Development and Application of Europe-Wide Outdoor Air Pollution Exposure Models for Epidemiological Studies of Mortality Effects

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Doctoral thesis, Utrecht University

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**Ontwikkeling en toepassing van modellen voor het schatten van de
blootstelling aan verontreiniging van de buitenlucht, ten behoeve
van epidemiologisch onderzoek naar effecten op sterfte**
(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1

General Introduction

Air Pollution and Health Effects

Exposure to air pollution has been associated with a variety of adverse health effects, ranging from subtle biochemical and physiological changes to severe illness and death¹. The Global Burden of Disease Study (GBD 2015) identified air pollution as a leading contributor to the global disease burden². Mortality is one of the most often considered outcomes in epidemiological studies and risk and health impact analyses, because it is the most serious outcome and population mortality information is usually available from routinely collected data. Epidemiological studies from different regions have reported acute and chronic effects of air pollution exposure on mortality particularly from cardiovascular diseases and respiratory diseases³⁻⁵. Acute effects of air pollution are usually investigated by time-series and case-crossover study designs linking short-term air pollution exposure to health outcomes⁶⁻⁸, while chronic effects are often investigated by cohort and case-control study designs investigating long-term air pollution exposure risks⁹⁻¹¹. The epidemiological findings are supported by observations from controlled human exposure studies, animal toxicology and mechanistic *in vitro* studies, which suggest that systemic inflammation and oxidative stress are the possible underlying mechanisms of the associations between air pollution and morbidity and mortality¹²⁻¹⁵. This evidence has led to the adoption of ambient air quality standards to safeguard the public from the most common toxic air pollutants. In 2005, the World Health Organization (WHO) published air quality guidelines for worldwide use¹⁶. Local and national air quality standards were developed by organizations such as the European Union (EU)¹⁷ and the US Environmental Protection Agency (EPA)¹⁸ according to specific approaches to balancing risks to health, technological feasibility, economic considerations and other political and social factors. Over the last decades, levels of air pollution have declined significantly in North America and Europe with the introduction of cleaner fuels and the implementation of pollution control technologies¹⁹. Questions about associations at these lower pollution levels have been raised²⁰. With the development of more accurate exposure assessment methods and the application of more sensitive statistical techniques, recent studies have suggested that the adverse health effects associated with air pollution persist at levels below the current air quality guidelines and standards^{5,21-23}. This has raised questions about the appropriateness of the existing standards and guideline values. In 2016, WHO has started the update of Global Air Quality Guidelines for ambient air²⁴.

Air pollution is a complex mixture of gases and particles from natural and anthropogenic sources. The current thesis focuses on ozone (O₃), nitrogen dioxide (NO₂), particulate matter (PM) and black carbon (BC). O₃ and most NO₂ are secondary pollutants formed through a series of complex atmospheric chemical reactions. The principle sources of anthropogenic emissions of NO₂ are the combustion processes in stationary sources (e.g., heating and electricity generation) and in mobile sources (e.g., motor vehicles). Most of NO₂ is first emitted as nitric oxide (NO) and then converted to NO₂ via reaction with atmospheric oxidants such as O₃, where O₃ is transformed into O₂. As a result, the O₃ concentrations are often low in busy urban centers, where strong emission sources of nitrogen oxides are present, and higher in suburban and adjacent rural areas¹. The photostationary cycle is described in reactions (1) to (3) below. When high sunlight intensity and chemically reactive hydrocarbons are present, the photochemical equilibrium is disturbed. NO converted to NO₂ without consuming O₃, as presented in reaction (4), and thus high concentrations of O₃ are produced.

PM is a complex mixture of components with diverse chemical and physical characteristics. PM has been classified by aerodynamic diameter for current regulatory purpose¹⁶: PM with an aerodynamic diameter $\leq 10 \mu\text{m}$ (PM₁₀) includes inhalable particles that are sufficiently small to penetrate to the thoracic region; PM with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ (PM_{2.5}) is able to penetrate into and deposit

in the smaller conducting airways and alveoli. The difference between PM_{10} and $PM_{2.5}$ is often referred to as coarse particles ($PM_{10-2.5}$). The coarse particles are composed largely of crustal materials, sea salt, resuspended dust from roads and industrial activities, and biological material. The fine particles are largely formed in the atmosphere from gases. The main precursor gases are sulfur dioxide (SO_2), NO_2 , ammonia and volatile organic compounds. For example, SO_2 is oxidized to sulfuric acid, NO_2 is oxidized to nitric acid, which in turn reacts with ammonia to form ammonium nitrate. The particles that are converted from gases in atmospheric reactions are called secondary particles. The fine fraction also includes primary particles generated from combustion processes, such as metals or organic compounds. Therefore, the fine fraction is typically composed of nitrate, sulfate, ammonium, organic compounds, trace metals and BC. BC is the sooty black material emitted from burning fossil fuels and biomass, for example in diesel engines, coal-fired power plants and wood burning. BC in this thesis was measured as $PM_{2.5}$ absorbance based on the blackness of $PM_{2.5}$ filters²⁵. $PM_{2.5}$ absorbance is a proxy for elemental carbon (EC), which is predominantly in the fine particle fraction²⁶. $PM_{2.5}$ is considered to be particularly important among the pollutants because it can penetrate deeply in the lungs, it has long atmospheric lifetime and travels across large geographical areas, and it can easily infiltrate into homes, where people spend a large amount of their time.

$PM_{2.5}$ has been associated with increases in mortality and morbidity more than any other regulated environmental pollutant^{2,15}. Epidemiological studies around the world have generally reported associations between $PM_{2.5}$ mass and mortality and morbidity, with substantial differences in the magnitude of effect estimates^{7,9,22,27-29}. Part of these differences may be related to the fact that the composition of $PM_{2.5}$ varies in time and space depending on sources of emission and atmospheric chemistry, which may in turn result in differences in toxicity and risk to health of $PM_{2.5}$ mass³⁰⁻³³. This implies current regulations that focus on mass concentrations may not be using the most efficient metrics. Understanding which components of the PM mixture are of greater health concerns than others would help inform targeted policies to control for those sources that contribute most of the toxic components in the PM mixture. So far, studies have associated adverse health effects with a series of $PM_{2.5}$ components including secondary inorganic aerosols (sulfate, nitrate), EC, metals and organic components³⁴⁻³⁹. Studies also used source apportionment techniques to identify the responsible sources of specific components such as coal combustion and traffic⁴⁰⁻⁴². However, the findings are inconsistent. The National Particle Component Toxicity (NPACT) studies funded by the Health Effect Institute (HEI) have performed a systematic evaluation on the relative toxicity of $PM_{2.5}$ components and source categories by combining epidemiologic and toxicologic analyses^{43,44}. The findings identified secondary sulfate and traffic sources were most consistently associated with health effects. However, other components and source categories could not be definitively excluded as having no adverse effects. Challenges in the analysis of component effects remain in the measurement errors of exposure assessment and the ability to disentangle effects of individual component or multiple components from the same source. Exposure assessment of PM component are more challenging than PM mass because of the scarcity of measurements and the high spatial heterogeneity for especially combustion-related components⁴⁵. The ability to detect health effects of individual components or pollution sources is limited because components originate from the same source are usually highly correlated in concentrations and a specific component can be generated from several different sources^{41,42,45}.

Long-term air pollution exposure assessment

Evaluating the mortality risk of long-term exposure to air pollution is usually addressed by cohort studies⁴. Assessing individual long-term exposure to air pollution remains challenging in these studies. Early cohort studies compared mortality outcomes between cities using group level average exposures. Specifically, individual exposure of all subjects living in a city was characterized as the average concentration of air pollution measured at one or a few monitoring sites within this city^{9,10,28}. However, numerous studies have documented that outdoor air pollution concentrations of especially NO_2 and BC

varied substantially at a small geographical scale^{25,46-48}. Within-city spatial contrasts may be larger than between-city spatial contrasts^{25,48}. The Women's Health Initiative study suggested larger cardiovascular mortality risks of PM_{2.5} related to within-city contrasts compared to between-city contrasts⁴⁹.

Fixed-site monitoring networks are expensive and therefore not spatially dense enough to characterize within-city contrasts. Several exposure assessment approaches beyond direct assignment of monitoring data have been developed to better characterize intra-urban variations over the recent decades. These approaches include exposure indicator variables (e.g., traffic intensity in proximity to residence⁵⁰ and distance to major roads⁵¹), interpolation techniques^{52,53} (e.g., kriging and inverse distance weighing), dispersion/chemical transport modeling^{54,55}, satellite monitoring^{29,56,57} and land use regression (LUR) modeling^{22,58}. One of the limitations of the exposure indicator variables is that they do not provide a quantitative pollution estimate. Although the interpolation techniques provide a spatially more resolved pattern than a simple average, the assumed smooth spatial variation of concentration may be too simple considering the complexity of local sources, street configurations and meteorological conditions. Dispersion/chemical transport models (DCTMs) are deterministic models based on physical principles and actual emission data, thus the models are subject to relatively low spatial resolution of meteorological data and require detailed input data including emission⁵⁹. Satellite modeling combines remote sensing and chemical transport modeling for estimating vertical gradients^{60,61}. Satellite observations are globally available but often coarse in spatial resolution, thus cannot represent fine-scale within-city variations. LUR is an empirical approach that models measured air pollution concentrations at (a limited number of) monitoring sites by (land use) variables collected via geographic information systems (GIS)^{62,63}. LUR models are developed based upon locally measured air pollution data and may be difficult to transfer from one study area to another. LUR modeling has been widely used in air pollution exposure assessment in epidemiological studies because of the ability to capture small-scale variation in concentrations, the lower demand on input data compared to DCTMs and the typically good performance.

One recent development in air pollution epidemiology is the use of very large populations with sufficient statistical power to quantify effects of air pollution at low concentrations, where the air pollution contrasts are small. For this, national administrative cohorts or pooled data from multiple cohorts are often used^{22,64-67}. Air pollution exposure estimates covering large geographical areas, such as a continent, at sufficiently fine spatial resolution are thus needed. LUR models have been extensively used to assess air pollution exposure at small spatial scales^{63,68,69}. For application in large geographical areas, modeling the background concentrations is challenging for LUR models because they cannot explicitly model secondary formation of pollutants⁷⁰. Recently so-called hybrid models have been developed incorporating satellite-derived data (SAT) and/or DCTM estimates as predictors with LUR to achieve a better prediction accuracy at large spatial scales⁷¹⁻⁷⁴. Both SAT and DCTM are able to model the dispersion and chemical transformations and are relatively coarse in spatial resolution, thus represent area-averaged background concentrations. For LUR models based upon surface monitoring data, developing large-scale models with increasing number of monitoring sites helps to improve the robustness of models and the accuracy of subsequent health effect estimation⁷⁵⁻⁷⁷.

Another development in air pollution epidemiology is the necessity to evaluate health effects of particle metrics beyond the regulated PM_{2.5} and PM₁₀, to identify the hazardous components within the complex PM mixture^{40,43}. Exposure assessment for PM composition is more challenging than for routinely measured pollutants because of the limited monitoring data and the scarcity of input information such as emission factors. Studies conducted in the US based on routine monitoring measurements of PM composition mainly exploited between-city contrasts while within-city contrasts were not well captured because of the limited number of monitors within a city^{35,78,79}. In the European Study of Cohorts for Air Pollution Effects (ESCAPE) based on purpose-designed monitoring campaigns, area-specific models were developed with 20 sites per area. In ESCAPE, model performance was good for traffic-related elements such as copper (Cu) and iron (Fe), but moderate to low for nickel (Ni), vanadium (V) and

potassium (K) because of the limited spatial variation within areas and the lack of key predictor variables representing specific sources⁸⁰. In addition, exposure models for PM composition might not be specific thus limiting the ability to disentangle the independent effects of PM composition and PM mass in the subsequent epidemiological studies^{80,81}. In recent years, dedicated short-term sampling and on-road mobile monitoring campaigns have been conducted to measure particle metrics such as UFP or BC, which are characterized by high temporal and spatial variabilities⁸²⁻⁸⁵. Developments in satellite data and DCTMs make it possible to model the background concentrations of specific PM composition and to separate the components to some extent⁸⁶.

LUR models are conventionally developed with linear regression algorithms^{87,88}, with some possible modifications on the modeling process (e.g., predefined direction of predictor effect)^{68,89,90}. Recent studies have attempted to use different modeling algorithms to address limitations of the linear regression algorithm and to achieve a better prediction accuracy. These approaches include the regularization algorithms^{91,92}, which address collinearity between predictor variables, and machine-learning algorithms^{72,93,94}, which can model potential non-linearity and interactions within the data more flexible than linear regression. The more flexible algorithms such as machine-learning algorithms may be helpful in modeling PM composition exposure where complex relationships between pollutant concentrations and predictor variables might be present. One study suggested random forest, a machine-learning method, provided more accurate exposure assessment compared to linear regression in predicting PM_{2.5} elemental composition concentrations⁹⁵. At the time the investigations described in the current thesis were conducted, few comparisons had been made regarding the prediction accuracy and interpretability of exposure models developed with different algorithms^{92,96,97}. No studies had assessed whether application of these different models in air pollution epidemiology would lead to different health effect estimates.

The ELAPSE project

The Effects of Low-level Air Pollution: A Study in Europe (ELAPSE) is a Europe-wide collaboration that focuses on analyses of health effects of air pollutants at low concentrations, defined as less than current EU limit values, US EPA National Ambient Air Quality Standards (NAAQS) and/or WHO Air Quality Guideline values⁹⁸. The ELAPSE study consists of a pooled cohort of more than 300,000 adults with detailed information on individual-level confounders and seven very large administrative cohorts of more than 28 million adults in total. In the pooled cohort, the data from existing cohorts in Sweden, Denmark, Germany, the Netherlands, Austria, France and Italy were pooled and analyzed centrally. Data from the administrative cohorts in Belgium, Denmark, England, the Netherlands, Norway and Switzerland and Rome, Italy were analyzed locally due to privacy regulations.

The analysis not only focuses on the routinely monitored pollutants PM_{2.5}, NO₂ and O₃, but also exploits the dedicated monitoring data of BC and PM_{2.5} elemental composition available from the ESCAPE monitoring campaign. ELAPSE exposure assessment characterizes fine-scale intra-urban as well as between-urban air pollution contrasts using hybrid Europe-wide models combining land use regression, dispersion models and satellite observations. The Europe-wide models further allow the analyses to be conducted in the full national study areas within ELAPSE because of the geographical coverage.

ELAPSE was designed to analyze a wide variety of outcomes including 1) natural cause and cause-specific mortality, 2) cancer incidence, 3) incidence of coronary and cerebrovascular events and 4) incidence of asthma and COPD.

Thesis aims and outline

This thesis has the following specific aims:

1. To systematically evaluate the evidence of associations of long-term exposure to PM₁₀ and PM_{2.5} with all-cause and cause-specific mortality with a focus on associations at low pollution levels
2. To develop Europe-wide LUR models for PM_{2.5}, NO₂, O₃, BC and PM_{2.5} elemental composition
3. To compare LUR models developed with different algorithms in terms of prediction accuracy and interpretability
4. To investigate associations between long-term exposure to PM_{2.5} components and mortality, and to compare the health effects estimated using exposure models developed with different algorithms

In **Chapter 2**, we performed a systematic review on associations of long-term exposure to PM₁₀ and PM_{2.5} with all-cause and cause-specific mortality with a focus on associations at low pollution levels to support the derivation of new air quality guidelines by the WHO. The remainder of the thesis was developed within the framework of the ELAPSE project to provide new empirical evidence at low pollution levels. In **Chapter 3**, we developed Europe-wide LUR models for PM_{2.5}, NO₂, BC and O₃ using supervised linear regression algorithm, and evaluated the spatiotemporal stability of the models. In **Chapter 4**, we compared the Europe-wide PM_{2.5} and NO₂ models developed with 16 different algorithms (linear regression, regularization and machine-learning algorithms), using the same measured air pollution data and potential predictor variables used in Chapter 3. We performed both cross-validation and external validation to strengthen the comparisons. In **Chapter 5**, we developed Europe-wide LUR models for PM_{2.5} elemental composition using supervised linear regression and random forest, a machine-learning algorithm. In **Chapter 6**, we assessed associations between PM_{2.5} elemental composition and mortality in the ELAPSE pooled cohort, using models developed in Chapter 5. We also compared the health effect estimates assessed using exposure models developed with supervised linear regression and random forest algorithms. In **Chapter 7**, the main findings of this thesis are summarized, followed by discussions on methodological issues in systematic reviews, spatial scale and statistical algorithms in developing exposure models, existing evidence on health effects of long-term PM component exposure, and the implications of this research.

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Chapter 2

Long-Term Exposure to PM and All-Cause and Cause-Specific Mortality: A Systematic Review and Meta-Analysis

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Abstract

As new scientific evidence on health effects of air pollution is generated, air quality guidelines need to be periodically updated. The objective of this review is to support the derivation of updated guidelines by the World Health Organization (WHO) by performing a systematic review of evidence of associations between long-term exposure to particulate matter with diameter under 2.5 μm ($\text{PM}_{2.5}$) and particulate matter with diameter under 10 μm (PM_{10}), in relation to all-cause and cause-specific mortality. As there is especially uncertainty about the relationship at the low and high end of the exposure range, the review needed to provide an indication of the shape of the concentration-response function (CRF).

We systematically searched MEDLINE and EMBASE from database inception to 9 October 2018. Articles were checked for eligibility by two reviewers. We included cohort and case-control studies on outdoor air pollution in human populations using individual level data. In addition to natural-cause mortality, we evaluated mortality from circulatory diseases (ischemic heart disease (IHD) and cerebrovascular disease (stroke) also specifically), respiratory diseases (Chronic Obstructive Pulmonary Disease (COPD) and acute lower respiratory infection (ALRI) also specifically) and lung cancer. A random-effect meta-analysis was performed when at least three studies were available for a specific exposure-outcome pair. Risk of bias was assessed for all included articles using a specifically developed tool coordinated by WHO. Additional analyses were performed to assess consistency across geographic region, explain heterogeneity and explore the shape of the CRF. An adapted GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment of the body of evidence was made using a specifically developed tool coordinated by WHO.

A large number ($N=107$) of predominantly cohort studies ($N=104$) were included after screening more than 3000 abstracts. Studies were conducted globally with the majority of studies from North America ($N=62$) and Europe ($N=25$). More studies used $\text{PM}_{2.5}$ ($N=71$) as the exposure metric than PM_{10} ($N=42$). $\text{PM}_{2.5}$ was significantly associated with all causes of death evaluated. The combined Risk Ratio (RR) for $\text{PM}_{2.5}$ and natural-cause mortality was 1.08 (95%CI 1.06, 1.09) per 10 $\mu\text{g}/\text{m}^3$. Meta analyses of studies conducted at the low mean $\text{PM}_{2.5}$ levels ($<25, 20, 15, 12, 10 \mu\text{g}/\text{m}^3$) yielded RRs that were similar or higher compared to the overall RR, consistent with the finding of generally linear or supra-linear CRFs in individual studies. Pooled RRs were almost identical for studies conducted in North America, Europe and Western Pacific region. PM_{10} was significantly associated with natural-cause and most but not all causes of death. Application of the risk of bias tool showed that few studies were at a high risk of bias in any domain. Application of the adapted GRADE tool resulted in an assessment of “high certainty of evidence” for $\text{PM}_{2.5}$ with all assessed endpoints except for respiratory mortality (moderate). The evidence was rated as less certain for PM_{10} and cause-specific mortality (“moderate” for circulatory, IHD, COPD and “low” for stroke mortality).

Compared to the previous global WHO evaluation, the evidence base has increased substantially. However, studies conducted in low- and middle- income countries (LMICs) are still limited. There is clear evidence that both $\text{PM}_{2.5}$ and PM_{10} were associated with increased mortality from all causes, cardiovascular disease, respiratory disease and lung cancer. Associations remained below the current WHO guideline exposure level of 10 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$.

Systematic review registration number (PROSPERO ID): CRD42018082577

1. Introduction

Air pollution is a major environmental hazard to human health and a leading cause of mortality and morbidity worldwide (WHO, 2006; USEPA, 2019). Particulate matter (PM), which comprises multiple components and size fractions, is an important health relevant outdoor air pollutant regulated in many countries. Most earlier routine air quality monitoring systems measured particulate matter with diameter under $10\text{ }\mu\text{m}$ (PM_{10}), whereas more recent networks have added particulate matter with diameter under $2.5\text{ }\mu\text{m}$ ($\text{PM}_{2.5}$) measurements. PM_{10} includes both fine particles ($\text{PM}_{2.5}$) and coarse ($\text{PM}_{10-2.5}$) particles. $\text{PM}_{2.5}$ originates primarily from combustion sources, while $\text{PM}_{10-2.5}$ is composed largely of crustal material, sea salt and biological material (WHO, 2006). The proportion of particles in these two size ranges varies substantially depending on local geography, meteorology and specific PM sources such as construction work, unpaved roads or nearby deserts, all contributing to large amounts of coarse particles. Health effects of fine and coarse particles may differ because of different chemical composition and different penetration into the respiratory tract. In the 2019 Integrated Science Assessment (ISA) by the US Environmental Protection Agency (EPA), the association between $\text{PM}_{2.5}$ and natural mortality was rated as “causal” while the association between $\text{PM}_{10-2.5}$ and natural-cause mortality was rated as “suggestive” (USEPA, 2019). Causal or likely causal relationship between long-term exposure to fine PM and all-cause, cardiovascular, respiratory and lung cancer mortality have also been reported by the International Agency for Research on Cancer (IARC, 2013) and Health Canada (HC, 2013). The Global Burden of Disease (GBD) study estimated that ambient $\text{PM}_{2.5}$ was the fifth-ranking mortality risk factor in 2015, with 4.2 million deaths caused by exposure to $\text{PM}_{2.5}$ (Cohen et al., 2017; WHO, 2018).

The World Health Organization (WHO) has published several volumes of Air Quality Guidelines (AQGs) to provide guidance to the public, especially to policy and other decision makers, on the health risks of air pollution. The latest version was published in 2006 with an annual average guideline exposure level of $10\text{ }\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ and $20\text{ }\mu\text{g}/\text{m}^3$ for PM_{10} (WHO, 2006). The guideline exposure levels represent the lower end of the range over which significant effects on survival were observed in the 2006 evaluation of the evidence. Guideline values are designed to advise national policy makers to what levels air pollution should be reduced to protect public health. The guideline was developed based on evaluation of a small number of cohort studies predominantly conducted in North America. Particularly, the American Cancer Society (ACS) study was important to derive the guideline. Concerns were raised regarding applying the guideline to other areas in the world where PM sources and population characteristics are different. A large number of new cohort studies has been published since 2006, including several large studies based on administrative databases (Hoek et al., 2013). A number of studies conducted in areas with PM levels below the current WHO guidelines (Cakmak et al., 2016; Dehbi et al., 2017; Gan et al., 2013; Pinault et al., 2016) suggested that health effects may occur at low pollution levels. This has increased the interest in the shape of the concentration-response function (CRF), including detection of a potential threshold in the CRF.

As new evidence is generated, the WHO air quality guidelines need to be periodically updated. The overall objective of the update of WHO Global AQGs is to develop public health recommendations for ambient air quality. To support the update of the guidelines, we performed a systematic review of evidence of associations between long-term exposure to PM and mortality. The most important goal of the systematic review was to provide quantitative information about the magnitude of risks, not to contribute to the debate about a potential causal relationship. The specific question formulated in terms of Population, Exposure, Comparator, Outcome, Study Design (PECOS) was: “In any population, including subgroups of susceptible individuals (P), what is the increase in risk of all-cause and cause-specific mortality (O) per 10 unit increase (C) in $\mu\text{g}/\text{m}^3$ of long-term exposure (in the order of months to years) to ambient concentrations of $\text{PM}_{2.5}$ and PM_{10} (E), observed in cohort and case-control studies (S)? In these studies, is an increased risk observed at low levels, specifically below the current WHO guideline?” In particular, we used meta-analysis to quantitatively pool risk estimates across studies, and

qualitatively summarized the concentration-response gradient evaluated in individual studies. The current review was based on a previous review which evaluated the epidemiological evidence for cardiovascular and respiratory mortality effects of long-term exposure to fine particulate matter (Hoek et al., 2013).

2. Methods

The study protocol was developed from a draft generic text provided by WHO to all systematic review teams. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO, registered ID: CRD42018082577).

2.1 Eligibility criteria and search strategy

We applied the following eligibility (inclusion and exclusion) criteria structured by PECOS items:

Population

Studies reporting general human population exposed to PM_{2.5} and PM₁₀ via inhalation through ambient air predominantly were included. Studies reporting on exposures of populations in the workplace exclusively were excluded. There were no restrictions on ages, geographical areas, occupations of population.

Exposure

Studies reporting long-term exposure (in the order of months to years) to ambient air PM_{2.5} and PM₁₀ expressed in a concentration unit ($\mu\text{g}/\text{m}^3$) were included. Studies that have translated other particle metrics such as total suspended particles (TSP) into PM₁₀ or PM_{2.5} using local and time specific conversion factors were also included. Studies reporting exposure to PM_{2.5} and PM₁₀ as a result of occupational exposure (measured in the workplace) or indoor exposure exclusively were excluded.

Comparator

In air pollution epidemiology, the association between a continuous exposure and the risk of death is evaluated. The risk of death is thus compared for subjects with relatively high and relatively low concentrations in each study. The comparator in each individual study was exposure to relatively low levels of PM_{2.5} and PM₁₀ in the same population (cohort studies) or in a control population (case-control studies).

Outcome

Health outcomes were selected by the Guideline Development Group (GDG) based on evidence on causality according to the latest determination (causal or likely causal) from the US Environmental Protection Agency (EPA), the International Agency for Research on Cancer (IARC), Health Canada (HC) or other integrated science assessments available. Additional most severe health outcomes with suggestive causality were also included based on other considerations such as contribution to burden of disease (prevalence of disease, disability weight, etc), policy implications and expected increase in exposure to a pollutant in the future.

Health outcomes selected in relation to long-term exposure to PM_{2.5} and PM₁₀ included (the 10th revision of the International Classification of Diseases (ICD-10) codes, version 2016 in brackets): all-cause mortality (A00 – Z99) and cause-specific mortality including circulatory diseases (I00 – I99), ischemic heart diseases (IHD, I20 – I25), cerebrovascular diseases (stroke, I60 – I69), respiratory diseases (J00–J99), chronic obstructive pulmonary diseases (COPD, J40 – J44, J47), acute lower respiratory infection (ALRI, J12 – J18, J20 – J22) and lung cancer mortality (C30 – C39). Natural-cause mortality or non-accidental mortality (A00 – R99) is mortality from all-causes except external causes such as accidents, suicide and homicide. We considered natural-cause mortality equivalent to all-cause mortality as

natural-cause mortality accounts for the majority of all-cause mortality and there is no clear evidence that air pollution is associated with accidental mortality. Equivalent definitions using ICD-9 or other versions of ICD-10 were included.

Study

Human epidemiological studies using prospective and retrospective cohort study designs, case-control and nested case-control study designs were included. Published journal articles in any language (abstract in English language) were included. If suitable articles were identified published in languages not known by the authors, further assistance was sought after.

Studies without individual level data (i.e. ecological studies with aggregated outcome, exposure and covariates data), studies where no original data were analyzed, methodological studies, non-human studies (in vivo, in vitro, other) and conference abstracts were excluded. Relevant reviews and systematic reviews were not included in the current systematic review but used to scan for references.

Ecological studies were excluded because they are not sufficiently informative for risks at the individual level. Studies analyzing exposure in categories were included in the review, but not in the meta-analysis, because of the uncertainty of transformations. Conference abstracts were excluded as they were expected to not contain sufficient information to perform data extraction and risk of bias assessment.

Studies matching the PECOS questions were searched systematically in the database MEDLINE using PubMed and the database EMBASE through EMBASE.com between database inception and 9 October 2018. Literature search strategies using free text and MeSH terms/ Emtree terms, considering exposure, health outcomes and study design, are presented in Appendix 1.

2.2 Study selection and data collection

We (GH and JC) independently screened references by titles and abstracts for potential relevance. We further assessed the full-text of the articles resulting from abstract screening independently for compliance with eligibility criteria in section 2.1. The specific reasons for excluding articles at this stage were recorded (Appendix 2). Any disagreement on inclusion was resolved by discussion.

We conducted data extraction in duplicate. When the data extraction did not agree, we went back to the original paper. We did not document the rate of agreement. We drafted a data extraction form in Excel and piloted the form with a few example studies by the two authors independently. We adapted the form based on these comparisons. The form was then reviewed by WHO with a few adaptations before being used in the current study (Appendix 3). The following characteristics of the included articles were extracted: citation details, study name, study design, study location; characteristics of the study population; follow up period(s); details on exposure; details on outcome assessment; details of confounders adjusted for; data to calculate the effect estimates and their confidence intervals; methods and results of assessment of the shape of the exposure response function; conflicts of interest. For a specific pollutant-outcome pair, most articles reported effect estimates from more than one single-pollutant models with increasing adjustment for potential confounders. When multiple estimates were reported, we extracted estimates from 1) the crude model (only adjusted for age and sex), 2) the most adjusted model, and 3) the authors favored model (usually shown in abstract). Additionally, we extracted estimates from two pollutant models with NO₂, O₃ or coarse particles as the second pollutant.

2.3 Risk of bias (RoB) assessment

A domain-based RoB assessment tool (WHO, 2020), developed by a group of experts convened by WHO, was used to assess all articles included in the meta-analyses. RoB assessments were conducted at outcome level; therefore, if a primary study reported on two relevant outcomes RoB was evaluated twice. There were six domains in the RoB assessment tool: confounding, selection bias, exposure assessment, outcome measurement, missing data, and selective reporting. Each domain contained several subdomains. Specifically, we examined the extent to which potential confounders were adjusted

for, whether the methods for measuring and controlling for the potential confounders were valid; whether there was a selection of participants into the study that related to exposure or outcome; whether the methods used for exposure assessment were valid; whether the outcome measurement methods were valid; whether missing data were related to exposure or outcome; and whether all results were reported. In evaluating each article, we assigned a 'low', 'moderate' or 'high' RoB for each subdomain. To come to an overall assessment for a domain, the following approach was applied: if any of the subdomains had a rating of high risk of bias, the entire domain was rated as high risk of bias; if all the subdomains had a rating of low risk of bias, the entire domain was rated as low risk of bias; when at least one subdomain had a rating of moderate risk of bias and none of the other subdomains was at high risk of bias, the entire domain was rated as moderate risk of bias. No overall risk of bias was determined across domains for a single article, because we were uncomfortable with assigning equal weight to the different domains.

To judge the RoB per study, the tool contained specific guidelines, for example on what should be considered critical and potential confounders for the different outcomes (WHO2020). Critical confounders (age, sex, individual- or area-level socioeconomic status, body mass index/smoking) and additional potential confounders (year of enrolment, ethnicity, diet, physical activity, marital status) were identified prior to the evaluation. An article can only be classified as low risk of bias if all critical and additional potential confounders were adjusted for; if not all critical potential confounders were adjusted for, the article was classified as high RoB; otherwise, a moderate RoB was assigned. For other subdomains, criteria were also specified, though not always as straightforward as the list of confounders (WHO, 2020).

RoB assessment was conducted independently by one reviewer (JC) and checked for accuracy by a second reviewer (GH). A 10% selection of articles were assessed by a WHO methods expert (RM) for cross-checking. Reviewer assessments and rationales were recorded in an Excel file (Appendix 4).

2.4 Meta-analysis

In case three or more studies were identified for the same pollutant and health outcome, a meta-analysis was performed. Because of the expected differences in both populations and pollution, we *a priori* decided to pool estimates by a random-effect meta-analysis (DerSimonian-Laird estimator). We used Risk Ratios (RRs) as the effect measure of associations between health outcomes and per 10 µg/m³ increase in particulate air pollution. Hazard Ratios (HRs) were considered equivalent to RRs. If RR estimates were reported for increments other than per 10 µg/m³ (e.g. per IQR increase), we converted the estimates to RR per 10 µg/m³. We calculated slope (Beta) and standard error (SE) per 1 µg/m³, multiplied by 10 and then exponentiated.

We used the standard equations below.

$$Beta = LN(RRo) / increment$$

$$SE = (LN(RRo_high) - LN(RRo_low)) / (2 \times 1.96 \times increment)$$

$$RRc = EXP(Beta \times 10)$$

$$RRc_low = EXP(Beta \times 10 - 1.96 \times SE \times 10)$$

$$RRc_high = EXP(Beta \times 10 + 1.96 \times SE \times 10)$$

RRo is the effect estimate originally reported in the paper with its low (RRo_low) and high (RRo_high) end of the confidence interval (CI); RRc is the estimate we converted to.

In the main meta-analysis we did not include studies conducted in patient groups because the patient population is very different from the general population, and the main interest for WHO of the review is to develop a quantitative summary estimate that applies to the general population, although this was not explicitly stated. In sensitivity analysis, we tested the combined effect estimates after including patient populations.

We only included in the meta-analysis the most recent published article when estimates for the same study population were reported in several articles, unless it has a smaller population or a different focus.

In meta-analysis, we used one estimate for a specific pollutant-health outcome from a single article. If an article reported two or more estimates for subgroups of the study population separately (e.g. male and female, age groups, regions) only, we combined the estimates by a fixed-effect meta-analysis. If an article reported more than one estimates from multiple single-pollutant models with increasing adjustment for potential confounders, we included the estimate from the authors favored model (usually shown in abstract). The authors favored model was always from adjusted models, but not necessarily the most adjusted model, for example in the case of testing for sensitivity to adding in variables that could both be a confounder and on the causal pathway from air pollution towards mortality, such as hypertension for cardiovascular mortality.

Statistical heterogeneity of effect estimates between studies were assessed using tau-squared, presented in the form of an 80% prediction interval around the mean effect in a random-effects meta-analysis (Borenstein et al., 2017). In addition, the χ^2 test (Cochran's Q) with a significance level <0.1 and the I^2 value, where I^2 values of 25%, 50% and 75% are taken as of low, moderate and high degree of heterogeneity, respectively (Woodward 2013).

The R program package 'metafor' was used to produce forest plots and to perform meta-analysis.

2.5 Additional analyses

In an attempt to explain heterogeneity, we further performed subgroup analysis for $PM_{2.5}$ and natural-cause mortality in pre-specified subgroups: geographical location (WHO Regions (African Region, Region of Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region)); sex (men, women, men + women); age groups (average age ≤ 65 years old or > 65 years old); level of mean $PM_{2.5}$ concentrations ($<10 \mu g/m^3$, $10-25 \mu g/m^3$, $>25 \mu g/m^3$). A meta regression was conducted by including all subgroup factors as covariates.

For each meta-analysis, a funnel plot was made to detect any evidence of publication bias. Egger's test was also applied.

We assessed the shape of the CRF by meta-analysing studies with mean $PM_{2.5}$ concentrations below certain cut-off values (10, 12, 15, 20, 25 $\mu g/m^3$) for $PM_{2.5}$ and natural-cause mortality. We further reviewed assessments within individual studies to assess the shape of the CRF, e.g. spline analyses, subset analyses, quartile/ quintile analyses or information from the discussion sections (Appendix 5).

For $PM_{2.5}$ and natural-cause mortality, further sensitivity analyses were conducted: 1) Effect estimates from two pollutant models adjusting for coarse particles, O_3 or NO_2 ; 2) Excluding studies at high risk of bias; 3) Excluding studies without individual level lifestyle confounders, specifically the large cohort studies based upon administrative databases; 4) Including studies in patient populations or infants.

2.6 Evaluation of certainty of evidence

A GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework, adapted by a group of experts convened by WHO, was used to assess the overall certainty of evidence across studies for each exposure-outcome pair. A common guidance document for all assessors was prepared to assist the rating, which is added in Appendix 6a. Briefly, we started the rating process at moderate certainty evidence because of the risk of unmeasured confounding in observational studies. Then, we downgraded or upgraded the certainty of evidence based on five and four GRADE domains respectively. Reasons for downgrading included 1. Limitations in studies; 2. Indirectness; 3. Inconsistency; 4. Imprecision; 5. Publication bias. Reasons for upgrading include 1. Large magnitude of effect size; 2. All plausible confounding decreases observed RR; 3. Concentration-response gradient. The assessments for the GRADE domains were mostly based on results of the Risk of Bias assessment,

heterogeneity, sensitivity and publication bias analyses, which were previously described in the methods section.

Reasons for downgrade:

Limitations in studies: the certainty of evidence was downgraded with one or two levels if serious or very serious risk of bias was present in studies that had a considerable weight in the meta-analysis. If high risk of bias studies differ in effect size from low/moderate risk of bias studies, consideration should be given to exclude high risk of bias studies from the meta-analysis.

Indirectness: the certainty of evidence was downgraded if the studies did not answer the PECOS question of the systematic review.

Inconsistency: the certainty of evidence was downgraded if severe heterogeneity was detected, for example, if there were studies in the body of evidence that show a harmful effect and also studies that show a preventive effect. Some heterogeneity is expected given differences in study location, type of population, level and composition of PM and methodological differences between studies. We assessed whether the 80% prediction interval of the meta-analytic risk estimate included unity and was more than twice the width of confidence interval. We further assessed whether heterogeneity could be explained by study-level factors and whether there was a sizable number of studies with HRs below 1. The latter criterium was assessed because a mere difference in magnitude of positive effect estimates between studies is of less concern than a mix of positive and negative associations.

Imprecision: the certainty of evidence was downgraded if the number of person-years of follow-up was less than 940 000 person-years.

Publication bias: the certainty of evidence was downgraded if publication bias was detected by visual inspection of the funnel plot in combination with the Egger's test. Careful consideration of heterogeneity as a cause for non-symmetric funnel plots and significant Egger tests was applied.

Reasons for upgrade:

Large effect size: the certainty of evidence had to be upgraded if the pooled effect size was large or very large. Calculation of a single E-value was proposed to evaluate how strong the relationship between an unmeasured confounder and both exposure and mortality needs to be to explain away the RRs we observed. We lacked the information to apply this procedure in our review. We had insufficient information to judge the strength of the relationships between exposure and confounders in the body of evidence. Furthermore, the relationship between a confounder and mortality is typically much stronger than between a confounder and air pollution exposure, so the use of a single E-value in our review is difficult to interpret. The certainty of evidence was therefore not upgraded based on this domain, consistent with RRs being typically low in well-executed air pollution epidemiological studies.

Confounding domain: the certainty of evidence was upgraded if all plausible confounding shifted the relative risk towards the null.

Concentration-response gradient domain: the certainty of evidence was upgraded if there was a concentration-response relationship between exposure and adverse mortality outcomes, either linearly or non-linearly."

3. Results

3.1 Article Selection and Description

After screening 3162 abstracts, we identified 216 records with potential relevance for the systematic review (Figure 1). We further excluded 54 records including 24 conference abstracts, 1 news report, 5 items with no full-text and 24 reviews. Reviews were not included in the study but used for references

screening and thus not excluded with search terms. Titles of the reviews were recorded in Appendix 2.1. We considered the 5 items with no full-text very unlikely to be relevant for this systematic review and did not put more efforts obtaining the full texts (documented in Appendix 2.2). Of 162 articles which remained for full-text assessment based on the eligibility criteria, we excluded 57 records with rationales documented in Appendix 2.2. We categorized excluded studies by PECOS items in the flowchart (Figure 1). With 2 additional records identified from scanning references of the identified reviews, we included 107 articles for further data extraction (Appendix 2.3). The descriptive information of the included articles is shown in Table 1. More detailed information is available in the data extraction file (Appendix 3).

There is a large number of studies now that have evaluated mortality effects of long-term exposure to PM_{2.5} or PM₁₀. The vast majority uses the cohort study design, with only three articles use a case-control study design (two in patient population and one in infants). Studies have been conducted in a wide range of countries, though the majority has been conducted in North America (N=62) and Europe (N=25). There is an increasing number of studies from Asia (N=19), but currently no studies from Africa, Central and South America. Widely different populations have been studied, including general population samples, elderly, specific occupational groups (nurses, agricultural workers). Studies further differ in their follow-up period, with the start of follow-up ranging from the 1970 to 2003 across studies. Several very large studies based upon administrative databases with more than a million subjects have been reported. Studies further differ in the detail of information available on potential confounders. Exposure assessment has evolved from assigning of city-average concentrations in the earlier studies to more individualized exposure assessment in later studies, using land use regression, dispersion modeling or interpolation.

3.2 Meta analyses

Main analyses

In addition to the forest plots showing articles included in the meta-analyses (Figure 2 – 5, Figure A7.1 – A7.11), we also presented all articles relevant for a specific exposure-outcome pair in a separate plot (Figure A7.12 – A7.26). The second set of plots (plot with all articles) were used to document our selection of a specific article in case of multiple articles from the same study population. Three studies that performed methodologically incorrect analyses were excluded from meta analyses as these results are biased (Kim et al., 2017; Zhang et al., 2014; Pun et al., 2017). Two of these studies assigned mean exposure over the follow-up on an individual basis, with subjects who did not die receiving the average of the full follow-up period (Kim et al., 2017; Zhang et al., 2014). Ostro et al., (2011) showed that assigning follow-up averages exposure to each individual while there was a downward trend in long-term ambient air pollution, resulted in severe overestimates of the air pollution risks. In Pun et al., (2017), HRs were biased upwards because of incorrect incorporation of exposure in analysis model: results affected by downward trend in exposure contrast in longer exposure window. The effect estimates extracted from these three studies were documented in the second set of plots (plot with all articles).

For PM_{2.5} and natural-cause mortality, the all-articles plot illustrates that several cohorts (e.g. ACS, CanCHEC) have been studied multiple times (Figure A7.12). The large majority of articles report a positive association between PM_{2.5} and natural-cause mortality. The overall summary estimate of the 25 studies is 1.08 (95% CI 1.06, 1.09). No single study has a large weight (Figure 3). Similar patterns were observed for other pollutant-outcome combinations. For PM₁₀ and ALRI mortality, no meta-analysis was performed as only two studies were identified (Figure A7.24).

The pooled effect estimates for all exposure-outcome pairs are shown in Table 2. PM_{2.5} was significantly associated with natural-cause mortality and all evaluated causes of death separately. HRs for all evaluated specific causes were moderately large than for natural-cause mortality. PM₁₀ was significantly associated with natural-cause, ischemic heart disease, respiratory and lung cancer mortality. For PM₁₀, effect estimates for the respiratory but not the cardiovascular outcomes were larger than for natural-

cause mortality. For all outcomes, the number of studies included in meta-analysis for PM_{10} is less than that for $PM_{2.5}$, thus might lead to less precise pooled effect estimates.

For most exposure-outcome pairs, there is a large degree of heterogeneity across studies as evidenced by the high I^2 and the larger 80% prediction interval compared to the 95% random effects interval. High heterogeneity is to be expected, given differences in study location, population characteristics, level and composition of PM and methodological differences between the studies (Table 1).

Figure 1. Flowchart of assessment of eligible studies

Table 1 Summary of articles included in the systematic review

ID	Author and Year	Study Population	Exposure	Mean/ median exposure ($\mu\text{g}/\text{m}^3$)	Outcome ^a	Study ^b	Study Period	Study Location	Study Size	Confounders adjusted for					
										age, sex	individual SES	individual smoking	other individual lifestyle	area-level SES	indirect adjustment for smoking
1	Abbey, 1999	Non-smoking, non-Hispanic white Seventh-day Adventists, age 27-95	PM ₁₀	51.24	A; R; LC	AHSMOG	1977-1992	California, U.S.	2,278 males; 4,060 females	y	y	y	y	n	n
2	Badaloni, 2017	general population age 30+	PM _{2.5} PM ₁₀	19.6 36.6	A; C	Rome longitudinal study	2001-2010	Rome, Italy	1,249,108	y	y	n	n	y	y
3	Beelen, 2009	general population age 55-69	PM _{2.5}		C	NLCS	1987-1996	the Netherlands	120,852	y	n	y	n	y	n
4	Beelen, 2008	general population age 55-69	PM _{2.5}	28.3	A; C; R; LC	NLCS-AIR	1987-1996	the Netherlands	120,852	y	n	y	n	y	n
5	Beelen, 2014a	population in 22 cohorts from 13 countries across Europe	PM _{2.5} / PM ₁₀		A	ESCAPE	1990s-2008	Europe	367,251	y	y	y	y	y	n
6	Beelen, 2014b	population in 22 cohorts from 13 countries across Europe	PM _{2.5} / PM ₁₀		C	ESCAPE	1990s-2008	Europe	367,383	y	y	y	y	y	n
7	Bentayeb, 2015	employees of the French national electricity and gas company	PM ₁₀ PM _{2.5}	25 17	A; C; R	Gazel	1989-2013	France	20,327	y	y	y	y	y	n
8	Bowe, 2018	US veterans with no previous history of diabetes	PM _{2.5}	11.8	A	U.S. veterans	2003-2012	U.S.	1,729,108	y	n	y	y	y	n
9	Brunekreef, 2009	general population age 55-69	PM _{2.5}	28.3	A; C; R; LC	NLCS-AIR	1987-1996	the Netherlands	120,227	y	n	y	n	y	n
10	Cakmak, 2018	non-immigrants aged 25-90 years	PM _{2.5}		A; C; R; LC	1991 CanCHEC	1991-2011	Canada	2,291,250	y	y	n	n	n	y
11	Cakmak, 2016	general population ≥ 25 years of age at baseline	PM _{2.5}	8.9	A; C	1991 CanCHEC	1991-2006	Canada	2,521,525	y	y	n	n	n	n
12	Carey, 2013	general population age 40-89	PM ₁₀ PM _{2.5}	19.7 12.9	A; C; R; LC	English national cohort	2002-2007	England	835,607	y	n	y	y	y	n
13	Cesaroni, 2013	general population age 30+	PM _{2.5}	43.6	A; C; R; LC	Rome longitudinal study	2001-2010	Rome, Italy	1,265,058	y	y	n	n	y	n
14	Chen, 2005	Non-smoking, non-Hispanic white SDAs, age ≥ 25 , lived within an airshed	PM ₁₀ PM _{2.5}	52.6 29	C	AHSMOG	1977-1998	3 metropolitan areas in California, U.S.	3,239	y	y	y	y	n	n
15	Chen H., 2016	AMI patients age ≥ 35	PM _{2.5}	10.7	A; C	EFFECT study	1999-2011	Ontario, Canada	8,873	y	y	y	y	y	n
16	Chen X., 2016	general population age ≥ 23 at baseline	PM ₁₀	144.34	A; LC	Northern China	1998-2009	4 cities in Northern China	39,054	y	y	y	y	n	n
17	Chen, 2017	general population age ≥ 23 at baseline	PM ₁₀	144.3	R	Northern China	1999 - 2009	4 cities in Northern China	39,054	y	y	y	y	n	n
18	Crouse, 2012	general population ≥ 25 years of age at baseline, immigrants	PM _{2.5}	8.7	A; C	1991 CanCHEC	1991-2001	Canada	2,145,400	y	y	n	n	y	n

(Table 1 Continued)

19	Crouse, 2015	general population ≥ 25 years of age at baseline	PM _{2.5}	8.9	A; C; R; LC	1991 CanCHEC	1991-2006	Canada	2,521,525	y	y	n	n	y	y
		NSHD: singleton births occurring in March 1946; SABRE: tri-ethnic population age 40-69 in 1989	PM ₁₀	16.7											
20	Dehbi, 2017		PM _{2.5}	9.9	C	NSHD, SABRE	1989-2015	England	7,529	y	y	y	n	y	n
21	Di, 2017	general population covered by Medicare age ≥ 65	PM _{2.5}	11	A	Medicare	2000-2012	continental USA	60,925,443	y	y	n	n	y	y
22	Dimakopoulou, 2014	Participants from 11 European cohorts	PM _{2.5} / PM ₁₀		R	ESCAPE	1985-2008	Europe	307,553	y	y	y	y	y	n
23	Dockery, 1993	white subjects age 25-74 at enrolment	PM _{2.5} / inhalable particles		A; LC	Harvard Six Cities	1974-1989	Six US cities	8,111	y	y	y	y	n	n
24	Dong, 2012	general population age ≥ 25 at baseline	PM ₁₀	154	R	Shenyang	1998-2009	Shenyang, China	9,941	y	y	y	y	n	n
25	Eckel, 2016	lung cancer patients	PM ₁₀	31.8	A; LC	lung cancer patients	1988-2009	California, USA	320,940	y	n	n	n	y	n
			PM _{2.5}	13.7					160,707						
26	Eftim, 2008	general population age ≥ 65	PM _{2.5}	13.6	A	Med-ACS	2000-2002	110 counties in USA	7,333,040	y	n	n	n	y	y
		general population age ≥ 65	PM _{2.5}	14.1	A	Med-SCS	2000-2002	6 counties in USA	341,099						
27	Enstrom, 2005	43- 99 yr (mean 65.7) old adults	PM _{2.5}	23.4	A	CA CPS I	1973-2002	11 counties in California, U.S.	35,783	y	y	y	y	n	n
28	Enstrom, 2017	general population age ≥ 30 living in households with at least one person age ≥ 45	PM _{2.5}	21.16	A	ACS-CPS II	1982-1988	U.S. 85 counties	292,277	y	y	y	n	n	n
29	Fischer, 2015	general population age ≥ 30	PM ₁₀	29	A; C; R; LC	DUELS	2004-2011	the Netherlands	7,218,363	y	y	n	n	y	y
30	Gan, 2011	general population age 45-86	PM _{2.5}	4.08	C	Canadian	1994-2002	Vancouver, Canada	466,727	y	n	n	n	y	n
31	Gan, 2013	general population age 45-85	PM _{2.5}	4.1	R	Canadian	1994-2002	Vancouver, Canada	467,994	y	n	n	n	y	n
32	Gehring, 2006	women age 50-59	PM ₁₀	43.7	A	German	1985-2003	North Rhine-Westphalia, Germany	4,752	n	y	y	y	n	n
33	Gerber, 2014	MI patients aged ≤ 65	PM _{2.5}	24	A; C	Israel Study of First Acute Myocardial Infarction	1992-2011	Israel	1,120	y	y	y	y	y	n
34	Hales, 2012	general population, age 30-74	PM ₁₀	8.3	A; C; R; LC	New Zealand Census-Mortality Study	1996-1999	New Zealand	1,364,454	y	y	y	n	y	n
35	Hansell, 2016	general population at all ages	PM ₁₀	20.7	A; C; R; LC	ONS longitudinal study	1971-2009	England and Wales	367,658	y	y	n	n	y	y
36	Hart, 2011	men in U.S. trucking industry, average age 42	PM ₁₀	26.8	A; C; R; LC	trucking companies	1985-2000	continental US	53,814	y	n	n	n	n	n
		married female nurses, age 54-79 in 2000	PM _{2.5}	14.1											
37	Hart, 2015	patients undergoing elective diagnostic coronary angiography or	PM _{2.5}	12	A	NHS	2000-2006	U.S.	108,767	y	y	y	y	y	n
38	Hartala, 2016		PM _{2.5}	14.6	A	Cleveland Clinic GeneBank study	2001-2010	Ohio, USA	5,854	y	y	y	n	n	n

(Table 1 Continued)

39	Heinrich, 2013	elective cardiac computed tomographic angiography	PM ₁₀				A; R; LC	German	1985-2008	North Rhine-Westphalia, Germany	4,752	y	y	n	n	n
40	Huss, 2010	general population age >30	PM ₁₀				C; LC	Swiss National Cohort	2000-2005	Switzerland	~4.6 million	y	y	n	y	n
41	Jerrett, 2005	general population age >=30 living in households with at least one person age >=45	PM _{2.5}				A; C; LC	ACS-CPS II	1982-2000	Los Angeles, USA	22,905	y	y	y	y	n
42	Jerrett, 2009	general population age >=30 living in households with at least one person age >=45	PM _{2.5}				A; C; R	ACS-CPS II	1982-2000	U.S. 86 metropolitan areas	448,850	y	y	y	y	n
43	Jerrett, 2013	general population age >=30 living in households with at least one person age >=45	PM _{2.5}	14.09			A; C; R; LC	ACS-CPS II	1982-2000	California, USA	73,711	y	y	y	y	n
44	Katanoda, 2011	general population age >=40	PM _{2.5} /SPM				R; LC	Three-prefecture Cohort Study	1983-1995	3 prefectures in Japan	63,520	y	y	y	n	n
45	Kim H., 2017	general population without previous CVD, age >=18	PM _{2.5}	25.03			A; C	NHIS-NSC	2007-2013	Seoul, Korea	136,094	y	y	n	y	n
46	Kim O., 2017	general population, employees, age 20-65	PM ₁₀	56			A; C; R	NHIS-NSC	2002-2013	South Korea	275,337	y	y	y	y	n
47	Kiountourtzoglou, 2015	old adults age >=65	PM _{2.5}	12.8			A	Medicare	2000-2010	U.S.	19,274,534	y	n	n	y	y
48	Koton, 2013	MI patients aged <=65	PM _{2.5}	23.9			A; C	Israel Study of First Acute Myocardial Infarction	1992-2011	Israel	1,120	y	y	y	y	n
49	Krewski, 2009	general population age >=30	PM _{2.5}	21.2			A; C; LC	ACS-CPS II	1982-2004	58 MSAs, U.S.	351,338	y	y	y	y	n
		general population age >=30	PM _{2.5}	14.02					1982-2004	116 MSAs, U.S.	499,968					
		general population age >=30	PM _{2.5}	14.3					1982-2000	New York, U.S.	44,056	y	y	y	y	n
		general population age >=30	PM _{2.5}						1982-2000	Los Angeles, U.S.	22,905					
50	Laden, 2006	white subjects age 25-74 at enrollment	PM _{2.5}				A; C; R; LC	Harvard Six Cities	1974-1998	six cities in U.S.	8,096	y	y	y	n	n
51	Lepeule, 2012	white subjects age 25-74 at enrollment	PM _{2.5}	15.9			A; C; R; LC	Harvard Six Cities	1974-2009	six cities in U.S.	8,096	y	y	y	n	n
52	Lipfert, 2006	male U.S. military veterans diagnosed as hypertension	PM _{2.5}	14.34			A	U.S. veterans	1976-2001	U.S.	~70,000	y	n	y	y	n
53	Lipsett, 2011	female public school professionals	PM ₁₀	30.6			A; C; R; LC	California Teachers Study	1995-2005	California, U.S.	101,784	y	n	y	y	n
54	Loop, 2018	> 45 yr blacks and whites free from CHD	PM _{2.5}	15.64			C	REGARDS	2003-2012	8 Southeastern U.S. states	17,126	y	y	y	n	n
55	Matheswaran, 2010	South London Stroke Register	PM ₁₀	25			A	patients	1995-2006	London	3,320	y	y	y	y	n
56	McDonnell, 2000	male, non-smoking, white, non-Hispanic, age >= 27 in	PM ₁₀	59.2			A; R; LC	AHSMOG	1977-1992	California, U.S.	1,266	y	y	y	n	n

(Table 1 Continued)

57	Miller, 2007	1977, lived within an airshed	PM _{2.5}	13.5	C	WHI	1994-2003	36 U.S. metropolitan areas	65,893	y				y	n	n
58	Næss, 2007a	postmenopausal women without previous CVD, age 51-90 years in 1992	PM ₁₀ PM _{2.5}	19 15	A; C; R; LC	Oslo Admin	1992-1998	Oslo, Norway	143,842	y				n	n	n
59	Næss, 2007b	inhabitants in Oslo, aged 50-74 in 1992	PM _{2.5}	14.2	C; R; LC	Oslo Admin	1992-1998	Oslo, Norway	105,359	y				n	n	n
60	Nishiwaki, 2013	residents aged 40-59, without a history of lung cancer, myocardial infarction, angina pectoris, or stroke	PM ₇		C; LC	JPHC	1990-2008	9 public health centers, Japan	78,057	y				n	n	n
61	Ostro, 2011	current and former female teachers and administrators, age >30 at baseline	PM _{2.5}	17.5	A; C; R	California Teachers Study	2002-2007	California, U.S.	44,847	y				y	y	n
62	Ostro, 2015	current and former female teachers and administrators, age <30 in 1995	PM _{2.5}	17.9	A; C; R	California Teachers Study	2001-2007	California, U.S.	101,884	y				y	n	n
63	Parker, 2018	adults ≥25	PM _{2.5}	11.8	A; C	NHIS	1997-2011	US	657,238	y				y	y	n
64	Peng, 2017	tuberculosis (TB) patients	PM _{2.5}	53.53	A; R	patients	2003-2013	Shanghai, China	4,444	y				y	n	n
65	Pinault, 2016	non-institutional Canadian population aged 25-90	PM _{2.5}	6.32	A; C; R; LC	CCHS-Mortality Cohort	2000-2011	Canada	299,500	y				y	y	n
66	Pinault, 2017	non-immigrants, non-institutionalized aged 25-90 years	PM _{2.5}	7.37	A; C; R; LC	2001 CanCHEC	2001-2011	Canada	2,448,500	y				n	y	n
67	Pope, 1995	general population age ≥30	PM _{2.5}	18.2	A; LC	ACS-CPS II	1982-1989	U.S. 50 MSAs	295,223	y				y	n	n
68	Pope, 2002	general population age ≥30	PM _{2.5}	21.1	A; LC	ACS-CPS II	1982-1998	U.S.	~359,000	y				y	n	n
69	Pope, 2004	general population age ≥30	PM _{2.5}	17.1	C; R	ACS-CPS II	1982-1998	U.S.	~319,000	y				y	n	n
70	Pope, 2015	general population age ≥30	PM _{2.5}	12.6	A; C	ACS-CPS II	1982-2004	U.S.	669,046	y				y	y	n
71	Puett, 2008	female registered nurses, age 30-55 at baseline, without cancer before 1992	PM ₁₀	21.6	A; C	NHS	1992-2002	13 states in U.S.	66,250	y				n	y	n
72	Puett, 2010	female registered nurses, age 30-55 at baseline, without cancer before 1992	PM _{2.5}	13.9	A; C	NHS	1992-2002	U.S.	66,250	y				n	y	n
73	Puett, 2011	male professionals, age 40-75, without MI	PM _{2.5} PM ₁₀	17.8 27.9	A; C	Health Professionals Followup Study	1986-2003	U.S.	17,545	y				n	y	n
74	Pun, 2017	Medicare beneficiaries age 65-120	PM _{2.5}	12.29	A; C; R; LC	Medicare	2000-2008	continental USA	18,937,461	n				n	n	n
75	Ritz, 2006	infant death during first year of life	PM ₁₀		A	infant	1989 - 2000	Southern California, USA	4,855 cases; 51,947 controls	y			y (maternal)	n	n	n

(Table 1 Continued)

76	Rosenlund, 2009	cases: MI patients age 15-79; controls: using registers stratified on sex, age	PM ₁₀	2.2	C	Stockholm Heart Epidemiology Program [SHEEP]	1985-1996	Stockholm, Sweden	43,275 cases; 511,065 controls	y	y	n	n	n	n
77	Rosenlund, 2006	cases: first-time MI patients age 45-70; controls: using registers stratified on sex, age	PM ₁₀	2.4	C	Stockholm Heart Epidemiology Program [SHEEP]	1992-1994	Stockholm, Sweden	1,397 cases; 1,870 controls	y	y	y	n	n	n
78	Ruttens, 2016	lung transplantation patients	PM ₁₀		A	lung transplantation patients	1987-2013	13 major lung transplant centers from 10 European countries	3,556 for macrolide-free group; 2,151 for macrolide group	y	n	n	n	n	n
79	Schwartz, 2008	white subjects age 25-74 at enrolment	PM _{2.5}	17.5	A	Harvard Six Cities	1974-1998	six cities in U.S.	8,096	y	y	y	n	n	n
80	Sese, 2018	Idiopathic pulmonary fibrosis patients	PM ₁₀ PM _{2.5}	19.46 26.23	A	COFI	2007-2014	France	192	n	n	y	n	n	n
81	Shi, 2016	Medicare cohort age >=65	PM _{2.5}	8.12	A	Medicare	2003-2008	New England, U.S.	10,938,852 person-years	n	n	n	y	y	y
82	Son, 2011	Infants with 37 - 44 weeks of gestation	PM ₁₀ PM _{2.5}	61 30.6	A; R	infant	2004 - 2007	Seoul, South Korea	352,405 for normal birth weight; 7,054 for low birth weight	y	y (maternal)	n	n	n	n
83	Spencer-Hwang, 2011	non-smoking kidney transplant patients	PM ₁₀	25.3	A; C	kidney transplant patients	1997-2003	US	32,239	y	y	n	y	n	n
84	Thurston, 2016a	general population age 50-71	PM _{2.5}	12.2	A; C; R	NIH-AARP	2000-2009	six US states and Atlanta and Detroit	517,041	y	y	y	y	n	n
85	Thurston, 2016b	general population age >=30	PM _{2.5}	15	C	ACS-CPS II	1982-2004	100 metropolitan areas in USA	445,860	y	y	y	y	y	n
86	Tomme, 2013	patients with Acute coronary syndrome	PM _{2.5} PM ₁₀	11 in England, 9.1 in Wales 17 in England, 14.6 in Wales	A	MINAP	2004 - 2010	England and Wales	154,204	y	n	y	n	y	n
87	Tomme, 2016	MI patients aged <=65	PM ₁₀ PM _{2.5}	23.2 14.6	A	MINAP	2003 - 2010	London	18,138	y	n	y	n	y	n
88	Tseng, 2015	civil service employees and teachers	PM _{2.5}		A; C	civil servants cohort	1989-2008	Greater Taipei, Taiwan	43,227	y	y	y	y	n	n
89	Turner, 2011	general population age >=30, never-smokers	PM _{2.5}	17.6	R; LC	ACS-CPS II	1982-2008	U.S.	120,917	y	y	y	y	n	n
90	Turner, 2016	general population age >=30	PM _{2.5}	12.6	A; C; R; LC	ACS-CPS II	1982-2004	U.S., esp. Iowa and North Carolina	669,046	y	y	y	y	y	n
91	Ueda, 2012	general population age >=30 without history of CHD or stroke	PM ₇	33.1-36.6 (40-60 th)	A; C	NIPPON	1980-2004	Japan	7,250	y	n	y	y	n	n

(Table 1 Continued)

92	Vedal, 2013	postmenopausal women, Ages 50–79, without a history of CVD	PM _{2.5}	12.9	C	WHI-OS	1994-2005	46 cities in the continental U.S. and Hawaii	73,094	y	y	y	n	n
93	Villeneuve, 2002	Caucasian subjects age 25–74 at enrolment	PM _{2.5}		A	Harvard Six Cities	1974-1991	six cities in U.S.	8,111	y	y	y	n	n
94	Villeneuve, 2015	healthy and free of cancer women age 40–59	PM _{2.5}	9.1	A; C; R; LC	CNBSS	1980-2005	Canada	89,835	y	y	y	y	n
95	Wang, 2017	Medicare beneficiaries ages ≥ 65	PM _{2.5}	10.7	A	Medicare	2000–2013	7 Southeastern states, U.S.	~13.1 million	y	n	n	y	n
96	Weichenathal, 2014	commercial pesticide applicators, farmers, and their families	PM _{2.5}	9.52	A; C; LC	AHS	1993-2009	Iowa and North Carolina, U.S.	83,378	y	y	y	n	n
97	Weichenathal, 2016	non-immigrants aged 25–90 years	PM _{2.5}	9.81	A; C; R; LC	1991 CanCHEC	1991-2009	Canada	193,300	y	y	n	n	y
98	Weichenathal, 2017	non-immigrants aged 25–90 years	PM _{2.5}	7.37	A; C; R	2001 CanCHEC	2001-2011	Canada	2,448,500	y	y	n	y	n
99	Wong, 2015	age ≥ 65	PM _{2.5}	35.3	A; C; R	HongKong elderly	1998-2011	Hong Kong	66,820	y	y	y	y	n
100	Yang, 2018	age ≥ 65	PM _{2.5}	42.2	A; C; R	HongKong elderly	1998-2011	Hong Kong	66,820	y	y	y	y	n
101	Yin, 2017	men age ≥ 40	PM _{2.5}	43.7	A; C; R; LC	Chinese men	1990-2006	45 districts in China	189,793	y	y	y	y	n
102	Zanobetti, 2007	Medicare data, MI patients age ≥ 65	PM ₁₀	28.8	A	MI patients	1985-1999	21 U.S. cities	196,000	y	n	n	y	n
103	Zanobetti, 2008	Medicare data, COPD patients age ≥ 65	PM ₁₀	29.4	A	COPD cohort	1985-1999	34 U.S. cities	1,039	y	n	n	y	n
104	Zeger, 2008	persons in the U.S. Medicare system, age ≥ 65	PM _{2.5} PM _{2.5} PM _{2.5}	14 10.7 13.1	A	Medicare	2000-2005	eastern U.S. central U.S. western U.S.	~12.5 million ~3.7 million ~3.1 million	n	n	n	y	y
105	Zhang, 2014	general population age ≥ 23 at baseline	PM ₁₀	144	A; C	Northern China	1998-2009	4 cities in Northern China	39,054	y	y	y	n	n
106	Zhang, 2011	general population age ≥ 25 at baseline	PM ₁₀	154	A; C	Shenyang	1998-2009	Shenyang, China	9,941	y	y	y	n	n
107	Zhou, 2014	men age ≥ 40	PM ₁₀	104	A; C; R; LC	Chinese men	1990-2006	45 districts in China	71,431	y	y	y	n	n

^a A = All-cause mortality/ natural-cause mortality; C = Cardiovascular mortality including subgroup of cardiovascular mortality (mortality from ischemic heart diseases, cerebrovascular diseases/ stroke); R = Respiratory mortality including subgroup of respiratory mortality (mortality from chronic obstructive pulmonary diseases, acute lower respiratory infection); LC = Lung Cancer mortality

^b All cohort studies except study ID 75, 76 and 77 (these three are case-control studies)

Figure 2. Forest plot of PM_{2.5} and natural-cause mortality

Figure 3. Forest plot of PM_{2.5} and circulatory mortality

Figure 4. Forest plot of PM_{2.5} and non-malignant respiratory mortality

Figure 5. Forest plot of PM_{2.5} and lung cancer mortality

Table 2. Pooled effect estimates for all pollutant-outcome combinations

	PM _{2.5}				PM ₁₀			
	N	pooled RR per 10µg/m ³	I ² (%)	Prediction interval	N	pooled RR per 10µg/m ³	I ² (%)	Prediction interval
Natural-cause	25	1.08 (1.06, 1.09)	88.9	(1.05, 1.11)	17	1.04 (1.03, 1.06)	94.0	(1.00, 1.09)
Circulatory	21	1.11 (1.09, 1.14)	72.1	(1.06, 1.17)	15	1.04 (0.99, 1.10)	98.5	(0.92, 1.19)
IHD	22	1.16 (1.10, 1.21)	77.5	(1.04, 1.29)	13	1.06 (1.01, 1.10)	73.4	(0.98, 1.14)
Stroke	16	1.11 (1.04, 1.18)	84.7	(0.98, 1.25)	9	1.01 (0.83, 1.21)	99.0	(0.67, 1.51)
Respiratory	17	1.10 (1.03, 1.18)	83.6	(0.95, 1.29)	13	1.12 (1.06, 1.19)	86.8	(0.99, 1.27)
COPD	11	1.11 (1.05, 1.17)	49.6	(1.02, 1.21)	5	1.19 (0.95, 1.49)	85.4	(0.78, 1.82)
ALRI	4	1.16 (1.01, 1.34)	83.0	(0.88, 1.54)	2	-	-	-
Lung cancer	15	1.12 (1.07, 1.16)	39.4	(1.05, 1.18)	13	1.08 (1.04, 1.13)	92.4	(0.99, 1.18)

N= number of studies

Analyses of the shape of concentration-response function (CRF)

Four studies assessed natural-cause mortality effects for participants exposed to PM_{2.5} concentrations below certain exposure levels (Figure A7.27). The positive associations remained below 10 µg/m³ in Medicare (1.09 (95%CI 1.01, 1.19)) and below 5 µg/m³ in CanCHEC (1.27 (95%CI 1.09, 1.49)). More assessments of the shape of the CRF by individual studies are documented in Appendix 5. These studies typically used non-parametric splines. The majority of studies which analyzed the CRF had no evidence of a threshold and showed linear or supra-linear functions.

We further combined effect estimates for studies with mean PM_{2.5} concentrations below certain cut-off exposure levels (Figure A7.28 – A7.32). The combined effect estimate is 1.17 (95% CI 1.12, 1.23) for the five studies with a mean concentration below 10 µg/m³. The limitation of this approach is that subjects exposed to pollution concentration higher than the cut-off exposure levels in the cohorts were also included.

Subgroup analyses

Virtually the same effect estimates were found for European Region, Region of the Americas and Western Pacific Region (Figure 6). Heterogeneity especially remained within the large group of North American studies. Virtually no difference in effect estimates was found between studies in men, women or combined (Figure A7.34). Studies performed in predominantly elderly showed somewhat smaller RRs but the confidence intervals overlapped (Figure A7.35). RRs tended to be larger in the studies with a mean PM_{2.5} concentration below 10 µg/m³ (Figure A7.36). No single factor can explain the source of high heterogeneity between studies. Meta-regression did not explain the source of high heterogeneity between studies (residual heterogeneity (I^2) = 86.53%), probably because little effect-modifier information is available on study-level factors.

Additional analyses

Two-pollutant models adjusting for NO₂ were specified by five studies and documented overall much lower RRs for PM_{2.5} compared to the single pollutant estimates in studies that specified two pollutant models (Figure A7.37 and A7.38: 1.07 (95% CI 1.05, 1.08) in single pollutant models versus 1.02 (95% CI 1.00, 1.04) in two-pollutant models). Two pollutant models can be difficult to interpret when the correlation between pollutants is high or exposure for pollutants is assessed with different methods or at a different spatial resolution. RRs remained stable after adjusting for coarse particles or O₃: 1.14 (95% CI 1.05, 1.24) based upon three studies and 1.08 (95% CI 1.04, 1.11) based upon seven studies respectively.

The combined effect estimate remained the same (1.08 (95%CI 1.06, 1.09)) after we excluded one study that was at high risk of bias in any domain for PM_{2.5} and natural-cause mortality combination. The combined estimate slightly increased with a slightly wider confidence interval (1.09 (95%CI 1.06, 1.11)) after we further excluded studies that score moderate on an item that all other studies score low (Figure A7.39). The combined effect estimate remained stable as these two studies had little weight on the meta-analysis.

Exclusion of the large administrative cohorts, which have limited information on individual lifestyle factors resulted in an identical effect for PM_{2.5} and natural-cause mortality, but with a slightly wider confidence interval: 1.08 (95% CI 1.05, 1.10) (Figure A7.40).

Inclusion of studies conducted in the very diverse patient populations resulted in a modest increase in effect estimates and a further increase in heterogeneity for PM_{2.5} and natural-cause mortality (Figure A7.41: 1.11 (95% CI 1.07, 1.14)). With the exception of a study in lung cancer patients, these typically smaller studies had less precise effect estimates than the general population studies. Including one small study reported effect estimate for PM_{2.5} and natural-cause mortality in infants with low precision did not change the overall effect estimate (Figure A7.42).

Figure 6. Meta-analysis of PM_{2.5} and natural-cause mortality: by geographical regions

3.3 Risk of Bias (RoB) assessment

Figure 7 shows a summary of RoB assessments for all studies included in the meta-analyses. The individual RoB assessments are presented in Appendix 4b. Most but not all of the cohort studies had similar evaluations because of the similar study design they used – following the classical cohort studies conducted in the USA, specifically the Six city study (Dockery et al., 1993) and the American Cancer Society study (Pope et al., 2002).

Confounding Most of the studies were rated as ‘moderate risk’ in this domain. The most critical subdomain was “Were all confounders considered adjusted for in the analysis?”. Individual-level smoking and BMI were usually not available in large administrative cohorts, and were indirectly adjusted for in some studies using an ancillary dataset (Badaloni et al., 2017; Crouse et al., 2015; Di et al., 2017; Fischer et al., 2015). Some studies were rated as ‘moderate risk’ because one or two of the confounders in the list of other/ additional potential confounders were not adjusted for. Studies that adjusted for a large number of individual- and area-level risk factors, such as the ACS study typically did not adjust for at least one of this list and we therefore rated the study as moderate risk of bias (Turner et al., 2016). This characterization is questionable however and some studies such as the ACS study would qualify as low risk of bias. Since the ACS study has adjusted for BMI and a large number of SES variables, it is highly likely that this will also adjust for effects of lack of physical activity. Similar examples apply to a large number of cohort studies, e.g. (Beelen et al., 2014; Carey et al., 2013; Thurston et al., 2016; Turner et al., 2016): ‘low risk’ might be more reasonable given the large number of covariates adjusted for.

Selection bias We found few studies where selection was related to exposure. Therefore, most of the studies were rated as ‘low risk’.

Exposure assessment The exposure assessment methods varied across the studies. We considered most of the exposure assessment methods appropriate when they had documented validity such as good agreement between model predictions and measurements. Change in spatial exposure contrasts is not a potential risk for studies assigning time-varying exposures. In cohort studies where exposures were assigned to the participants for the same period, several reported the stability of spatial contrast. For studies that did not report stability of the contrasts, we made an assessment based on previous studies in the same study area and time period. We generally assessed spatial exposure contrasts did not change much in well-developed areas in North America and Europe. In strongly developing areas such as Asia, spatial exposure contrasts might have changed in the past decade(s). If the change of spatial exposure contrasts was not accounted for, we rated as ‘moderate’ or ‘high’ risk of bias.

Outcome measurement Most of the studies used a mortality registry to link health outcomes of the participants. Some earlier studies used interviews to confirm the vital status of participants. Deaths were classified according to the International Classification of Diseases (ICD) in most of the studies using the underlying cause of death. The same outcome measurement methods were applied for all subjects within a particular study, irrespective of the level of exposure, therefore all studies were rated as ‘low risk’. We note that misclassification of cause of death may have contributed to additional noise in the data.

Missing data Studies measuring outcome by linkage to mortality registries were unlikely to have frequent missing outcome data. Most of the studies excluded subjects if they had missing exposure data. No studies used imputation of exposure. Percent of missing data of exposure was typically low. Therefore, most but not all of the studies were rated as ‘low risk’.

Selective reporting Studies typically reported all risk estimates for the outcomes and pollutants identified in the Methods section therefore were rated as ‘low risk’. One study (McDonnell et al., 2000) selectively reported effects for males only because effects for females were weak or inverse, thus was rated as “high risk”.

Figure 7. Summary of all RoB assessments (total number of assessments across all exposure-outcome pairs = 216)

3.4 Assessment of the certainty of evidence

Table 3 lists the application of the adapted GRADE tool to the body of evidence for PM_{2.5} and PM₁₀ related to natural-cause and circulatory mortality. The complete evaluations are documented in Appendix 6b. The starting point was at moderate certainty of evidence reflecting the risk of unmeasured confounding in observational studies. We concluded an upgrade of the evidence with one level for all assessed endpoints associated with PM_{2.5} except respiratory mortality, and for natural-cause, respiratory and lung cancer mortality associated with PM₁₀, resulting in a ‘high certainty of evidence’. A downgrade with one level was concluded for PM₁₀ and stroke mortality, resulting in a ‘low certainty of evidence’. A ‘moderate certainty of evidence’ was assessed for the remainder of the exposure-endpoint combinations. Most of the rationales for the assessments in the various GRADE domains are documented in the previous sections. Briefly:

A1 Limitations in studies (risk of bias) No downgrading was applied as few studies were identified as ‘high risk of bias’ and exclusion of these studies had little impact on the overall effect estimate (section 3.2). This decision is supported by the stability of risk estimates excluding the large administrative cohorts with no direct information on individual lifestyle (section 3.2).

A2 Indirectness No downgrading was applied as all studies answered the PECOS (Population, Exposure, Comparator, Outcome and Study) question directly as shown in Table 1.

A3 Inconsistency We downgraded the certainty of the evidence for PM₁₀ and circulatory mortality, PM₁₀ and stroke mortality, and PM_{2.5} and respiratory mortality because the 80% prediction interval included unity; the width of the prediction interval was more than twice the width of confidence interval and there was a sizable number of studies with HRs below 1. Heterogeneity was partly explained by the level of pollution and differences in population: higher HRs for studies with lower mean PM_{2.5} concentrations, somewhat lower HRs in elderly and higher HRs in patient populations.

A4 Imprecision No downgrading was applied as the included cohort studies followed a large population for several years, resulting in large number of person-years (Table 1). Several single studies included much more than 940 000 person-years. All exposure outcome pairs (except PM₁₀ and ALRI, 2 studies) fulfilled the criterium by a wide margin. The small width of the confidence interval around the summary HR further supports that no downgrade is needed.

A5 Publication bias

No downgrading was applied as no evidence of publication bias was found in funnel plots and Egger's tests. Upon visual inspection, no funnel plots showed that small studies with RRs below 1 were missing, indicating no evidence for publication bias (Figure A7.33). Egger's test has good performance for continuous outcomes but is less sensitive for the binary outcomes reported in the current review, especially for the outcomes with a small number of studies. The funnel plot is not sensitive with small number of studies for some outcome pollution pairs either. Cohort studies require a large effort often of different institutes and hence investigators generally try to get studies published irrespective of the results of the study. This qualitative interpretation cannot be investigated directly, because no registries of planned studies exist. We further do not imply that publication bias is absent in easier to conduct air pollution epidemiology studies. Most Funnel plots show a pattern with studies outside the area defined by uncertainty. This mostly reflects the large degree of heterogeneity across studies (Lau et al., 2006; Sterne et al., 2011). Egger's test is sometimes significant (e.g. natural-cause mortality and PM₁₀, IHD and PM₁₀), more reflecting heterogeneity than publication bias.

B1 Large RR No upgrading was applied as RRs are typically low in air pollution epidemiological studies. We did not apply the procedure based on a single E-value (section 2.6).

B2 All confounding decreases observed RR No upgrading as confounding may decrease or increase observed RRs depending on the direction of the association between exposure and confounder in individual studies.

B3 Concentration-response gradient Upgrading was applied for most combinations. We considered upgrading for a specific combination when there was at least one study reported evidence of a concentration-response gradient (Appendix 5).

Table 3 Detailed assessment of certainty of evidence for each exposure-outcome pair ('+' implies increase in confidence)

		reasons for downgrading										reasons for upgrading					overall	Final certainty assessment
		A1	rationale	A2	rationale	A3	rationale	A4	rationale	A5	rationale	B1	rationale	B2	rationale	B3		
PM _{2.5} and natural-cause	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM ₁₀ and natural-cause	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM _{2.5} and circulatory	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM ₁₀ and circulatory	0	little influence on the overall effect	0	no evidence of indirectness	-1	prediction interval includes unity and larger than twice the CI	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	0	Moderate

A1 = limitations in studies (risk of bias); A2 = indirectness; A3 = inconsistency; A4 = imprecision; A5 = publication bias
 B1 = large RR; B2 = all confounding decreases observed RR; B3= concentration-response gradient

4. Discussion

4.1 Summary of evidence

4.1.1 Quantitative effect estimates in meta-analysis

In meta analyses, PM_{2.5} was associated with significantly increased risks of all causes of mortality evaluated. PM₁₀ was associated with significantly increased risks of natural-cause and most but not all cause-specific mortality. The evidence base has increased substantially compared to the previous global WHO evaluation published in 2006 (WHO, 2006).

For natural-cause mortality, the combined effect estimate across 25 studies was 1.08 (95%CI:1.06, 1.09) per 10 µg/m³ increase in PM_{2.5}, which is slightly higher than the combined estimate of 1.06 (95% CI:1.04, 1.08) across 11 studies reported in a 2013 review used extensively by the European Environment Agency for European health impact assessment (Hoek et al., 2013). The previous estimate was based on studies predominantly conducted in North America with two studies from Europe (Beelen et al., 2008; Cesaroni et al., 2013). The evidence was strengthened by including new evidence generated in Asia (Tseng et al., 2015; Yang et al., 2018; Yin et al., 2017), North America (Bowe et al., 2018; Pinault et al., 2017), Europe (Beelen et al., 2014b; Carey et al., 2013), and longer follow-up (Cakmak et al., 2018; Di et al., 2017). For PM₁₀, the combined estimate increased from 1.035 (95%CI:1.004, 1.066) reported in the Hoek et al. (2013) review to 1.04 (95%CI:1.03, 1.06) in the current review. The previous review was based on only 6 cohort studies while the updated combined estimate was based on 17 cohort studies.

The combined effect estimate was larger for cardiovascular (particularly ischemic heart disease) than for natural-cause mortality associated with exposure to PM_{2.5}. This pattern is consistent with findings in the previous reviews (Chen et al., 2008; Hoek et al., 2013; Liu et al., 2018). One potential source of heterogeneity for effects on IHD is misclassification of the underlying cause of death as Heart Failure rather than IHD. Both WHO and GBD consider heart failure as a "junk category" and re-assign most to IHD (WHO, 2006; Cohen et al., 2017). For stroke mortality, a significant increased risk was found to be associated with PM_{2.5} but not with PM₁₀. A previous review derived the same conclusion but in addition, reported a significant increased risk for stroke incidence associated with both PM_{2.5} and PM₁₀ (Scheers et al., 2015).

In the Hoek et al. (2013) review no significant association was found for PM_{2.5} and non-malignant respiratory mortality across six studies (Hoek et al., 2013). An increased risk of non-malignant respiratory mortality associated with both PM_{2.5} and PM₁₀ in this review was found by including more recent findings. This increases the coherence with the time-series studies which have consistently shown short-term associations between PM and respiratory mortality (Brunekreef and Holgate 2002; WHO, 2006; Pope and Dockery 2006). Studies investigating long-term exposure and acute lower respiratory infection (ALRI) are still scarce.

Association between lung cancer and PM has been widely investigated as lung cancer is one of the most common cancers and has a poor prognosis. In this review we found significantly increased risk in lung cancer mortality associated with both PM_{2.5} and PM₁₀. This pattern is consistent with several previous reviews (Chen et al., 2008; Cui et al., 2015; Yang et al., 2016). The effect estimates were slightly higher than that reported in (Cui et al., 2015): 1.09 (95%CI 1.06, 1.11) for 10 µg/m³ increase in PM_{2.5} and 1.05 (95%CI 1.03, 1.07) for PM₁₀. In the review resulting from the IARC evaluation of carcinogenicity of outdoor air pollution, the estimates were 1.09 (95% CI 1.04, 1.14) and 1.08 (95% CI 1.00, 1.17) associated with 10 µg/m³ increase in PM_{2.5} and PM₁₀ respectively (Hamra et al., 2014). IARC has designated outdoor air pollution and particulate air pollution specifically as a Group 1 human carcinogen (IARC 2013). Studies investigating lung cancer incidence were not included in the current review.

In general, associations with PM_{2.5} were more consistent than with PM₁₀, particularly for cardiovascular outcomes. PM₁₀ is made up of fine (PM_{2.5}) and coarse particles. The less consistent association for PM₁₀ may reflect the smaller number of studies compared to PM_{2.5} and the lower risk of long-term exposure to coarse particles (Adar et al., 2014; Hoek et al., 2013). We note that we cannot compare the presented effect estimates for PM_{2.5} and PM₁₀ as the applied increment of 10 µg/m³ represents a larger contrast for PM_{2.5} than for PM₁₀.

4.1.2 Heterogeneity of effect estimates

In all meta analyses we observed a moderate to high degree of heterogeneity. This is to be expected given the wide diversity of studies conducted. Heterogeneity is likely due to a combination of differences in methodology, concentration and composition of PM, population, geographical location and time period. We primarily interpret this diversity of populations and methods as support for an association, as it decreases the likelihood that residual confounding explains the associations observed between PM and mortality. Documenting heterogeneity is important for health impact assessment of PM in different countries across the globe.

The exposure assessment methods varied across the studies, from assigned exposure to the nearest monitoring station, to land use regression or dispersion models. Exposures were assigned on very different spatial scales, ranging from residential address to US county. In the risk of bias assessment, we considered all exposure assessment methods appropriate if they had documented validity. However, differences of exposure assessment methodology may affect effect size estimation (Vodonas et al., 2018). For example, in studies characterizing exposure by an area-level value (Nishiwaki et al., 2013; Zhang et al., 2011), only a small number of exposure values were assigned to the population, resulting in difficulties to interpret associations.

The body of evidence includes several very large cohorts of several million subjects based upon administrative registry data, which is new compared to the REVIHAAP assessment (WHO, 2013). These large studies have strong statistical power but often lack individual lifestyle information. Importantly, we found identical RR with wider CI after excluding these studies without individual lifestyle factors. The wider CI is to be expected as the number of subjects in the meta-analysis decreased substantially and lowered the statistical power. Confounding may affect RR estimates for PM_{2.5} and PM₁₀ in both directions. While risk factors such as smoking, high BMI or low SES affect mortality in the same (adverse) direction, the correlations between these factors and air pollution exposure actually vary across studies. In the Rome cohort study and the Canadian studies (Badaloni et al., 2017; Cakmak et al., 2018), lifestyle tends to be more favorable among the higher exposed subjects living in metropolitan areas, potentially leading to underestimation of air pollution RRs in case of insufficient confounder control. In other studies such as the ESCAPE study (Beelen et al., 2014a), adjustment for confounding reduced air pollution effect estimates. For the entire body of evidence it is therefore not likely that important confounding has occurred.

The body of evidence was based on studies conducted globally, though the majority of studies was from Europe and North America. Differences in geographical location lead to differences in population, concentration and composition of PM. Previous studies have suggested some population groups are more susceptible (Di et al., 2017) and some components are more harmful than others (Vedal 2013). An important observation of our study is that the combined effect estimates were similar across the three WHO regions (Region of the Americas, European Region and Western Pacific Region) where studies have been conducted. This comparison has become possible because of the increase of studies in different regions and addressed concerns about the applicability of results from in the past primarily North-American studies to assess health risks in Europe and other regions.

4.1.3 Concentration-Response Function (CRF) at low pollution levels

As the levels of ambient air pollution have declined significantly over the last few decades in North America, Europe, and in other developed regions, it is important to examine whether associations with

adverse health effects continue to be observed at low levels. Two recently published studies indicated that health effects occur well below 12 $\mu\text{g}/\text{m}^3$ (the US-EPA NAAQS exposure level) (Brauer et al., 2019; Dominici et al., 2019). In our review, a meta-analysis of studies investigating natural-cause mortality conducted at mean annual average $\text{PM}_{2.5}$ levels below 25 $\mu\text{g}/\text{m}^3$ (the EU limit exposure level) yielded a significantly positive RR, very similar to the overall RR estimate from all studies. An analysis of studies conducted at mean annual average $\text{PM}_{2.5}$ levels below 10 $\mu\text{g}/\text{m}^3$ (the current WHO guideline exposure level) yielded an even higher RR, coherent with an increasing number of studies showing linear or supra-linear concentration response relationships (Cesaroni et al., 2013; Crouse et al., 2015; Di et al., 2017; Hart et al., 2015; Pinault et al., 2016; Pinault et al., 2017; Pope et al., 2002). Monotonically rising concentration response relationships were also reported in individual studies for mortality from other diseases related to long-term exposure to $\text{PM}_{2.5}$, including CVD, IHD, stroke, Respiratory disease, COPD and lung cancer (Cesaroni et al., 2013; H Chen et al., 2016; Crouse et al., 2012; Lepeule et al., 2012; Pinault et al., 2017; Thurston et al., 2016a; Weichenthal et al., 2014). Nonlinear CRFs were sometimes reported with usually wide CIs at both the higher and lower ends of the concentration distribution (Crouse et al., 2012; Gan et al., 2013; Villeneuve et al., 2015). Burnett et al., (2018) has recently reported on an analysis of a large number of cohorts included in the current review and showed a near-linear ensemble curve for natural-cause mortality and $\text{PM}_{2.5}$. The study involved analysis using a standardized code allowing non-linear functions applied by local analysts and subsequent combination of the curves. The study also showed near-linear ensemble CRFs for lower respiratory infection, stroke, COPD, lung cancer and IHD associated with long-term exposure to $\text{PM}_{2.5}$. While most studies suggested there is little evidence of a threshold for $\text{PM}_{2.5}$ and mortality from all causes and specific causes (Di et al., 2017; Lepeule et al., 2012; Pinault et al., 2016; Schwartz et al., 2008), a threshold of 11 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ and nonaccidental mortality was reported in (Villeneuve et al., 2015). Studies that evaluated the shape of the CRF for PM_{10} are more limited (Fischer et al., 2015).

4.1.4 Certainty of evidence

We applied an adapted GRADE method to assess certainty in the epidemiological body of evidence. In general, $\text{PM}_{2.5}$ was more consistently associated with mortality than PM_{10} , particularly for cardiovascular outcomes. PM_{10} is made up of fine ($\text{PM}_{2.5}$) and coarse particles. The less consistent association for PM_{10} may reflect the smaller number of studies compared to $\text{PM}_{2.5}$ and the lower risk of long-term exposure to coarse particles (Adar et al., 2014; Hoek et al., 2013).

The assignment of high certainty of evidence to most long-term $\text{PM}_{2.5}$ exposure and mortality associations agrees well with recent assessments made by the USEPA using a different methodology (USEPA, 2019). In the 2019 Integrated Science Assessment (ISA), the association between $\text{PM}_{2.5}$ and natural mortality was rated as “causal” based on assessment of different scientific disciplines beyond the epidemiological air pollution mortality studies. For long-term PM_{10} exposure and mortality associations, the assessments are generally stronger than the ISA assessments for coarse particles. The 2019 PM ISA evaluated evidence from studies of $\text{PM}_{10-2.5}$ and natural-cause mortality as “suggestive”. The assessment for coarse PM is not directly comparable to PM_{10} , as PM_{10} is the sum of $\text{PM}_{2.5}$ and coarse PM. We also rated the evidence for specific causes of death lower for PM_{10} than for $\text{PM}_{2.5}$. The high certainty assessment for lung cancer mortality agrees well with the assessment in 2013 by IARC, which designated outdoor air pollution and particulate air pollution specifically as a Group 1 human carcinogen (IARC, 2013).

The biological plausibility of associations between mortality and PM have been identified previously (USEPA, 2019). Inhalation of PM may result in injury, oxidative stress, and inflammation in the respiratory tract and lead to systemic inflammation and oxidative stress. Persistent or intermittent exposure to PM over months to years may lead to cumulative or chronic effects including mortality from respiratory, cardiovascular disease, lung cancer or possibly other diseases.

Application of the adapted GRADE approach was challenging in some domains. Limitations in studies were assessed based on results of the risk of bias assessments. Risk of Bias application is more complex

than following a simple checklist and requires careful interpretations to make a proper judgment. The criteria for the confounding domain were clear, but probably a more refined list of confounders would have distinguished studies better. The missing data and exposure contrast subdomains required careful examination as data were not always reported in the epidemiological paper, but occasionally in a companion paper. Change in exposure contrast during follow-up also required additional information to be inspected. Consideration of heterogeneity was complex, as distinguishing differences in magnitude of effect size and differences in direction of effect across studies was needed. Publication bias was difficult to assess as the tools are somewhat problematic for non-continuous outcomes, for a small number of studies and settings with heterogeneity. The imprecision criterium was based upon comparison with a set number of person-years determined with a power calculation. Probably, the evaluation of the meta-analytical confidence interval would have been more direct. We did not apply the upgrade procedure for large RR, based upon the suggested evaluation of an E-value. None of these challenges likely has materially affected the overall certainty of evidence assessment.

4.2 New studies published after last search

A number of studies has been published after the date of our final search (October 2018), which is more than a year ago. Table A7.1 lists the new studies including RR estimates. Some of the new evidence is from an update of the included cohorts with longer follow-up or with more advanced methodology, including the National Health Interview Survey cohort (Pope et al., 2018; Pope et al., 2019) and the National Institutes of Health-AARP Diet and Health Study (Hayes et al., 2019). These new studies are unlikely to change our estimates as the same populations were already included. Some new studies were conducted in the included cohorts with a different focus (Lim et al., 2019; Sun et al., 2019), which would not fulfil the criteria to replace the estimates used in the meta analyses.

Two recently published reports funded by the Health Effect Institute (HEI) suggested health effects of air pollution exist at low levels, even below the current annual U.S. national ambient air quality standard for PM_{2.5} of 12 µg/m³ (Brauer et al., 2019; Dominici et al., 2019). This is coherent with findings from a number of studies included in the current review. These two reports were conducted in the Medicare cohort and four Canadian cohorts (three CanCHEC and CCHS). Estimates in the Medicare report were identical as previously reported in (Di et al., 2017), which was included in our review. Estimates in the Canadian report were published separately in Christidis et al., (2019) and Pappin et al., (2019). Three of the four Canadian cohorts were included in our review with a shorter follow-up, with exception of the 1996 CanCHEC.

The Dutch Environmental Longitudinal Study (DUELS) and the Korean National Health Insurance Service-based National Sample Cohort were included in the current review with effect estimates reported only for PM₁₀ (Fischer et al., 2015; Kim et al., 2017). In the recent articles derived from these cohorts, health effect estimates associated with PM_{2.5} were reported (Fischer et al., 2020; Kim et al., 2019). However, the Korean cohort only reported PM_{2.5} estimates in a two-pollutant model adjusted for O₃. Evidence was also generated from new cohorts including the Chinese Longitudinal Healthy Longevity Survey (CLHLS) (Li et al., 2018), the Danish Diet, Cancer and Health cohort (Hvidtfeldt et al., 2019) and the ‘45 and up study’ cohort (Hanigan et al., 2019). Most of these studies have reported positive associations between PM_{2.5} and mortality. Importantly, sensitivity analysis including this new evidence did not change our combined estimates. The summary RR for PM_{2.5} and natural mortality was 1.08 (95%CI 1.07, 1.10) after including 5 new studies (Figure A7.43). The body of evidence is already based on a large number of well conducted studies without a large weight from a single study, therefore including new evidence is unlikely to change the combined effect estimate materially.

4.3 Strengths and limitations

A strength of our study is the efforts made throughout the design and the conduct of the systematic review to ensure its validity, including the incorporation of risk of bias assessment. Another strength is the large number of studies included in our systematic review, with the diversity of populations. This

decreases the likelihood that residual confounding explains the associations observed between PM and mortality.

This systematic review has a number of limitations. First, we acknowledge that our search strategy had limitations. The use of “NOT” operators in our search strategy and inclusion of study design might lead to missing relevant evidence. However, we also scanned references of identified reviews to identify papers that were potentially missed by our search strategy. Compared to a very recent review article (Pope et al., 2019), our systematic search only missed two studies published in the search period – one from a cohort we already included in our review (Wong et al., 2016), one from a patient group (Goss et al., 2004). We therefore think that the risk of missing key papers was small. Second, we found that relatively few studies were performed in low- and middle-income countries (LMICs) which typically experience higher air pollution levels than observed in the countries where the majority of cohort studies have been performed (Burns et al., 2019). Therefore, uncertainty about the shape of the CRF remains especially for the high end of the concentration distribution. To support health impact assessment in LMICs and global burden of disease assessment, new studies in LMICs are needed. Third, the review focused on PM_{2.5} and PM₁₀ without assessing particle composition. As most included studies have been conducted in areas with combustion as the main source of (primary and secondary) particles, it is not clear whether the risk estimates can be applied in settings where other sources are dominant such as desert dust (Kotsyfakis et al., 2019; Naidja et al., 2018). More research investigating which components/sources are most responsible for health effects is needed. Fourth, in a meta-analysis of published studies, we had limited possibilities to assess the shape of the CRF.

4.4 Implications

Results of this and other systematic reviews commissioned by WHO are currently being used in developing new air quality guidelines by WHO. Our results suggest that PM_{2.5} is associated with increased risk for mortality, even below the current WHO guideline exposure level of 10 µg/m³. If a threshold is present, it is at very low levels. These results suggest an update of the current guideline needs to be considered by WHO. An update of the PM₁₀ guideline needs to be considered as well.

The large heterogeneity of effect estimates across studies suggests that health impact assessment in specific locations may have fairly large uncertainty. The full body of evidence should be used with caution in regions where no or few studies have been conducted such as the African Region, South-East Asia Region, and Eastern Mediterranean Region. Particularly in areas where dust contributes significantly to overall PM_{2.5} levels, our combined RRs may not apply. Also, as the summary RR estimates were derived assuming a linear relationship, application of this relationship in e.g. burden of disease assessments may be problematic when evaluating settings with very high concentrations such as in polluted regions of Asia (Pant et al., 2016).

5. Conclusions

The evidence base has increased substantially compared to the previous global WHO evaluation, however studies conducted in low- and middle-income countries (LMICs) are still scarce. There is clear evidence that both PM_{2.5} and PM₁₀ are associated with increased mortality from all causes, cardiovascular disease, respiratory disease and lung cancer. The combined HRs for natural-cause mortality are 1.08 (95%CI:1.06, 1.09) per 10 µg/m³ increase in PM_{2.5}, and 1.04 (95%CI:1.03, 1.06) per 10 µg/m³ increase in PM₁₀. The associations with PM_{2.5} remained below the current WHO annual average guideline exposure level of 10 µg/m³.

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Supplementary Information

(For space reasons, not all appendices are presented in this thesis. For more information, please refer to the online appendices: <https://doi.org/10.1016/j.envint.2020.105974>)

Appendix 1 Search Strategy

A1.1 Search strategy for MEDLINE

Search timeline: 1966–09.10.2018		Abstracts
#20	19 NOT "time series"[Title]	1,855
#19	18 NOT "Air Pollution, Indoor"[Mesh] NOT "Occupational Exposure"[Mesh]	1,873
#18	17 NOT "Treatment Outcome"[MeSH]	1,915
#17	16 NOT "animals"[Mesh:NoExp]	2,157
#16	15 NOT "Clinical Trial"[pt]	2,235
#15	5 AND 9 AND 14	2,362
#14	OR/ 10-13	2,880,275
#13	case-control[Title/Abstract]	111,292
#12	cohort[Title/Abstract] OR follow up[Title/Abstract] OR Longitudinal[Title/Abstract] OR Prospective[Title/Abstract] OR Retrospective[Title/Abstract]	1,939,404
#11	Case-Control Studies[Mesh]	945,436
#10	Cohort Studies[Mesh]	1,785,591
#9	OR/ 5-8	1,650,591
#8	mortality[Title/Abstract] OR death[Title/Abstract]	1,182,902
#7	Death[Mesh]	139,544
#6	mortality [Subheading]	523,650
#5	Mortality[Mesh]	348,241
#4	OR/ 1-3	293,389
#3	particulate matter[Title/Abstract] OR particulate air pollution[Title/Abstract] OR PM[Title/Abstract] OR PM10[Title/Abstract] OR PM2.5[Title/Abstract] OR particles[Title/Abstract]	252,616
#2	Particulate Matter[nm]	13,598
#1	Particulate Matter[Mesh]	55,047

A1.2 Search strategy for EMBASE

Search timeline: 1974–09.10.2018		Abstracts
#16	15 NOT 'time series':ti	1,962
#15	14 NOT ('occupational exposure'/exp/mj OR 'indoor air pollution'/exp/mj)	1,971
#14	13 NOT ('case report'/de OR 'clinical trial'/de OR 'medical record review'/de OR 'nonhuman'/de)	2,027
#13	'12 AND 'human'/de	2,275
#12	4 AND 7 AND 11	2,509
#11	OR/ 8-10	3,088,391
#10	cohort:ab,ti OR 'follow up':ab,ti OR longitudinal:ab,ti OR prospective:ab,ti OR retrospective:ab,ti	2,921,977
#9	'case control study'/exp	147,341
#8	'cohort analysis'/exp	401,441
#7	OR/ 4-6	2,207,348
#6	'death':ab,ti OR 'mortality':ab,ti	1,641,979
#5	'death'/exp	669,233
#4	'mortality'/exp	958,142
#3	1 OR 2	302,300
#2	'particulate matter':ab,ti OR 'particulate air pollution':ab,ti OR pm:ab,ti OR pm10:ab,ti OR pm2.5:ab,ti OR particles:ab,ti	292,768
#1	"particulate matter"/exp	36,016

Appendix 6b Certainty of evidence assessment

Table A6 Detailed assessment of certainty of evidence for each exposure-outcome combination ('+' implies increase in confidence)

	reasons for downgrading						reasons for upgrading					overall	Final certainty assessment					
	A1	rationale	A2	rationale	A3	rationale	A4	rationale	A5	rationale	B1			rationale	B2	rationale	B3	rationale
	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0			insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure
PM _{2.5} and all-cause	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM ₁₀ and all-cause	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM _{2.5} and circulatory	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM ₁₀ and circulatory	0	little influence on the overall effect	0	no evidence of indirectness	-1	prediction interval includes unity and larger than twice the CI	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	0	Moderate
PM _{2.5} and IHD	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM ₁₀ and IHD	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval includes unity but less than twice the CI	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	0	No evidence of a clear increasing risk with exposure	0	Moderate
PM _{2.5} and stroke	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval includes unity but less than twice the CI	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	No evidence of a clear increasing risk with exposure	+1	High
PM ₁₀ and stroke	0	little influence on the overall effect	0	no evidence of indirectness	-1	prediction interval includes unity and larger than twice the CI	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	0	No evidence of a clear increasing risk with exposure	-1	Low

(Table A6 Continued)

PM _{2.5} and respiratory	0	little influence on the overall effect	0	no evidence of indirectness	-1	prediction interval includes unity and larger than twice the CI The bulk of the assessed studies has effect estimates well above unity with only two exceptions with wide CI	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	0	Moderate
PM ₁₀ and respiratory	0	little influence on the overall effect	0	no evidence of indirectness	0		0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM _{2.5} and COPD	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM ₁₀ and COPD	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval includes unity but less than twice the CI	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	0	No evidence of a clear increasing risk with exposure	0	Moderate
PM _{2.5} and ALRI	0	little influence on the overall effect	0	no evidence of indirectness	0	Only one out of four studies reported a negative effect estimate with CI includes unity, other three studies reported significantly positive estimates	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM _{2.5} and Lung cancer	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM ₁₀ and Lung cancer	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval includes unity but less than twice the CI	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High

A1 = limitations in studies (risk of bias); A2 = indirectness; A3 = inconsistency; A4 = imprecision; A5 = publication bias

B1 = large RR; B2 = all confounding decreases observed RR; B3 = dose-response gradient

Appendix 7 (selected figures and Table A7.1)

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Figure A7.12 PM_{2.5} and all-cause mortality: all articles

Figure A7.27 PM_{2.5} and all-cause mortality: studies evaluating associations by restricting to low concentrations

Figure A7.28 Meta-analysis of PM_{2.5} and all-cause mortality: studies with mean PM_{2.5} concentrations below 25 µg/m³

Figure A7.29 Meta-analysis of PM_{2.5} and all-cause mortality: studies with mean PM_{2.5} concentrations below 20 µg/m³

Figure A7.30 Meta-analysis of PM_{2.5} and all-cause mortality: studies with mean PM_{2.5} concentrations below 15 µg/m³

Figure A7.31 Meta-analysis of PM_{2.5} and all-cause mortality: studies with mean PM_{2.5} concentrations below 12 µg/m³

Figure A7.32 Meta-analysis of PM_{2.5} and all-cause mortality: studies with mean PM_{2.5} concentrations below 10 µg/m³

Figure A7.34 Meta-analysis of PM_{2.5} and all-cause mortality: by sex

Figure A7.35 Meta-analysis of PM_{2.5} and all-cause mortality: by age group

Figure A7.36 Meta-analysis of PM_{2.5} and all-cause mortality: by level of mean PM_{2.5} concentrations

Figure A7.37 Meta-analysis of PM_{2.5} and all-cause mortality: two-pollutant model estimates

Figure A7.38 Meta-analysis of PM_{2.5} and all-cause mortality: single pollutant model estimates in studies that specified two-pollutant models

Figure A7.39 Meta-analysis of PM_{2.5} and all-cause mortality: excluding studies at high risk of bias

Figure A7.40 Meta-analysis of PM_{2.5} and all-cause mortality: studies without individual lifestyle excluded

Figure A7.41 Meta-analysis of PM_{2.5} and all-cause mortality: studies in patient populations added

Figure A7.43 Meta-analysis of PM_{2.5} and all-cause mortality: studies published after last search added

Table A7.1 Articles published after last search or missed in the search strategy

Author and Year	Study	Study Period	Study Location	Study Population	Study size	Exposure	HR (95% CI)		
							All-cause	CVD	respiratory
Pope, 2018	NHIS	1986-2011	US	Age 18-84 living in a MSA	392,807	PM _{2.5}	1.04 (1.01, 1.07)		
Pope, 2019	NHIS	1986-2015	US	Age 18-84	1,599,329	PM _{2.5}	1.13 (1.11, 1.16)		1.08 (0.99, 1.18)
Li, 2018	CLHLS	2008-2014	China	aged ≥ 65	13,344	PM _{2.5}	1.08 (1.07, 1.10)		
Fischer, 2020	DUELS	2008-2015	the Netherlands	age ≥ 30	7.5 million	PM ₁₀	1.12 (1.09, 1.14)		
						PM _{2.5}	1.17 (1.14, 1.20)		
Kim, 2019 ^a	NHIS-NSC	2002-2013	South Korea	age > 18	436,933	PM _{2.5}	1.03 (1.03, 1.04)	1.05 (1.04, 1.06)	
Hvidtfeldt, 2019	DCH	1993-2015	Copenhagen and Aarhus, Denmark	aged 50-64 years residing in the areas of Copenhagen and Aarhus	49,564	PM _{2.5}	1.28 (1.11, 1.47)	1.66 (1.28, 2.16)	1.14 (0.85, 1.54)
						PM ₁₀	1.12 (1.03, 1.22)	1.30 (1.11, 1.53)	1.04 (0.87, 1.24)
Hanigan, 2019	45 and up study	2006-2015	Sydney, Australia	aged 45 - 79	75,268	PM _{2.5}	1.63 (0.84, 3.18)		
Hayes, 2019	NIH-AARP	1995-2011	six US states and Atlanta and Detroit	age 50 to 71 years	565,477	PM _{2.5}		1.12 (1.07, 1.17)	
Lim, 2019	NIH-AARP	1995-2011	six US states and Atlanta and Detroit	age 50 to 71 years	548,780	PM _{2.5}	1.03 (1.01, 1.06)	1.11 (1.06, 1.16)	1.09 (1.00, 1.18)
Christidis, 2019	CCHS	2000-2016	Canada	non-institutional Canadian population aged 25-90	540,900	PM _{2.5}	1.11 (1.04, 1.18)		
Pappin, 2019	1991 CanCHEC	1991-2016			2.5 million		1.04 (1.02, 1.07)		
	1996 CanCHEC	1996-2016			3 million		1.04 (1.02, 1.06)		
	2001 CanCHEC	2001-2016	Canada	non-immigrants aged 25-90 years	3 million	PM _{2.5}	1.08 (1.06, 1.11)		
	pooled	1991-2016			8.5 million		1.05 (1.04, 1.07)		
Sun, 2019	Hong Kong elderly	1998-2011	Hong Kong	age ≥ 65	66,820	PM _{2.5}		1.19 (1.05, 1.35)	1.02 (0.87, 1.19)
Wong, 2016 ^b	Hong Kong elderly	1998-2011	Hong Kong	age ≥ 65	66,820	PM _{2.5}	1.13 (1.08, 1.19)		1.14 (0.96, 1.36)
Goss, 2014 ^b	patient	1999-2000	U.S.	cystic fibrosis patients aged > 6	11,484	PM _{2.5}	1.32 (0.91, 1.92)		

Hazard Ratio per 10 µg/m³ increase in PM_{2.5} or PM₁₀

^b only reported estimates from two-pollutant model adjusted for O₃

^a studies published in the search period but were not identified

Chapter 3

Spatial PM_{2.5}, NO₂, O₃ and BC Models for Western Europe – Evaluation of Spatiotemporal Stability

Kees de Hoogh, Jie Chen, John Gulliver, Barbara Hoffmann, Ole Hertel, Matthias Ketzel, Mariska Bauwelinck, Aaron van Donkelaar, Ulla A. Hvidtfeldt, Klea Katsouyanni, Jochem Klompmaker, Randall V. Martin, Evangelia Samoli, Per E. Schwartz, Massimo Stafoggia, Tom Bellander, Maciej Strak, Kathrin Wolf, Danielle Vienneau, Bert Brunekreef and Gerard Hoek

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Abstract

Background

In order to investigate associations between air pollution and adverse health effects consistent fine spatial air pollution surfaces are needed across large areas to provide cohorts with comparable exposures. The aim of this paper is to develop and evaluate fine spatial scale land use regression models for four major health relevant air pollutants (PM_{2.5}, NO₂, BC, O₃) across Europe.

Methods

We developed West-European land use regression models (LUR) for 2010 estimating annual mean PM_{2.5}, NO₂, BC and O₃ concentrations (including cold and warm season estimates for O₃). The models were based on AirBase routine monitoring data (PM_{2.5}, NO₂ and O₃) and ESCAPE monitoring data (BC), and incorporated satellite observations, dispersion model estimates, land use and traffic data. Kriging was performed on the residual spatial variation from the LUR models and added to the exposure estimates. One model was developed using all sites (100%). Robustness of the models was evaluated by performing a five-fold hold-out validation and for PM_{2.5} and NO₂ additionally with independent comparison at ESCAPE measurements. To evaluate the stability of each model's spatial structure over time, separate models were developed for different years (NO₂ and O₃: 2000 and 2005; PM_{2.5}: 2013).

Results

The PM_{2.5}, BC, NO₂, O₃ annual, O₃ warm season and O₃ cold season models explained respectively 72%, 54%, 59%, 65%, 69% and 83% of spatial variation in the measured concentrations. Kriging proved an efficient technique to explain a part of residual spatial variation for the pollutants with a strong regional component explaining respectively 10%, 24% and 16% of the R² in the PM_{2.5}, O₃ warm and O₃ cold models. Explained variance at fully independent sites vs the internal hold-out validation was slightly lower for PM_{2.5} (65% vs 66%) and lower for NO₂ (49% vs 57%). Predictions from the 2010 model correlated highly with models developed in other years at the overall European scale.

Conclusions

We developed robust PM_{2.5}, NO₂, O₃ and BC hybrid LUR models. At the West-European scale models were robust in time, becoming less robust at smaller spatial scales. Models were applied to 100x100 m surfaces across Western Europe to allow for exposure assignment for 35 million participants from 18 European cohorts participating in the ELAPSE study.

Abbreviations

CTM Chemical Transport Models

SAT Satellite-derived predictions

FULL Models developed using 100% of the monitoring sites

HOV Hold-Out-Validation models developed on 80% of the number of sites

1. Introduction

Ambient air pollution remains one of the main causes of morbidity and mortality in the world (Cohen et al., 2017). WHO's global assessment of ambient air pollution exposure estimated that one in nine deaths annually are caused by ambient air pollution (WHO, 2016). More recently, there is evidence showing that associations between mortality and morbidity and long-term exposure to outdoor air pollution might have no threshold, and extend to concentrations below current air quality limit values of the US EPA and EU (Beelen et al., 2015). Recent studies conducted in North-America have shown that long-term exposure to PM_{2.5} is associated with mortality also at low exposures (i.e. below the current WHO guideline of 10 µg/m³) (Crouse et al., 2015; Di et al., 2017; Pinault et al., 2017). Particularly in North-America and Europe, tougher air quality policies have led to a reduction in emissions and a gradual decline in ambient air pollution concentrations (EEA, 2017). Little, however, is known about the shape of the exposure-response curve at low concentrations, and thus the impact of low level concentrations on large populations remains uncertain.

The ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) study aims to fill this gap by investigating the relationship between long term air pollution and morbidity and mortality at low PM_{2.5} (Particulate Matter <2.5 µg), nitrogen dioxide (NO₂), black carbon (BC) and ozone (O₃) exposures. Low levels are defined as air pollutant concentrations below EU and/or US air quality limit values and/or WHO guidelines. ELAPSE includes 11 cohorts with in-depth individual data on lifestyle and 7 large administrative/national cohorts across Europe (<http://www.elapseproject.eu/>). Cohorts were selected to represent a contrast in air pollution exposures between and within study areas. The 11 detailed individual-level cohorts will be analyzed as a pooled cohort, whereas the administrative cohorts will be analyzed separately. Taken together, the evidence should allow collective consideration and evaluation. This study therefore needs consistent models that can provide valid exposures at two different spatial extents in Western Europe: combining all study regions of the detailed individual-level cohorts for the pooled analysis; and the national extents for the administrative/national cohorts. The previously developed ESCAPE LUR models (Beelen et al., 2013; Eeftens et al., 2012a) do not meet the requirements for the ELAPSE project because they do not cover the full national study areas. Secondly, methodological work by Basagana and Wang has shown that more stable models can be developed based on a larger number of model training sites than the 20 sites that the ESCAPE PM models were based upon (Basagaña et al., 2012; Wang et al., 2013). Finally, ESCAPE did not evaluate ozone.

Cohorts in the ELAPSE study have different recruitment and follow-up periods going back as early as the 1990's. Epidemiological studies have used the back-extrapolation method to estimate exposures back in time (Beelen et al., 2014; Chen et al., 2017). The method uses a well validated air pollution surface as the base and assumes that the spatial structure of this surface remains stable over time. Monitoring data from routine monitoring sites are then used to re-scale the surface back or forward in time (Cesaroni et al., 2012; Chen et al., 2010). Few studies have been able to document the stability of spatial surfaces, mostly focusing on NO₂ and at the city level (Cesaroni et al., 2012; Eeftens et al., 2011; Wang et al., 2013) or national scale (Gulliver et al., 2013). We thus evaluated the stability of these surfaces over time by comparing modelled estimates with historic monitoring data and by developing models for other years.

The aims of the paper are to:

1. develop and evaluate performance of fine spatial scale hybrid land use regression models for four major health relevant pollutants PM_{2.5}, NO₂, BC, O₃ across Western Europe;
2. investigate the temporal stability of the spatial contrast at the West-European and national scale.

This paper follows our recently published West-European fine scale air pollution exposure models for PM_{2.5} and NO₂ (de Hoogh et al., 2016). Models were based on both 2010 ESCAPE and the European

Environment Agency (EEA) AirBase routine monitoring data, and documented the contribution of satellite data and chemical transport models (CTM) to LUR models. An important finding was that models performed well when validated with data from the other measurement network (i.e. ESCAPE model validated with AirBase sites and vice versa). In the current paper we substantially extended this work, firstly by adding BC and O₃ which are both health relevant pollutants. We also improved the testing of the robustness of models by evaluating structure and predictions using five-fold hold-out-validation (HOV), following a study on land use regression models for ultrafine particles (van Nunen et al., 2017). We further assessed improving the LUR models using kriging and added new predictor variables with improved granularity, including 1x1 km satellite-derived PM_{2.5} to the previously used 10x10 km satellite data. Finally we added an assessment of the temporal stability of the models.

2. Materials and methods

2.1 Air pollution monitoring data

PM_{2.5}, NO₂ and O₃ daily concentration data for 2010 were derived from the AirBase v8 dataset (EEA, 2015). Only sites with $\geq 75\%$ completeness of the total hours (NO₂ and O₃) or days (PM_{2.5}) were accepted, and an annual average was calculated for PM_{2.5} and NO₂. For O₃, we calculated the maximum running 8-hour mean for each day and then averaged to obtain an annual, warm season (April through September) and cold season (January through March and October through December) average maximum running 8-hour mean. For BC, which is not available through AirBase, we used the ESCAPE annual mean BC concentrations (measured as PM_{2.5} absorbance based on reflectance measurement of the filters) reflecting the time period 2009-2010. Previous studies (Cyrus et al., 2012; Eeftens et al., 2012b) using AirBase data documented no difference in average BC concentrations between 2000 and 2010, therefore we treated all BC measurements as 2010 annual mean concentrations. A detailed description of the ESCAPE measurement campaign can be found elsewhere (Eeftens et al., 2012b). Table S1 describes the number of sites and summary statistics of the air pollution measurement data. The locations of the monitoring sites used for the 2010 models are shown in Figure S1. For temporal stability analysis we additionally included NO₂ and O₃ daily concentration data for 2000 and 2005 from AirBase v8 and daily PM_{2.5} concentration data for 2013 from Air Quality e-Reporting (www.eea.europa.eu/data-and-maps/data/aqereporting-8). There were insufficient PM_{2.5} sites across Western Europe before 2010.

2.2 Predictor variables

2.2.1 Satellite derived air pollution data

In addition to the satellite-derived (SAT) PM_{2.5} product (v3.01) used in the previous paper (de Hoogh et al., 2016), we tested two additional different SAT PM_{2.5} products, which have become available only recently, as potential predictors. These were obtained from the global dataset reported in Van Donkelaar et al. (2015). Aerosol Optical Depth (AOD) retrievals from the NASA MODIS (Moderate Resolution Imaging Spectroradiometer), MISR (Multi-angle Imaging Spectroradiometer) and SeaWiFS instruments were related to near-surface concentrations using aerosol vertical profiles and scattering properties simulated by the GEOS-Chem CTM, to produce an annual average PM_{2.5} dataset at a 0.1° x 0.1° (~10km) resolution for 2010. In the previous paper we used a dataset inferred from 2009-2011 (optimized for 2010), here we additionally tested the inferred data from 2010 data only. We further included the current, purely geophysical, global PM_{2.5} dataset (V4.GL.02.NoGWR), which includes some information at the finer resolution of 0.01° x 0.01° (~1km) published by van Donkelaar et al. (2016). The pre-Geographically Weighted Regression dataset used here includes AOD from multiple satellite products (MISR, MODIS Dark Target, MODIS and SeaWiFS Deep Blue, and MODIS MAIAC) together with simulation-based sources, with information content below ~10km provided by the MAIAC AOD retrieval. PM_{2.5} satellite data was offered as a predictor to the PM_{2.5}

models. No BC satellite data were available and because BC is a major component of PM_{2.5}, PM_{2.5} satellite data were also offered to the BC models.

NO₂ SAT estimates for 2010 were derived from the tropospheric NO₂ columns measured with the OMI (Ozone Monitoring Instrument) on board the Aura satellite. Like PM_{2.5}, the satellite column-integrated retrievals were related to ground-level concentrations using the global GEOS-Chem model, producing an annual gridded NO₂ surface at a 10km resolution (Bechle et al., 2013, 2015; Novotny et al., 2011). NO₂ satellite predictors were offered to the NO₂ models. No O₃ satellite data were available but, because NO₂ is related to O₃ formation and scavenging, NO₂ satellite data was also offered to the O₃ models.

2.2.2 Chemical transport model (CTM) data

Pollutant estimates for 2010 from two long range CTM's were obtained as potential predictor variables for the models. Annual PM_{2.5}, NO₂ and O₃ estimates were derived from the MACC-II ENSEMBLE model at a 0.1° x 0.1° (~10km) resolution (Inness et al., 2013). The ENSEMBLE model provides a value at each pixel which is defined as the median value of seven individual CTMs: CHIMERE, EMEP, EURAD, LOTOS-EUROS, MATCH, MOCAGE and SILAM. Annual MACC-II ENSEMBLE averages for PM_{2.5}, NO₂ and O₃ were offered to the respective LUR models. We additionally acquired a second CTM dataset from the Danish Eulerian Hemispheric Model (DEHM_v31102016) for PM_{2.5}, NO₂, O₃ and BC at a monthly 50x50 km resolution (Brandt et al., 2012). Annual DEHM averages were calculated for all pollutants and offered to the respective LUR models, while warm and cold averages of O₃ were offered to the warm and cold season models.

2.2.3 Other predictor variables

The GIS predictor variables used in this study are described in more detail elsewhere (de Hoogh et al., 2016; Vienneau et al., 2013). In brief, road data, classified as 'all' and 'major' roads, were extracted from the 1:10,000 EuroStreets digital road network (version 3.1 based on TeleAtlas MultiNet TM, year 2008). Land cover data were extracted from European Corine Land Cover 2006 data (ETC-LC, 2013) except for Greece for which Corine Land Cover 2000 was used (ETC-LC, 2009). The 100 m resolution Corine datasets, with an initial 44 land classes, were grouped into six main land cover groups. Elevation was extracted from the SRTM Digital Elevation Database version 4.1 which has a resolution of one arc second (approximately 90 m) and a vertical error <16 m (CGIAR-CSI, 2013). We additionally obtained 1x1 km population data for 2011 from Eurostat (EC, 2011).

Both road and land cover databases were intersected with a 100x100 m base polygon and the sum of road length (for 'all' and 'major' roads) and sum of land cover area (for the six grouped land classes) were calculated. The 100x100 m polygons were converted to grids and a focalsum procedure was applied to calculate these predictor variables for different distances, i.e. "buffers". All potential predictor variables are listed in Table S2, and GIS analysis was conducted in ESRI ArcGIS 10.5.

2.3 Model development and evaluation

A two-stage statistical procedure was applied to explain the spatial variation in the measurement data. Firstly, separate standard LUR models were developed based on all measurements for each pollutant. LUR models were developed according to the ESCAPE protocol; i.e. supervised stepwise linear regression as used in our previous paper (de Hoogh et al., 2016). Predictor variables were only allowed to enter the model if they adhered to the predefined direction of effect (see Table S2). For example, road density, an indicator of traffic, has a positive (+) effect in the prediction of NO₂, PM_{2.5} and BC and therefore will increase concentrations. Other variables like altitude and natural land will have a negative (-) effect on the same pollutants, and will therefore decrease concentrations. We allowed significant predictor variables to enter the model when they added to the adjusted R² of the previous model step. Secondly, using the urban and rural background sites only, we explored the remaining broad scale variation in the residuals. Ordinary kriging was applied to the residuals using

the GSTAT R package (LUR + kriging). If kriging was not successful (i.e. we could not fit a kriging function through the residuals) we offered longitude and/or latitude to the LUR model as additional predictors.

For each pollutant, six LUR models for 2010 were developed. The main model was developed using all sites (FULL). To test the robustness and stability of this model we additionally developed five hold out validation (HOV) models (HOV1, HOV2,..., HOV5), each built on 80% of the monitoring sites with the remaining 20% used for validation. Sites were selected into five groups (20% of sites) at random, stratified by site type and country.

HOV was performed after the LUR modeling and after the kriging (when applicable) using the criteria R^2 and root mean square error (RMSE). The main model (FULL, developed on all available sites) was evaluated against the 5 HOV samples.

For $PM_{2.5}$ and NO_2 we were able to perform an additional independent comparison with the ESCAPE monitoring datasets. Comparisons were performed at different scales: 1) overall (all ESCAPE sites); 2) overall ELAPSE (ESCAPE sites falling in ELAPSE study areas); and 3) matched to individual ELAPSE study areas (both detailed individual-level and administrative cohorts). Since the BC model was developed using the ESCAPE measurements, no independent comparison was possible.

2.4 Stability of spatial structure

In back extrapolation we assume that the spatial structure remains the same going back in time. To investigate the stability of the spatial structure of the models, and to test this assumption, we developed models for NO_2 and O_3 (2000 and 2005) using the same methods described in section 2.3. For $PM_{2.5}$ it was not possible to develop models for 2000 and 2005 due to the lack of monitoring data (12 and 165 in 2000 and 2005 respectively), instead we developed a model for 2013 (number of included monitoring sites = 732). The FULL models were mapped at a 100x100 m resolution across the study area and for the different years we visually inspected the spatial patterns.

As we did not have access to cohort geocodes, we created a random point file of 150,000 points across the full rectangular extent of the study area. After intersecting with the study area boundary, approximately 44,000 points remained which was considered a sufficient number to evaluate the stability. These points were intersected with all the raster surfaces: 2010 for $PM_{2.5}$, NO_2 and O_3 (annual, cold season and warm season); 2013 for $PM_{2.5}$; and 2005 and 2000 for NO_2 and O_3 . Comparisons of model predictions were made for the West-European countries combined and at the national scale reporting R^2 , RMSE and fractional bias (FB). In addition we calculated population weighted annual means (see equation 1) (Briggs et al., 2007) for $PM_{2.5}$, NO_2 and O_3 , using the 1x1 km GEOSTAT population database (EC, 2011).

$$\text{Pop-w-exposure} = \Sigma(\text{pop} \times \text{conc}) / \Sigma \text{pop} \quad (\text{equation 1})$$

We additionally evaluated the correlation of annual average measurements (plus summer and winter average for O_3) for those AirBase stations with measurements going sufficiently back in time.

2.5 Population exposure

For 2010, we calculated the total population of West-European countries (based on the GEOSTAT 2011 population grid dataset (EC, 2011)) residing in $PM_{2.5}$ and NO_2 concentration classes.

3. Results

3.1 Air pollution models 2010

The performance statistics (squared Pearson correlation (R^2) and RMSE) and model structure of the FULL hybrid models for all pollutants are presented in Table 1 including the LUR component and,

where applicable, the combined LUR + kriging component. The variograms of the kriging models for PM_{2.5}, O₃ in the warm and cold season are shown in Figure S2. A detailed model description, including constants, coefficients, incremental R² and RMSE can be found in Table 2 for PM_{2.5} and the Supplementary material for the other pollutants (Table S3) and years (Table S4). Figure 1 shows the mapped surfaces at a 100x100 m resolution of the FULL models for all pollutants.

3.1.1 PM_{2.5} models

The PM_{2.5} LUR model developed on all available monitoring sites (FULL) explained 62% of spatial variation of the measured PM_{2.5} concentrations (Table 1). Apart from satellite and CTM estimates, the LUR model included altitude, all roads, natural areas, ports and residential area. The satellite variable was the strongest predictor in all models explaining approximately 48% of the spatial variation in measured PM_{2.5} concentrations. Comparing the predicted increase in PM_{2.5} across a change from the 1st to the 99th percentile of each predictor, satellite and CTM PM_{2.5} were associated with the largest contrast in PM_{2.5}. The model included large scale predictors (CTM, SAT at 10x10 km) and small-scale road, natural and residential land (50-200m) predictors. Kriging increased the explained variation to 72%.

The difference between the calibration and HOV R² of the FULL PM_{2.5} model was small (72% vs 66%) confirming that overfitting was unlikely to be a big problem in the model development (Table 2). Similar predictor variables as in the FULL model were retained in the validation models, with only ports and urban green not always present in each model. Consistently, predictions of the six models (FULL and 5 HOV) at the 44,000 randomly selected sites were very highly correlated documenting the robustness of the model (Figure S3).

The mapped FULL PM_{2.5} model (see Figure 1) showed predicted levels of PM_{2.5} > 20 µg/m³ in major cities and the Po area (the Po river basin running from the Western Alps to the Adriatic Sea) in Italy. Large parts of Northern Europe had low (<10 µg/m³) predicted PM_{2.5} concentrations.

We tested the three different PM_{2.5} satellite products in preliminary PM_{2.5} model development and found that the 0.1° x 0.1° inferred 2009-2011 product v3.01 produced the best results (see the Supplementary material section 1 and Table S5 for a more detailed description).

3.1.2 NO₂ models

The FULL NO₂ model explained 59% of the spatial variation (Table 1 and Table S3). In all models the CTM variable was the strongest predictor explaining approximately 29% of variation in NO₂ concentrations, followed by the small (100-300m) and larger scale (2000m) road variables. All roads, major roads, natural and residential predictor variables consistently appeared in every model. Predictions of the six models (FULL and 5 HOV) models at the 44,000 randomly selected sites were very highly correlated (Figure S3). None of the variogram models adequately fit the residuals at the NO₂ background monitoring sites, nor did including longitude and/or latitude help explain the residuals (p-value of coefficient not significant). The mapped NO₂ estimates (Figure 1) showed more variation compared to PM_{2.5}. Major roads and cities clearly stood out with predicted concentrations generally > 30 µg/m³. Away from sources in rural areas, NO₂ levels dropped below 15 µg/m³.

3.1.3 O₃ models

Around half of the spatial variation in the annual O₃ measurements was explained by the CTM (MACC-O₃) variable. Other variables consistently entering all 6 annual models were roads, residential land cover and altitude (Table S3). Ports entered the FULL model and 4 of the 5 HOV models. The CTM was associated with much larger contrast in O₃ than the other predictors. Predictions of the 6 models (FULL and 5 HOV) models at the 44,000 randomly selected sites were very highly correlated (Figure S3). No reliable kriging function could be fit through the residuals of O₃ background monitoring sites. However, latitude and longitude variables were fit to the models. The FULL model had a R² of 65% (HOV models ranging from 63 to 68%).

Table 1. Model structure^a and performance of 2010 LUR models

Pollutant	Stage	Method	N sites	R ²	RMSE ^b	Full LUR model ^c
PM _{2.5}	Training	LUR	543	62.2	3.17	3.19 + 13.24*SAT-PM25 + 7.08*MACC-PM25 - 3.82* ALT + 2.17*ALRD ₁₀₀ - 2.07*NAT ₅₀ + 2.39*POR ₈₀₀ + 1.41*RES ₂₀₀
		LUR +Kriging		72.2	2.71	
	HOV	LUR		58.7	3.30	
		LUR +Kriging		66.4	2.97	
BC ^d	Training	LUR	436	54.4	0.56	0.99 + 0.85* MACC-PM25 + 0.30* SAT-PM25 + 0.68*MJRD ₁₀₀ + 0.40* ALRD ₅₀ + 0.45* ALRD ₇₀₀ + 0.90*RES ₃₀₀₀ - 0.12*UGR ₁₀₀₀ - 1.16*Y
	HOV	LUR		51.4	0.58	
NO ₂ ^d	Training	LUR	2399	58.8	9.38	3.30 + 22.73*MACC-NO ₂ + 7.04* ALRD ₅₀ + 3.92* ALRD ₃₀₀ + 12.32* MJRD ₁₀₀ + 15.73*ALRD ₂₀₀₀ - 3.38*NAT ₄₀₀ + 4.1*POR ₇₀₀ + 5.8*RES ₃₀₀
	HOV	LUR		57.5	9.51	
O ₃ annual ^d	Training	LUR	1747	65.1	6.73	40.54 + 25.51*MACC-O ₃ - 2.49*ALRD ₅₀ - 4.75* ALRD ₂₀₀ - 3.24* MJRD ₂₀₀ - 1.57*POR ₄₀₀₀ - 1.94*RES ₅₀₀ - 4.13*RES ₂₀₀₀ + 8.82*ALT + 2.48*X - 10.05*Y
	HOV	LUR		63.4	6.87	
O ₃ warm	Training	LUR	1730	45.5	10.07	30.00 + 32.57*DEHM-O ₃ - 6.87* ALRD ₂₀₀ - 6.03* MJRD ₁₀₀ - 5.95*PORT ₅₀₀₀ - 4.79*RES ₂₀₀₀ + 5.70*ALT
		LUR +Kriging		69.6	7.51	
	HOV	LUR		44.5	10.15	
		LUR +Kriging		59.9	8.63	
O ₃ cold	Training	LUR	1716	67.7	7.43	1.00 + 37.62*MACC-O ₃ - 3.35* ALRD ₂₀₀ - 3.48* MJRD ₅₀ - 1.61* MJRD ₇₀₀ + 5.81*NAT ₇₀₀ - 4.18*RES ₁₂₀₀ - 1.10*TBU ₁₀₀ + 2.21*UGR ₁₀₀₀ + 6.84*ALT
		LUR +Kriging		83.3	5.33	
	HOV	LUR		66.5	7.55	
		LUR +Kriging		75.3	6.99	

a. Regression slope in $\mu\text{g}/\text{m}^3$, except BC (10^{-5}m^{-1}), multiplied by the difference between the 1st and 99th percentile of each predictor to allow comparison across predictors
b. RMSE in $\mu\text{g}/\text{m}^3$, except BC (10^{-5}m^{-1})

c. ALT = altitude, ALRD = all roads, MJRD = major roads, IND = industry, POR = ports, UGR = urban green, TBU = total build up, NAT = natural land, RES = residential, POP = sum of population, X = North-South trend, Y = East-West trend, SAT = satellite, MACC = MACC dispersion model, DEHM = DEHM CTM.

Number in subscript depicts the buffer size (e.g. ALRD₁₀₀ = sum of all road length within 100 m)

d. No valid variograms were possible on the residuals of these models

Table 2. Structure and performance of LUR models^a for PM_{2.5} for full dataset and five hold-out validation datasets for 2010

Theme	Variable ^b	FULL ^c	HOV1	HOV2	HOV3	HOV4	HOV5
Satellite	(Constant)	3.19	3.46	3.53	3.14	3.49	3.32
	SAT-PM25	13.24	12.98	12.39	13.19	12.68	13.55
CTM	MACC-PM25	7.08	7.32	7.45	7.17	7.09	6.93
Altitude	ALT	-3.82	-3.82	-4.10	-3.93	-3.54	-3.73
Roads	ALRD ₁₀₀	2.17	2.89		2.23	2.00	
	MJRD ₅₀						1.98
	MJRD ₁₀₀			2.26			
Urban green	UGR ₇₀₀		-1.08				
	UGR ₈₀₀					-0.98	
Nature	NAT ₅₀	-2.07	-2.24			-2.72	-2.26
	NAT ₁₀₀			-2.31	-2.12		
	NAT ₃₀₀						
Ports	NAT ₄₀₀						
Residential	POR ₈₀₀	2.39	3.19		2.95	2.46	2.35
	RES ₅₀		0.89				
	RES ₂₀₀	1.41		1.72	1.44	1.48	
	RES ₃₀₀						1.39
Training (LUR)	R ²	62.2	62.0	63.1	61.1	60.8	66.0
	RMSE	3.17	3.26	3.10	3.30	3.22	2.95
HOV (LUR)	R ²	58.7	62.2	53.9	67.4	68.1	50.3
	RMSE	3.30	2.93	3.67	2.68	3.01	3.94
Training (LUR + Kriging)	R ²	72.2	71.4	70.5	76.8	76.0	63.3
	RMSE	2.71	2.55	2.94	2.26	2.61	3.38
HOV (LUR + Kriging)	R ²	66.4	67.7	66.0	72.3	74.0	57.9
	RMSE	2.97	2.71	3.15	2.47	2.72	3.61

- Regression slope $\mu\text{g}/\text{m}^3$ were multiplied by the difference between the 1st and 99th percentile of each predictor to allow comparison across predictors
- ALT = altitude, ALRD = all roads, MJRD = major roads, IND = industry, POR = ports, UGR = urban green, TBU = total build up, NAT = natural land, RES = residential, POP = sum of population, X = North-South trend, Y = East-West trend, SAT = satellite, MACC = MACC dispersion model, DEHM = DEHM CTM. Number in subscript depicts the buffer size (e.g. ALRD₁₀₀ = sum of all road length within 100 m)
- FULL refers to all sites; HOV1 is first holdout validation dataset (80% stratified random sample)

Figure 1. Mapping of hybrid West European LUR models for PM_{2.5}, BC, NO₂ and O₃ warm season at 100x100 m ($\mu\text{g}/\text{m}^3$, BC 10^{-5}m^{-1}).

Like the annual O₃ model, the cold season O₃ model was dominated by the MACC predictor variable, explaining nearly 60% of the spatial variation in measured O₃ concentrations. Roads, residential land and altitude variable entered in all 6 cold season models. Kriging explained, on average, an additional 16% of the spatial variation, bringing the final performance of the FULL O₃ cold model to 83% (80% to 85% for the 5 validation models).

The O₃ warm season models also contained a CTM variable, but unlike the annual and cold season O₃ models where the annual MACC CTM variable entered, here the warm season DEHM CTM variable was the stronger predictor. Other variables entering in all models were roads, ports, residential land and altitude. The performance of LUR models was moderate (R² ranging from 44 to 48%) but with additionally fitted kriging functions, we increased the explained variation to 70% for the FULL model (67% to 73% for the 5 validation models).

Maps of the FULL O₃ models (Figure 1 and S4) showed similar general patterns for annual and cold season, with the highest predicted O₃ concentrations in Southern Europe and lower concentrations in more central areas (England, the Netherlands, Germany and northern Italy). Areas of high altitude also tended to have higher predicted O₃ levels compared areas of lower altitudes. Predicted O₃ concentrations for the warm season showed a somewhat different spatial pattern with a much clearer negative North-South gradient than the cold season model.

3.1.4 BC models

For the FULL BC LUR model we achieved an explained variation of 54% (FULL model) and between 52 and 57% for the 5 HOV models (Table 1, Table S3). For all 6 models, the CTM MACC-PM_{2.5} contributed 24 to 30% of the explained spatial variation. Roads, PM_{2.5} SAT estimates, urban green land, residential land and natural land were also included consistently in FULL and HOV models. Predictions of the 6 (FULL and 5 HOV) models at the 44,000 randomly selected sites were very highly correlated (Figure S3). The BC model included large contributions from large-scale predictors (CTM PM_{2.5}, Y-coordinate and residential density) and small-scale predictors (roads and residential density).

Due to the clustered nature of the BC monitoring data it was not possible to perform kriging. Latitude was best able to explain the residuals.

When mapped across Western Europe (Figure 1), BC predicted concentrations showed a distinct North – South division, with low ($\leq 0.8 \cdot 10^{-5} \text{m}^{-1}$) BC concentrations in Scandinavia and the north of the UK, and higher $> 0.8 \cdot 10^{-5} \text{m}^{-1}$ in the rest of Western Europe. Mediterranean Europe had the highest concentration $> 1.2 \cdot 10^{-5} \text{m}^{-1}$. Traffic sources were also clearly identifiable in the inset with major roads visible around Paris.

3.2 Comparison at ESCAPE sites

We performed an independent external comparison for PM_{2.5} and NO₂ FULL models using measured concentration data from the ESCAPE study. Table 3 shows the correlations at different scales including the mean and standard deviation of measured concentrations at the ESCAPE measurement sites.

The PM_{2.5} FULL model explained 65% of variance overall (n=416) with a small fractional bias (FB = -2%). The explained variance is almost identical to the HOV R² of 66% (Table 1). Restricting the analysis to the overall area with ELAPSE cohorts (n = 255) led to a slight decrease in the explained variance (59%) and a small overestimation (FB = -10%). The comparison at each ELAPSE study areas separately (detailed individual-level and administrative cohorts) revealed a large range in the explained variation, 8% for EPIC Oxford and English administrative cohort to 66% for HNR, also with the FB varying from -2 to -30%. We note that the number of sites is relatively small for the individual area comparisons.

NO₂ FULL models also showed reasonable associations for overall (49%) and overall ELAPSE (46%). The explained variance was modestly lower than the HOV R² of 57% (Table 1). FB indicated a small overestimation of 13% for the ELAPSE overall area. At the ELAPSE detailed individual-level cohorts the correlations for NO₂ were generally better than for PM_{2.5}: all were >47% except for HUBRO (7%) and EPIC VARESE (34%). FB showed overestimation for all areas, except for ELAPSE areas in Italy.

Table 3. Comparison of PM_{2.5} and NO₂ ELAPSE models at ESCAPE monitoring sites

Pollutant		PM _{2.5}			Measurements		N ^b
Name ESCAPE area		R ²	RMSE	FB ^a	Mean	SD	
Overall		64.8	3.41	-0.02	15.86	5.73	416
Overall ELAPSE		58.7	2.85	-0.10	14.16	4.43	255
ELAPSE cohorts							
HUBRO	Oslo, NO	18.4	2.04	-0.30	8.59	2.20	19
CEANS	Stockholm County, SE	39.0	1.32	-0.04	8.29	1.64	19
DCH	Copenhagen, DK	40.1	1.26	-0.18	11.12	1.58	20
EPIC-NL	NL	12.6	1.71	-0.02	17.35	1.80	34
EPIC OXFORD	London- Oxford, Manchester, UK	7.6	2.23	-0.26	10.55	2.29	39
HNR	Ruhr Area, GER	65.5	0.97	-0.06	18.52	1.61	20
KORA	Munich-Augsburg, GER	31.5	1.44	-0.16	14.34	1.70	20
VHM&PP	Vorarlberg, AU	22.4	1.74	-0.19	13.34	1.92	20
E3N	Paris, FR	38.7	3.30	-0.24	16.02	4.10	20
EPIC VARESE	n.a.	-	-	-	-	-	-
DNC	n.a.	-	-	-	-	-	-
Administrative ELAPSE cohorts							
Dutch	NL	12.6	1.71	-0.02	17.35	1.80	34
English	London- Oxford, Manchester, UK	7.6	2.23	-0.26	10.55	2.29	39
Rome	Rome, IT	43.0	2.51	0.16	19.77	3.24	20
Danish	n.a.	-	-	-	-	-	-
Norwegian							
Swiss ^c	Lugano, CH	-	-	-	-	-	-
Belgian ^c	Antwerp, BE	-	-	-	-	-	-
Pollutant		NO ₂			Measurements		N
ESCAPE area		R ²	RSME	FB	Mean	SD	
Overall		49.4	11.47	-0.08	29.32	16.12	1396
Overall ELAPSE		45.8	10.28	-0.13	29.74	13.95	780
ELAPSE cohorts							
HUBRO	Oslo, NO	7.0	12.74	-0.19	24.29	13.05	39
CEANS	Stockholm County, SE	55.0	5.03	-0.50	15.49	7.44	39
DCH	Copenhagen, DK	59.0	5.99	-0.54	17.82	9.21	41
EPIC-NL	NL	75.9	5.10	-0.26	28.76	10.32	68
EPIC OXFORD	London -Oxford, Manchester, Bradford, UK	53.9	8.64	-0.17	29.82	12.67	119
HNR	Ruhr Area, GER	54.0	6.74	-0.20	33.16	9.76	40
KORA	Munich-Augsburg, GER	64.0	5.79	-0.13	26.82	9.58	40
VHM&PP	Vorarlberg, AU	47.0	5.29	-0.10	22.59	7.17	40
E3N	Paris, Grenoble, Lyon, Marseille, FR	52.6	12.37	-0.01	34.42	17.90	160
EPIC VARESE	Varese, IT	34.0	13.78	0.10	36.53	16.54	20
DNC	n.a.	-	-	-	-	-	-
Administrative ELAPSE cohorts							
Dutch	NL	75.9	5.10	-0.26	28.76	10.32	68
English	London-Oxford, Manchester, Bradford, UK	53.9	8.64	-0.17	29.82	12.67	119
Rome	Rome, IT	51.0	9.72	0.23	42.64	13.71	40
Danish	n.a.	-	-	-	-	-	-
Norwegian	n.a.	-	-	-	-	-	-
Swiss	Basel, Geneva, Lugano, CH	13.7	7.55	-0.16	30.03	8.09	121
Belgian ^c	Antwerp, BE	-	-	-	-	-	-

a. FB = Fractional Bias calculated as $2 * (\text{mean observations} - \text{mean predictions}) / (\text{mean observations} + \text{mean predictions})$

b. N = number of ESCAPE monitoring sites (the same for black carbon and PM_{2.5})

c. Covers only a small part of the area, with insufficient number of sites

3.3 Air pollution models for different time periods and stability analysis

3.3.1 Models for 2000, 2005 (NO₂ and O₃) and 2013 (PM_{2.5})

The performance statistics of the PM_{2.5}, NO₂ and O₃ models for different years are presented in Table S4. The 2013 PM_{2.5} LUR models explained 64% of spatial variation in the PM_{2.5} measurements. The LUR models had some similarities with the 2010 models, with MACC, SAT, roads and natural land entering all models. Neither reliable kriging models nor longitude/latitude variables improved the models.

No NO₂ MACC CTM estimates were available for the years 2000 and 2005, so only DEHM NO₂ for 2000 and 2005 estimates were offered to the NO₂ model development. Otherwise the NO₂ models showed a similar structure with the 2010 NO₂ LUR models (CTM, roads, natural land, residential land and ports in all models), but performed slightly less well (R^2 NO₂ 2000 = 56%; R^2 NO₂ 2005 = 52%).

O₃ models for 2000 and 2005 were able to respectively explain 60% and 49% (annual), 82 and 42% (warm season), 52 and 70% (cold season) of the variation in measured concentrations. The 2000 and 2005 annual and warm O₃ models contained DEHM CTM variables whereas no DEHM variable entered the cold season models. Kriging models explained an additional ~ 25% of spatial variation in the 2000 warm season and the 2005 cold season models. Latitude and longitude variables were entered to the other models.

Figure 1 shows the maps of PM_{2.5} (2013, 2010), NO₂ and O₃ warm season (2010, 2005, 2000). Similar patterns over multiple years were observed with, for example, high predicted PM_{2.5} concentrations for both 2010 and 2013 in the Po valley in North Italy and low PM_{2.5} concentrations in Scandinavia. Spatial patterns in the NO₂ and O₃ concentrations maps for the 3 years also appeared broadly similar.

3.3.2 Comparison of model predictions for Western Europe across years

Table 4 (and Figure S5) shows the results of the stability tests at country level. Agreement in spatial variation was generally high at the overall EU country and combined ELAPSE country level (>76%) for all comparisons, except for the O₃ cold season surface (44% when 2000 model compared to 2010). At the national level, focusing on ELAPSE countries only, we observed some heterogeneity in the associations. Both 2000 and 2005 NO₂ surfaces showed a high agreement with the 2010 NO₂ surface (all ELAPSE countries >80%). The agreement between PM_{2.5} surfaces developed for 2010 and 2013 showed more variability, with four ELAPSE countries >80% (UK, Sweden, Belgium and Italy), the Netherlands 70% and the rest between 48 and 60%. There was a high variability between the associations of the different O₃ surfaces. The agreement between O₃ annual surfaces of 2000 and 2005 with 2010 was reasonable, all ELAPSE countries had >60% explained spatial variability, with the exception of Sweden (2000) with 45%. Except for the 2005 O₃ cold (all ELAPSE countries > 60%), the O₃ cold and warm season surfaces were less stable over time with large ranges of explained spatial variability. Italy performed poorly with 1.6%, 11.9% and 16.6% for respectively 2000 warm season, 2005 warm season and 2000 cold season (combined with the largest RMSE's).

NUTS areas are standard administrative divisions of EU countries for statistical purposes. We performed the stability analysis using the same 44,000 random points at the NUTS1 area level (see Figure S6) to gain a better understanding of the stability at the sub-national level. Similar to the national level, there was a good agreement for all areas for NO₂ 2000 and 2005 when compared to the 2010 surface ($R^2 > 0.60$). For more details see the Supplementary material section 2.

3.3.3 Comparison of measurements

We additionally evaluated the relationship between measured average concentrations for those AirBase stations with measurements going sufficiently back in time between 2010 to 2005 and 2000 (Table 5). In Western Europe the measured concentrations between the different years yielded high

Table 4. Stability analysis at country level: predictions of the 2010 LUR model versus models from other years at randomly selected points (in squared correlation, R^2 in percentages, RMSE in $\mu\text{g}/\text{m}^3$)

Region	PM _{2.5} 2013 R ² (%)	NO ₂ 2005 R ² (%)	NO ₂ 2005 RMSE	NO ₂ 2000 R ² (%)	NO ₂ 2000 RMSE	O ₃ 2005a ^a R ² (%)	O ₃ 2005a ^a RMSE	O ₃ 2005c ^a R ² (%)	O ₃ 2005c ^a RMSE	O ₃ 2000c ^a R ² (%)	O ₃ 2000c ^a RMSE	O ₃ 2005w ^a R ² (%)	O ₃ 2005w ^a RMSE	O ₃ 2000w ^a R ² (%)	O ₃ 2000w ^a RMSE	N	
All West-European countries	88.2	1.9	91.9	1.9	2.0	85.8	3.5	78.8	4.3	80.4	4.3	84.3	4.6	76.4	5.6	44.000	
ELAPSE countries																	
Combined	89.3	1.9	92.6	2.0	91.4	2.1	82.7	3.2	82.0	3.3	87.0	3.3	81.6	4.6	78.3	5.0	34762
Austria	60.1	2.0	86.7	1.3	87.4	1.9	81.9	3.7	82.7	4.1	80.9	3.4	82.5	3.4	64.5	3.9	1050
Belgium	84.1	1.0	90.9	1.4	84.6	2.3	81.5	1.9	87.4	1.9	89.6	1.9	86.5	2.0	70.6	2.5	352
Switzerland	52.5	1.9	91.5	1.2	92.6	1.8	94.6	2.4	95.2	2.7	88.2	3.3	87.9	3.5	88.7	4.6	503
Germany	57.6	1.2	85.0	1.3	80.5	2.2	64.0	2.7	69.2	3.0	75.5	3.1	47.3	3.8	63.7	4.4	4232
Denmark	48.8	1.1	88.8	0.8	84.8	1.6	73.0	1.2	71.1	1.3	71.0	1.6	63.6	1.5	73.2	1.6	527
France	57.4	1.5	89.0	1.1	82.9	1.9	83.2	2.7	80.4	3.5	87.6	3.0	76.3	3.4	86.8	4.1	6475
Italy	82.6	1.7	81.9	1.6	82.6	2.3	59.9	4.4	64.8	4.9	90.0	4.3	11.9	5.2	1.6	12.3	3548
Netherlands	70.1	0.9	87.9	1.6	81.9	2.7	60.4	2.2	71.8	2.1	73.0	2.3	79.3	2.2	53.1	2.6	454
Norway	59.3	0.9	83.3	0.5	83.4	0.8	88.6	1.7	79.4	2.4	79.0	2.2	71.7	3.1	79.4	2.4	3449
Sweden	86.2	0.9	93.1	0.5	91.3	0.8	65.5	1.6	45.1	2.2	78.9	1.7	76.6	1.6	87.4	1.7	5353
United Kingdom	89.8	1.2	95.3	1.1	93.0	2.0	71.8	2.0	78.1	2.1	81.9	3.3	52.2	2.5	53.0	3.3	2845
Non ELAPSE countries																	
Greece	64.4	1.2	86.5	0.9	83.3	1.6	40.9	3.7	49.5	3.8	14.2	6.6	34.7	3.9	19.4	5.1	1549
Finland	44.2	1.0	92.7	0.4	89.7	0.8	52.4	1.0	46.3	1.2	25.2	2.4	70.2	1.3	69.7	1.6	4008
Hungary	53.9	0.9	84.3	0.9	84.8	1.2	50.8	1.3	38.4	1.6	21.6	3.9	54.1	1.2	38.6	2.3	1118
Ireland	73.9	0.8	92.7	0.6	90.2	1.0	52.0	1.3	49.1	1.4	79.1	2.4	61.1	1.2	61.6	2.3	841
Lithuania	56.3	0.9	89.7	0.6	85.1	1.0	52.9	1.1	40.8	1.2	65.3	1.9	54.8	0.9	24.4	1.7	780
Luxembourg	68.3	0.9	89.0	1.3	77.9	2.2	73.9	1.3	75.4	1.4	74.1	2.6	47.2	1.8	57.7	1.4	31
Portugal	63.8	1.1	85.4	1.0	87.0	1.6	71.3	1.9	67.4	2.2	62.1	3.3	33.0	2.4	37.4	3.9	1015
Spain	69.4	1.1	77.8	1.2	79.7	1.7	65.6	2.8	58.5	3.6	62.8	4.4	42.9	3.4	38.9	7.0	5974

a. O3 a for annual, c for cold season and w for warm season.

Table 5. Correlations between concurrent AirBase measurements (background sites only) in 2010 with 2000 and 2005 (NO₂, O₃ annual, warm and cold season) and 2013 (PM_{2.5}) in R² (number of sites) for EU and separately for ELAPSE countries.

	NO ₂		O ₃ annual		O ₃ warm		O ₃ cold		PM _{2.5}	
	2000	2005	2000	2005	2000	2005	2000	2005	2013	2013
EU	85.8 (546)	86.7 (794)	71.6 (572)	72.3 (836)	68.3 (576)	67.7 (843)	77.9 (555)	79.5 (817)	79.3 (247)	
Austria	86.1 (66)	94.6 (77)	87.8 (77)	89.9 (86)	72.1 (79)	79.5 (88)	91.3 (75)	92.4 (84)	96.7 (8)	
Belgium	95.4 (16)	93.2 (26)	88.2 (22)	88.1 (28)	76.7 (22)	75.9 (29)	91.5 (22)	94.6 (25)	85.5 (19)	
Switzerland	97.7 (21)	94.7 (21)	90.9 (21)	89.2 (23)	75.0 (21)	86.0 (23)	97.5 (21)	92.1 (23)	n.a. (0)	
Germany	90.9 (185)	93.5 (213)	73.3 (181)	77.6 (206)	58.4 (182)	59.9 (206)	80.5 (175)	88.3 (201)	46.4 (63)	
Denmark	n.a. (2)	93.4 (6)	n.a. (0)	41.0 (6)*	n.a. (0)	18.6 (6)*	n.a. (0)	72.7 (6)	95.5 (3)*	
France	86.0 (169)	90.1 (261)	70.9 (179)*	82.5 (301)	66.3 (184)	82.0 (307)	80.1 (173)	85.7 (294)	52.5 (57)	
Great Britain	88.2 (27)	90.0 (44)	72.9 (35)	71.7 (55)	67.5 (31)	66.1 (51)	77.7 (35)	76.8 (54)	59.4 (28)	
Italy	65.9 (30)	73.7 (109)	38.0 (26)	20.5 (87)	20.3 (26)	1.2 (90)*	74.9 (23)	68.4 (88)	84.5 (44)	
Netherlands	89.2 (23)	92.5 (26)	30.0 (19)	30.0 (25)	1.1 (19)*	2.6 (25)*	59.5 (20)	69.6 (23)	68.3 (15)	
Norway	n.a. (2)	100 (3)	2.8 (6)	49.7 (7)	46.3 (6)*	72.4 (7)	73.2 (6)	91.1 (7)	15.5 (5)*	
Sweden	96.6 (5)	96.8 (8)	67.5 (6)	0.8 (12)*	40.9 (6)*	15.4 (11)*	93.2 (5)	30.1 (12)	84.5 (5)	

*not significant (p>0.05)

correlations. When focusing on ELAPSE participating countries, high correlations were also observed for the majority of the countries and years.

3.4 Population exposure

Based on our modelled concentrations (FULL models), a respective 8 million (2%) and 371 million (89%) people live in areas with estimated PM_{2.5} concentrations greater than the EU annual PM_{2.5} limit value of 25 µg/m³ and the WHO annual guideline of 10 µg/m³. 32 million (8%) of people live in areas with modelled NO₂ concentration greater than the EU and WHO annual NO₂ guideline of 40 µg/m³ (see Table S6). Table S7 shows that population weighted concentration levels across the whole of our study area do not drastically fluctuate over time and are generally low (PM_{2.5} ~ 11 µg/m³ and NO₂ < 20 µg/m³).

4. Discussion

We developed West-European LUR models at a 100x100 m spatial scale for four priority pollutants. The models including large scale satellite data and CTM and small-scale traffic and land use predictors explained between 54% (BC) and 83% (O₃ cold season) of the measured variability in concentrations. The explained variance at fully independent sites was only slightly less than the internal hold-out validation: 65% vs 66% for PM_{2.5} and 49% vs 57% for NO₂. Predictions from the 2010 model correlated highly with models developed for 2000 and 2005 (2013 for PM_{2.5}) at the overall European scale, with squared correlations larger than 76%, except for the O₃ cold season of 2000 (44%). The temporal correlation was more variable when evaluated at the country and especially at the NUTS1 level. Correlations between measured concentrations at the EU level between 2010 - 2005 and 2010 - 2000 for NO₂ and O₃ (R² between 68% to 87%) and for PM_{2.5} 2010 - 2013 (R² 79%) were even higher than modeled concentrations. Based on our modelled surfaces, 371 million and 32 million people in Western Europe live in areas with air pollution levels exceeding the WHO annual guidelines for PM_{2.5} and NO₂ respectively.

4.1 Interpretation of 2010 models

PM_{2.5} SAT and CTM available at a 10x10 km scale were the strongest predictors in the PM_{2.5} models, consistent with PM_{2.5} being a largely regionally varying pollutant. Eeftens et al. (2012a) reported that 81% of the variability in the ESCAPE annual average PM_{2.5} concentrations was due to between study area contrast. The modest contrast related to the small-scale road variable is consistent with the overall mean ratio of 1.14 comparing traffic and background sites within ESCAPE (Eeftens et al., 2012a). Roads, ports and residential areas represent the contribution of local sources, with altitude, and nature/urban green representing pollution sinks. Applying kriging to the residuals of the LUR model explained an extra 10% of the variation, suggesting that the SAT and CTM predictors did not fully capture the large scale variation of PM_{2.5} across Europe. Alternatively, the number of sites was insufficient to train the model. Kriging was not feasible for the 2013 model, possibly due to the larger number of sites.

In the BC models, satellite and CTM PM_{2.5} also contributed strongly, raising potential concerns when applying the PM_{2.5} and BC models in the epidemiological analysis as it might be difficult to tease apart their respective contribution to health effects. Compared to the PM_{2.5} models, small-scale road predictors contributed more to the BC prediction. The FULL model contained three road variables with a similar magnitude to the CTM and SAT predictors. This is consistent with the observation in ESCAPE that 52% of the variability was due to within-study area variability (Eeftens et al., 2012a). The overall ratio of BC concentrations measured at traffic/urban background sites was 1.38 (Eeftens et al., 2012a). The residuals of our initial model showed a clear north-south gradient, which was captured by a Y-coordinate in the model, documenting that the models did not predict the large scale contrast of BC across Europe sufficiently. MACC and satellites do not represent BC, whereas DEHM

modelled BC at a larger scale (50x50 km scale). It is likely that limitations in emission data for BC may have impacted the performance of the models.

After the CTM predictor variable, small-scale road variables were the strongest predictors in the NO₂ models. Motorized traffic is a dominant source of local NO₂ concentrations, as illustrated by the overall ratio of 1.63 for concentrations measured at traffic vs. urban background ESCAPE monitoring sites (Cyrus et al., 2012). In ESCAPE, 60% of the variability of NO₂ was due to within-study area variability (Cyrus et al., 2012). The NO₂ models could not be further improved by kriging or geographical coordinates, suggesting that the CTM adequately captured the large scale variation across Europe. We previously suggested that CTM's were better developed for NO₂ than for PM_{2.5} when discussing the contribution of CTM and SAT to PM_{2.5} and NO₂ LUR models (de Hoogh et al., 2016).

In O₃ models, CTM (the ensemble MACC for the annual and cold period and DEHM for the warm season) were the dominant predictor variables, consistent with O₃ being a regional pollutant. The model further predicted higher concentrations at higher altitude, in accordance with a previous European LUR model (Beelen et al., 2009). Predicted lower concentrations near roads was consistent with scavenging of O₃ by NO₂. In both the warm and cold season, kriging substantially improved the models, likely illustrating limitations in the CTM. Kriging did not contribute to the annual model, possibly because the annual average combined the two different spatial patterns of the cold and warm seasons.

Few studies have combined LUR and kriging in air pollution models. Young et al. (2016) evaluated the additional value of satellite data and/or kriging on NO₂ LUR models across the USA for 1990 – 2012. Models with both satellite data and kriging performed best, increasing the average cross-validation R² from 0.72 (just applying LUR) to 0.85. Satellite or kriging alone yielded respective average R²'s of 0.81 and 0.84. Although we found improvement of model performance with kriging for the PM_{2.5} and O₃ models, we did not see the same result in our NO₂ models. This might be due to the difference in scale of the two studies. Young et al. (2016) estimated NO₂ concentrations at a 25 x 25 km resolution, thereby not explaining intra-urban variation but rather focusing on more regional background. This study operates at a much smaller resolution (100x100 m) and, at least for NO₂, the residual concentrations after LUR were too variable, even at background sites, for reliable kriging functions. In a previous study distinguishing global, regional and urban scales, universal kriging improved PM₁₀, O₃ and NO₂ European models compared to regression models (Beelen et al., 2009). In that study, the analysis was based on 1 * 1 km estimates.

Relatively few studies have tested the robustness by developing HOV models and assessing the structure of the models. Johnson et al. (2010) evaluated PM_{2.5}, NO_x and benzene LUR models in New Haven, CT, USA by including hold-out validation using varying sizes of training/testing groups. van Nunen et al. (2017) performed a 10-fold cross validation when developing UFP LUR models in six study European areas. We observed that the model predictions from our FULL model correlated very highly with the 5 HOV models at the 44,000 independent sites, suggesting that the developed models were robust. The correlations in our study were higher than that observed for the UFP models based on short-term monitoring at 160 sites in some of the cities (van Nunen et al., 2017).

4.2 Comparison with other European models

Previously we published the development of hybrid PM_{2.5} and NO₂ LUR models for the same study area, showing that satellite-derived (SAT) estimates and CTM estimates contribute considerably to the explained variance in PM_{2.5} and NO₂ measurements (de Hoogh et al., 2016). The models presented in this paper confirm our previous findings. Moreover, by additionally including kriging to explain residuals at background monitoring sites, we improved the PM_{2.5} hybrid models from 62 to 72% (R²). This improvement was also observed when tested using the independent ESCAPE monitoring dataset, showing an improvement from 53 to 65% (R²). For NO₂ models, where the inclusion of longitude

explained some of the residuals, the R^2 remained the same (both 58%); but the improved NO_2 model described here yielded a higher independent validation (R^2) of 49% compared to 43% in de Hoogh et al. (2016). Additionally we evaluated the performance of SAT and CTM derived estimates by comparing monitored AIRBASE data and satellite derived $\text{PM}_{2.5}$ ($R^2 = 0.48$) and NO_2 ($R^2 = 0.13$) and CTM $\text{PM}_{2.5}$ ($R^2 = 0.41$) and NO_2 ($R^2 = 0.29$). SAT and CTM (MACC) surfaces explain less of the measured spatial variation than when these datasets are used within a hybrid LUR framework as presented in this paper.

Vienneau et al. (2013) also developed European NO_2 and PM_{10} LUR models, for 2005-2007, showing that the inclusion of satellite data substantially improved model performance. The NO_2 model explained a comparable fraction of the variation (46-56%) to our models. The CTM predictor outperformed the satellite data in our NO_2 model, a predictor variable not available in the study by Vienneau et al. (2013).

To date few studies have attempted to model pollutants other than NO_2 and PM. European O_3 LUR models have been previously developed by Beelen et al. (2009) for the year 2001 at the global ($R^2 = 0.53$), rural ($R^2 = 0.63$) and urban ($R^2 = 0.06$) scale. Our annual O_3 model performance for 2000 yielded a higher R^2 (0.63) possibly due to the inclusion of DEHM estimates in our model. In addition we further developed seasonal O_3 models.

4.3 Application of 2010 models in epidemiological studies

The models developed and described here will be used for the exposure assessment in ELAPSE for 7 administrative cohorts and a pooled cohort comprising of 11 local cohorts across 11 countries in Europe (Norway, Sweden, Denmark, United Kingdom, the Netherlands, Belgium, Germany, France, Switzerland, Austria and Italy). For the pooled cohort, the (moderately) high explained variance in hold-out validation and external validation over the full area suggests that exposure assessment is robust. For individual cohorts, comparison with ESCAPE data in the respective study areas showed more variable results, especially for $\text{PM}_{2.5}$. This implies that our West European model should be applied with caution in a small area (part of a country) unless local validation is possible. The difference between NO_2 and $\text{PM}_{2.5}$ could be due to the relatively small number of sites for $\text{PM}_{2.5}$ and the smaller contrast in $\text{PM}_{2.5}$ within cohorts compared to NO_2 .

For the administrative cohorts, direct comparisons of the Dutch, Rome and to some extent national English and Swiss (NO_2 only) study areas with the ESCAPE data are possible due to overlaps between the ESCAPE and ELAPSE study areas/regions. The West European ELAPSE models explained variation well, except for $\text{PM}_{2.5}$ in the Netherlands (possibly due to small variation) and NO_2 in Switzerland. The findings for Switzerland do not directly apply to the Swiss cohort, as the evaluation was limited to three cities whereas the Swiss cohort includes the entire population including those in rural and Alpine areas. We have no ready explanation for these findings, and can only speculate that a more locally generated model may better capture area-specific small-scale concentration differences than a pan-European model, which tends to smooth intra-urban differences over several very different study areas.

4.4 Spatial stability of models and measurements over time

This is one of the few studies which has tested the stability of spatial structure of air pollution exposure models at a continental scale, by developing models for different time points and comparing the respective estimates. Most studies evaluated LUR models at a national or sub-national scale by linear regression using historical monitoring data, allowing the constant and coefficient to change (Cesaroni et al., 2012; Chen et al., 2010; Eeftens et al., 2011; Gulliver et al., 2013; Gulliver and de Hoogh, 2015; Levy et al., 2015). Gulliver et al. (2016), however, produced separate NO_2 LUR models for 1991 and 2009 for the UK and found that the year-specific 1991 model yielded similar exposures as the back-extrapolated 2009 model. Wang et al. (2013) developed NO_2 LUR models for 2003 and 2010 for Vancouver, Canada, and when applied to measurements of the other year were able to

explain 52 to 61% (2003 model to 2010 measurements) and 44 to 49% (2010 model to 2003 measurements) of the spatial variation. These studies suggest that the spatial structure of the different models were similar, at least at a national or city level. It is difficult to compare the findings of the analyses carried out in this study with the studies conducted at the sub-continental scale. In this study we specifically assessed the stability of the spatial structure by comparing the concentration surfaces of the different models based on a set of ~44,000 random points spread across the study area. At the EU scale (all countries combined and ELAPSE countries combined) there was a high squared correlation (>76%) between the other year models (PM_{2.5} 2013, NO₂ and O₃ 2000, 2005) and the corresponding 2010 models, with the only exception the O₃ 2000 cold season model (~45%). Other countries that performed poorly for O₃ 2000 cold were Germany and the Netherlands. The poorer temporal correlation for O₃ may be due to the smaller spatial contrast when evaluating at a smaller spatial scale. Another explanation may be that there are different CTM predictions used in the LUR models for 2010 (MACC-O₃ for annual and cold O₃) compared to 2000 and 2005 for which only the DEHM model was available.

Correlations between annual average measured concentrations at sites that were in operation for an extended time period were even higher. The higher correlation for measurements was probably due to the only moderately high explained variance of the models and difference in availability of predictor variables across years. A difficulty in the interpretation of monitoring data is the limited number of sites with continuous data, especially for PM_{2.5}.

The temporal stability of the estimated spatial surface for most of the pollutants has positive consequences for further application in long-term epidemiological studies especially those including cohorts which started one or two decades ago and which will have had several follow-ups since then. The 2010 surfaces produced here can be used with some confidence as the base for back-extrapolation.

For several areas we now have study-area specific ESCAPE models and Europe wide ELAPSE models. The ESCAPE models are based upon a smaller number of training sites but may be more specific for the area. The spatial extent of ESCAPE PM models has limited the analysis of some ESCAPE cohorts (e.g. only Paris in the national French E3N cohort and Copenhagen in the Danish DCH cohort). The ELAPSE model can be applied to larger areas e.g. entire France, Denmark. In general, Europe wide models may be better when large areas are studied. In international multi-center studies, the use of a single harmonized model is important to standardize exposure assessment.

4. Conclusions

We were able to develop robust PM_{2.5}, NO₂, BC and O₃ LUR models. At the West-European scale models were robust in time, becoming less robust at smaller spatial extents. In terms of model performance we improved on previously published European NO₂ and PM_{2.5} models and developed new models for BC and O₃ explaining large fractions of the variance. We showed, by five-fold hold-out validation plus an independent comparison, that the models were spatially robust at the West-European and, to a lesser degree, at the national scale. At the West-European scale, PM_{2.5}, NO₂ and O₃ models were robust in time. For BC models we were not able to perform a stability analysis. At smaller spatial scales, models were less robust in time, especially for O₃. The models presented here will be used to assign exposures in the ELAPSE study and will be made available for other studies in Europe.

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Supplementary material

1. Analysis of different PM_{2.5} satellite products

We offered three different PM_{2.5} satellite products to the PM_{2.5} model development; (1) 10km product inferred 2009-2011; (2) 10km product for 2010; (3) 1km product for 2010. In preliminary models, the first data set led to better PM_{2.5} models compared to the other 2 datasets. We further investigated the raw squared correlation coefficients (R^2) of the 3 data products (annual mean) with the annual mean PM_{2.5} measurements from AirBase for the year 2010 (see Table S5 for more details). The difference in explained variance seems to be in the time period of the 3 products. The products 2 and 3 focusing on the year 2010 yielded similar correlations, irrespective of the 10 or 1km spatial resolution, explaining around 40% of variation. Product 1, which was inferred for 2009 to 2011 and optimized for 2010, explained 46% of variation. For the final PM_{2.5} model we therefore decided to only offer the first PM_{2.5} product.

2. Stability analysis at regional (NUTS1) level

NUTS areas are standard administrative divisions of EU countries for statistical purposes. The NUTS1 level is the first level. We also performed the stability analysis using the same 44,000 random points at the NUTS1 area level (see Figure S6). Like at the country level, there is a good agreement for all areas for NO₂ 2000 and 2005 when compared to the 2010 surface ($R^2 > 0.60$). For the other pollutants there is more heterogeneity in the correlation coefficients across areas. When comparing the PM_{2.5} surfaces (2010 vs. 2013), the majority of the NUTS1 areas have a correlation coefficient > 0.40 , with only a handful of areas dropping between 0.20 and 0.40. The comparison of the O₃ surfaces (2000, 2005 vs. 2013) shows a clear difference between annual and cold season versus the warm season. Both the 2000 and 2005 comparisons for warm season show a number of areas in the south of Europe with correlations of less than 0.20. This pattern is not observed in the annual and cold season comparisons.

Table S1. Descriptive statistics of PM_{2.5}, NO₂, BC, O₃ concentrations for 2010 used in the modeling procedure.

Air pollutant	Type	N ^a	Mean (µg/ m ³)	Median (µg/m ³)	Std. Deviation (µg/m ³)	Percentiles (µg/m ³)			
						5	25	75	95
PM _{2.5}	Traffic	149	16.28	16.63	4.93	8.33	12.75	19.67	23.76
	Background	341	15.75	15.77	5.16	7.25	12.65	18.78	23.92
	Industrial	53	15.12	15.27	5.45	7.51	10.36	19.18	25.73
	All	543	15.84	15.88	5.13	7.65	12.42	19.25	23.94
NO ₂	Traffic	740	40.23	38.69	14.62	19.90	30.39	47.75	66.06
	Background	1287	21.47	21.01	9.82	5.67	14.81	27.94	37.27
	Industrial	372	19.43	18.22	10.13	4.47	11.52	26.72	38.06
	All	2399	26.94	25.12	14.59	6.73	16.34	34.70	53.69
BC ^b	Traffic	207	2.28	2.16	0.90	0.98	1.65	2.83	3.99
	Background	229	1.51	1.47	0.54	0.74	1.08	1.85	2.44
	Industrial	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	All	436	1.88	1.78	0.83	0.84	1.26	2.33	3.50
O ₃ annual ^c	Traffic	228	65.01	63.86	12.26	45.80	57.10	73.44	88.72
	Background	1323	72.10	70.92	10.66	56.25	65.71	77.76	91.86
	Industrial	194	75.77	76.59	11.76	57.42	67.12	84.31	94.49
	All ^c	1747	71.59	70.61	11.35	53.75	64.54	78.31	91.85
O ₃ warm ^c	Traffic	225	81.62	81.34	15.03	57.65	70.69	92.51	106.04
	Background	1311	89.99	89.30	12.99	69.09	82.22	98.45	111.84
	Industrial	192	90.70	92.20	13.45	67.13	81.61	100.18	110.61
	All ^d	1730	88.98	88.95	13.62	66.39	80.97	97.96	111.08
O ₃ cold ^c	Traffic	223	48.31	47.13	12.29	29.96	39.44	57.52	72.03
	Background	1304	54.05	53.18	12.69	35.34	44.92	62.17	77.63
	Industrial	188	60.16	62.26	13.55	37.90	49.77	69.77	82.50
	All ^c	1716	53.98	53.04	13.05	34.11	44.34	62.72	77.42

a. Number of sites

b. BC monitoring data from ESCAPE (2009-2010), no industrial type monitoring sites were used. Measured as absorbance of PM_{2.5} (10⁻⁵m⁻¹)c. O₃ concentrations were calculated as the average of the daily maximum running 8-hour mean; warm season is from 1 April to 30 September; cold season is from 1 October to 31 March falling in the same year.

d. These include 2 sites with site type 'Unknown'

e. These include 1 site with site type 'Unknown'

Table S2. GIS predictor variables

Data set	Predictor variable	Name variable	Year	Buffer Size (radius in m) or point estimate	Pre-specified direction of effect for PM _{2.5} , NO ₂ , BC (O ₃)
PM _{2.5} (µg/m ³) derived from MODIS on board the Terra satellite: ~10km	Surface PM _{2.5} concentration derived from satellite	SAT-PM25	2010, 2013	Point	+
PM _{2.5} (µg/m ³) derived from MODIS on board the Terra satellite: ~1km	Surface PM _{2.5} concentration derived from satellite	SAT-PM25-1k	2010, 2013	Point	+
NO ₂ (µg/m ³) derived from OMI on board the Aura satellite: ~10km	Surface NO ₂ concentration derived from satellite	SAT-NO ₂	2010	Point	+(-)
PM _{2.5} , NO ₂ , O ₃ (µg/m ³) estimated by MACC-II Ensemble model: ~10km	Surface PM _{2.5} , NO ₂ and O ₃ concentration from dispersion model	MACC-PM25 MACC-NO ₂ MACC-O ₃	2010, 2013	Point	+(-)
PM _{2.5} , NO ₂ , O ₃ and BC (µg/m ³) estimated by DEHM: ~50km	Surface PM _{2.5} , NO ₂ , O ₃ and BC concentration from dispersion model	DEHM-PM _{2.5} DEHM-NO ₂ DEHM-O ₃ DEHM-BC	2000, 2005, 2010	Point	+(-)
EuroStreets roads (length in m)	Major roads All roads	MJRD ALRD	2010	50; 100; 200; 300; 400; 500; 700; 1000; 2000; 5000; 10000	+(-)
Corine land cover: 100m	Industry/commercial Ports Urban green Total built up ^a Natural land Residential ^b	IND POR UGR TBU NAT RES	2006	50; 100; 200; 300; 400; 500; 600; 700; 800; 1000; 1200; 1500; 1800; 2000; 2500; 3000; 3500; 4000; 5000; 6000; 7000; 8000; 10000	+(-) +(-) -(+) +(-) -(+) +(-)
GEOSTAT 2011 population grid dataset: ~1km	Sum of population	POP	2011	Point	+(-)
Altitude SRTM DTM: ~90 m	Altitude – transformed ^c	ALT		Point	-(+)
Trend	North-South and East- West trend	X, Y ^d		Point	n.a.

^aResidential + Ind/comm + Port + transport infrastructure, airports, mines, dumps and construction sites

^bcontinuous urban fabric (high density housing) + discontinuous urban fabric (low density housing)

^cTransformed altitude is calculated as $\sqrt{(\text{nalt}/\text{max}(\text{nalt}))}$, where $\text{nalt} = \text{altitude} - \text{min}(\text{altitude})$.

^dCoordinates were truncated : $X = x - x_{\min} / (x_{\max} - x_{\min})$; $Y = y - y_{\min} / (y_{\max} - y_{\min})$

Table S3. Structure and performance of LUR models for BC, NO₂ and O₃ for full dataset and five hold-out validation datasets**BC models^a**

Theme	Variables ^b	FULL	HOV1	HOV2	HOV3	HOV4	HOV5
CTM	Constant	0.99	0.85	0.99	0.94	0.99	1.10
	MACC-PM25	0.85	0.95	0.80	0.92	0.95	0.65
Satellite	SAT-PM25	0.30	0.34	0.39	0.32	0.22	0.34
Major roads	MJRD ₅₀		0.64				
	MJRD ₁₀₀	0.68		0.68	0.67	0.65	0.44
All roads	ALRD ₅₀	0.40			0.39	0.40	0.52
	ALRD ₁₀₀₀				0.34		
Residential	ALRD ₇₀₀	0.45	0.67	0.40		0.43	0.57
	RES ₂₅₀₀			0.93	0.86		
Urban green	RES ₃₀₀₀	0.90	0.86			0.86	0.94
	UGR ₁₀₀₀	-0.12	-0.18	-0.14	-0.11	-0.19	-0.08
Ycoord	Y	-1.16	-1.09	-1.16	-1.16	-1.16	-1.30
Training (LUR)	R ²	54.4	52.2	52.3	53.9	57.6	55.3
	RMSE	0.56	0.59	0.56	0.58	0.54	0.572
HOV (LUR)	R ²	51.4	56.7	56.9	53.8	43.2	49.3
	RMSE	0.58	0.52	0.62	0.52	0.67	0.54

NO₂ models^a

Theme	Variable ^b	FULL	HOV1	HOV2	HOV3	HOV4	HOV5
CTM	Constant	3.30	3.30	3.70	4.70	3.30	3.20
	MACC-NO ₂	22.73	22.73	23.30	22.73	22.16	22.73
All Roads	ALRD ₅₀	7.04		8.60	6.65	9.38	
	ALRD ₁₀₀		9.68				10.29
	ALRD ₃₀₀	3.92			7.50		
	ALRD ₁₀₀₀					12.27	
Major roads	ALRD ₂₀₀₀	15.73	16.71	16.71			15.73
	MJRD ₅₀		5.70				
	MJRD ₁₀₀	12.32		12.32	10.67	12.32	12.32
	MJRD ₂₀₀		6.95				
Natural	NAT ₄₀₀	-3.38			-3.97	-3.09	-3.14
	NAT ₅₀₀		-3.24	-3.89			
Ports	POR ₂₀₀			1.82			1.80
	POR ₇₀₀	4.10	4.51			2.87	
Residential	POR ₁₈₀₀				4.14		
	RES ₂₀₀				2.73		
	RES ₃₀₀	5.80		6.38			
	RES ₄₀₀		6.86				6.37
	RES ₂₅₀₀				14.10		
	RES ₈₀₀₀					7.09	
Total build up	TBU ₃₀₀					6.09	
Urban green	UGR ₁₀₀				-3.20		
	UGR ₂₀₀			-2.40			
Training (LUR)	R ²	58.8	59.1	58.3	58.4	59.0	59.6
	RMSE	9.38	9.38	9.39	9.38	9.36	9.36
HOV (LUR)	R ²	57.5	57.8	59.9	60.2	54.8	54.7
	RMSE	9.51	9.36	9.44	9.44	9.81	9.51

^a Regression slope in 10⁻⁵m⁻¹ (BC) or µg/m³ (NO₂) were multiplied by the difference between the 1st and 99th percentile of each predictor to allow comparison across predictors

^b ALT = altitude, ALRD = all roads, MJRD = major roads, IND = industry, POR = ports, UGR = urban green, TBU = total build up, NAT = natural land, RES = residential, POP = sum of population, X = North-South trend, Y = East-West trend, SAT = satellite, MACC = MACC dispersion model, DEHM = DEHM CTM. Number in subscript depicts the buffer size (e.g. ALRD₁₀₀ = sum of all road length within 100m)

(Table S3 Continued)

O₃ models^a

Theme	Variable ^b	Annual					Warm					Cold							
		FULL	HOV1	HOV2	HOV3	HOV4	HOV5	FULL	HOV1	HOV2	HOV3	HOV4	HOV5	FULL	HOV1	HOV2	HOV3	HOV4	HOV5
MACC DEHM Roads	Constant	40.54	42.72	40.91	40.02	39.30	40.16	30.00	30.00	30.00	32.00	29.00	29.00	1.00	0.23	1.10	1.60	0.19	0.14
	MACC-O ₃	25.51	25.04	24.93	25.38	26.35	26.45	32.57	32.57	32.57	31.71	33.43	33.43	37.62	37.62	37.62	36.87	37.62	37.62
	DEHM O ₃ ^c																		
	ALRD50	-2.49	-3.70	-7.04	-3.14	-7.13	-6.29	-6.87	-3.04	-3.35	-4.87	-6.09	-4.52	-3.53	-3.35	-3.14	-4.52	-3.53	-3.34
	ALRD200	-4.75			-4.25				-5.81	-6.18	-5.54								
Nature	ALRD500																		
	ALRD700		-5.83				-5.17						-3.40			-3.04			
	ALRD1000																		
	ALRD2000																		
	MJRD50			-3.69		-4.67	-3.03	-6.03	-5.85	-5.85	-5.96	-4.99	-7.24	-3.48	-3.32	-3.48	-4.09	-4.01	-2.66
Ports	MJRD100		-4.42		-3.48				-5.85										
	MJRD200	-3.24												-1.61	-1.90			-2.49	
	MJRD700													5.81	5.07		5.81	6.56	
	NAT700																		
	POR4000	-1.57		-1.67	-1.63	-1.63	-2.20	-5.95	-4.95	-5.45	-5.95	-5.68	-7.43				6.70		
Residential	POR5000																		
	RES100		-1.84																
	RES200																		
	RES400																		
	RES500	-1.94			-1.91	-4.29									-4.77	-3.58			-3.38
Industrial/ commercial	RES700																		
	RES800																		
	RES1000						-5.02												
	RES1200																		
	RES1500																		
Total build up Urban green Altitude Coordinate	RES2000	-4.13	-2.38	-6.02	-3.81			-4.79	-3.99	-4.01	-3.54			-4.18			-5.16		
	RES3000																		
	IND50		-2.42																
	IND200																		
	TBU100																		
Training (LUR + Kriging)	UGR1000																		
	ALT	8.82	7.82	10.02	9.33	8.67	8.38	5.70	4.99	6.56	5.99	5.13	5.27	-1.10	2.21	8.12	2.78	2.59	6.27
	X	2.48	1.65	3.57	2.55	2.62								2.21	6.13		7.13	6.98	
	Y	-10.05	-11.01	-10.93	-9.34	-10.07	-8.82												
	R ²	65.1	65.4	68.5	63.4	64.6	63.9	45.5	44.9	48.9	45.0	45.6	44.7	67.7	68.1	69.8	66.2	67.6	67.0
HOV	RMSE	6.73	6.66	6.39	6.93	6.81	6.81	10.07	10.09	9.69	10.10	10.17	10.18	7.43	7.35	7.25	7.60	7.53	7.43
	R ²	63.4	64.1	51.1	73.5	64.3	67.7	44.5	48.1	34.9	48.8	45.1	49.5	66.5	65.8	58.7	73.8	67.4	68.5
	RMSE	6.87	7.00	7.94	5.71	6.65	6.57	10.15	9.98	11.33	9.83	9.69	9.58	7.55	7.84	8.16	6.74	7.11	7.67
	R ²							69.6	69.5	73.3	70.0	68.5	67.3	83.3	84.4	85.2	50.3	83.8	82.4
	RMSE							7.51	7.49	6.98	7.44	7.73	7.81	5.33	5.13	5.05	5.78	5.32	5.42
HOV	R ²							59.9	61.5	48.0	61.9	6.50	65.8	75.3	71.6	71.8	83.3	76.8	75.1
	RMSE							8.63	8.60	10.13	8.48	7.74	7.88	6.49	7.15	6.75	5.39	5.99	6.82

a. Regression slope $\mu\text{g}/\text{m}^3$ were multiplied by the difference between the 1st and 99th percentile of each predictor to allow comparison across predictors

b. ALT = altitude, ALRD = all roads, MJRD = major roads, IND = industry, POR = ports, UGR = urban green, TBU = total build up, NAT = natural land, RES = residential, POP = sum of population, X = North-South trend, Y = East-West trend, SAT = satellite, MACC = MACC dispersion model, DEHM = DEHM CTM. Number in subscript depicts the buffer size (e.g. ALRD₁₀₀ = sum of all road length within 100m)

c. DEHM estimates were calculated for each season (annual, warm and cold)

Table S4. Details of 2000, 2005 (NO₂ and O₃) and 2013 (PM_{2.5}) FULL models^a

Theme	Variable ^b	PM _{2.5} 2013	NO ₂ 2000	NO ₂ 2005	O ₃ 2000a	O ₃ 2000w	O ₃ 2000c	O ₃ 2005a	O ₃ 2005w	O ₃ 2005c
CTM	Constant	0.45	6.48	8.39	56.06	35.88	59.90	72.00	61.92	56.60
	MACC-PM25	13.21								
Satellite	DEHM-NO ₂		11.55	12.49						
	DEHM-O ₃ ^c				11.19	32.33		7.24	20.34	
Roads	SAT-PM25	6.54								
Roads	ALRD ₅₀	1.09	14.07	9.96				-6.39	-10.29	-8.16
	ALRD ₁₀₀					-7.84	-6.07			
	ALRD ₂₀₀				-7.15			-6.76		
	ALRD ₁₀₀₀			9.20						
	ALRD ₂₀₀₀									
Roads	ALRD ₅₀₀₀		32.43		-16.57	-21.31		-21.84	-17.76	
	MJRD ₅₀				-6.78		-4.12			
	MJRD ₁₀₀			11.67		-6.92		-2.21	-5.96	
	MJRD ₅₀₀									-2.93
	MJRD ₁₀₀₀₀						-15.42			-16.64
Nature	NAT ₄₀₀			-3.23			3.87			
	NAT ₅₀₀		-4.05							
	NAT ₆₀₀									5.20
	NAT ₁₀₀₀	-3.17								
Urban green	NAT ₁₀₀₀₀						5.16			4.85
	UGR ₁₀₀					6.00				
Ports	UGR ₁₀₀₀	-1.09								
	POR ₃₀₀								-2.18	
Ports	POR ₁₀₀₀		4.42							
	POR ₆₀₀₀			3.73					-4.38	
Industrial/ commercial	IND ₂₀₀									-5.07
Residential	RES ₃₀₀			4.64						
Total build up	RES ₇₀₀		8.20							-7.30
	TBU ₃₀₀	1.51								
Total build up	TBU ₄₀₀							-3.53		
	TBU ₅₀₀				-5.67					
Total build up	TBU ₆₀₀									
	ALT				15.30	14.38	18.36	12.75	9.85	12.60
Altitude	X				9.94		-12.42			
X-coord	Y				-11.83			-14.40	-11.52	
Y-coord										
Training (LUR)	R ²	65.6	55.9	52.2	59.6	53.5	51.8	48.8	42.0	45.0
	RMSE	2.87	10.59	11.34	8.56	11.39	9.17	9.45	11.93	10.13
HOV (LUR)	R ²	0.64	53.8	50.1	58.0	52.2	50.1	46.6	40.6	43.3
	RMSE	2.93	10.57	11.57	8.69	11.53	9.31	9.62	12.04	10.25
Training (LUR + Kriging)	R ²					81.5				69.9
	RMSE					7.17				7.47
HOV (LUR + Kriging)	R ²					63.8				63.4
	RMSE					10.02				8.24

- Regression slope $\mu\text{g}/\text{m}^3$ were multiplied by the difference between the 1st and 99th percentile of each predictor to allow comparison across predictors
- ALT = altitude, ALRD = all roads, MJRD = major roads, IND = industry, POR = ports, UGR = urban green, TBU = total build up, NAT = natural land, RES = residential, POP = sum of population, X = North-South trend, Y = East-West trend, SAT = satellite, MACC = MACC dispersion model, DEHM = DEHM CTM. Number in subscript depicts the buffer size (e.g. ALRD₁₀₀ = sum of all road length within 100m)
- DEHM O₃ estimates were calculated for each season (annual, warm and cold)

Table S5. Comparison of predictions of different satellite derived PM_{2.5} (SAT) products with routine PM_{2.5} concentrations.

AirBase Site type	Inferred 2009-2011, 10x10km, v3.01		Inferred 2010, 10x10km, v3.01		Inferred 2010, 1x1km, v4.GL.02.NoGWR		
	R ²	RMSE	R ²	RMSE	R ²	RMSE	N
All sites	0.46	3.77	0.39	4.01	0.40	3.98	545
No industrial sites	0.47	3.71	0.38	4.02	0.38	4.00	492
Traffic only	0.46	3.62	0.42	3.75	0.42	3.76	149
Background only ^a	0.49	3.68	0.37	4.11	0.38	4.07	342

a. Monitoring site located away from major pollutant sources

Table S6. Population (2010) by classes of modelled air pollution estimates (PM_{2.5} and NO₂ FULL models)

Pollutant	Concentration class (µg/m ³)	Area (1,000,000 m ²)	Percentage of total (%)	Population ^a (millions)	Percentage of total (%)
PM _{2.5}	<5	1769.41	11.32	4.51	1.08
	5-<10	3592.20	22.98	42.31	10.12
	10-<15	7016.49	44.88	173.87	41.57
	15-<20	2762.81	17.67	155.38	37.15
	20-<25	404.38	2.59	33.68	8.05
	25-<30	87.30	0.56	7.96	1.90
	>30	2.17	0.01	0.53	0.13
Total		15634.76		418.24	
NO ₂	<10	7335.38	46.93	32.72	7.82
	10-<15	4156.22	26.59	60.36	14.43
	15-<20	2351.02	15.04	77.17	18.45
	20-<30	1500.96	9.60	139.49	33.35
	30-<40	240.35	1.54	76.54	18.30
	40-<60	45.95	0.29	30.92	7.39
	>60	1.54	0.01	1.07	0.26
Total		15631.42		418.26	

a. Population was derived from 2011 census data

Table S7. Population weighted annual concentration (µg/m³) averaged over Western Europe

Year	PM _{2.5}	Pollutant (µg/m ³)			
		NO ₂	O ₃ annual	O ₃ cold	O ₃ warm
2000		20.09	55.37	39.94	70.02
2005		15.41	57.97	43.48	71.86
2010	11.17	18.85	57.11	42.70	70.51
2013	10.58

Figure S1. Location of PM_{2.5}, NO₂, O₃ and BC monitoring sites for the year 2010

Figure S2. Variograms for PM_{2.5}, O₃ warm and O₃ cold models for 2010. n = nugget ($\mu\text{g}/\text{m}^3$), s = sill ($\mu\text{g}/\text{m}^3$), r = range (km), m (model); mat = matern; sph = spherical; gau = gaussian, exc = exclass (exponential class/stable)

Figure S3. Scatterplot matrix of predicted concentrations of FULL and HOV models for all pollutants at ~44,000 random points across Western Europe

Figure S4. Mapping of FULL hybrid LUR models for O₃ annual and warm season (2010, 2005, 2000).

Figure S5. Stability analysis at country level

Figure S6. Stability analysis at NUTS 1 level (on average ~600 random points per NUTS1 area)

Chapter 4

A Comparison of Linear Regression, Regularization, and Machine Learning Algorithms to Develop Europe-Wide Spatial Models of Fine Particles and Nitrogen Dioxide

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Abstract

Empirical spatial air pollution models have been applied extensively to assess exposure in epidemiological studies with increasingly sophisticated and complex statistical algorithms beyond ordinary linear regression. However, different algorithms have rarely been compared in terms of their predictive ability.

This study compared 16 algorithms to predict annual average fine particle ($PM_{2.5}$) and nitrogen dioxide (NO_2) concentrations across Europe. The evaluated algorithms included linear stepwise regression, regularization techniques and machine learning methods. Air pollution models were developed based on the 2010 routine monitoring data from the AIRBASE dataset maintained by the European Environmental Agency (543 sites for $PM_{2.5}$ and 2399 sites for NO_2), using satellite observations, dispersion model estimates and land use variables as predictors. We compared the models by performing five-fold cross-validation (CV) and by external validation (EV) using annual average concentrations measured at 416 ($PM_{2.5}$) and 1396 sites (NO_2) from the ESCAPE study. We further assessed the correlations between predictions by each pair of algorithms at the ESCAPE sites.

For $PM_{2.5}$, the models performed similarly across algorithms with a mean CV R^2 of 0.59 and a mean EV R^2 of 0.53. Generalized boosted machine, random forest and bagging performed best (CV $R^2 \sim 0.63$; EV R^2 0.58–0.61), while backward stepwise linear regression, support vector regression and artificial neural network performed less well (CV R^2 0.48–0.57; EV R^2 0.39–0.46). Most of the $PM_{2.5}$ model predictions at ESCAPE sites were highly correlated ($R^2 > 0.85$, with the exception of predictions from the artificial neural network). For NO_2 , the models performed even more similarly across different algorithms, with CV R^2 s ranging from 0.57 to 0.62, and EV R^2 s ranging from 0.49 to 0.51. The predicted concentrations from all algorithms at ESCAPE sites were highly correlated ($R^2 > 0.9$). For both pollutants, biases were low for all models except the artificial neural network. Dispersion model estimates and satellite observations were two of the most important predictors for $PM_{2.5}$ models whilst dispersion model estimates and traffic variables were most important for NO_2 models in all algorithms that allow assessment of the importance of variables.

Different statistical algorithms performed similarly when modelling spatial variation in annual average air pollution concentrations using a large number of training sites.

Abbreviations

ANN	Artificial Neural Network
BLR	Backward stepwise Linear Regression
CTM	Chemical Transport Models
CV	Cross Validation
DSA	Deletion/ Substitution/ Addition
EN25/50/75	Elastic Net with $\alpha=0.25/0.50/0.75$
EV	External Validation
FLR	Forward stepwise Linear Regression
GAM	Generalized Additive Model
GBM	Generalized Boosted Machine
KRLS	Kernel-based Regularized Least Squares
LASSO	Least Absolute Shrinkage and Selection Operator
LUR	Land Use Regression
NO ₂	Nitrogen dioxide
PM _{2.5}	Particulate Matter with an aerodynamic diameter smaller than 2.5 micrometers
RF	Random Forest
RMSE	Root-mean-square error
SAT	Satellite-derived
SLR	Supervised Linear Regression
SVR	Support Vector Regression
WLR	Stepwise Linear Regression

1. Introduction

Research in developed countries is currently focusing on health effects of long-term exposure to ambient air pollution at low concentrations, where the concentration contrast is small (Beelen et al., 2014; Di et al., 2017; Pinault et al., 2017). In order to do so, accurately assessing exposure for study subjects is particularly important.

Land Use Regression (LUR) models are frequently used to assess air pollution exposure in epidemiological studies on long-term health effects of air pollution. These are empirical models derived by combining air pollution concentrations monitored at a limited number of locations and potential predictor variables collected in a geographic information systems (GIS) (Hoek, 2017). In a LUR model, a linear regression with an automatic variable selection algorithm has often been used to maximize the within-sample explained variation of measured air pollution concentrations (Crouse et al., 2009; Hoek et al., 2008). Some LUR models are fitted with a supervised linear regression algorithm to include only predictor variables following the plausible direction of effect, e.g. a positive traffic slope, in order to increase the physical interpretability and potentially transferability of the models (Brauer et al., 2003; Briggs et al., 1997; Henderson et al., 2007).

There are several concerns about the standard linear regression algorithm. One is that the algorithm may overfit the data when there are relatively few monitoring sites to train a model and a large number of potential predictor variables offered (Basagaña et al., 2012; Friedman et al., 2001; Wang et al., 2012). Second, the algorithm may fail to capture potentially complex relationships within the data, since it assumes the relationship between air pollution and a predictor is linear across the whole range of the predictor values, and the impacts of different predictors to be independent (no interaction) (Friedman et al., 2001; Tibshirani et al., 2013). Third, the algorithm may result in unstable and uninterpretable

coefficient estimates when highly correlated predictors are included in one model (Crouse et al., 2009; Tibshirani et al., 2013).

A number of different algorithms beyond standard linear regression have increasingly been applied to fit LUR models in air pollution exposure assessment. The Deletion/ Substitution/ Addition (DSA) algorithm selects the subset of predictors that minimize the cross-validation mean squared errors (Basagaña et al., 2012; Beckerman et al., 2013). The Generalized Additive Model (GAM) algorithm estimates nonlinear relationships between air pollution and predictors (Y. Liu et al., 2009). The LASSO (Least Absolute Shrinkage and Selection Operator) algorithm addresses collinearity by shrinking the coefficients of correlated predictors toward zero (Kim et al., 2016). Machine learning algorithms can detect previously unknown relationships within the data by modelling nonlinearity and interactions. Applications of the machine learning algorithms include Artificial Neural Network (ANN) (Di et al., 2016b; Zou et al., 2015), Random Forests (RF) (Brokamp et al., 2018; Hu et al., 2017; Zhan et al., 2018), Support Vector Regression (SVR) (de Hoogh et al., 2018b; Stafoggia et al., 2017; Van den Bossche et al., 2018), Generalized Boosted Machine (GBM) (Reid et al., 2015; Zhan et al., 2017), and Kernel-based Regularized Least Squares (KRLS) (Weichenthal et al., 2016).

Few studies have compared the performance of different algorithms in building LUR models for exposure assessment. The generalized boosted machine algorithm outperformed 10 other algorithms in a study modelling spatiotemporal variation of daily PM_{2.5} concentrations during wildfires (Reid et al., 2015). The random forest algorithm outperformed the linear stepwise regression algorithm in a study modelling spatial variation of PM_{2.5} and its components (Brokamp et al., 2017). In other studies modelling spatial variation of air pollution concentrations, similar performance was found using the Deletion/ Substitution/ Addition algorithm and the linear regression algorithm (Basagaña et al., 2012), the Kernel-based Regularized Least Squares algorithm and the linear regression algorithm (Weichenthal et al., 2016), the linear regression algorithm, the LASSO algorithm and the Support Vector Regression algorithm (Van den Bossche et al., 2018). Only modest differences in performance across algorithms were found in a recent comprehensive algorithm comparison study based on mobile monitoring of ultrafine particles (Kerckhoffs et al., 2019).

Most of the previous air pollution exposure assessment studies evaluated model performance based on cross-validation, which assesses a model's predictive ability within the monitoring domain. For cross-validation to be meaningful, the monitoring sites need to be representative of the locations to which the model is applied (e.g. residential addresses versus routine monitoring sites other than in residential areas or on-road mobile monitoring). A model that performs well in cross-validation does not necessarily transfer well to application in epidemiological studies (Hystad et al., 2011; Kerckhoffs et al., 2016). Therefore, it is valuable to evaluate models using pollution data collected from monitoring sites which represent the application locations.

We have recently developed spatial air pollution models across Europe, using a Supervised Linear Regression (SLR) algorithm (de Hoogh et al., 2018a). The aim of the current study was to compare 16 different algorithms, including the SLR, in their ability to predict spatial variation of PM_{2.5} and NO₂ concentrations across Europe. To strengthen our comparisons, we used two ground-based monitoring datasets to perform both cross-validation (AIRBASE dataset; EEA) and external validation (ESCAPE (European Study of Cohorts for Air Pollution Effects) dataset) (Cyrys et al., 2012; Eeftens et al., 2012). The selected algorithms follow a recent evaluation of model development of mobile monitoring data by our group (Kerckhoffs et al., 2019).

2. Methods

Measured air pollution concentration data and GIS predictor variables were the same as in our recently published Europe-wide modelling study (de Hoogh et al., 2018a).

2.1 Air pollution monitoring data

To build the spatial empirical models, we used annual mean concentrations for $PM_{2.5}$ (available for 543 sites) and NO_2 (available for 2399 sites) for 2010 from the AIRBASE v8 dataset (EEA, 2015) (Figure S1). AIRBASE is a database maintained by the European Environmental Agency (EEA) containing monitoring data reported by EU member states and associated countries. Air pollution data are from routine regulatory networks in individual countries, measured by a diversity of methods. The monitoring locations are chosen to check for compliance with the European Union air quality standards (<http://ec.europa.eu/environment/air/quality/standards.htm>) at background sites, near busy roads or in industrial zones. The annual mean concentrations were aggregated by EEA based on the primary observations uploaded by countries and successfully tested by automated quality control. The primary observations were reported with different frequency (hour, day, or week). Based on the frequency of reported air pollution values, an annual average was calculated only when valid measurements coverage $\geq 75\%$ of a year. AIRBASE monitoring sites were randomly divided into five groups (20% each), stratified by site type and region (de Hoogh et al., 2018a). Main models were built using all measurements (100% sites) in the AIRBASE dataset. Each of the 5 hold-out validation models was developed based on 80% of the monitoring sites, with the remaining 20% used for validation.

Air pollution monitoring data from the ESCAPE study were used for external validation. Three 2-weekly measurement campaigns were held at 416 monitoring sites for $PM_{2.5}$ and 1396 sites for NO_2 , using Harvard Impactors and Ogawa badges respectively (Cyrus et al., 2012; Eeftens et al., 2012). The annual mean concentrations reflecting the period 2009-2010 were derived based on measurements in the three seasons with temporal adjustment. Measurement sites in ESCAPE were specifically selected to represent spatial variation of air pollution at home addresses of subjects in the included cohorts, thus the monitoring sites were clustered (Fig S1).

Summary statistics of the training and validation datasets are presented in Table S1.

2.2 Predictor variables

Potential predictor variables used in this study are described in more detail elsewhere (de Hoogh et al., 2016; de Hoogh et al., 2018a; Vienneau et al., 2013). The predictor variables are integrated into a 100 m gridded GIS database covering Western Europe. All potential predictor variables and summary statistics are shown in Table S2. We offered 150 potential predictor variables.

2.2.1 Satellite-derived air pollution estimates and chemical transport model estimates

Satellite-derived (SAT) estimates of $PM_{2.5}$ were obtained from global datasets (V3.GL.01; Van Donkelaar et al., 2015). A gridded surface of the 2010 annual average $PM_{2.5}$ was produced at a $0.1^\circ \times 0.1^\circ$ ($\sim 10 \times 10$ km) resolution by relating aerosol optical depth (AOD) retrievals from the NASA MODIS (Moderate Resolution Imaging Spectroradiometer), MISR (Multi-angle Imaging Spectroradiometer) and SeaWiFS (Sea-viewing Wide Field-of-view Sensor) instruments to near-surface concentrations using aerosol vertical profiles and scattering properties simulated by the GEOS-Chem chemical transport model. For NO_2 , SAT estimates for 2010 were derived from the tropospheric NO_2 columns measured with the OMI (Ozone Monitoring Instrument) on board the Aura satellite. The satellite column-integrated retrievals were related to ground-level concentrations using the global GEOS-Chem model to produce a 10×10 km resolution dataset (Bechle et al., 2013, 2015; Novotny et al., 2011).

Annual $PM_{2.5}$ and NO_2 chemical transport models (CTM) estimates for 2010 were derived from the MACC-II ENSEMBLE model at a $0.1^\circ \times 0.1^\circ$ ($\sim 10 \times 10$ km) resolution (Inness et al., 2013). In the ENSEMBLE model, the median value of seven individual regional CTMs (CHIMERE, EMEP, EURAD, LOTOS-EUROS, MATCH, MOCAGE and SILAM) was provided for each pixel.

2.2.2 Traffic, land use and altitude predictors

Road data were extracted from the 1:10,000 EuroStreets digital road network (version 3.1 based on TeleAtlas MultiNet TM, year 2008), classified into ‘all’ and ‘major’ roads. These were then intersected with a 100 m base polygon and the sum of the road lengths was calculated within each grid cell.

The European Corine Land Cover 2006 dataset (ETC-LC, 2009) was used to extract land cover variables for all study areas except for Greece, which has missing data. We used the Corine Land Cover 2000 (ETC-LC, 2013) to extract data for Greece. Six main groups (residential, industry, ports, urban green space, total built up land and natural land) were derived from the initial 44 land classes. A moving window procedure was used to calculate both road and land cover data for selected radii, which ranged from 50 m to 10,000 m (Focalstatistics using sum with a circle).

Elevation was obtained from the SRTM Digital Elevation Database version 4.1 with a resolution of 3 arc second (approximately 90 m) with vertical error of <16 m (CGIAR-CSI).

2.3 Model development

We applied 16 statistical algorithms to build the models. These algorithms cover almost all algorithms applied in previous LUR models and have been assessed in a model comparison paper using mobile monitoring ultrafine particle concentration data (Kerckhoffs et al., 2019).

For each algorithm, 6 models (1 main model plus 5 hold-out validation models) were developed for both pollutants (see Section 2.1). We used grid search to optimize hyperparameters (whose values were set before the training process) for each model, based on the minimum mean cross-validated error. This approach helped to minimize the risk of overfitting and ensured that the models we derived had the best predictive power. Hyperparameters for each algorithm were specified in Table S3.

Linear stepwise regression algorithms assume that the relationships between the pollutants and the predictors are linear and additive (Tibshirani et al., 2013). We used 3 automatic variable selection methods to choose the best subset of predictors. **Forward stepwise Linear Regression (FLR)** started with a null model, then the predictor that generated the highest increase in the adjusted R^2 was added to the model at each subsequent step. This process was repeated until the model adjusted R^2 stopped maximizing. **Backward stepwise Linear Regression (BLR)** began with all variables in the model and deleted the variable with the highest P-value one at a time. The procedure stopped when it generated a model that had only significant predictors (significance level of 0.1) with the maximum adjusted R^2 . **Stepwise Linear Regression (WLR)** allowed variables to be added or deleted as modelling progresses. The algorithm started off in a forward approach with a null model, and then removed variables if they became statistically insignificant (significance level of 0.1). We also used a **Supervised Linear Regression (SLR)** algorithm that was described previously in de Hoogh et al. (2018a). In this algorithm, a univariate linear regression model was run for each potential predictor to choose the model with the highest adjusted R^2 as the starting point. Additional significant predictor variables were allowed to enter the model if they added to the adjusted R^2 of the previous model step, and only if they adhered to the plausible direction of effect. Variables with variance inflation factor (VIF) larger than 3 were removed from the model to avoid multicollinearity.

Regularization or shrinkage algorithms are used to estimate reliable predictor coefficients when the predictors are highly correlated. By imposing different penalties, **ridge regression** keeps all predictors in the final model, while **LASSO** ensures sparsity of the results by shrinking some coefficients exactly to zero. **Elastic Net** is a hybrid of ridge regression and LASSO by adjusting the values of hyperparameter α (Friedman et al., 2009). Elastic net is the same as lasso when $\alpha=1$, it approaches ridge regression as α reduces towards 0. In this study, $\alpha=0.25$ (EN25), 0.5 (EN50) and 0.75 (EN75) were used to build separate elastic net models.

The **Generalized Additive Model (GAM) algorithm** (Wood and Wood, 2015) extends the standard linear regression by introducing non-linear functions for predictors while keeping the additive

assumption. We used “gam” function in the “mgcv” R package, which performs automatic smoothing parameter estimation and allows adding an extra penalty to remove redundant variables from the model. A smoothing spline was fit for potential predictors with at least 5 unique values. Variables with less than 5 differing values, i.e. the land use variables in the smallest buffers (TBU50, NAT50, IND50, POR50, UGR50, RES50), were deleted because the function could not estimate the smoothing parameters for them. The roughness of the smoothing spline was selected via restricted maximum likelihood method (REML).

Machine learning algorithms are able to model nonlinearity as well as the potentially complex interactions among predictors. One type of machine learning algorithms is the ensemble learning machine based on decision trees. **Bagging**, also known as the bootstrap aggregation, repeatedly draws separate subsets from the full training dataset. The final predictions were calculated by averaging the results from all the decision trees built on bootstrapped training subsets. **Random Forest (RF)** (Breiman et al., 2011) adds an additional layer of randomness to bagging by forcing each split to consider only a randomly chosen subset of candidate predictors, instead of the full set. Instead of building independent trees using bootstrapped samples, **Generalized Boosted Machine (GBM)** (Ridgeway et al., 2013) grows trees sequentially: each tree is fit on the residuals of the given model. Other types of machine learning algorithms include the **Support Vector Regression (SVR)** algorithm (Friedman et al., 2001; Meyer et al., 2017), which uses kernel functions to enlarge the feature space and produces non-linear boundaries by constructing a linear boundary in a transformed high-dimensional feature space; the **Kernel-based Regularized Least Squares (KRLS)** (Ferwerda et al., 2017; Hazlett and Hainmueller 2017) algorithm, whose kernel function measures the similarity between covariates while the regularization imposes a preference for a smoother function; and the **Artificial Neural Network (ANN)** (Ripley et al., 2016) algorithm, which consist of interconnected “neurons” (represent predictors) in layers that can account for possible nonlinearities and interactions.

We additionally use two approaches to make ensemble predictions that leverage information from all models. In Ensemble 1 model, the median value of 16 model predictions was provided for each site (Inness et al., 2013). In Ensemble 2 model, a weighted average of the 16 model predictions was provided for each site. The weight (w_i) of each model was calculated based on the inverse of average cross-validation absolute bias at all AIRBASE sites. The ensemble prediction at each site ($\hat{y}$) was defined as:

$$\hat{y} = \frac{\sum_{i=1}^{16} w_i y_i}{\sum_{i=1}^{16} w_i}$$

where y_i is the prediction of the individual models.

2.4 Model evaluation and comparison

We evaluated model performance by regression-based R^2 (R^2), mean square error based R^2 (MSE- R^2), and root-mean-square error (RMSE). R^2 was derived from correlations between predicted and observed values. MSE- R^2 can be seen as a rescaling of MSE. It measures fit about the 1:1 line rather than fit about the best fit line in regression-based R^2 . The formula was defined as:

$$\text{MSE} - R^2 = 1 - \frac{\text{MSE}}{\left(\frac{1}{n} \sum_{i=1}^n (y_i - \bar{y})^2\right)}$$

where $\bar{y}$ is the average of the observed values. MES- R^2 can yield negative values when the average of the observed values performs better than the predictions of the model (Wang et al., 2012). RMSE was computed as the square root of the mean of squared difference between predicted and observed values. **Training** R^2 and RMSE were calculated by comparing the predictions and the observations at all AIRBASE sites. **Cross-validated (CV)** R^2 , MSE- R^2 , and RMSE were computed by comparing the assembled predictions at 5 held-out sets to the corresponding observations at AIRBASE sites (see section 2.1). **External-validated (EV)** R^2 , MSE- R^2 , and RMSE were computed by comparing the

predictions, which were derived from the main models, and the observations at all ESCAPE sites. In external validation, bias (mean difference between predictions and measurements) was additionally calculated for each model to evaluate the transferability of models.

We also evaluated model performance in subsets of ESCAPE sites, including areas with low air pollution concentrations (annual average concentration below 10, 12, 15, 20 and 25 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$; annual average concentration below 20, 30 and 40 $\mu\text{g}/\text{m}^3$ for NO_2), sites of different types (street, rural background and urban background), and different regions (north, west, central, and south). External-validated R^2 , RMSE and bias were calculated for each evaluation.

The predicted concentrations can correlate poorly between models even if the models have similar explained variance (R^2). Therefore, for each pair of models, scatter plots of predicted concentrations at all ESCAPE sites were made to visually assess the correlations at these independent locations. Pearson correlation coefficients were also calculated. Scatter plots of the predictions versus observations at ESCAPE sites were also made for each of the models.

We compared the structure of models by looking at the number of predictors included in a model and the direction and magnitude of coefficients, where applicable. In linear regression models, regression slopes were multiplied by the difference between the 1st and 99th percentile of each predictor to allow comparison across predictors.

2.5 Sensitivity analysis

2.5.1 NO_2 models based on a reduced number of sites

The main NO_2 models were built on 2399 monitoring sites while the $\text{PM}_{2.5}$ models were developed on 543 sites. To separate the impacts of the number of training sites and the differences in pollutant characteristics, we built additional NO_2 models using a random subset of 543 measurements extracted from all AIRBASE NO_2 monitoring sites (stratified by region and site type). The NO_2 sample models were developed and evaluated by the methods described above.

2.5.2 Models with a reduced number of potential predictors

Three variable selection methods were applied to explore the effect of the number of potential predictors offered. For each set of potential predictors derived from the methods described below, we arbitrarily selected two linear regression-based algorithms (SLR and Elastic Net ($\alpha=0.75$)) and two machine learning algorithms (RF and ANN) to fit the models. The training R^2 , CV R^2 and EV R^2 were calculated for each model.

Firstly, the predictor variables were ranked by their absolute correlation coefficients with pollutant concentrations, based on univariate correlation. In separate models, the first 80, 40 and 20 variables with the highest absolute correlation were used as potential predictor variables.

Secondly, the predictor variables were ranked by their variable importance, calculated as percentage increase in mean squared errors after a random permutation of the values of a variable, derived from the RF algorithm. In separate models, the first 80, 40 and 20 variables were used as potential predictor variables.

Finally, we reduced the number of buffers for road length and land use variables. Only variables with radii of 50 m, 100 m, 300 m, 500 m, 1000 m, 2000 m, 5000 m, 10000 m were offered as potential predictors, resulting in a total of 64 predictors.

2.5.3 $\text{PM}_{2.5}$ models with kriging

In the recently published Europe-wide modelling study (de Hoogh et al., 2018a), kriging proved an efficient technique to explain a part of residual spatial variation for the $\text{PM}_{2.5}$ SLR model. To examine whether the residual variation explained by kriging had been captured by a more flexible algorithm, we performed kriging on the residuals from the selected $\text{PM}_{2.5}$ models (BLR, SLR, LASSO, GBM and

ANN). Ordinary kriging was applied to the residuals of background sites only, and added to the pollution estimates of the models. Models were evaluated by the metrics described in section 2.4. Scatter plots comparing the predictions at all ESCAPE sites were made, and Pearson correlation coefficients were calculated.

All statistical analyses were conducted in R v 3.4.1 (Team, 2013).

3. Results

3.1 PM_{2.5} models

All models had moderate to good performance when evaluated by cross-validation (CV), with CV R²s ranging from 0.48 to 0.63, and CV RMSEs ranging from 3.1 to 3.9 µg/m³ (Table 1). CV MSE-R²s were similar as CV R²s. Higher CV R²s and lower CV RMSEs were found for machine learning models based on decision trees (the GBM, the bagging, and the RF). The lowest CV R² and the highest CV RMSE were found for the ANN model. Among all linear regression-based models, the BLR model had the lowest CV R² and the highest CV RMSE, while it had the highest training R² among these linear models.

Model performance measured by external validation (EV) showed good agreement with the results measured by CV, though less of the variation (R²) in the external data was explained (Table 1). MSE-R²s were on average 5% lower than the R²s. The decision tree-based ensemble models performed moderately better than others whilst the BLR, the SVR, and the ANN models performed moderately worse. Biases were lower than 1 µg/m³ for all models, except the ANN. The better performance of the decision tree-based models disappeared when restricting validation dataset to sites with low PM_{2.5} concentrations (Table S4). For all algorithms, validation R² decreased and bias increased when restricting to lower pollution levels. Similar differences in model performance across algorithms were observed for street and urban background sites (Table S5). For all algorithms, bias was higher for background sites than for street sites. The pattern between algorithms was similarly when evaluated at regional scale (Table S6). We noted only small differences of both ensemble models performances compared to the best individual models.

Figure 1 shows the scatter plots of PM_{2.5} predictions at all ESCAPE sites by each pair of models. Most of the predicted concentrations were highly correlated, with correlation coefficients above 0.85. Almost identical predictions were found for several models, such as the LASSO and three Elastic Net models, the FLR and the WLR models, as well as the Bagging and the RF models. Predictions by the ANN model and other models were less correlated. All models tended to overpredict at low concentrations and underpredict at high concentrations (Figure S2).

For linear regression-based models (except for the Ridge regression model), the number of predictors included in the main model, the direction and magnitude of regression slope are summarized in Figure 2 (details shown in Table S7). The SLR model included the lowest number of predictors (7) in the model while the BLR retained the highest number (48). All models included CTM and SAT estimates as well as all roads, natural areas, ports, residential areas, and altitude as predictors. CTM and SAT estimates were positively correlated with PM_{2.5} in all linear regression models, while altitude was always negatively correlated with PM_{2.5}. All models except the SLR model included predictors with counterintuitive direction of slope, such as negative slopes for road length and ports. CTM and SAT estimates were consistently two of the most important predictors in all models, as shown by the large regression slopes, except in the BLR model. CTM and SAT estimates were also identified as the most important predictors in variable importance plots from the RF model and the GBM model, followed by altitude (Figure S4). A rapid drop in variable importance was observed after CTM and SAT estimates.

Table 1. Performance of PM_{2.5} spatial models using different model building algorithms

Algorithm ^a	Training (N = 543)		Cross Validation (N = 543)			External Validation (N = 416)			
	R ²	RMSE ^b ($\mu\text{g}/\text{m}^3$)	R ²	MSE-R ²	RMSE ($\mu\text{g}/\text{m}^3$)	R ²	MSE-R ²	RMSE ($\mu\text{g}/\text{m}^3$)	Bias ($\mu\text{g}/\text{m}^3$)
FLR	0.657	3.0	0.600	0.598	3.3	0.517	0.481	4.1	0.7
BLR	0.704	2.8	0.506	0.472	3.7	0.463	0.445	4.3	0.8
WLR	0.657	3.0	0.600	0.598	3.3	0.517	0.481	4.1	0.7
SLR	0.622	3.2	0.595	0.594	3.3	0.529	0.478	4.1	0.9
Ridge	0.665	3.0	0.592	0.592	3.3	0.535	0.485	4.1	0.7
EN25	0.643	3.1	0.608	0.607	3.2	0.545	0.483	4.1	0.8
EN50	0.642	3.1	0.609	0.608	3.2	0.546	0.486	4.1	0.8
EN75	0.641	3.1	0.609	0.609	3.2	0.547	0.486	4.1	0.8
LASSO	0.641	3.1	0.610	0.609	3.2	0.547	0.487	4.1	0.8
GAM	0.652	3.0	0.608	0.608	3.2	0.557	0.498	4.1	0.9
Bagging	0.954	1.2	0.627	0.626	3.1	0.575	0.531	3.9	0.4
RF	0.955	1.2	0.626	0.624	3.1	0.583	0.530	3.9	0.4
GBM	0.895	1.8	0.631	0.630	3.1	0.610	0.548	3.9	0.4
SVR	0.799	2.3	0.569	0.568	3.4	0.457	0.432	4.3	0.3
KRLS	0.726	2.7	0.590	0.586	3.3	0.525	0.466	4.2	0.6
ANN	0.723	2.7	0.477	0.428	3.9	0.391	0.286	4.8	1.2
Ensemble1	0.698	2.8	0.618	0.617	3.2	0.553	0.495	4.1	0.7
Ensemble2	0.762	2.6	0.622	0.622	3.2	0.573	0.513	4.0	0.7

^aFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network; Ensemble1 = Ensemble model based on median prediction; Ensemble2 = Ensemble model based on weighted average

^bRMSE = Root-mean-square error

Figure 1. Correlations between PM_{2.5} predictions at ESCAPE sites. The upper triangle shows the correlation coefficients, the lower triangle shows the scatter plots

FLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network

Figure 2. Predictors included in linear $PM_{2.5}$ models. The figures in the blanket show the number of predictors included in each model

Regression slopes were multiplied by the difference between the 1th and 99th percentile of each predictor to allow comparison across predictors

MACC = MACC dispersion model, SAT = Satellite-derived, MJRD = Major Roads, ALRD = All Roads, TBU = Total Build Up, NAT = Natural Land, IND = Industry, POR = Ports, UGR = Urban Green, RES = Residential, ALT = Altitude

FLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator

3.2 NO₂ models

Table 2 shows the performance of the different NO₂ models. Though the non-linear models had higher training R²s than the linear regression-based models, all models had similar performances when measured by cross-validation (CV R² 0.57 to 0.62, CV RMSE 9.0 to 9.6 µg/m³), and when measured by external validation (EV R² 0.49 to 0.51, EV RMSE 11.6 to 14.6 µg/m³). Biases were low (1.2 to 3.3 µg/m³) for all models except the ANN (8.8 µg/m³). Model performance also did not vary much across algorithms when restricting validation subsets to less polluted sites (Table S8) and specific type of sites (Table S9). For all algorithms, validation R² decreased and bias increased when restricting to lower pollution levels (Table S8). For all algorithms, validation R² was lower for street sites compared to background sites. A small negative bias was observed for street sites and a more substantial positive bias for background sites, again with small differences across algorithms. All algorithms performed similarly when evaluated at regional scale. Only small differences were found for both ensemble models performances compared to the best individual models.

The predictions at the ESCAPE sites by each pair of models were highly correlated, with Pearson correlation coefficients ranging from 0.91 to 1.00 (Figure 3). All models tended to overpredict at low concentrations and underpredict at high concentrations (Figure S3).

Even though the NO₂ model predictions were similar, their structures were different (Figure 4 and Table S11). The SLR model included the lowest number of predictors (8), while the EN25 model included the highest number (55). CTM estimates were positively associated with NO₂ in all models. All models included SAT estimates with a counterintuitive negative slope, except the SLR which did not include SAT at all. Counterintuitive slopes were also found for road length, ports, natural areas and residential areas in BLR model and regularization models. The variable importance plots derived from the RF and the GBM indicate that the CTM estimates and road variables were strong predictors (Figure S5).

3.3 Sensitivity analysis

3.3.1 NO₂ models based on a reduced number of sites

The performances of NO₂ models built on a subset of 543 sites (the number of PM_{2.5} sites) are summarized in Table S12. Compared to NO₂ models built on all 2399 sites, the CV R²s were virtually the same, while the EV R²s were about 0.05 lower. More variation in the model performances across different algorithms was found compared to the original NO₂ models. The ANN model performed the most poorly when evaluated by CV. The BLR and the ANN performed moderately worse than other models when evaluated by EV. Other models performed similarly when comparing CV and EV results.

3.3.2 Models with a reduced number of potential predictors

For PM_{2.5} models, the training R²s, CV R²s and EV R²s were relatively stable in relation to the number of potential predictors offered to fit the SLR, the EN75 and the RF algorithms (Figure S6). The ANN model had lower training R² but higher CV R² and EV R² when fitted with fewer potential predictors.

NO₂ models fitted with different algorithms show consistent patterns in relation to the number of potential predictors offered (Figure S7). The plots on the left show the relatively poor performance of NO₂ models built with only 20 predictors selected based on univariate correlation, where NO₂ CTM estimates ranked 30 and were not included in the first 20 predictors. The model training R²s, CV R²s and EV R²s all increased rapidly when the number of potential predictors offered increased from 20 to 40. The training R²s, CV R²s and EV R²s further increased mildly when 80 potential predictors were offered. In contrast, the training R²s, CV R²s and EV R²s were not affected by the number of potential predictors offered when variables were selected based on RF or a priori reduction of the number of buffers.

Table 2. Performance of NO₂ spatial models using different model building algorithms

Algorithm ^a	Training (N = 2399)		Cross Validation (N = 2399)			External Validation (N = 1396)			
	R ²	RMSE ^b ($\mu\text{g}/\text{m}^3$)	R ²	MSE- R ²	RMSE ($\mu\text{g}/\text{m}^3$)	R ²	MSE- R ²	RMSE ($\mu\text{g}/\text{m}^3$)	Bias ($\mu\text{g}/\text{m}^3$)
FLR	0.596	9.3	0.584	0.583	9.4	0.499	0.485	11.6	1.3
BLR	0.614	9.1	0.573	0.571	9.5	0.496	0.481	11.6	1.8
WLR	0.596	9.3	0.584	0.583	9.4	0.499	0.485	11.6	1.3
SLR	0.588	9.4	0.575	0.575	9.5	0.495	0.468	11.8	2.5
Ridge	0.606	9.2	0.586	0.586	9.4	0.500	0.471	11.7	2.5
EN25	0.605	9.2	0.588	0.588	9.4	0.504	0.483	11.6	2.0
EN50	0.606	9.2	0.588	0.588	9.4	0.505	0.485	11.6	1.9
EN75	0.606	9.2	0.588	0.588	9.4	0.505	0.485	11.6	1.9
LASSO	0.606	9.2	0.588	0.588	9.4	0.505	0.485	11.6	1.9
GAM	0.639	8.8	0.609	0.609	9.1	0.506	0.486	11.6	2.3
Bagging	0.950	3.6	0.612	0.612	9.1	0.490	0.449	12.0	3.2
RF	0.951	3.6	0.613	0.612	9.1	0.487	0.444	12.0	3.3
GBM	0.807	6.5	0.621	0.621	9.0	0.499	0.471	11.7	2.7
SVR	0.708	8.0	0.607	0.601	9.2	0.492	0.481	11.6	1.2
KRLS	0.687	8.2	0.613	0.613	9.1	0.505	0.480	11.6	2.4
ANN	0.623	9.0	0.570	0.568	9.6	0.488	0.181	14.6	8.8
Ensemble1	0.628	8.9	0.597	0.60	9.3	0.509	0.49	11.6	2.1
Ensemble2	0.706	8.0	0.611	0.61	9.1	0.518	0.49	11.5	2.5

^aFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network; Ensemble1 = Ensemble model based on median prediction; Ensemble2 = Ensemble model based on weighted average

^bRMSE = Root-mean-square error

Figure 3. Correlations between NO₂ predictions at ESCAPE sites. The upper triangle shows the correlation coefficients, the lower triangle shows the scatter plots

FLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network

Figure 4. Predictors included in linear NO₂ models. The figures in the blanket show the number of predictors included in each model

Regression slopes were multiplied by the difference between the 1th and 99th percentile of each predictor to allow comparison across predictors

MACC = MACC dispersion model, SAT = Satellite-derived, MJRD = Major Roads, ALRD = All Roads, TBU = Total Build Up, NAT = Natural Land, IND = Industry, POR = Ports, UGR = Urban Green, RES = Residential, ALT = Altitude
 FLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator

3.3.3 PM_{2.5} models with kriging

The kriging technique performed on residuals further increased the CV R²s and EV R²s of the linear models (BLR, SLR, LASSO) by 4.0% and 12.4% on average, while it increased less for the GBM and ANN models (the CV R² and EV R² of the GBM model increased by 0.8% and 3.8% respectively, the CV R² and EV R² of the ANN model increased by 2.3% and 6.1% respectively) (Table S13). The correlation coefficients of model predictions at ESCAPE sites were both 0.90 for SLM + kriging and GBM + kriging, and LASSO + kriging and GBM + kriging (Figure S8).

4. Discussion

We compared 16 algorithms to develop Europe-wide models predicting annual average PM_{2.5} and NO₂ concentrations in 2010. For both validation methods, PM_{2.5} models developed on 543 sites performed similarly across algorithms, though models developed with the generalized boosted machine, random forest and bagging performed slightly better than others in the full datasets. The PM_{2.5} predictions at all ESCAPE sites derived from different models were highly correlated, except for predictions from the artificial neural network. For both validation methods, NO₂ models developed on 2399 sites performed even more similarly across different algorithms. The NO₂ predictions at external sites were all highly correlated. For both pollutants, low biases were found when different models were applied on all ESCAPE sites, except for the ANN models.

4.1 Predictive ability

Our study found small differences in performance and in predictions at all external sites derived from different algorithms. The algorithms identified the same key predictor variables. The small differences between algorithms may be the result of the large number of training sites, the use of relatively stable annual average concentrations to develop models and the lack of complex relationships between predictors and annual average concentrations.

Previous algorithm comparison studies were based on either a smaller number of sites (Brokamp et al., 2017) or on mobile monitoring with much more variation in the measured concentration data (Kerckhoffs et al., 2019; Van den Bossche et al., 2018; Weichenthal et al., 2016). In our study, all algorithms may have the advantage of a lower risk of overfitting because of the combination of a large number of training sites and stable annual average concentrations. The NO₂ models built on 2399 sites performed more similarly across algorithms than the PM_{2.5} models built on 543 sites, which could be due to the fact that the NO₂ models were built on four times more training sites. This is supported by the sensitivity analysis where the performance of NO₂ models built on 543 sites (the same number of training sites available for PM_{2.5}) varied more across algorithms than the original NO₂ models built on 2399 sites.

The machine learning algorithms did not perform better in our study. However, their ability to model complex relationships among the data is a clear benefit in studies modelling spatiotemporal variations of air pollution, where the variability in concentration is often larger and the relationships between pollution concentration and predictors are more complicated (e.g. nonlinear relationships between pollution and satellite data exist under different meteorological conditions and emission features (Liu et al., 2009; Schaap et al., 2009)). The RF algorithm was fitted to assess spatiotemporal patterns of air pollution in Japan (Araki et al., 2018), the United States (Hu et al., 2017) and China (Zhan et al., 2018). The neural network algorithm was trained to predict daily PM_{2.5} concentrations over the continental United States from 2000 to 2012 (Di et al., 2016a). The SVR algorithm was used in recent European studies to estimate daily PM_{2.5} concentrations across Switzerland (de Hoogh et al., 2018b) and daily PM₁₀ concentrations in Italy (Stafoggia et al., 2017). The GBM algorithm outperformed 10 other algorithms, including linear-regression based algorithms, to model spatiotemporal variation of PM_{2.5} concentrations during a wildfire (Reid et al., 2015). In the Reid et al., algorithm comparison study, the

larger variability in pollution concentrations and the more complicated relationships between predictors and pollution may explain why the more sophisticated algorithms, which are able to model nonlinearity and complex interactions, outperformed the simple algorithms. However, if there are no strong nonlinear relationships or complex interactions in the data, as we have good reasons to assume is the case in our data based on annual average spatial variation, the more sophisticated algorithms do not add to the simple linear regression-based algorithms. In a recent algorithm comparison study trained on mobile and short-term measurements (Kerckhoffs et al., 2019), differences in performance evaluated by external long-term exposure estimates were also small. The investigators used spatial average concentrations for 368 short-term sites and over 8000 road segments, resulting in much less stable estimates of site-specific averages probably due to the shorter sampling time.

We noted only small differences of both ensemble models performances compared to the best individual models. The fact that ensemble models did not improve upon the individual algorithms in our setting could be due to the similar performances and highly correlated predictions across algorithms. Ensemble models are attractive because the researcher does not have to make (arbitrary) choices of what model to choose for final exposure assignment. We used global weights for the different algorithms. If there is evidence for spatially different performance of the different algorithm, spatially varying weights could be used.

Comparing PM_{2.5} and NO₂ models built on the same number of training sites, the ensemble learning algorithms (Bagging, RF and GBM) performed slightly better than other algorithms for PM_{2.5} but not for NO₂. We speculate that this might be due to the different characteristics of PM_{2.5} and NO₂. PM_{2.5} concentrations vary at large regional scales (Eeftens et al., 2012), whereas NO₂ concentrations, strongly influenced by local traffic emissions, vary more widely at smaller scales (Cyrus et al., 2012). The ensemble learning algorithms modelled detailed fluctuations of the measurements – as indicated by the extremely high training R²s, which may not transfer to the validation dataset for NO₂.

The results of the GAM models might not be comparable with other models because of the slightly different input variables. However, we would not expect much deviation from the current results as none of the deleted small buffer land use variables was identified as important predictors in other models. The ANN models as specified in the current study did not perform well among the algorithms. One possible reason is that the large number of predictors and relatively small number of observations in the training dataset required more careful training. Our sensitivity analysis also supported that with less potential predictors or more training data, the ANN algorithm tended to perform better. In this study, we used one hidden layer to build ANN models because, as suggested by Schalkoff (1997), one hidden layer is sufficient for avoiding overfitting in most applications. However, we cannot rule out the possibility of better performance by using more than one hidden layer.

Kriging is a technique which can be used to explain spatial variation within the data. In the sensitivity analysis, kriging on residual variation did not significantly improve the performance for PM_{2.5} GBM and ANN models, indicating the machine learning algorithms have some ability to address spatial autocorrelation in air pollution concentrations. The CV-R² of SLR, LASSO and GBM models became closer after adding kriging surfaces, indicating part of the residual variance of the SLR and LASSO models explained by kriging had been accounted for by a more flexible GBM algorithm. For NO₂, kriging did not explain the residual spatial variation (de Hoogh et al., 2018a).

4.2 Model structure and interpretation

Although our main interest is in the predictive performance of the models, it is informative to interpret the structure of the models. The importance of specific determinants such as traffic in the model may be helpful to compare risks across epidemiological studies in different areas.

The machine learning algorithms are often considered “black boxes” (Zhang and Ding, 2017) since the models derived from these algorithms are difficult to interpret. Even though some algorithms provide variable importance measures, such as the RF and the GBM (Breiman et al., 2011; Ridgeway et al.,

Table 3. Overview of algorithms as applied in this study

Algorithm ^a	Group	Model possible nonlinear relationships between pollutant and predictors	Model possible interactions among predictors	Variable selection	Computation time (mins) ^b	Model structure
FLR	Linear stepwise regression algorithms	No; a priori transformations can be offered e.g. inverse distance	No; selected product terms can be added in principle	Yes	<1	Shown magnitude and direction of predictor effects; biased coefficient estimates when predictors are highly correlated (except SLR, which excluded highly correlated predictors in a model)
BLR					4	
WLR					<1	
SLR					<1	
Ridge	Regularization or shrinkage algorithms	No; a priori transformations can be offered e.g. inverse distance	No; selected product terms can be added in principle	Yes, except for Ridge regression	<1	Shown magnitude and direction of predictor effects; reliable coefficient estimates even when predictors are highly correlated
EN25					<1	
EN50					<1	
EN75					<1	
LASSO					<1	
GAM	Generalized Additive Model algorithm	Yes	No	Yes, not in default method	2313	Difficult to interpret with multiple predictors
Bagging	Machine learning algorithms	Yes	Yes	No	41	Difficult to interpret, though RF and GBM provide variable importance measures
RF					96	
GBM					66	
SVR					8	
KRLS					5	
ANN					6	

^aFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network

^bComputation time was recorded for PM_{2.5} models developed on a standard office computer

2013), the magnitude and direction of the predictor effects are unknown. Models built with linear stepwise regression and regularization algorithms are easier to interpret, both in terms of included predictors and the magnitude and direction of predictor effects. An overview of the applied algorithms is shown in Table 3.

For both pollutants, the SLR models by definition included only predictors following the plausible direction of effect, resulting in a substantially smaller number of predictors than other models. Models developed with all other algorithms included predictors with counterintuitive directions of effect, though in most cases not for the key predictor variables. For example in the NO₂ models, satellite NO₂ was included with a negative slope possibly to compensate for overprediction by the other large spatial scale predictor variable (CTM estimates). Restricting the inclusion of predictors did not affect model performance in our study and may be considered more a philosophical choice (Brauer et al., 2003; Vienneau et al., 2010). However, model prediction may deviate when the models are applied in another domain than the Europe-wide training domain such as a smaller area within Europe. This is supported by our subset validation where the NO₂ SLR model outperformed automatic variable selection linear models at rural background sites.

In our study, correlated potential predictors were offered to build linear-regression based models. These predictors are usually the same land use feature/ road length in buffers with different radii. Offering highly correlated predictors would lead to incorrect selection of predictors in a model (Agier et al., 2016), and including highly correlated predictors in an ordinary least squares-based model would lead to biased coefficient estimates (Tibshirani et al., 2013). Clear evidence for this is found in the backward stepwise selection algorithm, which included very different predictor variables than all other algorithms, and had a lower explained variance in the validation dataset. The SLR algorithm deals with collinearity by deleting predictors with a variance inflation factor larger than 3, at the expense of including fewer predictor variables. The regularization algorithms impose a penalty to shrink the coefficients of the least informative predictors towards zero, which have been shown to be more efficient in identifying correct predictors than the ordinary least squares-based algorithms (Agier et al., 2016). Compared to the SLR algorithm, regularization algorithms included more buffers of the same variable, which is consistent with the notion of smooth changes of pollution with increasing buffer size: if a road length variable contributes to the pollution estimate, one would expect road length variables with other buffer sizes also to add to the pollution estimate. However, interpretation is hampered because the same land use feature/ road length with different radii entered the model with both plausible and implausible directions of effect.

4.3 Strengths and limitations

One strength of our study is that we compared multiple algorithms with very different assumptions. Most of the previous algorithm comparison studies only compared two or three algorithms (Basagaña et al., 2012; Brokamp et al., 2017; Van den Bossche et al., 2018; Weichenthal et al., 2016), therefore results between studies are difficult to compare. Studies have assessed more algorithms in different settings such as assessing spatiotemporal variation of PM_{2.5} during a wildfire (Reid et al., 2015), or assessing spatial variation of ultrafine particles using mobile monitoring data (Kerckhoffs et al., 2019). Our study gives new insight into the predictive ability of these algorithms because the number of training sites, variation in the monitoring data and complexity of relationships within the data can all affect relative performance of the algorithms.

Secondly, we used both cross-validation and external validation to strengthen our comparison. CV is commonly used to evaluate model performance in air pollution exposure assessment (Kim et al., 2016; Y. Liu et al., 2009). Because CV is restricted to the monitoring domain, a good performance evaluated by CV does not necessarily mean the model can accurately predict residential exposure, which is often used as surrogates for long-term exposure of subjects in epidemiological studies (Beelen et al., 2014; Di et al., 2017). Concerns about overestimating exposures at residential addresses have been raised for models based upon on-road mobile monitoring (Hoek, 2017; Kerckhoffs et al., 2016). In this situation,

CV alone cannot reflect true transferability because the mobile monitoring sites are located on roads and the measurements usually have significant variations. Validation of such models using an external dataset reflecting residential exposure is important (Kerckhoffs et al., 2019). In our study, monitoring data from the regulatory AIRBASE network were used to develop air pollution models. With the aim to check for compliance with the European Union air quality standards, the monitors in the AIRBASE network have not primarily been located with the goal of characterizing residential exposure in mind. On the other hand, the location of ESCAPE sites was purposely selected to be representative for air pollution exposure at home addresses of study subjects. In this sense, results of our EV using pollution data from the ESCAPE study reflects the transferability of models in application. Besides the choice of monitoring locations, there are also a number of differences between the two datasets that could impact the evaluation. Firstly, ESCAPE monitoring sites do not cover the same geographical area as the AIRBASE monitoring sites. Secondly, the two datasets differed in measurement techniques. A comprehensive comparison showed limited systematic differences between the ESCAPE and AIRBASE methods for NO₂ (Cyrus et al., 2012). NO₂ was mainly measured by chemiluminescence in AIRBASE versus Ogawa badges in ESCAPE. Chemiluminescence is subject to interference from other reactive nitrogen species that can vary spatially (Suzuki et al., 2011), which could, at least partially, explain the higher bias at low concentration and background ESCAPE sites. For PM_{2.5} no methods comparison was made. Thirdly, the ESCAPE measurements are based on 2-week sampling in three seasons with temporal adjustment versus continuous measurements in AIRBASE. Lastly, ESCAPE measurements were conducted following the same standard measurement methods and strict quality control procedures, while the AIRBASE were measured by inconsistent methods and reported with different frequency across countries. Nevertheless, the agreement in results showed by CV and EV help us to strengthen the comparison.

Thirdly, we used grid search to optimize hyperparameters for some algorithms before fitting the models, based on the best performance in 5-fold cross-validation. This approach helped to minimize the risk of overfitting and avoid overly optimistic performance estimates (Van den Bossche et al., 2018). This adds to a recent algorithm comparison performed by Kerckhoffs et al., (2019) which used default parameters for algorithms. Though the grid search approach added to the computation load in model development for the GAM and machine learning algorithms, the computation time is generally short for all algorithms, and was not a decisive factor for choosing one algorithm over another in this moderately small dataset (Table 3).

Despite similarities across algorithms, the model performances remained moderate in our study for both pollutants. This is probably a result of missing explanatory variables. A previous European PM_{2.5} model developed using supervised linear regression algorithm obtained a CV R² of 0.80 (Wang et al., 2014), which was driven by the inclusion of local traffic intensity and measured regional background concentrations. Such variables are often only available at local level, and were not available in the current study. The relevant influence of missing explanatory variables is also supported by our sensitivity analysis where performance of different NO₂ models all reduced dramatically when the CTM estimates were not offered as a potential predictor. Additionally, the overall model performance we evaluated in the study could be dominated by regional variation and might not reflect within-city variations well. Decreased and varying R²s were reported when the SLR model was validated at individual study areas (de Hoogh et al., 2018a). However, the overall model performance was our primary interest as the models developed in this study were aimed to estimate air pollution exposure for participants across Europe. Our sensitivity analyses showed moderate performances when models were validated at regional scale (Tables S6 and S10). Another limitation is that none of the algorithms explicitly include handling spatial autocorrelation in air pollution concentrations in model building. We addressed this with a 2-step kriging sensitivity analysis. Our results showed that kriging significantly improved model performance of linear regression algorithms, and suggest that the machine learning algorithms have some ability to handle autocorrelation within data. Our 2-step kriging approach likely underestimates the value of including spatial autocorrelation (Mercer et al., 2011). The predictive power

of these models might be further improved by applying universal kriging, which can be seen as a LUR with addition of correlated residuals.

4.4 Conclusion

Different statistical algorithms performed similarly when modelling spatial variation of annual average air pollution concentrations using a large number of training sites.

The results of our study and the previous algorithm comparisons suggest that the relative performance of algorithms may differ with the study setting, therefore generic recommendations for one algorithm cannot be made. To take appropriate decisions for a particular study, future studies may opt for models developed using more than one algorithm.

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Supplemental Information

Table S1. Summary statistics of air pollution measurements

Air pollutant	type	N	Mean ($\mu\text{g}/\text{m}^3$)	Median ($\mu\text{g}/\text{m}^3$)	SD ($\mu\text{g}/\text{m}^3$)	Percentiles ($\mu\text{g}/\text{m}^3$)				min ($\mu\text{g}/\text{m}^3$)	max ($\mu\text{g}/\text{m}^3$)
						5	25	75	95		
PM _{2.5}	Traffic	149	16.3	16.6	4.9	8.6	13.0	19.7	23.7	6.3	28.1
	BG ^a	341	15.8	15.8	5.2	7.3	12.7	18.7	23.7	2.1	33.4
	Industrial	53	15.1	15.3	5.5	7.8	10.4	18.8	25.4	6.7	26.0
	All	543	15.8	15.9	5.1	7.7	12.4	19.2	23.9	2.1	33.4
NO ₂	Traffic	740	40.2	38.7	14.6	20.6	30.4	47.7	65.6	3.0	101.8
	BG	1287	21.5	21.0	9.8	5.7	14.8	27.9	37.1	0.4	58.7
	Industrial	372	19.4	18.2	10.1	4.5	11.5	26.6	37.4	1.6	60.5
	All	2399	26.9	25.1	14.6	6.8	16.4	34.7	53.6	0.4	101.8
NO ₂ sample	Traffic	168	40.1	37.0	16.0	16.2	30.1	49.1	67.1	7.9	99.9
	BG	291	21.7	21.0	10.0	5.3	14.8	29.4	38.6	0.4	57.5
	Industrial	84	18.8	18.1	10.1	4.5	11.4	25.3	38.3	1.6	43.1
	All	543	27.0	24.7	15.1	6.2	16.2	34.9	54.3	0.4	99.9
PM _{2.5}	Street	196	17.1	17.1	6.0	8.8	12.3	20.5	29.8	7.9	36.3
	Rural BG	53	13.8	14.0	4.6	6.0	11.1	16.8	21.3	4.4	23.2
	Urban BG	167	15.1	14.8	5.4	7.5	10.9	18.5	24.2	5.6	32.6
	All	416	15.9	15.8	5.7	7.9	11.5	19.1	26.0	4.4	36.3
NO ₂	Street	713	37.0	32.8	17.1	16.1	24.7	47.0	71.2	9.8	109.0
	Rural BG	118	14.4	15.1	6.3	5.1	9.5	17.9	25.3	1.5	32.9
	Urban BG	565	22.7	22.0	10.0	7.8	14.6	29.5	41.1	3.0	57.6
	All	1396	29.3	26.3	16.1	9.4	17.6	36.7	62.1	1.5	109.0

^aBG = Background

Table S2. Potential predictor variables and statistics for grid estimate or selected buffers (100m, 1000m and 10000m)

Predictor variable	Name variable	Year	Buffer size (radius in m) or grid estimate	PM _{2.5} model predictors			NO ₂ model predictors		
				1 st percentile	Median	99 th percentile	1 st percentile	Median	99 th percentile
Dispersion model estimates (µg/m ³)	MACC_PM ₂₅ MACC_NO ₂	2010	grid	5	12	19	-	-	-
Satellite derived estimates (µg/m ³)	SAT_PM ₂₅ SAT_NO ₂	2010	grid	4	13	31	-	-	-
Length of Major roads (m)	MJRD			0	0	808	0	0	804
			50, 100, 200, 300, 400,	0	2639	16070	0	2091	14728
			500, 700, 1000, 2000,	0	135837	526443	0	109657	627774
		2010	5000, 10000	0	190	1112	0	200	1208
Length of All roads (m)	ALRD			0	11461	32668	0	9897	28910
				77525	453868	1472325	63050	391724	1675754
Surface area of total build up ^a (m ²)	TBU			0	5	5	0	5	5
				0	253	317	0	226	317
				41	6593	26013	67	4662	26248
Surface area of natural areas (m ²)	NAT			0	0	5	0	0	5
				0	0	297	0	0	317
				254	7020	26634	89	8692	29360
Surface area of industrial/commercial areas (m ²)	IND			0	0	5	0	0	5
			50, 100, 200, 300, 400,	0	2	178	0	2	181
			500, 600, 700, 800,	0	1087	4385	0	853	4470
		2006	1000, 1200, 1500,	0	0	1	0	0	0
			1800, 2000, 2500,	0	0	88	0	0	78
			3000, 3500, 4000,	0	0	2468	0	0	2007
Surface area of ports (m ²)	POR			0	0	5	0	0	4
			5000, 6000, 7000,	0	0	94	0	0	89
			8000, 10000	0	5	5	0	5	5
Surface area of urban green (m ²) ^b	UGR			0	198	317	0	175	317
Surface area of residential land ^c (m ²)	RES			24	4846	21049	27	3283	21319
Altitude – transformed ^d	ALT		point	-2	80	957	-1	106	1121
									204

^aResidential + Ind/comm + Port + transport infrastructure, airports, mines, dumps and construction sites

^bSurface area of urban green only has estimates for buffer size of 50m, 100m, 200m, 300m, 400m, 500m, 600m, 700m, 800m, 1000m

^cContinuous urban fabric (high density housing) + discontinuous urban fabric (low density housing)

^dTransformed altitude is calculated as $\sqrt{(\text{nalt}/\text{max}(\text{nalt}))}$, where nalt = altitude – $\text{min}(\text{altitude})$

Table S3. Hyperparameters^a selected in main models

Algorithm ^b	R package	PM _{2.5} models	NO ₂ models
FLR	SignifReg	-	-
BLR	SignifReg	-	-
WLR	SignifReg	-	-
SLR	stats	-	-
Ridge	glmnet	$\alpha = 0, \lambda = 0.66$	$\alpha = 0, \lambda = 0.87$
EN25	glmnet	$\alpha = 0.25, \lambda = 0.38$	$\alpha = 0.25, \lambda = 0.16$
EN50	glmnet	$\alpha = 0.50, \lambda = 0.22$	$\alpha = 0.50, \lambda = 0.07$
EN75	glmnet	$\alpha = 0.75, \lambda = 0.16$	$\alpha = 0.75, \lambda = 0.05$
LASSO	glmnet	$\alpha = 1, \lambda = 0.12$	$\alpha = 1, \lambda = 0.04$
GAM	mgcv	gamma = 3	gamma = 1
Bagging	randomForest	nbag = 3000, nodesize = 5	nbag = 500, nodesize = 5
RF	randomForest	mtry = 100, ntree = 750, nodesize = 5	mtry = 130, ntree = 2500, nodesize = 5
GBM	gbm	ntree = 4000, max.inter = 10, shrinkage = 0.001	ntree = 6000, max.inter = 10, shrinkage = 0.001
SVR	e1071	eps-regression, $\epsilon = 0.01$, cost = 2, kernel = "radial"	eps-regression, $\epsilon = 0.28$, cost = 1, kernel = "radial"
KRLS	KRLS	lambda = 0.3, sigma=500	lambda = 0.7, sigma=310
ANN ^c	nnet	size = 1, maxit = 10000	size = 1, maxit = 10000

^a α = hyperparameter to balance LASSO penalty and ridge penalty; λ = hyperparameter to control the shrinkage penalty; gamma = the lever of penalty added to smoothing parameter; nbag = number of bootstrapped subsets; nodesize = minimum number of observations in the terminal nodes; mtry = number of predictors at each split; ntree = number of trees; max.inter = maximum depth of interactions; shrinkage = the learning speed of a boosted model; ϵ = epsilon in the insensitive-loss function; cost = hyperparameter to control regularization; lambda = hyperparameter determines the trade-off between model fit and complexity; sigma = kernel bandwidth that governs the maximum distance between two observations that enters into the kernel calculation; size = number of neurons in the hidden layer; maxit = maximum number of iterations

^bFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network

^cOne hidden layer was used in ANN because, as suggested by Schalkoff (1997), this is sufficient for avoiding overfitting in most applications; data were normalized and rescaled before training to ensure equal initial contribution of each potential predictor (determined by its variability) (Iglewicz, 1983)

Table S4. Performance of PM_{2.5} models at ESCAPE sites with annual average PM_{2.5} concentration below certain values

Algorithm ^a	< 10 µg/m ³ (N = 74)			< 12 µg/m ³ (N = 118)			< 15 µg/m ³ (N = 191)			< 20 µg/m ³ (N = 327)			< 25 µg/m ³ (N = 390)		
	R ²	RMSE ^b (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)
FLR	0.273	4.3	3.9	0.360	4.1	3.7	0.493	3.9	3.3	0.547	3.4	2.2	0.522	3.5	1.4
BLR	0.335	4.4	3.8	0.325	4.1	3.5	0.400	4.1	3.3	0.468	3.7	2.2	0.437	3.8	1.4
WLR	0.273	4.3	3.9	0.360	4.1	3.7	0.493	3.9	3.3	0.547	3.4	2.2	0.522	3.5	1.4
SLR	0.376	4.4	4.2	0.421	4.3	4.0	0.516	4.0	3.6	0.541	3.5	2.4	0.517	3.6	1.5
Ridge	0.319	4.5	4.2	0.378	4.3	3.9	0.477	4.0	3.4	0.536	3.4	2.2	0.522	3.5	1.4
EN25	0.372	4.5	4.3	0.427	4.3	4.0	0.520	4.0	3.5	0.553	3.4	2.3	0.534	3.5	1.4
EN50	0.372	4.5	4.2	0.427	4.3	4.0	0.526	4.0	3.5	0.555	3.4	2.3	0.535	3.5	1.4
EN75	0.373	4.5	4.2	0.429	4.3	4.0	0.528	4.0	3.5	0.554	3.4	2.3	0.535	3.5	1.4
LASSO	0.374	4.5	4.2	0.429	4.3	4.0	0.529	4.0	3.5	0.554	3.4	2.3	0.535	3.5	1.4
GAM	0.339	4.4	4.1	0.398	4.2	3.9	0.522	4.0	3.5	0.563	3.4	2.4	0.542	3.5	1.5
Bagging	0.241	4.2	3.7	0.340	4.1	3.5	0.478	3.8	3.2	0.531	3.2	1.9	0.523	3.4	0.9
RF	0.252	4.2	3.7	0.356	4.1	3.6	0.495	3.8	3.2	0.542	3.2	1.9	0.534	3.4	1.0
GBM	0.216	4.2	3.7	0.354	4.1	3.6	0.486	3.7	3.1	0.571	3.1	1.9	0.556	3.3	1.0
SVR	0.213	4.4	3.9	0.300	4.2	3.7	0.453	3.9	3.3	0.460	3.4	1.9	0.444	3.6	1.0
KRLS	0.329	4.5	4.3	0.384	4.3	4.0	0.502	4.0	3.5	0.522	3.4	2.2	0.500	3.6	1.2
ANN	0.257	4.4	3.5	0.272	4.3	3.3	0.302	4.5	3.1	0.363	4.6	2.5	0.370	4.6	1.8
Ensemble1	0.348	4.4	4.1	0.410	4.2	3.9	0.523	3.9	3.5	0.562	3.4	2.2	0.542	3.5	1.4
Ensemble2	0.348	4.3	4.0	0.416	4.1	3.8	0.533	3.8	3.4	0.574	3.3	2.2	0.552	3.4	1.3

^aFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network; Ensemble1 = Ensemble model based on median prediction; Ensemble2 = Ensemble model based on weighted average

^bRMSE = Root-mean-square error

Table S5. Performance of PM_{2.5} models at different type of sites

Algorithm ^a	Street (N = 196)			Rural Background (N = 53)			Urban Background (N = 167)		
	R ²	RMSE ^b (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)
FLR	0.482	4.4	0.0	0.675	3.2	1.7	0.504	4.1	1.3
BLR	0.469	4.4	-0.1	0.508	4.0	2.4	0.449	4.2	1.2
WLR	0.482	4.4	0.0	0.675	3.2	1.7	0.504	4.1	1.3
SLR	0.495	4.4	0.1	0.669	3.2	1.7	0.520	4.1	1.6
Ridge	0.504	4.4	-0.1	0.662	3.3	1.9	0.532	4.0	1.3
EN25	0.519	4.3	-0.1	0.665	3.3	1.8	0.538	4.1	1.4
EN50	0.519	4.3	-0.1	0.669	3.3	1.8	0.541	4.1	1.5
EN75	0.520	4.3	-0.1	0.670	3.3	1.8	0.543	4.1	1.5
LASSO	0.520	4.3	-0.1	0.671	3.2	1.8	0.544	4.1	1.5
GAM	0.536	4.2	0.0	0.679	3.3	2.0	0.553	4.0	1.6
Bagging	0.537	4.3	-0.5	0.677	3.1	1.4	0.597	3.8	1.1
RF	0.552	4.2	-0.5	0.670	3.1	1.5	0.601	3.8	1.1
GBM	0.586	4.1	-0.5	0.711	3.0	1.5	0.616	3.7	1.1
SVR	0.423	4.7	-0.8	0.677	3.5	2.3	0.493	4.1	1.0
KRLS	0.487	4.5	-0.4	0.663	3.4	2.1	0.551	4.0	1.2
ANN	0.411	4.7	0.3	0.542	4.8	3.2	0.363	5.0	1.7
Ensemble1	0.522	4.3	-0.1	0.680	3.2	1.8	0.554	4.0	1.4
Ensemble2	0.544	4.3	-0.2	0.688	3.2	1.9	0.579	3.9	1.3

^aFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network; Ensemble1 = Ensemble model based on median prediction; Ensemble2 = Ensemble model based on weighted average

^bRMSE = Root-mean-square error

Table S6. Performance of PM_{2.5} models at different regions

Algorithm ^a	North (N = 99)			West (N = 119)			Central (N = 78)			South (N = 120)		
	R ²	RMSE ^b ($\mu\text{g}/\text{m}^3$)	Bias ($\mu\text{g}/\text{m}^3$)	R ²	RMSE ($\mu\text{g}/\text{m}^3$)	Bias ($\mu\text{g}/\text{m}^3$)	R ²	RMSE ($\mu\text{g}/\text{m}^3$)	Bias ($\mu\text{g}/\text{m}^3$)	R ²	RMSE ($\mu\text{g}/\text{m}^3$)	Bias ($\mu\text{g}/\text{m}^3$)
FLR	0.705	3.8	2.0	0.610	3.7	2.7	0.400	3.2	0.0	0.387	5.2	-1.8
BLR	0.611	3.9	1.8	0.519	4.1	2.8	0.301	3.5	-0.2	0.323	5.1	-1.5
WLR	0.705	3.8	2.0	0.610	3.7	2.7	0.400	3.2	0.0	0.387	5.2	-1.8
SLR	0.650	4.0	2.1	0.656	3.9	3.0	0.320	3.4	-0.1	0.546	4.8	-1.5
Ridge	0.739	3.8	2.2	0.575	3.7	2.6	0.391	3.2	-0.2	0.439	5.1	-1.7
EN25	0.716	4.0	2.1	0.634	3.7	2.7	0.359	3.3	-0.1	0.530	5.0	-1.7
EN50	0.715	3.9	2.0	0.636	3.7	2.7	0.358	3.3	-0.1	0.529	5.0	-1.7
EN75	0.715	4.0	2.0	0.637	3.7	2.8	0.350	3.3	-0.1	0.540	5.0	-1.7
LASSO	0.715	3.9	2.0	0.638	3.7	2.8	0.350	3.3	0.0	0.541	5.0	-1.7
GAM	0.741	3.8	1.9	0.613	3.8	2.8	0.397	3.2	0.2	0.505	4.9	-1.5
Bagging	0.650	3.7	1.5	0.568	3.6	2.2	0.095	3.9	0.4	0.700	4.4	-2.3
RF	0.675	3.6	1.5	0.555	3.6	2.2	0.125	3.8	0.3	0.699	4.5	-2.3
GBM	0.684	3.6	1.6	0.603	3.5	2.2	0.248	3.5	-0.1	0.697	4.5	-2.1
SVR	0.646	3.8	1.8	0.426	3.7	2.0	0.230	3.7	0.1	0.437	5.5	-2.5
KRLS	0.743	3.8	2.1	0.488	3.7	2.3	0.273	3.5	0.1	0.518	5.2	-2.0
ANN	0.665	3.7	2.0	0.332	5.9	4.0	0.472	3.6	-0.9	0.238	5.2	-0.8
Ensemble1	0.721	3.8	2.0	0.628	3.7	2.7	0.356	3.3	0.0	0.537	5.0	-1.7
Ensemble2	0.737	3.7	1.9	0.621	3.7	2.6	0.356	3.3	0.0	0.593	4.9	-1.8

^aFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network; Ensemble1 = Ensemble model based on median prediction; Ensemble2 = Ensemble model based on weighted average

^bRMSE = Root-mean-square error

Table S7. Predictors^a included and corresponding coefficients^b of parametric PM_{2.5} models

Algorithm ^c	main model
FLR	2.82+11.74*SAT_PM ₂₅ +4.12*TBU ₄₀₀ +8.97*MACC_PM ₂₅ -4.29*ALT+2.32*ALRD ₁₀₀ -2.72*ALRD ₁₀₀₀₀ -2.57*POR ₅₀₀₀ +6.43*POR ₈₀₀ -2.1*NAT ₅₀ -3.04*IND ₁₀₀ -3.46*POR ₁₈₀₀ +0*POR ₅₀ -4.77*RES ₈₀₀ +2.99*RES ₁₅₀₀
BLR	3.63-4.73*ALT+27.61*TBU ₁₂₀₀ -28.19*TBU ₁₅₀₀ -21.63*TBU ₁₀₀ +30.93*TBU ₂₀₀ +25*TBU ₄₀₀₀ -24.02*TBU ₅₀₀₀ -8.7*TBU ₇₀₀ +71.36*NAT ₁₀₀₀ -37.91*NAT ₁₂₀₀ +23*NAT ₂₀₀₀ -38.42*NAT ₂₅₀₀ -7.52*NAT ₂₀₀ +41.51*NAT ₃₀₀₀ -20.49*NAT ₃₅₀₀ -22.89*NAT ₄₀₀ +107.1*NAT ₅₀₀ -136.23*NAT ₆₀₀ +100.22*NAT ₇₀₀ -82.57*NAT ₈₀₀ -10.12*IND ₁₂₀₀ +12.68*IND ₁₅₀₀ +18.14*IND ₁₀₀ -38.81*IND ₂₀₀ +26.93*IND ₃₀₀ -5.56*IND ₄₀₀₀ -12.36*IND ₄₀₀ +8.08*IND ₆₀₀₀ -12.67*IND ₇₀₀₀ +9.1*IND ₈₀₀₀ +2.62*POR ₁₀₀ -35.7*POR ₃₀₀ +32.35*POR ₄₀₀ -3.21*POR ₅₀₀₀ +2.71*UGR ₁₀₀₀ +9.18*UGR ₄₀₀ -10.42*UGR ₆₀₀ +2.09*ALRD ₁₀₀ +8.48*MACC_PM ₂₅ +10.95*SAT_PM ₂₅ +18.52*RES ₁₀₀ -28.83*RES ₂₀₀ +8.8*RES ₃₀₀ -33.07*RES ₁₂₀₀ +36.61*RES ₁₅₀₀ -19.22*RES ₄₀₀₀ +28.69*RES ₆₀₀₀ -14.33*RES ₈₀₀₀
WLR	2.82+11.74*SAT_PM ₂₅ +4.12*TBU ₄₀₀ +8.97*MACC_PM ₂₅ -4.29*ALT+2.32*ALRD ₁₀₀ -2.72*ALRD ₁₀₀₀₀ -2.57*POR ₅₀₀₀ +6.43*POR ₈₀₀ -2.1*NAT ₅₀ -3.04*IND ₁₀₀ -3.46*POR ₁₈₀₀ +0*POR ₅₀ -4.77*RES ₈₀₀ +2.99*RES ₁₅₀₀
SLR	3.19 +13.24*SAT_PM ₂₅ +7.08*MACC_PM ₂₅ - 3.82*ALT + 2.17*ALRD ₁₀₀ -2.07*NAT ₅₀ +2.39*POR ₈₀₀ +1.41*RES ₂₀₀
Ridge	4.48-3.69*ALT-0.77*TBU ₁₀₀₀₀ -0.09*TBU ₁₀₀₀ +0.21*TBU ₁₂₀₀ +0.34*TBU ₁₅₀₀ +0.26*TBU ₁₈₀₀ +0.19*TBU ₁₀₀ +0.18*TBU ₂₀₀₀ -0.19*TBU ₂₅₀₀ +0.62*TBU ₂₀₀ -0.14*TBU ₃₀₀₀ -0.09*TBU ₃₅₀₀ +0.71*TBU ₃₀₀ -0.07*TBU ₄₀₀₀ +0.55*TBU ₄₀₀ -0.13*TBU ₅₀₀₀ +0.31*TBU ₅₀₀ +0.14*TBU ₆₀₀₀ +0.19*TBU ₆₀₀ -0.08*TBU ₇₀₀₀ +0.03*TBU ₇₀₀ -0.42*TBU ₈₀₀₀ -0.06*TBU ₈₀₀ -0.62*TBU ₅₀ -0.62*NAT ₁₀₀₀₀ +0.46*NAT ₁₀₀₀ +0.29*NAT ₁₂₀₀ +0.18*NAT ₁₅₀₀ +0.3*NAT ₁₈₀₀ -1.09*NAT ₁₀₀ +0.33*NAT ₂₀₀₀ -0.1*NAT ₂₅₀₀ -0.82*NAT ₂₀₀ -0.09*NAT ₃₀₀₀ -0.21*NAT ₃₅₀₀ -0.36*NAT ₃₀₀ -0.21*NAT ₄₀₀₀ -0.09*NAT ₄₀₀ -0.21*NAT ₅₀₀₀ +0.38*NAT ₅₀₀ -0.08*NAT ₆₀₀₀ -0.05*NAT ₆₀₀ +0.1*NAT ₇₀₀₀ -0.02*NAT ₇₀₀ +0.03*NAT ₈₀₀₀ -0.17*NAT ₈₀₀ -0.92*NAT ₅₀ +0.93*IND ₁₀₀₀₀ +0.12*IND ₁₀₀₀ +0.07*IND ₁₂₀₀ +0.03*IND ₁₅₀₀ +0*IND ₁₈₀₀ -0.41*IND ₁₀₀ +0.04*IND ₂₀₀₀ -0.06*IND ₂₅₀₀ -0.32*IND ₂₀₀ -0.1*IND ₃₀₀₀ -0.22*IND ₃₅₀₀ +0.12*IND ₃₀₀ -0.4*IND ₄₀₀₀ -0.13*IND ₄₀₀ -0.37*IND ₅₀₀₀ -0.31*IND ₅₀₀ -0.1*IND ₆₀₀₀ -0.12*IND ₆₀₀ +0.21*IND ₇₀₀₀ +0.02*IND ₇₀₀ +0.94*IND ₈₀₀₀ +0.31*IND ₈₀₀ -0.5*IND ₅₀ +0*POR ₁₀₀₀₀ +0.54*POR ₁₀₀₀ +0.09*POR ₁₂₀₀ -0.67*POR ₁₅₀₀ -0.72*POR ₁₈₀₀ +0.11*POR ₁₀₀ -0.74*POR ₂₀₀₀ -0.1*POR ₂₅₀₀ -0.16*POR ₂₀₀ -0.2*POR ₃₀₀₀ -0.35*POR ₃₅₀₀ -0.37*POR ₃₀₀ -0.31*POR ₄₀₀₀ +0.06*POR ₄₀₀ -0.75*POR ₅₀₀₀ +0.5*POR ₅₀₀ -0.44*POR ₆₀₀₀ +1.14*POR ₆₀₀ -0.34*POR ₇₀₀₀ +1.38*POR ₇₀₀ -0.17*POR ₈₀₀₀ +1.44*POR ₈₀₀ +0*POR ₅₀ +0.37*UGR ₁₀₀₀ -0.13*UGR ₁₀₀ +0.86*UGR ₂₀₀ +0.58*UGR ₃₀₀ +0.29*UGR ₄₀₀ -0.56*UGR ₅₀₀ -0.67*UGR ₆₀₀ -0.46*UGR ₇₀₀ -0.26*UGR ₈₀₀ -0.27*UGR ₅₀ -0.61*MJRD ₁₀₀₀₀ -0.01*MJRD ₁₀₀₀ +0.82*MJRD ₁₀₀ -0.19*MJRD ₂₀₀₀ +0.13*MJRD ₂₀₀ -0.37*MJRD ₃₀₀ -0.17*MJRD ₄₀₀ -0.05*MJRD ₅₀₀₀ -0.63*MJRD ₅₀₀ +0.41*MJRD ₇₀₀ +0.89*MJRD ₅₀ -0.99*ALRD ₁₀₀₀₀ +0.34*ALRD ₁₀₀₀ +1.6*ALRD ₁₀₀ -0.37*ALRD ₂₀₀₀ +0.17*ALRD ₂₀₀ +0.25*ALRD ₃₀₀ +0.22*ALRD ₄₀₀ -0.81*ALRD ₅₀₀₀ -0.59*ALRD ₅₀₀ +0.22*ALRD ₇₀₀ -0.54*ALRD ₅₀ +8.09*MACC_PM ₂₅ +10.2*SAT_PM ₂₅ -0.07*RES ₅₀ +0.22*RES ₁₀₀ +0.39*RES ₂₀₀ +0.37*RES ₃₀₀ +0.21*RES ₄₀₀ -0.03*RES ₅₀₀ -0.28*RES ₆₀₀ -0.56*RES ₇₀₀ -0.8*RES ₈₀₀ -0.81*RES ₁₀₀₀ -0.28*RES ₁₂₀₀ +0.32*RES ₁₅₀₀ +0.43*RES ₁₈₀₀ +0.42*RES ₂₀₀₀ -0.03*RES ₂₅₀₀ +0.03*RES ₃₀₀₀ +0.23*RES ₃₅₀₀ +0.3*RES ₄₀₀₀ +0.43*RES ₅₀₀₀ +0.71*RES ₆₀₀₀ +0.31*RES ₇₀₀₀ -0.28*RES ₈₀₀₀ -0.68*RES ₁₀₀₀₀
EN25	4.04 -3.56*ALT+0.17*TBU ₂₀₀ +0.54*TBU ₃₀₀ +0.25*TBU ₄₀₀ -0.2*NAT ₁₀₀₀₀ -1.08*NAT ₁₀₀ -0.25*NAT ₂₀₀ -0.01*NAT ₄₀₀₀ -0.79*NAT ₅₀ -0.33*IND ₅₀ -0.31*POR ₃₀₀₀ -0.85*POR ₃₅₀₀ -0.35*POR ₄₀₀₀ -0.82*POR ₅₀₀₀ -0.13*POR ₆₀₀₀ +0.1*POR ₆₀₀ +0.98*POR ₇₀₀ +1.23*POR ₈₀₀ -0.1*UGR ₆₀₀ -0.2*UGR ₇₀₀ -0.16*MJRD ₁₀₀₀₀ +0.39*MJRD ₁₀₀ +0.56*MJRD ₅₀ -0.8*ALRD ₁₀₀₀₀ +1.25*ALRD ₁₀₀ +7.58*MACC_PM ₂₅ +11.17*SAT_PM ₂₅ +0.1*RES ₁₀₀ +0.43*RES ₂₀₀ +0.11*RES ₃₀₀ +0.02*RES ₂₀₀₀
EN50	3.74 -3.66*ALT+0.81*TBU ₃₀₀ +0.07*TBU ₄₀₀ -1.29*NAT ₁₀₀ -0.77*NAT _p -0.23*IND ₅₀ -0.14*POR ₃₀₀₀ -1.22*POR ₃₅₀₀ -1.08*POR ₅₀₀₀ +0.83*POR ₇₀₀ +1.43*POR ₈₀₀ -0*UGR ₆₀₀ -0.21*UGR ₇₀₀ -0.04*MJRD ₁₀₀₀₀ +0.28*MJRD ₁₀₀ +0.58*MJRD ₅₀ -0.78*ALRD ₁₀₀₀₀ +1.31*ALRD ₁₀₀ +7.56*MACC_PM ₂₅ +11.62*SAT_PM ₂₅ +0*RES ₁₀₀ +0.7*RES ₂₀₀
EN75	3.73 -3.63*ALT+0.73*TBU ₃₀₀ -1.31*NAT ₁₀₀ -0.7*NAT ₅₀ -0.09*IND ₅₀ -1.26*POR ₃₅₀₀ -1.04*POR ₅₀₀₀ +0.69*POR ₇₀₀ +1.51*POR ₈₀₀ -0.17*UGR ₇₀₀ +0.21*MJRD ₁₀₀ +0.59*MJRD ₅₀ -0.7*ALRD ₁₀₀₀₀ +1.3*ALRD ₁₀₀ +7.44*MACC_PM ₂₅ +11.78*SAT_PM ₂₅ +0.81*RES ₂₀₀
LASSO	3.67 -3.65*ALT+0.74*TBU ₃₀₀ -1.29*NAT ₁₀₀ -0.69*NAT ₅₀ -0.08*IND ₅₀ -1.33*POR ₃₅₀₀ -1*POR ₅₀₀₀ +0.04*POR ₇₀₀ +2.2*POR ₈₀₀ -0.15*UGR ₇₀₀ +0.18*MJRD ₁₀₀ +0.59*MJRD ₅₀ -0.72*ALRD ₁₀₀₀₀ +1.33*ALRD ₁₀₀ +7.45*MACC_PM ₂₅ +11.9*SAT_PM ₂₅ +0.8*RES ₂₀₀

^aMACC = MACC dispersion model, SAT = satellite, MJRD = major roads, ALRD = all roads, TBU = total build up, NAT = natural land, IND = industry, POR = ports, UGR = urban green, RES = residential, ALT = altitude

^bRegression slope were multiplied by the difference between the 1st and 99th percentile of each predictor to allow comparison across predictors

^cFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator

Table S8. Performance of NO₂ models at ESCAPE sites with annual average NO₂ concentration below certain values

Algorithm ^a	< 20 µg/m ³			< 30 µg/m ³			< 40 µg/m ³		
	(N = 433)			(N = 844)			(N = 1116)		
	R ²	RMSE ^b (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)
FLR	0.339	9.6	7.9	0.463	8.8	6.6	0.488	8.4	5.1
BLR	0.313	9.8	8.0	0.451	9.2	6.9	0.473	8.9	5.5
WLR	0.339	9.6	7.9	0.463	8.8	6.6	0.488	8.4	5.1
SLR	0.385	10.2	8.7	0.492	9.5	7.6	0.508	9.2	6.3
Ridge	0.341	10.3	8.8	0.471	9.6	7.6	0.492	9.3	6.3
EN25	0.337	10.0	8.4	0.467	9.2	7.2	0.492	8.9	5.8
EN50	0.333	9.9	8.3	0.464	9.2	7.0	0.490	8.8	5.7
EN75	0.334	9.9	8.3	0.465	9.1	7.0	0.491	8.8	5.7
LASSO	0.334	9.9	8.2	0.465	9.1	7.0	0.490	8.8	5.7
GAM	0.367	9.3	7.4	0.491	9.3	6.8	0.507	9.2	5.8
Bagging	0.320	10.9	9.3	0.448	10.2	8.1	0.481	9.8	6.9
RF	0.323	11.0	9.5	0.447	10.3	8.3	0.480	9.9	7.0
GBM	0.344	10.0	8.4	0.476	9.6	7.5	0.498	9.4	6.3
SVR	0.311	9.3	7.6	0.455	8.7	6.4	0.483	8.5	5.0
KRLS	0.326	9.9	8.4	0.470	9.5	7.3	0.495	9.2	6.1
ANN	0.332	14.6	12.6	0.470	14.9	12.8	0.489	14.6	12.1
Ensemble1	0.352	9.9	8.4	0.478	9.2	7.2	0.500	8.9	5.9
Ensemble2	0.356	10.1	8.6	0.487	9.5	7.5	0.511	9.1	6.3

^aFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network; Ensemble1 = Ensemble model based on median prediction; Ensemble2 = Ensemble model based on weighted average

^bRMSE = Root-mean-square error

Table S9. Performance of NO₂ models at different type of sites

Algorithm ^a	Street (N = 713)			Rural Background (N = 118)			Urban Background (N = 565)		
	R ²	RMSE ^b (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)
FLR	0.392	13.7	-3.2	0.486	7.6	5.3	0.584	9.0	6.1
BLR	0.400	13.5	-2.7	0.466	8.1	5.7	0.573	9.4	6.6
WLR	0.392	13.7	-3.2	0.486	7.6	5.3	0.584	9.0	6.1
SLR	0.384	13.6	-2.0	0.594	8.9	7.2	0.612	9.7	7.2
Ridge	0.398	13.4	-2.0	0.534	8.7	6.8	0.596	9.8	7.4
EN25	0.403	13.5	-2.5	0.514	8.3	6.2	0.595	9.4	6.8
EN50	0.405	13.5	-2.6	0.505	8.2	6.1	0.593	9.4	6.7
EN75	0.404	13.5	-2.6	0.506	8.2	6.1	0.594	9.4	6.7
LASSO	0.404	13.5	-2.7	0.505	8.2	6.1	0.594	9.3	6.7
GAM	0.400	13.4	-1.8	0.541	8.4	5.9	0.604	9.5	6.7
Bagging	0.353	13.8	-0.6	0.535	8.9	7.0	0.570	9.9	7.3
RF	0.346	13.8	-0.5	0.537	9.0	7.2	0.570	9.9	7.4
GBM	0.363	13.7	-1.0	0.563	8.4	6.6	0.583	9.4	6.7
SVR	0.365	13.9	-3.0	0.536	8.6	6.9	0.581	8.5	5.4
KRLS	0.381	13.5	-1.7	0.568	8.4	6.7	0.576	9.4	6.6
ANN	0.388	14.3	5.1	0.527	13.3	11.3	0.579	15.1	13.0
Ensemble1	0.401	13.4	-2.3	0.530	8.3	6.4	0.603	9.3	6.8
Ensemble2	0.404	13.3	-1.7	0.544	8.5	6.6	0.611	9.5	7.1

^aFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network; Ensemble1 = Ensemble model based on median prediction; Ensemble2 = Ensemble model based on weighted average

^bRMSE = Root-mean-square error

Table S10. Performance of NO₂ models at different regions

Algorithm ^a	North (N = 240)			West (N = 319)			Central (N = 403)			South (N = 434)		
	R ²	RMSE ^b (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)	R ²	RMSE (µg/m ³)	Bias (µg/m ³)
FLR	0.446	10.6	7.4	0.596	9.7	3.5	0.484	9.5	1.7	0.464	14.7	-4.2
BLR	0.449	11.0	7.9	0.597	9.8	4.0	0.456	9.7	2.0	0.465	14.4	-3.5
WLR	0.446	10.6	7.4	0.596	9.7	3.5	0.484	9.5	1.7	0.464	14.7	-4.2
SLR	0.405	10.6	7.1	0.628	10.8	6.5	0.487	9.7	2.9	0.468	14.5	-3.4
Ridge	0.441	11.3	8.5	0.616	10.4	5.6	0.487	9.7	2.7	0.478	14.3	-3.3
EN25	0.445	11.0	8.1	0.614	9.9	4.6	0.480	9.6	2.3	0.474	14.4	-3.5
EN50	0.445	11.0	8.0	0.614	9.8	4.3	0.477	9.6	2.1	0.473	14.4	-3.5
EN75	0.445	11.0	8.0	0.614	9.8	4.3	0.478	9.6	2.1	0.473	14.4	-3.5
LASSO	0.445	11.0	8.0	0.614	9.8	4.3	0.477	9.6	2.1	0.472	14.4	-3.5
GAM	0.447	9.8	6.1	0.638	10.9	6.8	0.513	9.5	3.0	0.478	14.4	-3.8
Bagging	0.419	11.7	8.7	0.719	9.9	6.5	0.469	10.1	3.9	0.433	14.7	-2.9
RF	0.418	11.8	8.8	0.721	10.0	6.6	0.464	10.2	4.0	0.430	14.8	-2.8
GBM	0.430	10.7	7.5	0.707	10.0	6.5	0.477	10.0	3.7	0.457	14.6	-3.6
SVR	0.416	10.1	6.6	0.642	9.4	3.9	0.464	9.6	2.1	0.448	15.0	-4.6
KRLS	0.414	10.7	7.5	0.689	9.5	5.2	0.483	9.8	3.3	0.449	14.6	-3.4
ANN	0.431	15.7	12.6	0.605	15.0	12.1	0.449	13.7	9.8	0.467	14.4	3.4
Ensemble1	0.447	10.9	7.9	0.638	9.9	4.9	0.495	9.5	2.4	0.473	14.4	-3.5
Ensemble2	0.451	11.0	8.0	0.674	9.8	5.5	0.500	9.7	3.1	0.476	14.3	-3.1

^aFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network; Ensemble1 = Ensemble model based on median prediction; Ensemble2 = Ensemble model based on weighted average

^bRMSE = Root-mean-square error

Table S11. Predictors^a included and corresponding coefficients^b of parametric NO₂ models

Algorithm ^c	main model
FLR	3.00+8.82*ALRD ₂₀₀₀ +25.98*MACC_NO ₂ +6.83*ALRD ₁₀₀ +3.91*RES ₁₅₀₀ +10.74*MJRD ₁₀₀ +3.92*TBU ₄₀₀ +3.31*POR ₇₀₀ -4.47*SAT_NO ₂ +4.12*ALRD ₅₀ -2.71*NAT ₄₀₀ +5.26*RES ₂₅₀₀
BLR	2.46-50.66*TBU ₁₀₀₀₀ +10.74*TBU ₁₀₀ -78.03*TBU ₂₅₀₀ -16.9*TBU ₂₀₀ +189.36*TBU ₃₀₀₀ -190.53*TBU ₃₅₀₀ +79.97*TBU ₄₀₀₀ +17.7*TBU ₇₀₀ -4.22*TBU ₅₀ +17.3*NAT ₁₀₀₀₀ -23.17*NAT ₂₅₀₀ +44.66*NAT ₃₀₀₀ -29.89*NAT ₃₅₀₀ +28.23*NAT ₆₀₀₀ -38.78*NAT ₇₀₀₀ +14.73*IND ₁₀₀₀₀ +24.52*IND ₂₅₀₀ -58.15*IND ₃₀₀₀ +63.53*IND ₃₅₀₀ +14.83*IND ₃₀₀ -33.63*IND ₄₀₀₀ -13.52*IND ₇₀₀ +2.05*POR ₂₀₀ +2.81*POR ₃₅₀₀ -13.7*UGR ₂₀₀ +11.6*UGR ₃₀₀ +10.31*MJRD ₁₀₀ +7.33*MJRD ₂₀₀ -7.44*MJRD ₃₀₀ +8.24*ALRD ₂₀₀₀ +5.29*ALRD ₃₀₀ +6.85*ALRD ₅₀ +26.4*MACC_NO ₂ -4.32*SAT_NO ₂ -6.82*RES ₁₀₀ +17.73*RES ₂₀₀ -38.35*RES ₁₀₀₀ +27.64*RES ₁₂₀₀ +65.82*RES ₂₅₀₀ -148.65*RES ₃₀₀₀ +169.51*RES ₃₅₀₀ -83.31*RES ₄₀₀₀ +44.98*RES ₁₀₀₀₀
WLR	3.00+8.82*ALRD ₂₀₀₀ +25.98*MACC_NO ₂ +6.83*ALRD ₁₀₀ +3.91*RES ₁₅₀₀ +10.74*MJRD ₁₀₀ +3.92*TBU ₄₀₀ +3.31*POR ₇₀₀ -4.47*SAT_NO ₂ +4.12*ALRD ₅₀ -2.71*NAT ₄₀₀ +5.26*RES ₂₅₀₀
SLR	3.30+22.73*MACC_NO ₂ +7.04*ALRD ₅₀ +3.92*ALRD ₃₀₀ +12.32*MJRD ₁₀₀ +15.73*ALRD ₂₀₀₀ -3.38*NAT ₄₀₀ +4.1*POR ₇₀₀ +5.8*RES ₃₀₀
Ridge	3.65-0.06*ALT-1.34*TBU ₁₀₀₀₀ -0.82*TBU ₁₀₀₀ -0.07*TBU ₁₂₀₀ +0.19*TBU ₁₅₀₀ +0.33*TBU ₁₈₀₀ -0.1*TBU ₁₀₀ +0.39*TBU ₂₀₀₀ +0.19*TBU ₂₅₀₀ -0.23*TBU ₂₀₀ +0.21*TBU ₃₀₀₀ -0.75*TBU ₃₅₀₀ +0.61*TBU ₃₀₀ -1.51*TBU ₄₀₀₀ +0.8*TBU ₄₀₀ -2.07*TBU ₅₀₀₀ +1.3*TBU ₅₀₀ -1.76*TBU ₆₀₀₀ +1.07*TBU ₆₀₀ -1.3*TBU ₇₀₀₀ +0.67*TBU ₇₀₀ -0.22*TBU ₈₀₀₀ +0.11*TBU ₈₀₀ -1.65*TBU ₅₀ +3.31*NAT ₁₀₀₀₀ +0.66*NAT ₁₀₀₀ -0.1*NAT ₁₂₀₀ -0.52*NAT ₁₅₀₀ -0.65*NAT ₁₈₀₀ +0.1*NAT ₁₀₀ -0.81*NAT ₂₀₀₀ -0.92*NAT ₂₅₀₀ +0.16*NAT ₂₀₀ -0.61*NAT ₃₀₀₀ -0.85*NAT ₃₅₀₀ -1.61*NAT ₃₀₀ -0.55*NAT ₄₀₀₀ -1.56*NAT ₄₀₀ -0.1*NAT ₅₀₀₀ -0.6*NAT ₅₀₀ -0.21*NAT ₆₀₀₀ +0.01*NAT ₆₀₀ -0.2*NAT ₇₀₀₀ +0.32*NAT ₇₀₀ +0.62*NAT ₈₀₀₀ +0.82*NAT ₈₀₀ +1.15*NAT ₅₀ +4.4*IND ₁₀₀₀₀ +0.14*IND ₁₀₀₀ -0.42*IND ₁₂₀₀ -0.74*IND ₁₅₀₀ +0.53*IND ₁₈₀₀ +1.32*IND ₁₀₀ +0.86*IND ₂₀₀₀ -0.9*IND ₂₅₀₀ -0.38*IND ₂₀₀ -0.43*IND ₃₀₀₀ +0.1*IND ₃₅₀₀ +1.77*IND ₃₀₀ -0.52*IND ₄₀₀₀ +1.31*IND ₄₀₀ -1.2*IND ₅₀₀₀ +0.24*IND ₅₀₀ -0.72*IND ₆₀₀₀ -0.58*IND ₆₀₀ +0.37*IND ₇₀₀₀ -1.17*IND ₇₀₀ +1.31*IND ₈₀₀₀ -0.63*IND ₈₀₀ -0.68*IND ₅₀ -1.92*POR ₁₀₀₀₀ +0.47*POR ₁₀₀₀ +0.04*POR ₁₂₀₀ -0.45*POR ₁₅₀₀ -0.02*POR ₁₈₀₀ +0*POR ₁₀₀ -0.15*POR ₂₀₀₀ -0.18*POR ₂₅₀₀ +0.63*POR ₂₀₀ -0.1*POR ₃₀₀₀ +0.3*POR ₃₅₀₀ -0.46*POR ₃₀₀ +1.61*POR ₄₀₀₀ +0.16*POR ₄₀₀ +1.2*POR ₅₀₀₀ +0.47*POR ₅₀₀ +0.61*POR ₆₀₀₀ +0.34*POR ₆₀₀ +0.46*POR ₇₀₀₀ +0.9*POR ₇₀₀ -1.21*POR ₈₀₀₀ +0.52*POR ₈₀₀ +0*POR ₅₀ +0.26*UGR ₁₀₀₀₀ -3.51*UGR ₁₀₀ -2.55*UGR ₂₀₀ +2.04*UGR ₃₀₀ +2.78*UGR ₄₀₀ +0.25*UGR ₅₀₀ -0.81*UGR ₆₀₀ -0.7*UGR ₇₀₀ -0.27*UGR ₈₀₀ +0.39*UGR ₅₀ -3.55*MJRD ₁₀₀₀₀ +2.42*MJRD ₁₀₀₀ +6.28*MJRD ₁₀₀ -0.38*MJRD ₂₀₀₀ +3.86*MJRD ₂₀₀ -0.55*MJRD ₃₀₀ -1.33*MJRD ₄₀₀ +0.71*MJRD ₅₀₀₀ -1.45*MJRD ₅₀₀ -0.23*MJRD ₇₀₀ +2.57*MJRD ₅₀ +0.72*ALRD ₁₀₀₀₀ +1.91*ALRD ₁₀₀₀ +4.71*ALRD ₁₀₀ +4.54*ALRD ₂₀₀₀ +0.66*ALRD ₂₀₀ +2.51*ALRD ₃₀₀ +0.21*ALRD ₄₀₀ +3.49*ALRD ₅₀₀₀ -0.71*ALRD ₅₀₀ +0.43*ALRD ₇₀₀ +3.74*ALRD ₅₀ +21.46*MACC_NO ₂ -1.28*SAT_NO ₂ -0.58*RES ₅₀ +0.92*RES ₁₀₀ +1.38*RES ₂₀₀ +1.18*RES ₃₀₀ +0.46*RES ₄₀₀ +0.57*RES ₅₀₀ +0.18*RES ₆₀₀ -0.13*RES ₇₀₀ -0.55*RES ₈₀₀ -0.94*RES ₁₀₀₀ +0.33*RES ₁₂₀₀ +1.06*RES ₁₅₀₀ +1.15*RES ₁₈₀₀ +1.29*RES ₂₀₀₀ +2.04*RES ₂₅₀₀ +1.59*RES ₃₀₀₀ +0.87*RES ₃₅₀₀ +0*RES ₄₀₀₀ +0.27*RES ₅₀₀₀ +1.01*RES ₆₀₀₀ +1.44*RES ₇₀₀₀ +2.34*RES ₈₀₀₀ +2.03*RES ₁₀₀₀₀
EN25	3.19+0.17*TBU ₃₀₀ +0.36*TBU ₄₀₀ -1.32*TBU ₅₀₀₀ +2.11*TBU ₅₀₀ -0.01*TBU ₆₀₀₀ +0.11*TBU ₆₀₀ -1.75*TBU ₅₀ +2.82*NAT ₁₀₀₀₀ -0.54*NAT ₂₀₀₀ -2.21*NAT ₂₅₀₀ -0.72*NAT ₃₅₀₀ -0.04*NAT ₃₀₀ -1.96*NAT ₄₀₀ +0.42*NAT ₅₀ +3.9*IND ₁₀₀₀₀ -0.78*IND ₁₂₀₀ +0.32*IND ₁₀₀ -0.36*IND ₂₅₀₀ -0.24*IND ₃₀₀₀ +1.97*IND ₃₀₀ -0.37*IND ₄₀₀₀ -1.69*IND ₅₀₀₀ -0.04*IND ₇₀₀ -0.01*IND ₈₀₀ -1.69*POR ₁₀₀₀₀ +0*POR ₁₀₀ +0.67*POR ₂₀₀ +1.54*POR ₄₀₀₀ +2.15*POR ₇₀₀ -3.04*UGR ₁₀₀ +0.81*UGR ₄₀₀ -3.11*MJRD ₁₀₀₀₀ +1.81*MJRD ₁₀₀₀ +7.65*MJRD ₁₀₀ +2.51*MJRD ₂₀₀ -1.05*MJRD ₄₀₀ -1.33*MJRD ₅₀₀ +1.99*MJRD ₅₀ +1.73*ALRD ₁₀₀₀ +5.18*ALRD ₁₀₀ +5.3*ALRD ₂₀₀₀ +2.52*ALRD ₃₀₀ +2.14*ALRD ₅₀₀₀ +3.77*ALRD ₅₀ +24.34*MACC_NO ₂ -2.93*SAT_NO ₂ +1.51*RES ₂₀₀ +2*RES ₃₀₀ +0.64*RES ₅₀₀ +0.62*RES ₁₅₀₀ +0.55*RES ₁₈₀₀ +0.88*RES ₂₀₀₀ +4.47*RES ₂₅₀₀ +0.42*RES ₃₀₀₀ +2.53*RES ₈₀₀₀
EN50	3.04-3.71*TBU ₅₀₀₀ +3.47*TBU ₅₀₀ -0.01*TBU ₆₀₀₀ -2.15*TBU ₅₀ +3.19*NAT ₁₀₀₀₀ -0.01*NAT ₁₈₀₀ -0.07*NAT ₂₀₀₀ -2*NAT ₂₅₀₀ -1.65*NAT ₃₅₀₀ -2.06*NAT ₄₀₀ +0.49*NAT ₅₀ +4.39*IND ₁₀₀₀₀ -0.62*IND ₁₂₀₀ +0.38*IND ₁₀₀ -0.02*IND ₂₅₀₀ -0.44*IND ₃₀₀₀ +2.73*IND ₃₀₀ -1.86*IND ₅₀₀₀ -1.12*IND ₇₀₀ -1.91*POR ₁₀₀₀₀ +0*POR ₁₀₀ +0.78*POR ₂₀₀ +2.03*POR ₄₀₀₀ +1.95*POR ₇₀₀ -3.56*UGR ₁₀₀ +1.27*UGR ₄₀₀ -3.81*MJRD ₁₀₀₀₀ +2.3*MJRD ₁₀₀₀ +8.04*MJRD ₁₀₀ +2.51*MJRD ₂₀₀ -1.35*MJRD ₄₀₀ +0*MJRD ₅₀₀₀ -1.58*MJRD ₅₀₀ +1.87*MJRD ₅₀ +1.22*ALRD ₁₀₀₀ +5.01*ALRD ₁₀₀ +5.51*ALRD ₂₀₀₀ +2.77*ALRD ₃₀₀ +2.51*ALRD ₅₀₀₀ +3.89*ALRD ₅₀ +24.97*MACC_NO ₂ -3.38*SAT_NO ₂ +2.24*RES ₂₀₀ +1.77*RES ₃₀₀ +0.3*RES ₁₅₀₀ +0.58*RES ₁₈₀₀ +6.72*RES ₂₅₀₀ +3.79*RES ₈₀₀₀
EN75	3.05-2.93*TBU ₅₀₀₀ +3.18*TBU ₅₀₀ -1.97*TBU ₅₀ +3.01*NAT ₁₀₀₀₀ +0*NAT ₁₈₀₀ -0.03*NAT ₂₀₀₀ -2.36*NAT ₂₅₀₀ -1.18*NAT ₃₅₀₀ -2.01*NAT ₄₀₀ +0.42*NAT ₅₀ +4.17*IND ₁₀₀₀₀ -0.5*IND ₁₂₀₀ +0.21*IND ₁₀₀ -0.1*IND ₂₅₀₀ -0.43*IND ₃₀₀₀ +2.59*IND ₃₀₀ -1.86*IND ₅₀₀₀ +0*IND ₇₀₀ -0.88*IND ₈₀₀ -1.77*POR ₁₀₀₀₀ +0*POR ₁₀₀ +0.81*POR ₂₀₀ +1.82*POR ₄₀₀₀ +2.03*POR ₇₀₀ -3.35*UGR ₁₀₀ +1.06*UGR ₄₀₀ -3.55*MJRD ₁₀₀₀₀ +2.09*MJRD ₁₀₀₀ +8.28*MJRD ₁₀₀ +2.14*MJRD ₂₀₀ -1.11*MJRD ₄₀₀ -1.47*MJRD ₅₀₀ +1.82*MJRD ₅₀ +1.3*ALRD ₁₀₀₀ +5.06*ALRD ₁₀₀ +5.62*ALRD ₂₀₀₀ +2.7*ALRD ₃₀₀ +2.17*ALRD ₅₀₀₀ +3.85*ALRD ₅₀ +25.02*MACC_NO ₂ -3.38*SAT_NO ₂ +1.56*RES ₂₀₀ +2.5*RES ₃₀₀ +0.65*RES ₁₅₀₀ +6.82*RES ₂₅₀₀ +3.33*RES ₈₀₀₀
LASSO	3.04-3.41*TBU ₅₀₀₀ +3.36*TBU ₅₀₀ -2*TBU ₅₀ +2.99*NAT ₁₀₀₀₀ +0*NAT ₁₈₀₀ -0.05*NAT ₂₀₀₀ -2.36*NAT ₂₅₀₀ -1.16*NAT ₃₅₀₀ -1.98*NAT ₄₀₀ +0.4*NAT ₅₀ +4.18*IND ₁₀₀₀₀ -0.52*IND ₁₂₀₀ +0.24*IND ₁₀₀ -0.15*IND ₂₅₀₀ -0.32*IND ₃₀₀₀ +2.52*IND ₃₀₀ -1.79*IND ₅₀₀₀ -0.01*IND ₇₀₀ -0.93*IND ₈₀₀ -1.77*POR ₁₀₀₀₀ +0*POR ₁₀₀ +0.81*POR ₂₀₀ +1.89*POR ₄₀₀₀ +1.98*POR ₇₀₀ -3.36*UGR ₁₀₀ +1.08*UGR ₄₀₀ -3.57*MJRD ₁₀₀₀₀ +2.09*MJRD ₁₀₀₀ +8.37*MJRD ₁₀₀ +2.04*MJRD ₂₀₀ -1.07*MJRD ₄₀₀ -1.5*MJRD ₅₀₀ +1.79*MJRD ₅₀ +1.32*ALRD ₁₀₀₀ +5.05*ALRD ₁₀₀ +5.59*ALRD ₂₀₀₀ +2.7*ALRD ₃₀₀ +2.19*ALRD ₅₀₀₀ +3.85*ALRD ₅₀ +25.08*MACC_NO ₂ -3.44*SAT_NO ₂ +1.7*RES ₂₀₀ +2.27*RES ₃₀₀ +0.37*RES ₁₅₀₀ +7.24*RES ₂₅₀₀ +3.55*RES ₈₀₀₀

^aMACC = MACC dispersion model, SAT = satellite, MJRD = major roads, ALRD = all roads, TBU = total build up, NAT = natural land, IND = industry, POR = ports, UGR = urban green, RES = residential, ALT = altitude

^bRegression slope were multiplied by the difference between the 1st and 99th percentile of each predictor to allow comparison across predictors

^cFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator

Table S12. Performances of NO₂ sample models

Algorithm ^a	Model Performance (N = 543)		Cross Validation (N = 543)			External Validation (ESCAPE) (N = 1396)			
	R ²	RMSE ^b (µg/m ³)	R ²	MSE-R ²	RMSE (µg/m ³)	R ²	MSE-R ²	RMSE (µg/m ³)	Bias (µg/m ³)
FLR	0.648	8.9	0.607	0.606	9.5	0.451	0.451	11.9	0.2
BLR	0.722	7.9	0.521	0.478	10.9	0.419	0.404	12.4	0.7
WLR	0.648	8.9	0.607	0.606	9.5	0.451	0.451	11.9	0.2
SLR	0.638	9.1	0.608	0.606	9.4	0.460	0.420	12.3	3.2
Ridge	0.690	8.4	0.618	0.617	9.3	0.473	0.458	11.9	2.0
EN25	0.658	8.8	0.615	0.615	9.3	0.481	0.462	11.8	2.1
EN50	0.650	8.9	0.616	0.616	9.3	0.478	0.449	12.0	2.7
EN75	0.653	8.9	0.617	0.617	9.3	0.483	0.463	11.8	2.2
LASSO	0.654	8.9	0.617	0.617	9.3	0.484	0.466	11.8	2.0
GAM	0.703	8.2	0.595	0.589	9.7	0.474	0.466	11.8	1.4
Bagging	0.951	3.8	0.595	0.594	9.6	0.431	0.384	12.6	3.5
RF	0.950	3.8	0.596	0.595	9.6	0.432	0.383	12.7	3.5
GBM	0.886	5.6	0.605	0.603	9.5	0.445	0.412	12.4	2.9
SVR	0.820	6.6	0.619	0.615	9.3	0.436	0.412	12.4	2.4
KRLS	0.781	7.2	0.617	0.617	9.3	0.452	0.405	12.4	3.5
ANN	0.773	7.2	0.034*	-21.443*	71.3*	0.309	-0.905	22.2	12.2
Ensemble1	0.718	8.1	0.624	0.624	9.2	0.484	0.462	11.8	2.3
Ensemble2	0.773	7.3	0.613	0.613	9.4	0.484	0.460	11.8	2.5

^aFLR = Forward stepwise Linear Regression; BLR = Backward stepwise Linear Regression; WLM = Stepwise Linear Regression; SLR = Supervised Linear Regression; EN25 = Elastic Net with $\alpha=0.25$; EN50 = Elastic Net with $\alpha=0.50$; EN75 = Elastic Net with $\alpha=0.75$; LASSO = Least Absolute Shrinkage and Selection Operator; GAM = Generalized Additive Model; RF = Random Forest; GBM = Generalized Boosted Machine; SVR = Support Vector Regression; KRLS = Kernel-based Regularized Least Squares; ANN = Artificial Neural Network; Ensemble1 = Ensemble model based on median prediction; Ensemble2 = Ensemble model based on weighted average

^bRMSE = Root-mean-square error

*An extremely high value was predicted by hold-out validation model 1. After removing the outlier, the CV R² increased to 0.331, MSE-R² increased to -0.124, RMSE decreased to 16.0 µg/m³

Table S13. Performances of selected PM_{2.5} models with kriging surface added

Algorithm ^a	Training (N = 543)		Cross Validation (N = 543)			External Validation (N = 416)			
	R ²	RMSE ^b ($\mu\text{g}/\text{m}^3$)	R ²	MSE-R ²	RMSE ($\mu\text{g}/\text{m}^3$)	R ²	MSE-R ²	RMSE ($\mu\text{g}/\text{m}^3$)	Bias ($\mu\text{g}/\text{m}^3$)
BLR	0.704	2.8	0.506	0.472	3.7	0.463	0.445	4.3	0.8
BLR + kriging	0.873	1.8	0.547	0.509	3.6	0.574	0.557	3.8	0.6
SLR	0.622	3.2	0.595	0.594	3.3	0.529	0.478	4.1	0.9
SLR + kriging	0.762	2.5	0.635	0.630	3.1	0.667	0.638	3.4	0.3
LASSO	0.641	3.1	0.610	0.609	3.2	0.547	0.487	4.1	0.8
LASSO + kriging	0.768	2.5	0.648	0.642	3.1	0.669	0.632	3.5	0.3
GBM	0.895	1.8	0.631	0.630	3.1	0.610	0.548	3.9	0.4
GBM + kriging	0.936	1.3	0.639	0.639	3.1	0.648	0.630	3.5	0.2
ANN	0.723	2.7	0.477	0.428	3.9	0.391	0.286	4.8	1.2
ANN + kriging	0.766	2.5	0.500	0.421	3.9	0.452	0.369	4.5	1.1

^aSLR = Supervised Linear Regression; GBM = Generalized Boosted Machine^bRMSE = Root-mean-square error

Figure S1. location of AirBase and ESCAPE monitoring sites (de Hoogh et al., 2016)

Figure S2. Correlations between PM_{2.5} predictions and measurements at ESCAPE sites (r = Pearson correlation coefficient)

Figure S3. Correlations between NO_2 predictions and measurements at ESCAPE sites (r = Pearson correlation coefficient)

(A) Percentage increase in MSE (Mean Squared Errors) after a random permutation of the values of a variable (Random Forest)

(B) Increase in MSE after a split on a variable (Random Forest)

(C) Relative influence of predictors (Generalized Boosted Machine)

Figure S4. Variable importance plots of PM_{2.5} random forest and Generalized Boosted Machine models

(A) Percentage increase in MSE after a random permutation of the values of a variable (random Forest)

(B) Increase in MSE after a split on a variable (Random Forest)

(C) Relative influence of predictors (Generalized Boosted Machine)

Figure S5. Variable importance plots of NO₂ Random Forest and Generalized Boosted Machine models

Figure S6. Model Training-R², CV R² and EV R² of PM_{2.5} models with reduced number of potential predictors offered (the number of all potential predictors is 150)

SLR = Supervised Linear Regression; EN75 = Elastic Net with $\alpha=0.75$; RF = Random Forest; ANN = Artificial Neural Network; CV = Cross Validation; EV = External Validation

Figure S7. Model Training-R², CV R² and EV R² of NO₂ models with reduced number of potential predictors offered (the number of all potential predictors is 150)

SLR = Supervised Linear Regression; EN75 = Elastic Net with $\alpha=0.75$; RF = Random Forest; ANN = Artificial Neural Network; CV = Cross Validation; EV = External Validation

Figure S8. Correlation of $PM_{2.5}$ estimations at ESCAPE sites predicted by selected models plus kriging

BLR = Backward stepwise Linear Regression; SLR = Supervised Linear Regression; LASSO = Least Absolute Shrinkage and Selection Operator; GBM = Generalized Boosted Machine; ANN = Artificial Neural Network

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Chapter 5

Development of Europe-Wide Models for Particle Elemental Composition Using Supervised Linear Regression and Random Forest

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Abstract

We developed Europe-wide models of long-term exposure to 8 elements (copper, iron, potassium, nickel, sulfur, silicon, vanadium and zinc) in particulate matter with diameter $<2.5\ \mu\text{m}$ (PM_{2.5}) using standardized measurements for one-year periods between October 2008 and April 2011 in 19 study areas across Europe, with supervised linear regression (SLR) and random forest (RF) algorithms. Potential predictor variables were obtained from satellites, chemical transport models, land-use, traffic and industrial point source databases to represent different sources. Overall model performance across Europe was moderate to good for all elements with hold-out-validation R-squared ranging from 0.41 to 0.90. RF consistently outperformed SLR. Models explained within-area variation much less than the overall variation, with similar performance for RF and SLR. Maps proved a useful additional model evaluation tool. Models differed substantially between elements regarding major predictor variables, broadly reflecting known sources. Agreement between the two algorithm predictions was generally high at the overall European level and varied substantially at the national level. Applying the two models in epidemiological studies could lead to different associations with health. If both between- and within-area exposure variability are exploited, RF may be preferred. If only within-area variability is used, both methods should be interpreted equally.

1. Introduction

Exposure to particulate matter (PM) is associated with adverse health outcomes^{1,2}. PM is a complex mixture of components that differ spatially and temporally. Identifying which components are main contributors to adverse health effects is important for targeted policymaking. Multiple studies have attempted to associate health effects with PM components including metals, organic compounds, inorganic carbonaceous material and inorganic secondary aerosols³⁻⁵. Findings, however, are inconsistent. Epidemiological studies have been limited due to the scarcity of air quality monitors that routinely measure PM composition. In Europe, a PM monitoring campaign was conducted in 20 ESCAPE (European Study of Cohorts for Air Pollution Effects) study areas following a common sampling protocol⁶. Most study areas consisted of a metropolitan area with some small towns around the main city. The PM samples were analyzed for elemental composition⁷. Based on the measurements from 20 sites in each study area, area-specific land use regression (LUR) models were developed to assess long-term exposure to elemental composition⁸. The models were applied to cohorts within the study areas to assess health effects related to particle composition⁹.

The geographical extent of the study-area specific ESCAPE models is limited and predictions from these models cannot reliably be used for other cohorts, such as large multi-center studies. The models were furthermore developed on 20 sites per area. Methodological studies suggested that more stable models can be developed based on larger number of sites in the model training dataset^{10,11}. In addition, the ESCAPE study-area specific models had rather good performance for traffic-related elements such as copper (Cu) and iron (Fe), but had poor performance for elements such as sulfur (S), nickel (Ni) and vanadium (V) for which spatial variation was limited within areas and key predictors were missing⁸. The lack of large-scale European models for particle elemental composition hampers large-area epidemiological studies. Our previous studies showed the possibility to develop European LUR models with good performance using a combined dataset from the ESCAPE study areas for PM with diameter $<2.5\ \mu\text{m}$ (PM_{2.5}), Black Carbon (BC) and nitrogen dioxide (NO₂)^{12,13}.

The supervised Linear Regression (SLR) algorithm is often used in air pollution modeling^{14,15}, and was used to develop ESCAPE models of elemental composition⁸ and European models of PM_{2.5}, NO₂ and BC¹². The SLR algorithm shows good predictive ability and interpretability but has strong statistical assumptions such as linearity. SLR models can, however, take into account non-linear relationships by offering *a priori* transformed predictor variables (e.g. inverse distance to a source), include only predictor variables following plausible direction of effect (e.g. a positive traffic slope) and add interaction terms. A number of more flexible algorithms including machine-learning algorithms have

increasingly been applied in air pollution exposure assessment^{16,17}. Random Forest (RF) has been widely used in recent years^{18,19}. RF is a classification tree analysis. It can model potentially complex relationships including non-linearity and interactions within data but gives little information regarding the prediction process²⁰. A key feature of RF is the “bagging” procedure adopted in both observation and variable selection: this allows even marginally important predictors to contribute, even in presence of high multicollinearity. A previous study found RF outperformed linear regression in modeling spatial variation of particle elemental composition²¹.

LUR models for multiple particle components are more useful for epidemiological studies if they include more specific predictors. Developments in satellite and chemical transport modeling and availability of industrial point source data have made it possible to develop more specific models.

The aim of this study was to assess the performance of Europe-wide models for particle elemental composition, developed using SLR and RF algorithms. The models have been developed in the “Effects of Low-Level Air Pollution: A Study in Europe” (ELAPSE), a Europe-wide project investigating long-term health effects of low-level air pollution.

2. Materials and Methods

2.1 Air pollution data

The PM_{2.5} elemental composition concentration data originated from the ESCAPE monitoring campaigns conducted in 19 study areas across Europe (Figure S1). PM sampling and analysis methods have been described previously^{6,7}. Briefly, measurements were made at 20 sites in each study area (40 in the large Catalunya and Netherlands/Belgium areas) for three 2-week periods in a 1-year period between October 2008 and April 2011. Monitoring sites were selected to represent pollution levels at regional background, urban background, and street locations using a common sampling protocol. PM_{2.5} samples were collected on Teflon filters using Harvard Impactors and analyzed for elemental composition using energy-dispersive X-ray fluorescence. Annual average concentrations were calculated based on three 14-day average measurements spread over the seasons (warm, cold and intermediate) with temporal adjustment from a reference background site in each study area. Our measurement campaign was restricted temporally, as previous sampling campaigns used to develop land use regression models²². While this design does not formally estimate absolute annual average concentrations as in regulatory monitoring, it has been shown to be useful to assess spatial contrast of long-term average concentrations because of specific design elements^{6,22,23}. We performed temporal adjustment, using a continuous reference site located at a regional or urban background location (not directly influenced by local sources), where measurements were made for the full 12-month period. Three 14-day average samples were taken in different seasons at all locations, which are less sensitive to the very short-term variations caused by daily variation in weather. Five sites and the reference site were measured simultaneously representing all different site types (regional background, urban background and street)^{6,23}.

Eight elements were *a priori* selected within ESCAPE to represent major pollution sources: Cu, Fe and Zn representing non-tailpipe traffic emissions, S representing long-range transport, Ni and V representing mixed oil burning/industry, silicon (Si) representing crustal material, and potassium (K) representing biomass burning^{7,8}.

2.2 Potential predictor variables

2.2.1 Traffic, population, altitude and land use variables

We used the same road density, population and elevation variables as in our previous exposure modeling paper for PM_{2.5}, NO₂, ozone (O₃) and BC across Europe¹². In short, road data were extracted from the 1:10,000 EuroStreets digital road network (version 3.1 based on TeleAtlas MultiNet TM, year 2008), classified into ‘all’ and ‘major’ roads, and road density calculated in a 100x100 m grid. Population

density in 1x1 km grid for 2011 were obtained from Eurostat²⁴. Elevation was obtained from the SRTM Digital Elevation Database²⁵ version 4.1 with a resolution of 3 arc second (approximately 90 m) with vertical error of <16 m. X and/or Y coordinates were offered to represent the East-West/ North-South gradient.

Land use variables were newly extracted from an updated European CORINE Land Cover surface in 100x100 m grid²⁶. The initial 44 land cover classes were grouped to six main classes: residential, industry, ports, urban green space, total built up land and natural land.

2.2.2 Additional component/ source-specific variables

Special attention was taken in obtaining specific potential predictor variables representing different sources of the eight selected elements. We hypothesized that this would allow us to develop better and more specific models, such that the independent associations of the different elements with health could be studied better. For each component, only plausible variables were offered for model development. The restrictions of offering specific potential predictors are specified in Table S1.

Satellite-model (SAT) estimates of 2010 annual average sulfate (SO_4^{2-}), organic matter (OM), BC and mineral dust (SOIL) in $\text{PM}_{2.5}$ were extracted from a gridded surface ($0.01^\circ \times 0.01^\circ$, ~1.11km) over Europe. These estimates are an application of simulated relative composition to the total $\text{PM}_{2.5}$ estimates produced by the methods described elsewhere²⁷, and do not incorporate compositional ground-based measurements over Europe. In brief, $\text{PM}_{2.5}$ mass estimates were produced by relating a combined aerosol optical depth (AOD) retrieval involving multiple satellite products and simulation to near-surface $\text{PM}_{2.5}$ concentrations using the spatiotemporally varying geophysical relationship simulated by the GEOS-Chem Chemical Transport Model (CTM). Ground-based observations of total $\text{PM}_{2.5}$ were then incorporated into these initial values using geographically weighted regression, and the resulting total mass estimates partitioned into chemical composition using their relative contributions according to the GEOS-Chem CTM simulations.

Chemical Transport Model estimates of BC AOD, Sulfate AOD, total column SO_2 , and sea-salt AOD were obtained from the European Centre for Medium-Range Weather Forecasts²⁸. Daily estimates in 2010 were extracted from a gridded surface ($0.125^\circ \times 0.125^\circ$, ~13.9km) produced by the MACC-II ENSEMBLE model²⁹, and then aggregated to derive the annual average.

In addition to the unspecific industry land-use category, information on major industrial point sources was obtained including facility location, pollutant and emission amount from the European Pollutant Release and Transfer Register³⁰. The industrial facility points were intersected with a 100 m base polygon, and then the number of facility sites and emissions were summed within each 100x100 m cell. Density of general industries and industries emitting specific aerosols (metal, Cu, Ni, PM_{10} , SO_x , Zn) were calculated accordingly. Sum of emissions were calculated for PM_{10} , Cu, Ni, SO_x and Zn.

All predictor variables were integrated into a 100 m gridded GIS database covering Europe. For road density, land use and industrial information, a moving window procedure was used to calculate the sum of values for selected buffers (focal statistics using sum within a circle). The influence of industrial point sources was calculated by inverse distance weighting (1/d). The processing of variable surfaces was done in ArcMap 10.6.

2.3 Model Development

The number of monitoring sites available for particle composition ranged from 400 to 414 because of failed PM composition measurements⁸. We used both Supervised Linear Regression (SLR) and Random Forest (RF) algorithms to develop models.

The SLR approach has been described in detail before¹². Briefly, a univariate linear regression model was applied for each potential predictor to find the predictor that explained the maximum variance in the measurements. At each subsequent step, the significant predictor variable ($P < 0.1$) that generated

the highest increase in model adjusted coefficient of determination (adjusted R^2) was added. Predictors only entered the model if they adhered to the plausible direction of effect (Table S1). This process was repeated until the model adjusted R^2 could not be increased anymore. Predictor variables with variance inflation factor (VIF) larger than 3 were removed from the model to avoid multicollinearity.

RF is an ensemble machine learning technique based on decision trees³¹. It builds independent trees in parallel, each based on a random sample drawn from the full set of measurements. At each node, a random subset of potential predictors is split. The final predictions are derived by averaging predictions from all decision trees. RF does not perform variable selection. It produces variable importance, calculated as percentage increase in mean squared errors after a random permutation of the values of a variable. We used the R package ‘randomForest’ to develop the RF models.

One-step and two-step modeling processes were used to offer geographical coordinates (X and Y) to the models. Following our previous exposure modeling procedure¹², for SLR we used a 2-step approach, in which we first developed a SLR model without offering X or Y, then added X and Y only if they increased the model adjusted R^2 . The rationale for the 2-step procedure is that we preferred spatial variation to be explained first by specific predictor variables and the residual variation to be further explained by the X, Y coordinates added in the second step. In RF we applied one-step modeling as our primary approach: X and Y were offered together with the other predictor variables. This allowed us to take advantage of the possibilities of RF algorithm to model the potential interactions between coordinates and other predictors. For comparison, we also developed one-step models for SLR and 2-step models for RF: we first developed a RF model without offering X or Y, then developed a second RF model with X, Y coordinates only, explaining variations in the residuals of the step1 RF model. The predictions of these two RF models were later added together. We further performed a sensitivity analysis offering a few non-linear transformations of the X- and Y-coordinates to the SLR model, including X^2 , Y^2 , $\sqrt{X}$, $\sqrt{Y}$ and XY , to allow more flexible functions of the coordinates than the linear function. We were not able to perform kriging due to the clustered nature of the monitoring data¹².

2.4 Model Evaluation and Comparison

For each model, we calculated Model r^2 (squared Pearson correlation) and RMSE (root-mean-square error) by comparing main model predictions to the measurements.

We performed five-fold hold-out validation (HOV). The full set of measurements were randomly divided into 5 groups (20% each), stratified by site type (Street, Rural and Urban Background) and region (North, West, Central and South). For each element-model combination, 5 additional HOV models were built, each based on 80% of the monitoring sites, with the remaining 20% for validation. HOV regression-based r^2 and RMSE were computed by comparing the stacked predictions at the 5 hold-out validation test sets to the corresponding measurements. We also calculated mean square error-based R^2 (MSE- R^2), defined as:

$$\text{MSE} - R^2 = 1 - \frac{\text{MSE}}{\left(\frac{1}{n} \sum_{i=1}^n (y_i - \bar{y})^2\right)}$$

where $\bar{y}$ is the average of the measurements. MSE- R^2 can be seen as a rescaling of MSE. It measures fit about the 1:1 line rather than fit about the best fit line in regression-based r^2 . The HOV r^2 and RMSE are relevant for multi-city studies that exploit both within and between city variability of air pollution contrasts.

To test how the European models predict within-area variability, we calculated within-area r^2 and RMSE by comparing the stacked HOV predictions and measurements within each individual study area. Since the monitors are spatially clustered over Europe and nearby locations might have auto-correlations in their measurements, we additionally performed leave-one-area-out cross-validation (LOAOCV)^{32,33}. We developed Europe-wide models by excluding all observations from one study area at a time and applied the models to the sites that were left out. Therefore, 19 additional models were developed for each

pollutant-algorithm combination. Within-area r^2 and RMSE were computed by comparing the predictions and measurements in the area that was excluded from model development. We focus interpretation on the average of the within-area r^2 s and RMSEs because the performance statistics of the individual study areas may be affected strongly by random error since they were based on only 20 sites in each study area.

For each main model, predictor variables selected in SLR models and the 15 most important variables in RF models were compared.

Each main model was mapped at a 100x100 m resolution across the whole study area, allowing for visual comparison between maps. Additionally, we compared predictions from models at 41,936 random locations across Europe used previously¹². Comparisons of model predictions were made for the entire study area and at the national scale reporting Pearson correlation coefficient (r) and RMSE. Truncations were performed to deal with unrealistic predictions of the SLR approach: predictions at the high end were truncated to the maximum final two-step modeled value, calculated by fitting the model with the maximum predictor values at monitoring sites for positive slopes (or the minimum predictor values for negative slopes); the negative predictions were set to zeros.

3. Results and Discussion

3.1 Distribution of PM_{2.5} component measurements

Boxplots of the annual mean concentration for PM_{2.5} components in the full dataset and in individual study areas are shown in Figure S2. For the majority of pollutants, pollution concentrations varied substantially within and between study areas. A positive north–south gradient was observed with higher pollution levels in southern study areas. A more detailed interpretation of the measured concentrations can be found elsewhere⁷.

3.2 Model performance

Performance of models across Europe is shown in Table 1. Models for most components had moderate to good performance based upon HOV. Model performance was almost the same evaluating by regression-based r^2 or MSE-based R^2 (Table S2), consistent with the observation that the fitted regression slopes between observed vs. predicted values are close to the 1-1 line (Figure S3). Models with the highest HOV r^2 s were developed for PM_{2.5} S, having large between-area concentration variability for which large-scale predictor variables from CTM were available to explain the contrast. Sulfate (represented by S) is a secondary pollutant formed by oxidation of sulfur dioxide for which the ratio of between- and within-area variability is larger than for the other elements⁷. RF models consistently outperformed SLR models for all elements. This agrees with a previous study, which found more accurate exposure assessed for elemental components by RF than SLR, based on 24 monitoring sites²¹. The better performance of RF is different from two previous comparisons^{16,17}, where similar performance of spatial models was observed for SLR and RF. One study compared Europe-wide models for PM_{2.5} and NO₂ developed using similar predictor variables as in the current study¹⁶, the second study compared LUR models for ultrafine particles based upon mobile monitoring¹⁷. One possible explanation for the difference in findings is that there might be more complex relationships between predictors and elemental composition than with the mass of PM_{2.5}, NO₂ and UFP. RF can capture unknown non-linear relationships and interactions not predefined in SLR, without introducing overfitting of the data. Another important difference is that in the current study, the data were clustered within Europe whereas in the earlier study on PM_{2.5} and NO₂, models were developed based upon routine monitoring, with a more even distribution of sites across Europe. We hypothesize that the RF model accounted for spatial trends across Europe better than the linear model.

For most components, HOV r^2 s were similar for the one-step model and the final two-step model and higher than for the first step of the two-step model, documenting that spatial trends account for the

residual variance not explained by the available predictors. Offering *a priori* transformed X- and Y-coordinates did not further improve performance for SLR models. The differences between model r^2 and HOV r^2 in SLR models were small, suggesting the models do not over-fit. The perfect performance on training set (Model r^2) for RF models is “by design” and basically meaningless. This is because the RF algorithm generally does not prune the individual trees, relying instead on the ensemble of trees to control overfitting²⁰.

While the models performed well to explain overall variability across Europe, models performed less well in explaining variation within individual study areas (Table 2). Results are similar by performing 5-fold HOV and leave-one-area-out cross-validation, suggesting the model performance is stable regardless of CV methods. The better overall performance is explained by a combination of larger variability of concentrations between areas than within areas and the better availability of predictor variables for describing between- compared to within-area variability. Specifically, the addition of large-scale satellite and chemical transport models has contributed to assess the study-area background. The average within-area r^2 s were moderate for Cu and Fe and relatively poor for other components. Cu and Fe represent mechanically generated traffic-related particles and thus their particle size distribution within PM_{2.5} is skewed towards coarse particles^{7,34}. Therefore, Cu and Fe do not travel far and may show large within-area variation. The better within-area performance for Cu and Fe is thus possibly due to the combination of higher within-area variation of the concentrations in most areas and the availability of data on traffic networks within individual areas. Within-area r^2 s were poor for components that have limited within-area variation such as S. S represents secondary inorganic aerosols (sulfates) produced by atmospheric chemistry of precursor gases (sulfur oxides) originating from combustion of sulfur-containing fossil fuels (e.g., in power plants)³⁵. Much of transported sulfate are in the sub-micron range and travel far, resulting in fairly uniform spatial variation in the scale of cities. Ni and V are often emitted from coal, oil or residual oil burning in buildings and ships. The emission height of buildings and ships are relatively low so that within-city variation can be observed. Despite the consistently better performance of RF models than SLR models in overall HOV, the average within-area r^2 s were similar across models for each element. This further supports our hypothesis that the RF model accounted for spatial trends across Europe better than the SLR model. Within-area r^2 s varied substantially across study areas and were low in areas with small contrasts in measured concentrations shown by low RMSE (Figure S4).

In summary, the generally moderate within-area performance of the developed models is likely related to a combination of limited availability of predictor variables e.g. targeting especially non-exhaust traffic emissions, the clustered nature of the monitoring data and the lack of exposure contrasts within specific areas. Especially predictor variables at the local scale are insufficient.

3.3 Model structure

Predictor variables selected in SLR models and the 15 most important variables in RF models are shown in Figure 1. For each element, some consistency was found between SLR models and RF models in terms of the variable categories that were included. To some extent, however, different buffer sizes were included. Variables within each algorithm were very similar. X, Y coordinates usually contributed to the models when offered and were considered relatively important variables in the one-step RF.

The major predictors in the models differed substantially between the eight elements, broadly reflecting the different sources.

In Cu and Fe models, traffic-related predictor variables dominated the other source categories in SLR models while they were also considered relatively important in RF models. This is consistent with previous LUR models of Cu and Fe where a large proportion of the variability in the measured concentrations was explained by traffic related variables^{8,36,37}. Some of the industrial point sources were picked up in the SLR models for Cu and Fe, possibly reflecting emission released by metallurgic

industries³⁵. A previous study suggested that industrial sources were major predictors for Cu and Fe models in PM with diameter < 1 μm (PM₁)³⁸.

In Zn models, predictors representing industrial Zn emission and combustion sources contributed a large proportion to the overall r^2 . This is consistent with LUR models in other studies³⁶⁻³⁸. In ESCAPE modeling, specific industrial predictors were not available⁸. The large contribution of industrial point sources to the Zn models is consistent with results of source apportionment analyses in MESA (Multi-Ethnic Study of Atherosclerosis) showing that Zn-rich features were indicative of incinerators at nearby fixed locations³⁴. Previous studies have used Zn as a tracer for metallurgic industries and non-metallurgic industries for frit production³⁵.

In Ni and V models, ports were important predictors, as a proxy for shipping emissions. Density of Ni-emitting industries and more general industrial density predictors were included in the SLR model for Ni and V, consistent with the identification that Ni and V shared the same mixed industrial/fuel-oil combustion source³⁹. Large-scale satellite-model dust showed a large contribution in the Ni and V models, which possibly accounts for the observed north-south trend in the absence of a specific large-scale Ni and V CTM or satellite predictors. We offered satellite-model dust to all elements as windblown dust can be a source for all components.

In S models, variation in the measured concentrations was predominantly explained by large-scale satellite and chemical transport model estimates and predictors in large buffers. Sulfate from the CTM and satellite-model dust were virtually equally important in the models. Satellite-model sulfate did not enter the model possibly because sulfate from the CTM was in the model and they are highly correlated. Satellite-model dust likely accounts for the observed north-south trend in concentration. In area-specific ESCAPE models, less well performing models were developed for S mainly due to the small within-study area variability⁸. Predictors representing industrial point sources also contributed to the S models, indicative of transformation of emissions from combustion³⁴.

In K models, satellite-model estimates for organic matter explained a large proportion of the variation, indicative of the main source of biomass burning for fine particle K³⁵. Small-scale variables contributed little to K models, resulting in limited ability in explaining within-area variability. In our current models, we are still missing fine spatial scale biomass burning source terms because of the lack of reliable predictor variables.

Si models were dominated by satellite-model dust estimates and population density, reflecting its crustal dust source³⁵. Road length and industry areas from CORINE land cover also contributed to the models. These variables contributed a large fraction also in models for Si in PM₁³⁸. In a previous study in New York, Si was strongly associated with an indicator for areas of industrial structures. This indicator includes a wide range of industrial, manufacturing and commercial activities thus it is difficult to identify the main source³⁶.

3.4 Maps and prediction at random locations

The truncation frequency for prediction at random locations is shown in Table S3. A large number of negative SLR predictions were truncated to zero for some elements – e.g., 41.3% of the 41,936 random locations across Europe for Cu in the final two-step SLR model predictions. Most of the negative values were located in the low population density areas of Northern Europe, covered mostly by natural land. When we applied the final two-step SLR models to a large Europe-wide pooled dataset of ESCAPE cohorts with 393,064 subjects (including a Swedish and Danish cohort), truncation frequencies were much smaller: 10.5% for PM_{2.5} Cu, 0.5% for PM_{2.5} Fe, 11.3% for PM_{2.5} Ni, 14.2% for PM_{2.5} V, 2.7% for PM_{2.5} Zn. Therefore, we do not expect this to be a big issue when applying the SLR models to participants in epidemiological studies. No truncation was needed for RF models.

Although we *a priori* considered one-step RF models as our main RF models, we observed large concentration jumps along horizontal or vertical lines in several maps (Figure S5). This counterintuitive

Table 1. Performance of PM_{2.5} composition models over Europe

	Inclusion of X, Y coordinates	Component	Cu	Fe	K	Ni	S	Si	V	Zn
		No. of sites	414	413	414	402	404	400	402	413
<u>Model building</u>										
SLR	One-step	Model r ²	0.56	0.55	0.61	0.62	0.79	0.52	0.70	0.48
		Model RMSE ^a	3.3	65.5	64.6	0.9	146.5	59.7	1.7	11.8
	Two-step, step1	Model r ²	0.52	0.53	0.52	0.56	0.80	0.48	0.66	0.47
		Model RMSE	3.4	67.4	71.1	1.0	142.2	61.9	1.8	11.9
	Two-step, step2	Model r ²	0.56	0.53	0.60	0.60	0.82	0.50	0.69	0.48
		Model RMSE	3.3	67.4	65.0	0.9	135.4	61.1	1.7	11.8
RF ^b	One-step	Model r ²	0.95	0.95	0.97	0.95	0.98	0.95	0.97	0.95
		Model RMSE	1.1	20.8	16.8	0.3	40.2	19.9	0.5	3.5
	Two-step, step1	Model r ²	0.95	0.95	0.97	0.95	0.98	0.94	0.97	0.96
		Model RMSE	1.1	20.9	17.4	0.3	41.8	20.3	0.5	3.4
	Two-step, step2	Model r ²	0.98	0.98	0.99	0.98	0.99	0.98	0.99	0.99
		Model RMSE	0.6	12.4	9.5	0.2	27.0	12.2	0.3	1.8
<u>Hold-Out Validation</u>										
SLR	One-step	HOV r ²	0.47	0.48	0.58	0.57	0.76	0.50	0.63	0.41
		HOV RMSE	3.6	70.5	66.4	1.0	156.4	60.8	1.8	12.5
	Two-step, step1	HOV r ²	0.44	0.46	0.50	0.51	0.76	0.46	0.60	0.42
		HOV RMSE	3.7	71.7	72.6	1.0	154.9	63.4	1.9	12.4
	Two-step, step2	HOV r ²	0.48	0.48	0.59	0.56	0.79	0.46	0.63	0.41
		HOV RMSE	3.6	70.5	66.1	1.0	147.0	62.9	1.8	12.5
RF	One-step	HOV r ²	0.60	0.60	0.82	0.74	0.91	0.62	0.85	0.68
		HOV RMSE	3.2	61.7	44.1	0.7	97.0	52.9	1.2	9.3
	Two-step, step1	HOV r ²	0.59	0.59	0.79	0.74	0.90	0.60	0.84	0.68
		HOV RMSE	3.2	62.4	47.4	0.7	102.1	54.2	1.2	9.2
	Two-step, step2	HOV r ²	0.59	0.61	0.80	0.76	0.90	0.62	0.86	0.71
		HOV RMSE	3.2	61.3	45.8	0.7	99.5	53.1	1.1	8.7

SLR = Supervised Linear Regression; RF = Random Forest; r² = squared Pearson correlation; RMSE = Root-Mean-Square Error; HOV = Five-fold Hold-Out Validation

^aunit of RMSE: ng/m³

^bPerformance of Random Forest on training set cannot be interpreted

Table 2. Performance of PM_{2.5} composition models to assess within-area variation: average within-area r^2

avg. WA r^2	Inclusion of X, Y coordinates	Evaluation method	Cu	Fe	K	Ni	S	Si	V	Zn
SLR	One-step	Five-fold HOV	0.34	0.35	0.09	0.18	0.14	0.18	0.21	0.20
		LOAOCV	0.37	0.38	0.09	0.15	0.22	0.21	0.23	0.18
	Two-step, step1	Five-fold HOV	0.34	0.34	0.08	0.17	0.14	0.20	0.18	0.21
		LOAOCV	0.35	0.35	0.09	0.15	0.22	0.20	0.20	0.18
	Two-step, step2	Five-fold HOV	0.35	0.36	0.07	0.17	0.14	0.20	0.19	0.19
		LOAOCV	0.36	0.36	0.09	0.15	0.22	0.20	0.21	0.18
	One-step	Five-fold HOV	0.31	0.31	0.05	0.21	0.21	0.19	0.27	0.24
		LOAOCV	0.35	0.35	0.12	0.18	0.21	0.17	0.27	0.18
	Two-step, step1	Five-fold HOV	0.31	0.30	0.06	0.21	0.22	0.17	0.27	0.24
		LOAOCV	0.34	0.34	0.07	0.16	0.21	0.16	0.23	0.19
RF	Two-step, step2	Five-fold HOV	0.29	0.29	0.07	0.21	0.23	0.17	0.29	0.25
		LOAOCV	0.34	0.34	0.07	0.16	0.21	0.16	0.23	0.20

SLR = Supervised Linear Regression; RF = Random Forest; r^2 = squared Pearson correlation; avg. WA r^2 is the average of 19 study area-specific r^2 s (area-specific r^2 s evaluated by five-fold HOV are shown in Figure S4); HOV = Hold-Out Validation; LOAOCV = Leave-One-Area-Out Cross-Validation

Figure 1. Regression slopes (shown in red) of predictors selected in Supervised Linear Regression (SLR) and relative variable importance (shown in blue) of the 15 most important predictors in Random Forest (RF).

Values between two algorithms are not quantitatively comparable. Regression slopes in SLR were multiplied by the range of each predictor to allow comparison across predictors. Relative variable importance in RF was calculated as percentage increase in mean squared errors after a random permutation of the values of a variable. SO₄=Sulfate, SO₂=Sulfur dioxide, OM=Organic Matter, SO₁₀=Satellite Dust, BC=Black Carbon, BCAOD=CTM Black Carbon, SUAOD=CTM Sulfate, TCSO₂=CTM Sulfate, POP=Population, ALT=Altitude, MURD=Major Roads, ALRD=All Roads, TBU=Total Build Up, NAT=Natural Land, IND=Industry, POR=Ports, UGR=Urban Green, RES=Residential, Cu_{emi}=Cu emission amount, PM₁₀ emission amount, SO_x emission amount, Zn_{emi}=Zn emission amount, industry=number of total industrial sites, Ni=number of industrial sites emitting Ni, X_{coord}=east-west gradient, Y_{coord}=north-south gradient. Number in subscript depicts the buffer size. SLR1 = one-step SLR; SLR2.1 = two-step SLR, step one; SLR2.2 = two-step SLR, step two; RF1 = one-step RF; RF2.1 = two-step RF, step one

pattern possibly reflects the role of the X, Y coordinates in RF modeling and relative importance attributed to these variables. Using X and Y in RF introduces strong boundary effects because, depending on the value where trees are split, large difference in predictions will be produced below and above that value. The concentration jumps were also observed in the final two-step RF model maps with X, Y coordinates. The RF models without offering X, Y coordinates produced clearly different maps while the HOV r^2 s were marginally lower than for the RF models with coordinates (Table 1). We therefore prefer the first step in the two-step RF and the final two-step SLR (maps in Figure 2), and show maps deriving from the other procedures in the appendix (Figure S5). The maps showing strong boundary effects might require smoothing before application in epidemiological studies. Our results clearly indicate the value in evaluating plausibility of maps as an important last step in air pollution exposure assessment studies. Comparing models solely by HOV statistics is not sufficient. We did not observe sharp gradients in the SLR model maps.

There are clear agreements between maps produced by our main SLR and RF for some elements and differences for other elements (Figure 2). In both maps for Cu, high levels of pollution are shown in big cities, and transport networks can be clearly seen in the inset map of the area around Paris. Maps for PM_{2.5} S are broadly similar with higher pollution levels in the south and east, while quite different patterns were observed for east Germany and Spain. Both maps for Zn show high concentrations close to industrial sites. The same industrial sites were picked up in the area around Paris shown in the inset. Comparing the predictions at a total of 41,936 random locations, agreement was high at all European countries-level and the ELAPSE countries combined-level for PM_{2.5} Cu, PM_{2.5} K, PM_{2.5} S, PM_{2.5} Zn ($r > 0.7$), and moderately high for other elements (Table 3). Correlation between all model predictions at the ELAPSE countries combined-level is presented in Figure S6. For most components, correlations were high for predictions derived from the same algorithm, and lower for predictions derived from different algorithms.

While correlations between predictions derived from SLR and RF were moderate to high at the European level, they are lower than the very high correlations (r generally > 0.9) reported previously for Europe-wide models of PM_{2.5} and NO₂¹⁶. Agreement between predictions from the two algorithms at national level varied substantially across countries (Table 3). There was no consistently good agreement between predictions for a specific country. Poor agreement between predictions were observed for area-component combinations that had small contrasts in measured concentrations shown by low RMSE (e.g. most components in Norway and Sweden).

Computation time for mapping differed substantially for RF and SLR – around 40 hours for RF and less than 1 hour for SLR to map pollution concentrations across Europe on a standard office computer.

3.5 Strengths and limitations

With the development of Europe-wide models, we are able to assess long-term exposures to PM_{2.5} components in a large European project, which consists of several nation-wide cohorts and smaller cohorts in which participants were recruited in specific study areas. The use of a single harmonized model allows a standardized exposure assessment in international multi-center studies.

Our Europe-wide models had the advantage of a large training dataset with large contrasts in measured concentrations by combining measurements from individual ESCAPE study areas. In contrast, the previous ESCAPE area-specific models could not be developed for some composition-area combinations because of missing data (e.g. in Lugano), small within-area variability (e.g. S) and poor precision of the measurements in areas with low concentrations (Ni and V)⁸. The moderate to good performance of our models across Europe suggests that the models would perform well in multi-center studies that exploit both within and between area variability of air pollution contrasts.

Another strength of our study is that we made efforts in collecting specific large-scale predictors, from satellites and chemical transport models, representing different pollution sources such as soil, industrial sources and biomass burning, which could not be applied in prior area-specific models. The availability

Table 3. Correlations between predictions by our main Supervised Linear Regression (two-step, step2) and Random Forest (two-step, step1) models at 41,936 random locations

Region	PM _{2.5} Cu		PM _{2.5} Fe		PM _{2.5} K		PM _{2.5} Ni		PM _{2.5} S		PM _{2.5} Si		PM _{2.5} V		PM _{2.5} Zn		N
	r	RMSE ^a	r	RMSE	r	RMSE	r	RMSE	r	RMSE	r	RMSE	r	RMSE	r	RMSE	
All European countries	0.72	1.1	0.66	20.5	0.75	51.3	0.56	0.5	0.88	162.6	0.56	22.8	0.64	1.0	0.73	7.1	41936
ELAPSE countries																	
Combined	0.79	1.0	0.77	19.1	0.70	56.1	0.53	0.5	0.89	142.0	0.75	12.5	0.66	0.8	0.73	7.0	27411
Austria	0.77	1.1	0.80	16.2	0.80	35.0	0.28	0.1	0.95	69.5	0.08	9.5	0.82	0.2	0.89	4.4	1051
Belgium	0.82	0.9	0.89	11.9	0.05	21.0	0.83	0.4	0.79	47.4	0.71	8.2	0.76	0.8	0.70	11.4	355
Switzerland	0.80	1.1	0.89	13.1	0.76	24.1	0.36	0.1	0.48	95.0	0.38	9.2	0.49	0.2	0.65	5.8	500
Germany	0.74	1.0	0.80	14.9	0.43	30.6	0.66	0.3	0.67	60.1	0.59	8.2	0.80	0.4	0.58	6.9	4233
Denmark	0.77	0.3	0.77	9.3	0.68	15.0	0.21	0.2	0.73	36.0	0.45	7.2	0.24	0.3	0.49	2.0	522
France	0.62	1.1	0.75	14.2	0.31	26.9	0.39	0.4	0.72	69.0	0.48	9.0	0.77	0.6	0.59	6.8	6476
Italy	0.72	1.3	0.53	23.2	0.69	33.6	0.51	0.6	0.83	183.0	0.70	19.5	0.63	1.3	0.67	9.0	3550
Netherlands	0.74	0.9	0.83	14.2	0.55	17.2	0.64	0.4	0.60	45.0	0.68	8.9	0.48	0.7	0.66	14.2	451
Norway	0.37	0.0	0.61	5.6	-0.68 ^b	8.6	0.43	0.2	0.25	104.9	0.03	4.3	0.80	0.3	0.46	4.0	2649
Sweden	0.56	0.2	0.77	5.8	-0.68 ^b	22.6	0.68	0.1	0.88	86.7	0.31	4.9	0.73	0.4	0.38	3.6	4786
United Kingdom	0.85	0.6	0.87	12.0	-0.74 ^b	25.9	0.59	0.3	0.86	72.1	0.12	9.6	0.57	0.5	0.68	4.1	2838
Non-ELAPSE countries																	
Greece	0.55	1.0	0.57	16.8	0.38	28.7	0.44	0.8	0.18	123.5	0.34	25.6	0.46	1.9	0.54	7.0	1541
Finland	0.25	0.3	0.58	7.4	0.49	28.7	0.48	0.1	0.85	67.3	0.28	4.9	0.33	0.3	0.55	4.2	3208
Hungary	0.68	0.9	0.61	11.7	0.74	29.0	0.34	0.2	0.60	87.4	0.57	8.2	0.67	0.3	0.79	5.0	1123
Ireland	0.52	0.3	0.65	5.8	-0.70 ^b	16.9	0.46	0.2	0.45	48.5	-0.08	4.8	0.41	0.4	0.26	1.8	844
Lithuania	0.63	0.8	0.68	7.0	0.65	25.3	0.26	0.1	0.16	52.5	0.59	4.7	0.29	0.2	0.89	1.8	783
Luxembourg	0.76	0.8	0.83	8.4	-0.08	16.2	0.82	0.1	0.82	26.5	0.77	4.9	0.80	0.2	0.83	2.1	33
Portugal	0.41	1.6	0.01	21.0	-0.03	23.5	0.71	0.4	0.72	72.9	0.22	7.3	0.80	0.7	0.60	6.6	1021
Spain	0.59	1.2	0.34	17.2	0.06	32.7	0.41	0.6	0.59	102.0	0.49	10.7	0.59	1.1	0.56	8.0	5972

r = Pearson correlation coefficient; RMSE = Root-Mean-Square Error

^aunit of RMSE: ng/m³^bWe do not have clear explanations of these high negative correlations. These values possibly reflect the poor performance of both models at low concentrations. Scatter plots documented the poor agreement between predictions by the two models with lots of scatters.

(1) PM_{2.5} Cu

(2) PM_{2.5} Fe

(3) PM_{2.5} K

(4) PM_{2.5} Ni

(5) PM_{2.5} S

(6) PM_{2.5} Si

(7) PM_{2.5} V

(8) PM_{2.5} Zn

Figure 2. Maps of PM_{2.5} components developed by our main Supervised Linear Regression (two-step, step2) and Random Forest (two-step, step1) models

of these predictors increased the specificity of our models, which is useful to study associated health effects of specific single components.

While inclusion of industrial point source data was an improvement over the simple land use categories available in CORINE land cover, a dispersion model for point sources would have been the method of choice. We did not have the possibility to use Europe-wide small-scale dispersion modeling, and we did not have information on chimney height and wind direction around chimneys. We therefore used inverse distance weighting to create variables from industrial point sources, which can lead to overestimation of pollution levels in areas very close to the industrial sites⁴⁰. The misclassification is expected to be minimal given that it is unlikely that many people live very close to the large point source chimneys included in the European Pollutant Release and Transfer Register databases. The small truncation frequency (<0.1%) above the maximum values in a total of around 42,000 random locations across Europe suggested the overestimation might not have a large impact.

The prediction ability of our Europe-wide model at small-scale, however, is limited, especially in areas without main sources present. The lack of specificity of the small-scale land use predictors might have contributed to the poor predictive ability for some elements. The poor within-area predictive ability suggests our Europe-wide models should be applied with caution in small-scale individual study areas, with the possible exception of the Cu and Fe models. Our model is more suited for multi-center studies.

Moderate to high overall correlations between our Europe-wide SLR and previous area-specific ESCAPE model predictions at monitoring sites were observed except for K and Zn (Table S4). The within-area correlations between SLR and ESCAPE varied considerably and the average correlations were high for Cu and Fe. The results suggested applying the newly developed Europe-wide models in epidemiological studies could lead to different findings from the ESCAPE study. The leave-one-out-cross-validation (LOOCV) r^2 s of the area-specific ESCAPE models are not quantitatively comparable with the within-area 5-fold cross-validation r^2 s in this study as the LOOCV is based on a small number of sites and tends to overestimate predictive ability^{10,11}.

Given the discrepancies in predictions derived from the two methods, applying the two sets of models in epidemiological studies could lead to different associations with health. SLR and RF model performances were similar for the within-area concentration variability, while RF model explained overall concentration variability (including between-area variability) better than SLR. In SLR, we did not add fixed or random intercepts for study area as such models could not be applied outside the specific study areas. In a previous study on PM_{2.5} and NO₂³³, we found that adding indicators for study area or the measured regional background in each study area, improved the overall explained variability. Therefore, when applied in epidemiological studies, it depends on the contrast exploited in the epidemiological study which method is the preferred method. If both between- and within-area variability are exploited, RF would be the method of choice based on the cross-validation statistics. If an epidemiological study only includes within-area exposure contrast, then both methods should be interpreted equally, without *a priori* preference for one of the methods. Given the moderate performance of both models, it would be important to observe robustness of the findings in epidemiological studies. If health effects are found with only one model, this should be interpreted cautiously.

Because of the lack of external validation data, we cannot draw strong conclusions about the preferred method. We note that RF models might be more difficult to interpret in terms of how predictor variables act in the models, although the “importance” statistics provide useful information on the relative importance of individual predictors. The classification nature of RF led to visible boundary effects in some exposure maps, which might require smoothing before application in epidemiological studies. On the other hand, SLR might fail to capture some complex non-linear relationships and/or interactions between predictors and pollutant, or might induce overfitting if multiple non-linear and interaction terms were added to the model. Despite the discrepancies in predictions, we believe our models are stable and the results are robust, as different cross-validation methods and several sensitivity analyses showed moderate to good performance especially at the overall Europe-wide scale and similar results.

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Supplementary Information

Table S1. Overview of potential predictor variables

Group	Predictor variable	Variable Name	Unit	Buffer size (radius in m) or point estimate	Direction of effect	Restricted to components
Altitude ^a	Altitude	ALT		Point (~90m spacing)	-	All
	Road length of major roads in a buffer	MJRD		50, 100, 200, 300, 400,		
	Road length of all roads in a buffer	ALRD	meter	500, 700, 1000, 2000, 5000, 10000	+	All
CTM estimate	Black carbon Aerosol Optical Depth	BCAOD				Cu, Fe, K, Ni, V, Zn
	Sulfate Aerosol Optical Depth	SUAOD		Point (~13.9km spacing)	+	Ni, S, V
	Total column SO ₂	TCSO2				Ni, S, V
	Sulfate	SO4				Ni, S, V
SAT estimate	Organic Matter	OM				Cu, Fe, K, Ni, V, Zn
	Mineral Dust	SOIL	µg/m ³	Point (~1.11km spacing)	+	All
	Black Carbon	BC				Cu, Fe, K, Ni, V, Zn
	Population density	POP		Point (1km spacing)	+	All
Land use	Percent area of continuous urban fabric - high/low density	RES		50, 100, 200, 300, 400, 500, 600, 700, 800, 1000,	+	
	Percent area of total build up	TBU		1200, 1500, 1800, 2000,	+	
	Percent area of natural lands	NAT	%	2500, 3000, 3500, 4000,	-	All
	Percent area of industrial/ commercial lands	IND		5000, 6000, 7000, 8000,	+	
	Percent area of ports	POR		10000	+	
	Percent area of urban green	UGR			-	
	Inverse distance weighted sum emission amount of Cu within a buffer	Cu_emi				Cu
	Inverse distance weighted sum emission amount of Ni within a buffer	Ni_emi				Ni, V
Industry	Inverse distance weighted sum emission amount of PM ₁₀ within a buffer	PM _{10_emi}	ton	2000, 4000, 10000	+	All
	Inverse distance weighted sum emission amount of SO _x within a buffer	SO _{x_emi}				Ni, S, V
	Inverse distance weighted sum emission amount of Zn within a buffer	Zn_emi				Zn

(Table S1 Continued)

	Inverse distance weighted number of industrial sites within a buffer	industry		
	Inverse distance weighted number of industrial sites emitting metal aerosols within a buffer	metal		
	Inverse distance weighted number of industrial sites emitting Cu within a buffer	Cu		
	Inverse distance weighted number of industrial sites emitting Ni within a buffer	Ni	count	2000, 4000, 10000
	Inverse distance weighted number of industrial sites emitting PM ₁₀ within a buffer	PM ₁₀		
	Inverse distance weighted number of industrial sites emitting SO _x within a buffer	SO _x		
	Inverse distance weighted number of industrial sites emitting Zn within a buffer	Zn		
North-south/ east-west gradient ^b	east-west gradient	X _{coord}		
	north-south gradient	Y _{coord}		
		Point	+/-	All

CTM = chemical transport model, SAT = satellite-model

^a Transformed altitude is calculated as $\sqrt{(\text{nalt}/\max(\text{nalt}))}$, where $\text{nalt} = \text{altitude} - \min(\text{altitude})$.

^b Transformed X, Y coordinates are calculated as $X_{\text{coord}} = (X - X_{\min})/(X_{\max} - X_{\min})$, $Y_{\text{coord}} = (Y - Y_{\min})/(Y_{\max} - Y_{\min})$

Table S2. Performance of PM_{2.5} composition models over Europe

Inclusion of X, Y coordinates		Component	Cu	Fe	K	Ni	S	Si	V	Zn	
		No. of sites	414	413	414	402	404	400	402	413	
Five-fold Hold-Out Validation											
SLR	One-step	Regression-based r^2	0.47	0.48	0.58	0.57	0.76	0.50	0.63	0.41	
		MSE-based R^2	0.47	0.48	0.58	0.57	0.76	0.50	0.63	0.41	
	Two-step, step1	Regression-based r^2	0.44	0.46	0.50	0.51	0.76	0.46	0.60	0.42	
		MSE-based R^2	0.44	0.46	0.50	0.51	0.76	0.45	0.59	0.42	
	Two-step, step2	Regression-based r^2	0.48	0.48	0.59	0.56	0.79	0.46	0.63	0.41	
		MSE-based R^2	0.48	0.48	0.59	0.56	0.79	0.46	0.63	0.41	
	One-step	Regression-based r^2	0.60	0.60	0.82	0.74	0.91	0.62	0.85	0.68	
		MSE-based R^2	0.59	0.60	0.82	0.74	0.91	0.62	0.85	0.67	
	RF	Two-step, step1	Regression-based r^2	0.59	0.59	0.79	0.74	0.90	0.60	0.84	0.68
			MSE-based R^2	0.58	0.59	0.78	0.74	0.90	0.60	0.86	0.68
Two-step, step2		Regression-based r^2	0.59	0.61	0.80	0.76	0.90	0.62	0.86	0.71	
		MSE-based R^2	0.59	0.61	0.80	0.76	0.90	0.62	0.86	0.71	

SLR = Supervised Linear Regression; RF = Random Forest; r² = squared Pearson correlation; MSE-based R² = Mean Square Error-based R²

Table S3. Truncation frequency (%) for model predictions at 41,936 random locations

Inclusion of X, Y coordinates			Cu	Fe	K	Ni	S	Si	V	Zn
SLR	one-step	exceed maximum	0	0	0	0	0	0	0	0.1
		negative	38.9	36.3	12	26.2	0	3.9	23.7	18.1
	Two-step, step1	exceed maximum	0	0	0	0	0	0	0	0.1
		negative	53.6	10	0	26.7	0	0	24.3	19.4
	Two-step, step2	exceed maximum	0	0	0	0	0	0	0	0.1
		negative	41.3	10	11.5	21.8	0	0	20.5	19.8
RF	one-step	exceed maximum	0	0	0	0	0	0	0	0
		negative	0	0	0	0	0	0	0	0
	Two-step, step1	exceed maximum	0	0	0	0	0	0	0	0
		negative	0	0	0	0	0	0	0	0
	Two-step, step2	exceed maximum	0	0	0	0	0	0	0	0
		negative	0	0	0	0	0	0	0	0

SLR = Supervised Linear Regression; RF = Random Forest

Table S4. Correlation of predictions at monitoring sites between Europe-wide models^a and ESCAPE models

	Overall r^2	Average of within-area r^2	Range of within-area r^2
Cu	0.63	0.50	(0.02, 0.77)
Fe	0.55	0.47	(0.07, 0.75)
K	0.26	0.10	(0.00, 0.47)
Ni	0.69	0.22	(0.00, 0.78)
S	0.84	0.22	(0.00, 0.73)
Si	0.49	0.27	(0.00, 0.68)
V	0.73	0.27	(0.00, 0.79)
Zn	0.13	0.22	(0.00, 0.74)

SLR = two-step Supervised Linear Regression step2; ESCAPE = area-specific ESCAPE model predictions; r^2 = squared Pearson correlation^a We only presented correlations between ESCAPE and SLR predictions, as correlations between ESCAPE and RF predictions cannot be interpreted because RF models have “by design” perfect predictions at training sites.

Figure S1. Distribution of 416 ESCAPE monitoring sites across 19 study areas. Each area has 20 sites (40 sites in the Netherlands/Belgium and Catalunya)

Figure S2. Boxplots of annual mean concentrations for PM_{2.5} composition (ng/m³) in individual study areas and in the full dataset (box shown in red). Individual study areas are shown from north to south.

NOS: Oslo (Norway); SST: Stockholm County (Sweden); FIH: Helsinki/Turku (Finland); DCO: Copenhagen (Denmark); LKA: Kaunas (Lithuania); UKM: Manchester (United Kingdom); UKO: London/Oxford (United Kingdom); BNL: Netherlands/Belgium; GRU: Ruhr Area (Germany); GMU: Munich/Augsburg (Germany); AUV: Vorarlberg (Austria); FPA: Paris (France); HUG: Gyor (Hungary); SWL: Lugano (Switzerland); ITU: Turin (Italy); IRO: Rome (Italy); SCA: Catalunya (Spain); GRA: Athens (Greece); GCR: Heraklion (Greece).

Figure S3. Scatter plots of the stacked predictions at 5 held-out sites versus measurements, obtained from 5-fold hold-out validation analyses

SLR = Supervised Linear Regression; RF = Random Forest

AUV: Vorarlberg (Austria); BNL: Netherlands/Belgium; DCO: Copenhagen (Denmark); FIH: Helsinki/Turku (Finland); FPA: Paris (France); GCR: Heraklion (Greece); GMU: Munich/Augsburg (Germany); GRA: Athens (Greece); GRU: Ruhr Area (Germany); HUG: Gyor (Hungary); IRO: Rome (Italy); ITU: Turin (Italy); LKA: Kaunas (Lithuania); NOS: Oslo (Norway); SCA: Catalunya (Spain); SST: Stockholm County (Sweden); SWL: Lugano (Switzerland); UKM: Manchester (United Kingdom); UKO: London/Oxford (United Kingdom)

(1) PM_{2.5} Cu (Left two-step SLR step2, Right two-step RF step 1)

(2) PM_{2.5} Fe (Left two-step SLR step2, Right two-step RF step 1)

(3) PM_{2.5} K (Left two-step SLR step2, Right two-step RF step 1) (4) PM_{2.5} Ni (Left two-step SLR step2, Right two-step RF step 1) (5) PM_{2.5} S (Left two-step SLR step2, Right two-step RF step 1)

(6) PM_{2.5} Si (Left two-step SLR step2, Right two-step RF step 1) (7) PM_{2.5} V (Left two-step SLR step2, Right two-step RF step 1) (8) PM_{2.5} Zn (Left two-step SLR step2, Right two-step RF step 1)

Figure S4. Within-area r^2 s (bars and scale on left) and Root-Mean-Square Errors (RMSEs) (plus signs and scale on right) of PM_{2.5} composition models evaluated by five-fold hold-out-validation

(a) One-step Supervised Linear Regression

One-step Random Forest

(b) Two-step Supervised Linear Regression, step1 **Two-step Random Forest, step1**

(c) Two-step Supervised Linear Regression, step2

Two-step Random Forest, step2

Study areas are shown from north to south. NOS: Oslo (Norway); SST: Stockholm County (Sweden); FIH: Helsinki/Turku (Finland); DCO: Copenhagen (Denmark); LKA: Kaunas (Lithuania); UKM: Manchester (United Kingdom); UKO: London/Oxford (United Kingdom); BNL: Netherlands/Belgium; GRU: Ruhr Area (Germany); GMU: Munich/Augsburg (Germany); AUV: Vorarlberg (Austria); FPA: Paris (France); HUG: Gyor (Hungary); SWL: Lugano (Switzerland); ITU: Turin (Italy); IRO: Rome (Italy); SCA: Catalunya (Spain); GRA: Athens (Greece); GCR: Heraklion (Greece); AVG = average.

Figure S5. Maps of PM_{2.5} components

(a) Supervised Linear Regression models

(1) PM_{2.5} Cu

(2) PM_{2.5} Fe

(3) PM_{2.5} K

(4) PM_{2.5} Ni

(5) PM_{2.5} S

(6) PM_{2.5} Si

(7) PM_{2.5} V

(8) PM_{2.5} Zn

(b) Random Forest models

(1) PM_{2.5} Cu

(2) PM_{2.5} Fe

(3) PM_{2.5} K

(4) PM_{2.5} Ni

(5) PM_{2.5} S

(6) PM_{2.5} Si

(7) PM_{2.5} V

(8) PM_{2.5} Zn

Figure S6. Pearson correlation between model predictions at random locations across ELAPSE countries (N=27,411)

SLR1 = One-step Supervised Linear Regression; SLR2.1 = Two-step Supervised Linear Regression, step1; SLR2.2 = Two-step Supervised Linear Regression, step2; RF1 = One-step Random Forest; RF2.1 = Two-step Random Forest, step1; RF2.2 = Two-step Random Forest, step2.

Chapter 6

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

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Abstract

Background Inconsistent associations between long-term exposure to particles with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ [fine particulate matter (PM_{2.5})] components and mortality have been reported, partly related to challenges in exposure assessment.

Objectives We investigated the associations between long-term exposure to PM_{2.5} elemental components and mortality in a large pooled European cohort; to compare health effects of PM_{2.5} components estimated with two exposure modeling approaches, namely supervised linear regression (SLR) and random forest (RF) algorithms.

Methods We pooled data from eight European cohorts with 323,782 participants, average age 49 y at baseline (1985–2005). Residential exposure to 2010 annual average concentration of eight PM_{2.5} components (copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc) was estimated with Europe-wide SLR and RF models at a 100x100m scale. We applied Cox proportional hazards models to investigate the associations between components and natural and cause-specific mortality. In addition, two-pollutant analyses were conducted by adjusting each component for PM_{2.5} mass and nitrogen dioxide (NO₂) separately.

Results We observed 46,640 natural-cause deaths with 6,317,235 person-years and an average follow-up of 19.5 y. All SLR-modeled components were statistically significantly associated with natural-cause mortality in single-pollutant models with hazard ratios (HRs) from 1.05 to 1.27. Similar HRs were observed for RF-modeled copper, iron, potassium, sulfur, vanadium and zinc with wider confidence intervals (CIs). HRs for SLR-modeled nickel, sulfur, silicon, vanadium and zinc remained above unity and (almost) significant after adjustment for both PM_{2.5} and NO₂. HRs only remained (almost) significant for RF-modeled potassium and vanadium in two-pollutant models. The HRs for vanadium were 1.03 (95% CI: 1.02, 1.05) and 1.06 (95% CI: 1.02, 1.10) for SLR- and RF-modeled exposures respectively per 2 ng/m³ adjusting for PM_{2.5} mass. Associations with cause-specific mortality were less consistent in two-pollutant models.

Conclusion Long-term exposure to vanadium in PM_{2.5} was most consistently associated with increased mortality. Associations for the other components were weaker for exposure modeled with RF than SLR in two-pollutant models.

1. Introduction

The Global Burden of Disease (GBD 2015) study estimated that exposure to ambient particles with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) was the fifth-ranking mortality risk factor, contributing to 4.2 million deaths per year (Cohen et al., 2017). $\text{PM}_{2.5}$ is a mixture of a large number of components related to specific sources. Identifying which components of $\text{PM}_{2.5}$ are main contributors to adverse health effects is important for targeted policy making. Although some studies have attempted to associate long-term exposure to specific $\text{PM}_{2.5}$ components with mortality risks, the results are inconclusive. The California Teachers Study (Ostro et al., 2015) found an increased risk of ischemic heart disease (IHD) mortality in associations with exposure to nitrate, elemental carbon (EC), copper and secondary organics in $\text{PM}_{2.5}$. The American Cancer Society (ACS) Cancer Prevention Study-II (CPS-II) suggested that long-term $\text{PM}_{2.5}$ exposure from coal combustion and its key emission tracer elements (i.e., selenium and arsenic) were associated with increased IHD mortality risk, whereas exposure to silicon and potassium was not associated with mortality (Thurston et al., 2013; Thurston et al., 2016). In the Medicare population, the excess mortality risk associated with long-term $\text{PM}_{2.5}$ exposure increased with relative concentration of EC, vanadium, copper, calcium and iron and decreased with nitrate, organic carbon and sulfate (Wang et al., 2017). The large European Study of Cohorts for Air Pollution Effects (ESCAPE) reported a robust relationship between natural-cause mortality and $\text{PM}_{2.5}$ sulfur, and some evidence of associations with iron and copper in $\text{PM}_{2.5}$ (Beelen et al., 2015). No statistically significant association with $\text{PM}_{2.5}$ components was found for cardiovascular mortality in the ESCAPE study (Wang et al., 2014).

Long-term exposure assessment for particle components is more challenging than for $\text{PM}_{2.5}$ mass because of limited regulatory routine monitoring (with the exception of nitrate, ammonium and sulfate) and less data on emission rates used as input to dispersion models (Holmes and Morawska, 2006). To date, the available epidemiological evidence used different exposure assessment methods, including direct monitoring (Ostro et al., 2011; Thurston et al., 2013; Thurston et al., 2016), chemical transport models at 4x4 km scale (Ostro et al., 2015) and fine spatial scale land use regression (LUR) models (Beelen et al., 2015; Wang et al., 2014). Different exposure assessment methods may lead to component-specific differences in exposure estimation error, potentially leading to bias (Adams et al., 2015). Studies have suggested that risk estimates of $\text{PM}_{2.5}$ mass differed between exposure assessment methods (Jerrett et al., 2017; McGuinn et al., 2017). Studies comparing exposure assessment methods in their associations with health outcomes mainly focused on the comparison among direct monitoring, satellite products, dispersion/chemical transport models and LUR models. Recent developments in exposure assessment include combining different methods such as land-use or chemical transport modeling and monitoring data using a variety of approaches including linear regression and machine learning algorithms (Hoek, 2017). Comparisons have been made among exposure predictions developed with different algorithms in terms of prediction accuracy (Brokamp et al., 2017; Chen et al., 2019; Kerckhoffs et al., 2019). However, a simulation study suggested that improving the prediction accuracy of exposure models did not always improve the accuracy of health effect estimation, when bias is introduced into health effect estimation by the classical-like measurement error and the impact of Berkson-like measurement error on the health effect estimation error diminishes for large number of subjects (Szpiro et al., 2011). To our knowledge, no studies have compared exposure models developed with different algorithms regarding their relation with health outcomes.

The present study is part of the Effects of Low-level Air Pollution: a Study in Europe (ELAPSE). ELAPSE builds on the elemental composition, mortality and covariate data of the ESCAPE study (Beelen et al., 2014; Beelen et al., 2015; Wang et al., 2014). In ESCAPE each cohort was analyzed separately, whereas in ELAPSE respective ESCAPE cohorts were pooled to represent a contrast in low-level air pollution exposures. In addition, the follow-up data for mortality were extended from typically up to 2008 in ESCAPE to up to 2011–2017 in ELAPSE, which substantially increased the number of deaths and hence study power. Measurements for black carbon (BC) and elemental composition at

individual ESCAPE study areas were pooled to develop Europe-wide exposure models covering combined study areas for application in the ELAPSE (Chen et al., 2020; De Hoogh et al., 2018). The combined ability to do pooled analyses, plus accounting for new insights in the robustness of LUR models related to the number of air pollution monitoring sites (Basagaña et al., 2012; Wang et al., 2012), strengthened the exposure assessment in ELAPSE. The Europe-wide models furthermore allowed better coverage of those ESCAPE cohorts in large study areas of which typically only a fraction was covered by dedicated monitoring campaigns (e.g., only Paris in the national French *Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale* (E3N) cohort) (de Hoogh et al., 2013; Tsai et al., 2015). The Europe-wide models for assessing 2010 annual average PM_{2.5} composition concentrations at a 100x100m scale were developed using two algorithms – the supervised linear regression (SLR) and the random forest (RF) algorithms, which is a machine learning algorithm (Chen et al., 2020). The RF models outperformed the SLR models at the Europe-wide level by 11–30% across components in hold-out-validation R^2 , whereas the two models performed similarly in explaining variability within individual ESCAPE study areas. Despite the similar within-area performance, the exposure predictions at random sites derived from SLR and RF models correlated only moderately at the national level (the average of correlation coefficients at 11 ELAPSE countries range from 0.41 to 0.77 across components). We refer to correlations <0.4 as low, 0.4–0.7 as moderate, and >0.7 as high. Although the focus of ELAPSE is on low-level air pollution defined as below the current air quality guidelines and standards, low-level is difficult to define for PM elemental composition because there are currently no guidelines/standards for PM elemental composition.

We previously observed significantly positive associations between PM_{2.5} and natural and cause-specific mortality using the same pooled cohort in the framework of ELAPSE (Strak et al., submitted). Hazard ratio for natural cause mortality was 1.13 (95% CI: 1.11, 1.16) per 5 µg/m³ increase in PM_{2.5}. The first aim of this study was to evaluate whether specific components of PM_{2.5} were associated with mortality. The second aim was to compare the health effects of PM_{2.5} components estimated with two different exposure modeling approaches, namely, the SLR and RF algorithms.

2. Methods

2.1 Study populations

The ELAPSE pooled cohort contains eight cohorts across six European countries able to participate in data pooling, areas with low-level air pollution exposure, and relatively recent recruitment dates (Table 1 and Figure S1). The cohorts are the following: the *Cardiovascular Effects of Air Pollution and Noise in Stockholm* (CEANS) cohort in Sweden, which was constructed from four sub-cohorts: the *Stockholm Diabetes Prevention Program* (SDPP) (Eriksson et al., 2008), the *Stockholm Cohort of 60-Year-Olds* (SIXTY) (Wändell et al., 2007), the *Stockholm Screening Across the Lifespan Twin study* (SALT) (Magnusson et al., 2013) and the *Swedish National Study on Aging and Care in Kungsholmen* (SNACK) (Lagergren et al., 2004); the *Diet, Cancer and Health cohort* (DCH) (Tjønneland et al., 2007) in Denmark; the *Danish Nurse Cohort* (DNC) (Hundrup et al., 2012) in Denmark, consisting at baseline of two surveys conducted in 1993 and 1999; the *European Prospective Investigation into Cancer and Nutrition-Netherlands* (EPIC-NL) cohort in the Netherlands, including the *Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands* (MORGEN) and *Prospect* (Beulens et al., 2010); the *Heinz Nixdorf Recall study* (HNR) in Germany (Schmermund et al., 2002); the *Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale* (E3N) in France (Clavel-Chapelon and Group, 2015); the *Cooperative Health Research in the Region of Augsburg* (KORA) in Germany, consisting at baseline of two cross-sectional population-representative surveys conducted in 1994–1995 (S3) and 1999–2001 (S4); and the *Vorarlberg Health Monitoring and Prevention Programme* (VHM&PP) in Austria (Ulmer et al., 2007). The study areas of most cohorts constituted a large city and its surrounding areas. Some cohorts, such as the French E3N cohort and the Danish DNC cohort, covered large regions of the country. All included cohort studies were approved by the medical ethics committees in their respective countries. Detailed information of each individual cohort is provided in

Tables S1–S8. A lot of variable harmonization was done in the ESCAPE collaboration which formed the basis of the present study (Beelen et al., 2014; Cesaroni et al., 2014; Raaschou-Nielsen et al., 2013; Stafoggia et al., 2014). In ELAPSE, a joint codebook with exact definitions of variables were prepared, starting from the ESCAPE codebook. We asked each cohort to transfer the data to Utrecht University and checked the definition of variables according to the joint codebook. The variables in our confounder models did not require much harmonization. In the E3N cohort, smoking intensity was in classes. We assigned the midpoint as the actual value. Area-level socio-economic status (SES) was newly collected in ELAPSE. We specified the desired area-level SES variables with respect to spatial scale and variables before pooling the cohort data. The detailed harmonization process for area-level SES variables is described in the Supplemental Material in the section “Area-level socio-economic status (SES) variable harmonization”.

2.2 Air pollution exposure assessment

Eight components were *a priori* selected in ESCAPE to represent major pollution sources: copper (Cu), iron (Fe) and zinc (Zn) representing non-tailpipe traffic emissions; sulfur (S) representing long-range transport of secondary inorganic aerosols; nickel (Ni) and vanadium (V) representing mixed oil burning/industry; silicon (Si) representing crustal material; and potassium (K) representing biomass burning (de Hoogh et al., 2013; Tsai et al., 2015). We assessed exposure to these eight elements in PM_{2.5} at the participants’ baseline residential addresses using Europe-wide LUR models developed with two algorithms. The models have been described in detail elsewhere (Chen et al., 2020). Briefly, we estimated 2010 annual mean concentrations of PM_{2.5} elemental composition based on the standardized ESCAPE monitoring data. We offered large-scale satellite-model and chemical transport model estimates of components as predictors to represent background concentrations and land use, traffic, population and industrial point source data to model local spatial variability. We applied the supervised linear regression (SLR) (De Hoogh et al., 2018) and the random forest (RF) algorithms (Chen et al., 2019) to develop models for each component. The models explained a moderate to large fraction of the measured concentration variation at the European scale, ranging from 41% to 90% across components. Model performance evaluated by 5-fold hold-out validation reported in Chen et al. (2020) was extracted and is shown in Table S9. The RF models consistently outperformed the SLR models in explaining overall variability, including both between- and within- study area variability. The models explained within-area variability less well, with similar performance for SLR and RF models. The SLR and RF model predictions correlated moderately at the national level (the averaged correlation coefficients at six countries covered by the ELAPSE pooled cohort range from 0.43 to 0.78 across the components).

Exposure to 2010 annual mean concentration of PM_{2.5} mass and NO₂ was assessed by Europe-wide LUR models developed previously (De Hoogh et al., 2018). The models were developed based on the European Environmental Agency AirBase routine monitoring data, with satellite-derived and chemical transport model air pollutants estimates, and land-use, traffic and population data as predictors. The PM_{2.5} model explained 72% of measured spatial variation in the annual average concentration across Europe, whereas the NO₂ model explained 59%.

We applied the exposure models to create 100x100 m grids of the predicted concentrations of the pollutants covering the entire study area, and transferred the relevant parts to the participating centers for exposure assignment. Careful procedures were applied to ensure that correct exposure assignment occurred, including clarification of the correct coordinate system. Checking involved exposure assignment to a set of randomly selected coordinates by the participating centers and the coordinating center independently and by comparison of the exposure assignment. After assignment, anonymized data were returned to Utrecht University for checking and pooling.

We selected 2010 as the primary year of exposure modeling because 2009–2010 was the period of ESCAPE monitoring that we used to develop PM_{2.5} composition models (Chen et al., 2020). For PM_{2.5}, this was the earliest year of a sufficiently wide coverage of PM_{2.5} monitoring across Europe (De Hoogh et al., 2018). For consistency, we used the year 2010 for NO₂ as well. We assumed that the spatial

variability of the relevant pollution concentrations remained reasonably stable to the baseline period (year 1985–2005). We also assumed that, for a mortality outcome, the exposure in the past few years was the most relevant exposure. We considered very high and negative predicted concentrations of elemental composition unrealistic. Truncations were performed to deal with unrealistic predicted concentrations (Chen et al., 2020). We defined a maximum predicted concentration for each component calculated by fitting the SLR model with the maximum predictor values at ESCAPE monitoring sites for positive slopes (or the minimum predictor values for negative slopes). We considered predicted concentrations larger than the maximum modeled values as unrealistic predictions and truncated them to the maximum predicted concentrations. The high unrealistic predictions were mostly related to a close distance to industrial sources. Negative predictions were set to zero. Truncation was performed in the main model population for SLR-modeled exposure: 11.3% for Cu, 0.5% for Fe, 11.6% for Ni, 14.3% for V, and 2.6% for Zn (Table S10). The truncation was mostly performed for predictions below zero and mostly located in the North-European cohorts (i.e., CEANS, DNC) and KORA and VHM&PP. The high truncation frequency in some cohorts indicates that these cohorts did not contribute much information to the analyses. Only 2, 24, and 240 observations ($\leq 0.1\%$ of all observations) were truncated because of high SLR predictions for Cu, Ni, and Zn, respectively. No truncation was needed for RF-modeled exposure because the RF predictions were within the reasonable range, probably due to the flexible nature of the RF algorithm.

2.3 Mortality outcome definition

Identification of outcomes was based upon linkage to mortality registries. Natural mortality was defined based on the underlying cause of death recorded on death certificates according to the *International Classification of Diseases, Ninth Revision* (ICD-9) codes 001–779 and the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) codes A00–R99. We further defined mortality from cardiovascular disease (ICD-9 codes 400–440, ICD-10 codes I10–I70), respiratory disease (ICD-9 codes 460–519, ICD-10 codes J00–J99) and lung cancer (ICD-9 code 162, ICD-10 code C34).

2.4 Statistical analyses

2.4.1 Main analyses

To estimate hazard ratios (HRs) and 95% confidence interval (CIs) for associations of the PM_{2.5} component exposure with natural and cause-specific mortality, we applied Cox proportional hazards models following the general ELAPSE analytical framework (Hvidtfeldt et al., 2021b; Liu et al., 2021a; Liu et al., 2021b; Samoli et al., 2021). We used strata for sub-cohorts contributing to the pooled cohort to account for differences in baseline hazard between the sub-cohorts unexplained by the available covariates. We used strata because the assumption of proportional hazards did not hold with respect to sub-cohort. Strata had a substantially better model performance compared to alternative specifications such as sub-cohort indicators. The decision to account for between cohort heterogeneity using strata implies that we mostly evaluated within-cohort exposure contrasts. Each PM_{2.5} component was included as a linear function in the Cox models as a reasonable summary of the association, allowing comparison with previous studies. HRs were calculated with a fixed increment for each PM_{2.5} component following the increments selected in previous publications from ESCAPE and ELAPSE (Beelen et al., 2015; Hvidtfeldt et al., 2021a): PM_{2.5} Cu – 5 ng/m³, PM_{2.5} Fe – 100 ng/m³, PM_{2.5} K – 50 ng/m³, PM_{2.5} Ni – 1 ng/m³, PM_{2.5} S – 200 ng/m³, PM_{2.5} Si – 100 ng/m³, PM_{2.5} V – 2 ng/m³, PM_{2.5} Zn – 10 ng/m³. Censoring occurred at the time of the event of interest, death from other causes, emigration, loss to follow-up for other reasons, or at the end of follow-up, whichever came first. We *a priori* specified three confounder models with increasing control for individual and area-level covariates: Model 1 included only age (as the time scale), sub-cohort (as strata), sex (as strata), and year of enrollment; Model 2 added individual-level covariates including marital status (married/cohabiting, divorced/separated, single, widowed), smoking status (never, former, current), smoking duration (years of smoking) for current smokers, smoking intensity (cigarettes/day) for current smokers, squared smoking intensity, body mass index

(BMI) categories (<18.5 , $18.5\text{--}24.9$, $25\text{--}29.9$, and >30 kg/m²), and employment status (employed vs. unemployed); Model 3 further adjusted for neighborhood-level mean income in 2001. We determined the confounder models 2 and 3 by balancing the need to adjust for a comprehensive set of confounders and the availability in a large number of cohorts. BMI was included as a categorical variable because there is evidence of nonlinear relationships between continuous BMI and mortality (Di Angelantonio et al., 2016). We considered model 3 as the main model. Participants with missing exposure or incomplete information on model 3 covariates were excluded from all main analyses to ensure comparability between the model results.

Two-pollutant models were conducted with the main model 3 adjusting each component for PM_{2.5} mass and NO₂ separately. We adjusted for PM_{2.5} mass to investigate whether the association with individual components reflecting specific sources remained after adjustment for generic PM_{2.5} mass for which we have strong evidence of associations (Beelen et al., 2014). We adjusted for NO₂ in an attempt to disentangle the individual component effect from traffic exhaust emission for which NO₂ is used as a marker. Adjustment for NO₂ is especially important when assessing associations with the traffic non-exhaust components Cu, Fe and Zn. However, two-pollutant models can be difficult to interpret when the two pollutants reflect the same source or are strongly correlated. We did not model combinations of PM_{2.5} components in two-pollutant models because many were highly correlated (Figure S2) and we preferred to limit the complexity of analyses. The PM_{2.5} mass and NO₂ estimates used in the two-pollutant models were developed with the SLR algorithm (De Hoogh et al., 2018). We previously documented that, for PM_{2.5} mass and NO₂ separately, SLR and RF models had similar performance, and that SLR- and RF-modeled exposure at external validation sites were highly correlated (PM_{2.5} mass: Pearson $r = 0.89$; NO₂: $r = 0.93$) (Chen et al., 2019). Consequently, only the SLR-modeled PM_{2.5} and NO₂ exposures were linked to the individual cohorts.

We assessed the shape of the concentration-response functions (CRFs) for PM_{2.5} components and natural-cause mortality with natural cubic splines with 3 degrees of freedom. The CRFs can be difficult to interpret when there is limited variability in exposure contrasts.

In our interpretations, we attached more importance to two-pollutant models than single-pollutant models, acknowledging the difficulties in interpreting two-pollutant models. Given the similar performance of the SLR and RF model in explaining within-area variation (Table S9), and the fact that our analyses exploited primarily within-cohort exposure contrasts, we interpreted the two exposure methods equally. Therefore, we considered it more convincing when consistent associations between specific PM_{2.5} components and mortality were observed by applying two different exposure methods.

2.4.2 Sensitivity analyses

To evaluate the potential bias introduced by excluding participants with missing information on Model 3 covariates, we fitted Model 1 and Model 2 with participants with complete information on model 1 and model 2 covariates respectively.

To assess the sensitivity of our findings to using the 2010 exposures, we restricted analyses to follow-up periods starting from 2000, 2005 and 2008, with successively less temporal misalignment of the exposure model at the expense of shorter follow-up and fewer deaths.

To address potential residual confounding by socio-economic status (SES) factors, we further adjusted for individual level education, occupational status and additional neighborhood-level SES variables in cohorts that had such information.

All sensitivity analyses were performed for natural-cause mortality only.

All analyses were performed in R (version 3.4.0), using the packages *survival*, *coxme*, *Matrix*, *foreach*, *glmnet*, *multcomp*, *survey*, *splines*, *Hmisc*, *mfp*, *VIM*, *ggplot2*, *frailtySurv*, *survsim*, *eha* and *stamod*. Statistical significance was based on a 95% confidence interval of effect estimate, not including unity.

3. Results

3.1 Characteristics of the study population

The total study population in the main model 3 (the most adjusted model) consisted of 323,782 subjects, contributing 6,317,235 person-years at risk. Most of the cohorts started in the mid-1990s with follow-up until 2011–2015. Fifteen percent of the total population was excluded from all main analyses owing to missing exposure (0.5%), individual-level covariates (12.7%) or neighborhood-level mean income (1.8%). The excluded population was slightly younger (baseline age 46.4 ± 14.7) than the model 3 population (baseline age 48.7 ± 13.4). The proportion of females in the excluded population (64%) was slightly lower than in the model 3 population (66%). Table 1 and Tables S1 to S8 show the baseline characteristics of the participants in the individual sub-cohorts. The sub-cohorts differed in the number of participants, average years of follow-up, mean baseline age, percentage of female participants, lifestyle factors and neighborhood-level income, supporting the analysis accounting for difference in baseline hazards between sub-cohorts.

3.2 Exposure distribution and correlations

For Cu, Fe, K, S and Zn, concentrations were lower in the North European cohorts (i.e., CEANS, DCH and DNC; Figure S1) than in the other cohorts (Figure 1 and Table S11). The within-cohort contrast was substantial for Cu, Fe and Si and limited for K, Ni, S, V and Zn for both SLR- and RF-modeled exposures. Exposure distributions for the pooled cohort were similar for SLR- and RF-modeled estimates, although for most components the variability was smaller for RF. Our selected fixed increment reflected a larger exposure contrast than the interquartile ranges for most elements. For individual cohorts, large differences between the two algorithms were found, for example, S in the HNR study.

Correlations between exposure estimates derived from SLR and RF models were high for Cu and Fe (average within-cohort Spearman $r = 0.81$ for Cu, $r = 0.84$ for Fe) (Table 2). Correlations between SLR- and RF-modeled exposure were moderate for S, Si, Zn and low for K, Ni, V, with large variation between cohorts. We focused on within-cohort correlations because the epidemiological analysis exploited mostly within-cohort exposure contrast.

Correlations of composition with $PM_{2.5}$ mass were mostly low to moderate (average of cohort-specific Spearman r ranging from 0.13 to 0.49) for both SLR- and RF-modeled exposures (Table S12). Correlations with NO_2 were mostly high for Cu and Fe (average of cohort-specific Spearman $r > 0.7$) for both methods (Table S13). Correlations with $PM_{2.5}$ mass and/or NO_2 differed substantially in magnitude between cohorts, reflecting differences in study area size and the presence of major sources. Average of cohort-specific correlations between Cu and Fe were high, whereas both Cu and Fe were moderately correlated with Zn (Figure S2). Correlation between Ni and V modeled with the same algorithm was moderate, whereas the correlation was low when Ni and V were modeled with different algorithms.

Table 1. Population characteristics based on the observations included in model 3

Sub-cohort ^a	Population size (N) ^b	Persons in main model, Model 3 [n (%)] ^c	Baseline period	Follow-up	Average years of follow-up	Age at baseline (Mean $\pm$ SD)	Female (%)	Current smokers (%)	Overweight or obese [(BMI $\geq$ 25 kg/m ² (%)]	Married or living with partner (%)	Employed (%)
Pooled cohort	381,036	323,782 (85.0)	-	-	19.5	48.7 $\pm$ 13.4	66	24	43	72	70
CEANS-SDPP	7,835	7,716 (98.5)	1992–1998	2011	15.9	47.1 $\pm$ 4.9	61	26	52	84	91
CEANS-SIXTY	4,180	3,965 (94.9)	1997–1999	2014	15.5	60.0 $\pm$ 0.0	52	21	64	74	68
CEANS-SALT	6,724	6,174 (91.8)	1998–2003	2011	10.4	57.8 $\pm$ 10.6	55	21	40	68	64
CEANS-SNACK	3,248	2,830 (87.1)	2001–2004	2011	7.4	72.9 $\pm$ 10.4	62	14	53	46	23
DCH	56,308	52,779 (93.7)	1993–1997	2015	18.2	56.7 $\pm$ 4.4	53	36	56	71	78
DNC-1993	19,664	17,017 (86.5)	1993	2013	18.7	56.2 $\pm$ 8.4	100	37	28	68	70
DNC-1999	8,769	8,117 (92.6)	1999	2013	14.4	47.9 $\pm$ 4.2	100	29	30	76	95
EPIC-NL Morgen	20,711	18,292 (88.3)	1993–1997	2013	16.8	42.9 $\pm$ 11.3	55	35	49	65	69
EPIC-NL Prospect	16,194	14,570 (90.0)	1993–1997	2013	16.4	57.7 $\pm$ 6.1	100	23	55	77	51
HNR	4,809	4,733 (98.4)	2000–2003	2015	12.0	59.7 $\pm$ 7.8	50	24	74	75	40
E3N	53,521	38,537 (72.0)	1989–1991	2011	16.8	53.0 $\pm$ 6.8	100	13	21	83	68
KORA-S3	4,566	2,572 (56.3)	1994–1995	2011	15.6	49.4 $\pm$ 13.9	51	20	67	80	55
KORA-S4	4,257	2,281 (53.6)	1999–2001	2014	12.9	49.3 $\pm$ 13.8	51	23	69	79	59
VHM&PP	170,250	144,199 (84.7)	1985–2005	2014	23.1	42.1 $\pm$ 15.0	56	20	42	69	70

^a The Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) cohort (including SDPP, SIXTY, SALT, SNACK) is in Sweden; the Diet, Cancer and Health cohort (DCH) is in Denmark; the Danish Nurse Cohort (DNC) (consisting of two surveys conducted in 1993 and 1999) is in Denmark; the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort is in the Netherlands (including MORGEN and Prospect); the Heinz Nixdorf Recall study (HNR) is in Germany; the Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Éducation Nationale (E3N) is in France; the Cooperative Health Research in the Region of Augsburg (KORA) is in Germany (consisting of two surveys S3 and S4); the Voralberg Health Monitoring and Prevention Programme (VHM&PP) is in Austria.

^b Population size is the number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort

^c The missing data for individual cohorts are indicated in Table S1–S8.

Figure 1. Distribution of component exposure at participant addresses estimated from Supervised Linear Regression and Random Forest models

The boundary of the box closest to zero indicates P25; furthest from zero – P75; bold vertical line inside the box – P50; whiskers indicate P5 and P95; see Table S11 for exposure distribution of components for the pooled cohort. Sub-cohorts are shown from north to south.

Table 2. Spearman correlation coefficients between component exposure at participant addresses estimated from Supervised Linear Regression and Random Forest models (N=323,782)

Sub-cohort	PM _{2.5} Cu	PM _{2.5} Fe	PM _{2.5} K	PM _{2.5} Ni	PM _{2.5} S	PM _{2.5} Si	PM _{2.5} V	PM _{2.5} Zn
Average ^a	0.81	0.84	0.22	0.33	0.59	0.56	0.27	0.60
CEANS-SDPP	0.27	0.72	0.16	0.24	0.48	-0.01	0.16	0.27
CEANS-SIXTY	0.86	0.89	-0.09	0.44	0.39	0.76	-0.07	0.45
CEANS-SALT	0.88	0.91	-0.09	0.47	0.38	0.81	-0.11	0.44
CEANS-SNACK	0.86	0.90	0.49	0.47	0.79	0.70	0.39	0.53
DCH	0.94	0.89	-0.37	0.69	0.78	0.53	0.58	0.61
DNC-1993	0.80	0.79	0.31	0.45	0.72	0.43	0.35	0.63
DNC-1999	0.77	0.78	0.35	0.43	0.70	0.41	0.34	0.63
EPIC-NL-Morgen	0.92	0.93	0.82	0.89	0.20	0.59	0.7	0.52
EPIC-NL-Prospect	0.94	0.94	0.11	0.09	0.58	0.82	-0.22	0.71
HNR	0.81	0.70	-0.33	0.53	0.56	0.72	0.53	0.79
E3N	0.90	0.89	0.62	0.51	0.67	0.55	0.72	0.83
KORA-S3	0.71	0.84	0.23	-0.17	0.62	0.79	-0.03	0.55
KORA-S4	0.77	0.85	-0.03	0.10	0.59	0.85	0.22	0.67
VHM&PP	0.88	0.74	0.89	-0.51	0.79	-0.16	0.22	0.74

^a Average of cohort-specific correlation coefficients. Cohort-specific correlations are shown because the analyses mostly exploit within-cohort exposure contrasts (i.e. stratified by sub-cohort id).

3.3 Associations of PM_{2.5} composition with mortality

Natural mortality

During the follow-up, we observed 46,640 (14.4%) deaths from natural causes. Figure 2 and Table S14 show associations of PM_{2.5} composition with natural mortality. In the single-pollutant models, all components were significantly associated with natural mortality except for RF-modeled Ni and Si. For Cu, Fe, K, S, V and Zn, the HR point estimates were similar for SLR- and RF-modeled exposures with generally wider confidence intervals (CIs) for RF. For Ni and Si, HRs were above unity for SLR-modeled and essentially unity for RF-modeled exposures.

In two-pollutant models, HRs strongly attenuated for most components, while HRs remained stable for PM_{2.5} mass and NO₂ (Figure 2 and Table S14). For Cu and Fe, HR point estimates were similar for SLR- and RF-modeled exposures after adjustment for PM_{2.5} mass, with wider CIs observed for RF-modeled exposures. HRs for Cu and Fe decreased substantially and became mostly nonsignificant after adjustment for NO₂ with HRs being above unity for SLR and below unity for RF. HRs for K were attenuated though still significantly above unity for SLR and RF after adjustment for NO₂, whereas after adjustment for PM_{2.5} mass, the HRs reduced to unity for SLR but remained above unity for RF. For Ni, S, Si and Zn, HRs remained above unity and (almost) significant for SLR in two-pollutant models, whereas HRs reduced to essentially unity for RF. The HRs for V were reduced but remained above unity and (almost) significant in two-pollutant models, with similar estimates observed for SLR and RF.

We observed the strongest associations of natural mortality with all PM_{2.5} components in the minimally adjusted models (Model 1) (Table S15). HRs attenuated substantially after adjusting for individual level covariates (Model 2), except for K which remained stable. HRs increased slightly or remained stable

after further adjustment for area-level covariates (Model 3). This pattern was observed both for SLR- and RF-modeled exposures. For Cu, Fe, K, S, V and Zn, the HR point estimates were similar between SLR- and RF-modeled exposures for all three models, with generally wider CIs for RF. For Ni and Si, the effect estimates were larger for SLR- than for RF-modeled exposure in all models.

We generally observed linear or supra-linear concentration-response relationships for SLR-modeled elements and natural mortality (Figure S3). For some RF-modeled elements, there is no strong evidence of linear associations between exposure and mortality, mainly because of the limited variability in exposure concentrations.

Cause-specific mortality

We observed 15,492 (4.8%) deaths from cardiovascular diseases during the follow-up. HRs were significantly above unity for all components in single pollutant models except for RF-modeled Ni and Si, for which HRs were (nonsignificantly) below unity (Table S16). The magnitude of HR point estimates was similar to the HRs observed for natural mortality. In two-pollutant models, HRs for most components attenuated substantially, whereas HRs for PM_{2.5} and NO₂ remained stable. HRs for PM_{2.5} and NO₂ tended to be higher in models with RF-modeled than in SLR-modeled component exposure. With adjustment for NO₂, HRs for Cu and Fe remained above unity for SLR but became unity or below unity for RF. HR point estimates for SLR-modeled Ni, S and Si were above unity in two-pollutant models adjusting for PM_{2.5} mass or NO₂, whereas HRs were unity or below unity for RF. The HRs for V attenuated but remained above unity though nonsignificant after adjustment for PM_{2.5} mass or NO₂, with similar estimates for SLR and RF.

We observed 2,846 (0.9%) deaths from nonmalignant respiratory diseases during the follow-up. HRs above unity were observed for Cu, Fe, Ni and V with a similar magnitude for SLR- and RF-modeled exposures in single pollutant models (Table S17). For S, Si and Zn, HRs were above unity for SLR-modeled exposures, and were higher compared to RF-modeled exposures. HRs were close to unity for RF-modeled Si and Zn. In two-pollutant models, HRs remained stable after adjustment for PM_{2.5} mass. HRs were non-significantly below unity after adjustment for NO₂ for components modeled with both algorithms except for Ni and V, for which HRs attenuated but were still above unity for both SLR and RF. HRs for NO₂ were stable in all models. HRs for PM_{2.5} varied from below to above unity in the different models, most of them were insignificant.

We observed 3,776 (1.2%) deaths from lung cancer during the follow-up. HRs were above unity for all components in single pollutant models, though HRs for RF-modeled exposures were non-significant except for K, S and V (Table S18). In two-pollutant models with adjustment for PM_{2.5} mass or NO₂, HRs stayed stable for SLR-modeled S, whereas HRs reduced substantially though remained non-significantly above unity for RF-modeled S. HRs for most other components reduced to unity or below unity and became non-significant in two-pollutant models. HRs for PM_{2.5} mass and NO₂ remained stable in all models except for reduced HRs for SLR-modeled S.

Sensitivity analyses

Table S15 shows results derived from Model 1 using Model 1 and Model 3 populations, respectively, and results derived from Model 2 using Model 2 and Model 3 populations, respectively. The effect estimates were almost identical for the same model using different population, suggesting little selection bias was introduced by excluding subjects with missing covariates.

When restricting analyses to participants with follow-up time to after year 2000 (69% of total person-years at risk, 84% of total death), after year 2005 (46% of total person-years at risk, 64% of total death), and after year 2008 (32% of total person-years at risk, 47% of total death), we observed robust associations between PM_{2.5} composition and natural mortality (Table S19).

The effect estimates were not affected by additional adjustment for individual level education, occupational status (Table S20) and additional neighborhood-level SES variables (Table S21) in cohorts that had such information.

Figure 2. Associations of PM_{2.5} composition with natural mortality in single pollutant and two-pollutant models

Total number of observations = 323,782; person-years at risk = 6,317,235; number of death from natural mortality = 46,640.
HR = Hazard Ratio, SLR = Supervised Linear Regression model, RF = Random Forest model
HR (95% confidence interval) presented for the following increments: PM_{2.5} Cu – 5 ng/m³, PM_{2.5} Fe – 100 ng/m³, PM_{2.5} K – 50 ng/m³, PM_{2.5} Ni – 1 ng/m³, PM_{2.5} S – 200 ng/m³, PM_{2.5} Si – 100 ng/m³, PM_{2.5} V – 2 ng/m³, PM_{2.5} Zn – 10 ng/m³; see Table S14 for corresponding numeric data
Main model adjusted for sub-cohort id, age, sex, year of enrollment, smoking (status, duration, intensity, intensity²), BMI categories, marital status, employment status and 2001 neighborhood-level mean income
In two-pollutant models, PM_{2.5} mass and NO₂ exposures were estimated using SLR only.

4. Discussion

We observed an elevated risk of mortality associated with long-term exposure to most PM_{2.5} elemental components in single pollutant models. In two-pollutant models with adjustment for PM_{2.5} mass or NO₂, effect estimates were attenuated for almost all component-outcome pairs. Effect estimates for SLR- and RF-modeled exposures agreed well in single pollutant models, except for Ni and Si, for which effect estimates for RF were lower. Effect estimates for RF modeled exposures were generally lower than for SLR in two-pollutant models.

4.1 Comparison with previous studies

Only a limited number of epidemiological studies have assessed associations between mortality and long-term exposure to PM_{2.5} elemental components. Among the components studied, sulfate has received the most attention. Sulfate is a secondary pollutant produced by atmospheric reactions of sulfur dioxide (SO₂) emitted by combustion of S-containing liquid and solid fuels. Because sulfate is primarily in the fine particle fraction, sulfate may travel for large distances, resulting in a relatively small within study area variability. Another important source is sea salt sulfate which is predominately in the coarse fraction but has a small fraction also in PM_{2.5} that is long-range transported (Belis et al., 2013). The California Teachers Study (Ostro et al., 2011) reported an increased hazard ratio (HR) of 1.06 (95% CI: 0.97, 1.16) for natural cause mortality in association with a 2.2 µg/m³ increase in PM_{2.5} sulfate concentration, translating into a HR of 1.02 per 200 ng/m³ (the exposure contrast used in our analyses), assuming all S is present as sulfate (sulfate to S ratio of 3). Analyses of the ACS CPS-II data suggested that long-term PM_{2.5} S exposure was associated with all-cause mortality (HR ranged from 1.01 to 1.03 per 528.8 ng/m³ depending on the models) (Thurston et al., 2013). In ESCAPE, robust associations of PM_{2.5} S exposure with natural mortality were found (Beelen et al., 2015). The effect estimate observed in ESCAPE was similar to the estimate in the present study (HR 1.14, 95% CI: 1.06, 1.23 per 200 ng/m³ in ESCAPE; HR 1.14, 95% CI: 1.11, 1.17 and HR 1.13, 95% CI: 1.08, 1.18 per 200 ng/m³ for SLR- and RF-modeled exposures, respectively, in ELAPSE). In the present study we obtained a much narrower confidence interval, probably due to the longer follow-up and the pooling of cohort data. The effect estimate of S in our study was much larger than the estimates from the U.S. cohorts. One major difference is that the U.S. cohorts investigated between-area contrasts only whereas both ELAPSE and ESCAPE focused on within-area contrasts. Because the transported sulfate has relatively uniform spatial variation at the city scale, the exposure contrast was much smaller in our study than in the U.S. studies, thus a small effect in our study could be inflated when adopting it to the same increment of exposure as in the U.S. studies. Another explanation might be that we measured elemental composition between 2008 and 2011, when emission of SO₂ had decreased compared to the baseline of all cohorts (EEA, 2015). The health effects in our study populations may be partly related to exposure levels and contrasts of 20 y ago (most cohorts have baselines in the 1990s). Therefore, our S-related magnitude of health effect estimates may be overestimated.

In the present study, we also found robust associations between S and lung cancer mortality, which was observed in ACS CPS-II as well (Thurston et al., 2013). The effect estimates for lung cancer mortality were larger than for natural-cause mortality, with wider confidence intervals. In ESCAPE, robust associations were observed for S and lung cancer incidence (Raaschou-Nielsen et al., 2016). We observed elevated associations of S with cardiovascular mortality, which is consistent with previous findings in ESCAPE (Wang et al., 2014; Wolf et al., 2015) and in one of the ELAPSE sub-cohorts (i.e. the DCH cohort). The latter study reported an elevated risk of cardiovascular mortality associated with long-term exposure to secondary inorganic aerosols (Hvidtfeldt et al., 2019). The Women's Health Initiative-Observational Study (WHI-OS) found no association of sulfur with cardiovascular deaths (HR 1.01, 95% CI: 0.92, 1.12 per 0.25 µg/m³), but a statistically significant association with cardiovascular events (HR 1.09, 95% CI: 1.05, 1.14 per 0.25 µg/m³) (Vedal et al., 2013). In the California Teachers Study, IHD mortality was associated with long-term exposure to sulfate (Ostro et al., 2011) and high-S content fuel combustion (Ostro et al., 2015).

Both Ni and V are suggested to be tracers of mixed industrial/ fuel-oil combustion and derived mainly from shipping emissions in Europe (Viana et al., 2008). Our study found a positive association of natural mortality with long-term exposure to Ni (HR 1.08, 95% CI 1.06, 1.11 per 1 ng/m³) for SLR- and no association for RF-modeled exposures (HR 1.01, 95% CI 0.97, 1.05 per 1 ng/m³). Our study found positive associations of natural mortality with long-term exposure to V (HR 1.06, 95% CI 1.04, 1.08 and HR 1.09, 95% CI 1.05, 1.14 per 2 ng/m³ for SLR- and RF-modeled exposures respectively). The effect estimates are similar to the estimates in ESCAPE for natural mortality (HR for Ni 1.05, 95% CI 0.97, 1.13 per 1 ng/m³; HR for V 1.07, 95% CI 0.93, 1.23 per 2 ng/m³) (Beelen et al., 2015), with much narrower CIs in ELAPSE. In ESCAPE, the accuracy of exposure estimates for Ni and V was limited because of the absence of specific sources of Ni and V in several study areas combined with limited measurement precision especially in areas with low pollution levels (de Hoogh et al., 2013). The Europe-wide models made use of both within and between area measurement contrasts and resulted in models with good performance for Ni and V (Chen et al., 2020). Compared to ESCAPE, the ELAPSE models further added industrial source data as potential predictors which improved the model performance. The improved exposure assessment may have allowed us to better detect the potential component-mortality associations. Our study also observed consistently positive associations between V and cause-specific mortality. Only a few studies have reported associations of mortality or morbidity with long-term exposure to Ni and V. In ESCAPE, association was found between PM₁₀ Ni exposure and lung cancer incidence (Raaschou-Nielsen et al., 2016). In the Medicare population, stronger associations between long-term PM_{2.5} exposure and mortality were found for PM_{2.5} with higher V content (Wang et al., 2017). In the ACS CPS-II, associations between IHD mortality and Ni were reported (Thurston et al., 2013). The observed associations of Ni and V with mortality could be due to the components per se or to other components in emissions from oil combustion. Studies have suggested V in PM_{2.5} can induce oxidative stress, which is considered central to producing many of the negative health effects attributed to PM (Kelly and Fussell, 2020; Zhang et al., 2009). However, there is no stronger support from experimental studies for effects of V than for Ni, Fe and Cu, for which oxidative stress is also a major pathway.

In the present study, the effect estimates for the traffic-related components Cu and Fe remained after adjustment for PM_{2.5} mass but were reduced substantially after adjustment for NO₂. The modestly wider confidence intervals for models with PM_{2.5} mass compared to the single pollutant models suggest these models provide interpretable results. Confidence intervals in two-pollutant models with NO₂ widened somewhat more, due to the high correlations of Cu and Fe with NO₂ in our study. Therefore, the substantial attenuation in effect estimates for Cu and Fe should be interpreted with caution, because effects of NO₂ vs. those from Cu or Fe cannot be separated well. The high correlations of Cu and Fe with NO₂ (average R of 0.75) in our study are consistent with correlations observed in the measured elemental components (R>0.75) that were used to develop the models (Tsai et al., 2015), suggesting the high correlations were not artificially introduced by the modeling methodology. Previous studies found mixed results regarding associations of mortality with Cu and Fe. Using LUR models developed in ESCAPE, the Rome longitudinal study found associations of mortality with Cu and Fe in PM_{2.5} as well as tracers of tailpipe (i.e., PM_{2.5} absorbance) (Badaloni et al., 2017), but in the Badaloni study, no adjustment for NO₂ was made. Positive associations were observed in the California Teachers Study between Fe and IHD mortality, but not with natural-cause, cardiopulmonary or pulmonary mortality (Ostro et al., 2011). Although the Ostro study did not adjust for NO₂ or PM_{2.5} mass, adjustment for organic carbon did substantially reduced HRs. Analyses of ACS CPS-II data showed that traffic-related exposure was less strongly associated with excess mortality compared to coal combustion-related exposure (Thurston et al., 2013). However the ACS CPS-II study might have underestimated the effects of traffic-related air pollution because it investigated between-city variation, which represents only a small part of the expected overall variation in traffic-related air pollution.

Although Zn was *a priori* selected in ESCAPE to represent non-tailpipe traffic emissions, our Europe-wide models showed that a large fraction of the variation in the Zn measurements was explained by

predictors representing industrial Zn emission (Chen et al., 2020), consistent with Zn being also a tracer for particles from industrial sources. This is consistent with source apportionment analyses in the ACS CPS-II, where Zn was considered as a source identifier for the metals industry (Thurston et al., 2016). The moderate correlations between Zn and NO₂ (average R of 0.51 and 0.54 for SLR- and RF-modeled Zn, respectively), suggest that Zn was not only related to traffic emission. The Rome longitudinal study found positive associations between PM_{2.5} Zn and mortality from natural causes, cardiovascular diseases and IHD, using LUR models developed in ESCAPE (Badaloni et al., 2017). The ACS CPS-II also found some evidence of positive associations between Zn and mortality (Thurston et al., 2013). In the California Teachers Study, positive associations between Zn and IHD mortality were reported, but not with natural-cause, cardiopulmonary or pulmonary mortality (Ostro et al., 2011). Our study did not find clear evidence for associations of Zn with natural-cause or cause-specific mortality in two-pollutant models.

K was selected to represent biomass burning emission in ESCAPE (Tsai et al., 2015). While our new model included a plausible background predictor for biomass combustion (satellite-modeled organic matter), the model may have limited ability to capture within-area variability of biomass combustion emission because of the lack of reliable fine-scale predictor variables (Chen et al., 2020). Our study found elevated HRs for K exposure associated with mortality from natural-cause, cardiovascular diseases and lung cancer. HRs decreased after adjustment for PM_{2.5} mass to close to unity for SLR-based exposure, while they remained (significantly) elevated for RF exposures. K was reported to be associated with coronary events in ESCAPE (Wolf et al., 2015). K in ESCAPE was rather related to traffic (e.g., from resuspension of road dust) than to biomass burning. The California Teachers Study found positive associations between IHD mortality and K (Ostro et al., 2011), whereas the ACS CPS-II consistently observed null association between K and mortality (Thurston et al., 2013).

Si was selected to represent crustal material, which is abundant in coarse particles. There was little evidence for an association between long-term coarse PM exposure and mortality (Adar et al., 2014; Hoek et al., 2013). The 2019 Integrated Science Assessment (ISA) rated the association between PM_{coarse} exposure and natural-cause mortality as “suggestive” (EPA, 2019). Our study found positive associations in single and two-pollutant models for PM_{2.5} Si based upon SLR models, whereas associations were null or negative for RF models. The ACS CPS-II found that Si was consistently not associated with mortality across all models (Thurston et al., 2013). A negative and marginal association was observed for CVD events with Si in WHI-OS (Vedal et al., 2013). In contrast, analyses in the California Teachers Study showed positive associations of IHD mortality with Si (Ostro et al., 2011).

4.2 Effect estimates using SLR- and RF-modeled exposures

For most components, we observed generally consistent elevated mortality risks for SLR- and RF-modeled exposures in single pollutant models. However, less consistent associations for exposures by RF than SLR were found in two-pollutant models especially after adjusting for NO₂. We do not have a clear explanation for these differences. There is no clear pattern of differences related to the spatial distribution of the components. We found differences both for components with a strong local contribution such as Cu and components with a predominantly large-scale variation such as S. The less consistent association for RF-modeled exposure in two-pollutant models is not due to different correlation of components with PM_{2.5} mass or NO₂, which were similar for RF- and SLR-modeled exposures. The two sets of models had similar performance in explaining within-area variability in internal cross-validations (Chen et al., 2020), which is the exposure contrast primarily exploited in the current analysis. The comparison of performance of the two algorithms is limited because we did not have external validation measurements. We therefore had no prior knowledge of which models had lower biases. We observed that the predicted variability of exposure was less for RF, explaining the wider confidence intervals in the epidemiological analyses using RF-modeled exposures. We note that RF models are more difficult to interpret in terms of how predictor variables act in the models, so a full analysis of the difference of specific predictors in the two algorithms is not possible.

4.3 Strengths and limitations

One important strength is the highly standardized dataset used in this study, which was pooled from eight European cohorts with detailed individual and area-level covariate information, including smoking and BMI, which involved harmonizing variables between cohorts. The pooling of data allowed for more statistical power in our current analyses compared to the previous ESCAPE analyses. Another strength is the improvement in exposure assessment compared to ESCAPE. Analyses in ESCAPE may have had limited ability to detect component-specific mortality associations for Ni and V because of the lack of specific predictors in the exposure models for these components (de Hoogh et al., 2013). The Europe-wide PM_{2.5} composition models were able to make use of specific predictors representing pollution sources such as industrial sources, which explained a large proportion of the variation in measurements of specific components such as Zn (Chen et al., 2020). The Europe-wide models were developed based on a large number of measurement sites combined from individual ESCAPE study areas. A previous study has suggested that underestimation of the effect estimates was less serious when a large number of measurement sites was used for LUR modeling (Basagana et al., 2013).

One main limitation of our study is that the exposure models were developed based on measurements made in 2008–2011, whereas most included cohorts started in the mid-1990s. In the present study, we were not able to apply back-extrapolated exposure for PM_{2.5} components because we had insufficient information on the concentration of PM_{2.5} components in Europe over time. However, our results were robust when restricting the follow-up period to more recent start dates (year 2000, 2005 and 2008), indicating the impact of temporal misalignment by applying 2010 exposures was limited. Several studies in Europe have reported that the spatial contrast of NO₂ remained stable for periods up to 10 y (Cesaroni et al., 2012; Eeftens et al., 2011; Gulliver et al., 2013), suggesting that spatial contrast for traffic-related components such as Cu and Fe may be stable over time. For Cu and Fe contrasts may actually be more stable, given that non-tailpipe emissions have not been regulated, as opposed to tailpipe emissions. We cannot rule out the possibility that spatial contrast for components from other sources may have been less stable. For example the magnitude of our sulfur-related health estimates might be overestimated because of decreased SO₂ emission over the years (EEA, 2015), which possibly resulted in a smaller contrast in sulfate exposure. The spatial pattern of major sources has likely not changed in a major way (Belis et al., 2013; Viana et al., 2008). Another limitation of the present study is that we did not consider residential mobility during follow-up. This may have resulted in measurement error, likely nondifferential and resulting in bias toward the null (Armstrong, 1998). The decision to focus on within-cohort exposure contrasts limited our ability to assess associations with components with relatively small within-area exposure contrasts such as S. However, we considered the potential confounding related to unmeasured differences between cohorts more critical. Last, the exposure maps for RF-modeled K, Ni and V showed strong boundary effects that might affect the exposure estimates for some participants in the E3N cohort (Chen et al., 2020). However, we expected limited impact on the health effect estimation because few people live at the borders and the correlations between SLR- and RF-modeled estimates did not stand out for these three elements, nor the E3N cohort.

5. Conclusions

Long-term exposures to especially vanadium in PM_{2.5} was associated with increased mortality risk, with associations observed for both SLR- and RF-modeled exposures. For the other components, associations were generally weaker when exposure was assessed with RF compared to SLR in two-pollutant models. The consistency between SLR and RF could reflect the suitability of the models for estimating components rather than being evidence of a stronger effect on mortality.

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Supplementary Information

Area-level socio-economic status (SES) variable harmonization

In the ELAPSE study manual (version 2, 31-10-2016) we identified that area-level SES variables were needed as potential confounders in the epidemiological analysis of the pooled cohort and the administrative cohorts. The Area-level SES Workgroup identified that harmonized SES data were not available from European databases for the neighborhood-scale. Therefore all local partners were asked to obtain the area-level SES data. We specified what data should be obtained and linked to the cohort data.

The area-level SES variables we aimed to obtain included composite score (combining different dimensions in one overall score), mean household income, low household income rate, income support rate, unemployment rate, low education rate, high education rate and ethnicity.

All variables were collected for a small area (neighborhood) and large area (region) to allow for confounding at commonly used spatial scales in previous cohort studies, realizing that not all data are necessary.

A **neighborhood** is a part of a city, with about 1,000 – 10,000 people. Ideally, we use a standard definition, referring to externally defined areas. If this is not available, postal codes were used, if they refer to the approximate number of people defined above. Examples include “buurt” and “wijk” in the Netherlands including on average 1,400 and 6,000 subjects; parish or census district (~4,300 subjects) in Denmark. Quite a few of the ESCAPE cohorts have used municipality (or local administrative unit 2 (LAU2, former NUTS5)) in the ESCAPE project. We now aimed at a finer spatial scale, given that many of the included ESCAPE cohorts include a large metropolitan area with surrounding smaller towns. For smaller towns (e.g. below 10,000 subjects), the town (community) level was deemed to be fine. In some countries, data are available for multiple scales within the specified range. Availability of type of data (in multiple years) and comparability with other cohorts were criteria to select the scale. A very fine scale e.g. below 1,000 subjects is problematic for computational reasons (random effect models), particularly if the outcome is relatively rare.

The **region** is important for national cohorts. Each cohort defined this locally and judged whether a region scale is needed. When both a neighborhood and region scale is used, neighborhood should be nested within region.

SES has multiple dimensions, including income, education, occupation and employment. We use national composite scores that combine the different dimensions and in addition the main individual components as the association with air pollution and health may differ between dimensions. SES scores at regional scale were calculated by aggregating the raw variables to region level and then calculate the SES score.

Table S1. Characteristics of the Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) cohort

All participants resided in Stockholm County, Sweden. The cohort is comprised of four sub-cohorts: The Stockholm Diabetes Preventive Program (SDPP) is a population-based prospective study of 7,949 subjects aged 35–54 years. The Stockholm Cohort of 60-year-olds (SIXTY) sub-cohort consists of a random population sample of one-third of all men and women living in Stockholm County turning 60 years between August 1997 and March 1999. The Screening Across the Lifespan Twin Study (SALT) sampled 7,043 individuals from the Swedish Twin Register born 1958 and earlier, who lived in Stockholm County. Lastly, The Swedish National Study of Aging and Care in Kungsholmen (SNAC-K) randomly sampled individuals 60+ years of age from a central area in Stockholm.

		CEANS, sub-cohorts			
Variable		SDPP	SIXTY	SALT	SNAC-K
Baseline year, range		1992–1998	1997–1999	1998–2003	2001–2004
Enrolled, N ^a		7,835	4,180	6,724	3,248
Included in mortality analyses		7,716 ^b	3,965 ^c	6,174 ^d	2,830 ^e
Deaths, N (%)					
	Natural cause	337 (4.4)	593 (15.0)	891 (14.4)	960 (33.9)
	Cardiovascular diseases	74 (1.0)	163 (4.1)	326 (5.3)	416 (14.7)
	Respiratory diseases	12 (0.2)	38 (1.0)	57 (0.9)	61 (2.2)
	Lung Cancer	39 (0.5)	46 (1.2)	55 (0.9)	26 (0.9)
Age at baseline, yrs (mean ± SD)		47.1 ± 4.9	60.0 ± 0.0	57.8 ± 10.6	72.9 ± 10.4
Women, N (%)		4,721 (61.2)	2,065 (52.1)	3,416 (55.3)	1,767 (62.4)
Employed, N (%)		7,005 (90.8)	2,684 (67.7)	3,976 (64.4)	656 (23.2)
Marital status, N (%)					
	Single	1,271 (16.5)	182 (4.6)	863 (14.0)	459 (16.2)
	Married	6,445 (83.5)	2,930 (73.9)	4,179 (67.7)	1,300 (45.9)
	Divorced	-	649 (16.4)	693 (11.2)	388 (13.7)
	Widowed	-	204 (5.1)	439 (7.1)	683 (24.1)
Smoking status, N (%)					
	Current	2,035 (26.4)	839 (21.2)	1,311 (21.2)	404 (14.3)
	Previous	2,811 (36.4)	1,520 (38.3)	2,058 (33.3)	1,079 (38.1)
	Never	2,870 (37.2)	1,606 (40.5)	2,805 (45.4)	1,347 (47.6)
Smoking intensity ^{af} , g/d (mean ± SD)		13.5 ± 7.4	13.4 ± 7.6	12.7 ± 8.0	11.7 ± 8.2
Smoking duration ^{af} , yrs (mean ± SD)		27.9 ± 8.6	36.3 ± 9.9	37.9 ± 9.3	43.3 ± 13.6
BMI, kg/m ² , N (%)					
	< 18.5	54 (0.7)	26 (0.7)	94 (1.5)	78 (2.8)
	18.5–24.9	3,688 (47.8)	1,397 (35.2)	3,622 (58.7)	1,251 (44.2)
	25.0–29.9	3,007 (39.0)	1,767 (44.6)	2,054 (33.3)	1,134 (40.1)
	30.0+	967 (12.5)	775 (19.5)	404 (6.5)	367 (13.0)
Neighborhood income ^g (mean ± SD)		24.3 ± 4.2	24.7 ± 6.9	25.3 ± 6.6	28.7 ± 2.2

^aThe number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort

^bSubjects were excluded due to missing exposure (11), smoking status (6), smoking duration (23), smoking intensity (7), BMI (25), marital status (34), employment status (29), neighborhood income (4).

^cSubjects were excluded due to missing exposure (4), smoking status (124), smoking duration (171), smoking intensity (124), marital status (122), employment status (158).

^dSubjects were excluded due to missing exposure (2), smoking status (170), smoking duration (447), smoking intensity (170), BMI (253), marital status (103), employment status (29).

^eSubjects were excluded due to fail in logical checks (1), missing smoking status (88), smoking duration (183), smoking intensity (139), BMI (290), marital status (7), employment status (73), neighborhood income (4).

^fFor current smokers

^gEUR per 1,000, year 2001

References: (Eriksson et al., 2008; Lagergren et al., 2004; Lichtenstein et al., 2006; Wandell et al., 2007)

Table S2. Characteristics of the Diet, Cancer and Health (DCH) cohort

Participants were recruited among persons aged 50–64 years from the areas of greater Copenhagen and Aarhus, Denmark, who were born in Denmark and free of cancer at baseline.

Variable	DCH
Baseline year, range	1993–1997
Enrolled, N ^a	56,308
Included in mortality analyses ^b	52,779
Deaths, N (%)	
Natural cause	10,490 (19.9)
Cardiovascular diseases	2,143 (4.1)
Respiratory diseases	861 (1.6)
Lung Cancer	1,282 (2.4)
Age at baseline, yrs (mean ± SD)	56.7 ± 4.4
Women, N (%)	27,709 (52.5)
Employed, N (%)	41,313 (78.3)
Marital status, N (%)	
Single	3,220 (6.1)
Married	37,665 (71.4)
Divorced	8,980 (17.0)
Widowed	2,914 (5.5)
Smoking status, N (%)	
Current	19,175 (36.3)
Previous	14,685 (27.8)
Never	18,919 (35.8)
Smoking intensity ^c , g/d (mean ± SD)	16.5 ± 9.0
Smoking duration ^c , yrs (mean ± SD)	36.3 ± 7.7
BMI, kg/m ² , N (%)	
< 18.5	414 (0.8)
18.5–24.9	22,781 (43.2)
25.0–29.9	21,941 (41.6)
30.0+	7,643 (14.5)
Neighborhood income ^d (mean ± SD)	20.1 ± 3.4

^aThe number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort

^bSubjects were excluded due to missing exposure (907), smoking status (75), smoking duration (433), smoking intensity (1062), BMI (42), marital status (461), employment status (309), neighborhood income (930).

^cFor current smokers

^dEUR per 1,000, year 2001

Reference: (Tjønneland et al., 2007)

Table S3. Characteristics of the Danish Nurse Cohort (DNC)

The cohort was sampled among members of The Danish Nurse Organization (DNO) including both working and retired nurses. Questionnaires were mailed in 1993 to members aged 45+ years and again in 1999 with the inclusion of new members (45+ years).

		DNC, sub-cohorts	
Variable		DNC-1993	DNC-1999
Baseline year		1993	1999
Enrolled, N ^a		19,664	8,769
Included in mortality analyses		17,017 ^b	8,117 ^c
Deaths, N (%)			
	Natural cause	3,997 (23.5)	309 (3.8)
	Cardiovascular diseases	937 (5.5)	50 (0.6)
	Respiratory diseases	359 (2.1)	14 (0.2)
	Lung Cancer	351 (2.1)	30 (0.4)
Age at baseline, yrs (mean $\pm$ SD)		56.2 $\pm$ 8.4	47.9 $\pm$ 4.2
Women, N (%)		17,017 (100.0)	8,117 (100.0)
Employed, N (%)		11,907 (70.0)	7,693 (94.8)
Marital status, N (%)			
	Single	1,799 (10.6)	757 (9.3)
	Married	11,511 (67.6)	6,154 (75.8)
	Divorced	2,111 (12.4)	1,043 (12.8)
	Widowed	1,596 (9.4)	163 (2.0)
Smoking status, N (%)			
	Current	6,373 (37.5)	2,320 (28.6)
	Previous	4,864 (28.6)	2,646 (32.6)
	Never	5,780 (34.0)	3,151 (38.8)
Smoking intensity ^d , g/d (mean $\pm$ SD)		13.9 $\pm$ 8.2	13.3 $\pm$ 7.3
Smoking duration ^d , yrs (mean $\pm$ SD)		31.6 $\pm$ 9.9	27.1 $\pm$ 7.1
BMI, kg/m ² , N (%)			
	< 18.5	499 (2.9)	142 (1.7)
	18.5–24.9	11,742 (69.0)	5,539 (68.2)
	25.0–29.9	3,893 (22.9)	1,897 (23.4)
	30.0+	883 (5.2)	539 (6.6)
Neighborhood income ^e (mean $\pm$ SD)		19.2 $\pm$ 2.6	19.0 $\pm$ 2.4

^aThe number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort

^bSubjects were excluded due to missing exposure (32), smoking status (922), smoking duration (1641), smoking intensity (1314), BMI (156), marital status (201), employment status (590), neighborhood income (81).

^cSubjects were excluded due to missing exposure (11), smoking status (30), smoking duration (165), smoking intensity (190), BMI (40), marital status (42), employment status (310).

^dFor current smokers

^eEUR per 1,000, year 2001

Reference: (Hundrup et al., 2012)

Table S4. Characteristics of the European Prospective Investigation into Cancer and Nutrition, the Netherlands (EPIC-NL)

The EPIC-NL combines two Dutch EPIC-cohorts: The Monitoring Project on Risk Factors and chronic diseases in the Netherlands (MORGEN) cohort which consists of a general population sample aged 20–59 years from three Dutch towns (Amsterdam, Doetinchem and Maastricht). Prospect is a prospective cohort study among women aged 49–70, residing in the city of Utrecht or its vicinity, who participated in the nation-wide Dutch breast cancer screening programme between 1993 and 1997.

		EPIC-NL, sub-cohorts	
Variable		MORGEN	PROSPECT
Baseline year		1993–1997	1993–1997
Enrolled, N ^a		20,711	16,194
Included in mortality analyses		18,292 ^b	14,570 ^c
Deaths, N (%)			
	Natural cause	1,180 (6.5)	1,997 (13.7)
	Cardiovascular diseases	261 (1.4)	459 (3.2)
	Respiratory diseases	63 (0.3)	126 (0.9)
	Lung Cancer	160 (0.9)	168 (1.2)
Age at baseline, yrs (mean ± SD)		42.9 ± 11.3	57.7 ± 6.1
Women, N (%)		10,051 (54.9)	14,570 (100.0)
Employed, N (%)		12,571 (68.7)	7,402 (50.8)
Marital status, N (%)			
	Single	4629 (25.3)	836 (5.7)
	Married	11,916 (65.1)	11,179 (76.7)
	Divorced	1,380 (7.5)	1,172 (8.0)
	Widowed	367 (2.0)	1,383 (9.5)
Smoking status, N (%)			
	Current	6,357 (34.8)	3,335 (22.9)
	Previous	5,153 (28.2)	4,795 (32.9)
	Never	6,782 (37.1)	6,440 (44.2)
Smoking intensity ^d , g/d (mean ± SD)		15.7 ± 8.6	13.7 ± 8.7
Smoking duration ^d , yrs (mean ± SD)		24.8 ± 10.6	36.8 ± 7.6
BMI, kg/m ² , N (%)			
	< 18.5	188 (1.0)	87 (0.6)
	18.5–24.9	9,122 (49.9)	6,505 (44.6)
	25.0–29.9	6,869 (37.6)	5,790 (39.7)
	30.0+	2,113 (11.6)	2,188 (15.0)
Neighborhood income ^e (mean ± SD)		12.2 ± 1.6	13.1 ± 1.4

^aThe number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort

^bSubjects were excluded due to fail in logical checks (28), missing exposure (11), smoking status (34), smoking duration (326), smoking intensity (1517), BMI (5), marital status (75), employment status (830), neighborhood income (2).

^cSubjects were excluded due to fail in logical checks (1), missing smoking status (100), smoking duration (374), smoking intensity (716), BMI (20), marital status (101), employment status (104), neighborhood income (883).

^dFor current smokers

^eEUR per 1,000, year 2001

Reference: (Beulens et al., 2010)

Table S5. Characteristics of the Heinz Nixdorf Recall study (HNR)

The cohort consists of randomly sampled persons aged 45 to 75 years from the Ruhr area, Germany primarily in the three adjacent large cities Bochum, Essen, and Mülheim.

Variable		HNR
Baseline year, range		2000–2003
Enrolled, N ^a		4,809
Included in mortality analyses ^b		4,733
Deaths, N (%)		
	Natural cause	694 (14.7)
	Cardiovascular diseases	190 (4.0)
	Respiratory diseases	44 (0.9)
	Lung Cancer	63 (1.3)
Age at baseline, yrs (mean ± SD)		59.7 ± 7.8
Women, N (%)		2,382 (50.3)
Employed, N (%)		1,895 (40.0)
Marital status, N (%)		
	Single	274 (5.8)
	Married	3,538 (74.8)
	Divorced	472 (10.0)
	Widowed	449 (9.5)
Smoking status, N (%)		
	Current	1,113 (23.5)
	Previous	1,619 (34.2)
	Never	2,001 (42.3)
Smoking intensity ^c , g/d (mean ± SD)		18.6 ± 12.0
Smoking duration ^c , yrs (mean ± SD)		34.5 ± 9.4
BMI, kg/m ² , N (%)		
	< 18.5	16 (0.3)
	18.5–24.9	1,237 (26.1)
	25.0–29.9	2,171 (45.9)
	30.0+	1,309 (27.7)
Neighborhood income ^d (mean ± SD)		25.2 ± 8.2

^aThe number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort

^bSubjects were excluded due to missing smoking status (10), smoking duration (49), smoking intensity (14), BMI (29), marital status (12), employment status (15).

^cFor current smokers

^dEUR per 1,000, year 2001

Reference: (Schmermund et al., 2002)

Table S6. Characteristics of the Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N)

The cohort was selected among French women aged 40 to 65 years who were insured through a national health system that primarily covered teachers. The cohort is nation-wide.

Variable	E3N
Baseline year, range	1989–1991
Enrolled, N ^a	53,521
Included in mortality analyses ^b	38,537
Deaths, N (%)	
Natural cause	1,941 (5.0)
Cardiovascular diseases	266 (0.7)
Respiratory diseases	59 (0.2)
Lung Cancer	132 (0.3)
Age at baseline, yrs (mean ± SD)	53.0 ± 6.8
Women, N (%)	38,537 (100.0)
Employed, N (%)	26,158 (67.9)
Marital status, N (%)	
Single	6,436 (16.7)
Married	32,101 (83.3)
Divorced	-
Widowed	-
Smoking status, N (%)	
Current	4,988 (12.9)
Previous	7,411 (19.2)
Never	26,138 (67.8)
Smoking intensity ^c , g/d (mean ± SD)	11.3 (9.2)
Smoking duration ^c , yrs (mean ± SD)	28.5 (7.6)
BMI, kg/m ² , N (%)	
< 18.5	1,386 (3.6)
18.5–24.9	29,205 (75.8)
25.0–29.9	6,574 (17.1)
30.0+	1,372 (3.6)
Neighborhood income ^d (mean ± SD)	11.2 ± 3.0

^aThe number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort

^bSubjects were excluded due to fail in logical checks (14), missing exposure (629), smoking duration (8211), smoking intensity (9729), BMI (2644), marital status (1989), neighborhood income (222).

^cFor current smokers

^dEUR per 1,000, year 2001

Reference: (Clavel-Chapelon and Group, 2015)

Table S7. Characteristics of the Cooperative Health Research in the Region of Augsburg (KORA)

Two cross-sectional population-representative surveys were conducted in 1994-1995 (survey S3) and 1999-2001 (survey S4) in the city of Augsburg and two adjacent rural counties including inhabitants of German nationality aged 25 to 74.

		KORA, sub-cohorts	
Variable		S3	S4
Baseline year, range		1994–1995	1999–2001
Enrolled, N ^a		4,566	4,257
Included in mortality analyses		2,572 ^b	2,281 ^c
Deaths, N (%)			
	Natural cause	391 (15.2)	215 (9.4)
	Cardiovascular diseases	159 (6.2)	72 (3.2)
	Respiratory diseases	33 (1.3)	20 (0.9)
	Lung Cancer	25 (1.0)	19 (0.8)
Age at baseline, yrs (mean ± SD)		49.4 ± 13.9	49.3 ± 13.8
Women, N (%)		1,308 (50.9)	1,173 (51.4)
Employed, N (%)		1,423 (55.3)	1,356 (59.4)
Marital status, N (%)			
	Single	227 (8.8)	184 (8.1)
	Married	2,060 (80.1)	1,807 (79.2)
	Divorced	108 (4.2)	151 (6.6)
	Widowed	177 (6.9)	139 (6.1)
Smoking status, N (%)			
	Current	519 (20.2)	523 (22.9)
	Previous	740 (28.8)	720 (31.6)
	Never	1,313 (51.0)	1,038 (45.5)
Smoking intensity ^d , g/d (mean ± SD)		16.5 ± 9.5	15.7 ± 9.5
Smoking duration ^d , yrs (mean ± SD)		25.2 ± 12.1	24.3 ± 11.6
BMI, kg/m ² , N (%)			
	< 18.5	13 (0.5)	8 (0.4)
	18.5–24.9	837 (32.5)	710 (31.1)
	25.0–29.9	1,116 (43.4)	996 (43.7)
	30.0+	606 (23.6)	567 (24.9)
Neighborhood income ^e (mean ± SD)		36.7 ± 4.4	38.0 ± 7.3

^aThe number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort

^bSubjects were excluded due to fail in logical checks (10), missing smoking duration (84), smoking intensity (129), BMI (52), neighborhood income (1825).

^cSubjects were excluded due to missing smoking status (5), smoking duration (84), smoking intensity (18), BMI (37), marital status (5), employment status (6), neighborhood income (1892).

^dFor current smokers

^eEUR per 1,000, year 2001

Reference: (Holle et al., 2005)

Table S8. Characteristics of the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP)

The VHM&PP is a population-based cohort recruited among all adults of the province of Vorarlberg, Austria. Vorarlberg is the western-most province of Austria consisting of towns and villages (30,000 inhabitants and smaller) and significant altitude differences.

Variable		VHM&PP
Baseline year, range		1985–2005
Enrolled, N ^a		170,250
Included in mortality analyses ^b		144,199
Deaths, N (%)		
	Natural cause	22,645 (15.7)
	Cardiovascular diseases	9,976 (6.9)
	Respiratory diseases	1,099 (0.8)
	Lung Cancer	1,380 (1.0)
Age at baseline, yrs (mean $\pm$ SD)		42.1 $\pm$ 15.0
Women, N (%)		81,017 (56.2)
Employed, N (%)		100,585 (69.8)
Marital status, N (%)		
	Single	24,832 (17.2)
	Married	99,400 (68.9)
	Divorced	9,762 (6.8)
	Widowed	10,205 (7.1)
Smoking status, N (%)		
	Current	28,871 (20.0)
	Previous	8,995 (6.2)
	Never	106,333 (73.7)
Smoking intensity ^c , g/d (mean $\pm$ SD)		15.6 $\pm$ 8.9
Smoking duration ^c , yrs (mean $\pm$ SD)		13.4 $\pm$ 8.3
BMI, kg/m ² , N (%)		
	< 18.5	4,450 (3.1)
	18.5–24.9	78,575 (54.5)
	25.0–29.9	45,533 (31.6)
	30.0+	15,641 (10.8)
Neighborhood income ^d (mean $\pm$ SD)		22.9 $\pm$ 1.7

^aThe number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort

^bSubjects were excluded due to missing exposure (396), smoking duration (5789), smoking intensity (6376), BMI (11), marital status (9970), employment status (15056), neighborhood income (1895).

^cFor current smokers

^dEUR per 1,000, year 2001

Reference: (Ulmer et al., 2007)

Table S9. Performance of Europe-wide PM_{2.5} composition models in five-fold hold-out validation^a

	Cu	Fe	K	Ni	S	Si	V	Zn
Performance of PM _{2.5} composition models over Europe: r ²								
SLR	0.48	0.48	0.59	0.56	0.79	0.46	0.63	0.41
RF	0.59	0.61	0.80	0.76	0.90	0.62	0.86	0.71
Performance of PM _{2.5} composition models to assess within-area variation: average within-area r ²								
SLR	0.35	0.36	0.07	0.17	0.14	0.20	0.19	0.19
RF	0.29	0.29	0.07	0.21	0.23	0.17	0.29	0.25

^a Values extracted from Chen et al. (2020)r² = squared Pearson correlation, SLR = Supervised Linear Regression model, RF = Random Forest model**Table S10. Truncation frequency (Truncation performed for model 3 population, N=323,782)**

Pollutant	Exposure model	N below zero (%)	N above maximum (%)
PM _{2.5} Cu	SLR	36,683 (11.3) ^a	2 (0) ^b
	RF	0 (0)	0 (0)
PM _{2.5} Fe	SLR	1,645 (0.5) ^c	0 (0)
	RF	0 (0)	0 (0)
PM _{2.5} K	SLR	0 (0)	0 (0)
	RF	0 (0)	0 (0)
PM _{2.5} Ni	SLR	37,470 (11.6) ^d	24 (0) ^e
	RF	0 (0)	0 (0)
PM _{2.5} S	SLR	0 (0)	0 (0)
	RF	0 (0)	0 (0)
PM _{2.5} Si	SLR	0 (0)	0 (0)
	RF	0 (0)	0 (0)
PM _{2.5} V	SLR	46,243 (14.3) ^f	0 (0)
	RF	0 (0)	0 (0)
PM _{2.5} Zn	SLR	8,154 (2.5) ^g	240 (0.1) ^h
	RF	0 (0)	0 (0)

N = Number of observations; SLR = Supervised Linear Regression model, RF = Random Forest model

^a 7464 (97%) in CEANS-SDPP, 1754 (44%) in CEANS-SIXTY, 2348 (38%) in CEANS-SALT, 2 (<1%) in CEANS-SNACK, 3158 (6%) in DCH, 7237 (43%) in DNC-1993, 3564 (44%) in DNC-1999, 1 (<1%) in EPIC-NL-Morgen, 110 (<1%) in E3N, 11045 (8%) in VHM&PP^b 2 (<1%) in E3N^c 563 (7%) in CEANS-SDPP, 30 (1%) in CEANS-SIXTY, 53 (1%) in CEANS-SALT, 58 (<1%) in DCH, 640 (4%) in DNC-1993, 301 (4%) in DNC-1999,^d 51 (1%) in CEANS-SDPP, 2 (<1%) in CEANS-SIXTY, 3 (<1%) in CEANS-SALT, 3 (<1%) in DCH, 94 (1%) in DNC-1993, 32 (<1%) in DNC-1999, 438 (1%) in E3N, 382 (15%) in KORA-S3, 250 (11%) in KORA-S4, 36215 (25%) in VHM&PP^e 4 (<1%) in DCH, 3 (<1%) in DNC-1993, 2 (<1%) in EPIC-NL-Prospect, 10 (<1%) in E3N, 5 (<1%) in VHM&PP^f 37 (1%) in CEANS-SIXTY, 68 (1%) in CEANS-SALT, 183 (6%) in CEANS-SNACK, 80 (<1%) in DCH, 12 (<1%) in DNC-1993, 5 (<1%) in DNC-1999, 582 (2%) in E3N, 1102 (43%) in KORA-S3, 1078 (47%) in KORA-S4, 43096 (30%) in VHM&PP^g 127 (<1%) in E3N, 8027 (6%) in VHM&PP^h 1 (<1%) in DNC-1993, 16 (<1%) in EPIC-NL-Morgen, 3 (<1%) in HNR, 220 (1%) in E3N

Table S11. Exposure distribution of PM_{2.5} composition in the pooled cohort

Exposure	Exposure model	Mean	SD	IQR	Min	P5	P25	Median	P75	P95	Max
PM _{2.5} Cu	SLR	3.5	2.6	3.7	0.0	0.0	1.4	3.5	5.1	7.3	42.4
	RF	3.9	1.6	1.9	0.9	1.9	2.7	3.9	4.6	6.7	19.2
PM _{2.5} Fe	SLR	87.0	45.5	55.9	0.0	20.9	56.3	84.3	112.2	158.3	453.9
	RF	83.8	33.5	34.2	21.0	43.9	62.5	75.0	96.8	154.1	311.8
PM _{2.5} K	SLR	166.7	52.4	82.2	31.8	89.8	123.1	165.0	205.3	255.6	321.4
	RF	212.3	101.6	200.1	74.4	89.7	112.0	210.7	312.1	371.0	480.6
PM _{2.5} Ni	SLR	0.8	0.7	0.8	0.0	0.0	0.3	0.6	1.1	2.2	12.7
	RF	0.8	0.6	0.9	0.1	0.2	0.3	0.8	1.2	1.9	3.8
PM _{2.5} S	SLR	658.4	139.9	212.9	299.0	438.3	554.1	649.7	766.9	884.2	1251.9
	RF	688.9	132.5	123.2	484.2	528.2	613.2	641.3	736.4	926.8	1314.1
PM _{2.5} Si	SLR	96.2	20.6	23.9	37.5	68.7	82.4	93.7	106.3	133.7	255.3
	RF	85.9	25.0	23.3	38.1	60.6	71.0	78.7	94.2	132.7	299.7
PM _{2.5} V	SLR	1.3	1.4	1.7	0.0	0.0	0.4	0.8	2.1	4.1	17.8
	RF	1.3	1.1	1.6	0.3	0.3	0.3	1.3	1.9	3.5	7.3
PM _{2.5} Zn	SLR	16.8	11.0	10.6	0.0	3.8	10.9	15.3	21.5	31.0	145.4
	RF	19.6	7.4	9.7	9.5	11.2	13.5	20.2	23.2	30.6	73.9

SLR = Supervised Linear Regression model, RF = Random Forest model, SD = standard deviation, IQR = interquartile range, P5 to P95 are percentiles.
Unit for pollutants: ng/m³

Table S12. Spearman correlation coefficient between PM_{2.5} composition and PM_{2.5} mass (N=323,782)

Sub-cohort	PM _{2.5} Cu		PM _{2.5} Fe		PM _{2.5} K		PM _{2.5} Ni		PM _{2.5} S		PM _{2.5} Si		PM _{2.5} V		PM _{2.5} Zn	
	SLR	RF	SLR	RF	SLR	RF	SLR	RF	SLR	RF	SLR	RF	SLR	RF	SLR	RF
Average^a	0.44	0.49	0.47	0.45	0.21	0.42	0.25	0.18	0.48	0.41	0.38	0.22	0.13	0.13	0.42	0.43
CEANS-SDPP	0.19	0.60	0.31	0.36	-0.07	0.39	-0.23	0.07	0.55	0.48	0.21	-0.19	-0.23	0.32	-0.18	0.44
CEANS-SIXTY	0.49	0.60	0.54	0.52	0.06	0.54	0.31	0.34	0.48	0.34	0.48	0.37	-0.03	0.24	0.45	0.43
CEANS-SALT	0.49	0.57	0.51	0.52	0.06	0.53	0.29	0.35	0.47	0.31	0.47	0.41	-0.02	0.28	0.41	0.42
CEANS-SNACK	0.50	0.64	0.53	0.65	0.55	0.55	0.19	0.51	0.46	0.25	0.45	0.31	0.43	0.30	0.39	0.57
DCH	0.74	0.72	0.76	0.66	-0.19	0.54	0.52	0.64	0.66	0.65	0.65	0.41	0.32	0.60	0.68	0.67
DNC-1993	0.42	0.40	0.38	0.37	0.17	0.42	0.22	0.27	0.42	0.50	0.36	0.22	0.11	0.28	0.48	0.34
DNC-1999	0.30	0.29	0.27	0.23	0.11	0.36	0.12	0.19	0.30	0.38	0.20	0.12	0.00	0.22	0.36	0.21
EPIC-NL-Morgen	0.22	0.24	0.28	0.24	0.50	0.49	0.14	0.06	0.46	0.61	0.28	0.46	-0.16	-0.52	0.55	0.55
EPIC-NL-Prospect	0.40	0.32	0.37	0.33	0.44	0.43	0.11	0.41	0.63	0.54	0.30	0.23	0.23	0.22	0.34	0.29
HNR	0.39	0.44	0.44	0.63	-0.34	0.54	0.28	0.52	0.48	0.27	0.35	0.29	0.30	0.41	0.46	0.59
E3N	0.62	0.63	0.67	0.56	0.31	-0.12	0.41	0.20	0.43	0.50	0.51	0.08	0.17	0.24	0.64	0.66
KORA-S3	0.28	0.28	0.41	0.33	0.26	0.36	0.22	-0.32	0.27	0.19	0.26	0.19	0.06	-0.36	0.22	0.16
KORA-S4	0.34	0.48	0.46	0.48	0.28	0.25	0.41	-0.35	0.33	0.19	0.44	0.43	0.00	-0.36	0.37	0.18
VHM&PP	0.72	0.63	0.62	0.38	0.76	0.59	0.54	-0.31	0.79	0.56	0.38	-0.21	0.65	-0.04	0.68	0.44

^a Average of cohort-specific correlation coefficients

Table S13. Spearman correlation coefficients between PM_{2.5} composition and NO₂ (N=323,782)

Sub-cohort	PM _{2.5} Cu		PM _{2.5} Fe		PM _{2.5} K		PM _{2.5} Ni		PM _{2.5} S		PM _{2.5} Si		PM _{2.5} V		PM _{2.5} Zn	
	SLR	RF	SLR	RF	SLR	RF	SLR	RF	SLR	RF	SLR	RF	SLR	RF	SLR	RF
Average^a	0.71	0.77	0.78	0.74	0.09	0.38	0.46	0.33	0.46	0.33	0.68	0.37	0.27	0.22	0.51	0.54
CEANS-SDPP	0.29	0.81	0.84	0.70	0.07	0.79	0.16	0.30	0.31	-0.06	0.73	-0.20	0.04	0.33	0.39	0.62
CEANS-SIXTY	0.83	0.89	0.90	0.86	-0.24	0.69	0.53	0.58	0.46	0.32	0.82	0.65	-0.13	0.21	0.58	0.70
CEANS-SALT	0.85	0.89	0.90	0.87	-0.28	0.68	0.52	0.62	0.44	0.33	0.82	0.71	-0.11	0.25	0.56	0.69
CEANS-SNACK	0.74	0.84	0.77	0.88	0.72	0.72	0.27	0.66	0.47	0.36	0.68	0.56	0.63	0.30	0.54	0.70
DCH	0.90	0.88	0.88	0.79	-0.24	0.63	0.55	0.62	0.57	0.58	0.63	0.31	0.36	0.61	0.62	0.68
DNC-1993	0.57	0.61	0.59	0.51	-0.12	0.42	0.27	0.25	0.33	0.28	0.50	0.17	0.02	0.27	0.39	0.51
DNC-1999	0.35	0.36	0.35	0.28	-0.13	0.28	0.13	0.13	0.19	0.18	0.26	0.08	-0.07	0.17	0.23	0.29
EPIC-NL-Morgen	0.88	0.90	0.88	0.88	-0.39	-0.45	0.72	0.71	0.27	-0.30	0.76	0.51	0.65	0.46	0.27	-0.35
EPIC-NL-Prospect	0.86	0.89	0.89	0.88	-0.12	0.71	0.57	0.09	0.41	0.56	0.85	0.77	0.32	-0.21	0.66	0.73
HNR	0.69	0.71	0.71	0.72	-0.16	0.34	0.17	0.63	0.41	0.32	0.52	0.33	0.33	0.42	0.26	0.50
E3N	0.81	0.82	0.86	0.81	0.28	-0.16	0.58	0.36	0.58	0.59	0.76	0.31	0.36	0.43	0.73	0.72
KORA-S3	0.72	0.69	0.72	0.72	0.58	0.14	0.60	0.05	0.63	0.42	0.67	0.58	0.32	-0.23	0.6	0.52
KORA-S4	0.68	0.69	0.73	0.74	0.56	-0.09	0.60	0.14	0.63	0.39	0.67	0.60	0.32	0.00	0.61	0.57
VHM&PP	0.83	0.79	0.88	0.76	0.71	0.67	0.72	-0.52	0.72	0.63	0.80	-0.24	0.75	0.10	0.76	0.65

^aAverage of cohort-specific correlation coefficients

Table S14. Associations of PM_{2.5} composition with natural mortality in single pollutant and two-pollutant models

Exposure	Exposure model	Single pollutant HR	Two-pollutant model adjusting for PM _{2.5}		Two-pollutant model adjusting for NO ₂	
			component	PM _{2.5} ^a	component	NO ₂ ^a
PM _{2.5} Cu	SLR	1.120 (1.094, 1.147)	1.043 (1.011, 1.076)	1.105 (1.073, 1.137)	1.023 (0.983, 1.065)	1.074 (1.047, 1.102)
	RF	1.154 (1.111, 1.198)	1.035 (0.989, 1.083)	1.122 (1.093, 1.151)	0.943 (0.887, 1.002)	1.107 (1.081, 1.134)
PM _{2.5} Fe	SLR	1.139 (1.110, 1.169)	1.065 (1.031, 1.100)	1.099 (1.070, 1.129)	1.024 (0.974, 1.076)	1.075 (1.044, 1.106)
	RF	1.132 (1.090, 1.176)	1.055 (1.013, 1.099)	1.122 (1.096, 1.148)	0.921 (0.869, 0.976)	1.114 (1.089, 1.139)
PM _{2.5} K	SLR	1.049 (1.035, 1.064)	0.998 (0.981, 1.015)	1.136 (1.105, 1.169)	1.027 (1.012, 1.041)	1.077 (1.060, 1.094)
	RF	1.056 (1.042, 1.070)	1.021 (1.006, 1.037)	1.114 (1.086, 1.143)	1.031 (1.017, 1.046)	1.072 (1.055, 1.090)
PM _{2.5} Ni	SLR	1.084 (1.063, 1.106)	1.043 (1.020, 1.066)	1.114 (1.087, 1.140)	1.030 (1.006, 1.055)	1.074 (1.055, 1.093)
	RF	1.011 (0.971, 1.053)	0.993 (0.953, 1.034)	1.134 (1.110, 1.159)	0.949 (0.909, 0.990)	1.093 (1.076, 1.110)
PM _{2.5} S	SLR	1.142 (1.113, 1.173)	1.049 (1.009, 1.090)	1.102 (1.068, 1.137)	1.074 (1.039, 1.109)	1.061 (1.042, 1.081)
	RF	1.127 (1.079, 1.177)	0.999 (0.951, 1.051)	1.134 (1.106, 1.162)	1.013 (0.964, 1.064)	1.085 (1.067, 1.103)
PM _{2.5} Si	SLR	1.268 (1.205, 1.336)	1.151 (1.087, 1.217)	1.108 (1.082, 1.134)	1.071 (0.995, 1.152)	1.072 (1.050, 1.095)
	RF	0.967 (0.921, 1.014)	0.969 (0.924, 1.017)	1.134 (1.109, 1.159)	0.906 (0.863, 0.952)	1.095 (1.078, 1.112)
PM _{2.5} V	SLR	1.061 (1.044, 1.079)	1.033 (1.015, 1.052)	1.120 (1.094, 1.145)	1.026 (1.007, 1.045)	1.077 (1.060, 1.095)
	RF	1.092 (1.050, 1.135)	1.056 (1.015, 1.099)	1.128 (1.104, 1.153)	1.026 (0.985, 1.069)	1.084 (1.067, 1.101)
PM _{2.5} Zn	SLR	1.051 (1.039, 1.064)	1.015 (0.999, 1.031)	1.118 (1.089, 1.147)	1.021 (1.006, 1.036)	1.074 (1.055, 1.093)
	RF	1.062 (1.036, 1.089)	0.992 (0.964, 1.021)	1.137 (1.110, 1.165)	1.002 (0.974, 1.030)	1.087 (1.069, 1.105)

Total number of observations = 323,782; person-years at risk = 6,317,235; number of death from natural mortality = 46,640.

HR = Hazard Ratio, SLR = Supervised Linear Regression model, RF = Random Forest model

HR (95% confidence interval) presented for the following increments: PM_{2.5} Cu – 5 ng/m³, PM_{2.5} Fe – 100 ng/m³, PM_{2.5} K – 50 ng/m³, PM_{2.5} Ni – 1 ng/m³, PM_{2.5} S – 200 ng/m³, PM_{2.5} Si – 100 ng/m³, PM_{2.5} V – 2 ng/m³, PM_{2.5} Zn – 10 ng/m³, PM_{2.5} mass – 5 µg/m³, NO₂ – 10 µg/m³; main model adjusted for sub-cohort id, age, sex, year of enrollment, smoking (status, duration, intensity, intensity²), BMI categories, marital status, employment status and 2001 neighborhood-level mean income

^aSingle pollutant HRs are 1.134, 95% CI: 1.109, 1.159 per 5 µg/m³ increase in PM_{2.5} mass and 1.087, 95% CI 1.071, 1.103 per 10 µg/m³ in NO₂. PM_{2.5} mass and NO₂ exposure were estimated using SLR only.

Table S15. Associations of PM_{2.5} composition with natural mortality with increasing control for covariates

Exposure	Exposure model	Model 1 HR N = 323,782 ^a	Model 2 HR N = 323,782 ^a	Model 3 HR N = 323,782 ^a	Model 1 HR N = 378,979 ^b	Model 2 HR N = 330,667 ^c
PM _{2.5} Cu	SLR	1.175 (1.148, 1.202)	1.103 (1.078, 1.128)	1.120 (1.094, 1.147)	1.168 (1.144, 1.193)	1.099 (1.075, 1.125)
	RF	1.257 (1.211, 1.305)	1.130 (1.088, 1.173)	1.154 (1.111, 1.198)	1.239 (1.198, 1.280)	1.119 (1.079, 1.160)
PM _{2.5} Fe	SLR	1.216 (1.186, 1.248)	1.121 (1.092, 1.150)	1.139 (1.110, 1.169)	1.202 (1.175, 1.231)	1.117 (1.089, 1.145)
	RF	1.258 (1.212, 1.306)	1.119 (1.078, 1.162)	1.132 (1.090, 1.176)	1.233 (1.192, 1.275)	1.107 (1.067, 1.148)
PM _{2.5} K	SLR	1.049 (1.035, 1.063)	1.043 (1.029, 1.056)	1.049 (1.035, 1.064)	1.053 (1.040, 1.066)	1.042 (1.028, 1.055)
	RF	1.059 (1.046, 1.073)	1.048 (1.034, 1.061)	1.056 (1.042, 1.070)	1.062 (1.049, 1.075)	1.050 (1.036, 1.063)
PM _{2.5} Ni	SLR	1.163 (1.142, 1.185)	1.087 (1.066, 1.109)	1.084 (1.063, 1.106)	1.164 (1.145, 1.184)	1.087 (1.066, 1.108)
	RF	1.122 (1.078, 1.168)	1.027 (0.986, 1.069)	1.011 (0.971, 1.053)	1.108 (1.068, 1.149)	1.018 (0.978, 1.060)
PM _{2.5} S	SLR	1.204 (1.173, 1.236)	1.135 (1.106, 1.165)	1.142 (1.113, 1.173)	1.182 (1.155, 1.210)	1.119 (1.091, 1.148)
	RF	1.219 (1.167, 1.274)	1.120 (1.072, 1.170)	1.127 (1.079, 1.177)	1.141 (1.101, 1.182)	1.076 (1.034, 1.119)
PM _{2.5} Si	SLR	1.534 (1.458, 1.614)	1.264 (1.200, 1.330)	1.268 (1.205, 1.336)	1.477 (1.411, 1.546)	1.243 (1.183, 1.307)
	RF	1.055 (1.007, 1.105)	0.986 (0.941, 1.034)	0.967 (0.921, 1.014)	1.033 (0.990, 1.078)	0.978 (0.934, 1.024)
PM _{2.5} V	SLR	1.129 (1.111, 1.148)	1.066 (1.048, 1.084)	1.061 (1.044, 1.079)	1.135 (1.118, 1.152)	1.066 (1.048, 1.084)
	RF	1.205 (1.159, 1.252)	1.099 (1.058, 1.143)	1.092 (1.050, 1.135)	1.204 (1.161, 1.248)	1.094 (1.052, 1.137)
PM _{2.5} Zn	SLR	1.074 (1.062, 1.087)	1.045 (1.033, 1.058)	1.051 (1.039, 1.064)	1.072 (1.060, 1.083)	1.044 (1.031, 1.056)
	RF	1.084 (1.058, 1.111)	1.050 (1.024, 1.076)	1.062 (1.036, 1.089)	1.084 (1.060, 1.108)	1.047 (1.022, 1.073)

^a Model 3 population = 323,782, person-years at risk = 6,317,235; number of death from natural mortality = 46,640.

^b Model 1 population = 378,979, person-years at risk = 7,291,866; number of death from natural mortality = 52,849. We excluded 54 (<0.1%) subjects after logical checks and 2,003 (0.5%) subjects due to missing exposure. Missing data for each cohort are shown in Tables S1 to S8.

^c Model 2 population = 330,667, person-years at risk = 6,433,069; number of death from natural mortality = 47,524. We further excluded 48312 (12.7%) subjects from Model 1 population due to missing individual level covariates. Missing data for each cohort are shown in Tables S1 to S8.

HR = Hazard Ratio, SLR = Supervised Linear Regression model, RF = Random Forest model

HR (95% confidence interval) presented for the following increments: PM_{2.5} Cu – 5 ng/m³, PM_{2.5} Fe – 100 ng/m³, PM_{2.5} K – 50 ng/m³, PM_{2.5} Ni – 1 ng/m³, PM_{2.5} S – 200 ng/m³, PM_{2.5} Si – 100 ng/m³, PM_{2.5} V – 2 ng/m³, PM_{2.5} Zn – 10 ng/m³; Model 1 adjusted for age, sub-cohort id, sex and year of enrollment; Model 2 further adjusted for smoking (status, duration, intensity, intensity²), BMI categories, marital status and employment status; Model 3 further adjusted for 2001 neighborhood-level mean income

Table S16. Associations of PM_{2.5} composition with cardiovascular mortality in single pollutant and two-pollutant models

Exposure	Exposure model	Single pollutant HR	Two-pollutant model adjusting for PM _{2.5}		Two-pollutant model adjusting for NO ₂	
			component	PM _{2.5} ^a	component	NO ₂ ^a
PM _{2.5} Cu	SLR	1.126 (1.080, 1.173)	1.033 (0.977, 1.092)	1.116 (1.064, 1.171)	1.045 (0.974, 1.122)	1.064 (1.014, 1.115)
	RF	1.168 (1.086, 1.257)	1.011 (0.926, 1.105)	1.134 (1.086, 1.183)	0.941 (0.835, 1.060)	1.110 (1.061, 1.161)
PM _{2.5} Fe	SLR	1.147 (1.094, 1.204)	1.055 (0.994, 1.119)	1.111 (1.064, 1.161)	1.035 (0.940, 1.139)	1.071 (1.014, 1.132)
	RF	1.129 (1.048, 1.217)	1.042 (0.963, 1.127)	1.130 (1.089, 1.173)	0.887 (0.792, 0.994)	1.127 (1.081, 1.176)
PM _{2.5} K	SLR	1.054 (1.032, 1.077)	0.997 (0.967, 1.027)	1.141 (1.086, 1.199)	1.030 (1.006, 1.054)	1.072 (1.039, 1.105)
	RF	1.075 (1.052, 1.098)	1.042 (1.015, 1.070)	1.092 (1.045, 1.142)	1.054 (1.029, 1.080)	1.054 (1.021, 1.088)
PM _{2.5} Ni	SLR	1.080 (1.038, 1.124)	1.023 (0.978, 1.070)	1.129 (1.086, 1.173)	1.012 (0.964, 1.063)	1.085 (1.050, 1.121)
	RF	0.943 (0.866, 1.026)	0.947 (0.870, 1.031)	1.137 (1.097, 1.178)	0.903 (0.829, 0.984)	1.096 (1.065, 1.127)
PM _{2.5} S	SLR	1.149 (1.098, 1.201)	1.036 (0.967, 1.110)	1.113 (1.054, 1.176)	1.090 (1.029, 1.154)	1.054 (1.017, 1.092)
	RF	1.090 (1.005, 1.181)	0.925 (0.844, 1.015)	1.156 (1.110, 1.204)	0.952 (0.867, 1.044)	1.099 (1.064, 1.135)
PM _{2.5} Si	SLR	1.267 (1.148, 1.399)	1.128 (1.015, 1.255)	1.119 (1.077, 1.163)	1.033 (0.895, 1.192)	1.083 (1.040, 1.127)
	RF	0.915 (0.835, 1.003)	0.936 (0.854, 1.025)	1.135 (1.095, 1.177)	0.868 (0.791, 0.953)	1.098 (1.067, 1.129)
PM _{2.5} V	SLR	1.066 (1.028, 1.104)	1.027 (0.989, 1.066)	1.128 (1.087, 1.171)	1.022 (0.982, 1.063)	1.082 (1.050, 1.116)
	RF	1.091 (1.002, 1.187)	1.056 (0.969, 1.150)	1.134 (1.094, 1.176)	1.022 (0.936, 1.116)	1.088 (1.057, 1.120)
PM _{2.5} Zn	SLR	1.054 (1.030, 1.079)	1.003 (0.973, 1.033)	1.134 (1.084, 1.186)	1.018 (0.990, 1.048)	1.077 (1.041, 1.114)
	RF	1.074 (1.026, 1.125)	0.982 (0.930, 1.038)	1.145 (1.099, 1.192)	1.002 (0.950, 1.058)	1.089 (1.055, 1.124)

Total number of observations = 323,782; person-years at risk = 6,317,235; number of death from cardiovascular mortality = 15,492.

HR = Hazard Ratio, SLR = Supervised Linear Regression model, RF = Random Forest model

HR (95% confidence interval) presented for the following increments: PM_{2.5} Cu – 5 ng/m³, PM_{2.5} Fe – 100 ng/m³, PM_{2.5} K – 50 ng/m³, PM_{2.5} Ni – 1 ng/m³, PM_{2.5} S – 200 ng/m³, PM_{2.5} Si – 100 ng/m³, PM_{2.5} V – 2 ng/m³, PM_{2.5} Zn – 10 ng/m³, PM_{2.5} mass – 5 µg/m³, NO₂ – 10 µg/m³; main model adjusted for sub-cohort id, age, sex, year of enrollment, smoking (status, duration, intensity, intensity²), BMI categories, marital status, employment status and 2001 neighborhood-level mean income

^aSingle pollutant HRs are 1.137, 95% CI: 1.097, 1.178 per 5 µg/m³ increase in PM_{2.5} mass and 1.090, 95% CI 1.060, 1.120 per 10 µg/m³ in NO₂. PM_{2.5} mass and NO₂ exposure were estimated using SLR only.

Table S17. Associations of PM_{2.5} composition with non-malignant respiratory mortality in single pollutant and two-pollutant models

Exposure	Exposure model	Single pollutant HR	Two-pollutant model adjusting for PM _{2.5}		Two-pollutant model adjusting for NO ₂	
			component	PM _{2.5} ^a	component	NO ₂ ^a
PM _{2.5} Cu	SLR	1.085 (0.984, 1.197)	1.088 (0.955, 1.239)	0.996 (0.881, 1.127)	0.861 (0.728, 1.018)	1.189 (1.073, 1.317)
	RF	1.124 (0.961, 1.315)	1.108 (0.921, 1.333)	1.016 (0.911, 1.134)	0.791 (0.611, 1.023)	1.184 (1.075, 1.304)
PM _{2.5} Fe	SLR	1.148 (1.031, 1.277)	1.173 (1.027, 1.340)	0.968 (0.863, 1.086)	0.952 (0.778, 1.166)	1.130 (1.010, 1.263)
	RF	1.184 (1.018, 1.378)	1.175 (0.999, 1.383)	1.013 (0.917, 1.119)	0.955 (0.759, 1.201)	1.119 (1.023, 1.224)
PM _{2.5} K	SLR	0.973 (0.918, 1.032)	0.929 (0.863, 1.001)	1.125 (1.002, 1.263)	0.944 (0.888, 1.004)	1.121 (1.054, 1.192)
	RF	1.020 (0.961, 1.082)	1.003 (0.933, 1.078)	1.047 (0.936, 1.171)	0.975 (0.914, 1.041)	1.115 (1.045, 1.190)
PM _{2.5} Ni	SLR	1.142 (1.063, 1.227)	1.150 (1.064, 1.243)	0.978 (0.884, 1.081)	1.099 (1.007, 1.199)	1.059 (0.986, 1.137)
	RF	1.209 (1.036, 1.411)	1.200 (1.026, 1.402)	1.033 (0.941, 1.134)	1.124 (0.953, 1.325)	1.087 (1.021, 1.158)
PM _{2.5} S	SLR	1.113 (0.995, 1.244)	1.147 (0.975, 1.350)	0.966 (0.843, 1.106)	0.996 (0.867, 1.143)	1.105 (1.027, 1.190)
	RF	1.063 (0.879, 1.287)	1.016 (0.816, 1.265)	1.046 (0.940, 1.163)	0.909 (0.735, 1.123)	1.119 (1.047, 1.195)
PM _{2.5} Si	SLR	1.252 (1.016, 1.544)	1.241 (0.987, 1.562)	1.009 (0.912, 1.117)	0.972 (0.728, 1.298)	1.110 (1.023, 1.205)
	RF	0.982 (0.812, 1.186)	0.980 (0.811, 1.184)	1.050 (0.957, 1.152)	0.907 (0.746, 1.103)	1.112 (1.046, 1.182)
PM _{2.5} V	SLR	1.082 (1.019, 1.148)	1.079 (1.014, 1.149)	1.012 (0.918, 1.115)	1.046 (0.980, 1.117)	1.084 (1.015, 1.157)
	RF	1.110 (0.963, 1.278)	1.097 (0.949, 1.268)	1.037 (0.943, 1.139)	1.028 (0.884, 1.196)	1.100 (1.032, 1.171)
PM _{2.5} Zn	SLR	1.031 (0.975, 1.091)	1.020 (0.951, 1.095)	1.029 (0.917, 1.155)	0.971 (0.905, 1.041)	1.123 (1.045, 1.206)
	RF	1.006 (0.898, 1.127)	0.972 (0.853, 1.107)	1.061 (0.955, 1.179)	0.913 (0.802, 1.039)	1.126 (1.054, 1.203)

Total number of observations = 323,782; person-years at risk = 6,317,235; number of death from non-malignant respiratory mortality = 2,846.

HR = Hazard Ratio, SLR = Supervised Linear Regression model, RF = Random Forest model

HR (95% confidence interval) presented for the following increments: PM_{2.5} Cu – 5 ng/m³, PM_{2.5} Fe – 100 ng/m³, PM_{2.5} K – 50 ng/m³, PM_{2.5} Ni – 1 ng/m³, PM_{2.5} S – 200 ng/m³, PM_{2.5} Si – 100 ng/m³, PM_{2.5} V – 2 ng/m³, PM_{2.5} Zn – 10 ng/m³, PM_{2.5} mass – 5 µg/m³, NO₂ – 10 µg/m³; main model adjusted for sub-cohort id, age, sex, year of enrollment, smoking (status, duration, intensity, intensity²), BMI categories, marital status, employment status and 2001 neighborhood-level mean income

^aSingle pollutant HRs are 1.050, 95% CI: 0.957, 1.152 per 5 µg/m³ increase in PM_{2.5} mass and 1.104, 95% CI 1.040, 1.172 per 10 µg/m³ in NO₂. PM_{2.5} mass and NO₂ exposure were estimated using SLR only.

Table S18. Associations of PM_{2.5} composition with lung cancer mortality in single pollutant and two-pollutant models

Exposure	Exposure model	Single pollutant HR	Two-pollutant model adjusting for PM _{2.5}		Two-pollutant model adjusting for NO ₂	
			component	PM _{2.5} ^a	component	NO ₂ ^a
PM _{2.5} Cu	SLR	1.114 (1.024, 1.211)	0.983 (0.879, 1.100)	1.199 (1.076, 1.337)	1.021 (0.884, 1.180)	1.068 (0.978, 1.166)
	RF	1.127 (0.989, 1.285)	0.957 (0.817, 1.121)	1.204 (1.092, 1.327)	0.914 (0.737, 1.134)	1.109 (1.020, 1.205)
PM _{2.5} Fe	SLR	1.125 (1.027, 1.233)	1.003 (0.894, 1.125)	1.185 (1.070, 1.312)	1.012 (0.852, 1.202)	1.073 (0.974, 1.181)
	RF	1.113 (0.978, 1.266)	1.004 (0.872, 1.156)	1.185 (1.085, 1.295)	0.918 (0.754, 1.118)	1.106 (1.024, 1.196)
PM _{2.5} K	SLR	1.076 (1.022, 1.133)	1.014 (0.951, 1.081)	1.171 (1.059, 1.295)	1.060 (1.005, 1.118)	1.064 (1.009, 1.122)
	RF	1.061 (1.008, 1.117)	1.005 (0.947, 1.067)	1.182 (1.075, 1.298)	1.037 (0.982, 1.096)	1.065 (1.008, 1.125)
PM _{2.5} Ni	SLR	1.091 (1.028, 1.159)	1.043 (0.975, 1.116)	1.160 (1.061, 1.268)	1.056 (0.981, 1.136)	1.052 (0.990, 1.119)
	RF	1.007 (0.885, 1.146)	0.962 (0.844, 1.098)	1.191 (1.096, 1.295)	0.932 (0.811, 1.071)	1.089 (1.031, 1.151)
PM _{2.5} S	SLR	1.265 (1.148, 1.395)	1.201 (1.044, 1.382)	1.063 (0.945, 1.196)	1.258 (1.116, 1.419)	1.005 (0.943, 1.070)
	RF	1.203 (1.024, 1.414)	1.029 (0.855, 1.237)	1.178 (1.074, 1.294)	1.112 (0.932, 1.327)	1.064 (1.006, 1.125)
PM _{2.5} Si	SLR	1.292 (1.082, 1.544)	1.124 (0.923, 1.369)	1.160 (1.060, 1.270)	1.153 (0.901, 1.475)	1.049 (0.977, 1.126)
	RF	1.034 (0.878, 1.218)	1.022 (0.867, 1.204)	1.186 (1.093, 1.287)	0.974 (0.823, 1.154)	1.081 (1.025, 1.139)
PM _{2.5} V	SLR	1.071 (1.019, 1.126)	1.040 (0.986, 1.096)	1.163 (1.067, 1.268)	1.047 (0.990, 1.106)	1.058 (1.000, 1.119)
	RF	1.133 (1.009, 1.273)	1.082 (0.960, 1.219)	1.173 (1.079, 1.275)	1.077 (0.951, 1.220)	1.066 (1.010, 1.126)
PM _{2.5} Zn	SLR	1.053 (1.010, 1.098)	1.004 (0.952, 1.059)	1.182 (1.072, 1.303)	1.029 (0.980, 1.081)	1.061 (1.002, 1.125)
	RF	1.070 (0.988, 1.159)	0.997 (0.911, 1.091)	1.188 (1.086, 1.299)	1.032 (0.947, 1.124)	1.071 (1.015, 1.131)

Total number of observations = 323,782; person-years at risk = 6,317,235; number of death from lung cancer mortality = 3,776.

HR = Hazard Ratio, SLR = Supervised Linear Regression model, RF = Random Forest model

HR (95% confidence interval) presented for the following increments: PM_{2.5} Cu – 5 ng/m³, PM_{2.5} Fe – 100 ng/m³, PM_{2.5} K – 50 ng/m³, PM_{2.5} Ni – 1 ng/m³, PM_{2.5} S – 200 ng/m³, PM_{2.5} Si – 100 ng/m³, PM_{2.5} V – 2 ng/m³, PM_{2.5} Zn – 10 ng/m³, PM_{2.5} mass – 5 µg/m³, NO₂ – 10 µg/m³; main model adjusted for sub-cohort id, age, sex, year of enrollment, smoking (status, duration, intensity, intensity²), BMI categories, marital status, employment status and 2001 neighborhood-level mean income

^a Single pollutant HRs are 1.187, 95% CI: 1.093, 1.288 per 5 µg/m³ increase in PM_{2.5} mass and 1.079, 95% CI 1.025, 1.135 per 10 µg/m³ in NO₂. PM_{2.5} mass and NO₂ exposure were estimated using SLR only.

Table S19. Sensitivity analysis: Associations of PM_{2.5} composition with natural mortality with restricted follow-up period

Exposure	Exposure model	Hazard Ratio (95% confidence interval)		
		Full follow-up ^a	After 2000 ^b	After 2005 ^c
PM _{2.5} Cu	SLR	1.120 (1.094, 1.147)	1.117 (1.089, 1.146)	1.099 (1.067, 1.132)
	RF	1.154 (1.111, 1.198)	1.143 (1.098, 1.190)	1.132 (1.080, 1.186)
PM _{2.5} Fe	SLR	1.139 (1.110, 1.169)	1.135 (1.104, 1.167)	1.119 (1.083, 1.156)
	RF	1.132 (1.090, 1.176)	1.126 (1.081, 1.172)	1.117 (1.067, 1.171)
PM _{2.5} K	SLR	1.049 (1.035, 1.064)	1.040 (1.025, 1.056)	1.025 (1.007, 1.043)
	RF	1.056 (1.042, 1.070)	1.048 (1.033, 1.064)	1.039 (1.022, 1.057)
PM _{2.5} Ni	SLR	1.084 (1.063, 1.106)	1.085 (1.062, 1.107)	1.079 (1.053, 1.105)
	RF	1.011 (0.971, 1.053)	1.047 (1.003, 1.092)	1.049 (0.999, 1.101)
PM _{2.5} S	SLR	1.142 (1.113, 1.173)	1.130 (1.098, 1.163)	1.095 (1.060, 1.132)
	RF	1.127 (1.079, 1.177)	1.118 (1.066, 1.172)	1.110 (1.051, 1.173)
PM _{2.5} Si	SLR	1.268 (1.205, 1.336)	1.237 (1.170, 1.306)	1.218 (1.143, 1.298)
	RF	0.967 (0.921, 1.014)	0.982 (0.934, 1.032)	0.975 (0.921, 1.033)
PM _{2.5} V	SLR	1.061 (1.044, 1.079)	1.061 (1.042, 1.080)	1.053 (1.032, 1.075)
	RF	1.092 (1.050, 1.135)	1.112 (1.068, 1.159)	1.096 (1.045, 1.149)
PM _{2.5} Zn	SLR	1.051 (1.039, 1.064)	1.044 (1.030, 1.058)	1.041 (1.026, 1.057)
	RF	1.062 (1.036, 1.089)	1.051 (1.023, 1.079)	1.049 (1.017, 1.081)

^aTotal number of observations = 323,782; person-years at risk = 6,317,235; number of death from natural mortality = 46,640.^bFollow-up period restricted to after year 2000, number of observations = 315,197 (97%); person-years at risk = 4,380,951 (69%); number of death from natural mortality = 39,321 (84%)^cFollow-up period restricted to after year 2005, number of observations = 303,022 (94%); person-years at risk = 2,905,753 (46%); number of death from natural mortality = 29,629 (64%)^dFollow-up period restricted to after year 2008, number of observations = 293,717 (91%); person-years at risk = 2,011,584 (32%); number of death from natural mortality = 21,785 (47%)SLR = Supervised Linear Regression model, RF = Random Forest model. HR (95% confidence interval) presented for the following increments: PM_{2.5} Cu – 5 ng/m³, PM_{2.5} Fe – 100 ng/m³, PM_{2.5} K – 50 ng/m³, PM_{2.5} Ni – 1 ng/m³, PM_{2.5} S – 200 ng/m³, PM_{2.5} Si – 100 ng/m³, PM_{2.5} V – 2 ng/m³, PM_{2.5} Zn – 10 ng/m³, PM_{2.5} mass – 5 µg/m³, NO₂ – 10 µg/m³; main model adjusted for sub-cohort id, age, sex, year of enrollment, smoking (status, duration, intensity²), BMI categories, marital status, employment status and 2001 neighborhood-level mean income

Table S20. Sensitivity analysis: Associations between PM_{2.5} composition and natural mortality with additional adjustment for individual level socio-economic status

Exposure	Exposure model	Full population ^a	w/o VHM (N = 178,387)		w/o DCH (N = 271,003)		w/o DCH, E3N, EPIC_NL, HNR (N = 181,082)	
			Main model ^b	Main model + education	Main model	Main model + Occupational Status	Main model	Main model + Collar Blue
PM _{2.5} Cu	SLR	1.120 (1.094, 1.147)	1.076 (1.039, 1.114)	1.078 (1.041, 1.116)	1.083 (1.055, 1.112)	1.082 (1.054, 1.111)	1.111 (1.077, 1.146)	1.117 (1.083, 1.153)
	RF	1.154 (1.111, 1.198)	1.086 (1.037, 1.138)	1.090 (1.041, 1.141)	1.095 (1.047, 1.145)	1.094 (1.046, 1.144)	1.168 (1.098, 1.242)	1.184 (1.113, 1.259)
PM _{2.5} Fe	SLR	1.139 (1.110, 1.169)	1.081 (1.045, 1.119)	1.082 (1.046, 1.120)	1.095 (1.062, 1.128)	1.094 (1.062, 1.128)	1.139 (1.097, 1.183)	1.151 (1.108, 1.195)
	RF	1.132 (1.090, 1.176)	1.073 (1.028, 1.121)	1.076 (1.030, 1.123)	1.079 (1.030, 1.129)	1.077 (1.029, 1.128)	1.148 (1.079, 1.221)	1.162 (1.092, 1.236)
PM _{2.5} K	SLR	1.049 (1.035, 1.064)	0.980 (0.947, 1.015)	0.980 (0.947, 1.015)	1.050 (1.035, 1.064)	1.050 (1.035, 1.064)	1.058 (1.042, 1.074)	1.060 (1.045, 1.077)
	RF	1.056 (1.042, 1.070)	1.003 (0.973, 1.034)	1.005 (0.975, 1.036)	1.049 (1.035, 1.063)	1.049 (1.035, 1.063)	1.066 (1.049, 1.082)	1.069 (1.053, 1.085)
PM _{2.5} Ni	SLR	1.084 (1.063, 1.106)	1.048 (1.024, 1.072)	1.050 (1.026, 1.075)	1.018 (0.987, 1.049)	1.017 (0.986, 1.048)	1.051 (1.010, 1.093)	1.056 (1.015, 1.098)
	RF	1.011 (0.971, 1.053)	1.053 (1.009, 1.099)	1.059 (1.014, 1.105)	0.873 (0.827, 0.920)	0.870 (0.825, 0.917)	0.776 (0.718, 0.838)	0.758 (0.702, 0.820)
PM _{2.5} S	SLR	1.142 (1.113, 1.173)	1.087 (1.040, 1.136)	1.086 (1.039, 1.135)	1.112 (1.080, 1.145)	1.112 (1.080, 1.144)	1.134 (1.097, 1.172)	1.139 (1.102, 1.177)
	RF	1.127 (1.079, 1.177)	1.065 (1.003, 1.129)	1.065 (1.003, 1.130)	1.077 (1.029, 1.127)	1.076 (1.029, 1.126)	1.108 (1.045, 1.176)	1.124 (1.060, 1.193)
PM _{2.5} Si	SLR	1.268 (1.205, 1.336)	1.135 (1.067, 1.207)	1.135 (1.066, 1.207)	1.177 (1.107, 1.252)	1.176 (1.106, 1.251)	1.311 (1.210, 1.420)	1.348 (1.244, 1.460)
	RF	0.967 (0.921, 1.014)	1.039 (0.986, 1.094)	1.039 (0.986, 1.095)	0.918 (0.867, 0.973)	0.918 (0.866, 0.972)	0.903 (0.839, 0.971)	0.896 (0.833, 0.964)
PM _{2.5} V	SLR	1.061 (1.044, 1.079)	1.029 (1.010, 1.049)	1.031 (1.012, 1.050)	0.995 (0.963, 1.028)	0.994 (0.962, 1.027)	1.029 (0.987, 1.073)	1.034 (0.992, 1.078)
	RF	1.092 (1.050, 1.135)	1.067 (1.025, 1.110)	1.072 (1.030, 1.116)	0.956 (0.902, 1.013)	0.953 (0.899, 1.010)	0.934 (0.863, 1.010)	0.934 (0.863, 1.010)
PM _{2.5} Zn	SLR	1.051 (1.039, 1.064)	1.017 (1.000, 1.034)	1.017 (1.000, 1.034)	1.030 (1.016, 1.043)	1.029 (1.016, 1.043)	1.078 (1.056, 1.100)	1.083 (1.062, 1.105)
	RF	1.062 (1.036, 1.089)	1.017 (0.985, 1.050)	1.016 (0.984, 1.049)	1.046 (1.020, 1.073)	1.045 (1.019, 1.072)	1.111 (1.065, 1.158)	1.124 (1.079, 1.172)

^aTotal number of observations = 323,782; person-years at risk = 6,317,235; number of death from natural mortality = 46,640.^bMain model adjusted for sub-cohort id, age, sex, year of enrollment, smoking (status, duration, intensity²), BMI categories, marital status, employment status and 2001 neighborhood-level mean incomeSLR = Supervised Linear Regression model, RF = Random Forest model. HR (95% confidence interval) presented for the following increments: PM_{2.5} Cu – 5 ng/m³, PM_{2.5} Fe – 100 ng/m³, PM_{2.5} K – 50 ng/m³, PM_{2.5} Ni – 1 ng/m³, PM_{2.5} S – 200 ng/m³, PM_{2.5} Si – 100 ng/m³, PM_{2.5} V – 2 ng/m³, PM_{2.5} Zn – 10 ng/m³, PM_{2.5} mass – 5 µg/m³, NO₂ – 10 µg/m³.

Table S21. Sensitivity analysis: Associations between PM_{2.5} composition and natural mortality with additional adjustment for neighborhood-level socio-economic status^a

Exposure	Exposure model	w/o CEANS (N = 302,968)			w/o EPIC_NL, HNR, KORA (N = 281,333)			w/o EPIC_NL, HNR, KORA (N = 281,333)			w/o CEANS, HNR, KORA (N = 293,510)		
		Main model ^b	Main model + unemployment rate	Main model	Main model + low educational level rate	Main model	Main model + high educational level rate	Main model	Main model + high educational level rate	Main model	Main model + Ethnicity	Main model	Main model + Ethnicity
PM _{2.5} Cu	SLR	1.121 (1.094, 1.148)	1.118 (1.091, 1.145)	1.127 (1.100, 1.154)	1.129 (1.102, 1.157)	1.127 (1.100, 1.154)	1.132 (1.104, 1.159)	1.123 (1.096, 1.150)	1.132 (1.104, 1.159)	1.123 (1.096, 1.150)	1.109 (1.081, 1.138)	1.123 (1.096, 1.150)	1.109 (1.081, 1.138)
	RF	1.157 (1.113, 1.203)	1.151 (1.107, 1.197)	1.171 (1.125, 1.219)	1.177 (1.130, 1.226)	1.171 (1.125, 1.219)	1.185 (1.137, 1.234)	1.159 (1.114, 1.206)	1.185 (1.137, 1.234)	1.159 (1.114, 1.206)	1.129 (1.081, 1.178)	1.159 (1.114, 1.206)	1.129 (1.081, 1.178)
PM _{2.5} Fe	SLR	1.143 (1.113, 1.174)	1.139 (1.109, 1.171)	1.149 (1.119, 1.181)	1.154 (1.123, 1.186)	1.149 (1.119, 1.181)	1.160 (1.128, 1.192)	1.145 (1.115, 1.177)	1.160 (1.128, 1.192)	1.145 (1.115, 1.177)	1.131 (1.098, 1.164)	1.145 (1.115, 1.177)	1.131 (1.098, 1.164)
	RF	1.141 (1.096, 1.188)	1.136 (1.091, 1.182)	1.152 (1.106, 1.201)	1.160 (1.112, 1.209)	1.152 (1.106, 1.201)	1.168 (1.120, 1.218)	1.139 (1.093, 1.186)	1.168 (1.120, 1.218)	1.139 (1.093, 1.186)	1.105 (1.058, 1.155)	1.139 (1.093, 1.186)	1.105 (1.058, 1.155)
PM _{2.5} K	SLR	1.048 (1.034, 1.062)	1.046 (1.032, 1.060)	1.051 (1.037, 1.066)	1.051 (1.036, 1.065)	1.051 (1.037, 1.066)	1.050 (1.036, 1.065)	1.049 (1.035, 1.064)	1.050 (1.036, 1.065)	1.049 (1.035, 1.064)	1.050 (1.036, 1.065)	1.049 (1.035, 1.064)	1.050 (1.036, 1.065)
	RF	1.054 (1.040, 1.068)	1.053 (1.040, 1.067)	1.056 (1.043, 1.070)	1.057 (1.043, 1.071)	1.056 (1.043, 1.070)	1.056 (1.042, 1.070)	1.055 (1.042, 1.069)	1.056 (1.042, 1.070)	1.055 (1.042, 1.069)	1.053 (1.039, 1.067)	1.055 (1.042, 1.069)	1.053 (1.039, 1.067)
PM _{2.5} Ni	SLR	1.086 (1.065, 1.108)	1.084 (1.063, 1.106)	1.099 (1.077, 1.122)	1.112 (1.088, 1.135)	1.099 (1.077, 1.122)	1.114 (1.091, 1.138)	1.087 (1.066, 1.109)	1.114 (1.091, 1.138)	1.087 (1.066, 1.109)	1.074 (1.051, 1.097)	1.087 (1.066, 1.109)	1.074 (1.051, 1.097)
	RF	1.023 (0.980, 1.067)	1.024 (0.982, 1.068)	1.018 (0.974, 1.064)	1.023 (0.978, 1.070)	1.018 (0.974, 1.064)	1.028 (0.983, 1.076)	1.017 (0.974, 1.062)	1.028 (0.983, 1.076)	1.017 (0.974, 1.062)	0.976 (0.932, 1.021)	1.017 (0.974, 1.062)	0.976 (0.932, 1.021)
PM _{2.5} S	SLR	1.138 (1.108, 1.169)	1.135 (1.105, 1.166)	1.146 (1.115, 1.177)	1.146 (1.116, 1.177)	1.146 (1.115, 1.177)	1.146 (1.115, 1.177)	1.139 (1.109, 1.170)	1.146 (1.115, 1.177)	1.139 (1.109, 1.170)	1.127 (1.097, 1.158)	1.139 (1.109, 1.170)	1.127 (1.097, 1.158)
	RF	1.123 (1.074, 1.174)	1.114 (1.065, 1.166)	1.132 (1.082, 1.185)	1.132 (1.082, 1.185)	1.132 (1.082, 1.185)	1.131 (1.081, 1.184)	1.128 (1.078, 1.181)	1.131 (1.081, 1.184)	1.128 (1.078, 1.181)	1.111 (1.061, 1.163)	1.128 (1.078, 1.181)	1.111 (1.061, 1.163)
PM _{2.5} Si	SLR	1.287 (1.219, 1.358)	1.279 (1.211, 1.352)	1.301 (1.232, 1.373)	1.313 (1.243, 1.388)	1.301 (1.232, 1.373)	1.324 (1.252, 1.399)	1.292 (1.223, 1.365)	1.324 (1.252, 1.399)	1.292 (1.223, 1.365)	1.256 (1.184, 1.331)	1.292 (1.223, 1.365)	1.256 (1.184, 1.331)
	RF	0.951 (0.902, 1.004)	0.945 (0.896, 0.998)	0.964 (0.916, 1.014)	0.963 (0.915, 1.013)	0.964 (0.916, 1.014)	0.964 (0.916, 1.014)	0.947 (0.896, 1.000)	0.964 (0.916, 1.014)	0.947 (0.896, 1.000)	0.924 (0.874, 0.976)	0.947 (0.896, 1.000)	0.924 (0.874, 0.976)
PM _{2.5} V	SLR	1.065 (1.047, 1.083)	1.063 (1.045, 1.081)	1.070 (1.051, 1.089)	1.077 (1.058, 1.097)	1.070 (1.051, 1.089)	1.079 (1.060, 1.099)	1.066 (1.048, 1.084)	1.079 (1.060, 1.099)	1.066 (1.048, 1.084)	1.055 (1.036, 1.074)	1.066 (1.048, 1.084)	1.055 (1.036, 1.074)
	RF	1.095 (1.053, 1.139)	1.095 (1.053, 1.139)	1.107 (1.062, 1.154)	1.111 (1.066, 1.159)	1.107 (1.062, 1.154)	1.113 (1.067, 1.160)	1.096 (1.053, 1.140)	1.113 (1.067, 1.160)	1.096 (1.053, 1.140)	1.061 (1.017, 1.106)	1.096 (1.053, 1.140)	1.061 (1.017, 1.106)
PM _{2.5} Zn	SLR	1.050 (1.038, 1.063)	1.049 (1.036, 1.062)	1.074 (1.059, 1.088)	1.074 (1.060, 1.089)	1.074 (1.059, 1.088)	1.074 (1.060, 1.089)	1.056 (1.043, 1.070)	1.074 (1.060, 1.089)	1.056 (1.043, 1.070)	1.051 (1.038, 1.065)	1.056 (1.043, 1.070)	1.051 (1.038, 1.065)
	RF	1.058 (1.033, 1.085)	1.055 (1.029, 1.082)	1.113 (1.078, 1.149)	1.113 (1.078, 1.149)	1.113 (1.078, 1.149)	1.112 (1.078, 1.148)	1.058 (1.032, 1.085)	1.112 (1.078, 1.148)	1.058 (1.032, 1.085)	1.055 (1.029, 1.082)	1.058 (1.032, 1.085)	1.055 (1.029, 1.082)

^aSee Table S20 for effect estimates in the full population. Total number of observations = 323,782; person-years at risk = 6,317,235; number of death from natural mortality = 46,640.

^bMain model adjusted for sub-cohort id, age, sex, year of enrollment, smoking (status, duration, intensity²), BMI categories, marital status, employment status and 2001 neighborhood-level mean income
SLR = Supervised Linear Regression model, RF = Random Forest model. HR (95% confidence interval) presented for the following increments: PM_{2.5} Cu – 5 ng/m³, PM_{2.5} Fe – 100 ng/m³, PM_{2.5} K – 50 ng/m³, PM_{2.5} Ni – 1 ng/m³, PM_{2.5} S – 200 ng/m³, PM_{2.5} Si – 100 ng/m³, PM_{2.5} V – 2 ng/m³, PM_{2.5} Zn – 10 ng/m³, PM_{2.5} mass – 5 µg/m³, NO₂ – 10 µg/m³.

Figure S1. Map of study areas

Figure S2. Average of cohort-specific Spearman correlation coefficients between PM_{2.5} composition

Figure S3. Natural spline (3 degree of freedom) for associations between $PM_{2.5}$ composition and natural cause mortality

Histogram shows the exposure distribution (exposure distribution for each individual cohort is shown in Figure 1); Shaded: 95% confidence intervals; Y-axis truncated at 0.5 and 1.5 for all components; Hazard ratios are expressed relative to minimum exposure.

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Chapter 7

General Discussion

The main objective of this thesis is to develop Europe-wide land use regression models for key pollutants PM_{2.5}, NO₂, O₃, black carbon (BC) and PM_{2.5} elemental composition, as well as to evaluate the mortality effects of PM₁₀, PM_{2.5} and PM_{2.5} composition. We compared exposure models developed with different statistical algorithms, and the health effects assessed by applying the different exposure models. This research has benefited from the unique air pollution dataset collected by a purpose-designed monitoring campaign conducted in 2008-2010 in the framework of the European Study of Cohorts for Air Pollution Effects (ESCAPE)^{1,2}, and the large population in the Effects of Low-level Air Pollution: A Study in Europe (ELAPSE) pooled cohort with detailed individual-level covariates³. This research advances our knowledge on two of the current challenges in air pollution epidemiology: the health effects of air pollution at low concentrations and the most responsible components within PM for the adverse health effects. A systematic review of the literature of long-term exposure to PM air pollution and mortality was conducted to assess the current state of knowledge and assess research challenges.

This chapter begins with a summary of the main findings in this thesis. Then methodological issues related to confidence assessment of epidemiological evidence in systematic reviews, spatial scale and statistical algorithms for developing exposure models, existing evidence on health effects of long-term PM composition exposure, and the implications of this research are discussed.

1. Main findings

In **Chapter 2**, we systematically reviewed the existing evidence on associations of long-term exposure to PM₁₀ and PM_{2.5} with natural-cause and cause-specific mortality. We identified 107 studies, of which 104 were cohort studies. The majority of studies were conducted in North America (N = 62) and Europe (N = 25). We performed meta-analysis to derive a combined risk ratio (RR) of 1.08 (95% CI 1.06, 1.09) per 10 µg/m³ for PM_{2.5} and natural-cause mortality. Substantial heterogeneity was found across studies, probably related to differences in study populations, methodology, exposure level and composition of particles. Meta-analyses of studies conducted at low mean PM_{2.5} levels (<25, 20, 15, 12, 10 µg/m³ respectively) yielded RRs that were similar or higher compared to the overall RR, consistent with the finding of generally linear or supra-linear concentration-response functions (CRFs) in individual studies. There is evidence that associations between PM_{2.5} and increased mortality risk remained below the current EU limit exposure level (25 µg/m³)⁴, the US Environmental Protection Agency (EPA) National Ambient Air Quality Standards (NAAQS; 12 µg/m³)⁵, and the World Health Organization (WHO) air quality guideline value (10 µg/m³)⁶. Studies at low concentrations were mostly performed in North-America.

The ELAPSE project is conducted to provide new empirical evidence on associations between low-level air pollution and adverse health effects in Europe. In order to assess air pollution exposure for ELAPSE cohort participants, Europe-wide hybrid land use regression (LUR) models for 2010 annual mean concentrations of PM_{2.5}, NO₂, BC and O₃ at 100x100 m resolution were developed in **Chapter 3**. The models were developed with a supervised linear regression (SLR) incorporating satellite observations, chemical transport model estimates, land use and traffic data as potential predictor variables. Kriging was performed to further explain spatial variations in residuals of the LUR models. Kriging significantly improved the PM_{2.5} and O₃ but not the NO₂ and BC models. The PM_{2.5}, NO₂, O₃ warm season and BC models explained 66%, 58%, 60% and 51% of the variability in measured concentrations in five-fold cross-validation, respectively. The spatial structures of the models were stable in time at the West-European scale, allowing for application in long-term epidemiological studies with cohorts started one or two decades ago.

In view of the increasing number of air pollution exposure assessment studies exploring application of sophisticated and complex statistical algorithms beyond ordinary linear regression, we compared 16 different algorithms (linear regression, regularization and machine-learning algorithms) to develop

Europe-wide PM_{2.5} and NO₂ models in **Chapter 4**, using the same air pollution measurements and potential predictor variables used in Chapter 3. We observed similar performance across algorithms evaluated by both five-fold cross-validation and external validation. The predicted concentrations from all algorithms at external validation sites were highly correlated ($R^2 > 0.85$).

In **Chapter 5**, we developed Europe-wide LUR models for eight *a priori* selected elemental components in PM_{2.5} – copper (Cu), iron (Fe), potassium (K), nickel (Ni), sulfur (S), silicon (Si), vanadium (V) and zinc (Zn), using supervised linear regression (SLR) and random forest (RF), a machine-learning algorithm. The models performed moderate to well across Europe, explaining 41% to 90% of the overall variability in measured concentrations in five-fold cross-validation. RF consistently outperformed SLR to explain overall concentration variability in the validation. Models explained within study area variation much less than the overall variation, with similar performance for RF and SLR for the within study variation. Maps proved a useful additional tool to evaluate the plausibility of model predictions beyond cross-validation statistics. Models differed substantially between elements in terms of the major predictor variables, broadly reflecting known sources. Agreement between the two algorithm predictions was high at the overall European level for Cu, K, S and Zn ($r > 0.7$), and varied substantially at the national level.

In **Chapter 6**, we assessed associations between PM_{2.5} elemental composition and mortality in the ELAPSE pooled cohort ($N = 323,782$). We applied exposures derived from both supervised linear regression (SLR) and random forest (RF) models developed in Chapter 5 and compared their relation with health outcomes. All SLR-modeled components were statistically significantly associated with natural-cause mortality in single pollutant models with hazard ratios (HRs) from 1.05–1.27. Similar HRs were observed for RF-modeled Cu, Fe, K, S, V and Zn with wider confidence intervals (CIs). For both SLR- and RF-modeled V, HRs attenuated but remained above unity and (borderline) significant after adjustment for PM_{2.5} mass or NO₂. The HRs for V were 1.03 (95% CI: 1.02, 1.05) and 1.06 (95% CI: 1.02, 1.10) for SLR- and RF-modeled exposures, respectively, per 2 ng/m³ adjusting for PM_{2.5} mass. Associations for the other components were weaker for exposure modeled with RF than SLR in two-pollutant models.

2. Risk of bias and certainty of evidence assessments in systematic reviews

Risk of bias assessment tools are increasingly used in systematic reviews for appraisal of individual studies. The optimal method for assessing risk of bias within individual observational studies is currently an active area of research with no clear consensus⁷⁻⁹. Different risk of bias assessment tools include different bias domains and/or define the same domains differently. Risk of bias assessments of individual studies are part of evidence synthesis, and act as a domain for downgrading the overall quality of evidence in the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system¹⁰. The GRADE approach is a framework for rating the overall certainty of evidence in the collection of systematically reviewed studies (a ‘body of evidence’). There are other frameworks currently being used by government and public health agencies for certainty assessment in evidence synthesis. For example, the International Agency for Research on Cancer (IARC) goes beyond direct evidence from epidemiologic studies to come to a final assessment regarding human carcinogenicity¹¹. IARC synthesizes evidence from epidemiologic studies, animal studies, pharmacokinetic/mechanistic experiments, and surveys of human exposure. Likewise, the US EPA considers evidence across disciplines including atmospheric science, toxicology, epidemiology, and aquatic and terrestrial ecology, to develop an Integrated Science Assessment (ISA) for the criteria air pollutants¹².

In the systematic review conducted in Chapter 2, we applied a domain-based risk of bias assessment tool¹³ and an adapted GRADE framework (see online Appendix 6a of Chapter 2: <https://ars.els-cdn.com/content/image/1-s2.0-S0160412020319292-mmc7.docx>) that were specifically developed for the review purpose coordinated by the WHO. The intention of applying these assessment tools is to

increase transparency and replicability, and to limit subjectivity in the evaluations. However, we struggled with applying these assessment tools when conducting the systematic review. Concerns have been raised regarding the implementation of these tools in the context of environmental epidemiological studies^{14,15}.

One major concern is the mechanistic application of these standardized algorithms without clear explanation of the reasoning behind the judgements¹⁴. Assessment of study validity is complex, and it requires substantive knowledge of the topic being examined. Mechanistically checking a list of study attributes without a thoughtful and informative guidance by subject-matter expertise is likely to yield erroneous conclusions and may dismiss important evidence. Algorithmic assessments of the same studies with different tools can result in opposite conclusions¹⁶. Therefore, in my opinion, the main value of risk of bias assessment derives from the clear reasoning behind the judgements, which inherently depends on subjective expert evaluation. To prevent purely mechanistic assessments, two suggestions are given below:

First, to identify the critical domains that have potential to introduce bias before conducting risk of bias assessments. The vulnerable aspects of a particular research topic are usually well-known to experts in that field and thus scrutiny should be focused on these domains. For example, misclassification in outcome measurement is unlikely to play a major role in mortality studies because mortality data are often derived from death registries and the causes of death are coded according to the international classification of diseases (ICD) typically using broad groups of causes (e.g., natural-cause, cardiovascular, respiratory). Whereas in morbidity studies, outcome measurement should be more carefully examined depending on the source of incidence data (e.g, self-reports, hospital discharge records), because the date of disease onset is not always well documented. The different data sources may introduce different biases and thus contribute to heterogeneity of effect estimates across studies.

Second, to characterize the direction, magnitude and relative importance of individual biases. Risk of bias tools typically only determine whether a risk for specific biases occurs without quantifying it. Furthermore, the tools assess *risk* of bias, not whether the bias actually occurs. Characterizing the biases helps to provide an informative summary and assessment when evaluating the evidence in an individual study or in a set of studies. For example, if an elevated risk is found and only classical nondifferential measurement errors in the exposure variables are present, we will still have confidence in the evidence of a positive association because these errors generally bias effect estimates towards null. If biases compensate for one another when one tends to produce an upward bias and the other produces a downward bias, confidence in the evidence for a positive association is still supported¹⁷. Identifying which of the potential biases are most influential also helps to give clear guidance for optimizing future studies on a topic.

Another major concern is that most risk of bias assessment tools and the GRADE framework consider hypothetical randomized controlled trials (RCTs) as ideal study¹⁵. This is because these tools are initially implemented for evaluating evidence to develop clinical guidelines^{18,19}. As a result, observational studies are considered to produce evidence of a lower certainty compared to RCTs in the GRADE framework, and some of the domains in the risk of bias assessment tools are not applicable to observational studies.

Although RCTs are typically considered the strongest study design in epidemiology because of its ability to eliminate or strongly reduce confounding²⁰, it is unethical and often impossible to randomize people to potentially harmful exposures with no perceived benefits in the context of environmental epidemiology. Besides, RCTs would have to involve impossibly long follow-up periods and large sample sizes to have sufficient statistical power for observing chronic disease onset or rare outcomes²¹. Moreover, as participants in RCTs often differ from the general population, the results of an RCT may not be generalizable. Observational studies, in contrast, are conducted in real life and thus – when based on random samples of the target population – reflect the nature of population-level exposures²². Outcomes with long latencies can be evaluated with long follow-up time, which is possible both

prospectively in cohort studies and retrospectively in case-control studies. Furthermore, a series of sensitivity analyses is usually done in observational studies to ensure the robustness of findings and for critical appraisal²³. Observational studies focus on characterizing concentration-response relationships, rather than simply comparing the outcome between exposed and unexposed groups as in RCTs. Given the challenges in conducting and interpreting RCTs in the context of environmental epidemiology, I argue, evidence from observational studies should not automatically be considered as weaker than evidence from RCTs.

One domain for downgrading the overall certainty of evidence in the GRADE framework is inconsistency/heterogeneity. However, heterogeneity is present in observational epidemiologic studies by nature because of factors such as different populations, exposure assessment methods, pollution mixtures, time periods, geographic locations or study designs. In fact, apparently conflicting results from epidemiological studies do not necessarily indicate that some are false positives or false negatives²⁴. This might, for example, reflect differences in exposure levels or susceptibility of the populations. On the contrary, consistent findings from environmental epidemiological studies conducted in different populations under different study designs should be considered as a domain for upgrading the overall certainty of evidence, because it is unlikely that the same biases will occur in multiple studies with different underlying patterns of confounding. For example, it is more convincing that associations between respiratory symptoms and air pollution from truck traffic were observed in different locations across the world. The associations found in Western Europe and North America were not different from those found in other parts of the world²⁵.

Statistical methodology is not included as a domain in the risk of bias assessment tools but is important for observational studies. Observational studies generally use models to assess the relationships between exposure and outcome and to control for potential biases. Misuse of models or violation of statistical assumptions may lead to biased or erroneous results. A methodological study conducted within the American Cancer Society cohort suggested failure to account for spatial autocorrelation can lead to an understatement of the uncertainty of the air pollution association with mortality²⁶. Other concerns include over-adjustment for covariates, adjusting for causal intermediates, incorrect assignment of exposure²⁷. Adding the statistical methodology domain may make it possible to infer the direction of resulting biases¹⁵.

To conclude, RCTs should not be considered as ideal study design when studying environmental exposures. The risk of bias and certainty of evidence assessment tools need to be adapted for better evaluation of observational studies. Mechanistic application of the tools is not informative for assessment of individual studies or the body of evidence. Clear reasoning behind the judgements is needed. The less mechanistic frameworks provided by IARC and the US EPA for evidence assessment provide a better starting point, particularly as these frameworks integrate assessments from more disciplines than epidemiology.

3. Air pollution exposure model development

Spatial scale

Air pollution exposure models with different spatial scales are developed to meet the requirements of the epidemiological studies. In chapter 3 and chapter 5, we developed Europe-wide LUR models for application in the ELAPSE project. ELAPSE is a multi-center project involving collaboration of cohorts from eleven countries across Europe^{3,28-31}. One advantage of applying harmonized exposure models in such international studies is the consistency of exposure assessment methodology. Applying different exposure assessment approaches may affect conclusions drawn in epidemiological studies³², and may affect interpretations of multi-pollutant analyses if different exposure methods were applied for different pollutants in the same study³³. Similarly, large-scale national or continental exposure models at a fine resolution have been developed previously to provide consistent exposure estimates for large

study populations in North-American studies^{34,35}. In the global studies such as the Global Burden of Diseases (GBD) assessment³⁶ and the International Study of Asthma and Allergies in Childhood (ISAAC)³⁷, global air pollution exposure models were used. Models applied in the global projects are usually derived from satellite estimates at a coarse resolution (e.g., $0.1^\circ \times 0.1^\circ$, $\sim 10 \times 10$ km)³⁸⁻⁴⁰. Although using models at a coarse resolution might be sufficiently accurate for pollutants that have relatively small spatial variability such as long-range transported sulfate^{41,42}, it might introduce large uncertainties and potentially bias epidemiological associations when estimating exposure to pollutants that vary considerably at local scale (e.g., traffic-related pollutants)^{1,2,41}. The Women's Health Initiative study showed larger cardiovascular mortality risks of PM_{2.5} related to within-city contrasts compared to between-city contrasts⁴³. Effect estimates would be underestimated if only between-city contrasts were exploited. Therefore, it is necessary to develop models for a large domain with fine spatial resolution.

The Europe-wide models for BC and PM composition developed in this thesis are based on pooled measurements from individual ESCAPE study areas^{1,41}. Area-specific models were developed previously for the same pollutants for application in the ESCAPE study^{44,45}. One reason for developing Europe-wide models in this thesis is that the ESCAPE models do not meet the requirements for the ELAPSE project. Most ESCAPE study areas were a large city with surrounding smaller rural communities. The ELAPSE project covers a larger study area than the ESCAPE individual study areas. For example, ESCAPE models were developed for the city of Copenhagen and surrounding areas, while the ELAPSE project includes the population distributed across entire Denmark. Local LUR models are typically not transferable from one area to another^{46,47}, though some studies suggested local calibration with data from a few monitoring sites may improve the transferability^{48,49}. Large-area models can probably be applied within the domain the models were developed, in our case Western Europe.

One benefit of developing Europe-wide models by pooling measurements from the ESCAPE study areas is the increasing number of training sites in the modeling process. Methodological studies suggested more training sites in model development result in more robust LUR models with better performance^{50,51}, and therefore more accurate health effect estimates⁵². Another benefit is the ability to make use of large-scale satellite and chemical transport model (CTM) estimates for assessing the background concentrations of air pollutants at approximately 10×10 km resolution. This benefit applies for pollutants that lack the main sources and have very low concentrations in individual areas. For these pollutants, no area-specific models could be developed in areas without the main source present, or poor models were developed mainly explained by predictors that are not representing the sources⁴⁴. When developing Europe-wide models for these pollutants, the model was informed by areas where specific sources were present. Large-scale satellite or chemical transport model estimates contributed to assess the low background concentrations in areas where sources are lacking (Chapter 5). This is still helpful when applied in epidemiological studies exploiting between-area contrasts in pollution concentrations. On the other hand, the potential predictor variables offered for developing large-scale models are restricted to variables that are available for all study areas. For example, traffic intensity variables are only available for part of ESCAPE study areas⁵³. Traffic intensity variables would have been a better predictor representing traffic emissions than road length used in our Europe-wide models^{54,55}. The ESCAPE area-specific models for NO₂ on average improved 10% by offering traffic intensity data compared to road length data⁵⁶. Therefore, in epidemiological studies involving only a single community, local models might be a better choice than larger scale models as these models will have been developed with the most extensive information available locally. The advantage of local models applies primarily when a sufficient number of sites is available for model training. Wang and co-workers suggested that for study areas in the ESCAPE study, fairly robust models could be developed with about 40 sites and more⁵⁰.

Depending on the requirements of the epidemiologic study, the most appropriate exposure model should be applied. To adapt to the development in quantifying health effects of air pollution at low

concentrations using large populations, large-scale national or continental models at sufficiently fine spatial resolution are needed.

Statistical algorithms

LUR models are often developed with the ordinary least square linear regression algorithm^{57,58}. There are four assumptions associated with a linear regression model: 1) the relationship between X and the mean of Y is linear (linearity); 2) the variance of residuals is the same for any value of X (homoscedasticity); 3) observations are independent of each other (independence); 4) for any fixed value of X, Y is normally distributed (normality)⁵⁹. Violation of the assumptions would reduce the accuracy of LUR model estimates and/or affect regression coefficient estimation. Other concerns of applying a multiple linear regression algorithm in developing spatial models include overfitting, collinearity, spatial non-stationarity and spatial autocorrelation. In chapter 4, we compared 16 different algorithms to predict spatial variation in annual average of PM_{2.5} and NO₂ across Europe. We observed similar performance for models developed with the different algorithms. Two of the concerns that were not fully addressed in chapter 4 are spatial non-stationarity and spatial autocorrelation. Spatial non-stationarity implies inconstant relationships among variables across space. This property leads to spatial instability of regression coefficients and can be associated with heteroskedastic regression residuals⁶⁰. For example, one might expect that regression coefficient for road length might not be the same in Portugal and in the Netherlands. One approach to resolve spatial non-stationarity is the geographically weighted regression (GWR) algorithm⁶¹. In a GWR, spatially varying coefficients are estimated for predictors by developing local regression models at numerous local neighborhoods. GWR has been applied to model ground-level air pollution exposures based on satellite observations⁶²⁻⁶⁴, but not much in LUR modeling⁶⁵. Spatial autocorrelation can be defined as similarity of observations over short distances⁶⁶, and can result in autocorrelated residuals if the model does not fully explain the spatial patterns. Some studies suggested the residuals of LUR models were independent for models developed in metropolitan areas even though significant spatial autocorrelation was present in the measured concentrations^{67,68}. One study resolved spatial autocorrelation in sulfur dioxide model residuals with a spatial autoregressive model⁶⁹. In developing spatiotemporal models for PM_{2.5}, convolutional layers aggregating neighboring information were used in a neural network algorithm to account for spatial and temporal autocorrelation⁷⁰. In chapter 3, kriging was performed on the residuals from the supervised linear regression models to account for the spatial autocorrelation⁵⁵. In chapter 4, we observed kriging on the residual of the generalized boosted machine and neural network models, both are machine-learning algorithms, did not significantly improve the model performance. This indicated that the machine-learning algorithms have some ability to address spatial autocorrelation.

Machine-learning algorithms have increasingly been applied in air pollution exposure assessment^{34,70-73}. Although similar performance was observed for machine-learning algorithms and supervised linear regression algorithm in chapter 4, when modeling spatial variation in annual average PM_{2.5} and NO₂ concentrations, machine-learning models accounted for spatial trends across Europe better than the linear models for PM_{2.5} composition (chapter 5). The different findings could be explained by the different distribution of monitoring sites for model development. While the PM_{2.5} and NO₂ models were developed on a large number of fairly evenly distributed routine monitoring sites, the PM_{2.5} composition models were based on clustered ESCAPE monitoring sites. Another possible explanation is that there might be more complex relationships between predictors and elemental composition than with the mass of PM_{2.5} and NO₂. Studies generally reported a similar or better performance of machine-learning algorithms compared to linear regression algorithm. In a study developing local-scale PM_{2.5} composition exposure models based on 24 sites, random forest, a machine-learning model, outperformed linear models⁷⁴. In another study modeling ultrafine particle (UFP) concentrations based on mobile monitoring, similar performance was observed for machine-learning and linear models⁷⁵. More work is needed to understand the performance of different algorithms in different conditions.

Machine-learning algorithms are attractive because they relax the assumptions of linear regression models and offer a flexible way to model the relationships including non-linearity and interactions⁵⁹. They further require less theoretical knowledge (e.g., *a priori* transformation of predictor variables to fit the linearity assumption) than linear regression models. However, the opaque modeling process of the machine-learning models results in difficulty in interpretation. Although some machine-learning algorithms provide useful information such as relative importance of individual predictors, it is not as straightforward as the regression coefficients of predictors derived from linear regression models.

Understanding how the machine-learning algorithms work would help to interpret the derived models. For example, in Chapter 5 we observed strong boundary effects in exposure surfaces produced by random forest models. This can be explained by the classification nature of the random forest algorithm: depending on the value where decision trees are split, large difference in predictions will be produced below and above that value. Therefore, smoothing might be required before applying the exposure surfaces in epidemiological studies. Even without fully understanding the method, it is important to graphically document what the complex model predicts. In chapter 5 we illustrated the importance of mapping the predicted exposures. Providing scatterplots or three-dimensional surfaces of predicted concentrations versus important predictor variables is another tool to understand the predictions of the model⁷⁶. In addition, models developed with machine-learning algorithms could be improved significantly with careful tuning and/or training⁵⁹. For example in chapter 4, the neural network performed the worst among the tested algorithms, whereas it achieved high predictive accuracy in modeling the spatiotemporal variation of PM_{2.5} over the continental US⁷⁰. In the latter study, the authors trained the neural network with more sophisticated methodology including adding convolutional layers. We cannot rule out the possibility of better performance of our Europe-wide models with more sophisticated training.

Another suggestion for future application of statistical algorithms in air pollution exposure modeling is not assuming one algorithm *a priori*, but to find the best predictive model for the data. A study selected the optimal prediction model from 11 statistical algorithms to estimate population exposure to PM during wildfires⁷⁷. Ensemble predictions can also be attractive because they leverage information from several individual models. In chapter 4 we developed two simple ensemble models by calculating the median value or a weighted average of the 16 individual model predictions. In a study modeling UFP concentrations, a ‘Super Learner’ algorithm was applied to combine results from a wide range of different modeling techniques⁷⁵. Neither our simple ensemble models nor the ‘Super Learner’ algorithm improve upon the individual models. However, the idea to combine individual models and average out biases is attractive. Further research is needed.

Health effects related to air pollution exposure modelled with different algorithms have been even less compared than predicted exposure. In chapter 6 we illustrated that while supervised linear regression and random forest had similar performance in predicting particle component exposures, the estimated associations with linear regression were generally more consistent than with random forest. The estimated associations with health depend not only on the validity of the model, but also on the type of exposure measurement error (Berkson, classical), the predicted exposure contrast and the relationship with potential confounders. Szpiro et al. has provided a theoretical discussion of the discrepancy between models with the best exposure prediction and models with the least bias⁷⁸.

Different statistical algorithms have their pros and cons. Understanding these would help to develop models with better prediction accuracy and help to interpret the models. With the development in computing capability, it is attractive to select the best model from a number of algorithms, or to develop an ensemble model from several models.

4. Long-term exposure to PM composition and health

Only a few epidemiological studies have investigated health effects of long-term exposure to PM composition. The number of studies has been small because of the scarcity of measurements relative to regulated pollutants such as PM_{2.5} and NO₂ and methodological challenges. So far, mixed findings have been reported for associations between health outcomes and a series of PM_{2.5} components including secondary inorganic aerosols (sulfate, nitrate, ammonium), elemental carbon (EC), metals and organic components. Some of the discrepancies can be explained by the different populations, exposure assessment methods and statistical modeling approaches applied in the studies.

Sulfate, sometimes quantified as elemental sulfur, is most consistently associated with a variety of health outcomes across studies. Two pivotal studies in the early 1990s – the Harvard Six Cities study⁷⁹ and the American Cancer Society study⁸⁰ – reported associations between long-term sulfate exposure and mortality from all causes, lung cancer and cardiopulmonary diseases. Later studies conducted in the North America and Europe continued to find elevated risk of mortality and morbidity in relation to long-term sulfate exposure^{27,81-86}. Sulfate is long-range transported and thus has relatively uniform concentrations within cities. The relatively large-scale spatial variation of sulfate allows the U.S. studies, which typically relied on central site ambient air pollution monitoring networks, to assess the health effects related to sulfate exposure. However, it is difficult to disentangle effects of sulfate from that of PM_{2.5} mass because of the high proportion of sulfate in PM combined with its relatively low fine spatial scale variability^{87,88}. In the ESCAPE meta-analysis of 19 European cohorts, association between PM_{2.5} sulfur and all-cause mortality was robust to adjustment for PM_{2.5} mass⁸¹. In the ELAPSE pooled cohort, we observed the associations of PM_{2.5} sulfur with mortality attenuated substantially after adjustment for PM_{2.5} mass. The HR for SLR-modeled sulfur remained positive in two-pollutant model, whereas the HR for RF-modeled sulfur reduced to unity (Chapter 6).

Studies on other secondary inorganic aerosols are fewer compared to sulfate. In a cohort of more than 100,000 current and former female public school professionals in the California Teachers Study, nitrate was associated with mortality from cardiovascular and Ischemic Heart Disease (IHD), but not with pulmonary disease mortality⁸⁹. Nitrate was also reported to be positively associated with mortality rate in studies within the U.S. Medicare beneficiaries and the U.S. veterans⁹⁰⁻⁹². In the large Danish Diet, Cancer and Health cohort⁸⁵, a positive association was observed between long-term nitrate exposure and mortality from all causes and respiratory diseases. The Danish study also reported negative associations between ammonium and mortality when taking into account overall secondary inorganic aerosols in multipollutant models. The negative associations can possibly be explained by the differences in exposure estimate precision combined with high correlation between pollutants instead of protective effect. We did not assess associations with nitrate or ammonium in the ELAPSE study.

There is mounting evidence on associations between adverse health outcomes and long-term exposure to black carbon particles, including black carbon (BC), black smoke (BS), absorption coefficient of PM (Abs) and elemental carbon (EC)⁹³. These black carbon metrics are all indicators for carbon-rich combustion sources and are often used interchangeably in the literature. Important sources of BC include coal combustion, diesel-powered motorized traffic and off-road machinery and wood burning. BC is a primary pollutant emitted especially as fine and ultrafine particles. A meta-analysis conducted in 2013 reported statistically significantly positive pooled estimate for all-cause mortality and EC⁹⁴. The EC exposure used in the meta-analysis includes BC or BS used as markers for soot in individual studies. Several later studies associated long-term EC exposure with risk of brain tumors and cardiovascular health outcomes^{27,85,89,95-98}. In ELAPSE, we found significantly positive associations between BC and mortality and incidence of stroke, asthma and COPD hospital admissions in the pooled cohort^{28,29,99}. Findings for organic carbon (OC) are more mixed. While some studies suggested long-term OC exposure related to cardiovascular outcomes^{27,84}, others did not^{83,90,98}. OC is a mixture of primary organic carbon particles and secondary organic aerosol formed in the atmosphere. Because of the more secondary nature of OC compared to EC, OC has less fine spatial scale variation compared to

EC/BC¹⁰⁰. OC consists of different components derived from very different sources (e.g., traffic, biomass burning). The varying relationships between OC and health endpoints can be partly explained by the different impacts of the specific components on health. One technical difficulty remains in reliably measuring the carbonaceous particles concentrations, which makes results across studies difficult to compare⁹³. Furthermore, the carbonaceous particles are highly correlated with NO₂ in concentrations, especially in the developed countries where an important source of both pollutants is diesel powered vehicles. The high correlations make it difficult to disentangle individual health effects. Another concern is that studies using limited number of monitors to represent exposure over large metropolitan areas do not sufficiently capture the large spatial gradients of the carbonaceous particles within a city^{83,98}. In the Women's Health Initiative-Observational Study (WHI-OS) and the Multi-Ethnic Study of Atherosclerosis (MESA)⁸⁴, the authors tried to address the sparseness of the EPA's Chemical Speciation monitoring Network (CSN) by adding additional monitoring data derived from a different measurement approach. However, the different measurement approach and sampling time used by the extra monitoring campaign might, on the contrary, increase the exposure measurement errors¹⁰¹. In the earlier California Teacher's study, the spatial variability issues were accounted for by restricting the analyses to participants living within 8- and 30-km buffers of a monitor²⁷. While the 30-km buffer might still be too large for capturing high spatial variation, the 8-km buffer reduced the sample size significantly and thus the statistical power⁸⁹. Recent studies typically applied fine spatial scale models to estimate exposure at the individual level (i.e., the outdoor concentrations at participants' residences)^{85,89,102}. Validity of the fine-scale air pollution models needs to be carefully examined, because the estimated effect of pollutant can be transferred from a less precisely modelled constituent to a more adequately modelled constituent in multi-pollutant models¹⁰³.

Mixed results have been reported for associations between health outcomes and long-term exposure to a variety of metals, including copper, iron, zinc, nickel, vanadium, potassium, calcium, lead, manganese, aluminum and sodium^{81,83,84,89,91}. One challenge in studying health effects of metal composition is to reliably estimate their concentrations. Metals usually have low concentrations, sometimes with a large number of measurements below the limits of detection^{41,83}. The low concentration of metals might hinder the assessment of their health impacts, as exposure estimates derived from models based on these low-concentration measurements are likely to be imprecise⁴⁴. This issue applies especially to metals such as nickel, vanadium, lead, but much less for the traffic-related iron, zinc and copper. Some of the metals are difficult to model, because the GIS databases do not readily contain the relevant predictor variables such as shipping emissions or wood burning⁴⁴. For these metals direct monitoring may be attractive. However, characterizing individual- or population-level metal exposures with one or a few monitors within a city may introduce large measurement error for metals with high spatial heterogeneity^{27,83}. This may bias the epidemiological findings unless there is a large contrast in exposure between cities. Another challenge is to separate the effects of individual components within PM, which is not restricted to metal composition. Individual components or elements are typically linked to one or more specific sources while several elements often share the same source. Studies have linked source categories directly to health outcomes using source apportionment results as an alternative approach to studying specific components^{83,89,98}. An analysis in the American Cancer Society Cancer Prevention Study II (ACS CPS-II) suggested exposure to coal combustion-related air pollution explained most associations between PM_{2.5} mass and increased risk of mortality from all causes, IHD and lung cancer^{83,98}. In the California Teachers study, associations with IHD mortality were observed for sources including gas- and diesel-fueled vehicles, meat cooking and high-sulfur fuel combustion⁸⁹. Other studies used source apportionment results of elements as tracers for specific sources to assist in the interpretation of the health effects^{81,84}. For example, in the Rome longitudinal study, higher mortality risk was found to be associated with increased exposure to copper, iron and zinc, representing non-tailpipe traffic emissions¹⁰⁴. Applying the same set of exposure models, analyses conducted within the ESCAPE and TRANSPHORM (Transport related Air Pollution and Health impacts – Integrated Methodologies for Assessing Particulate Matter) concluded long-term exposure to transition metals

originating from traffic and industry may be related to chronic systemic inflammation¹⁰⁵. Linking source categories to health endpoints may represent the combined effects of multiple pollutants from the same source and is more readily translatable into air quality policy. However, it may introduce additional uncertainties and assumptions. Source apportionment results can be different depending on the different methodologies¹⁰⁶. Furthermore, it is difficult to compare the quantitative effect estimates for pollution sources across studies that are varied in time and space. In ELAPSE, we did not directly assess which source categories are most responsible for health effects but used source apportionment results in Europe to assist in the interpretations as was done in ESCAPE^{81,107-109}. Future studies are suggested to link both source categories and individual components to the health endpoints, with a focus on examining consistencies and differences between the two approaches, following the National Particle Component Toxicity (NPACT) study^{83,98}. When source apportionment results are used, researchers should recognize and discuss the uncertainties introduced by the apportionment method.

The analyses within the ACS CPS-II found no association with mortality for soil and biomass combustion source categories and their elemental tracers (calcium, silicon and potassium)⁹⁵. Consistently, a negative and marginal association was observed for CVD events with silicon in the WHI-OS⁸⁴. Silicon is a specific tracer for crustal material that is a large component of soil and resuspended road dust. However, a distinction between soil and road dust is often not possible because of the overlapping source profiles⁴². Crustal materials are often abundant in coarse particles. There is little evidence for an association between long-term coarse PM exposure and adverse health effects^{94,110}. The 2019 Integrated Science Assessment (ISA) rated the association between PM_{coarse} exposure and natural-cause mortality as “suggestive”¹¹¹. In contrast, a few studies have reported adverse cardiovascular effects of long-term exposure to silicon^{27,108}. In the California Teachers Study, the authors interpreted the silicon exposure as a proxy either for toxic constituents found in road dust or for exposures to traffic-related pollutants²⁷.

Recent studies have tried to associate adverse health effects with oxidative potential of particulate matter¹¹²⁻¹¹⁴, as it was proposed that oxidative potential may be a more health relevant metric than PM mass^{115,116}. However, it remains challenging to specifically model the concentrations for oxidative potential, because emission factors are not available and specific sources are not known¹¹⁷. We did not assess health effects of oxidative potential in ELAPSE, because Europe-wide data were not available.

Although multiple groups of PM components and sources have been linked to a variety of adverse health outcomes, the collective evidence has not yet isolated elements or sources that are most strongly and unequivocally related to specific health endpoints¹¹⁸. Similarly, the US EPA concluded in the Integrated Science assessment (ISA) for PM that there was evidence for associations of mortality with multiple elements, without a clear pattern of particularly important components¹¹¹. Further research is needed to address the methodological challenges in this field and to provide more evidence about the relative harm of the specific components. Methodological challenges discussed in this section include: 1) more limited routine monitoring compared to regulated pollutants, which limits the possibilities to develop large-scale models and to assess historical exposures, as we experienced within ELAPSE; 2) Multiple comparison issues may apply if a large number of elements are included in an epidemiological study (risk of chance findings); 3) Multi-collinearity.

5. Implications

Application of air pollution models in the ELAPSE project

Europe-wide air pollution models developed in Chapter 2 and Chapter 5 for PM_{2.5}, NO₂, BC, O₃ and PM_{2.5} elemental composition were applied in the ELAPSE project to characterize individual exposures. Compared to the ESCAPE area-specific LUR models^{44,45,56}, the Europe-wide models allow for the consistent exposure estimation for all participants in the ELAPSE project. The models further cover

study areas that were not covered by the ESCAPE models. Moreover, methodological studies suggested more stable exposure models can be developed based on larger number of model training sites^{51,119}.

The ELAPSE project aims to investigate health effects of long-term exposure to low concentrations of outdoor air pollution in Europe³. ‘Low concentration’ is defined as less than the current EU limit values, the US EPA NAAQS and/or the WHO air quality guideline values, respectively. The study assesses the shape of the CRFs with a focus at the shape at low exposures. The ELAPSE project consists of a pooled cohort of more than 300,000 participants and seven large administrative cohorts of more than 28 million adults. In the pooled cohort, data from eight existing cohorts in seven European countries with detailed lifestyle data were combined and analyzed centrally. Analyses of the administrative cohorts were conducted locally, with fewer possibilities to control for individual-level confounders. A summary of the main findings of the ELAPSE project is given below.

In the **pooled cohort**, 325,367 adults were followed for an average of 19.5 years. Almost all subjects had 2010 annual average exposures to PM_{2.5} below the EU Limit Value (25 µg/m³). More than 50,000 and 25,000 subjects had exposures below the US-EPA NAAQS (12 µg/m³) and WHO AQG (10 µg/m³), respectively. Nearly all subjects had 2010 annual average exposures to NO₂ below the WHO AQG and EU Limit Values (40 µg/m³). Long-term exposure to PM_{2.5}, NO₂, BC were (borderline) significantly positively associated with mortality from natural-cause, cardiovascular and respiratory diseases¹²⁰. Hazard ratios (HR, 95% CI) for natural-cause mortality were 1.130 (1.106, 1.155) for a 5 µg/m³ increase in PM_{2.5}, 1.086 (1.070, 1.102) for a 10 µg/m³ increase in NO₂ and 1.081 (1.065, 1.098) for a 0.5*10⁻⁵/m increase in BC. For these pollutants, a supra-linear CRF with steeper slopes at low exposures was observed, with no evidence of a threshold. Consistently, HRs were slightly larger in subsets of participants restricted to low exposures. The HR for natural-cause mortality was 1.296 (1.140, 1.474) for subjects with PM_{2.5} exposures below the US standard of 12 µg/m³. The HR for natural-cause mortality was 1.101 (1.083, 1.119) for subjects with NO₂ exposures below the WHO and EU limit value of 40 µg/m³. Negative associations were found between mortality and ozone. This may be related to the narrow range of ozone exposure in the pooled cohort combined with the high negative correlations between ozone and especially NO₂ and BC. Associations between mortality and long-term exposure to elemental composition of PM_{2.5} were documented in Chapter 6. We identified that exposure to vanadium in PM_{2.5} was most consistently associated with increased natural-cause mortality.

Significantly positive associations were found between long-term PM_{2.5}, NO₂ and BC exposure and incidence of cerebrovascular events and asthma and COPD hospital admissions^{28,29,99}. NO₂ was furthermore significantly associated with acute coronary heart disease and PM_{2.5} with lung cancer incidence^{31,99}. The CRFs generally displayed a linear to supra-linear association with no evidence of a threshold, except the sublinear association between NO₂ and acute coronary heart disease. Subset analyses suggested that adverse health effects of PM_{2.5} remained below 20 µg/m³ and in some cases 12 µg/m³. Associations with NO₂ remained below 30 and possibly 20 µg/m³. In two-pollutant models, NO₂ was most consistently associated with acute coronary heart disease, stroke, asthma and COPD hospital admissions. PM_{2.5} was not associated with these outcomes in two-pollutant models. PM_{2.5} was the only pollutant that was associated with lung cancer incidence in two-pollutant models. A further analysis showed that the associations between lung cancer incidence and PM_{2.5} composition were most robust for sulfur, potassium, nickel and vanadium³⁰. Associations with ozone were negative, though not statistically significant in two-pollutant models.

In the **administrative cohorts**, analyses were conducted locally in Norway, Denmark, England, the Netherlands, Belgium, Switzerland and Rome (Italy)¹²¹. Cohort-specific results were then pooled into a random-effects meta-analysis. All cohorts contributed to 28,146,444 subjects of observation with 3,593,741 deaths from natural causes. Almost all participants had exposures below the EU limit values for both PM_{2.5} (25 µg/m³) and NO₂ (40 µg/m³). More than 3.9 million (mostly from the Scandinavian cohorts) and 1.9 million (mostly from the Norwegian cohort) subjects had 2010 PM_{2.5} exposure below the US-EPA NAAQS (12 µg/m³) and the WHO air quality guideline (10 µg/m³), respectively.

Significantly positive associations were found between PM_{2.5}, NO₂ and BC and mortality from natural-cause, cardiovascular diseases, respiratory diseases and lung cancer. Pooled HRs of natural-cause mortality were 1.053 (95% CI: 1.021, 1.085), 1.044 (95% CI: 1.019, 1.069) and 1.039 (95% CI: 1.018, 1.059) per 5 µg/m³ increment in PM_{2.5}, 10 µg/m³ in NO₂ and 0.5*10⁻⁵/m in BC, respectively. Large heterogeneity was observed in the cohort-specific HRs. HRs were similar for cardiovascular and respiratory mortality, and highest for lung cancer mortality. Warm season ozone was negatively associated with both natural-cause and cause-specific mortality. Cohort-specific CRFs displayed differently between cohorts, though associations were generally linear for PM_{2.5} and supra-linear for NO₂, with no indication of a threshold. The subset analyses supported the observations from the shape of the associations. For PM_{2.5} and NO₂, HRs were modestly larger when the analysis was restricted to subjects exposed to low concentrations, i.e., HRs below 10 µg/m³ (the WHO guidelines) for PM_{2.5} and 20 µg/m³ for NO₂ were 1.078 (1.046, 1.111) and 1.061 (0.985, 1.143), respectively. Copper and iron in PM_{2.5} were positively associated with mortality, especially for respiratory and lung cancer mortality.

The ELAPSE findings are generally consistent with findings from other recent studies on health effects of low-level air pollution¹²²⁻¹²⁵, including the other two studies funded by the Health Effects Institute¹²⁶: the Mortality–Air Pollution Associations in Low-Exposure Environments (MAPLE) study¹²⁷ and the analyses in the Medicare enrollees¹²⁸. The MAPLE study includes approximately 8.5 million participants from three Canadian Census Health and Environment Cohorts (CanCHEC), and about half million Canadian Community Health Survey (CCHS) participants with additional lifestyle and behavioral information¹²⁷. The pooled HR across the three CanCHEC cohorts for nonaccidental mortality was 1.053 (1.041, 1.065) per 10 µg/m³ increment in long-term average PM_{2.5} exposure. In the CCHS cohort, an HR of 1.11 (1.04, 1.18) per 10 µg/m³ increase in PM_{2.5} for the nonaccidental mortality risk was reported. A supra-linear association was observed for long-term average PM_{2.5} and nonaccidental mortality, with a steep increase across lower concentrations (i.e., <5 µg/m³), followed by a leveling off or a smaller increase after ~10 µg/m³. No apparent threshold or sublinear association was suggested. In the Medicare cohort of around 61 million Americans aged 65 years and older, hazard ratios were derived from two-pollutant analyses¹²⁸. A 7.3% (95% CI: 7.1% – 7.5%) and a 1.1% (95% CI: 1.0% – 1.2%) higher risk of all-cause mortality were reported for a 10 µg/m³ and a 10 ppb increase in annual average PM_{2.5} and average O₃ concentrations in the warm season, respectively. When restricting the analyses to person-years with low exposures (concentrations less than 12 µg/m³ PM_{2.5} and 50 ppb O₃), the mortality risk was 13.6% (95% CI: 13.1% – 14.1%) and 1.0% (95% CI: 0.9% – 1.1%) for the same increase in PM_{2.5} and O₃ respectively. The CRFs from the two-pollutant models showed almost linear curves, with no indication of a threshold down to 5 µg/m³ PM_{2.5} and 30 ppb O₃. A recent study modeled an ensemble shape of the association between PM_{2.5} and natural-cause mortality using data from 41 cohorts from 16 countries¹²⁹. The curve displayed a supra-linear association over lower exposures and then a near-linear association at higher concentrations.

The findings from the ELAPSE project and other studies on health effects of low-level air pollution provide novel and potentially important insight into the shape of concentration-response functions at low concentrations. These studies might contribute to the future research on health effects of air pollution, global burden of disease assessments and revision of air quality guidelines and standards.

Policy recommendations

In 2015, an expert consultation was organized by the WHO calling for the need to update existing air quality guidelines¹³⁰. The latest WHO air quality guidelines were released in 2006 based on studies mainly conducted in North America and Europe⁶. New evidence has emerged since then and showed associations between adverse health effects and air pollutants at levels below the existing WHO guideline values. A series of systematic reviews were conducted by different groups (including our group) coordinated by the WHO focusing on long-term and short-term health effects of PM, O₃, NO₂, SO₂ and CO¹³¹⁻¹³⁴. The reviews documented clear associations between all pollutants and mortality and

morbidity outcomes. These reviews have been applied in developing the updated WHO air quality guidelines. Among these pollutants, PM_{2.5} has received particular attention because it has been associated with increased risks in mortality and morbidity more than any other regulated air pollutant^{36,111}. IARC has classified ambient PM as carcinogenic, with evidence of increased risk for cancer at levels below the current PM_{2.5} guideline value¹³⁵. The systematic review documented in chapter 2 showed clear evidence for associations between mortality and long-term exposure to PM_{2.5} at levels below the current WHO guideline value of 10 µg/m³. This is further confirmed by findings of the ELAPSE project and other recent studies on health effects of low-level air pollution, as discussed above. One of the key findings of the ELAPSE project is the supra-linear concentration-response relationships between PM_{2.5} exposure and health effects, with no indication of a threshold below which there is no effects of PM_{2.5} on health. The supra-linear associations were not only observed for mortality outcomes, but also for a variety of incident endpoints including cerebrovascular events, acute coronary heart disease, lung cancer incidence, and asthma and COPD hospital admissions^{28,29,31,99}. The evidence suggests the need to tighten the current guideline value.

Another ongoing discussion is whether PM mass is the most efficient metric for regulation purposes. Components of PM vary in space and time, and some components may be more responsible for the observed health effects than others. PM_{2.5} concentrations in parts of Africa would exceed the guideline value largely with probably little harm, because dust is a dominant component of ambient PM there^{136,137}. Although regulatory control of PM might be improved with robust quantification of the toxicity of various constituents of the PM mixture and of their sources⁹⁰, the existing evidence is not sufficient to support such component-specific regulations, as discussed in section 4. Consistently, the 2019 PM ISA concluded that there is no indication of any one source or component is consistently more closely related to specific health outcomes than PM_{2.5} mass¹¹¹. More studies are needed to further contribute to the understanding of the associations between PM composition and health outcomes in order to recommend relevant regulatory controls.

6. Conclusions

A systematic review of long-term exposure to PM_{2.5} and PM₁₀ documented significantly positive associations with mortality. Associations at low levels were predominantly found in North-American studies. Effect estimates were heterogenous, probably related to differences in particle composition, exposure level and methodological differences. We developed Europe-wide LUR models for assessing long-term exposure to PM_{2.5}, NO₂, O₃, black carbon (BC) and PM_{2.5} elemental composition. We found only limited differences in model performance using supervised linear regression and a range of algorithms including machine-learning methods. Models were applied in the ELAPSE project to assign exposure at the individual level. Both PM_{2.5} and PM₁₀ were associated with increased mortality from all causes, cardiovascular disease, respiratory disease and lung cancer. Associations remained below the current WHO air quality guideline level of 10 µg/m³ for PM_{2.5}. Long-term exposures to especially vanadium in PM_{2.5} was associated with increased mortality risk, with associations observed for both random forest- and supervised linear regression-modeled exposures. For the other elemental components studied, associations were generally weaker when exposure was assessed with random forest compared to supervised linear regression in two-pollutant models.

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Summary

Air pollution concentrations in North America and Europe have decreased substantially over the past decades. Despite that, recent studies suggested that the well-documented adverse health effects of air pollution may persist at levels below the current air quality guidelines and standards. This has raised questions about the appropriateness of the existing standards and guideline values for regulated pollutants including particulate matter with an aerodynamic diameter ≤ 2.5 and $10\ \mu\text{m}$ ($\text{PM}_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2) and ozone (O_3). $\text{PM}_{2.5}$ is considered to be particularly important among the pollutants. The composition of $\text{PM}_{2.5}$ varies in time and space, which may result in differences in toxicity and risk to health of $\text{PM}_{2.5}$. Mixed findings have been reported for associations between specific $\text{PM}_{2.5}$ components and health endpoints.

Recent developments in air pollution epidemiology require air pollution exposure estimates covering large geographical areas at sufficiently fine spatial resolution. Land use regression (LUR) models have been widely used in air pollution exposure assessment and are often developed with linear regression algorithms. More flexible modeling algorithms, such as regularization algorithms and machine-learning algorithms, have been applied recently. Few studies have compared exposure models developed with different algorithms. No study has compared the health effects related to these different exposure models.

The Effects of Low-level Air Pollution: A Study in Europe (ELAPSE) is a Europe-wide collaboration which focuses on analyses of health effects of air pollutants at low concentrations, defined as less than the current European and United States' air quality standards and WHO air quality guideline values.

This thesis has the following specific aims:

1. To systematically evaluate the evidence of associations of long-term exposure to PM_{10} and $\text{PM}_{2.5}$ with all-cause and cause-specific mortality with a focus on associations at low pollution levels
2. To develop Europe-wide LUR models for $\text{PM}_{2.5}$, NO_2 , O_3 , black carbon (BC) and $\text{PM}_{2.5}$ elemental composition
3. To compare LUR models developed with different algorithms in terms of prediction accuracy and interpretability
4. To investigate associations between long-term exposure to $\text{PM}_{2.5}$ components and mortality, and to compare the health effects estimated using exposure models developed with different algorithms

In **Chapter 2**, we conducted a systematic review on associations of long-term exposure to $\text{PM}_{2.5}$ and PM_{10} with natural-cause and cause-specific mortality. We identified 107 eligible articles, of which 104 were reporting results of cohort studies. The majority of studies were conducted in North America ($N = 62$) and Europe ($N = 25$). By including the most recently published article for the same study population in the meta-analysis, we estimated a meta-analytical risk ratio (RR) of 1.08 (95% CI 1.06, 1.09) per $10\ \mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ and natural-cause mortality ($N = 25$). Substantial heterogeneity was found across studies, probably related to differences in study populations, methodology, exposure level and composition of particles. Meta-analytical RRs per $10\ \mu\text{g}/\text{m}^3$ derived from studies conducted at low mean $\text{PM}_{2.5}$ levels (<25 , 20, 15, 12, $10\ \mu\text{g}/\text{m}^3$ respectively) were higher compared to the overall RR and increased as $\text{PM}_{2.5}$ concentration decreased (meta-analytical RRs at low concentrations ranged from 1.09 to 1.17). This is consistent with the finding of generally linear or supra-linear concentration-response functions (CRFs) in individual studies. Studies at low concentrations were predominantly conducted in North America where concentrations are lower than in most of Europe, in part because of lower population density. There is evidence that associations between $\text{PM}_{2.5}$ and increased mortality risk remained below the current EU air quality limit exposure level ($25\ \mu\text{g}/\text{m}^3$), the USEPA National Ambient Air Quality Standards (NAAQS; $12\ \mu\text{g}/\text{m}^3$), and even the WHO air quality guideline value ($10\ \mu\text{g}/\text{m}^3$).

The ELAPSE project is conducted to provide new empirical evidence on associations between low-level air pollution and health outcomes in Europe, characterizing air quality with PM_{2.5} and additionally NO₂, BC and O₃. In **Chapter 3**, we developed Europe-wide hybrid LUR models for 2010 annual mean concentrations of PM_{2.5}, NO₂, BC and O₃ at 100x100 m resolution to assess air pollution exposure for ELAPSE cohort participants. The models were developed using a supervised linear regression algorithm with satellite observations, chemical transport model estimates, land use and traffic data as potential predictor variables. Kriging was performed to further explain spatial variations in residuals of the LUR models. Kriging significantly improved the PM_{2.5} and O₃ models but not the NO₂ and BC models. In five-fold cross-validation, the PM_{2.5}, NO₂, O₃ warm season and BC models explained 66%, 58%, 60% and 51% of the variability in measured concentrations, respectively. The spatial structures of the models were stable in time at the West-European scale, supporting application in long-term epidemiological studies with cohorts started one or two decades ago.

in **Chapter 4**, we compared 16 different algorithms (linear regression, regularization and machine-learning algorithms) to develop Europe-wide PM_{2.5} and NO₂ models, using the same air pollution measurements and potential predictor variables used in Chapter 3. We observed similar performance across algorithms evaluated by five-fold cross-validation and an additional validation using an external dataset. The predicted concentrations from all algorithms at external validation sites were highly correlated ($R^2 > 0.85$).

In **Chapter 5**, we developed Europe-wide LUR models for elemental components in PM_{2.5}. Eight elements were *a priori* selected to represent major sources: copper (Cu), iron (Fe) and zinc (Zn) representing non-tailpipe traffic emissions; sulfur (S) representing long-range transport of secondary inorganic aerosols generated from combustion of sulfur containing solid and liquid fuels; nickel (Ni) and vanadium (V) representing mixed oil burning/industry; silicon (Si) representing crustal material; and potassium (K) representing biomass burning. Models for each element were developed with supervised linear regression and random forest, a machine-learning algorithm. The models performed moderate to well across Europe, explaining 41% to 90% of the overall spatial variability in measured concentrations in five-fold cross-validation. Random forest models consistently outperformed supervised linear regression models in explaining the overall variability. Models explained within study area variation much less than the overall variation. Random forest and supervised linear regression models explained similar within study variation. Maps proved a useful additional tool to evaluate the plausibility of model predictions beyond cross-validation statistics. Models differed substantially between elements in terms of the major predictor variables. The major predictor variables included in the models broadly reflected the major sources of the corresponding elements. Agreement between the two algorithm predictions was high at the overall European level for Cu, K, S and Zn ($r > 0.7$), and varied substantially at the national level.

In **Chapter 6**, we assessed associations between exposure to PM_{2.5} elemental components and mortality in the ELAPSE pooled cohort ($N = 323,782$). Exposure models developed in Chapter 5 with both supervised linear regression (SLR) and random forest (RF) algorithms were applied for comparison. All SLR-modeled components were statistically significantly associated with natural-cause mortality in single pollutant models with hazard ratios (HRs) from 1.05–1.27 over representative concentration ranges. Similar HRs were observed for RF-modeled Cu, Fe, K, S, V and Zn with wider confidence intervals (CIs). For both SLR- and RF-modeled V, HRs attenuated but remained above unity and (borderline) significant after adjustment for PM_{2.5} mass or NO₂. The HRs for V were 1.03 (95% CI: 1.02, 1.05) and 1.06 (95% CI: 1.02, 1.10) for SLR- and RF-modeled exposures, respectively, per 2 ng/m³ adjusting for PM_{2.5} mass. Associations for the other components were weaker for exposure modeled with RF than SLR in two-pollutant models.

In **Chapter 7**, methodological issues related to confidence assessment of epidemiological evidence in systematic reviews, spatial scale and statistical algorithms for developing air pollution exposure models, existing evidence on health effects of long-term PM composition exposure are being discussed. The main ELAPSE findings by applying the air pollution models developed in this thesis were summarized. Finally, some policy recommendations were given based on the current state of knowledge.

Samenvatting

De concentraties luchtverontreiniging in Noord-Amerika en Europa zijn de afgelopen decennia aanzienlijk afgenomen. Desondanks suggereren recente studies dat de nadelige gezondheidseffecten van luchtverontreiniging kunnen aanhouden bij concentraties onder de huidige luchtkwaliteitsrichtlijnen en -normen. Dit roept vragen op over de geschiktheid van de bestaande normen en richtlijnen voor gereguleerde luchtvervuilende stoffen, waaronder fijnstof met een aerodynamische diameter van ≤ 2.5 en $10 \mu\text{m}$ ($\text{PM}_{2.5}$ en PM_{10}), stikstofdioxide (NO_2) en ozon (O_3). $\text{PM}_{2.5}$ wordt beschouwd als een bijzonder belangrijke luchtvervuilende stof. De samenstelling van $\text{PM}_{2.5}$ varieert in tijd en ruimte, wat kan leiden tot verschillen in de toxiciteit en gezondheidsrisico's van $\text{PM}_{2.5}$. Er zijn inconsistente bevindingen gerapporteerd voor associaties tussen specifieke componenten van $\text{PM}_{2.5}$ en gezondheidsuitkomsten.

Recente ontwikkelingen in epidemiologisch onderzoek van luchtverontreiniging vereisen schattingen van de blootstelling aan luchtverontreiniging met een hoge ruimtelijke resolutie in grote geografische gebieden. Land use regressie (LUR) modellen worden veel gebruikt bij het schatten van de blootstelling aan luchtverontreiniging en worden vaak ontwikkeld met lineaire regressie algoritmen. Recentelijk zijn flexibeler, niet-lineaire modelleer algoritmen toegepast, zoals 'machine learning' algoritmen. Weinig studies hebben blootstellingsmodellen vergeleken die zijn ontwikkeld met verschillende algoritmen. Geen enkele studie heeft de gezondheidseffecten van luchtverontreiniging, samenhangend met blootstelling aan luchtverontreiniging zoals geschat met verschillende blootstellingsmodellen vergeleken.

ELAPSE (Effects of Low-level Air Pollution: A Study in Europe) is een Europa-brede samenwerking van onderzoeksinstituten die zich richt op het analyseren van gezondheidseffecten van luchtverontreiniging bij lage concentraties, gedefinieerd als concentraties lager dan de huidige Europese en Amerikaanse luchtkwaliteitsnormen en de advieswaarden van de WHO.

Dit proefschrift heeft de volgende specifieke doelstellingen:

1. Het systematisch evalueren van associaties tussen langdurige blootstelling aan PM_{10} en $\text{PM}_{2.5}$ en totale sterfte en oorzaak specifieke sterfte, met een focus op associaties bij lage concentraties luchtverontreiniging
2. Het ontwikkelen van LUR modellen voor heel Europa voor $\text{PM}_{2.5}$, NO_2 , O_3 , black carbon (BC) en een aantal elementaire componenten van $\text{PM}_{2.5}$
3. Het vergelijken van de voorspellingsnauwkeurigheid en interpreteerbaarheid van LUR modellen die zijn ontwikkeld met verschillende algoritmen
4. Het bestuderen van associaties tussen langdurige blootstelling aan componenten van $\text{PM}_{2.5}$ en sterfte, en het vergelijken van de gezondheidseffecten die zijn geschat met blootstellingsmodellen die zijn ontwikkeld met verschillende algoritmen

In **Hoofdstuk 2** hebben we een systematisch review uitgevoerd van studies die associaties onderzochten tussen langdurige blootstelling aan $\text{PM}_{2.5}$ en PM_{10} en natuurlijke en oorzaak specifieke sterfte. We identificeerden 107 artikelen die in aanmerking kwamen, waarvan 104 artikelen de resultaten van cohortonderzoeken rapporteerden. De meeste studies waren uitgevoerd in Noord-Amerika ($N = 62$) en Europa ($N = 25$). Wanneer er meer dan één artikel verscheen over dezelfde onderzoekspopulatie kozen we ervoor alleen het meest recente artikel op te nemen in de meta-analyse. Zodoende hebben we een meta-analytisch relatief risico (RR) van 1.08 (95% CI 1.06, 1.09) per $10 \mu\text{g}/\text{m}^3$ geschat voor $\text{PM}_{2.5}$ en natuurlijke sterfte ($N = 25$ studies). We vonden aanzienlijke heterogeniteit tussen de studies, die waarschijnlijk is gerelateerd aan verschillen in onderzoekspopulaties, methodologie, blootstellingsniveaus en de samenstelling van de fijnstofdeeltjes. Meta-analytische RR's per $10 \mu\text{g}/\text{m}^3$, afgeleid van studies die zijn uitgevoerd bij lage gemiddelde $\text{PM}_{2.5}$ concentraties (respectievelijk <25 , 20, 15, 12, $10 \mu\text{g}/\text{m}^3$), waren hoger dan het relatieve risico voor alle studies en namen toe naarmate de gemiddelde $\text{PM}_{2.5}$ concentratie lager was (meta-analytische RR's bij lage concentraties varieerden van 1.09 tot 1.17). Dit komt overeen met de bevinding van in het algemeen lineaire of supra-lineaire concentratie-respons functies (CRF's) in individuele studies. Studies met lage concentraties

luchtverontreiniging werden voornamelijk uitgevoerd in Noord-Amerika, waar de concentraties lager zijn dan in het grootste deel van Europa, deels vanwege de lagere bevolkingsdichtheid. Er zijn aanwijzingen voor associaties tussen $PM_{2.5}$ en een verhoogd sterfterisico bij concentraties onder de huidige EU grenswaarde voor $PM_{2.5}$ ($25 \mu g/m^3$), de US EPA National Ambient Air Quality Standards (NAAQS; $12 \mu g/m^3$), en zelfs de advieswaarde van de WHO ($10 \mu g/m^3$).

Het ELAPSE project wordt uitgevoerd om associaties tussen lage concentraties aan luchtverontreiniging ($PM_{2.5}$, NO_2 , BC en O_3) en gezondheidsuitkomsten in Europa te onderzoeken. In **Hoofdstuk 3** hebben we Europa-brede hybride LUR modellen ontwikkeld voor de jaargemiddelde concentraties van $PM_{2.5}$, NO_2 , BC en O_3 in 2010 met een resolutie van 100×100 m om de blootstelling aan luchtverontreiniging voor deelnemers van het ELAPSE cohort te schatten. De modellen zijn ontwikkeld met behulp van een gesuperviseerd lineair regressie algoritme met satellietwaarnemingen, schattingen van chemische transportmodellen, landgebruik en verkeersgegevens als mogelijk voorspellende variabelen. Met behulp van ‘kriging’ hebben we de ruimtelijke variaties in de residuen van de LUR modellen verder verklaard. ‘Kriging’ heeft de $PM_{2.5}$ en O_3 modellen aanzienlijk verbeterd, maar niet de NO_2 en BC modellen. In vijfvoudige kruisvalidatie verklaarden de $PM_{2.5}$, NO_2 , O_3 en BC modellen respectievelijk 66%, 58%, 60% en 51% van de variabiliteit in gemeten concentraties. De ruimtelijke structuren van de modellen waren stabiel in de tijd op West-Europese schaal. Dit ondersteunt de toepassing van deze modellen in langlopende epidemiologische studies met cohorten die één of twee decennia geleden zijn gestart.

In **Hoofdstuk 4** vergeleken we 16 verschillende algoritmen (lineaire regressie, regularisatie en ‘machine learning’ algoritmen) om Europa-brede $PM_{2.5}$ en NO_2 modellen te ontwikkelen, met behulp van dezelfde luchtverontreinigingsmetingen en mogelijk voorspellende variabelen die in Hoofdstuk 3 werden gebruikt. We vonden dat de algoritmen gelijkwaardig presteerden, geëvalueerd door vijfvoudige kruisvalidatie en een aanvullende validatie met behulp van een externe dataset. De voorspelde concentraties van alle algoritmen op externe validatielocaties waren sterk gecorreleerd ($R^2 > 0.85$).

In **Hoofdstuk 5** hebben we Europa-brede LUR modellen ontwikkeld voor een aantal elementaire componenten van $PM_{2.5}$. Acht elementen werden *a priori* geselecteerd om de belangrijkste bronnen te vertegenwoordigen: koper (Cu), ijzer (Fe) en zink (Zn), die niet-uitlaat verkeersemisies vertegenwoordigen; zwavel (S) staat voor transport over lange afstand van secundaire anorganische aerosolen afkomstig van verbranding van zwavelhoudende vaste en vloeibare brandstoffen; nikkel (Ni) en vanadium (V) vertegenwoordigen een mix van olieverbranding/industrie; silicium (Si), dat aardkorstmateriaal vertegenwoordigt; en kalium (K), dat de verbranding van biomassa vertegenwoordigt. Voor elk element zijn modellen ontwikkeld met gesuperviseerde lineaire regressie en ‘random forest’, een ‘machine learning’ algoritme. De modellen presteerden matig tot goed in heel Europa en verklaarden 41% tot 90% van de totale ruimtelijke variabiliteit in gemeten concentraties in vijfvoudige kruisvalidatie. ‘Random forest’ modellen presteerden beter dan gesuperviseerde lineaire regressiemodellen bij het verklaren van de algehele variabiliteit. De LUR modellen verklaarden de variatie binnen een studiegebied veel minder goed dan de algehele variatie. ‘Random forest’ en gesuperviseerde lineaire regressie modellen waren vergelijkbaar in het verklaren van de binnen-studie variatie. Het gebruik van kaarten bleek een nuttig aanvullend hulpmiddel te zijn om de aannemelijkheid van de modelvoorspellingen te evalueren, naast kruisvalidatie statistieken. De modellen voor de verschillende elementen verschilden aanzienlijk wat betreft de belangrijkste voorspellende variabelen. De belangrijkste voorspellende variabelen die in de modellen waren opgenomen weerspiegelden in grote lijnen de belangrijkste bronnen van de overeenkomstige elementen. De overeenkomst tussen de twee algoritme voorspellingen was hoog op Europees niveau voor Cu, K, S en Zn ($r > 0.7$), en varieerde aanzienlijk op nationaal niveau.

In **Hoofdstuk 6** hebben we associaties onderzocht tussen blootstelling aan elementaire componenten van $PM_{2.5}$ en sterfte in het gepoolde ELAPSE cohort (met een totale populatie omvang van 323,782

deelnemers). Ter vergelijking hebben we blootstellingsmodellen toegepast die zijn ontwikkeld in Hoofdstuk 5 met zowel gesuperviseerde lineaire regressie (SLR) als ‘random forest’ (RF) algoritmen. Alle SLR-gemodelleerde componenten waren statistisch significant geassocieerd met natuurlijke sterfte in modellen met één element, met hazard ratio's (HR's) van 1.05–1.27 over representatieve concentratie bereiken. Vergelijkbare HR's met bredere betrouwbaarheidsintervallen (CI's) werden gevonden voor RF-gemodelleerde Cu, Fe, K, S, V en Zn. De HR's voor zowel SLR- als RF- gemodelleerde V verzwakten na correctie voor PM_{2.5}-massa of NO₂, maar bleven groter dan één en (borderline) significant. De HR's voor V waren 1.03 (95% CI: 1.02, 1.05) en 1.06 (95% CI: 1.02, 1.10) per 2 ng/m³ voor respectievelijk SLR- en RF-gemodelleerde blootstelling, gecorrigeerd voor PM_{2.5}-massa. Associaties voor de andere componenten waren zwakker voor blootstelling gemodelleerd met RF dan SLR in modellen met twee elementen.

In **Hoofdstuk 7** bespreken we methodologische kwesties met betrekking tot de betrouwbaarheidsbeoordeling van epidemiologische studies in systematische reviews, de ruimtelijke schaal en statistische algoritmen voor het ontwikkelen van modellen voor blootstelling aan luchtverontreiniging, en bestaande aanwijzingen voor gezondheidseffecten van langdurige blootstelling aan de componenten van fijnstof. De belangrijkste bevindingen van ELAPSE, door toepassing van de luchtverontreinigingsmodellen die in dit proefschrift zijn ontwikkeld, worden samengevat. Ten slotte worden enkele beleidsaanbevelingen gedaan gebaseerd op de huidige stand van kennis.

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Curriculum Vitae

Jie Chen was born on the 25th of December, 1990 in Quanzhou, Fujian province, China. After graduating from high school in 2009, she studied Preventive Medicine at Peking University, China. She obtained her Bachelor of Science degree in 2014 and continued to study for a Master's degree in Environmental Health at Peking University, under the supervision of Prof. Wei Huang. During her master's study, she participated in several research projects focusing on acute health effects of air pollution and developed an interest in environmental epidemiology. In 2016, she started her PhD at the Institute for Risk Assessment Sciences, Utrecht University. She was supervised by Prof. Dr. Bert Brunekreef, Dr. Gerard Hoek and Dr. Maciek Strak. She has been working within the Health Effects Institute (HEI)-financed project 'Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE), which is coordinated by Utrecht University. Her research focused on air pollution exposure assessment and health effect evaluation. She has been working as the project manager of ELAPSE since 2019. She was also a member of the systematic review team, working for the update of the WHO Global Air Quality Guidelines (under the supervision of Dr. Gerard Hoek). Jie is currently doing her postdoctoral research within ELAPSE.

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