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Long-term Concentrations of Nitrogen Dioxide and Mortality

A Meta-analysis of Cohort Studies

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Background: Concentrations of outdoor nitrogen dioxide (NO_2) have been associated with increased mortality. Hazard ratios (HRs) from cohort studies are used to assess population health impact and burden. We undertook meta-analyses to derive concentration–response functions suitable for such evaluations and assessed their sensitivity to study selection based upon cohort characteristics.

Methods: We searched online databases and existing reviews for cohort studies published to October 2016 that reported HRs for NO_2 and mortality. We calculated meta-analytic summary estimates using fixed/random-effects models.

Results: We identified 48 articles analyzing 28 cohorts. Meta-analysis of HRs found positive associations between NO_2 and all cause (1.02 [95% confidence interval (CI): 1.01, 1.03]; prediction interval [PI]: [0.99, 1.06] per 10 µg/m³ increment in NO_2), cardiovascular (1.03 [95% CI: 1.02, 1.05]; PI: [0.98, 1.08]), respiratory (1.03 [95% CI: 1.01, 1.05]; PI: [0.97, 1.10]), and lung cancer mortality (1.05 [95% CI: 1.02, 1.08]; PI: [0.94, 1.17]) with evidence of substantial heterogeneity between studies. In subgroup analysis, summary HRs varied by age at cohort entry, spatial resolution of pollution estimates, and adjustment for smoking and body mass index at the individual level; for some subgroups, the HR was close to unity, with lower confidence limits below 1.

Conclusions: Given the many uncertainties inherent in the assessment of this evidence base and the sensitivity of health impact calculations to small changes in the magnitude of the HRs, calculation of the impact on health of policies to reduce long-term exposure to NO_2 should use prediction intervals and report ranges of impact rather than focusing upon point estimates.

Keywords: Cohort, Long-term exposure, Meta-analysis, Mortality, Nitrogen dioxide

Epidemiologic studies have reported associations between long-term concentrations (typically averaged over a year or more) of outdoor air pollution and a range of health end points. Outdoor air pollution comprises a mixture of particles and gases, emitted directly from the combustion of fossil fuels or formed from secondary chemical reactions in the air. The evidence for ambient particulate matter monitored as $PM_{2.5}$ (mass per m³ of particles of aerodynamic diameter generally less than 2.5 µm) has been extensively reviewed and judged sufficient to infer a causal, adverse effect on a range of health outcomes.[1,2]

Nitrogen dioxide (NO_2) is a respiratory toxicant gas which in outdoor air is derived primarily from the oxidation of nitric oxide (NO). In urban areas, the predominant source of NO and NO_2, as well as carbon particles, carbon monoxide, and other pollutants, is motor vehicle exhaust. A growing number of cohort studies have exploited spatial variability in long-term NO_2 concentrations estimated using pollution models based upon the interpolation of monitoring data, land-use regression, or dispersion models[3] to investigate associations with mortality or disease incidence. Recent systematic reviews and meta-analyses have assessed the evidence from cohort studies published to 2013–2014 and reported associations between NO_2 concentrations and mortality from all-cause, cardiovascular, and respiratory diseases[4,5] and lung cancer.[6] An assessment of the evidence for oxides of nitrogen conducted by the US Environmental Protection Agency Integrated Science Assessment[7] including toxicologic and epidemiologic evidence across a wide range of health end points concluded that "the evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term exposure to NO_2 and mortality among adults." This extensive review included cohort studies published up to 2014 but did

not undertake meta-analyses nor attempt to establish concentration–response functions for use in health impact calculations. A similar conclusion was reached by Health Canada following their review.[8]

Summary risk estimates [hazard ratios (HRs)] from meta-analyses of cohort studies are used in policy evaluations to assess the health impact and burden of current, and future, pollutant concentrations.[9] These calculations usually apply to the general population of a defined geographical area, and the results are often widely reported/discussed in the mainstream media outlets. In air pollution epidemiology, HRs are generally small (close to 1) indicating low individual risk. However, because of the ubiquitous nature of ambient air pollution and the very large populations exposed, small HRs can translate into important, and substantial, consequences for health at the population level. The process used to derive the summary HRs, including decisions on included studies, appropriate analytical model, assessment of heterogeneity, and effect modification, are therefore important.

In this study, we undertook a systematic search of the literature to identify cohort studies examining the association between long-term concentrations of NO_2 and mortality. We used stratified meta-analyses to assess the sensitivity of summary HRs to the selection of studies with different cohort and study characteristics and considered the implications for the selection of concentration–response functions for use in health impact assessment in a general population. We also calculated prediction intervals and considered their relevance for health impact assessment exercises. Our study updates previous reviews by including studies published to October 2016 and incorporating a wider range of causes of death.

METHODS

To identify publications reporting results from cohort studies of NO_2 and mortality, we conducted a broad search of the online medical databases supplemented with citation searches of recently published literature reviews.

Search Strategy

We applied the search string "cohort & ('no2' or 'nitrogen dioxide' or 'air pollution') & mortality" to: (1) Ovid Medline (R) without Revisions for the period 1996 to October Week two 2016 and Embase for the period 1996 to 2016 Week 42; (2) Web of Science (1970 to October 2016); and (3) Pubmed (1966 to October 2016). We also searched citations in five review articles.[4–6,10,11] Studies identified in each search were combined and duplicates removed leaving 959 studies to be assessed.

Inclusion/Exclusion Criteria

Studies were screened by study title and abstract. Inclusion criteria were (1) cohort studies including individual-level covariate information; and (2) a "long-term" exposure metric for NO_2, i.e., annual or multi-year averages. Exclusion criteria were (1) conference abstracts, conference papers, notes,

editorials, and letters; (2) cross-sectional, case–control and nested case–control study designs; (3) mean daily or monthly NO_2 exposure metrics (short-term exposure [time series] studies); and (4) study population selected because of close proximity to specific pollution sources (e.g., waste incinerators). After applying these inclusion/exclusion criteria, 73 studies remained and were subject to full-text review.

Suitability of these studies for inclusion in the quantitative assessment was assessed as follows: studies were excluded if (1) they reported results for NO_X rather than NO_2 (n = 5); (2) replicated results from previous publications (n = 7); or (3) did not provide quantitative HRs together with a measure of precision (standard errors or 95% confidence intervals) and adequate information to enable standardization of the HR per 10 µg/m^3 increase in NO_2 (n = 13). Forty-eight studies remained from which data characterizing the outcome, HR, and other relevant information were extracted. Figure 1, adapted from Moher et al,[12] summarizes the literature search and study assessment.

Data Extraction and Coding

We extracted cohort and estimate level information from each paper and entered it into an EXCEL database. These data included cohort name, country, cohort description, date of enrolment of cohort members, age at enrollment, number of subjects, follow-up period, exposure period, and exposure assessment method (measured/modeled). The level of covariate adjustment was also recorded including individual-level age, sex, smoking, and body mass index (BMI) and level of adjustment for a marker of socioeconomic status (e.g., education level, income, etc.) at either the individual or ecologic level. All HRs were standardized to 10 µg/m^3 increase in NO_2. Where the units used in the original study were ppb, a conversion factor of 1.88 µg/m^3 per 1 ppb was used (assuming 25°C and 1013 mb atmospheric pressure).

Meta-analysis

Where studies reported results for various follow-up periods for the same cohort, we selected studies using the most recent follow-up period. If results for the same outcomes were available for the full cohort and a subset, we used results from the full cohort unless these results were considered to be out of date (e.g., statistical analysis, exposure assessment, date of last follow-up). Two studies from the same cohort were only included if they provided results for different outcomes.

We conducted analyses in STATA Version 12 (StataCorp. 2011). All studies reported HRs together with 95% confidence intervals. Therefore, estimates of the standard error were derived using each limit value and the two estimates averaged. Forest plots were used to display study information and HRs graphically. Articles used different terms to describe causes of death and were grouped together for meta-analysis according to terms and International Classification of Diseases codes where available (eTable 1; http://links.lww.com/EDE/B348). We calculated meta-analytic
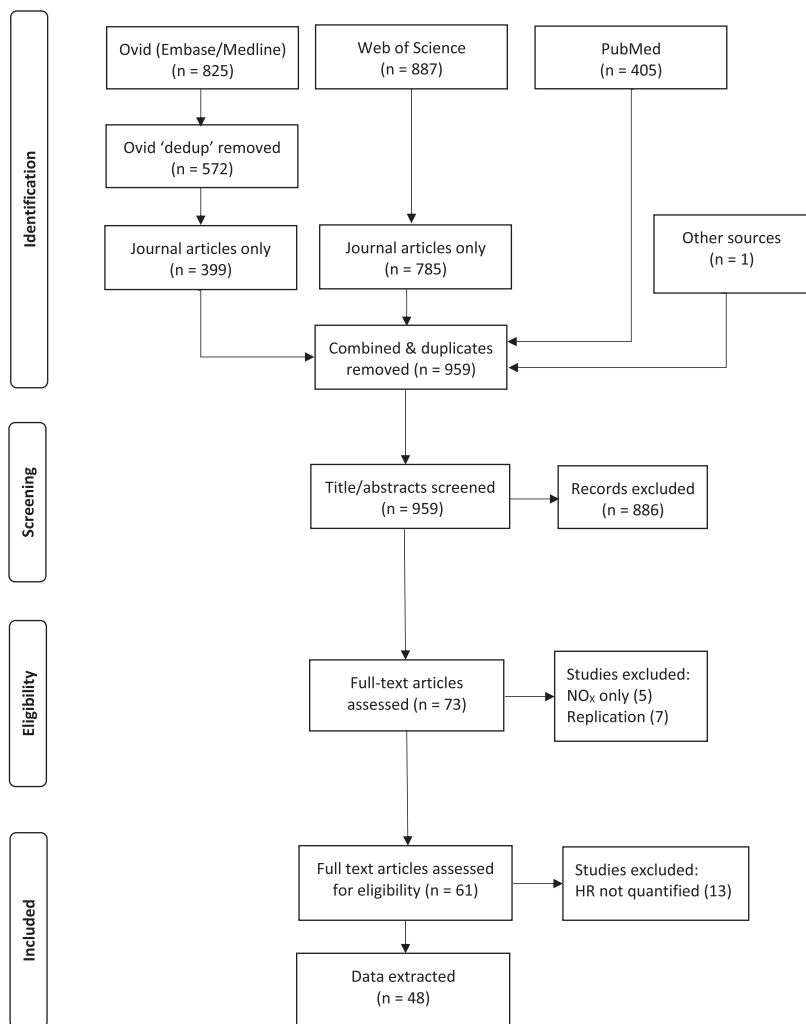
FIGURE 1. Summary of literature search and study assessment. Adapted from PLoS Med. 2009;6:e1000097.

summary estimates using fixed and random-effects models using the program "metan" in STATA and assessed heterogeneity using the I^2 statistic. Prediction intervals were calculated when heterogeneity was identified.[13] Small study bias was assessed using Begg and Berlin[14] and Egger et al[15] tests and the Trim and Fill procedure.[16]

A series of stratified analyses assessed potential effect modification by both cohort and study characteristics. Cohort characteristics included (1) study population—general population cohorts versus cohorts using subjects with preexisting disease; and (2) age at recruitment, cohorts based upon adults across a wide age range at recruitment versus cohorts in selected ages at cohort entry. As the focus of our investigation was the identification of concentration–response functions for use in health impact assessments, we selected cohorts conducted in the general population and without narrow age restriction at cohort entry for further stratified analyses by study characteristics. These included (1) adjustment for individual measures of BMI and smoking versus no adjustment or use of area-level estimates of BMI and/or smoking; and (2) use of land-use regression models to estimate residential NO_2 concentrations versus area-based concentration estimates. Our evaluation of differences between strata was based upon the sizes and confidence intervals of the respective summary HRs and the differences between HRs assessed using the method of Altman and Bland.[17]

RESULTS

The 48 articles identified in the review analyzed 28 cohorts (including the European Study of Cohorts for Air Pollution Effects (ESCAPE) study comprising 22 separate cohorts).[18–65] eTable 2; http://links.lww.com/EDE/B348 provides a description of each article/cohort including cohort size and geographical location, subject characteristics, exposure assessment and control for key individual confounders. Cohorts were studied in Europe (13 including the ESCAPE consortium of cohorts), North America (10), Taiwan (1), China (2), and Japan (2).

HRs for NO_2 and all-cause mortality were reported in 32 studies (22 cohorts including ESCAPE) and cause-specific mortality in 41 studies (24 cohorts including ESCAPE).

All-cause Mortality

Of the 32 studies reporting results for all-cause mortality (eFigure 1; http://links.lww.com/EDE/B348), 11 studies, selected according to our a priori algorithm, were excluded from the meta-analyses: 3 studies[39,41,54] because their results were included in the ESCAPE meta-analysis[21] and 8 studies as the same cohorts were analyzed in other publications included in our review.[27,32,42,44,47,48,63,65] In one article,[43] results for two cohorts were reported; we did not use the HR for the American Cancer Society Cancer Prevention Study-II (ACS CPS II) cohort reported in this study, but selected the more recent reanalyses of the ACS CPS II cohort[61] instead. Following these exclusions, results from 20 separate cohorts (including the ESCAPE consortium of 22 individual cohorts) reported results for NO_2 and all-cause mortality. In the fixed-effects meta-analysis (eFigure 2a; http://links.lww.com/EDE/B348), three large administrative cohorts[26,31,36] and the ACS study[61] accounted for 80% and 11% of the weight, respectively. Meta-analysis indicated a high level of heterogeneity between study HRs ($I^2 = 84\%$). The random-effects summary HR was 1.02 (95% confidence interval [CI]: 1.01, 1.03; prediction interval [PI]: 0.99, 1.06) per 10 µg/m³ increment in NO_2 (Table 1 and eFigure 2b; http://links.lww.com/EDE/B348). Begg and Egger tests for small study bias returned *P* values of 0.3 and 0.9, respectively. Application of the trim and fill technique indicated the need to impute two additional study estimates to adjust for small study bias assuming a fixed random-effects model although the adjusted HR (and 95% CI) remained unchanged.

Five studies investigated associations with mortality in cohorts selected on the basis of preexisting disease: survivors of stroke,[51] coronary heart disease,[56] acute coronary syndrome,[59] attendees at respiratory clinic,[45] and hypertensive US veterans[49] (eFigure 3; http://links.lww.com/EDE/B348). Meta-analysis of these studies gave a summary HR of 1.04 per 10 µg/m³ increment in NO_2 compared with 1.02 for the 15 cohorts recruiting subjects from the general population (Table 1).

Eleven of the 15 cohorts recruited adults within a broad age range and four cohorts limited recruitment to narrower age ranges: 35–50,[23] 55–69 years,[24] 25–59 years,[35] and 65–84 years of age[62] (eFigure 4; http://links.lww.com/EDE/B348). A stratified meta-analysis indicated a substantial difference in the summary HRs between cohorts recruiting adults over a broad age range compared with cohorts restricting age at entry, 1.02 versus 1.08 per 10 µg/m³ increment in NO_2, respectively (Table 1).

For the 11 cohorts that recruited adults within a broad age range, Figure 2 shows the cohort-specific HRs and meta-analytic summary estimates stratified by (1) level of covariate adjustment, i.e., those controlling for required confounding factors including individual BMI and smoking status and those who did not; (2) the spatial resolution

TABLE 1. Summary HRs (95% CI) for All-cause Mortality Without and With Stratification by Selected Study Characteristics

Cohort Stratification		No. Cohorts	HR (95% CI) per 10 µg/m³	I^2 (%)	P^a	Figure[b]
All Cohorts			n = 32 (Removed = 12)			e1
Cohorts excluding duplicates						
Selected cohorts[c]	Fixed	20	1.03 (1.02, 1.03)	84	NA	e2a
	Random		1.02 (1.01, 1.03)			e2b
			(0.99, 1.06)[d]			
Stratification by cohort characteristics						
Preexisting disease	Yes	5	1.04 (0.98, 1.10)	76	0.82	e3
	No	15	1.02 (1.01, 1.03)	86		
Stratification by cohort characteristics excluding preexisting disease cohorts						
Age-restricted[c,e]	Yes	4	1.08 (1.02, 1.15)	79	0.04	e4
	No	11	1.02 (1.01, 1.03)	88		
Stratification by study characteristics excluding preexisting disease and age-restricted cohorts						
Individual BMI and smoking adjustment[c,e,f]	Yes	7	1.00 (0.98, 1.03)	89	0.03	2A
	No	4	1.03 (1.02, 1.04)	67		
Residential NO_2 exposure estimates[c,e,f]	Yes	6	1.03 (1.02, 1.03)	67	0.19	2B
	No	5	1.00 (0.96, 1.04)	90		

[a]*P* value for differences in summary hazard ratios.
[b]Corresponding figure giving study information.
[c]Excluding studies identified as previous/smaller analyses of the same cohort and cohorts included in ESCAPE.
[d]Prediction interval.
[e]Excluding preexisting disease cohorts.
[f]Excluding age-restricted cohorts.
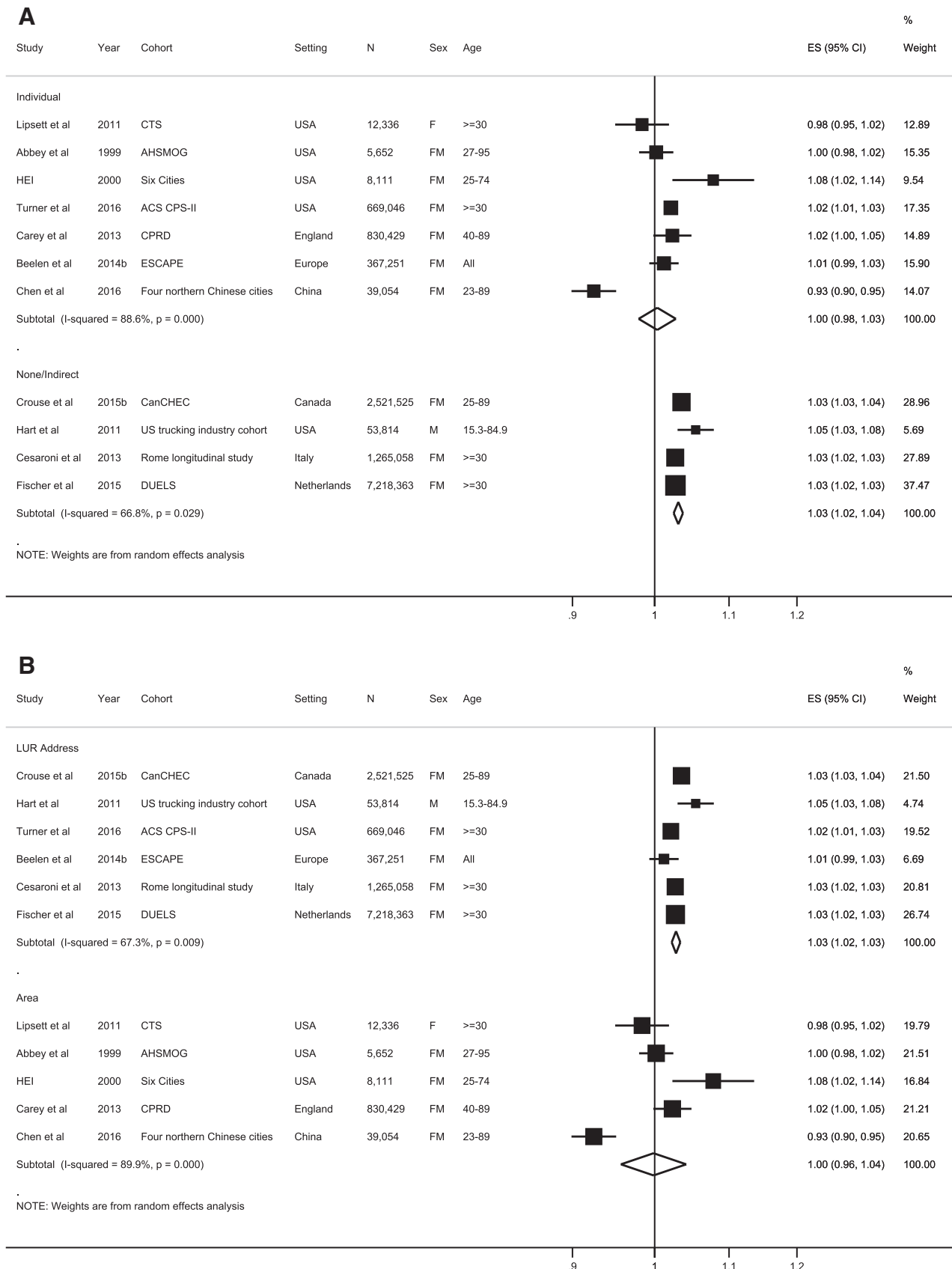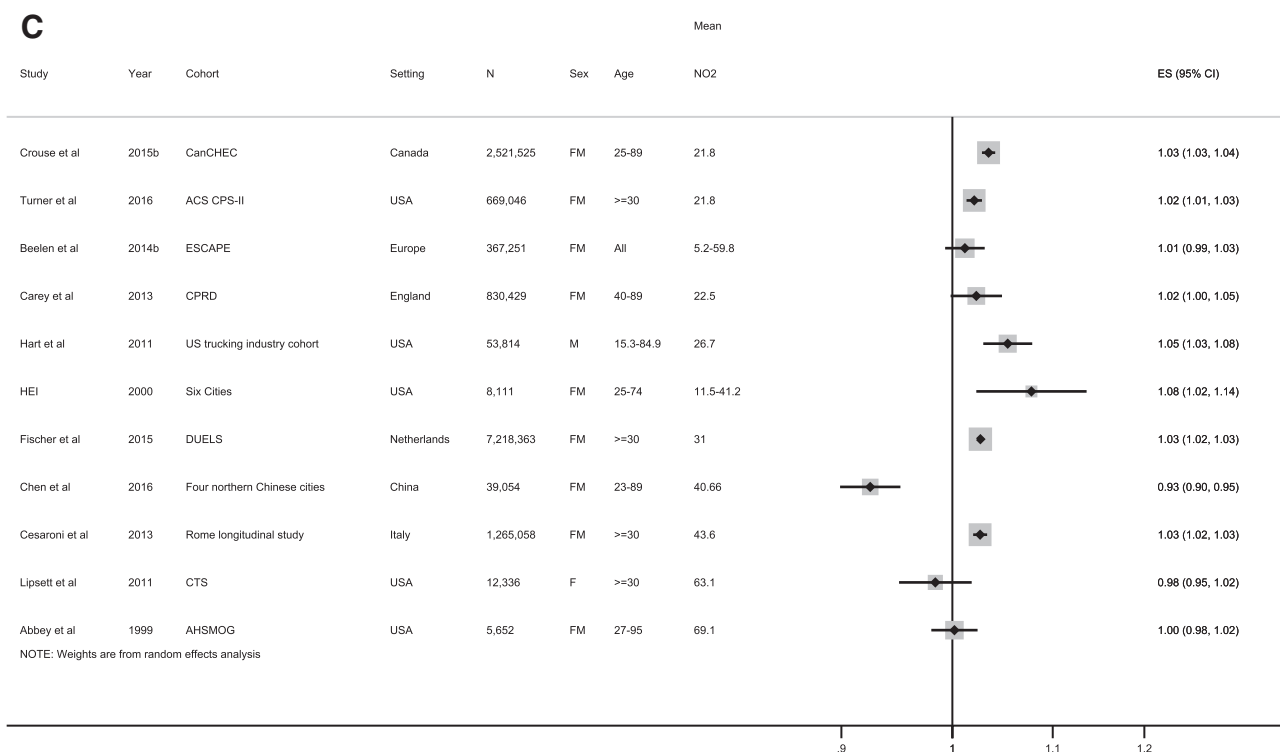NA indicates not applicable

A

Study	Year	Cohort	Setting	N	Sex	Age	ES (95% CI)	% Weight
Individual								
Lipsett et al	2011	CTS	USA	12,336	F	>=30	0.98 (0.95, 1.02)	12.89
Abbey et al	1999	AHSMOG	USA	5,652	FM	27-95	1.00 (0.98, 1.02)	15.35
HEI	2000	Six Cities	USA	8,111	FM	25-74	1.08 (1.02, 1.14)	9.54
Turner et al	2016	ACS CPS-II	USA	669,046	FM	>=30	1.02 (1.01, 1.03)	17.35
Carey et al	2013	CPRD	England	830,429	FM	40-89	1.02 (1.00, 1.05)	14.89
Beelen et al	2014b	ESCAPE	Europe	367,251	FM	All	1.01 (0.99, 1.03)	15.90
Chen et al	2016	Four northern Chinese cities	China	39,054	FM	23-89	0.93 (0.90, 0.95)	14.07
Subtotal (I-squared = 88.6%, p = 0.000)							1.00 (0.98, 1.03)	100.00
.								
None/Indirect								
Crouse et al	2015b	CanCHEC	Canada	2,521,525	FM	25-89	1.03 (1.03, 1.04)	28.96
Hart et al	2011	US trucking industry cohort	USA	53,814	M	15.3-84.9	1.05 (1.03, 1.08)	5.69
Cesaroni et al	2013	Rome longitudinal study	Italy	1,265,058	FM	>=30	1.03 (1.02, 1.03)	27.89
Fischer et al	2015	DUELS	Netherlands	7,218,363	FM	>=30	1.03 (1.02, 1.03)	37.47
Subtotal (I-squared = 66.8%, p = 0.029)							1.03 (1.02, 1.04)	100.00
.								

NOTE: Weights are from random effects analysis

.9   1   1.1   1.2

B

Study	Year	Cohort	Setting	N	Sex	Age	ES (95% CI)	% Weight
LUR Address								
Crouse et al	2015b	CanCHEC	Canada	2,521,525	FM	25-89	1.03 (1.03, 1.04)	21.50
Hart et al	2011	US trucking industry cohort	USA	53,814	M	15.3-84.9	1.05 (1.03, 1.08)	4.74
Turner et al	2016	ACS CPS-II	USA	669,046	FM	>=30	1.02 (1.01, 1.03)	19.52
Beelen et al	2014b	ESCAPE	Europe	367,251	FM	All	1.01 (0.99, 1.03)	6.69
Cesaroni et al	2013	Rome longitudinal study	Italy	1,265,058	FM	>=30	1.03 (1.02, 1.03)	20.81
Fischer et al	2015	DUELS	Netherlands	7,218,363	FM	>=30	1.03 (1.02, 1.03)	26.74
Subtotal (I-squared = 67.3%, p = 0.009)							1.03 (1.02, 1.03)	100.00
.								
Area								
Lipsett et al	2011	CTS	USA	12,336	F	>=30	0.98 (0.95, 1.02)	19.79
Abbey et al	1999	AHSMOG	USA	5,652	FM	27-95	1.00 (0.98, 1.02)	21.51
HEI	2000	Six Cities	USA	8,111	FM	25-74	1.08 (1.02, 1.14)	16.84
Carey et al	2013	CPRD	England	830,429	FM	40-89	1.02 (1.00, 1.05)	21.21
Chen et al	2016	Four northern Chinese cities	China	39,054	FM	23-89	0.93 (0.90, 0.95)	20.65
Subtotal (I-squared = 89.9%, p = 0.000)							1.00 (0.96, 1.04)	100.00
.								

NOTE: Weights are from random effects analysis

.9   1   1.1   1.2

FIGURE 2. (*Continued*)

C

Study	Year	Cohort	Setting	N	Sex	Age	Mean NO2	ES (95% CI)
Crouse et al	2015b	CanCHEC	Canada	2,521,525	FM	25–89	21.8	1.03 (1.03, 1.04)
Turner et al	2016	ACS CPS-II	USA	669,046	FM	>=30	21.8	1.02 (1.01, 1.03)
Beelen et al	2014b	ESCAPE	Europe	367,251	FM	All	5.2-59.8	1.01 (0.99, 1.03)
Carey et al	2013	CPRD	England	830,429	FM	40–89	22.5	1.02 (1.00, 1.05)
Hart et al	2011	US trucking industry cohort	USA	53,814	M	15.3-84.9	26.7	1.05 (1.03, 1.08)
HEI	2000	Six Cities	USA	8,111	FM	25-74	11.5-41.2	1.08 (1.02, 1.14)
Fischer et al	2015	DUELS	Netherlands	7,218,363	FM	>=30	31	1.03 (1.02, 1.03)
Chen et al	2016	Four northern Chinese cities	China	39,054	FM	23-89	40.66	0.93 (0.90, 0.95)
Cesaroni et al	2013	Rome longitudinal study	Italy	1,265,058	FM	>=30	43.6	1.03 (1.02, 1.03)
Lipsett et al	2011	CTS	USA	12,336	F	>=30	63.1	0.98 (0.95, 1.02)
Abbey et al	1999	AHSMOG	USA	5,652	FM	27-95	69.1	1.00 (0.98, 1.02)

NOTE: Weights are from random effects analysis

FIGURE 2. (*Continued*). HRs for all-cause mortality stratified by: A, level of adjustment for smoking and BMI; (B) spatial resolution of NO$_2$ concentration estimates; (C) study mean/median NO$_2$ concentrations. ES - Hazard ratio; CanCHEC – Canadian Census Health and Environment Cohort; DUELS – Dutch Environmental Longitudinal Study; CTS – California Teachers Society; ASHMOG - Adventist Health Study of Smog; CPRD – Clinical Practice Research Database; LUR Land Use Regression.

of the estimated NO$_2$ concentrations, i.e., land-use regression models predicting concentrations at subjects' residential addresses versus estimates for larger geographical areas derived from models or interpolation of data from monitoring stations; and (3) ordered by study mean/median NO$_2$ concentration. HRs from studies that controlled for individual measures of BMI and smoking were more variable and less precise than HRs from studies lacking this level of covariate adjustment. Summary HRs for the two subgroups are presented in Table 1 and indicate a larger summary HR ($P = 0.03$) for studies without control for individual measures of BMI and smoking compared with studies that did (1.03 vs. 1.00 per 10 µg/m^3 increment in NO$_2$). Studies that used estimated area-level concentrations of NO$_2$ were more variable and less precise than studies that used land-use regression-based residential concentration estimates and when meta-analyzed gave a smaller summary HR (1.00) compared with studies using residential land-use regression estimates (1.03). Three administrative cohorts constructed from national registries rather than recruitment of individuals accounted for 3/4 studies that did not adjust for individual-level BMI and smoking and 3/6 studies that used residential concentration estimates from land-use regression models. When ordered by study mean/median NO$_2$ concentration (Figure 2C), there was a suggestion of a downward trend in the size of the HR as study mean NO$_2$

concentrations increased. Meta-regression confirmed this impression (data not shown).

Cause-specific Mortality
Cardiovascular

Twenty-two studies reported results for cardiovascular mortality (eFigure 5; http://links.lww.com/EDE/B348). Two studies[54,57] were excluded from the meta-analyses as their results were included in the ESCAPE meta-analysis[22] and four studies were excluded as the same cohorts were analyzed in other publications included in our review.[20,32,44,63] One study from China[64] reported a (precisely estimated) HR in excess of 2.4 per 10 µg/m^3 increment in NO$_2$. The authors were cautious about the validity of this extreme finding in the Shenyang cohort, and therefore, the study was excluded from further analyses.

The random-effects summary HR for the remaining 15 studies was 1.03 (95% CI: 1.02, 1.05; PI: 0.98, 1.08) per 10 µg/m^3 increment in NO$_2$ (Table 2). Heterogeneity between-study estimates was high (83%). No evidence of small study bias was detected (data not shown). After exclusion of the age-restricted cohorts, larger summary HRs were observed in studies with limited age ranges at cohort enrolment (vs. broader age ranges); in cohorts without individual adjustment for BMI and smoking (vs. studies with individual adjustment); and in studies using residential land-use

TABLE 2. Summary HRs (95% CI) for Cardiovascular, Respiratory, and Lung Cancer Mortality, Without and With Stratification by Selected Cohort and Study Characteristics

Cohort Stratification		Cardiovascular Mortality					Respiratory Mortality					Lung Cancer Mortality				
		No. Cohorts	HR (95% CI) per 10 μg/m³	I² (%)	Pᵃ	Figureᵇ	No. Cohorts	HR (95% CI) per 10 μg/m³	I² (%)	Pᵃ	Figureᵇ	No. Cohorts	HR (95% CI) per 10 μg/m³	I² (%)	Pᵃ	Figureᵇ
All Cohorts			n = 22 (Removed = 7)			e5		n = 18 (Removed = 5)			e21		n = 20 (Removed = 4)			e33
Cohorts after excluding duplicates																
All cohortsᶜ	Fixed	15	1.03 (1.02, 1.03)	83	NA	e6a	13	1.03 (1.02, 1.04)	76	NA	e22a	16	1.07 (1.06, 1.08)	88	NA	e34a
	Random		1.03 (1.02, 1.05) (0.98, 1.08)ᵈ			e6b		1.03 (1.01, 1.05) (0.97, 1.10)ᵈ			e22b		1.05 (1.02, 1.08) (0.94, 1.17)ᵈ			e34b
Stratification by cohort characteristics																
Preexisting diseaseᶜ	Yes	1	NA	NA	NA	e7	1	NA	NA	NA	e23	0	NA	NA	NA	NA
	No	14	1.03 (1.02, 1.04)	83			12	1.03 (1.01, 1.05)	78			16	1.05 (1.02, 1.08)	88		
Stratification by cohort characteristics excluding preexisting disease cohorts																
Age-restrictedᶜ,ᵉ	Yes	3	1.10 (0.93, 1.29)	90	0.41	e8	2	NA	NA	NA	e24	3	1.15 (0.92, 1.42)	81	0.68	e35
	No	11	1.02 (1.01, 1.04)	81			10	1.03 (1.01, 1.05)	78			13	1.05 (1.02, 1.08)	90		
Stratification by study characteristics excluding preexisting disease and age-restricted cohorts																
Key confounder adjustmentᶜ,ᵉ,ᶠ	Yes	5	1.01 (0.99, 1.04)	68	0.50	e9	5	1.01 (0.97, 1.05)	69	0.001	e25	6	1.02 (0.96, 1.08)	72	0.20	e36
	No	6	1.03 (1.01, 1.04)	82			5	1.04 (1.01, 1.06)	85			7	1.06 (1.03, 1.10)	86		
Residential NO₂ exposure estimatesᶜ,ᵉ,ᶠ	Yes	7	1.03 (1.01, 1.04)	87	0.15	e10	6	1.02 (1.01, 1.03)	0	0.57	e26	5	1.04 (1.00, 1.09)	96	0.77	e37
	No	4	1.01 (1.00, 1.03)	0			4	1.04 (0.98, 1.10)	83			8	1.05 (1.00, 1.11)	65		

ᵃP value for differences in summary hazard ratios.
ᵇCorresponding figure giving study information.
ᶜExcluding studies identified as previous/smaller analyses of the same cohort and cohorts included in ESCAPE.
ᵈPrediction interval.
ᵉExcluding preexisting disease cohorts.
ᶠExcluding age-restricted cohorts.
NA indicates Not Applicable, HR hazard ratio, CI confidence interval.

regression estimates (compared to area-level concentrations of NO_2; Table 2).

Respiratory

Of the 18 studies reporting HRs for respiratory mortality (eFigure 21; http://links.lww.com/EDE/B348), five were excluded from the meta-analysis (included in the ESCAPE study[41]; analyzed in other publications included in the review[32,44,63]; and the Chinese Shenyang cohort study[34] which reported an HR of 2.97 per 10 µg/m³ increment in NO_2). The random-effects summary HR (13 studies) was 1.03 (95% CI: 1.01, 1.05; PI: 0.97, 1.10) per 10 µg/m³ increment in NO_2. Heterogeneity between study estimates was high ($I^2 = 76\%$). Following exclusion of the two age-restricted cohorts, a larger summary HR was observed in cohorts without individual adjustment for BMI and smoking compared with those with individual adjustment (1.04 vs. 1.01 per 10 µg/m³ increment in NO_2; $P = 0.001$). A larger summary HR was also observed in studies using area-level concentrations of NO_2 (compared with residential land-use regression estimates; Table 2).

Lung Cancer

Twenty studies reported results for lung cancer mortality (eFigure 33; http://links.lww.com/EDE/B348). Four studies, selected according to our a priori algorithm, were excluded as the same cohorts were analyzed in other publications included in the review.[43,44,47,63] In the fixed-effects meta-analysis, two large administrative cohorts[31,36] and the ACS study[61] accounted for over 80% of the weight. Heterogeneity between study HRs was high ($I^2 = 88\%$). The random-effects summary HR for the 16 studies was 1.05 (95% CI: 1.02, 1.08; PI: 0.94, 1.17) per 10 µg/m³ increment in NO_2 (Table 2). There was no evidence of publication bias. After exclusion of the age-restricted cohorts, larger summary HRs were observed in studies with limited age ranges at cohort enrollment (vs. broader age ranges) and in cohorts without individual adjustment for BMI and smoking (vs. studies with individual adjustment; Table 2). Stratification by spatial resolution of the estimated NO_2 concentrations suggested little difference in the respective summary HRs (Table 2 and eFigure 37; http://links.lww.com/EDE/B348).

Other Causes

Sufficient studies were available for meta-analysis for coronary heart disease (CHD) (12), cerebrovascular (8), and chronic obstructive pulmonary disorder (COPD; 8) after exclusions. Details of exclusions are given in the supplementary material; http://links.lww.com/EDE/B348 and results are presented in Table 3. Summary HRs for CHD and COPD were 1.05 and 1.03, respectively, but close to 1 for cerebrovascular mortality. Heterogeneity was also present except for COPD. For CHD, the summary HR observed for cohorts with individual measures of BMI and smoking was the same as those without. A larger summary HR was observed in studies using

estimates of residential versus small area NO_2 concentrations for CHD but reversed for COPD.

Five studies (three from Japan, one from the United States, and one from England) analyzing four cohorts reported HRs for pneumonia mortality and NO_2 (eFigure 32; http://links.lww.com/EDE/B348). The meta-analytic summary HR (studies n = 4) was 1.08 (95% CI: 1.06, 1.09) with no evidence of heterogeneity ($I^2 = 0\%$). Three studies[31,55,61] in three cohorts (CanCHEC, DCH, and ACS) reported HRs for diabetes-associated mortality giving a random-effects summary HR of 1.04 (95% CI: 1.00, 1.07) per 10 µg/m³ increment in NO_2, respectively (eFigure 38; http://links.lww.com/EDE/B348). A single study based on data from the ACS[52] reported a hazard ratio for brain cancer mortality of 0.93 (95% CI: 0.89, 0.98) per 10 µg/m³ increment in NO_2.

DISCUSSION

Our study identified 48 articles reporting results for all-cause and cause-specific mortality from 28 cohorts. The majority of the cohorts were in North America and Europe with only a few cohorts in Asia. Concentrations of NO_2 were positively associated with all-cause mortality and mortality from cardiovascular and respiratory diseases and lung cancer. Summary hazard ratios were generally in the range 1.02–1.5 per 10 µg/m³ with lower confidence limits above 1. There was substantial heterogeneity between HRs for all categories of death except COPD and pneumonia mortality. There was evidence of effect modification by subject age range at cohort recruitment and control for individual measures of smoking and BMI. Studies using cohorts comprising subjects with preexisting respiratory and cardiovascular disease tended to report higher HRs than the studies in the general population.

Our study adds to previous quantitative reviews by incorporating studies published to October 2016 and a wider range of cause-specific mortality. A review in 2014[4] included studies of NO_2 and NO_X published between 2004 and January 2013 but was restricted to studies (n = 23) which also included HRs for particles. Hoek et al[5] also reviewed studies published to January 2013 reporting results for NO_2 and fine and coarse particles and carbon. Our study identified 20 cohort studies of NO_2 and mortality published during the period 2013 to October 2016, an indication of the growing evidence base, though a number of these more recent studies included reanalyses of existing cohorts. Only seven of the 48 studies (five separate cohorts) identified were outside of North America and Europe and illustrated the limited geographical spread of the current evidence base. Nonetheless, the addition of new studies can facilitate meta-analysis of less common causes of death and incorporate results from updated cohorts with longer follow-up periods, enhanced exposure estimation, or inclusion of new variables in the analyses. Therefore, ongoing review of studies remains appropriate.

Our summary HR for all-cause mortality (cohorts n = 20) 1.02 (95% CI: 1.01, 1.03) per 10 µg/m³ increment in

TABLE 3. Summary HRs (95% CI) for CHD, Cerebrovascular, and COPD Mortality Without and With Stratification by Selected Cohort and Study Characteristics

Cohort Stratification	CHD Mortality					Cerebrovascular Mortality					COPD Mortality				
	No. Cohorts	HR (95% CI) per 10 µg/m³	I²(%)	Pᵃ	Figureᵇ	No. Cohorts	HR (95% CI) per 10 µg/m³	I²(%)	Pᵃ	Figureᵇ	No. Cohorts	HR (95% CI) per 10 µg/m³	I²(%)	Pᵃ	Figureᵇ
All Cohorts		n = 17 (Removed n = 5)			e11		n = 12 (Removed = 4)			e16		n = 9 (Removed = 1)			e27
Cohorts after excluding duplicates															
All cohortsᶜ Fixed	12	1.05 (1.04, 1.06)	67	NA	e12a	8	1.00 (0.99, 1.02)	62	NA	e17a	8	1.03 (1.01, 1.04)	0	NA	e28a
Random		1.05 (1.03, 1.06) (1.00, 1.10)ᵈ			e12b		1.01 (0.98, 1.03) (0.95, 1.07)ᵈ			e17b		1.03 (1.01, 1.04) (1.01, 1.05)ᵈ			e28b
Stratification by cohort characteristics															
Preexisting diseaseᶜ Yes	0	NA	NA	NA	NA	0	NA	NA	NA	NA	0	NA	NA	NA	NA
No	12	1.05 (1.03, 1.06)	67			8	1.01 (0.98, 1.03)	62			8	1.03 (1.01, 1.04)	0		
Stratification by cohort characteristics excluding preexisting disease cohorts															
Age-restrictedᶜ,ᵉ Yes	2	NA	NA	NA	e13	2	NA	NA	NA	e18	1	NA	NA	NA	e29
No	10	1.05 (1.03, 1.06)	59			6	1.00 (0.99, 1.01)	0			7	1.03 (1.01, 1.04)	5		
Stratification by study characteristics excluding preexisting disease and age-restricted cohorts															
Key confounder adjustmentᶜ,ᵉ,ᶠ Yes	5	1.04 (1.00, 1.08)	68	0.78	e14	3	0.99 (0.98, 1.01)	0	0.30	e19	2	NA	NA	NA	e30
No	5	1.04 (1.03, 1.06)	13			3	1.01 (0.99, 1.02)	0			5	1.03 (1.02, 1.05)	0		
Residential NO₂ exposure estimatesᶜ,ᵉ,ᶠ Yes	7	1.05 (1.03, 1.07)	61	0.47	e15	5	1.00 (0.99, 1.01)	0	NA	e20	4	1.02 (1.00, 1.04)	10	0.20	e31
No	3	1.03 (0.97, 1.09)	50			1	NA	NA			3	1.04 (1.01, 1.07)	0		

ᵃP value for differences in summary hazard ratios.
ᵇCorresponding figure giving study information.
ᶜExcluding studies identified as previous/smaller analyses of the same cohort and cohorts included in ESCAPE.
ᵈPrediction interval.
ᵉExcluding preexisting disease cohorts.
ᶠExcluding age-restricted cohorts.
NA - Not Applicable

NO_2 was smaller than reported in Faustini et al[4] (n = 12; 1.04 [95% CI: 1.02, 1.06]) and Hoek et al[5] (n = 11; 1.06 [1.04, 1.08]). Because of the ubiquitous nature of ambient air pollution and the very large populations exposed, small HRs can translate into substantial consequences for health at the population level. Hence, small variations in summary HRs can translate into important differences in population impact. The process used to derive the summary HRs therefore needs careful consideration.

The selection of study results for meta-analysis depends upon which studies are identified (which in turn depends upon the search strategy, review period, inclusion/exclusion criteria, etc.) and the protocol for estimate selection and highlights the importance of preparing, a priori, an analytical protocol for study and estimate selection without reference to the direction and magnitude of the HRs. The choice of model, fixed or random, also needs consideration.[66] In a fixed-effects model, a single underlying HR is assumed, whereas in a random-effects model, a distribution of HRs is assumed. For NO_2, a fixed-effects model would seem to be an appropriate a priori choice: NO_2 does not vary in its composition from one location to another nor would one expect its toxicity to vary, unlike particulate matter. However, studies vary in many other respects including modeling of pollution concentrations, population characteristics, and statistical model/confounders, suggesting that a random effects is most appropriate. The two modeling approaches also differ in the assignment of study weights; a fixed-effects model assigns weights based upon the precision of study estimates, whereas a random-effects model also incorporates between-study variability. As a consequence, in a random-effects model, smaller studies are given larger weight in the meta-analysis. This may or may not be appropriate depending upon the characteristics of the studies. For example, smaller studies may have a greater range of individual confounders and possibly higher data quality than very large studies based upon large administrative databases with limited data on individual risk factors. In such a scenario, the reweighting that can arise in a random-effects model may be appropriate.

In common with previous reviews,[4,5] our study found high levels of heterogeneity between study HRs for almost all causes of death assessed. Heterogeneity is an indicator of the extent to which study estimates are sufficiently consistent to be summarized using a weighted average in a fixed-effects model. The presence of heterogeneity indicates that the variability between study estimates is too great to be explained by chance alone but it does not necessarily rule out a causal interpretation.[67] Large variations in study size (as here where sample sizes ranged from 2000+ to 7.5 million) can lead to an artificially high I^2 statistic, a measure of heterogeneity.[68] An investigation of the sources of this heterogeneity is needed to inform the interpretation of the evidence.[69] Such an investigation also prevents these issues becoming lost in the statistical summary[70] provided by a random-effects analysis.[71]

The presence of high levels of heterogeneity between cohort estimates in our study is therefore an important finding in its own right and should be incorporated into any assessment of the evidence.

We assessed a range of potential effect modifiers. We first compared HRs from studies in subjects with preexisting disease with other cohorts. For all-cause mortality, we observed a larger, less-precise summary HR in subjects with preexisting disease (1.04) versus the rest (1.02). This comparison was limited however in two ways: (1) the small number of studies; and (2) such cohorts tend to be smaller and therefore carry little weight in any meta-analyses. Inclusion or otherwise in a meta-analysis should not be guided by a statistical assessment of differences between HRs; rather, it should be determined by the purpose of the analysis—hazard identification or calculation of a concentration–response function for input to a health impact calculation in the general population. To assess other potential effect modifiers, we chose to exclude studies in subjects with preexisting disease. Sensitivity analyses including these cohorts did not alter materially our findings (data not shown).

A small number of studies[23,24,35,62,63] used restricted age ranges for subjects at cohort entry limiting our ability to compare their results with cohorts including subjects with broad adult age ranges on entry. There was a tendency for cohorts restricting subjects' ages at cohort entry to report higher NO_2 HRs for all-cause, cardiovascular, and respiratory mortality compared with cohorts with much broader age ranges upon entry. This observation, based upon a small number of studies, may be a chance finding. Alternatively, age at cohort entry may be correlated with smoking status and disease status as well as NO_2 concentrations and proximity to traffic; further work is required to better understand this potentially important effect modifier.

In recent years, a number of studies have used administrative databases to construct retrospective cohorts.[25,26,31,36] "Administrative" cohorts tend to use very large numbers of subjects with broad population coverage. They may lack individual measures of potential confounders, e.g., smoking status and BMI utilizing instead small area measures derived from other sources. Residual confounding is generally acknowledged as a potential weakness in these studies and investigators have attempted to evaluate this using statistical methods or survey data.[26,36] Our stratified meta-analyses, separating studies with individual measures of smoking status and BMI from those who did not, found smaller HRs in the former with lower confidence limits below 1 for all causes of death except from CHD. A number of explanations for this finding are possible: (1) chance, the differences observed reflecting the results of studies that happen to be available at the time of the review; (2) other confounders, the two groups of studies give different results because of differences between studies other than the BMI and smoking characterization; (3) measurement error related to different scales of measurement

of confounders and exposure estimates; and (4) adjustment for these potential confounders at the small area level does not provide adequate control compared with that provided by individual measures. A sensitivity analysis using the English CPRD cohort (Carey I.M., personal communication, 2016) found that adjustment for individual-level smoking status and BMI after adjustment for a small area-level marker of socioeconomic status attenuated the all-cause mortality HR by a further 15%. The possibility remains, therefore, that studies unable to control for key individual confounders may be overstating the size of the association between long-term NO_2 and all-cause mortality.

Meta-analysis stratified by the spatial resolution of the modeled NO_2 concentrations showed for all-cause and cardiovascular-related deaths, a trend toward larger HRs for cohorts that used land-use regression models capable of estimating NO_2 concentrations at the subjects' residential address compared with other pollution models that estimated concentrations at a lower spatial resolution. This pattern was reversed for respiratory deaths. Such differences, though small, would have important implications for health impact assessments. Land-use regression models are capable of revealing gradients in NO_2 concentrations that are missed by models that estimate concentrations for larger geographic areas. The improved precision of the estimate of a subject's long-term exposure to a pollutant is achieved by reducing both systematic and random measurement error in the exposure estimate. Random measurement error has long been acknowledged as a problem in epidemiological studies. If the *estimated* exposure can be expressed as a linear combination of the true exposure plus random error, that error is described as additive and "classical" but if the *true* exposure can be expressed as a linear combination of the estimated exposure plus random error, the error is described as additive and Berkson. Additive classical error leads on average to the underestimation of hazard ratios (bias towards the null), whereas Berkson error leads to wider confidence intervals due to reduced statistical power. Measurement error introduced by spatial smoothing behaves like Berkson error whereas error introduced by parameter estimation behaves like classical error.[72,73] Thus, even if greater spatial resolution in modeled NO_2 concentrations results in more precise exposure estimates (i.e., less measurement error), the effect on hazard ratio estimation will depend on whether it is the overall Berkson or the classical component of measurement error that is reduced.[72] Hence, it does not follow necessarily that land-use regression models will suffer less from bias toward the null than models with coarser spatial resolution. Of the six studies that used land-use regression models to estimate NO_2 concentrations (Figure 2B), three administrative cohorts dominated the meta-analysis (combined weight >69%). These three studies were also limited in their ability to control for individual measures of BMI and smoking and accounted for over 94% of the weight in the meta-analysis of studies with limited control for confounders (Figure 2A), and

therefore, one should be cautious in the interpretation of these findings.

The calculation and use of prediction intervals in meta-analyses has been advocated.[13,68] In a random-effects model, study HRs are assumed to follow a distribution. The 95% CI for the summary HR represents, therefore, the range within which the mean of this distribution lies. It does not convey the uncertainty in the HR from any one study. A prediction interval allows for the fact that the health effects of NO_2 may differ from one setting to another (e.g., due to the susceptibility of the underlying population; the assessment of NO_2 concentrations; the pollutant mixture; underlying disease prevalence; competing risk factors; model specification etc.). It provides an appropriate indication of the precision of the estimated HR in a future setting.[68] Given the sensitivity of health impact calculations to small changes in the magnitude of the HR and the imprecision inherent in any meta-analyses of HRs, subsequent impact calculations should utilize prediction intervals and report ranges of impact rather than focusing upon point estimates.

Evidence gathered from experimental studies in animals and human volunteers and from epidemiologic studies employing biomarkers of effects of exposure to air pollutants offers limited support for the assertion that long-term exposure to NO_2 is causally associated with an increase in risk of death.[7,8] Such evidence as there is for toxicological effects of NO_2 on mortality comes largely from studies of the association with short-term exposure. These studies have, so far, provided no means of distinguishing the effects of NO_2 from those of PM: both might well act via the same mechanisms including the induction of increased levels of oxidative free radicals and inflammation. Evidence for effects on the cardiovascular system, e.g., effects on levels of clotting factors and on the rate of progression of arterial disease, is better developed for PM than for NO_2.

Only a small number of the studies identified in our review reported HRs for NO_2 adjusted for PM. In some studies the correlation between pollutants was high (>0.8) limiting their ability to disentangle associations between the pollutants and mortality. The difficulties in interpreting coefficients in multipollutant models have received attention.[74,75] These difficulties include (1) correlation between pollutants (arising due to common sources and meteorologic conditions), which can lead to unstable parameter estimation; (2) differential measurement error between pollutants which can lead to the "transfer" of an association from the less well-measured (but true) pollutant to the better-measured (but incorrect) pollutant; and (3) statistical models which do not generally assess interactions between pollutants in order to interpret correctly model main effects. Statistical methods for dealing with correlated predictors have been proposed as well as the use of combined pollutant estimates to be used in formulating a multipollutant approach to regulatory policy.[74,75] Given the current limited evidence base and the statistical issues described, it remains infeasible to distinguish

associations between NO_2 and mortality from those for PM, especially fine particles arising from vehicle exhaust.

Previous reviews of both the toxicologic and epidemiologic literature have concluded that the evidence was not sufficient to infer a causal relationship between long-term exposure to NO_2 and mortality.[7,8] This caution was due in part to a lack of consistency in study findings and concerns relating to potential confounding by copollutants especially particles in traffic exhaust. Our study confirms the need for continued caution in respect of causality particularly since the revised meta-analyses suggest HRs close to one, with the possibility of further attenuation if meta-analyses are restricted to studies with individual measures of BMI and smoking. The substantial heterogeneity between study results also weakens the argument for causality. Unlike particles where unit mass concentrations might vary between locations in size, composition, and nature (primary/secondary), a unit mass concentration of NO_2 gas is the same everywhere. We therefore consider that as the evidence stands at present, the causal basis for estimating the burden of NO_2 on mortality and loss of life expectancy remains weak.

Our study found positive associations between long-term concentrations of NO_2 and risk of mortality from a range of diseases. However, there was substantial heterogeneity between estimates and evidence of differences in the magnitude and precision of HRs depending upon the degree of control for individual confounding factors and the spatial resolution of the NO_2 concentration estimates. This has important implications for the selection of HRs for use in health impact assessment calculations. Given the many uncertainties inherent in the assessment of this evidence base and the sensitivity of health impact calculations to small changes in the magnitude of the HR, subsequent impact calculations should take account of these issues by utilizing prediction intervals and reporting ranges of impact rather than focusing upon a point estimate.

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