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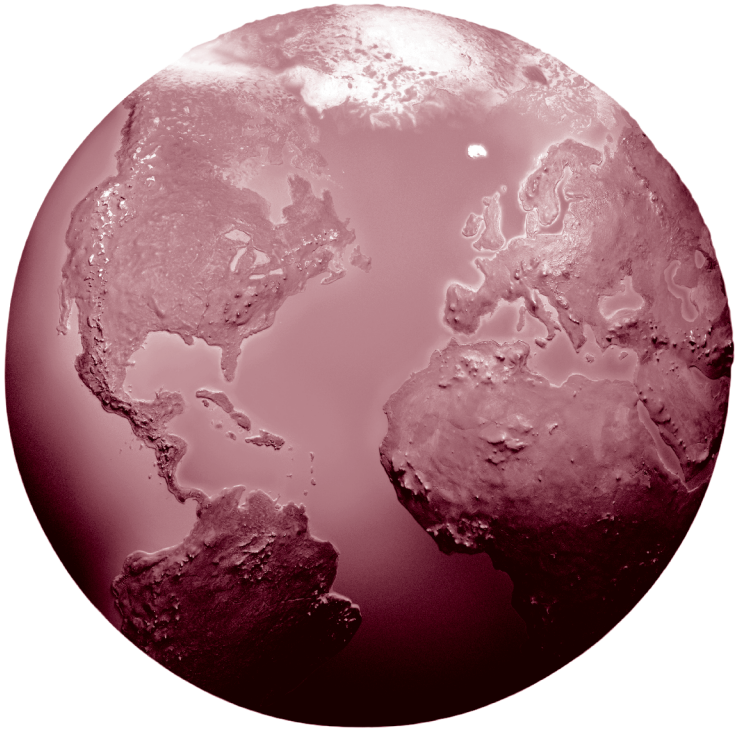

COMMENTARY BY THE HEI LOW-EXPOSURE EPIDEMIOLOGY STUDIES REVIEW PANEL SUMMARIZING AND EVALUATING THE INVESTIGATORS' REPORT:

Mortality and Morbidity Effects of Long-Term Exposure to Low-Level $PM_{2.5}$, BC, NO_2, and O_3: An Analysis of European Cohorts in the ELAPSE Project

Brunekreef et al.

Health Effects Institute

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Research Report 208
Health Effects Institute
Boston, Massachusetts

Trusted Science • Cleaner Air • Better Health

CONTENTS

ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the institute

- Identifies the highest-priority areas for health effects research;
- Competitively funds and oversees research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI's research and analyses to public and private decision makers.

HEI typically receives balanced funding from the U.S. Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 340 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 260 comprehensive reports published by HEI, as well as in more than 1,000 articles in the peer-reviewed literature.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. For this study, a special panel — HEI's Low-Exposure Epidemiology Studies Oversight Panel — has worked with the Research Committee in project selection and oversight. The Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research. For this study, a special review panel — HEI's Low-Exposure Epidemiology Studies Review Panel — is fulfilling this role.

All project results and accompanying comments by the Review Committee (or, in this case, the Low-Exposure Epidemiology Studies Review Panel) are widely disseminated through HEI's website (*www.healtheffects.org*), printed reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

Research Report 208, *Mortality and Morbidity Effects of Long-Term Exposure to Low-Level $PM_{2.5}$, BC, NO_2, and O_3: An Analysis of European Cohorts — Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE)*, Brunekreef et al.

INTRODUCTION

Ambient air pollution is an important contributor to the global burden of disease (GBD 2020; HEI 2020). Although levels of air pollution have been declining over the past few decades in many parts of the world, several studies published in the past decade reported associations between risk of mortality and long-term exposures to fine particulate matter ($PM_{2.5}$*) at even relatively low concentrations (e.g., Beelen et al. 2014a, b; Crouse et al. 2012, 2015; Hales et al. 2012; Pinault et al. 2016). To inform future risk assessment and regulation, it is important to confirm whether associations with adverse health effects continue to be observed as levels of air pollution decline still further. It is also important to understand better the shape of the concentration–response function at those low levels. Both of these issues remain as major uncertainties for setting air quality standards. The growing body of evidence demonstrating effects on health associated with exposures to air pollution at levels below current air quality standards in North America and Europe, the large overall contributions of air pollution to the global burden of disease, and general interests in reducing greenhouse gas emissions suggest that stronger air quality standards and guidelines may be considered in the future.

As described in detail in the Preface to this Report, in 2016 HEI funded three studies under RFA 14-3 to explore this issue of effects on health associated with exposures to low concentrations of air pollution. Dr. Brunekreef's ELAPSE study was one of these three studies. Additional information about the RFA and the two other studies conducted in North America is included in the Preface.

This Commentary was prepared by the HEI Low-Exposure Epidemiology Studies Review Panel and members of the HEI Scientific Staff, who were convened to review these three HEI-funded studies. The Commentary includes the scientific and regulatory background for the research, a summary of the study's approach and key results, and the Panel's evaluation of the Investigators' Report (IR) highlighting strengths and weaknesses of the study.

This Commentary is intended to aid the sponsors of HEI and the public by highlighting both the strengths and limitations of the study and by placing the Investigators' Report into scientific and regulatory context.

SCIENTIFIC AND REGULATORY BACKGROUND

The setting of ambient air quality standards — at levels considered adequate to protect public health — is a central component of programs designed to reduce air pollution and improve public health under the U.S. Clean Air Act (U.S. CAA), the European Union (EU) Ambient Air Quality Directives, the World Health Organization (WHO) Air Quality Guidelines, and similar measures around the world. Although the process for setting such standards varies, they all contain several common components:

- identifying, reviewing, and synthesizing the scientific evidence on sources, exposures, and health effects of air pollution;
- conducting risk and policy assessments to estimate what public health effects are likely to be seen at different levels of the standard;
- identifying and setting standards based on the risk analysis;
- air quality monitoring to determine areas that do not meet the standards; and
- implementing air quality control interventions to meet the standards by reducing exposure.

Dr. Brunekreef's 3-year study, "Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE)," began in May 2016. Total expenditures were $2,089,795. The draft Investigators' Report from Brunekreef and colleagues was received for review in May 2020. A revised report was submitted in November and reviewed in December by the HEI Low-Exposure Epidemiology Studies Review Panel, who suggested a few more minor revisions. A second revised final report was submitted and accepted for publication in January 2021. During the review process, the Panel and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Panel's Commentary.

* A list of abbreviations and other terms appears at the end of this volume.

SETTING AIR QUALITY STANDARDS IN THE UNITED STATES

The U.S. CAA requires that in setting the National Ambient Air Quality Standards (NAAQS), the U.S. Environmental Protection Agency (U.S. EPA) Administrator reviews all available science and sets the NAAQS for all major (criteria) pollutants (e.g., PM, nitrogen dioxide [NO_2], and ozone [O_3]) at a level "requisite to protect the public health with an adequate margin of safety." In practice, that review has had two principal steps:

- Synthesis and evaluation of all available science in what is now called an Integrated Science Assessment. This document reviews the widest range of exposure, dosimetry, toxicology, mechanistic, clinical, and epidemiologic evidence. It then — according to a predetermined set of criteria (U.S. EPA 2015) — draws on all lines of evidence to make a determination of whether the exposure is causal, likely to be causal, or suggestive for a series of health outcomes.
- Assessment of the risks based on that science is then conducted in a Risk and Policy Assessment. This further analysis draws on the Integrated Science Assessment to identify the strongest evidence — most often from human clinical and epidemiological studies — of the lowest concentration levels at which health effects are observed, the likely implications of such levels for health across the population, and the degree to which the newest evidence suggests that there are effects observed below the then-current NAAQS for a particular pollutant.

The Risk and Policy Assessment also examines the uncertainties around estimates of health impacts, and the shape of the concentration–response curve, especially at levels near and below the then-current NAAQS. Although a range of possible shapes of the concentration–response curves has been considered, including whether there is a threshold at a level below which effects are not likely, the U.S. EPA's conclusions in these reviews thus far have not found evidence of a threshold (although studies to date have not always had the power to detect one) (U.S. EPA 2004, 2013). Also, although the standard is set ostensibly to protect public health with an adequate margin of safety, it has been generally understood that there are likely additional, albeit more uncertain, health effects of exposure below the NAAQS.

Both of these documents are subjected to extensive public comments and review by the Clean Air Scientific Advisory Committee, which was established under the U.S. CAA. The Clean Air Scientific Advisory Committee is charged with both peer-reviewing the documents, which includes advising the Administrator on the strength and uncertainties in the science as well as on making the decision whether to retain or change the NAAQS. The current longer-term NAAQS for $PM_{2.5}$, NO_2, and O_3 are as follows (*https://www.epa.gov/criteria-air-pollutants/naaqs-table*):

- $PM_{2.5}$: annual mean averaged over three years of 12 μg/m^3;
- NO_2: annual mean of 53 ppb (approximately 100 μg/m^3);
- O_3: annual fourth-highest daily maximum 8-hour concentration, averaged over three years of 70 ppb (approximately 140 μg/m^3).

SETTING AIR QUALITY STANDARDS IN EUROPE

Similar to the United States and around the world, the EU has the overarching goal to protect its citizens and susceptible subpopulations from the adverse effects of major ambient air pollutants. The EU's clean air policy is based on three main pillars (European Commission 2018): (1) the Ambient Air Quality Directives (European Union 2004, 2008), which set out air quality standards and require Member States to assess air quality in a harmonized and comparable manner and to implement air quality plans to improve or maintain the quality of air; (2) the National Emissions Ceiling Directive (European Union 2016), which establishes national emission reduction commitments; and (3) source-specific legislation establishing specific emission standards for key sources of air pollution.

The directives have established EU air quality standards in the form of limit values and target values. Limit values are not to be exceeded and target values are to be attained where possible. The air quality standards currently in place were established in two complementary Ambient Air Quality Directives in 2004 and 2008 (European Union 2004, 2008).

In the 2008 directive, a limit value for $PM_{2.5}$ was added for the first time. The limit value for $PM_{2.5}$ is an annual average of 25 μg/m^3, which is higher than the U.S. annual standard of 12 μg/m^3 and the WHO health-based guideline of 10 μg/m^3, established in 2005 (World Health Organization 2006). The limit value for NO_2 is an annual average of 40 μg/m^3, which is more stringent than that in the United States.

Although the U.S. EPA is mandated by law to conduct comprehensive reviews on individual pollutants on a regular basis, there is no such regular process in Europe, and the EU relies on the WHO and others for the rigorous evaluation of the scientific evidence to inform retaining or tightening the air quality standards.

Just recently, in 2019, a fitness check of the EU Ambient Air Quality Directives was published (European Commission 2019a). It assessed whether or not all the directives' provisions are fit for purpose, looking in particular at the monitoring and assessment methods, the air quality stan-

dards, the provisions for public information, and the extent to which the directives facilitated action to prevent or reduce adverse impacts. The fitness check applied five criteria: relevance, effectiveness, efficiency, coherence, and EU added value. Based on this fitness check, the Commission concluded that the Ambient Air Quality Directives have been partly effective in improving air quality and achieving air quality standards.

Also in 2019, the European Green Deal (European Commission 2019b) was published. This is the European Commission's response to the climate and environmental challenges Europe (and the world) is facing. The European Green Deal has the overarching aim of reducing sources of carbon dioxide sufficiently to make Europe climate neutral by 2050. It also aims for a zero-emission strategy of air pollutants and foresees a revision of the European Air Quality Directive. To reach this target, the Commission will adopt a zero-pollution action plan for air, water, and soil in 2021.

In line with the conclusions from the fitness check, it is expected that the Commission in its plan will propose to revise air quality standards so that they align more closely with the WHO recommendations, which are due to be updated in 2021 (EEA, 2020). More information on the existing legislation in the EU can be found here: *https://ec.europa.eu/environment/air/quality/existing_leg.htm.*

THE ADVENT OF HEI STUDIES OBSERVING ASSOCIATIONS BELOW CURRENT AIR QUALITY STANDARDS AND GUIDELINES

As the quality and availability of data on levels of $PM_{2.5}$ improved over the course of the first decade of this century, results from new studies began to emerge starting in 2012 (e.g., in Canada and New Zealand) suggesting that associations of $PM_{2.5}$ and mortality could be observed down to levels well below the NAAQS of 12 μg/m^3 and the EU limit value of 25 μg/m^3 (Crouse et al. 2012; Hales et al. 2012). These studies found robust associations, with some evidence of even steeper slopes of effect at the lowest levels. If replicated in other populations and by other investigators, these findings could change the basis for future determinations of the levels at which to set the NAAQS as well as EU and other air quality standards.

At the same time, these findings posed several questions, for example:

- Would the results be robust to the application of a range of alternative analytic models and their uncertainty?
- Could other important determinants of population health, such as age, socio-economic position, health status, and access to medical care, as well as differences in air pollution sources and time–activity patterns, modify or confound the associations seen?
- Would the results change if risk estimates were more fully corrected for the effects of important potential confounding variables, such as smoking, in the absence of such data at the individual level?
- What might be the effects of co-occurring pollutants on health effect associations at low ambient concentrations?

As described in the Preface, the advent of these studies and the desire to address these important questions were the basis for the HEI Request for Applications (RFA 14-3) that sought and ultimately supported this study by Dr. Brunekreef and colleagues and the two other studies that make up HEI's Program to Assess Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution.

STUDY SUMMARY

STUDY OBJECTIVES

The main purpose of the ELAPSE study was to examine whether exposure to low concentrations of ambient air pollution is associated with adverse effects on human health, where "low" is defined as concentrations lower than the current EU Limit Values, U.S. EPA NAAQS, and/or the WHO Air Quality Guideline values for $PM_{2.5}$, NO_2, and O_3. The study had four specific objectives, namely:

1. To estimate long-term average exposure to $PM_{2.5}$, black carbon (BC), NO_2, O_3, and $PM_{2.5}$ composition by developing new hybrid models that combine monitoring data, land use, satellite observations, and dispersion models for participants in a pooled cohort consisting of participants from 15 existing cohorts from the European Study of Cohorts for Air Pollution Effects (ESCAPE) and in seven large administrative cohorts.

To investigate the shape of the relationship between long-term exposure to $PM_{2.5}$, BC, NO_2, and O_3 and four broad health effect categories — (1) natural- and cause-specific mortality including cardiovascular and nonmalignant as well as malignant respiratory and diabetes mortality; and morbidity measured as (2) coronary and cerebrovascular events; (3) lung cancer incidence; and (4) asthma and chronic obstructive pulmonary disease (COPD) incidence — using a number of different methods to characterize the concentration–response function (linear, nonlinear, or threshold).

2. To investigate, in the context of the second objective, variability of the concentration–response function

across populations and different exposure assessment methods, as well as the impact of different methods for addressing exposure measurement error, the role of co-occurring pollutants, and the effect of indirect approaches for confounder control in administrative cohorts.

3. To compare epidemiological effect estimates between those obtained using the ELAPSE and Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE) exposure modeling frameworks, respectively (MAPLE is the Canadian companion study funded by HEI within RFA14-3).

Briefly, the ELAPSE study consists of two parallel sets of epidemiologic analysis. As described below, Brunekreef and colleagues created Europewide exposure models for all pollutants of interest and assigned estimates of exposure to participants in two sets of cohorts. The first set includes 15 well-characterized cohorts pooled together. Fourteen of these cohorts were analyzed previously as part of the ESCAPE project (see Sidebar). The second set of cohorts includes seven large European administrative cohorts analyzed individually, and with their epidemiological results meta-analyzed to produce summary effect estimates. The purpose of working with these two cohort groups was to address the various strengths and limitations of using each individually. Specifically, the key strength of the pooled cohorts is the rich amount of individual-level information available for participants (despite somewhat smaller sample sizes), whereas the key strength of the administrative cohorts is their large sample sizes and national representativeness (at the expense of having fewer individual-level variables for participants).

Health outcomes in this study included mortality from all-natural causes, cardiovascular disease, diabetes, cardiometabolic disorders, and respiratory diseases, as well as incidences of lung cancer, coronary and cerebrovascular events, asthma, and COPD. The investigators applied standard Cox proportional hazard models to describe associations between exposures to the pollutants and these outcomes. They considered many sensitivity analyses, related broadly to different approaches to exposure specification, confounder control, and exploration of concentration–response functions. Note that not all analyses nor health outcomes were examined in both cohort groups.

METHODS AND STUDY DESIGN

Exposure Modeling

Main Models The investigators' main analyses involved the development of Europewide, hybrid land use regression (LUR) exposure models based on a consistent modeling approach for the whole area. These models are considered "hybrid" because they included outputs from dispersion models and satellite data along with ground-based observations and land use data. Both LUR and dispersion modeling are alternative approaches for modeling air pollution patterns that have only recently been combined using hybrid approaches (Hoek 2017). Briefly, LUR is a spatial modeling technique that uses observations of pollutant concentrations from point locations as the dependent variable and data describing characteristics such as road density and land use as the independent variables in a multivariate regression model to estimate pollutant concentrations at unsampled locations. Dispersion models estimate air pollution patterns by combining data on emission sources, geophysical characteristics of the area, and meteorological conditions. These models assume deterministic relation-

WHAT IS ESCAPE?

The ESCAPE project was a collaboration of more than 30 existing European cohort studies. The study took place between 2008 and 2012 and was led by Bert Brunekreef. Briefly, the study sought to quantify health impacts of exposure to air pollution and considered the effects of within-city and within-area contrasts in exposure as well as many different health outcomes. Among the key features was the harmonized exposure assessment, including an extensive air pollution measurement campaign across all areas. Key differences between the analyses conducted as part of the ELAPSE study compared to the ESCAPE project are summarized in Commentary Table 1. Specifically, in the ELAPSE study, the investigators conducted a pooled analysis (instead of cohort-specific analyses), developed Europewide exposure models (instead of local exposure models), incorporated residential history into the exposure assessment, added O_3 to the list of pollutants examined, and incorporated updated mortality and morbidity data (Commentary Table 1).

Commentary Table 1. Selected Study Characteristics Between the ESCAPE, ELAPSE Pooled, and ELAPSE Administrative Analyses

Study Characteristics	ESCAPE	ELAPSE Pooled	ELAPSE Administrative
Study design	Cohort-specific analyses and meta-analyses	Pooled cohort analysis	Cohort-specific analyses and meta-analyses
Pollutants	$PM_{2.5}$, BC, NO_2, PM_{10}, coarse PM, NO_x, and the copper, iron, zinc, and sulfur content of $PM_{2.5}$	$PM_{2.5}$, BC, NO_2, O_3, and the copper, iron, zinc, and sulfur content of $PM_{2.5}$	$PM_{2.5}$, BC, NO_2, O_3, and the copper, iron, zinc, and sulfur content of $PM_{2.5}$
Monitoring data	ESCAPE network	AirBase (the European air quality database) and ESCAPE network	AirBase (the European air quality database) and ESCAPE network
Exposure models	Within-city, within-area, and within-country	Europewide	Europewide
Total number of cohorts	30	15[a]	7
Total population	~370,000	~325,000	~28 million
Health endpoints[b]	Pregnancy and birth outcomes Respiratory disease outcomes Cardiovascular disease outcomes Cancer incidence and cause-specific mortality	Natural and cause-specific mortality including cardiovascular, non-malignant respiratory and diabetes mortality Coronary and cerebrovascular events Lung cancer incidence Asthma and COPD incidence	Natural and cause-specific mortality including cardiovascular, nonmalignant and malignant respiratory and diabetes mortality
Typical covariates included (but differed according to cohort and outcome considered)	Information on age, sex, individual and area-level socio-economic status, and health behaviors: smoking status, body mass index	Information on age, sex, individual and area-level socio-economic status, and health behaviors: smoking status, body mass index	Information on age, sex, individual and area-level socio-economic status; the English cohort had health behaviors: smoking status, body mass index

[a] The investigators selected cohorts from the original ESCAPE study that carried the most weight for analyses of the mortality and morbidity endpoints for the current study; were willing to pool data; were at the lower end of the ESCAPE exposure range, and were recruited relatively recently. See Investigators' Report (IR), page 11.

[b] Not all health endpoints were considered in each cohort category; see Investigators' Report Table 1 for a detailed overview.

ships between emissions and concentrations as compared to the empirical nature of LUR models.

Here, the investigators used AirBase routine monitoring data to derive annual average concentrations for $PM_{2.5}$, NO_2, and O_3. AirBase is the European air quality database maintained by the European Environment Agency. It contains air quality monitoring data and information submitted by participating countries throughout Europe. The database consists of a multi-annual time series of air quality measurement data and statistics for several air pollutants. The investigators developed their LUR model for BC with monitoring data collected from the network of monitors deployed as part of the ESCAPE project. Spatial data describing roads, land use, elevation, and population density, as well as satellite data, were all used as predictor variables in the LURs. The investigators also made use of pollutant estimates from two long-range chemical transport models, namely the MACC-II ENSEMBLE (Inness et al. 2013) and the Danish Eulerian Hemispheric Model (Brandt et al. 2012). They also applied universal kriging, which is an interpolation technique that considers the distance and direction between sample points (i.e., pollution monitors), to aid in explaining spatial variation in estimated concentrations.

The models were developed with monitoring data from the year 2010 because that was the earliest year with sufficient $PM_{2.5}$ data across Europe. For consistency, models for the other pollutants were based on data from this same year. All models were created at a spatial resolution of 100 m × 100 m. Brunekreef and colleagues created exposure models for annual, warm-season, and cold-season O_3, but correlations were high between the other pollutants and annual and winter season O_3 estimates, and so they focused on warm-season O_3 throughout their study. Other reasons for this were that concentrations and concentration contrasts are higher in summer and people spend more time outdoors in the warm season.

They examined the validity of the final exposure models by comparing indicators of performance and model fit among additional models produced while randomly excluding observations from 20% of the monitoring sites, with subsets of observations at relatively low concentrations, and validating with external ESCAPE monitoring data for $PM_{2.5}$ and NO_2. They also evaluated the performance of 14 algorithms including supervised linear regression to develop LUR models for $PM_{2.5}$ and NO_2. They observed that the performance of most algorithms was similar, with little indication of better performance of more sophisticated algorithms compared with supervised linear regression.

Additional Models to Examine Spatial Stability Over Time The investigators developed additional NO_2 and O_3 models for 2000 and 2005, as well as a $PM_{2.5}$ model for 2013 to examine spatial stability over time.

Additional Models to Account for Temporal Changes The investigators used estimates from the Danish Eulerian Hemispheric Model, which is an atmospheric chemical transport model developed to study the long-range transport of air pollution across the Northern Hemisphere, to extrapolate pollutant concentrations from 2010 back to 1990 (preceding the earliest baseline year for any of the study cohorts) and forward to 2017 (the latest end of follow-up year for any of the cohorts).

Additional Area-Specific Models The investigators made use of previously developed local-, region-, or country-specific pollution models, where available (IR Table 2; Beelen et al. 2013; Eeftens et al. 2012) for comparing results and patterns with the new Europewide models.

MAPLE $PM_{2.5}$ Exposure Model Additionally, the investigators used 2010 $PM_{2.5}$ estimates at a 1 × 1 km spatial resolution produced through the MAPLE study (see Preface or Brauer et al. 2019). The MAPLE model is based primarily on satellite aerosol optical depth and uses a global chemical transport model (GEOS-Chem) to calculate surface concentrations. Brauer and colleagues used geographically weighted regression to calibrate the surface concentrations to ground monitoring data (van Donkelaar et al. 2015, 2016). The MAPLE study has further refined the exposure estimation method by incorporating long-term measurements of aerosol optical depth from the ground at selected Canadian stations. Although the ELAPSE model includes satellite $PM_{2.5}$ data, it does not include the refinements added by geographically weighted regression and ground-based aerosol optical depth monitoring.

Study Populations

This study combines 15 well-characterized cohorts, mostly from the ESCAPE project, pooled together and seven large European administrative cohorts analyzed separately to perform new analyses on the health effects of air pollution at low levels of exposure. Commentary Table 2 presents selected characteristics of all cohorts used in these analyses. An administrative cohort is created through linked "administrative" data (e.g., census records and national mortality databases). Unlike conventional "research" cohorts, where individuals are invited to participate and to respond to questionnaires, the data used to compile administrative cohorts were not originally collected for research purposes nor for linking together.

Commentary Table 2. Selected Characteristics of the ELAPSE Cohorts

Cohort	Country	Geographic Coverage	Follow-Up Period	Sample Size
Pooled Cohorts				
CEANS-SDPP	Sweden	Stockholm county	1992–1998 to 2011	7,835
CEANS-SIXTY	Sweden	Stockholm county	1997–1999 to 2014	4,180
CEANS-SALT	Sweden	Stockholm county	1998–2002 to 2011	6,724
CEANS-SNACK	Sweden	Stockholm county	2001–2004 to 2011	3,248
DCH	Denmark	Copenhagen and Aarhus	1993–1997 to 2015	56,308
DNC-1993	Denmark	National	1993 to 2013	19,664
DNC-1999	Denmark	National	1999 to 2013	8,769
E3N	France	National	1993–1996 to 2011	53,521
EPIC-NL-MORGEN	The Netherlands	Four cities	1993–1997 to 2013	20,711
EPIC-NL-PROSPECT	The Netherlands	Four cities	1993–1997 to 2013	16,194
EPIC-VARESE	Italy	City of Varese	1993–1997 to 2014	12,028
HNR	Germany	Ruhr area	2000–2003 to 2015	4,809
KORA-S3	Germany	Augsburg area	1994–1995 to 2011	4,566
KORA-S4	Germany	Augsburg area	1999–2001 to 2014	4,257
VHM&PP	Austria	Vorarlberg Region	1985–2005 to 2014	170,250
Administrative Cohorts				
Belgian	Belgium (BE)	National	2001 to 2011	6,491,801
Danish	Denmark (DK)	National	2000 to 2015	3,409,517
Dutch	The Netherlands (NL)	National	2008 to 2012	10,532,360
English	England (EN)	National	2011 to 2017	1,491,124
Norwegian	Norway (NO)	National	2001 to 2016	2,516,192
Italian	Italy (IT)	City of Rome	2001 to 2015	1,263,712
Swiss	Switzerland (CH)	National	2000 to 2014	4,293,521

The advantage of working with administrative cohorts is that they tend to cover an entire country and are therefore nationally representative. Although the seven administrative cohorts were analyzed separately in this study, meta-analysis was used to produce summary effect estimates. Participants in the 15 conventional cohorts were combined into a single "pooled" dataset for analysis purposes. The investigators also evaluated the consistency of epidemiological results from these two cohort groups.

The purpose of reporting findings from separate analyses based on the two cohort groups was to address the various strengths and limitations of using each individually. For example, although the administrative cohorts are representative of whole populations, have substantially greater statistical power (i.e., approximately 28 million participants compared with approximately 325,000 participants in the pooled cohort), and control effectively for contextual confounders (i.e., area-based neighborhood- or community-level variables), they include relatively few

individual-level confounders. Conversely, the pooled cohorts have detailed information on individual-level characteristics and health behaviors, in addition to contextual confounders, but have relatively smaller sample sizes and may be less representative in their coverage of the full populations (e.g., some of these cohorts were composed exclusively of women).

Pooled Cohorts Brunekreef and colleagues chose to pool 15 cohorts, 14 of which were analyzed previously as part of the ESCAPE project, in an effort to gain statistical power for epidemiological analyses and to investigate more efficiently the shapes of concentration–response functions. The specific cohorts used for this study were selected based on willingness to pool data, had populations with exposures to relatively low concentrations of pollution, and were relatively recent in their recruitment. The Danish Nurse Cohort joined the ELAPSE study separately with independent funding. Most of these cohorts are located in a region that included one or multiple large cities and surrounding smaller towns.

Administrative Cohorts The administrative cohorts comprised 28 million participants spread across seven large administrative cohorts in seven European countries. These cohorts were formed by linking census data, population registries, and death registries. The administrative cohorts contributed primarily to the mortality analyses. In some previous studies with these cohorts, different exposure assessment and analytical methods were applied, thus making comparisons among results challenging. This work harmonized these cohorts to enhance comparability.

Exposure Assignment

As noted above, the investigators produced 100 m × 100 m spatial surfaces (i.e., maps) of estimates of annual average concentrations for each pollutant. They used exposure estimates for the year 2010 assigned to participant address at the time of recruitment as the main exposure variable in epidemiological models. Residential history data were available for all administrative cohort participants and for about half of the pooled cohort participants. As such, they assigned exposures for each year of follow-up using the annual, temporally adjusted estimates to all available addresses for use in separate sensitivity analyses, as noted below.

Main Epidemiological Analyses

Health outcomes in this study included natural cause, cardiovascular, diabetes, cardiometabolic and respiratory mortality, as well as incidences of lung cancer, coronary and cerebrovascular events, asthma, and COPD. The investigators applied standard Cox proportional hazard models to describe associations between exposures to the pollutants and mortality and morbidity. Main analyses were limited to each pollutant individually. The geographic scale of the contextual variables ranged from neighborhood in some cases to that of the municipality in others. Model specification differed slightly between those conducted with the pooled cohort versus those conducted with the administrative cohorts and according to health outcome considered, as noted below. Broadly, however, the investigators explored increasing levels of confounder control with individual-level and contextual covariates for both the pooled cohort and the administrative cohorts, namely:

- **Model 1:** included age (time axis), sex (as baseline hazard stratification), calendar year of enrollment, and cohort (as baseline hazard stratification) in the pooled cohort analyses;
- **Model 2:** added individual-level variables available to all cohorts in the pooled cohort, and all variables available in each administrative cohort;
- **Model 3:** added contextual variables (as covariates, not as random effects).

Ultimately, the investigators selected the most fully adjusted models (i.e., Model 3) available for use in the main analyses and limited these to only those participants with complete covariate information. In the case of the pooled cohort, the final model was defined by balancing the need to adjust for specific confounders and the desire to include as many cohorts as possible. All cohorts in the pooled cohort included information on age, sex, smoking status, body mass index, and individual-level and contextual indicators of socioeconomic status. In the case of the administrative cohorts, which were analyzed individually and then meta-analyzed using random effects models, the investigators preferred models with maximal adjustment per cohort rather than a common model with fewer covariates. As such, they included all available individual-level and contextual covariates in these models. The administrative cohorts, with the exception of the English cohort, did not include information on smoking or body mass index, which are both important risk factors for mortality. To address this limitation, the investigators applied indirect adjustment methods to adjust the hazard ratios of natural-cause mortality for these missing covariates. Indirect adjustment is a technique to help overcome the issue of unmeasured confounding in epidemiological studies where important risk factor information is missing (e.g., information on smoking or diet). The method allows researchers to adjust hazard ratios by examining the relationship between the missing risk factors and exposure in

an ancillary data set that does include information on those risk factors (along with all other variables also included in the survival models) (Erickson et al. 2019).

Additional Epidemiological Analyses

The investigators conducted many additional analyses and sensitivity analyses to assess the robustness of the findings reported with the main models, including analyses limited to subsets of participants within selected ranges of exposure concentrations to investigate associations at low levels. Below is a comprehensive enumeration of additional analyses conducted, according to two categories of analyses, namely: **alternative approaches to exposure estimation** and **variations on covariate adjustment**.

Lastly, the investigators also examined the shapes of **concentration–response functions** to investigate associations at low levels. Note that not all of these additional analyses were conducted for all health outcomes, nor necessarily for both cohort groups.

Alternative Approaches to Exposure Estimation In addition to using the exposure estimates derived for the year 2010 from the central, Europewide models applied to baseline years, the investigators also explored models using:

- time-varying exposures (i.e., a 1-year moving window of exposure);
- local exposure models (where available);
- estimates for $PM_{2.5}$ created for the MAPLE study;
- estimates for O_3 at a larger spatial scale; and,
- estimates for $PM_{2.5}$ composition, specifically the copper, iron, zinc, and sulfur content of fine particulate matter. These analyses were not planned originally, and results for the compositional models were included only in Appendix 4. As such, they are not discussed further in this commentary.

Variations on Covariate Adjustments In addition to the three levels of model adjustment described above, the investigators also examined models that:

- evaluated effect modification by age at baseline, smoking status, and body mass index;
- were adjusted for every two-pollutant combination of $PM_{2.5}$, BC, NO_2, and O_3;
- adjusted for dietary variables (i.e., alcohol and fruit intake);
- adjusted for road traffic noise; and,
- adjusted for indicator variables for "region" to allow for variation in health outcomes not accounted for by the other confounder variables in the models.

Concentration–Response Functions The team investigated the shapes of concentration–response functions using natural splines with two, three, and four degrees of freedom, with penalized splines, and with shape-constrained health impact functions (SCHIFs). SCHIFs were developed by Nasari and colleagues (2016) to extend the log-linear model (which relates the logarithm of the hazard ratio to exposure in a linear manner) to nonlinear transformations of exposure (including near-linear, supralinear, and sublinear). The Brunekreef team used the SCHIF method in addition to the more traditional methods to estimate concentration–response curves to harmonize the analytic approaches across the other studies funded under this RFA and conducted in Europe and North America, in particular with the Canadian (MAPLE) team. The Canadian team asserted that a major advantage of the SCHIF over nonparametric smoothing functions is the resulting specific parameter estimates that can be applied in related analyses, for example in cost–benefit evaluations. The SCHIFs are constrained to produce functions that increase monotonically with concentration and forms that are biologically plausible, for example, not allowing multiple upward and downward inflections (Brauer et al. 2019).

SUMMARY OF KEY RESULTS

MODELING AND EXPOSURE ESTIMATION RESULTS

The final, Europewide hybrid LUR exposure models explained 66%, 51%, 58%, and 60% of the variability in concentrations of $PM_{2.5}$, BC, NO_2, and O_3, respectively. As noted above, the investigators developed additional NO_2 and O_3 models for the years 2000 and 2005, as well as a $PM_{2.5}$ model for 2013 to examine spatial stability over time. Here, squared correlations (R^2) between concentrations predicted at random sites across the models for different years overall were generally high (i.e., >78%). The within-country squared correlations were more modest: >49% for $PM_{2.5}$, >80% for NO_2, and >47% for O_3 (except Italy, i.e., 12%). Additionally, the investigators observed similar patterns for correlations between the Airbase monitoring data in different years. All of this suggested that the main exposure models had good spatial stability (across the full study area) and good temporal stability (throughout the study period).

Key epidemiological results are presented below separately for analyses with the pooled cohort and with the

administrative cohorts. Not all analyses were conducted on both cohort groups.

POOLED COHORT HEALTH ANALYSIS

In 2010, almost all participants in the pooled cohort had $PM_{2.5}$ and NO_2 annual average exposures below the EU limit values of 25 and 40 μg/m^3, respectively, with more than 50,000 and 25,000 participants experiencing residential $PM_{2.5}$ exposures below the U.S. EPA NAAQS (12 μg/m^3) and the WHO guideline (10 μg/m^3). Mean concentrations (and standard deviations [SD]) in μg/m^3 (BC was measured in 1.5×10^{-5}/m) for participants in the pooled cohort for $PM_{2.5}$, BC, NO_2, and O_3 were 15.02 (3.22), 1.52 (0.42), 25.00 (8.05), and 67.46 (6.86), respectively.

The investigators reported significant positive associations between $PM_{2.5}$, BC, and NO_2, and all causes of death examined in their main models (with the exception of respiratory mortality and $PM_{2.5}$) (Commentary Table 3; See also IR Table 5). They reported the largest mortality effect estimates for diabetes mortality (e.g., hazard ratio (HR) for $PM_{2.5}$ per 5 μg/m^3: 1.32; 95% confidence interval (CI): 1.14–1.51). They reported inverse associations between O_3 and all causes of death examined.

The HRs for natural-cause mortality remained elevated and significant for $PM_{2.5}$ even when all observations higher than 12 μg/m^3 were removed from the analysis (Commentary Table 4 and IR Table 7), although effect estimates tended to be higher than those reported with the full dataset. For NO_2, HRs remained elevated and significant even when all observations higher than 20 μg/m^3 were removed, and for BC, HRs remain elevated and significant even when all observations higher than 1.5×10^{-5}/m were removed. HRs for O_3 attenuated toward unity at concentrations below 80 μg/m^3 (IR Table 7).

In the incidence analyses the investigators found significant positive associations between $PM_{2.5}$, BC, and NO_2

Commentary Table 3. Associations Between Air Pollution and Selected Causes of Mortality from Main Epidemiological Models Among Participants in the Pooled and Administrative ELAPSE Cohorts[a]

	Natural Cause		Cardiovascular		Respiratory		Diabetes	
Cohort (deaths)	Pooled[b] (47,131)	Administrative[c] Meta-analysis (3,593,741)	Pooled[b] (15,542)	Administrative[c] Meta-analysis (1,186,101)	Pooled[b] (2,865)	Administrative[c] Meta-analysis (371,990)	Pooled[b] (1,034)	Administrative[c] Meta-analysis (78,622)
$PM_{2.5}$								
	1.130 (1.106, 1.155)	1.053 (1.021, 1.085)	1.135 (1.095, 1.176)	1.041 (1.010, 1.072)	1.054 (0.961, 1.156)	1.064 (1.013, 1.118)	1.316 (1.144, 1.514)	1.038 (0.974, 1.106)
BC								
	1.081 (1.065, 1.098)	1.039 (1.018, 1.059)	1.085 (1.055, 1.116)	1.022 (1.004, 1.040)	1.084 (1.020, 1.151)	1.053 (1.021, 1.085)	1.240 (1.112, 1.382)	1.015 (0.969, 1.065)
NO_2								
	1.086 (1.070, 1.102)	1.044 (1.019, 1.069)	1.089 (1.060, 1.120)	1.025 (1.006, 1.044)	1.101 (1.038, 1.168)	1.058 (1.024, 1.093)	1.238 (1.112, 1.378)	1.013 (0.958, 1.070)
O_3								
	0.896 (0.878, 0.914)	0.953 (0.929, 0.979)	0.887 (0.854, 0.922)	0.976 (0.954, 0.998)	0.890 (0.821, 0.966)	0.948 (0.910, 0.988)	0.744 (0.645, 0.859)	0.984 (0.917, 1.057)

[a] Results are expressed as hazard ratios and 95% confidence intervals. (Source IR: Tables 5 and 19.) HRs presented for the following increments: $PM_{2.5}$: 5 μg/m^3; BC: 0.5×10^{-5}/m; NO_2: 10 μg/m^3; and O_3: 10 μg/m^3.

[b] For the pooled cohort—Model 3: adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income.

[c] For the administrative cohorts—Model 3: adjusted for age, sex, year of baseline visit, and cohort-specific individual and area-level SES variables.

Commentary Table 4. Associations Between Air Pollution and Natural-Cause Mortality in Subset Analyses Among Participants in the Pooled Cohort

Pollutant / Subset	N	HR[a] (95% CI)
$PM_{2.5}$		
Full dataset	325,367	1.130 (1.106, 1.155)
<12 μg/m^3	52,528	1.296 (1.140, 1.474)
<10 μg/m^3	25,422	1.146 (0.931, 1.410)
NO_2		
Full dataset	325,367	1.086 (1.070, 1.102)
<30 μg/m^3	247,039	1.114 (1.088, 1.140)
<20 μg/m^3	88,510	1.099 (1.033, 1.170)
BC		
Full dataset	325,367	1.081 (1.065, 1.098)
$<1.5 \times 10^{-5}$/m	142,032	1.125 (1.086, 1.165)
$<1 \times 10^{-5}$/m	35,406	1.041 (0.942, 1.150)

[a] HR (95% confidence interval) presented for the following increments: $PM_{2.5}$: 5 μg/m^3, NO_2, 10 μg/m^3, BC: 0.5×10^{-5}/m; Model 3 adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity squared), BMI, marital status, employment status, and 2001 neighborhood-level mean income.

and incidence of stroke, asthma, and COPD hospital admissions. Additionally, they reported significant associations between NO_2 and acute coronary heart disease and between $PM_{2.5}$ and lung cancer incidence (Commentary Table 5). They reported that results with the full pooled cohort were similar in magnitude in subset analyses limited to participants with exposures below 10 μg/m^3 for $PM_{2.5}$ and below 20 μg/m^3 for NO_2.

In two-pollutant models, the HRs for natural-cause mortality were attenuated, but remained elevated and statistically significant for $PM_{2.5}$ and NO_2. Associations with O_3 were also attenuated but remained negative in the two-pollutant models with $PM_{2.5}$, BC, and NO_2. It should be noted that BC and NO_2 were highly correlated in all cohorts, $PM_{2.5}$ was moderately to highly correlated with BC and NO_2, and O_3 was negatively correlated with $PM_{2.5}$, NO_2, and BC.

In spline plots examining the shape of associations between exposure and natural-cause mortality, the investigators observed generally supralinear patterns (i.e., steeper slopes at lower exposures) with no evidence of concentrations below which no associations were found for $PM_{2.5}$, BC, and NO_2. That is, increased risks for mortality were associated with even the lowest observed concentrations. Commentary Figure 1 shows the results for $PM_{2.5}$; the curves for BC and NO_2 had similar shapes, though were somewhat more u-shaped. Lastly, the investigators pre-

Commentary Table 5. Associations Between Air Pollution and Incidence of Acute Coronary Heart Disease, Stroke, Lung Cancer, Asthma, and COPD Among Participants in the Pooled Cohort[a,b]

	Acute Coronary Heart Disease[c]	Stroke[c]	Lung Cancer[d]	Asthma[e]	COPD[f]
$PM_{2.5}$	1.02 (0.95, 1.10)	1.10 (1.01, 1.21)	1.13 (1.05, 1.23)	1.22 (1.04, 1.43)	1.17 (1.06, 1.29)
BC	1.02 (0.99, 1.06)	1.06 (1.02, 1.10)	1.02 (0.97, 1.07)	1.15 (1.08, 1.23)	1.11 (1.06, 1.15)
NO_2	1.04 (1.01, 1.07)	1.08 (1.04, 1.12)	1.02 (0.97, 1.07)	1.17 (1.10, 1.25)	1.11 (1.06, 1.16)
O_3	0.94 (0.90, 0.98)	0.96 (0.91, 1.01)	0.95 (0.89, 1.02)	0.90 (0.81, 0.99)	0.99 (0.93, 1.05)

[a] Results are expressed as hazard ratios and 95% confidence intervals. $PM_{2.5}$ per 5 μg/m^3, NO_2 per 10 μg/m^3, BC per 0.5×10^{-5}/m, O_3 per 10 μg/m^3.

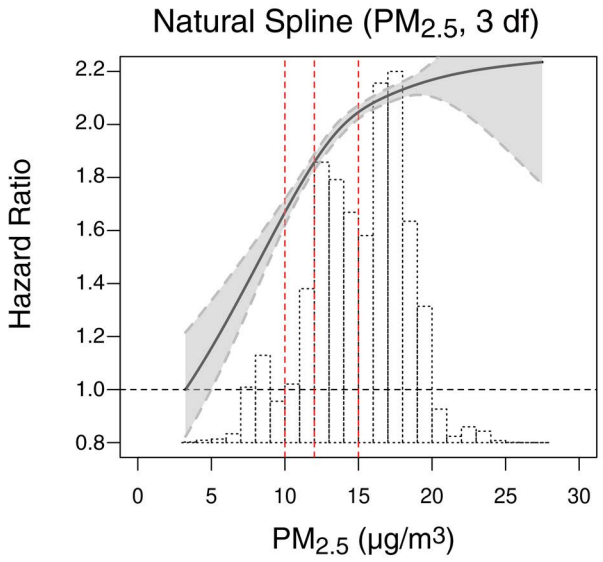
[b] Adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity squared), BMI category, marital status, employment status, and 2001 neighborhood-level mean income (acute coronary heart disease, stroke, asthma, and COPD incidence additionally adjusted for educational status). (Source: IR Table 13.)

[c] Acute coronary heart disease and stroke, n = 137,148.

[d] Lung cancer, n = 307,550.

[e] Asthma, n = 98,326.

[f] COPD, n = 98,508.



Commentary Figure 1. Associations between $PM_{2.5}$ and natural-cause mortality among participants in the pooled cohort. Concentration–response curve shown as a natural cubic spline with three degrees of freedom (df). Shaded area represents 95% confidence interval. Red dotted lines are, from right to left, the "old" U.S. EPA NAAQS, the current U.S. EPA NAAQS, and the 2005 WHO air quality guideline values. *X*-axis truncated at 30 µg/m^3. Hazard ratios are expressed relative to minimum exposure (i.e., 3.24 µg/m^3). Histograms represent exposure distributions. WHO = World Health Organization; NAAQS = U.S. National Ambient Air Quality Standards. (Source: IR Figure 4.)

sented associations between mortality and exposures to $PM_{2.5}$ estimated by models from the MAPLE study. The exposure estimates from the MAPLE model were slightly lower than those from the main ELAPSE model, but the two were highly correlated ($r = 0.7$), suggesting similar spatial patterns. Generally, the effect estimates were slightly larger in models that used the ELAPSE exposure model, but the 95% CIs overlapped with those that used the MAPLE exposure model in all cases.

ADMINISTRATIVE COHORT HEALTH ANALYSIS

In 2010, almost all participants had $PM_{2.5}$ and NO_2 annual average exposures below the EU limit values, and more than 3.9 million and 1.9 million, respectively, experienced residential $PM_{2.5}$ exposures below the U.S. EPA NAAQS and the WHO guideline. Mean concentrations of $PM_{2.5}$ ranged from ~12–19 µg/m^3 across all but the Norwegian cohort (8.26 µg/m^3) (IR Appendix 3, Table A1).

The investigators reported significant positive associations between $PM_{2.5}$, BC, and NO_2 and natural-cause, cardiovascular, respiratory, and lung cancer mortality with moderate to high heterogeneity between cohorts (Commentary Table 3; note results for lung cancer not presented here). Here they found weaker evidence of associations with diabetes and cerebrovascular mortality than were reported with the pooled cohort. Similar to the analyses with the pooled cohort, they reported inverse associations between O_3 and all causes of death examined. Also similar to the results with the pooled cohort, effect estimates for mortality were somewhat larger than those reported with the full datasets when analyses were limited to participants in the lowest concentration ranges for each of $PM_{2.5}$, BC, and NO_2.

HRs for natural-cause mortality, however, remained significantly associated with BC and NO_2 in two-pollutant models adjusted additionally for either $PM_{2.5}$ or O_3. The HRs for $PM_{2.5}$ and for BC were attenuated to unity (i.e., HR = 1.0 indicating no difference) in two-pollutant models with NO_2. In two-pollutant models for O_3, associations were attenuated to unity and not statistically significant.

The shape of association between exposure and natural-cause mortality differed among the seven administrative cohorts, although associations were generally linear to supralinear, with effects observed at all pollution concentrations considered.

As with the pooled cohort, the investigators reported comparable associations between mortality and exposures to $PM_{2.5}$ produced through the MAPLE study among the administrative cohorts. For example, the meta-analytic HR for natural-cause mortality with ELAPSE exposures was 1.058 (95% CI: 1.022–1.095), compared with HR 1.047 (95% CI: 1.003–1.094) with MAPLE exposures (IR Table 26). The fact that the associations observed with the independently developed exposure model were similar to those observed with the ELAPSE-developed exposures corroborated the robustness of the associations.

EVALUATION BY THE HEI LOW-EXPOSURE EPIDEMIOLOGY STUDIES REVIEW PANEL

In its independent review of the study, the HEI Low-Exposure Epidemiology Studies Review Panel concluded that this was an impressive, well-designed, comprehensively analyzed, and properly interpreted study. The Panel found that having produced exposure models at 100 m × 100 m spatial resolution for all pollutants across Europe was an impressive achievement and that the harmonized exposure models were a strong improvement over the region-specific models used in earlier studies. The Panel

felt that a particular strength of the study was the investigation of so many important health endpoints. The Panel also appreciated the extensive and thorough set of sensitivity analyses examining differences in effect sizes for associations between long-term exposures to several key air pollutants and several health outcomes, exploring different levels of confounder adjustment, exploring different exposure specifications, and exploring different approaches to modeling concentration–response functions.

The findings from this Report contribute to our knowledge of effects on health associated with long-term exposures to relatively lower concentrations of ambient air pollution. As noted previously, almost all participants in both the pooled and administrative cohorts had $PM_{2.5}$ and NO_2 annual average exposures below EU limit values. The investigators reported positive associations between exposures to $PM_{2.5}$, BC, and NO_2 and natural-cause, respiratory, and cardiovascular mortality in both cohorts (Commentary Table 3). The shapes of the concentration–response functions between exposures and mortality differed somewhat between cohorts, although associations were generally linear to supralinear with no evidence of thresholds below which no effects were found. These and other aspects of the study design and approach as well as interpretations of the findings and results, are described and discussed in the following sections.

EVALUATION OF STUDY DESIGN AND APPROACH

Air Pollution Models and Exposure Estimation

The Panel found that the development of the pollution models used for exposure estimation was a major achievement of this study. Brunekreef and colleagues created the first-ever, Europewide, hybrid LUR models for each of $PM_{2.5}$, BC, NO_2, and O_3 (annual, and warm and cold seasons). The Panel concluded that the investigators' application of a single, harmonized model for each pollutant was an improvement over the approaches applied in earlier analyses, such as those conducted as part of the ESCAPE project, in which exposure models were developed for individual countries and regions in Europe. Importantly, each of the new models was developed at a fine spatial resolution of 100 m × 100 m. The Panel was very satisfied with this level of spatial detail in models for $PM_{2.5}$. $PM_{2.5}$ has generally lower spatial variability than BC, NO_2, and O_3, which are influenced more by traffic and other local sources. Models for BC, NO_2, and O_3 were considered acceptable at a 100-m resolution, but the panel felt that that resolution may not have fully captured the finer-scale spatial patterns of these pollutants.

The investigators examined the validity of the exposure models by comparing indicators of model performance (e.g., R^2 between observed and predicted values) among subsets of held-out observations at lower concentrations. In all cases of these subsets, the R^2 values were lower than those produced with the full set of observations, suggesting that generally, the exposure models were less effective at estimating concentrations in the lowest pollution areas. There were, however, challenges to evaluating the performance of the models at the lowest concentrations. For example, only 86 of the 543 pollution monitoring sites that measured $PM_{2.5}$ were located in areas with concentrations lower than 10 μg/m^3, and only 841 of 2,399 sites that measured NO_2 were in areas with concentrations lower than 20 μg/m^3. That is, there were relatively few observations to evaluate and validate model performance for areas with concentrations below these levels. As noted above, the investigators also evaluated the performance of 14 different algorithms to develop LUR models for $PM_{2.5}$ and NO_2. Here, they observed that the performance of most algorithms was similar, with little indication of better performance of more sophisticated algorithms compared with supervised linear regression.

As described above, using exposure data from 2010, at time of recruitment, nearly all participants in the various cohorts were assigned estimates of exposure to annual $PM_{2.5}$ in the range of ~12–19 μg/m^3. Importantly, only participants in cohorts from two countries, namely Sweden (in the pooled cohort) and Norway (among the administrative cohorts) had annual mean concentrations lower than 10 μg/m^3 based on the year 2010. On the one hand, these exposures are all somewhat higher than those reported in a recent U.S.-based cohort study of ~61 million older adults for whom annual average $PM_{2.5}$ concentrations for the years 2000–2012 ranged from 6.2 to 15.6 μg/m^3 (5th and 95th percentiles, respectively) (Di et al. 2017). Additionally, a recent national Canadian cohort study (Brauer et al. 2019) reported even lower annual mean exposures of 6.7 μg/m^3 among ~3 million adults for the year 2001. On the other hand, from a global perspective, these values are indeed relatively low: in 2019, over 90% of the world's population was exposed to annual average concentrations of $PM_{2.5}$ greater than 10 μg/m^3, with most exposed to concentrations greater than 20 μg/m^3 (Health Effects Institute 2020). Moreover, many African and Asian countries experience annual mean exposures to $PM_{2.5}$ greater than 45 μg/m^3. That is, "low" concentrations of pollution is a relative term, and the analyses presented in this Report should be considered within that global context.

The investigators reported, in sensitivity analyses with time-varying exposures that incorporated residential histories, associations and effect sizes comparable to those reported in the main models (based on exposure data from 2010 assigned at baseline). The Panel cautioned, however,

that there are important limitations to the approach of back-extrapolating exposure estimates as far back as 1990. Essentially, it should be acknowledged that levels of uncertainty in these estimates increase the further they go back in time. This uncertainty is related in part to the fact that relatively few monitoring stations were in operation during the earlier periods and because most of the model input variables that were fixed in 2010 would likely change in nonlinear, nonspatially uniform ways over that 20-year period (e.g., construction of new roads, changes in urban form and housing density). Additionally, the investigators documented that concentrations of both $PM_{2.5}$ and NO_2 have been decreasing over time, but it is not clear the extent to which these decreases have been linear, nor if they have been consistent across regions. Moreover, reductions in pollutant concentrations over time could impact the magnitude of associations reported if the variation in concentrations also shrank (i.e., if the range between high and low exposures shrank), even if correlations between periods were strong. All these details have implications for analyses based on back-extrapolated exposure estimates here and elsewhere.

Evaluation of Epidemiological Analysis

A key epidemiological contribution of this study is the fact that the investigators reported on associations between exposures and many important health endpoints. Specifically, the investigators considered associations with mortality from all-natural causes, from cardiometabolic diseases (i.e., all cardiovascular diseases and diabetes combined), all cardiovascular diseases, ischemic heart disease, cerebrovascular disease, diabetes, respiratory disease, and from COPD (excluding asthma). Additionally, they examined incidence of lung cancer, acute coronary heart disease, and cerebrovascular, COPD, and asthma events. It is a major achievement for the investigators to have analyzed associations of so many different health endpoints with four different pollutants, being very vigilant about checking for the robustness of their findings to different modeling choices.

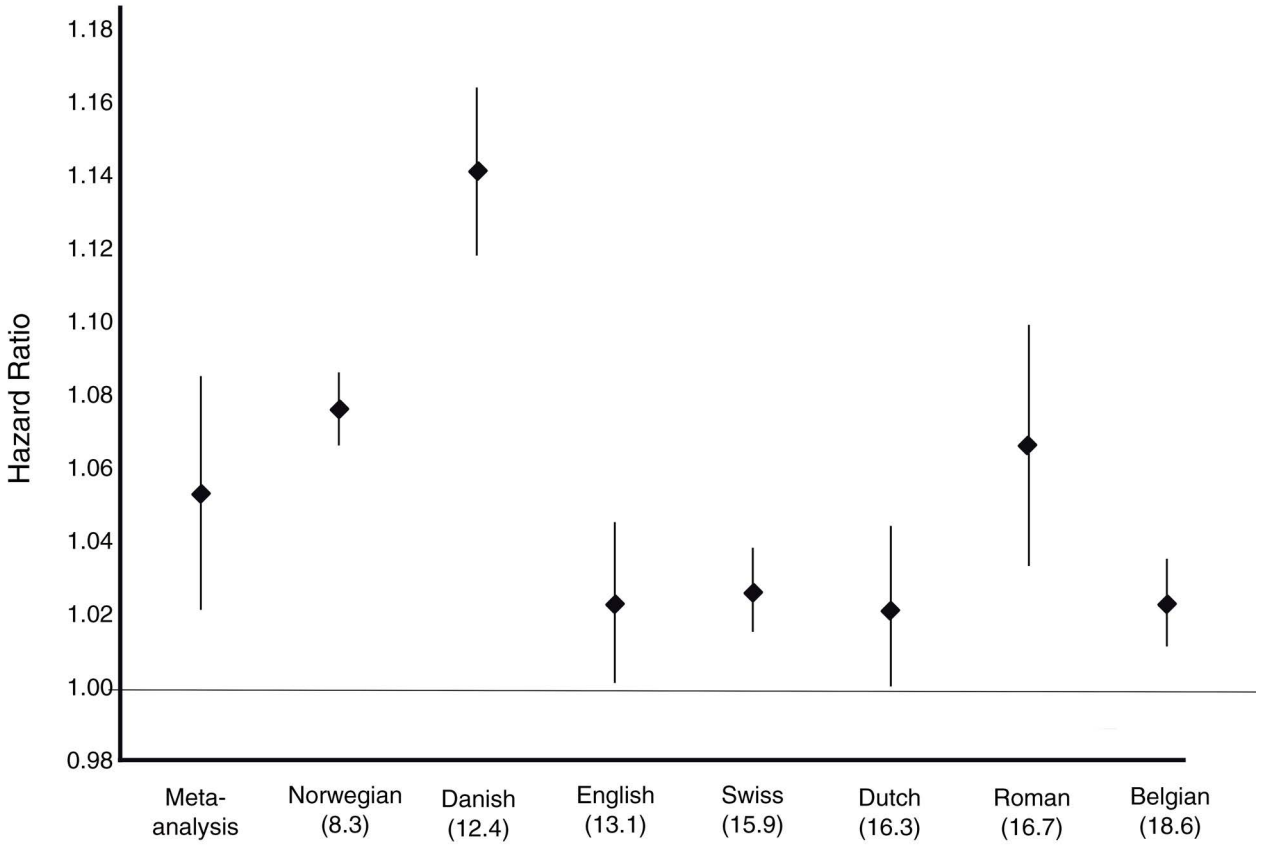
In addition to natural-cause mortality summary effect estimates for the full pooled and administrative cohorts, Brunekreef and colleagues presented results for seven of the administrative cohorts individually. Providing these regional results was a valuable contribution that allowed for some regional comparisons between exposure patterns and risk estimates. For example, they showed that annual mean concentrations of $PM_{2.5}$ ranged from ~17–19 $\mu g/m^3$ in the Roman and Belgian cohorts, to ~12–13 $\mu g/m^3$ in the Danish and English cohorts, to ~8 $\mu g/m^3$ in the Norwegian cohort. Moreover, they presented the heterogeneity in effect estimates for associations between mortality and exposures among the administrative cohorts, namely relatively high effect estimates (across pollutants and causes of death) for the Danish cohort, and generally lower effect estimates among the English, Swiss, Dutch, and Belgian cohorts (e.g., Commentary Figure 2). Note also in that figure, that for Norway, with mean exposures of only 8.3 $\mu g/m^3$, they reported an HR of 1.076; 95% CI: 1.066–1.086. In sum, a key strength of the report is the presentation of evidence of both overall, summary estimates of associations between exposures and health outcomes as well as local and regional results.

Overall, the Panel was impressed with the numerous sensitivity analyses conducted and generally found them helpful in supporting the robustness and interpretation of the findings. Broadly, these sensitivity analyses related to different approaches to exposure specification (e.g., estimating exposures only at baseline versus using time-varying estimates), confounder control (e.g., adjusting for additional confounders and noise), and exploration of concentration–response functions.

The additional adjustments for road traffic noise in some models were deemed by the Panel to provide an especially worthwhile and interesting contribution to the Report. In most cases, the air pollution associations were robust to noise adjustment. In the Swiss cohort, however, effect estimates for cardiovascular mortality were attenuated substantially by this adjustment. Here, the investigators suggested that differences in measurement error, populations, and correlations with the pollutants may have contributed to differences in the effect of noise on these associations across cohorts.

An additional analysis that the Panel appreciated was the comparison of associations between cause-specific mortality and $PM_{2.5}$ using the independent exposure model created by the MAPLE team. The fact that the exposure patterns and epidemiological results produced with the MAPLE exposure model were similar to those reported with the main ELAPSE model (except for some countries, notably Norway where the MAPLE HR is fully null) generally reinforced the robustness of the study's main findings.

Although results from the subset analyses restricted to participants with mean exposures below selected concentrations provide additional (and generally interesting) support for evidence of associations between exposure and health at low concentrations, it is important to acknowledge that these analyses are based on notably reduced and less-balanced mixes of cohorts. For the pooled cohort, all cohorts contributed to the $PM_{2.5}$ analysis for exposures below 15 $\mu g/m^3$, but the Dutch and German cohorts con-



Commentary Figure 2. Associations between $PM_{2.5}$ and natural-cause mortality: hazard ratios and meta-analysis of seven administrative cohorts, fully adjusted Model 3. HRs per 5 μg/m^3. Numbers next to cohort names indicate mean concentrations of $PM_{2.5}$ in μg/m^3 assigned to participants. (Source: IR Figure 14 and Appendix 3, Table A1.)

tributed little. Moreover, only the Swedish, Danish, French, and Austrian cohorts contributed to the analyses below 10 and 12 μg/m^3, and the former analysis was composed primarily of participants in the Swedish cohort. The sample sizes for these latter two analyses were also limited to only 52,528 and 25,422 participants (down from the 325,367 included in the full, pooled cohort; cf. Commentary Table 4). For the administrative cohorts, all cohorts contributed to the $PM_{2.5}$ analysis below 15 μg/m^3. Several cohorts were excluded from analyses below 12 μg/m^3, and the analysis below 10 μg/m^3 was dominated by the Norwegian cohort. Sample sizes for analyses with the administrative cohorts for $PM_{2.5}$ below 10 and 12 μg/m^3 were limited to only ~2 and ~4 million participants, respectively (down from just over 28 million across all administrative cohorts). The limited representation of participants from many cohorts (countries) in the subset analyses therefore may limit the generalizability of findings from these particular analyses.

An important design issue to acknowledge is that the survival models were stratified by cohort in the pooled cohort analysis. These analyses were stratified by cohort (along with by sex and age) to account for differences in baseline hazards between the cohorts (e.g., the baseline risk of dying from all-natural causes may differ between countries). Although the Panel concurred that this was the appropriate approach given the differences in populations, it is important to highlight the implications for how exposure contrasts are therefore treated in the analyses. Ultimately, this approach entails that exposure contrasts are captured only between participants within each individual cohort but not across them. As such, the risk associated with exposure for a participant with low exposure in one country is not really compared with that of someone with low exposure in another country.

DISCUSSION OF THE FINDINGS AND INTERPRETATION

Overall, the Panel found that the investigators have carefully reported and discussed the results of multiple analyses in detail, from separate cohorts (administrative or otherwise), together with a comprehensive set of sensitivity analyses. The presentation of this volume of information within a clear and structured narrative presents challenges, namely balancing the focus on overall patterns and trends versus on regional variations and heterogeneity in associations between places or cohorts. In this context, the Panel commends the investigators for preparing a comprehensive report and for the careful, fair, and balanced interpretation of the extensive array of results.

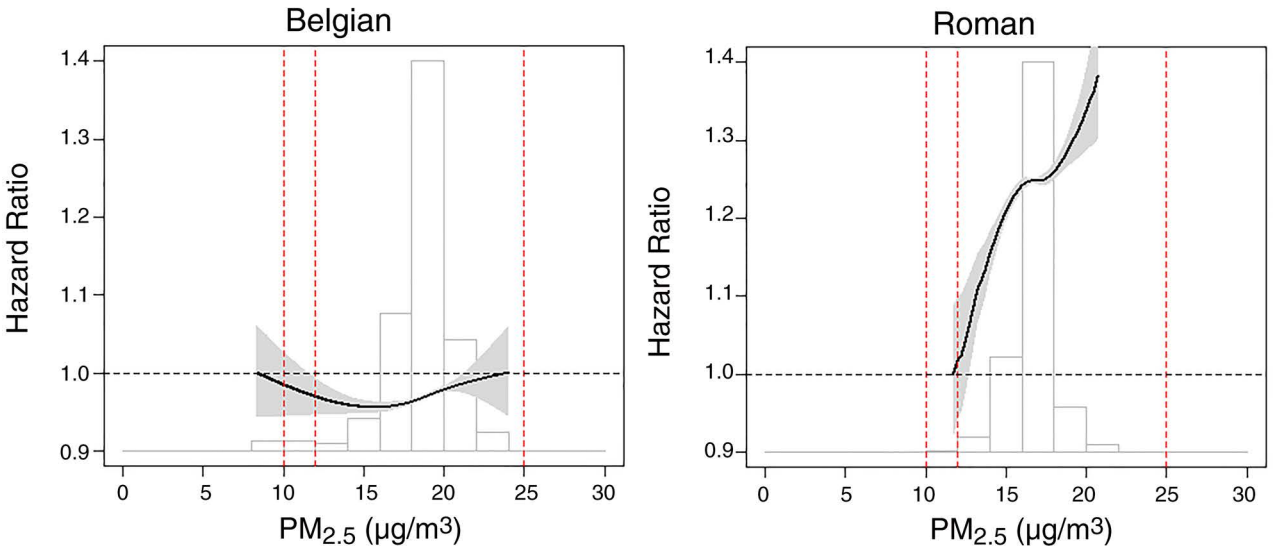
To some extent, the lack of detail provided on the cohorts, including data on recruitment, is a limitation of the Report (although those details have been reported in earlier journal articles). For example, the eligibility criteria for inclusion/exclusion in the various cohorts was not always clear, nor were patterns of participation, nor of attrition or loss of follow-up. It was also unclear whether the given cohorts were population-based (i.e., drawn from all possible people in a given age range and location) nor if they were nationally representative (or if participants tended to be of higher or lower socioeconomic position, for instance). These missing details do not necessarily impact the internal validity of the individual cohorts, unless they obscure the possibility of selection biases, but they may have implications for combining or pooling them and may affect the generalizability of the findings.

Generally, the Panel appreciated that the Report explored several approaches to modeling concentration–response functions and that these models were assessed carefully. They did feel however, that the Report was lacking in interpretation and explanation of the heterogeneity in the shapes reported between the administrative cohorts (beyond acknowledging that the cohorts differed in mean exposures) (e.g., Commentary Figure 3). As a result, readers are left wondering to what extent the heterogeneity in shapes is due to differences in population characteristics, pollutant mixtures, variability in exposure misclassification, or some other unknown factors.

The Panel noted that systematic differences in the exposure distributions for different cohorts/countries in the pooled analyses, however, means that the concentration–response function value at a given exposure is driven primarily by the cohort contributing observations at that exposure level. Most strikingly, as noted above, the results for the lowest $PM_{2.5}$ exposures are informed almost exclusively by the Norwegian and Swedish (i.e., Stockholm) cohorts.

Although the Panel thought the careful attention to the potential shape of the concentration–response function and the use of splines was a strength of the work, they found the SCHIF approach to be difficult to interpret. Although the desire to use a function that is constrained to take a plausible functional form is understandable and the Panel appreciated that the investigators sought to harmonize their results with those from the MAPLE team, the Panel felt that the use of the minimum exposure as the reference exposure made the SCHIF uncertainty estimates difficult, if not impossible, to interpret from a practical perspective. In particular, while one can use the fitted curves to estimate the risk under one exposure relative to another exposure (by reading off two hazard ratios and dividing), one can only assess uncertainty for an exposure compared to the reference exposure, which may not be of much practical use when using the minimum as the reference. That is, the choice of the reference causes the seemingly counterintuitive result that uncertainty is lowest at the place on the curve where exposure data are most sparse (i.e., at the lowest concentrations), when this is simply the result of the chosen reference value.

An unexpected finding in this Report is the near consistent inverse associations between warm season O_3 and the risk of the various health outcomes (e.g., Commentary Tables 3 and 5). The investigators reported that O_3 was highly (negatively) correlated with $PM_{2.5}$ and NO_2, and that concentrations did not decrease substantially over time. Moreover, O_3 remained inversely associated with the various health outcomes in multipollutant models, although these were generally attenuated. They also note that the associations with O_3 were observed over a relatively narrow range of exposure (i.e., 98% of the pooled cohort had exposures between 60 and 100 $\mu g/m^3$ and 68% were in the range 80–100 $\mu g/m^3$). They concluded that their study was therefore less suited to assessing associations with O_3 than those based in other locations (e.g., Canada or the United States) where greater variability in exposures have been reported. Findings from subsequent analyses carried out by the ELAPSE investigators (not included in the Report, but as reported in a recent publication [Strak et al., in press]) show that the inverse association with O_3 in the pooled cohort was attenuated when the large Austrian cohort (VHM&PP) that experienced the highest O_3 concentrations was not included, but only when coupled with adjustment for any of the copollutants. With additional adjustment for noise, the inverse association was attenuated to unity. Although interesting, interpretation of the impact of this restriction of the study sample population and additional covariate adjustments on the associations with O_3 is complicated and requires further investigation and deliberation.



Commentary Figure 3. Associations between natural-cause mortality and $PM_{2.5}$ in the Belgian and Roman administrative cohorts. Concentration–response curves are shown as natural cubic splines with three degrees of freedom (df). Hazard ratios expressed relative to minimum exposure. Shaded area represents 95% confidence interval. Red dotted lines are, from right to left, the "old" U.S. EPA NAAQS, the current U.S. EPA NAAQS, and the 2005 WHO air quality guideline values. *X*-axis truncated at 30 µg/m^3. Hazard ratios are expressed relative to minimum exposure (i.e., 3.24 µg/m^3). Histograms represent exposure distributions. (Source: IR Figure 15.)

As noted above, the investigators reported null associations between natural-cause mortality and both $PM_{2.5}$ and BC in their two-pollutant models adjusted for NO_2 among participants in the administrative cohort. In the case of the pooled cohort, however, the effect estimates for $PM_{2.5}$ and BC, while attenuated, remained positive and significant in such models. Ultimately, the impact of NO_2 adjustment on these estimates is open to interpretation, with no clear answer.

Together, the results of this single Report provide a veritable body of evidence for associations between exposures and health based on different populations and age ranges, and from countries with different cultures, geographies, and health care systems. Despite analytic challenges and limitations associated with combining and pooling various datasets and effect estimates, more can be learned from a multicohort study such as this than one based on only a single, large national cohort.

CONCLUSIONS

Based on its thorough review, the Panel concluded that this Report provided very good evidence of associations between long-term exposures to relatively low concentrations of ambient air pollution and several important health endpoints, at concentrations below the current levels of the current EU limit values. They note, however, that there remains limited evidence for associations at the lowest concentrations, with only data from Norway and Stockholm providing the bulk of the evidence in those settings.

As described above, a key highlight of this study, which is not present in most others, is the presentation of results from several different countries (pooled and individually) and the reporting of the cross-country heterogeneity in associations. The large number of cohorts included is, however, both a boon and challenge for readers seeking to synthesize the key messages of the study, to weigh and interpret the heterogeneity in results between places, and to identify overarching conclusions. In sum, this Report provided a comprehensive overview, discussion, and interpretation of the many analyses conducted. The Report includes a wealth of findings that will be of great interest and value to a wide readership of researchers and decision makers.

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ABBREVIATIONS AND OTHER TERMS

AIC	Akaike information criterion
AOD	aerosol optical density
BC	black carbon
BIC	Bayesian information criterion
BMI	body mass index
CI	confidence interval
CRF	concentration–response function
COPD	chronic obstructive pulmonary disease
DAG	directed acyclic graph
DEHM	Danish Eulerian Hemispheric Model
ESCAPE	European Study of Cohorts for Air Pollution Effects
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
EU	European Union
GEOS-Chem	global three-dimensional chemical transport model
GIS	geographic information system
HR	hazard ratio
ICD	International Classification of Diseases
LUR	land use regression
MAPLE	Mortality–Air Pollution Associations in Low-Exposure Environments study
NAAQS	National Ambient Air Quality standards (U.S.)
NO_2	nitrogen dioxide
NUTS-1	Nomenclature of Territorial Units for Statistics
O_3	ozone
P	percentile
PM_{10}	particulate matter ≤10 μm in aerodynamic diameter
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
R^2	coefficient of determination
RMSE	root mean squared error
SAT	satellite-derived
SCHIF	Shape-Constrained Health Impact Function
SES	socioeconomic status
Swiss TPH	Swiss Tropical and Public Health Institute
U.S. EPA	U.S. Environmental Protection Agency
WHO	World Health Organization

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