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, 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); $PM_{2.5\text{-}1}$
$PM_{10\text{-}2.5}$	$PM_{10\text{-}2.5}$
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]	**22/10**	**5/1 (26)**	**0.78 (0.47, 1.09)**	66.9	**0.60 (0.33, 0.87)**	0
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)		0.01 (-1.10, 1.12)	
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	-	Insufficient estimates for meta-analysis			
NO_2 + TSP	3/0	-				
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 the methods section. 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)**	93.8	**0.20 (-0.24, 0.65)**	95.2
AMR A	1/0	1/0 (1)	1.19 (0.20, 2.19)		0.78 (-0.35, 1.92)	
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 the methods section. 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)**	72	**0.82 (0.22, 1.42)**	58.8
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)		-0.36 (-2.47, 1.81)	
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 the methods section. 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 the methods section. 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 the methods section. 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/m^3 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/m^3 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

Author,Year [RMID]	City, Country	Study Period	Access ID	Particle Co-pollutant	Correlation, NO_2 + PM	ES (95% CI)
Amr A,Multi-city						
Burnett,2004 [3000]	12 Canadian cities, Canada	1981-1999	22161	None		0.62 (0.19, 1.05)
			22164	PM_{10}	None reported	0.74 (0.24, 1.23)
Amr A,Single city						
Ostro,1999 [3]	Coachella Valley,USA	1989-1992	4055	None		1.46 (-0.36, 3.29)
			4061	PM_{10}	-0.13	0.39 (-1.75, 2.53)
Moolgavkar,2003 [162]	Cook County,USA	1987-1995	12723	None		0.57 (0.33, 0.81)
			22023	PM_{10}	0.49	0.47 (0.17, 0.77)
	Los Angeles County,USA	1987-1995	12744	None		0.52 (0.40, 0.64)
			12753	PM_{10}	0.70	0.73 (0.40, 1.05)
Kelsall,1997 [236]	Philadelphia,USA	1974-1988	574	None		0.07 (-0.15, 0.29)
			3740	TSP	0.67	-0.31 (-0.58, -0.05)
Amr B,Single city						
Borja-Aburto,1998 [214]	Mexico City,Mexico	1993-1995	567	None		0.59 (-0.26, 1.44)
			20142	$PM_{2.5}$	0.57	0.01 (-1.10, 1.11)
Eur A,Single city						
Peters,2009 [621]	Erfurt,Germany	1995-2001	22212	None		0.41 (-1.17, 1.99)
			21697	PNC	0.62	-1.47 (-3.41, 0.47)
Michelozzi,1998 [219]	Rome,Italy	1992-1995	1196	None		0.43 (0.10, 0.76)
			22265	TSP	0.507	0.29 (-0.07, 0.65)
Hoek,2000 [175]	Netherlands,Netherlands	1986-1994	5504	None		1.02 (0.76, 1.28)
			5552	PM_{10}	0.62	1.69 (0.92, 2.46)
Sear B,Single city						
Wong,2008 [313]	Bangkok,Thailand	1999-2003	16196	None		1.40 (0.89, 1.91)
			16270	PM_{10}	0.71	0.42 (-0.55, 1.39)
Wpr B,Single city						
Chen,2010 [2052]	Anshan,China	2004-2006	21120	None		1.29 (-0.06, 2.64)
			21121	PM_{10}	0.55	0.89 (-0.91, 2.69)
Wong,2008 [313]	Hong Kong,China	1996-2002	16208	None		0.90 (0.58, 1.21)
			16294	PM_{10}	0.80	0.86 (0.42, 1.29)
	Shanghai,China	2001-2004	16220	None		0.97 (0.66, 1.27)
			16318	PM_{10}	0.75	0.94 (0.50, 1.37)
	Wuhan,China	2001-2004	16232	None		1.95 (1.30, 2.60)
			16342	PM_{10}	0.75	1.68 (0.87, 2.49)
Kwon,1999 [1643]	Seoul,South Korea	1991-1995	14389	None		0.35 (0.05, 0.66)
			22296	TSP	0.774	0.26 (-0.05, 0.56)

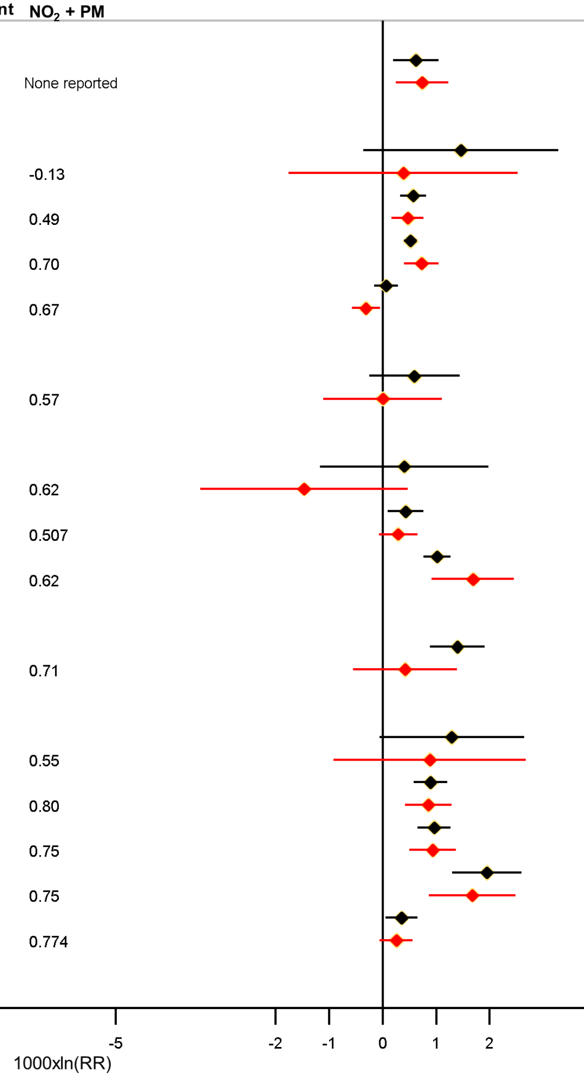


Figure S2: All available studies providing two-pollutant model estimates for meta-analysis for all-cause mortality, all ages, 1 hour NO_2

Author, Year [RMID]	City, Country	Study Period	Access ID	Particle Co-pollutant	Correlation, NO_2 + PM	ES (95% CI)
Amr A, Single city						
Ostro, 1999 [3]	Coachella Valley, USA	1989-1992	4056	None		1.19 (0.20, 2.17)
			4063	PM_{10}	-0.13	0.78 (-0.35, 1.91)
Amr B, Single city						
Ostro, 1996 [256]	Santiago, Chile	1989-1991	439	None		-0.09 (-0.19, 0.00)
			3377	PM_{10}	0.73	-0.28 (-0.38, -0.19)
Eur A, Multi-city						
Samoli, 2006 [1671]	30 European Cities, EU	1990-1997	16845	None		0.30 (0.22, 0.38)
			16847	PM_{10}	0.11-0.69	0.27 (0.16, 0.38)
			16846	BS	0.11-0.78	0.33 (0.23, 0.43)
Touloumi, 1997 [240]	6 European Cities (inc Athens), EU	n/a-n/a	1211	None		0.26 (0.18, 0.34)
			1216	BS		0.12 (0.00, 0.24)
Wpr A, Multi-city						
Simpson, 2005 [133]	4 Australian Cities, Australia	1996-1999	22274	None		0.63 (0.21, 1.04)
			13884	Visibility	0.29-0.62	0.52 (0.05, 0.99)

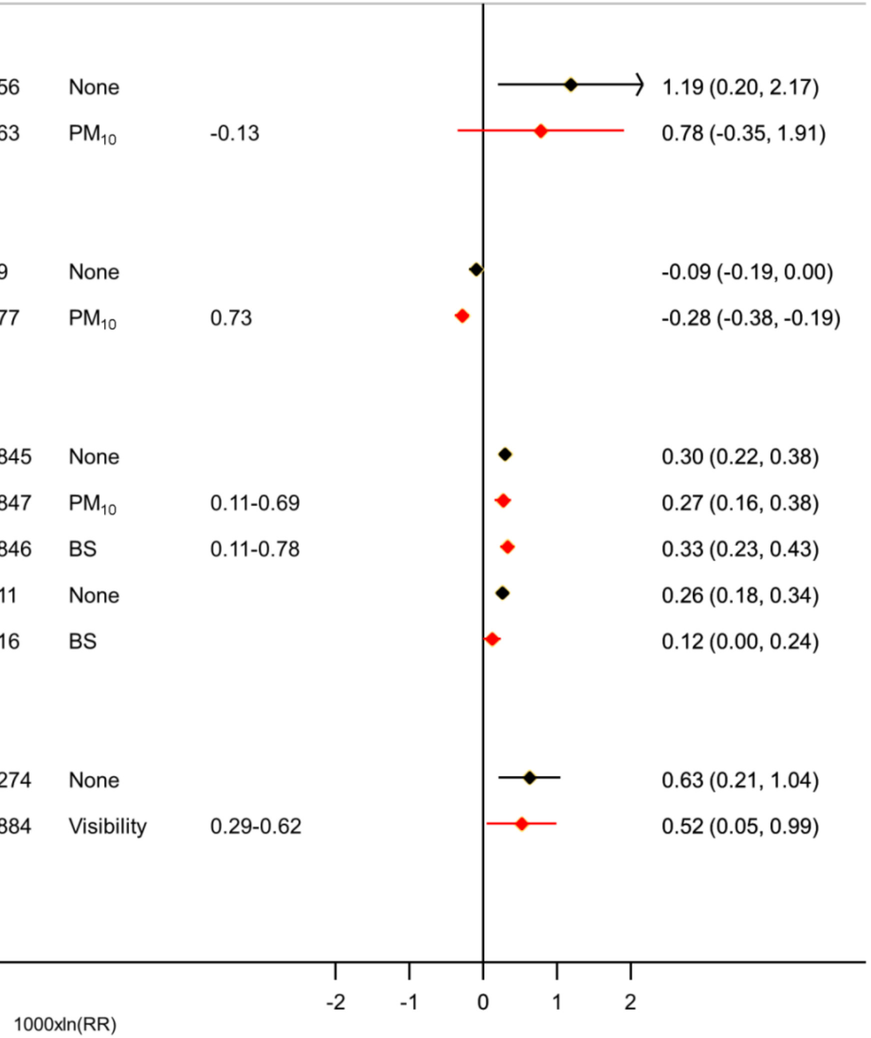


Figure S3: All available studies providing two-pollutant model estimates for meta-analysis for all cardiovascular mortality, all ages, 24 hour NO_2

Author,Year [RMID]	City, Country	Study Period	Access ID	Particle Co-pollutant	Correlation, NO_2 + PM	ES (95% CI)
Amr A,Single city						
Moolgavkar,2003 [162]	Cook County,USA	1987-1995	12877	None		0.52 (0.15, 0.89)
			22072	PM_{10}	0.49	0.26 (-0.20, 0.73)
Moolgavkar,2003 [162]	Los Angeles County,USA		12900	None		0.52 (0.35, 0.69)
			22090	PM_{10}	0.70	0.68 (0.22, 1.13)
			22100	$PM_{2.5}$	0.73	0.26 (-0.31, 0.83)
Amr B,Single city						
Borja-Aburto,1998 [214]	Mexico City,Mexico	1993-1995	570	None		0.73 (-0.87, 2.33)
			20145	$PM_{2.5}$	0.57	-0.36 (-2.51, 1.79)
Eur A,Single city						
Hoek,2000 [175]	Netherlands,Netherlands	1986-1994	5513	None		0.92 (0.50, 1.34)
			5584	BS	0.87	0.43 (-0.20, 1.06)
			5576	PM_{10}	0.62	1.66 (0.50, 2.82)
Zeghnoun,2001 [1374]	Rouen,France	1990-1995	22295	None		3.67 (0.92, 6.42)
			7861	BS	0.77	3.97 (-0.67, 8.60)
Sear B,Single city						
Wong,2008 [313]	Bangkok,Thailand	1999-2003	16200	None		1.76 (0.47, 3.06)
		1999-2003	16273	PM_{10}	0.71	-0.51 (-2.92, 1.90)
Wpr B,Single city						
Chen,2010 [2052]	Anshan,China	2004-2006	21125	None		2.09 (0.22, 3.96)
			21126	PM_{10}	0.55	-0.15 (-2.70, 2.40)
Wong,2008 [313]	Hong Kong,China	1996-2002	16212	None		1.22 (0.64, 1.81)
			16297	PM_{10}	0.80	1.32 (0.54, 2.10)
	Shanghai,China	2001-2004	16224	None		1.00 (0.55, 1.46)
			16321	PM_{10}	0.75	0.98 (0.33, 1.62)
Chen,2008 [1956]	Shanghai,China	2001-2004	15756	None		1.00 (0.55, 1.46)
			15757	PM_{10}	0.71	0.98 (0.33, 1.62)
Wong,2008 [313]	Wuhan,China	2001-2004	16236	None		2.10 (1.17, 3.02)
			16345	PM_{10}	0.75	1.40 (0.24, 2.56)
Qian,2007 [1945]	Wuan,China	2000-2004	15257	None		1.64 (0.87, 2.41)
			15310	PM_{10}	0.58	0.98 (0.00, 1.95)

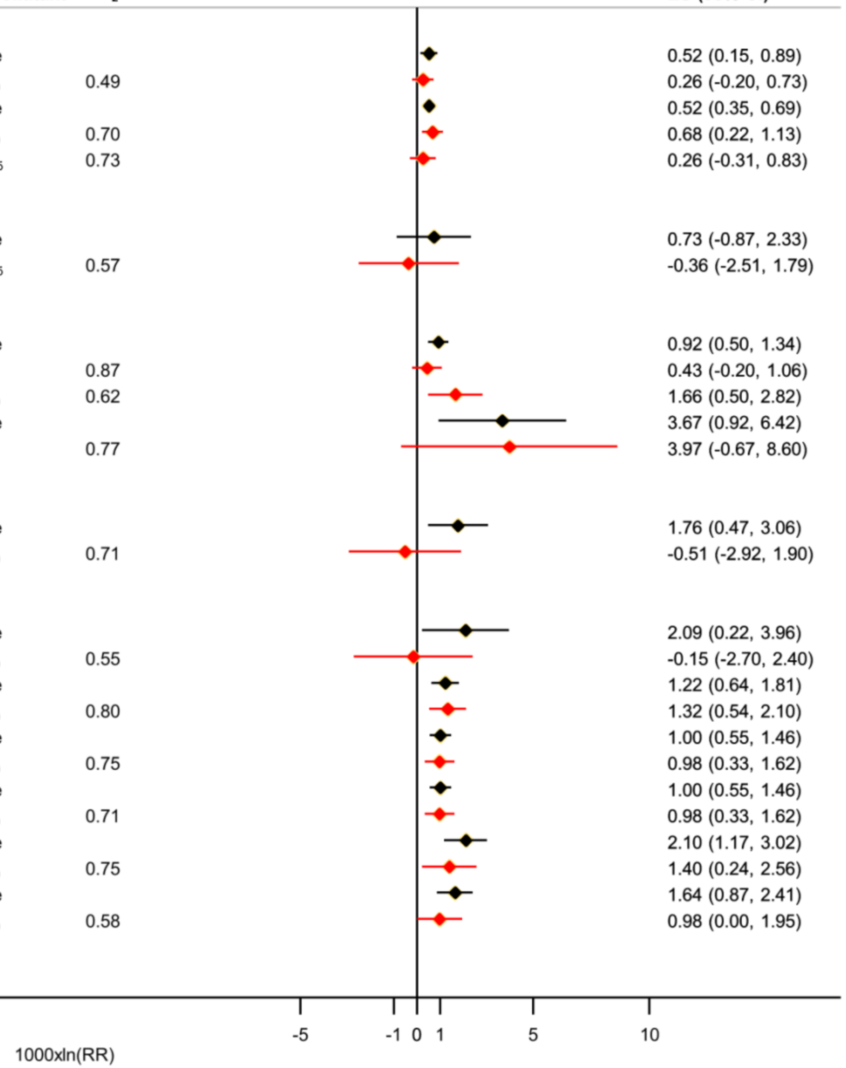


Figure S4: All available studies providing two-pollutant model estimates for meta-analysis for all cardiovascular mortality, all ages, 1 hour NO_2

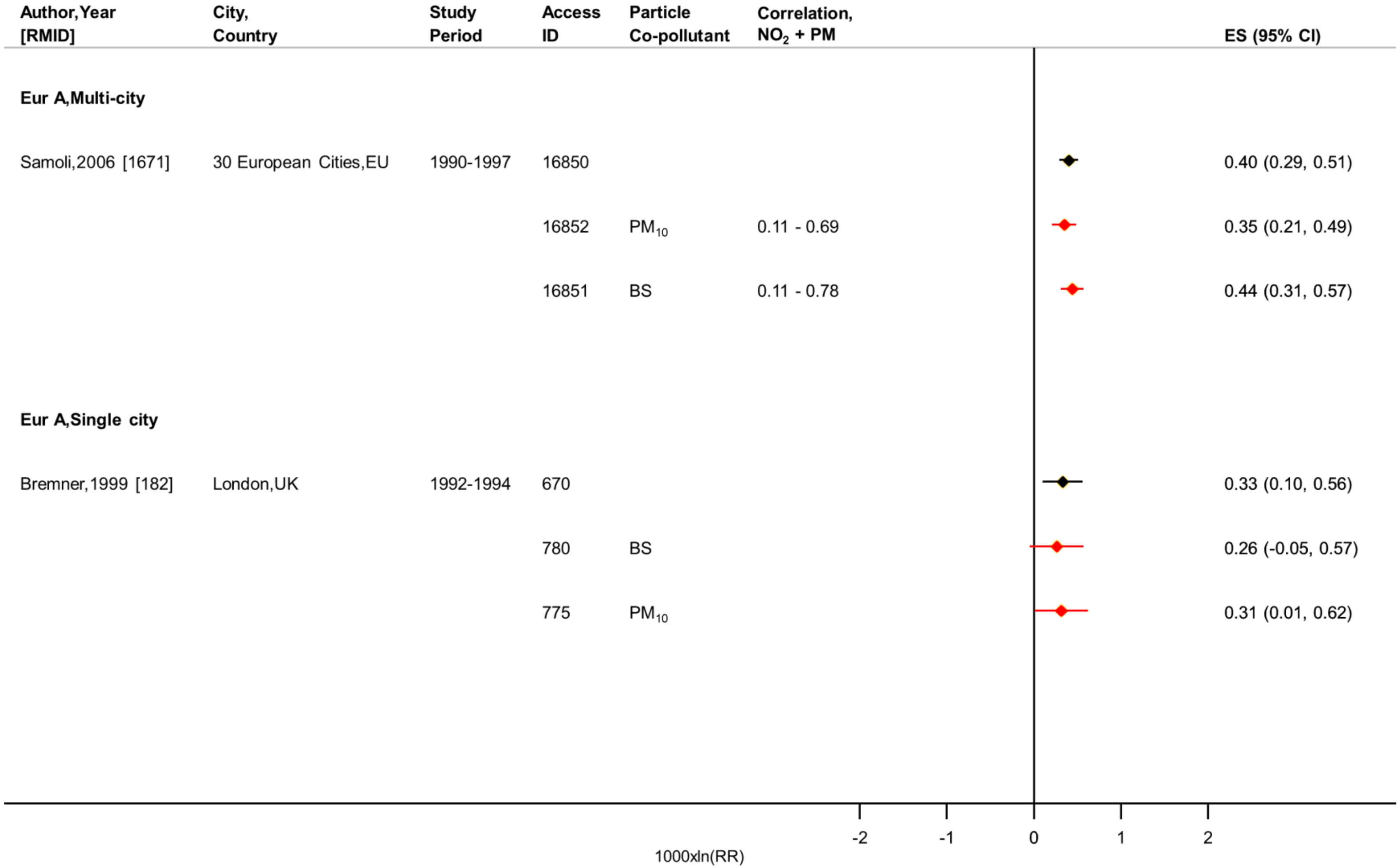


Figure S5: All available studies providing two-pollutant model estimates for meta-analysis for all respiratory mortality, all ages, 24 hour NO_2

Author,Year [RMID]	City, Country	Study Period	Access ID	Particle Co-pollutant	Correlation, NO_2 + PM	ES (95% CI)
Amr B,Single city						
Borja-Aburto,1998 [214]	Mexico City,Mexico	1993-1995	569	None		1.20 (-1.44, 3.83)
			20144	$PM_{2.5}$	0.57	0.61 (-2.87, 4.08)
Sear B,Single city						
Wong,2008 [313]	Bangkok,Thailand	1999-2003	16204	None		1.04 (-0.60, 2.69)
			16276	PM_{10}	0.71	0.32 (-2.70, 3.33)
Wpr B,Single city						
Chen,2010 [2052]	Anshan,China	2004-2006	21130	None		-0.18 (-5.54, 5.18)
			21131	PM_{10}	0.55	-1.73 (-9.27, 5.80)
Wong,2008 [313]	Hong Kong,China	1996-2002	16216	None		1.14 (0.42, 1.87)
			16300	PM_{10}	0.80	0.87 (-0.11, 1.84)
	Shanghai,China	2001-2004	16228	None		1.21 (0.42, 2.01)
			16324	PM_{10}	0.75	1.31 (0.21, 2.41)
Chen,2008 [1956]	Shanghai,China	2001-2004	15748	None		1.21 (0.42, 2.01)
			15749	PM_{10}	0.71	1.31 (0.21, 2.41)
Wong,2008 [313]	Wuhan,China	2001-2004	16240	None		3.61 (1.75, 5.47)
			16348	PM_{10}	0.75	2.80 (0.46, 5.14)
Qian,2007 [1945]	Wuhan,China	2000-2004	15266	None		2.21 (0.52, 3.89)
			15313	PM_{10}	0.58	1.28 (-0.83, 3.40)

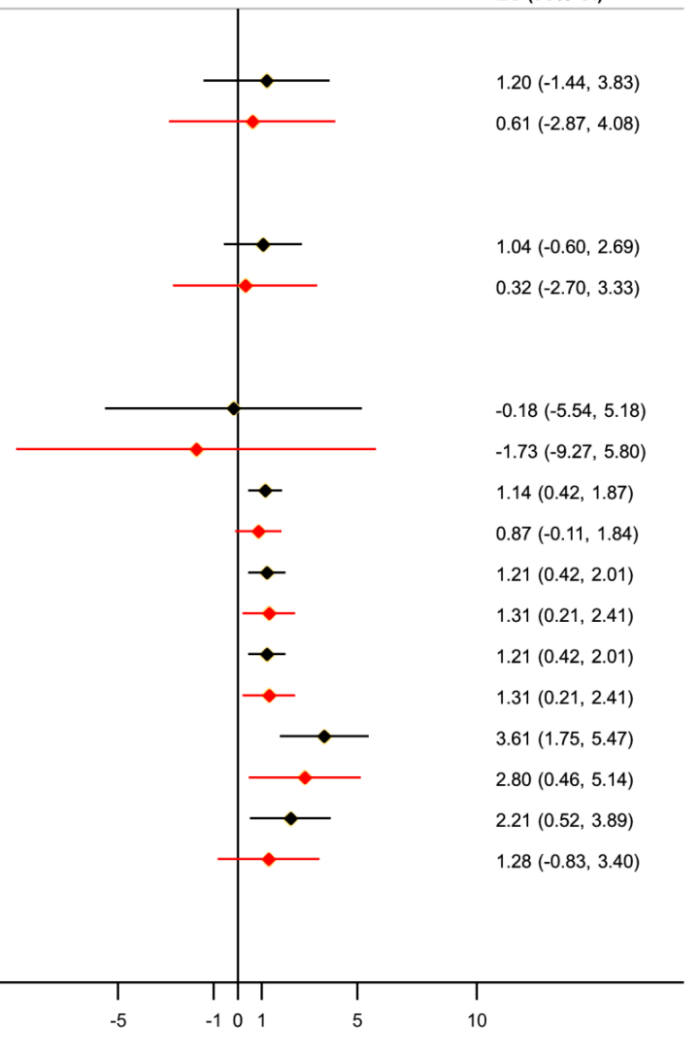


Figure S6: All available studies providing two-pollutant model estimates for meta-analysis for stroke mortality, all ages, 24 hour NO_2

Author,Year [RMID]	City, Country	Study Period	Access ID	Particle Co-pollutant	Correlation, NO_2 + PM	ES (95% CI)
Sear B,Single city						
HEI,2010 [3003]	Bangkok,Thailand	1999-2003	22198	None		2.76 (0.70, 4.83)
			22247	PM_{10}	0.71	1.59 (-2.22, 5.40)
Wpr B,Single city						
Ren,2008 [2001]	Hangzhou,China	2002-2004	17521	None		2.05 (0.54, 3.56)
			17522	PM_{10}	0.692	1.27 (-0.86, 3.41)
Hong,2002 [1448]	Seoul,South Korea	1991-1997	8760	None		1.47 (0.37, 2.57)
			8767	TSP	0.50	1.47 (0.00, 2.94)
HEI,2010 [3003]	Shanghai,China	2001-2004	22190	None		0.69 (0.08, 1.30)
			22224	PM_{10}	0.71	0.79 (-0.07, 1.64)
Haidong,2004 [349]	Shanghai,China	2001-2001	14215	None		2.86 (0.10, 5.62)
			14216	PM_{10}	0.65	1.98 (-1.61, 5.57)
Kan,2003 [130]	Shanghai,China	2001-2002	12338	None		2.86 (0.10, 5.62)
			12339	PM_{10}	0.65	1.98 (-1.61, 5.57)
HEI,2010 [3003]	Wuhan,China	2001-2004	22195	None		2.15 (1.06, 3.23)
			22214	PM_{10}	0.75	1.50 (0.14, 2.86)
Qian,2007 [1945]	Wuhan,China	2000-2004	15260	None		1.48 (0.56, 2.40)
			15311	PM_{10}	0.58	0.93 (-0.23, 2.08)

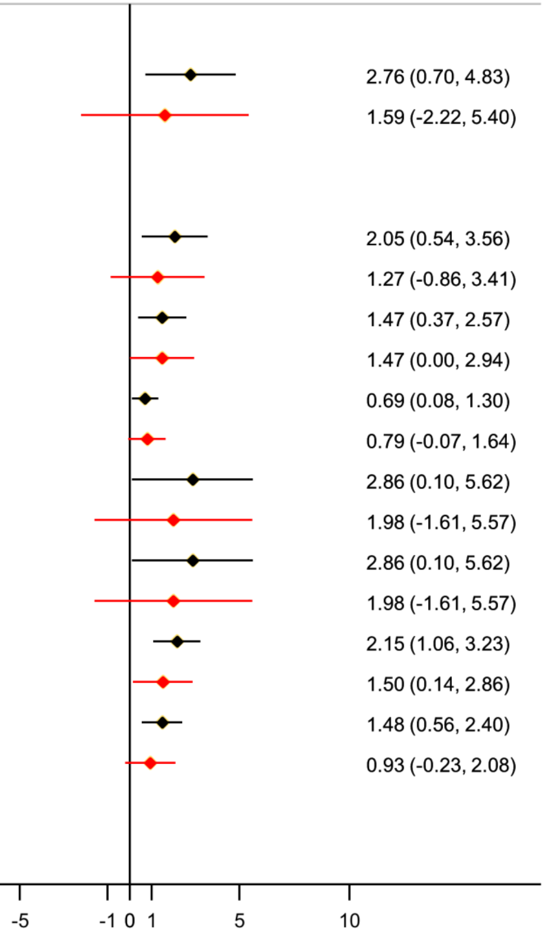
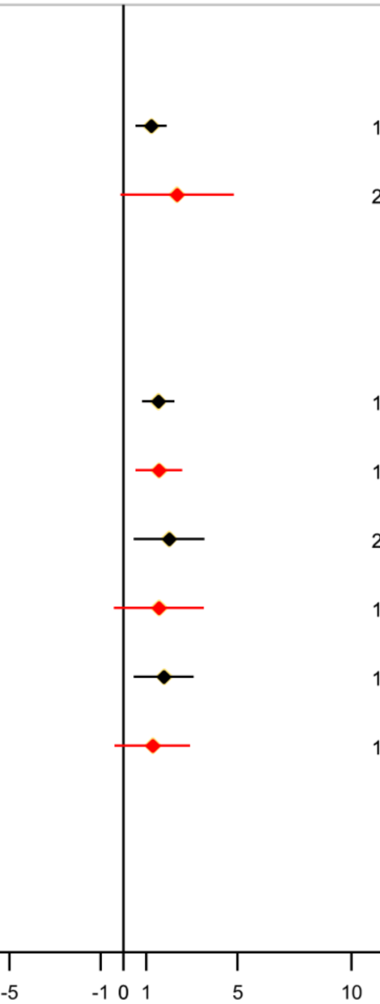


Figure S7: All available studies providing two-pollutant model estimates for meta-analysis for cardiac mortality, all ages, 24 hour NO_2

Author,Year [RMID]	City, Country	Study Period	Access ID	Particle Co-pollutant	Correlation, NO_2 + PM	ES (95% CI)
Amr A,Single city						
Moolgavkar,2000 [163]	Maricopa,USA	1987-1995	6981	None		1.20 (0.51, 1.89)
			22294	PM_{10}	0.22	2.33 (-0.15, 4.81)
Wpr B,Single city						
HEI,2010 [3003]	Shanghai,China	2001-2004	22191	None		1.53 (0.82, 2.24)
			22225	PM_{10}	0.71	1.55 (0.52, 2.58)
HEI,2010 [3003]	Wuhan,China	2001-2004	22196	None		2.00 (0.44, 3.56)
			22215	PM_{10}	0.71	1.55 (-0.42, 3.52)
Qian,2007 [1945]	Wuhan,China	2000-2004	15263	None		1.75 (0.44, 3.07)
			15312	PM_{10}	0.58	1.27 (-0.38, 2.92)



1000xln(RR)

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

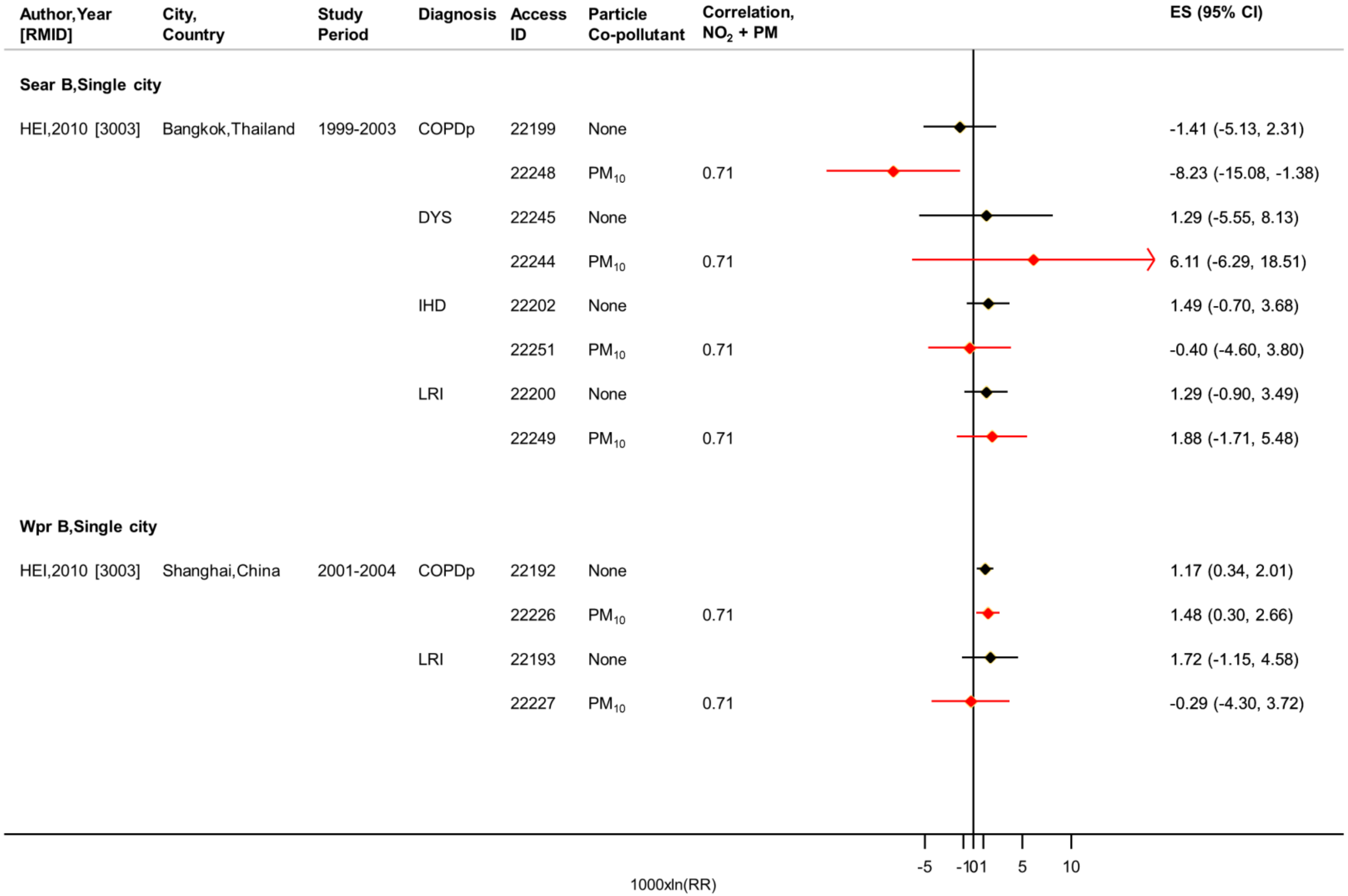


Figure S9: Studies and two-pollutant model estimates selected for meta-analysis for all cardiovascular mortality, all ages, 24 hour NO_2

Author, Year [RMID]	City, Country	Study Period	Access ID	Particle Co-pollutant	Correlation, NO_2 + PM	ES (95% CI)
Amr A, Single city						
Moolgavkar, 2003 [162]	Cook County, USA	1987-1995	12877	None		0.52 (0.15, 0.89)
			22072	PM_{10}	0.49	0.26 (-0.20, 0.73)
	Los Angeles County, USA		12900	None		0.52 (0.35, 0.69)
			22090	PM_{10}	0.70	0.68 (0.22, 1.13)
Amr B, Single city						
Borja-Aburto, 1998 [214]	Mexico City, Mexico	1993-1995	570	None		0.73 (-0.87, 2.33)
			20145	$PM_{2.5}$	0.57	-0.36 (-2.51, 1.79)
Eur A, Single city						
Zeghnoun, 2001 [1374]	Rouen, France	1990-1995	22295	None		3.67 (0.92, 6.42)
			7861	BS	0.77	3.97 (-0.67, 8.60)
Hoek, 2000 [175]	Netherlands, Netherlands	1986-1994	5513	None		0.92 (0.50, 1.34)
			5576	PM_{10}	0.62	1.66 (0.50, 2.82)
Sear B, Single city						
Wong, 2008 [313]	Bangkok, Thailand	1999-2003	16200	None		1.76 (0.47, 3.06)
			16273	PM_{10}	0.71	-0.51 (-2.92, 1.90)
Wpr B, Single city						
Chen, 2010 [2052]	Anshan, China	2004-2006	21125	None		2.09 (0.22, 3.96)
			21126	PM_{10}	0.55	-0.15 (-2.70, 2.40)
Wong, 2008 [313]	Hong Kong, China	1996-2002	16212	None		1.22 (0.64, 1.81)
			16297	PM_{10}	0.80	1.32 (0.54, 2.10)
	Shanghai, China	2001-2004	16224	None		1.00 (0.55, 1.46)
			16321	PM_{10}	0.75	0.98 (0.33, 1.62)
	Wuhan, China	2001-2004	16236	None		2.10 (1.17, 3.02)
			16345	PM_{10}	0.75	1.40 (0.24, 2.56)

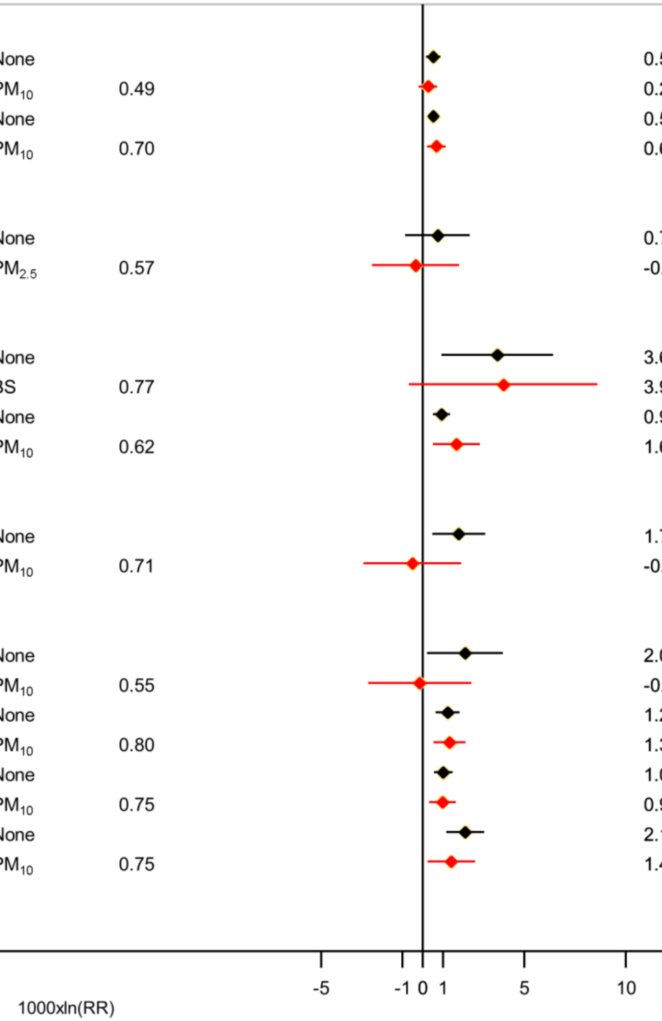


Figure S10: Studies and two-pollutant model estimates selected for meta-analysis for all respiratory mortality, all ages, 24 hour NO_2

Author,Year [RMID]	City, Country	Study Period	Access ID	Particle Co-pollutant	Correlation, NO_2 + PM	ES (95% CI)
Amr B,Single city						
Borja-Aburto,1998 [214]	Mexico City,Mexico	1993-1995	569	None		1.20 (-1.44, 3.83)
			20144	$PM_{2.5}$	0.57	0.61 (-2.87, 4.08)
Sear B,Single city						
Wong,2008 [313]	Bangkok,Thailand	1999-2003	16204	None		1.04 (-0.60, 2.69)
			16276	PM_{10}	0.71	0.32 (-2.70, 3.33)
Wpr B,Single city						
Chen,2010 [2052]	Anshan,China	2004-2006	21130	None		-0.18 (-5.54, 5.18)
			21131	PM_{10}	0.55	-1.73 (-9.27, 5.80)
Wong,2008 [313]	Hong Kong,China	1996-2002	16216	None		1.14 (0.42, 1.87)
			16300	PM_{10}	0.80	0.87 (-0.11, 1.84)
	Shanghai,China	2001-2004	16228	None		1.21 (0.42, 2.01)
			16324	PM_{10}	0.75	1.31 (0.21, 2.41)
	Wuhan,China	2001-2004	16240	None		3.61 (1.75, 5.47)
			16348	PM_{10}	0.75	2.80 (0.46, 5.14)

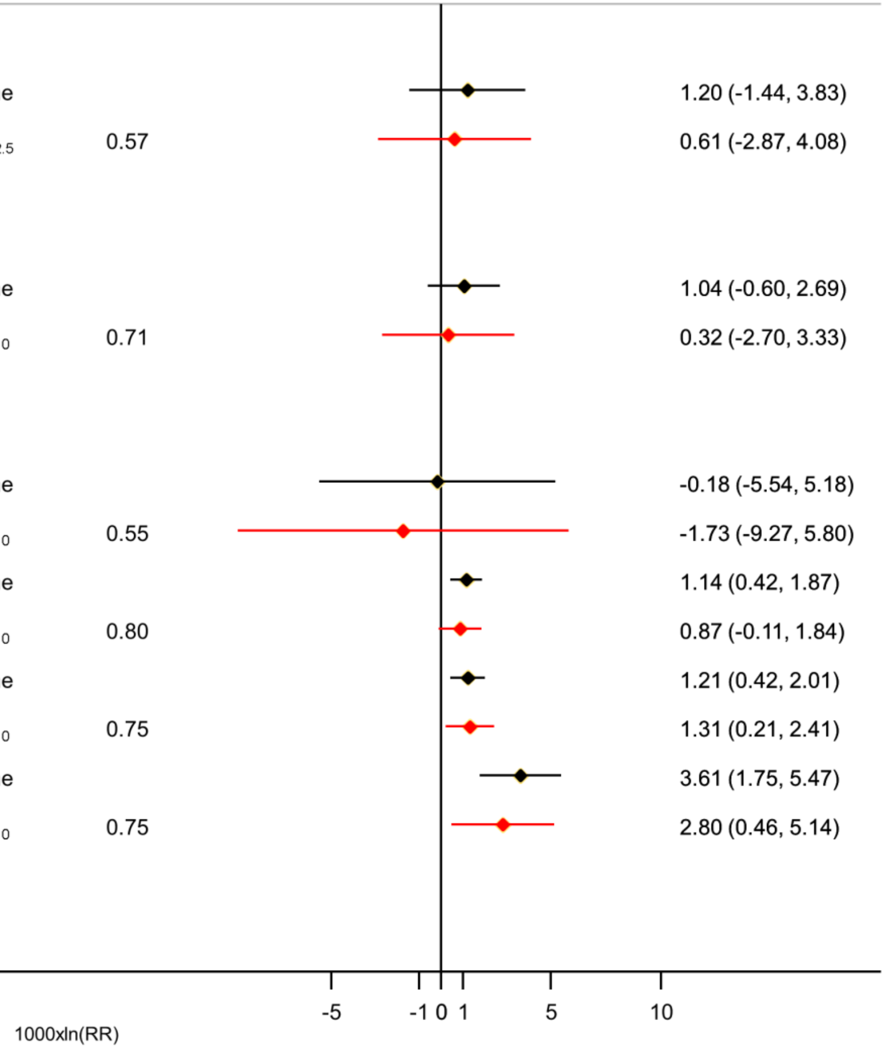


Figure S11: All studies providing two-pollutant model estimates for all-cause mortality, all-ages, ultrafine particles (UFP) adjusted for 24 hour NO_2

Author,Year [RMID]	City, Country	Study Period	Access ID	Correlation, UFP + NO_2	ES (95% CI)
Eur A,Single city					
Wichmann,2000 [1205]	Erfurt,Germany	1995-1998	22277		35.44 (-2.37, 73.25)
			22278	0.61	30.91 (-12.71, 74.52)
Breitner,2009 [1954]	Erfurt,Germany	1995-2002	16186		70.00 (14.30, 125.69)
			16189	0.62	79.87 (15.60, 144.15)
Peters,2009 [621]	Erfurt,Germany	1995-2001	22210		29.34 (3.08, 55.61)
			22211	0.62	40.26 (9.20, 71.31)

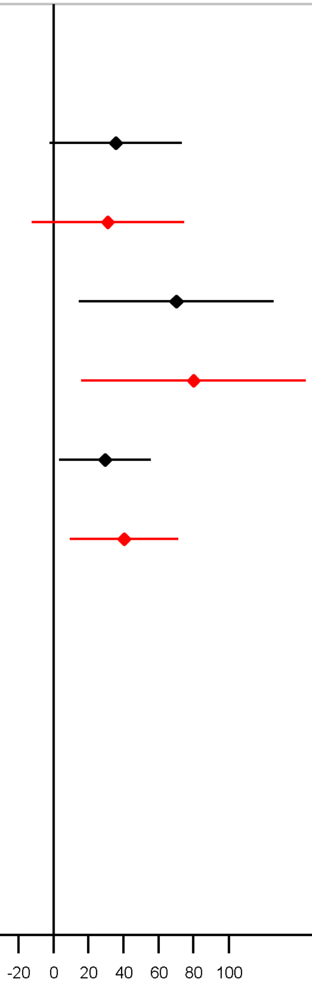


Figure S12: All studies providing two-pollutant model estimates for all cardiovascular mortality, all-ages, PM adjusted for 24 hour NO_2

Pollutant	Author,Year [RMID]	City, Country	Study Period	Access ID	Correlation PM + NO_2	ES (95% CI)
Black Smoke	**Eur A,Single city**					
	Hoek,2000 [175]	Netherlands,Netherlands	1986-1994	5508		0.79 (0.40, 1.18)
				5583	0.87	0.62 (0.02, 1.21)
PM_{10}	**Amr A,Single city**					
	Moolgavkar,2003 [162]	Cook County,USA	1987-1995	12872		0.40 (0.07, 0.73)
				22071	0.49	0.30 (-0.05, 0.65)
		Los Angeles County,USA	1987-1995	12892		0.50 (0.05, 0.94)
				22095	0.70	0.40 (-0.16, 0.96)
	Eur A,Single city					
	Hoek,2000 [175]	Netherlands,Netherlands	1986-1994	5507		0.19 (-0.16, 0.54)
				5575	0.62	-0.32 (-0.80, 0.17)
	Sear B,Single city					
	Wong,2008 [313]	Bangkok,Thailand	1999-2003	16202		1.88 (0.80, 2.97)
				16284	0.71	2.24 (0.24, 4.25)
	Wpr B,Single city					
	Chen,2010 [2052]	Anshan,China	2004-2006	21796		0.67 (0.29, 1.05)
				21798	0.55	0.69 (0.19, 1.19)
	Wong,2008 [313]	Hong Kong,China	1996-2002	16214		0.61 (0.11, 1.11)
				16308	0.80	-0.13 (-0.78, 0.52)
	Wong,2008 [313]	Shanghai,China	2001-2004	16226		0.27 (0.10, 0.44)
				16332	0.75	0.01 (-0.22, 0.24)
	Chen,2008 [1956]			15725		0.27 (0.10, 0.44)
				15731	0.71	0.01 (-0.22, 0.24)
	Wong,2008 [313]	Wuhan,China	2001-2004	16238		0.57 (0.31, 0.83)
				16356	0.75	0.33 (0.00, 0.66)
$PM_{2.5}$	**Amr A,Single city**					
	Moolgavkar,2003 [162]	Los Angeles County,USA	1987-1995	12895		0.90 (0.16, 1.63)
				22101	0.73	0.20 (-1.10, 1.50)
	Amr B,Single city					
	Borja-Aburto,1998 [214]	Mexico City,Mexico	1993-1995	560		2.17 (-0.01, 4.34)
				20125	0.57	1.67 (-2.92, 6.25)

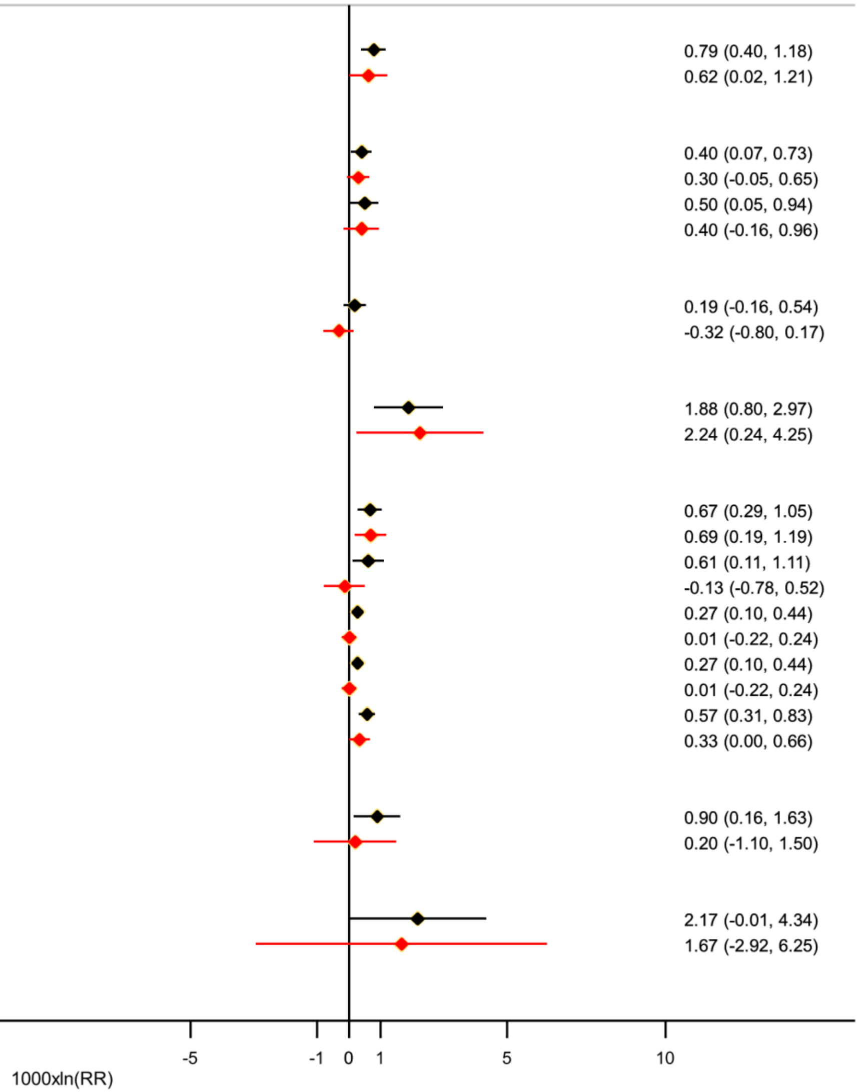


Figure S13: All studies providing two-pollutant model estimates for all respiratory mortality, all-ages, PM adjusted for 24 hour NO_2

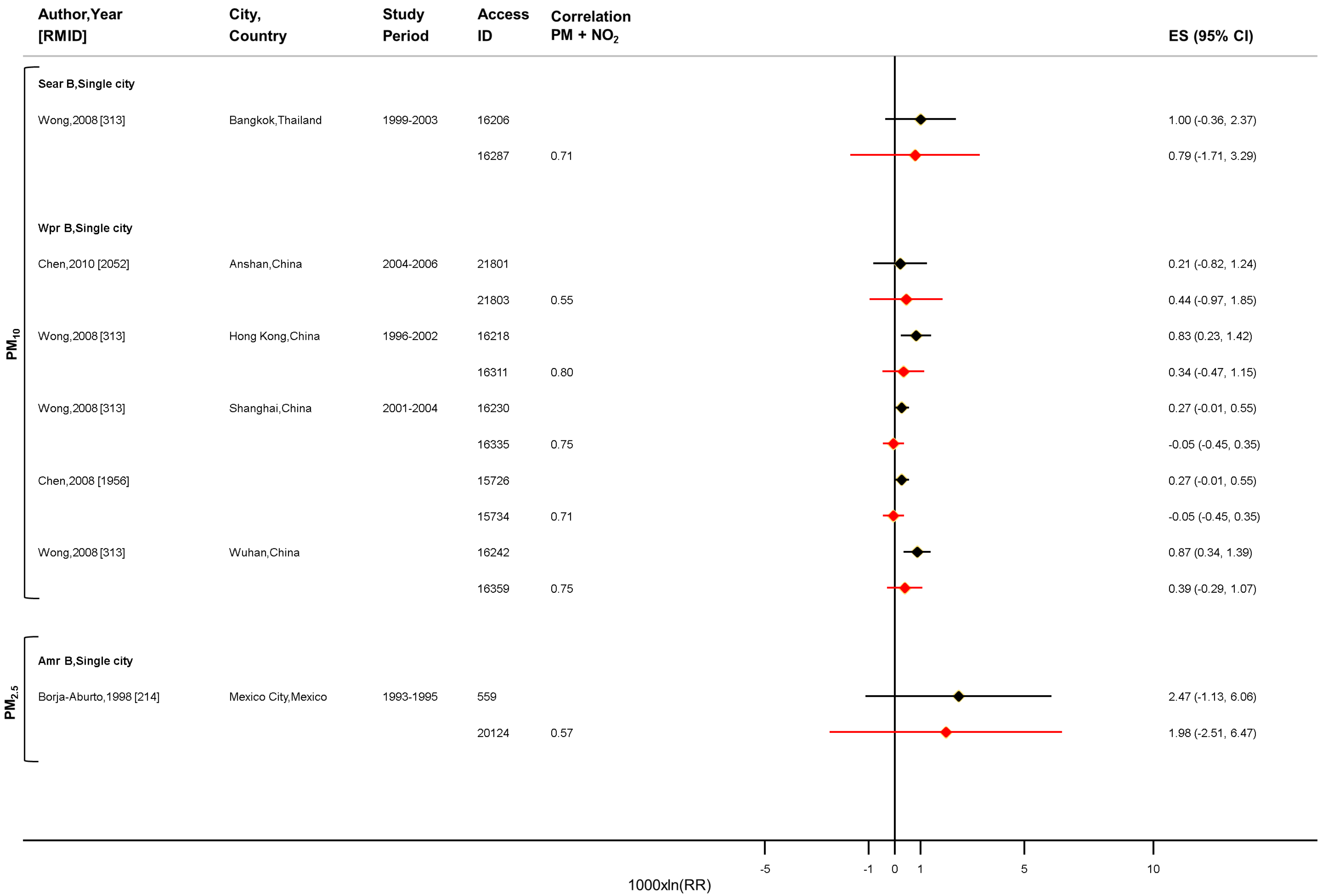
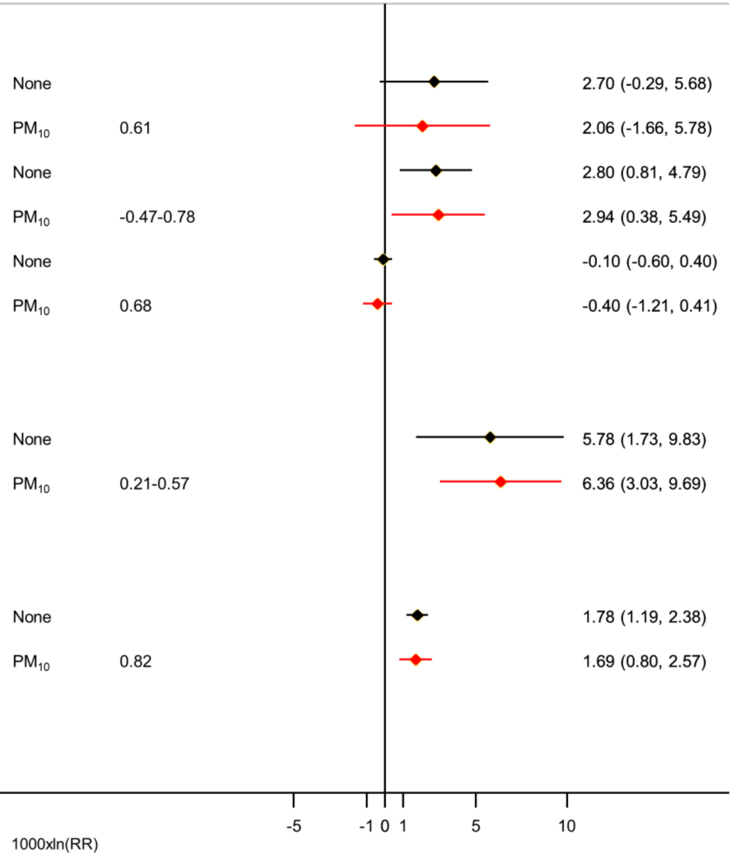


Figure S14: Studies providing two-pollutant model estimates for meta-analysis for all respiratory hospital admissions, various age groups, 24 hour NO_2

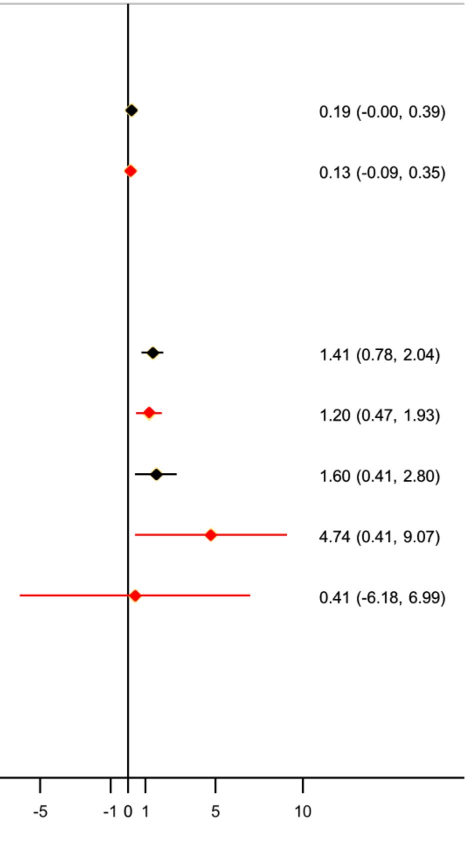
Author,Year [RMID]	City, Country	Study Period	Age*	Access ID	Particle Co-pollutant		ES (95% CI)
Eur A,Single city							
Hagen,2000 [1071]	Drammen,Norway	1994-1997	AA	4371	None		2.70 (-0.29, 5.68)
				3681	PM_{10}	0.61	2.06 (-1.66, 5.78)
Oftedal,2003 [1556]	Drammen,Norway	1994-2000	AA	12620	None		2.80 (0.81, 4.79)
				12632	PM_{10}	-0.47-0.78	2.94 (0.38, 5.49)
Wong,2002 [1429]	London,UK	1992-1994	E	22188	None		-0.10 (-0.60, 0.40)
				22189	PM_{10}	0.68	-0.40 (-1.21, 0.41)
Wpr A,Multi-city							
Barnett,2005 [2039]	7 Australia & New Zealand cities	1998-2001	C	18986	None		5.78 (1.73, 9.83)
				19024	PM_{10}	0.21-0.57	6.36 (3.03, 9.69)
Wpr B,Single city							
Wong,2002 [1429]	Hong Kong,China	1995-1997	E	8202	None		1.78 (1.19, 2.38)
				8319	PM_{10}	0.82	1.69 (0.80, 2.57)



* 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

Author,Year [RMID]	City, Country	Study Period	Age*	Access ID	Particle Co-pollutant		ES (95% CI)
Amr B,Single city							
Gouveia,2000 [207]	Sao Paulo,Brazil	1992-1994	C	5454	None		0.19 (-0.00, 0.39)
			C	22004	PM_{10}	0.40	0.13 (-0.09, 0.35)
Wpr A,Multi-city							
Simpson,2005 [134]	4 Australian Cities, Australia	1996-1999	E	13922	None		1.41 (0.78, 2.04)
			E	13945	Visibility	0.29 – 0.62	1.20 (0.47, 1.93)
Barnett,2005 [2039]	7 Australia & New Zealand cities	1998-2001	C	18977	None		1.60 (0.41, 2.80)
			C	19020	$PM_{2.5}$	0.34 - 0.68	4.74 (0.41, 9.07)
			C	19021	PM_{10}	0.21 - 0.57	0.41 (-6.18, 6.99)



* 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

Author,Year [RMID]	City, Country	Study Period	Access ID	Particle Co-pollutant	Correlation, NO_2 + PM	ES (95% CI)
Eur A,Multi-city						
Sunyer,1997 [398]	3 European Cities,EU	1986-1992	1658	None		0.51 (0.12, 0.91)
	2 European Cities,EU		1688	BS	0.29 – 0.49	0.71 (-0.90, 2.31)
Eur A,Single city						
Andersen,2007 [519]	Copenhagen,Denmark	1999-2004	18396	None		8.99 (2.13, 15.85)
			18397	PM_{10}	0.42	2.35 (-6.47, 11.17)
Andersen,2008 [1950]	Copenhagen,Denmark	2001-2004	16168	None		3.42 (-7.26, 14.10)
			16169	PNC	0.68	-2.65 (-16.23, 10.93)
Anderson,1998 [380]	London,UK	1987-1992	2128	None		0.65 (0.16, 1.14)
			1888	BS		1.17 (0.43, 1.90)
Wpr B,Single city						
Lee,2002 [1466]	Seoul,South Korea	1997-1999	8586	None		5.00 (3.41, 6.60)
			8587	PM_{10}	0.738	4.38 (2.42, 6.33)

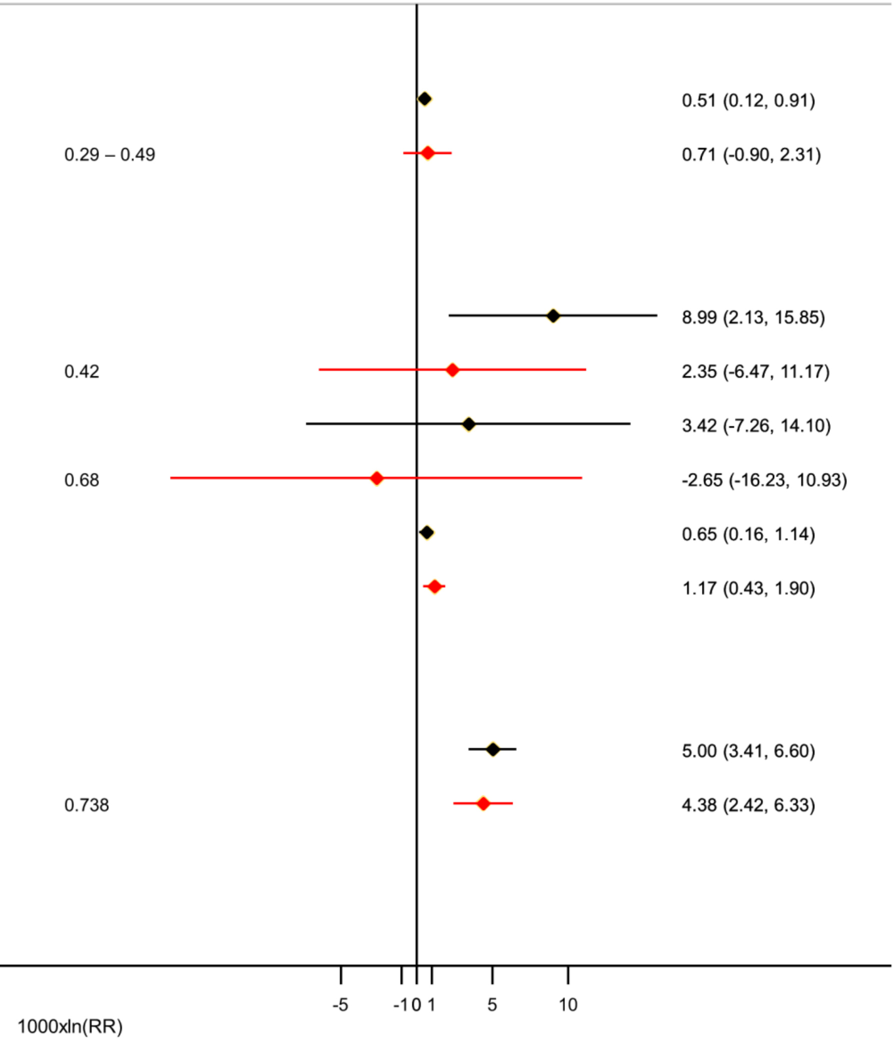
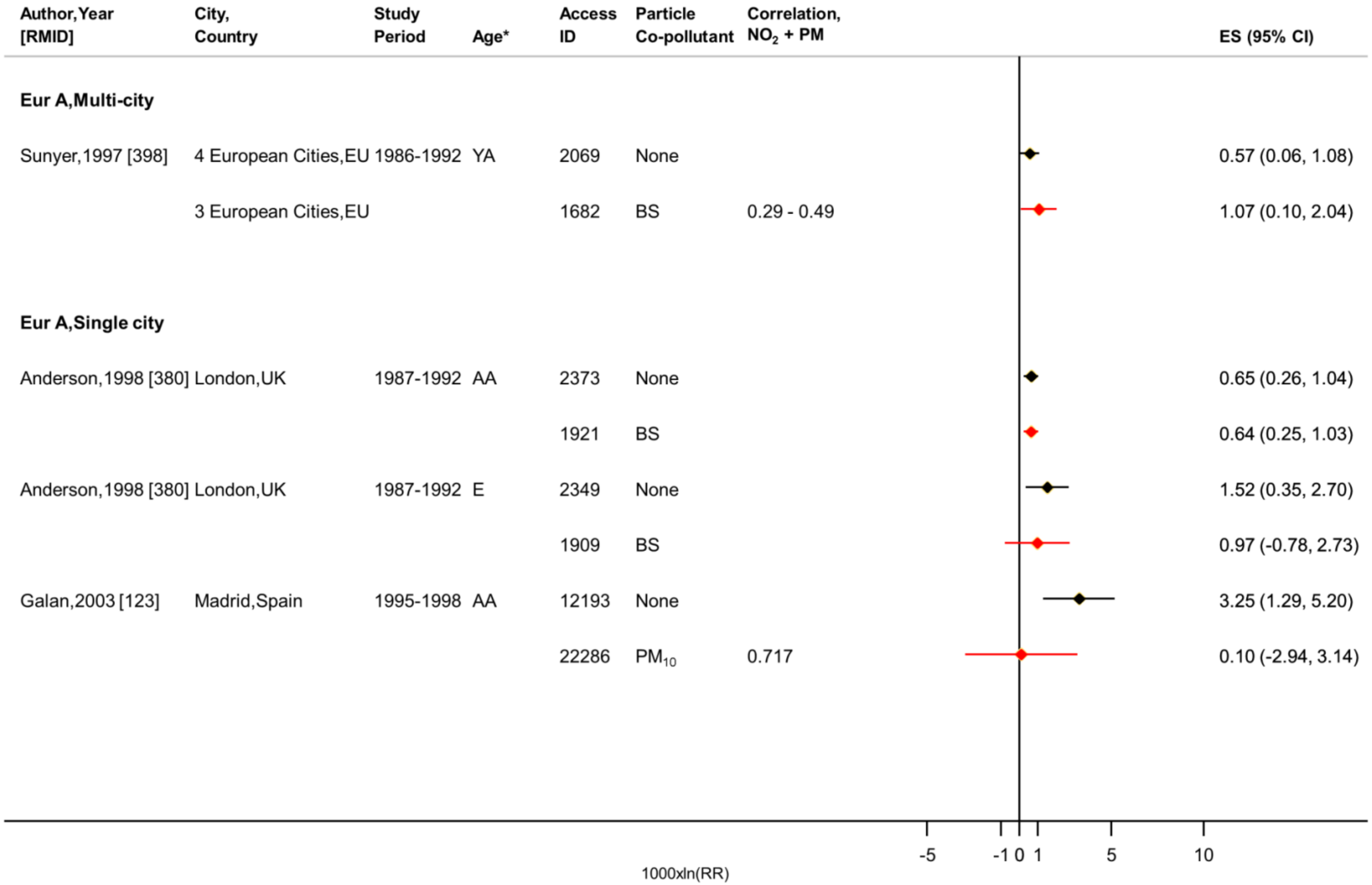


Figure S17: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for asthma, various age groups, 24 hour NO_2



* 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

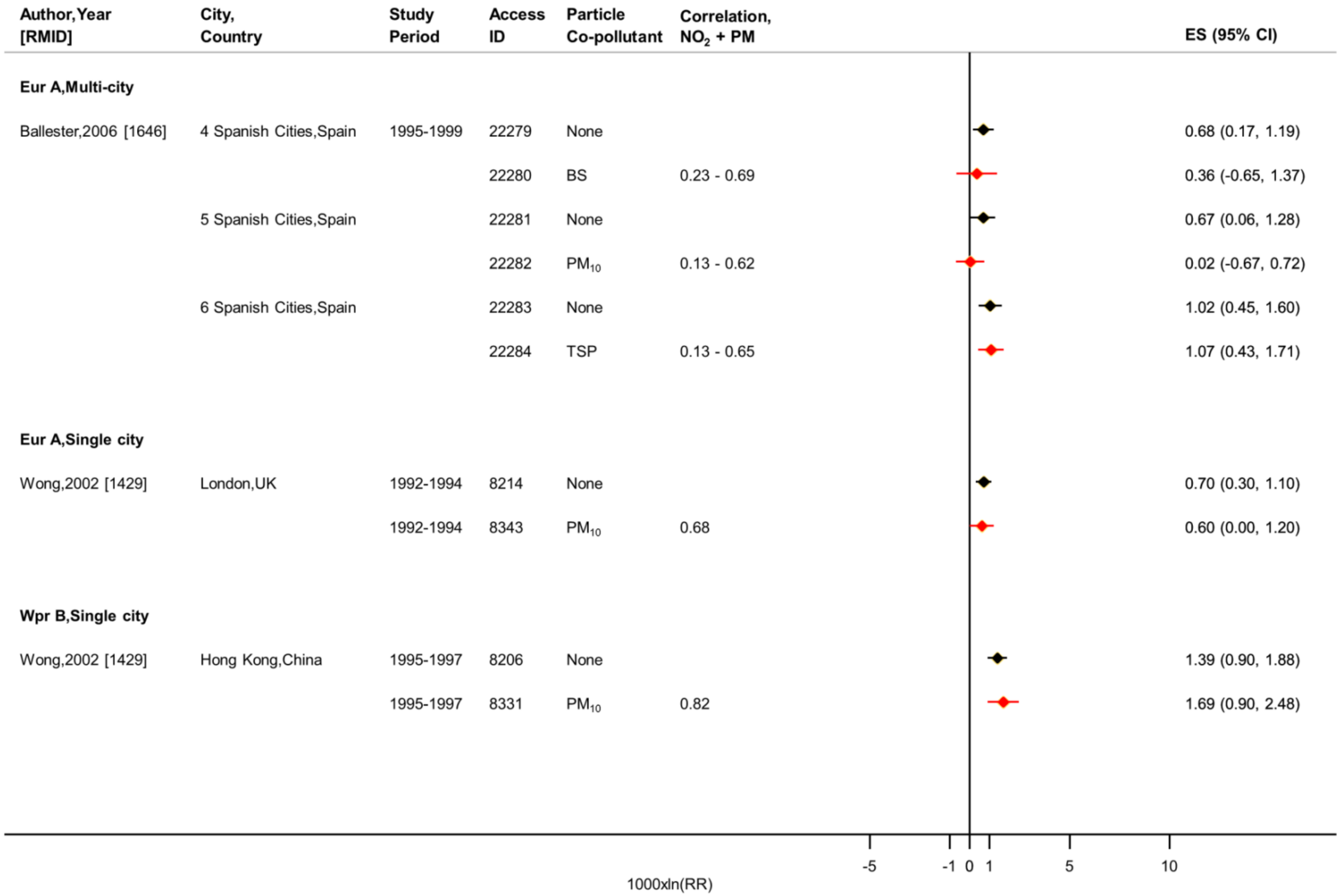
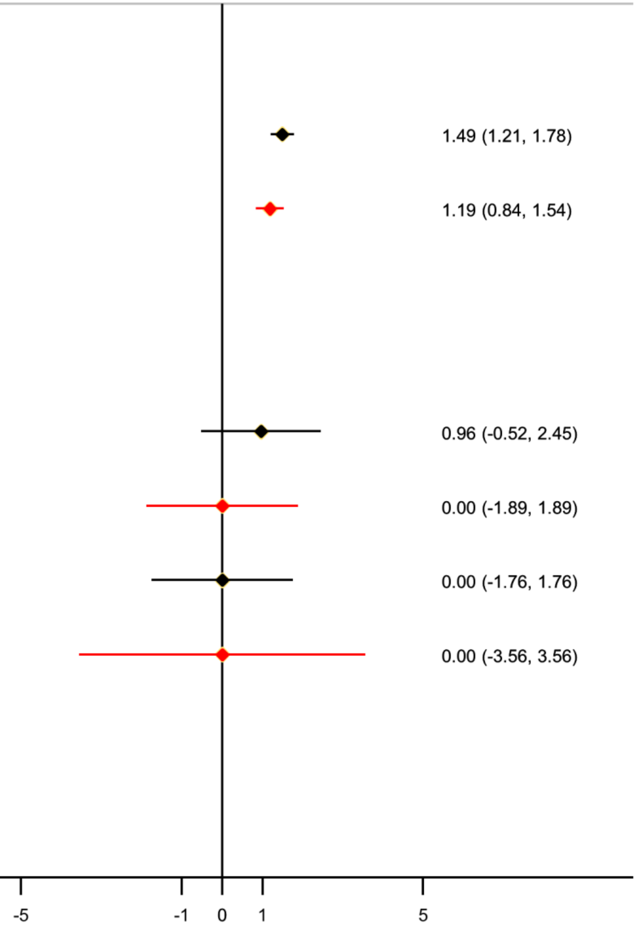


Figure S19: Studies providing two-pollutant model estimates for meta-analysis for hospital admissions for cardiac disease, elderly, 24 hour NO_2

Author,Year [RMID]	City, Country	Study Period	Access ID	Particle Co-pollutant	Correlation, NO_2 + PM	ES (95% CI)
Amr A,Single city						
Moolgavkar,2000 [1196]	Cook County,USA	1987-1995	6841	None		1.49 (1.21, 1.78)
			6846	PM_{10}	0.49	1.19 (0.84, 1.54)
Eur A,Single city						
Andersen,2007 [519]	Copenhagen,Denmark	1999-2004	18381	None		0.96 (-0.52, 2.45)
			18383	PM_{10}	0.42	0.00 (-1.89, 1.89)
Andersen,2008 [1950]	Copenhagen,Denmark	2001-2004	16127	None		0.00 (-1.76, 1.76)
			16137	PNC	0.66	0.00 (-3.56, 3.56)



1000xln(RR)

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

Author,Year [RMID]	City, Country	Study Period	Access ID	Lag	Season	ES (95% CI)
Amr A,Multi-city						
Brook,2007 [485]	10 Canadian cities,Canada	1980-2000	15647	lag 1	all	0.66 (0.40, 0.91)
			15649	lag 1	summer	1.16 (0.76, 1.55)
			15650	lag 1	winter	0.46 (0.25, 0.66)
Burnett,2004 [3000]	12 Canadian Cities,Canada	1981-1999	22140	lag 0-2	all	0.52 (0.29, 0.75)
			22300	lag 0-2	summer	0.95 (0.51, 1.40)
			22301	lag 0-2	winter	0.28 (0.04, 0.52)
Amr A,Single city						
Moolgavkar,2003 [162]	Cook County,USA	1987-1995	12723	lag 1	all	0.57 (0.33, 0.81)
			12780	lag 1	summer	1.04 (0.50, 1.57)
			12805	lag 4	winter	0.78 (0.30, 1.26)
	Los Angeles County,USA	1987-1995	12744	lag 1	all	0.52 (0.40, 0.64)
			12836	lag 2	summer	0.83 (0.47, 1.19)
			22328	lag 5	winter	0.52 (-1.51, 2.55)
Eur A,Single city						
Wichmann,2000 [1205]	Erfurt,Germany	1995-1998	7480	lag 4	all	1.43 (-0.40, 3.26)
			7498	lag 4	summer	-0.20 (-3.63, 3.23)
			7496	lag 4	winter	1.96 (-0.05, 3.97)
Peters,2009 [621]		1995-2001	21687	lag 3	all	0.69 (-0.88, 2.27)
			22325	lag 3	summer	-1.65 (-3.74, 0.44)
			22323	lag 3	winter	1.05 (-0.05, 2.16)
Anderson,1996 [268]	London,UK	1987-1992	641	lag 1	all	0.14 (-0.02, 0.30)
			643	lag 1	summer	0.25 (-0.04, 0.55)
			642	lag 1	winter	0.10 (-0.10, 0.30)
Hoek,2000 [175]	Netherlands,Netherlands	1986-1994	5503	lag 1	all	0.57 (0.40, 0.75)
			5544	lag 0-6	summer	1.37 (0.76, 1.98)
			5543	lag 0-6	winter	0.82 (0.46, 1.18)
Michelozzi,1998 [219]	Rome,Italy	1992-1995	1196	lag 2	all	0.43 (0.10, 0.76)
			1202	lag 2	summer	1.09 (0.48, 1.71)
			1200	lag 2	winter	0.07 (-0.32, 0.46)
Michelozzi,2000 [1299]		1992-1995	7320	lag 1-2	all	0.40 (0.10, 0.70)
			7324	lag 1-2	summer	1.09 (0.50, 1.69)
			7322	lag 1-2	winter	0.10 (-0.30, 0.50)
Ocana-Riola,1999 [190]	Seville,Spain	1992-1996	1031	lag 0	all	-1.10 (-2.26, 0.05)
			1032	lag 4	summer	1.71 (0.04, 3.37)
			1033	lag 0	winter	-2.57 (-3.98, -1.15)
Wpr A,Single city						
Simpson,1997 [233]	Brisbane,Australia	1987-1993	1142	lag 0	all	-0.27 (-1.39, 0.86)
			1143	lag 0	summer	-0.96 (-3.11, 1.19)
			1144	lag 0	winter	0.31 (-1.13, 1.74)
Simpson,2000 [148]	Melbourne,Australia	1991-1996	5634	lag 1	all	1.25 (0.63, 1.88)
			5636	lag 1	summer	1.88 (0.73, 3.03)
			5635	lag 1	winter	0.78 (-0.05, 1.62)
Wpr B,Multi-city*						
Wong,2008 [313]	Shanghai,China	2001-2004	16220	lag 0-1	all	0.97 (0.66, 1.27)
			22302	lag 0-1	summer	0.46 (-0.07, 0.99)
			22303	lag 0-1	winter	1.23 (0.84, 1.63)
Wpr B,Single city						
Wong,2001 [1327]	Hong Kong,China	1995-1997	5978	lag 1	all	0.67 (0.23, 1.12)
			6002	lag 1	summer	0.44 (-0.22, 1.09)
			6003	lag 1	winter	1.16 (0.47, 1.85)
Kan,2008 [1973]	Shanghai,China	2001-2004	17349	lag 0-1	all	0.97 (0.66, 1.27)
			17350	lag 0-1	summer	0.46 (-0.07, 0.99)
			17351	lag 0-1	winter	1.23 (0.84, 1.63)

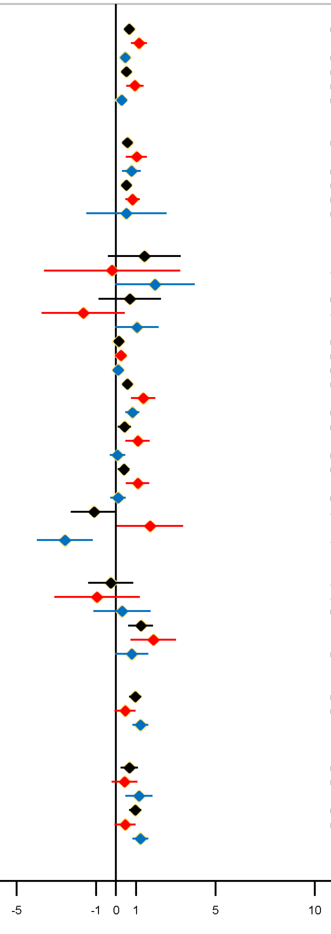


Figure S21: All available studies providing estimates from both all-year and season-specific models for 24 hour NO_2 and all cardiovascular mortality in all ages

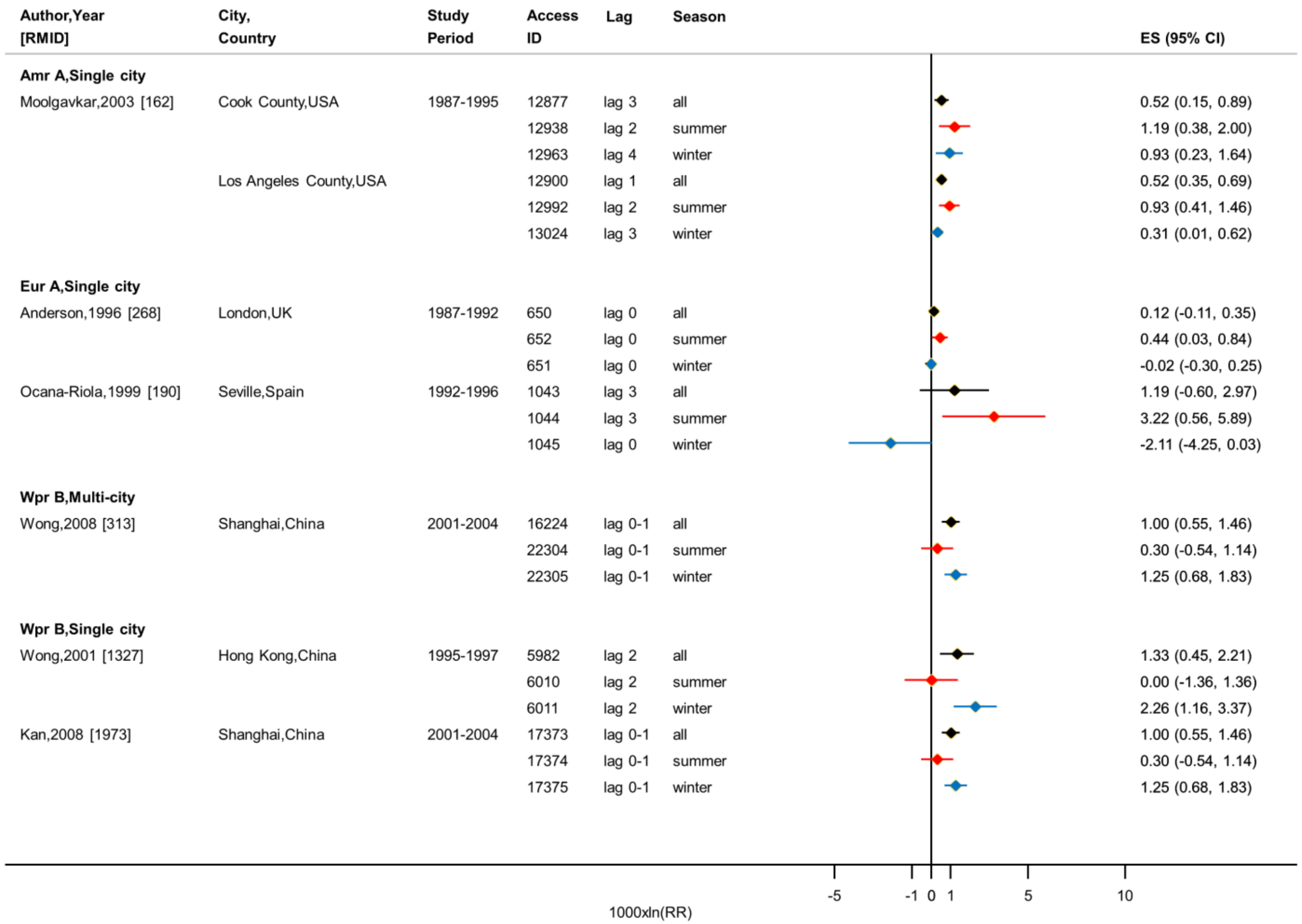


Figure S22: All available studies providing estimates from both all-year and season-specific models for 24 hour NO_2 and all respiratory mortality in all-ages

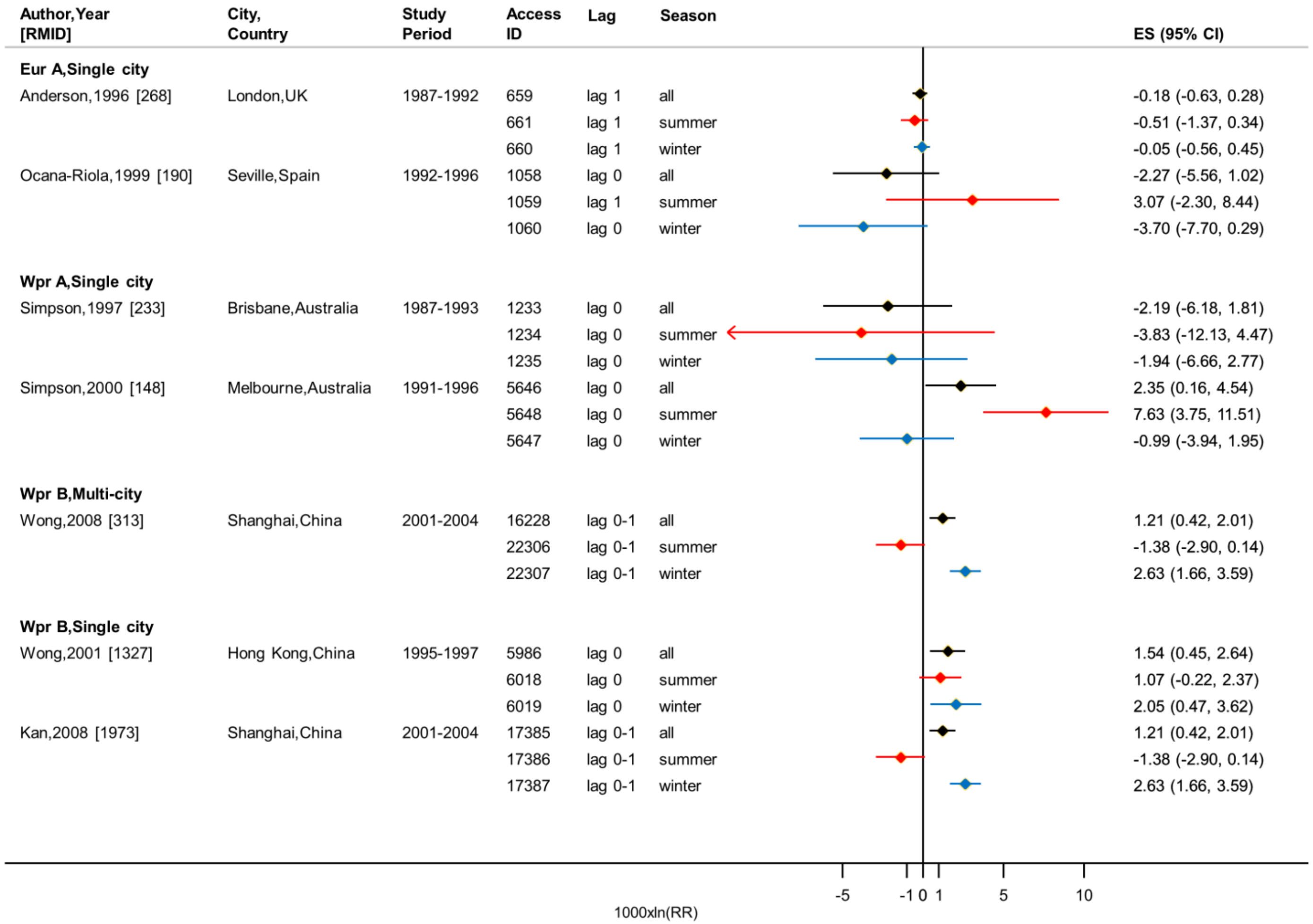


Figure S23: All available studies providing estimates from both all-year and season-specific models for 24 hour NO_2 and all respiratory and all cardiovascular hospital admissions in all-ages

Author,Year [RMID]	Diagnosis	City, Country	Study Period	Access ID	Lag	Season	ES (95% CI)
Eur A,Single city							
De Leon,1996 [417]	All respiratory	London,UK	1987-1992	1404	lag 2	all	0.22 (0.01, 0.43)
				1396	lag 2	summer	0.47 (0.07, 0.88)
				1388	lag 2	winter	0.13 (-0.12, 0.37)
Sear D,Single city							
Jayaraman,2008 [739]	All respiratory	Delhi,India	2004-2005	18727	lag 3	all	0.40 (-0.80, 1.60)
				18739	lag 3	summer	51.76 (22.47, 81.05)
Wpr B,Single city							
Wong,1999 [364]	All respiratory	Hong Kong,China	1994-1995	2982	lag 0-3	all	1.98 (1.29, 2.67)
				3005	lag 0-3	winter	0.40 (-1.21, 2.01)
	All cardiovascular			2994	lag 0-1	all	1.29 (0.70, 1.89)
				3008	lag 0-3	winter	9.80 (-0.10, 19.71)
Chen,2010 [124]	All respiratory	Shanghai,China	2005-2007	21109	lag 6	all	0.47 (-0.25, 1.19)
				21115	lag 5	summer	0.05 (-0.91, 1.01)
				21114	lag 5	winter	0.65 (-0.37, 1.67)
	All cardiovascular			21108	lag 5	all	0.80 (0.10, 1.49)
				21113	lag 5	summer	-0.26 (-1.18, 0.66)
				21112	lag 5	winter	1.65 (0.68, 2.62)

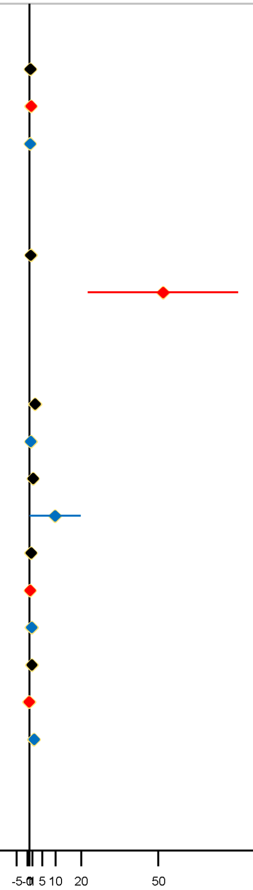


Figure S24: Ranking of NO_2 estimates for all-cause mortality in all-ages by mean levels of 24 hour NO_2 (multi-city studies shown using black bars)

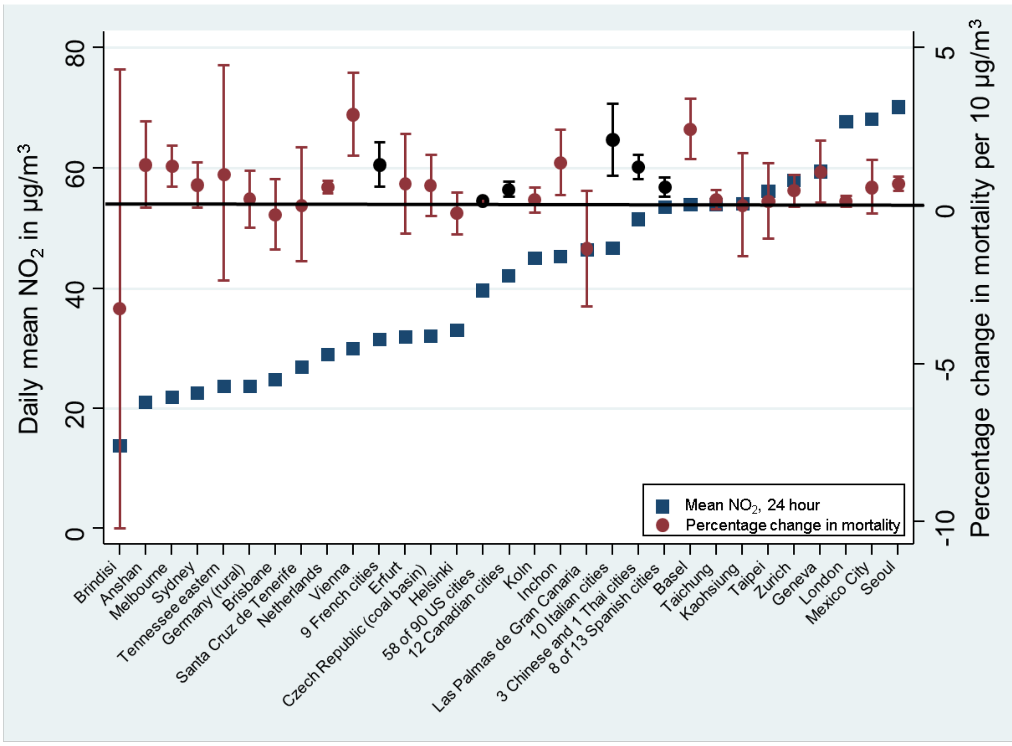


Figure S25: Ranking of NO_2 estimates for all-cause mortality in all-ages by mean levels of PM_{10} (multi-city studies shown using black bars)

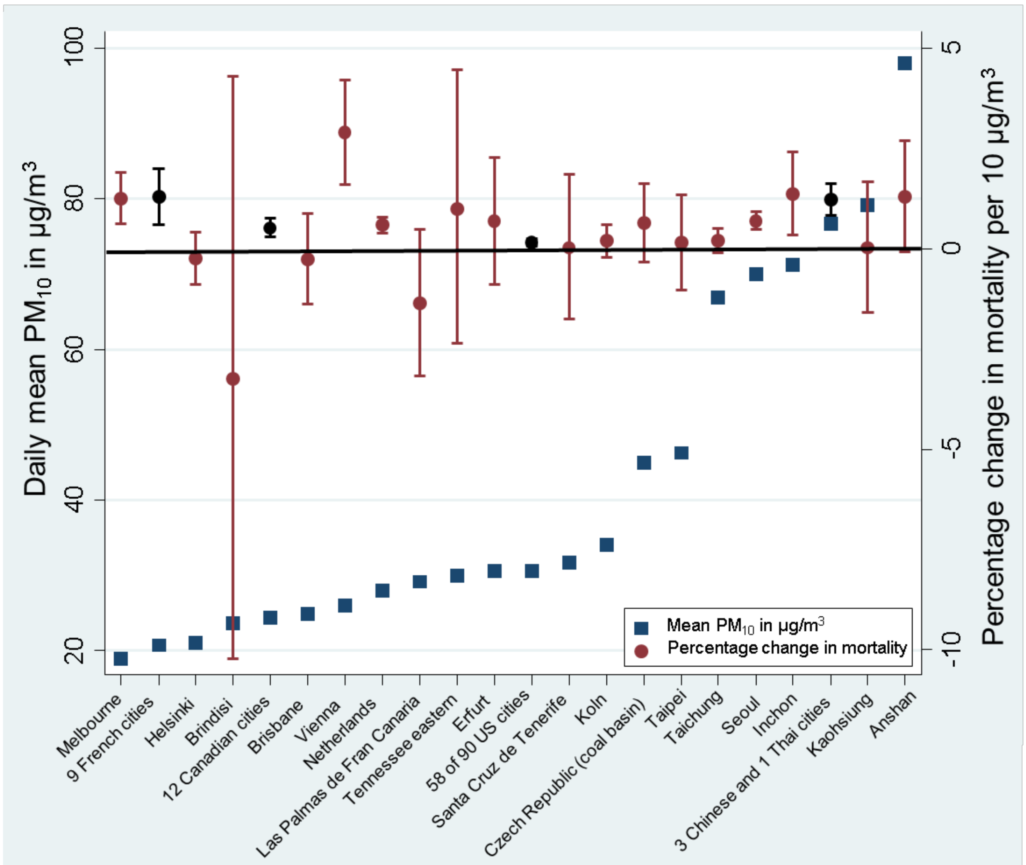


Figure S26: Ranking of NO_2 estimates for all-cause mortality in all-ages by the NO_2/PM_{10} concentration ratio (multi-city studies shown using black bars)

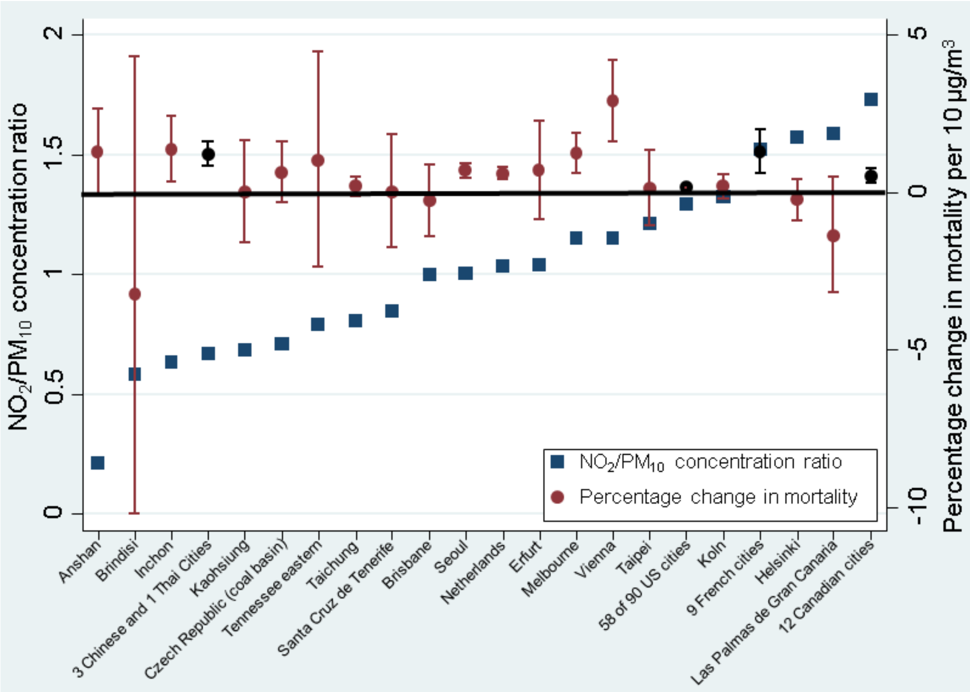
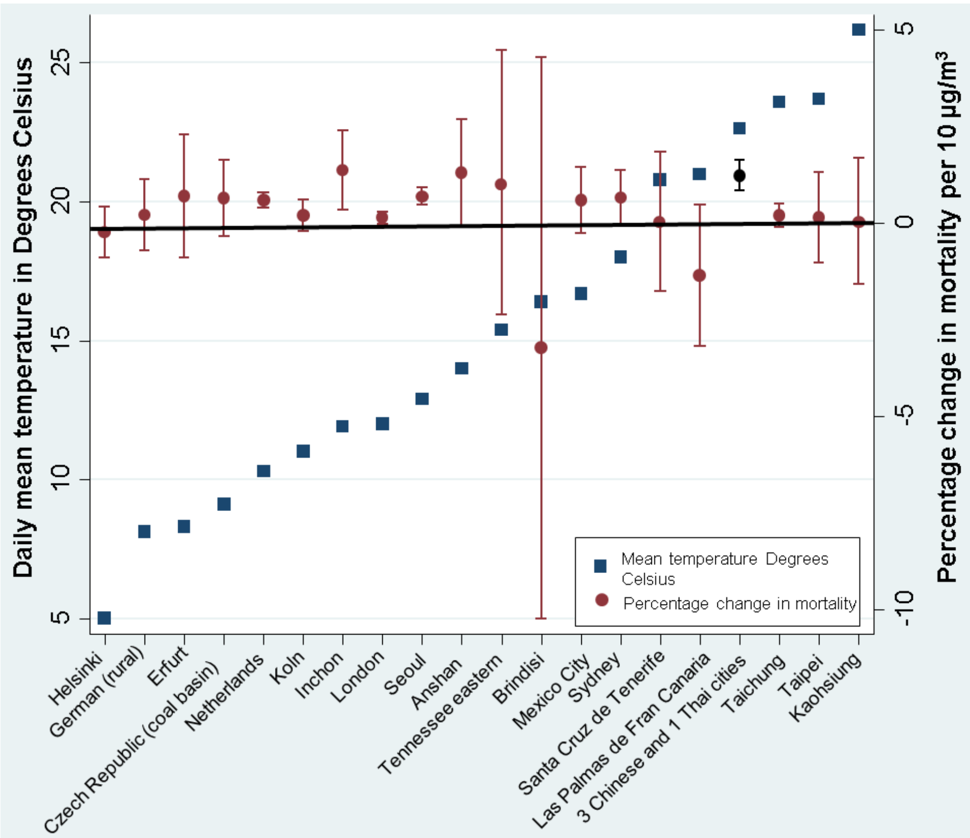


Figure S27: Ranking of NO_2 estimates for all-cause mortality in all-ages by daily mean temperature (multi-city studies shown using black bars)



Reference List

Listed in order of Reference Manager ID (RMID)

(1) Ostro BD, Hurley S, Lipsett MJ. Air pollution and daily mortality in the Coachella Valley, California: A study of PM10 dominated by coarse particles. Environ Res 1999; 81(NO-3):231-238.
RMID: 3

(2) Kan H, Chen BC. Air pollution and daily mortality in Shanghai: A time-series study. Arch Environ Health 2003; 58(6):360-367.
RMID: 76

(3) Galan I, Tobias A, Banegas JR, Aranguez E. Short-term effects of air pollution on daily asthma emergency room admissions. Eur Respir J 2003; 22(5):802-808.
RMID: 123

(4) Chen RJ, Chu C, Tan JG, Cao JS, Song WM, Xu XH et al. Ambient air pollution and hospital admission in Shanghai, China. Journal of Hazardous Materials 2010; 181(1-3):234-240.
RMID: 124

(5) Kan H, Jia J, Chen BH. Acute stroke mortality and air pollution: New evidence from Shanghai, China. Journal of Occupational Health 2003; 45(5):321-323.
RMID: 130

(6) Simpson R, Williams G, Petroeschevsky A, Best T, Morgan G, Denison L et al. The short-term effects of air pollution on daily mortality in four Australian cities. Aust N Z J Public Health 2005; 29(3):205-212.
RMID: 133

(7) Simpson R, Williams G, Petroeschevsky A, Best T, Morgan G, Denison L et al. The short-term effects of air pollution on hospital admissions in four Australian cities. Aust N Z J Public Health 2005; 29(3):213-221.
RMID: 134

(8) Burnett RT, Brook J, Dann T, Delocla C, Philips O, Cakmak S et al. Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. Inhal Toxicol 2000; 12:15-39.
RMID: 135

(9) Kan H, Jia J, Chen BH. The association of daily diabetes mortality and outdoor air pollution in Shanghai, China. Journal of Environmental Health 2004; 67(3):21-25.
RMID: 150

(10) Moolgavkar SH. Air pollution and daily mortality in two U. S. counties: Season-specific analyses and exposure-response relationships. Inhal Toxicol 2003; 15(9):877-907.
RMID: 162

(11) Moolgavkar SH. Air pollution and daily mortality in three US counties. Environ Health Perspect 2000; 108(8):777-784.
RMID: 163

(12) Hoek G, Brunekreef B, Verhoeff A, van Wijnen J, Fischer P. Daily mortality and air pollution in the Netherlands. J Air Waste Manage Assoc 2000; 50(8):1380-1389.
RMID: 175

(13) Chock DP, Winkler SL. A study of the association between daily mortality and ambient air pollutant concentrations in Pittsburgh, Pennsylvania. J Air Waste Manage Assoc 2000; 50(8):1481-1500.
RMID: 177

(14) Bremner SA, Anderson HR, Atkinson RW, McMichael AJ, Strachan DP, Bland JM et al. Short-term associations between outdoor air pollution and mortality in London 1992-4. Occupational & Environmental Medicine 1999; 56(4):237-244.
RMID: 182

(15) Gouveia N, Fletcher T. Respiratory diseases in children and outdoor air pollution in Sao Paulo, Brazil: a time series analysis. Occupational & Environmental Medicine 2000; 57(7):477-483.
RMID: 207

(16) Loomis DP, Castillejos M, Gold DR, McDonnell W, Borja-Aburto VH. Air pollution and infant mortality in Mexico City. Epidemiol 1999; 10(2):118-123.
RMID: 210

(17) Borja-Aburto VH, Castillejos M, Gold DR, Bierzwinski S, Loomis D. Mortality and ambient fine particles in southwest Mexico City, 1993-1995. Environ Health Perspect 1998; 106(12):849-855.
RMID: 214

(18) Michelozzi P, Forastiere F, Fusco D, Perucci CA, Ostro B, Ancona C et al. Air pollution and daily mortality in Rome, Italy. Occupational & Environmental Medicine 1998; 55(9):605-610.
RMID: 219

(19) Farhat SCL, Paulo RLP, Shimoda TM, Conceicao GMS, Lin CA, Braga ALF et al. Effect of air pollution on pediatric respiratory emergency room visits and hospital admissions. Brazilian Journal of Medical and Biological Research 2005; 38(2):227-235.
RMID: 235

(20) Kelsall JE, Samet JM, Zeger SL, Xu J. Air pollution and mortality in Philadelphia, 1974-1988. Am J Epidemiol 1997; 146(9):750-762.
RMID: 236

(21) Touloumi G, Katsouyanni K, Zmirou D, Schwartz J, Spix C, De Leon AP et al. Short-term effects of ambient oxidant exposure on mortality: a combined analysis within the APHEA project. Air Pollution and Health: a European Approach. Am J Epidemiol 1997; 146(2):177-185.
RMID: 240

(22) Ostro BD, Sanchez JM, Aranda C, Eskeland GS. Air pollution and mortality: results from a study of Santiago, Chile. J Expo Anal Environ Epidemiol 1996; 6(1):97-114.
RMID: 256

(23) Wong CM, Vichit-Vadakan N, Kan HD, Qian ZM. Public Health and Air Pollution in Asia (PAPA): A multicity study of short-term effects of air pollution on mortality. Environ Health Perspect 2008; 116(9):1195-1202.
RMID: 313

(24) Kan H, Jia J, Chen B. A time-series study on the association of stroke mortality and air pollution in Zhabei, Shanghai. Journal of Hygiene Research 2006; 33(1):36-38.
RMID: 349

(25) Anderson HR, Ponce dL, Bland JM, Bower JS, Emberlin J, Strachan DP. Air pollution, pollens, and daily admissions for asthma in London 1987- 92. Thorax 1998; 53(10):842-848.
RMID: 380

(26) Sunyer J, Spix C, Quenel P, Ponce-de-Leon A, Barumandzadeh T, Touloumi G et al. Urban air pollution and emergency admissions for asthma in four European cities: The APHEA project. Thorax 1997; 52(9):760-765.
RMID: 398

(27) Brook JR, Burnett RT, Dann TF, Cakmak S, Goldberg MS, Fan XH et al. Further interpretation of the acute effect of nitrogen dioxide observed in Canadian time-series studies. Journal of Exposure Science and Environmental Epidemiology 2007; 17:S36-S44.
RMID: 485

(28) Andersen ZJ, Wahlin P, Raaschou-Nielsen O, Scheike T, Loft S. Ambient particle source apportionment and daily hospital admissions among children and elderly in Copenhagen. Journal of Exposure Science and Environmental Epidemiology 2007; 17(7):625-636.
RMID: 519

(29) Peters A, Breitner S, Cyrys J, Stolzel M, Pitz M, Wolke G et al. The influence of improved air quality on mortality risks in Erfurt, Germany. Research Report - Health Effects Institute [137], 5-77. 2009.
Ref Type: Report
RMID: 621

(30) Samoli E, Nastos PT, Paliatsos AG, Katsouyanni K, Priftis KN. Acute effects of air pollution on pediatric asthma exacerbation: Evidence of association and effect modification. Environ Res 2011; 111(3):418-424.
RMID: 872

(31) Hagen JA, Nafstad P, Skrondal A, Bjorkly S, Magnus P. Associations between outdoor air pollutants and hospitalization for respiratory diseases. Epidemiol 2000; 11(2):136-140.
RMID: 1071

(32) Cifuentes L, Vega J, Kopfer K, Lava LB. Effect of the fine fraction of particulate matter versus the coarse mass and other pollutants on daily mortality in Santiago, Chile. J Air Waste Manage Assoc 2000; 50(8):1287-1298.
RMID: 1152

(33) Ballester F, Tenias JM, Perez-Hoyos S. Air pollution and emergency hospital admissions for cardiovascular diseases in Valencia, Spain. J Epidemiol Community Health 2001; 55(1):57-65.
RMID: 1184

(34) Moolgavkar SH. Air pollution and hospital admissions for diseases of the circulatory system in three US metropolitan areas. J Air Waste Manage Assoc 2000; 50(7):1199-1206.
RMID: 1196

(35) Wichmann HE, Spix C, Tuch T, Wolke G, Peters A, Heinrich J et al. Daily Mortality and Fine and Ultrafile Particles in Erfurt, Germany Part I: Role of Particle Number and Particle Mass. 98. 2000. Health Effects Institute.
Ref Type: Report
RMID: 1205

(36) Zeghnoun A, Czernichow P, Beaudeau P, Hautemaniere A, Froment L, Le Tertre A et al. Short-term effects of air pollution on mortality in the cities of Rouen and Le Havre, France, 1990-1995. Arch Environ Health 2001; 56(4):327-335.
RMID: 1374

(37) Wong CM, Atkinson RW, Anderson HR, Hedley AJ, Ma S, Chau PYK et al. A tale of two cities: Effects of air pollution on hospital admissions in Hong Kong and London compared. Environ Health Perspect 2002; 110(1):67-77.
RMID: 1429

(38) Hong Y-C, Lee J-T, Kim H, Kwon H-J. Air pollution: A new risk factor in ischemic stroke mortality. Stroke 2002; 33(9):2165-2169.
RMID: 1448

(39) Lee JT, Kim H, Song HY, Hong YC, Cho YS, Shin SY et al. Air pollution and asthma among children in Seoul, Korea. Epidemiol 2002; 13(4):481-484.
RMID: 1466

(40) D'Ippoliti D, Forastiere F, Ancona C, Agabiti N, Fusco D, Michelozzi P et al. Air pollution and myocardial infarction in Rome - A case- crossover analysis. Epidemiol 2003; 14(5):528-535.
RMID: 1509

(41) Kan HD, Chen BH. A case-crossover analysis of air pollution and daily mortality in Shanghai. Journal of Occupational Health 2003; 45(2):119-124.
RMID: 1531

(42) Oftedal B, Nafstad P, Magnus P, Bjorkly S, Skrondal A. Traffic related air pollution and acute hospital admission for respiratory diseases in Drammen, Norway 1995-2000. Eur J Epidemiol 2003; 18(7):671-675.
RMID: 1556

(43) Lee JT, Kim H, Cho YS, Hong YC, Ha EH, Park H. Air pollution and hospital admissions for ischemic heart diseases among individuals 64+years of age residing in Seoul, Korea. Arch Environ Health 2003; 58(10):617-623.
RMID: 1622

(44) Yang QY, Chen Y, Krewski D, Burnett RT, Shi YL, McGrail KM. Effect of short-term exposure to low levels of gaseous pollutants on chronic obstructive pulmonary disease hospitalizations. Environ Res 2005; 99(1):99-105.
RMID: 1638

(45) Kwon H-J, Cho S-H. Air pollution and daily mortality in Seoul. Korean Journal of Preventative Medicine 1999; 32(2):191-199.
RMID: 1643

(46) Chang JH, et al. Effect of air pollution on daily clinic treatments for respiratory cardiovascular disease in central Taiwan, 1997-1999. Zhonghua Occupational Medicine

Journal 2002; 9(2):111-120.
RMID: 1645

(47) Ballester F, Rodriguez P, Iniguez C, Saez M, Daponte A, Galan I et al. Air pollution and cardiovascular admissions association in Spain: results within the EMECAS project. J Epidemiol Community Health 2006; 60(4):328-336.
RMID: 1646

(48) Samoli E, Aga E, Touloumi G, Nislotis K, Forsberg B, Lefranc A et al. Short-term effects of nitrogen dioxide on mortality: an analysis within the APHEA project. Eur Respir J 2006; 27(6):1129-1137.
RMID: 1671

(49) Wellenius GA, Bateson TF, Mittleman MA, Schwartz J. Particulate air pollution and the rate of hospitalization for congestive heart failure among Medicare beneficiaries in Pittsburgh, Pennsylvania. Am J Epidemiol 2005; 161(11):1030-1036.
RMID: 1924

(50) Qian Z, He Q, Lin HM, Kong L, Liao D, Yang N et al. Short-term effects of gaseous pollutants on cause-specific mortality in Wuhan, China. J Air Waste Manag Assoc 2007; 57(7):785-793.
RMID: 1945

(51) Andersen ZJ, Wahlin P, Raaschou-Nielsen O, Ketzel M, Scheike T, Loft S. Size distribution and total number concentration of ultrafine and accumulation mode particles and hospital admissions in children and the elderly in Copenhagen, Denmark. Occup Environ Med 2008; 65(7):458-466.
RMID: 1950

(52) Breitner S, Stolzel M, Cyrys J, Pitz M, Wolke G, Kreyling W et al. Short-Term Mortality Rates during a Decade of Improved Air Quality in Erfurt, Germany. Environ Health Perspect 2009; 117(3):448-454.
RMID: 1954

(53) Chen GH, Song GX, Jiang LL, Zhang YH, Zhao NQ, Chen BH et al. Short-term effects of ambient gaseous pollutants and particulate matter on daily mortality in Shanghai, China. Journal of Occupational Health 2008; 50(1):41-47.
RMID: 1956

(54) Ren YJ, Li XY, Chen K, Liu QM, Xiang HQ, Jin DF et al. [A case-crossover study on air pollutants and the mortality of stroke]. Zhonghua Liu Xing Bing Xue Za Zhi = Zhonghua Liuxingbingxue Zazhi 2008; 29(9):878-881.
RMID: 2001

(55) Barnett AG, Williams GM, Schwartz J, Neller AH, Best TL, Petroeschevsky AL et al. Air pollution and child respiratory health - A case-crossover study in Australia and new Zealand. American Journal of Respiratory and Critical Care Medicine 2005; 171(11):1272-1278.
RMID: 2039

(56) Lin M, Stieb DM, Chen Y. Coarse particulate matter and hospitalization for respiratory infections in children younger than 15 years in Toronto: A case-crossover analysis. Pediatrics 2005; 116(2):E235-E240.
RMID: 2040

(57) Chen RJ, Pan GW, Kan HD, Tan JG, Song WM, Wu ZY et al. Ambient air pollution and daily mortality in Anshan, China: A time-stratified case-crossover analysis. Science of the Total Environment 2010; 408(24):6086-6091.
RMID: 2052

(58) Park AK, Hong YC, Kim H. Effect of changes in season and temperature on mortality associated with air pollution in Seoul, Korea. J Epidemiol Community Health 2011; 65(4):368-375.
RMID: 2067

(59) Burnett RT, Stieb D, Brook JR, Cakmak S, Dales R, Raizenne M, Vincent R, Dann T. Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. *Arch Environ Health.* 2004; **59**(5):228-36.
RMID: 3000

(60) HEI Public Health and Air Pollution in Asia Program. (2010) Public Health and Air Pollution in Asia (PAPA): Coordinated Studies of Short-Term Exposure to Air Pollution and Daily Mortality in Four Cities. HEI Research Report 154. Health Effects Institute, Boston, MA.
RMID: 3003

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 the online supplementary material.

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 $\mu g/m^3$ 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 $\mu g/m^3$ 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 $\mu g/m^3$ 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 $\mu g/m^3$ 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 $\mu g/m^3$ 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 $\mu g/m^3$ 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 $\mu g/m^3$ 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 $\mu g/m^3$ 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 $\mu g/m^3$ 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/m^3 (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/m^3 (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/cm^3 (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/m^3 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/m^3 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/m^3 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/m^3 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/m^3 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/m^3 NO_2	RR 1.01005 (1.00782, 1.01228) adjusted for PM_{10}		RR 1.00101 (1.00057, 1.00145) per 10 μg/m^3 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	

References

Bhaskaran K, Hajat S, Armstrong B, Haines A, Herrett E, Wilkinson P, Smeeth L. (2011) The effects of hourly differences in air pollution on the risk of myocardial infarction: case crossover analysis of the MINAP database. BMJ. 343:d5531. doi: 10.1136/bmj.d5531.

Chen R, Samoli E, Wong CM, Huang W, Wang Z, Chen B, Kan H; CAPES Collaborative Group. (2012) Associations between short-term exposure to nitrogen dioxide and mortality in 17 Chinese cities: the China Air Pollution and Health Effects Study (CAPES). Environ Int. 45:32-8. doi:10.1016/j.envint.2012.04.008.

Chen R, Zhang Y, Yang C, Zhao Z, Xu X, Kan H. (2013a) Acute effect of ambient air pollution on stroke mortality in the China air pollution and health effects study. Stroke. 44(4):954-60. doi: 10.1161/STROKEAHA.111.673442.

Chen R, Wang X, Meng X, Hua J, Zhou Z, Chen B, Kan H. (2013b) Communicating air pollution-related health risks to the public: an application of the Air Quality Health Index in Shanghai, China. Environ Int. 168-73. doi: 10.1016/j.envint.2012.11.008.

Chiusolo M, Cadum E, Stafoggia M, Galassi C, Berti G, Faustini A, Bisanti L, Vigotti MA, Dessì MP, Cernigliaro A, Mallone S, Pacelli B, Minerba S, Simonato L, Forastiere F; EpiAir Collaborative Group. (2011) Short-Term Effects of Nitrogen Dioxide on Mortality and Susceptibility Factors in 10 Italian Cities: The EpiAir Study. Environ Health Perspect. 119(9):1233-8. doi: 10.1289/ehp.1002904.

Faustini A, Stafoggia M, Colais P, Berti G, Bisanti L, Cadum E, Cernigliaro A, Mallone S, Scarnato C, Forastiere F; EpiAir Collaborative Group. (2013) Air pollution and multiple acute respiratory outcomes. Eur Respir J. 42(2):304-13. doi: 10.1183/09031936.00128712.

Guo Y, Li S, Tian Z, Pan X, Zhang J, Williams G.(2013) The burden of air pollution on years of life lost in Beijing, China, 2004-08: retrospective regression analysis of daily deaths. BMJ. 347: f7139. doi: 10.1136/bmj.f7139.

HEI Collaborative Working Group on Air Pollution, Poverty, and Health in Ho Chi Minh City[1], Le TG, Ngo L, Mehta S, Do VD, Thach TQ, Vu XD, Nguyen DT, Cohen A. (2012) Effects of short-term exposure to air pollution on hospital admissions of young children for acute lower respiratory infections in Ho Chi Minh City, Vietnam. Res Rep Health Eff Inst. (169):5-72

Iskandar A, Andersen ZJ, Bønnelykke K, Ellermann T, Andersen KK, Bisgaard H. (2012) Coarse and fine particles but not ultrafine particles in urban air trigger hospital admission for asthma in children. Thorax. 67(3):252-7. doi: 10.1136/thoraxjnl-2011-200324.

Moolgavkar SH[1], McClellan RO, Dewanji A, Turim J, Luebeck EG, Edwards M. (2013) Time-series analyses of air pollution and mortality in the United States: a subsampling approach. Environ Health Perspect. 121(1):73-8. doi: 10.1289/ehp.1104507.

Nuvolone D, Balzi D, Chini M, Scala D, Giovannini F, Barchielli A. (2011) Short-term association between ambient air pollution and risk of hospitalization for acute myocardial infarction: results of the cardiovascular risk and air pollution in Tuscany (RISCAT) study. Am J Epidemiol. 174(1):63-71. doi: 10.1093/aje/kwr046.

Zhang F, Li L, Krafft T, Lv J, Wang W, Pei D. (2011) Study on the association between ambient air pollution and daily cardiovascular and respiratory mortality in an urban district of Beijing. Int J Environ Res Public Health. 8(6):2109-23. doi: 10.3390/ijerph8062109.