by adjustment for PM_{10} (or Black Smoke) –Table S2. Table 3 provides meta-analysis results for all-cause mortality and 1 hour NO_2 adjusted for different PM metrics. Control for PM_{10} led to attenuation of the estimate and loss of statistical significance, whilst the association was robust to control for Black Smoke and visibility (measured as black suspended particles, bsp).

Table 2: Random-effects summary estimates (as percentage change (95% confidence intervals)) for mortality or hospital admissions associated with a 10 μg/m³ increase 24 hour average pollution

	All SC/MC[a]	Selected SC/MC (cities)[b]	24 hour NO_2		24 hour PM	
			Single-pollutant	Adjusted for PM	Single-pollutant	Adjusted for NO_2
All-cause mortality, all ages						
PM_{10}	13/3	4/1 (21)	0.92 (0.58, 1. 72)	0.85 (0.52, 1.18)	0.51 (0.29, 0.74)	0.18 (-0.11, 0.47)
$PM_{2.5}$	2/3	2/1 (14)	0.53 (0.42, 0.64)	0.57 (0.24, 0.89)	0.74 (0.34, 1.14)	0.54 (-0.25, 1.34)
$PM_{10-2.5}$	0/3	0/1 (12)	0.62 (0.19, 1.06)	0.73 (0.28, 1.18)	0.65 (-0.10, 1.42)	0.31 (-0.49, 1.11)
Visibility	0/1	0/1 (12)	0.60 (0.34, 0.87)	0.66 (0.33, 1.00)	40.93 (23.39, 60.97)*	12.42 (-4.47, 32.29)*
All cardiovascular mortality, all ages						
PM_{10}	10/0	4/0 (8)	0.99 (0.49, 1.49)	0.87 (0.28, 1.46)	0.48 (0.18, 0.78)	0.19 (-0.21, 0.59)
All respiratory mortality, all ages						
PM_{10}	7/0	2/0 (5)	1.44 (0.63, 2.27)	1.15 (0.47, 1.84)	0.58 (0.22, 0.93)	0.13 (-0.18, 0.44)
All respiratory hospital admissions, children (5-14 years)						
PM_{10}	0/1	0/1 (5)	5.95 (1.74, 10.33)	6.56 (3.08, 10.17)	-	-
Cardiac hospital admissions, all ages						
PM_{10}	2/1	2/1 (7)	0.93 (0.46, 1.40)	0.75 (-0.13, 1.64)	-	-
BS	0/1	0/1 (4)	0.68 (0.17, 1.20)	0.36 (-0.65, 1.38)	-	-
TSP	0/1	0/1 (6)	1.03 (0.45, 1.61)	1.08 (0.43, 1.72)	-	-

a -Numbers of available pairs of single-city (SC) / multi-city (MC) estimates from all studies
b -Numbers of pairs of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions. Estimates were selected for meta-analysis from all available. The number of cities represented by the summary estimates is given in brackets.
* The results for visibility (measured as Coefficient of Haze (COH units)) are not comparable to other PM results.

Table 3: Random-effects summary estimates (as percentage change (95% confidence intervals)) for mortality or hospital admissions associated with a 10 μg/m³ increase in air pollution

	All SC/MC[a]	Selected SC/MC (cities)[b]	1 hour NO_2		24 hour PM	
			Single-pollutant	Adjusted for PM	Single-pollutant	Adjusted for NO_2
All-cause mortality, all ages						
PM_{10}	2/1	2/1 (32)	0.22 (-0.15, 0.60)	0.10 (-0.40, 0.61)	0.52 (0.29, 0.75)	0.48 (0.31, 0.66)
BS	0/2	0/1 (30)	0.30 (0.22, 0.38)	0.33 (0.23, 0.43)	0.60 (0.30, 0.90)	0.26 (0.00, 0.52)
Visibility	0/1	0/1 (4)	0.63 (0.21, 1.05)	0.52 (0.05, 1.00)	35.70 (3.97, 77.12)*	10.24 (-20.03, 51.97)*
All cardiovascular mortality, all ages						
PM_{10}	1/1	0/1 (29)	0.40 (0.29, 0.51)	0.35 (0.21, 0.49)	0.76 (0.47, 1.05)	0.17 (-0.10, 0.44)
BS	1/1	0/1 (29)	0.40 (0.29, 0.51)	0.44 (0.31, 0.57)	0.62 (0.35, 0.90)	0.32 (0.05, 0.59)
All respiratory mortality, all ages						
PM_{10}	0/1	0/1 (29)	0.38 (0.17, 0.59)	0.37 (0.08, 0.66)	0.71 (0.22, 1.20)	0.20 (-0.29, 0.69)
BS	0/1	0/1 (29)	0.38 (0.17, 0.59)	0.26 (-0.12, 0.64)	0.84 (0.11, 1.58)	0.57 (-0.34, 1.48)
All respiratory hospital admissions, children (< 5 years)						
PM_{10}	1/1	1/1 (6)	0.77 (-0.59, 2.15)	0.13 (-0.09, 0.35)	-	-
$PM_{2.5}$	0/1	0/1 (4)	1.62 (0.41, 2.84)	4.85 (0.41, 9.50)	-	-
All respiratory hospital admissions, elderly (65 + years)						
Visibility	0/1	0/1 (4)	1.42 (0.79, 2.06)	1.21 (0.47, 1.95)	-	-
Cardiac hospital admissions, elderly						
Visibility	0/1	0/1 (4)	1.21 (0.84, 1.58)	0.73 (0.31, 1.16)	-	-

See Table 2 for footnotes
* The results for visibility (measured as black suspended particles ($10^{-4}.m^{-1}$)) are not comparable to other PM results.

NO_2 and mortality from specific causes

NO_2 estimates adjusted for PM were available for several specific causes of death in all ages: all cardiovascular (Figures S3 and S4), all respiratory (Figure S5), stroke (Figure S6), cardiac (Figure S7), ischaemic heart disease, dysrhythmia, chronic obstructive pulmonary disease including asthma, and lower respiratory infections (Figure S8). Sufficient numbers of estimates for meta-analysis were available for all cardiovascular (Table S3), all respiratory (Table S4), and stroke (Table S5) mortality.

Eight studies providing 14 pairs of estimates showed positive associations between all cardiovascular deaths and 24 hour NO_2 including after adjustment mainly for PM_{10} (Figure S3). However, attenuation of estimates and loss of statistical significance was observed in the few studies with control for $PM_{2.5}$ or Black Smoke. Meta-analysis of 10 pairs of estimates found a 1.07% (95% CI: 0.43, 1.72) increase in the risk of death from all cardiovascular diseases per 10 $\mu g/m^3$ increase in 24 hour NO_2 (Table S3 and Figure S9). This was attenuated (0.82% (95% CI 0.22, 1.42)) Table S3) following adjustment for PM, but comparable to our earlier result (0.88% (95% CI: 0.63, 1.13)).[12] Control of the NO_2-association with all cardiovascular mortality for specific PM metrics showed an association which was robust to adjustment for PM_{10} (Table 2). There were too few estimates to permit meta-analysis for other PM metrics controlled for in the studies. The available data for 1 hour NO_2 and all cardiovascular mortality was sparse and limited to two studies representing 29 European cities which showed positive NO_2-associations that were robust to adjustment for both PM_{10} and Black Smoke (Table 3 and Figure S4).

Evidence for all respiratory mortality and 24 hour NO_2 adjusted for PM came from six cities (Figure S5). Meta-analysis produced a 1.42% (95% CI: 0.64, 2.21) increased risk of all respiratory deaths per 10 $\mu g/m^3$ increase in 24 hour NO_2 (Table S4 and Figure S10). The corresponding estimate adjusted for particles was attenuated (1.13% (95% CI: 0.46, 1.81)) but was comparable with the single-pollutant estimate (1.09% (95% CI: 0.75, 1.42)) derived from the larger body of time-series evidence examined in our previous paper.[12] There was no evidence of heterogeneity (I^2=0%) between the geographic specific estimates either before or after adjustment for PM (Table S4). Evidence for associations between all respiratory mortality and 1 hour NO_2 came solely from the multi-city APHEA II study of 29 European cities,[19] which showed a positive association that was robust to adjustment for PM_{10} but not Black Smoke (Table 3).

PM and mortality

Meta-analyses were undertaken separately for PM adjusted for the different averaging times of NO_2 to allow comparison with the relevant meta-analyses for NO_2 using data from the same studies, cities and time periods. Figure 2 shows positive, single-pollutant associations between various mass metrics of PM and all-cause mortality. In the majority of studies, attenuation of estimates was observed following control for 24 hour NO_2. Estimates for ultrafine particles and all-cause mortality were robust to adjustment for 24 hour NO_2 (Figure S11), but the data came

from three studies conducted in the same city, Erfurt, Germany. Results of meta-analysis for all-cause mortality and PM metrics are shown in Tables 2 and 3 for adjustment for 24 hour and 1 hour NO_2, respectively. In contrast to the results for NO_2, the summary estimates for PM were attenuated, in most cases by more than half and confidence intervals overlapped zero. Evidence of high heterogeneity between region-specific summary estimates for PM_{10} and all-cause mortality was identified (Table S6). Summary estimates for deaths from all cardiovascular or all respiratory diseases and PM were also sensitive to control for NO_2 (Tables 2 and 3; study estimates in Figures S12-S13; Tables S7 and S8 for region-specific results).

NO_2 and hospital admissions

Few cause- and age-specific combinations of hospital admissions for 24 hour or 1 hour NO_2 with control for PM had sufficient numbers of estimates for meta-analysis - all respiratory diseases in children and the elderly, asthma in children, and cardiac disease in all ages and the elderly - and half were based solely on a multi-city estimate from a single study.

Positive associations were identified between all respiratory hospital admissions in different age groups and 24 hour or 1 hour NO_2, which remained after control for PM (Tables 2 and 3; Figures S14-S15 for available study estimates).

Evidence for the association between hospitalisation for asthma in different ages and daily NO_2 adjusted for PM came from seven studies (Figures S16-S17), six of which were conducted in Europe. Sufficient estimates for meta-analysis were only available for asthma admissions in children and 24 hour NO_2 adjusted for any particles (measured as Black Smoke, PM_{10} and PNC): a 2.81% (95% CI: -1.28, 7.06) increase in risk per 10 $\mu g/m^3$ 24 hour NO_2 was attenuated following adjustment for particles (2.24% (95% CI: -1.12, 5.71)).

Five studies provided evidence for the relationship between 24 hour NO_2 adjusted for PM and hospitalisation for cardiac disease in all ages (Figure S18) and the elderly (Figure S19). Meta-analysis for the all age category (Table 2) identified positive estimates which were attenuated and confidence intervals overlapped zero after control for PM_{10} and Black Smoke. One multi-city study of four Australian cities provided evidence for the relationship between 1 hour NO_2 and cardiac admissions in the elderly. The association (1.21% (95% CI: 0.84, 1.58)) was weakened by control for BSP (an indicator of fine particles), but remained statistically significant (0.73% (95% CI: 0.31, 1.16)).

Sources of variation in NO_2 estimates

We examined season-specific NO_2 estimates of mortality from studies which reported all-year estimates to explore possible effect modification by season. Some studies, mainly from Western Europe, Canada and the USA, reported stronger associations between daily mortality and NO_2 in the summer months (Figure S20-S22). The extent of the correlations between concentrations of NO_2 and PM in the different seasons is unclear because very few studies reported these data,

and only one study reported season-specific estimates adjusted for PM. Similarly, limited evidence is available on which to base an assessment of seasonal variation of associations between hospitalisation for cardiovascular and respiratory diseases and 24 hour NO_2 (Figure S23).

We explored reasons for the observed high heterogeneity by ranking study estimates for all-cause mortality and 24 hour NO_2 (from the full dataset)[12] by different potential effect modifiers (Figures S24-S27). None of the variables used to represent the pollution and meteorological environments in the cities examined accounted for the observed between-study variability.

DISCUSSION

Sixty time-series studies of NO_2 were used to determine whether NO_2 is associated with daily mortality or hospital admissions independently of daily PM. In general, our results demonstrate that after controlling for PM, daily NO_2 remained significantly associated with increases in the risk of adverse health outcomes. The evidence appears clearest for daily deaths from all-causes and from all cardiovascular and all respiratory diseases, and for all respiratory hospital admissions, outcomes for which more co-pollutant estimates were available. Robustness of the NO_2-associations to control for PM was observed at both high and low correlations between NO_2 and PM, and no clear relationship could be discerned between the correlations and changes in the size of the adjusted NO_2 estimates. In contrast to the results for NO_2, the associations between daily PM and the main mortality outcomes (all-cause, all cardiovascular, all respiratory) were very sensitive to the inclusion of NO_2 in two-pollutant models.

Two/multi-pollutant models are increasingly being used to draw conclusions about whether or not NO_2 is independently associated with adverse health outcomes. This comprehensive review provides systematic evaluation and formal meta-analysis of the full body of two-pollutant estimates of NO_2 adjusted for PM, across several cause- and age-specific health outcomes, both globally and by different geographical regions. Whilst earlier reviews[7-8, 13, 20-23] included some assessment of these data, they were either limited in scope to specific health outcomes and/or examined together two- and multi-pollutant model NO_2 estimates, or did not undertake meta-analysis whatsoever. Another key strength of this review is the protocol-led approach to identifying and assembling studies and estimates, which aimed to minimise selection bias in the different stages of the review.

The subset of studies of NO_2 analysed in this paper were generally comparable to the studies examined in our earlier paper in terms of the magnitudes of summary estimates and overlap in confidence intervals.[12] For example, the single-pollutant summary estimates for all-cause mortality, the outcome with the most data, were similar across both datasets, suggesting that the studies reporting two-pollutant model estimates were typical of the wider body of time-series evidence of NO_2.

Whilst evidence of NO_2-associations which are robust to control for PM mass have been identified, it is possible that there may be some residual confounding by PM. The components of PM - primary combustion particles, for example ultrafine particles or Black Carbon - which have been proposed as the real causal agents of the NO_2-associations were not included in co-pollutant models of NO_2 because concentration data for these pollutants were either unavailable or sparse, reflecting the fact that these PM metrics are not routinely measured. PM_{10} was by far the most used metric - in 67% of the studies. Summary estimates of NO_2 were generally robust to adjustment for PM_{10}. However, PM_{10} may not adequately reflect the toxic component of PM because it reflects a number of sources, which do not include combustion / traffic, that are not shared with NO_2. Where the data permitted meta-analysis, robustness of the NO_2 associations to adjustment for $PM_{2.5}$ and Black Smoke was observed. Few data were available to permit an assessment of the extent to which the NO_2-associations are sensitive to control for combustion derived particles such as Black Carbon or ultrafine particles. This has also been noted by others.[7-8,24]

Given that the sources and composition of PM vary by location, and hence its toxicity, it cannot be assumed that PM represents the same thing in each study (city/country). In view of the differential toxicity of PM, it is preferable to examine individual studies that used more than one particle metric to investigate possible confounding of the NO_2 associations by PM when answering the research question, because they 'tested' the robustness of the NO_2-associations to different fractions / components of the ambient aerosol in the same location. Unfortunately, such studies were few in number (8), but their findings support the view that the associations of NO_2 with major health outcomes are robust to adjustment for PM measured in different ways.

We observed confounding of the associations between daily PM and mortality outcomes by NO_2. This suggests that NO_2, rather than the PM metrics examined, is a better predictor of the observed mortality effects in the cities examined. An alternative interpretation may be that daily variation in NO_2 in the cities better represents the mortality effects of daily variations in the complex urban air pollution mixture or an unknown toxic entity than the metrics of PM used in the analyses. Some caution is however needed in drawing conclusions about the analysis of PM estimates because it only reflects a subset of the available studies on PM. Whether the results are a feature of the subset of studies examined is unclear, and formal meta-analysis of the full body of PM estimates, similar to the current review, is warranted. This may provide further insights into whether the different fractions/component of PM might show different sensitivity to adjustment for NO_2.

Our results for PM are in contrast to the predominant views in the literature: although confounding of the PM-mortality associations by NO_2 has been observed in some time-series studies[19, 25-26] and noted in reviews[6], the general consensus is that the PM-mortality estimates are robust to adjustment for co-pollutants[6]. The associations have been regarded as reflecting a causal relationship, and experimental evidence has been used to support this. There is a lack of

experimental evidence for NO_2 at current ambient concentrations and for cardiovascular endpoints, and this has contributed to uncertainty regarding whether NO_2 is causally related to health.

We also found evidence of high heterogeneity between the geographic specific summary estimates of NO_2, which suggests that it cannot be assumed that the results for one city (region) represent the results for all cities (regions). For all-cause mortality and 24 hour NO_2, the high heterogeneity between WHO region-specific estimates was completely removed after control for PM (I^2 from 66.9% to 0%), suggesting that some study estimates were a bit extreme in comparison with others in the meta-analysis, but were less so after adjustment for PM. Geographical variation in effect estimates may be due to variations in population characteristics and in pollution sources, mixtures, and ambient concentrations. However, none of the variables used to represent the pollution and meteorological environments in the cities examined accounted for the high between-study variability we observed. Further work is therefore required to investigate potential explanations for the heterogeneity.

Results from the studies published since our literature search cut-off are summarised and discussed in Appendix 1 of the supplementary material. The studies indicate that, in general, the associations between NO_2 and mortality and hospital admissions remain after control for PM. This is in keeping with the findings set-out in this paper.

In addition to the issue of confounding, studies have examined the potential for factors (for example, season, socio-economic status, age, etc.) to modify the relationship between daily NO_2 and mortality or hospital admissions. Few studies have however examined modification of the associations of NO_2 with health by particulate air pollution. The available evidence suggests that the size of an NO_2 association may be dependent on concentrations of PM_{10}.[19] However, studies have also observed the potential for daily NO_2 to modify the relationship between PM and mortality.[33] The few available data on this issue come largely from the US and Europe, but interaction between NO_2 and PM (on cardiac hospitalisation) has also been observed in Hong Kong.[34] Further research on this aspect of the NO_2-PM issue is needed.

Our review supports the conclusions of recent narrative reviews,[7-8] but also provides meta-analytical estimates based on two-pollutant model estimates of NO_2 from the worldwide data. Taken together with the recent quantitative reviews of cohort studies on long-term exposure to NO_2 and mortality[27-28] and of short-term exposure to NO_2 and respiratory symptoms in children with asthma from panel studies,[8, 29] the evidence suggests a need for re-evaluation of the approach to health risk assessment (hazard identification and health impact assessment) for air pollution, an activity which has long been dominated by PM.[30] The current review suggests that the relationship between temporal variations in PM and mortality may not be as robust to control for NO_2 as previously thought. We note also that attenuation of PM-mortality estimates following control for NO_2 has been observed in long-term exposure studies.[31-32] These findings

could have implications for the calculation of health impacts attributable to these pollutants and for possible double counting of effects.

In summary, we identified evidence of associations between NO_2 and adverse health outcomes that are independent of PM mass. However, there was limited evidence on adjustment of the NO_2-associations for primary combustion particles which are thought to be responsible for the NO_2-associations. Therefore, some uncertainty remains regarding possible confounding and health impact assessments should reflect this.

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Two authors of the review – ICM and RWA – undertook the literature search.
ICM read all papers, checked data prior to meta-analysis, and carried out all analyses.
RWA produced the statistical code in STATA used by ICM in the analyses.
ICM is responsible for the overall content as lead author of the paper.

DATA SHARING STATEMENT: No additional data are available.

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Legend (and footnotes) to Figures

Figure 1: All available studies providing two-pollutant model estimates for meta-analysis for all-cause mortality, all ages, 24 hour NO_2

Footnotes to Figure 1

1000xln(RR) approximates to a percentage change per 10 μg/m^3
* Single-pollutant model estimate for days with both NO_2 and visibility (Coefficient of Haze, COH) data in Burnett et al, 2004 [RMID 3000].

Figure 2: All studies providing two-pollutant model estimates for all-cause mortality, all ages, PM adjusted for 24 hour NO_2

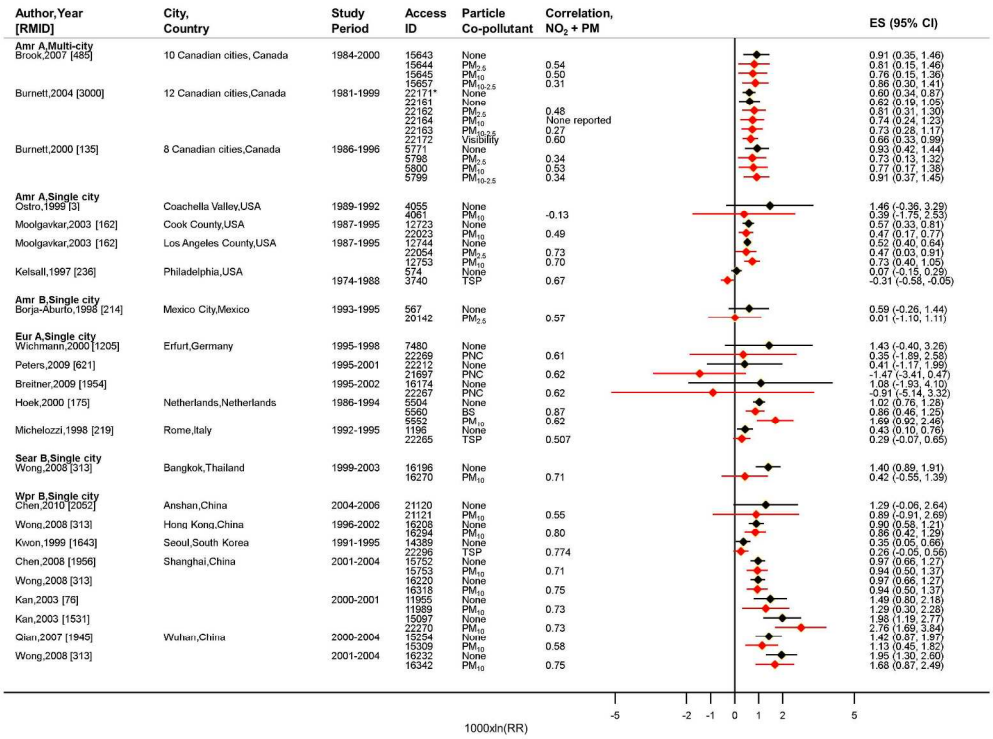


Figure 1: All available studies providing two-pollutant model estimates for meta-analysis for all-cause mortality, all ages, 24 hour NO2
485x359mm (300 x 300 DPI)

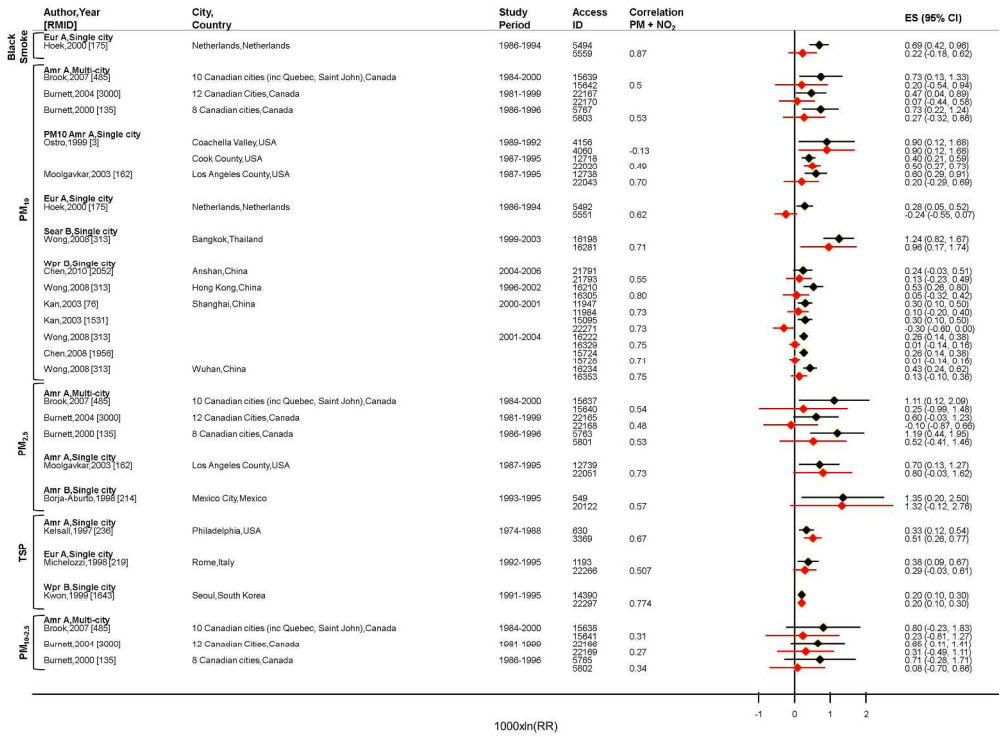


Figure 2: All studies providing two-pollutant model estimates for all-cause mortality, all ages, PM adjusted for 24 hour NO2
483x367mm (300 x 300 DPI)

Distinguishing the associations of short-term exposure to outdoor nitrogen dioxide with mortality and hospital admissions from those of particulate matter

IC Mills, RW Atkinson, HR Anderson, RL Maynard, DP Strachan

Online Supplementary Material

Contents list

5. List of figures

Literature search criteria

Bibliographic databases were searched to identify peer-reviewed time-series (and case crossover) studies of the relationship between daily concentrations of NO_2 and daily mortality or hospital admissions.

Bibliographic databases searched: PubMed, EMBASE or Web of Science (which includes the Science Citation Index).

The search terms used are shown below and minor refinements were made for use in each bibliographic database.

> (air pollution OR pollution OR nitric oxide* OR nitrogen dioxide?) AND (timeseries OR time series OR time-series OR daily OR case-crossover) AND (mortality OR death* OR dying OR hospital admission* OR admission* OR emergency room OR visit* OR attendance* OR 'a&e' OR 'a and e' OR accident and emergency OR general pract* OR physician* OR consultation* OR emergency department*)

No restriction on language was applied. The bibliographic databases were searched for peer-reviewed papers published up to May 2011.

List of countries by WHO Region and mortality strata

Reproduced from The World Health Report 2002 (http://www.who.int/whr/2002/en/, accessed 7th February 2015)

African Region

Algeria — AFR-D
Angola – AFR-D
Benin – AFR-D
Botswana – AFR-E
Burkina Faso – AFR-D
Burundi – AFR-E
Cameroon – AFR-D
Cape Verde – AFR-D
Central African Republic – AFR-E
Chad – AFR-D
Comoros – AFR-D
Congo – AFR-E
Côte d'Ivoire – AFR-E
Democratic Republic of the Congo – AFR-E
Equatorial Guinea – AFR-D
Eritrea – AFR-E
Ethiopia – AFR-E
Gabon – AFR-D
Gambia – AFR-D
Ghana – AFR-D
Guinea – AFR-D
Guinea-Bissau – AFR-D
Kenya – AFR-E
Lesotho – AFR-E
Liberia – AFR-D
Madagascar – AFR-D
Malawi – AFR-E
Mali – AFR-D
Mauritania – AFR-D
Mauritius – AFR-D
Mozambique – AFR-E
Namibia – AFR-E
Niger – AFR-D
Nigeria – AFR-D
Rwanda – AFR-E
Sao Tome and Principe – AFR-D
Senegal – AFR-D
Seychelles – AFR-D
Sierra Leone – AFR-D
South Africa – AFR-E
Swaziland – AFR-E
Togo – AFR-D
Uganda – AFR-E
United Republic of Tanzania – AFR-E
Zambia – AFR-E
Zimbabwe – AFR-E

Region of the Americas

Antigua and Barbuda – AMR-B
Argentina – AMR-B
Bahamas – AMR-B
Barbados – AMR-B
Belize – AMR-B
Bolivia – AMR-D
Brazil – AMR-B
Canada – AMR-A
Chile – AMR-B
Colombia – AMR-B
Costa Rica – AMR-B
Cuba – AMR-A
Dominica – AMR-B
Dominican Republic – AMR-B
Ecuador – AMR-D
El Salvador – AMR-B
Grenada – AMR-B
Guatemala – AMR-D
Guyana – AMR-B
Haiti – AMR-D
Honduras – AMR-B
Jamaica – AMR-B
Mexico – AMR-B
Nicaragua – AMR-D
Panama – AMR-B
Paraguay – AMR-B
Peru – AMR-D
Saint Kitts and Nevis – AMR-B
Saint Lucia – AMR-B
Saint Vincent and the Grenadines – AMR-B
Suriname – AMR-B
Trinidad and Tobago – AMR-B
United States of America – AMR-A
Uruguay – AMR-B
Venezuela, Bolivarian Republic of – AMR-B

Eastern Mediterranean Region

Afghanistan – EMR-D
Bahrain – EMR-B
Cyprus – EMR-B
Djibouti – EMR-D
Egypt – EMR-D
Iran, Islamic Republic of – EMR-B
Iraq – EMR-D
Jordan – EMR-B
Kuwait – EMR-B
Lebanon – EMR-B
Libyan Arab Jamahiriya – EMR-B
Morocco – EMR-D
Oman – EMR-B
Pakistan – EMR-D
Qatar – EMR-B
Saudi Arabia – EMR-B
Somalia – EMR-D
Sudan – EMR-D
Syrian Arab Republic – EMR-B
Tunisia – EMR-B
United Arab Emirates – EMR-B
Yemen – EMR-D

Mortality strata
A. Very low child, very low adult
B. Low child, low adult
C. Low child, high adult
D. High child, high adult
E. High child, very high adult

European Region

Albania – EUR-B
Andorra – EUR-A
Armenia – EUR-B
Austria – EUR-A
Azerbaijan – EUR-B
Belarus – EUR-C
Belgium – EUR-A
Bosnia and Herzegovina – EUR-B
Bulgaria – EUR-B
Croatia – EUR-A
Czech Republic – EUR-A
Denmark – EUR-A
Estonia – EUR-C
Finland – EUR-A
France – EUR-A
Georgia – EUR-B
Germany – EUR-A
Greece – EUR-A
Hungary – EUR-C
Iceland – EUR-A
Ireland – EUR-A
Israel – EUR-A
Italy – EUR-A
Kazakhstan – EUR-C
Kyrgyzstan – EUR-B
Latvia – EUR-C
Lithuania – EUR-C
Luxembourg – EUR-A
Malta – EUR-A
Monaco – EUR-A
Netherlands – EUR-A
Norway – EUR-A
Poland – EUR-B
Portugal – EUR-A
Republic of Moldova – EUR-C
Romania – EUR-B
Russian Federation – EUR-C
San Marino – EUR-A
Slovakia – EUR-B
Slovenia – EUR-A
Spain – EUR-A
Sweden – EUR-A
Switzerland – EUR-A
Tajikistan – EUR-B
The former Yugoslav Republic of Macedonia – EUR-B
Turkey – EUR-B
Turkmenistan – EUR-B
Ukraine – EUR-C
United Kingdom – EUR-A
Uzbekistan – EUR-B
Yugoslavia – EUR-B

South-East Asia Region

Bangladesh – SEAR-D
Bhutan – SEAR-D
Democratic People's Republic of Korea – SEAR-D
India – SEAR-D
Indonesia – SEAR-B
Maldives – SEAR-D
Myanmar – SEAR-D
Nepal – SEAR-D
Sri Lanka – SEAR-B
Thailand – SEAR-B

Western Pacific Region

Australia – WPR-A
Brunei Darussalam – WPR-A
Cambodia – WPR-B
China – WPR-B
Cook Islands – WPR-B
Fiji – WPR-B
Japan – WPR-A
Kiribati – WPR-B
Lao People's Democratic Republic – WPR-B
Malaysia – WPR-B
Marshall Islands – WPR-B
Micronesia, Federated States of – WPR-B
Mongolia – WPR-B
Nauru – WPR-B
New Zealand – WPR-A
Niue – WPR-B
Palau – WPR-B
Papua New Guinea – WPR-B
Philippines – WPR-B
Republic of Korea – WPR-B
Samoa – WPR-B
Singapore – WPR-A
Solomon Islands – WPR-B
Tonga – WPR-B
Tuvalu – WPR-B
Vanuatu – WPR-B
Viet Nam – WPR-B

Metrics of particulate matter (PM) used in two-pollutant model analyses

Category of PM metric	Particulate pollutants which map to category
PM_{10}	PM_7; PM_{10}; PM_{13}; ln(PM_7); ln (PM_{13}); √(PM_{10}); ln(PM_{14});
$PM_{2.5}$	$PM_{2.5}$; PM<1; $PM_{0.5}$; Re-suspended Particulate Matter (RSPM); $PM_{2.5-1}$
$PM_{10-2.5}$	$PM_{10-2.5}$
Black Smoke	Black Smoke; ln(BS); sqrt(BS)
Particle Number Concentration (PNC)	10-100nm; PNC; <100nm; Nucleation <30nm; Aitken 30-100nm; Accumulation 100-290nm; NC 0.03-0.05; NC 0.05-0.1; NC 0.01-0.03; NC 0.01-0.1; $PM_{2.5}$ NC; $PM_{2.5-10}$ NC; PM_{10} NC; PNC size mode 12nm; PNC size mode 23nm; PNC size mode 57nm; PNC size mode 212nm; PNC size mode to 100nm; NC128; NC346; NC total; NC31; 10-100nm surface area
Carbon	Black Carbon (BC); Elemental Carbon (EC); Organic Carbon (OC); $PM_{2.5}$ OC; $PM_{2.5}$ EC; $PM_{2.5}$ OM; Total Carbon;
Total Suspended Particles (TSP)	TSP; ln(TSP); TSP-PM_{10}; PM_{20}; SPM; sqrt(TSP); blackness of TSP filters
Visibility	Coefficient of haze (COH); light scattering ($PM_{2.5}$ indicator = nephelometry measure instead of gravimetric); dry light scattering (PM<1 indicator); bsp ($PM_{2.5}$ indicator = an indicator for particles 01-2 um (nephelometry measure instead of gravimetric)); visibility ($PM_{2.5}$ indicator = digital photography visibility); $PM_{2.5}$ nephelpmetry ($PM_{2.5}$ indicator=(nephelometry measure*100,000-.01)/0.28.)

Table S1: Meta-analysis results for all-cause mortality in all-ages associated with a 10 µg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**22/10**	**5/1 (26)**	**0.78 (0.47, 1.09)**		**0.60 (0.33, 0.87)**	
AMR A	5/10	4/1 (16)	0.48 (0.24, 0.72)		0.55 (0.12, 0.99)	
AMR B	1/0	1/0 (1)	0.59 (-0.26, 1.45)	66.9	0.01 (-1.10, 1.12)	0
EUR A	6/0	3/0 (3)	0.71 (0.20, 1.22)		0.43 (-0.86, 1.73)	
SEAR B	1/0	1/0 (1)	1.41 (0.89, 1.93)		0.42 (-0.55, 1.40)	
WPR B	9/0	5/0 (5)	1.00 (0.54, 1.46)		0.85 (0.37, 1.33)	
NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	13/3	4/1 (21)	0.92 (0.58, 1. 72)	88.7	0.85 (0.52, 1.18)	72
NO_2 + $PM_{2.5}$	2/3	2/1 (14)	0.53 (0.42, 0.64)	0	0.57 (0.24, 0.89)	6.9
NO_2 + $PM_{10-2.5}$	0/3	0/1 (12)	0.62 (0.19, 1.06)	-	0.73 (0.28, 1.18)	-
NO_2 + Visibility	0/1	0/1 (12)	0.60 (0.34, 0.87)	-	0.66 (0.33, 1.00)	-
NO_2 + BS	1/0	-				
NO_2 + TSP	3/0	-	Insufficient estimates for meta-analysis			
NO_2 + PNC	3/0	-				

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S2: Meta-analysis results for all-cause mortality in all-ages associated with a 10 µg/m³ increase in 1 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2 single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI) [c]	I^2 (%)[d]	Random Effects (95% CI) [c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**2/4**	**2/2 (36)**	**0.32 (-0.02, 0.66)**		**0.20 (-0.24, 0.65)**	
AMR A	1/0	1/0 (1)	1.19 (0.20, 2.19)	93.8	0.78 (-0.35, 1.92)	95.2
AMR B	1/0	1/0 (1)	-0.09 (-0.19, 0.00)		-0.28 (-0.38, -0.19)	
EUR A	0/3	0/1 (30)	0.30 (0.22, 0.38)		0.27 (0.16, 0.38)	
WPR A	0/1	0/1 (4)	0.63 (0.21, 1.05)		0.52 (0.05, 1.00)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	2/1	2/1 (32)	0.22 (-0.15, 0.60)	95.4	0.10 (-0.40, 0.61)	96.5
NO_2 + BS	0/2	0/1 (30)	0.30 (0.22, 0.38)	-	0.33 (0.23, 0.43)	-
NO_2 + Visibility	0/1	0/1 (4)	0.63 (0.21, 1.05)	-	0.52 (0.05, 1.00)	-

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S3: Meta-analysis results for all cardiovascular mortality in all-ages associated with a 10 μg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI) [c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**14/0**	**5/0 (10)**	**1.07 (0.43, 1.72)**		**0.82 (0.22, 1.42)**	
AMR A	3/0	2/0 (2)	0.52 (0.37, 0.68)		0.47 (0.06, 0.88)	
AMR B	1/0	1/0 (1)	0.73 (-0.87, 2.36)	72	-0.36 (-2.47, 1.81)	58.8
EUR A	3/0	2/0 (2)	1.97 (-0.66, 4.66)		1.81 (0.67, 2.97)	
SEAR B	1/0	1/0 (1)	1.78 (0.47, 3.11)		-0.51 (-2.88, 1.92)	
WPR B	6/0	4/0 (4)	1.37 (0.87, 1.87)		1.13 (0.67, 1.58)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	10/0	4/0 (8)	0.99 (0.49, 1.49)	80.1	0.87 (0.28, 1.46)	61
NO_2 + $PM_{2.5}$	2/0	2/0 (2)	Insufficient estimates for meta-analysis			
NO_2 + BS	2/0	2/0 (2)	Insufficient estimates for meta-analysis			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 μg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S4: Meta-analysis results for all respiratory mortality in all-ages associated with a 10 µg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI) [c]	I^2 (%)[d]	Random Effects (95% CI) [c]	I^2 (%) [d]
Overall, NO_2 + PM (any PM metric)[e]	**8/0**	**3/0 (6)**	**1.42 (0.64, 2.21)**		**1.13 (0.46, 1.81)**	
AMR B	1/0	1/0 (1)	1.21 (-1.43, 3.91)	0	0.61 (-2.83, 4.17)	0
SEAR B	1/0	1/0 (1)	1.05 (-0.60, 2.73)		0.32 (-2.66, 3.39)	
WPR B	6/0	4/0 (4)	1.57 (0.63, 2.51)		1.20 (0.50, 1.90)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	7/0	2/0 (5)	1.44 (0.63, 2.27)	0	1.15 (0.47, 1.84)	0
NO_2 + $PM_{2.5}$	1/0	1/0 (1)	Insufficient estimates for meta-analysis			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S5: Meta-analysis results for stroke mortality in all-ages associated with a 10 µg/m³ increase in 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	NO_2, single-pollutant		NO_2 adjusted for PM	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
Overall, NO_2 + PM (any PM metric)[e]	**8/0**	**2/0 (5)**	**1.76 (0.68, 2.85)**	25.6	**1.12 (0.50, 1.74)**	0
SEAR B	1/0	1/0 (1)	2.80 (0.70, 4.94)		1.60 (-2.20, 5.55)	
WPR B	7/0	4/0 (4)	1.47 (0.67, 2.27)		1.11 (0.48, 1.74)	
Overall, NO_2 + PM (specific PM metric)[f]						
NO_2 + PM_{10}	7/0	2/0 (4)	1.83 (0.76, 2.92)	9.3	1.04 (0.36, 1.73)	0
NO_2 + TSP	1/0	1/0 (1)	Insufficient estimates for meta-analysis			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs of single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ NO_2.
d -I^2 statistic for heterogeneity between WHO region specific estimates
e -Overall (global) summary estimate of NO_2 adjusted for PM and by WHO regions. Protocol for selection of PM metrics defined in Chapter 4 (Methods). Estimate numbers for Overall refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
f – Overall summary estimate of NO_2 adjusted for specific metrics of PM.
AMR, region of the Americas; EUR, European region; WPR, Western Pacific region; SEAR, South East Asian region.

Table S6: Meta-analysis results for all-cause mortality in all-ages associated with a 10 µg/m³ increase in metrics of Particulate Matter (PM) - estimates adjusted for 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	PM, single-pollutant		PM adjusted for 24 hour NO_2	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
PM_{10}						
Overall[e]	**12/3**	**4/1 (21)**	**0.51 (0.29, 0.74)**	**82.9**	**0.18 (-0.11, 0.47)**	**71.9**
AMR A	3/3	3/1 (15)	0.49 (0.31, 0.66)		0.33 (-0.04, 0.71)	
EUR A	1/0	1/0 (1)	0.28 (0.05, 0.52)		-0.24 (-0.55, 0.07)	
SEAR B	1/0	1/0 (1)	1.25 (0.82, 1.68)		0.96 (0.17, 1.76)	
WPR B	7/0	4/0 (4)	0.35 (0.22, 0.47)		0.05 (-0.06, 0.17)	
$PM_{2.5}$						
Overall[e]	**2/3**	**2/1 (14)**	**0.74 (0.34, 1.14)**	**19.6**	**0.54 (-0.25, 1.34)**	**23.9**
AMR A	1/3	1/1 (13)	0.66 (0.23, 1.08)		0.33 (-0.54, 1.22)	
AMR B	1/0	1/0 (1)	1.36 (0.20, 2.53)		1.33 (-0.12, 2.80)	
$PM_{10-2.5}$	**0/3**	**0/1 (12)**	**0.65 (-0.10, 1.42)**	**-**	**0.31 (-0.49, 1.11)**	**-**
Visibility	**0/1**	**0/1 (12)**	**40.93 (23.39, 60.97)**	**-**	**12.42 (-4.47, 32.29)**	**-**
Black Smoke	**1/0**	**-**	**Insufficient estimates for meta-analysis**			
PNC	**3/0**	**-**				
TSP	**3/0**	**-**				

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the selected estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage change (95% confidence interval) in the risk of death per 10 µg/m³ increase in 24 hour measures of PM. Estimates presented for 'Overall' and by WHO Region.
d -I^2 statistic for heterogeneity between WHO region-specific effect estimates
e -Estimate numbers for 'Overall' refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO regions.
AMR, region of the Americas; Eur, European region; WPR, Western Pacific region; SEAP, South East Asian region.

Table S7: Meta-analysis results for all cardiovascular mortality in all-ages associated with a 10 μg/m³ increase in metrics of Particulate Matter (PM) - estimates adjusted for 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	PM, single-pollutant		PM adjusted for 24 hour NO_2	
			Random Effects (95% CI)[c]	I^2 (%)[d]	Random Effects (95% CI)[c]	I^2 (%)[d]
PM_{10}						
Overall[e]	**9/0**	**4/0 (8)**	**0.48 (0.18, 0.78)**	**66.5**	**0.19 (-0.21, 0.59)**	**67.1**
AMR A	2/0	2/0 (2)	0.43 (0.17, 0.70)		0.33 (0.03, 0.62)	
EUR A	1/0	1/0 (1)	0.19 (-0.16, 0.54)		-0.32 (-0.80, 0.17)	
SEAR B	1/0	1/0 (1)	1.90 (0.80, 3.01)		2.27 (0.24, 4.34)	
WPR B	5/0	4/0 (4)	0.48 (0.26, 0.70)		0.22 (-0.09, 0.54)	
$PM_{2.5}$	**2/0**	**-**	**Insufficient estimates for meta-analysis**			
Black Smoke	**1/0**	**-**				

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the selected estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage increase (95% confidence interval) in the risk of death per 10 μg/m³ increase in 24 hour measures of PM. Estimates presented for 'Overall' and by WHO Region.
d -I^2 statistic for heterogeneity between WHO region-specific effect estimates
e -Estimate numbers for 'Overall' refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO Regions.
AMR, region of the Americas; Eur, European region; WPR, Western Pacific region; SEAP, South East Asian region.

Table S8: Meta-analysis results for all respiratory mortality in all-ages associated with a 10 µg/m³ increase in metrics of Particulate Matter (PM) - estimates adjusted for 24 hour NO_2

	All SC/MC[a]	Selected SC/MC (cities)[b]	PM, single-pollutant		PM adjusted for 24 hour NO_2	
			Random Effects (95% CI) [c]	I^2 (%)[d]	Random Effects (95% CI) [c]	I^2 (%)[d]
PM_{10}						
Overall[e]	**6/0**	**2/0 (6)**	**0.58 (0.22, 0.93)**	**0**	**0.13 (-0.18, 0.44)**	**0**
SEAR B	1/0	1/0 (1)	1.01 (-0.36, 2.40)		0.79 (-1.70, 3.34)	
WPR B	5/0	4/0 (4)	0.54 (0.17, 0.92)		0.12 (-0.19, 0.43)	
$PM_{2.5}$	**1/0**	**-**	**Insufficient estimates for meta-analysis**			

a -Numbers of pairs of single-city (SC) / multi-city (MC) estimates available from all studies
b -Numbers of pairs single-city (SC) / multicity (MC) estimates selected for meta-analysis. The number of cities represented by the selected estimates is given in brackets.
c – Random-effects summary estimates presented as a percentage increase (95% confidence interval) in the risk of death per 10 µg/m³ increase in 24 hour measures of PM. Estimates presented for 'Overall' and by WHO Region.
d -I^2 statistic for heterogeneity between WHO region-specific effect estimates
e -Estimate numbers for 'Overall' refer to: (i) the number of single-city (SC) / multi-city (MC) estimates available from all studies; (ii) for selected estimates, it is the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO Regions.
WPR, Western Pacific region; SEAR, South East Asian region.

Figure S1: Studies and two-pollutant model estimates selected for meta-analysis for all-cause mortality, all ages, 24 hour NO_2

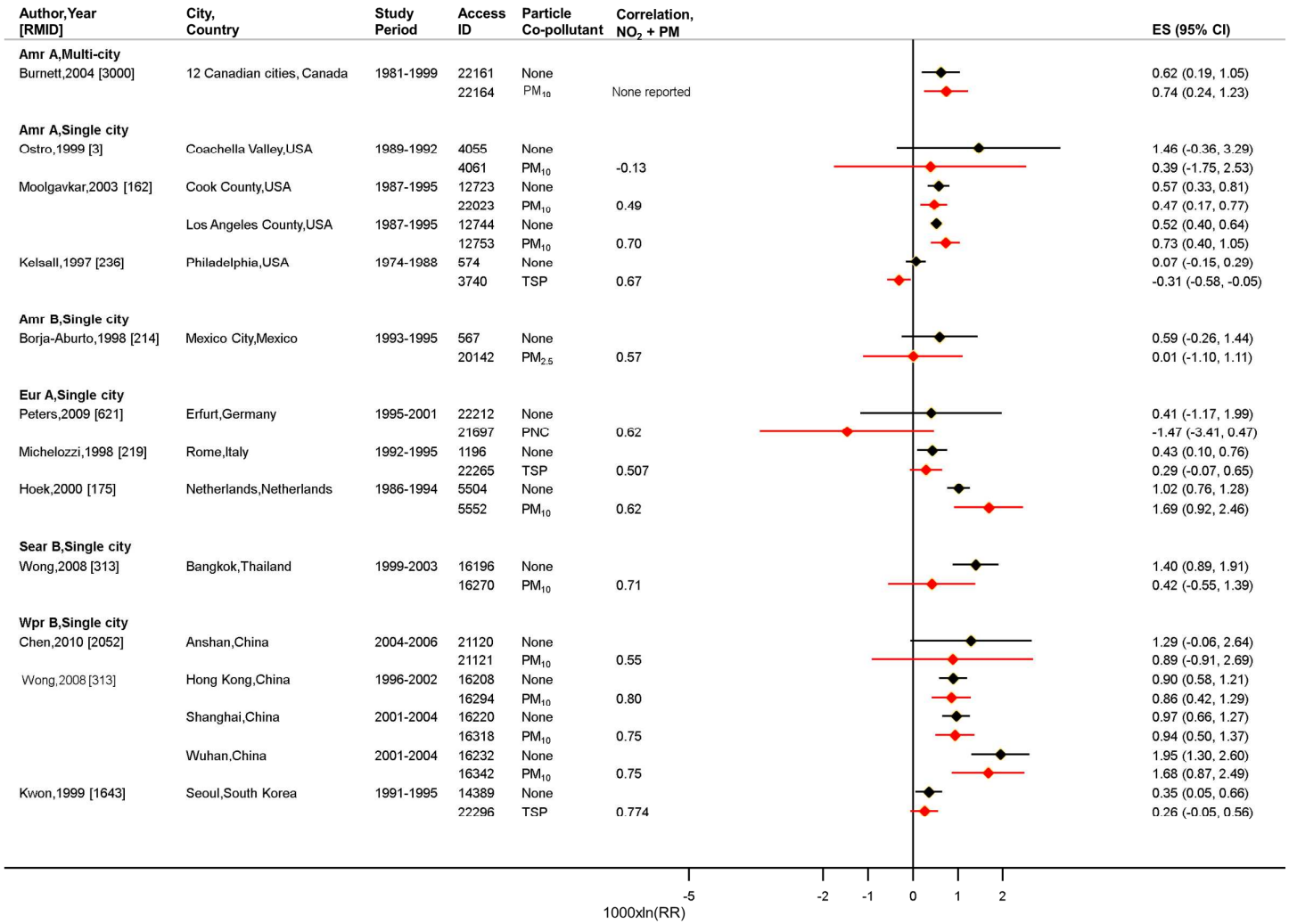


Figure S2: All available studies providing two-pollutant model estimates for meta-analysis for all-cause mortality, all ages, 1 hour NO_2

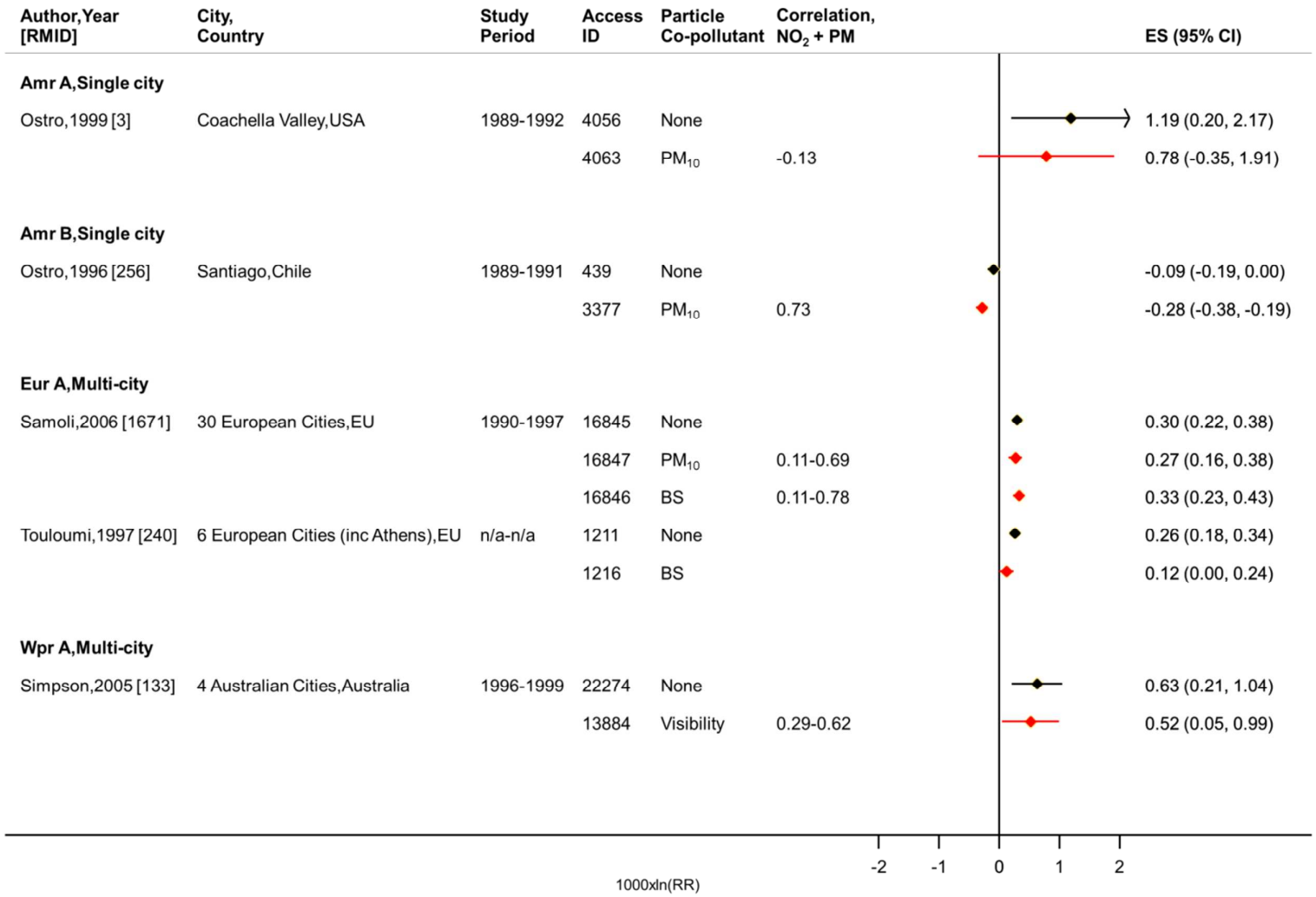


Figure S3: All available studies providing two-pollutant model estimates for meta-analysis for all cardiovascular mortality, all ages, 24 hour NO_2

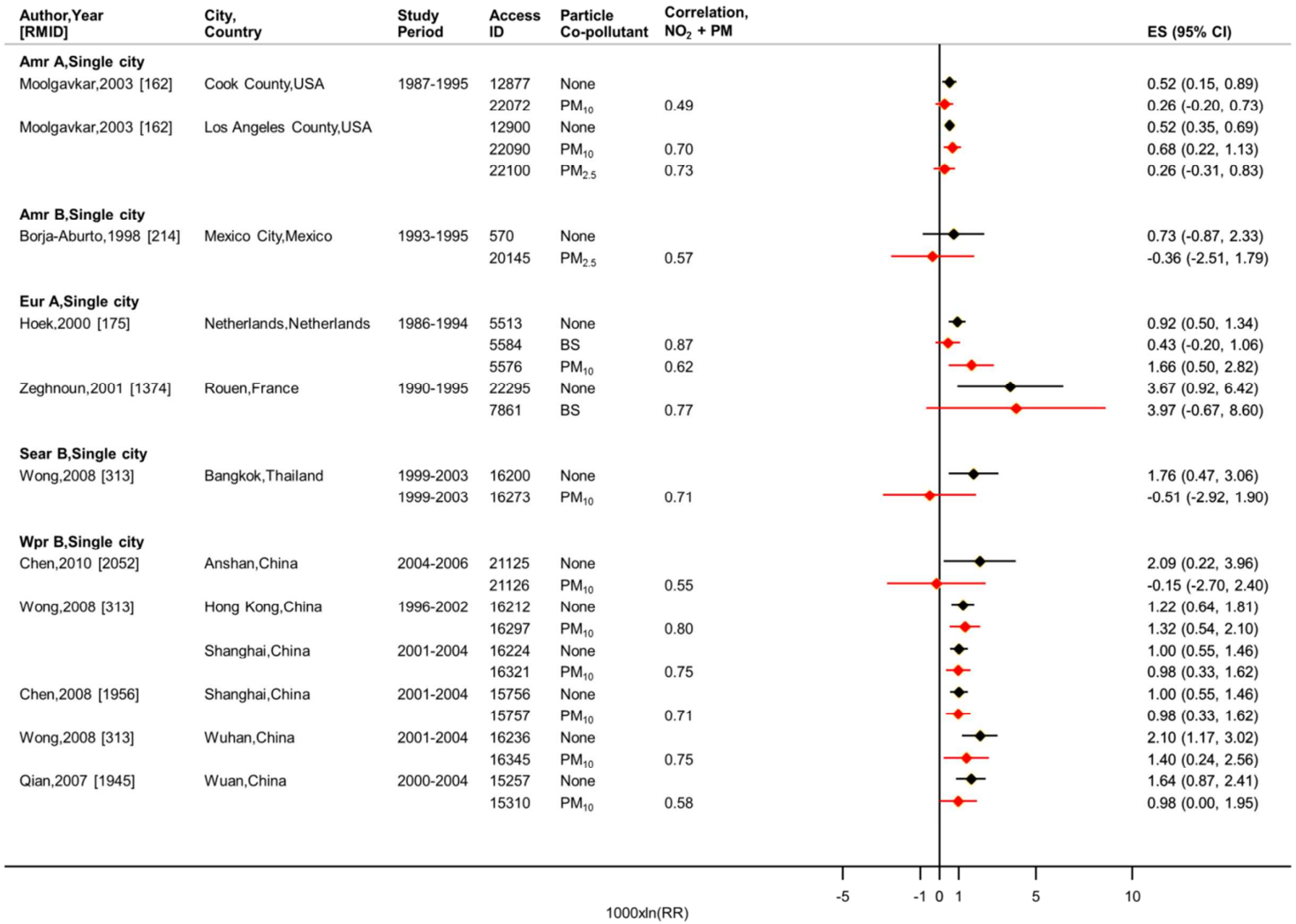


Figure S4: All available studies providing two-pollutant model estimates for meta-analysis for all cardiovascular mortality, all ages, 1 hour NO_2

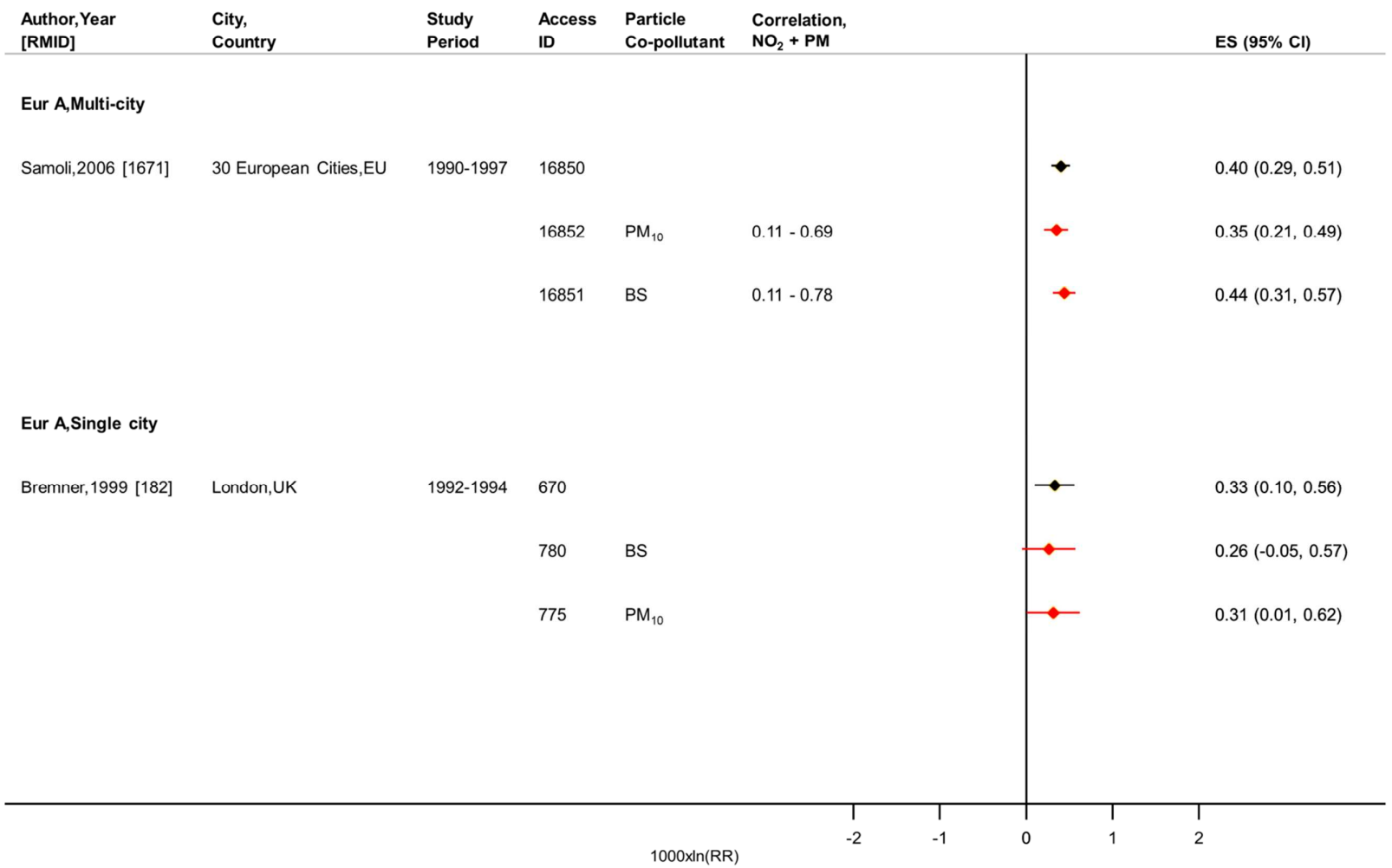


Figure S5: All available studies providing two-pollutant model estimates for meta-analysis for all respiratory mortality, all ages, 24 hour NO_2

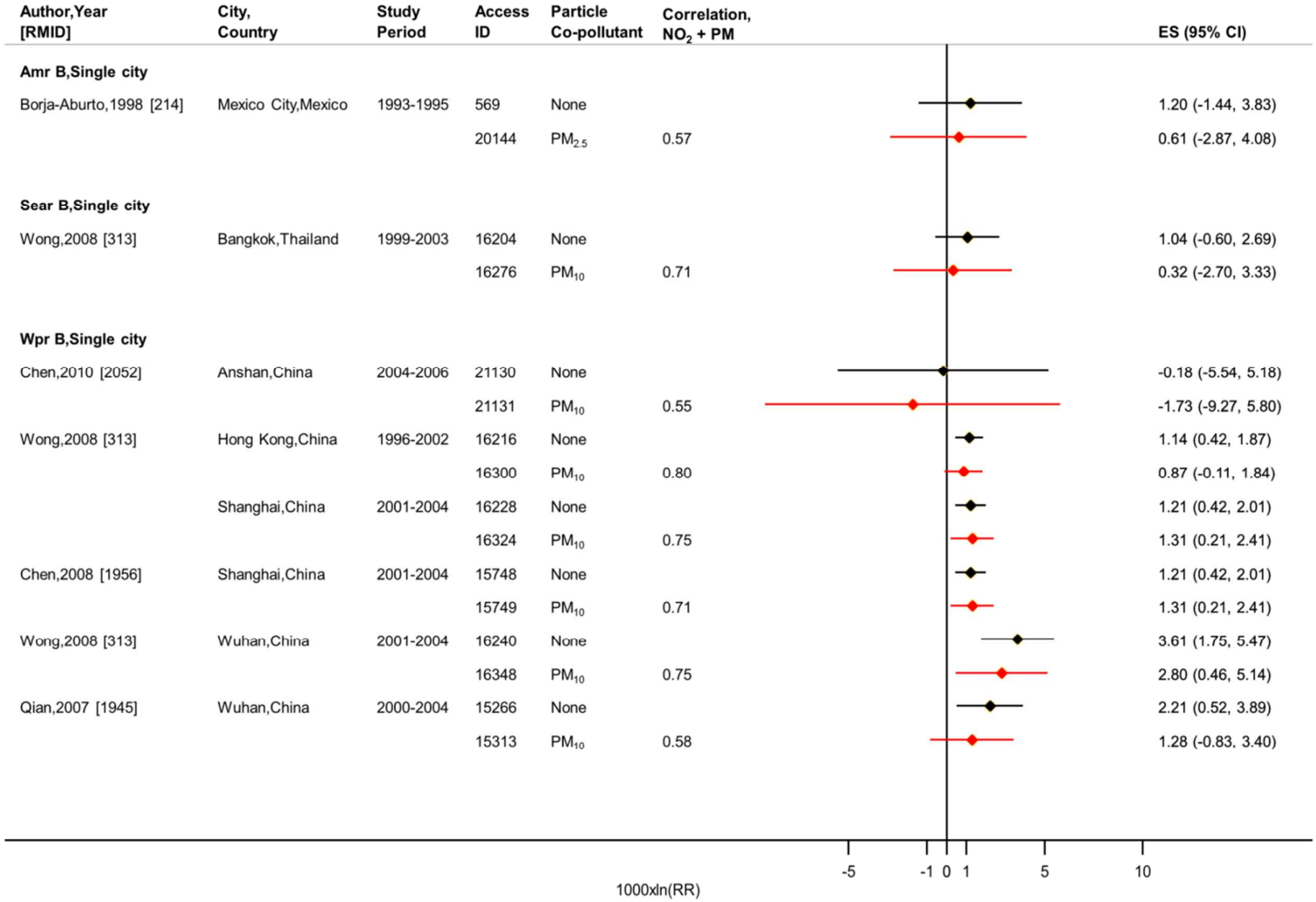


Figure S6: All available studies providing two-pollutant model estimates for meta-analysis for stroke mortality, all ages, 24 hour NO_2

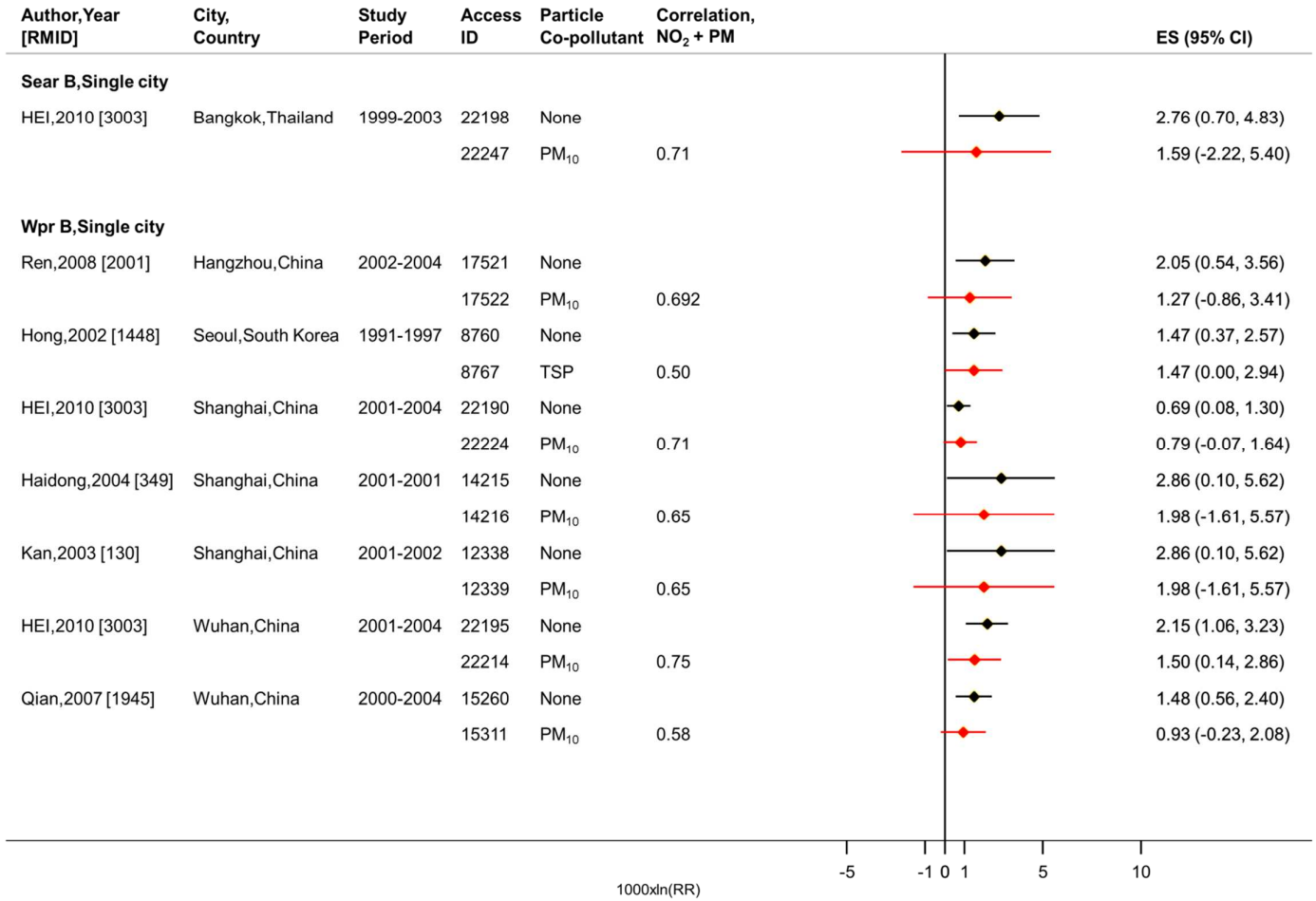


Figure S7: All available studies providing two-pollutant model estimates for meta-analysis for cardiac mortality, all ages, 24 hour NO_2

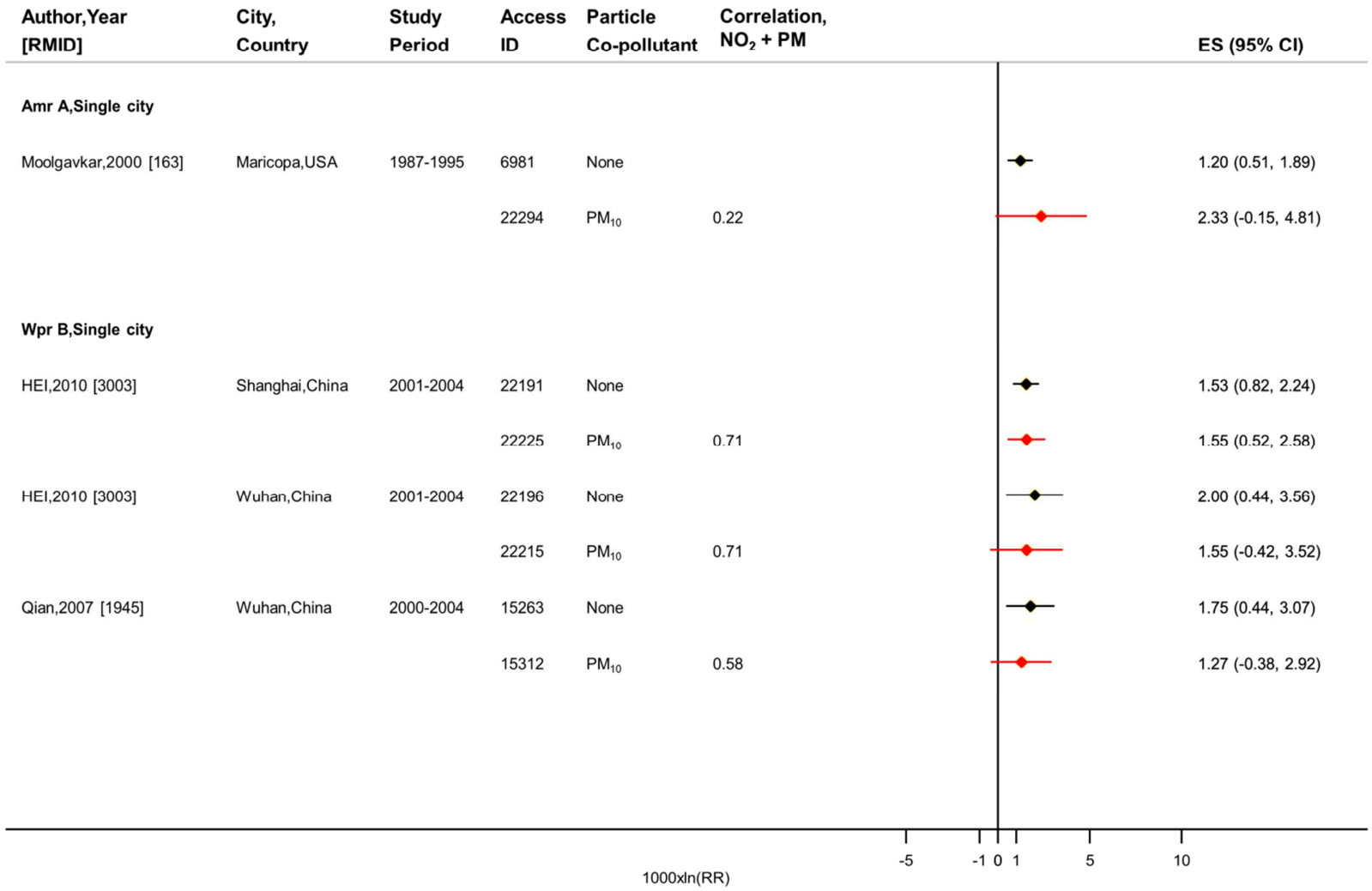


Figure S8: All available studies providing two-pollutant model estimates for meta-analysis for COPD (including asthma), Lower Respiratory Infections (LRI), ischaemic heart disease (IHD), dysrhythmia (DYS) mortality, all ages, 24 hour NO_2

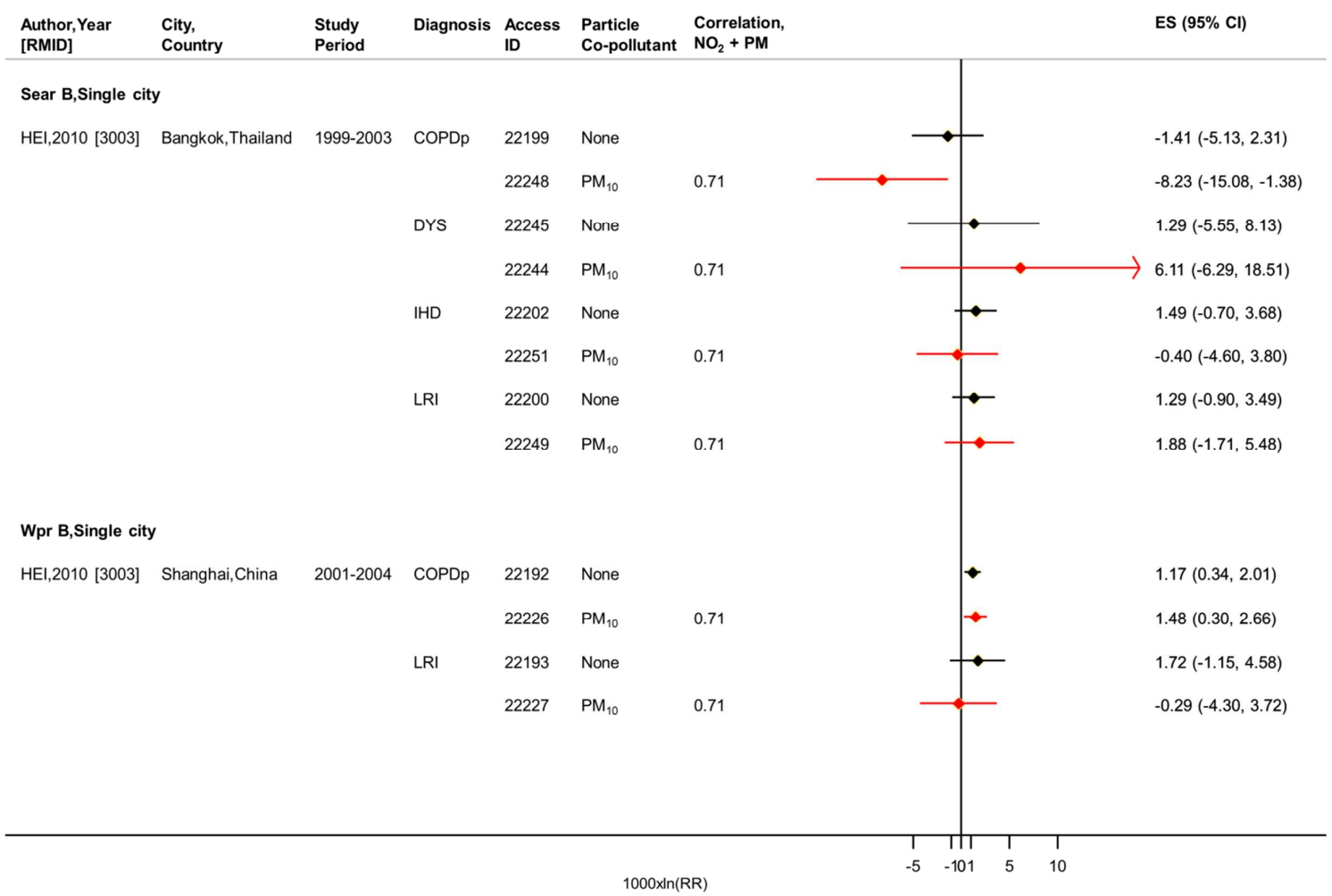


Figure S9: Studies and two-pollutant model estimates selected for meta-analysis for all cardiovascular mortality, all ages, 24 hour NO_2

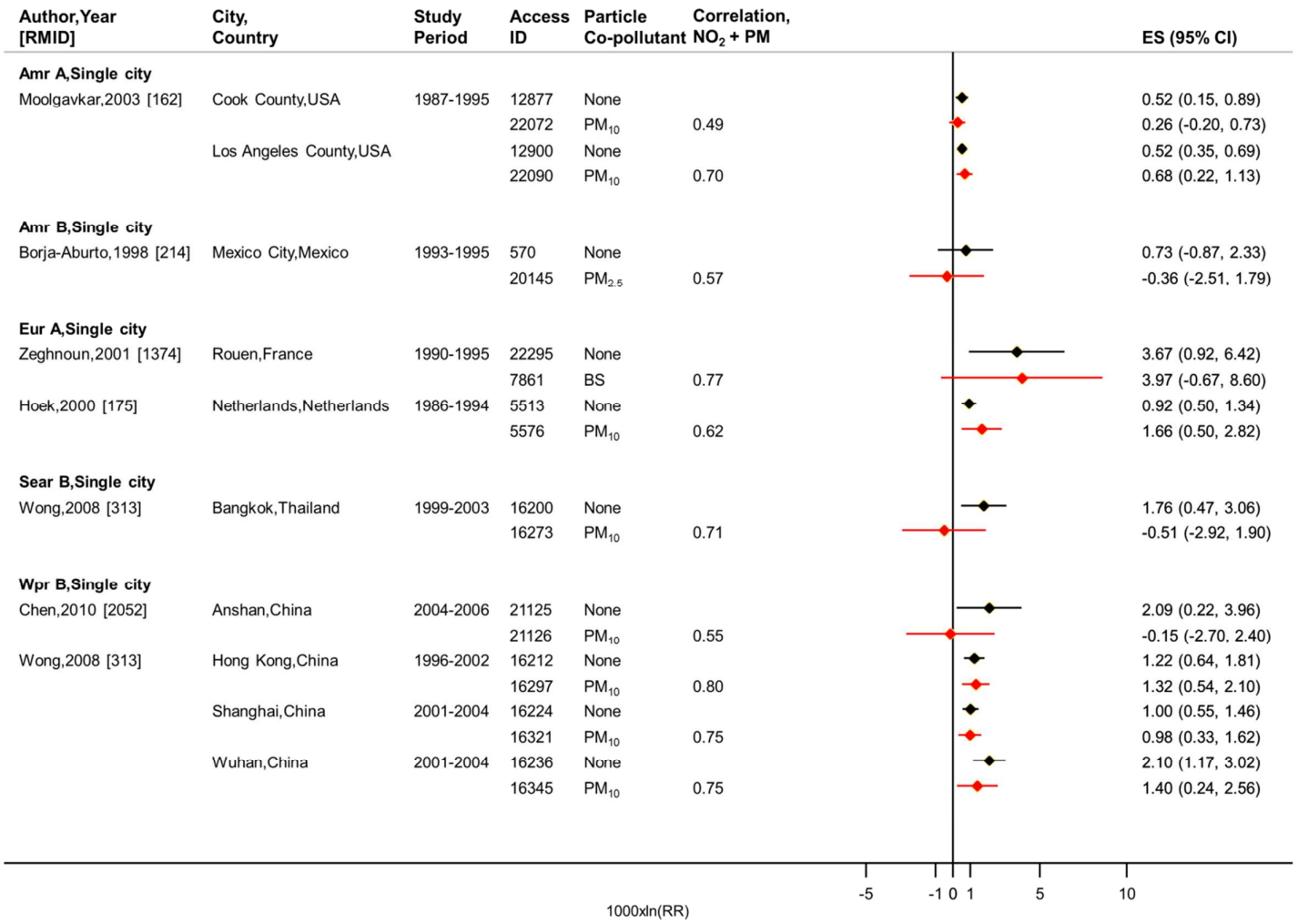


Figure S10: Studies and two-pollutant model estimates selected for meta-analysis for all respiratory mortality, all ages, 24 hour NO_2

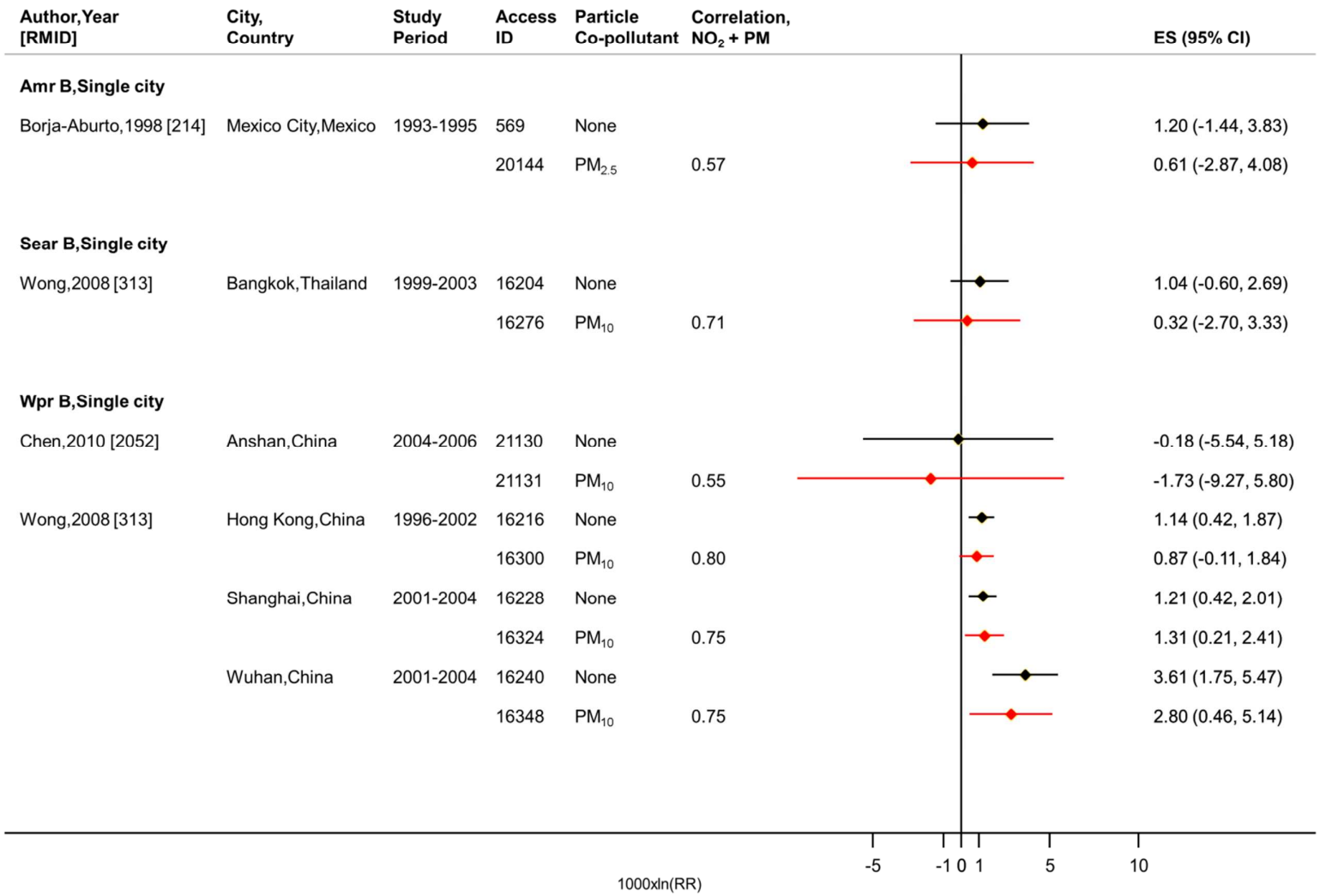


Figure S11: All studies providing two-pollutant model estimates for all-cause mortality, all-ages, ultrafine particles (UFP) adjusted for 24 hour NO_2

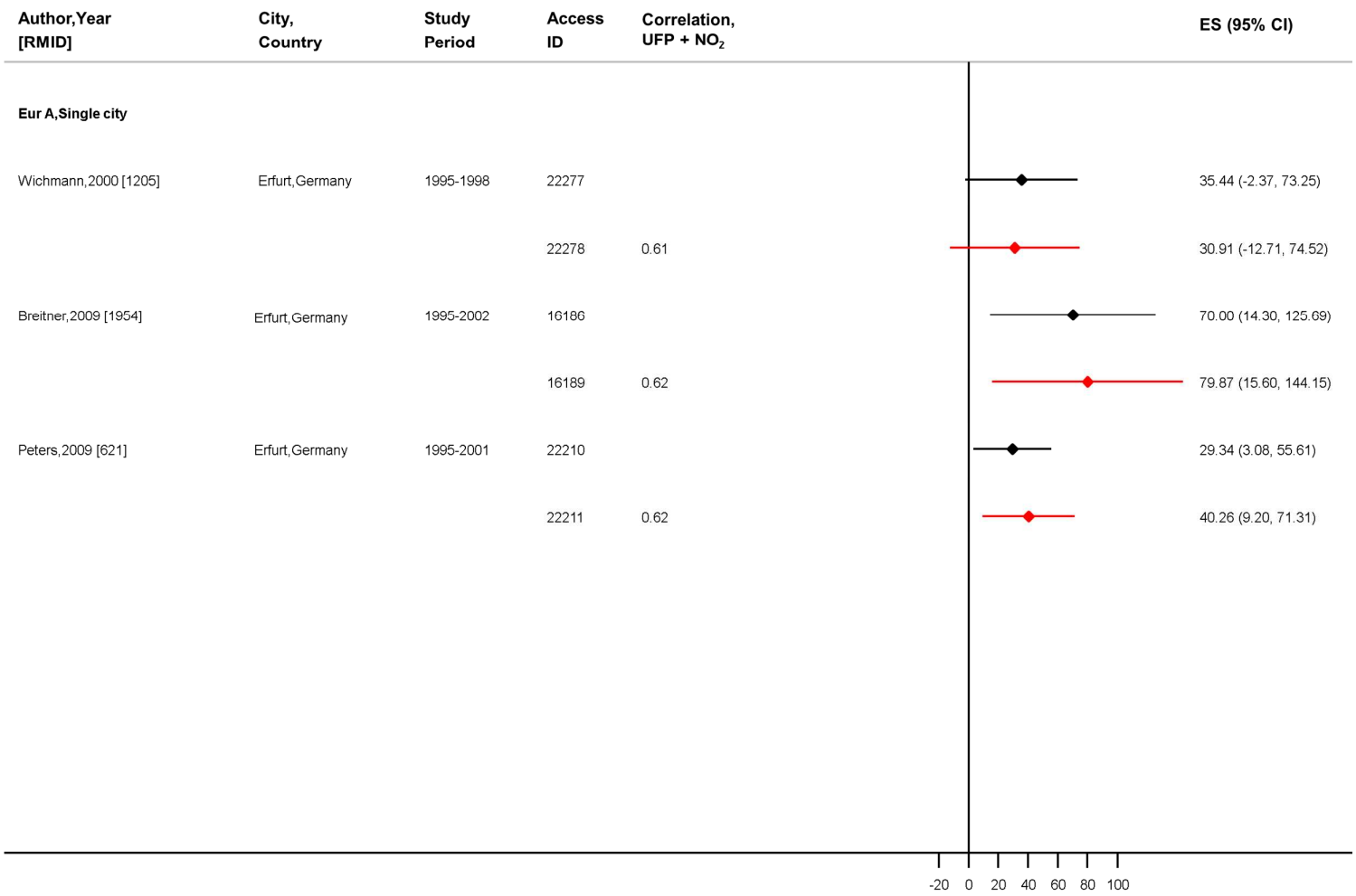


Figure S12: All studies providing two-pollutant model estimates for all cardiovascular mortality, all-ages, PM adjusted for 24 hour NO_2

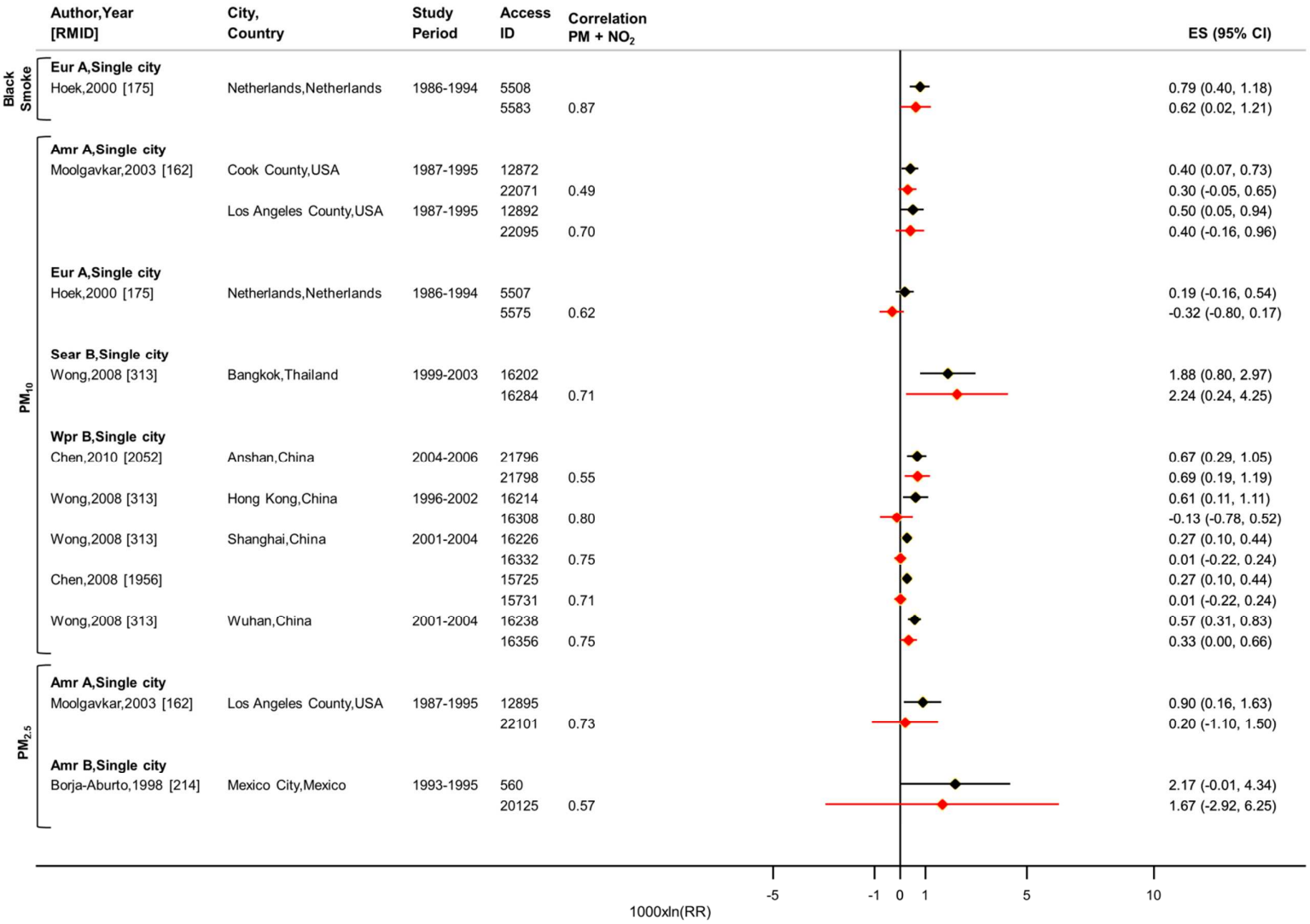


Figure S13: All studies providing two-pollutant model estimates for all respiratory mortality, all-ages, PM adjusted for 24 hour NO_2

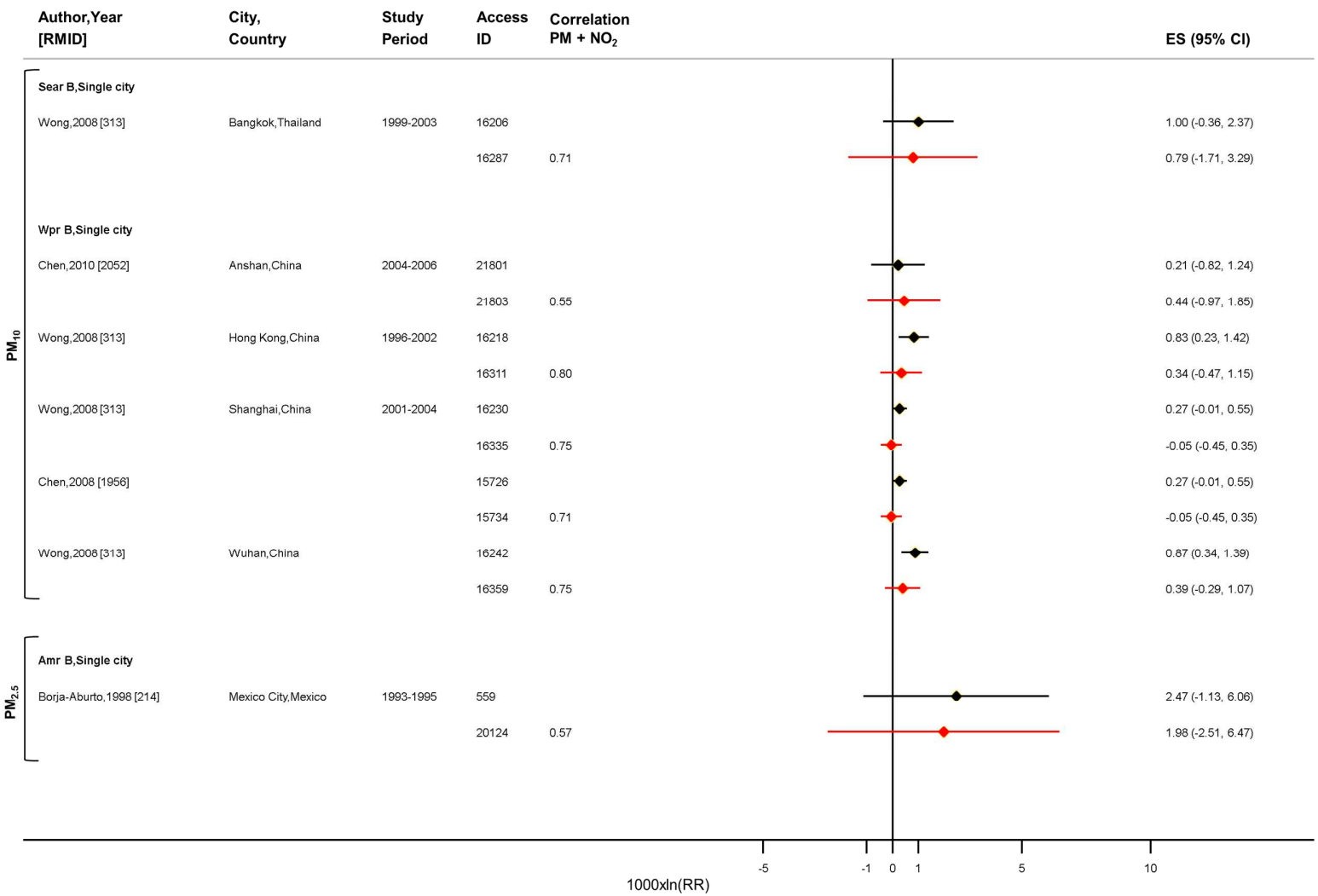
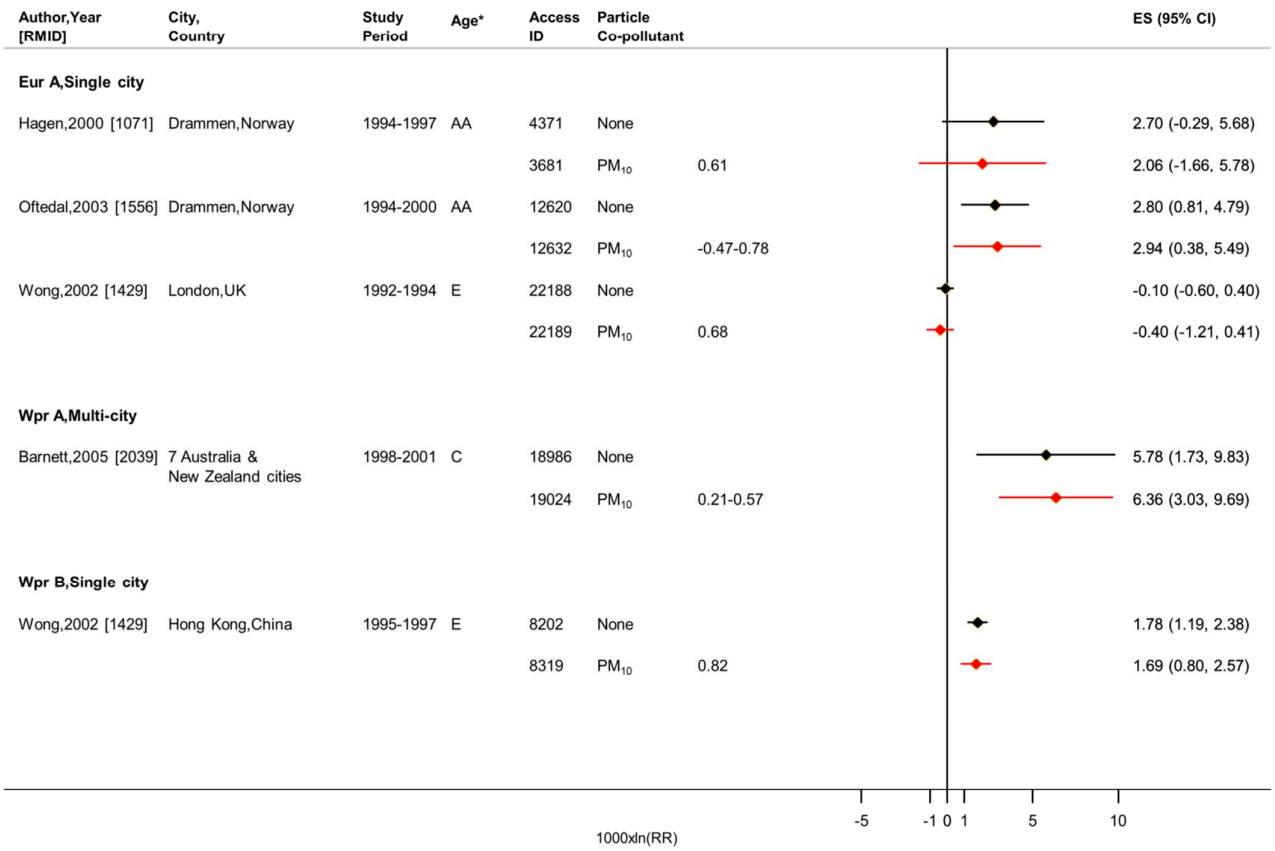
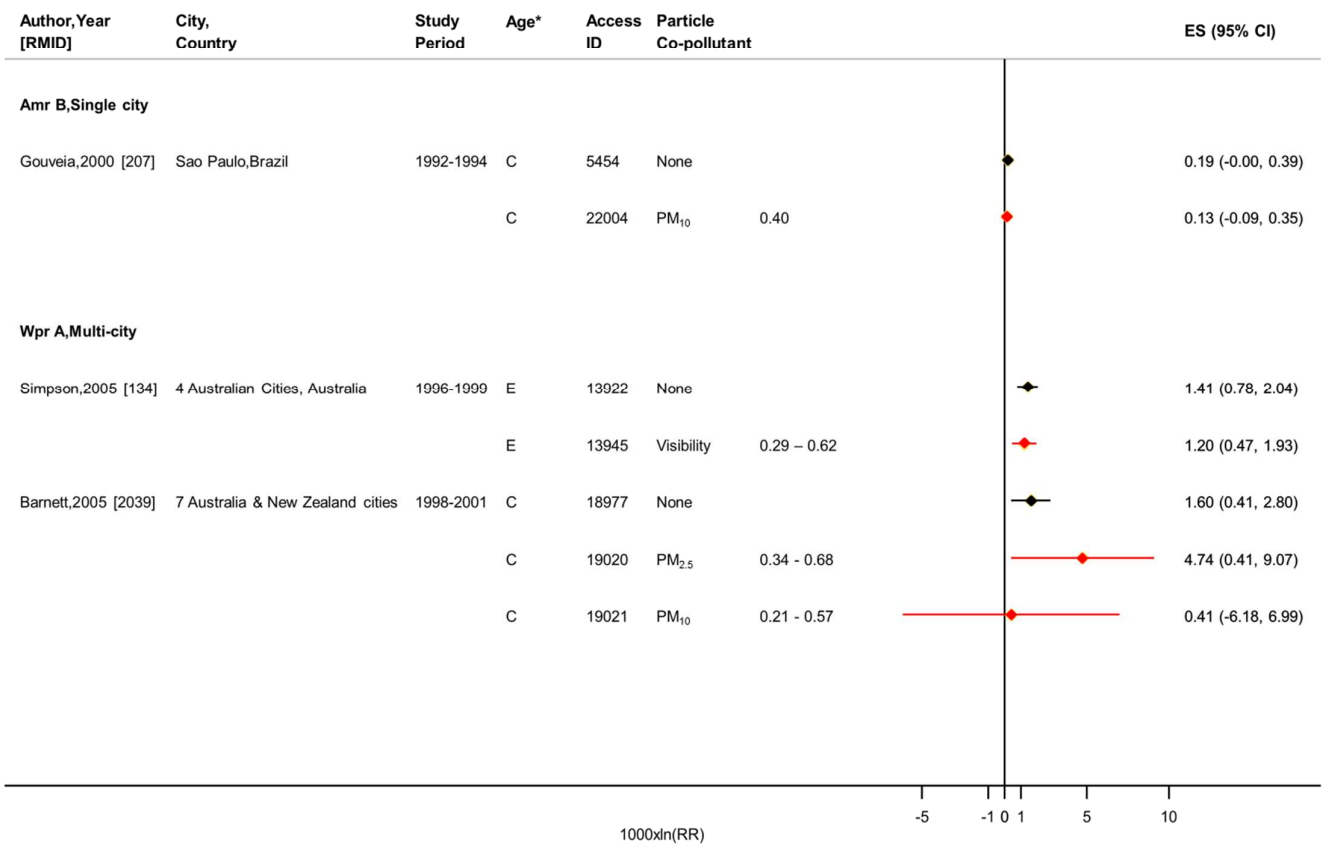


Figure S14: Studies providing two-pollutant model estimates for meta-analysis for all respiratory hospital admissions, various age groups, 24 hour NO_2



* Age: AA = all ages; E = Elderly; C = Children

Figure S15: Studies providing two-pollutant model estimates for meta-analysis for all respiratory hospital admissions, various age groups, 1 hour NO_2



* Age: C = Children; E = Elderly

Figure S16: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for asthma, children, 24 hour NO_2

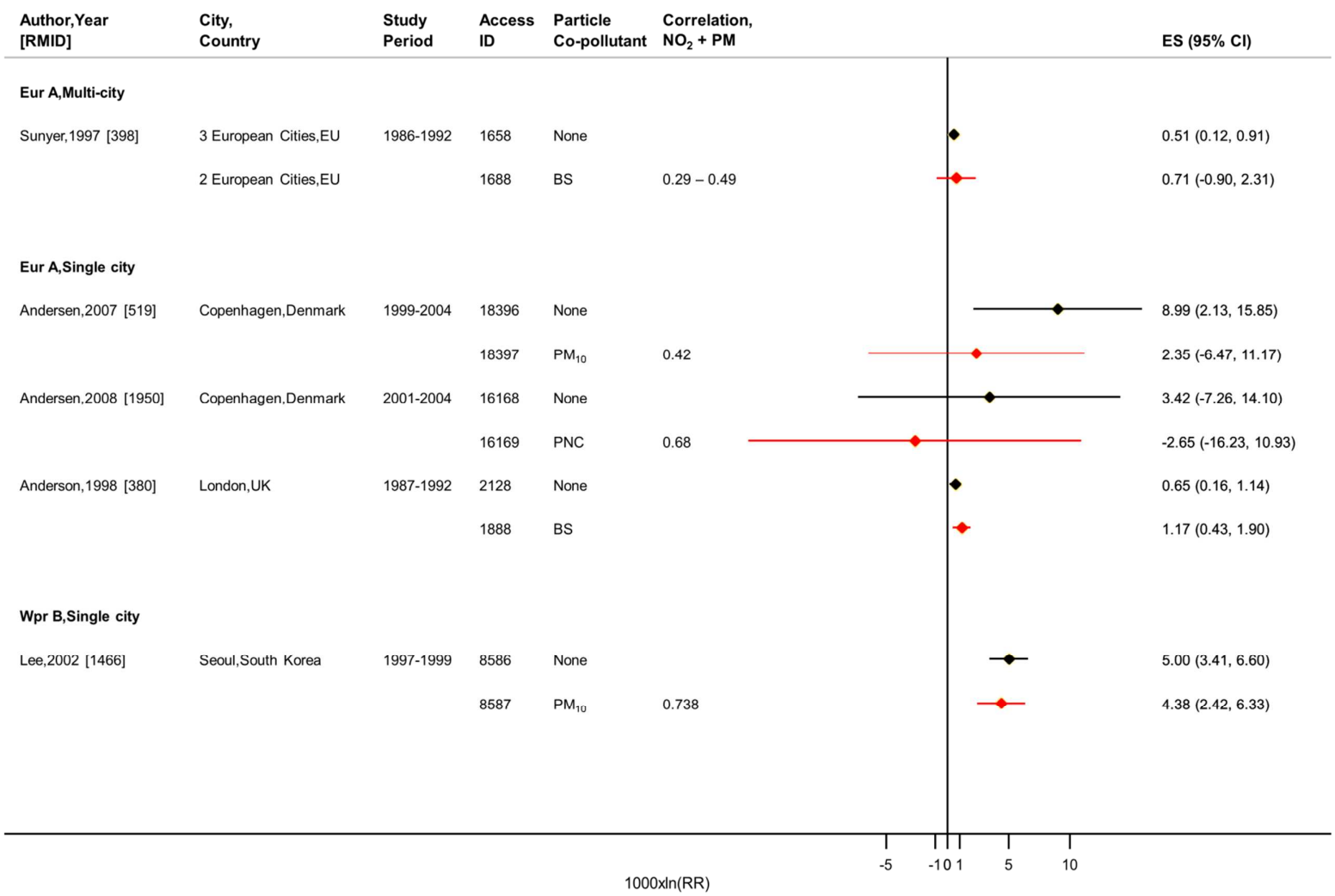
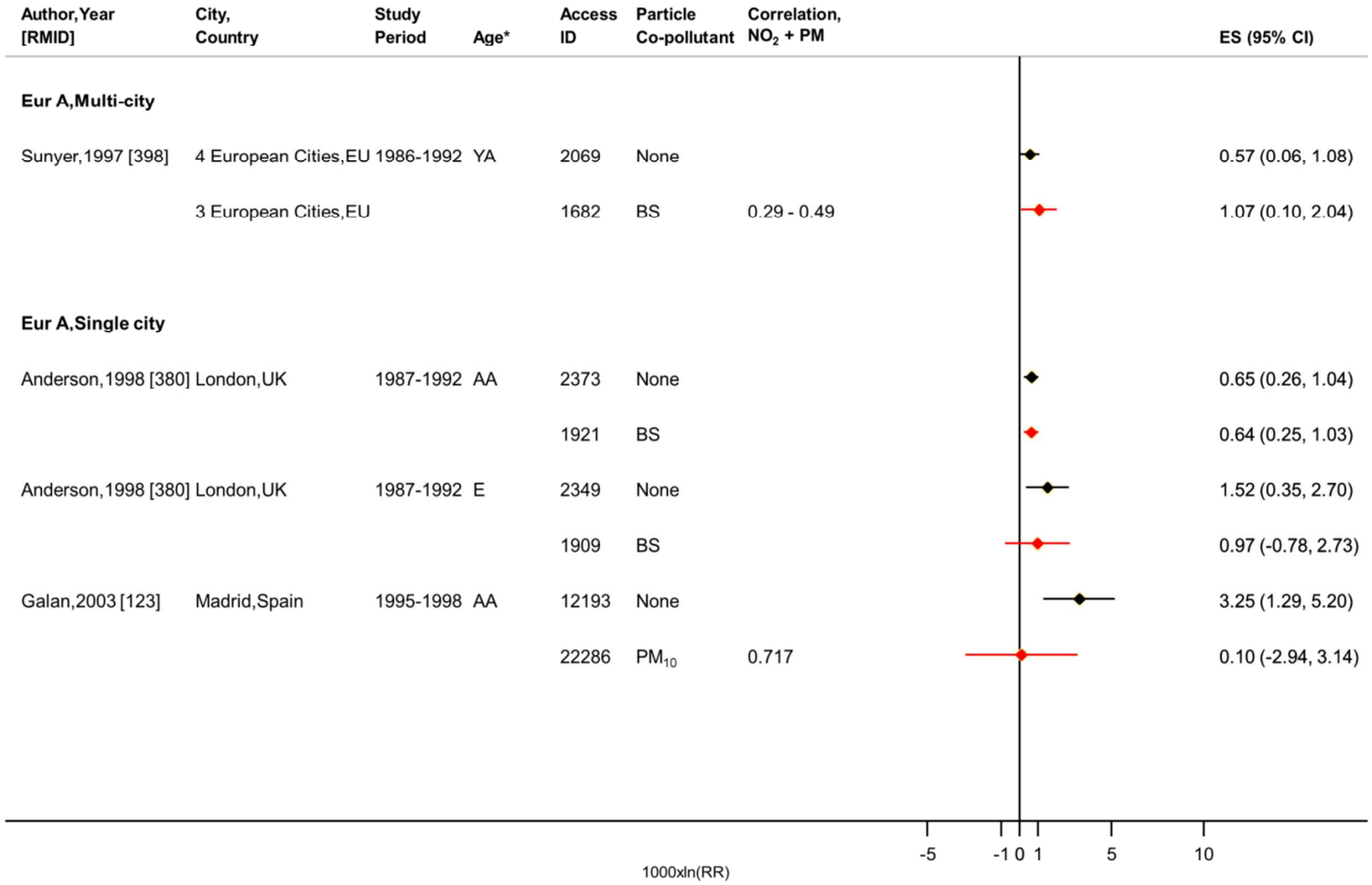


Figure S17: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for asthma, various age groups, 24 hour NO_2



* Age: AA = All-ages; E = Elderly; YA = Young adults

Figure S18: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for cardiac disease, all-ages, 24 hour NO_2

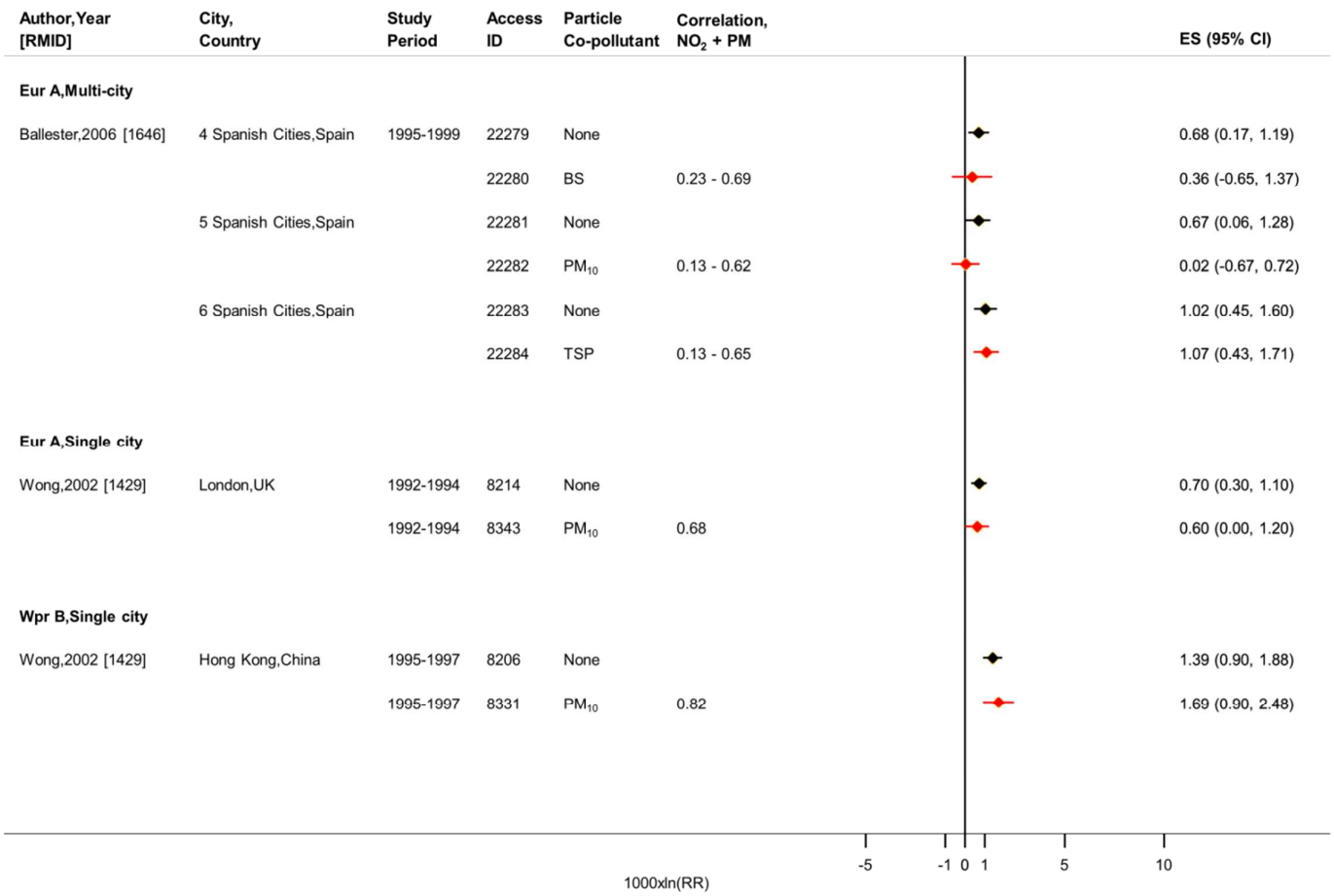


Figure S19: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for cardiac disease, elderly, 24 hour NO_2

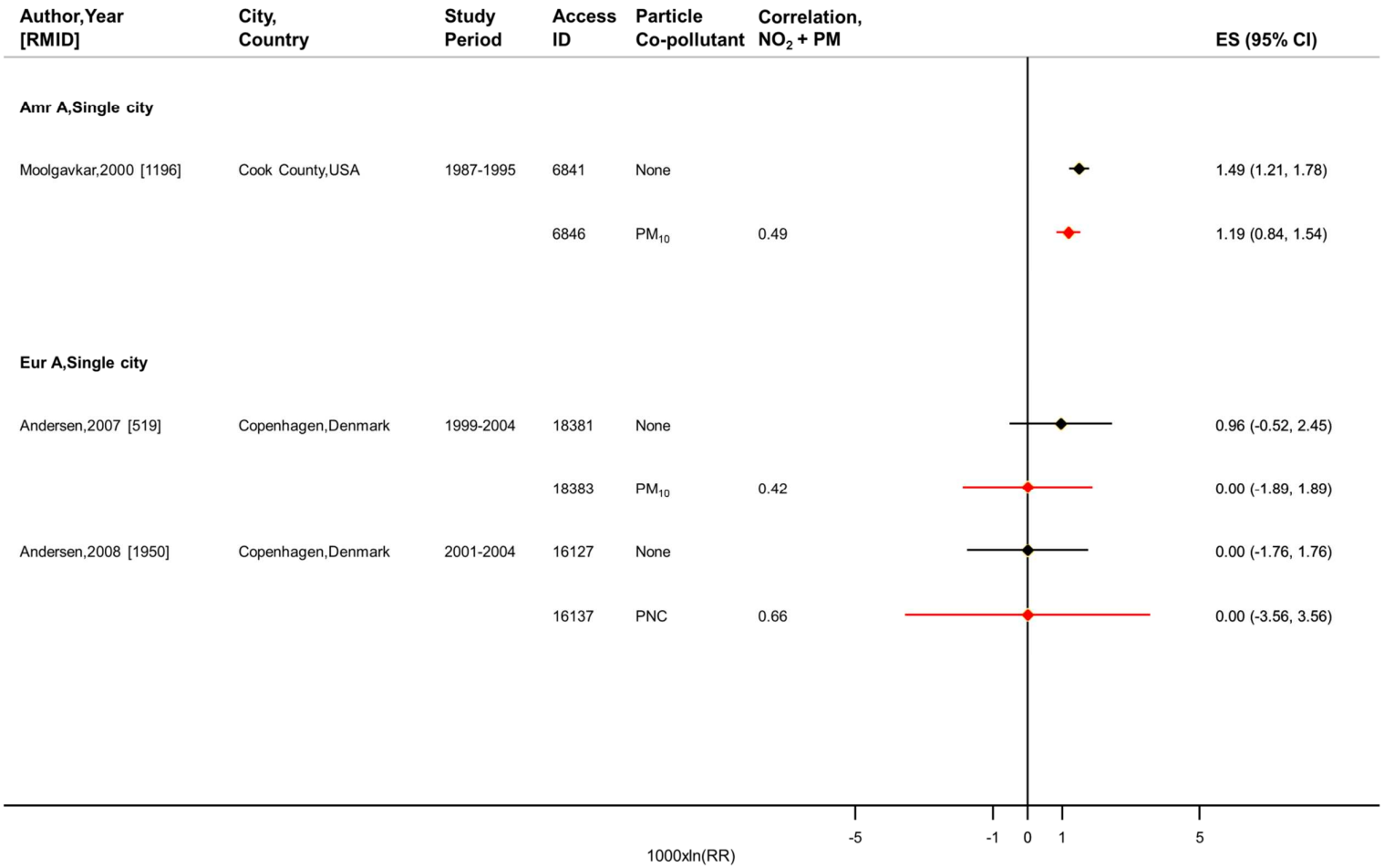


Figure S20: All available studies providing estimates from both single-pollutant and season-specific models for 24 hour NO_2 and all-cause mortality in all-ages

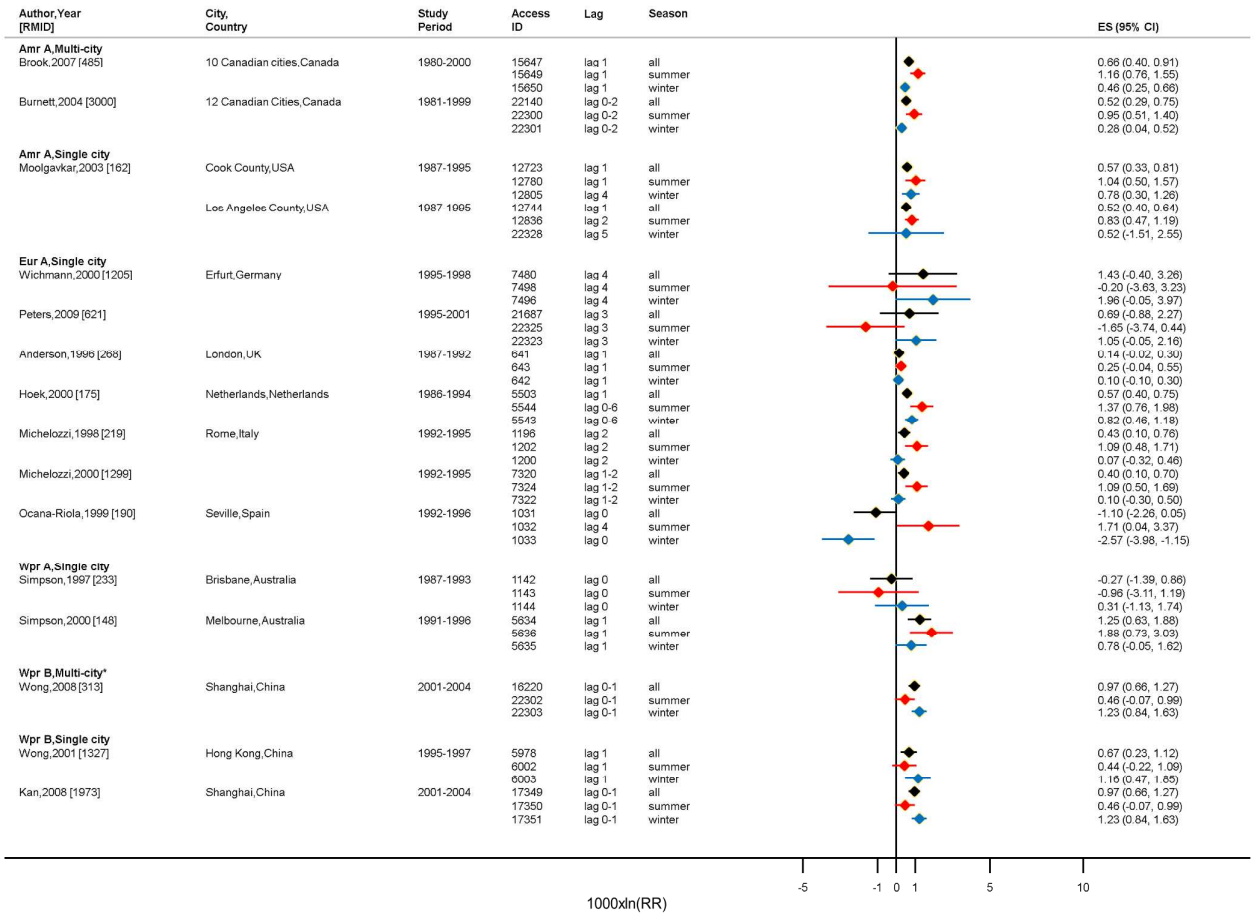


Figure S21: All available studies providing estimates from both single and season-specific models for 24 hour NO_2 and all cardiovascular mortality in all ages

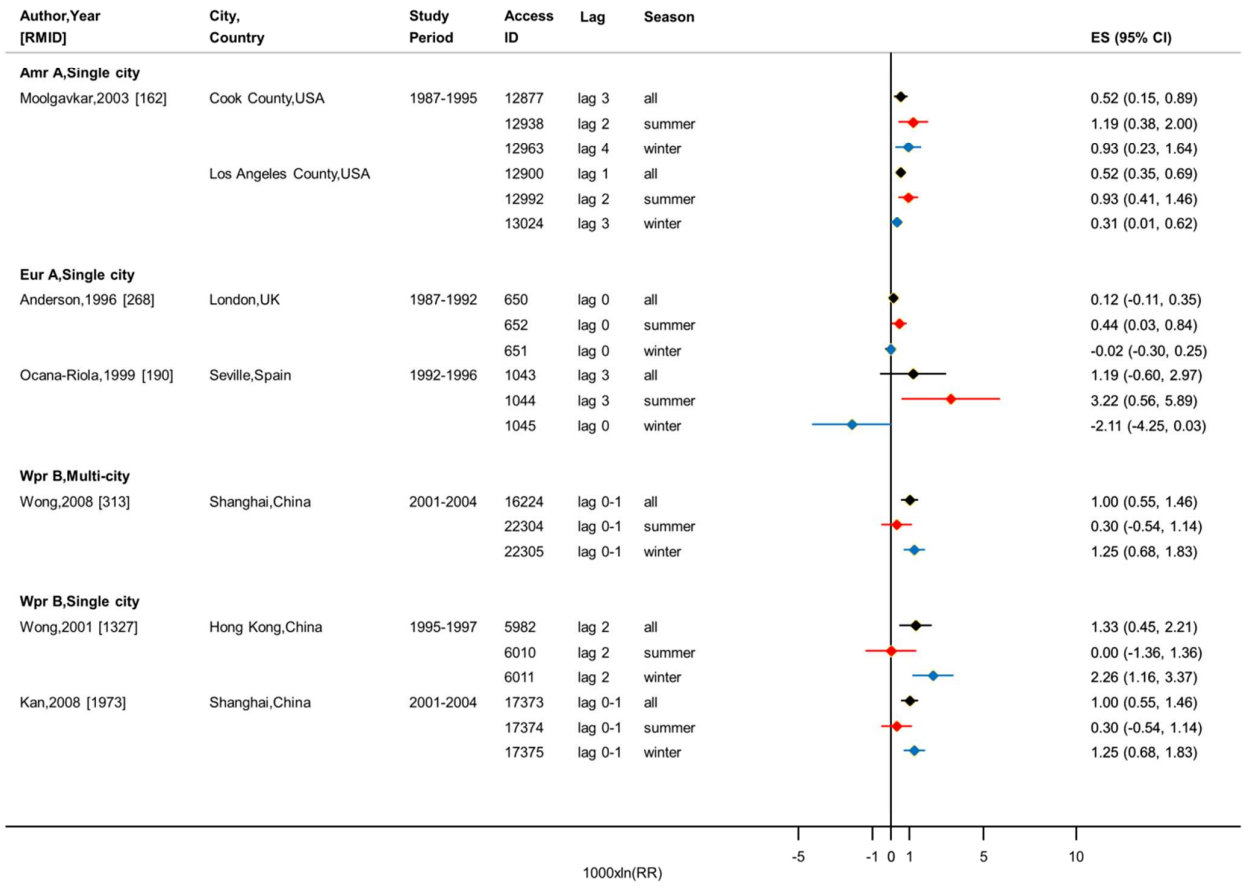


Figure S22: All available studies providing estimates from both single-pollutant and season-specific models for 24 hour NO_2 and all respiratory mortality in all-ages

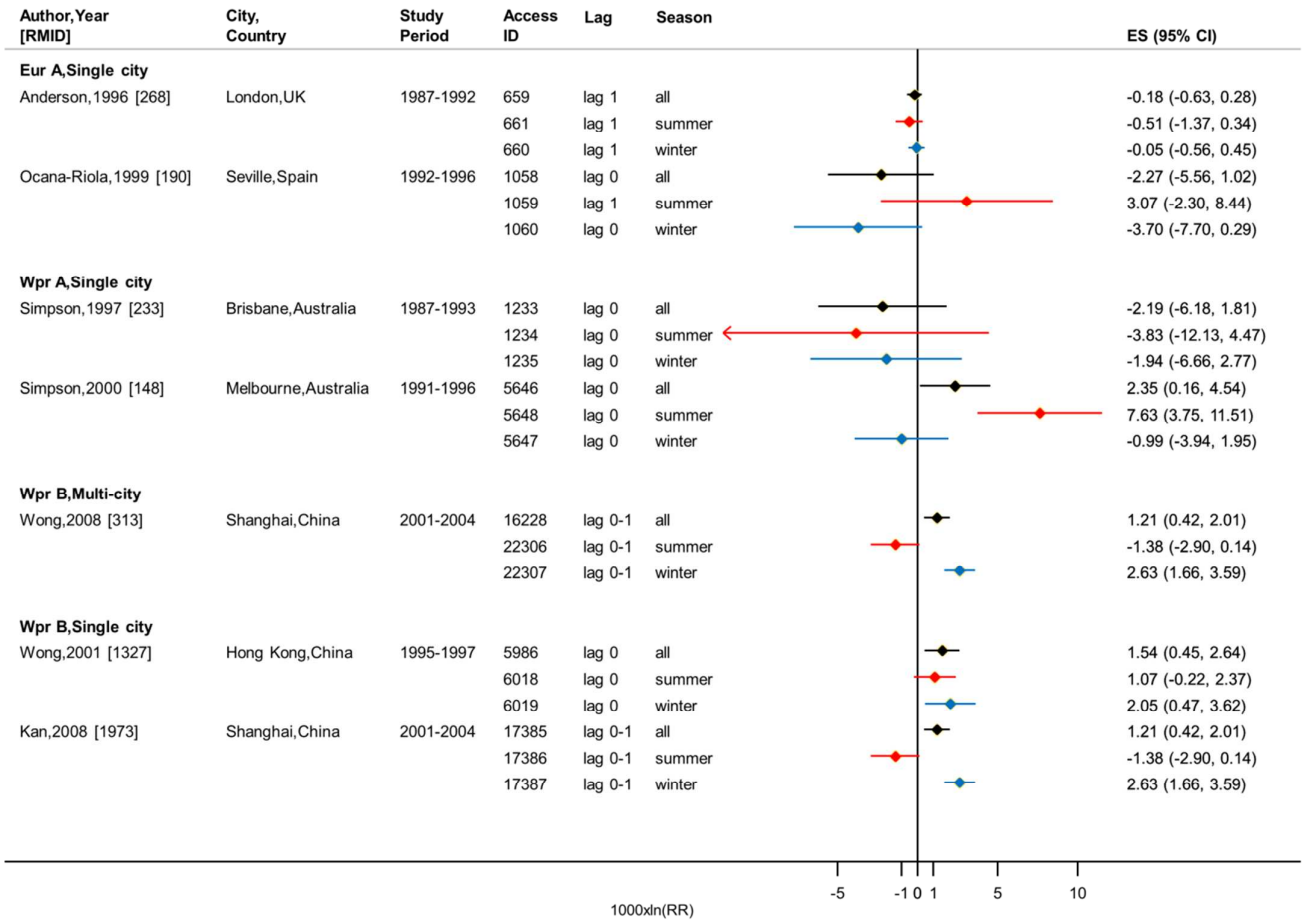


Figure S23: All available studies providing estimates from both single-pollutant and season-specific models for 24 hour NO_2 and all respiratory and all cardiovascular hospital admissions in all-ages

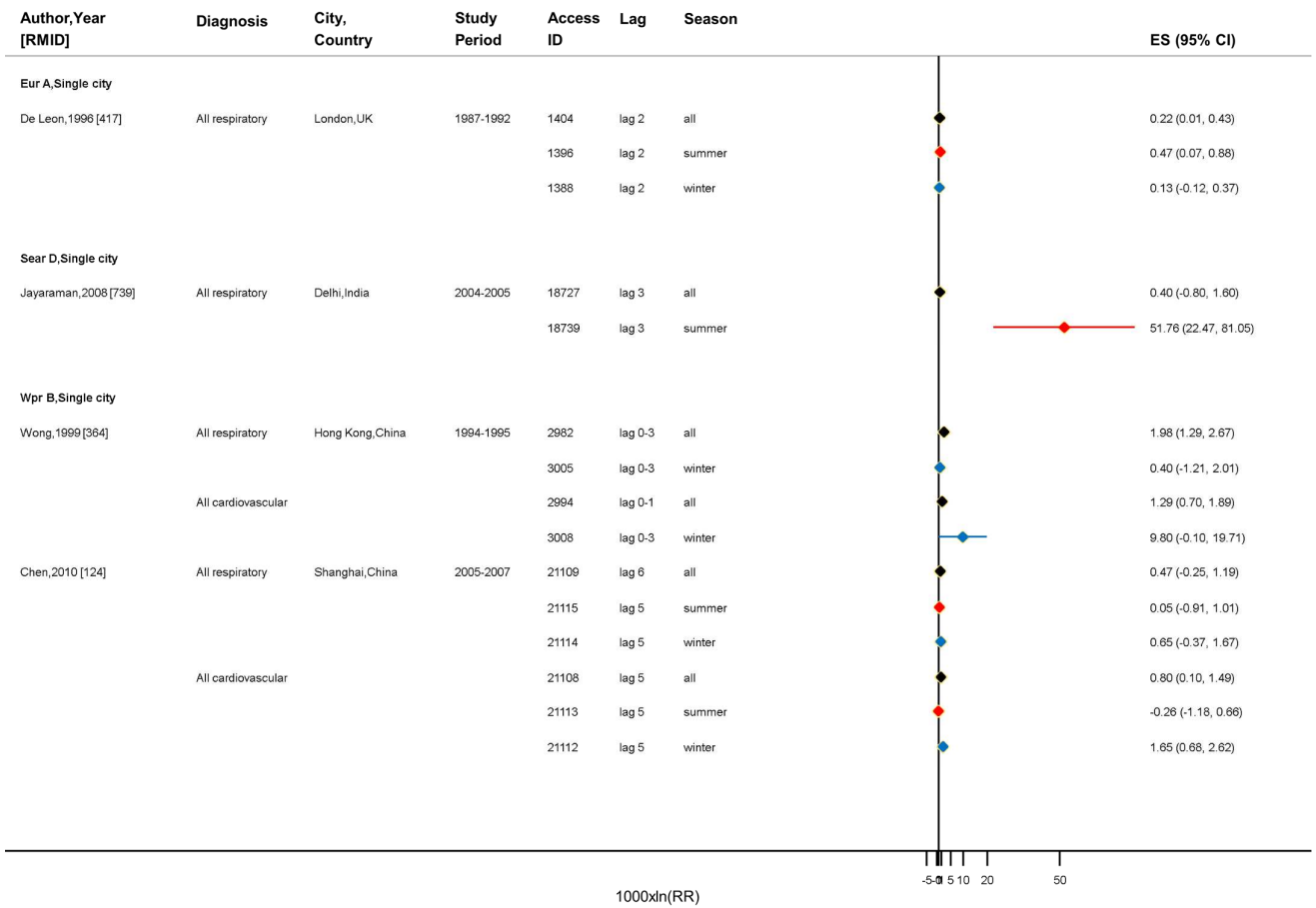


Figure S24: Ranking of NO_2 estimates for all-cause mortality in all-ages by mean levels of 24 hour NO_2 (multi-city studies shown using black bars)

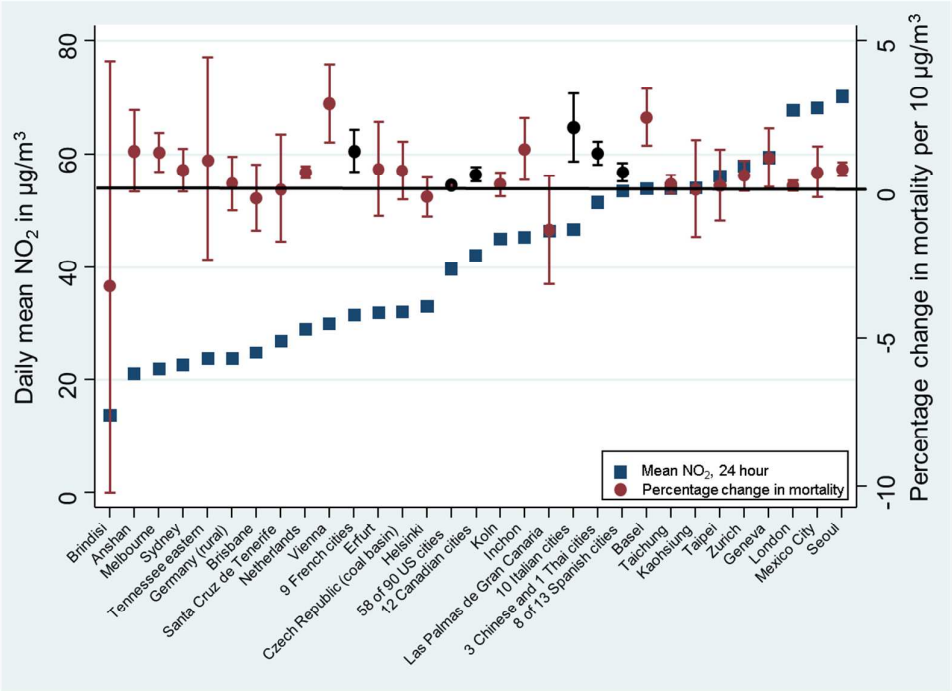


Figure S25: Ranking of NO_2 estimates for all-cause mortality in all-ages by mean levels of PM_{10} (multi-city studies shown using black bars)

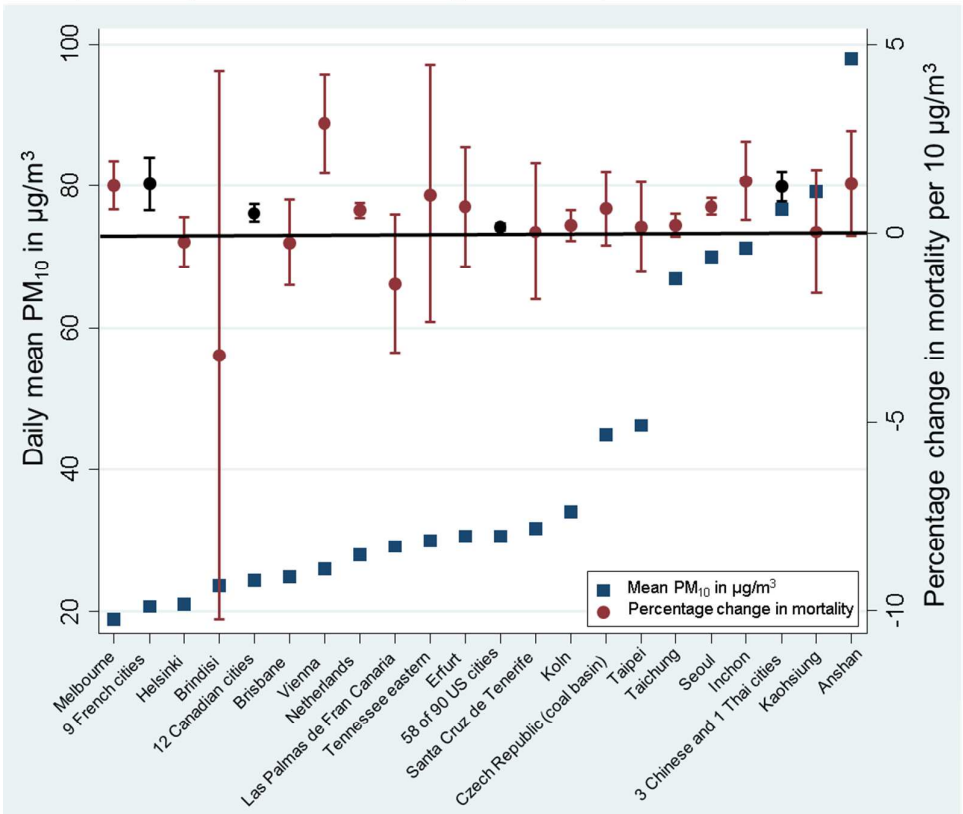


Figure S26: Ranking of NO_2 estimates for all-cause mortality in all-ages by the NO_2/PM_{10} concentration ratio (multi-city studies shown using black bars)

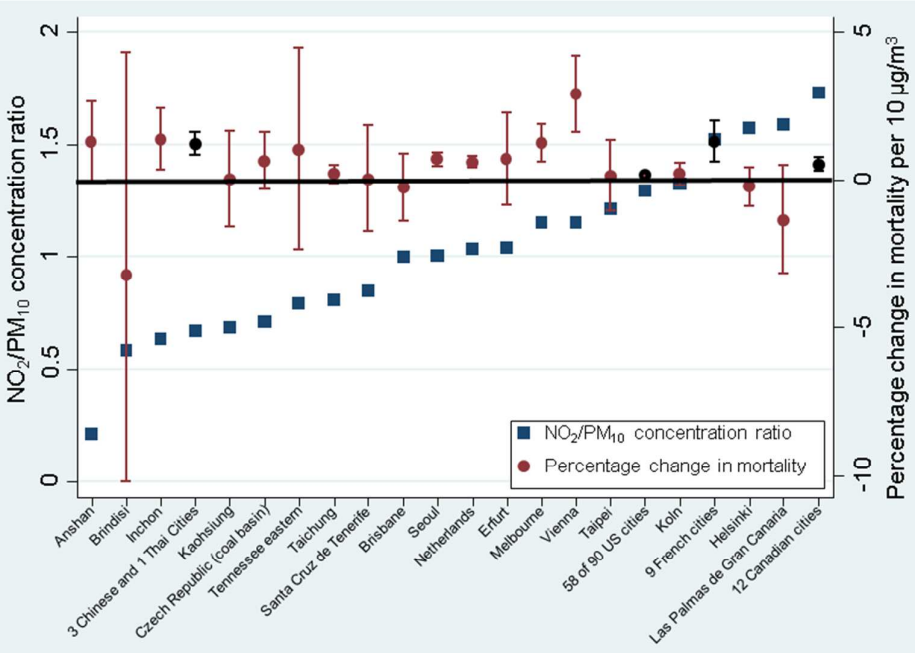
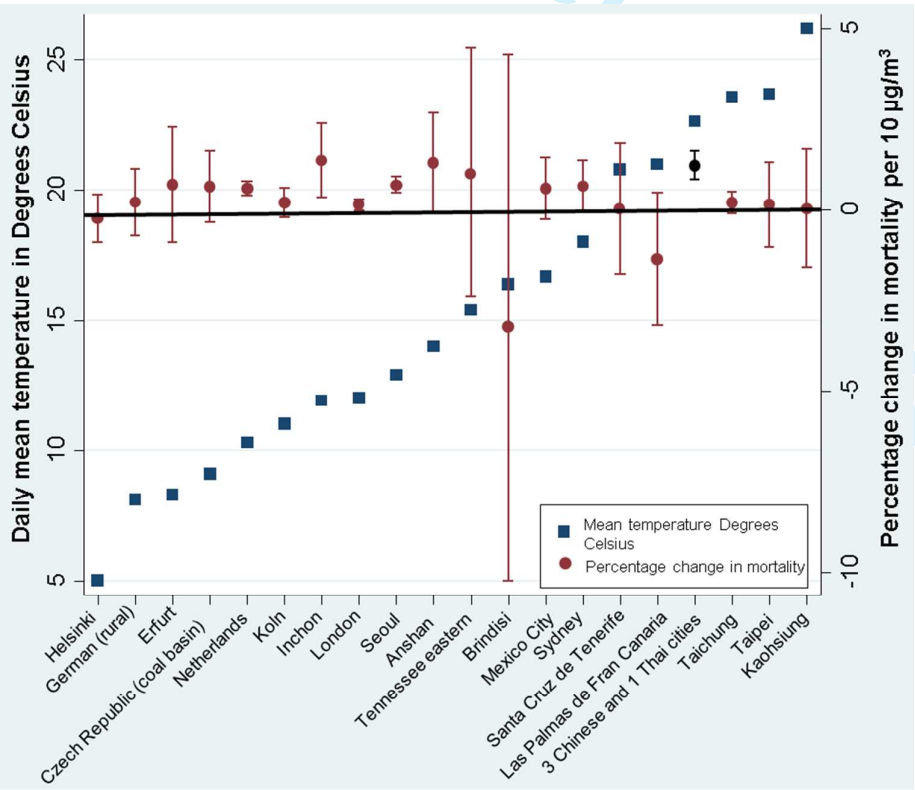


Figure S27: Ranking of NO_2 estimates for all-cause mortality in all-ages by daily mean temperature (multi-city studies shown using black bars)



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APPENDIX 1
Update literature search and commentary

In May 2015, BMJ Open published our systematic review and meta-analysis in which we demonstrated that short-term exposure to NO_2 is associated with mortality and hospital admissions for cardiovascular and respiratory diseases in different age groups (doi:10.1136/bmjopen-2014-006946). Whether the NO_2 associations are independent of the effects of particulate matter (PM) is the subject of the current manuscript under consideration by BMJ Open. The manuscript builds upon our earlier paper and forms the second part of our two-part study. Both parts of the study are based on a literature search with a cut-off of May 2011.

During the peer-review of the first (already published) paper, we faced criticisms regarding our literature cut-off similar to those made about the second manuscript. At that time, we addressed the points by undertaking a *partial* update of the literature:

(i) using the same search string
(ii) searching only one (of three) bibliographic databases – PubMed
(iii) focusing only on papers published in the English language
(iv) focusing on the period from 1st April 2011 to 26th July 2014, the date of the search

After applying the same inclusion criteria, we identified 37 studies of all-year NO_2.

To address the latest comments regarding the literature cut-off, we re-examined the 37 studies to:

(i) identify papers which reported estimates of NO_2 adjusted for a metric of PM
(ii) assess how the adjusted estimates compare with the results of our study
(iii) determine whether the papers published since our cut-off alter the messages in our manuscript.

Twelve of the 37 studies (that is 32%) reported numerical estimates of NO_2 adjusted for a metric of PM: see reference list. Table 1 provides an overview of the data, by outcome, diagnosis, averaging time, multi-city status of the study and location in which the study was conducted. Table 2 summarises the quantitative results of each study, and the paragraphs which follow provide commentary on the information presented in the tables.

Seven studies examined mortality outcomes whilst five examined hospital admissions. Eleven studies used 24 hour average NO_2 and the majority of the studies used PM_{10} to control for the effects of particles. These findings are in keeping with our manuscript: (i) 29% of the studies published up to May 2011 reported estimates of NO_2 adjusted for PM; (ii) 67% of the studies used PM_{10} to control for the effects of particles. Table 1 also shows that six of the 12 studies used a multi-city design and the majority of the new data comes from the Western Pacific Region B, which includes China. The growth in studies from this region of the world was identified in our review and cities in this region are represented in our meta-analytic estimates.

Many of the new studies include locations which are represented in our meta-analyses and there is also some overlap in study time periods between studies included in our review and newly published evidence. Some of the new studies are however based on a larger number of cities from a particular country, but also include cities represented in our meta-analyses (Moolgavkar et al, 2013; Chen et al, 2012). Chiusolo et al (2011) report further analyses of

existing data. Only one single-city study provided data for a less well studied part of the world: Ho Chi Minh city, Vietnam (HEI, 2012).

The results of the studies presented in Table 2 indicate that, in general, the associations between NO_2 and mortality and hospital admissions remain after control for PM and support an independent effect of NO_2 (adjusted for PM). This is in keeping with the key findings of our manuscript, and does not alter the conclusions of our review of studies published up to May 2011. Whilst we acknowledge that a more up-to-date review is desirable, it would be unlikely to significantly alter the relevance or importance of our review. To our knowledge, no quantitative systematic review of the two-/multi-pollutant model estimates of NO_2 has been published since 2002 (Stieb et al), and this was only for all-cause mortality. Since then, the evidence of adverse effects of NO_2 has increased and strengthened. Our analyses therefore contribute new quantitative evidence to the science-policy debate, indicating that NO_2 is associated with adverse health outcomes independently of PM (measured mainly as PM_{10}, $PM_{2.5}$, and Black Smoke). Table 2 also shows that the estimates of PM are more sensitive to control for NO_2 in joint models than the estimates of NO_2 are. This observation provides some support for the findings in our manuscript, and, as discussed in our manuscript, is an issue which warrants further investigation.

The resources required to undertake a detailed systematic ascertainment and quantitative meta-analysis of the growing time-series literature limits the ability of our systematic review to incorporate the very latest published evidence. Further work would be required to search additional databases (as was done in our manuscript), sift and translate relevant foreign language papers (also done for our review), enter quantitative estimates in our database, and apply our estimate selection protocol before judgements could be made about the specific meta-analyses that would or would not need to be updated in light of the new evidence. Furthermore, as the current manuscript builds upon our earlier paper and forms the second part of our two-part study, it is desirable to base the two papers on the same literature cut-off to enable comparison of results.

Table 1: Summary of time-series studies of daily NO_2 and mortality or hospital admissions published since May 2011

		Total		Multi-city study		Single-city study	
Outcome		**Mortality**	**Hospital admission**	**Mortality**	**Hospital admission**	**Mortality**	**Hospital admission**
Total		7	5	4	2	3	3
Disease[a]	Respiratory	3	3	2	1	1	2
	Cardiovascular	4	2	3	1	1	1
	All-cause	5		2		2	
WHO Region[b]	American A	1		1			
	European A	1	4	1	2		2
	Western Pacific B	5		2		3	
	American B						
	Western Pacific A						
	South East Asia B		1				1
Averaging time	24 hours	7	4	4	1	3	3
	Maximum 1 hour		1		1		
	Other						

a - Respiratory includes all-respiratory diseases, asthma, COPD only, COPD (including asthma), lower respiratory infections, and upper respiratory diseases; Cardiovascular includes all-cardiovascular diseases, cardiac disease, heart failure, ischaemic heart disease, dysrhythmia, and stroke.

b - WHO regions: A: very low child and adult mortality; B: low child mortality and low adult mortality; C: low child mortality and high adult mortality; D: high child mortality and high adult mortality. A list of countries which form part of each WHO region is given in Appendix 3.

Table 2: Summary of results of time-series studies of mortality and hospital admissions reporting estimates of NO_2 adjusted for a metric of PM.

Author (year) Study location Study period	Outcome Diagnosis Age group	NO_2 effect estimate (95% confidence interval)		Correlation NO_2/PM	PM effect estimate (95% confidence interval)	
		Single-pollutant	Adjusted for PM		Single-pollutant	Adjusted for NO_2
Bhaskaran et al (2011) 15 conurbations in England and Wales 2003-06	Hospital admissions Myocardial infarction Adults / Elderly	1.1% (0.3, 1.8) per 10 µg/m³ NO_2 Lag 1-6 hours Hourly average	0.8% (0, 1.6) adjusted for PM_{10}	NO_2/PM_{10} 0.48	1.2% (0.3, 2.1) per 10 µg/m³ PM_{10} Lag 1-6 hours Hourly averaging time	0.8% (-0.1, 1.8)
Chen et al (2013a) 8 Chinese cities 1996-2008, years varied across the cities	Mortality Stroke (ICD10 I60-69) All ages	1.47% (0.88, 2.06) per 10 µg/m³ NO_2 Lag 0-1 24 hour average	1.17% (0.47, 1.88) adjusted for PM_{10}	$PM_{10}/SO_2/NO_2$ across cities ranged from 0.51 to 0.87	0.54% (0.28, 0.81) per 10 µg/m³ PM_{10} Lag 0-1 24 hour average	0.14% (-0.04, 0.31)
Chen et al (2013b) Shanghai 2001-2008	Mortality All-cause (ICD10 A00-99) All ages	0.66% (0.47, 0.86) per 10 µg/m³ NO_2 Lag 0 24 hour average	0.81% (0.53, 1.11) adjusted for PM_{10}	None reported	0.15% (0.07, 0.23) per 10 µg/m³ PM_{10} Lag 0 24 hour average	-0.08% (-0.2, 0.04)
Chen et al (2012) 17 Chinese cities 1996-2010, years varied across the cities	Mortality All-cause (ICD10 A00-99) All ages	1.63% (1.09, 2.17) per 10 µg/m³ NO_2 Lag 0-1 24 hour average	1.28% (0.72, 1.84) adjusted for PM_{10}	NO_2/PM_{10} 0.66	0.35% (0.18, 0.52) per 10 µg/m³ PM_{10} Lag 0-1 24 hour average	0.16% (0.00, 0.32)
	Mortality All cardiovascular (I90-99) All ages	1.80% (1.00, 2.59)	1.19% (0.30, 2.08) adjusted for PM_{10}		0.44% (0.23, 0.64)	0.23% (0.03, 0.43)
	Mortality All respiratory (J00-98) All ages	2.52% (1.44, 3.59)	1.75% (0.76, 2.75) adjusted for PM_{10}		0.56% (0.31, 0.81)	0.24% (0.00, 0.49)
Chiusolo et al (2011) 10 Italian cities 2001-2005	Mortality All-causes (ICD9 <800) ≥ 35 years	2.09% (0.96, 3.24%) per 10 µg/m³ NO_2 Lag 0-5 24 hour average	1.95% (0.50, 3.43%) adjusted for PM_{10}	None reported	-	-

Author (year) Study location Study period	Outcome Diagnosis Age group	NO_2 effect estimate (95% confidence interval)		Correlation NO_2/PM	PM effect estimate (95% confidence interval)	
		Single-pollutant	Adjusted for PM		Single-pollutant	Adjusted for NO_2
	Mortality Cardiac (ICD9 390-429) ≥ 35 years	2.63% (1.53, 3.75)	2.58% (1.05, 4.13) adjusted for PM_{10}		-	-
	Mortality All respiratory (ICD9 460-519) ≥ 35 years	3.48% (0.75, 6.29)	3.39% (0.77, 6.08) adjusted for PM_{10}		-	-
	Mortality Cerebrovascular (ICD9 430-438) ≥ 35 years	2.35% (-013, 4.89)	2.55% (-0.71, 5.92) adjusted for PM_{10}		-	-
Faustini et al (2013) 6 Italian cities 2001-05	Hospital Admissions All respiratory ≥ 35 years	1.19% (0.23–2.15) per 10 µg/m³ NO_2 Lag 0-5 24 hour average	0.86% (0.30–2.02) adjusted for PM_{10}	NO_2/PM_{10} 0.22-0.79	0.59% (0.10–1.08) per 10 µg/m³ PM_{10} Lag 0-1 24 hour average	0.45% (-0.12–1.01)
	Hospital Admissions COPD ≥ 35 years	1.20% (0.17–2.23)	1.02% (-0.45–2.51) adjusted for PM_{10}		0.67% (-0.02–1.35)	0.54% (-0.41–1.49)
	Hospital Admissions Lower respiratory tract infections ≥ 35 years	1.79% (-1.16–4.83)	2.01% (-1.78–5.94) adjusted for PM_{10}		1.91% (0.06–3.79)	2.14% (-0.74–5.11)
Guo et al (2014) Shanghai 2004-08	Mortality All-causes All ages	1.6% (0.4 to 2.8) per 30 µg/m³ (IQR) NO_2 Lag 0-1 24 hour average	1.6% (−0.2 to 3.5) adjusted for $PM_{2.5}$	$NO_2/PM_{2.5}$ 0.61	1.3% (0.1 to 2.6) per 94 µg/m³ (IQR) $PM_{2.5}$, Lag 0-1 24 hour average	0.3% (−1.4 to 2.0) $PM_{2.5}$
			0.5% (−1.3 to 2.3) adjusted for PM_{10}	NO_2/PM_{10} 0.67	1.7% (0.6 to 2.9) per 106 µg/m³ (IQR) PM_{10}	1.3% (−0.4 to 3.0) PM_{10}
HEI (2012) Ho Chi Minh city, Vietnam	Hospital admissions Acute lower respiratory	4.32% (0.04, 8.79) per 10 µg/m³ NO_2	4.81% (0.04, 9.80) adjusted for PM_{10}	NO_2/PM_{10} 0.78	0.26% (-0.94, 1.47) per 10 µg/m³ PM_{10}	-0.31% (-1.65, 1.04)

Author (year) Study location Study period	Outcome Diagnosis Age group	NO_2 effect estimate (95% confidence interval)		Correlation NO_2/PM	PM effect estimate (95% confidence interval)	
		Single-pollutant	Adjusted for PM		Single-pollutant	Adjusted for NO_2
2003-05	infections Children <5 years	Lag 1-6 24 hour average			Lag 1-6 24 hour average	
Iskandar et al (2012) Copenhagen 2001-08	Hospital admissions Asthma (ICD10 J45-46) Children 0-18 years	OR 1.10 (1.04 to 1.16) per 6.53 ppb (IQR) NO_2 Lag 0-4 24 hour average	OR 1.08 (1.01 to 1.15) adjusted for PM_{10}	NO_2/PM_{10} 0.43	OR 1.07 (1.03 to 1.12) per 13.4 µg/m³ (IQR) PM_{10} Lag 0-4	OR 1.04 (1.00 to 1.09)
			OR 1.12 (1.05 to 1.19) adjusted for $PM_{2.5}$	$NO_2/PM_{2.5}$ 0.33	OR 1.09 (1.04 to 1.13) per 4.8 µg/m³ (IQR) $PM_{2.5}$ Lag 0-4	OR 1.06 (1.02 to 1.11)
			OR 1.13 (1.05 to 1.22) adjusted for ultrafine particles	NO_2/ultrafine particles 0.51	OR 1.06 (0.98 to 1.14) per 3812.86 particles/cm³ (IQR) ultrafine particles Lag 0-4	OR 0.97 (0.89 to 1.06)
Moolgavkar et al (2013) 108 metropolitan US areas 1987-2000	Mortality All-cause All ages	1.03% (0.91, 1.18) per 10 ppb NO_2 Lag 1 24 hour average	0.94% (0.60, 1.26) Based on 72 cities	None reported	0.40% (0.30, 0.53) per 10 µg/m³ PM_{10} Lag 1 24 hour average	0.20% (0.03, 0.36) Based on 72 cities
Nuvolone et al (2013) 6 urban areas in Tuscany 2002-05	Hospital admissions Myocardial infarction (ICD9 410)	OR 1.022 (1.004, 1.041) per 10 µg/m³ NO_2 Lag 2 24 hour average	OR 1.025 (0.999, 1.053) adjusted for PM_{10}	NO_2/PM_{10} 0.44-0.71	OR 1.013 (1.000, 1.026) per 10 µg/m³ PM_{10} Lag 2 24 hour average	OR 1.001 (0.980, 1.021)
Zhang et al (2011) Beijing 2003-08	Mortality All cardiovascular (I90-99) All ages	RR 1.00271 (1.00086, 1.00457) per 10 µg/m³ NO_2 Lag 0 24 hour average	RR 0.99866 (0.99765, 0.99967) adjusted for PM_{10}	NO_2/PM_{10} 0.615	RR 1.00164 (1.00144, 1.00184) per 10 µg/m³ PM_{10} Lag 0 24 hour average	RR 1.00181 (1.00157, 1.00205)
	Mortality All respiratory (J00-98) All ages	RR 1.00947 (1.00759, 1.01135) per 10 µg/m³ NO_2	RR 1.01005 (1.00782, 1.01228) adjusted for PM_{10}		RR 1.00101 (1.00057, 1.00145) per 10 µg/m³ PM_{10} Lag 0	RR 0.99974 (0.99922, 1.00027)

Author (year) Study location Study period	Outcome Diagnosis Age group	NO_2 effect estimate (95% confidence interval)		Correlation NO_2/PM	PM effect estimate (95% confidence interval)	
		Single-pollutant	Adjusted for PM		Single-pollutant	Adjusted for NO_2
		Lag 0 24 hour average			24 hour average	

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4 and Supplementary Material
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4 and Supplementary Material
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4 and Supplementary Material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4 and Supplementary Material
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 and Supplementary Material
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 and Supplementary

PRISMA 2009 Checklist

			Material
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6 and Supplementary Material

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-7 and Supplementary Material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-11 and Supplementary Material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-11 and Supplementary Material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-11 and Supplementary Material
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	See previous related paper – reference 12 in

PRISMA 2009 Checklist

			manuscript for publication bias in full dataset. Data from the subset of studies examined in current manuscript were insufficient to permit assessment of publication bias.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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