Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project

Massimo Stafoggia, Bente Oftedal, Jie Chen, Sophia Rodopoulou, Matteo Renzi, Richard W Atkinson, Mariska Bauwelinck, Jochem O Klompmaker, Amar Mehta, Danielle Vienneau, Zorana J Andersen, Tom Bellander, Jørgen Brandt, Giulia Cesaroni, Kees de Hoogh, Daniela Fecht, John Gulliver, Ole Hertel, Barbara Hoffmann, Ulla A Hvidtfeldt, Karl-Heinz Jöckel, Jeanette T Jørgensen, Klea Katsouyanni, Matthias Ketzel, Doris Tove Kristoffersen, Anton Lager, Karin Leander, Shuo Liu, Petter L S Ljungman, Gabriele Nagel, Göran Pershagen, Annette Peters, Ole Raaschou-Nielsen, Debora Rizzuto, Sara Schramm, Per E Schwarze, Gianluca Severi, Torben Sigsgaard, Maciek Strak, Yvonne T van der Schouw, Monique Verschuren, Gudrun Weinmayr, Kathrin Wolf, Emanuel Zitt, Evangelia Samoli, Francesco Forastiere, Bert Brunekreef, Gerard Hoek*, Nicole A H Janssen**

Summary

Background Long-term exposure to ambient air pollution has been associated with premature mortality, but associations at concentrations lower than current annual limit values are uncertain. We analysed associations between low-level air pollution and mortality within the multicentre study Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE).

Methods In this multicentre longitudinal study, we analysed seven population-based cohorts of adults (age ≥30 years) within ELAPSE, from Belgium, Denmark, England, the Netherlands, Norway, Rome (Italy), and Switzerland (enrolled in 2000–11; follow-up until 2011–17). Mortality registries were used to extract the underlying cause of death for deceased individuals. Annual average concentrations of fine particulate matter ($PM_{2·5}$), nitrogen dioxide (NO_2), black carbon, and tropospheric warm-season ozone (O_3) from Europe-wide land use regression models at 100 m spatial resolution were assigned to baseline residential addresses. We applied cohort-specific Cox proportional hazard models with adjustment for area-level and individual-level covariates to evaluate associations with non-accidental mortality, as the main outcome, and with cardiovascular, non-malignant respiratory, and lung cancer mortality. Subset analyses of participants living at low pollutant concentrations (as per predefined values) and natural splines were used to investigate the concentration-response function. Cohort-specific effect estimates were pooled in a random-effects meta-analysis.

Findings We analysed 28 153 138 participants contributing 257 859 621 person-years of observation, during which 3 593 741 deaths from non-accidental causes occurred. We found significant positive associations between non-accidental mortality and $PM_{2·5}$, NO_2, and black carbon, with a hazard ratio (HR) of 1·053 (95% CI 1·021–1·085) per 5 μg/m³ increment in $PM_{2·5}$, 1·044 (1·019–1·069) per 10 μg/m³ NO_2, and 1·039 (1·018–1·059) per $0·5\times10^{-5}$/m black carbon. Associations with $PM_{2·5}$, NO_2, and black carbon were slightly weaker for cardiovascular mortality, similar for non-malignant respiratory mortality, and stronger for lung cancer mortality. Warm-season O_3 was negatively associated with both non-accidental and cause-specific mortality. Associations were stronger at low concentrations: HRs for non-accidental mortality at concentrations lower than the WHO 2005 air quality guideline values for $PM_{2·5}$ (10 μg/m³) and NO_2 (40 μg/m³) were 1·078 (1·046–1·111) per 5 μg/m³ $PM_{2·5}$ and 1·049 (1·024–1·075) per 10 μg/m³ NO_2. Similarly, the association between black carbon and non-accidental mortality was highest at low concentrations, with a HR of 1·061 (1·032–1·092) for exposure lower than $1·5\times10^{-5}$/m, and 1·081 (0·966–1·210) for exposure lower than $1·0\times10^{-5}$/m.

Interpretation Long-term exposure to concentrations of $PM_{2·5}$ and NO_2 lower than current annual limit values was associated with non-accidental, cardiovascular, non-malignant respiratory, and lung cancer mortality in seven large European cohorts. Continuing research on the effects of low concentrations of air pollutants is expected to further inform the process of setting air quality standards in Europe and other global regions.

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*Shared last authorship

Department of Epidemiology, Lazio Region Health Service, ASL Roma 1, Rome, Italy (M Stafoggia PhD, M Renzi MSc, G Cesaroni MSc, F Forastiere PhD); **Institute of Environmental Medicine** (M Stafoggia, Prof T Bellander PhD, K Leander PhD, P L S Ljungman PhD, Prof G Pershagen MD) **and Department of Global Public Health** (A Lager PhD), **Karolinska Institutet, Stockholm, Sweden; Department of Environmental Health** (B Oftedal PhD) **and Division for Infection Control and Environmental Health** (P E Schwarze PhD), **Norwegian Institute of Public Health, Oslo, Norway; Institute for Risk Assessment Sciences, Utrecht University, Utrecht, Netherlands** (J Chen PhD, M Strak PhD, Prof B Brunekreef PhD, G Hoek PhD); **Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece** (S Rodopoulou PhD, Prof K Katsouyanni PhD, E Samoli PhD); **Population Health Research Institute, St George's, University of London, London, UK** (Prof R W Atkinson PhD); **Interface Demography–Department of Sociology, Vrije Universiteit Brussel, Brussels, Belgium** (M Bauwelinck MSc);

National Institute for Public Health and the Environment, Bilthoven, Netherlands (J O Klompmaker PhD, M Strak, Prof M Verschuren PhD, N A H Janssen PhD)**; Harvard T H Chan School of Public Health, Boston, MA, USA** (J O Klompmaker)**; Section of Epidemiology** (A Mehta PhD) **and Section of Environmental Health** (Prof Z J Andersen PhD, J T Jørgensen PhD, S Liu MPH)**, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; Swiss Tropical and Public Health Institute, Basel, Switzerland** (D Vienneau PhD, K de Hoogh PhD)**; University of Basel, Basel, Switzerland** (D Vienneau, K de Hoogh)**; Centre for Occupational and Environmental Medicine, Region Stockholm, Stockholm, Sweden** (Prof T Bellander, Prof G Pershagen)**; Department of Environmental Science** (Prof J Brandt PhD, Prof M Ketzel PhD, Prof O Raaschou-Nielsen) **and Department of Bioscience** (Prof O Hertel PhD)**, Aarhus University, Roskilde, Denmark; iClimate Aarhus University Interdisciplinary Centre for Climate Change, Aarhus, Denmark** (Prof J Brandt)**; School of Public Health, Faculty of Medicine, Imperial College London, London, UK** (D Fecht PhD, Prof J Gulliver PhD, Prof K Katsouyanni, F Forastiere)**; Centre for Environmental Health and Sustainability and School of Geography, Geology and the Environment, University of Leicester, Leicester, UK** (Prof J Gulliver)**; Institute for Occupational, Social and Environmental Medicine, Centre for Health and Society, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany** (Prof B Hoffmann MD)**; Danish Cancer Society Research Center, Copenhagen, Denmark** (U A Hvidtfeldt PhD, Prof O Raaschou-Nielsen PhD)**; Institute for Medical Informatics, Biometry and Epidemiology, Medical Faculty, University of Duisburg-Essen, Essen, Germany** (K-H Jöckel PhD)**; Global Centre for Clean Air Research, University of Surrey, Guildford, UK** (Prof M Ketzel)**; Norwegian**

Research in context

Evidence before this study

We searched PubMed without language restrictions from database inception up to Dec 7, 2021, using the search terms "air pollution", "long-term", "mortality" and "cardiovascular" or "respiratory" or "lung cancer". We then screened abstracts and full texts to select relevant articles. Our literature review showed that epidemiological evidence from cohort studies is increasing. The strongest evidence was found for long-term effects of fine particulate matter ($PM_{2·5}$) and nitrogen dioxide (NO_2) on total and cardiovascular mortality and for $PM_{2·5}$ on lung cancer mortality, but results had a high degree of heterogeneity, and uncertainty from limited adjustment for co-pollutants. Evidence of association with respiratory mortality, and associations for other pollutants (PM_{10}, sulphur dioxide, black carbon, and ozone [O_3]) is less consistent and limited. Furthermore, the magnitude and linearity of associations had not been confirmed in previous studies.

Added value of this study

We pooled results from seven large cohorts in Europe, from six countries and one metropolitan area, representing a total of 28 million participants. We designed our study to investigate the shape of the relationship between long-term exposure to $PM_{2·5}$, NO_2, black carbon, and warm-season O_3 with non-accidental and cause-specific mortality, including cardiovascular, non-malignant respiratory, and lung cancer mortality, focusing on low pollution exposures. Exposure was assigned at the residential address of each participant from a uniform European-wide model, and common protocols (and scripts) for statistical analyses were applied in each cohort. We found that low concentrations of $PM_{2·5}$, NO_2, and black carbon were positively associated with non-accidental and cause-specific mortality. Results were robust to indirect adjustment for the lifestyle variables of body-mass index and smoking.

Implications of all the available evidence

Associations were observed at concentrations lower than current annual limit values of the EU, US Environmental Protection Agency, and WHO air quality guidelines for $PM_{2·5}$ and NO_2. Most associations presented a concentration-response function with the steepest part of the slope at low rather than high exposures, without an indication of a threshold. The evidence supports policies to further reduce air pollution and a re-evaluation of existing limit values and guidelines.

Introduction

Epidemiological cohort studies have consistently found associations between long-term exposure to outdoor air pollution and several mortality endpoints.[1–8] Recent evaluations have suggested that these associations might persist at low concentrations, defined as concentrations that are lower than the current limit values set by the EU, the US Environmental Protection Agency (EPA) standards, and WHO 2005 air quality guidelines.[4,7,9–12] To detect associations at low concentrations, large populations are needed. Evidence for associations of mortality with concentrations of fine particulate matter ($PM_{2·5}$) below current air quality standards primarily consists of a few large population-based studies conducted in North America.[4,7,13,14] To assess the robustness of these findings, large multicentre population-based studies are needed in other parts of the world with low air pollution concentrations.

Although most previous studies on low-level air pollution have focused on $PM_{2·5}$, the need to assess associations with mortality for other major air pollutants, including nitrogen dioxide (NO_2), ozone (O_3), and black carbon (a measure of primary combustion particles), is increasingly being shown.[1,4,11–13,15] For air pollution management, different pollutants from various sources should be assessed. The objective of this multicentre study was to investigate the shape of the relationship between long-term exposure to $PM_{2·5}$, NO_2, black carbon, and warm-season O_3 and non-accidental and cause-specific mortality, including cardiovascular, non-malignant, and malignant respiratory mortality, focusing on low pollution levels. We used standardised methods for exposure assessment and statistical analysis in seven large European cohorts with 28 million participants.

Methods

Study populations and mortality outcomes

In this multicentre longitudinal study, we collected data from six population-based nationwide cohorts in Belgium, Denmark, England, the Netherlands, Norway, and Switzerland, and from one citywide cohort in Rome, Italy (appendix pp 2–3, 17). Briefly, cohorts were enrolled between 2000 and 2011 based on data from population or census registries and followed up until 2011–17. Participants aged 30 years or older were enrolled, and followed up until death, emigration out of the study area, or end of the study, whichever came first. Mortality registries were used to extract the underlying cause of death for deceased individuals. Four study outcomes were selected as defined by the International Classification of Diseases, 9th revision (ICD-9) or 10th revision (ICD-10) codes: non-accidental (ICD-9: 1–779; ICD-10: A00–R99), cardiovascular (ICD-9: 400–440; ICD-10: I10–I70), non-malignant respiratory (ICD-9: 460–519; ICD-10: J00–J99), and lung cancer mortality (ICD-9: 162; ICD-10: C34). Non-accidental mortality was analysed as our main outcome. All cohorts recorded baseline information on age, sex, residential address, and area-level socioeconomic status (SES) indicators for each participant. Five cohorts recorded data on marital status and occupation, and four cohorts had data on country of origin and education (table 1). Only the English cohort had individual data on smoking and

body-mass index (BMI). In the other cohorts we used data from smaller external surveys in the study area with information on smoking and BMI for indirect adjustment of effect estimates (appendix pp 4–9). We assessed all enrolled participants with available data on analysed covariates and exposures (table 1).

We used centrally developed Europe-wide exposure models, harmonised the definition of confounders, and standardised the analytical strategy by centrally developing and distributing common R scripts to all cohort analysts.

The study was conducted in accordance with the Declaration of Helsinki. The original cohort studies were approved by appropriate institutional review boards complying with all relevant national, state, and local regulations. Informed consent was waived due to the nature of data sources.

Estimation of air pollution exposure

Annual mean concentrations of $PM_{2.5}$, NO_2, black carbon, and warm-season O_3 (from April to September inclusive) were centrally estimated for western Europe with land use regression models for the year 2010.[16] The linear regression models were trained on pollution concentrations measured at large numbers of sites by the AirBase network of the European Environmental Agency ($PM_{2.5}$, NO_2, and O_3) or by the European Study of Cohorts for Air Pollution Effects (black carbon),[17] with satellite data, dispersion models, land use variables, and traffic data as potential predictors. The models performed reasonably well in 5-fold cross-validation, with percentages of explained variability in held-out air pollution monitors between 51% (black carbon) and 66% ($PM_{2.5}$), which reduced to 34% at black carbon concentrations lower than $1{\cdot}5\times10^{-5}$/m and 38% at

Institute of Public Health, Cluster for Health Services Research, Oslo, Norway (D T Kristoffersen PhD); **Department of Cardiology, Danderyd University Hospital, Stockholm, Sweden** (P L S Ljungman); **Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany** (Prof G Nagel MD, G Weinmayr PhD); **Institute of Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany** (Prof A Peters PhD, K Wolf PhD); **Ludwig Maximilians Universität München, Munich, Germany** (Prof A Peters); **Department of Neurobiology,**

	Belgian cohort	Danish cohort	Dutch cohort	English cohort	Norwegian cohort	Rome cohort	Swiss cohort
Cohort details							
Total participants	6 491 801	3 323 612	10 532 360	1 491 124	2 516 192	1 263 712	4 293 521
Participants with complete data	5 474 548 (84·3%)	3 083 235 (92·8%)	10 465 727 (99·4%)	1 368 740 (91·8%)	2 309 001 (91·8%)	1 263 712 (100·0%)	4 188 175 (97·5%)
Follow-up*	2001 to 2011	2000 to 2015	2008 to 2012	2011 to 2017	2001 to 2016	2001 to 2015	2000 to 2014
Person-years at end of follow-up*	54 575 223	42 586 584	50 436 539	9 084 293	32 531 421	15 301 265	53 344 296
Non-accidental mortality, n (rate per 1000 person-years)*	707 146 (13·0)	714 629 (16·8)	604 309 (12·0)	145 988 (16·1)	524 592 (16·1)	235 543 (15·4)	661 534 (12·4)
Cardiovascular mortality, n (rate per 1000 person-years)*	234 553 (4·3)	232 699 (5·5)	165 000 (3·3)	36 615 (4·0)	183 971 (5·7)	91 278 (6·0)	241 985 (4·5)
Respiratory mortality, n (rate per 1000 person-years)*	82 341 (1·5)	90 158 (2·1)	63 104 (1·3)	20 946 (2·3)	56 857 (1·7)	14 972 (1·0)	43 612 (0·8)
Lung cancer mortality, n (rate per 1000 person-years)*	52 211 (1·0)	51 881 (1·2)	49 294 (1·0)	9 346 (1·0)	27 525 (0·8)	19 572 (1·3)	36 680 (0·7)
Individual-level covariates*							
Age, years	52·6 (15·2)	53·0 (15·1)	53·6 (15·1)	58·9 (12·8)	53·9 (15·9)	55·1 (15·4)	52·7 (15·2)
Women	2 704 580 (49·4%)	1 594 177 (51·7%)	5 373 585 (51·3%)	718 019 (52·5%)	1 175 702 (50·9%)	688 172 (54·5%)	2 179 587 (52·0%)
Current smokers	NA	NA	NA	492 684 (36·0%)	NA	NA	NA
Body-mass index, kg/m²	NA	NA	NA	27·5 (5·6)	NA	NA	NA
Born in study region	5 302 118 (96·9%)	2 907 280 (94·3%)	8 665 292 (82·8%)	NA	NA	NA	3 480 232 (83·1%)
Household income levels†	NA	Deciles	Deciles	NA	Quartiles	NA	NA
Marital status							
Single	675 491 (12·3%)	NA	1 978 248 (18·9%)	NA	411 200 (17·8%)	192 769 (15·3%)	585 510 (14·0%)
Married	3 739 836 (68·3%)	NA	6 599 500 (63·1%)	NA	1 369 694 (59·3%)	838 161 (66·3%)	2 900 333 (69·3%)
Divorced	541 609 (9·9%)	NA	1 053 822 (10·1%)	NA	283 817 (12·3%)	88 645 (7·0%)	362 642 (8·7%)
Widowed	517 534 (9·5%)	NA	834 157 (8·0%)	NA	244 290 (10·6%)	144 137 (11·4%)	339 690 (8·1%)
Education level‡							
Low	1 301 659 (23·8%)	NA	NA	NA	720 257 (31·2%)	314 675 (24·9%)	1 027 268 (24·5%)
Medium	2 839 960 (51·9%)	NA	NA	NA	1 057 520 (45·8%)	743 188 (58·8%)	2 208 181 (52·7%)
High	1 332 929 (24·3%)	NA	NA	NA	531 224 (23·0%)	205 156 (16·2%)	952 726 (22·7%)
Occupational status§							
Employed	2 919 418 (53·3%)	1 841 848 (59·7%)	NA	NA	1 519 637 (65·8%)	578 751 (45·8%)	2 573 280 (61·4%)
Unemployed	276 948 (5·1%)	78 924 (2·6%)	NA	NA	27 381 (1·2%)	62 859 (5·0%)	90 238 (2·2%)
Homemaker	463 245 (8·5%)	1 162 463 (37·7%)‡	NA	NA	0	265 546 (21·0%)	612 344 (14·6%)
Retired	1 814 947 (33·2%)	0‡	NA	NA	761 983 (33·0%)	296 398 (23·5%)	912 313 (21·8%)

Data are n (%) or mean (SD) unless stated otherwise. NA=not available. *For the participants with complete data. †Data were retained in classes to comply with privacy regulations. ‡Low education denotes primary school or less, medium education denotes secondary school, and high education denotes university degree or more. §Occupational status has three classes in the Danish cohort: employed, pensioner (ie, retired, other, student, cash support, or sick), and unemployed.

Table 1: **Description of the seven administrative cohorts and participant characteristics**

Care Sciences, and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden (D Rizzuto PhD); Stockholm Gerontology Research Center, Stockholm, Sweden (D Rizzuto); Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, University Hospital Essen, Germany (S Schramm MD); Exposome and Heredity Team, University Paris-Saclay, UVSQ, INSERM, Gustave Roussy, Villejuif, France (G Severi PhD); Department of Statistics, Computer Science and Applications "G Parenti", University of Florence, Italy (G Severi); Department of Public Health, Environment Occupation and Health, Danish Ramazzini Centre, Aarhus University, Aarhus, Denmark (Prof T Sigsgaard); Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands (Prof Y T van der Schouw PhD, Prof M Verschuren); Agency for Preventive and Social Medicine, Bregenz, Austria (E Zitt MD)

Correspondence to: Dr Massimo Stafoggia, Department of Epidemiology, Lazio Region Health Service, ASL Roma 1, 00147 Rome, Italy **m.stafoggia@deplazio.it**

See Online for appendix

$PM_{2.5}$ concentrations lower than 12 μg/m³ (appendix p 11).[16] Annual mean predictions of the four pollutants were then calculated on a 100×100 m grid and assigned to the baseline residential addresses of the cohort participants. In our main analysis we used exposure of the baseline address as the relevant exposure. If a participant changed address during follow-up, but remained in the study area, we included them in the analysis. Participants who moved out of the study area were censored on the day of emigration. In additional sensitivity analyses with time-varying exposures, we allowed exposures to change by year, and accounted for residential changes in the analyses. For use in the sensitivity analyses, annual mean concentrations were estimated for each year of follow-up by applying back-extrapolation and forward-extrapolation procedures on the basis of a validated chemical transport model.[18] Further details on the exposure models are provided in the appendix (p 10).

Statistical analysis

Data were analysed by cohort, followed by a random-effects meta-analysis. Data needed to be analysed in a national secure environment in all countries, precluding data pooling.

We applied multiple Cox proportional hazard models with adjustment for individual-level and area-level covariates. We specified three confounder models a priori, following the general modelling strategy of the ELAPSE study.[19,20] Model 1 included age (time axis), sex (as strata), and calendar year of enrolment. Model 2 added all individual-level variables available in each administrative cohort (table 1, appendix p 14) to achieve maximal adjustment. Model 3 added to model 2 multiple area-level SES variables such as income, education, and unemployment at both the regional and neighbourhood scale (appendix p 14). Regions were defined as large-scale areas, such as counties and administrative regions, which was applicable for the six national cohorts. Neighbourhoods were defined as smaller units, representing parts of a city, with about 1000–10 000 people, with some differences across cohorts. All models were run on the populations with complete data on covariates in model 3, to allow comparison across models. We used a robust estimator of variance to account for the dependence of observations belonging to the same neighbourhood (appendix p 15).

Within each cohort, we first modelled linear effects for each pollutant (ie, we fit a model where the logarithm of the hazard ratio [HR] changed linearly in proportion to air pollution concentration). Our primary exposure variable was based on models for 2010. We then estimated the shape of the concentration-response function by modelling each pollutant with a natural spline with three degrees of freedom, and by estimating the recently developed shape-constrained health impact function (SCHIF).[9] In this paper, we present natural splines and SCHIF curves for the main outcome of interest, non-accidental mortality. Additionally, we specified linear models in subsets of the concentration range for all pollutants, defined by removing individuals with concentrations higher than a certain value from the analysis. For $PM_{2.5}$, subsets were defined by annual cutoff values of 25 μg/m³ (EU limit value), 20 μg/m³, 15 μg/m³, 12 μg/m³ (US EPA national ambient air quality standard), and 10 μg/m³ (WHO 2005 air quality guideline value); and for NO_2, 40 μg/m³ (EU limit value and WHO 2005 air quality guideline), 30 μg/m³, and 20 μg/m³ (20 μg/m³ threshold taken from the health risks of air pollution in Europe project [HRAPIE]).[21] For black carbon, subsets were defined by annual cutoff values between $3{\cdot}0\times10^{-5}$/m and $1{\cdot}0\times10^{-5}$/m. These values were chosen to represent realistic cutpoints within the distributions that were observed in the ELAPSE study.

We conducted sensitivity analyses to check the robustness of the main results to different model choices and co-exposures. Details are reported in the appendix (pp 16, 31–35). Briefly, we back-extrapolated air pollutant concentrations to baseline year, as an alternative to the year 2010 used in the main approach. We fitted time-varying Cox models to account for residential history and time trends in pollutant exposure and mortality during follow-up. We applied two-pollutant models to distinguish the effects of different pollutants. To indirectly adjust for smoking and BMI (detailed methods in the appendix, pp 15–16), we used available survey data (appendix pp 4–9) or area-level prevalence of chronic obstructive pulmonary disease and lung cancer for smoking and diabetes for BMI. Area-level prevalence data were from hospital discharge files from national and regional registries (appendix p 16). Results of these adjustments for lifestyle variables are presented for non-accidental mortality. We also adjusted for co-exposure to traffic noise (available in five cohorts) in a sensitivity analysis of cardiovascular mortality because epidemiological evidence has shown associations between road traffic noise and cardiovascular endpoints.[22] O_3 was excluded from most additional analyses post hoc due large uncertainty in the model 3 results for O_3.

We pooled cohort-specific estimates with a random-effects meta-analysis using the restricted maximum-likelihood estimator of the between-cohorts variance.[23] We estimated HRs, and 95% CIs, per fixed increments in air pollutants chosen a priori and consistent with previous studies: 5 μg/m³ for $PM_{2.5}$, 10 μg/m³ for NO_2 and O_3, and $0{\cdot}5\times10^{-5}$/m for black carbon.[1,19,20] Results were considered statistically significant when the 95% CI excluded unity. We evaluated the presence of heterogeneity in the cohort-specific results by applying the Cochran's Q test based on a χ^2 distribution, which was then quantified by calculating the I^2 statistic.[24] We obtained meta-analytical curves of the concentration-response functions between the pollutants and non-accidental mortality by applying the meta-smoothing approach (appendix p 15),[25] according to which predictions (and standard errors) of the natural spline models were derived per 0·1-unit increment in the

pollutant-specific concentrations in each cohort (per 0·01-unit increment for black carbon) and consequently meta-analysed. 95% CIs were used to interpret statistical significance of the concentration-response functions. All analyses were conducted with R software (version 3.6.0) and were based on common scripts developed and distributed by a statistical group within the ELAPSE project.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 29 912 322 participants in all seven cohorts, we analysed 28 153 138 participants with complete data, contributing 257 859 621 person-years of observation, during which 3 593 741 deaths from non-accidental causes were observed (table 1, appendix pp 4–9, 14).

Air pollution concentrations in 2010 varied substantially between cohorts, with a clear north-to-south gradient (figure 1). More than 3·9 million participants had a $PM_{2·5}$ exposure below the US EPA standard (12 μg/m³) and more than 1·9 million participants had a $PM_{2·5}$ exposure below the WHO 2005 guideline value (10 μg/m³), mostly from Norway and Denmark. In the Norwegian cohort, 1 642 644 (71·1%) of 2 309 001 participants had $PM_{2·5}$ exposures below the WHO 2005 guideline value. All cohorts had exposures mostly below the EU limit values for both $PM_{2·5}$ (25 μg/m³) and NO_2 (40 μg/m³). Correlations between pollutants were generally moderate, except between NO_2 and black carbon (strongly positive as both are mainly from traffic) and between NO_2 and warm-season O_3 (strongly negative, due to atmospheric chemistry), with negligible differences in Spearman's *r* values between the city cohort of Rome and the rural nationwide cohort in Norway (NO_2 and black carbon, *r*=0·91 *vs* 0·92; NO_2 and O_3, *r*=–0·80 *vs*–0·81; appendix p 18).

We found significant positive associations between $PM_{2·5}$, NO_2, and black carbon and all mortality outcomes in our main model 3. Pooled HRs for non-accidental mortality were 1·053 (95% CI 1·021–1·085) per 5 μg/m³ increment in $PM_{2·5}$, 1·044 (1·019–1·069) per 10 μg/m³ NO_2, and 1·039 (1·018–1·059) per $0·5\times10^{-5}$/m black carbon (table 2). The $0·5\times10^{-5}$/m increment for black carbon is approximately equivalent to 0·44 μg/m³.[26] In comparison, associations with $PM_{2·5}$, NO_2, and black carbon were slightly weaker for cardiovascular mortality, similar for non-malignant respiratory mortality, and stronger for lung cancer mortality. Mortality HRs for these three pollutants were greater than 1 for most individual cohorts (figure 2, appendix pp 20–22). The cohort-specific HRs were heterogeneous, with relatively high effect estimates for the Norwegian and Danish cohorts, and lower estimates

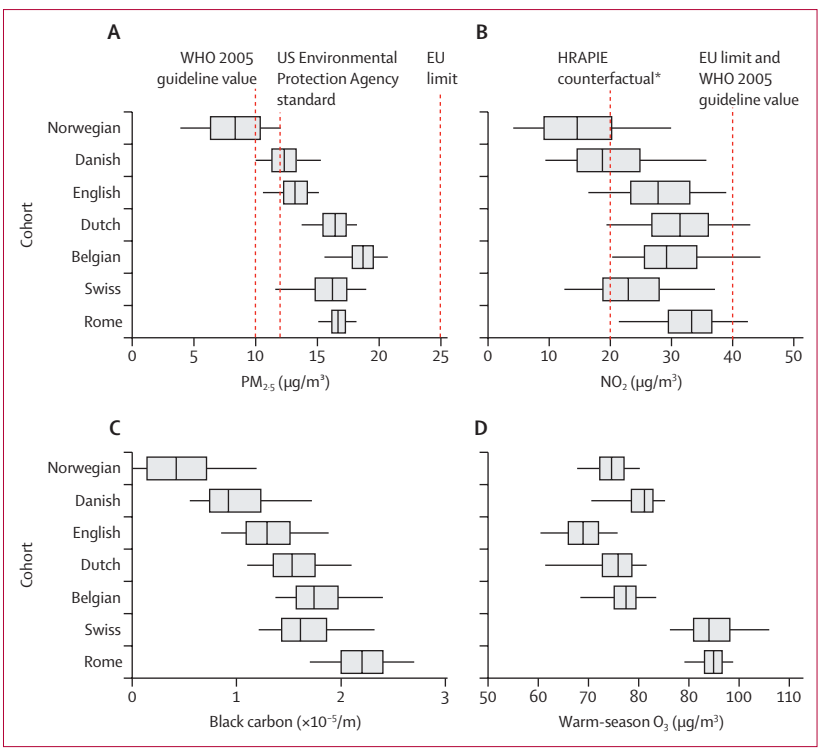

Figure 1: **Distribution of air pollutant exposures at participant addresses in 2010**
The boundary of the box closest to zero indicates the 25th percentile; the boundary furthest from zero indicates the 75th percentile; the bold line in the middle of the box indicates the 50th percentile (median); whiskers indicate 5th and 95th percentiles. HRAPIE=health risks of air pollution in Europe project. NO_2=nitrogen dioxide. O_3=ozone. $PM_{2·5}$=fine particulate matter. *HRAPIE-suggested counterfactual below which no health impact is quantified.[21]

for the other cohorts. Warm-season O_3 was negatively associated with both non-accidental and cause-specific mortality (table 2). The negative associations with O_3 might be due to the strong negative correlation with NO_2. However, all O_3 associations are difficult to interpret because of the small range in exposure. Increasing levels of adjustment for individual-level and area-level confounders did not alter the main results (appendix p 19).

All cohorts contributed to the analysis of the concentration-response function for exposures lower than 15 μg/m³ for $PM_{2·5}$, and all but the Rome cohort had at least some participants at $PM_{2·5}$ exposures lower than 12 μg/m³. The Danish, English, Norwegian, and Swiss cohorts contributed to the analysis for $PM_{2·5}$ exposures lower than 10 μg/m³. All cohorts contributed to the analysis of NO_2 exposures lower than 20 μg/m³, and to the analysis of black carbon exposures lower than $2·0\times10^{-5}$/m. The pooled concentration-response functions showed increasing risks of non-accidental mortality with increasing $PM_{2·5}$, NO_2, and black carbon, with the steepest part of the curves occurring at low exposures (supralinear concentration-response function) and no evidence of a threshold for the association with mortality (figure 3). Cohort-specific natural splines showed more heterogeneous shapes across the seven

	Increment	Hazard ratio (95% CI)			
		Non-accidental mortality	Cardiovascular mortality	Non-malignant respiratory mortality	Lung cancer mortality
$PM_{2·5}$	5 μg/m³	1·053 (1·021–1·085)	1·041 (1·010–1·072)	1·064 (1·013–1·118)	1·102 (1·036–1·172)
NO_2	10 μg/m³	1·044 (1·019–1·069)	1·025 (1·006–1·044)	1·058 (1·024–1·093)	1·093 (1·053–1·134)
Black carbon	$0·5 \times 10^{-5}$/m*	1·039 (1·018–1·059)	1·022 (1·004–1·040)	1·053 (1·021–1·085)	1·078 (1·038–1·118)
O_3	10 μg/m³	0·953 (0·929–0·979)	0·976 (0·954–0·998)	0·948 (0·910–0·988)	0·924 (0·887–0·963)

Results are from the random-effects meta-analysis; results from cohort-specific models were adjusted for individual-level and area-level covariates available in the administrative cohorts. These include, in almost all cases, age, sex, marital status, educational level, occupational status, and individual-level and area-level income or socioeconomic position (appendix p 14). $PM_{2·5}$=fine particulate matter. NO_2=nitrogen dioxide. O_3=ozone. *The $0·5 \times 10^{-5}$/m increment for black carbon is approximately equivalent to 0·44 μg/m³.[21]

Table 2: **Association between air pollutants and mortality outcomes in the seven administrative cohorts**

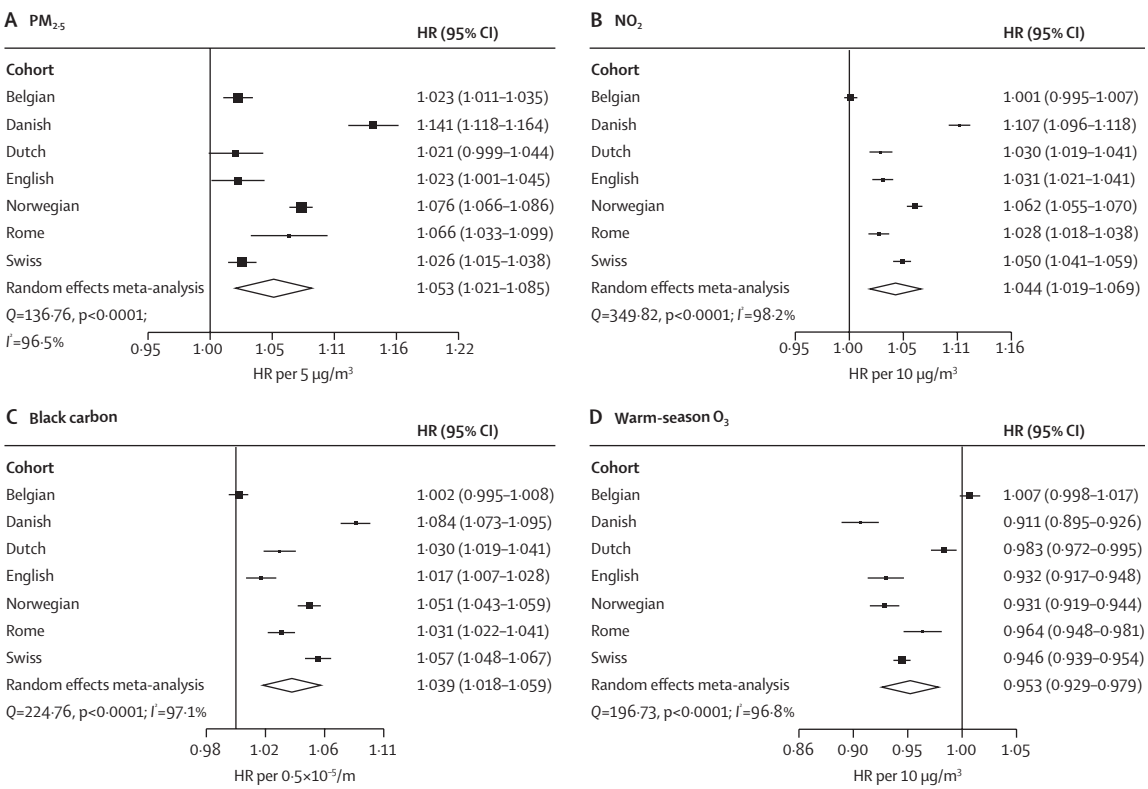

Figure 2: **Forest plots of the association between air pollutants and non-accidental mortality**
Cohort-specific and meta-analytical results. Results are expressed per fixed increments of the pollutants, equal to 5 μg/m³ for $PM_{2·5}$, 10 μg/m³ for NO_2 and O_3, and $0·5 \times 10^{-5}$/m for black carbon. Results are from models adjusted for individual-level and area-level covariates available in the administrative cohorts. These include, in almost all cases, age, sex, marital status, educational level, occupational status, and individual-level and area-level income or socioeconomic position (appendix p 14). The size of the squares is proportional to the weight each cohort has in the meta-analysis. Diamonds are centred on the point estimate and extend to the 95% CIs. HR=hazard ratio. NO_2=nitrogen dioxide. O_3=ozone. $PM_{2·5}$=fine particulate matter.

cohorts for associations with non-accidental mortality, but were mostly consistent with linear or supralinear slopes when confidence intervals were sufficiently narrow for an evaluation (appendix pp 23–24). Cohort-specific SCHIFs for $PM_{2·5}$, NO_2, and black carbon also supported positive functions for non-accidental mortality, generally showing the strongest effects at low concentrations (appendix pp 25–26), with some exceptions (eg, the Swiss and Belgian cohorts).

The subset analyses supported the spline and SCHIF analyses. Associations with non-accidental mortality remained stable when limiting the analysis to decreasing concentrations of pollutants (table 3), although some estimates at the lowest concentrations did not reach statistical significance probably due to reduced power. Similar results from subset analyses were observed for cause-specific mortality (appendix p 27). For $PM_{2·5}$ and NO_2, moderately increased HRs were found when

the analysis was restricted to low exposures: HRs for non-accidental mortality at concentrations lower than those in the WHO 2005 air quality guidelines for $PM_{2·5}$ (10 μg/m³) and NO_2 (40 μg/m³) were 1·078 (1·046–1·111) per 5 μg/m³ $PM_{2·5}$ and 1·049 (1·024–1·075) per 10 μg/m³ NO_2. Similarly, the effect estimate for black carbon at low exposure (<$1·5\times10^{-5}$/m) was moderately larger than for the full range of exposure (table 3).

Results of the two-pollutant models for non-accidental and cause-specific mortality showed an attenuation of $PM_{2·5}$ HRs after adjustment for either NO_2 or black carbon, whereas HRs for NO_2 and black carbon remained stable after adjustment for $PM_{2·5}$. HRs for O_3 approached unity and became non-significant on adjustment for NO_2 or black carbon, and, in some instances, on adjustment for $PM_{2·5}$, while NO_2 effects were robust and slightly increased with O_3 co-exposure (appendix p 29).

Indirect adjustment for smoking and BMI had a negligible effect on the main results for non-accidental mortality; some cohorts (Danish, Dutch, Norwegian, and Swiss) showed a mild attenuation in HRs, whereas others (Belgian and Rome) showed an increase in HRs. Similarly, adjustment for area-level rates of chronic obstructive pulmonary disease, lung cancer, and diabetes as proxies for smoking and BMI had little effect on the main associations with non-accidental mortality (appendix p 30).

Other sensitivity analyses did not alter the main findings: back-extrapolation of exposure to baseline year produced similar or slightly smaller effect estimates than those obtained with 2010 exposures (appendix p 31); marginal reductions in effect estimates were obtained when we applied time-varying analyses, with exposures modelled as either linear terms (appendix p 32) or splines (appendix pp 33–34); and adjustment for traffic noise did not markedly alter the association between air pollutants and cardiovascular mortality (appendix p 35).

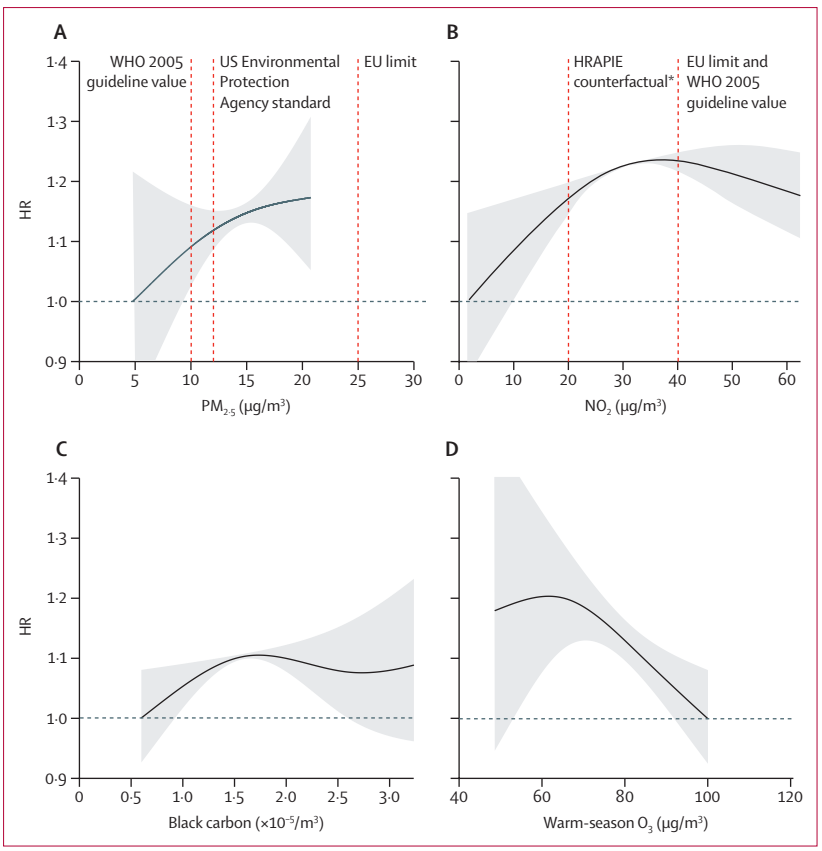

Figure 3: **Meta-analytical concentration-response functions of the association between air pollutants and non-accidental mortality**
Cohort-specific models were adjusted for individual-level and area-level covariates available in the administrative cohorts (appendix p 11). Meta-analytical curves were obtained by meta-smoothing with natural splines with three degrees of freedom. The shaded regions are 95% CIs. HR=hazard ratio. NO_2=nitrogen dioxide. O_3=ozone. $PM_{2·5}$=fine particulate matter. *HRAPIE-suggested counterfactual below which no health impact is quantified.[21]

Discussion

In this analysis of seven large administrative European cohorts, low concentrations of $PM_{2·5}$, NO_2, and black carbon were positively associated with non-accidental and cause-specific mortality. Associations were observed at concentrations markedly lower than official limit values and guideline values for $PM_{2·5}$ and NO_2. Associations typically showed a concentration-response function with the steepest part of the slopes at low exposures, without an indication of a threshold. Associations with O_3 were mostly negative but were attenuated to unity in two-pollutant models with NO_2 or black carbon, whereas NO_2 associations were unaffected and sometimes strengthened by O_3 co-exposure. In a sensitivity analysis of non-accidental mortality, results were robust to indirect adjustment for lifestyle covariates such as smoking and BMI.

Low concentrations of $PM_{2·5}$ and NO_2 have been associated with mortality in a few large studies, especially in North America.[4,7,13,14] In the USA, Di and colleagues enrolled a cohort of more than 60 million Medicare beneficiaries and reported an increase in all-cause mortality of 3·6% (3·5–3·7) per 5 μg/m³ increment in $PM_{2·5}$ exposure, which rose to 6·6% (6·3–6·8) when the analysis was restricted to $PM_{2·5}$ concentrations lower than 12 μg/m³.[4] There was no indication of a threshold down to concentrations of 5 μg/m³. In Canada, Crouse and colleagues reported similar findings in the population-based Canadian Census Health and Environment Cohort: long-term exposures to $PM_{2·5}$ and NO_2 concentrations were associated with non-accidental mortality, with HRs of 1·035 (95% CI 1·029–1·041) per 5 μg/m³ increments of $PM_{2·5}$ and 1·052 (1·045–1·059) per 8·1 parts per billion (ppb) of NO_2 (~15 μg/m³), and evidence of steeper associations at concentrations below 10 μg/m³ ($PM_{2·5}$) and 25 μg/m³ (NO_2).[13] Additionally, there was no indication of a threshold down to concentrations of 1 μg/m³ for both $PM_{2·5}$ and NO_2. A previous analysis in the Danish cohort included in our study, which used a different exposure model, reported significant associations for both $PM_{2·5}$ and NO_2 with

	Number of cohorts	Number of participants	HR (95% CI)
$PM_{2.5}$, µg/m³			
Full dataset	7	28 153 138	1·053 (1·021–1·085)
<25	7	28 146 444	1·053 (1·021–1·085)
<20	7	27 210 961	1·053 (1·022–1·086)
<15	7	9 703 270	1·051 (0·998–1·108)
<12	6*	4 026 706	1·095 (1·002–1·197)
<10	4†	1 920 292	1·078 (1·046–1·111)
NO_2, µg/m³			
Full dataset	7	28 153 138	1·044 (1·019–1·069)
<40	7	26 085 008	1·049 (1·024–1·075)
<30	7	16 791 623	1·063 (1·031–1·097)
<20	7	5 881 351	1·061 (0·985–1·143)
Black carbon, $\times 10^{-5}$/m			
Full dataset	7	28 153 138	1·039 (1·018–1·059)
<3·0	7	28 108 712	1·040 (1·019–1·060)
<2·5	7	27 684 442	1·042 (1·021–1·063)
<2·0	7	24 278 537	1·045 (1·022–1·067)
<1·5	6*	13 181 589	1·061 (1·032–1·092)
<1·0	4†	4 160 568	1·081 (0·966–1·210)

Results are from the random-effects meta-analysis; results from cohort-specific models were adjusted for individual-level and area-level covariates available in the administrative cohorts. These include, in almost all cases, age, sex, marital status, educational level, occupational status, and individual-level and area-level income or socioeconomic position (appendix p 14). HRs are expressed per fixed increments of the pollutants: 5 µg/m³ for $PM_{2.5}$, 10 µg/m³ for NO_2, and $0{\cdot}5 \times 10^{-5}$/m for black carbon. HR=hazard ratio. $PM_{2.5}$=fine particulate matter. NO_2=nitrogen dioxide. *All cohorts except the Rome cohort. †The Danish, English, Norwegian, and Swiss cohorts.

Table 3: **Association between air pollutants and non-accidental mortality in subset analysis of the seven administrative cohorts**

all-cause and cause-specific mortality at concentrations lower than the WHO 2005 guideline value of 10 µg/m³ for $PM_{2.5}$ and the HRAPIE counterfactual value of 20 µg/m³ for NO_2.[8] Our study in seven large population-based cohorts provides strong support for associations of low pollutant exposures with mortality for both $PM_{2.5}$ and NO_2 in a European context. As originally discussed by Pope and colleagues in 2009,[27] and more recently argued by Pope and colleagues in 2015[28] and Burnett and colleagues in 2020,[29] the supralinear shape of the concentration-response function estimated in our cohorts suggests that incremental pollution reduction strategies might provide health benefits even in areas with relatively clean air.

Our linear effect estimates for $PM_{2.5}$ and NO_2 were larger than those reported in two recent systematic reviews commissioned by WHO. The combined HR for the effect of $PM_{2.5}$ exposure on non-accidental mortality across 25 studies in one of the WHO systematic reviews was 1·08 (1·06–1·09) per 10 µg/m³ increase in $PM_{2.5}$.[11] Our combined estimate was 1·108 (1·042–1·178) expressed per 10 µg/m³. Our HR estimate for NO_2 (1·044 [1·019–1·069] per 10 µg/m³) is larger than the combined estimate from 24 studies in the other WHO systematic review (1·02 [1·01–1·04] per 10 µg/m³).[30] Both in the systematic reviews and in our current analysis, substantial heterogeneity in effect estimates across cohorts was observed. The reasons for this heterogeneity are not well understood, but probably include differences in exposure assessment, $PM_{2.5}$ composition, control for covariates, and age of the population. Thus $PM_{2.5}$ at low concentrations, or in different countries or regions of countries, might represent particles with different toxicity. However, the debate on which PM components are more or less toxic than others is unresolved.[31,32]

Few studies have investigated the association between long-term exposure to black carbon and mortality.[26,33–35] We found significant associations with black carbon, even at low exposures, which were robust to $PM_{2.5}$ adjustment. Two-pollutant models of black carbon with NO_2 are difficult to interpret because of the high correlation between the two. Since both NO_2 and black carbon are components of emissions from combustion processes, the consistent associations we found between NO_2 and black carbon with mortality point toward combustion sources including tailpipe emissions as sources of adverse health effects. $PM_{2.5}$ associations were strongly attenuated when adjusted for NO_2, and attenuated in two-pollutant models with black carbon, suggesting an important role of multipollutant mixtures directly emitted from combustion sources in our study. For O_3, we did not observe the previously reported positive associations in studies in North America.[4,13,15,36–38] Associations in single-pollutant models of O_3 in our study were inverse, but attenuated towards unity and became insignificant in two-pollutant models with NO_2 or black carbon, and occasionally on adjustment for $PM_{2.5}$. The relatively small range in O_3 exposure within our cohorts (IQRs <15 µg/m³ for all cohorts, figure 1D) makes our study less informative on O_3 associations than the Medicare study, which covered a concentration range of 30–60 ppb (approximately 60–120 µg/m³),[4] or the Canadian study, with a range of 10–60 ppb (20–120 µg/m³).[13]

This multicentre study has several strengths. We standardised the air pollution exposure assessment, the definition of models, and the analytical strategy: exposures were derived uniformly across western Europe with the latest land use regression models and assigned to the residential addresses of participants, and the statistical analyses were conducted on the basis of predefined common analytical protocols, with R scripts developed by a statistical working group and distributed to all analysts. These protocols included an extended set of analyses aimed at checking the robustness of the main results to model specification and exposure definition. In particular, for non-accidental mortality, we assessed the sensitivity of estimates by indirectly adjusting for key covariates usually omitted in large administrative cohorts (ie, BMI and smoking), using information from external survey studies or area-level prevalences of related conditions. We also applied back-extrapolation procedures to assign exposures from the baseline year,

and as time-varying exposures during follow-up, to provide further support for the main conclusions about the shape of the exposure-response functions at low concentrations.

We were able to combine results from seven large population-based prospective cohorts, with 28 million participants and 258 million person-years included in the analysis. The inclusion of cohorts in seven different countries reduces the likelihood of bias related to spatial patterns in unmeasured covariates that are concordant with air pollution patterns. Being registry based, these populations had less selective recruitment and dropout compared with traditional cohort studies. The present cohorts also included populations in rural areas, which are often not represented in traditional cohort studies.

The study was explicitly designed to investigate the shape of the concentration-response functions at low pollutant concentrations, and was adequately powered to do so, including more than 3·9 million participants with $PM_{2·5}$ exposure below the annual US EPA standard (12 μg/m³), more than 1·9 million with $PM_{2·5}$ exposure below the annual limit in the WHO 2005 guideline (10 μg/m³), and 26·1 million with NO_2 exposure below the WHO 2005 guideline and EU limit value (40 μg/m³). Furthermore, we applied three alternative methods to investigate associations between air pollutants and mortality at low exposures, namely natural splines, SCHIFs, and a subset analysis, providing a broad scope of evidence for associations of mortality with $PM_{2·5}$, NO_2, and black carbon down to low concentrations.

A limitation of large population-based cohorts like ours is confounding adjustment. Except for the English cohort, no cohorts had data on smoking and BMI available at the individual level, and we cannot entirely exclude residual confounding from unmeasured covariates. We did adjust for a fairly extensive set of individual-level and area-level SES indicators. This adjustment is important as the relationship between air pollution exposure and lifestyle is predominantly mediated by SES.[39] The limited effect of missing lifestyle variables on air pollution effect estimates we observed is consistent with the North American studies.[4,7,14] We also note that in some of our cohorts, effect estimates increased after indirect adjustment. Lack of adjustment for individual lifestyle might bias in either direction.

For $PM_{2·5}$, there were large differences in exposure between cohorts, with most of the low concentration exposures occurring in Scandinavian cohorts, potentially limiting the generalisability of our results in other populations. However, we note that six of seven cohorts contributed data on exposures lower than 12 μg/m³ (table 3) and the forest plots did not suggest that the meta-analytical effect estimates were driven by the findings in Norway or Denmark. For $PM_{2·5}$, the findings in the Norwegian cohort strongly support that associations persist at very low exposures. The high correlation between NO_2 and black carbon limited the possibility to assess the independent effects of NO_2 and primary combustion particles. The small range in O_3 exposure produced non-informative estimates of associations between O_3 and the study outcomes.

We investigated outdoor air pollution concentrations, with no information on individual time–activity patterns, nor indoor–outdoor infiltration. Indeed, people spend a lot of time indoors, but PM and, to a somewhat lesser extent, NO_2, penetrate readily indoors. This is different for O_3, which is highly reactive, partly explaining the null effects of O_3 in our study. Furthermore, air pollution concentrations were estimated for 2010 and assigned to the baseline addresses, potentially introducing additional exposure misclassification. However, the sensitivity models on back-extrapolation and time-varying analyses confirmed our main findings. Additionally, the percentage of variability in held-out monitors explained by the land use regression models decreased at low concentrations (appendix p 11); however, this was paralleled by decreased model residuals.

In conclusion, long-term exposure to low concentrations of $PM_{2·5}$, NO_c, and black carbon was associated with non-accidental, cardiovascular, non-malignant respiratory, and lung cancer mortality in seven large prospective cohort studies in Europe, notably, at $PM_{2·5}$ and NO_2 exposures lower than annual limit values of the EU, US EPA, and WHO 2005 air quality guidelines.

Contributors

MSta is the corresponding author. BB, GH, JC, and MStr are the coordinators of the ELAPSE project, under which the study was conducted. MSta, JC, ZJA, TB, JG, BH, PLSL, GP, YTvdS, GW, ES, FF, BB, GH, and NAHJ equally contributed to the study concept. MSta and MR pooled results from all cohorts, performed the meta-analysis, and wrote the first draft of the manuscript. SR, KW, and ES developed the statistical codes and provided key methodological support. BO, DTK, MR, RWA, MB, JOK, AM, and DV analysed cohort-specific data. The data were accessed and verified by MB and MV for the Belgian cohort, ZJA and AM for the Danish cohort, JOK and NAHJ for the Dutch cohort, RWA and DF for the English cohort, BO and DTK for the Norwegian cohort, MSta and MR for the Rome cohort, and DV and KdH for the Swiss cohort. KdH and OH provided air pollution exposure data. JB, GC, DF, UAH, K-HJ, JTJ, KK, MK, DTK, AL, KL, SL, GN, AP, OR-N, DR, SS, PES, GS, TS, MV, and EZ provided clinical or epidemiological interpretations of the study findings. All authors contributed to critical revision of the Article for important intellectual content. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The exposure maps are available on request from KdH (c.dehoogh@swisstph.ch). The cohort data could not be shared among the ELAPSE project members including named authors, nor can the data be shared externally due to strict national data protection regulations and the General Data Protection Regulation of the EU. The ELAPSE study protocol is available online. A detailed statistical analysis plan is available from the corresponding author on reasonable request.

For the **ELAPSE protocol** see http://www.elapseproject.eu/

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