Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project

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Summary

Background Few studies on long-term exposure to air pollution and mortality have been reported from Europe. Within the multicentre European Study of Cohorts for Air Pollution Effects (ESCAPE), we aimed to investigate the association between natural-cause mortality and long-term exposure to several air pollutants.

Methods We used data from 22 European cohort studies, which created a total study population of 367 251 participants. All cohorts were general population samples, although some were restricted to one sex only. With a strictly standardised protocol, we assessed residential exposure to air pollutants as annual average concentrations of particulate matter (PM) with diameters of less than 2·5 μm ($PM_{2·5}$), less than 10 μm (PM_{10}), and between 10 μm and 2·5 μm (PM_{coarse}), $PM_{2.5}$ absorbance, and annual average concentrations of nitrogen oxides (NO_2 and NO_x), with land use regression models. We also investigated two traffic intensity variables—traffic intensity on the nearest road (vehicles per day) and total traffic load on all major roads within a 100 m buffer. We did cohort-specific statistical analyses using confounder models with increasing adjustment for confounder variables, and Cox proportional hazards models with a common protocol. We obtained pooled effect estimates through a random-effects meta-analysis.

Findings The total study population consisted of 367 251 participants who contributed 5 118 039 person-years at risk (average follow-up 13·9 years), of whom 29 076 died from a natural cause during follow-up. A significantly increased hazard ratio (HR) for $PM_{2·5}$ of 1·07 (95% CI 1·02–1·13) per 5 μg/m³ was recorded. No heterogeneity was noted between individual cohort effect estimates (I^2 p value=0·95). HRs for $PM_{2·5}$ remained significantly raised even when we included only participants exposed to pollutant concentrations lower than the European annual mean limit value of 25 μg/m³ (HR 1·06, 95% CI 1·00–1·12) or below 20 μg/m³ (1·07, 1·01–1·13).

Interpretation Long-term exposure to fine particulate air pollution was associated with natural-cause mortality, even within concentration ranges well below the present European annual mean limit value.

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Introduction

Studies have shown the effects of long-term exposure to air pollution on mortality,[1,2] with most, especially those in the USA, reporting on the mass concentration of particulate matter (PM) smaller than 10 μm (PM_{10}) or 2·5 μm ($PM_{2·5}$) in diameter. Few European studies have investigated $PM_{2·5}$, partly because of the low availability of routine monitoring data. However, some European studies have shown associations between mortality and nitrogen dioxide (NO_2) or nitrogen oxides (NO_x).[3–8]

In urban areas, NO_2, NO_x, and $PM_{2·5}$ absorbance (a marker for black carbon or soot) have larger spatial concentration contrasts than PM because they are more closely related to motorised traffic. Interest in the health effects of coarse particles (2·5–10 μm in diameter) has also increased.[9] However, the comparability of previous studies is limited by the different exposure methods used.[10]

In the framework of the multicentre European Study of Cohorts for Air Pollution Effects (ESCAPE), we added standardised exposure assessment for PM, NO_2, and NO_x to health data from 22 ongoing cohort studies across Europe. The objective of ESCAPE was to investigate the association between long-term exposure to air pollution and mortality. In this Article, we report associations for natural-cause mortality. Cause-specific results will be published separately.

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Methods

Procedures

We analysed the association between natural-cause mortality and air pollution in each cohort separately with a common statistical protocol and STATA script, which was explained in a training workshop for all local analysts. We sent cohort-specific results to the co-ordinating institute (Institute for Risk Assessment Sciences, Utrecht University, Netherlands) for central assessment (see appendix pp 1–9 for more details). We combined cohort-specific effect estimates by random-effects meta-analysis. Pooling of the cohort data was not possible because of data transfer and privacy issues.

Study populations

We selected 22 cohorts from 13 countries across Europe (table 1 and appendix pp 1–9). All cohorts were samples from the general population. The study areas of most cohorts were a large city with surrounding smaller rural communities. Some cohorts included large regions of the country, such as EPIC-MORGEN in the Netherlands, EPIC-Oxford (which covered much of the UK), the VHM&PP cohort in Austria, and SAPALDIA in three cities in Switzerland. All included cohort studies were approved by the institutional medical ethics committees and undertaken in accordance with the Declaration of Helsinki. Each cohort study followed the rules for ethics and data protection set up in the country in which they were based.

Mortality outcome definition

In all cohorts, follow-up was based on linkage to mortality registries. Natural-cause mortality was defined on the basis of the underlying cause of death recorded on death certificates as International Classification of Diseases (ICD)-9 codes 001–779 and ICD-10 codes A00–R99. We excluded causes of death not conceivably related to air pollution exposure, such as injury, accidents, and suicide, which account for roughly 5% of total deaths in general.

	Total n*	Deaths from natural mortality	Mean age at baseline, years (SD)	Baseline period	Total follow-up time in person-years (mean per observation)	Study area description
EPIC-Umeå, Sweden	22 136	912	46·0 (10·2)	1992–96	281 711 (12·7)	City of Umeå and surrounding rural areas
FINRISK, Finland	10 224	602	47·9 (13·2)	1992, 1997, 2002, 2007	108 434 (10·6)	Greater Helsinki area and Turku city and its rural surroundings
HUBRO, Norway	18 102	1182	48·3 (15·2)	2000–01	173 798 (9·6)	City of Oslo
SNAC-K, Sweden	2401	395	70·3 (8·1)	2001–04	15 568 (6·5)	City of Stockholm
SALT/Twin gene, Sweden	5473	581	58·0 (9·9)	1998–2002	47 767 (8·7)	Stockholm County
60-y/IMPROVE, Sweden	3612	303	60·4 (0·1)	1997–99	40 612 (11·2)	Stockholm County
SDPP, Sweden	7408	248	47·1 (5·0)	1992–98	102 831 (13·9)	Stockholm County
DCH, Denmark	35 458	3770	56·7 (4·4)	1993–97	469 571 (13·2)	City of Copenhagen and surrounding areas
EPIC-MORGEN, Netherlands	16 446	795	43·9 (10·9)	1993–97	217 722 (13·2)	Cities of Amsterdam, Maastricht, and Doetinchem, and surrounding rural areas
EPIC-PROSPECT, Netherlands	15 670	1269	57·7 (6·0)	1993–97	202 809 (12·9)	City of Utrecht and surrounding rural areas
SALIA, Germany	4352	618	54·5 (0·6)	1985–87, 1990–94	81 093 (18·6)	Areas in the cities of Dortmund, Duisburg, Essen, Gelsenkirchen, and Herne situated in the Ruhr area, and the adjacent towns of Borken and Dülmen
EPIC-Oxford, UK	38 941	2185	45·8 (13·7)	1993–2001	491 542 (12·6)	Urban and rural areas in a buffer of 400 km around London/ Oxford area
KORA, Germany	8399	673	49·5 (13·8)	1994–95, 1999–2001	88 592 (10·5)	City of Augsburg and two adjacent rural counties
VHM&PP, Austria	117 824	13 081	41·9 (14·9)	1985–2005	2 039 328 (17·3)	State of Vorarlberg, excluding high mountain areas (>600 m above sea level) and areas within 300 m of the state border
SAPALDIA, Switzerland†	3473 *(1250)*	201 *(65)*	41·1 (11·8)	1991	55 935 (16·1) *(20 294 [16·2])*	Cities of Geneva, Lugano, and Basel
E3N, France†	14 313 *(10 915)*	661 *(516)*	53·0 (6·7)	1993–96	192 761 (13·5) *(147 021 [13·5])*	Cities of Paris, Grenoble, Lyon, and Marseille and surrounding rural areas
EPIC-Varese, Italy	9871	323	51·7 (8·3)	1993–97	111 415 (11·3)	City of Varese and surrounding rural areas
EPIC-Turin, Italy	7261	302	50·4 (7·5)	1993–98	97 549 (13·4)	City of Turin
SIDRIA-Turin, Italy	5054	129	44·2 (6·2)	1999	55 667 (11·0)	City of Turin
SIDRIA-Rome, Italy	9177	239	44·3 (6·0)	1999	102 856 (11·2)	City of Rome
EPIC-San Sebastian, Spain	7464	352	49·4 (7·7)	1992–95	93 626 (12·5)	City of San Sebastian and surrounding area in Basque Country
EPIC-Athens, Greece	4192	255	49·4 (11·7)	1994–99	46 852 (11·2)	Greater Athens area

The order of studies in the table follows a north to south gradient. *Number of observations without missing value in any confounder variable of model 3 (main model). †Italicised numbers in brackets in these rows represent observations for which particulate matter data were available.

Table 1: **Description of the included cohort studies**

Exposure assessment

We estimated air pollutant concentrations at the baseline residential addresses of study participants with land use regression models and a standardised procedure, which is described elsewhere.[11,12] Briefly, air pollution was monitored between October, 2008, and May, 2011 in all study areas to obtain annual average concentrations of NO_2, NO_x, $PM_{2.5}$, and PM_{10}, and $PM_{2.5}$ absorbance.[13,14] The concentration of PM_{coarse} was calculated as the concentration of PM_{10} minus that of $PM_{2.5}$. PM measurements were restricted to 19 of the 22 study areas for budgetary reasons (appendix pp 10–12). Land use regression models were developed to explain the spatial variation of measured annual average air pollution concentrations within each area. Depending on cohort, the models explained 57–89% of the variability in the annual average concentrations of $PM_{2.5}$, 67–90% of that for PM_{10}, 44–81% of that for PM_{coarse}, 56–97% of that for $PM_{2.5}$ absorbance, 58–90% of that for NO_2, and 49–91% of that for NO_x (appendix pp 10–12). We then used the results of the land use regression models to estimate ambient air pollution concentration at the participants' baseline addresses. In addition to pollutant concentrations, we also used traffic intensity on the nearest road (vehicles per day) and total traffic load (intensity multiplied by length) on all major roads within a 100 m buffer as indicators of exposure to pollution. We analysed these traffic variables separately to identify the effects of living near busy roads for comparison with previous studies.[3] Appendix pp 10–12 shows a detailed description of exposure assessment procedures, including back-extrapolation of concentrations to the baseline year and fit of land use regression models.

Statistical analyses

Cohort-specific analyses

We used Cox proportional hazards models for the cohort-specific analyses. We used age as the timescale because of evidence of better adjustment for potential confounding by age.[15] Censoring was done at the time of death for non-natural causes, emigration, loss to follow-up for other reasons, or at end of follow-up, whichever came first. We analysed air pollution exposure as a linear variable. Potential confounders were available from questionnaires at baseline. We specified three confounder models a priori, with an increasing amount of adjustment from model 1 to model 3. These models were decided on the basis of previous cohort studies of air pollution and mortality and the availability of data for most of the cohorts. Model 1 included only age (time axis), sex, and

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	% women	% never smokers	Mean number of cigarettes per day (SD)	Mean years of smoking, mean (SD)	Mean BMI, kg/m² (SD)	Fruit intake*	Alcohol intake†	% married or living with partner	% low educational level	% employed or self-employed
EPIC-Umeå, Sweden	52·2%	62·0%	2·4 (5·6)	8·8 (13·0)	25·0 (4·0)	163·0 (132·6)	3·2 (4·0)	82·3%	28·0%	85·4%
FINRISK, Finland	53·8%	45·4%	3·8 (7·8)	8·6 (12·2)	26·4 (4·6)	66·3%	0·9 (1·3)	70·1%	31·0%	69·2%
HUBRO, Norway	56·1%	45·9%	6·8 (8·4)	11·6 (14·4)	25·7 (4·1)	39·9%	50·8%	49·8%	17·6%	73·4%
SNAC-K, Sweden	60·0%	44·3%	7·1 (9·5)	9·8 (15·2)	26·0 (4·1)	NA	21·8%	54·2%	21·2%	28·6%
SALT/Twin gene, Sweden	55·7%	38·7%	8·5 (9·7)	16·7 (17·3)	28·6 (4·1)	NA	NA	68·0%	21·5%	NA
60-y/IMPROVE, Sweden	52·5%	41·0%	8·0 (9·1)	15·2 (16·4)	26·8 (4·2)	64·2%	8·9 (9·7)	71·6%	27·5%	51·4%
SDPP, Sweden	61·7%	37·4%	8·5 (8·8)	12·3 (12·4)	25·6 (4·0)	92·4%	1·3 (1·9)	83·6%	25·5%	91·8%
DCH, Denmark	54·1%	36·3%	6·3 (10·4)	18·7 (17·1)	26·0 (4·1)	183·2 (151·2)	21·7 (22·8)	69·2%	29·6%	80·1%
EPIC-MORGEN, Netherlands	54·4%	35·0%	10·4 (11·1)	14·3 (13·7)	25·2 (4·0)	171·9 (129·2)	12·7 (18·0)	67·7%	11·9%	NA
EPIC-PROSPECT, Netherlands	100%	45·0%	5·7 (7·4)	15·2 (16·5)	25·5 (4·1)	231·6 (139·2)	9·0 (12·4)	76·9%	22·2%	NA
SALIA, Germany	100%	74·5%	2·6 (6·6)	4·4 (10·5)	NA	NA	NA	NA	28·8%	NA
EPIC-Oxford, UK	77·5%	63·3%	5·0 (8·3)	6·7 (11·2)	24·0 (3·9)	259·9 (204·5)	9·1 (11·7)	70·8%	36·5%	72·5%
KORA, Germany	50·8%	43·7%	9·2 (13·3)	12·0 (14·2)	27·2 (4·6)	59·5%	16·3 (22·3)	75·7%	12·6%	58·3%
VHM&PP, Austria	56·1%	69·9%	NA	NA	24·8 (4·3)	NA	NA	68·4%	NA	69·3%
SAPALDIA, Switzerland	52·0%	42·4%	11·5 (14·5)	10·7 (12·4)	23·7 (4·0)	NA	NA	54·3%	15·0%	84·4%
E3N, France	100%	49·3%	NA	NA	22·8 (3·2)	242·0 (164·7)	12·0 (15·1)	NA	5·0%	NA
EPIC-Varese, Italy	86·0%	59·7%	4·0 (6·4)	9·4 (13·3)	25·7 (4·2)	303·8 (172·2)	11·4 (15·7)	86·9%	61·1%	NA
EPIC-Turin, Italy	47·7%	42·6%	7·2 (8·2)	17·6 (16·3)	25·3 (3·8)	318·2 (182·2)	18·1 (20·3)	85·6%	43·6%	NA
SIDRIA-Turin, Italy	51·8%	37·5%	9·3 (10·2)	11·3 (10·6)	NA	NA	NA	95·4%	17·5%	72·2%
SIDRIA-Rome, Italy	52·8%	34·6%	10·1 (10·5)	11·7 (10·4)	NA	NA	NA	100%	44·9%	NA
EPIC-San Sebastian, Spain	53·6%	53·9%	6·9 (10·0)	11·4 (14·3)	27·3 (3·9)	330·2 (258·5)	18·3 (24·0)	87·5%	70·6%	NA
EPIC-Athens, Greece	55·0%	39·5%	1·7 (15·0)	10·8 (13·1)	27·5 (4·5)	402·6 (258·2)	9·2 (14·5)	78·0%	23·6%	66·9%

The order of studies in the table follows a north to south gradient. A detailed description of each cohort is in appendix pp 13–34. BMI=body-mass index. *Mean (SD) grams per day, or percentage of people with daily fruit consumption. For the SDPP cohort, the value is the percentage of people with daily or weekly fruit consumption. †Mean (SD) grams per day, or percentage of people with daily alcohol consumption. For the FINRISK cohort, the value is the number of glasses of alcoholic drink in the past week. For the SDPP cohort, the value is the number of glasses of alcoholic drink per day. For the HUBRO cohort, the value is the percentage of participants with weekly alcohol consumption. NA=not available or available with a large amount of missing data (eg, BMI in SALIA and smoking variables in E3N).

Table 2: **Population characteristics at baseline of the included cohort studies (based on number of observations in main confounder model 3)**

	N*	$PM_{2.5}$, μg/m³, mean (SD)	$PM_{2.5}$ absorbance, 10^{-5} m^{-1}, mean (SD)	PM_{10}, μg/m³, mean (SD)	PM_{coarse}, μg/m³, mean (SD)	NO_2, μg/m³, mean (SD)	NO_x, μg/m³, mean (SD)	Traffic intensity on nearest road, motor vehicles per day, mean (SD)	Traffic intensity on major roads within 100 m buffer, motor vehicles* km/day, mean (SD)
EPIC-Umeå, Sweden	22136	NA	NA	NA	NA	5·2 (2·5)	8·7 (5·7)	845 (1523)	102 (418)
FINRISK, Finland	10224	7·7 (1·1)	0·9 (0·2)	14·0 (3·1)	6·6 (2·3)	15·3 (4·8)	24·2 (8·8)	1663 (4393)	630 (1517)
HUBRO, Norway	18102	8·9 (1·3)	1·2 (0·3)	13·5 (3·1)	4·0 (2·0)	20·9 (8·0)	38·2 (15·4)	2494 (5069)	822 (1844)
SNAC-K, Sweden	2401	7·9 (1·3)	0·8 (0·2)	16·3 (6·0)	8·5 (4·7)	17·3 (4·8)	33·2 (12·3)	3597 (8847)	2260 (3593)
SALT/Twin gene, Sweden	5473	7·3 (1·3)	0·6 (0·2)	15·0 (3·9)	7·3 (3·0)	10·9 (4·2)	18·9 (9·3)	1471 (3400)	576 (1596)
60-y/IMPROVE, Sweden	3612	7·2 (1·3)	0·6 (0·2)	15·0 (3·8)	7·3 (2·9)	10·7 (4·2)	18·6 (9·4)	1459 (3519)	509 (1449)
SDPP, Sweden	7408	6·6 (1·2)	0·5 (0·1)	13·7 (3·2)	6·3 (2·4)	8·4 (1·7)	14·4 (3·2)	857 (1591)	109 (421)
DCH, Denmark	35458	11·3 (0·9)	1·2 (0·2)	17·1 (1·9)	5·7 (1·0)	16·3 (7·0)	26·6 (18·3)	2977 (7207)	1266 (1908)
EPIC-MORGEN, Netherlands	16446	16·9 (0·6)	1·4 (0·2)	25·4 (1·7)	8·6 (1·1)	23·8 (7·0)	36·5 (11·8)	1543 (4092)	920 (1983)
EPIC-PROSPECT, Netherlands	15670	16·8 (0·5)	1·4 (0·2)	25·3 (1·2)	8·5 (0·7)	26·7 (4·6)	39·6 (10·5)	1029 (3458)	686 (1532)
SALIA, Germany	4352	18·0 (1·4)	1·5 (0·4)	27·3 (2·2)	9·8 (1·7)	30·0 (7·8)	50·7 (20·4)	2110 (5005)	846 (1981)
EPIC-Oxford, UK	38941	9·8 (1·1)	1·1 (0·3)	16·1 (2·0)	6·4 (0·9)	24·4 (7·9)	40·8 (15·6)	1386 (4324)	374 (1289)
KORA, Germany	8399	13·6 (0·9)	1·7 (0·2)	20·3 (2·4)	6·2 (1·1)	18·7 (3·9)	32·6 (7·4)	1645 (3607)	450 (1133)
VHM&PP, Austria	117824	13·6 (1·2)	1·7 (0·2)	20·6 (2·4)	6·7 (0·9)	19·9 (5·5)	40·0 (9·6)	1694 (3616)	297 (1000)
SAPALDIA, Switzerland	3473 (1250)	17·3 (1·6)	2·0 (0·4)	24·0 (2·3)	6·8 (1·2)	28·8 (6·1)	48·7 (13·6)	3478 (5438)	1099 (2095)
E3N, France	14313 (10915)	15·0 (1·9)	1·8 (0·7)	25·3 (4·2)	8·5 (2·6)	30·5 (12·7)	55·6 (28·2)	6529 (8271)	1228 (2758)
EPIC-Varese, Italy	9871	NA	NA	NA	NA	43·7 (17·3)	86·6 (41·9)	NA	NA
EPIC-Turin, Italy	7261	30·1 (1·7)	3·1 (0·4)	46·4 (4·2)	16·4 (2·7)	53·1 (10·8)	96·1 (21·0)	3905 (9195)	466 (914)
SIDRIA-Turin, Italy	5054	31·0 (1·7)	3·2 (0·4)	48·1 (4·1)	17·0 (2·5)	59·8 (10·5)	107·3 (24·1)	4271 (10184)	805 (1372)
SIDRIA-Rome, Italy	9177	19·4 (1·8)	2·7 (0·5)	36·5 (5·0)	16·7 (3·4)	39·1 (9·1)	82·1 (23·9)	2965 (6758)	1414 (2847)
EPIC-San Sebastian, Spain	7464	NA	NA	NA	NA	23·8 (6·6)	47·1 (12·5)	NA	673 (2614)
EPIC-Athens, Greece	4192	20·4 (2·6)	2·3 (0·5)	45·2 (13·7)	20·7 (2·6)	37·9 (13·7)	75·2 (40·8)	9034 (12466)	11000 (15000)

NA=not available. *Number of observations without missing values in any confounder variable of model 3 (main model). Numbers in brackets in this column represent observations for which particulate matter data were available.

Table 3: **Descriptions of the different pollutants and two traffic intensity indicators at participant addresses in each cohort**

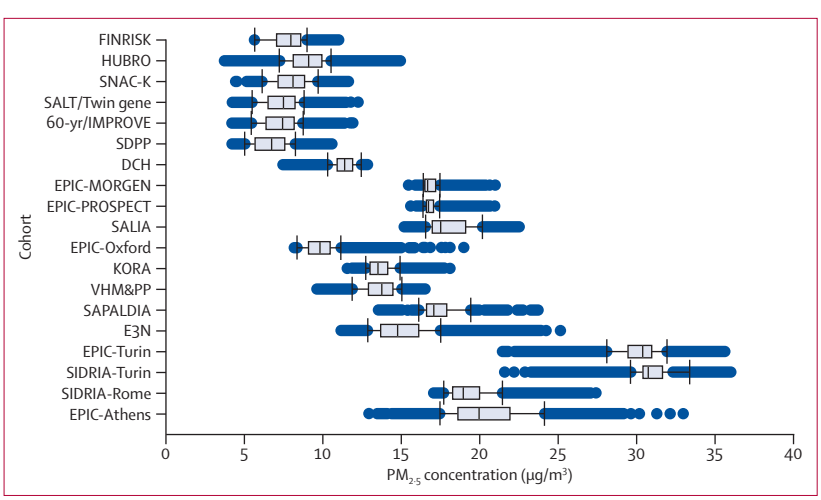

Figure 1: **Description of exposure to $PM_{2.5}$ concentration (μg/m³) at participant addresses in each cohort**
PM concentrations not available for the EPIC-Umeå, EPIC-Varese, or EPIC-San Sebastian cohorts. The boundary of the box closest to 0 indicates the 25th percentile, the line within the box marks the median, and the boundary of the box furthest from 0 indicates the 75th percentile. Whiskers (error bars) above and below the box indicate the 90th and 10th percentiles. The blue circles are individual points between the minimum and 10th percentile and between the 90th percentile and the maximum. PM=particulate matter.

calendar time (year[s] of enrolment). Model 2 added individual level variables: smoking status (never, former, or current), smoking intensity, smoking duration, environmental tobacco smoke, intake of fruit and vegetables, alcohol consumption (linear and squared term), body-mass index (BMI; linear and squared term), educational level (low, medium, or high), occupational class (white or blue collar classification), employment status, and marital status. Model 3 added area-level socio-economic status variables (mostly mean income of the neighbourhood or municipality).

We chose model 3 as the main confounder model. Only participants with complete information for this model's variables were included in the main analyses.

Threshold analyses were done by consecutively including participants who had exposure estimates below prespecified thresholds in the analyses (eg, starting at 25 μg/m³ [the European annual mean limit value], 20 μg/m³, 15 μg/m³, and 10 μg/m³ for $PM_{2.5}$). Concentrations based on the ESCAPE measurement period were used for these threshold analyses. We studied the shape of the association between each pollutant and mortality within each cohort by inputting the exposure term as a natural cubic spline with three

equally spaced inner knots, and by comparing the model fit of the linear and the spline models through a likelihood-ratio test.

To disentangle the effects of different pollutants, we included two pollutants simultaneously in an analysis. We did these two-pollutant models for $PM_{2.5}$, PM_{coarse}, and NO_2, and limited them to cohort study areas for which the estimated correlation between two pollutants at the participant addresses was less than 0·7.

In sensitivity analyses, we added prevalent hypertension, physical activity, and two additional classical cardiovascular risk factors—prevalent diabetes and cholesterol concentration—to model 3. We used extended confounder models in sensitivity analyses because some potential effects of air pollution might be mediated by these factors.

We used stratified analyses to investigate effect modification by prespecified variables: age during follow-up (<60, 60–75, or ≥75 years), sex, smoking status, educational level, fruit intake (<150, 150–300, or ≥300 g per day), and BMI (<25, 25–30, or ≥30 kg/m²).

We tested whether back-extrapolation of the concentrations to the baseline year had any effect on the results. We did sensitivity analyses restricted to participants who did not move during follow-up. We used random effects of the spatial area units in each cohort to check for spatial clustering of residuals of the models.

All cohort-specific analyses were done in STATA versions 10–12, except for models with random effects, for which we used R software, version 2.11–2.15.

Meta-analysis

We did meta-analyses of cohort-specific effect estimates with the DerSimonian-Laird method with random effects.[16] We calculated hazard ratios (HRs) and 95% CIs for fixed increments that were chosen to cover the range in concentrations within the different cohorts and to keep increments broadly comparable between pollutants. We analysed the two traffic indicator variables in combination with background NO_2 concentration.

We quantified heterogeneity between cohorts by the I^2 statistic and tested it with the χ^2 test from Cochran's Q statistic.[17]

We tested effect modification with a meta-analysis of the pooled estimates from the different strata and by computing the χ^2 test of heterogeneity. We investigated whether effect estimates differed for cohorts for which the amount of variance explained by the land use regression model cross-validation was smaller or larger than 60% (since 60% was assumed to be an acceptable amount of explained variance, and the median explained variance by cross-validation was 62%).

All tests were two-sided and p values less than 0·05 were judged to be significant. We used STATA version 12.1 for all meta-analyses.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The total study population consisted of 367 251 participants contributing 5 118 039 person-years at risk (average follow-up 13·9 years [range 6·5–18·6 years]), of whom 29 076 died from natural causes during follow-up (table 1). Cohorts were mainly recruited in the 1990s, and differed in the number of participants, the mean baseline age, availability of confounders, and percentage

	Number of cohorts	Model 1*	Model 2*	Model 3*	p value for model 3	I^2 (p value)†
$PM_{2.5}$	19‡	1·18 (1·08–1·30)	1·09 (1·03–1·14)	1·07 (1·02–1·13)	0·02	0 (0·95)
$PM_{2.5}$ absorbance	19‡	1·11 (1·04–1·18)	1·04 (0·99–1·09)	1·02 (0·97–1·07)	0·38	0 (0·99)
PM_{10}	19‡	1·12 (1·03–1·21)	1·05 (1·01–1·10)	1·04 (1·00–1·09)	0·08	0 (0·61)
PM_{coarse}	19‡	1·14 (1·03–1·26)	1·05 (0·99–1·12)	1·04 (0·98–1·10)	0·22	32·3 (0·09)
NO_2	22	1·06 (1·02–1·10)	1·02 (0·99–1·04)	1·01 (0·99–1·03)	0·18	0·7 (0·45)
NO_x	22	1·06 (1·03–1·09)	1·03 (1·00–1·05)	1·02 (1·00–1·04)	0·08	22·1 (0·17)
Traffic intensity on the nearest road	20§	1·02 (1·00–1·03)	1·01 (0·99–1·02)	1·01 (1·00–1·03)	0·19	20·4 (0·20)
Traffic intensity on major roads within 100 m buffer	21‖	1·03 (1·00–1·07)	1·02 (0·98–1·05)	1·01 (0·98–1·05)	0·49	28·4 (0·11)

Data are HR (95% CI), unless indicated otherwise. HRs are presented for the following increments: 5 μg/m³ for $PM_{2.5}$, 10^{-5} m^{-1} for $PM_{2.5}$ absorbance, 10 μg/m³ for PM_{10}, 5 μg/m³ for PM_{coarse}, 10 μg/m³ for NO_2, 20 μg/m³ for NO_x, 5000 motor vehicles per day for the traffic intensity on the nearest road, and 4 000 000 motor vehicles*m per day for the total traffic load on all major roads within a 100 m buffer. Only observations with complete information for model 3 variables were included in the analyses. The number of observations in particulate matter and NO_2 or NO_x analyses were the same for the different confounder models: 322 159 and 367 251, respectively. HR=hazard ratio. *Model 1 was adjusted for sex and calendar time; model 2 was adjusted as in model 1, but also adjusted for smoking status, smoking intensity, smoking duration, environmental tobacco smoke, fruit intake, vegetables intake, alcohol consumption, body-mass index (BMI), educational level, occupational class, employment status, and marital status; and model 3 was adjusted as in model 2 but also adjusted for area-level socioeconomic status. †I^2 and Cochran's test for heterogeneity for model 3 of effect estimates between cohorts. ‡Particulate matter not available for EPIC-Umeå, EPIC-Varese, and EPIC-San Sebastian. For E3N and SAPALDIA, particulate matter was available for part of the cohort (see table 3). §Not available for EPIC-Varese and EPIC-San Sebastian. ‖Not available for EPIC-Varese.

Table 4: **Results of random-effects meta-analyses for the association between natural cause mortality and exposure to air pollution and traffic intensity indicators (using main confounder models 1, 2, and 3)**

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See **Online** for appendix

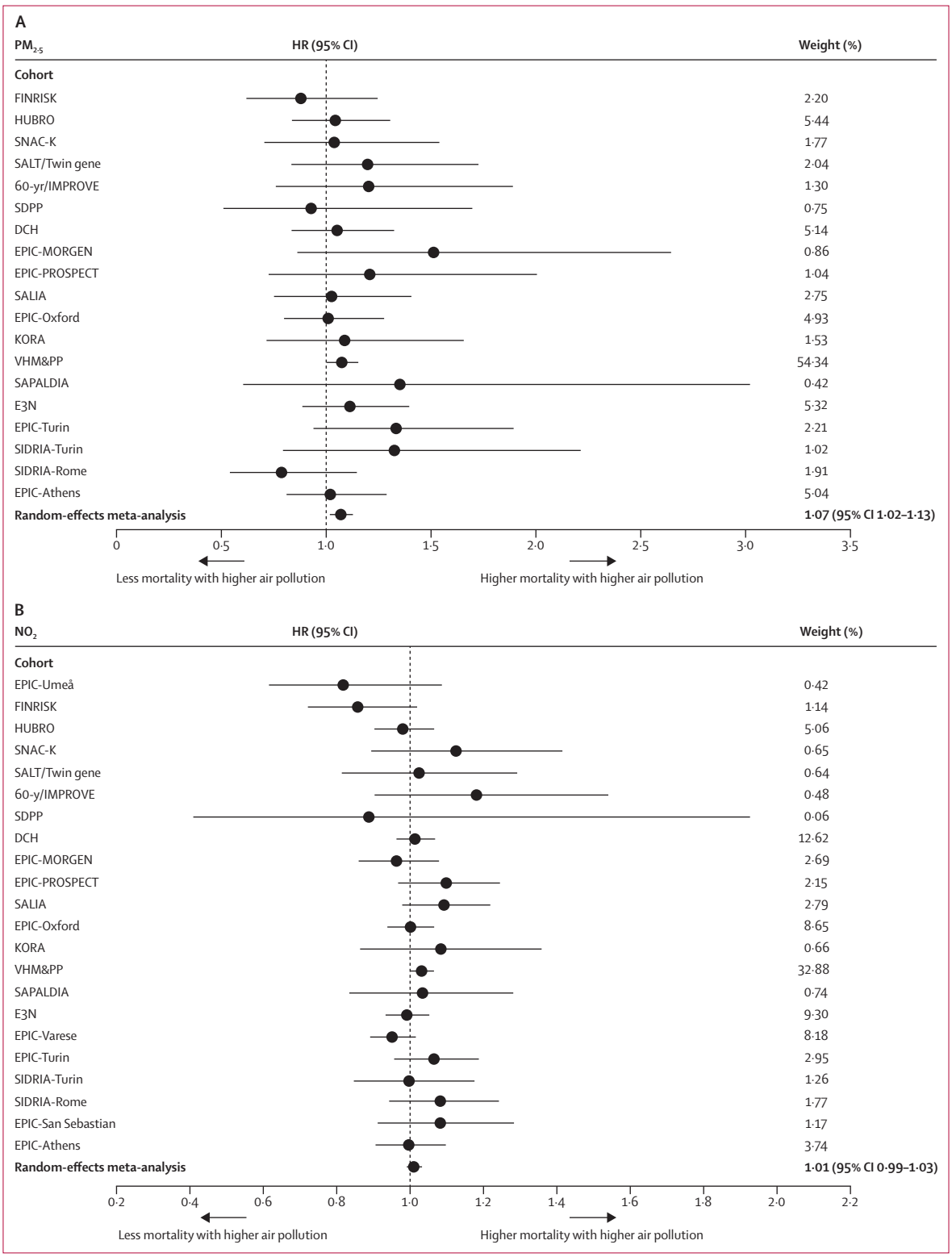

Figure 2: **Adjusted association between natural cause mortality and exposure to $PM_{2·5}$ and NO_2 (with main model 3)—results from cohort-specific analyses and random-effects meta-analyses**

(A) Exposure to $PM_{2·5}$. (B) Exposure to NO_2. HR=hazard ratio. HRs are presented per 5 μg/m³ for $PM_{2·5}$ and per 10 μg/m³ for NO_2. The number of observations was 322 159 in the $PM_{2·5}$ analysis and 367 251 in the NO_2 analysis. Particulate matter concentrations were not available for the EPIC-Umeå, EPIC-Varese, or EPIC-San Sebastian cohorts. For E3N and SAPALDIA, particulate matter concentrations were available for part of the cohort.

of non-movers during follow-up (table 2 and appendix pp 13–34). Age, sex, smoking status, and socioeconomic status (at an area level) were available for all cohorts. Smoking intensity and duration were available as continuous variables for all cohorts, except for VHM&PP and E3N. VHM&PP had data for occupation and employment status, but not for education. On average, we had complete confounder information for 90·3% of the participants.

Concentrations of air pollutants varied between and within study areas (table 3, figure 1, and appendix pp 35–38) and increased from northern to southern Europe cohorts. The average NO_2 concentration ranged from 5·2 μg/m³ (EPIC-Umeå) to 59·8 μg/m³ (SIDRIA-Turin), and the average $PM_{2·5}$ concentration from 6·6 μg/m³ (SDPP) to 31·0 μg/m³ (SIDRIA-Turin; table 3). Median differences between area-specific 10th and 90th percentiles were 17·6 μg/m³ for NO_2 concentrations and 3·3 μg/m³ for $PM_{2·5}$ concentrations (figure 1). Correlations between exposure measures were generally greater than 0·5 (appendix pp 39–44).

We recorded raised risks for all exposures to air pollutants, with a statistically significant increased pooled risk for $PM_{2·5}$ per 5 μg/m³ (1·07, 95% CI 1·02–1·13, p=0·02; table 4, figure 2, and appendix pp 45–50). HRs for confounder model 1 (adjusted only for calendar year and sex) were highest for all pollution indicators, and decreased after adjustment for individual level confounders (table 4). Sensitivity analyses showed that smoking variables were especially responsible for this decrease. Inclusion of area-level socioeconomic status variables (in model 3) led to only a small further decrease in HRs (table 4).

No heterogeneity between individual cohort effect estimates was recorded since the I^2 statistic was 0 or small (table 4).

In threshold analyses, for $PM_{2·5}$, pooled HRs remained statistically significantly raised when only participants with concentrations below 25 μg/m³ and 20 μg/m³ were included. Below 15 μg/m³, the HR was raised but not significantly so (table 5). This finding is complemented by the results of the spline models, which showed that the association did not deviate significantly from a linear association (appendix pp 51).

Pooled effect estimates for $PM_{2·5}$ in two-pollutant models adjusted for NO_2 (14 cohorts) and PM_{coarse} (16 cohorts) did not differ from the single-pollutant models (table 6). PM_{coarse} effects adjusted for $PM_{2·5}$ (11 cohorts) were reduced to unity. NO_2 effect estimates were not affected by $PM_{2·5}$ (14 cohorts), but were reduced by PM_{coarse} (11 cohorts), in two-pollutant analyses (table 6).

The pooled HR for $PM_{2·5}$ without the influential VHM&PP cohort, which was defined as having a weight greater than 50% in meta-analysis (figure 2), was similar (1·07, 95% CI 0·99–1·15) to the pooled HR for $PM_{2·5}$ in the main analysis (1·07, 1·02–1·13). A sensitivity analysis restricting the VHM&PP study population to the participants included after 1990 (similar to other cohorts) resulted in a slightly higher pooled HR for $PM_{2·5}$ of 1·08 (95% CI 1·01–1·15).

	Number of cohorts	Number of observations	HR (95% CI)	HR (95% CI) based on all participants (no threshold) in the same cohorts*
10 μg/m³	9	68 527	1·02 (0·87–1·19)	1·06 (1·00–1·13)
15 μg/m³	11	241 293	1·04 (0·98–1·11)	1·07 (1·01–1·13)
20 μg/m³	17	304 759	1·07 (1·01–1·13)	1·06 (1·01–1·12)
25 μg/m³	17	309 310	1·06 (1·00–1·12)	1·06 (1·01–1·12)
No threshold	19 (all)	322 159	1·07 (1·02–1·13)	1·07 (1·02–1·13)

At the threshold of 10 μg/m³, FINRISK, HUBRO, SNAC-K, SALT/Twin gene, 60-y/IMPROVE, SDPP, DCH, EPIC-Oxford, and VHM&PP were included. At the 15 μg/m³ threshold, the same studies were included, with the addition of KORA and E3N. At the 20 and 25 μg/m³ thresholds, all the aforementioned studies were included, with the addition of EPIC-MORGEN, EPIC-PROSPECT, SALIA, SAPALDIA, SIDRIA-Rome, and EPIC-Athens. HRs are presented per 5 μg/m³ for $PM_{2·5}$. HR=hazard ratio. *Example of reading the table: nine cohorts contributed to the 10 μg/m³ threshold analysis, providing an HR of 1·02. When the same nine cohorts were used for a standard analysis (disregarding thresholds—ie, including all participants), the HR was 1·06.

Table 5: **Results from random-effects meta-analyses for the adjusted association between natural cause mortality and exposure to $PM_{2·5}$ below various threshold values**

	One-pollutant model	Two-pollutant model	Number of cohorts
$PM_{2·5}$			
Adjusted for NO_2*	1·07 (1·01–1·13)	1·06 (0·98–1·15)	14
Adjusted for PM_{coarse}†	1·08 (1·02–1·14)	1·07 (1·01–1·14)	16
PM_{coarse}			
Adjusted for NO_2‡	1·06 (0·96–1·18)	1·07 (0·94–1·21)	11
Adjusted for $PM_{2·5}$†	1·04 (0·97–1·12)	1·01 (0·92–1·11)	16
NO_2			
Adjusted for $PM_{2·5}$*	1·01 (0·99–1·04)	1·01 (0·97–1·05)	14
Adjusted for PM_{coarse}‡	1·01 (0·97–1·05)	0·98 (0·93–1·03)	11

Data are HR (95% CI), unless otherwise indicated. HR=hazard ratio. HRs are presented for the following increments: 5 μg/m³ for $PM_{2·5}$ and PM_{coarse}, and 10 μg/m³ for NO_2. The analyses were limited to studies for which correlation between two pollutants was less than 0·7. *Included studies: FINRISK, HUBRO, SALT/Twin gene, 60-yr/IMPROVE, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, KORA, VHM&PP, E3N, SIDRIA-Turin, SIDRIA-Rome, and EPIC-Athens. †Included studies: FINRISK, HUBRO, SALT/Twin gene, 60-yr/IMPROVE, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, KORA, VHM&PP, SAPALDIA, E3N, EPIC-Turin, SIDRIA-Turin, and EPIC-Athens. ‡Included studies: FINRISK, HUBRO, SNAC-K, SALT/Twin gene, 60-yr/IMPROVE, SDPP, EPIC-PROSPECT, EPIC-Oxford, EPIC-Turin, SIDRIA-Turin, and EPIC-Athens.

Table 6: **Results from random-effects meta-analyses from one-pollutant and two-pollutant models for adjusted association between natural-cause mortality and various pollutants**

Additional adjustment for hypertension, physical activity, diabetes, and cholesterol did not change pooled HRs compared with those for the main model (appendix pp 52).

Back-extrapolation for NO_2 was possible in most cohorts, whereas for seven cohorts spread over Europe back-extrapolation for PM_{10} was possible. $PM_{2·5}$ monitoring in Europe was not available for the baseline periods. Cohort size-weighted average PM_{10} concentrations decreased for the seven cohorts with historical PM_{10} data and were 34·8 μg/m³ at baseline and 22·2 μg/m³ in 2008–11. HRs did not differ between the back-extrapolated concentrations at baseline in the year of recruitment and the concentrations based on 2008–11 measurements. The pooled HR for back-extrapolated PM_{10} concentrations based on the difference method was 1·07 (95% CI 0·94–1·21), whereas the pooled HR for back-extrapolated PM_{10} concentrations based on

the ratio method was 1·04 (0·96–1·13)—essentially the same as the 1·04 (0·93–1·16) for the main ESCAPE exposure for these seven cohorts (p=0·93). Analyses restricted to participants who did not move during follow-up in the 14 cohorts with moving information available (on average 66·4% of the participants did not move during follow-up) resulted in a slightly higher pooled HR for $PM_{2·5}$ of 1·10 (95% CI 1·02–1·20) than the HR from the main analysis for the same 14 cohorts including all participants (1·06, 1·00–1·12). HRs for $PM_{2·5}$ with and without random effects were similar: 1·08 (95% CI 1·00–1·16) with random effects, and 1·07 (0·98–1·15) without random effects (available for 15 cohorts).

Pooled HRs for $PM_{2·5}$ differed significantly between men and women in the cohorts that included both sexes. HRs were raised in men (1·14, 95% CI 1·04–1·24) but not in women (0·99, 0·92–1·07; p=0·02), with no heterogeneity between individual cohort effect estimates within each sex stratum (p value for women=0·77; p value for men=0·38). Most of the cohorts contained roughly the same percentage of men and women (table 2) and the results did not change when the analysis was restricted to these cohorts. No statistically significant effect modification occurred for the other assessed characteristics (appendix pp 53). $PM_{2·5}$ effect estimates were similar for the six cohorts for which the amount of variance explained by land use regression model cross-validation was smaller than 60% (1·07, 95% CI 1·01–1·14) and for the 13 cohorts for which it was larger than 60% (1·07, 0·97–1·17; p=0·92).

Discussion

Long-term exposure to $PM_{2·5}$ was associated with natural-cause mortality in many European cohort studies, with no indication of heterogeneity between individual cohort effect estimates. Associations remained raised and statistically significant over concentration ranges well below the existing European annual mean limit value of 25 μg/m³ (European Commission air quality standards).

For more on the **European Commission air quality standards** see http://ec.europa.eu/environment/air/quality/standards.htm

ESCAPE is the first multicentre study of long-term exposure to air pollution and mortality, covering a large study population in different settings across Europe. Exposure assessment and statistical analyses were highly standardised (panel).

Although we recorded a decrease in HRs between models adjusted only for calendar year and sex compared with those adjusted for individual confounders, HRs of the main model remained stable with use of more extended sets of confounders, including hypertension and physical activity, diabetes and cholesterol, and area-level socioeconomic status. Confounder control was at least as intense as in previous studies, including the large US American Cancer Society study.[18] However, residual confounding by, for example, smoking, can never be excluded completely. The $PM_{2·5}$ HR for never-smokers (1·05, 95% CI 0·98–1·12) was similar to the overall HR of 1·07 (1·02–1·13; p=0·65).

In this Article, we report associations for natural-cause mortality. Cause-specific results from ESCAPE analyses will be published and discussed separately. Briefly, increased effect estimates for $PM_{2·5}$ were recorded for lung cancer incidence[19] (HR 1·18, 95% CI 0·96–1·46, per 5 μg/m³), and stroke mortality, but not for ischaemic heart disease or respiratory mortality.

Most, but not all, studies showed statistically significant associations between $PM_{2·5}$ or PM_{10} and all-cause or natural-cause mortality.[2,20] Effect estimates differed substantially across studies. The American Cancer Society study recorded an effect estimate of 1·06 (95% CI 1·02–1·11) per 10 μg/m³ $PM_{2·5}$ for all-cause mortality.[18] A recent meta-analysis of mortality and long-term exposure to air pollution showed a random effects summary estimate for all-cause mortality of 1·06 (95% CI 1·04–1·08) per 10 μg/m³ $PM_{2·5}$.[20] Expressed per 10 μg/m³, for $PM_{2·5}$ our effect estimate is 1·13 (1·01–1·25), and is somewhat higher than the combined estimate from previous studies, although the confidence intervals do overlap widely. Our higher estimate is possibly related to the fact that we analysed within-area rather than between-area contrasts in pollution related to the decision to not pool data, which could have led to some loss of statistical power. However, with use of a strictly standardised protocol, we achieved many of the advantages that a pooled analysis would have had. Additionally, our approach allows us to use optimised cohort-specific confounder models. An analysis within the American Cancer Society study population in Los Angeles County (CA, USA) also reported larger effect estimates than the overall between-area analyses.[21] We used 2008–11 air pollution data to develop our exposure models, which we applied to the participants' baseline addresses (1985–2007, with most studies starting in the mid-1990s). Four studies in the Netherlands, Italy (Rome), the UK, and Canada (Vancouver) have shown that during periods of about 10 years and longer, existing land use regression models predicted historic spatial contrasts well.[22–25] Furthermore, sensitivity analyses with PM_{10} concentrations back-extrapolated to the baseline year resulted in similar pooled HRs as with the non-back-extrapolated concentrations, which shows that HRs with the present exposures were not inflated. Pooled effect estimates for $PM_{2·5}$ in two-pollutant models adjusted for NO_2 and PM_{coarse} did not differ from the single-pollutant $PM_{2·5}$ effect estimates, which suggests an independent effect of $PM_{2·5}$ exposure on mortality.

Effect estimates for the more traffic-related air pollutants NO_2 and $PM_{2·5}$ absorbance, and the two traffic indicator variables, were raised slightly, although mostly not statistically significantly. Our effect estimates for NO_2 (1·01, 95% CI 0·99–1·03) and $PM_{2·5}$ absorbance (1·02, 0·97–1·07) were lower than pooled effect estimates in two recent reviews.[20,26] In these reviews, expressed per 1 μg/m³ elemental carbon, which is equivalent to our increment for $PM_{2·5}$ absorbance, pooled effect estimates were 1·06

(95% CI 1·05–1·07) and 1·06 (1·04–1·09).[20,26] For NO_2, the pooled estimate per 10 μg/m³ was 1·06 (1·03–1·08).[20]

The health effects of coarse particles have attracted renewed attention because tailpipe emissions have been reduced, and therefore non-tailpipe emissions, such as tyre or brake wear, are becoming more important. Little evidence exists for an association between mortality and long-term exposure to coarse particles.[9] However, only a few studies have been done, which did not take into account small-scale spatial variation. We noted very scarce evidence for an increased risk of mortality in relation to PM_{coarse}. The small effect estimate for PM_{coarse} was reduced to essentially unity after adjustment for $PM_{2·5}$, which is consistent with findings from the Nurses' Health study.[27]

$PM_{2·5}$ was the pollutant that was most consistently associated with natural-cause mortality in our study. A range of predictor variables explained the spatial variation of $PM_{2·5}$ in ESCAPE study areas, including not only traffic variables but also population density, industrial sources, urban green space, and elevation (the latter two variables were negatively associated with air pollution concentrations).[11] This finding suggests that the effect of $PM_{2·5}$ in our study is caused not only by traffic emissions but also by other factors. By contrast, the spatial variation in $PM_{2·5}$ absorbance was explained more exclusively by traffic variables.[11]

The absence of statistically significant heterogeneity across cohorts supports the use of one risk estimate for health effect assessment across Europe. Our effect estimate was two-times bigger than the relative risk used in the recent Aphekom project to estimate years of life lost in a series of European cities.[28] Although this result could be interpreted to mean that such published impact assessments are seriously underestimating the risk, we would like to point out that a recent meta-analysis supported the use of the relative risk estimate used in Aphekom,[20] and our results should be interpreted in the light of the wider published literature.

Several plausible biological pathways whereby air pollutants could affect mortality have been investigated. The main pathway is probably that fine particles can lead to systemic inflammatory and oxidative stress responses.[2] One recent study has shown an association between black carbon and telomere length—a measure of biological ageing.[29]

We found no effect modification by smoking status, education level, fruit intake, or BMI, as reported in some previous studies.[2] We did find that pooled HRs for $PM_{2·5}$ were raised in men but not in women. Sex-stratified results in previous studies have varied, although risks do tend to be higher for men, as we noted in our study.[8,18] No explanation for such sex differences has yet been proposed. We studied effect modification by various factors that might be associated with sex, such as smoking status, educational level, fruit intake, and BMI, but no effect modification was recorded that could potentially explain the sex differences that we recorded in our study.

For $PM_{2·5}$, HRs remained statistically significantly raised when only participants with concentrations below 20 μg/m³ were included. The current European annual mean limit value for $PM_{2·5}$ is 25 μg/m³. Our findings suggest that significant adverse health effects occur at concentrations well below accepted limits. The WHO air quality guideline for annual mean $PM_{2·5}$ is 10 μg/m³ and our findings support the idea that significant health benefits can be achieved by moving towards that guideline. The $PM_{2·5}$ threshold analysis focused on the concentration distributions in 2008–11 and not on cumulative exposures during the follow-up periods because no historical $PM_{2·5}$ records are available in the study areas. Therefore, the thresholds in the analyses might represent slightly higher thresholds over the follow-up periods. In the seven cohorts for which we had data, PM_{10} concentrations had decreased from baseline to the ESCAPE measurement period by 12 μg/m³. If the ratio of $PM_{2·5}$ to PM_{10} has not changed, this figure translates into a roughly 8 μg/m³ decrease in $PM_{2·5}$ concentration.[30] Previous analyses suggested a monotonic (eg, linear or log-linear) concentration response association between long-term exposure to $PM_{2·5}$ and mortality risk, without an apparent threshold below which there is no risk.[2]

In conclusion, our findings show that long-term exposure to fine particulate air pollution is associated with natural-cause mortality, even at concentration ranges well below the present European annual mean limit value.

Panel: Research in context

Systematic review

We reviewed the published scientific literature up to May, 2007, when we submitted our grant proposal to the European Union. We searched PubMed for articles and reviews published in English with search terms "air pollution and mortality" and "ambient air and mortality". A brief description of the findings of our scientific literature review was part of the study proposal. Additionally, four coauthors of this Article, including RB and GH, did a new systematic review that has recently been published.[20] For this review, we did a search in the Medline and Scopus databases with the search terms "air pollution", "cohort", and "mortality" until January, 2013 . The results of this review were also used to place our findings in context with previous studies. At the time of inception of our study, some studies had already shown associations between long-term exposure to air pollution and mortality, but they had limitations, including small size of some cohort studies, poor retrospective exposure assessment, and no or scarce information about potential confounders.

Interpretation

Our study supports the association between long-term exposure to ambient particulate matter air pollution and mortality, even at concentrations below the existing European Union limit values. Our study overcomes several limitations of previous studies, since it has a large sample size, broad European coverage, retrospective exposure assessment, and contains adjustment for a wide range of potential confounder variables. Particulate matter air pollution is ubiquitous and, on the basis of our results, further reductions in particulate matter air pollution can be expected to reduce the mortality risk.

Contributors

RB contributed to the study design, exposure assessment, statistical script, and data analyses, and drafted the report. OR-N and KK contributed to the study design. MS and GW contributed to the statistical script and data analyses. ZJA contributed to the study design, statistical script, and data analyses. BH contributed to the statistical script and provided local cohort data. ESa, CSc, TS, and MA contributed to the statistical script. PF, MN, LM, MKo, KTE, TE, ME, KM, MW, KdH, AI, HP, CdQ, M-YT, and AR contributed to exposure assessment. PV contributed to the design and provided local cohort data. WWX contributed to the design and data analyses. KD contributed to the design, exposure assessment, statistical script, and data analyses. AO, ATu, BO, JP, ESc, AV, SG, FR, EM, IT, and MKa contributed to the data analyses. BF, ASH, WN, PN, UDF, NLP, C-GO, LF, GP, KO, PHP, BB-d-M, UK, JH, TK, AP, HC, NP-H, NK, FCC, VK, CSa, FF, PA, MD, and ATr provided local cohort data. TL contributed to exposure assessment and provided local cohort data. DS, RH, CG, GC, and CB contributed to exposure assessment and data analyses. KW contributed to exposure assessment, statistical script, and data analyses. GN contributed to data analyses and provided local cohort data. BB contributed to the design and drafted the report. GH contributed to the design, statistical script, and drafted the report. All authors contributed to critical reading of, and commented on, the report, helped to interpret the data, and approved the final draft.

Conflicts of interest

We declare that we have no conflicts of interest.

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