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Pooled analysis

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Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: pooled analysis

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ABSTRACT OBJECTIVE

To investigate the associations between air pollution and mortality, focusing on associations below current European Union, United States, and World Health Organization standards and guidelines.

DESIGN

Pooled analysis of eight cohorts.

SETTING

Multicentre project Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) in six European countries.

PARTICIPANTS

325 367 adults from the general population recruited mostly in the 1990s or 2000s with detailed lifestyle data. Stratified Cox proportional hazard models were used to analyse the associations between air pollution and mortality. Western Europe-wide land use regression models were used to characterise

residential air pollution concentrations of ambient fine particulate matter (PM_{2.5}), nitrogen dioxide, ozone, and black carbon.

MAIN OUTCOME MEASURES

Deaths due to natural causes and cause specific mortality.

RESULTS

Of 325 367 adults followed-up for an average of 19.5 years, 47 131 deaths were observed. Higher exposure to PM_{2.5}, nitrogen dioxide, and black carbon was associated with significantly increased risk of almost all outcomes. An increase of 5 µg/m³ in PM_{2.5} was associated with 13% (95% confidence interval 10.6% to 15.5%) increase in natural deaths; the corresponding figure for a 10 µg/m³ increase in nitrogen dioxide was 8.6% (7% to 10.2%). Associations with PM_{2.5}, nitrogen dioxide, and black carbon remained significant at low concentrations. For participants with exposures below the US standard of 12 µg/m³ an increase of 5 µg/m³ in PM_{2.5} was associated with 29.6% (14% to 47.4%) increase in natural deaths.

CONCLUSIONS

Our study contributes to the evidence that outdoor air pollution is associated with mortality even at low pollution levels below the current European and North American standards and WHO guideline values. These findings are therefore an important contribution to the debate about revision of air quality limits, guidelines, and standards, and future assessments by the Global Burden of Disease.

Introduction

Epidemiological cohort studies have consistently found associations between long term exposure to outdoor air pollution and a range of morbidity and mortality endpoints. Concentrations of health relevant regulated pollutants, including fine particles and nitrogen dioxide, have decreased in the past decades in developed countries. Recent evaluations

WHAT IS ALREADY KNOWN ON THIS TOPIC

In the framework of the update of the World Health Organization air quality guidelines, systematic reviews of studies of the effect of long term exposure to major outdoor air pollutants (fine particles, nitrogen dioxide, and ozone) have been done

Findings showed that long term exposure to ambient air pollution was significantly associated with natural and cause specific mortality, but associations at concentrations below current limit values were not well understood

WHAT THIS STUDY ADDS

Long term exposure to outdoor air pollution was positively associated with mortality even at levels well below the EU limit values, US Environmental Protection Agency national ambient air quality standards, and WHO air quality guidelines for fine particles and nitrogen dioxide

This new evidence supports reconsideration of existing guideline values and standards

The finding of associations at low levels of air pollution and mortality also supports policies to reduce air pollution below current legal limit values

by the World Health Organization and the Global Burden of Disease study have suggested that health effects might persist at these lower concentrations.¹⁻³ However, there is uncertainty about the shape of the concentration-response function at the low end of the air pollution concentration distribution, related to the scarcity of observations at the lowest concentrations. Associations with mortality at low pollution levels in large populations were primarily investigated in a few North American studies, specifically the Canadian census cohort, the Canadian Community Health survey, the US Medicare cohort, and the US National Health Interview Survey study.⁴⁻¹⁰ All the studies found associations below the current annual average US standard of 12 $\mu\text{g}/\text{m}^3$ and WHO guideline value of 10 $\mu\text{g}/\text{m}^3$ for fine particles with an aerodynamic diameter of $<2.5 \mu\text{m}$ ($\text{PM}_{2.5}$), but only two studies were able to adjust for detailed individual lifestyle factors.^{7,9} Most of the studies suggested a steeper concentration response function at the lowest levels, but the National Health Interview Survey study⁹ suggested little association below about 5 $\mu\text{g}/\text{m}^3$. Most studies focused primarily on $\text{PM}_{2.5}$, whereas increasing evidence shows that pollutants related to local combustion sources, including nitrogen dioxide and black carbon, might be relevant to health. Few studies have assessed the mortality effects of long term exposure to ozone.

Within the project Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) we assessed associations of low level air pollution concentrations with natural and cause specific mortality. Low level air pollution was defined as concentrations below current European Union limit values, US Environmental Protection Agency national ambient air quality standards, or the 2005 WHO air quality guidelines. We investigated $\text{PM}_{2.5}$, nitrogen dioxide, ozone, and black carbon at a fine spatial resolution. To have sufficient statistical power to detect associations at low exposure levels, we pooled data from eight European cohorts with information on important individual risk factors, including smoking and body mass index.

Methods

Study population

The eight cohorts were selected from six European countries (see supplementary figure): Sweden (Stockholm county), Denmark (Copenhagen and Aarhus, and nationwide), France (nationwide), the Netherlands (four cities), Germany (Ruhr and Augsburg areas), and Austria (Vorarlberg region). All the cohorts, except the Danish cohort,¹¹ were previously part of the European Study of Cohorts for Air Pollution Effects (ESCAPE).¹² Not all ESCAPE cohorts were included, either because of relatively high annual air pollution concentrations or because the data could not be pooled. Several of the included cohorts (ie, from Sweden, Denmark, the Netherlands, and Augsburg, Germany) combined multiple original cohorts, termed subcohorts. All cohorts and subcohorts included general population samples and specific subgroups, such as Danish nurses (DNC cohort).

Most cohorts were from large cities and surrounding regions. Supplementary appendix section 1 describes the cohorts in more detail. Recruitment of most of the cohorts was in the 1990s or 2000s (supplementary table S1).

To pool data, we used a common codebook to harmonise individual and area level covariates and outcome variables between cohorts. Information on covariates was only available at baseline.

Assessment of exposure to air pollution

We assessed air pollution concentrations at the baseline residential address of the study participants using land use regression models, described in detail elsewhere.¹³ Briefly, we estimated 2010 annual mean $\text{PM}_{2.5}$, nitrogen dioxide, black carbon, and (warm season) ozone concentrations using the European Environmental Agency AirBase routine monitoring data ($\text{PM}_{2.5}$, nitrogen dioxide, and ozone) and ESCAPE monitoring data (black carbon). Predictors were satellite derived and chemical transport model air pollutant estimates at $10 \times 10 \text{ km}$, and fine scale land use and road traffic data. Western Europe-wide models were developed on a $100 \times 100 \text{ m}$ grid and were assigned to the participants using their geocoded residential address. The $\text{PM}_{2.5}$, nitrogen dioxide, black carbon, and ozone models generally explained a large fraction of measured spatial variation of the annual average concentration: 72%, 59%, 54%, and 69%, respectively. In the ELAPSE paper on exposures¹³ we reported performance of the models by comparing with the external ESCAPE measurements by cohort (typically 20 sites for $\text{PM}_{2.5}$ and 40 sites for nitrogen dioxide). The root means square error of this comparison was between 1.0 $\mu\text{g}/\text{m}^3$ and 1.7 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, except for the French cohort, where the value was 3.3 $\mu\text{g}/\text{m}^3$. For nitrogen dioxide, the root means square error was between 5 $\mu\text{g}/\text{m}^3$ and 7 $\mu\text{g}/\text{m}^3$, except for the nationwide French cohort (12 $\mu\text{g}/\text{m}^3$). Differences were therefore modest, and some of the variability was probably related to the small number of sites in each ESCAPE area. To enable time varying exposure analysis, we extrapolated concentrations to every year of follow-up using the estimated annual concentrations from the Danish eulerian hemispheric model, which models monthly average concentrations across Europe at $26 \times 26 \text{ km}$ spatial resolution back to 1990.¹⁴

Mortality data

Mortality was defined based on the underlying cause of death recorded on death certificates in mortality registries as ICD-9 and ICD-10 (international classification of diseases, ninth and 10th revisions, respectively) codes. We analysed mortality from natural causes (ICD-9: 001-779; ICD-10: A00-R99) and cause specific mortality for cardiovascular disease (ICD-9: 400-440; ICD-10: I10-I70), ischaemic heart disease (ICD-9: 410-414; ICD-10: I20-I25), cerebrovascular disease (ICD-9: 430-438; ICD-10: I60-I69), respiratory disease (ICD-9: 460-519; ICD-10: J00-J99), chronic

obstructive pulmonary disease (ICD-9: 490-492, 494, 496; ICD-10: J40-J44, J47), diabetes (ICD-9: 249-250; ICD-10: E10-E14), and cardiometabolic diseases (cardiovascular disease or diabetes). The end of follow-up for mortality was until 2011-15, depending on the cohort (supplementary table S1).

Statistical analysis

We analysed the associations between air pollution and mortality using Cox proportional hazards models stratified by sex and cohort or subcohort, with age as underlying timescale. Censoring occurred at the time of the event of interest, death from other causes, emigration, loss to follow-up for other reasons, or end of follow-up, whichever came first. Strata for cohorts or subcohorts were applied because of concerns about differences not fully accounted for by the available covariates and departures from the proportional hazard assumption.¹⁵

We specified three confounder models a priori, with an increasing level of adjustment for individual and area level variables. Model 1 included age (as the timescale), sex (strata), and year of enrolment. Model 2 further included smoking status, duration and intensity of smoking (linear and squared for intensity), body mass index, marital status, and employment status. Model 3 further expanded model 2 with neighbourhood or municipal level mean income in 2001. We determined models 2 and 3 based on the ESCAPE confounder models¹² and detailed sensitivity analyses, in which we balanced the need to adjust for a comprehensive set of covariates and the availability of these covariates for most participants. Model 3 was considered the main model.

In addition to the main linear model, we assessed the shape of the concentration-response association between air pollution and mortality using both natural cubic splines with three degrees of freedom and the shape constrained health impact function (SCHIF). The SCHIF method assesses several different shapes of the association as variations of sigmoidal functions to produce biologically plausible concentration-response functions, resulting in an “optimal” and “ensemble” of all fitted shapes.¹⁶ The SCHIF shapes are smoother and less affected by sparse data than natural cubic splines. We also performed analyses with exposure grouped into quarters for natural, cardiovascular, and respiratory mortality.

Furthermore, we performed several sensitivity analyses. The associations with linear models were analysed in subsets of concentrations by excluding observations above specific values. We evaluated cut-offs including current EU limit values (25 µg/m³ PM_{2.5}, 40 µg/m³ nitrogen dioxide), US Environmental Protection Agency national ambient air quality standards (12 µg/m³ PM_{2.5}), and WHO air quality guidelines (10 µg/m³ PM_{2.5}, 40 µg/m³ nitrogen dioxide).

To disentangle the effect of individual pollutants, we specified linear models of two pollutants for all combinations of the four pollutants. We did not specify

three pollutant models because of the high correlations between pollutants within cohorts.

As some potential confounders were not available in all cohorts, we tested the sensitivity of our findings by adjusting for additional variables such as education and performing a leave one out cohort analysis.

We assessed effect modification by covariates available in all cohorts and subcohorts. Because we stratified for sex in our main model, we changed the formulation to include sex as a covariate in the model. We then added pollution as an interaction variable, as with the other effect modifiers (restoring strata for sex as in the main model).

We assessed the sensitivity of our findings to using the exposure in 2010 by analysing the back extrapolated concentrations at each cohort's baseline year and by time varying exposures from enrolment to end of follow-up. Residential history was incorporated in the time varying exposure analyses. In the time varying analysis, one and five year period strata were used in the Cox models to account for time trends in mortality and air pollution.

Because air pollution and noise might be correlated, we conducted additional adjustment for road traffic noise. Details on assessment of noise exposure are provided elsewhere.¹⁷

We used multiple imputation by chained equations¹⁸ to fill in missing values for confounders, provided that a cohort had information for a variable for part of the cohort (supplementary appendix, section 2).

Analyses were performed in R (version 3.4.0).¹⁹ Supplementary appendix, section 3, lists the packages used in the analyses.

Patient and public involvement

As we used existing cohorts recruited more than a decade ago, we could not involve patients in the design of the study and the paper. We will prepare press releases and share the findings through publications, talks, and social media, addressing larger audiences that include members of the public, patients, health professionals, and stakeholders.

Results

Population and exposure characteristics

Cohorts differed in all characteristics, supporting the analysis using strata for cohorts and subcohorts (table 1 and supplementary tables S1 and S2). Observations were pooled from 381036 participants. Owing to missing covariate data, 325367 participants were included in the main analysis. The Austrian VHM&PP cohort contributed 45% of participants. Nearly all participants were exposed to PM_{2.5} levels below the EU limit value (25 µg/m³), more than 50000 were exposed to levels below the US Environmental Protection Agency national ambient air quality standards (12 µg/m³), and more than 25000 were exposed to levels below the WHO air quality guidelines (10 µg/m³). More than 310000 participants were exposed to nitrogen dioxide levels below the EU limit values and WHO air quality guidelines (40 µg/m³).

Table 1 | Characteristics of study populations from eight European cohorts. Values are numbers (percentages) unless stated otherwise

Cohorts and subcohorts	No of people in model 1	People in main model 3	Person years of follow-up	Natural deaths	Women (%)	Mean (SD) age at baseline (years)	Current smokers (%)	Mean (SD) No of cigarettes/day*	Mean (SD) years of smoking*	Overweight or obese (%)	Married or cohabiting (%)	Not employed† (%)	Mean (SD) small area income, ×€1000
Total	381 036	325 367 (85.4)	6 339 553	47 131 (14.5)	66.0	48.7 (13.4)	24.2	15.2 (8.9)	25.5 (13.1)	43.3	71.7	30.0	20.1 (5.8)
Stockholm county, Sweden													
CEANS-SDPP	7835	7727 (98.6)	122 606	337 (4.4)	61.2	47.1 (4.9)	26.4	13.5 (7.4)	27.9 (8.6)	51.5	83.5	9.2	24.3 (4.2)
CEANS-SIXTY	4180	3969 (95.0)	61 328	593 (14.9)	52.1	60.0 (0.0)	21.1	13.4 (7.6)	36.3 (9.9)	64.1	73.9	32.3	24.7 (6.9)
CEANS-SALT	6724	6176 (91.9)	64 140	891 (14.4)	55.3	57.8 (10.6)	21.2	12.7 (8.0)	37.9 (9.3)	39.8	67.7	35.6	25.3 (6.6)
CEANS-SNACK	3248	2830 (87.1)	20 970	960 (33.9)	62.4	72.9 (10.4)	14.3	11.7 (8.2)	43.3 (13.6)	53.0	45.9	76.8	28.7 (2.2)
Denmark (Copenhagen and Aarhus)													
DCH	56 308	53 647 (95.3)	974 868	10 644 (19.8)	52.4	56.7 (4.4)	36.3	16.4 (9.0)	36.3 (7.7)	56.1	71.5	21.7	20.2 (3.4)
Denmark (nationwide)													
DNC-1993	19 664	17 043 (86.7)	318 351	4003 (23.5)	100	56.2 (8.4)	37.5	13.9 (8.2)	31.6 (9.9)	28.1	67.6	30.0	19.2 (2.6)
DNC-1999	8769	8128 (92.7)	117 390	313 (3.9)	100	47.9 (4.2)	28.6	13.3 (7.3)	27.1 (7.1)	30.0	75.8	5.3	19.0 (2.4)
Netherlands (four cities)													
EPIC-NL-Morgen	20 711	18 302 (88.4)	308 257	1180 (6.4)	55.0	42.9 (11.2)	34.7	15.7 (8.6)	24.8 (10.6)	49.1	65.1	31.3	12.2 (1.6)
EPIC-NL-Prospect	16 194	14 570 (90.0)	239 372	1997 (13.7)	100	57.7 (6.1)	22.9	13.7 (8.7)	36.8 (7.6)	54.8	76.7	49.2	13.1 (1.4)
Germany (Ruhr area)													
HNR	4809	4733 (98.4)	56 857	694 (14.7)	50.3	59.7 (7.8)	23.5	18.6 (12.0)	34.5 (9.4)	73.5	74.8	60	25.2 (8.2)
France (nationwide)													
E3N	53 521	39 006 (72.9)	650 664	2260 (5.8)	100	53.0 (6.8)	13.0	11.4 (9.2)	28.6 (7.6)	20.7	83.3	32.3	11.2 (3.0)
Germany (Augsburg area)													
KORA-S3	4566	2572 (56.3)	40 080	391 (15.2)	50.9	49.4 (13.9)	20.2	16.5 (9.5)	25.2 (12.1)	67.0	80.1	44.7	36.7 (4.4)
KORA-S4	4257	2281 (53.6)	29 528	215 (9.4)	51.4	49.3 (13.8)	22.9	15.7 (9.5)	24.3 (11.6)	68.5	79.2	40.6	38.0 (7.3)
Austria (Vorarlberg region)													
VHM&PP	170 250	144 383 (84.8)	3 335 141	22 653 (15.7)	56.2	42.1 (15.0)	20.0	15.6 (8.9)	13.4 (8.3)	42.4	68.9	30.2	22.9 (1.7)

€1.00 (€0.85; \$1.18).

*For current smokers.

†Includes participants who are unemployed, home workers, or retired.

Large north to south upward gradients in exposure to air pollution were observed between cohorts (figure 1 and table S3). Variations in black carbon and nitrogen dioxide within cohorts were especially substantial. Contrast for ozone was low within cohorts.

PM_{2.5} was moderately to highly correlated with black carbon and nitrogen dioxide within most cohorts (supplementary table S4). Black carbon and nitrogen dioxide were highly correlated in most cohorts. Ozone was negatively correlated with PM_{2.5} and especially nitrogen dioxide and black carbon in all cohorts, with a particularly high negative correlation in the large Austrian cohort. The within cohort correlation is important since strata were used for cohorts and subcohorts in the epidemiological analysis.

Associations with mortality

Main analysis

Associations between PM_{2.5}, nitrogen dioxide, and black carbon and almost all outcomes were significantly positive in linear analysis (table 2). Effect estimates for PM_{2.5} were similar for deaths from natural causes and cardiovascular disease and lower for deaths from respiratory disease but similar for nitrogen dioxide and black carbon. The highest hazard ratios were found for deaths due to diabetes, with wider confidence intervals owing to a small number of deaths. Associations were significantly negative for ozone and all outcomes, related to the negative correlation between ozone and the other pollutants (participants with high exposure to ozone had low exposures to PM_{2.5}, black carbon, and nitrogen dioxide).

Hazard ratios (95% confidence intervals) from the main linear model (model 3) presented for the following increments: PM_{2.5} 5 µg/m³, nitrogen dioxide 10 µg/m³, black carbon 0.5×10⁻⁵/m, and ozone 10 µg/m³. These increments were chosen to reflect contrast in exposure for the pollutants, in accordance with the ESCAPE study. Main model adjusted for cohort or subcohort, age, sex, year of baseline visit, smoking status (current, former, never), smoking duration (years), smoking intensity (cigarettes/day, both linear and quadratic terms), body mass index (<18.5, 18.5–24.9, 25–29.9, >30), marital status (single, married or cohabiting, divorced or separated, widowed), employment status (yes or no), and 2001 small area level mean income. Natural mortality: 001-779 (ICD-9) and A00–R99 (ICD-10); cardiovascular disease mortality: 400-440 (ICD-9) and I10-I70 (ICD-10); ischaemic heart disease mortality: 410-414 (ICD-9) and I20-I25 (ICD-10); cerebrovascular disease mortality: 430-438 (ICD-9) and I60-I69 (ICD-10); respiratory mortality: 460-519 (ICD-9) and J00-J99 (ICD-10); chronic obstructive pulmonary disease mortality: 490-492, 494, 496 (ICD-9) and J40-J44, J47 (ICD-10); diabetes mortality: 249-250 (ICD-9) and E10-E14 (ICD-10); and cardiometabolic disease mortality: defined as mortality due to either cardiovascular disease or diabetes.

Figure 2 and supplementary figure S1 show the concentration-response functions for PM_{2.5}, nitrogen

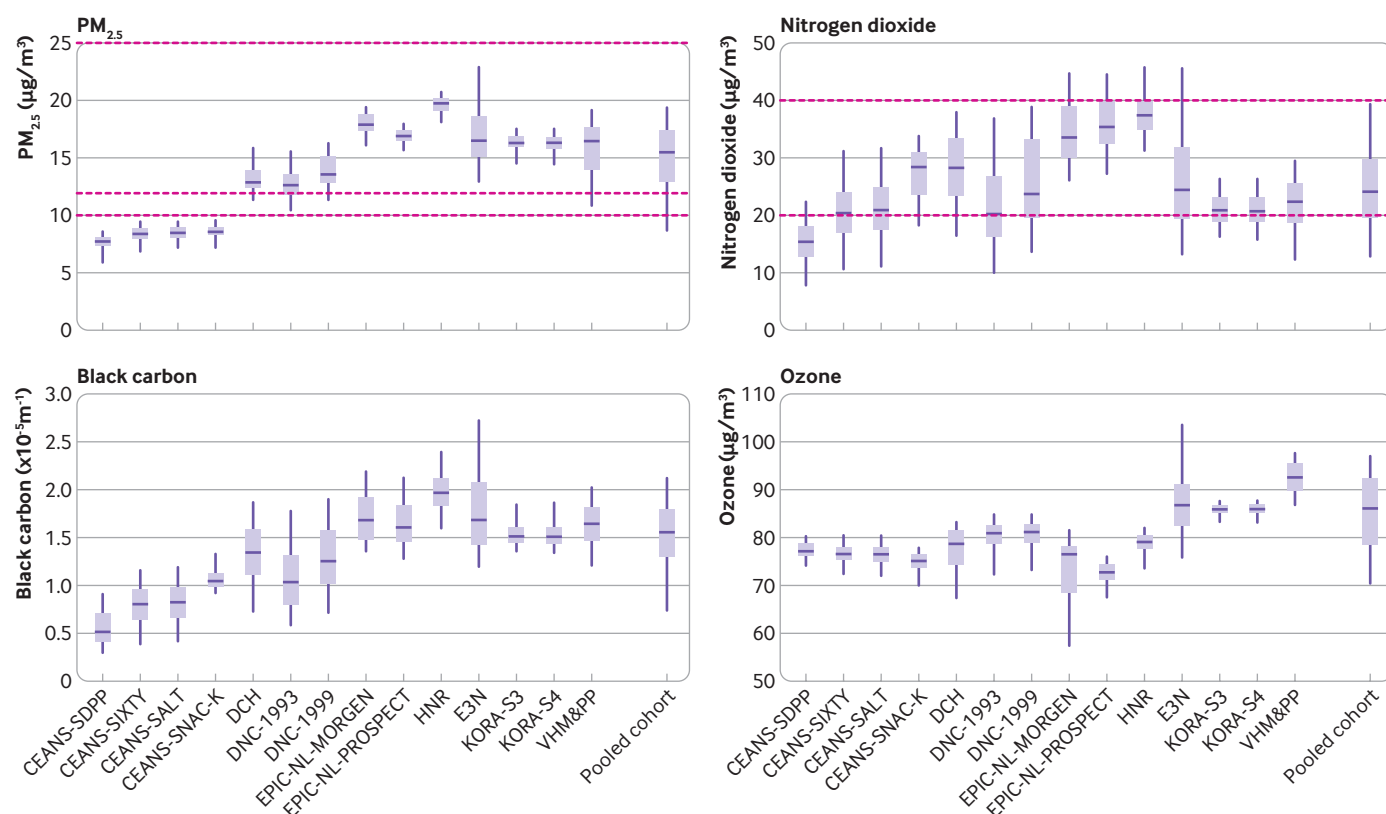


Fig 1 | Annual average exposure at participant ($n=325\,367$) addresses. In boxes, the boundary closest to zero indicates 25th centile and furthest from zero indicates 75th centile. Lines in boxes represent the median and whiskers are 5th and 95th centiles. Dashed lines for fine particulate matter ($PM_{2.5}$) indicate World Health Organization air quality guidelines ($10\,\mu\text{g}/\text{m}^3$), US Environmental Protection Agency national ambient air quality standards ($12\,\mu\text{g}/\text{m}^3$), and EU limit value ($25\,\mu\text{g}/\text{m}^3$). Dashed lines for nitrogen dioxide indicate WHO air quality guidelines ($40\,\mu\text{g}/\text{m}^3$) and WHO health risks of air pollution in Europe (HRAPIE) health impact quantification threshold ($20\,\mu\text{g}/\text{m}^3$). Cohorts were ordered from north (top) to south (bottom). CEANS cohorts are from Stockholm county, Sweden, DCH from Copenhagen and Aarhus, Denmark, DNC from Denmark nationwide, EPIC-NL from four cities in the Netherlands, HNR from the Ruhr area, Germany, E3N from France nationwide, KORA from the Augsburg area, Germany, and VHM&PP from the Vorarlberg region, Austria

dioxide, and deaths from natural causes using natural splines. Associations for natural deaths were observed over the full range of exposures. Associations tended to be steeper at low concentrations, levelling off at high concentrations. At the extremes of the distribution, patterns occurred that were difficult to interpret, related to large uncertainty about the shape of the curve as indicated by wide confidence intervals. For the association between $PM_{2.5}$ and deaths due to respiratory disease and chronic obstructive pulmonary disease, the pattern was difficult to interpret as a decreasing trend occurred associated with relatively frequently occurring exposures. Concentration-response functions for cause specific mortality were in general similar to those for natural deaths, indicating mostly supralinear curves, with associations remaining at low levels (figure 2 and supplementary figures S2-S6). The analyses of exposure grouped into quarters confirmed the linear to supralinear curves in the splines, except for $PM_{2.5}$ and deaths due to respiratory disease (supplementary table S5).

The SCHIF shapes were generally in agreement with the shapes of the natural splines, indicating that evidence still exists for an association at low levels and the positive associations between pollution and

natural and cause specific mortality are generally steeper at the low end of the distribution for $PM_{2.5}$, nitrogen dioxide, and black carbon (supplementary figures S7-S12). The SCHIF shapes for nitrogen dioxide and deaths due to respiratory disease and chronic obstructive pulmonary disease suggest a flatter slope at low than at high concentrations.

Sensitivity analyses

Table 3 shows the hazards ratios for natural deaths observed in subsets of successively lower air pollution concentrations. Associations remained positive and statistically significant for $PM_{2.5}$ even when all observations higher than $12\,\mu\text{g}/\text{m}^3$ were removed from the analysis. The hazard ratios for participants with exposures below $10\,\mu\text{g}/\text{m}^3$ was similar to those for all observations but with wider confidence intervals. For nitrogen dioxide, associations remained significantly positive below $20\,\mu\text{g}/\text{m}^3$, well below current standards. Similar patterns were found for cause specific mortality (table 3), with wider confidence intervals associated with smaller number of deaths.

Associations for $PM_{2.5}$ and nitrogen dioxide were attenuated but remained significant after adjustment for each other and for ozone as well as for black

Table 2 | Risk of death associated with exposure to air pollution in 325 367 participants from eight European cohorts. Values are hazard ratios (95% confidence intervals) unless stated otherwise

	Natural deaths	CVD	IHD	Cerebrovascular disease	Respiratory disease	COPD	Diabetes	Cardiometabolic disease
No of deaths	47 131	15 542	7265	3740	2865	1711	1034	16 576
PM _{2.5}	1.130 (1.106 to 1.155)	1.135 (1.095 to 1.176)	1.111 (1.056 to 1.169)	1.128 (1.048 to 1.214)	1.054 (0.961 to 1.156)	1.131 (1.002 to 1.278)	1.316 (1.144 to 1.514)	1.146 (1.107 to 1.186)
Nitrogen dioxide	1.086 (1.070 to 1.102)	1.089 (1.060 to 1.120)	1.098 (1.053 to 1.145)	1.068 (1.011 to 1.129)	1.101 (1.038 to 1.168)	1.141 (1.056 to 1.233)	1.238 (1.112 to 1.378)	1.098 (1.069 to 1.128)
Black carbon	1.081 (1.065 to 1.098)	1.085 (1.055 to 1.116)	1.078 (1.033 to 1.125)	1.075 (1.016 to 1.138)	1.084 (1.020 to 1.151)	1.119 (1.034 to 1.211)	1.240 (1.112 to 1.382)	1.095 (1.065 to 1.125)
Ozone	0.896 (0.878 to 0.914)	0.887 (0.854 to 0.922)	0.870 (0.821 to 0.921)	0.882 (0.817 to 0.953)	0.890 (0.821 to 0.966)	0.861 (0.774 to 0.957)	0.744 (0.645 to 0.859)	0.877 (0.845 to 0.910)

CVD=cardiovascular disease; IHD=ischemic heart disease; COPD=chronic obstructive pulmonary disease; PM_{2.5}=fine particulate matter with an aerodynamic diameter of <2.5 µm.

carbon in models of two pollutants for deaths due to natural causes and cardiovascular disease (supplementary tables S6 and S7). For deaths due to respiratory disease, only associations for nitrogen dioxide were robust to adjustment for other pollutants (supplementary table S8). The negative association with ozone attenuated towards unity but remained statistically significant.

Air pollution concentrations have decreased substantially in Europe since the 1990s (supplementary figure S13). Exposures to PM_{2.5} especially were substantially higher at baseline than in 2010 (supplementary figure S14); exposures to nitrogen dioxide and black carbon were moderately higher at baseline (supplementary appendix, section 7). When exposure to baseline air pollution was used instead of the 2010 exposure, hazard ratios especially for PM_{2.5} were found to be smaller than in the main analysis, although still statistically significant (supplementary table S9). Hazard ratios in the time varying exposure analyses were similar to those of the analysis using the 2010 exposure (supplementary table S10). As time trends were different across Europe, different trends were specified for each cohort. Natural spline analysis conducted in time varying exposure analyses supported the findings that mortality associations remained at low levels and were not associated with the use of the 2010 exposure as an exposure estimate (supplementary figure S15).

Further adjustment for education, diet, and occupational status did not affect effect estimates obtained with the main model (supplementary table S11). Effect estimates were not (PM_{2.5}) or were mildly (nitrogen dioxide, black carbon) affected by exclusion of specific cohorts, such as the large Austrian VHM&PP cohort (supplementary figure S16). The hazard ratio for ozone was substantially closer to unity when excluding the Austrian cohort. Effect estimates for deaths due to natural causes and cardiovascular disease were only mildly attenuated by additional adjustment for road traffic noise (supplementary table S12). The negative ozone associations were attenuated to unity in models of two pollutants (adjusting the ozone association for one of the other pollutants, one at a time) without the Austrian cohort and with additional adjustment for road traffic noise (supplementary tables S13 and S14). Hazard ratios were unchanged after using multiple imputation to estimate missing covariate data in the full study population (supplementary table S15).

Indications of effect modification were found for sex (higher hazard ratio in men; supplementary figure S17), smoking status for PM_{2.5} (higher hazard ratio in current smokers, but also significant associations in never smokers), age for nitrogen dioxide (higher hazard ratio in those aged <65 years). Effect estimates remained significant in all strata of participants except those with a very low body mass index (<18.5).

Discussion

By performing targeted analyses within a large European pooled cohort with detailed data on

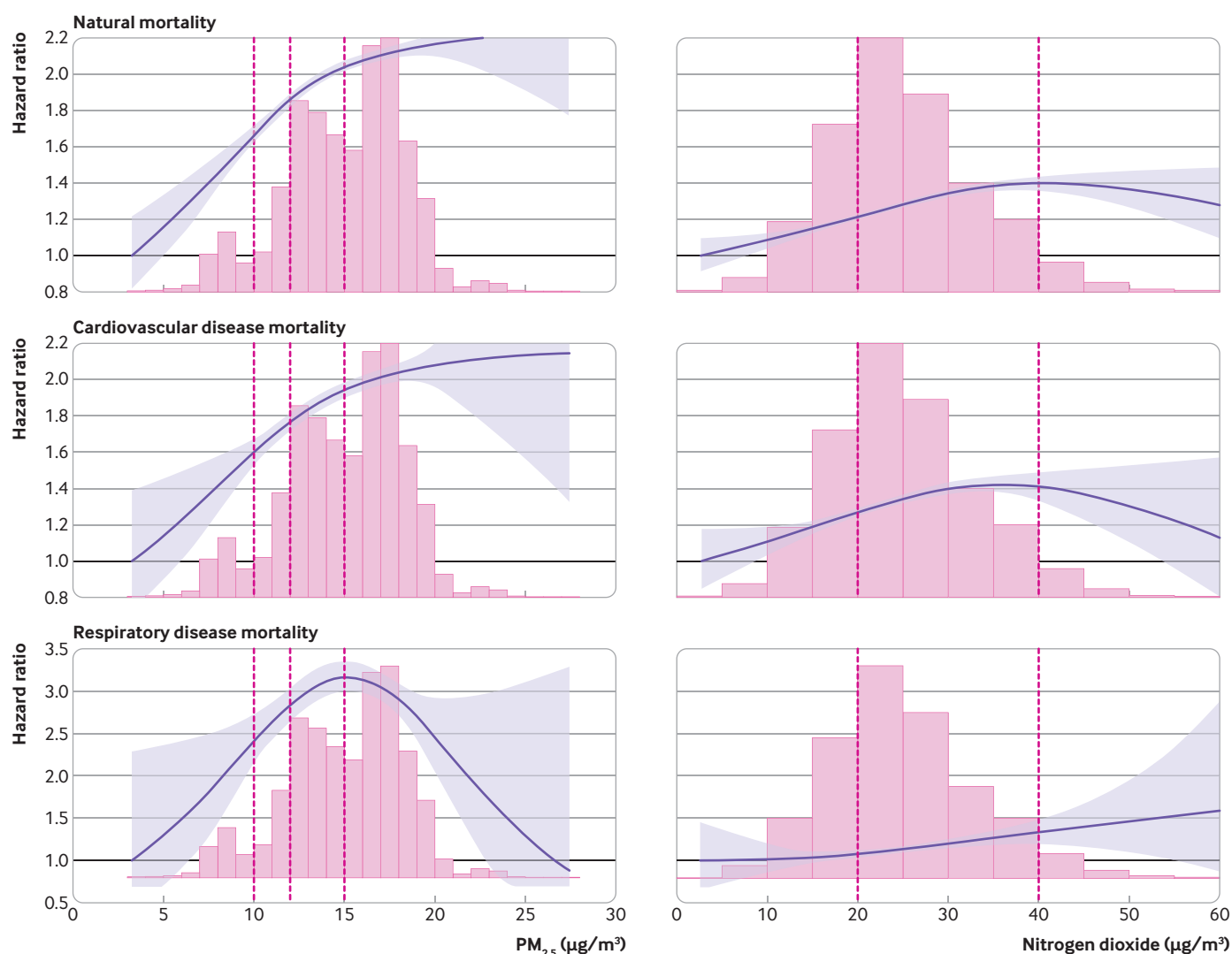


Fig 2 | Natural cubic splines (three degrees of freedom) for associations between exposure to air pollution and deaths due to natural causes, cardiovascular disease, and respiratory disease. Purple shaded areas represent 95% confidence intervals. Histogram of exposure added to illustrate sparse data regions. Dashed lines for fine particulate matter (PM_{2.5}) indicate World Health Organization air quality guidelines (10 µg/m³), the primary US Environmental Protection Agency standard (12 µg/m³), and the secondary US EPA standard (15 µg/m³), all as annual averages. For nitrogen dioxide the red lines indicate the WHO suggested limit for burden of disease quantification (20 µg/m³) and EU limit value and WHO air quality guidelines (40 µg/m³). Patterns at the extremes are difficult to interpret owing to wide confidence intervals

individual lifestyle covariates, we found significant positive associations between residential exposure to PM_{2.5}, nitrogen dioxide, and black carbon and deaths due to natural causes, cardiovascular disease, and respiratory disease. For these pollutants, we generally observed associations that were stronger at low exposure levels. Subset analyses documented that these associations remained even at levels for PM_{2.5} and nitrogen dioxide below current EU limit values, US Environmental Protection Agency national ambient air quality standards, and WHO air quality guidelines.

Comparison with other studies

The estimated hazard ratio for mortality associated with PM_{2.5} in our study is larger than the estimate from the ESCAPE study,¹² estimates from recent North American administrative cohorts^{5 6 8 20} and a recent Danish study,²¹ and estimates from meta-analyses²²⁻²⁴

(supplementary table S16), but almost identical to the results of the Canadian community health survey study.⁷ The recent WHO systematic review documented heterogeneity in PM_{2.5} effect estimates between studies, attributed to study location, level, and composition of particulate matter and to methodological differences.²⁴ In our cohort, similarly to the Canadian community health survey, individual lifestyle data were available, which are missing in large administrative cohorts. The sensitivity analysis using PM_{2.5} estimates at baseline year of exposure showed clearly smaller effect estimates. These estimates are more in line with effect estimates reported in a recent systematic review, suggesting that the effect estimate using the 2010 concentrations as exposure variable might be overestimating the true effect estimate. Effect estimates from time varying exposure analyses were similar to those of our main analyses. Our effect estimates for

Table 3 | Subset analysis of risk of death associated with exposure to air pollution

		Mortality hazard ratio (95% CI)		
Pollutant by subset	No	Natural deaths	Cardiovascular disease	Respiratory disease
PM _{2.5}				
Full dataset	325 367	1.130 (1.106 to 1.155)	1.135 (1.095 to 1.176)	1.054 (0.961 to 1.156)
Pollution level (µg/m ³):				
<25	325 339	1.131 (1.107 to 1.156)	1.135 (1.096 to 1.176)	1.050 (0.957 to 1.152)
<20	316 540	1.138 (1.113 to 1.164)	1.141 (1.101 to 1.183)	1.071 (0.975 to 1.177)
<15	151 250	1.257 (1.193 to 1.324)	1.276 (1.167 to 1.397)	1.322 (1.075 to 1.625)
<12	52 528	1.296 (1.140 to 1.474)	1.238 (0.999 to 1.535)	1.417 (0.849 to 2.365)
<10	25 422	1.146 (0.931 to 1.410)	0.863 (0.618 to 1.205)	1.489 (0.622 to 3.564)
Nitrogen dioxide				
Full dataset	325 367	1.086 (1.070 to 1.102)	1.089 (1.060 to 1.120)	1.101 (1.038 to 1.168)
Pollution level (µg/m ³):				
<40	310 643	1.101 (1.083 to 1.119)	1.104 (1.071 to 1.137)	1.099 (1.030 to 1.173)
<30	247 039	1.114 (1.088 to 1.140)	1.117 (1.074 to 1.161)	1.049 (0.953 to 1.154)
<20	88 510	1.099 (1.033 to 1.170)	1.171 (1.052 to 1.303)	1.044 (0.809 to 1.347)
Black carbon				
Full dataset	325 367	1.081 (1.065 to 1.098)	1.085 (1.055 to 1.116)	1.084 (1.020 to 1.151)
Pollution level (×10 ⁻⁵ /m):				
<3	324 757	1.084 (1.067 to 1.101)	1.087 (1.056 to 1.119)	1.085 (1.021 to 1.154)
<2.5	320 632	1.091 (1.074 to 1.109)	1.090 (1.058 to 1.123)	1.100 (1.034 to 1.171)
<2	296 371	1.107 (1.087 to 1.128)	1.107 (1.070 to 1.145)	1.119 (1.044 to 1.200)
<1.5	142 032	1.125 (1.086 to 1.165)	1.150 (1.072 to 1.234)	1.127 (0.990 to 1.284)
<1	35 406	1.041 (0.942 to 1.150)	0.895 (0.738 to 1.086)	1.186 (0.798 to 1.763)
Ozone				
Full dataset	325 367	0.896 (0.878 to 0.914)	0.887 (0.854 to 0.922)	0.890 (0.821 to 0.966)
Pollution level (µg/m ³):				
<120	325 367	0.896 (0.878 to 0.914)	0.887 (0.854 to 0.922)	0.890 (0.821 to 0.966)
<100	320 522	0.891 (0.872 to 0.910)	0.880 (0.846 to 0.915)	0.891 (0.820 to 0.969)
<80	98 840	0.979 (0.940 to 1.018)	1.021 (0.938 to 1.111)	0.890 (0.772 to 1.025)
PM _{2.5} =fine particulate matter with an aerodynamic diameter of <2.5 µm.				
Hazard ratios (95% confidence intervals) from the main linear model (model 3) presented for the following increments: PM _{2.5} 5 µg/m ³ , nitrogen dioxide 10 µg/m ³ , black carbon 0.5×10 ⁻⁵ /m, and ozone 10 µg/m ³ . These increments were chosen to reflect contrast in exposure for the pollutants, in accordance with the ESCAPE study. Main model adjusted for cohort or subcohort, age, sex, year of baseline visit, smoking status (current, former, never), smoking duration (years), smoking intensity (cigarettes/day, both linear and quadratic terms), body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30), marital status (single, married or cohabiting, divorced or separated, widowed), employment status (yes or no), and 2001 small area level mean income.				

PM_{2.5}=fine particulate matter with an aerodynamic diameter of <2.5 µm.

Hazard ratios (95% confidence intervals) from the main linear model (model 3) presented for the following increments: PM_{2.5} 5 µg/m³, nitrogen dioxide 10 µg/m³, black carbon 0.5×10⁻⁵/m, and ozone 10 µg/m³. These increments were chosen to reflect contrast in exposure for the pollutants, in accordance with the ESCAPE study. Main model adjusted for cohort or subcohort, age, sex, year of baseline visit, smoking status (current, former, never), smoking duration (years), smoking intensity (cigarettes/day, both linear and quadratic terms), body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30), marital status (single, married or cohabiting, divorced or separated, widowed), employment status (yes or no), and 2001 small area level mean income.

nitrogen dioxide were also higher than those in recent meta-analyses (supplementary table S12).

Our study contributes to the evidence that outdoor air pollution is associated with mortality even at levels below the current European and North American standards and WHO guideline values. When we applied two methods allowing non-linear concentration-response functions and linear analyses in subsets of exposure, we found no indication of a level below which no association was found. The finding of associations at low levels is consistent with that of several other recent cohort studies.^{4–8 25–29} The steeper slope of the PM_{2.5} mortality association at low levels is consistent with previous North American studies.^{4–8} In some other cohort studies, the shape of the PM_{2.5} function was sublinear^{30 31} or linear.^{25–27} In a comprehensive meta-analysis that combined evidence from a large number of cohorts, a supralinear association was observed for PM_{2.5}.³² Considerably less evidence is available about associations between low level nitrogen dioxide and mortality. In two large administrative cohorts in Canada and the Netherlands, associations with nitrogen dioxide were also found well below the WHO guideline value.^{5 33} Our study found associations at levels twofold lower than the current WHO guideline values for long term exposure to nitrogen dioxide.

Models of two pollutants showed that both PM_{2.5} and nitrogen dioxide were associated with mortality.

Whereas PM_{2.5} primarily reflects pollution transported over large distances, nitrogen dioxide reflects local fossil fuel combustion sources, especially motorised traffic.

Our results for ozone did not confirm previously reported positive associations with mortality.³⁴ This might be related to the very small range of ozone exposure within our study, rendering our study less informative for assessing health effects of ambient ozone. The negative associations we found in single pollutant models might reflect the high negative correlation with especially nitrogen dioxide and black carbon. Ozone and nitrogen dioxide are negatively correlated because when ozone is close to combustion sources (eg, major roads), it reacts with nitric oxide emitted from the combustion source to form oxygen and nitrogen dioxide. Ozone therefore tends to be low near roadways, whereas black carbon emitted by traffic is high. Nitrogen dioxide is in part directly emitted from traffic and in part formed by the atmospheric reactions, so it is also high near roadways. In models of two pollutants and models adjusting for noise, the negative associations with ozone were attenuated to unity, especially when excluding the large Austrian cohort and adjusting for nitrogen dioxide and noise together. The very high negative correlation between ozone and nitrogen dioxide in the Austrian cohort renders models of two pollutants difficult to interpret.

Strengths and limitations of this study

An important strength of ELAPSE is the pooling of data from multiple European cohorts with detailed information on individual covariates (eg, smoking, body mass index), which allowed for more statistical power and analysis of the shapes of concentration-response functions. A part of the pooling process was an extensive, highly standardised procedure of harmonisation of individual and small area level variables between all cohorts. Another strength of the study is that we used state-of-the-art models to enable a uniform assessment of exposure to air pollution at a fine, 100×100 m scale for all four pollutants. Compared with the ESCAPE study,¹² we had longer follow-up time.

A limitation of our study is the use of the 2010 exposure in our main analyses. The rationale for using the 2010 exposure was that in earlier years we did not have enough monitoring stations in Europe to develop the fine spatial scale models for PM_{2.5}. The 2010 exposure represents exposure towards the end of follow-up for most cohorts. Given the downward trends in air pollution, a concern is that 2010 exposure might not correctly reflect the long term exposure leading to increased mortality. Previous studies, however, have documented that spatial contrasts in nitrogen dioxide and black carbon remain constant for at least a decade,^{35–38} supporting the use of 2010 exposures in the analysis. Our sensitivity analyses with time varying exposure resulted in similar findings to the main model.

For PM_{2.5}, mainly, northern European cohorts contributed to the effect estimates in the lowest exposure range and we therefore could not distinguish between the characteristics of the particulate matter mixture or the population characteristics affecting the steeper slope at low levels. More overlap was found in exposure to nitrogen dioxide and black carbon between cohorts and we observed steeper slopes at low levels as well.

The difficulty in interpreting the non-linear function observed for deaths due to respiratory disease could be related to competing risks of death that we did not account for in our study.

Bias from exposure misclassification and residual confounding cannot be excluded. As exposure status was determined fully independently from the outcome, misclassification is likely non-differential and thus biased towards the null. We adjusted for several commonly used potential confounders, and adjustment for socioeconomic status might reduce confounding by other risk factors.

The coding for the causes of the death in the current study were brought in line with the previous ESCAPE analyses. These differ slightly from the ones used by the Global Burden of Disease. Owing to that, we do not expect major differences.

Conclusions

Our study contributes to the evidence that outdoor air pollution is associated with mortality even at levels

below the current European and North American standards and WHO guideline values. These findings are therefore an important contribution to the debate about revision of air quality limits, guidelines and standards, and future assessments by the Global Burden of Disease.

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The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplementary information: figure showing location of included cohorts

Supplementary information: supplementary appendix