

## Online-only Supplements

Title: Short term associations of ambient nitrogen dioxide with daily total, cardiovascular, and respiratory mortality: a multi-location analysis in 398 cities

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## **eReferences**

## 1. eMethods

### 1.1 Health and exposure data

We obtained mortality data from the Multi-City Multi-Country (MCC) database, which has been described in previous publications <sup>1,2</sup>. The current analysis was limited to locations where NO<sub>2</sub> ground measurements were available, which included a total of 398 cities in 22 countries and/or regions with different study periods, including Australia (3 cities, 1988–2009), Brazil (one city, 1997–2011), Canada (25 cities, 1986–2015), Chile (3 cities, 2005–2013), China (15 cities, 1996–2015), Colombia (1 city, 1998–2013), Czech Republic (1 city, 1994–2015), Estonia (4 cities, 1997–2015), Finland (1 city, 1994–2014), Germany (12 cities, 1993–2015), Greece (1 city, 2001–2010), Japan (47 cities, 2011–2015), Portugal (7 cities, 1990–2018), South Korea (8 cities, 1992–2015), Spain (48 cities, 1990–2014), Sweden (1 city, 1990–2010), Switzerland (8 cities, 1995–2013), Taiwan (3 cities, 1994–2014), Thailand (18 cities, 1999–2008), United Kingdom (39 cities, 1990–2016), and United States (147 cities, 1973–2006). Mortality data were obtained from local authorities within each country/region. Causes of death were classified according to the 9th or 10th version of International Classification of Diseases (ICD) codes, wherever available. In each location, mortality is represented by daily counts of either non-external causes or, where not available, all-cause only (ICD-9: 0-799; ICD-10: A0-R99). We also collected mortality data for two main causes: cardiovascular disease (ICD-10, codes I00-I99) and respiratory disease (ICD-10, codes J00-J99) <sup>3</sup>. Mortality from non-external causes were not available in Chile, Estonia, Germany, Greece, Japan, Portugal, Romania, Sweden, and United States. Deaths from cardiovascular and respiratory diseases were recorded in 362 cities from 14 countries, and were not available in Australia, Brazil, Chile, Estonia, Germany, and Romania (Table 1).

Daily data of particulate matter and other gaseous pollutants, including inhalable particles (PM<sub>10</sub>), fine particulate matter (PM<sub>2.5</sub>), ozone (O<sub>3</sub>), sulfur dioxide (SO<sub>2</sub>) and carbon monoxide (CO), were also obtained where available, to adjust for potential

confounding by co-pollutants. There were 370 cities with PM<sub>10</sub> data, 313 cities with PM<sub>2.5</sub> data, 364 cities with O<sub>3</sub> data, 358 cities with SO<sub>2</sub> data, and 298 cities with CO data. In brief, measurements for air pollutants were obtained from fixed-site monitoring networks operated in the same standard by local authorities. The majority of monitors were located in urban areas, and daily time-series of NO<sub>2</sub> was derived from one or more monitoring stations in each city; when more than one monitor, an average daily measurement was derived. Only those cities with daily measurements reporting above 75% of hourly data, in more than 300 days of a year, and with a coverage over a 3-year period were included. The overall missing rate for total mortality, NO<sub>2</sub> and temperature time-series was 0.13%, 4.41% and 1.24%, respectively. A detailed summary of missing rates for health and exposure data was provided in eTable 7.

## 1.2 Lag structure

We selected and compared a list of lag structures for NO<sub>2</sub> and temperature that were reported in previous studies <sup>2,4-6</sup>. The lags of NO<sub>2</sub> include: 1) lag 0, the present day; 2) lag 1, the previous day; 3) lag 2, the day before lag 1; 4) lag 3, the day before lag 2; and 5) lag 0–1, the two-day moving average of the present day and the previous day; 6) lag 0–2, the three-day moving average of the present day and the previous two days; 7) lag 0–3, the four-day moving average of the present day and the previous three days

For temperature, we tested the traditional single lag days and moving averages, including 1) lag 0, the present day; 2) lag 0 and lag 1, separate terms of the present and previous day; 3) lag 0–3, the 4-day moving average of the present and previous 3 days; 4) lag 0 and lag 1–3, separate terms of the present day and the average of the previous 3 days; 5) lag 0–7, the moving average of the present and previous 7 days; 6) lag 0–14, the moving average of the present and previous 14 days, and 7) lag 0–21, the moving average of the present and previous 21 days.

### **1.3 Heterogeneity and effect modification analyses**

We explored potential effect modifiers on the associations between NO<sub>2</sub> and total mortality based on the main models. First, we conducted separate analyses by regions classified by the World Health Organization (WHO) (eTable 2), which include Western-Pacific Region (WPRO), Regional Office for the Americas (AMRO), and Regional Office for Europe (EURO). Then, the statistical significance for differences among groups were determined by likelihood ratio tests. Second, using the aforementioned approach, we conducted additional analyses by regions in terms of Gross Domestic Product (GDP) per capita at country level (eTable 2). Third, we assessed potential effect modification in the NO<sub>2</sub>-mortality associations by including annual-mean levels of all air pollutants and temperature, relative humidity, latitude of locations, region (WHO and GDP), and GDP per capita in meta-regression models all together.

### **1.4 Concentration–response curves**

To estimate the overall shape of the associations between NO<sub>2</sub> concentrations and total, cardiovascular, and respiratory mortality in 398 cities, we estimated the concentration–response (C–R) relationship curves using the same approach as in previous studies<sup>7,8</sup>. The model specifications were the same as in the main model other than the replacement of the linear term of NO<sub>2</sub> with an assumed nonlinear term. Following the distribution of annual mean NO<sub>2</sub> concentrations at the city level, we first used a quadratic B-spline for NO<sub>2</sub> with two common knots at 20 µg/m<sup>3</sup> and 40 µg/m<sup>3</sup> (corresponding to 25% and 75% percentiles of annual mean NO<sub>2</sub> concentrations across all cities). This spline specification would allow enough flexibility to capture potential non-linearity of the association in a wide range of concentrations across cities. Finally, we combined the city-specific components of the spline estimates using random-effect models. In the sensitivity analysis, we placed knots at different NO<sub>2</sub> concentrations for the curve of NO<sub>2</sub> with total mortality, including (15, 40) µg/m<sup>3</sup>, (25, 40) µg/m<sup>3</sup> and (25, 45) µg/m<sup>3</sup>.

## **2. eResults**

### **2.1 Descriptive Statistics**

eFigure 1 illustrates the locations of cities included in present analysis and the average values of annual mean concentrations of NO<sub>2</sub> during the periods with available NO<sub>2</sub> ground measurements at city level. eTable 1 summarizes the descriptive statistics of environmental data. The summary of missing rates for health and exposure data is provided in eTable 7.

### **2.2 Heterogeneity, regional analyses, and effect modifications**

Among all cities, heterogeneity was found in the NO<sub>2</sub>-mortality association across country and city-specific estimates, with I<sup>2</sup> statistics of 47.7%, and Cochran Q P-value < .001.

In regional analyses (eTable 4), the NO<sub>2</sub>-mortality association was largest in the AMRO with an average increment of 0.53% in total mortality per 10 µg/m<sup>3</sup> increase of NO<sub>2</sub> concentrations, and was smallest in the EURO (corresponding estimate: 0.36%). The associations did not vary between different groups classified by GDP, with estimates of 0.48%, 0.49%, and 0.50% corresponding to low, medium, and high GDP areas, respectively. There were no significant effect modifications by annual levels of air pollutants, temperature, relative humidity, GDP, region and latitude of locations.

### **2.3 The impact of missing values**

There were two types of missing data in the current study: one was caused by complete unavailability of measurements for certain variables in a city/country; and the other was caused by a small amount of missing values scattered during the study time

period of each city.

For the first type of missing data, the NAs in eTable 1 denote lack of co-pollutant or relative humidity data in corresponding countries/regions, which are determined by the data availability in different countries/regions. Regarding to this kind of missingness, countries or regions with unavailable co-pollutants data were excluded accordingly; therefore, the number of countries/regions in eTable 3 varied by co-pollutants. We did not control relative humidity in cities without such data, and a sensitivity analysis was conducted to test influence of this missing information on results (eTable 5).

For the second type of missing data, there were also some missing values for air pollutant measurements in certain periods of consecutive days, which were mainly caused by data logging errors or abnormal operations of the monitoring equipment. This kind of missing is likely to be independent from any other predictors and especially the outcome. Multiple imputation or other imputation methods has been used to handle the issue of missing values in previous studies with small sample size, but it is unfeasible and not cost-effective in this large multi-location studies across dozens of countries. We thereby provided a summary of missing rates of mortality and exposure data at the country level (eTable 7). The overall missing rates for total mortality, NO<sub>2</sub> and temperature were 0.13%, 4.41% and 1.24%, respectively. Thus, this amount of missingness is unlikely to produce appreciable influences on our estimates in main models.

### 3. eTables

**eTable 1. Descriptive statistics of annual-mean concentration of nitrogen dioxide, weather conditions and other air pollutants in each country or region throughout the study period. Values are shown as median [25%-75% percentiles].**

Country /Region	NO <sub>2</sub> (µg/m <sup>3</sup> )	PM <sub>10</sub> (µg/m <sup>3</sup> )	PM <sub>2.5</sub> (µg/m <sup>3</sup> )	O <sub>3</sub> (µg/m <sup>3</sup> )	SO <sub>2</sub> (µg/m <sup>3</sup> )	CO (mg/m <sup>3</sup> )	Temperature (°C)	Humidity (%)
Australia	21.4 [14.1-27.9]	18.2 [14.5-23.2]	6.0 [4.3-8.4]	29.9 [22.1-37.9]	3.3 [1.4-5.7]	0.4 [0.2-0.7]	18.1 [14.7-21.2]	70.1 [62.5-77.2]
Brazil	84.9 [62.6-115.3]	39.6 [29.0-54.0]	NA	75.4 [51.9-104.5]	10.7 [7.3-15.4]	1.9 [1.3-2.8]	20.6 [18-22.9]	74.8 [67.0-81.0]
Canada	23.7 [15.6-33.8]	NA	6.7 [4.3-10.3]	41.4 [28.9-54.9]	3.5 [1.5-7.3]	0.3 [0.2-0.5]	7.4 [-0.9-15.7]	73.2 [65.6-80.9]
Chile	21.6 [13.9-32.4]	46.8 [34.3-70.7]	21.5 [14.2-38]	25.2 [13.8-33.7]	NA	0.6 [0.3-1.1]	13.7 [10.7-17.2]	NA
China	46.5 [36.2-60.4]	95.2 [67.2-133.6]	49.7 [30.1-80]	82.3 [49.9-121.5]	37.1 [24.9-65.3]	1.0 [0.7-1.3]	16.3 [6.5-23.5]	66.2 [54.9-77]
Colombia	30.5 [23.3-37.9]	61.3 [49-74.5]	NA	24.1 [18.4-30.9]	19.8 [10.8-28.5]	NA	13.9 [13.2-14.5]	NA
Czech Republic	30.8 [24.2-38.7]	29.4 [19.9-44.7]	NA	69.3 [47.4-95]	7.2 [4.2-15.2]	NA	9.2 [2.7-15.3]	78.0 [68.0-86.0]
Estonia	11.4 [7.6-16.7]	14.4 [9.3-21.8]	6.6 [3.8-10.6]	48.9 [36.7-61.8]	1.3 [0.6-3.3]	NA	6 [-0.1-13.6]	83.5 [73.8-90.8]
Finland	6.8 [4.3-11.7]	14.7 [8.9-25.5]	12.6 [7.4-21.7]	51.3 [40.0-63.0]	6.2 [3.5-11.6]	0.3 [0.2-0.3]	5.9 [0-13.8]	79.2 [67.8-87.7]
Germany	29.6 [21.8-38.4]	20.1 [14.3-28.7]	12.0 [8.0-18.8]	38.1 [21-54.6]	4.7 [3.1-8.5]	0.4 [0.3-0.6]	10.5 [4.8-15.9]	NA
Greece	50.2 [39.6-61.6]	39.5 [29.5-53.1]	20.3 [15.0-26.4]	75.1 [52.8-97.5]	NA	1.8 [1.3-2.6]	17.9 [12.9-24.9]	66.0 [54.0-75.4]
Japan	16.7 [12.1-23.4]	16.7 [11.8-23.8]	12.6 [8.4-18.3]	56.2 [41.3-72.2]	4.9 [3.5-7.2]	NA	16.1 [7.6-22.7]	69.8 [60.9-77.9]
Portugal	14.9 [10.0-21.7]	18.8 [12.9-28.3]	8.2 [5.4-12.8]	54.1 [41.1-66.5]	2.0 [1.3-3.5]	0.3 [0.2-0.4]	15.4 [11.5-19.9]	NA
Romania	25.6 [17.7-36.2]	27.7 [18.9-40.1]	15.5 [10.2-22.5]	36.8 [24.2-50.3]	7.1 [5.1-10.0]	0.2 [0.1-0.5]	11.4 [3.4-18.9]	76.3 [66.5-85.9]
South Korea	43.7 [33.0-57.5]	46.0 [33.3-63.0]	NA	41.2 [28.3-56.7]	13.9 [10.5-18.7]	0.6 [0.5-0.8]	14.9 [5.7-21.9]	65.7 [53.2-76.0]

Spain	26.4 [20.2-33.9]	26.2 [19.4-35.4]	10.0 [7.0-14.1]	51.6 [37.5-63.9]	5.0 [3.8-6.7]	0.4 [0.3-0.5]	14.9 [10.2-20.7]	NA
Sweden	26.8 [20.0-34.8]	12.5 [9.3-17.9]	6.6 [4.7-9.5]	61.9 [48.9-76.0]	NA	0.9 [0.6-1.5]	6.8 [1.2-13.9]	79.6 [68.4-87.6]
Switzerland	32.3 [24.0-42.0]	21.3 [14.2-31.6]	16.2 [10.6-24.7]	72.8 [47.0-98.1]	3.8 [1.8-7.5]	0.6 [0.4-0.9]	10.7 [4.4-16.5]	75.4 [66.3-83.2]
Taiwan	42.2 [31.6-54.7]	58.8 [38.7-81.5]	32.3 [20.6-44.6]	65 [44.5-91.6]	13.4 [9.6-18.7]	0.7 [0.6-0.9]	24.9 [20.4-28.0]	75.3 [70.3-80.2]
Thailand	22.0 [16.3-30.4]	44.1 [32.6-63.1]	NA	31.9 [22.6-45.3]	9.1 [6.1-12.8]	0.6 [0.5-0.9]	28 [26.4-29]	74.2 [67.7-79.9]
United Kingdom	25.6 [17.9-35.6]	18.7 [13.7-25.9]	9.2 [6.4-14.5]	43.0 [30.1-55.7]	5.5 [2.7-9.9]	0.3 [0.2-0.5]	10.4 [6.6-14.7]	NA
United States	28.7 [20.8-38.6]	24.1 [17-33.5]	10.9 [7.4-16]	52.1 [36.3-68.5]	10.5 [5.9-17.7]	0.8 [0.6-1.2]	14.7 [7.2-21.8]	65.3 [55.2-75.5]
Total	26.9 [19.5-36.2]	27.6 [19.7-38.6]	11.4 [7.7-17.0]	49.7 [34.9-65.1]	8.7 [5.4-14.3]	0.6 [0.4-0.9]	14.4 [7.8-20.6]	68.5 [59.0-77.6]

Abbreviations: NO<sub>2</sub>=nitrogen dioxide; PM<sub>10</sub>=particulate matter with an aerodynamic diameter less than or equal to 10 µm; PM<sub>2.5</sub>=particulate matter with an aerodynamic diameter less than or equal to 2.5 µm; O<sub>3</sub>=ozone; SO<sub>2</sub>=sulfur dioxide; CO=carbon monoxide.

NA=not available.

**eTable 2. Summary of the locations, GDP and region specification of the 22 countries/regions included in this analysis.**

<b>Country/Region</b>	<b>Cities</b>	<b>GDP per capita</b>	<b>WHO region</b>	<b>GDP region</b>
Australia	3	54066	WPRO	3
Brazil	1	9925	AMRO	1
Canada	25	45149	AMRO	3
Chile	3	14999	AMRO	1
China	15	8879	WPRO	1
Colombia	1	6378	AMRO	1
Czech Republic	1	20380	EURO	1
Estonia	4	20388	EURO	1
Finland	1	46317	EURO	3
Germany	12	44350	EURO	3
Greece	1	18930	EURO	1
Japan	47	38387	WPRO	2
Portugal	5	21490	EURO	1
Romania	8	10808	EURO	1
South Korea	7	31617	WPRO	2
Spain	48	28170	EURO	2
Sweden	1	53792	EURO	3
Switzerland	8	80450	EURO	3
Taiwan	3	24283	WPRO	2
Thailand	18	6593	WPRO	1
United Kingdom	39	40361	EURO	3
United States	147	59958	AMRO	3

Abbreviations: GDP=Gross Domestic Product; WHO=World Health Organization.

Notes: Regions by GDP: Regions classified by GDP per capita in 2017 according to World Bank ([data.worldbank.org](http://data.worldbank.org)). Regions by WHO: classified by the World Health Organization, including the Western Pacific Region (Western-Pacific Regional Office, WPRO), and the European Region (Regional Office for Europe, EURO).

**eTable 3. Percent changes in total mortality associated with a 10 µg/m<sup>3</sup> increase in nitrogen dioxide on lag 1 day, with and without adjustment of co-pollutants. Results are shown as percentage (95% confidence interval).**

<b>Models</b>	<b>N</b>	<b>Estimates</b>	<b>P* for difference</b>
Single-pollutant + PM <sub>10</sub>	370	0.47 (0.36 to 0.58) 0.38 (0.26 to 0.51)	0.082
Single-pollutant + PM <sub>2.5</sub>	313	0.47 (0.35 to 0.59) 0.37 (0.25 to 0.48)	0.076
Single-pollutant +SO <sub>2</sub>	364	0.44 (0.34 to 0.54) 0.45 (0.34 to 0.55)	0.578
Single-pollutant +O <sub>3</sub>	358	0.45 (0.34 to 0.56) 0.47 (0.36 to 0.57)	0.617
Single-pollutant +CO	298	0.46 (0.34 to 0.57) 0.48 (0.37 to 0.60)	0.597

Abbreviations as in Table 2. N=number of cities with available data.

\* *P*-value for difference was calculated by evaluating a binary variable (with and without the adjustment for co-pollutant) in likelihood ratio tests with both single- and two- pollutant model estimates. *P*-values < 0.05 were considered statistically significant for differences.

**eTable 4. Percentage change in total mortality associated with a 10 µg/m<sup>3</sup> increase in nitrogen dioxide (lag 1) stratified by WHO/GDP regions and P-values for testing difference among regions. Results are shown as percentage (95% confidence interval).**

<b>Classifications</b>	<b>Regions</b>	<b>Mortality</b>	<b>P-values*</b>
WHO	AMRO	0.53 (0.42 to 0.65)	0.007
	WPRO	0.49 (0.36 to 0.61)	
	EURO	0.36 (0.24 to 0.48)	
GDP	1	0.48 (0.43 to 0.54)	0.791
	2	0.49 (0.44 to 0.55)	
	3	0.50 (0.45 to 0.56)	

Abbreviations as in eTable 2.

\* P-values were obtained by likelihood ratio tests comparing the fit of a meta-regression model with the region variable to the simple meta-analysis model. P-values < 0.05 were considered statistically significant for regional differences.

**eTable 5. Percentage change in total mortality per 10 µg/m<sup>3</sup> increase in nitrogen dioxide (lag 1), with and without adjustment of relative humidity. Results are shown as percentage (95% confidence interval).**

<b>Endpoints</b>	<b>Adjustments</b>	<b>N</b>	<b>Estimates</b>	<b>P*</b>
Total	RH adjusted	290	0.51 (0.44 to 0.59)	0.440
	RH unadjusted		0.54 (0.47 to 0.61)	
Cardiovascular	RH adjusted	271	0.44 (0.32 to 0.56)	0.757
	RH unadjusted		0.46 (0.34 to 0.58)	
Respiratory	RH adjusted	271	0.63 (0.53 to 0.73)	0.668
	RH unadjusted		0.67 (0.57 to 0.76)	

Abbreviations: RH=relative humidity.

\* P-values for difference was calculated by evaluating a binary variable (with and without the adjustment for humidity) in likelihood ratio tests with both model estimates.

P-values < 0.05 were considered statistically significant for differences.

**eTable 6. Percentage change in mortality per 10 µg/m<sup>3</sup> increase in nitrogen dioxide (lag 1) for different time periods. Results are shown as percentage (95% confidence interval).**

<b>Endpoints</b>	<b>Time periods</b>	<b>N</b>	<b>Estimates</b>	<b>P*</b>
Total	Before 2000 (included)	223	0.457 (0.286 to 0.629)	0.795
	After 2000		0.458 (0.289 to 0.628)	
Cardiovascular	Before 2000 (included)	205	0.382 (0.169 to 0.596)	0.313
	After 2000		0.351 (0.150 to 0.553)	
Respiratory	Before 2000 (included)	205	0.367 (0.004 to 0.730)	0.446
	After 2000		0.379 (0.022 to 0.723)	

Notes: \* P-values for difference was calculated by evaluating a binary variable (before or after the year 2000) in likelihood ratio tests with both model estimates. P-values < 0.05 was considered statistically significant for differences.

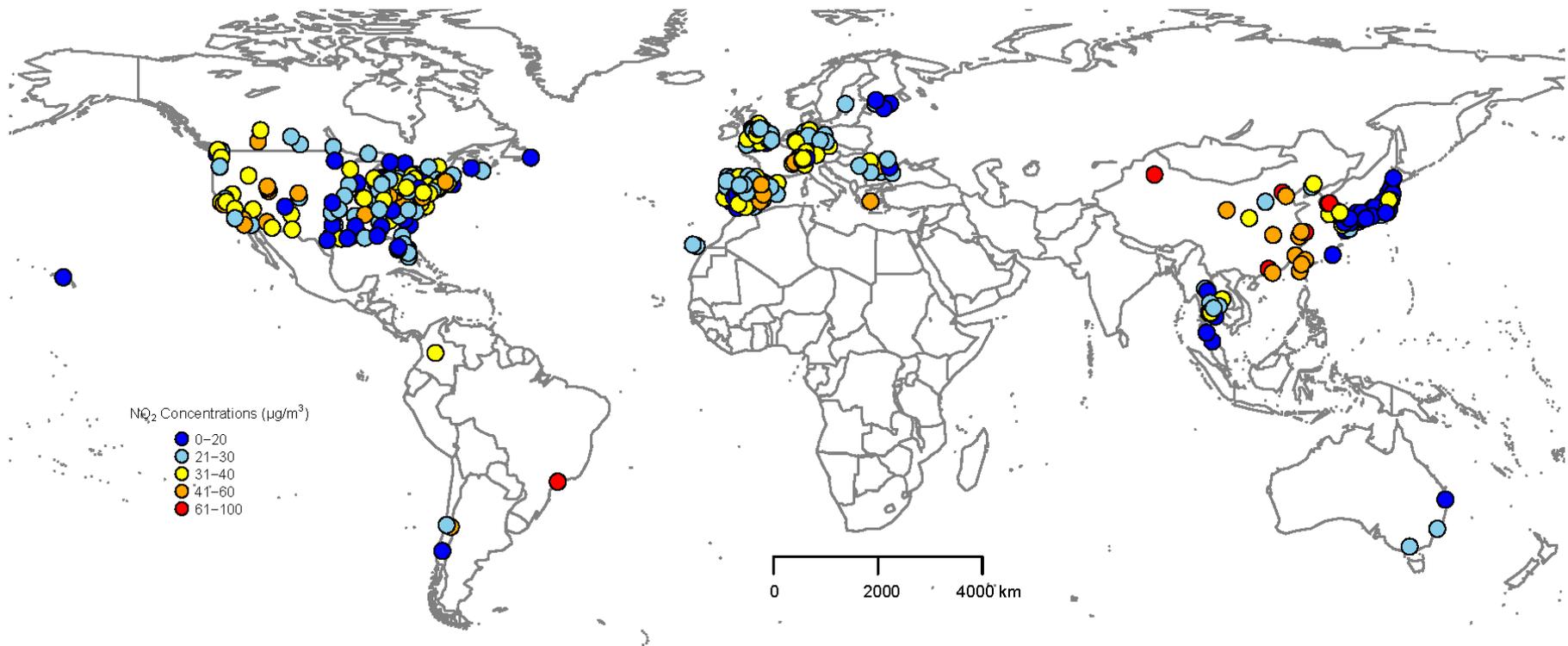
**eTable 7. Summary statistics on missing rates of health and exposure data at the country level.**

<b>Country /Region</b>	<b>Total</b>	<b>Cardiovascular</b>	<b>Respiratory</b>	<b>NO<sub>2</sub> (µg/m<sup>3</sup>)</b>	<b>PM<sub>10</sub> (µg/m<sup>3</sup>)</b>	<b>PM<sub>2.5</sub> (µg/m<sup>3</sup>)</b>	<b>O<sub>3</sub> (µg/m<sup>3</sup>)</b>	<b>SO<sub>2</sub> (µg/m<sup>3</sup>)</b>	<b>CO (mg/m<sup>3</sup>)</b>	<b>Temp (°C)</b>	<b>Humidity (%)</b>
Australia	0.00%	NA	NA	4.00%	3.18%	5.84%	3.11%	3.82%	1.64%	0.00%	0.00%
Brazil	0.00%	NA	NA	0.00%	0.00%	NA	0.00%	0.04%	0.00%	0.84%	0.84%
Canada	0.94%	0.94%	0.94%	7.46%	NA	3.58%	3.00%	5.74%	6.92%	0.54%	0.24%
Chile	0.00%	NA	NA	10.89%	7.73%	12.13%	14.11%	NA	11.18%	7.83%	NA
China	0.40%	0.40%	0.40%	4.48%	0.41%	1.21%	0.04%	0.67%	1.21%	0.43%	0.43%
Colombia	0.00%	0.00%	0.05%	3.76%	0.14%	NA	4.96%	0.70%	NA	3.34%	NA
Czech Republic	0.00%	0.00%	0.00%	0.00%	0.00%	NA	0.00%	0.00%	NA	0.00%	0.00%
Estonia	0.00%	NA	NA	0.00%	0.00%	0.00%	0.00%	0.00%	NA	0.00%	0.00%
Finland	0.01%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	4.97%	5.03%
Germany	0.00%	NA	NA	5.04%	3.37%	3.55%	3.86%	7.39%	3.99%	0.01%	NA
Greece	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	NA	0.00%	0.00%	0.00%
Japan	0.00%	0.00%	0.00%	0.83%	2.58%	1.17%	1.14%	3.40%	NA	0.05%	0.12%
Portugal	0.08%	0.69%	1.58%	10.31%	7.71%	12.15%	2.56%	10.87%	1.98%	4.87%	NA
Romania	0.00%	NA	NA	4.43%	3.11%	2.56%	2.93%	4.17%	3.29%	0.00%	0.00%
South Korea	0.64%	0.63%	0.63%	0.92%	1.41%	NA	0.92%	0.92%	0.92%	0.63%	0.63%
Spain	0.00%	0.00%	0.00%	7.84%	9.02%	5.02%	5.46%	6.33%	11.39%	0.72%	NA
Sweden	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	NA	0.00%	0.00%	0.00%
Switzerland	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Taiwan	0.02%	0.00%	0.00%	0.00%	0.02%	0.05%	0.00%	0.00%	0.00%	0.00%	0.01%

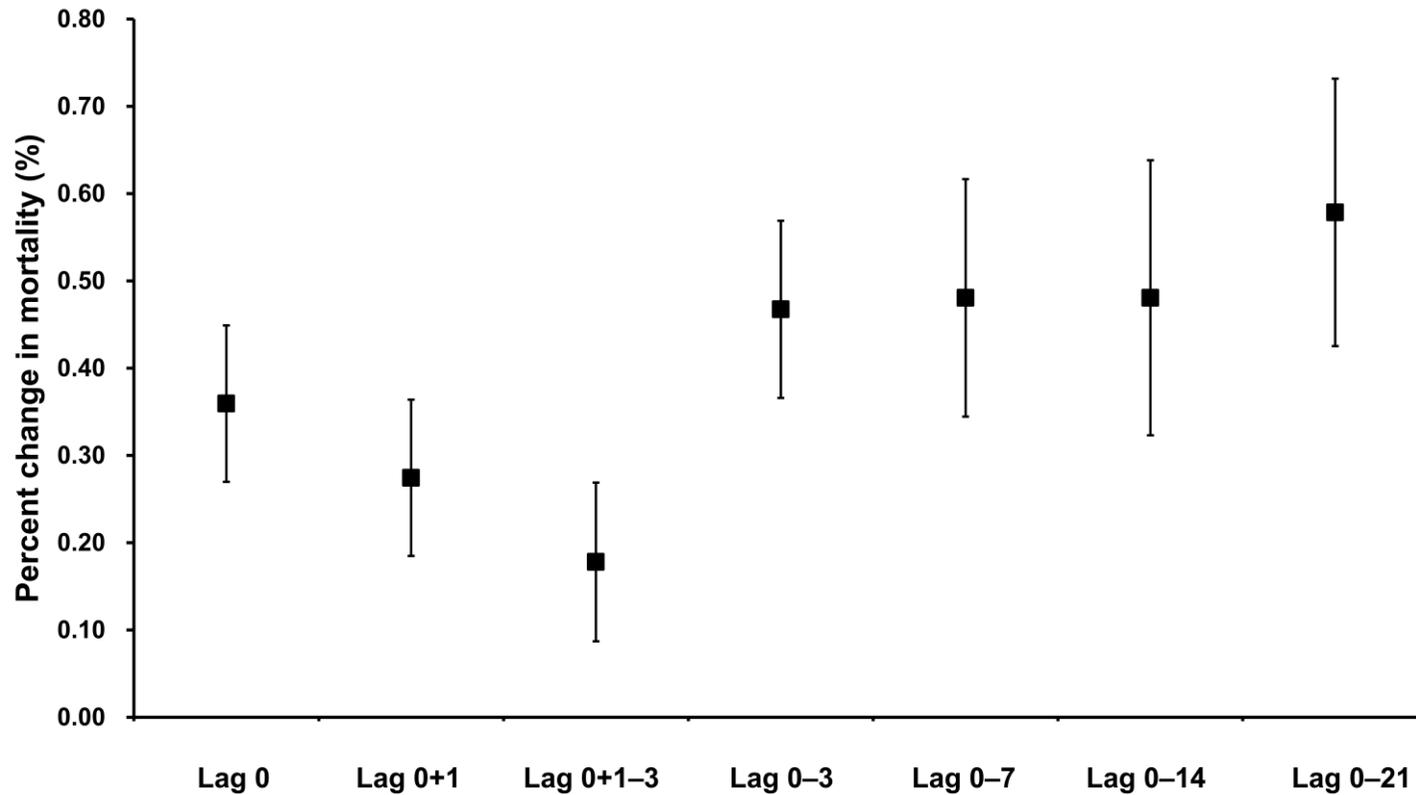
Thailand	0.00%	0.00%	0.00%	10.05%	10.39%	NA	9.99%	15.25%	12.05%	2.12%	3.77%
United Kingdom	0.00%	0.00%	0.00%	15.72%	11.89%	13.65%	15.74%	10.13%	6.28%	0.00%	NA
United States	0.71%	0.71%	0.71%	11.38%	10.62%	5.69%	3.41%	4.96%	5.76%	0.82%	6.16%
Pooled	0.13%	0.21%	0.27%	4.41%	3.41%	3.92%	3.24%	3.91%	3.70%	1.24%	1.08%

Abbreviations as in eTable 1.

NA=not available.

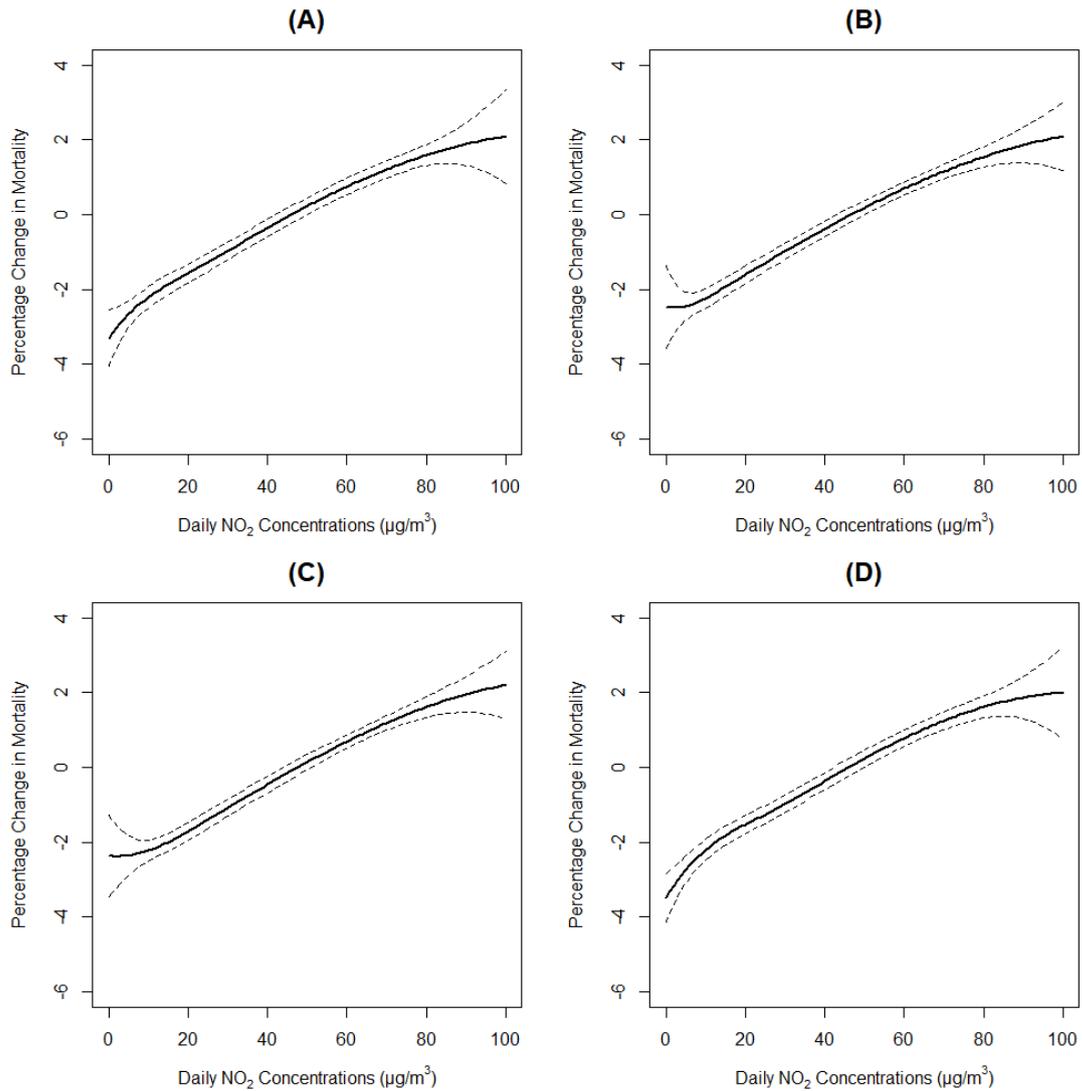


**eFigure 1. Geographic distributions of the 398 cities within the 22 countries included in the analysis, and the corresponding annual mean NO<sub>2</sub> concentrations (µg/m<sup>3</sup>).**



**eFigure 2. Percentage changes in total mortality associated with a 10  $\mu\text{g}/\text{m}^3$  increase in nitrogen dioxide (lag 1), with different modelling approaches to control for temperature.** Lag 0, the present day; Lag 0+1, the present day and the previous day; Lag 0+1-3, the present day and the mean of the previous 3 days; Lag 0-3, moving average of the present day and the previous 3 days; Lag 0-7, moving average of the present day

and the previous 7 days; Lag 0–14, moving average of the present day and the previous 14 days; Lag 0–21, moving average of the present day and the previous 21 days.



**eFigure 3. Concentration–response relationship curves between NO<sub>2</sub> concentrations (lag 1) and total mortality using alternative knots.** The y-axis can be interpreted as the relative change from the mean effect of NO<sub>2</sub> on mortality; the fraction of the curve below zero denotes a smaller estimate compared with the mean effect. (A) knots at (20, 40) µg/m<sup>3</sup> (main analysis); (B) knots at (15, 40) µg/m<sup>3</sup>; (C) knots at (25, 40) µg/m<sup>3</sup>; and (D) knots at (25, 45) µg/m<sup>3</sup>.

#### 4. eReference

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