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Long-term low-level ambient air pollution exposure and risk of lung cancer – A pooled analysis of 7 European cohorts

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ABSTRACT

Background/aim: Ambient air pollution has been associated with lung cancer, but the shape of the exposure-response function - especially at low exposure levels - is not well described. The aim of this study was to address the relationship between long-term low-level air pollution exposure and lung cancer incidence.
Methods: The "Effects of Low-level Air Pollution: a Study in Europe" (ELAPSE) collaboration pools seven cohorts from across Europe. We developed hybrid models combining air pollution monitoring, land use data, satellite observations, and dispersion model estimates for nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$), black carbon (BC), and ozone (O_3) to assign exposure to cohort participants' residential addresses in 100 m by 100 m grids. We applied stratified Cox proportional hazards models, adjusting for potential confounders (age, sex, calendar year, marital status, smoking, body mass index, employment status, and neighborhood-level socio-economic status). We fitted linear models, linear models in subsets, Shape-Constrained Health Impact Functions (SCHIF), and natural cubic spline models to assess the shape of the association between air pollution and lung cancer at concentrations below existing standards and guidelines.
Results: The analyses included 307,550 cohort participants. During a mean follow-up of 18.1 years, 3956 incident lung cancer cases occurred. Median (Q1, Q3) annual (2010) exposure levels of NO_2, $PM_{2.5}$, BC and O_3 (warm season) were 24.2 $\mu g/m^3$ (19.5, 29.7), 15.4 $\mu g/m^3$ (12.8, 17.3), 1.6 $10^{-5}m^{-1}$ (1.3, 1.8), and 86.6 $\mu g/m^3$ (78.5, 92.9), respectively. We observed a higher risk for lung cancer with higher exposure to $PM_{2.5}$ (HR: 1.13, 95% CI: 1.05, 1.23 per 5 $\mu g/m^3$). This association was robust to adjustment for other pollutants. The SCHIF, spline and subset analyses suggested a linear or supra-linear association with no evidence of a threshold. In subset analyses, risk estimates were clearly elevated for the subset of subjects with exposure below the EU limit value of 25 $\mu g/m^3$. We did not observe associations between NO_2, BC or O_3 and lung cancer incidence.
Conclusions: Long-term ambient $PM_{2.5}$ exposure is associated with lung cancer incidence even at concentrations below current EU limit values and possibly WHO Air Quality Guidelines.

1. Introduction

Lung cancer is the most frequent cancer worldwide, accounting for 12% of all cancer diagnoses and the leading cause of cancer deaths (Bray et al., 2018). In high-income countries, the age-standardized incidence rate for men and women in 2018 was 40.4 and 19.1 per 100,000 person-years, respectively. Large regional differences exist, with an estimated incidence rate in Northern Europe of 34.0 in men and 26.9 in women per 100,000 person-years compared to 43.1 and 15.7 in Southern Europe (Bray et al., 2018). This incidence variation across geographical regions strongly reflects country-specific smoking prevalence. However, environmental risk factors such as indoor and ambient air pollution in addition to asbestos, radon, and arsenic exposure, are also established independent risk factors (Brambilla et al., 2014).

Over the years, epidemiological evidence of an effect of air pollution on lung cancer has accumulated, most notably for particulate matter (PM) exposure (Hamra et al., 2014). In 2013 the International Agency for Research on Cancer (IARC) classified outdoor air pollution as carcinogenic to humans (Group 1) (Straif et al., 2013). The large European Study of Cohorts for Air Pollution Effects (ESCAPE), which was based on 17 European cohorts analyzed in a standardized way and subsequently meta-analyzed, reported higher hazards with higher exposures to particulate matter with an aerodynamic diameter of <10 μm (PM_{10}) and <2.5 μm ($PM_{2.5}$) for incidence of all lung cancers and stronger associations specifically for adenocarcinomas (Raaschou-Nielsen et al., 2013). Despite the evidence linking PM exposure and lung cancer risk, uncertainty remains regarding the shape of the exposure-response function - especially at lower exposure levels (Cohen et al., 2017).

The aim of this study was to assess the relationship of long-term low-level air pollution exposure and lung cancer incidence. In addition to $PM_{2.5}$, we included nitrogen dioxide (NO_2), black carbon (BC) and ozone (O_3) for which a relationship with lung cancer has not been established. The Effects of Low-level Air Pollution: a Study in Europe (ELAPSE) builds on the ESCAPE collaboration by pooling data across cohorts selected to represent a contrast in low-level air pollution exposures between and within study areas. In contrast to ESCAPE, that used meta-analysis of individual cohort effect estimates, we performed a pooled data analysis, applied a more comprehensive standardized exposure assessment and had a longer follow-up. By pooling data of more than 300,000 individuals, we aimed to conduct an in-depth investigation of the exposure-response function at low exposure levels.

2. Methods

2.1. Study population

The ELAPSE collaboration contains eight of the ESCAPE cohorts and one additional cohort with the following criteria for inclusion: availability of data on low-level air pollution and the ability to share data for pooling. Of these nine cohorts, seven contained information on lung cancer incidence and the most important potential confounders. The cohorts included in the final analysis originated in Sweden (*Cardiovascular Effects of Air Pollution and Noise in Stockholm* [CEANS], which is the collective name of the following four sub-cohorts: Swedish National Study on Aging and Care in Kungsholmen [SNAC-K] (Lagergren et al., 2004); Stockholm Screening Across the Lifespan Twin study [SALT] (Magnusson et al., 2013); Stockholm 60 years old study [Sixty] (Wändell et al., 2007); and Stockholm Diabetes Prevention Program [SDPP]) (Eriksson et al., 2008); Denmark (*Diet, Cancer and Health cohort* [DCH]

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(Tjønneland et al., 2007) and *Danish Nurse Cohort* [DNC] (Hundrup et al., 2012), the Netherlands (*Dutch European Investigation into Cancer and Nutrition* [EPIC-NL] consisting of EPIC-Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands [EPIC-MORGEN] and [EPIC-Prospect]) (Beulens et al., 2010). France (*Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale* [E3N or EPIC-France]) (Clavel-Chapelon, 2015); Germany (*Heinz Nixdorf Recall study* [HNR]) (Schmermund et al., 2002); and Austria (*Vorarlberg Health Monitoring and Prevention Programme* [VHM&PP]) (Ulmer et al., 2007). We organized the harmonization of individual level variables from each cohort by identifying a list based on the ESCAPE confounder models, supplemented with additional variables. All seven cohorts had information available at baseline on age, sex, smoking status, amount and duration of smoking in current smokers (E3N and VHM&PP only in classes), body mass index (BMI), employment status and area-level socio-economic status (SES). Availability of variables and the specific definitions varied between cohorts. The dietary variables (i.e., alcohol and fruit intake), were defined with actual quantitative consumption (e.g., in grams/day) in some cohorts and with frequency of consumption (e.g., daily, weekly, seldom) in others. We harmonized these variables by classifying them into low, medium and high consumption. We describe each included cohort in more detail in the online appendix.

2.2. Exposure assessment

We assessed air pollution exposures for the pooled cohorts using Europe-wide hybrid land use regression (LUR) models, which incorporated air pollution monitoring data, satellite observations, dispersion model estimates, land use, and traffic variables as predictors. The exposure modelling and validation has been described in detail previously (de Hoogh et al., 2018). Briefly, for the modelling of $PM_{2.5}$, NO_2 and O_3 (warm season) we used 2010 AirBase routine monitoring data maintained by the European Environmental Agency (EEA) and for BC, which was not available through EEA, we used ESCAPE monitoring data (Eeftens et al., 2012); to develop and evaluate models. The exposure model has been validated using five-fold Hold Out Validation (HOV) in random subsets (20%) of the monitoring datasets, stratified by site type (background, traffic) and region of Europe (de Hoogh et al., 2018). The models generally explained a large fraction of measured spatial variation in the annual average concentration in HOV, e.g. 59% for NO_2, 72% for $PM_{2.5}$, 54% for BC, and 69% for O_3 average concentration in the warm season. We applied models for 2010 to create surfaces (100 m × 100 m grids) and linked these to the baseline residential address of each of the cohort members.

Our main model exposure represents exposure towards the end of follow-up (2010). We also estimated pollutant concentrations for each year from recruitment to end of follow-up for $PM_{2.5}$, NO_2, BC and O_3 using back-extrapolation back until 1990. We back-extrapolated by using estimated concentrations from the Danish Eulerian Hemispheric Model (DEHM) (Brandt et al., 2012). Results from the DEHM include hourly values of a number of chemical species, which were averaged into monthly concentrations across Europe at 26 km × 26 km spatial resolution (down-scaled from an original 50 km × 50 km resolution using a bi-linear interpolation) back to at least 1990. The rationale to perform back-extrapolation by modelled concentrations was to estimate long-term exposure over many years rather than a single year and this was possible because of the consistent availability of estimates across Europe for the full study period for all pollutants. In contrast, routine monitoring was less consistently available in the past, not available for BC and only available from about 2008 for $PM_{2.5}$. We used monitoring data to compare temporal patterns of modelled and measured concentrations for countries with measurements (de Hoogh et al., 2018). For application to the cohorts, we used the trends predicted by the DEHM for all four pollutants to calculate annual average concentrations for all years from recruitment up to end of follow-up, allowing different spatial trends within Europe (Online appendix Fig. S1). To allow for varying trends per country, we used the population weighted average concentrations of all 26 × 26 km cells within the Nomenclature of Territorial Units for Statistics (NUTS-1) spatial scale for national cohorts. NUTS-1 is a large scale, e.g. there are four NUTS-1 areas within the Netherlands. For smaller study areas, we used the population weighted average concentrations of all 26 × 26 km cells in the (approximated) study area. We back-extrapolated concentrations, using both a difference- and a ratio-method with 2010 as the baseline.

2.3. Outcome

We followed up the cohort participants for lung cancer incidence in cancer registries, death certificates or medical records with the exception of E3N in which we applied self-reports from biannual questionnaires or death certificates. Self-reported cases were confirmed through pathological reports and reviewed by a lung oncologist. We excluded persons registered with cancer before baseline (except non-melanoma skin cancer). We included primary cancers located in the bronchus and the lung (ICD9 codes 162.2–162.9 and ICD10 code C34) and obtained the histological characterization of the cancer to identify adenocarcinomas (ICDO3 8140–8384; fifth digit morphology code 3) and squamous-cell carcinomas (ICDO3 8050–8084; fifth digit morphology code 3).

2.4. Statistical analysis

We calculated hazard ratios (HR) with 95% confidence intervals (CI) by Cox Proportional Hazards models with age as the underlying time scale, censoring each cohort member at time of first occurrence of any cancer other than lung cancer, date of death, emigration, loss to follow-up or at the end of follow-up. One exception was the HNR cohort, for which we only followed up participants for lung cancer specifically - and not other types of cancers. Therefore, censoring at first occurrence of any cancer other than lung cancer was not possible. We included strata per individual (sub) cohort to account for baseline hazard heterogeneity across the cohorts and to relax the proportional hazards assumption. In addition to the approach using a stratified term, we evaluated alternative approaches (not accounting for the separate (sub) cohort, using indicator variables per cohort, or a frailty term for cohort identification). All methods, except the absence of any control, resulted in almost identical results, but the strata option had the lowest Akaike information criterion (AIC) compared to the alternative approaches.

We modelled the association between various air pollutants and lung cancer incidence in three á priori specified models with increasing levels of confounder adjustment: *Model 1*: accounting for age (applied as the underlying time-scale), (sub) cohort ID (included as strata), sex (included as strata), and adjustment for year of enrolment in order to account for time-trends in exposure and outcome; *Model 2* further adjusted for individual-level factors marital status (married/cohabiting, divorced, single, widowed), smoking status (never, former, current), smoking duration (years of smoking) for current smokers, smoking intensity (cigarettes/day) for current smokers, square of smoking intensity, BMI (<18.5, 18.5–24, 25–29, and 30 + kg/m^2), and employment status (yes vs. no); *Model 3* (main model) further adjusted for neighborhood-level socio-economic status (SES; mean income in 2001, the most consistently available variable and year across cohorts). The spatial scale of a 'neighborhood' varied from smaller neighborhoods and city districts (CEANS, EPIC-NL, E3N, HNR) to municipalities (DNS, DCH, and VHM&PP). We excluded participants with incomplete information on model 3 variables from all analyses.

We used four alternative approaches to investigate the shape of the exposure-response function and potential exposure threshold values below which no association existed: (1) Shape Constrained Health Impact Functions (SCHIF) as suggested by Nasari et al. (2016) The method implies fitting several parametric Cox models based on transformations of the exposure with biologically plausible shapes and

subsequently constructing an ensemble of all models based on a weighted average of the predicted log-HR. The transformations are based on sigmoidal functions providing supra-linear (i.e. steeper at low than at high concentrations), near linear, and sub-linear (i.e. less steep at low than at high concentrations) shapes. The weights are based on the Akaike information criterion (AIC) of each model. We derived uncertainty estimates of the predictions by bootstrapping. (2) Modelling each pollutant as a natural cubic spline with 3 degrees of freedom. (3) Subset analyses, in which we excluded subjects exposed to concentrations above a certain value and compared estimates to those of the full exposure range using cut-points based on existing limit and guideline values where possible. For $PM_{2.5}$ we evaluated 25 (the EU limit value), 20, 15, 12 (the US-EPA NAAQS) and 10 (the WHO guideline value). (4) Threshold analyses, in which the pollutant variable was set to zero for exposures below a certain (threshold) value, thus assuming no effect below the threshold. We evaluated the performance of threshold models by comparison of the AIC with the corresponding linear model.

Additionally, we assessed sensitivity of our findings by applying alternative exposure definitions to the linear main model. (1) Exposures back-extrapolated to the baseline address for all cohorts as described above. (2) Time-varying air pollution exposure back-extrapolated according to address history from enrolment to end of follow-up in cohorts with the available information (excluding DNC, E3N and HNR). We specified a 1-year calendar time period strata to handle varying time trends in air pollution and lung cancer. (3) The local LUR exposure models developed for ESCAPE (excluding DNC, parts of DCH, which were not part of ESCAPE, and E3N) for comparison.

Sensitivity analyses further included: (1) A mixed Cox model option with a random intercept per cohort (level 1) and per neighborhood (level 2) considered as nested within cohort. This alternative approach compared to modelling cohort ID in strata was evaluated in order to exploit more between-cohort exposure contrasts. (2) Investigating the possible impact of potential confounders, which were only available in some cohorts, by comparing estimates in identical subsets of the data with and without adjustment. Potential additional confounders included educational level (three categories), occupational class (white collar/blue collar), and the following alternative neighborhood-level SES indicators: unemployment rate, ethnicity, and low/high educational level rate. Additionally, we investigated whether including only smoking duration and intensity for current smokers affected the estimates. This was done in cohorts with detailed smoking information in former smokers (i.e. excluding VHM&PP). (3) Comparing effect estimates in datasets with and without the HNR cohort to ensure that the results were not affected by the different censoring date definition in this specific

Table 1
Descriptio m

	Total participants	Baseline period	End of follow-up	Baseline age (mean/SD) years	NO_2 (mean/SD)[a] μg/m^3	$PM_{2.5}$ (mean/SD)[a] μg/m^3	BC (mean/SD)[a] (10^{-5} m^{-1})	O_3 (mean/SD)[a] μg/m^3	All lung cancers	Adeno-carcinomas	Squamos-cell carcinomas
CEANS Stockholm, Sweden	18,963	1992–2004	31-12-2011	55.8 (11.1)	19.6 (6.7)	8.1 (1.0)	0.7 (0.3)	76.8 (2.5)	144	47	16
SDPP	7315	1992–1998	31-12-2011	47.0 (4.9)	15.4 (4.3)	7.6 (0.9)	0.6 (0.2)	77.6 (1.9)	42	15	6
SIXTY	3663	1997–1999	31-12-2011	60 (0)	20.6 (6.1)	8.3 (0.9)	0.8 (0.3)	76.7 (2.5)	38	11	5
SALT	5626	1998–2003	31-12-2011	57.3 (10.4)	21.2 (6.2)	8.4 (0.9)	0.8 (0.3)	76.7 (2.5)	43	12	4
SNAC-K	2359	2001–2004	31-12-2011	72.5 (10.4)	27.4 (5.1)	8.6 (0.8)	1.1 (0.2)	75.1 (2.7)	21	9	1
DCH, Copenhagen/Aarhus, Denmark	53647	1993–1997	31-12-2015	56.7 (4.4)	28.0 (6.8)	13.2 (1.4)	1.3 (0.4)	77.5 (5.1)	1496	616	300
DNC, Denmark	23,018	1993/1999	31-12-2012	53.4 (8.2)	23.1 (8.4)	13.1 (1.6)	1.2 (0.4)	80.5 (3.9)	325	145	36
DNC-1993	15,581	1993	31-12-2012	56.0 (8.3)	21.8 (8.0)	12.7 (1.5)	1.1 (0.4)	80.4 (4.0)	299	127	35
DNC-1999	7437	1999	31-12-2012	47.9 (4.1)	25.8 (8.5)	13.8 (1.5)	1.3 (0.4)	80.6 (3.8)	26	18	1
EPIC-NL, Netherlands	31,442	1993–1997	31-12-2012	49.2 (11.9)	35.1 (5.8)	17.5 (1.1)	1.7 (0.3)	73.1 (6.1)	361	129	67
MORGEN	17,802	1993–1997	31-12-2012	42.7 (11.2)	34.5 (6.1)	18.0 (1.0)	1.7 (0.3)	73.5 (7.7)	170	48	42
Prospect	13,640	1993–1997	31-12-2012	57.6 (6.0)	35.9 (5.4)	16.9 (0.8)	1.7 (0.3)	72.7 (2.7)	191	81	25
HNR, Ruhr area, Germany	3611	2000–2003	26-04-2017	59.1 (7.7)	37.8 (4.7)	19.6 (0.9)	2.0 (0.2)	78.9 (2.8)	69	20	15
E3N, France	36,597	1989–1991	08-12-2014	52.8 (6.7)	26.3 (9.7)	17.0 (2.9)	1.8 (0.5)	87.7 (8.0)	174	68	11
VHM&PP, Vorarlberg, Austria	140,272	1985–2005	31-12-2014	41.7 (14.9)	22.0 (5.3)	15.7 (2.6)	1.6 (0.3)	92.6 (3.6)	1387	516	295
Pooled cohort	307,550	1985–2005	2011–2017	48.3 (13.4)	25.0 (8.0)	15.0 (3.2)	1.5 (0.4)	85.3 (9.0)	3956	1541	740

CEANS: Cardiovascular Effects of Air Pollution and Noise in Stockholm; SDPP: The Stockholm Diabetes Preventive Program; SIXTY: The Stockholm cohort of 60-year-olds; SALT: Screening Across the Lifespan Twin Study; SNAC-K: The Swedish National Study of Aging and Care in Kungsholmen; DCH: Diet, Cancer and Health; DNC: Danish Nurses Cohort; EPIC-NL: European Prospective Investigation into Cancer and Nutrition, the Netherlands; MORGEN: Monitoring Project on Risk Factors and chronic diseases in the Netherlands; HNR: Heinz Nixdorf Recall study; E3N (EPIC-France): Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; VHM&PP: Vorarlberg Health Monitoring and Prevention Programme.

[a] 2010 exposure model.

cohort. (4) Comparing datasets with and without the E3N cohort in case the self-reported case status would affect the conclusions. (5) Investigating effect measure modification by smoking status by including an interaction term in the model tested by the Wald test. (6) Two- and three-pollutant models to test the sensitivity of the estimates of one pollutant to inclusion of another.

We evaluated violation of the proportional hazards assumption of the Cox Models for all covariates by test of a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on time. We performed analyses in R, version 3.4.0 and packages: *survival* (version 2.42–3), *coxme* (version 2.2–10), *Matrix* (version 1.2–14), *foreach* (version 1.4.4), *glmnet* (version 2.0–16), *multcomp* (version 1.4–8), *survey* (version 3.33–2), *splines* (version 3.4.0), *Hmisc* (version 4.1–1), *mfp* (version 1.5.2), *mice* (version 2.46.0), *VIM* (version 4.7.0), *ggplot2* (version 2.2.1), *MASS* (version 7.3–50), and *rms* (version 5.1–2).

3. Results

In total, the pooled study population comprised 307,550 individuals who experienced 3956 incident lung cancer events during 5,561,379 person-years of follow-up (Table 1). The participants were recruited in the period 1985–2005 and the mean age at baseline ranged from 41.7 to 72.5 years across the individual (sub) cohorts with a pooled mean of 48.3 years. The exposures varied between the individual cohorts with generally lower mean levels of $PM_{2.5}$, NO_2 and BC in northern compared to more southern cohorts (Fig. S2). The mean O_3 levels were highest in the French and Austrian cohorts.

Baseline characteristics of participants are presented in Table 2. The pooled cohort comprised 66% women. Twenty-four percent of cohort participants were current smokers at baseline ranging from 13% to 37% across the individual (sub) cohorts. The fraction of overweight or obese, not employed, and married participants varied substantially between (sub) cohorts, ranging from 21% to 73%, 5% to 76%, and 46% to 84%, respectively.

The fully adjusted linear analyses (Model 3) showed an association between exposure to $PM_{2.5}$ and risk of lung cancer with a HR of 1.13 (95% CI: 1.05, 1.23) per increments of 5 μg/m^3. No association was evident for NO_2, BC or O_3, except in Model 1, which was adjusted only for age, sex, and year of baseline visit (Table 3). The attenuation in effect estimates between Model 1 and 2 was mainly due to adjustment for the smoking variables. The inclusion of neighborhood SES in Model 3 did not affect the HRs notably. Of the two histological subtypes analyzed, the increase in lung cancer risk with higher $PM_{2.5}$ exposure was more pronounced for adenocarcinomas.

Table 4 shows the results of the subset analyses in which we removed subjects exposed to concentrations above a certain value. The risk estimates were similar across subsets of $PM_{2.5}$ exposure-levels with wide confidence intervals for the subsets below 12 μg/m^3 and 10 μg/m^3, related to a lower number of observations. Importantly, risk estimates were clearly elevated for the subset of subjects with exposure below the EU limit value of 25 μg/m^3. The corresponding results for NO_2, BC and O_3 are provided in the online appendix Table S1, showing associations somewhat larger at low concentrations of NO_2, with wider confidence intervals. Consistently, the SCHIF function indicated a linear to supra-linear ensemble model for $PM_{2.5}$ with no evidence of a threshold (Fig. 1), which is supported by the natural spline function (Fig. S3). Model performance (AIC) did not suggest a threshold below which no association was evident (Table S2), although differences in AIC between the linear and threshold models were small, consistent with the small number of observations below 10 μg/m^3.

Exposure to $PM_{2.5}$ was moderately to highly correlated with exposure to BC and NO_2 in most individual (sub) cohorts (Table S3). The correlation between $PM_{2.5}$ and O_3 in the warm season was generally moderately negative but varied considerably between individual (sub) cohorts. The effect estimate for the association between $PM_{2.5}$ and lung cancer was not sensitive to inclusion of co-pollutants (Fig. S4). The HRs for $PM_{2.5}$ adjusted for NO_2 and BC were 1.18 (95% CI: 1.07, 1.31) and 1.19 (95% CI: 1.07, 1.32), respectively.

Means, standard deviations and effect estimates of exposures back-extrapolated to the baseline year are provided in the online appendix (Table S4). Generally, NO_2, BC and O_3 concentrations were only mildly higher for back-extrapolated exposures compared to 2010 concentration estimates, whereas the back-extrapolated concentration values of $PM_{2.5}$ were higher and more variable than the 2010-exposure. The risk

Table 2
Baseline characteristics of the included (sub)cohort studies.

	% Women	% Current smokers	Cigarettes/day[a]	Years of smoking[a]	% BMI ≥ 25 kg/m^2	% Not employed	% Married/cohabiting	Mean income neighborhood[b]
CEANS Stockholm, Sweden	56	22	13.1 (7.8)	33.4 (10.9)	51	29	73	25.2 (5.6)
SDPP	59	26	13.5 (7.4)	27.8 (8.6)	51	9	84	24.3 (4.2)
SIXTY	50	21	13.3 (7.7)	36.2 (10.1)	47	32	75	24.7 (6.9)
SALT	53	21	12.7 (8.1)	37.6 (9.1)	41	33	68	25.4 (6.6)
SNAC-K	62	15	11.7 (8.3)	43.2 (13.5)	53	76	46	28.7 (2.2)
DCH, Copenhagen/Aarhus, Denmark	52	36	16.4 (9.0)	36.3 (7.7)	56	22	72	20.2 (3.4)
DNC, Denmark	100	34	13.7 (7.9)	30.3 (9.5)	29	21	71	19.2 (2.5)
DNC-1993	100	37	13.8 (8.1)	31.4 (9.9)	28	29	68	19.2 (2.6)
DNC-1999	100	28	13.2 (7.4)	27.1 (7.1)	30	5	76	19.0 (2.4)
EPIC-NL, Netherlands	74	30	15.0 (8.7)	28.6 (11.3)	51	38	70	12.6 (1.6)
MORGEN	54	35	15.7 (8.6)	24.5 (10.6)	49	31	65	12.2 (1.6)
PROSPECT	100	23	13.6 (8.7)	36.7 (7.7)	55	49	77	13.6 (1.4)
HNR, Ruhr area, Germany	50	25	19.1 (12.5)	33.9 (9.2)	73	57	75	25.1 (8.1)
E3N, France	100	13	11.3 (9.2)	28.5 (7.6)	21	32	83	11.2 (3.0)
VHM&PP, Vorarlberg, Austria	56	20	15.6 (8.9)	13.4 (8.2)	42	29	69	22.9 (1.7)
Pooled cohort	66	24	15.2 (8.9)	25.3 (13.1)	43	29	72	19.9 (5.3)

CEANS: Cardiovascular Effects of Air Pollution and Noise in Stockholm; SDPP: The Stockholm Diabetes Preventive Program; SIXTY: The Stockholm cohort of 60-year-olds; SALT: Screening Across the Lifespan Twin Study; SNAC-K: The Swedish National Study of Aging and Care in Kungsholmen; DCH: Diet, Cancer and Health; DNC: Danish Nurses Cohort; EPIC-NL: European Prospective Investigation into Cancer and Nutrition, the Netherlands; MORGEN: Monitoring Project on Risk Factors and chronic diseases in the Netherlands; HNR: Heinz Nixdorf Recall study; E3N: Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; VHM&PP: Vorarlberg Health Monitoring and Prevention Programme.

[a] Among current smokers.

[b] Euros × 1000, year 2001.

Table 3
Pooled analyses of air pollutants exposure and risk of all lung cancers, adenocarcinomas, and squamous-cell carcinomas.

		Model 1[a] N = 307,550			Model 2[b] N = 307,550			Model 3[c] N = 307,550		
	Increment	HR	95% CI		HR	95% CI		HR	95% CI	
All lung cancers (N = 3956)										
NO_2	10 μg/m^3	1.10	1.05	1.15	1.00	0.95	1.05	1.02	0.97	1.07
$PM_{2.5}$	5 μg/m^3	1.21	1.11	1.31	1.12	1.03	1.21	1.13	1.05	1.23
BC	0.5 10^{-5} m^{-1}	1.10	1.05	1.16	1.01	0.96	1.06	1.02	0.97	1.07
O_3w	10 μg/m^3	0.82	0.77	0.88	0.95	0.89	1.01	0.95	0.89	1.02
Adenocarcinoma (N = 1541)										
NO_2	10 μg/m^3	1.08	1.00	1.17	1.01	0.94	1.09	1.02	0.94	1.10
$PM_{2.5}$	5 μg/m^3	1.22	1.07	1.39	1.16	1.02	1.32	1.16	1.02	1.32
BC	0.5 10^{-5} m^{-1}	1.06	0.98	1.15	0.99	0.92	1.07	1.00	0.92	1.08
O_3w	10 μg/m^3	0.83	0.75	0.92	0.92	0.83	1.03	0.92	0.83	1.03
Squamous-cell (N = 740)										
NO_2	10 μg/m^3	1.04	0.92	1.17	0.93	0.83	1.05	0.97	0.86	1.09
$PM_{2.5}$	5 μg/m^3	1.10	0.91	1.32	1.02	0.85	1.22	1.04	0.87	1.25
BC	0.5 10^{-5} m^{-1}	1.07	0.95	1.21	0.96	0.86	1.09	0.99	0.88	1.12
O_3w	10 μg/m^3	0.79	0.68	0.91	0.94	0.80	1.09	0.94	0.81	1.10

HR, hazard ratio; CI, confidence interval; O_3w, Ozone in the warm season.
[a] Adjusted for study (strata), age, sex (strata), year of baseline visit.
[b] Further adjusted for smoking status, duration, intensity, intensity^2, BMI, marital status, and employment status.
[c] Further adjusted for 2001 mean income at the neighborhood level.

Table 4
Subset analyses of $PM_{2.5}$ and lung cancer.

			All lung cancers[a]		
Subset[b]	No Obs	No cases	HR	95% CI	
Full dataset	307,550	3956	1.13	1.05	1.23
<25 μg/m^3	307,524	3956	1.13	1.05	1.23
<20 μg/m^3	299,514	3897	1.15	1.06	1.25
<15 μg/m^3	145,078	2147	1.09	0.90	1.30
<12 μg/m^3	49,834	589	1.21	0.75	1.96
<10 μg/m^3	23,554	185	2.01	0.80	5.04

HR, hazard ratio; CI, confidence interval.
[a] Adjusted for study (strata), age, sex (strata), year of baseline visit, smoking status, duration, intensity, intensity (Brambilla et al., 2014), BMI, marital status, employment status and 2001 mean income at the neighborhood level.
[b] Concentrations above a certain value were excluded and compared to analyses of the full exposure range.

estimates were unaffected by the back-extrapolation for NO_2, BC and O_3 whereas lower effect estimates were observed for back-extrapolated $PM_{2.5}$ exposures compared to the main approach with 2010-exposures. The HR (95% CI) for back-extrapolated $PM_{2.5}$ was 1.06 (1.02, 1.10) for the ratio method and 1.06 (1.01, 1.12) for the difference method. Spearman correlation coefficients between the 2010 exposure concentrations and those back-extrapolated to baseline were 0.95, 0.76, 0.90, and 0.95 for NO_2, $PM_{2.5}$, BC, and O_3 based on the ratio method and correspondingly 0.99, 0.67, 0.97, and 0.95 based on the difference method. In the analysis of time-varying exposure back-extrapolated to the address history, we observed similar effect estimates for $PM_{2.5}$ compared to the 2010 main exposure in the same subgroup (Table S4).

The air pollution concentrations from ELAPSE and local study area specific LUR models from ESCAPE were moderately to highly correlated with the exception of the Swedish CEANS (Fig. S5). The contrast in BC exposure was generally larger for the ELAPSE compared to the ESCAPE exposure. For $PM_{2.5}$, the contrast varied for the different cohorts. For VHM&PP, DCH and the EPIC_NL cohorts the contrast was larger for the ELAPSE exposure compared to ESCAPE, whereas ESCAPE exposure had a larger exposure contrast in the CEANS and HNR cohorts. For NO_2, the exposure contrasts did not vary markedly. The HRs for NO_2 and BC in relation to lung cancer were generally similar in analyses based on the ESCAPE LUR model compared to the ELAPSE exposure model (Table S5). For $PM_{2.5}$, the effect estimate was higher when based on the ESCAPE compared to the ELAPSE exposure model. The HR (95% CI) for the association between $PM_{2.5}$ and lung cancer using the ESCAPE exposure model was 1.34 (1.11, 1.61) compared to 1.20 (1.07, 1.35) using the ELAPSE exposure model in the cohorts and individuals for which both exposure models were available.

The HRs were stable in different sensitivity analyses including comparison of the main model stratified by cohort ID to the mixed Cox model approach (Fig. S6) as well as additional adjustments for educational level, occupational class, alternative neighborhood level SES indicators, smoking variables (Table S6), and exclusion of the HNR and E3N cohort (Table S7). The $PM_{2.5}$ effect estimate was sensitive to exclusion of the large VHM&PP cohort, which contributed about one third of the cases, (HR: 1.01; 95% CI: 0.88, 1.14) and the E3N cohort (HR: 1.17; 95% CI: 1.08, 1.28). In an analysis excluding both VHM&PP and E3N (N = 130,681) we found a HR of 1.08 (95% CI: 0.92, 1.26). The $PM_{2.5}$ effect estimates for the individual cohorts are provided in the online appendix (Fig. S7). The uncertainty in these individual cohort estimates is, however, large with the exception of the DCH and VHM&PP cohort. In the analyses of effect modification by smoking, we observed an elevated HR between $PM_{2.5}$ and lung cancer in both never smokers (HR: 1.15; 95% CI: 1.01, 1.31) and current smokers (HR: 1.15; 95% CI: 1.08, 1.26) (Table S8).

We detected deviation from the proportional hazards assumption for smoking intensity and duration. A sensitivity analysis incorporating these in strata (grouping intensity per 10 cigarettes per day and the duration in categories per 5 years) did not show results deviating from the main analysis.

4. Discussion

In this large pooled cohort analysis covering seven cohorts from across Europe, we observed a higher risk of lung cancer incidence with higher exposure to $PM_{2.5}$. The results indicate that long-term ambient $PM_{2.5}$ exposure at the residential address may contribute to lung cancer incidence even at concentrations lower than current EU limit values (25 μg/m^3) and possibly WHO Air Quality Guidelines (10 μg/m^3). The observed associations were more pronounced for adenocarcinomas of the lung.

The results of our study suggest a linear to supra-linear shape of the $PM_{2.5}$ concentration-response function with no evidence of a threshold. Evidence based on studies focusing on the concentration-response function of $PM_{2.5}$ and lung cancer incidence is scarce (overview provided in Table S9). A Canadian population-based cohort study including

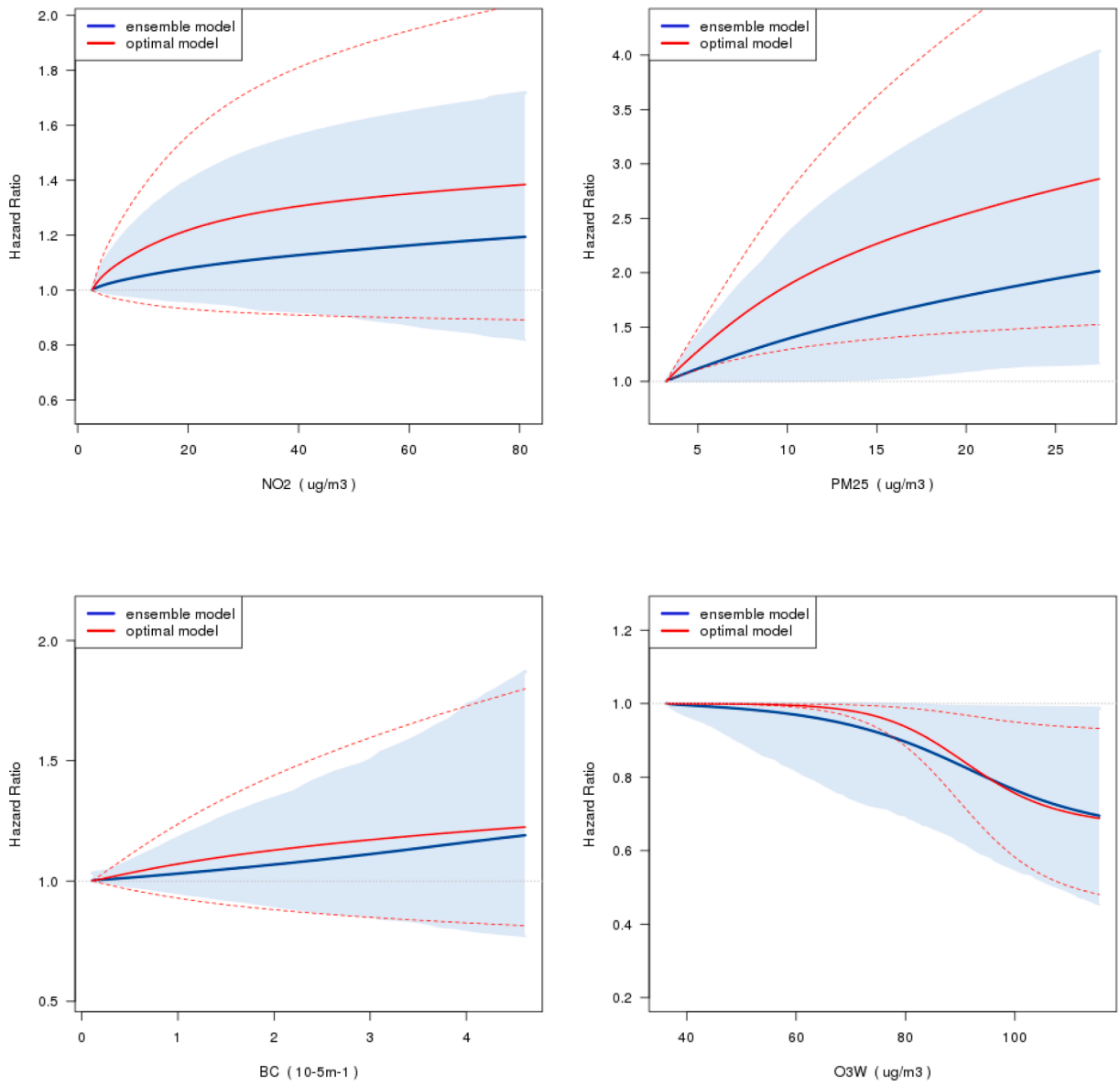

Fig. 1. Shape-Constrained Health Impact Functions. Optimal hazard function (red solid line) with uncertainty bounds (dashed red lines). Ensemble hazard function (blue solid line) with uncertainty bounds (blue-shaded area). The optimal model is a single model whereas the ensemble model is a weighted average from multiple models. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

more than 100,000 incident lung cancer cases observed a sublinear relationship between $PM_{2.5}$ and lung cancer incidence with an indication of a threshold at 10 μg/m^3 (Bai et al., 2019). The findings of our study are in line with the ESCAPE analysis in which an overall HR of 1.18 (95% CI: 0.96, 1.46) per 5 μg/m^3 $PM_{2.5}$ was reported for lung cancer incidence with subset estimates of 1.13 (95% CI: 0.90, 1.43), 1.14 (95% CI: 0.90, 1.45), 1.11 (95% CI: 0.85, 1.45), and 1.20 (95% CI: 0.55, 2.66) for subsets of <25, 20, 15, and 10 μg/m^3 $PM_{2.5}$, respectively (Raaschou-Nielsen et al., 2013). Results of the analyses of ESCAPE also suggested a linear or supra-linear association with no evidence of a threshold. Our new analyses are substantially more precise than the ESCAPE study. A large meta-analysis from 2014 covering broader study areas including North America and Europe reported an association of 1.04 (95% CI: 1.02, 1.07) per 5 μg/m^3 increase in $PM_{2.5}$, with the lowest estimates observed in European study areas (Hamra et al., 2014); which is somewhat lower than the effects estimates of our study as well as the ESCAPE study. The majority of other previous studies investigating the concentration-response function of $PM_{2.5}$ and lung cancer focus on lung cancer mortality. A recent analysis based on data from 41 cohorts from 16 countries across the world provided an in-depth analysis of the shape of the association between $PM_{2.5}$ exposure and non-accidental mortality overall, and for five specific causes of death including lung cancers (Burnett et al., 2018). The included cohorts covered a broad exposure range and several had exposures below the WHO ambient air-quality guideline of 10 μg/m^3. In line with our results, a linear relationship was observed for lung cancer mortality with no evidence of a threshold. In a newly published study of more than 4.5 million US veterans followed between 2006 and 2016, results indicated a supra-linear relation between $PM_{2.5}$ and lung cancer mortality (Bowe et al., 2019). A mortality-study based on the Canadian CANCHEC cohort reported a sublinear relation below 5 μg/m^3 $PM_{2.5}$ (Pinault et al., 2017). Likewise, a lung cancer mortality-study based on a Chinese male cohort suggested a sub-linear relation (Yin et al., 2017). The Chinese study, however, covered a much broader range of exposure (3.5–89.8 μg/m^3) than the North American or European studies, with an apparent linear increase up to 30 μg/m^3. Generally, results may not be comparable across different continents due to marked differences in exposure ranges and possibly in composition of PM. The aforementioned comprehensive re-

analysis of mortality studies by Burnett and colleagues (Burnett et al., 2018) did not, however, show varying results depending on inclusion of the large Chinese Male Cohort. Variations in results across the studies may also stem from differences in the choice of spatial and temporal scale of $PM_{2.5}$ exposure assessment as recently suggested (Crouse et al., 2020). The present study had few observations in the very low end of the exposure range, reflected in the wide confidence bounds for subsets below 10 $\mu g/m^3$ and very similar AICs across the threshold models for $PM_{2.5}$ (Table S2). Thus, while we do not in the ELAPSE study have the data to demonstrate or discard a threshold of 10 $\mu g/m^3$, our study provides strong evidence that associations well below the current EU limit value of 25 $\mu g/m^3$ are present. In line with our results, both the meta-analysis by Hamra et al. (2014) and the ESCAPE study reported stronger associations for adenocarcinomas compared to squamous-cell carcinomas.

Similarly to the findings of the ESCAPE study, we did not observe an association between NO_2 exposure and lung cancer incidence (Raaschou-Nielsen et al., 2013). A more recent meta-analysis of 20 studies reported an overall meta-estimate of 1.04 (95% CI: 1.01, 1.08) per 10 $\mu g/m^3$ NO_2 (Hamra et al., 2015); however, analyses according to region of study showed a relative risk of 1.02 (95% CI: 0.99, 1.06) per 10 $\mu g/m^3$ NO_2 in European studies. Another large meta-analysis of NO_2 and cause-specific mortality reported a HR of 1.05 (95% CI: 1.02, 1.08) per 10 $\mu g/m^3$ NO_2 in relation to lung cancer mortality (Atkinson et al., 2018). The heterogeneity between study-specific HRs, however, was high and analyses restricted to cohorts adjusting for key confounders such as smoking, were not in support of an association. The results of this meta-analysis also suggested potential effect modification by age range at cohort entry with larger HRs observed in cohorts of limited age ranges at baseline as opposed to more general adult populations. Previous findings on BC and lung cancer incidence mainly stem from studies of workers exposed to diesel exhaust (i.e. trucking industry, railroad workers, underground miners) (Grahame et al., 2014). Generally, these studies point to an elevated risk of lung cancer in relation to higher exposure to BC (Garshick et al., 2012; Vermeulen et al., 2014). In ESCAPE, a HR of 1.12 (95% CI: 0.88, 1.42) per 10^{-5}/m increase for $PM_{2.5}$ absorbance was reported. There are fewer studies on long-term exposure to O_3 and lung cancer. Along with our findings, a meta-analysis covering six cohort studies (primarily American) did not find an association between neither all season-O_3 nor warm season O_3 and lung cancer mortality (Atkinson et al., 2016). A recent Chinese study reported an elevated risk of lung cancer with higher exposure to O_3 (Guo et al., 2016); whereas a Canadian case-control study of more than 2000 incident lung cancers reported an odds ratio of 1.04 (95% CI: 0.92, 1.18) per 10 $\mu g/m^3$ increase in O_3 (Hystad et al., 2013).

The mechanisms by which air pollution may promote lung cancer include inflammation and oxidative stress (Straif et al., 2013). Through these mechanisms, inhaled concentrations of particulate matter may induce DNA damage, promotion of cell turnover and proliferation in the lung tissue. Also, epigenetic changes of the genome, and in particular promotor hypermethylation, are suspected of mediating the effects of air pollutants on lung cancer (Straif et al., 2013).

The strengths of this study include the very large sample size obtained by pooling seven cohorts combined with detailed information on individual lifestyle. Compared to ESCAPE, we included close to 2000 additional lung cancer cases. We included cohorts representing a broad range of exposure, which is of special importance for $PM_{2.5}$ for which the exposure contrast is small within the cohorts - but large between cohorts (Fig. S2). Pooling allowed us to apply non-parametric methods to assess the shape of the concentration response function over the full range of exposure. The size of the study population also allowed for subset analyses exploring the association between ambient air pollution and lung cancer at the lower end of the exposure distribution - which even large individual cohorts do not have the power to address. In addition, the large sample size enabled multi-pollutant models to disentangle potential inter-dependencies between pollutants. Also, we were able to include a broad range of potential confounders harmonized across cohorts for this specific project. The hybrid models developed within the ELAPSE collaboration ensured comparable exposure estimates for the entire study population. However, some misclassification is inevitable when applying an outdoor air pollution model for exposure assignment due to uncertainties in input data and because exposure modelled at the residential address is not equivalent to personal exposure (Evangelopoulos et al., 2020). We have no information on time-activity patterns, ventilation rates, and indoor sources, so we cannot investigate to what extent participating cohorts were different from each other in these domains. We consider the potential misclassification of exposure associated with these uncertainties to be non-differential with respect to lung cancer incidence, which would cause bias of the effect estimate towards the null. In addition, the exposure model was developed for the year 2010 and subsequently applied to the baseline address of each study participant. Previous studies from Europe have shown that the spatial distribution of NO_2, black smoke and traffic intensities was stable over several years (Beelen et al., 2007; Cesaroni et al., 2012; Gulliver et al., 2011). The exposure model applied in our study was validated and compared for different time points in order to evaluate the stability of the spatial structure (de Hoogh et al., 2018). The predictions from the 2010 model showed high correlations with models developed for 2000 and 2005 (2013 for $PM_{2.5}$) at the European scale. In order to take into account time-trends in air pollutants, we back-extrapolated the 2010-exposures to the baseline year of the cohort participants. Additionally, to address the issue of moving patterns, we performed a sensitivity analysis including back-extrapolated exposures applied to the address history in cohorts with the available information. This analysis showed somewhat lower but still significant effect estimates for $PM_{2.5}$ compared to the 2010 exposure. This probably reflects that the exposures in 2010 were lower than at baseline.

Another important issue to consider is that the pooled cohort comprises seven individual cohorts, which may differ in their underlying risk of lung cancer due to features that we were not able to account for in this study although we used strata for (sub) cohort to allow for unmeasured confounders across cohorts. For example, the results of the subset analyses, in which we address the association in the lower end of the exposure range, are based mainly on Northern European cohorts. We are not able to conclude that differences in HRs between the Nordic and Southern cohorts are due to lower levels of air pollution exposure or to variations in residual confounding reflecting differences in sensitivity between cohorts. For lung cancer, the most important potential confounders to consider are smoking, occupational exposures, and radon exposure. We were able to account for smoking status at baseline as well as for smoking duration and intensity for current smokers, but not for changes in smoking habits during follow-up. We also performed a sensitivity analyses adjusting for occupational class. Radon exposure levels are likely inversely associated with air pollution concentrations, because concentrations of radon are usually lower in apartment buildings, which are more common in city areas (Kropat et al., 2014). Thus, we would expect adjustment for radon to lead to higher HRs for $PM_{2.5}$ and lung cancer.

The findings of this study confirm a role of outdoor airborne particulate matter in lung cancer incidence, even at concentrations lower than current EU limit values and possibly below WHO Air Quality Guidelines.

CRediT authorship contribution statement

Ulla Arthur Hvidtfeldt: Formal analysis, Methodology, Software, Visualization, Writing - original draft. **Gianluca Severi:** Data curation, Resources, Writing - review & editing. **Zorana Jovanovic Andersen:** Writing - review & editing. **Richard Atkinson:** Writing - review & editing. **Mariska Bauwelinck:** Data curation, Writing - review & editing. **Tom Bellander:** Writing - review & editing. **Marie-Christine Boutron-Ruault:** Data curation, Resources, Writing - review & editing.

Jørgen Brandt: Data curation, Methodology, Writing - review & editing. **Bert Brunekreef:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing - review & editing. **Giulia Cesaroni:** Methodology, Writing - review & editing. **Jie Chen:** Data curation, Methodology, Project administration, Software, Writing - review & editing. **Hans Concin:** Project administration, Resources. **Francesco Forastiere:** Conceptualization, Funding acquisition, Writing - review & editing. **Carla H. Gils:** Writing - review & editing. **John Gulliver:** Conceptualization, Funding acquisition, Methodology, Validation, Visualization, Writing - review & editing. **Ole Hertel:** Data curation, Methodology, Writing - review & editing. **Gerard Hoek:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing - review & editing. **Barbara Hoffmann:** Conceptualization, Data curation, Funding acquisition, Resources, Writing - review & editing. **Kees Hoogh:** Data curation, Methodology, Writing - review & editing. **Nicole Janssen:** Writing - review & editing. **Karl-Heinz Jöckel:** Data curation, Investigation, Resources, Writing - review & editing. **Jeanette Therming Jørgensen:** Data curation, Writing - review & editing. **Klea Katsouyanni:** Methodology, Writing - review & editing. **Matthias Ketzel:** Data curation, Methodology, Writing - review & editing. **Jochem O. Klompmaker:** Writing - review & editing. **Norun Hjertager Krog:** Writing - review & editing. **Alois Lang:** Data curation, Writing - review & editing. **Karin Leander:** Resources, Writing - review & editing. **Shuo Liu:** Writing - review & editing. **Petter L.S. Ljungman:** Conceptualization, Data curation, Writing - review & editing. **Patrik K.E. Magnusson:** Investigation, Project administration, Writing - review & editing. **Amar Jayant Mehta:** Writing - review & editing. **Gabriele Nagel:** Data curation, Writing - review & editing. **Bente Oftedal:** Writing - review & editing. **Göran Pershagen:** Data curation, Writing - review & editing. **Raphael Simon Peter:** Data curation, Writing - review & editing. **Annette Peters:** Data curation, Funding acquisition, Project administration, Resources, Writing - review & editing. **Matteo Renzi:** Writing - review & editing. **Debora Rizzuto:** Data curation, Writing - review & editing. **Sophia Rodopoulou:** Data curation, Methodology, Software, Writing - review & editing. **Evangelia Samoli:** Methodology, Software, Writing - review & editing. **Per Everhard Schwarze:** Writing - review & editing. **Torben Sigsgaard:** Methodology, Writing - review & editing. **Mette Kildevæld Simonsen:** Resources. **Massimo Stafoggia:** Methodology, Writing - review & editing. **Maciek Strak:** Writing - review & editing. **Danielle Vienneau:** Writing - review & editing. **Gudrun Weinmayr:** Methodology, Writing - review & editing. **Kathrin Wolf:** Data curation, Software, Writing - review & editing. **Ole Raaschou-Nielsen:** Conceptualization, Data curation, Methodology, Supervision, Writing - review & editing. **Daniela Fecht:** Conceptualization, Data curation, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Co-author Bente Oftedal owns stocks in the Norwegian company Equinor. However, this ownership does not interfere with her research on health effects of air pollution, including this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106249.

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