Long-term Exposure to Air Pollution and Cardiovascular Mortality

An Analysis of 22 European Cohorts

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Background: Air pollution has been associated with cardiovascular mortality, but it remains unclear as to whether specific pollutants are related to specific cardiovascular causes of death. Within the multicenter European Study of Cohorts for Air Pollution Effects (ESCAPE), we investigated the associations of long-term exposure to several air pollutants with all cardiovascular disease (CVD) mortality, as well as with specific cardiovascular causes of death.

Methods: Data from 22 European cohort studies were used. Using a standardized protocol, study area–specific air pollution exposure at the residential address was characterized as annual average concentrations of the following: nitrogen oxides (NO_2 and NO_x); particles with diameters of less than 2.5 μm ($PM_{2.5}$), less than 10 μm (PM_{10}), and 10 μm to 2.5 μm (PM_{coarse}); $PM_{2.5}$ absorbance estimated by land-use regression models; and traffic indicators. We applied cohort-specific Cox proportional hazards models using a standardized protocol. Random-effects meta-analysis was used to obtain pooled effect estimates.

Results: The total study population consisted of 367,383 participants, with 9994 deaths from CVD (including 4,992 from ischemic heart disease, 2264 from myocardial infarction, and 2484 from cerebrovascular disease). All hazard ratios were approximately 1.0, except for particle mass and cerebrovascular disease mortality; for $PM_{2.5}$, the hazard ratio was 1.21 (95% confidence interval = 0.87–1.69) per 5 $\mu g/m^3$ and for PM_{10}, 1.22 (0.91–1.63) per 10 $\mu g/m^3$.

Conclusion: In a joint analysis of data from 22 European cohorts, most hazard ratios for the association of air pollutants with mortality from overall CVD and with specific CVDs were approximately 1.0, with the exception of particulate mass and cerebrovascular disease mortality for which there was suggestive evidence for an association.

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Cohort studies assessing effects of long-term exposure to air pollution on cardiovascular mortality have generally found increased risks.[1–4] Studies in the United States have mostly reported associations for particles with diameters of less than 2.5 μm ($PM_{2.5}$),[5] whereas studies in Europe (including studies in The Netherlands,[6] France,[7] Norway,[2] Denmark,[8] United Kingdom,[9] and Italy)[10] have also reported associations with long-term exposure to nitrogen oxides (NO_2 and NO_x), which are more related to traffic pollutants than particle mass. Effect estimates differ across studies, with some studies showing little or no association of various air pollutants with all cardiovascular mortality.[6,9,11–13] There is therefore an interest in investigating the mortality effects of a range of air pollutants.

The category of cardiovascular diseases (CVDs) is broad, and it is unlikely that the risk associated with air pollution exposure is uniform for the specific cardiovascular mortality causes. However, only a few studies have investigated specific causes of cardiovascular mortality, including ischemic heart disease and cerebrovascular disease.[1,2,8,14–16]

The aim of the current study was to investigate the effects of long-term exposure to air pollution on all cardiovascular mortality, as well as the more specific causes of ischemic heart disease mortality, myocardial infarction (MI) mortality, and cerebrovascular disease mortality, for a range of air pollution measures. In the framework of the collaborative European Study of Cohorts for Air Pollution Effects (ESCAPE), data from 22 ongoing cohort studies were used, with a standardized exposure assessment of particle mass and nitrogen oxides.

METHODS

The association between air pollution and cardiovascular mortality was analyzed in each cohort separately, following the standardized analysis protocol of the ESCAPE study.[17] A standardized statistical protocol and STATA script were used, as explained in a training workshop for all local analysts. Cohort-specific results were sent to the coordinating institute (IRAS, Utrecht University) for central evaluation. We combined cohort-specific effect estimates by random-effects meta-analysis. Pooling of the cohort data was not possible due to data transfer and privacy issues. Random-effects meta-analysis has the advantage of taking into account inter-area and intercohort differences not entirely addressed by the available confounders.

Study Populations

Twenty-two ongoing cohorts from 13 countries across Europe were included (Table 1, and eAppendix 1; http://links.lww.com/EDE/A767). All cohorts were included samples from the general population. The study areas of most cohorts consisted of a large city with surrounding smaller rural communities. Some (multicenter) cohorts included large regions of the country, such as EPIC-MORGEN in The Netherlands, SALIA in the Ruhr area in Germany, EPIC-Oxford covering much of the United Kingdom, the VHM&PP cohort in Austria, and SAPALDIA in three cities in Switzerland. The use of cohort data in ESCAPE was approved by the local ethical and data protection authorities. Each cohort study followed the rules for ethics and data protection set up in the country in which it was based.

Mortality Outcome Definition

In all cohorts, follow-up was based on linkage to mortality registries. Outcomes were defined on the basis of the underlying cause of death recorded on death certificates: all CVD mortality (*International Classification of Diseases [ICD]-9*: 400–440; *ICD-10*: I10-I70), ischemic heart disease mortality (*ICD-9*: 410–414; *ICD-10*: I20-I25), MI mortality (*ICD-9*: 410; *ICD-10*: I21, I22), and cerebrovascular disease mortality (*ICD-9*: 430–438; *ICD-10*: I60-I69) (eAppendix 2; http://links.lww.com/EDE/A767).

Exposure Assessment

Air pollution concentrations at the baseline residential addresses of study participants were estimated by land-use regression models following a standardized procedure described elsewhere.[18,19] In brief, air pollution was monitored for 1 year between October 2008 and May 2011 in all study areas to obtain the following annual average concentrations: NO_2 and NO_x; particles with aerodynamic diameters of less than 2.5 μm ($PM_{2.5}$) and less than 10 μm (PM_{10}) plus $PM_{2.5}$ absorbance (determined as the reflectance of $PM_{2.5}$ filters).[20,21] PM_{coarse} was calculated as PM_{10} minus $PM_{2.5}$. PM and NO_x were both measured in 19 of the 22 study areas; NO_x alone was measured in the remaining three areas. Study area–specific land-use regression models were developed to explain the spatial variation of measured annual average air pollution concentrations within each area using traffic and land-use predictor variables from a Geographic Information System. The results of the land-use regression models were then used to estimate ambient air pollution concentration at the participants' baseline addresses. In addition to air pollution concentrations, traffic intensity on the nearest road (vehicles per day) and total traffic load (intensity × length) on all major roads within a 100-m buffer were used as indicators of exposure. A detailed description of exposure-assessment procedures, including back-extrapolation of concentrations to the baseline year and fit of land-use regression models, is presented in eAppendix 3 (http://links.lww.com/EDE/A767).

Statistical Analyses

Cohort-specific Analyses

Cox proportional hazards models were used for the cohort-specific analyses. We used age as the time scale because of evidence that this better adjusts for potential confounding by age.[22] Censoring occurred at the time of death for non-CVD causes, emigration, loss to follow-up for other reasons, or at end of follow-up, whichever came first. Air pollution exposure was analyzed as a linear variable. Information on potential confounders was available from questionnaires at baseline.

A priori, we specified three confounder models with increasing level of adjustment. Confounder models were decided based on previous cohort studies of air pollution and mortality, as well as availability of data in a majority of the cohorts. Model 1 included only age (time axis), sex, and calendar time (year(s) of enrollment). Model 2 added individual-level variables: smoking status (never/former/current), smoking intensity, smoking duration, environmental tobacco smoke, fruits intake, vegetables intake, alcohol consumption (linear and squared term), body mass index (BMI) (linear and squared term), educational level (low, medium, or high), occupational class (white/blue collar classification), employment status, and marital status. Model 3 added to Model 2 area-level socioeconomic status (SES) variables (mostly mean income of neighborhood or municipality). Model 3 was selected as the main confounder model. Only subjects with complete information for Model 3 variables were included in the analyses.

In sensitivity analyses, we added prevalent hypertension, physical activity, diabetes mellitus, and cholesterol level to Model 3. Extended confounder models were used in sensitivity analyses because some potential effect of air pollution might be mediated by hypertension, diabetes mellitus, and cholesterol level.

We further evaluated the impact of the addition of modeled road traffic noise to Model 3 because noise and air pollution have been shown to be correlated and may both affect CVD mortality. Road traffic noise was modeled at the highest exposed facade at the baseline address (eAppendix 3; http://links.lww.com/EDE/A767). Noise was used as continuous variable and as categorical variable (5 dB categories).[1]

Effect modification by a priori-specified variables was investigated by stratified analyses for age during follow-up (<60, 60–75, ≥ 75 year), sex, smoking status, educational level, fruits intake (<150, 150–300, ≥300 g/day), and BMI (<25, 25–30, ≥ 30 kg/m^2). These variables were selected based on previous studies.[5,23]

We tested whether back-extrapolation of the air pollution concentrations to the baseline year affected the results (details in eAppendix 3; http://links.lww.com/EDE/A767). Sensitivity analyses restricted to subjects who did not move during follow-up were conducted. We conducted analyses

TABLE 1. Description of the Included Cohort Studies: Description of the Study Area, Total Study Population,[a] Number of Deaths per Outcome,[a] Age at Baseline, Baseline Period, and Follow-up Time

Cohort	Study Area Description	No. Deaths					Age in Years Mean (SD)	Baseline Period	Follow-up Time in Person-years Total (Mean)
		Total No.	All CVD Causes	Ischemic Heart Disease	Myocardial Infarction	Cerebrovascular			
EPIC-Umeå, Sweden	City of Umeå and surrounding rural areas	22,136	230	169	117	56	46.0 (10.2)	1992–1996	281,711 (12.7)
FINRISK, Finland	Greater Helsinki Area and Turku city and its rural surroundings	10,224	225	137	66	61	47.9 (13.2)	1992; 1997; 2002; 2007	108,434 (10.6)
HUBRO, Norway	City of Oslo	18,234	332	145	103	98	48.3 (15.2)	2000–2001	175,076 (9.6)
SNAC-K, Sweden	City of Stockholm	2,401	140	61	31	30	70.3 (8.1)	2001–2004	15,568 (6.5)
SALT/Twin gene, Sweden	Stockholm County	5,473	206	95	57	57	58.0 (9.9)	1998–2002	47,767 (8.7)
60-y/IMPROVE, Sweden	Stockholm County	3,612	81	46	21	21	60.4 (0.1)	1997–1999	40,612 (11.2)
SDPP, Sweden	Stockholm County	7,408	55	35	23	13	47.1 (5.0)	1992–1998	102,831 (13.9)
DCH, Denmark	City of Copenhagen and surrounding areas	35,458	678	270	166	177	56.7 (4.4)	1993–1997	469,571 (13.2)
EPIC-MORGEN, The Netherlands	Cities of Amsterdam, Maastricht, and Doetinchem and surrounding rural areas	16,446	185	101	79	39	43.9 (10.9)	1993–1997	217,722 (13.2)
EPIC-PROSPECT, The Netherlands	City of Utrecht and surrounding rural areas	15,670	290	88	71	91	57.7 (6.0)	1993–1997	202,809 (12.9)
SALIA, Germany	Areas in the cities of Dortmund, Duisburg, Essen, Gelsenkirchen, and Herne situated in the Ruhr Area and adjacent towns Borken and Dülmen	4,352	206	94	56	34	54.5 (0.6)	1985–1987; 1990–1994	81,093 (18.6)
EPIC-Oxford, United Kingdom	Urban and rural areas in a buffer of 400 km around London–Oxford area	38,941	661	350	156	209	45.8 (13.7)	1993–2001	491,542 (12.6)
KORA, Germany	City of Augsburg and two adjacent rural counties	8,399	270	130	83	63	49.5 (13.8)	1994–1995; 1999–2001	88,592 (10.5)
VHM&PP, Austria	State of Vorarlberg, excluding high mountain areas (>600 m) and areas within 300 m of state border	117,824	5,858	3,043	1,099	1,384	41.9 (14.9)	1985–2005	2,039,328 (17.3)
SAPALDIA, Switzerland	Cities of Geneva, Lugano, and Basel	3,473	42	25	17	5	41.1 (11.8)	1991	55,935 (16.1)
	Analyses for which PM data are available	1,250	14	8	NA	NA			20,294 (16.2)
E3N, France	Cities of Paris, Grenoble, Lyon, and Marseille and surrounding rural areas	14,313	118	15	4	34	53.0 (6.7)	1993–1996	192,761 (13.5)

(*Continued*)

TABLE 1. (*Continued*)

Cohort	Study Area Description	Total No.	No. Deaths: All CVD Causes	No. Deaths: Ischemic Heart Disease	No. Deaths: Myocardial Infarction	No. Deaths: Cerebrovascular	Age in Years, Mean (SD)	Baseline Period	Follow-up Time in Person-years, Total (Mean)
	Analyses for which PM data are available	10,915	89	14	3	26			147,021 (13.5)
EPIC-Varese, Italy	City of Varese and surrounding rural areas	9,871	79	22	13	31	51.7 (8.3)	1993–1997	111,415 (11.3)
EPIC-Turin, Italy	City of Turin	7,261	46	19	7	8	50.4 (7.5)	1993–1998	97,549 (13.4)
SIDRIA-Turin, Italy	City of Turin	5,054	29	10	7	8	44.2 (6.2)	1999	55,667 (11.0)
SIDRIA-Rome, Italy	City of Rome	9,177	64	40	26	10	44.3 (6.0)	1999	102,856 (11.2)
EPIC-San Sebastian, Spain	City of San Sebastian and surrounding area in Basque Country	7,464	83	40	29	25	49.4 (7.7)	1992–1995	93,626 (12.5)
EPIC-Athens, Greece	Greater Athens Area	4,192	116	57	33	30	49.4 (11.7)	1994–1999	46,852 (11.2)
Total		367,383	9,994	4,992	2,264	2,484	50.5 (41.1–70.3)[b]		5,119,317 (13.9)

Order of studies is based on North-to-South gradient.
[a]Number of observations without missing values in any confounder variable of Model 3 (main model).
[b]Mean age at baseline (range) in total study population.
NA indicates not available.

without the large Austrian cohort.We checked for spatial clustering of residuals of the models using random effects of the spatial area units (often neighborhood or municipality) in each cohort. The two traffic indicator variables were analyzed in combination with background NO_2 concentration.

All cohort-specific analyses were done in STATA versions 10 to 12 (StataCorp, College Station, TX) except models with random effects, which were done using R software (R Foundation for Statistical Computing, 2004 [ISBN 3-900051-00-3], Vienna, Austria).

Meta-analysis

Meta-analyses of cohort-specific effect estimates were conducted using the DerSimonian–Laird[24] method with random effects. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for fixed increments. Heterogeneity between cohorts was quantified by the I^2 statistic and tested by the χ^2 test from Cochran's Q statistic.[25]

Effect modification was tested by meta-analysis of the pooled estimates from the various strata, and by computing the χ^2 test of heterogeneity.

We tested whether effect estimates differed for cohorts for which the variance explained by the land-use regression model cross-validation was smaller or larger than 60% for $PM_{2.5}$. In addition, we tested whether effect estimates differed by region of Europe ("North": Sweden, Norway, Finland, Denmark; "West and Middle": United Kingdom, The Netherlands, Germany, France, Austria, and Switzerland; and "South": Italy and Greece). All meta-analyses were conducted in STATA, version 12 (StataCorp).

RESULTS

Characteristics of the Study Population

The total study population consisted of 367,383 participants contributing 5,119,317 person-years at risk (average time of follow-up = 13.9 years). Of the participants, 29,076 died from a natural cause during follow-up, with 9994 deaths due to CVD (4992 to ischemic heart disease, 2264 to MI, and 2484 cerebrovascular disease) (Table 1). The ratio of specific causes to all CVD deaths varied substantially among cohorts. Cohorts were recruited mostly in the 1990s. Cohorts differed in the number of participants, the mean baseline age, and the availability of information on confounders (Table 2, and eAppendix 4; http://links.lww.com/EDE/A767). Age, sex, smoking status, and area-level SES were available for all cohorts. Smoking intensity and duration were available as continuous variables for all cohorts except for the Austrian and French. The Austrian cohort had data on occupation and employment status but not on education.

Air Pollution Exposure

Air pollution concentrations varied among and within study areas (eAppendix 5; http://links.lww.com/EDE/A767). Concentrations showed an increase from northern to southern

TABLE 2. Population Characteristics at Baseline of the Included Cohort Studies

Cohort	Women %	Never-smokers %	No. Cigarettes per day Mean (SD)	No. Years of Smoking Mean (SD)	BMI (kg/m^2) Mean (SD)	Fruit Intake[a]	Alcohol Intake[b]	Married/ Living with Partner %	Low Educational Level %	Employed/ Self-employed %
EPIC-Umeå, Sweden	52	62	2.4 (5.6)	8.8 (13.0)	25.0 (4.0)	163.0 (132.6)	3.2 (4.0)	82	28	85
FINRISK, Finland	54	45	3.8 (7.8)	8.6 (12.2)	26.4 (4.6)	66%	0.9 (1.3)	70	31	69
HUBRO, Norway	56	46	6.7 (8.4)	11.5 (14.4)	25.7 (4.1)	40%	51%	50	18	NA
SNAC-K, Sweden	60	44	7.1 (9.5)	9.8 (15.2)	26.0 (4.1)	NA	22%	54	21	29
SALT/Twin gene, Sweden	56	39	8.5 (9.7)	16.7 (17.3)	28.6 (4.1)	NA	NA	68	22	NA
60-y/IMPROVE, Sweden	53	41	8.0 (9.1)	15.2 (16.4)	26.8 (4.2)	64%	8.9 (9.7)	72	28	51
SDPP, Sweden	62	37	8.5 (8.8)	12.3 (12.4)	25.6 (4.0)	92%	1.3 (1.9)	84	26	92
DCH, Denmark	54	36	6.3 (10.4)	18.7 (17.1)	26.0 (4.1)	183.2 (151.2)	21.7 (22.8)	69	30	80
EPIC-MORGEN, The Netherlands	54	35	10.4 (11.1)	14.3 (13.7)	25.2 (4.0)	171.9 (129.2)	12.7 (18.0)	68	12	NA
EPIC-PROSPECT, The Netherlands	100	45	5.7 (7.4)	15.2 (16.5)	25.5 (4.1)	231.6 (139.2)	9.0 (12.4)	77	22	NA
SALIA, Germany	100	75	2.6 (6.6)	4.4 (10.5)	NA	NA	NA	NA	29	NA
EPIC-Oxford, United Kingdom	78	63	5.0 (8.3)	6.7 (11.2)	24.0 (3.9)	259.9 (204.5)	9.1 (11.7)	71	37	73
KORA, Germany	51	44	9.2 (13.3)	12.0 (14.2)	27.2 (4.6)	60%	16.3 (22.3)	76	13	58
VHM&PP, Austria	56	70	NA	NA	24.8 (4.3)	NA	NA	68	NA	69
SAPALDIA, Switzerland	52	42	11.5 (14.5)	10.7 (12.4)	23.7 (4.0)	NA	NA	54	15	84
E3N, France	100	49	NA	NA	22.8 (3.2)	242.0 (164.7)	12.0 (15.1)	NA	5	NA
EPIC-Varese, Italy	86	60	4.0 (6.4)	9.4 (13.3)	25.7 (4.2)	303.8 (172.2)	11.4 (15.7)	87	61	NA
EPIC-Turin, Italy	48	43	7.2 (8·2)	17.6 (16.3)	25.3 (3.8)	318.2 (182.2)	18.1 (20.3)	86	44	NA
SIDRIA-Turin, Italy	52	38	9.3 (10·2)	11.3 (10.6)	NA	NA	NA	95	18	72
SIDRIA-Rome, Italy	53	35	10.1 (10·5)	11.7 (10.4)	NA	NA	NA	100	45	NA
EPIC-San Sebastian, Spain	54	54	6.9 (10·0)	11.4 (14.3)	27.3 (3.9)	330.2 (258.5)	18.3 (24.0)	88	71	NA
EPIC-Athens, Greece	55	40	1.7 (15·0)	10.8 (13.1)	27.5 (4.5)	402.6 (258.2)	9.2 (14.5)	78	24	67
Total[c]	63 (48–100)	47 (35–75)	6.7 (1.7–11.5)	11.9 (4.4–18.7)	25.7 (22.8–28.6)	—	—	75 (50–100)	29 (5–71)	69 (29–92)

Order of studies is North-to-South. Detailed description of each cohort can be found in eAppendix 4; http://links.lww.com/EDE/A767.

[a]Mean (SD) (g/day) or percentage with daily fruit consumption. For SDPP, it is percentage daily/weekly fruit consumption.

[b]Mean (SD) (g/day) or percentage with daily alcohol consumption. For FINRISK, it is number of glasses of alcoholic drink during last week. For SDPP, it is the number of glasses of alcoholic drink per day. For HUBRO, it is percentage with weekly alcohol consumption.

[c]Mean (range) in whole study population.

NA indicates not available.

Europe cohorts. The average NO_2 concentration ranged from 5.2 μg/m^3 (EPIC-Umeå) to 59.8 μg/m^3 (SIDRIA-Turin) and the average $PM_{2.5}$ concentration from 6.6 μg/m^3 (SDPP) to 31.0 μg/m^3 (SIDRIA-Turin). Median differences between area-specific 5th and 95th percentiles in NO_2 and $PM_{2.5}$ concentrations were 21.1 and 4.3 μg/m^3, respectively. Contrasts were within-city contrasts for most study areas but could also include between-city contrasts for the cohorts covering larger geographical areas. Correlations between exposure measures were moderate to high in each cohort (eAppendix 6; http://links.lww.com/EDE/A767).

Main Results

Most HRs for the association between mortality outcomes and the air pollutants were approximately 1.0 (Table 3, Figure, and eAppendix 7; http://links.lww.com/EDE/A767), with the exception of the association of particulate mass and cerebrovascular disease mortality (Table 3 and Figure). The HR for $PM_{2.5}$ was 1.21 (95% CI = 0.87–1.69) per 5 μg/m^3 and for PM_{10} the HR was 1.22 (0.91–1.63) per 10 μg/m^3. In addition, associations between all outcomes and traffic intensity on the nearest road were slightly increased; the HR for total CVD mortality was 1.02 (0.99–1.05) per 5000 motor vehicles per day, an association that remained after adjustment for noise (eAppendix 8; http://links.lww.com/EDE/A767).

HRs for confounder Model 1 (adjusted only for calendar year and sex) were highest; after adjustment for individual-level confounders, HRs decreased. Sensitivity analyses showed that smoking variables were primarily responsible for this decrease. Inclusion of area-level SES variables led to a small further decrease in HRs.

No heterogeneity among cohorts was found for total CVD mortality, except for the HRs for traffic intensity on major roads in a 100-m buffer. HRs for random-effects (default method) and fixed-effects CVD meta-analyses were similar (data not shown). For the more specific causes, low to moderate heterogeneity was found ($I^2 < 50\%$).

Sensitivity Analyses

Additional adjustment for hypertension and physical activity, diabetes mellitus and cholesterol, and noise did not change the pooled HRs compared with the main model HRs (eAppendix 8; http://links.lww.com/EDE/A767). Back-extrapolation for NO_2 was possible in 18 cohorts, whereas back-extrapolation for PM_{10} was possible for seven cohorts spread over Europe. HRs were not different between the back-extrapolated concentrations at baseline in the year of recruitment and the concentrations based on 2008–2011 measurements. Pooled HRs for CVD mortality for back-extrapolated NO_2 concentrations based on the difference and the ratio method were 1.02 (95% CI = 0.97–1.07) and 1.01 (0.98–1.05)—essentially the same as the 1.02 (0.97–1.07) for the main ESCAPE exposure for the 18 cohorts with back-extrapolated NO_2 concentrations. For cerebrovascular disease mortality, pooled HRs for back-extrapolated PM_{10} concentrations based on the difference and the ratio method were 1.36 (0.92–2.02) and 1.22 (0.93–1.59) also the same as the 1.21 (0.79–1.85) for the main ESCAPE exposure for the seven cohorts with back-extrapolated PM_{10} concentrations. Analyses restricted to subjects who did not move during follow-up resulted in similar HRs as for the main analyses (data not shown). HRs for total CVD mortality without the influential Austrian cohort were similar to those from the main analyses. HRs for cerebrovascular disease mortality for $PM_{2.5}$ and PM_{10} increased to 1.32 (0.93–1.89) and 1.30 (0.96–1.77), respectively. HRs with and without accounting for spatial clustering of residuals were similar. $PM_{2.5}$ effect estimates for cerebrovascular disease mortality were similar for the cohorts for which the variance explained by land-use regression model cross-validation was smaller or larger than 60%: 1.24 (0.71–2.15) (N = 6) and 1.22 (0.78–1.92) (N = 12), respectively. $PM_{2.5}$ effect estimates for cerebrovascular disease mortality were also not statistically different among the cohorts in different regions. For the other pollutants also, effect estimates did not differ based on validation R^2 or region.

Effect Modification

For none of the evaluated variables, was there an indication of effect modification, except for $PM_{2.5}$, for which men had higher HRs than women (eAppendix 9; http://links.lww.com/EDE/A767). For NO_2, there was no difference in HRs between men and women.

DISCUSSION

We found that most HRs for the association between air pollutants and mortality from overall CVD and specific CVDs were approximately 1.0, with the exception of particulate mass and cerebrovascular disease mortality for which there was suggestive evidence for an association.

An association between $PM_{2.5}$ exposure and overall cardiovascular mortality was first identified in the Harvard Six Cities study (risk ratio [RR] = 1.28 [95% CI = 1.13–1.44] per 10 μg/m^3),[4] and the American Cancer Society study (RR = 1.09 [1.03–1.16] per 10 μg/m^3),[3] both from the United States. Overall, subsequent cohort studies have confirmed these associations.[5,23] A recent review documented large heterogeneity of effect estimates across studies, with several studies showing no association.[23] A recent study of a national United Kingdom cohort found associations between ambient air pollution and all-cause mortality, but associations were approximately 1.0 for cardiovascular mortality.[9]

Associations between exposure to NO_2 or elemental carbon (which correlates highly with $PM_{2.5}$ absorbance) and overall cardiovascular mortality were observed in studies conducted in Europe, Japan, Canada, and the United States.[6–8,26–31] The number of studies on the association between long-term coarse particle exposure and cardiovascular mortality is still small, and there is no clear evidence that coarse particles are associated with overall cardiovascular mortality.[3,11]

TABLE 3. Association of Exposure to Air Pollution and Traffic Indicators with Mortality Due to CVD, Ischemic Heart Disease, MI, and Cerebrovascular Disease: Results from Random-effects Meta-analyses (HR [95% CI]) and I^2 (P Value) of Test for Heterogeneity of Effect Estimates Among Cohorts Using Main Confounder Models 1, 2, and 3[a]

Exposure	Model 1[b] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[b] HR (95% CI)	I^2 (P)[c]
Total CVD deaths				
$PM_{2.5}$[d]	1.18 (1.00–1.38)	1.04 (0.93–1.17)	0.99 (0.91–1.08)	0 (0.48)
$PM_{2.5}$ absorbance[d]	1.09 (0.95–1.25)	0.99 (0.91–1.08)	0.97 (0.89–1.06)	0 (0.67)
PM_{10}[d]	1.10 (0.95–1.26)	1.04 (0.92–1.16)	1.02 (0.92–1.14)	20.2 (0.21)
PM coarse[d]	1.11 (0.95–1.30)	1.04 (0.92–1.17)	1.02 (0.91–1.13)	26.9 (0.14)
NO_2	1.07 (1.00–1.14)	1.03 (0.97–1.08)	1.01 (0.97–1.06)	20.1 (0.20)
NO_x	1.06 (1.02–1.11)	1.03 (0.99–1.07)	1.02 (0.99–1.06)	0 (0.53)
Traffic intensity on the nearest road[e]	1.03 (1.00–1.06)	1.02 (0.99–1.06)	1.02 (0.99–1.05)	30.3 (0.10)
Traffic intensity on major roads 100-m buffer[f]	1.02 (0.93–1.12)	1.00 (0.90–1.11)	0.99 (0.89–1.11)	55.5 (0.001)
Ischemic heart disease deaths				
$PM_{2.5}$[d]	1.09 (0.87–1.37)	1.00 (0.78–1.27)	0.98 (0.74–1.30)	40.3 (0.04)
$PM_{2.5}$ absorbance[d]	1.07 (0.86–1.32)	0.99 (0.82–1.20)	0.98 (0.78–1.23)	34.2 (0.07)
PM_{10}[d]	0.98 (0.85–1.14)	0.94 (0.80–1.10)	0.93 (0.77–1.13)	34.7 (0.07)
PM coarse[d]	0.98 (0.81–1.19)	0.92 (0.77–1.10)	0.92 (0.77–1.11)	41.3 (0.03)
NO_2	1.05 (0.96–1.14)	1.00 (0.92–1.09)	1.00 (0.91–1.09)	34.3 (0.06)
NO_x	1.06 (0.99–1.12)	1.02 (0.96–1.09)	1.02 (0.95–1.09)	20.3 (0.19)
Traffic intensity on the nearest road[e]	1.03 (1.00–1.06)	1.02 (0.99–1.06)	1.02 (0.99–1.06)	4.3 (0.40)
Traffic intensity on major roads 100-m buffer[f]	1.05 (0.92–1.19)	1.02 (0.89–1.17)	1.02 (0.88–1.18)	55.4 (0.001)
MI deaths				
$PM_{2.5}$[d]	1.07 (0.82–1.41)	0.98 (0.72–1.33)	0.96 (0.70–1.32)	28.7 (0.13)
$PM_{2.5}$ absorbance[d]	1.11 (0.82–1.50)	0.99 (0.77–1.28)	0.97 (0.75–1.25)	19.9 (0.22)
PM_{10}[d]	0.97 (0.84–1.12)	0.95 (0.82–1.10)	0.94 (0.81–1.09)	0 (0.66)
PM coarse[d]	0.95 (0.76–1.19)	0.89 (0.73–1.09)	0.88 (0.71–1.10)	35.9 (0.07)
NO_2	1.03 (0.92–1.14)	0.98 (0.89–1.08)	0.98 (0.88–1.09)	26.9 (0.12)
NO_x	1.03 (0.94–1.12)	0.99 (0.91–1.08)	0.99 (0.90–1.07)	19.0 (0.21)
Traffic intensity on the nearest road[e]	1.04 (1.00–1.08)	1.03 (0.99–1.07)	1.03 (0.99–1.07)	0 (0.71)
Traffic intensity on major roads 100-m buffer[f]	1.08 (0.94–1.25)	1.05 (0.90–1.22)	1.04 (0.89–1.22)	36.9 (0.05)
Cerebrovascular disease deaths				
$PM_{2.5}$[d]	1.34 (0.94–1.91)	1.28 (0.91–1.80)	1.21 (0.87–1.69)	38.0 (0.05)
$PM_{2.5}$ absorbance[d]	1.23 (0.91–1.66)	1.12 (0.86–1.47)	1.01 (0.82–1.24)	7.0 (0.37)
PM_{10}[d]	1.33 (0.99–1.79)	1.28 (0.94–1.74)	1.22 (0.91–1.63)	49.4 (0.009)
PM coarse[d]	1.29 (0.96–1.72)	1.22 (0.93–1.62)	1.17 (0.90–1.52)	46.4 (0.02)
NO_2	1.09 (0.96–1.23)	1.05 (0.94–1.18)	1.01 (0.93–1.10)	16.7 (0.24)
NO_x	1.07 (0.95–1.19)	1.04 (0.93–1.16)	1.00 (0.93–1.08)	14.4 (0.27)
Traffic intensity on the nearest road[e]	1.03 (0.99–1.08)	1.03 (0.99–1.07)	1.02 (0.98–1.07)	0 (0.60)
Traffic intensity on major roads 100-m buffer[f]	1.07 (0.94–1.21)	1.05 (0.92–1.19)	1.04 (0.90–1.19)	26.0 (0.14)

[a]HRs are presented for the following increments: 10 μg/m^3 for NO_2, 20 μg/m^3 for NO_x, 5 μg/m^3 for $PM_{2.5}$, 10^{-5} m^{-1} for $PM_{2.5}$ absorbance, 10 μg/m^3 for PM_{10}, 5 μg/m^3 for PM_{coarse}, 5000 motor vehicles per day for the traffic intensity on the nearest road, and 4,000,000 motor vehicles*m/day for the total traffic load on all major roads within a 100-m buffer.

[b]Model 1: adjusted for sex and calendar time: Model 2: as in Model 1, also adjusting for smoking status, smoking intensity, smoking duration, environmental tobacco smoke, fruit intake, vegetable intake, alcohol consumption, body mass index, educational level, occupational class, employment status, and marital status: Model 3: as in Model 2, also adjusting for area-level socioeconomic status.

[c]I^2 and Cochran's test for heterogeneity for Model 3.

[d]PM not available for EPIC-Umeå, EPIC-Varese, and EPIC-San Sebastian. For E3N and SAPALDIA, PM was available for part of the cohort (Table 1).

[e]Not available for EPIC-Varese and EPIC-San Sebastian.

[f]Not available for EPIC-Varese.

The diversity of diseases included in the broad category of CVDs makes it unlikely that the risk associated with air pollution exposure is the same for all diseases.[5] Studies have therefore evaluated specific cardiovascular causes, with focus on ischemic heart disease, and cerebrovascular disease mortality. Most studies investigating ischemic heart disease mortality found increased risks for $PM_{2.5}$ or PM_{10} exposure,[14,15,32–34] and for NO_2 or NO_x exposure.[2,8,29–31] A few studies, however, found no association between air pollution exposure and ischemic heart disease mortality.[1,11] Fewer

studies have investigated cerebrovascular disease mortality. In the Dutch cohort study and in the Women's Health Initiative Study, a strong association was found between cerebrovascular disease mortality and black smoke and $PM_{2.5}$, respectively.[1,15] In contrast, no such association was found in the American Cancer Society study,[14] a Norwegian cohort study,[2] a recent Danish cohort study,[8] and recent large Canadian population-based studies.[30,34]

In previous cohort studies assessing effects of long-term exposure to air pollution on mortality, it has generally been found that effect estimates were larger for cardiovascular mortality than for all-cause or natural-cause mortality,[23] with a few exceptions.[6,9,35,36] However, the heterogeneity in effect estimates across studies was much larger for CVD mortality than for natural-cause mortality.[23] In our study, we found the opposite; in the same cohorts, using the same exposure and statistical methods, an association of natural-cause mortality with $PM_{2.5}$ (HR = 1.07 [95% CI = 1.02–1.13] per 5 μg/m^3) was found.[37] We do not have a clear explanation for the lack of an association with cardiovascular mortality within the ESCAPE project, whereas we did find an association with all natural-cause mortality. This discrepancy could be due to the fact that cardiovascular causes of death contributed no more than 30% of all deaths in 15 of the 22 cohorts. In the Harvard Six Cities and in the American Cancer Society studies, participants were born on average several decades earlier than in most of our cohorts, and the relative contribution of cardiovascular mortality to total mortality in these two cohorts was much larger.

We speculate that changes in cardiovascular risk profiles over time (eg, reduced smoking and increased medication and medical treatment)[38] have altered the relation between air pollution and CVD mortality. There is some support for this speculation in a recent German study showing stronger association for early-period versus later-period exposures.[31] These changes over time result in a lower fatality rate for cardiovascular events, suggesting that risk factors may increasingly have a different association with incident cardiovascular events and cardiovascular mortality.[38] We found an association between PM_{10} and incident (fatal plus not-fatal) coronary events (HR = 1.12 [95% CI = 1.01–1.25] for an increase of 10 μg/m^3 in PM_{10}) in a subset of 11 cohorts within the ESCAPE

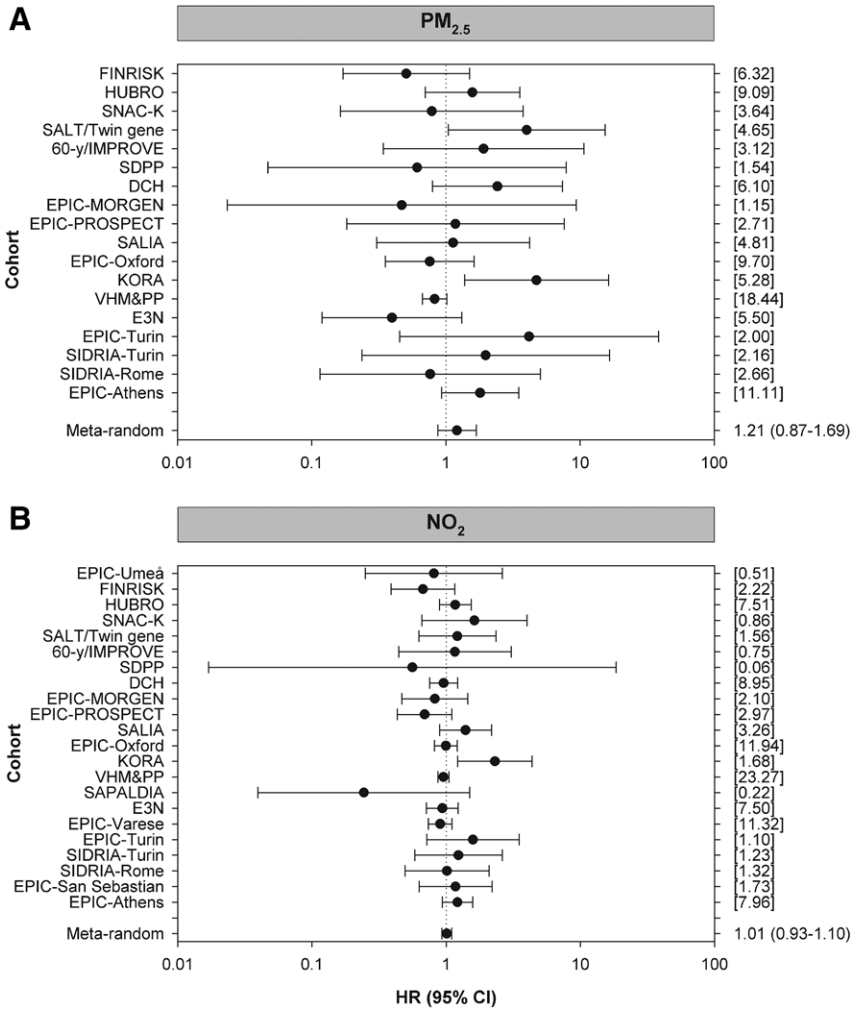

FIGURE. Adjusted association of cerebrovascular disease mortality with exposure to (A) $PM_{2.5}$ and (B) NO_2: Results from cohort-specific analyses and from random-effects meta-analyses. Numbers between brackets represent the weight of each cohort in the meta-analysis. HRs are presented per 5 μg/m^3 for $PM_{2.5}$ and per 10 μg/m^3 for NO_2. PM not available for EPIC-Umeå, EPIC-Varese, and EPIC-San Sebastian. For E3N and SAPALDIA, PM was available for part of the cohort (Table 1).

project, using the same exposure and statistical methods.[39] Furthermore, in the same subset of 11 cohorts, $PM_{2.5}$ was associated with stroke incidence (HR = 1.19 [95% CI = 0.88–1.62]) (M. Stafoggia, unpublished data, 2014). For the incidence of both coronary events and stroke, the number of cases was approximately six times higher than the number of ischemic heart disease and CVD deaths, respectively, in our analysis. Incident events may be less affected by medication use than cardiovascular deaths, which are likely often preceded by nonfatal events. This suggests that a large number of incident coronary and stroke events do not lead to cardiovascular death soon after the event. Compared with our natural-cause mortality analysis, we observed more substantial heterogeneity of effect estimates across cohorts, especially for the more specific causes.

Another limitation is that we have to rely on data from mortality registries. There may be coding differences in death certificates among countries and among ESCAPE study areas. Such differences might have contributed to the heterogeneous results among ESCAPE cohorts. Heterogeneity in effect estimates due to coding differences might also have affected the overall pooled analyses, possibly leading to the lack of an association with cardiovascular mortality. We did observe increased effect estimates in models adjusted only for age and sex; these estimates were reduced after adjustment for confounders. It is unlikely that we over-adjusted our models, because our confounder models were similar to previous studies and because smoking (a well-established risk factor) was mainly responsible for the drop in effect estimates. We further found no evidence for CVD mortality associations in never-smokers.

CIs were small for overall CVD mortality and wider for specific causes. The increased HRs for cerebrovascular disease mortality could be a chance finding among the many associations studied. However, the consistency across models and the coherence with the stroke incidence analysis support these associations.

One source of variability of effect estimates among previous studies is likely related to varying degrees of exposure misclassification. A strength of ESCAPE is that air pollution exposure assessment within the ESCAPE study areas was conducted in a standardized way.

A limitation of our study is that the land-use regression models used for exposure assessment were based on air pollution measurements in the period 2008–2011, whereas the cohort studies included in ESCAPE started in the past (1985–2007, with most studies starting in the mid-1990s). Analyses using exposures back-extrapolated to the recruitment date showed similar HRs. Four recent studies in The Netherlands,[40] Rome,[41] United Kingdom,[42] and Vancouver[43] have shown that, for periods up to 10 years and longer, spatial air pollution contrasts often remained the same, even with a decrease in concentrations over time. Thus, land-use regression models based on current air pollution data may be valid predictors of historic spatial contrasts. Measurement error is an unlikely explanation of the lack of associations, because we did observe an association with natural-cause mortality using the same exposure variables and the same set of cohorts.

In conclusion, most HRs for the association of air pollutants with mortality from overall cardiovascular and from specific CVDs were approximately 1.0 in 22 European cohort studies, with the exception of particulate mass and cerebrovascular disease mortality for which there was suggestive evidence for an association.

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REFERENCES

1. Beelen R, Hoek G, Houthuijs D, et al. The joint association of air pollution and noise from road traffic with cardiovascular mortality in a cohort study. *Occup Environ Med*. 2009;66:243–250.
2. Nafstad P, Håheim LL, Wisløff T, et al. Urban air pollution and mortality in a cohort of Norwegian men. *Environ Health Perspect*. 2004;112:610–615.
3. Pope CA 3rd, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA*. 2002;287:1132–1141.
4. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med*. 2006;173:667–672.
5. Brook RD, Rajagopalan S, Pope CA, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the american heart association. *Circulation*. 2010;121:2331–2378.
6. Beelen R, Hoek G, van den Brandt PA, et al. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort. *Environ Health Perspect*. 2008;116:196–202.
7. Filleul L, Rondeau V, Vandentorren S, et al. Twenty five year mortality and air pollution: results from the French PAARC survey. *Occup Environ Med*. 2005;62:453–460.

8. Raaschou-Nielsen O, Andersen ZJ, Jensen SS, et al. Traffic air pollution and mortality from cardiovascular disease and all causes: a Danish cohort study. *Environ Health*. 2012;11:60.
9. Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG, Anderson HR. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *Am J Respir Crit Care Med*. 2013;187:1226–1233.
10. Cesaroni G, Badaloni C, Gariazzo C, et al. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect*. 2013;121:324–331.
11. Puett RC, Hart JE, Suh H, Mittleman M, Laden F. Particulate matter exposures, mortality, and cardiovascular disease in the health professionals follow-up study. *Environ Health Perspect*. 2011;119:1130–1135.
12. Ueda K, Nagasawa SY, Nitta H, Miura K, Ueshima H; NIPPON DATA80 Research Group. Exposure to particulate matter and long-term risk of cardiovascular mortality in Japan: NIPPON DATA80. *J Atheroscler Thromb*. 2012;19:246–254.
13. Ostro B, Reynolds P, Goldberg D, et al. Assessing long-term exposure in the California teachers study. *Environ Health Perspect*. 2011;119: A242–A243.
14. Pope CA 3rd, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation*. 2004;109:71–77.
15. Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med*. 2007;356:447–458.
16. Puett RC, Hart JE, Yanosky JD, et al. Chronic fine and coarse particulate exposure, mortality, and coronary heart disease in the Nurses' Health Study. *Environ Health Perspect*. 2009;117:1697–1701.
17. Raaschou-Nielsen O, Andersen ZJ, Beelen R, et al. Air pollution and lung cancer incidence in 17 European cohorts within the ESCAPE study. *Lancet Oncol*. 2013;14:813–822.
18. Eeftens M, Beelen R, de Hoogh K, et al. Development of Land Use Regression models for PM(2.5), PM(2.5) absorbance, PM(10) and PM(coarse) in 20 European study areas; results of the ESCAPE project. *Environ Sci Technol*. 2012;46:11195–11205.
19. Beelen R, Hoek G, Vienneau D, et al. Development of NO_2 and NO_x land use regression models for estimating air pollution exposure in 36 study areas in Europe—the ESCAPE project. *Atmos Environ*. 2013;72: 10–23.
20. Eeftens M, Tsai M, Ampe C, et al. Spatial variation of PM2.5, PM10, PM2.5 absorbance and PM coarse concentrations between and within 20 European study areas and the relationship with NO2—results of the ESCAPE project. *Atmos Environ*. 2012;62:303–317.
21. Cyrys J, Eeftens M, Heinrich J, et al. Variation of NO_2 and NO_x concentrations between and within 36 European study areas: results from the ESCAPE study. *Atmos Environ*. 2012;62:374–390.
22. Thiébaut AC, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med*. 2004;23: 3803–3820.
23. Hoek G, Krishnan MK, Beelen R, Peters A, Ostro B, Kaufman J. Long-term air pollution exposure and cardio- respiratory mortality. *Environ Health*. 2013;12:43.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
25. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
26. Gehring U, Heinrich J, Krämer U, et al. Long-term exposure to ambient air pollution and cardiopulmonary mortality in women. *Epidemiology*. 2006;17:545–551.
27. Smith KR, Jerrett M, Anderson HR, et al. Public health benefits of strategies to reduce greenhouse-gas emissions: health implications of short-lived greenhouse pollutants. *Lancet*. 2009;374:2091–2103.
28. Gan WQ, Koehoorn M, Davies HW, Demers PA, Tamburic L, Brauer M. Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. *Environ Health Perspect*. 2011;119:501–507.
29. Yorifuji T, Kashima S, Tsuda T, et al. Long-term exposure to traffic-related air pollution and mortality in Shizuoka, Japan. *Occup Environ Med*. 2010;67:111–117.
30. Chen H, Goldberg MS, Burnett RT, Jerrett M, Wheeler AJ, Villeneuve PJ. Long-term exposure to traffic-related air pollution and cardiovascular mortality. *Epidemiology*. 2013;24:35–43.
31. Heinrich J, Thiering E, Rzehak P, et al. Long-term exposure to NO_2 and PM_{10} and all-cause and cause-specific mortality in a prospective cohort of women. *Occup Environ Med*. 2013;70:179–186.
32. Puett RC, Schwartz J, Hart JE, et al. Chronic particulate exposure, mortality, and coronary heart disease in the nurses' health study. *Am J Epidemiol*. 2008;168:1161–1168.
33. Lipsett MJ, Ostro BD, Reynolds P, et al. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. *Am J Respir Crit Care Med*. 2011;184:828–835.
34. Crouse DL, Peters PA, van Donkelaar A, et al. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Environ Health Perspect*. 2012;120:708–714.
35. Hales S, Blakely T, Woodward A. Air pollution and mortality in New Zealand: cohort study. *J Epidemiol Community Health*. 2012;66:468–473.
36. Elliott P, Shaddick G, Wakefield JC, de Hoogh C, Briggs DJ. Long-term associations of outdoor air pollution with mortality in Great Britain. *Thorax*. 2007;62:1088–1094.
37. Beelen R, Raaschou-Nielsen O, Stafoggia M, et al. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet*. 2013. DOI: 10.1016/S0140-6736(13)62158-3.
38. Nichols M, Townsend N, Scarborough P, Rayner M. Trends in age-specific coronary heart disease mortality in the European Union over three decades: 1980–2009. *Eur Heart J*. 2013;34:3017–3027.
39. Cesaroni G, Forastiere F, Stafoggia M, et al. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. *BMJ* 2014, DOI: 10.1136/bmj.f7412.
40. Eeftens M, Beelen R, Fischer P, Brunekreef B, Meliefste K, Hoek G. Stability of measured and modelled spatial contrasts in NO(2) over time. *Occup Environ Med*. 2011;68:765–770.
41. Cesaroni G, Porta D, Badaloni C, et al. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. *Environ Health*. 2012;11:48.
42. Gulliver J, de Hoogh K, Hansell A, Vienneau D. Development and back-extrapolation of NO_2 land use regression models for historic exposure assessment in Great Britain. *Environ Sci Technol*. 2013;47:7804–7811.
43. Wang R, Henderson SB, Sbihi H, Allen RW, Brauer M. Temporal stability of land use regression models for traffic-related air pollution. *Atmos Environ*. 2013;64:312–319.