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

Shuo Liu, PhD, ORCID: 0000-0003-0374-7292

Section of Environmental Health, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

shli@sund.ku.dk

Youn-Hee Lim, PhD, ORCID: 0000-0002-1290-5814

Section of Environmental Health, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

younhee.lim@sund.ku.dk

Jie Chen, PhD, ORCID: 0000-0001-9644-8026

Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands

j.chen1@uu.nl

Maciek Strak, PhD

Institute for Risk Assessment Sciences, Utrecht University, the Netherlands

National Institute for Public Health and the Environment, Bilthoven, the Netherlands

maciek.strak@rivm.nl

Kathrin Wolf, PhD, ORCID: 0000-0002-4343-201X

Institute of Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany

kathrin.wolf@helmholtz-muenchen.de

Gudrun Weinmayr, PhD

Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany

gudrun.weinmayr@uni-ulm.de

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Sophia Rodopolou, PhD

Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece

srodopoyl@med.uoa.gr

Kees de Hoogh, PhD

Swiss Tropical and Public Health Institute, Basel, Switzerland

University of Basel, Basel, Switzerland

c.dehoogh@swisstph.ch

Tom Bellander, PhD

Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Centre for Occupational and Environmental Medicine, Region Stockholm, Stockholm, Sweden

tom.bellander@ki.se

Jørgen Brandt, PhD, ORCID: 0000-0002-7580-9547

Department of Environmental Science, Aarhus University, Roskilde, Denmark

iClimate, interdisciplinary Centre for Climate Change, Aarhus University, Roskilde, Denmark

jbr@envs.au.dk

Hans Concin, MD

Agency for Preventive and Social Medicine (aks), Bregenz, Austria

hans.concin@aks.or.at

Emanuel Zitt, MD, ORCID: 0000-0001-6944-6041

Agency for Preventive and Social Medicine (aks), Bregenz, Austria

Department of Internal Medicine 3, LKH Feldkirch, Feldkirch , Austria

Emanuel.zitt@aks.or.at

Daniela Fecht, PhD

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

MRC Centre for Environment and Health, School of Public Health, Imperial College London, London, UK

d.fecht@imperial.ac.uk

Francesco Forastiere, PhD

Department of Epidemiology, Lazio Region Health Service / ASL Roma 1, Rome, Italy

Science Policy & Epidemiology Environmental Research Group King's College London, London UK

fran.forastiere@gmail.com

John Gulliver, PhD

Centre for Environmental Health and Sustainability & School of Geography, Geology and the Environment, University of Leicester, Leicester, UK

MRC Centre for Environment and Health, School of Public Health, Imperial College London, London, UK

jg435@leicester.ac.uk

Ole Hertel, DSc, PhD, ORCID: 0000-0003-0972-7735

Department of Ecoscience, Aarhus University, Roskilde, Denmark

oh@ecos.au.dk

Barbara Hoffmann, MD

Institute for Occupational, Social and Environmental Medicine, Centre for Health and Society, Medical Faculty, Heinrich Heine University Düsseldorf, Germany

b.hoffmann@uni-duesseldorf.de

Ulla A. Hvidtfeldt, PhD

Danish Cancer Society Research Center, Copenhagen, Denmark

ullah@cancer.dk

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

W.M.Monique Verschuren, PhD, ORCID: 0000-0003-2134-4227

National Institute for Public Health and the Environment, Bilthoven, the Netherlands and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands.

monique.verschuren@rivm.nl

Karl-Heinz Jöckel, PhD

Institute for Medical Informatics, Biometry and Epidemiology, Medical Faculty, University of Duisburg-Essen, Essen, Germany

k-h.Joeckel@uk-essen.de

Jeanette T. Jørgensen, PhD

Section of Environmental Health, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

jethe@sund.ku.dk

Rina So, M.A, ORCID: 0000-0002-2113-3887

Section of Environmental Health, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

rina.so@sund.ku.dk

Heresh Amini, PhD, ORCID: 0000-0002-4825-1322

Section of Environmental Health, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

heresh.amini@sund.ku.dk

Thomas Cole-Hunter, PhD, ORCID: 0000-0002-6827-6084

Section of Environmental Health, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

t.cole-hunter@sund.ku.dk

Amar J. Mehta, ScD

Section of Epidemiology, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

Statistics Denmark, Copenhagen, Denmark

amar.mehta@sund.ku.dk

Laust H. Mortensen, PhD

Section of Epidemiology, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

Statistics Denmark, Copenhagen, Denmark

lamo@sund.ku.dk

Matthias Ketzel, PhD, ORCID: 0000-0001-9519-1935

Department of Environmental Science, Aarhus University, Frederiksborgvej 399, DK-4000 Roskilde, Denmark

Global Centre for Clean Air Research (GCARE), University of Surrey, Guildford GU2 7XH, United Kingdom

mke@envs.au.dk

Anton Lager, PhD

Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden

anton.lager@ki.se

Karin Leander, PhD

Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

karin.leander@ki.se

Petter Ljungman, MD

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Department of Cardiology, Danderyd University Hospital, Stockholm, Sweden

petter.ljungman@ki.se

Gianluca Severi, PhD

University Paris-Saclay, UVSQ, Inserm, Gustave Roussy, "Exposome and Heredity" team, CESP UMR1018, 94805, Villejuif, France

Department of Statistics, Computer Science and Applications “G. Parenti” (DISIA), University of Florence, Italy

gianluca.severi@inserm.fr

Marie-Christine Boutron-Ruault, MD

University Paris-Saclay, UVSQ, Inserm, Gustave Roussy, "Exposome and Heredity" team, CESP UMR1018, 94805, Villejuif, France

marie-christine.boutron@gustaveroussy.fr

Patrik K.E. Magnusson, PhD

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

patrik.magnusson@ki.se

Gabriele Nagel, PhD, ORCID: 0000-0001-6185-8535

Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany

Gabriele.Nagel@uni-ulm.de

Göran Pershagen, MD, PhD, ORCID: 0000-0002-9701-1130

Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Centre for Occupational and Environmental Medicine, Region Stockholm, Stockholm, Sweden

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

goran.pershagen@ki.se

Annette Peters, PhD, ORCID: 0000-0001-6645-0985

Institute of Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany

Chair of Epidemiology, Ludwig Maximilians Universität München, , Germany

peters@helmholtz-muenchen.de

Ole Raaschou-Nielsen, PhD, ORCID: 0000-0002-1223-0909

Danish Cancer Society Research Center, Copenhagen, Denmark

Department of Environmental Science, Aarhus University, Roskilde, Denmark

ole@cancer.dk

Debora Rizzuto, PhD, ORCID: 0000-0001-6199-9629

Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet, Stockholm, Sweden

Stockholm Gerontology Research Center, Stockholm, Sweden.

debora.rizzuto@ki.se

Yvonne T. van der Schouw, PhD, ORCID: 0000-0002-4605-435X

Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

y.t.vanderschouw@umcutrecht.nl

Sara Schramm, MD, ORCID: 0000-0001-6493-6009

Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, University Hospital Essen, Germany

sara.schramm@uk-essen.de

Mette Sørensen, PhD, ORCID: 0000-0002-7302-4789

Danish Cancer Society Research Center, Copenhagen, Denmark

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Department of Natural Science and Environment, Roskilde University, Roskilde, Denmark

mettes@cancer.dk

Massimo Stafoggia, PhD, ORCID: 0000-0003-2843-2908

Department of Epidemiology, Lazio Region Health Service / ASL Roma 1, Rome, Italy

Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

m.stafoggia@deplazio.it

Anne Tjønneland, MD, PhD, DMSc, ORCID: 0000-0003-4385-2097

Danish Cancer Society Research Center, Copenhagen, Denmark

Diet, Genes and Environment (DGE), Copenhagen, Denmark

annet@cancer.dk

Klea Katsouyanni, PhD

Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Science Policy & Epidemiology Environmental Research Group King's College, London, London UK

kkatsouy@med.uoa.gr

Wei Huang, ScD

Department of Occupational and Environmental Health, School of Public Health, Peking University, Beijing, China

whuang@bjmu.edu.cn

Evangelia Samoli, PhD

Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece

esamoli@med.uoa.gr

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Bert Brunekreef, PhD

Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands

B.Brunekreef@uu.nl

Gerard Hoek, PhD

Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands

g.hoek@uu.nl

Zorana J. Andersen, PhD, ORCID: 0000-0003-4138-9828

Department of Public Health, University of Copenhagen, Copenhagen, Denmark

zorana.andersen@sund.ku.dk

Correspondence and requests for reprints should be addressed to Zorana J. Andersen, PhD, University of Copenhagen, Øster Farimagsgade 5, Copenhagen 1014, Denmark. E-mail: zorana.andersen@sund.ku.dk.

Author Contributions: Study was conceptualized and designed by Zorana J. Andersen, Gerard Hoek, Bert Brunekreef, and Shuo Liu. Bert Brunekreef is Principal Investigator (PI) of the ELAPSE project. Statistical analysis and manuscript writing were conducted by Shuo Liu. Zorana J. Andersen helped in editing the manuscript. Bert Brunekreef, Gerard Hoek, Jie Chen, and Maciej Strak coordinated the ELAPSE project, helped in preparing pooled data for analyses, and provided support with the access to pooled cohort data. Sophia P. Rodopoulou, Evangelia Samoli, and Klea Katsouyanni contributed with the statistical analyses strategy and scripts for the statistical analyses. Kees de Hoogh, Jie Chen, and Gerard Hoek worked for the exposure assessment. All authors contributed to the interpretation of the results. All authors have read and revised the manuscript for the important intellectual content, and approved the final draft of the manuscript.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Supported by the Health Effects Institute (#4954-RFA14-3/16-5-3) and a scholarship from the China Scholarship Council (No. 201806010406). SALT and TwinGene are sub-studies of The Swedish Twin Registry (STR), which is managed by Karolinska Institutet and receives additional funding through the Swedish Research Council (No. 2017-00641). The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. The China Scholarship Council, the Swedish Research Council, the German Federal Ministry of Education and Research, and the State of Bavaria were not involved in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Running head the ELAPSE Project

Descriptor number 6.1

Word count for the manuscript 3500

This article has an online data supplement, which is accessible from this issue's table of content online 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

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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 (ALRI) 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 ($PM_{2.5}$) or ozone (O_3) 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.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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 'Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE), we pooled data from eight cohorts among six European countries. Annual mean residential concentrations in 2010 for fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC), and ozone (O_3) 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 to normal weight, unemployed, or non-smoking 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.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Word count for abstract: 253

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

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Introduction

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 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 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 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), with studies from US (8, 16-21), Canada (22), Japan (23, 24), China (25), or UK (26). All but one (25) of these studies reported positive associations

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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

The 'Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE) 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 (COPD) (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: (a) Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) cohort in Sweden, which combined four sub-cohorts: Stockholm Diabetes Prevention Program (SDPP) (31), Stockholm Cohort of 60-year-olds (SIXTY) (32), Stockholm Screening Across the Lifespan Twin study (SALT) (33), and Swedish National Study on Aging and Care in Kungsholmen (SNACK) (34); (b) Diet, Cancer

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

and Health cohort (DCH) in Denmark (35); (d) Danish Nurse Cohort (DNC) in Denmark (36), including two cohort recruitment rounds in 1993 and 1999; (c) Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N) in France (37); (e) European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort in the Netherlands, which included two sub-cohorts: Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands (Morgen) and Prospect (38); (f) Heinz Nixdorf Recall study (HNR) in Germany (39); (g) Cooperative Health Research in the Region of Augsburg (KORA) in Germany (40), combining two sub-cohorts from baseline rounds in 1994–1995 (S3) and 1999–2001 (S4); and (h) Vorarlberg Health Monitoring and Prevention Programme (VHM&PP) in Austria (41). The cohorts were recruited in the 1990's or early 2000's, 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 modelling 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 participants' baseline residential addresses 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 × 100 m grids) and performed well in five-fold hold-out validation, explaining 72%, 59%, 54%, and 69% of 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 warm season from April to September.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

We additionally back-extrapolated pollutants' concentrations for each year from baseline to the end of follow-up (29, 30), incorporating dynamic residential address history during follow-up. Back-extrapolation method was applied by utilizing the estimated monthly average concentrations, at a 26 km × 26 km spatial resolution (downscaled from a original 50 km × 50 km resolution using bi-liear interpolation), from the Danish Eulerian Hemispheric Model (DEHM) back to 1990 (44). Predicted modelling exposure data from DEHM provided 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 analysed 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 event of interest, death

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

from other causes, emigration, loss to follow-up, or the end of follow-up (that ranges from 2011 to 2015 depending on the sub-cohorts), whichever came first. The start of follow-up was the year of enrolment 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), sub-cohort (strata), and year of enrollement; 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 ≥ 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 socio-economic status (SES): mean income in 2001. We determined Model 2 and 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 pre-defined 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 the EU and US limit values and the 2005 WHO guidelines. We did not conduct 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 non-informative effect estimate. We modelled 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 likelihood ratio test. We assessed potential effect modification on the associations by age (<70,

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

≥70 years old), overweight status (BMI ≥ 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 (assess by AIC-Akaike Information Criteria) in Model 3 with alternative models using different adjustment approaches for sub-cohorts: without adjustment, indicator variables, a frailty term, and a random intercept under a mixed Cox model. Secondly, 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 (MICE) 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 ratios (HR) and 95% confidence intervals (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 then excluded. Study locations and population proportion for eight included cohorts in our study were shown in Figure E1. Of 325,367 remained participants in the final analyses, 712 died from pneumonia and influenza combined, 695 from ALRI, 682

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

from pneumonia, and 30 from influenza, during a mean follow-up of 19.5 years (Table 1 and 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 sub-cohorts (Table 1), supporting the use of strata for sub-cohorts 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/sub-cohorts 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 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 sub-cohorts 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 EU limit value of 40 $\mu g/m^3$, and to $PM_{2.5}$ levels (99.99%) below the EU limit value of 25 $\mu g/m^3$. Further, the concentration of $PM_{2.5}$ in CEANS cohort was below the 2005 WHO guidelines and US limit values of 10 and 12 $\mu g/m^3$, respectively (Figure 1). We also observed varying exposure levels across cohorts and sub-cohorts for the baseline year exposure in Figure E2. Comparing 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 sub-cohorts (0.67–0.93) except for in CEANS-SNACK (0.43; Table E3). $PM_{2.5}$ was moderately correlated with exposure to BC and NO_2 in most sub-cohorts, and O_3 was negatively correlated with other pollutants in all sub-cohorts, having high correlations with NO_2 and BC in some sub-cohorts (Table E3).

NO_2 and BC were associated with 10-12% increases in respiratory infectious diseases mortality, but 95% confidence intervals (CI) included unity (Table 2). Specifically, in the fully

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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 (1.10; 0.98–1.24), and pneumonia mortality (1.11; 0.99–1.26). The corresponding estimates for BC for each 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 either $PM_{2.5}$ 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 confidence intervals 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 non-linear with a wide confidence interval (Table 3 and Figure 2), where we found a positive association at lower levels (below 15 μg/m^3) and no association at higher cutoff levels (below 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 sub-cohorts by $PM_{2.5}$ levels below or above 15 μg/m^3, and did not observe significant differences within each sub-cohort (Table E5). However, the majority of participants (74% to 100%) in the three Nordic cohorts (CEANS, DCH, DNC) were exposed to $PM_{2.5}$ levels below 15 μg/m^3, in contrast to other cohorts (0.02% to 37%) (Table E5 and 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 non-linear relationship for $PM_{2.5}$ could be due to an unequal distribution of sub-cohorts at the range of $PM_{2.5}$ concentrations. Associations with O_3 were negative and linear (Figure 2).

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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 to normal weight participants (p-value for interaction=0.02 for NO_2 and 0.10 for BC), in current smokers as compared to former and never smokers (p-value=0.17 for NO_2 and 0.07 for BC), and in employed participants as compared to non-employed (p-value=0.29 for NO_2 and 0.08 for BC) (Table 4). Due to the non-linear relationship for $PM_{2.5}$ we did not consider the significant effect modificion 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 sub-cohorts (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 appling 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 associated with 10-12% increases in ALRI mortality, which was mainly driven by pneumonia mortality. Confidence intervals 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 infection 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 confidence intervals.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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, combining with previous findings, suggest that air pollution from fossil fuel combustion sources (such as motorised 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 non-linear exposure-response function, with a positive slope at $PM_{2.5}$ levels below 15 $\mu g/m^3$ and a 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 et al. found a sub-linear curve for the association of $PM_{2.5}$ with pneumonia mortality in the Canadian Census Health and Environment Cohort study (22). Burnett et al. 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 et al. estimated the burden of death from pneumonia due to $PM_{2.5}$ using non-linear exposure-response function models in a cohort study of US 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 below 15 $\mu g/m^3$) showed a positive linear association (Figure E3).

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Evidence on long-term exposure to O_3 and pneumonia mortality shows mixed results. Three US 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; 0.73–0.97, per 10 μg/m^3 increase) (26). Notably, the UK study used annual mean O_3 levels, while all three US 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 sub-cohorts (Figure 1). Another explanation may be the generally low levels of O_3 exposure (ranging from 36 to 116 μg/m^3) in our study, as a previous study suggested a possible threshold of 56 ppb (around 110 μg/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 sub-cohorts (Table E3), we thus need to be cautious in interpreting the two-pollutant results for O_3. Notably, we examined the sssociations 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 a 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 potential susceptibility of overweight 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

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

comparisons with studies on chronic respiratory disease mortality and COVID-19 (viral respiratory infectious disease). Results on smoking are in agreement with Beelen et al. 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 et al. in UK Biobank study found that smokers and obese people had elevated risks of COVID-19 hospital admission compared to never smokers and healthy weight participants as references, respectively (54). Yang et al. found that participants with high BMI ($\geq$ 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 anti-oxidative stress capacity and impairment of immune defenses (10, 13). Our results on higher susceptibility of employed as compared to 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 confidence intervals. 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 year 2010 at the baseline of the cohorts recruited in 1990s and early 2000s, due to lack of monitoring stations for $PM_{2.5}$ in Europe prior to 2010. However, a study reported stable spatial distribution of NO_2 over 10 years in the Netherlands

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

(56). Similarly, in our study the predictions from 2010 model were highly correlated ($R^2 > 76\%$) with 2000 and 2005 models for NO_2 and O_3, and 2013 model for $PM_{2.5}$ at the European scale (43), indicating limited impacts of temporal misalignment by exposures based on the year 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 reasonable accurate estimates for included study regions and pollutants, while acknowledging some degrees of exposure misclassification. The potential for exposure misclassification also exists when using modelled 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 in our LUR models. Additionally, we mostly evaluated associations with exposure contrasts within sub-cohorts due to the use of strata for sub-cohorts 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 US counties over the 1984-1989 period. In a recent nationwide study on air pollution and mortality, Di et al. found that effect estimates for $PM_{2.5}$ and O_3 were insensitive to adjustment for annual mean temperature and relative humidity (58). Removal of the two nationwide cohorts (E3N and DCH) furthermore made no difference. We also lacked the information on influenza vaccinations, which could be a confounder for association between air pollution and pneumonia and influenza related mortality. We do not have information on the differences in ICD coding

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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.

In conclusion, 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.

Acknowledgements

The research described in this article was conducted under contract to the Health Effects Institute (HEI), an organization jointly funded by the United States Environmental Protection Agency (EPA) (Assistance Award No. R-82811201) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of HEI, or its sponsors, nor do they necessarily reflect the views and policies of the EPA or motor vehicle and engine manufacturers. HEI has reviewed and approved the study design. HEI was not involved in data collection and analysis, decision to publish, or preparation of the manuscript. The authors would also like to thank all participants in the pooled cohort studies and the respective study teams of the ELAPSE project for their hard work and effort. We thank Marjan Tewis for the data management tasks in creating the pooled cohort database.

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 (London, England)* 2018; 392: 1736-1788.

2. Marshall DC, Goodson RJ, Xu Y, Komorowski M, Shalhoub J, Maruthappu M, Salciccioli JD. Trends in mortality from pneumonia in the Europe union: a temporal analysis of the European detailed mortality database between 2001 and 2014. *Respiratory research* 2018; 19: 81.

3. Torres A, Cillóniz C, Blasi F, Chalmers JD, Gaillat J, Dartois N, Schmitt HJ, Welte T. 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, Cousens S, Mathers C, Black RE. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet (London, England)* 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. *Environmental health : a global access science source* 2021; 20: 6.

6. Nhung NTT, Amini H, Schindler C, Kutlar Joss M, Dien TM, Probst-Hensch N, Perez L, Kunzli N. 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. *American journal of respiratory and critical care medicine* 2010; 181: 47-53.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

8. Eum KD, Kazemiparkouhi F, Wang B, Manjourides J, Pun V, Pavlu V, Suh H. Long-term NO2 exposures and cause-specific mortality in American older adults. *Environment international* 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. *European respiratory review : an official journal of the European Respiratory Society* 2021; 30.

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, Perez-Padilla R, Rice MB, Riojas-Rodriguez H, Sood A, Thurston GD, To T, Vanker A, Wuebbles DJ. 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, Perez-Padilla R, Rice MB, Riojas-Rodriguez H, Sood A, Thurston GD, To T, Vanker A, Wuebbles DJ. 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, Vedal S, Kaufman JD. 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 (Cambridge, Mass)* 2015; 26: 310-320.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

14. Chen J, Hoek G. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. *Environment international* 2020: 105974.

15. Huangfu P, Atkinson R. Long-term exposure to NO2 and O3 and all-cause and respiratory mortality: A systematic review and meta-analysis. *Environment international* 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, Garcia C, Bell ML, Thurston GD. Long-Term Exposure to Ozone and Cause-Specific Mortality Risk in the United States. *American journal of respiratory and critical care medicine* 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. *American journal of epidemiology* 2017; 186: 961-969.

19. Turner MC, Jerrett M, Pope CA, 3rd, Krewski D, Gapstur SM, Diver WR, Beckerman BS, Marshall JD, Su J, Crouse DL, Burnett RT. Long-Term Ozone Exposure and Mortality in a Large Prospective Study. *American journal of respiratory and critical care medicine* 2016; 193: 1134-1142.

20. Pope CA, 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. 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, 3rd, Lefler JS, Ezzati M, Higbee JD, Marshall JD, Kim SY, Bechle M, Gilliat KS, Vernon SE, Robinson AL, Burnett RT. Mortality Risk and Fine Particulate Air Pollution in a Large, Representative Cohort of U.S. Adults. *Environmental health perspectives* 2019; 127: 77007.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

22. Pinault LL, Weichenthal S, Crouse DL, Brauer M, Erickson A, Donkelaar AV, Martin RV, Hystad P, Chen H, Fines P, Brook JR, Tjepkema M, Burnett RT. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. *Environmental research* 2017; 159: 406-415.

23. Yorifuji T, Kashima S, Tsuda T, Ishikawa-Takata K, Ohta T, Tsuruta K, Doi H. Long-term exposure to traffic-related air pollution and the risk of death from hemorrhagic stroke and lung cancer in Shizuoka, Japan. *The Science of the total environment* 2013; 443: 397-402.

24. Katanoda K, Sobue T, Satoh H, Tajima K, Suzuki T, Nakatsuka H, Takezaki T, Nakayama T, Nitta H, Tanabe K, Tominaga S. An Association Between Long-Term Exposure to Ambient Air Pollution and Mortality From Lung Cancer and Respiratory Diseases in Japan. *Journal of Epidemiology* 2011; 21: 132-143.

25. Yang Y, Tang R, Qiu H, Lai PC, Wong P, Thach TQ, Allen R, Brauer M, Tian L, Barratt B. Long term exposure to air pollution and mortality in an elderly cohort in Hong Kong. *Environment international* 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. *American journal of respiratory and critical care medicine* 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, Magnusson PKE, Rizzuto D, Hvidtfeldt UA, Raaschou-Nielsen O, Wolf K, Hoffmann B, Brunekreef B, Strak M, Chen J, Mehta A, Atkinson RW, Bauwelinck M, Varraso R, Boutron-Ruault MC, Brandt J, Cesaroni G, Forastiere F, Fecht D, Gulliver J, Hertel O, de Hoogh K, Janssen NAH, Katsouyanni K, Ketzel M, Klompmaker JO, Nagel G, Oftedal B, Peters A, Tjønneland A, Rodopoulou SP, Samoli E,

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Kristoffersen DT, Sigsgaard T, Stafoggia M, Vienneau D, Weinmayr G, Hoek G, Andersen ZJ. Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project. *The European respiratory journal* 2021;57(6):2003099.

29. Liu S, Jørgensen JT, Ljungman P, Pershagen G, Bellander T, Leander K, Magnusson PKE, Rizzuto D, Hvidtfeldt UA, Raaschou-Nielsen O, Wolf K, Hoffmann B, Brunekreef B, Strak M, Chen J, Mehta A, Atkinson RW, Bauwelinck M, Varraso R, Boutron-Ruault MC, Brandt J, Cesaroni G, Forastiere F, Fecht D, Gulliver J, Hertel O, de Hoogh K, Janssen NAH, Katsouyanni K, Ketzel M, Klompmaker JO, Nagel G, Oftedal B, Peters A, Tjønneland A, Rodopoulou SP, Samoli E, Bekkevold T, Sigsgaard T, Stafoggia M, Vienneau D, Weinmayr G, Hoek G, Andersen ZJ. Long-term exposure to low-level air pollution and incidence of chronic obstructive pulmonary disease: The ELAPSE project. *Environment international* 2021; 146: 106267.

30. Hvidtfeldt UA, Severi G, Andersen ZJ, Atkinson R, Bauwelinck M, Bellander T, Boutron-Ruault MC, Brandt J, Brunekreef B, Cesaroni G, Chen J, Concin H, Forastiere F, van Gils CH, Gulliver J, Hertel O, Hoek G, Hoffmann B, de Hoogh K, Janssen N, Jöckel KH, Jørgensen JT, Katsouyanni K, Ketzel M, Klompmaker JO, Krog NH, Lang A, Leander K, Liu S, Ljungman PLS, Magnusson PKE, Mehta AJ, Nagel G, Oftedal B, Pershagen G, Peter RS, Peters A, Renzi M, Rizzuto D, Rodopoulou S, Samoli E, Schwarze PE, Sigsgaard T, Simonsen MK, Stafoggia M, Strak M, Vienneau D, Weinmayr G, Wolf K, Raaschou-Nielsen O, Fecht D. Long-term low-level ambient air pollution exposure and risk of lung cancer - A pooled analysis of 7 European cohorts. *Environment international* 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. *Diabetic medicine : a journal of the British Diabetic Association* 2008; 25: 834-842.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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 & metabolism* 2007; 33: 30-36.

33. Magnusson PK, Almqvist C, Rahman I, Ganna A, Viktorin A, Walum H, Halldner L, Lundström S, Ullén F, Långström N, Larsson H, Nyman A, Gumpert CH, Råstam M, Anckarsäter H, Cnattingius S, Johannesson M, Ingelsson E, Klareskog L, de Faire U, Pedersen NL, Lichtenstein P. The Swedish Twin Registry: establishment of a biobank and other recent developments. *Twin research and human genetics : the official journal of the International Society for Twin Studies* 2013; 16: 317-329.

34. Lagergren M, Fratiglioni L, Hallberg IR, Berglund J, Elmståhl S, Hagberg B, Holst G, Rennemark M, Sjölund BM, Thorslund M, Wiberg I, Winblad B, Wimo A. A longitudinal study integrating population, care and social services data. The Swedish National study on Aging and Care (SNAC). *Aging clinical and experimental research* 2004; 16: 158-168.

35. Tjønneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, Overvad K. 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. *Scandinavian journal of public health* 2007; 35: 432-441.

36. Hundrup YA, Simonsen MK, Jørgensen T, Obel EB. Cohort profile: the Danish nurse cohort. *International journal of epidemiology* 2012; 41: 1241-1247.

37. Clavel-Chapelon F. Cohort Profile: The French E3N Cohort Study. *International journal of epidemiology* 2015; 44: 801-809.

38. Beulens JW, Monninkhof EM, Verschuren WM, van der Schouw YT, Smit J, Ocke MC, Jansen EH, van Dieren S, Grobbee DE, Peeters PH, Bueno-de-Mesquita HB. Cohort profile: the EPIC-NL study. *International journal of epidemiology* 2010; 39: 1170-1178.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

39. Schmermund A, Möhlenkamp S, Stang A, Grönemeyer D, Seibel R, Hirche H, Mann K, Siffert W, Lauterbach K, Siegrist J, Jöckel KH, Erbel R. 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. *American heart journal* 2002; 144: 212-218.

40. Holle R, Happich M, Löwel H, Wichmann HE. KORA--a research platform for population based health research. *Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany))* 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, Bauwelinck M, Bellander T, Brandt J, Cesaroni G, Concin H, Fecht D, Forastiere F, Gulliver J, Hertel O, Hoffmann B, Hvidtfeldt UA, Janssen NAH, Jöckel KH, Jørgensen J, Katsouyanni K, Ketzel M, Klompmaker JO, Lager A, Leander K, Liu S, Ljungman P, MacDonald CJ, Magnusson PKE, Mehta A, Nagel G, Oftedal B, Pershagen G, Peters A, Raaschou-Nielsen O, Renzi M, Rizzuto D, Samoli E, van der Schouw YT, Schramm S, Schwarze P, Sigsgaard T, Sørensen M, Stafoggia M, Tjønneland A, Vienneau D, Weinmayr G, Wolf K, Brunekreef B, Hoek G. 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. *Environmental health perspectives* 2021; 129: 47009.

43. de Hoogh K, Chen J, Gulliver J, Hoffmann B, Hertel O, Ketzel M, Bauwelinck M, van Donkelaar A, Hvidtfeldt UA, Katsouyanni K, Klompmaker J, Martin RV, Samoli E, Schwartz PE, Stafoggia M, Bellander T, Strak M, Wolf K, Vienneau D, Brunekreef B, Hoek G. Spatial PM(2.5), NO(2), O(3)

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

and BC models for Western Europe - Evaluation of spatiotemporal stability. *Environment international* 2018; 120: 81-92.

44. Brandt J, Silver JD, Frohn LM, Geels C, Gross A, Hansen AB, Hansen KM, Hedegaard GB, Skjøth CA, Villadsen H, Zare A, Christensen JH. An integrated model study for Europe and North America using the Danish Eulerian Hemispheric Model with focus on intercontinental transport of air pollution. *Atmospheric Environment* 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. *Statistics in medicine* 2004; 23: 3803-3820.

46. Samoli E, Rodopoulou S, Hvidtfeldt UA, Wolf K, Stafoggia M, Brunekreef B, Strak M, Chen J, Andersen ZJ, Atkinson R, Bauwelinck M, Bellander T, Brandt J, Cesaroni G, Forastiere F, Fecht D, Gulliver J, Hertel O, Hoffmann B, de Hoogh K, Janssen NAH, Ketzel M, Klompmaker JO, Liu S, Ljungman P, Nagel G, Oftedal B, Pershagen G, Peters A, Raaschou-Nielsen O, Renzi M, Kristoffersen DT, Severi G, Sigsgaard T, Vienneau D, Weinmayr G, Hoek G, Katsouyanni K. Modeling multi-level survival data in multi-center epidemiological cohort studies: Applications from the ELAPSE project. *Environment international* 2021; 147: 106371.

47. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Statistics in medicine* 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, Atkinson R, Bauwelinck M, Bekkevold T, Bellander T, Boutron-Ruault MC, Brandt J, Cesaroni G, Concin H, Fecht D, Forastiere F, Gulliver J, Hertel O, Hoffmann B, Hvidtfeldt UA, Janssen NAH, Jöckel KH, Jørgensen JT, Ketzel M, Klompmaker JO, Lager A, Leander K, Liu S, Ljungman P, Magnusson PKE, Mehta AJ, Nagel G, Oftedal B, Pershagen G, Peters A, Raaschou-Nielsen O, Renzi M, Rizzuto D, van der Schouw YT, Schramm S, Severi G, Sigsgaard T, Sørensen M, Stafoggia M,

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Tjønneland A, Verschuren WMM, Vienneau D, Wolf K, Katsouyanni K, Brunekreef B, Hoek G, Samoli E. Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: pooled analysis. *BMJ (Clinical research ed)* 2021; 374: n1904.

50. Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA, 3rd, Apte JS, Brauer M, Cohen A, Weichenthal S, Coggins J, Di Q, Brunekreef B, Frostad J, Lim SS, Kan H, Walker KD, Thurston GD, Hayes RB, Lim CC, Turner MC, Jerrett M, Krewski D, Gapstur SM, Diver WR, Ostro B, Goldberg D, Crouse DL, Martin RV, Peters P, Pinault L, Tjepkema M, van Donkelaar A, Villeneuve PJ, Miller AB, Yin P, Zhou M, Wang L, Janssen NAH, Marra M, Atkinson RW, Tsang H, Quoc Thach T, Cannon JB, Allen RT, Hart JE, Laden F, Cesaroni G, Forastiere F, Weinmayr G, Jaensch A, Nagel G, Concin H, Spadaro JV. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proceedings of the National Academy of Sciences of the United States of America* 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, 3rd, Ito K, Thurston G, Krewski D, Shi Y, Calle E, Thun M. Long-term ozone exposure and mortality. *The New England journal of medicine* 2009; 360: 1085-1095.

53. Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, Jerrett M, Hughes E, Armstrong B, Brunekreef B. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environmental health perspectives* 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, behavior, and immunity* 2020; 87: 184-187.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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 NO₂ over time. *Occupational and environmental medicine* 2011; 68: 765.

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, Dominici F, Schwartz JD. Air Pollution and Mortality in the Medicare Population. *The New England journal of medicine* 2017; 376: 2513-2522.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Figure 1. Distribution of annual average concentrations of air pollution for the year 2010 by cohorts and sub-cohorts (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 dotted dash lines represent different limited values in the EU, U.S., and 2005 WHO guidelines. For $PM_{2.5}$, they indicate the annual average limited/guideline values of WHO (2005 version; 10 μg/m^3), U.S. (12 μg/m^3), and EU (25 μg/m^3). For NO_2, they indicate the annual average limited/guideline values of WHO (2005 version) and EU (40 μg/m^3), and WHO HRAPIE (health risks of air pollution in Europe) (20 μg/m^3).

O_3 was in the warm season from April 1 through September 30.

Definition of abbreviation: $PM_{2.5}$, particulate matters with aerodynamic diameters of less than 2.5 μm; NO_2, nitrogen dioxide; BC, black carbon; O_3, ozone.

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 set equal to one for the minimum pollutant exposures.

Solid black lines indicate hazard ratio values and black dashed lines indicate their 95% confidence intervals. Green dotted lines indicate the 5th and 95th percentiles of air pollutants' concentrations. Red dotted dash lines represent different limited/guideline values in EU, U.S., and WHO (2005 version). X-axes are truncated at 60 μg/m^3 and 3 10^{-5}m^{-1} for NO_2 and BC.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Table 1. Baseline demographic characteristics of participants by the pooled cohort, cohorts and sub-cohorts.

Cohort/sub-cohort	N	Deaths, N§	Follow-up time, years	Age, years	Female (%)	Current smokers (%)	Smoking duration, years*	Smoking intensity, n/day*	Over weight (%)ϕ	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

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Results of participants' characteristics at baseline are presented as Mean ± SD, Number, or Percentage.

*: Smoking duration and smoking intensity are only for current smokers. We set these variable to zero for never and former smokers.

ϕ: BMI ≥ 25 kg/m^2 indicates overweight according to the World Health Organization (WHO) 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).

§: The number of deaths of pneumonia and influenza combined.

Definition of abbreviation: BMI, body mass index; SD, standard deviation.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Table 2. Associations between long-term air pollution exposure and specific respiratory infection mortality (N=325,367).

	Model 1*	Model 2*	Model 3*	Model 3ϕ
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)

Model 1 adjusted for age (time axis), sex (strata), sub-cohort (strata), and calendar year of baseline; Model 2 additionally adjusted for smoking (status, duration, intensity, and intensity^2), BMI (category), marital status, and employment status;

Model 3 further adjusted for area-level mean year income.

*: Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] for the following increases: 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.

ϕ: Results are presented for interquartile range (IQR) increases: 10.2 μg/m^3 for NO_2, 4.5 μg/m^3 for $PM_{2.5}$, 0.5 10^{-5}m^{-1} for BC and 14.1 μg/m^3 for O_3.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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 μg/m^3	310,643	682	1.11 (0.97, 1.26)
	< 30 μg/m^3	247,039	517	1.07 (0.88, 1.30)
	< 20 μg/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 μg/m^3	325,339	711	0.94 (0.78, 1.13)
	< 20 μg/m^3	316,540	704	0.96 (0.80, 1.15)
	< 15 μg/m^3	151,250	393	1.33 (0.88, 2.00)
	< 12 μg/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 μg/m^3	325,367	712	0.92 (0.78, 1.09)
	< 100 μg/m^3	320,522	709	0.93 (0.79, 1.11)
	< 80 μg/m^3	98,840	268	0.91 (0.68, 1.21)

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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	$PM_{2.5}$	BC	O_3	*P* values for interaction
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Age, years							NO_2: 0.90; $PM_{2.5}$: 0.04*; BC: 0.13; O_3:0.03*
< 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)	
≥ 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)	
Overweightϕ							NO_2: 0.02*; $PM_{2.5}$: 0.15; BC: 0.10; O_3:0.09
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)	
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)	
Smoking status							
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)	NO_2: 0.17; $PM_{2.5}$: 0.01*; BC: 0.07; O_3: 0.20
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)	
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)	
Employment status							NO_2: 0.29; $PM_{2.5}$: <0.001*; BC: 0.08; O_3: 0.71
Employedϕ	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)	
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)	

Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] 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.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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.

ϕ: BMI $\geq$ 25 kg/m^2 indicates overweight according to WHO categories. Employed status includes employed and self-employed.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

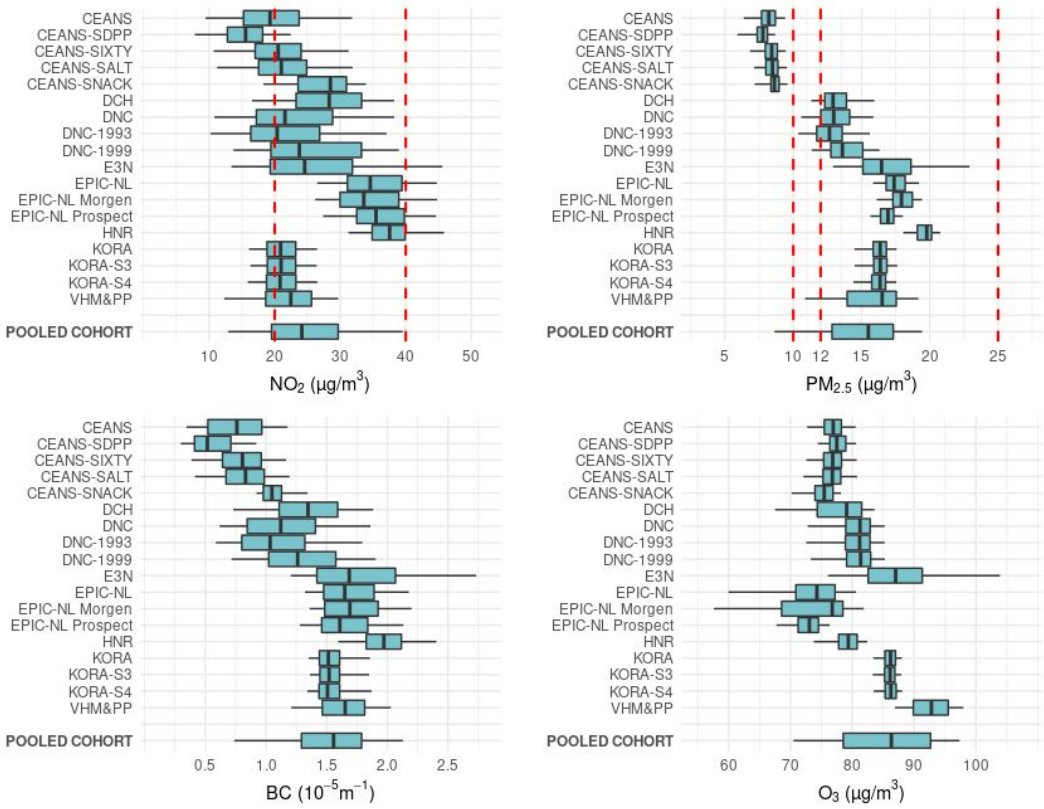


Figure 1. Distribution of annual average concentrations of air pollution for the year 2010 by cohorts and sub-cohorts (N=325,367).

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 dotted dash lines represent different limited values in the EU, U.S., and 2005 WHO guidelines. For $PM_{2.5}$, they indicate the annual average limited/guideline values of WHO (2005 version; 10 µg/m^3), U.S. (12 µg/m^3), and EU (25 µg/m^3). For NO_2, they indicate the annual average limited/guideline values of WHO (2005 version) and EU (40 µg/m^3), and WHO HRAPIE (health risks of air pollution in Europe) (20 µg/m^3).

O_3 was in the warm season from April 1 through September 30.

Definition of abbreviation: $PM_{2.5}$, particulate matters with aerodynamic diameters of less than 2.5 µm; NO_2, nitrogen dioxide; BC, black carbon; O_3, ozone.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

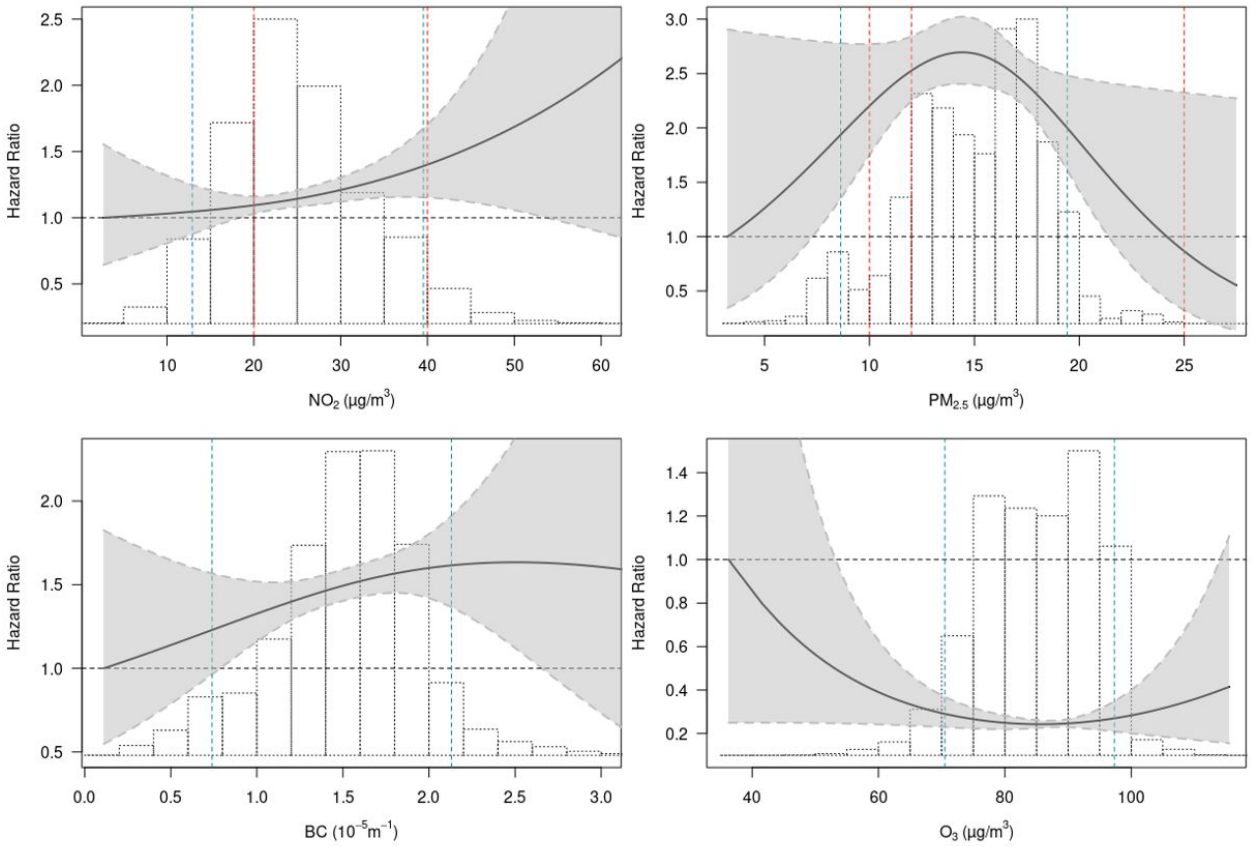


Figure 2. Concentration-response curves for the associations between long-term exposure to air pollution and pneumonia and influenza mortality.

Natural cubic splines with two degrees of freedom were fit for air pollutants based on Model 3, where the hazard ratios equal to one were for minimum pollutant exposures.

Solid black lines indicate hazard ratio values and black dashed lines indicate their 95% confidence intervals. Green dotted lines indicate the 5th and 95th percentiles of air pollutants' concentrations. Red dotted dash lines represent different limited values in EU, U.S., and 2005 WHO guidelines. The histograms show the distributions of exposures in 2010. X-axes are truncated at 60 μg/m^3 and 3 10^{-5}m^{-1} for NO_2 and BC.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

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

Running head: the ELAPSE project

Shuo Liu, Youn-Hee Lim, Jie Chen, Maciek Strak, Kathrin Wolf, Gudrun Weinmayr, Sophia Rodopolou, Kees de Hoogh, Tom Bellander, Jørgen Brandt, Hans Concin, Emanuel Zitt, Daniela Fecht, Francesco Forastiere, John Gulliver, Ole Hertel, Barbara Hoffmann, Ulla A. Hvidtfeldt, W.M.Monique Verschuren, Karl-Heinz Jöckel, Jeanette T. Jørgensen, Rina So, Heresh Amini, Thomas Cole-Hunter, Amar J. Mehta, Laust H. Mortensen, Matthias Ketzel, Anton Lager, Karin Leander, Petter Ljungman, Gianluca Severi, Marie-Christine Boutron-Ruault, Patrik K.E. Magnusson, Gabriele Nagel, Göran Pershagen, Annette Peters, Ole Raaschou-Nielsen, Debora Rizzuto, Yvonne T. van der Schouw, Sara Schramm, Mette Sørensen, Massimo Stafoggia, Anne Tjønneland, Klea Katsouyanni, Wei Huang, Evangelia Samoli, Bert Brunekreef, Gerard Hoek, Zorana J. Andersen

Correspondence and requests for reprints should be addressed to Zorana J. Andersen, PhD, University of Copenhagen, Øster Farimagsgade 5, Copenhagen 1014, Denmark. E-mail: zorana.andersen@sund.ku.dk.

Online Data Supplement.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Table E1. An overview of studies on air pollution and pneumonia related mortality in adults.

Author, year	Cohort/Study	Population Size (N)	Disease	ICD codes	Number of deaths	Pollutant	Effect estimates
Pope et al., 2019	National Health Interview Surveys (1986–2014, NHIS), USA	1,599,329 adults (ages 18–84)	Pneumonia and influenza mortality	ICD-10: J09–J18	6,018	$PM_{2.5}$ (10.7 μg/m^3)	HR (95% CI): 1.47 (1.27, 1.71) per 10 μg/m^3
Kazemiparkouhi et al., 2020	American Medicare beneficiary study, USA	22.2 million Medicare beneficiaries (ages 65–120)	Pneumonia mortality	ICD-10: J12–J18	174,932	O_3 warm season (median: 55 ppb)	RR (95% CI): 1.024 (1.018, 1.030) per 10 ppb
Eum et al., 2019	American Medicare beneficiary study, USA	14.1 million Medicare beneficiaries (ages 65–120)	Pneumonia mortality	ICD-10: J12–J18	112,863	NO_2 (median: 14.2 ppb)	OR (95% CI): 1.275 (1.263, 1.287) per 10 ppb
Pun et al., 2017	American Medicare beneficiary study, USA	18,937,461 Medicare beneficiaries (ages 65–120)	Pneumonia mortality	ICD-10: J12–J18	126,635	$PM_{2.5}$ (median: 12.5 μg/m^3)	RR (95% CI): 1.445 (1.394, 1.498) per 10 μg/m^3
Lim et al., 2019	NIH-AARP Diet and Health Study, USA	548,780 participant aged 50–71 years	Pneumonia and influenza mortality	ICD-9: 480–48; ICD-10: J09–J18	1,889	Mean: $PM_{2.5}$ (11.0 μg/m^3); NO_2 (11.1 ppb); O_3 annual (39.0 ppb); O_3 warm season (46.2 ppb);	RR (95% CI): 1.53 (1.26, 1.86) per 10 μg/m^3 1.22 (1.11, 1.35) per 10 ppb 1.00 (0.90, 1.11) per 10 ppb 1.05 (0.99, 1.10) per 10 ppb
Turner et al., 2016	Cancer Prevention Study II (CPS-II), USA	669,046 participants aged ≥30 years	Pneumonia and influenza mortality	ICD-9: 480–487; ICD-10: J10–J18	6,599	Mean: $PM_{2.5}$ (12.6 μg/m^3); NO_2 (11.6 ppb); O_3 annual (38.2 ppb); O_3 warm season (47.1 ppb);	HR (95% CI) (single-pollutant): 1.31 (1.20, 1.44) per 10 μg/m^3 1.11 (1.05, 1.18) per 10 ppb 1.15 (1.08, 1.23) per 10 ppb 1.14 (1.10, 1.19) per 10 ppb

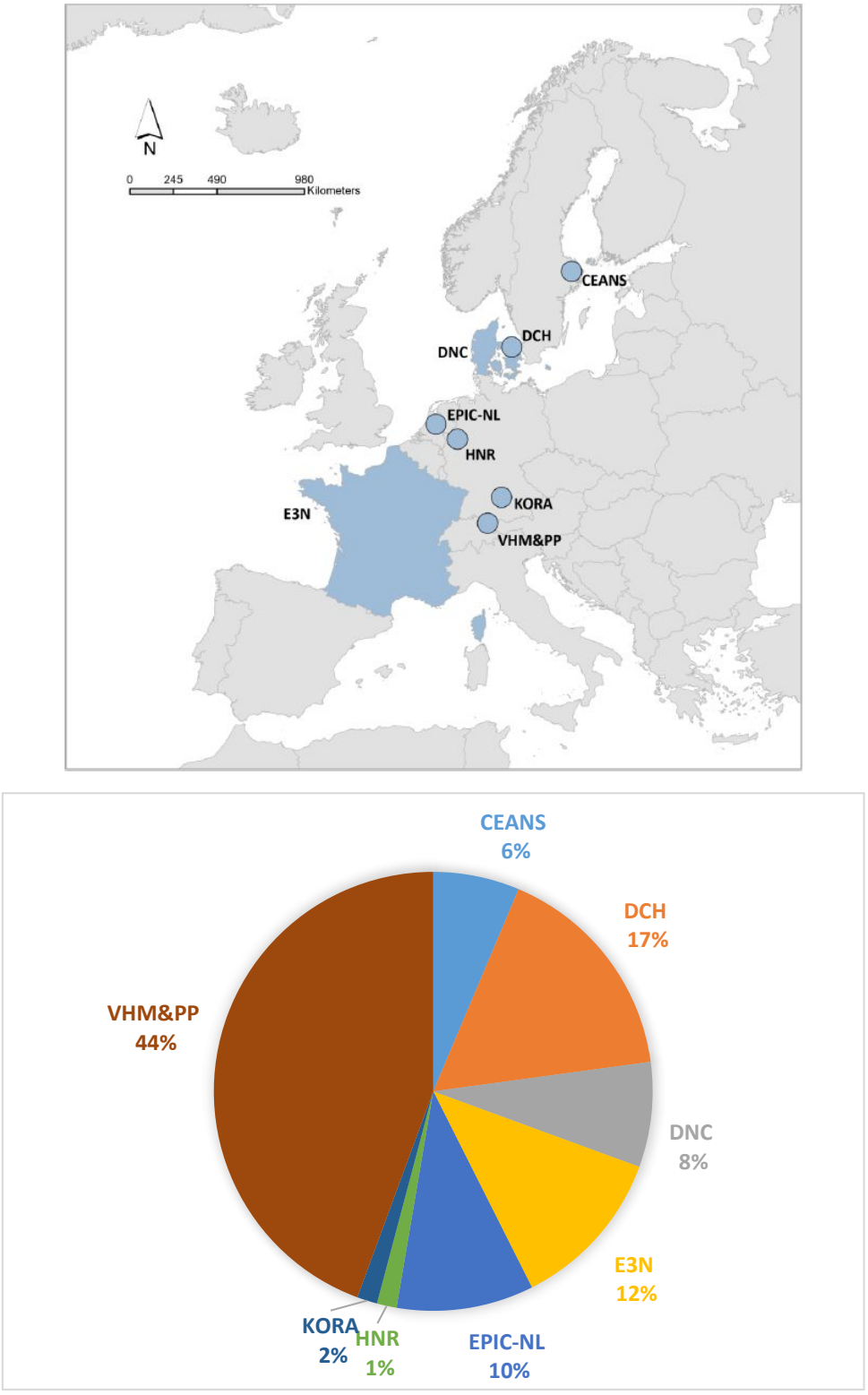
AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Pope et al., 2004	Cancer Prevention Study II (CPS-II), USA	319,000 participants aged ≥30 years	Pneumonia and influenza mortality	ICD-9: 480–487	NA	Mean: $PM_{2.5}$ (17.1 μg/m^3);	RR (95% CI): 1.07 (0.95, 1.20) per 10 μg/m^3
Pinault et al., 2017	The 2001 CanCHEC, Canada	2,448,500 participants aged 25–90 years	Pneumonia mortality	ICD-10: J10–J19	4,600	$PM_{2.5}$ (mean: 7.37 μg/m^3)	HR (95% CI): 1.210 (1.004, 1.457) per 10 μg/m^3
Carey et al., 2013	Clinical Practice Research Datalink database (CPRD), UK	Patients consulting their family practitioner aged 40–89 years: 830,842 ($PM_{2.5}$); 830,429 (NO_2); 824,654 (O_3)	Pneumonia mortality	ICD-10: J12–J18	4,071 ($PM_{2.5}$); 4,065 (NO_2); 4,042 (O_3)	Mean: $PM_{2.5}$ (12.9 μg/m^3); NO_2 (22.5 μg/m^3); O_3 annual (51.7 μg/m^3)	HR (95% CI): 1.08 (1.03, 1.13) per 1.9 μg/m^3 1.09 (1.03, 1.16) per 10.7 μg/m^3 0.95 (0.91, 0.99) per 3.0 μg/m^3
Yang et al., 2018	Hong Kong elderly cohort, China	66,820 elderly people aged ≥65 years	Pneumonia mortality	ICD-10: J12–J18	NA	Median: $PM_{2.5}$ (42.2 μg/m^3); BC (12.1 μg/m^3); NO_2 (104 μg/m^3)	HR (95% CI): 0.99 (0.94, 1.05) per 5.5 μg/m^3 0.99 (0.93, 1.05) per 9.6 μg/m^3 0.98 (0.90, 1.06) per 25.6 μg/m^3
Yorifuji et al., 2013	Shizuoka elderly cohort, Japan	13,412 elderly residents	Pneumonia and influenza mortality	ICD-10: J10–J29	159	Mean: NO_2 (22 μg/m^3)	HR (95% CI): 1.15 (0.99, 1.35) per 10 μg/m^3
Katanoda et al., 2011	Three-prefecture Cohort Study, Japan	63,520 aged ≥40 years	Pneumonia mortality	NA	512	Mean range in 6 study areas: $PM_{2.5}$ (16.8 to 41.9 μg/m^3); NO_2 (1.2 to 33.7 ppb)	HR (95% CI): 1.17 (1.04, 1.32) per 10 μg/m^3 1.16 (1.12, 1.21) per 10 ppb

Definition of abbreviation: $PM_{2.5}$, particulate matters with aerodynamic diameters of less than 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Figure E1. Map of study locations and proportion of study population for eight cohorts included in our study (source: map is from Strak et al. 2021; doi: 10.1136/bmj.n1904).



AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Table E2. Study characteristic of each sub-cohort with corresponding specific respiratory infection mortality rates.

Cohort/sub-cohort	Population size*	N#	Enrolmented year	End of follow-up	Mean age at baseline	Mean age at end of follow-up	Deaths, N (rate)ϕ			Study area
							Pneumonia and Influenza	ALRI	Pneumonia	
Pooled Cohort	381,036	325,367	/	/	48.7	68.2	712 (11.2)	695 (11.0)	682(10.8)	Eight cohorts in six countries
CEANS	21,987	20,702	/	/	56.3	69.3	43 (16.0)	42 (15.6)	42 (15.6)	Stockholm county, Sweden
SDPP	7,835	7,727	1992-1998	2011	47.1	63.0	0 (0)	0 (0)	0 (0)	
SIXTY	4,180	3,969	1997-1999	2014	60.0	75.5	6 (9.8)	5 (8.2)	5 (8.2)	
SALT	6,724	6,176	1998-2002	2011	57.8	68.2	15 (23.4)	15 (23.4)	15 (23.4)	
SNACK	3,248	2,830	2001-2004	2011	72.9	80.3	22 (104.9)	22 (104.9)	22 (104.9)	
DCH	56,308	53,647	1993-1997	2015	56.7	74.8	157 (16.1)	153 (15.7)	153 (15.7)	Copenhagen and Aarhus, Denmark
DNC	28,433	25,171	/	/	53.5	70.8	113 (25.9)	111 (25.5)	109 (25.0)	Denmark-wide
1993	19,664	17,043	1993	2013	56.2	74.9	108 (33.9)	105 (33.0)	104 (32.7)	
1999	8,769	8,128	1999	2013	47.9	62.4	5 (4.3)	6 (5.1)	5 (4.3)	
E3N	53,521	39,006	1989-1991	2011	53.0	69.7	18 (2.8)	22 (3.4)	16 (2.5)	France-wide
EPIC-NL	36,905	32,872	/	/	49.5	66.1	55 (10.0)	56 (10.2)	54 (9.9)	Four cities, the Netherlands
Morgen	20,711	18,302	1993-1997	2013	42.9	59.8	19 (6.2)	20 (6.5)	19 (6.2)	
Prospect	16,194	14,570	1993-1997	2013	57.7	74.1	36 (15.0)	36 (15.0)	35 (14.6)	
HNR	4,809	4,733	2000-2003	2015	59.7	71.7	11 (19.3)	11 (19.3)	11 (19.3)	Ruhr area, Germany
KORA	8,823	4,853	/	/	49.4	63.7	26 (37.4)	26 (37.4)	26 (37.4)	Augsburg area,

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

S3	4,566	2,572	1994-1995	2011	49.4	65.0	15 (37.4)	15 (37.4)	15 (37.4)	Germany
S4	4,257	2,281	1999-2001	2014	49.3	62.3	11 (37.3)	11 (37.3)	11 (37.3)	
VHM&PP	170,250	144,383	1985-2005	2014	42.1	65.2	289 (11.2)	274 (8.2)	271 (8.1)	Vorarlberg region, Austria

*: Population size is the number of participants for which information was transferred to Utrecht University for construction of the pooled cohort.

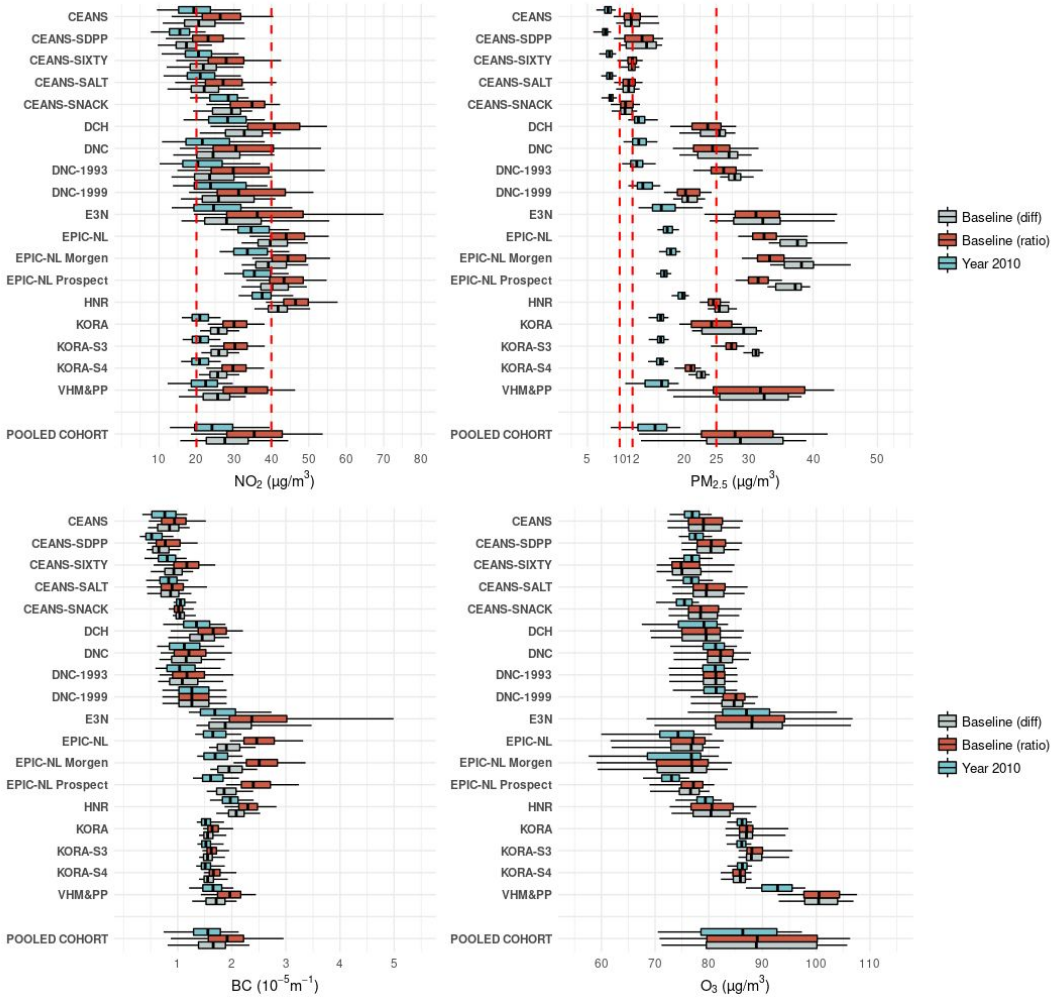
#: N indicates the number participants included in our model analysis.

ϕ: Rate is crude mortality rate for the pooled cohort during the follow-up period, expressed in units of deaths per 100,000 participants per year.

Definition of abbreviation: ALRI, acute lower respiratory infection.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Figure E2. Description of air pollutants by cohorts and sub-cohorts for the year 2010 and the baseline years (N=325,342).



The bold lines in the middle of the box indicate the median values (the 50th percentiles). 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 dotted dash lines represent different limited/guideline values in the EU, U.S., and 2005 WHO guidelines.

The number of participants for available baseline exposures, which were back-extrapolated using ratio and difference methods, was 325,342. For comparison, we restricted the same participants for 2010 exposure in this graph.

Definition of abbreviation: $PM_{2.5}$, particulate matters with aerodynamic diameters of less than 2.5 µm; NO_2, nitrogen dioxide; BC, black carbon; O_3, ozone.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Table E3. Pearson correlations between air pollutants for year 2010 exposure in the pooled cohort and sub-cohorts.

Pollutants	Cohort	NO_2	$PM_{2.5}$	BC	O_3	Cohort	NO_2	$PM_{2.5}$	BC	O_3
NO_2	**Pooled cohort**	1				**CEANS-SALT**	1			
$PM_{2.5}$		0.52	1				0.67	1		
BC		0.67	0.80	1			0.84	0.55	1	
O_3		-0.61	0.04	0.03	1		-0.74	-0.47	-0.76	1
NO_2	**CEANS-SDPP**	1				**CEANS-SIXTY**	1			
$PM_{2.5}$		0.60	1				0.69	1		
BC		0.67	0.49	1			0.84	0.59	1	
O_3		-0.70	-0.18	-0.33	1		-0.71	-0.44	-0.71	1
NO_2	**CEANS-SNACK**	1				**DCH**	1			
$PM_{2.5}$		0.75	1				0.72	1		
BC		0.43	0.29	1			0.91	0.66	1	
O_3		-0.66	-0.5	-0.74	1		-0.61	-0.56	-0.57	1
NO_2	**DNC-1993**	1				**DNC-1999**	1			
$PM_{2.5}$		0.64	1				0.61	1		
BC		0.92	0.70	1			0.93	0.64	1	
O_3		-0.42	-0.32	-0.42	1		-0.21	-0.16	-0.20	1
NO_2	**E3N**	1				**EPIC-NL-Morgen**	1			
$PM_{2.5}$		0.81	1				0.22	1		
BC		0.92	0.74	1			0.84	0.41	1	
O_3		-0.50	-0.49	-0.38	1		-0.78	0.15	-0.55	1
NO_2	**EPIC-NL-Prospect**	1				**HRN**	1			
$PM_{2.5}$		0.48	1				0.65	1		
BC		0.91	0.41	1			0.88	0.64	1	
O_3		-0.86	-0.43	-0.84	1		-0.83	-0.66	-0.81	1

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

NO_2	**KORA-S3**	1				**KORA-S4**	1			
$PM_{2.5}$		0.52	1				0.58	1		
BC		0.78	0.46	1			0.73	0.54	1	
O_3		-0.75	-0.38	-0.77	1		-0.73	-0.37	-0.71	1
NO_2	**VHM&PP**	1								
$PM_{2.5}$		0.65	1							
BC		0.91	0.76	1						
O_3		-0.83	-0.69	-0.88	1					

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Table E4. Associations between air pollution and specific respiratory infection mortality in two-pollutant models (N=325,367).

	Model 3	Model 3 + NO_2	Model 3 + $PM_{2.5}$	Model 3 + BC	Model 3 + O_3
Pneumonia and Influenza (712 deaths)					
NO_2	1.12 (0.99, 1.26)	/	1.21 (1.05, 1.40)	1.17 (0.89, 1.53)	1.14 (0.97, 1.34)
$PM_{2.5}$	0.96 (0.80, 1.15)	0.80 (0.64, 1.01)	/	0.81 (0.64, 1.02)	0.89 (0.72, 1.10)
BC	1.10 (0.97, 1.24)	0.95 (0.72, 1.25)	1.19 (1.02, 1.39)	/	1.10 (0.94, 1.28)
O_3	0.92 (0.78, 1.09)	1.04 (0.84, 1.30)	0.87 (0.72, 1.06)	1.00 (0.81, 1.24)	/
Acute lower respiratory infection (695 deaths)					
NO_2	1.10 (0.98, 1.24)	/	1.20 (1.04, 1.39)	1.15 (0.88, 1.51)	1.13 (0.97, 1.33)
$PM_{2.5}$	0.93 (0.78, 1.12)	0.79 (0.63, 0.99)	/	0.79 (0.63, 1.00)	0.87 (0.70, 1.08)
BC	1.08 (0.96, 1.22)	0.95 (0.72, 1.26)	1.19 (1.02, 1.39)	/	1.09 (0.93, 1.28)
O_3	0.95 (0.80, 1.12)	1.06 (0.85, 1.33)	0.89 (0.73, 1.08)	1.02 (0.83, 1.27)	/
Pneumonia (682 deaths)					
NO_2	1.11 (0.99, 1.26)	/	1.23 (1.06, 1.42)	1.17 (0.89, 1.54)	1.14 (0.97, 1.34)
$PM_{2.5}$	0.93 (0.77, 1.12)	0.77 (0.61, 0.97)	/	0.78 (0.61, 0.99)	0.85 (0.69, 1.06)
BC	1.09 (0.97, 1.24)	0.95 (0.71, 1.26)	1.21 (1.04, 1.42)	/	1.09 (0.93, 1.28)
O_3	0.92 (0.78, 1.09)	1.04 (0.83, 1.31)	0.86 (0.71, 1.05)	1.00 (0.80, 1.24)	/

Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] 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.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

*Two-pollutant results are difficult to interpret because of high correlations between NO_2, BC and O_3 in some sub-cohorts and non-linear relationship for $PM_{2.5}$ exposure.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Table E5. Characteristics of participants at baseline and air pollutants for the year 2010 by the quartiles of $PM_{2.5}$ concentrations (N=325,367).

Characteristic	Pooled cohort		CEANS-SALT		CEANS-SDPP		CEANS-SIXTY		CEANS-SNACK	
	<15	≥15	<15	≥15	<15	≥15	<15	≥15	<15	≥15
N	151,250	174,117	6,176	0	7,727	0	3,969	0	2,830	0
Percentage, %	46	54	100	0	100	0	100	0	100	0
Deaths, N*	393	319	15	0	0	0	6	0	22	0
$PM_{2.5}$, $\mu g/m^3$	12.2 ± 2.1	17.5 ± 1.6	8.4 ± 0.8	0	7.6 ± 0.9	0	8.3 ± 0.9	0	8.6 ± 0.8	0
Age, years	50.8 ± 12.7	46.9 ± 13.8	57.8 ± 10.6	0	47.1 ± 4.9	0	60.0 ± 0	0	72.9 ± 10.4	0
Female, %	64	68	55	0	61	0	52	0	62	0
Current smokers, %	26	22	21	0	26	0	21	0	14	0
Overweight, %#	45	42	40	0	52	0	65	0	53	0
Married or cohabiting, %	73	71	68	0	84	0	74	0	46	0
Employed, %	73	67	64	0	91	0	68	0	23	0
Mean income, euro†	21.1 ± 4.8	19.2 ± 6.4	25.3 ± 6.6	0	24.3 ± 4.2	0	24.7 ± 6.9	0	28.7 ± 2.2	0
	DCH		DNC-1993		DNC-1999		E3N		EPIC-NL-Morgen	
	<15	≥15	<15	≥15	<15	≥15	<15	≥15	<15	≥15
N	45,236	8,411	15,362	1,681	6,026	2,102	9,091	29,915	56	18,246
Percentage, %	84	16	90	10	74	26	23	77	0.3	99.7
Deaths, N*	116	41	94	14	4	1	3	15	0	19

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

$PM_{2.5}$, μg/m^3	12.7 ± 0.9	15.8 ± 0.6	12.4 ± 1.2	15.7 ± 0.5	13.1 ± 1.1	15.8 ± 0.6	13.7 ± 1.3	18.0 ± 2.5	14.4 ± 0.6	18.0 ± 1.0
Age, years	56.7 ± 4.4	56.6 ± 4.3	56.4 ± 8.3	54.8 ± 9.0	48.1 ± 4.4	47.5 ± 3.3	53.3 ± 6.7	52.9 ± 6.8	47.3 ± 10.8	42.9 ± 11.2
Female, %	52	54	100	100	100	100	100	100	59	55
Current smokers, %	35	45	37	41	28	29	12	13	27	35
Overweight, %#	56	55	28	27	30	29	21	21	61	60
Married or cohabiting, %	74	57	69	53	77	73	87	82	70	65
Employed, %	78	81	69	75	94	96	63	69	55	69
Mean income, euro†	20.4 ± 3.6	19.2 ± 1.9	19.2 ± 2.6	19.3 ± 2.7	18.9 ± 2.2	19.3 ± 27.7	9.9 ±1.8	11.6 ± 3.2	11.3 ± 1.2	12.2 ± 1.6
	EPIC-NL-Prospect		**HNR**		**KORA-S3**		**KORA-S4**		**VHM&PP**	
	<15	**≥15**	**<15**	**≥15**	**<15**	**≥15**	**<15**	**≥15**	**<15**	**≥15**
N	177	14,393	1	4,732	232	2,340	228	2,053	54,139	90,244
Percentage, %	1	99	0.02	99.98	9	91	10	90	37	63
Deaths, N*	1	35	0	11	2	13	2	9	128	161
$PM_{2.5}$, μg/m^3	14.2 ± 0.8	16.9 ± 0.7	14.8	19.6 ± 0.9	14.4 ± 0.4	16.5 ± 0.7	14.3 ± 0.5	16.4 ± 0.7	12.8 ± 1.7	17.5 ± 1.1
Age, years	58.1 ± 5.6	57.7 ± 6.1	—	59.7 ± 7.8	46.6 ± 14.4	49.7 ± 13.9	49.7 ± 13.6	49.3 ± 13.9	42.0 ± 15.0	42.1 ± 15.1
Female, %	100	100	—	50	50	51	50	52	56	56
Current smokers, %	11	23	—	24	18	20	23	23	20	20
Overweight, %#	60	55	—	74	66	67	71	69	41	43
Married or cohabiting, %	87	77	—	75	79	80	86	79	69	69
Employed, %	51	51	—	40	59	55	58	60	71	69
Mean income, euro†	13.6 ± 1.6	13.1 ± 1.4	—	25.2 ± 8.2	36.6 ± 3.7	36.7 ± 4.5	34.4 ± 3.7	38.4 ± 7.4	22.6 ± 1.9	23.0 ± 1.5

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Results are presented as Mean ± SD for continuous variables and proportion (%) for categorical variables.

*: The number of deaths of pneumonia and influenza.

ϕ: Smoking duration and smoking intensity are only for current smokers. We set these variable to zero for never and former smokers.

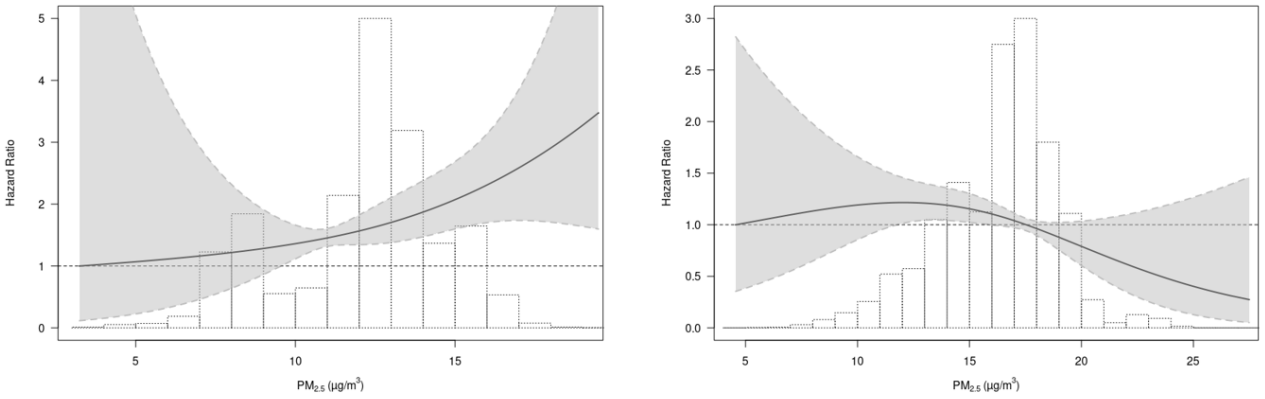
#: BMI ≥ 25 kg/m^2 indicates overweight according to the World Health Organization (WHO) categories.

†: Area-level mean year income in euros × 1,000 in the year 2001. It is at municipality-level in 2001 for DCH and DNC and at neighbourhood/city district level in 1994 for CEANS.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Figure E3. Associations between long-term exposure to $PM_{2.5}$ and pneumonia and influenza combined mortality in different cohort groups based on Model 3.

Cohorts	$PM_{2.5}$ levels, $\mu g/m^3$	No. of participants	No. of deaths	HR (95%CI)
CEANS, DCH, DNC	12.1 ± 2.5	99,520	313	1.58 (1.07, 2.35)
E3N, EPIC-NL, HNR, KORA, VHM&PP	16.3 ± 2.6	225,847	399	0.82 (0.67, 1.01)



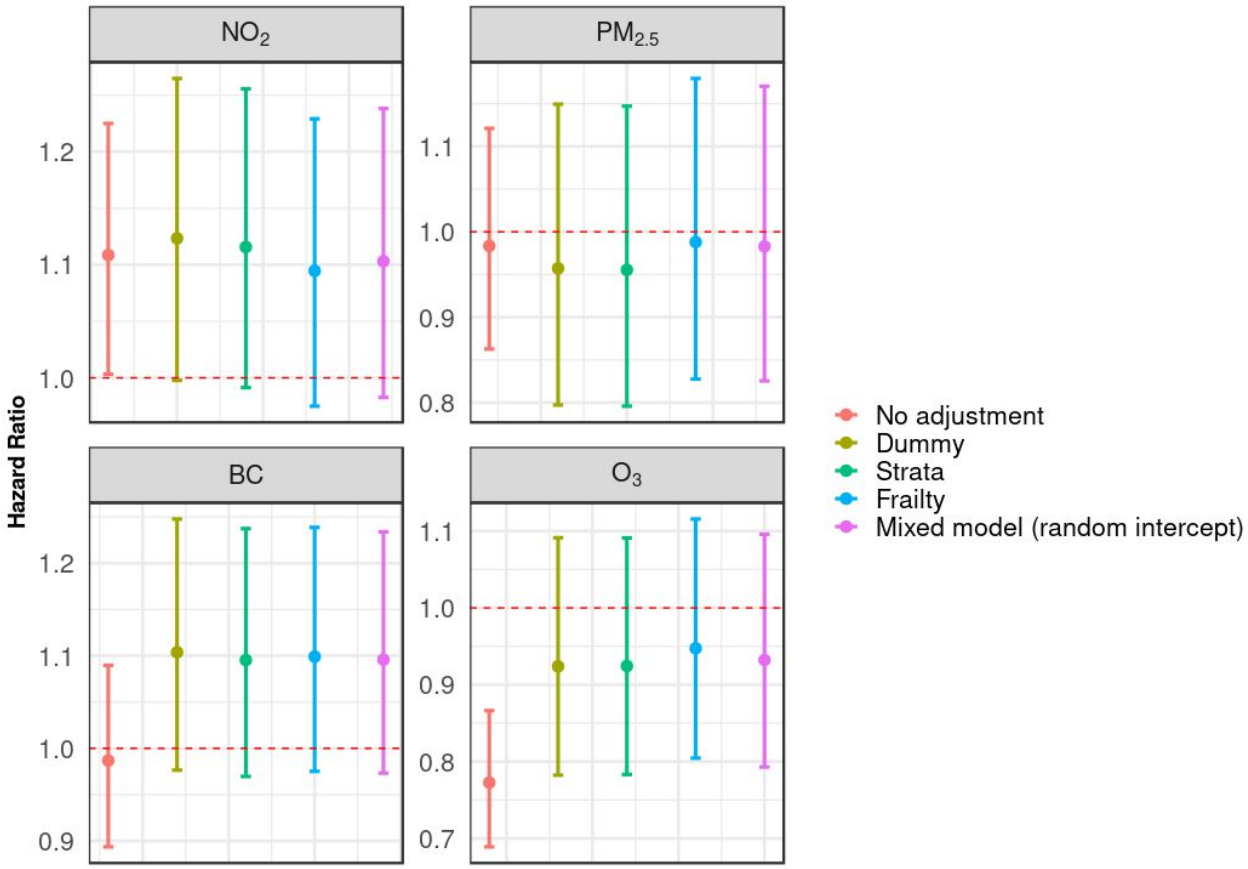
Natural cubic splines with two degrees of freedom were fit for concentration-response curves for the associations in different groups of cohorts, where the hazard ratios equal to one were for minimum exposures of $PM_{2.5}$. Left graph was for the cohorts of CEANS, DCH, and DNC, in which $PM_{2.5}$ levels were almost all below 15 $\mu g/m^3$.

Solid black lines indicate hazard ratio values and black dashed lines indicate their 95% confidence intervals. The histograms show the distributions of exposures in 2010.

Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] for a 5 $\mu g/m^3$ increase for $PM_{2.5}$,

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Figure E4. Comparing the results of different approaches for adjusting the heterogeneity between sub-cohorts based on the association with pneumonia and influenza mortality in Model 3.



The green error bars are our main result in Models adjusted for sub-cohort with strata.

Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] for the following increases: 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.

The Akaike Information Criteria (AIC) values for different approaches in models with NO_2 exposure were 13456.08 for no adjustment, 13372.25 for dummy variables, 11349.30 for strata, 13374.46 for a frailty term, and 13373.31 for a random intercept.

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Table E6. Associations between year 2010 exposure and back-extrapolated baseline year exposure and specific respiratory infection mortality in Model 3 (N=325,342).

	Year 2010 exposure	Baseline year exposure	
	(N=325,342)	Ratio method	Difference method
Pneumonia and Influenza (712 deaths)			
NO_2	1.12 (0.99, 1.26)	1.07 (0.99, 1.16)	1.11 (0.99, 1.25)
$PM_{2.5}$	0.96 (0.80, 1.15)	0.96 (0.89, 1.05)	0.95 (0.83, 1.08)
BC	1.10 (0.97, 1.24)	1.03 (0.94, 1.14)	1.07 (0.95, 1.21)
O_3	0.92 (0.78, 1.09)	0.98 (0.84, 1.14)	0.98 (0.84, 1.14)
ALRI (695 deaths)			
NO_2	1.10 (0.98, 1.24)	1.06 (0.98, 1.15)	1.09 (0.97, 1.23)
$PM_{2.5}$	0.93 (0.77, 1.12)	0.96 (0.88, 1.04)	0.95 (0.83, 1.09)
BC	1.08 (0.96, 1.22)	1.02 (0.93, 1.13)	1.06 (0.94, 1.19)
O_3	0.95 (0.80, 1.12)	0.99 (0.86, 1.15)	0.99 (0.85, 1.16)
Pneumonia (682 deaths)			
NO_2	1.11 (0.99, 1.26)	1.06 (0.98, 1.15)	1.11 (0.98, 1.25)
$PM_{2.5}$	0.93 (0.77, 1.12)	0.96 (0.88, 1.04)	0.95 (0.82, 1.09)
BC	1.09 (0.97, 1.24)	1.02 (0.93, 1.13)	1.07 (0.95, 1.21)
O_3	0.92 (0.78, 1.10)	0.99 (0.86, 1.15)	0.97 (0.83, 1.14)

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

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Table E7. Associations between time-varying annual exposure and specific respiratory infection mortality in four cohorts (CEANS, DCH, EPIC-NL, and VHM&PP; N=185,585) with available information based on Model 3.

	Year 2010 exposure	Time-varying exposure*	
	(N=185,585)	Ratio method	Difference method
Pneumonia and Influenza (395 deaths)			
NO_2	1.18 (1.00, 1.40)	1.12 (0.95, 1.31)	1.12 (0.95, 1.31)
$PM_{2.5}$	0.87 (0.67, 1.12)	0.93 (0.73, 1.19)	0.91 (0.70, 1.18)
BC	1.13 (0.95, 1.33)	1.08 (0.91, 1.29)	1.07 (0.91, 1.26)
O_3	0.92 (0.73, 1.14)	0.97 (0.87, 1.08)	0.97 (0.87, 1.08)
ALRI (386 deaths)			
NO_2	1.16 (0.98, 1.38)	1.12 (0.95, 1.31)	1.11 (0.95, 1.31)
$PM_{2.5}$	0.84 (0.65, 1.09)	0.92 (0.72, 1.17)	0.88 (0.68, 1.15)
BC	1.11 (0.93, 1.31)	1.08 (0.90, 1.29)	1.07 (0.91, 1.26)
O_3	0.95 (0.76, 1.18)	0.97 (0.87, 1.09)	0.97 (0.87, 1.09)
Pneumonia (384 deaths)			
NO_2	1.16 (0.98, 1.37)	1.12 (0.95, 1.32)	1.12 (0.95, 1.31)
$PM_{2.5}$	0.84 (0.65, 1.09)	0.92 (0.72, 1.17)	0.88 (0.68, 1.15)
BC	1.10 (0.93, 1.31)	1.09 (0.91, 1.30)	1.07 (0.91, 1.26)
O_3	0.95 (0.76, 1.18)	0.97 (0.87, 1.09)	0.97 (0.87, 1.09)

*: Time-varying analyses were additionally adjusted for calendar year of follow-up (strata one year) based on Model 3 to account for secular time trend in respiratory infection mortality and air pollution.

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

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC

Table E8. Results for sensitivity analysis of associations between year 2010 exposure and pneumonia and influenza mortality in Model 3.

	Number of participants	Number of deaths	HR (95%CI)			
			NO_2	$PM_{2.5}$	BC	O_3
All cohorts	325,367	712	1.12 (0.99, 1.26)	0.96 (0.80, 1.15)	1.10 (0.97, 1.24)	0.92 (0.78, 1.09)
Exclude CEANS-SDPP	317,640	712	1.12 (0.99, 1.26)	0.96 (0.80, 1.15)	1.10 (0.97, 1.24)	0.92 (0.78, 1.09)
Exclude CEANS	304,665	669	1.13 (1.00, 1.28)	0.95 (0.79, 1.15)	1.10 (0.97, 1.24)	0.93 (0.78, 1.10)
Exclude DCH	271,720	555	1.02 (0.89, 1.18)	0.85 (0.70, 1.03)	1.00 (0.86, 1.16)	0.98 (0.80, 1.20)
Exclude DNC	300,196	599	1.15 (1.00, 1.32)	0.94 (0.77, 1.13)	1.10 (0.96, 1.27)	0.92 (0.76, 1.10)
Exclude E3N	286,361	694	1.11 (0.98, 1.25)	0.95 (0.79, 1.15)	1.08 (0.95, 1.23)	0.93 (0.78, 1.10)
Exclude EPIC-NL	292,495	657	1.13 (1.00, 1.27)	0.98 (0.82, 1.18)	1.12 (0.99, 1.27)	0.95 (0.80, 1.13)
Exclude HNR	320,634	701	1.11 (0.99, 1.25)	0.95 (0.79, 1.14)	1.09 (0.97, 1.24)	0.93 (0.79, 1.10)
Exclude KORA	320,514	686	1.12 (0.99, 1.26)	0.96 (0.80, 1.15)	1.10 (0.97, 1.24)	0.92 (0.78, 1.09)
Exclude VHM&PP	180,984	423	1.10 (0.95, 1.27)	1.25 (0.89, 1.75)	1.13 (0.97, 1.30)	0.92 (0.76, 1.13)
All cohorts after multiple imputation	381,036	827	1.13 (1.01, 1.26)	0.96 (0.80, 1.13)	1.10 (0.98, 1.22)	0.94 (0.80, 1.09)

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

AJRCCM Articles in Press. Published March 08, 2022 as 10.1164/rccm.202106-1484OC