ORIGINAL ARTICLE

Long-term Air Pollution Exposure and Pneumonia-related Mortality in a Large Pooled European Cohort

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Abstract

Rationale: Ambient air pollution exposure has been linked to mortality from chronic cardiorespiratory diseases, while evidence on respiratory infections remains more limited.

Objectives: We examined the association between long-term exposure to air pollution and pneumonia-related mortality in adults in a pool of eight European cohorts.

Methods: Within the multicenter project ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe), we pooled data from eight cohorts among six European countries. Annual mean residential concentrations in 2010 for fine particulate matter, nitrogen dioxide (NO_2), black carbon (BC), and ozone were estimated using Europe-wide hybrid land-use regression models. We applied stratified Cox proportional hazard models to investigate the associations between air pollution and pneumonia, influenza, and acute lower respiratory infections (ALRI) mortality.

Measurements and Main Results: Of 325,367 participants, 712 died from pneumonia and influenza combined, 682 from pneumonia, and 695 from ALRI during a mean follow-up of 19.5 years. NO_2 and BC were associated with 10–12% increases in pneumonia and influenza combined mortality, but 95% confidence intervals included unity (hazard ratios, 1.12 [0.99–1.26] per 10 $\mu g/m^3$ for NO_2; 1.10 [0.97–1.24] per 0.5 $10^{-5}m^{-1}$ for BC). Associations with pneumonia and ALRI mortality were almost identical. We detected effect modification suggesting stronger associations with NO_2 or BC in overweight, employed, or currently smoking participants compared with normal weight, unemployed, or nonsmoking participants.

Conclusions: Long-term exposure to combustion-related air pollutants NO_2 and BC may be associated with mortality from lower respiratory infections, but larger studies are needed to estimate these associations more precisely.

Keywords: air pollution; respiratory infections; long-term exposure; adults

Acute lower respiratory infections (ALRI), including pneumonia (infection of lung alveoli), as well as infections of the airways, such as bronchitis and influenza, are common respiratory diseases that pose a large burden and can be life-threatening, ranking as the fourth leading cause of death worldwide in 2017 (1). Pneumonia is the most common ALRI, caused by viruses, bacteria, or fungi. While there is a general decline in the pneumonia mortality rate in European countries (2), pneumonia remains the most frequent cause of death from infection, especially in children and older people (3, 4). Short-term exposure to air

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pollution has been found to trigger hospital admission or emergency room visits for pneumonia (5, 6). However, it remains uncertain whether long-term exposure to air pollution can lead to increased risks of contracting or dying from pneumonia or other ALRI in adults due to the general lack of cohorts with data on incidence or mortality from these infections (7, 8). An association of long-term exposure to air pollution with increased respiratory infection risk and severity is biologically plausible (9). Experimental studies show that particulate matter (PM) exposure can impair cell immunity and weaken host defense mechanisms, increasing susceptibility to respiratory infections (10). This is caused by direct cellular damage and indirectly via oxidative stress and inflammation in the lung and system (11–13).

Two systematic reviews of 71 cohort studies on PM with diameter <2.5 μm ($PM_{2.5}$) and 41 cohort studies on nitrogen dioxide (NO_2) reported clear evidence of associations with all-cause and respiratory mortality (14, 15). However, only a limited number of studies investigated the association with respiratory infection mortality (such as pneumonia mortality), mainly due to a lack of cohorts with sufficient power to study these rarer endpoints. So far, several cohort studies in adults have examined the associations of different air pollutants with pneumonia-related mortality (Table E1 in the online supplement), with studies from the United States (8, 16–21), Canada (22), Japan (23, 24), China (25), or United Kingdom (26). All but one (25) of these studies reported positive associations with pneumonia mortality, but several aspects remain uncertain, including the shape of the concentration–response function, which pollutants are most relevant, and which groups are most susceptible. Strong associations were found between long-term exposure to NO_2 and $PM_{2.5}$ with increased risks of hospitalization for radiologically confirmed pneumonia in adults aged 65 years or older (7). Furthermore, emerging concerns on the link between long-term air pollution exposure and mortality due to the coronavirus disease 2019 (COVID-19) infection (27), which may develop into severe or fatal pneumonia,

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

At a Glance Commentary

Scientific Knowledge on the Subject: Ambient air pollution exposure has been linked to mortality from chronic cardiorespiratory diseases. However, a limited number of studies investigated the association between air pollution and mortality from respiratory infectious diseases, mainly due to a lack of adult cohorts with sufficient power to investigate these rarer outcomes.

What This Study Adds to the Field: In a large pooled adult cohort of eight European cohorts, we found that long-term exposure to nitrogen dioxide (NO_2) and black carbon (BC) were associated with pneumonia, influenza, and acute lower respiratory infections mortality, with higher risks observed in overweight participants and current smokers, as well as in employed subjects. There was no evidence of an exposure threshold for these associations. No association was observed between fine particulate matter or ozone exposures and the investigated endpoints. This study provides suggestive evidence that combustion-related air pollutants NO_2 and BC, even at low levels, below current limit values, may be risk factors for pneumonia-related mortality.

especially among older people and people with comorbidities, raise renewed interest and demand for more data on air pollution and respiratory infections.

The ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) project recently showed that long-term exposure to low levels of air pollution increased risks of numerous chronic lung diseases, including adult-onset asthma (28), chronic obstructive pulmonary disease (29), and lung cancer (30). We aimed to examine the association of long-term exposure to $PM_{2.5}$, NO_2, black carbon (BC), and ozone (O_3) with pneumonia-related mortality among adults in a pool of eight European cohorts within ELAPSE.

Methods

Study Population

Within the ELAPSE project, we analyzed pooled data from eight cohorts among six European countries, which contained information of potential confounders and were pooled, harmonized, and stored at a secure server. The cohorts include: *1*) CEANS (Cardiovascular Effects of Air Pollution and Noise in Stockholm) cohort in Sweden, which combined four subcohorts: SDPP (Stockholm Diabetes Prevention Program) (31), SIXTY (Stockholm Cohort of 60-year-olds) (32), SALT (Stockholm Screening Across the Lifespan Twin study) (33), and SNACK (Swedish National Study on Aging and Care in Kungsholmen) (34); *2*) DCH (Diet, Cancer, and Health) cohort in Denmark (35); *3*) DNC (Danish Nurse Cohort) in Denmark (36), including two cohort recruitment rounds in 1993 and 1999; *4*) E3N (Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale) in France (37); *5*) EPIC-NL (European Prospective Investigation into Cancer and Nutrition-Netherlands) cohort in The Netherlands, which included two subcohorts: Morgen (Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands) and Prospect (38); *6*) HNR (Heinz Nixdorf Recall study) in Germany (39); *7*) KORA (Cooperative Health Research in the Region of Augsburg) in Germany (40), combining two subcohorts from baseline rounds in 1994–1995 (S3) and 1999–2001 (S4); and *8*) VHM&PP (Vorarlberg Health Monitoring and Prevention Program) in Austria (41). The cohorts were recruited in the 1990s or early 2000s, from one or several large cities and their surrounding towns, except for the two nationwide cohorts, E3N and DNC (Table E2), and detailed information of each cohort was described previously (42). All cohorts were approved by the medical ethics committees in their respective countries.

Air Pollution Exposure Assessment

The exposure modeling information was described in detail previously (29, 30, 43). In brief, we estimated annual mean concentrations of $PM_{2.5}$, NO_2, BC, and O_3 for 2010 at baseline residential addresses of participants utilizing standardized Europe-wide hybrid land-use regression (LUR) models (43), which incorporated monitoring data, satellite data, chemical transport model estimates, land use, and traffic variables as predictors. The LUR models were at a fine spatial scale (100 m $\times$ 100 m grids) and performed well in fivefold holdout validation, explaining 72%, 59%, 54%, and 69% of the measured spatial variation for $PM_{2.5}$, NO_2, BC, and O_3, respectively. BC was measured by the reflectance of $PM_{2.5}$ filters for 2009 and 2010 and was expressed in absorbance units. O_3 concentrations were estimated as the maximum running 8-hour averages in the warm season from April to September.

We additionally back-extrapolated pollutant concentrations for each year from baseline to the end of follow-up (29, 30), incorporating dynamic residential address history during follow-up. The back-extrapolation method was applied by utilizing the estimated monthly average concentrations, at a 26 km $\times$ 26 km spatial resolution (downscaled from an original 50 km $\times$ 50 km resolution using bilinear interpolation), from the DEHM (Danish Eulerian Hemispheric Model) back to 1990 (44). Predicted modeling exposure data from DEHM provided a complete database to perform harmonious back-extrapolation for all four pollutants, whereas routine AirBase monitoring data were less consistent, not available for BC, and only available from around 2008 for $PM_{2.5}$. We back-extrapolated pollutant concentrations for cohorts with available information on residential history, using both a difference method and a ratio method with 2010 as the reference year.

Mortality Outcome Definition

We identified mortality outcomes based on the linkage to the mortality registries, in which death certificates for the underlying cause of death were recorded. Cause of death was coded with the International Classification of Diseases (ICD)-9 and ICD-10 classification of diseases. We analyzed mortality using three definitions of respiratory infectious diseases: ALRI (ICD-9: 480–486, 466; ICD-10: J12-J18, J20-J22), pneumonia (ICD-9: 480–486; ICD-10: J12-J18), and influenza (ICD-9: 487–488; ICD-10: J09-J11). We defined three outcomes: pneumonia and influenza combined, ALRI, and pneumonia only.

Statistical Analysis

We applied Cox proportional hazards models with age as the underlying timescale (45) to examine the associations between

long-term air pollution exposure and three mortality outcomes (pneumonia and influenza combined, ALRI, and pneumonia), following the general ELAPSE analytical framework (46). Censoring occurred at the time of the event of interest, death from other causes, emigration, loss to follow-up, or the end of follow-up (that ranges from 2011 to 2015 depending on the subcohorts), whichever came first. The start of follow-up was the year of enrollment, which varied from the early 1990s to the early 2000s (Table E2). Air pollution exposure was included as a linear term. The associations were examined using three models, including *a priori* defined individual and area-level covariates: Model 1 included age (time axis), sex (strata), subcohort (strata), and year of enrollment; Model 2 further included smoking status (never, former, current), smoking duration (years) for current smokers, smoking intensity (linear and squared term; cigarettes/day) for current smokers, body mass index (BMI; categories: $<$18.5, 18.5–24.9, 25.0–29.9, and $\geqslant$30 kg/m^2), marital status (married/cohabiting, divorced/separated, single, widowed), and employment status (employed/self-employed, other); and Model 3 (main model) further adjusted for area-level socioeconomic status: mean income in 2001. We determined Model 2 and Model 3 by balancing the need to adjust for a comprehensive set of covariates and the availability of covariates across eight cohorts. Only participants with complete exposure and covariates information on Model 3 were included in the analyses to ensure comparability among the model results.

To investigate whether associations persisted at low-level exposures, we performed subset analyses using Model 3 by excluding participants with exposure levels above certain predefined values (40, 30, 20 μg/m^3 for NO_2; 25, 20, 15, 12 μg/m^3 for $PM_{2.5}$; 3, 2.5, 2, 1.5 10^{-5}m^{-1} for BC; and 120, 100, 80 μg/m^3 for O_3), partially based on existing European Union (E.U.) and U.S. limit values and the 2005 World Health Organization (WHO) guidelines. We did not conduct a subset analysis for $PM_{2.5}$ exposures below the 2005 WHO guidelines of 10 μg/m^3 as only 54 deaths were observed, resulting in a noninformative effect estimate. We modeled pollutants as natural cubic splines with two degrees of freedom in Model 3 to assess the shape of the concentration–response functions for the associations and tested for the deviation of linearity by comparing with linear models using the likelihood ratio test. We assessed potential effect modification on the associations by age ($<$70, $\geqslant$70 years old), overweight status (BMI $\geqslant$25 kg/m^2 or not), smoking status, and employment status by including an interaction term into Model 3 tested by the Wald test. In addition, we performed two-pollutant models in Model 3 to disentangle the effect of individual pollutants.

We performed several sensitivity analyses to examine the robustness of the associations. At first, we compared the result and model performance (assessed by Akaike Information Criteria) in Model 3 with alternative models using different adjustment approaches for subcohorts: without adjustment, indicator variables, a frailty term, and a random intercept under a mixed Cox model. Second, we compared the results of year 2010 exposure in Model 3 with results of back-extrapolated baseline year exposures and time-varying annual exposures. Time-varying analyses were performed for cohorts with available information on residential address history, including CEANS, DCH, EPIC-NL, and VHM&PP, with 1-year strata of calendar time to account for time trends in air pollution and mortality. We also compared effect estimates in Model 3 in different datasets by excluding one cohort each time. Finally, we applied multiple imputation by chained equations to fill in missing covariate values in Model 3 (47) and calculated the combined effect estimates from five imputed complete datasets using the Rubin's rules (48), following the same ELAPSE analytical procedure (49).

The results are presented as hazard ratio (HR) and 95% confidence interval (CI) for increases of 10 μg/m^3 for NO_2, 5 μg/m^3 for $PM_{2.5}$, 0.5 10^{-5} m^{-1} for BC, and 10 μg/m^3 for O_3. All statistical analyses were performed in R software (version 3.4.0).

Results

The pooled cohort included 381,036 participants. Of those, 55,669 participants with missing covariate data in Model 3 were excluded. Study locations and population proportion for eight included cohorts in our study are shown in Figure E1. Of 325,367 remaining participants in the final analyses, 712 died from pneumonia and influenza combined, 695 from ALRI, 682 from pneumonia, and 30 from influenza during a mean follow-up of 19.5 years (Table 1; Table E2). The VHM&PP was the largest cohort, accounting for 44.4% of the population (Figure E1). Baseline characteristics of participants varied widely across subcohorts (Table 1), supporting the use of strata for subcohorts to adjust for differences in baseline hazard. The mean age was 48.7 years, ranging from 42.1 in VHM&PP to 72.9 in CEANS-SNACK. The majority of participants (66%) were female, as three cohorts/subcohorts were female-only by design (DNC, E3N, and EPIC-NL-Prospect). The proportion of current smokers ranged from 13% in E3N to 37% in DNC-1993. Almost half of the participants (43%) were overweight, with the highest proportion (74%) in HNR and the lowest (21%) in E3N.

Figure 1 represents the distribution of air pollution levels by cohorts and subcohorts in 2010. The exposure distributions varied between cohorts with the lowest concentrations of $PM_{2.5}$ and BC in Nordic cohorts (CEANS, DCH, and DNC). Almost all participants were exposed to NO_2 levels (95.5%) below the 2005 WHO guidelines and E.U. limit value of 40 μg/m^3, and to $PM_{2.5}$ levels (99.99%) below the E.U. limit value of 25 μg/m^3. Further, the concentration of $PM_{2.5}$ in the CEANS cohort was below the 2005 WHO guidelines and U.S. limit values of 10 and 12 μg/m^3, respectively (Figure 1). We also observed varying exposure levels across cohorts and subcohorts for the baseline year exposure in Figure E2. Compared with the 2010 exposure, the concentrations of $PM_{2.5}$ were much higher at baseline, and smaller differences were observed for other pollutants. Pearson correlations between NO_2 and BC were moderate to high in subcohorts (0.67–0.93) except for CEANS-SNACK (0.43; Table E3). $PM_{2.5}$ was moderately correlated with exposure to BC and NO_2 in most subcohorts, and O_3 was negatively correlated with other pollutants in all subcohorts, having high correlations with NO_2 and BC in some subcohorts (Table E3).

NO_2 and BC were associated with 10–12% increases in respiratory infectious diseases mortality, but 95% CI included unity (Table 2). Specifically, in the fully adjusted Model 3, a 10 μg/m^3 increase in NO_2 was associated with increased risks of pneumonia and influenza combined mortality (HR, 1.12; 95% CI, 0.99–1.26), ALRI mortality (HR, 1.10; CI, 0.98–1.24), and pneumonia mortality (HR, 1.11; CI, 0.99–1.26). The corresponding estimates for BC for each

Table 1. Baseline Demographic Characteristics of Participants by the Pooled Cohort, Cohorts, and Subcohorts

Cohort/ Subcohort	*N*	Deaths, *n**	Follow-up Time (yr)	Age (yr)	Female (%)	Current Smokers (%)	Smoking Duration† (yr)	Smoking Intensity† (*n*/d)	OverWeight‡ (%)	Married/ Cohabiting (%)	Employed (%)	Mean Income§ (Euro)
Pooled cohort	325,367	712	19.5	48.7 ± 13.4	66	24	6.2 ± 12.7	3.7 ± 7.8	43	72	70	20.1 ± 5.8
CEANS	20,702	43	13.0	56.3 ± 11.4	58	22	7.5 ± 14.9	2.9 ± 6.5	51	72	69	25.3 ± 5.6
SDPP	7,727	0	15.9	47.1 ± 4.9	61	26	7.4 ± 13.0	3.6 ± 7.1	52	84	91	24.3 ± 4.2
SIXTY	3,969	6	15.5	60.0 ± 0.0	52	21	7.7 ± 15.5	2.8 ± 6.5	65	74	68	24.7 ± 6.9
SALT	6,176	15	10.4	57.8 ± 10.6	55	21	8.0 ± 16.1	2.7 ± 6.4	40	68	64	25.3 ± 6.6
SNACK	2,830	22	7.4	72.9 ± 10.4	62	14	6.2 ± 16.0	1.7 ± 5.2	53	46	23	28.7 ± 2.2
DCH	53,647	157	18.2	56.7 ± 4.4	52	36	13.2 ± 18.1	6.0 ± 9.6	56	72	78	20.2 ± 3.4
DNC	25,171	113	17.3	53.5 ± 8.3	100	35	10.5 ± 15.5	4.8 ± 8.1	29	70	78	19.1 ± 2.5
1993	17,043	108	18.7	56.2 ± 8.4	100	37	11.8 ± 16.4	5.2 ± 8.4	28	68	70	19.2 ± 2.6
1999	8,128	5	14.4	47.9 ± 4.2	100	29	7.8 ± 12.8	3.8 ± 7.2	30	76	95	19.0 ± 2.4
E3N	39,006	18	16.7	53.0 ± 6.8	100	13	3.7 ± 10.0	1.5 ± 5.1	21	83	68	11.2 ± 3.0
EPIC-NL	32,872	55	16.7	49.5 ± 11.9	75	29	8.5 ± 14.5	4.4 ± 8.3	52	70	61	12.6 ± 1.6
Morgen	18,302	19	16.8	42.9 ± 11.2	55	35	8.6 ± 13.3	5.5 ± 9.0	50	65	69	12.2 ± 1.6
Prospect	14,570	36	16.4	57.7 ± 6.1	100	23	8.4 ± 15.9	3.1 ± 7.1	55	77	51	13.1 ± 1.4
HNR	4,733	11	12.0	59.7 ± 7.8	50	24	8.1 ± 15.3	4.4 ± 9.8	74	75	40	25.2 ± 8.2
KORA	4,853	26	14.3	49.4 ± 13.9	51	21	5.3 ± 11.5	3.5 ± 8.0	68	80	57	37.3 ± 6.0
S3	2,572	15	15.6	49.4 ± 13.9	51	20	5.1 ± 11.5	3.3 ± 7.9	67	80	55	36.7 ± 4.4
S4	2,281	11	12.9	49.3 ± 13.8	51	23	5.6 ± 11.6	3.6 ± 8.0	69	79	59	38.0 ± 7.3
VHM&PP	144,383	289	23.1	42.1 ± 15.0	56	20	2.7 ± 6.5	3.1 ± 7.4	43	69	70	22.9 ± 1.7

Definition of abbreviations: BMI = body mass index; CEANS = Cardiovascular Effects of Air Pollution and Noise in Stockholm; DCH = Diet, Cancer, and Health; DNC = Danish Nurse Cohort; E3N = Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; EPIC-NL = European Prospective Investigation into Cancer and Nutrition-Netherlands; HNR = Heinz Nixdorf Recall study; KORA = Cooperative Health Research in the Region of Augsburg; SALT = Stockholm Screening Across the Lifespan Twin study; SDPP = Stockholm Diabetes Prevention Program; SIXTY = Stockholm Cohort of 60-year-olds; SNACK = Swedish National Study on Aging and Care in Kungsholmen; VHM&PP = Vorarlberg Health Monitoring and Prevention Program.

Results of participant characteristics at baseline are presented as mean ± SD, number, or percentage.

*The number of deaths of pneumonia and influenza combined.

†Smoking duration and smoking intensity are only for current smokers. We set these variables to zero for never and former smokers.

‡BMI ⩾25 kg/m^2 indicates overweight according to the World Health Organization categories.

§Area-level mean year income in euros ×1,000 in the year 2001. The spatial scale of an area varied from neighborhoods and city districts (CEANS, E3N, EPIC-NL, and HNR) to municipalities (DNC, DCH, KORA, and VHM&PP).

0.5 $10^{-5}m^{-1}$ increase were 1.10 (0.97–1.24), 1.08 (0.96–1.22), and 1.09 (0.97–1.24), respectively. Associations with $PM_{2.5}$ and O_3 had wider confidence intervals and were closer to unity. In two-pollutant models, positive associations with NO_2 and BC were robust to adjustment for $PM_{2.5}$ or O_3. The associations with BC were attenuated to null, while the associations with NO_2 were enhanced when adjusting for each other (Table E4).

Associations of both NO_2 and BC with pneumonia and influenza combined mortality did not change below predefined cutoffs (Table 3), but CIs became wide at the lower cutoffs for which few cases remained. There was no evidence of a threshold for these two pollutants (Figure 2). For $PM_{2.5}$, the association was nonlinear with a wide confidence interval (Table 3; Figure 2), where we found a positive association at lower levels (<15 μg/m^3) and no association at higher cutoff levels (<25 μg/m^3) (Table 3), resulting in an overall inverted U-shaped relationship with a significant deviation from linearity ($P = 0.03$) (Figure 2). We described characteristics of participants in different subcohorts by $PM_{2.5}$ levels below or above 15 μg/m^3 and did not observe significant differences within each subcohort (Table E5). However, the majority of participants (74–100%) in the three Nordic cohorts (CEANS, DCH, DNC) were exposed to $PM_{2.5}$ levels <15 μg/m^3, in contrast to other cohorts (0.02–37%) (Table E5; Figure 1). Additionally, in the three Nordic cohorts, we found a positive linear slope of exposure–response function between $PM_{2.5}$ and pneumonia and influenza combined mortality, and a negative linear slope for the other cohorts (Figure E3). The nonlinear relationship for $PM_{2.5}$ could be due to an unequal distribution of subcohorts at the range of $PM_{2.5}$ concentrations. Associations with O_3 were negative and linear (Figure 2).

We observed that the associations between pneumonia and influenza combined mortality with NO_2 and BC were stronger in participants who were overweight as compared with normal-weight participants (P value for interaction = 0.02 for NO_2 and 0.10 for BC), in current smokers as compared with former and never smokers (P value = 0.17 for NO_2 and 0.07 for BC), and in employed participants as compared with nonemployed (P value = 0.29 for NO_2 and

0.08 for BC) (Table 4). Due to the nonlinear relationship for $PM_{2.5}$, we did not consider the significant effect modification results with this pollutant.

The associations for all pollutants were robust to different sensitivity analyses. We found similar effect estimates, except for BC and O_3 with no adjustment method, and the best model performance with strata when comparing models with different approaches to adjust for subcohorts (Figure E4). The effect estimates were somewhat attenuated when using either back-extrapolated baseline year exposures (Table E6) or time-varying exposures (Table E7). The associations were unaffected after applying multiple imputation, as well as by excluding each cohort separately, except for DCH, where attenuation of associations to unity was observed (Table E8).

Discussion

In this pooled analysis of 325,367 adults from eight European cohorts, we found that long-term exposure to NO_2 and BC were

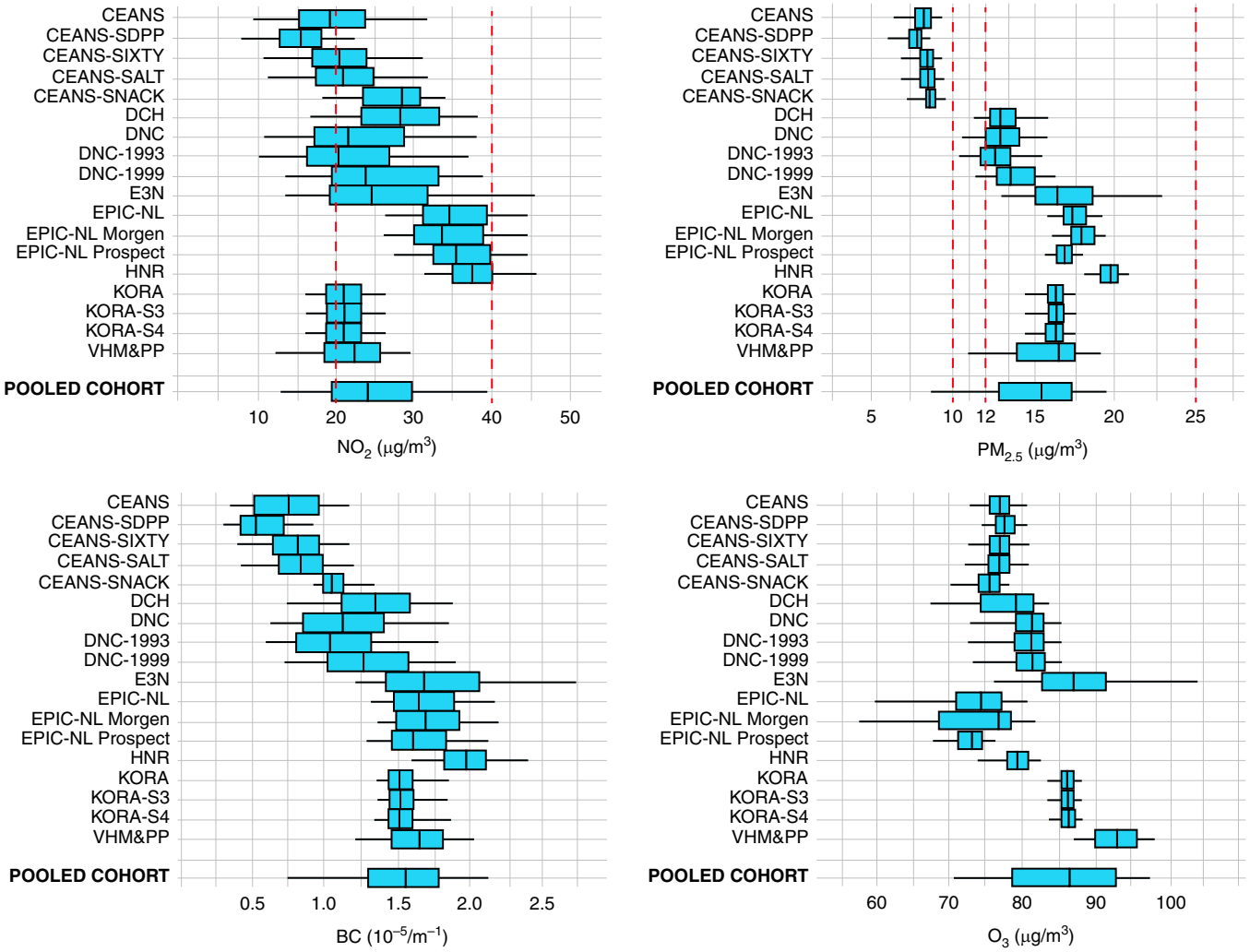

Figure 1. Distribution of annual average concentrations of air pollution for the year 2010 by cohorts and subcohorts ($N = 325,367$). The bold lines in the middle of the box indicate the median values (the 50th percentile). The lower and upper hinges correspond to the 25th and 75th percentiles. The lower and upper whiskers extend to the 5th and 95th percentiles. Red dashed lines represent different limited values in the European Union, United States, and 2005 World Health Organization (WHO) guidelines. For fine particulate matter ($PM_{2.5}$), they indicate the annual average limited/guideline values of WHO (2005 version; 10 $\mu g/m^3$), United States (12 $\mu g/m^3$), and European Union (25 $\mu g/m^3$). For nitrogen dioxide (NO_2), they indicate the annual average limited/guideline values of WHO (2005 version) and European Union (40 $\mu g/m^3$), and WHO health risks of air pollution in Europe (20 $\mu g/m^3$). Ozone (O_3) was in the warm season from April 1 through September 30. BC = black carbon. CEANS = Cardiovascular Effects of Air Pollution and Noise in Stockholm; DCH = Diet, Cancer, and Health; DNC = Danish Nurse Cohort; E3N = Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; EPIC-NL = European Prospective Investigation into Cancer and Nutrition-Netherlands; HNR = Heinz Nixdorf Recall study; KORA = Cooperative Health Research in the Region of Augsburg; SALT = Stockholm Screening Across the Lifespan Twin Study; SDPP = Stockholm Diabetes Prevention Program; SIXTY = Stockholm Cohort of 60-year-olds; SNACK = Swedish National Study on Aging and Care in Kungsholmen; VHM&PP = Vorarlberg Health Monitoring and Prevention Program.

Table 2. Associations between Long-Term Air Pollution Exposure and Specific Respiratory Infection Mortality ($N = 325{,}367$)

	Model 1*	Model 2*	Model 3*	Model 3†
Pneumonia and influenza (712 deaths)				
NO_2	1.12 (1.00–1.26)	1.06 (0.94–1.19)	1.12 (0.99–1.26)	1.12 (0.99–1.26)
$PM_{2.5}$	0.96 (0.80–1.15)	0.92 (0.77–1.11)	0.96 (0.80–1.15)	0.96 (0.81–1.13)
BC	1.11 (0.99–1.25)	1.05 (0.93–1.19)	1.10 (0.97–1.24)	1.10 (0.97–1.24)
O_3	0.86 (0.73–1.01)	0.94 (0.79–1.11)	0.92 (0.78–1.09)	0.89 (0.71–1.13)
Acute lower respiratory infection (695 deaths)				
NO_2	1.11 (0.99–1.25)	1.05 (0.93–1.18)	1.10 (0.98–1.24)	1.10 (0.98–1.24)
$PM_{2.5}$	0.94 (0.78–1.13)	0.90 (0.75–1.09)	0.93 (0.78–1.12)	0.94 (0.80–1.11)
BC	1.10 (0.98–1.24)	1.04 (0.92–1.17)	1.08 (0.96–1.22)	1.08 (0.96–1.22)
O_3	0.88 (0.75–1.04)	0.96 (0.81–1.14)	0.95 (0.80–1.12)	0.93 (0.73–1.17)
Pneumonia (682 deaths)				
NO_2	1.12 (1.00–1.26)	1.06 (0.94–1.19)	1.11 (0.99–1.26)	1.12 (0.99–1.26)
$PM_{2.5}$	0.94 (0.78–1.13)	0.90 (0.75–1.09)	0.93 (0.77–1.12)	0.94 (0.79–1.11)
BC	1.11 (0.99–1.26)	1.05 (0.93–1.19)	1.09 (0.97–1.24)	1.09 (0.97–1.24)
O_3	0.86 (0.73–1.02)	0.94 (0.80–1.11)	0.92 (0.78–1.09)	0.89 (0.70–1.14)

Definition of abbreviations: BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = fine particulate matter.
Model 1 adjusted for age (time axis), sex (strata), subcohort (strata), and calendar year of baseline; Model 2 additionally adjusted for smoking (status, duration, intensity, and intensity^2), body mass index (category), marital status, and employment status; Model 3 further adjusted for area-level mean year income.
*Results are presented as hazard ratio (95% confidence interval) for the following increases: 10 $\mu g/m^3$ for NO_2, 5 $\mu g/m^3$ for $PM_{2.5}$, 0.5 $10^{-5}m^{-1}$ for BC, and 10 $\mu g/m^3$ for O_3.
†Results are presented for interquartile range increases: 10.2 $\mu g/m^3$ for NO_2, 4.5 $\mu g/m^3$ for $PM_{2.5}$, 0.5 $10^{-5}m^{-1}$ for BC, and 14.1 $\mu g/m^3$ for O_3.

associated with 10–12% increases in ALRI mortality, which was mainly driven by pneumonia mortality. CIs were wide, however, and just included unity. We present novel findings that overweight, current smoking, and employment may increase susceptibility to adverse effects of air pollution on risk of dying from respiratory infectious diseases. The associations persisted at low-level concentrations, with no evidence of a threshold. Associations with $PM_{2.5}$ and O_3 were closer to unity with wider CIs.

Table 3. Associations between Long-Term Air Pollution Exposure and Pneumonia and Influenza Mortality Below Various Cut-Off Values in Model 3

Pollutants	Cut-off Levels	Number of Participants	Number of Deaths	HR (95% CI)
NO_2				
	All levels	325,367	712	1.12 (0.99–1.26)
	<40 $\mu g/m^3$	310,643	682	1.11 (0.97–1.26)
	<30 $\mu g/m^3$	247,039	517	1.07 (0.88–1.30)
	<20 $\mu g/m^3$	88,510	172	1.12 (0.67–1.87)
$PM_{2.5}$				
	All levels	325,367	712	0.96 (0.80–1.15)
	<25 $\mu g/m^3$	325,339	711	0.94 (0.78–1.13)
	<20 $\mu g/m^3$	316,540	704	0.96 (0.80–1.15)
	<15 $\mu g/m^3$	151,250	393	1.33 (0.88–2.00)
	<12 $\mu g/m^3$	52,528	128	1.14 (0.42–3.10)
BC				
	All levels	325,367	712	1.10 (0.97–1.24)
	<3 $10^{-5}m^{-1}$	324,757	711	1.08 (0.96–1.23)
	<2.5 $10^{-5}m^{-1}$	320,632	709	1.10 (0.97–1.25)
	<2 $10^{-5}m^{-1}$	296,371	666	1.11 (0.96–1.28)
	<1.5 $10^{-5}m^{-1}$	142,032	335	1.17 (0.89–1.53)
O_3				
	All levels	325,367	712	0.92 (0.78–1.09)
	<120 $\mu g/m^3$	325,367	712	0.92 (0.78–1.09)
	<100 $\mu g/m^3$	320,522	709	0.93 (0.79–1.11)
	<80 $\mu g/m^3$	98,840	268	0.91 (0.68–1.21)

Definition of abbreviations: BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = fine particulate matter.

Our results on long-term exposure to NO_2 and pneumonia-related mortality are in accordance with current evidence. Seven previous studies investigated the association of long-term exposure to NO_2 with pneumonia or pneumonia and influenza combined mortality (Table E1), and all (8, 17, 19, 23, 24, 26) but one (25) reported positive associations. Five of these studies (19, 23–26) were included in a recent WHO systematic review, reporting a pooled estimate of 1.06 (1.02–1.10) per 10 $\mu g/m^3$ increase (15), somewhat smaller than our estimate of 1.12 (0.99–1.26). Our study is the first to detect positive associations between long-term exposure to BC and pneumonia-related mortality, with an HR of 1.10 (0.97–1.24) per 0.5 $10^{-5}m^{-1}$, which is in contrast to a single other study (25). Our results on NO_2 and BC, combined with previous findings, suggest that air pollution from fossil fuel combustion sources (such as motorized traffic) may be most relevant to increased susceptibility to infectious lung diseases mortality.

For $PM_{2.5}$, most previous studies reported positive associations with pneumonia mortality (18, 22, 24, 26) or pneumonia and influenza combined mortality (17, 19–21). In our study, one reason for the lack of a positive association with $PM_{2.5}$ is the nonlinear exposure–response function, with a positive slope at $PM_{2.5}$ levels below 15 $\mu g/m^3$ and a

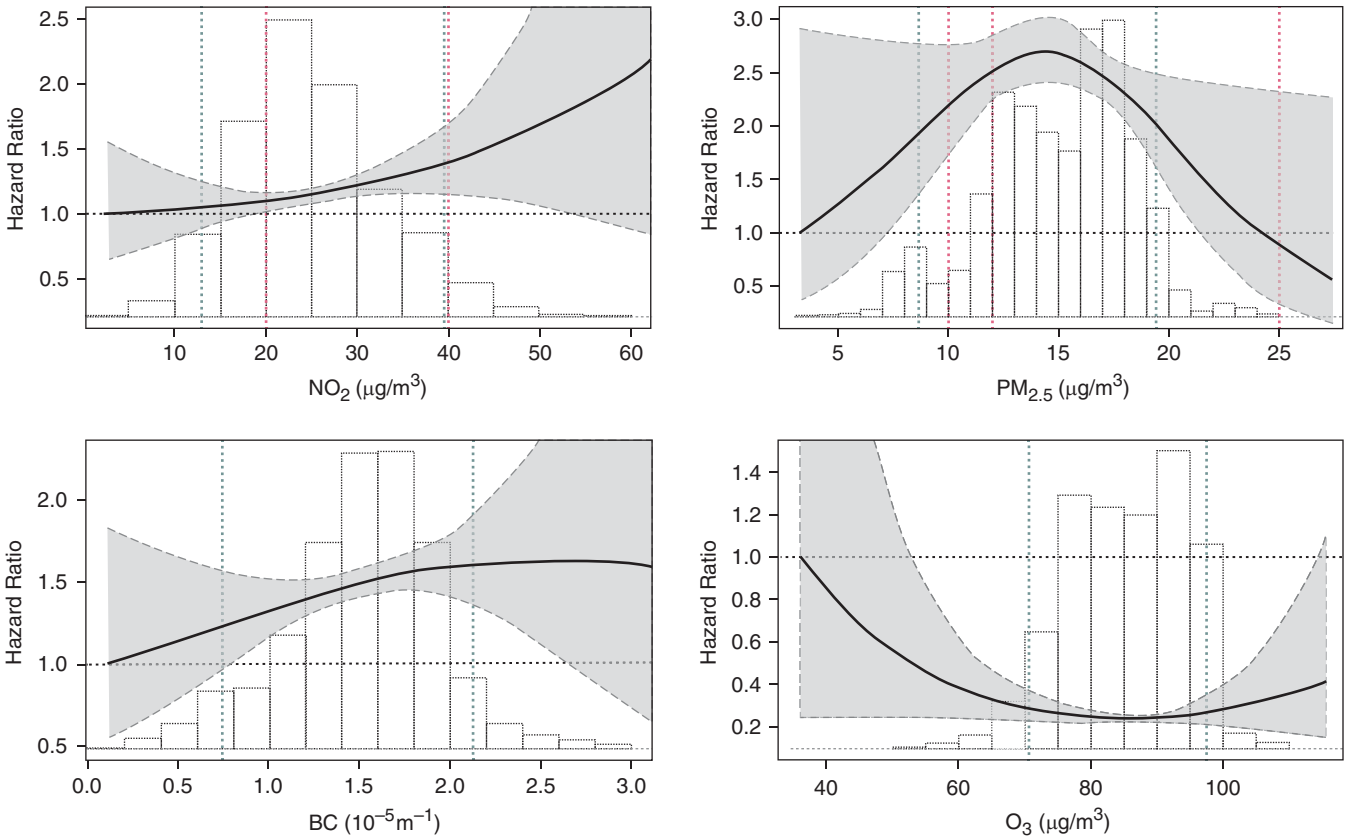

Figure 2. Concentration–response curves for the associations between long-term exposure to air pollution and pneumonia and influenza mortality. Natural cubic splines with two degrees of freedom were fit for air pollutants based on Model 3, with hazard ratios (HRs) set equal to one for the minimum pollutant exposures. Solid black lines indicate HR values and black dashed lines indicate their 95% confidence intervals. Green dotted lines indicate the 5th and 95th percentiles of air pollutant concentrations. Red dotted dash lines represent different limited/guideline values in the European Union, United States, and World Health Organization (2005 version). *X*-axes are truncated at 60 $\mu g/m^3$ and 3 $10^{-5}m^{-1}$ for nitrogen dioxide (NO_2) and black carbon (BC). O_3 = ozone; $PM_{2.5}$ = fine particulate matter.

negative slope above 15 $\mu g/m^3$. Comparisons of exposure–response functions with other studies are limited, as only a few provided these. Pinault and colleagues found a sublinear curve for the association of $PM_{2.5}$ with pneumonia mortality in the Canadian Census Health and Environment Cohort study (22). Burnett and colleagues reported a near-linear exposure–response relationship for lower respiratory infection mortality and $PM_{2.5}$ using data from 41 cohorts (50). In contrast, Bowe and colleagues estimated the burden of death from pneumonia due to $PM_{2.5}$ using nonlinear exposure–response function models in a cohort study of U.S. veterans (51). In our study, the findings of an inverted U-shaped exposure–response curve for $PM_{2.5}$ is difficult to interpret because $PM_{2.5}$ levels in three Nordic cohorts (mainly <15 $\mu g/m^3$) showed a positive linear association (Figure E3).

Evidence on long-term exposure to O_3 and pneumonia mortality shows mixed results. Three U.S. studies based on Medicare data (16), NIH-AARP Diet and Health Study (17), and Cancer Prevention Study II (CPS-II) (19) all detected positive associations, whereas a national English cohort reported negative associations (HR, 0.84; CI, 0.73–0.97, per 10 $\mu g/m^3$ increase) (26). Notably, the United Kingdom study used annual mean O_3 levels, while all three U.S. studies reported associations with warm-season O_3, of which two studies also investigated annual O_3 and one observed associations with annual mean O_3 (19) but the other one did not (17). In our study, we have not found clear explanations for the inverse exposure–response function for O_3. One explanation may be the small exposure contrasts within each subcohort (Figure 1). Another explanation may be the generally low levels of O_3 exposure (ranging from 36 to 116 $\mu g/m^3$) in our study, as a previous study suggested a possible threshold of 56 ppb (around 110 $\mu g/m^3$) for the effect of warm-season O_3 on mortality (52). The inverse relationship with O_3 could also be due to the strong negative correlations for O_3 with NO_2 and BC in some subcohorts (Table E3); we thus need to be cautious in interpreting the two-pollutant results for O_3. Notably, we examined the associations with warm-season O_3 estimated from the DEHM dispersion models, which were at a much lower spatial resolution of 50×50 km than the resolution in the ELAPSE models of 100×100 m. By using the DEHM dispersion models, we found a positive association of O_3 with pneumonia and influenza combined mortality, with an HR of 1.29 (0.98–1.70), based on 323,888 participants and 709 deaths, which was in line with the several earlier studies (16, 17, 19). Overall, more research on the effects of long-term exposure to low levels of O_3 on pneumonia-related mortality is needed.

We present novel findings of the potential susceptibility of overweight

Table 4. Effect Modification on the Association between Year 2010 Exposure and Pneumonia and Influenza Mortality by Baseline Characteristics

Baseline Characters	*N*	Deaths, *n*	NO_2 HR (95% CI)	$PM_{2.5}$ HR (95% CI)	BC HR (95% CI)	O_3 HR (95% CI)	*P* Values for Interaction
Age, yr							NO_2: 0.90;
<70	313,221	454	1.11 (0.96–1.28)	0.82 (0.65–1.02)	1.02 (0.89–1.18)	0.87 (0.72–1.04)	$PM_{2.5}$: 0.04*;
⩾70	12,146	258	1.09 (0.90–1.32)	1.16 (0.88–1.53)	1.22 (1.00–1.47)	1.17 (0.91–1.51)	BC: 0.13;
							O_3: 0.03*
Overweight†							NO_2: 0.02*;
No	184,552	343	1.01 (0.87–1.17)	0.87 (0.69–1.09)	1.02 (0.87–1.19)	0.99 (0.82–1.19)	$PM_{2.5}$: 0.15;
Yes	140,815	369	1.26 (1.08–1.47)	1.05 (0.84–1.31)	1.20 (1.02–1.40)	0.85 (0.71–1.03)	BC: 0.10;
							O_3: 0.09
Smoking status							NO_2: 0.17;
Current smoker	78,584	208	1.27 (1.06–1.53)	1.36 (1.00–1.85)	1.26 (1.05–1.52)	0.82 (0.66–1.02)	$PM_{2.5}$: 0.01*;
Former smoker	59,488	152	1.08 (0.87–1.33)	1.07 (0.77–1.49)	1.12 (0.91–1.38)	0.94 (0.73–1.22)	BC: 0.07;
Never smoker	187,295	352	1.03 (0.87–1.21)	0.83 (0.68–1.02)	0.96 (0.81–1.14)	1.02 (0.83–1.26)	O_3: 0.20
Employment status							NO_2: 0.29;
Employed†	227,765	194	1.21 (1.00–1.46)	1.69 (1.23–2.31)	1.26 (1.04–1.53)	0.90 (0.73–1.12)	$PM_{2.5}$:
Others	97,602	518	1.08 (0.94–1.23)	0.81 (0.67–0.99)	1.03 (0.89–1.18)	0.94 (0.78–1.12)	<0.001*;
							BC: 0.08;
							O_3: 0.71

Definition of abbreviations: BC = black carbon; BMI = body mass index; CI = confidence interval; HR = hazard ratio; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = fine particulate matter.

Results are presented as hazard ratio (95% confidence interval) for the following increases: 10 $\mu g/m^3$ for NO_2, 5 $\mu g/m^3$ for $PM_{2.5}$, 0.5 10^{-5} m^{-1} for BC, and 10 $\mu g/m^3$ for O_3.

Effect modification analyses were conducted based on Model 3 and evaluated by introducing interaction terms. *P* values for whether there were statistically significant differences between strata were tested by the Wald test.

*A statistically significant *P* value (at 5% level) for effect modification analyses.

†BMI ⩾25 kg/m^2 indicates overweight according to World Health Organization categories. Employed status includes employed and self-employed.

participants and smokers and those who are employed in showing stronger associations with dying from respiratory infections. There are no other studies that explored effect modification of the association between air pollution and infectious disease mortality, so we draw some comparisons with studies on chronic respiratory disease mortality and COVID-19 (viral respiratory infectious disease). Results on smoking are in agreement with Beelen and colleagues, who reported stronger associations of respiratory mortality with black smoke in current smokers in the NLCS-AIR study, though without reaching statistically significant interaction ($P = 0.11$) (53). Hamer and colleagues in the United Kingdom Biobank study found that smokers and obese people had elevated risks of COVID-19 hospital admission compared with never smokers and healthy-weight participants as references, respectively (54). Yang and colleagues found that participants with high BMI (⩾26.3 kg/m^2) had higher risks for respiratory mortality related to exposure to $PM_{2.5}$ and BC (25). A recent study proposed a hypothesis that obesity, acting as an effect modifier of air pollution-induced lung injury, could play a role in the relationship between exposure to air pollution and COVID-19 severity (55). Plausible mechanisms for how overweight/obesity and smoking can enhance risks of infection due to air pollution may be underlying depletion of antioxidative stress capacity and impairment of immune defenses (10, 13). Our results on higher susceptibility of employed as compared with unemployed participants may reflect higher risks of infection related to contact with more people, at work or transport to and from work, in employed participants.

The main strength of our study is the pooled data from eight European cohorts allowing for investigating mortality from lower respiratory infections, a rather rare outcome, as well as detailed information on individual and area-level potential confounders. However, the number of deaths from respiratory infections was still small in this large population, resulting in wide CIs. Another strength of this study is the harmonized exposure data based on the Europe-wide hybrid LUR models at a fine spatial scale, especially for data on BC, facilitating just the second study on this pollutant with pneumonia mortality.

One limitation of this study is the use of exposure data for 2010 at the baseline of the cohorts recruited in the 1990s and early 2000s due to the lack of monitoring stations for $PM_{2.5}$ in Europe before 2010. However, a study reported stable spatial distribution of NO_2 over 10 years in The Netherlands (56). Similarly, in our study, the predictions from the 2010 model were highly correlated ($R^2 > 76\%$) with 2000 and 2005 models for NO_2 and O_3, and 2013 models for $PM_{2.5}$ at the European scale (43), indicating limited impacts of temporal misalignment by exposures based on 2010. In sensitivity analyses, we also observed that associations were insensitive to either using back-extrapolated baseline year exposures (Table E6) or time-varying exposures for four cohorts with address history information (Table E7). We, therefore,

assume that the chosen approach to exposure assessment yields reasonably accurate estimates for included study regions and pollutants while acknowledging some degrees of exposure misclassification. The potential for exposure misclassification also exists when using modeled exposures at the residential address and ignoring time spent outdoors and commuting to work, which are inevitably not equivalent to personal exposure from outdoor sources, as well as relatively moderate model performance ($R^2 = 0.59$ and 0.54) for NO_2 and BC, respectively, in our LUR models. Additionally, we mostly evaluated associations with exposure contrasts within subcohorts due to the use of strata for subcohorts in analyses. We did not adjust for spatial contrasts in long-term exposure to high or low temperatures because such contrasts are absent within most of our single city-based cohorts. Spatial variation in temperature is occasionally but not usually included in analyses of long-term effects of air pollution on all-cause and cause-specific (including respiratory) mortality and morbidity. An early study found no association between annual mean temperature and pneumonia admissions among the elderly (57), including all admissions and all U.S. counties over the 1984–1989 period.

In a recent nationwide study on air pollution and mortality, Di and colleagues found that effect estimates for $PM_{2.5}$ and O_3 were insensitive to adjustment for annual mean temperature and relative humidity (58). The removal of the two nationwide cohorts (E3N and DCH) made no difference. We also lacked the information on influenza vaccinations, which could be a confounder for the association between air pollution and pneumonia and influenza-related mortality. We do not have information on the differences in ICD coding instructions between cohorts and study periods. Finally, we acknowledge that the large number of analyses, including main, subset, two-pollutant, effect-modification models, and a number of sensitivity analyses, may result in a risk of some false discoveries. We did not apply procedures such as Bonferroni corrections to redefine statistical significance, as we focus on the size of the effect estimates and not on statistical significance.

Conclusions

Our findings from the ELAPSE pooled cohort provide suggestive evidence that long-term exposure to NO_2 and BC may increase the risk of mortality from pneumonia and related infectious diseases in adults and suggest that overweight, current smoking, and employed participants may be especially vulnerable. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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References

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1736–1788.
2. Marshall DC, Goodson RJ, Xu Y, Komorowski M, Shalhoub J, Maruthappu M, *et al.* Trends in mortality from pneumonia in the Europe union: a temporal analysis of the European detailed mortality database between 2001 and 2014. *Respir Res* 2018;19:81.
3. Torres A, Cillóniz C, Blasi F, Chalmers JD, Gaillat J, Dartois N, *et al.* Burden of pneumococcal community-acquired pneumonia in adults across Europe: a literature review. *Respir Med* 2018;137:6–13.
4. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, *et al.* Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015;385:430–440.
5. Yee J, Cho YA, Yoo HJ, Yun H, Gwak HS. Short-term exposure to air pollution and hospital admission for pneumonia: a systematic review and meta-analysis. *Environ Health* 2021;20:6.
6. Nhung NTT, Amini H, Schindler C, Kutlar Joss M, Dien TM, Probst-Hensch N, *et al.* Short-term association between ambient air pollution and pneumonia in children: a systematic review and meta-analysis of time-series and case-crossover studies. *Environ Pollut* 2017;230:1000–1008.
7. Neupane B, Jerrett M, Burnett RT, Marrie T, Arain A, Loeb M. Long-term exposure to ambient air pollution and risk of hospitalization with community-acquired pneumonia in older adults. *Am J Respir Crit Care Med* 2010;181:47–53.
8. Eum KD, Kazemiparkouhi F, Wang B, Manjourides J, Pun V, Pavlu V, *et al.* Long-term NO_2 exposures and cause-specific mortality in American older adults. *Environ Int* 2019;124:10–15.
9. Bourdrel T, Annesi-Maesano I, Alahmad B, Maesano CN, Bind MA. The impact of outdoor air pollution on COVID-19: a review of evidence from in vitro, animal, and human studies. *Euro Respir Rev* 2021;30: 200242.
10. Ciencewicki J, Jaspers I. Air pollution and respiratory viral infection. *Inhal Toxicol* 2007;19:1135–1146.
11. Schraufnagel DE, Balmes JR, Cowl CT, De Matteis S, Jung SH, Mortimer K, *et al.* Air pollution and noncommunicable diseases: a review by the Forum of International Respiratory Societies' Environmental Committee, part 1: the damaging effects of air pollution. *Chest* 2019; 155:409–416.
12. Schraufnagel DE, Balmes JR, Cowl CT, De Matteis S, Jung SH, Mortimer K, *et al.* Air pollution and noncommunicable diseases: a review by the Forum Of International Respiratory Societies' Environmental Committee, part 2: air pollution and organ systems. *Chest* 2019;155: 417–426.
13. Hajat A, Allison M, Diez-Roux AV, Jenny NS, Jorgensen NW, Szpiro AA, *et al.* Long-term exposure to air pollution and markers of inflammation, coagulation, and endothelial activation: a repeat-measures analysis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Epidemiology* 2015; 26:310–320.
14. Chen J, Hoek G. Long-term exposure to PM and all-cause and cause-specific mortality: a systematic review and meta-analysis. *Environ Int* 2020;143:105974.
15. Huangfu P, Atkinson R. Long-term exposure to NO_2 and O_3 and all-cause and respiratory mortality: a systematic review and meta-analysis. *Environ Int* 2020;144:105998.
16. Kazemiparkouhi F, Eum KD, Wang B, Manjourides J, Suh HH. Long-term ozone exposures and cause-specific mortality in a US Medicare cohort. *J Expo Sci Environ Epidemiol* 2020;30:650–658.
17. Lim CC, Hayes RB, Ahn J, Shao Y, Silverman DT, Jones RR, *et al.* Long-term exposure to ozone and cause-specific mortality risk in the United States. *Am J Respir Crit Care Med* 2019;200:1022–1031.
18. Pun VC, Kazemiparkouhi F, Manjourides J, Suh HH. Long-Term PM2.5 exposure and respiratory, cancer, and cardiovascular mortality in older US adults. *Am J Epidemiol* 2017;186:961–969.

19. Turner MC, Jerrett M, Pope CA III, Krewski D, Gapstur SM, Diver WR, *et al.* Long-term ozone exposure and mortality in a large prospective study. *Am J Respir Crit Care Med* 2016;193:1134–1142.
20. Pope CA III, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, *et al.* Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;109:71–77.
21. Pope CA III, Lefler JS, Ezzati M, Higbee JD, Marshall JD, Kim SY, *et al.* Mortality risk and fine particulate air pollution in a large, representative cohort of U.S. adults. *Environ Health Perspect* 2019;127:77007.
22. Pinault LL, Weichenthal S, Crouse DL, Brauer M, Erickson A, Donkelaar AV, *et al.* Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. *Environ Res* 2017;159:406–415.
23. Yorifuji T, Kashima S, Tsuda T, Ishikawa-Takata K, Ohta T, Tsuruta K, *et al.* Long-term exposure to traffic-related air pollution and the risk of death from hemorrhagic stroke and lung cancer in Shizuoka, Japan. *Sci Total Environ* 2013;443:397–402.
24. Katanoda K, Sobue T, Satoh H, Tajima K, Suzuki T, Nakatsuka H, *et al.* An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. *J Epidemiol* 2011;21:132–143.
25. Yang Y, Tang R, Qiu H, Lai PC, Wong P, Thach TQ, *et al.* Long term exposure to air pollution and mortality in an elderly cohort in Hong Kong. *Environ Int* 2018;117:99–106.
26. Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG, Anderson HR. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *Am J Respir Crit Care Med* 2013;187: 1226–1233.
27. Ali N, Islam F. The effects of air pollution on COVID-19 infection and mortality-a review on recent evidence. *Front Public Health* 2020; 8:580057.
28. Liu S, Jørgensen JT, Ljungman P, Pershagen G, Bellander T, Leander K, *et al.* Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project. *Eur Respir J* 2021;57:2003099.
29. Liu S, Jørgensen JT, Ljungman P, Pershagen G, Bellander T, Leander K, *et al.* Long-term exposure to low-level air pollution and incidence of chronic obstructive pulmonary disease: the ELAPSE project. *Environ Int* 2021;146:106267.
30. Hvidtfeldt UA, Severi G, Andersen ZJ, Atkinson R, Bauwelinck M, Bellander T, *et al.* Long-term low-level ambient air pollution exposure and risk of lung cancer - a pooled analysis of 7 European cohorts. *Environ Int* 2021;146:106249.
31. Eriksson AK, Ekbom A, Granath F, Hilding A, Efendic S, Ostenson CG. Psychological distress and risk of pre-diabetes and Type 2 diabetes in a prospective study of Swedish middle-aged men and women. *Diabet Med* 2008;25:834–842.
32. Wändell PE, Wajngot A, de Faire U, Hellénius ML. Increased prevalence of diabetes among immigrants from non-European countries in 60-year-old men and women in Sweden. *Diabetes Metab* 2007;33:30–36.
33. Magnusson PK, Almqvist C, Rahman I, Ganna A, Viktorin A, Walum H, *et al.* The Swedish Twin Registry: establishment of a biobank and other recent developments. *Twin Res Hum Genet* 2013;16:317–329.
34. Lagergren M, Fratiglioni L, Hallberg IR, Berglund J, Elmståhl S, Hagberg B, *et al.* A longitudinal study integrating population, care and social services data. The Swedish National study on Aging and Care (SNAC). *Aging Clin Exp Res* 2004;16:158–168.
35. Tjønneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, *et al.* Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. *Scand J Public Health* 2007;35:432–441.
36. Hundrup YA, Simonsen MK, Jørgensen T, Obel EB. Cohort profile: the Danish nurse cohort. *Int J Epidemiol* 2012;41:1241–1247.
37. Clavel-Chapelon F; E3N Study Group. Cohort profile: the French E3N cohort study. *Int J Epidemiol* 2015;44:801–809.
38. Beulens JW, Monninkhof EM, Verschuren WM, van der Schouw YT, Smit J, Ocke MC, *et al.* Cohort profile: the EPIC-NL study. *Int J Epidemiol* 2010;39:1170–1178.
39. Schmermund A, Möhlenkamp S, Stang A, Grönemeyer D, Seibel R, Hirche H, *et al.* Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL study. Risk factors, evaluation of coronary calcium and lifestyle. *Am Heart J* 2002;144:212–218.
40. Holle R, Happich M, Löwel H, Wichmann HE; MONICA/KORA Study Group. KORA–a research platform for population based health research. *Gesundheitswesen* 2005;67 Suppl 1:S19–25.
41. Ulmer H, Kelleher CC, Fitz-Simon N, Diem G, Concin H. Secular trends in cardiovascular risk factors: an age-period cohort analysis of 698,954 health examinations in 181,350 Austrian men and women. *J Intern Med* 2007;261:566–576.
42. Chen J, Rodopoulou S, de Hoogh K, Strak M, Andersen ZJ, Atkinson R, *et al.* Long-term exposure to fine particle elemental components and natural and cause-specific mortality-a pooled analysis of eight European cohorts within the ELAPSE project. *Environ Health Perspect* 2021;129:47009.
43. de Hoogh K, Chen J, Gulliver J, Hoffmann B, Hertel O, Ketzel M, *et al.* Spatial $PM_{2.5}$, NO_2, O_3 and BC models for Western Europe - evaluation of spatiotemporal stability. *Environ Int* 2018; 120:81–92.
44. Brandt J, Silver JD, Frohn LM, Geels C, Gross A, Hansen AB, *et al.* An integrated model study for Europe and North America using the Danish Eulerian Hemispheric Model with focus on intercontinental transport of air pollution. *Atmos Environ* 2012;53: 156–176.
45. Thiébaut AC, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med* 2004;23:3803–3820.
46. Samoli E, Rodopoulou S, Hvidtfeldt UA, Wolf K, Stafoggia M, Brunekreef B, *et al.* Modeling multi-level survival data in multi-center epidemiological cohort studies: applications from the ELAPSE project. *Environ Int* 2021;147:106371.
47. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med* 1999;18:681–694.
48. Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987.
49. Strak M, Weinmayr G, Rodopoulou S, Chen J, de Hoogh K, Andersen ZJ, *et al.* Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: pooled analysis. *BMJ* 2021;374:n1904.
50. Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA III, *et al.* Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci USA* 2018;115: 9592–9597.
51. Bowe B, Xie Y, Yan Y, Al-Aly Z. Burden of cause-specific mortality associated with PM2.5 air pollution in the United States. *JAMA Netw Open* 2019;2:e1915834.
52. Jerrett M, Burnett RT, Pope CA III, Ito K, Thurston G, Krewski D, *et al.* Long-term ozone exposure and mortality. *N Engl J Med* 2009;360: 1085–1095.
53. Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, *et al.* Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environ Health Perspect* 2008;116:196–202.
54. Hamer M, Kivimäki M, Gale CR, Batty GD. Lifestyle risk factors, inflammatory mechanisms, and COVID-19 hospitalization: a community-based cohort study of 387,109 adults in UK. *Brain Behav Immun* 2020;87:184–187.
55. Lubrano C, Risi R, Masi D, Gnessi L, Colao A. Is obesity the missing link between COVID-19 severity and air pollution? *Environ Pollut* 2020;266:115327.
56. Eeftens M, Beelen R, Fischer P, Brunekreef B, Meliefste K, Hoek G. Stability of measured and modelled spatial contrasts in NO(2) over time. *Occup Environ Med* 2011;68:765–770.
57. Morris RD, Munasinghe RL. Geographic variability in hospital admission rates for respiratory disease among the elderly in the United States. *Chest* 1994;106:1172–1181.
58. Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, *et al.* Air pollution and mortality in the Medicare population. *N Engl J Med* 2017; 376:2513–2522.