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HEALTH EFFECTS OF AIR POLLUTION - INNOVATIVE APPROACHES FOR SPATIO-TEMPORAL EVALUATIONS

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Health effects of air pollution - Innovative approaches for spatio-temporal evaluations

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To the three loves of my life

ABSTRACT

Air pollution is one of the major risk factors to human health, causing both short- and long-term effects and the global burden on mortality is estimated in more than 4 million deaths every year. Most of the evidence on the short-term effects is based on studies conducted in major cities, because data or estimates of air pollutants exposures in non-urban settings have been historically lacking. This is a limitation, because a large fraction of the population lives outside the cities, where the vulnerability profile is different from that of urban populations.

In the last decade, several attempts were made to estimate daily concentrations of particulate matter (PM) with high spatial resolution over large geographical domains. However, applications in Italy and Sweden, and on other pollutants as nitrogen dioxide (NO_2) and ozone (O_3), are almost lacking, leaving a gap in the knowledge of their health effects outside cities.

This thesis has been designed to fill this gap, by providing daily estimates of multiple air pollutants at the national level, and exploring the spatial heterogeneity in their health effects.

Italy represented a testing ground for the development of innovative mixed-effects regression models which combined PM measurements with satellite data, land-use parameters and meteorological fields, and produced daily estimates of PM_{10} (PM with diameter smaller than 10 μm) for each squared kilometer of the country, and each day in 2006-2012 (**Study I**). More recently, machine learning methodologies have been tested in the U.S., therefore, we have updated estimates of PM_{10} till 2015 and produced new estimates of $PM_{2.5}$ (PM < 2.5 μm), using a random forest (RF) algorithm (**Study II**). We replicated the same approach in Sweden, to which we added models for NO_2 and O_3, and a few spatiotemporal predictors aimed at capturing sources of air pollutants' variations missed in the previous studies (**Study III**).

We collected national data on hospital discharges for all Italian public and private hospitals during 2013-2015. We created municipality-specific time-series of daily counts of acute admissions for multiple cardiovascular (CVD) endpoints, which we related to daily mean PM_{10} and $PM_{2.5}$ concentrations. We found evidence of adverse effects of PM on total CVD admissions and on specific outcomes such as heart failure and atrial fibrillation. Also, we estimated highest effects at the lowest PM concentrations, also in non-urban municipalities (**Study IV**).

Similarly, we collected daily mortality counts at small area level in the Stockholm county, that we analyzed in relation to daily mean exposure to PM_{10}, $PM_{2.5}$, NO_2 and O_3. We found evidence of an association between daily O_3 and non-accidental mortality in the year-round analysis, and significant associations with PM and O_3 in the warm (April-September) period only. Effects were slightly higher in more densely inhabited areas, but we found associations also in non-urban areas outside the Stockholm city (**Study V**).

In conclusion, we developed novel spatiotemporal models to estimate air pollutant concentrations at fine spatial and temporal resolution in Italy and Sweden. These allowed us to document adverse short-term effects on mortality and morbidity at very low concentrations and in areas (and among populations) previously neglected by epidemiological investigations.

LIST OF SCIENTIFIC PAPERS

I. **Stafoggia M**, Schwartz J, Badaloni C, Bellander T, Alessandrini E, Cattani G, De' Donato F, Gaeta A, Leone G, Lyapustin A, Sorek-Hamer M, de Hoogh K, Di Q, Forastiere F, Kloog I. Estimation of daily PM_{10} concentrations in Italy (2006-2012) using finely resolved satellite data, land use variables and meteorology. *Environ Int*. 2017; 99: 234-244.

II. **Stafoggia M**, Bellander T, Bucci S, Davoli M, de Hoogh K, De' Donato F, Gariazzo C, Lyapustin A, Michelozzi P, Renzi M, Scortichini M, Shtein A, Viegi G, Kloog I, Schwartz J. Estimation of daily PM_{10} and $PM_{2.5}$ concentrations in Italy, 2013-2015, using a spatiotemporal land-use random-forest model. *Environ Int*. 2019; 124: 170-179.

III. **Stafoggia M**, Johansson C, Glantz P, Renzi M, Shtein A, de Hoogh K, Kloog I, Davoli M, Michelozzi P, Bellander T. A Random Forest approach to estimate daily particulate matter, nitrogen dioxide, and ozone at fine spatial resolution in Sweden. *Atmosphere* 2020; 11: 239.

IV. **Stafoggia M**, Renzi M, Forastiere F, Ljungman P, Davoli M, de' Donato FK, Gariazzo C, Michelozzi P, Scortichini M, Solimini A, Viegi G, Bellander T, on behalf of the BEEP Collaborative Group. Short-term effects of particulate matter on cardiovascular morbidity in Italy. A national analysis. *Accepted for publication in the European Journal of Preventive Cardiology*.

V. **Stafoggia M,** Bellander T. Short-term effects of air pollutants on daily mortality in the Stockholm county - A spatiotemporal analysis. *Environ Res.* 2020; 188: 109854.

CONTENTS

LIST OF ABBREVIATIONS

AOD	Aerosol optical depth
CAMS	Copernicus Atmosphere Monitoring Service
CI	Confidence interval
CLC	Corine Land Cover
CVD	Cardiovascular disease
ECMWF	European Centre for Medium-Range Weather Forecasts
ERF	Exposure response function
GIS	Geographic Information System
ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision
IDW	Inverse distance weighting
IPW	Inverse probability weighting
ISA	Imperviousness surface areas
LAN	Light-at-night
LUR	Land-use regression
MACC-II	Monitoring Atmospheric Composition and Climate – Interim Implementation
MAIAC	Multi-Angle Implementation of Atmospheric Correction
MODIS	MODerate resolution Imaging Spectroradiometer
NDVI	Normalized Difference Vegetation Index
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
O_3	Ozone
OMI	Ozone-Monitoring Instrument
PBL	Planetary boundary layer
PM	Particulate matter
$PM_{2.5}$	PM with an aerodynamic diameter less than 2.5 μm
$PM_{2.5-10}$	PM with an aerodynamic diameter between 2.5 and 10 μm
PM_{10}	PM with an aerodynamic diameter less than 10 μm
RF	Random forest
RMSPE	Root mean squared prediction error
SAMS	Small areas for market statistics
SCB	Statistiska centralbyrån
SVM	Support Vector Machine
UFP	Ultrafine particles, PM with an aerodynamic diameter less than 0.1 μm
VIIRS	Visible Infrared Imaging Radiometer Suite
VOCs	Volatile organic compounds
WHO	World Health Organization

1. INTRODUCTION

Air pollution is recognized as one of the major risk factors to human health. The most recent update of the Global Burden of Disease compared 84 behavioral, environmental and occupational risk factors in terms of attributable mortality and disability-adjusted life-years lost globally, and ranked ambient air pollution as the 10th leading cause of mortality (Stanaway et al. 2018). Similarly, the World Health Organization (WHO) has estimated more than 4 million deaths as attributable to ambient air pollution every year worldwide (Prüss-Ustün et al. 2016).

Epidemiological investigations of the adverse health effects of air pollution have a long history, tracing back 70 years when the first documented macroscopic episodes of air pollution peaks were related to mortality in Donora, U.S. in 1948 (Schrenk et al. 1949) and in London in 1952 (Logan 1953). Only a few decades later, however, researchers realized that even small concentrations of air particles and gases might trigger adverse effects in the general population (Ostro 1984). In this period the first time-series studies were designed, initially in single cities in the U.S. and Europe (Hatzakis et al. 1986; Schwartz and Marcus 1990), then in multiple locations (Biggeri et al. 2001; Katsouyanni et al. 1996; Samet et al. 2000). Concurrently, the first cohort studies started to test the hypothesis that not only daily peaks but also chronic exposures to air pollutants might cause adverse effects in the long term (Dockery et al. 1993; Pope et al. 1995).

Despite the abundance of scientific evidence produced in the last 50 years, there is still uncertainty, if not skepticism (Goldman and Dominici 2019), on the causal role of air pollution in deteriorating human health or triggering acute responses in the body. This is partially attributable to the complexity of understanding the spatial and temporal variability of different air pollutants, a necessary requisite to properly attribute exposures to individuals and populations in the epidemiological studies.

Most of this thesis will focus on this aspect, namely what are the driving forces of the spatial and temporal distribution of air pollutants across large geographical domains, how these components can be represented by proxy variables in order to define suitable exposure models, and why such spatiotemporal exposures are relevant for epidemiological investigations. Along the thesis, the major challenges about the definition of spatiotemporal exposure models, and the design of epidemiological studies for evaluating short-term effects, will be presented and discussed.

1.1 AIR POLLUTANTS

The air we breathe contains a complex mixture of solid, liquid or gaseous compounds.

Broadly speaking, air pollutants in the solid phase are called "particles", and are usually classified on the basis of their size into PM_{10} (particles with aerodynamic diameter smaller than 10 μm, sometimes called "inhalable" particles), $PM_{2.5}$ (particles smaller than 2.5 μm, also called "fine" particles), $PM_{2.5\text{-}10}$ (particles between 2.5 and 10 μm in diameter, referred to as "coarse" particles), and UFP ("ultrafine particles", particles $\leq$ 0.1 μm). Different particles have different physical and chemical properties, and are originated by different sources. For example, UFP and $PM_{2.5}$ in urban environments are mostly of primary origin, i.e. they are directly generated by anthropogenic sources such as industrial activities, motor vehicles and domestic heating. In contrast, fine particles in non-urban areas are mostly secondary, meaning that they are generated by chemical reactions involving gaseous precursors such as sulfur dioxide, nitrogen oxides (NO_x), ammonia, and volatile organic compounds (VOCs). Finally, coarse particles are mostly of primary origin, composed by sea salt and crustal materials, and, in cities, brought by long-range transportation patterns or originated by mechanical processes of dust resuspension.

Nitrogen dioxide (NO_2) is a gaseous air pollutant composed of nitrogen and oxygen derived from burning fossil fuels (coal, oil, gas or diesel) at high temperatures. Therefore, the largest sources of ambient NO_2 are motor vehicles and industrial plants, and NO_2 concentrations are highest in urban and industrial areas, and lowest in rural and remote settings.

Tropospheric ozone (O_3) is a highly reactive component of the photochemical air mixture. In the stratosphere it protects the earth by shielding it from the ultraviolet radiations emitted by the sun. However, at ground level, it is an oxidant air pollutant generated by photochemical reactions of NO_x and VOCs and can be harmful to human health. It displays an inverse relationship with NO_2, because, near combustion sources, the directly emitted nitrogen oxide reacts with O_3 producing NO_2 and depleting ozone, while away from the sources NO_x emissions and VOCs react, increasing O_3 concentrations.

1.2 SPATIAL AND TEMPORAL VARIABILITY OF AIR POLLUTANTS

Air pollutants vary in space and time as a consequence of the distribution of their sources and the prevalent meteorological conditions.

The source profile of air pollutants is different between urban and non-urban areas. In cities, anthropogenic sources are the most relevant ones, and each pollutant (or fraction of PM) can be dominated by a specific mixture of sources. Exhaust emissions from vehicular traffic, non-exhaust emissions from tires and brakes erosion or dust resuspension, heating of domestic or commercial buildings, emissions from industrial activities, are the main contributors to urban air pollution. These sources can be highly variable across space (i.e. vehicular traffic) and display long-term, seasonal and weekly time trends mirroring human activities. As a consequence, while data on measurements of the sources can be difficult to retrieve, proxy variables of vehicular traffic (i.e. road network or average traffic load by road type), domestic heating (i.e. resident population by small areas) and industrial emissions (i.e. distance from the closest industrial site) can be easy to access and might represent valid surrogates. Outside the cities, natural sources and long-range transport patterns are the main drivers of air pollution variability, and proxy variables of land cover, combined with satellite retrievals and orography/altitude parameters can be extremely useful to capture the main spatial contrasts in air pollutants.

Synoptic weather conditions and atmospheric dynamics influence the amount of pollution in the atmosphere (Beaver and Palazoglu 2009; Dayan and Levy 2005; Demuzere et al. 2009; Russo et al. 2015). For example, conditions of thermal inversion (when a layer of cool air lies below one of warmer air) prevent emissions from dispersing and pollutants build up under the inversion. On the other hand, single meteorological variables also influence air pollution concentrations, transformation and chemical reactions (Csavina et al. 2014; Shenfeld 1970; Zhang et al. 2015). Temperature and sunlight (solar radiation) for example play a key role in the chemical reactions occurring in the atmosphere. Solar radiation is required for the photochemical production of oxidants forming smog. Precipitation has a scavenging effect in washing out particles in the atmosphere. Finally, humidity and water vapor are involved in many thermal and photochemical reactions in the atmosphere. The amount of water vapor in the atmosphere depends, in fact, by proximity to water bodies and by wind direction and air temperature. Finally, wind velocity, turbulence and stability of the atmosphere may affect the transport, dilution and dispersion of air pollutants.

1.3 MODELS FOR EXPOSURE ASSESSMENT

Modelling spatial and temporal variability of air pollution for epidemiological studies remains a challenging task. Initial studies relied on averages of monitoring stations as proxies of individual exposure, and focused on comparisons between locations (Dockery et al. 1993; Pope et al. 1995). However, it was soon realized that within-city variability was larger, and more related to health effects, than between-city differences (Eeftens et al. 2012; Miller et al. 2007), therefore new methods based on monitors were introduced, such as proximity to monitors and geo-statistical approaches for spatial interpolation. More recently, satellite retrievals have been exploited for two main reasons: first, they allowed to cover geographical areas previously neglected because of lack of data, such as rural and remote settings; second, they provided a fine temporal resolution to capture not just spatial but also daily variation. Land-use regression (LUR) techniques have had an exponential growth in the last three decades, because they present several advantages: first, they are trained on observations; second, they are fairly easy to apply with conventional statistical software; third, they allow to increase the spatial resolution of the final estimates by incorporating predictors at fine scale. Concurrently, dispersion and chemical transport models have been sometimes used in epidemiological applications as a valid alternative, as they provided fairly good approximations of air pollution fields over space and time, especially for air pollutants with limited spatial variability. In the last years, “hybrid” or “ensemble” models have been introduced, the idea being to exploit the relative advantages of some of the previous methods by averaging more of them, sometimes using complex machine learning statistical methodologies.

1.3.1 Monitor-based approaches

The approximation of individual or population exposure by use of an average of monitors common to all subjects within a location, or the closest monitor to the receptor point (residential address), have the clear advantage of simplicity, but make the assumption that exposure does not vary over space, or that monitors are representative of the mean exposure of the general population. This is reasonable in short-term epidemiological studies conducted in small cities with several monitoring stations, because day-to-day contrasts in exposures are likely to be similar in different places and well captured by the available sampling points. In practical terms, it can often be the only option when health data (mortality or hospitalizations records, for example) are available at the city level, with no detail on individual addresses or small-area classifications.

Approaches based on spatial interpolation, such as ordinary kriging (Künzli et al. 2005) and inverse-distance weighting (IDW)(Beelen et al. 2008), have been used to overcome some of the limitations mentioned above. These are quite easy to implement but have the limitation of producing over smoothed surfaces of exposure, with negative consequences on the resulting health effects estimates.

1.3.2 Satellite data

Satellite retrievals are an appealing source of information to complement monitoring stations and to capture spatial and temporal variability of air pollutants, because they are virtually available everywhere every day, with fine enough spatial and temporal resolution to design proper epidemiological studies for short-term and long-term health effects. The main limitations of satellite retrievals are the discrepancy between columnar estimates and ground-level concentrations, the interference of clouds and water bodies, and the complexity of downloading and processing huge amount of spatiotemporal data.

Depending on the pollutant, different products from different sensors are available at different spatial resolutions. In this thesis, the main parameter of interest has been the “aerosol optical depth” (AOD), a measure of the light extinction from particles suspended in the column of air. Put it simply, the more light is absorbed/refracted by suspended particles, the less it reaches the sensor, which translates this information into a parameter, AOD, directly proportional to the number of particles present in the column of air, from ground to the atmosphere. AOD is currently measured both from the moderate resolution imaging spectroradiometer (MODIS) onboard the NASA Terra and Aqua satellites, and onboard the ESA Sentinel satellite. However, historical data are available only from the former.

Columnar NO_2 and O_3 are measured by the ozone-monitoring instrument (OMI) on board the Aura satellite. These estimates, however, are less useful because they are provided at a coarse spatial resolution, not sufficient to capture the highly variable NO_2 concentrations in urban environments. For ozone, also, these are less useful because of the interference from the high concentrations in the stratosphere, which limit the possibility to estimate ground-level concentrations with accuracy.

1.3.3 Land-use regression

The first application of a land-use regression (LUR) model dates back to 1997 (Briggs et al. 1997). Since then, their use has grown exponentially (Nieuwenhuijsen 2015). LURs are statistical regression models which combine observations from a limited set of monitors with land-use variables defined using geographic information system (GIS) techniques. First, a statistical relationship is established between such variables, generally chosen as representative of air pollution sources, and the measured concentrations at specific sampling points. Then, the same variables are computed at receptor points (individual addresses or centroids of a fixed grid), and the model output is predicted there, so obtaining estimates of air pollutants exposures at each point. Key aspects for a good LUR model are: a) the number and positioning of sampling points, which should cover a large variability of the target pollutant; b) the definition of a large set of explanatory variables, capturing different sources at fine spatial resolution; c) the strategy for variable selection, which should be inclusive of all the main sources, but not too much, in order to avoid "overfitting" of the data; and d) the strategy for cross-validation, aimed at checking the performance of the model on external points.

In most cases, LURs have been developed in specific cities to represent long-term (e.g. annual) average concentrations, and represented good approximations of chronic exposures to investigate long-term effects in prospective cohort studies (Beelen et al. 2014; Cesaroni et al. 2013). More recently, temporal covariates have been incorporated in the models, with the effort to modulate the spatial contrasts over time, and obtaining estimates for each day to be related to short-term health effects (Vedal et al. 2013; Yanosky et al. 2014). In addition, conventional multivariate regression models have been replaced by more flexible approaches based on machine learning, such as random forests (Hu et al. 2017), extreme gradient boosting (Chen et al. 2019), support vector machines (Leong et al. 2020) and neural networks (Di et al. 2016).

The appealing features of LURs are the simplicity of application and the high spatial resolution of the final outputs. The main limitation is the extrapolation of the model output, often based on few sampling sites, to many receptor points, sometimes in the order of hundreds of thousands (Basagana et al. 2013), with the inevitable consequence of introducing measurement error in exposures, and bias and/or imprecision in the health effects estimates (Gryparis et al. 2009).

1.3.4 Dispersion models

Dispersion and chemical transport models represent a shift in paradigm compared with LURs, because they, rather than establishing statistical relationships with observations, try to model the dispersion of emissions from source to receptors using deterministic approaches. They have been historically used for regulatory and monitoring purposes, with some applications in epidemiology (Cesaroni et al. 2013; Nyberg et al. 2000; Raaschou-Nielsen et al. 2012). They can provide outputs with very high temporal (hourly) and spatial (few meters) resolutions, however they are computationally intensive and require a high level of expertise, generally beyond the scope of epidemiological researchers. In addition, they are not based on measurements, therefore their results rely on the correctness of the assumptions behind the mathematical formulas, although recently it has become common practice for modelers to combine actual measurements with theoretical formulas, by use of "data assimilation".

1.3.5 Hybrid approaches

The latest generation of models to predict spatial and temporal variability in air pollutants is the one of "hybrid" or "ensemble" approaches, which acknowledge the pros and cons of the previous methods, and try to exploit their full potential by averaging them or use some of them as predictor variables for others. For example, satellite data have been often used in LURs as covariates (Novotny et al. 2011; Vienneau et al. 2013), dispersion models have been used as covariates for LURs (Korek et al. 2017), and multiple machine learning methods have been used as individual learners in "ensemble" approaches (Di et al. 2019; Shtein et al. 2020).

1.4 HEALTH EFFECTS OF AIR POLLUTION, AN OVERVIEW

1.4.1 Short-term versus long-term effects

Health effects of air pollution have historically been distinguished into “short-term” (i.e. acute effects due to short-term exposures) and “long-term” (i.e. chronic effects due to long-term exposures).

The etiological hypothesis of short-term effects studies, and its translation into the statistical question directly addressed by the epidemiological analysis, are depicted in **Figure 1.1**.

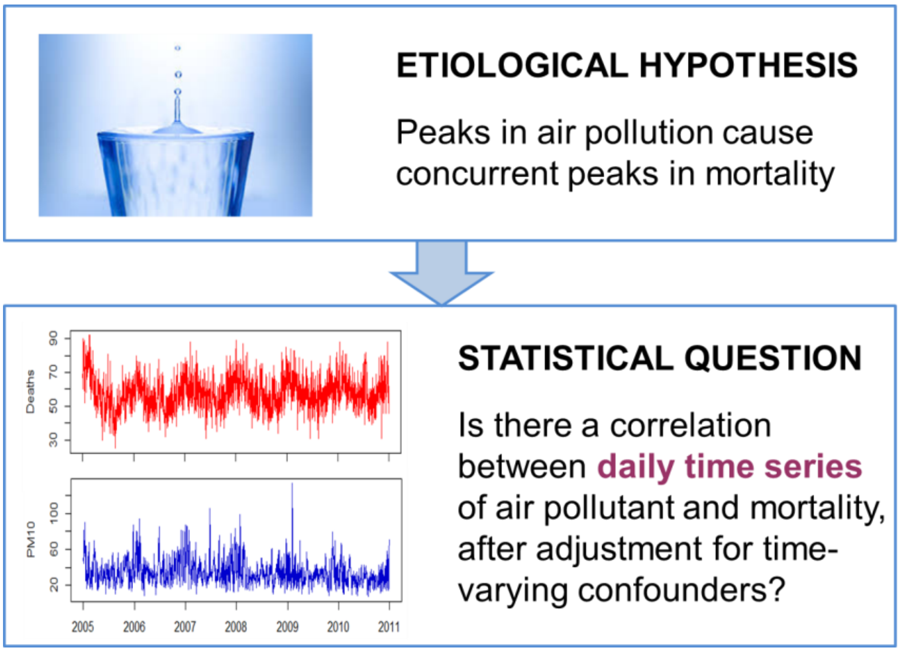

Figure 1.1 Conceptual scheme of the etiological hypothesis, and the corresponding statistical question, underlying short-term effects studies

It is assumed that short-term (e.g. daily) peaks in air pollution might trigger an acute response in the population, especially among susceptible individuals (in the figure, it is represented by the metaphor of an almost filled glass, which spills water because of the last drop). This translates into the statistical question: “is there a statistical correlation between daily time series of air pollutants’ concentrations and daily counts of a health outcome (for example, mortality), upon adjustment for time-varying confounders?”. The best study design, largely applied in epidemiological applications, is the time-series approach, with Poisson multivariate regression, where daily counts of an outcome (usually cause-specific mortality or disease-specific hospital admissions) are regressed against daily mean concentrations of an air pollutant, possibly with a latency of few days, and adjustment is made in the regression by adding terms for long-term and seasonal time trends, meteorology, influenza epidemics and days of the week.

The most interesting feature of this study design is that, since the interest lies in day-to-day contrasts in exposures within the same population, perfect adjustment for known or unknown time-fixed covariates (e.g. sex distribution) or slowly varying ones (e.g. age structure, smoking habits, prevalence of chronic conditions, socio-economic status, etc.) is achieved by design.

The main limitation of this approach is the ecological fallacy of assuming a common exposure for all the individuals of the population on a given day, an assumption that might not be true in areas characterized by large exposure variability, especially if daily data on the health outcome of interest can be retrieved at a spatial resolution finer than the city or the municipality as a whole. Under these circumstances, a spatiotemporal exposure model might be warranted, and area-specific time-series, or the case-crossover design (Maclure 1991), can be preferable alternatives to the conventional time series design, because they allow to reduce exposure measurement error and exploit the full extent of exposure variability, an important advantage when the effect under estimation is very small.

The etiological hypothesis of long-term effects studies, and its statistical counterpart, are depicted in **Figure 1.2**.

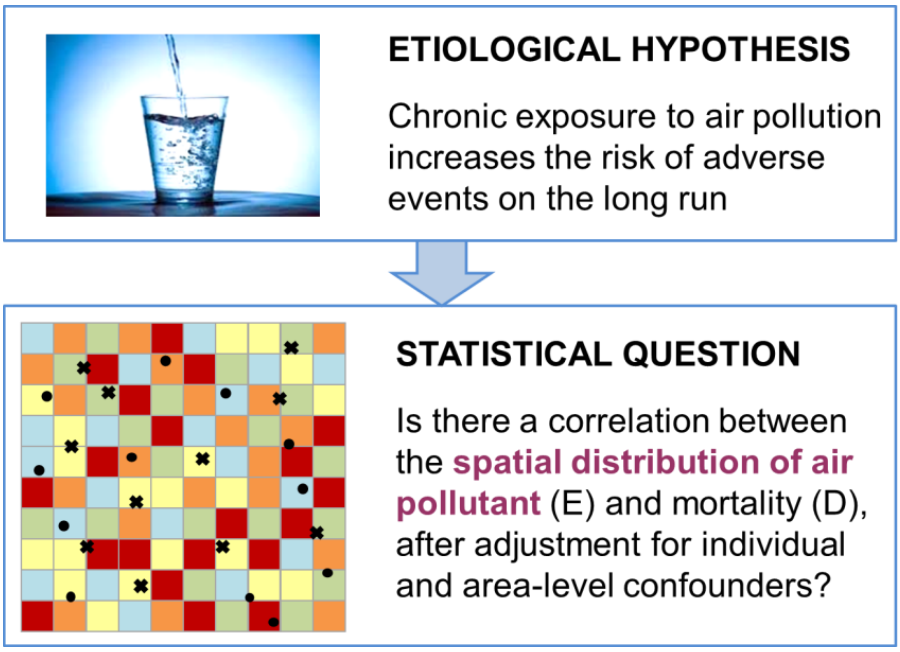

Figure 1.2 Conceptual scheme of the etiological hypothesis, and the corresponding statistical question, underlying long-term effects studies

In this case, the researcher seeks to understand whether long-term exposure to air pollution, over years or decades, might be responsible for a chronic process of health deterioration (the filling of the glass), ultimately leading to an observable health effect in the population. This translate into the statistical question: “is mortality higher for subjects residing in areas with higher-than-average air pollution, compared to subjects less exposed, holding other factors constant?”. In this situation the exposure contrast of interest is purely spatial, and, since exposed and unexposed individuals are different, individual-level and area-level covariates become eligible confounders to be adjusted for. Among the different study designs applicable, the prospective cohort study is the elective one, and multivariate survival models have been the most common choice in the literature, in small cohorts rich of individual-level covariates, in large administrative population-based longitudinal studies, and in large multi-center projects combining many cohorts from different countries.

Prospective cohort studies for long-term health effects present the opposite strengths and limitations compared to time-series designs. They are focused on the individual and exposure is often available at fine spatial resolution, sometimes at the residential address level. On the other hand, they are more prone to confounding from omitted covariates because the design, per se, does not control for any individual-level or area-level covariate.

1.4.2 Epidemiological evidence and biological mechanisms

Respiratory effects

There is a large convergence of the epidemiologic literature in showing a relationship between short-term exposure to several air pollutants and respiratory outcomes, such as asthma exacerbation, chronic obstructive pulmonary disease exacerbation, respiratory infections, increased respiratory symptoms, and mortality (U.S. Environmental Protection Agency 2009). Such evidence is corroborated by toxicological studies reporting asthma-related responses, enhanced lung inflammation and greater susceptibility to bacterial infection in animals exposed to fine particles (Harkema et al. 2004; Morishita et al. 2004; Saldiva et al. 2002).

Similarly, effects of long-term exposure to air pollutants have been estimated on lung function growth, asthma prevalence or development in children, and pulmonary inflammation (U.S. Environmental Protection Agency 2019). Also these results have been supported by animal toxicological studies showing impaired lung development (Mauad et al. 2008), increased airway responsiveness and inflammation (De Grove et al. 2018), oxidative stress (Deiuliis et al. 2012), and morphological changes in airways (Kim et al. 2016) upon chronic exposure to air pollutants, especially $PM_{2.5}$.

Cardiovascular effects

The cardiovascular effects of air pollution exposure are even larger than those reported for respiratory outcomes. Epidemiological studies on the short-term effects documented associations with mortality, hospital admissions and emergency-room visits for total cardiovascular diseases, heart failure, ischemic heart diseases, stroke and, recently, rarer outcomes such as pulmonary embolism and deep vein thrombosis (U.S. Environmental Protection Agency 2019). These findings were confirmed by controlled human exposure studies which reported changes in endothelial function and blood pressure, decreased cardiac contractility and left ventricular pressure in relation to short-term exposure to air pollutants (U.S. Environmental Protection Agency 2019).

Prospective cohort studies conducted in the U.S., Canada and Europe reported strong associations between long-term exposure to multiple air pollutants, including PM_{10}, $PM_{2.5}$ and NO_2, and CVD mortality (Cesaroni et al. 2013; Chen et al. 2016; Pope et al. 2015), as well as incidence of ischemic heart diseases and stroke (Crouse et al. 2015; Turner et al. 2016). Only few studies focused on alternative cardiovascular outcomes, such as coronary events among post-menopausal women (Chi et al. 2016), progression of atherosclerosis (Künzli et al. 2010), heart failure (Atkinson et al. 2013), blood pressure (Chan et al. 2015), hypertension (Zhang et al. 2016b) and subclinical cardiovascular biomarkers (Zhang et al. 2016a), and reported evidence of an association with long-term PM exposure.

In general, there is a wide consensus among cardiovascular experts that a mixture of several mechanisms is involved in the air pollution-CVD relationship, including atherosclerotic processes and vascular dysfunction, systemic inflammation and oxidative stress, thrombogenicity, mechanisms inducing heart failure, and epigenetic changes (Newby et al. 2015). These are consistent with both short-term (trigger) and long-term (accumulation) effects.

Other health effects

Other health effects of air pollution include cancer incidence and mortality, neurodegenerative diseases among the elderly, neurodevelopment in children, adverse outcomes in pregnant women and on newborns (U.S. Environmental Protection Agency 2019).

1.5 RESEARCH GAPS MOTIVATING THIS THESIS

Most of the existing studies on the short-term health effects of air pollutants have been conducted in large cities and have commonly used air pollutants measurements from routine monitoring stations to assign a common daily exposure to all subjects. In contrast, spatially resolved exposure estimates from LUR or dispersion models have been historically used to describe annual averages and to investigate long-term effects only.

One of the reasons behind such research gap has been the absence of exposure models capable to describe the air pollutants' variability over space and time at a fine resolution and covering large geographical domains. Therefore, researchers have usually made the implicit assumption, possibly generated by lack of viable alternatives, that daily variability in air pollutants is constant over space, at least within a city, and that short-term effect estimates reported in urban environments could be generalized to the entire population.

This is a major limitation, for at least three reasons. First, it precludes the possibility to study non-urban populations. These are of high public health interest because of their non-negligible size and because they are likely characterized by a different vulnerability profile (in terms of socioeconomic status, lifestyle characteristics, access to healthcare services, composition of the air mixture, etc.) compared to urban ones. Second, it limits the statistical power to estimate exposure-response functions at low levels of air pollution. In fact, air pollutants' concentrations in non-urban areas are lower than those reported in cities, and national and international agencies (e.g. WHO) are currently seeking for new evidence on the shape of the relationship between air pollution and health at the lower end of the air pollutants' distributions. Third, it makes it impossible to investigate the extent of the spatial heterogeneity in the short-term health effects within urban areas. It is, in fact, plausible that individual-level risk factors (smoking, alcohol consumption, physical inactivity, old age, etc.), area-level risk factors (socio-economic status, disease prevalence, accessibility to health infrastructures, etc.) and environmental determinants other than air pollution (proximity to green spaces, noise exposure, urban heat islands, road density, etc.) might concur in altering daily air pollution variability and its health effects, over space, even on a small scale.

2. AIMS

The overarching aim of this thesis was to investigate the short-term effects of particulate matter, NO_2 and O_3 on mortality and hospital admissions, using innovative approaches for spatio-temporal investigations.

Specific aims were:

- To provide novel estimates of air pollution concentrations at fine spatial and temporal resolution over large geographical domains useful for epidemiological investigations (Studies **I**, **II** and **III**);
- To investigate short-term effects of particulate matter at the national level, in order to cover large and previously neglected populations, and explore concentration-response relationships at low levels (Study **IV**);
- To investigate the spatial heterogeneity of the short-term effects of air pollutants in a region encompassing both urban and non-urban areas (Study **V**).

3. MATERIALS AND METHODS

3.1 EXPOSURE ASSESSMENT

Studies **I**, **II** and **III** describe in details the process of data selection and model building for the estimation of daily air pollutants' concentrations at the national level in Italy and Sweden. The first step has been, for both countries, to define fixed grids of 1x1-km size as target areas, and to collect monitoring data of PM_{10}, $PM_{2.5}$ (both countries), NO_2 and O_3 (Sweden only) available from the national environmental protection agencies or downloaded from the Airbase database collected by the European Environmental Agency (https://www.eea.europa.eu/data-and-maps/data/aqereporting-8). The study periods of the analyses were 2006-2012 (study **I**), 2013-2015 (study **II**) and 2005-2016 (study **III**). **Figure 3.1** displays the study areas, with a zoom of the metropolitan areas of Rome and Stockholm, and the location of the monitoring stations.

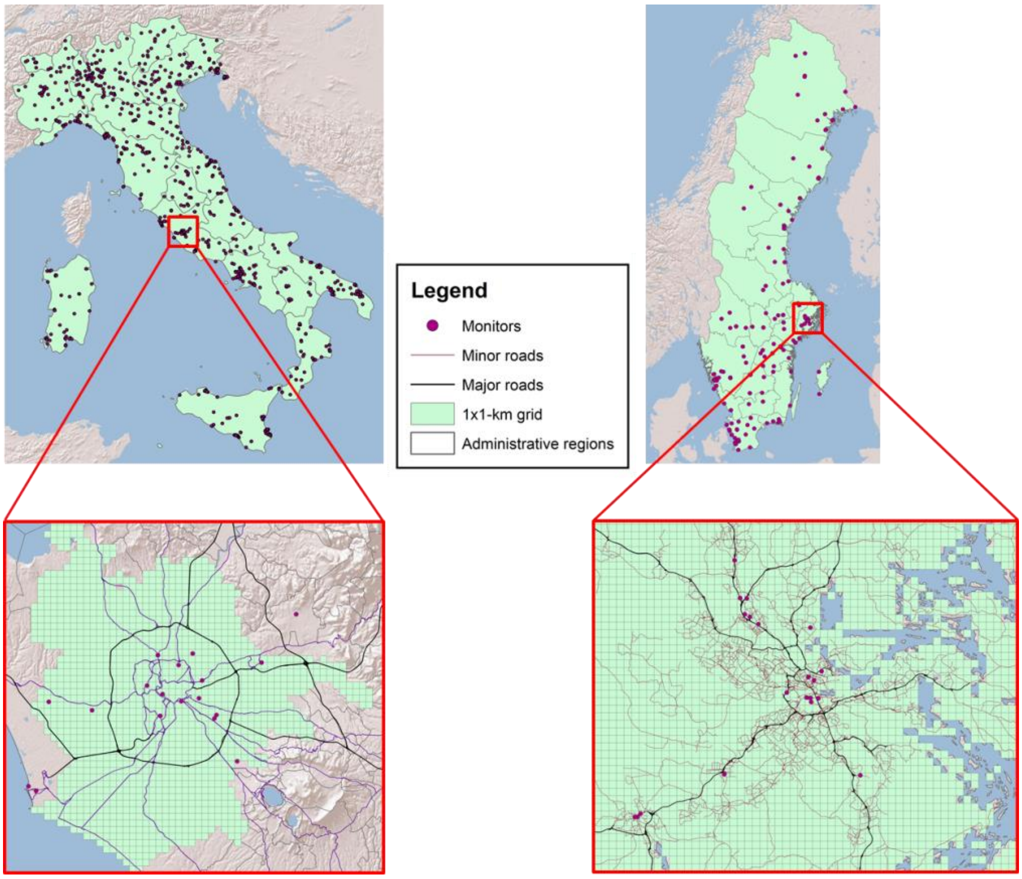

Figure 3.1 Study areas, 1x1-km fixed grids and monitoring stations

For each grid cell we built a number of spatial variables (i.e. variables changing from cell to cell, but assumed constant over the study period) aimed at capturing spatial sources of air pollution variability, possibly linked to the main emission sources and land use. In addition, we defined a number of spatiotemporal variables (i.e. variables changing from cell to cell and day to day) aimed at capturing spatial and temporal sources of air pollution variability (such as seasonal patterns, meteorological conditions, etc.). All them are briefly reported below, and described in details in studies **I**, **II** and **III**.

3.1.1 Satellite data

Aerosol Optical Depth (AOD)

In studies **I**, **II** and **III** we have used AOD estimates from the algorithm Multi-Angle Implementation of Atmospheric Correction (MAIAC), developed by NASA at 1x1-km resolution from collection 6 MODIS Aqua L1B data (Lyapustin et al. 2011b, 2011a, 2018).

MAIAC AOD data can be unavailable on a large sample of grid cells and days because of cloud coverage, water/snow glint reflectance and satellite calibration. Therefore, in studies **II** and **III** we also downloaded modelled AOD estimates from the Monitoring Atmospheric Composition and Climate – Interim Implementation (MACC-II) project, developed within the Copernicus Atmosphere Monitoring Service (CAMS). CAMS provides predicted total AOD as the sum of five types of tropospheric aerosols: sea salt, dust, organic and black carbon, and sulfates. CAMS AOD was downloaded for 2006-2015 (study **II**, Italy) and 2005-2016 (study **III**, Sweden) at the finest spatial resolution available, equal to 0.125°×0.125° (approximately 10×10-km).

Normalized Difference Vegetation Index (NDVI)

NDVI is a satellite-based indicator assessing whether the target being observed contains live green vegetation or not. Generally, healthy vegetation will absorb most of the visible light that falls on it, and reflects a large portion of the near-infrared light. Unhealthy or sparse vegetation reflects more visible light and less near-infrared light. Bare soils on the other hand reflect moderately in both the red and infrared portion of the electromagnetic spectrum. We downloaded monthly data on NDVI from the NASA website, using the publicly available MODIS NDVI product (MOD13A3) at 1x1-km spatial resolution. The monthly resolution was chosen under the assumption that NDVI values do not change considerably within months.

Light-at-night (LAN)

LAN data are a proxy indicator for major conurbations and human activities. They were collected from the Visible Infrared Imaging Radiometer Suite (VIIRS) Day/Night Band, year 2015, at a spatial resolution of ~750 m.

3.1.2 Meteorological data

In study **I** meteorological data were collected from ground-level measurements available from several sources: airport data of the World Meteorological Organization, data from sites owned by region-specific environmental protection agencies, and additional data from personal stations included in the Weather Underground network. Grid cells were matched to the closest weather station with non-missing meteorological observations on a specific day. We used the following daily parameters: air temperature, relative humidity, visibility and wind speed.

For studies **II** and **III** meteorological parameters (daily mean air temperature, sea-level barometric pressure, precipitations, relative humidity, wind speed and direction) and planetary boundary layer (PBL) height were retrieved by the ERA-Interim reanalysis project (Dee et al. 2011), the latest global atmospheric reanalysis produced by the European Centre for Medium-Range Weather Forecasts (ECMWF). Data have been downloaded at the spatial resolution of

0.125°×0.125° for the hours 0.00 and 12.00 for each day in 2006–2015 (study **II**) and 2005-2016 (study **III**).

3.1.3 Dispersion models

For study **III** we retrieved parameters of global atmospheric composition from ERA-Interim project (total column ozone, 2005–2016), MACC-II re-analysis ($PM_{2.5}$, PM_{10}, and total column nitrogen oxides, 2005–2012), and CAMS near-real time models ($PM_{2.5}$, PM_{10}, and total column nitrogen oxides, 2013–2016). Each parameter was downloaded for the 8 three-hour windows from 0:00 to 21:00 each day in 2005–2016, at the finest spatial resolution available (0.125°×0.125°, approximately 10x10-km).

3.1.4 Other predictors

Other predictors used in the three studies of exposure assessment are reported in **Table 3.1**.

Table 3.1 Other spatial and spatiotemporal predictors used in studies **I**, **II** and **III**

Variable	Description	Source	Resolution	Study
Administrative areas	Regions, provinces/counties, municipalities	ISTAT SCB	Polygons	**I, II, III**
Geo-climatic zones	Alpine ridge, Po valley, high Adriatic, Appennine, high Tyrrenum, mid Tyrrenum, low Adriatic and Ionium, low Tyrrenum and Sicily, Sardinia	ISPRA	9 macro-areas	**I, II**
Population density	Resident population, Census 2011 (Italy) Resident population, 2016 (Sweden)	ISTAT SCB	Census blocks DeSO	**I, II, III**
Industrial emissions	Point emission sources, year 2010, tons/year of PM_{10}, SO_2, NO_2, CO, NH_3; Distance between each cell and the closest plant	ISPRA	743 points	**I, II**
Elevation	Mean elevation (meters)	CLMS / EU-DEM	30 m	**I, II, III**
Imperviousness surface areas (ISA)	Indicator of artificial areas (houses, airports, harbors, roads, industrial and commercial areas, construction sites), year 2012	CLMS	20 m	**I, II, III**
Corine Land Cover (CLC)	Land cover data, 2012. Defined as % of each grid cell covered by: high/low development, urban green, industries, arable land, pastures, deciduous, evergreen, forest, shrubs, water	EEA	100 m	**I, II, III**
Roads	Road density (meters within the cell) and proximity (distance from the closest road) by road type: highway, major, secondary, local	TeleAtlas	Lines	**I, II, III**
Proximity to other features	Distance between grid cells centroids and other features: ports, airports, sea, lakes	-	Polygons	**I, II, III**
Saharan dust	Days in 5 macro-areas of Italy (North, Centre, South, Sicily, Sardinia) classified as dust-affected (DUST=1) or not (DUST=0) based on a combination of multiple meteorological models	(Pey et al. 2013)	5 macro-areas	**I, II**

3.1.5 Statistical methods for air pollution estimation

The objective of the three exposure studies was to train spatiotemporal models on air pollutants' measurements, using all (or a subset of) the above spatial and spatiotemporal covariates as predictors, and predict the model for all the grid cells of the national domains and all days of the study periods. This has been achieved with slight differences among studies.

Study **I**

We have adopted a strategy based on five steps:

1. *Inverse Probability Weighting (IPW)*: define a model for the probability of non-missing AOD, to account for the fact that missingness in AOD data can be related to PM_{10} concentrations (for example, when it is due to cloud coverage or snow contamination). In such cases, we need to overweight observations without AOD and downweight those with AOD, so that the final prediction is balanced and representative of the whole spatiotemporal domain. The model in step 1, detailed in study **I**, provides estimates of such probabilities, that are used as (inverse) weights in models of later steps:

$$\hat{p}_{non.missing\ AOD} \sim f(elevation + PBL + air.temperature + month)$$

$\frac{1}{\hat{p}}$ = IPW: Inverse probability weigths used in following steps

2. *Calibration*: define a mixed-effects multivariate regression model for the relationship between measured PM_{10} concentrations and the spatial and spatiotemporal covariates. In such a model, random intercepts by day and random slopes of AOD by day are used to account for the changing relationship between AOD and PM_{10} every day. In addition, the model incorporates weights from the previous step for balancing observations based on the predicted probability of non-missing AOD.
3. *Prediction*: Predict the previous model in all grid cells and days with AOD data.
4. *Imputation*: define a mixed-effects multivariate regression model to impute daily PM_{10} concentrations over cells/days where AOD is not available. This is achieved by establishing a relationship between predictions of the previous step and averages of PM_{10} observations from all the monitors distant up to 50 km from each cell centroid.
5. *Downscaling*: define a machine-learning model, the support-vector machine (SVM), to establish a relationship between residuals of the calibration model and predictors calculated around each monitors (e.g. 150-m buffer) aimed at capturing local sources. While the output of this model cannot be applied everywhere (because such small-scale data are not available over all spatial locations of Italy), such data are available in many cohort studies, where it is desirable to predict air pollution at individual addresses.

Further details of the individual steps are described in study **I**.

Study **II**

The analytical strategy of studies **II** and **III** was different from study **I**, because we applied a preliminary stage of AOD imputation, by using CAMS AOD to impute MAIAC AOD when this was missing. In addition, we collected data, and obtained predictions, also for $PM_{2.5}$ and $PM_{2.5-10}$, which required a preliminary step of data integration. A summary of the analytical steps undertaken in study **II** for Italy is reported in **Figure 3.2**.

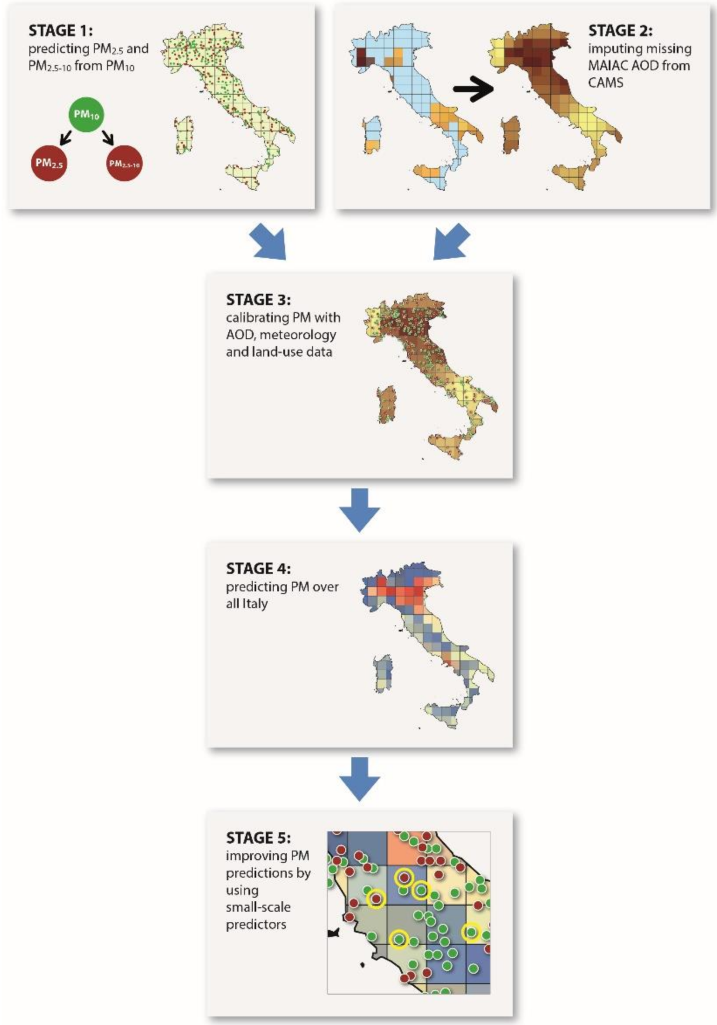

Figure 3.2 Graphical representation of the analytical steps in study **II**

Briefly, we applied a first step (stage 1) to predict $PM_{2.5}$ and $PM_{2.5-10}$ daily concentrations from co-located PM_{10} data. This allowed to increase the number of monitoring stations of fine and coarse particles to use in the following calibration step. In parallel, we applied a second step (stage 2) to establish a statistical relationship between co-located MAIAC and CAMS AOD, aimed at predicting MAIAC when this was missing, so obtaining a full AOD surface. Third, for each year in 2013-2015 and each one of the three pollutants PM_{10}, $PM_{2.5}$ and $PM_{2.5-10}$, we defined a calibration model where imputed AOD, spatial and spatiotemporal covariates were used as predictors (stage 3). This model was applied to predict daily PM over all 1x1-km grid cells of Italy and all days in 2013-2015 (stage 4). Finally, we applied a downscaling model on the residuals of the calibration model (stage 5), as described in study **I**.

Another major difference between studies **II** and **III** compared with study **I** was that we trained machine learning models, specifically random forests, in each stage. Briefly, random forests represent a family of methods that consist in building an ensemble (or forest) of decision trees. Different versions of random forests have been proposed in the literature, depending on how data are sampled and decision trees are grown at each iteration (Breiman 2001; Cutler and Zhao 2001; Geurts et al. 2006). In the proper random forest design (Breiman 2001), each tree is built using a bootstrap sample of the data, and each node of the tree is split according to the best of a subset of randomly chosen predictors (Liaw and Wiener 2002). Finally, outputs from each tree are averaged to obtain an ensemble prediction of the target variable. The model also provides an estimate of the "importance" of each predictor by quantifying how much prediction error increases when data for that variable are permuted while all others are left unchanged (Liaw and Wiener 2002).

Study **III**

Study **III** followed the same analytical strategy as study **II**. There were, however, substantial differences, listed below:

- *Spatial domain*: we ran models for the first time in Sweden, a spatial domain of 460,296 squared kilometers;
- *New air pollutants*: we ran models also for NO_2 and O_3;
- *Long study period*: we expanded the study period to twelve years (2005-2016). In addition, the calibration model (stage 3) was run on the full period altogether, rather than by each year separately;
- *Additional covariates*: we added atmospheric composition variables downloaded from Copernicus; in addition, for many spatiotemporal covariates, we used lagged terms up to three days, to account for a potential latency between such variables and PM/gases concentrations at ground level.

Cross-validation

Common to the three studies was the strategy for cross-validation. As the ultimate goal of the spatiotemporal models was to predict air pollutants in places and days with no observations, a careful cross-validation was essential to guarantee a proper extrapolation of the model fit to external receptors. This was achieved by a 10-fold cross-validation by monitors. Specifically, the total set of monitoring stations was randomly split into ten groups; the calibration model was applied, in turn, on nine groups ("training" set) and predicted to the tenth group ("testing" set); the procedure was reiterated ten times, so to obtain a prediction for every left-out observation; finally we checked the correlation between observed air pollutants' concentrations and predictions in held-out monitors: we estimated the R^2 (percent of variability of measured concentrations captured by predictions), the root mean squared prediction error (RMSPE), and the intercept and slope of the simple linear regression between measured and predicted concentrations.

3.2 EPIDEMIOLOGICAL ANALYSIS

We evaluated the short-term association between daily air pollutants' concentrations and cardiovascular admissions in Italy (study **IV**) and cause-specific mortality in the Stockholm county (study **V**).

3.2.1 Hospitalizations data in Italy

The Italian Ministry of Health provided data on hospital discharge records for all the Italian hospitals, both public and private, for 2006-2015, for a total of 109,832,220 admissions. For the aims of the study **IV**, we selected only acute (e.g. unscheduled) hospitalizations for cardiovascular diseases (International Classification of Diseases, 9th Revision – ICD-9: 390-459) for the years 2013-2015, because the focus of the paper was on $PM_{2.5}$, for which reliable estimates were obtained only for the last period (study **II**).

In addition to total CVD admissions, we considered the following groups of diseases, selected from the primary diagnoses of discharge:

- cardiac diseases (ICD-9: 390-429)
    - hypertension (ICD-9: 401-405)
    - ischemic heart diseases (ICD-9: 410-414)
        - acute myocardial infarction (ICD-9: 410)
    - arrhythmias (ICD-9: 427)
        - atrial fibrillation (ICD-9: 427.31)
    - heart failure (ICD-9: 428)
- cerebrovascular diseases (ICD-9: 430-438)
    - hemorrhagic stroke (ICD-9: 431)
    - ischemic stroke (ICD-9: 433-435)

For each group of diseases and each of the 8,084 municipalities of Italy, we built a time series of daily counts of acute hospital admissions. In addition, we generated time series by age (0-64, 65-74, 75-84 and 85+ years) and sex, evaluated as potential effect modifiers in the PM-CVD admissions relationship.

One of the key aspects of study **IV**, and of the thesis, was to describe a potential heterogeneity in the short-term effects of PM across space. To this aim, we classified the 8,084 Italian municipalities into two different urbanization scores:

- For the first one we used four spatial parameters considered valid proxies for population clustering at the municipality level: resident population (from Census data, year 2011), "light-at-night" (LAN) parameter (from the "VIIRS" satellite, year 2015), percentage of built areas (from Corine Land Cover database, year 2012), and density of high traffic roads (from TeleAtlas TomTom 2012 road network). These variables were combined in order to produce a quantitative score for each municipality.

- For the second one, we used an alternative indicator of urbanization, as defined by EUROSTAT for each municipality of Europe. This is based on the combination of absolute resident population and population density (Census 2011), and classifies municipalities into "Cities" (densely populated areas), "Towns and suburbs" (intermediate density areas) and "Rural areas" (thinly populated areas).

Comparative maps of Italy by the two scores are reported in **Figure 3.3**.

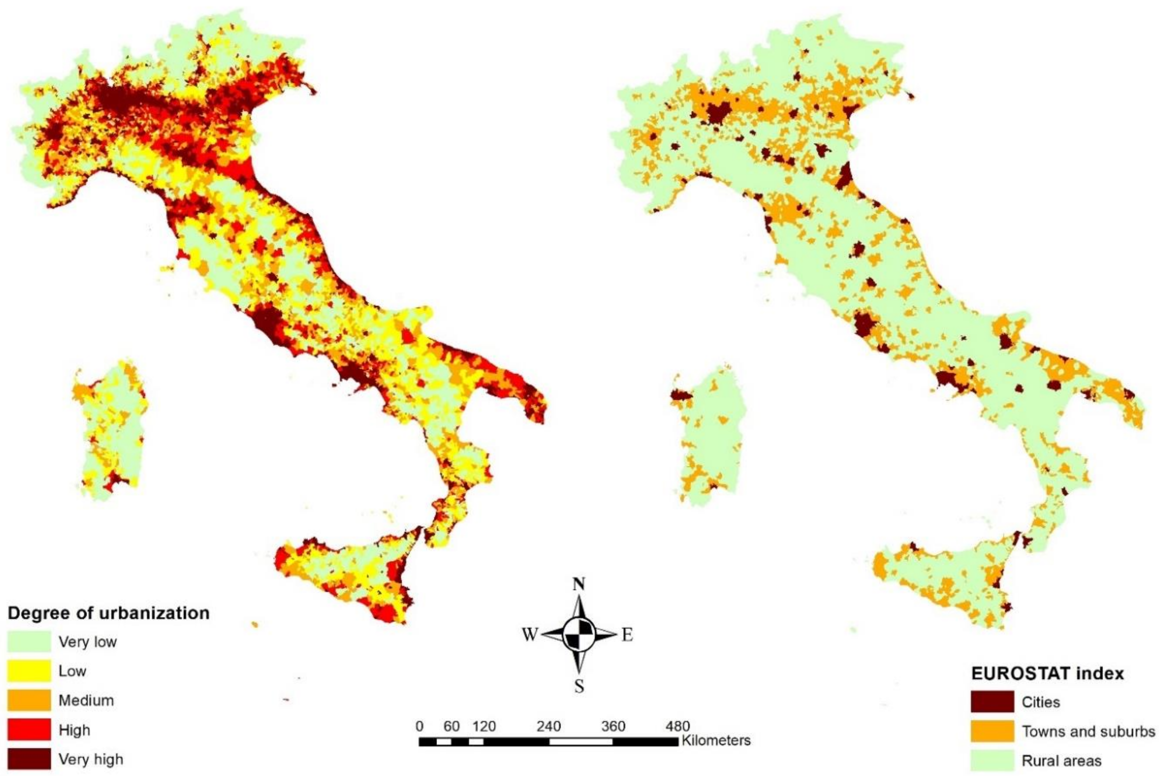

Figure 3.3 Italian municipalities (N = 8,084) by quintiles of the urbanization score (left) and by the EUROSTAT index of urbanization (right)

3.2.2 Mortality data in the Stockholm county

Statistics Sweden (Statistiska centralbyrån – SCB) provided data on all deaths occurring in the Stockholm county between 2005 and 2016, with information on the date of death, the primary cause, the location of death (whether in-hospital or out-of-hospital), age and sex of the deceased subject, the municipality of residence, and the small area for market statistics (SAMS) of mortality. For the aims of Study **V**, we included subjects 75+ years old, and considered all non-accidental (International Classification of Diseases, 10th revision – ICD-10 between A00-R99), cardiovascular (ICD-10: I00-I99) and respiratory causes (ICD-10: J00-J99).

In order to investigate whether associations differed across space, we adopted three different approaches: first, we compared associations between those residing in or out the Stockholm municipality; second, we categorized the SAMS based on the resident population, to identify more and less urbanized areas; third, we reported estimates for each of the 26 municipalities of the Stockholm county.

3.2.3 Statistical methods for short-term effects of air pollutants

Study **IV**

Daily estimates of PM_{10} and $PM_{2.5}$ exposures were attributed to each of the 8,084 municipalities of Italy as a weighted average of PM concentrations of all the 1x1-km grid cells intersecting the municipality, with weights proportional to the intersection areas.

We applied a 2-stage hierarchical model to estimate the associations of daily PM_{10} and $PM_{2.5}$ concentrations with disease-specific hospital admissions across Italy:

- First, we estimated the associations separately in each of the 110 provinces of Italy. For each province, we applied a pooled analysis on the time-series of municipalities belonging to the same province. Specifically, we stacked together the time series of all municipalities for that province, and ran an over-dispersed Poisson regression model, using the following formula (simplified version of the one in study **IV**):

$$E\left[\ln\left(Y_{i,j}^{d,p}\right)\right] = intercept + \beta^p PM_{i-lag,j}^{m,p} + confounders$$

  where the natural logarithm of $Y_{i,j}^{d,p}$ (count of admissions on day *i* in the municipality *j* belonging to province *p* for disease group *d*) was regressed against $PM_{i-lag,j}^{m,p}$ (mean concentrations of PM for metric *m* (either "10" or "2.5") on day *i-lag* (with lag being the time latency) for municipality *j* belonging to province *p*) upon adjustment for temporal confounders: time trends, meteorology, days of the week, influenza epidemics, holidays and summer population decrease;

- Second, we pooled province-specific estimates β^p with a random-effects meta-analysis using the restricted maximum-likelihood estimator of the between-province variance (Hardy and Thompson 1996).

In the first stage of analyses, we evaluated several aspects of the PM-CVD association:

1. *Temporal latency*: we examined whether different outcomes displayed different temporal latencies with the exposures. This was accomplished by fitting distributed lag models up to 9 days before admissions, and by selecting a priori lags 0, 0-1, 2-5 and 0-5 as referent time windows to represent immediate, delayed or prolonged effects;
2. *Exposure-response function*: we modelled PM with a natural spline with 2 inner knots located at terciles of the province-specific distributions, in order to describe the shape of the association with each study outcome;
3. *Effect modification*: we repeated the analyses by age group (0-64, 65-74, 75-84 and 85+ years) and sex, to identify potentially vulnerable subgroups, and by the two indicators of urbanization described above, to check whether associations existed even outside the major urban areas.

Study **V**

We derived daily estimates of air pollutants' concentrations (PM_{10}, $PM_{2.5}$, NO_2 and O_3) for each SAMS as a weighted average of concentrations of the 1-km grids intersecting the SAMS.

We applied a case-crossover design to estimate the short-term association between daily air pollutants and cause-specific mortality. The case-crossover design is a special case of matched case-control study, where each deceased subject represents a risk set, the case is chosen as the subject himself on the date of death, and the controls are suitably chosen as alternative days when the even did not happen (Maclure 1991). In this analysis, control periods were selected using the “time-stratified” approach (Lumley and Levy 2000), according to which the study period is divided into monthly strata, and control days for each case were chosen as the same days of the week in the stratum. We considered the case-crossover design as the best option because we had estimates of exposures at very fine spatial resolution, and the alternative of running time-series analyses separately for each SAMS would have been much less efficient.

We investigated:

- the *lag structure* between daily air pollution and mortality, using single-lag and average-lag models;
- the *difference in effects between two different sets of exposures*: first, the spatiotemporal exposures obtained under study **III**, where each subject was given the daily exposure of the SAMS of death; second, a temporal-only exposure where all subjects dying on the same day were given the same exposure, calculated as the average of the urban background monitors. The purpose of this analysis was to test whether there was any added value in using our spatiotemporal estimates of air pollution in the epidemiological analyses, compared to the standard approach of using daily averages from monitoring stations, which assume the same day-to-day variability of air pollutants across space;
- *effect modification* by: season of death, distinguished into the warm period (April to September) and the cold period (October to March); age (75-84 and 85+ years old), sex, location of death (in-hospital or out-of-hospital);
- the *spatial heterogeneity* in health effects, by reporting associations: 1) among those residing in versus those resideing out the Stockholm municipality; 2) in SAMS with a resident population below versus above the median value (~3,000 inhabitants per km^2); 3) for each of the 26 municipalities of the Stockholm county;
- the *shape of the exposure-response relationship* between air pollution and non-accidental mortality by fitting natural splines of lag 0-5 air pollutants with two inner knots located at the terciles of the exposure variables. This was repeated for the two types of exposures (spatiotemporal and monitor-based) and for the warm period only (as it was the one displaying the highest effects in the main analysis).

4. RESULTS AND COMMENTS

4.1 PARTICULATE MATTER EXPOSURE IN ITALY

Table 4.1 reports a summary of PM_{10} and $PM_{2.5}$ data available in Italy during 2006-2015 (studies **I** and **II**). The coarse fraction has been calculated as the difference between PM_{10} and $PM_{2.5}$ from co-located monitors. In grey are reported the years for which estimates of air pollutants were not performed in studies **I** and **II** because of the limited number of monitors.

Table 4.1 PM data in Italy, 2006-2015

Year	PM_{10}			$PM_{2.5}$			$PM_{2.5-10}$		
	n. sites	mean	SD	n. sites	mean	SD	n. sites	mean	SD
2006	308	35.1	24.4	29	27.3	20.4	26	14.7	12.8
2007	405	33.3	22.1	46	23.9	17.9	46	12.5	10.1
2008	460	30.5	20.8	68	20.4	15.7	68	11.6	9.7
2009	504	29.9	19.1	93	20.2	15.4	92	10.9	9.4
2010	545	27.8	18.1	123	19.2	14.4	122	9.4	7.9
2011	533	30.0	20.7	136	21.5	17.0	136	9.6	7.8
2012	504	27.8	18.5	132	19.6	15.7	132	9.9	7.7
2013	506	25.5	18.1	198	17.4	14.7	198	8.2	7.1
2014	519	24.1	16.9	221	15.7	12.0	221	8.7	8.2
2015	524	26.7	18.2	229	18.3	14.7	229	8.6	6.8

Figure 4.1 compares the spatial distribution of predicted $PM_{2.5}$ concentrations (annual averages, year 2015) using two different methods: an inverse-distance weighted (IDW) average on the left, which utilizes only information from monitoring stations, and the random forest (RF) prediction on the right, which combines multiple sources of data (study **II**).

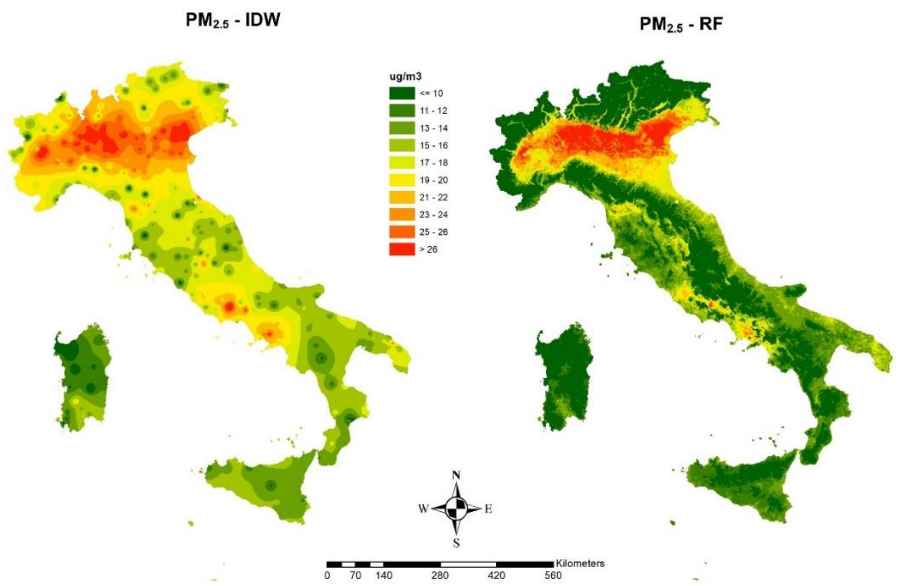

Figure 4.1 Estimates of annual mean $PM_{2.5}$ concentrations (in $\mu g/m^3$) from two spatiotemporal models: Inverse-Distance Weighting (IDW, left) and Random Forest (RF, right) – Italy, year 2015

Day-to-day variability in air pollutants' concentrations is displayed in **Figure 4.2**, for PM_{10} in 2012 (study **I**, left) and $PM_{2.5}$ in 2015 (study **II**, right). The plots display the daily time series of the measured concentrations at the monitoring stations (blue line), the predictions at the same sites (red line) and the predictions at the national level, obtained as averages of the 307,635 1x1-km grid cells of Italy (green line). Both methods, the mixed model (MM) applied in study **I** and the random forest (RF) applied in study **II**, were able to approximate very well the temporal trends of the monitoring stations. In addition, our models allowed to describe the daily mean concentrations and variability of PM in places not covered by the routine monitoring networks, usually more remote and isolated, therefore characterized by lower concentrations, as evident from the green lines. This was extremely relevant from an epidemiological perspective, because enabled us to investigate health effects in understudied populations of Italy, providing new evidence on the shape of the exposure-response functions at low PM levels (further described later in study **IV**).

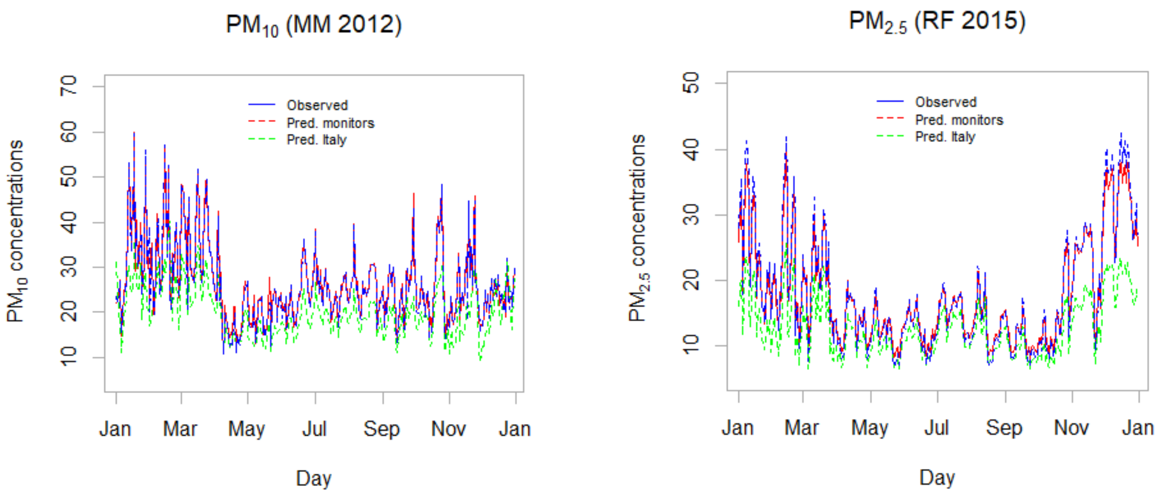

Figure 4.2 Daily mean PM_{10} and $PM_{2.5}$ concentrations (in $\mu g/m^3$): measurements at the monitoring stations (blue lines), predictions at the same sites (red lines), and predictions at the national level (green lines) – Italy, year 2012 (predictions obtained with mixed model – MM, left) and year 2015 (predictions obtained with random forest – RF, right)

Finally, **Table 4.2** shows the statistics of model fit (R^2, RMSPE, intercept and slope) for PM_{10} (years 2006-2012, mixed model, study **I**) and both PM_{10} and $PM_{2.5}$ (years 2013-2015, random forest, study **II**) obtained comparing measurements with predictions in left-out monitors. We also report statistics separately for the spatial and temporal components of the model:

- for the <u>spatial component</u>, we averaged daily observed and predicted PM concentrations within each cell, then we regressed annual mean observed VS predicted PM values;
- for the <u>temporal component</u>, for both the observed and the predicted series of PM concentrations, we subtracted the annual averages from the daily values, then we regressed daily observed VS predicted PM deviations.

Table 4.2 Model fit statistics in study **I** (mixed-effects model, top) and study **II** (random forest, bottom)

	Spatiotemporal				Spatial		Temporal	
	R^2	RMSPE	Int.	slope	R^2	RMSPE	R^2	RMSPE
STUDY I – PM_{10}, years 2006-2012								
PM_{10} overall	0.64	10.2	1.20	0.95	0.56	4.8	0.67	9.0
By season								
Winter	0.69	13.8	0.15	0.99	-	-	0.69	12.4
Spring	0.62	9.4	1.40	0.94	-	-	0.64	8.2
Summer	0.52	8.3	2.80	0.89	-	-	0.60	7.3
Autumn	0.60	10.0	1.49	0.94	-	-	0.62	8.7
By monitor type								
Traffic	0.62	10.6	1.52	0.99	0.45	5.7	0.65	9.2
Industrial	0.53	10.1	3.13	0.89	0.50	4.9	0.55	9.0
Background	0.70	9.7	0.03	0.95	0.64	4.5	0.72	8.7
STUDY II – PM_{10} and $PM_{2.5}$, years 2013-2015								
PM_{10} overall	0.74	9.1	-0.01	1.01	0.71	3.3	0.74	8.5
By season								
Winter	0.73	11.3	-0.52	1.03	-	-	0.73	10.6
Spring	0.74	8.6	0.39	0.99	-	-	0.74	8.1
Summer	0.69	7.4	-0.16	1.01	-	-	0.69	7.1
Autumn	0.75	8.6	0.16	1.00	-	-	0.75	8.0
By monitor type								
Traffic	0.76	9.4	0.03	1.04	0.69	3.6	0.77	8.7
Industrial	0.73	8.3	0.03	1.03	0.77	2.9	0.73	7.9
Background	0.73	9.0	-0.13	0.99	0.70	3.0	0.73	8.5
$PM_{2.5}$ overall	0.79	6.1	-0.59	1.02	0.79	2.6	0.79	5.6
By season								
Winter	0.76	9.3	-0.65	1.03	-	-	0.74	8.3
Spring	0.79	4.6	-0.36	1.00	-	-	0.80	4.3
Summer	0.59	3.5	-0.74	1.03	-	-	0.71	3.5
Autumn	0.79	5.6	-0.47	1.01	-	-	0.78	5.1
By monitor type								
Traffic	0.80	6.4	-0.44	1.06	0.76	2.6	0.81	5.9
Industrial	0.79	5.5	-0.76	1.07	0.81	2.4	0.77	5.0
Background	0.79	6.0	-0.67	0.99	0.81	2.4	0.79	5.6

In general, both the mixed-effects and the random forest models were able to capture most of the observed variability in left-out monitors, explaining 64%, 74% and 79% of PM variability for PM_{10} (2006-2012), PM_{10} (2013-2105) and $PM_{2.5}$ (2013-2015), respectively. Both models explained a larger fraction of temporal than spatial PM variability, and displayed a better fit in winter and autumn months. While the mixed model fitted data from background monitors much better than traffic and industrial ones, no substantial differences in fit were found for the random forest. Finally, all models showed little bias in their predictions in left-out monitors, as represented by intercepts close to zero, and slopes close to one.

4.2 AIR POLLUTION EXPOSURE IN SWEDEN AND STOCKHOLM

The number of monitoring stations available in Sweden during 2005-2016 was limited, with annual monitors remaining stable for PM_{10} and NO_2, and slightly increasing for $PM_{2.5}$ and O_3 (study **III**). Descriptive statistics for the four pollutants and $PM_{2.5\text{-}10}$, calculated subtracting $PM_{2.5}$ from PM_{10} at co-located monitors, are reported in **Table 4.3**, and highlight very low concentrations of PM and NO_2, with the former decreasing over time and the latter remaining stable. Finally, ozone levels were stable around a mean of 55 μg/m^3.

Table 4.3 Air pollution data in Sweden, 2005-2016

Year	PM_{10}			$PM_{2.5}$			$PM_{2.5\text{-}10}$		
	n. sites	mean	SD	n. sites	mean	SD	n. sites	mean	SD
2005	61	19.1	13.3	7	12.0	6.9	7	7.8	7.5
2006	72	20.1	13.1	17	11.8	7.3	17	8.5	8.1
2007	64	19.0	13.1	18	9.2	5.8	18	9.8	8.5
2008	58	18.2	12.1	17	8.8	4.4	17	9.5	8.8
2009	54	17.1	12.0	25	8.1	5.0	25	9.4	8.6
2010	61	16.2	11.4	24	7.4	5.1	24	8.5	8.2
2011	59	18.2	12.4	25	8.6	6.8	25	9.6	8.3
2012	60	15.6	11.1	24	7.2	4.8	24	8.5	8.4
2013	66	16.5	12.0	21	6.2	3.5	21	10.5	9.9
2014	63	16.4	11.3	28	8.1	6.0	28	8.3	6.8
2015	55	14.6	10.3	27	6.6	4.7	27	7.9	6.5
2016	62	14.0	10.3	29	5.9	3.6	29	8.1	7.7

Year	NO_2			O_3		
	n. sites	mean	SD	n. sites	mean	SD
2005	60	19.9	16.3	23	56.6	18.8
2006	67	21.4	16.9	29	58.6	20.4
2007	55	19.9	16.2	29	55.1	16.8
2008	60	20.1	15.4	24	54.8	19.3
2009	58	20.2	15.4	26	54.0	17.8
2010	58	23.1	18.1	26	54.9	18.0
2011	58	21.5	16.7	27	56.5	19.3
2012	60	21.2	15.9	22	52.2	18.3
2013	58	22.1	16.5	30	55.7	18.4
2014	50	20.3	15.5	30	53.8	18.0
2015	45	20.0	15.5	30	54.8	16.0
2016	53	20.7	15.7	30	52.3	17.2

Table 4.4 reports the Spearman correlation coefficients between the five air pollutants and the main predictors used in the calibration RF model in study **III**. In general, we found weak correlations between predictors and air pollutants' concentrations, with CAMS atmospheric composition variables, PBL height, cloud coverage, barometric pressure and NDVI being the most correlated spatiotemporal parameters, and resident population, ISA, LAN, elevation, road density, % evergreen and % urban areas being the most correlated spatial ones.

Table 4.4 Spearman's correlations between air pollutants and predictors

Predictor	PM_{10}	$PM_{2.5}$	$PM_{2.5\text{-}10}$	NO_2	O_3
Spatiotemporal					
atmospheric composition var.	0.35	0.44	0.21	0.12	0.35
PBL (at midnight)	-0.14	-0.14	-0.10	-0.21	0.09
PBL (at midday)	0.06	-0.08	0.14	-0.13	0.35
cloud coverage	-0.17	-0.04	-0.20	-0.06	-0.21
barometric pressure	0.18	0.18	0.14	0.10	-0.02
NDVI	-0.13	-0.11	-0.12	-0.31	0.07
Spatial					
resident population	0.17	-0.01	0.24	0.34	-0.15
ISA	0.17	0.16	0.14	0.27	-0.16
LAN	0.08	-0.02	0.13	0.27	-0.11
elevation	-0.18	-0.16	-0.15	-0.23	0.14
all roads length	0.17	0.10	0.18	0.44	-0.16
% evergreen	-0.17	-0.12	-0.16	-0.29	0.15
% urban area	0.12	0.07	0.13	0.32	-0.18

Predicted mean concentrations of NO_2 (left) and O_3 (right) are reported in **Figure 4.3**, for Sweden and Stockholm. The maps display the mean predictions of the RF model (study **III**) for the year 2016.

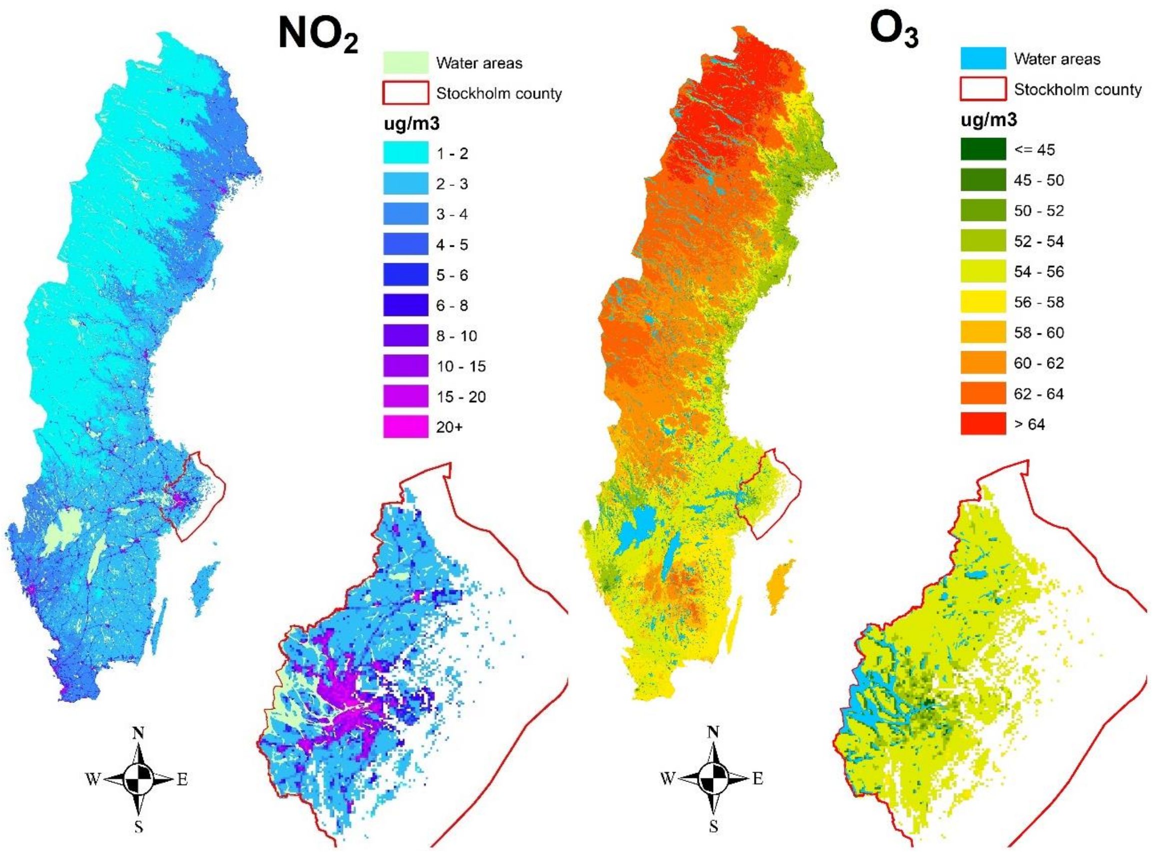

Figure 4.3 Estimates of annual mean NO_2 (left) and O_3 (right) concentrations (in μg/m^3) for Sweden and Stockholm, obtained with the random forest model (study **III**) – year 2016

4.3 SHORT-TERM EFFECTS OF PM ON HOSPITALIZATIONS AT THE NATIONAL LEVEL

Study population

We selected 2,154,810 acute admissions for cardiovascular diseases in Italy during 2013-2015, of which the most frequent diseases were cerebrovascular diseases (25.2%), ischemic heart diseases (23.7%) and heart failure (21.9%). While most patients resided in major urban centers (54.6%), there was still a large fraction of individuals living in areas never investigated in previous studies on air pollution, such as rural and remote towns (13.3%), sub-urban settings (12.2%) and small cities (20.0%).

Main effects of air pollutants by cause and lag

Figure 4.4 reports the results of the associations between daily mean PM_{10} and $PM_{2.5}$ concentrations, at different lags, and daily admissions for a selection of CVD outcomes: results are expressed as relative CVD increases, and 95% Confidence Intervals (95% CI), per 10 μg/m^3 increments in PM. We found significant effects of both PM_{10} and $PM_{2.5}$ on total cardiovascular diseases, cardiac diseases, ischemic heart diseases, myocardial infarction, heart failure, atrial fibrillation and ischemic stroke. However, the time lag of the effect of PM was different, as both PM metrics displayed a long latency of effect on cardiac diseases and heart failure (up to five days after exposure), while the effects on the other CVD endpoints were immediate, statistically significant mostly within one-two days after exposure. No evidence of an association was detected with total arrhythmias or total cerebrovascular diseases (outcomes not reported in fig. 4.4 but presented in study **III**).

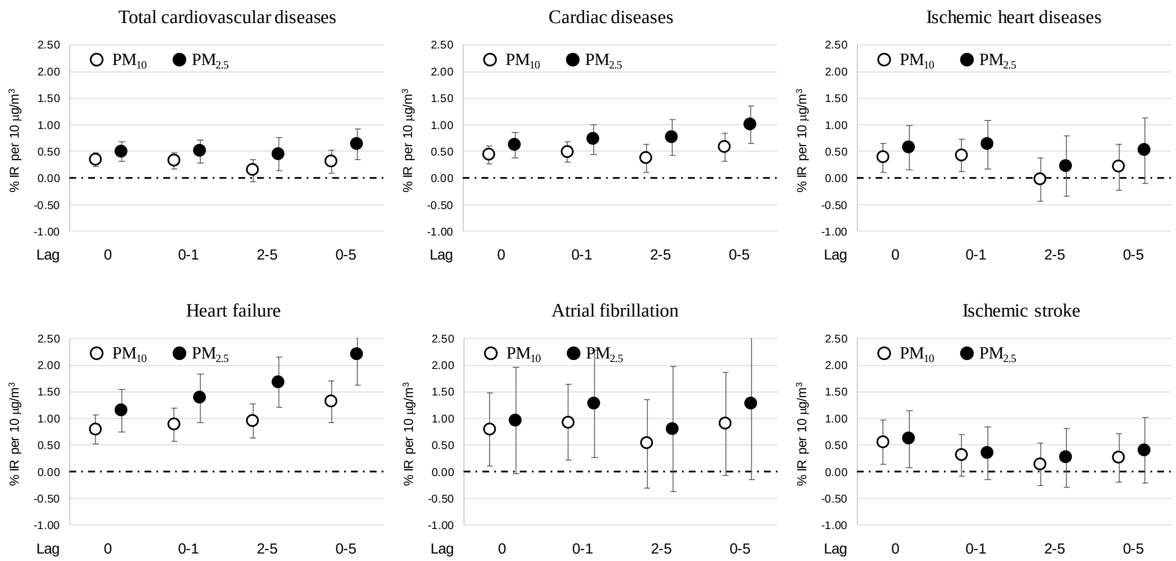

Figure 4.4 Associations between daily mean PM_{10} and $PM_{2.5}$ concentrations, at different lags, and daily admissions for selected CVD outcomes: results are expressed as relative CVD increases (% increments of risk - %IR), and 95% Confidence Intervals (95% CI), per 10 μg/m^3 increments in PM.

Exposure-response functions

The “meta-curves” representing pooled exposure-response functions between the two PM exposures (at lag 0) and selected CVD outcomes are displayed in **Figure 4.5**. We found evidence of non-linear effects in most cases, with steeper slopes of the PM-outcome associations in the lower ranges of exposures (down to 15 μg/m^3 for PM_{10} and 10 μg/m^3 for $PM_{2.5}$), far below the WHO air quality guidelines for daily mean PM_{10} (50 μg/m^3) and $PM_{2.5}$ (25 μg/m^3).

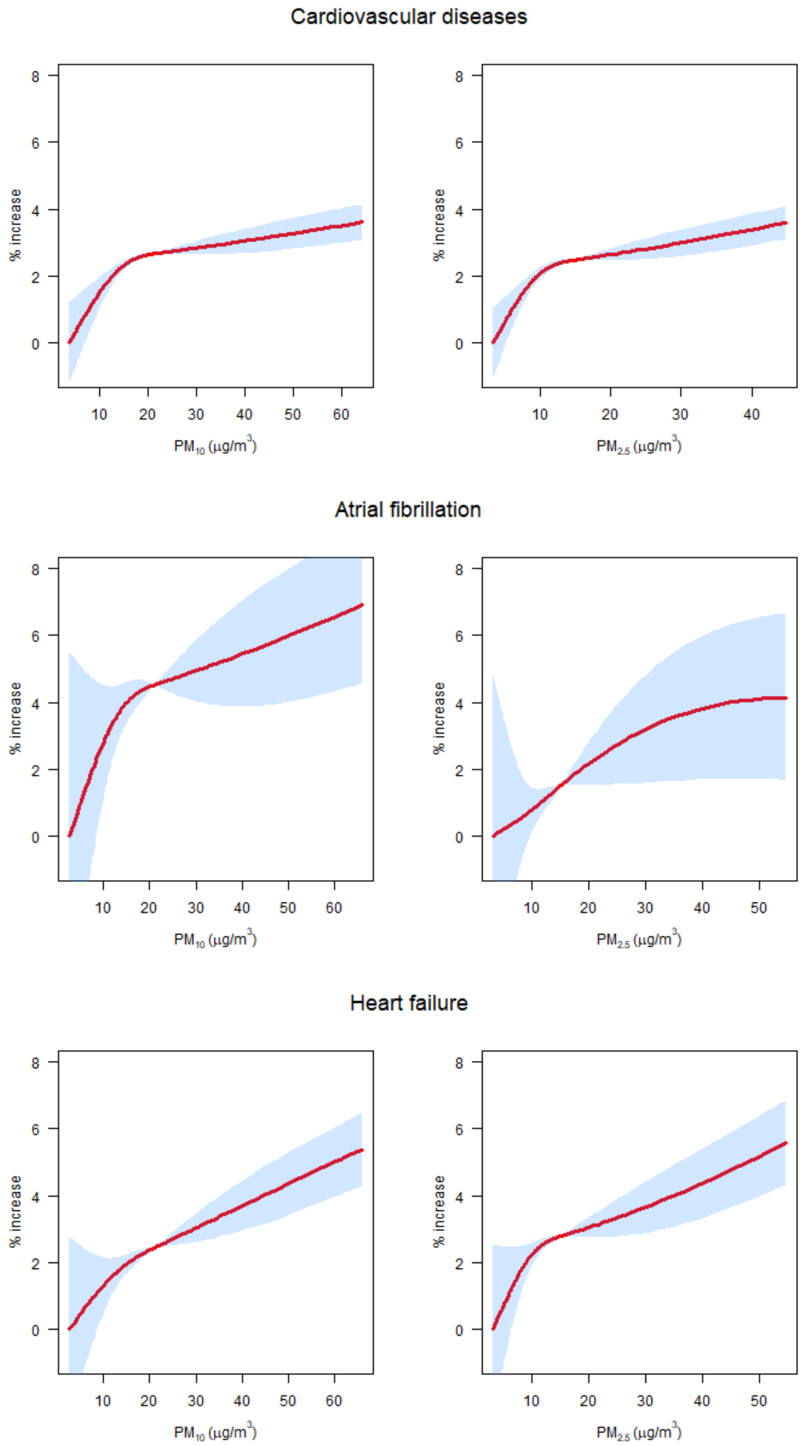

Figure 4.5 Exposure-response functions. % increases of admissions per increasing levels of PM (lag 0), by cause: PM_{10} on the left, $PM_{2.5}$ on the right

Spatial heterogeneity of the PM-CVD admissions associations

Finally, **Figure 4.6** reports results on the differential associations between daily PM concentrations and selected CVD outcome by urbanization level of the municipality of residence, using both the urbanization score and the EUROSTAT indicator described in the Methods. In general, associations were homogeneous across groups of municipalities characterized by different degrees of urbanization, with risks of PM-related cardiovascular admissions, especially for atrial fibrillation, ischemic heart diseases and myocardial infarction, high and statistically significant also among populations residing in the rural areas of the country.

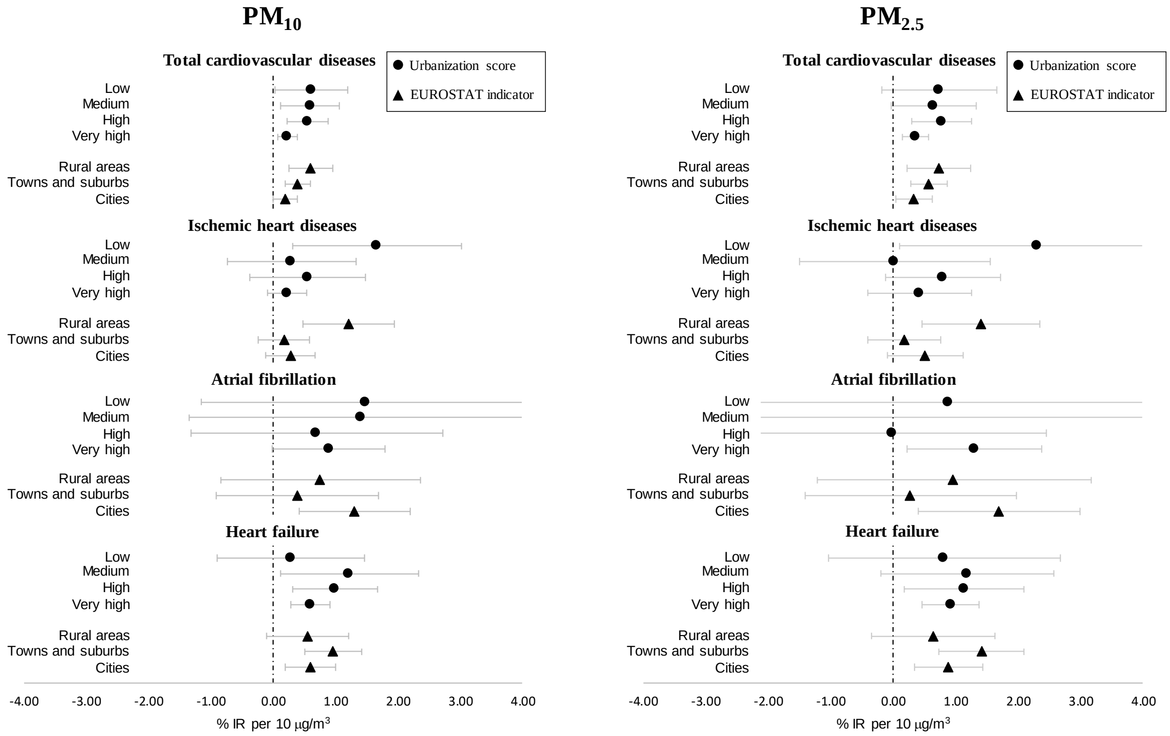

Figure 4.6 Associations between daily PM concentrations and CVD selected outcomes, by levels of the urbanization score (dots) and the EUROSTAT indicator (triangles) of the municipality of residence: % increases of admissions per 10 $\mu g/m^3$ increments in PM (lag 0), by cause

4.4 SHORT-TERM EFFECTS OF PM ON MORTALITY AT THE COUNTY LEVEL

Study population and air pollution exposure

We analyzed data on 125,468 subjects aged 75+ years old who died in the Stockholm county from non-accidental causes during 2005-2016. Of them, 43% died from cardiovascular causes and 8% from respiratory causes, 62% died out-of-hospital, and less than half resided in the Stockholm municipality at the time of death.

Average concentrations of PM_{10}, $PM_{2.5}$ and NO_2 were higher in the central area of the county, where Stockholm city is located, with decreasing patterns south and especially north of the county. Ozone, as expected, displayed an opposite trend, with higher concentrations on the islands and on the rural and remote areas in the north and south of the county (see study **III** for a detailed presentation of the exposure maps). In terms of temporal distribution, the daily time series showed a higher degree of daily variability in air pollutants (all except ozone) captured by our spatiotemporal model described in study **III**, compared to daily means of urban background monitoring stations. This is reported in **Figure 4.7** for $PM_{2.5}$ and NO_2, for the year 2016.

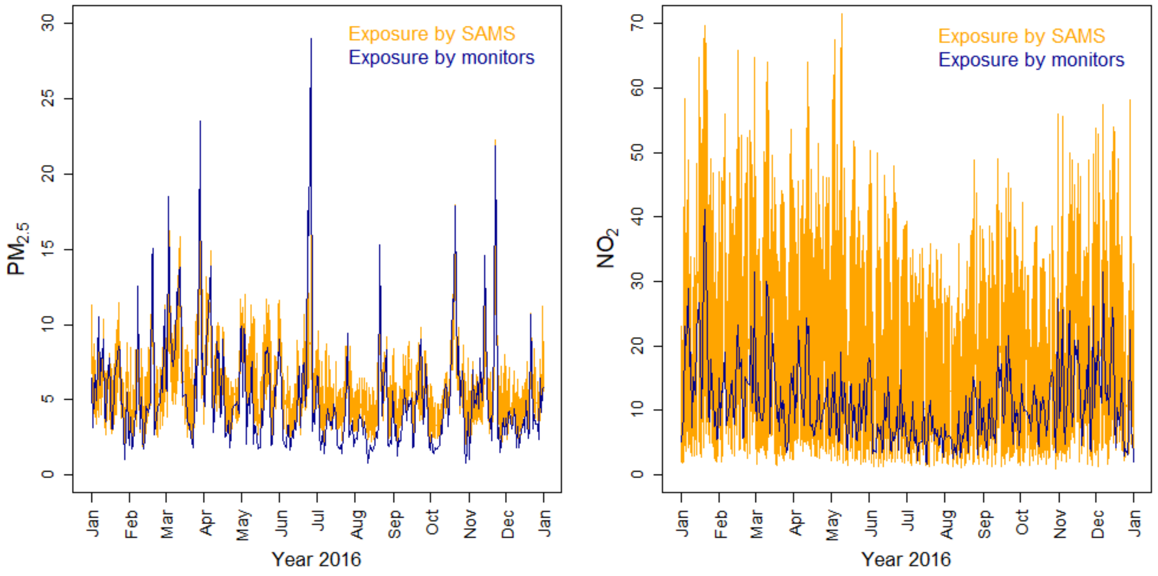

Figure 4.7 Time-series of daily $PM_{2.5}$ and NO_2 concentrations, year 2016, from different metrics: spatiotemporal at Small-Area for Market Statistics (SAMS) level (orange) and average of urban background monitors (blue)

Main effects of air pollutants by cause, lag and season

We did not find evidence of associations between short-term exposures to PM and NO_2 with non-accidental mortality nor with cause-specific mortality in the full year analysis. In contrast, ozone was significantly associated with non-accidental mortality, which increased by 1.50% (95% confidence interval – 95% CI: 0.29%, 2.71%) per 10 $\mu g/m^3$ increments in lag 0-5 O_3. The corresponding estimate for the exposure based on the average of urban background monitors was 1.19% (95% CI: 0.29%, 2.10%).

When we restricted the analysis to the warmer months (April to September), we found consistent associations of PM and O_3 with non-accidental and cardiovascular mortality, while the effects of NO_2 on all three outcomes and of all four pollutants on respiratory mortality were positive but non-significant. In particular, non-accidental mortality on warm months increased by 5.00% (0.79%, 9.38%), 2.92% (0.67%, 5.22%) and 2.14% (0.25%, 4.06%) per 10 $\mu g/m^3$ increments in $PM_{2.5}$, PM_{10} and O_3, respectively. Interestingly, respiratory mortality during cold months increased by 6.96% (1.13%, 13.12%) per 10 $\mu g/m^3$ increases in lag 0-5 O_3.

Exposure-response functions

The exposure-response functions (ERF) reported in **Figure 4.8** show increasing effects of $PM_{2.5}$, PM_{10} and O_3 on non-accidental mortality during the warm months, with no clear evidence of departures from linearity. When comparing the curves obtained using the spatiotemporal exposures to those derived by monitor averages, we didn't find meaningful differences in the shapes nor in the exposure ranges. In contrast, large differences in the two exposures were found for NO_2, for which daily average concentrations from urban background monitors never exceeded 35 μg/m^3 whereas estimates from our spatiotemporal model reached daily values > 70 μg/m^3. However, ERFs were flat and non-significant in both cases.

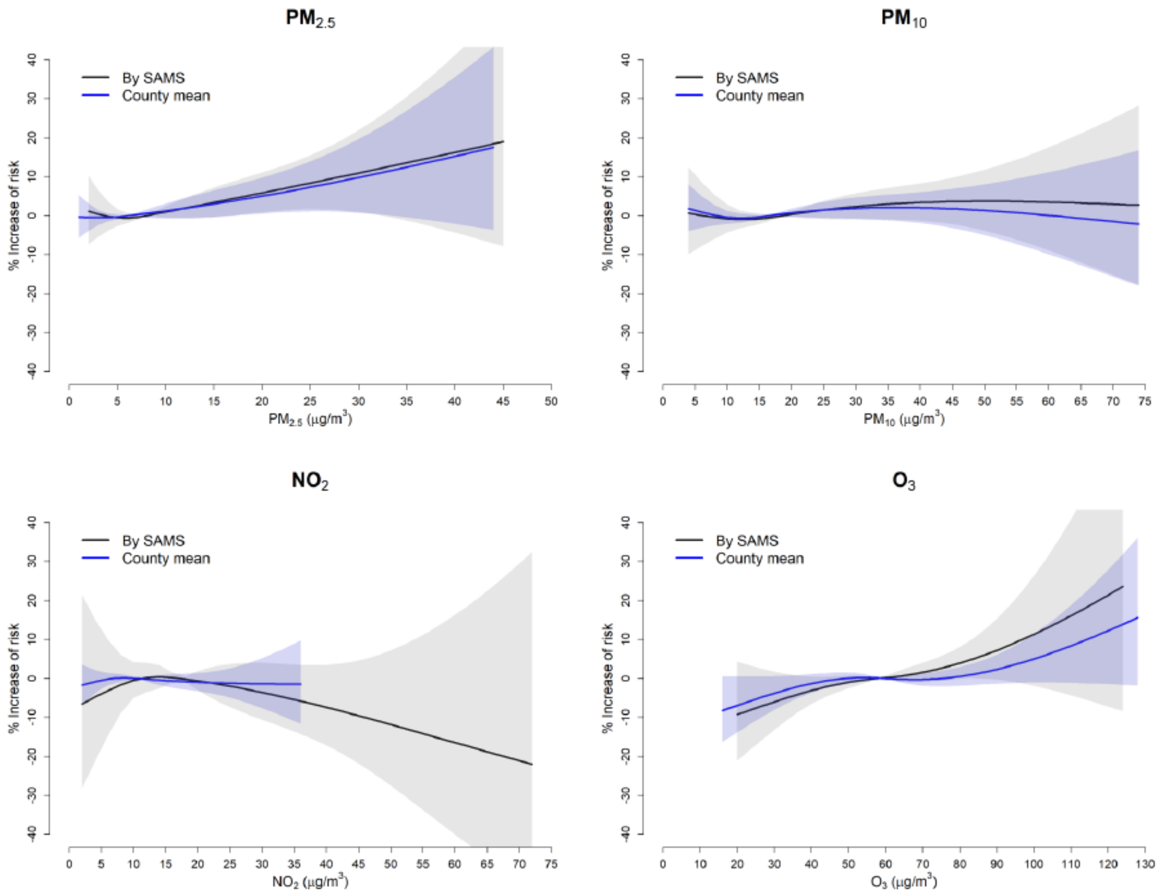

Figure 4.8 Exposure-response functions. % increases of risk of non-accidental mortality in the warm period (April-September) per increasing levels of air pollutants (lag 0-5), by type of exposure. Plots centered in the mean

Spatial heterogeneity of the air pollution-mortality associations

Finally, the estimates of the association between air pollutants and non-accidental mortality (warm period) for the 26 municipalities of the Stockholm county are displayed in **Figure 4.9**. The estimates were obtained by adding to the base model interaction terms between the indicator variables for municipality and the exposure term. In general, we found a high degree of variability in the point estimates of the relative risks, with null associations in the northern and southern areas of the county, and positive associations, with RRs of mortality per 10 μg/m^3 increment of exposure even above 1.20, in some of the central and more densely populated municipalities. However, most of the associations were not statistically significant, and the likelihood-ratio test comparing the models with and without interaction terms was largely non-significant, thus rejecting the study hypothesis of spatial heterogeneity in the health effects of air pollution in the Stockholm county. Similar results were found when we applied alternative approaches for evaluating spatial heterogeneity (the Cochrane Q test of heterogeneity on municipality-specific estimates obtained from stratified analyses, or test for the presence of residual variance from mixed-effects models).

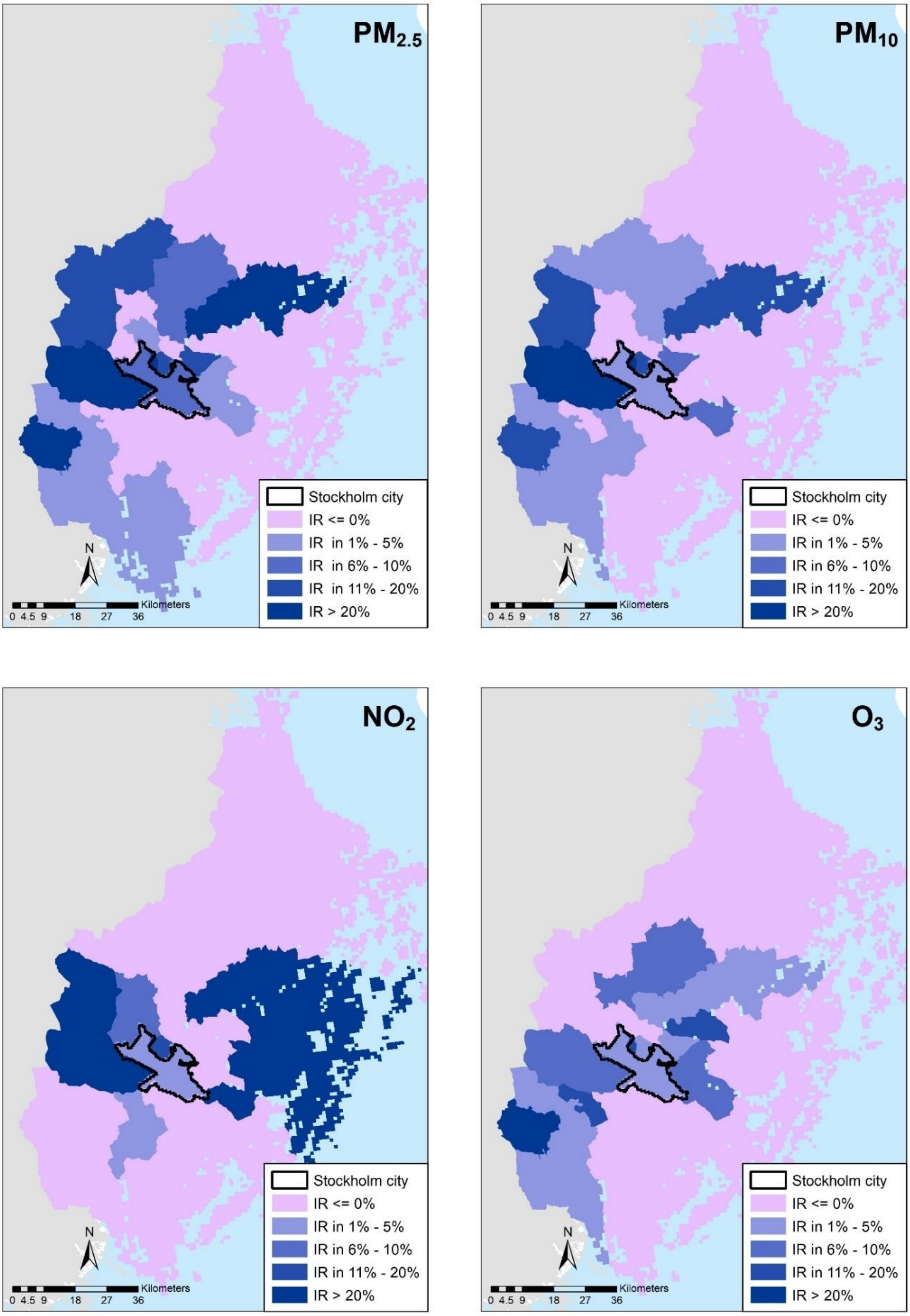

Figure 4.9 Association between air pollutants (lag 0-5) and non-accidental mortality in the warm period (April-September), by municipality. Results are expressed as % increases of risks per 10 μg/m^3 increments in air pollutants

5. DISCUSSION

The collection of studies in this thesis presents new methods for air pollution exposure assessment in Italy and Sweden, and examples of the application of such exposures to evaluate short-term effects on mortality and morbidity outcomes. The individual studies discuss the strengths and limitations of each study, and put the epidemiological findings in the perspective of the existing literature. Here the same studies will be discussed with the broader perspective to highlight the main challenges behind air pollution exposure modelling, and the complexity of interpreting the resulting epidemiological findings on short-term health effects.

5.1 EXPOSURE ASSESSMENT

The accuracy of the spatiotemporal exposure models developed in studies I-III (and in most exercises of exposure assessment described in the Introduction) depends on at least two key aspects: the availability of good data and the validity of the assumptions underlying the models.

5.1.1 Quality of input data

Air pollution measurements

The Directive of the European Commission 2008/50/CE establishes rules for the numbers of monitoring sites, their positioning and the reference methods to be applied for the measurements of the different air pollutants. The Directive states that sampling points are chosen to represent average population exposure both in urban areas and in suburban and rural settings. On this regard, the monitors available in Italy and Sweden should be, in principle, consistent with the main objectives of this thesis, i.e. the epidemiological investigation of the short-term effects of air pollution in the populations of Italy and Stockholm. However, when building spatiotemporal models aimed at predicting concentrations in large portions of the territory with only few monitors, the sparsity of the stations can be problematic because the model has less information on air pollutants' variability and sources there, with little guarantee of an accurate prediction in the corresponding areas.

The map below (**Figure 5.1**) represents an attempt to describe the spatial distribution of model uncertainty in the predictions of $PM_{2.5}$ concentrations for the year 2016 in Sweden. In particular, for each monitor the annual RMSPE has been computed by comparing daily $PM_{2.5}$ observations with cross-validated predictions. Then, the monitor-specific RMSPE has been divided by the annual average $PM_{2.5}$ concentration in that monitor in order to derive a relative measure. Finally, an inverse distance weighted prediction has been mapped for the full Swedish domain. The map suggests that model uncertainty was higher in the more remote areas of northern and western Sweden, where only sparse monitors were available. While we acknowledge that propagation of model uncertainty is not only driven by the distance from the monitors, still this can be regarded as a suggestion that air pollution estimates in large remote areas with few sampling points can be affected by a large degree of inaccuracy. However, from an epidemiological perspective, this should have a limited impact on the health effects estimates, because a very small fraction of the population lives there.

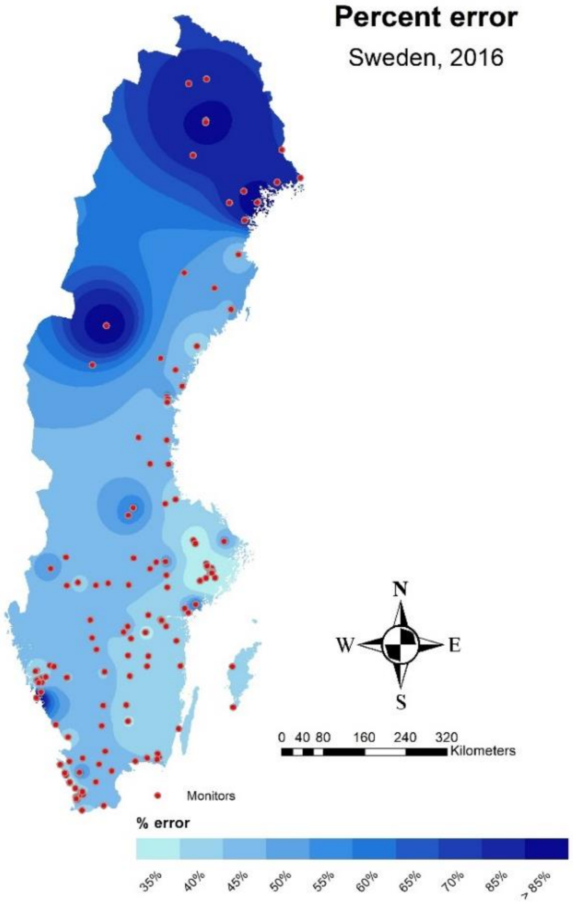

Figure 5.1 Annual mean % errors in $PM_{2.5}$ estimates calculated for each monitor and spatialized to the whole domain with an IDW model – Sweden, 2016

Predictors based on GIS techniques: spatial parameters

The majority of predictors used in the exposure models described in studies I-III are spatial, i.e. they vary across locations but are assumed constant over time, and are aimed at capturing the main emission sources of air pollution, such as road traffic, domestic heating, other anthropogenic activities, and industrial emissions. This is also the case for all those applications aimed at estimating annual average air pollutant concentrations for long-term effects studies. Since data on the actual emissions are generally lacking or poorly resolved in space and time, we have to rely on spatial proxies and apply GIS techniques to make such variables available for all the grid cells of our study domains. The most common data are population density, road networks, land-use/land-cover terms, elevation and, if available, industrial emissions. The main advantage in the use of these variables is the availability from official statistics (resident population) or opensource database (Corine, Imperviousness surface areas), the completeness across the whole study area, the high spatial resolution of most of them and the ease to process the source files using standard GIS techniques. However, the main drawback in most cases is the low explanatory power in air pollution modelling, because some of them are weak proxies of the targeted sources (for example, industrial emissions) while others characterize areas where very few monitors are available (natural classes from Corine). This is apparent in studies II and III, where the spatial terms ranked among the lowest in terms of relative importance in the random forest model (study II) and displayed very low correlations with measured air pollutants, with only few exceptions (study III).

Predictors based on external models: spatiotemporal parameters

In studies II and III we have replaced meteorological observations from sparse monitors with outputs from regional meteorological models. Also, we downloaded AOD estimates at different wavelengths to impute missing satellite retrievals (both studies) and atmospheric composition variables on columnar PM, NO_x and O_3 (study III only). These variables proved extremely useful in producing full meteorological fields, filling missing AOD data and training random forest models for air pollution predictions. This is apparent from the high ranking of most of these variables in their relative importance, and in the extremely good fitting statistics achieved when CAMS AOD was used to impute missing MAIAC AOD. There are clear advantages in the use of these variables that should be acknowledged, and explain why hybrid approaches have become standard in air pollution exposure assessment nowadays. These include the availability of such model outputs at global scale from opensource repositories, the high temporal resolution, in the order of three-hour time windows, the acceptable spatial resolution for large-scale modelling, the completeness of spatiotemporal fields, and the good correlations with measurements. At the same time, there are challenges in the download, processing and interpretation of such variables, which might explain why the final model fit of most exposure assessment studies, including those presented here, is sub-optimal: a) the spatial resolution is coarse when it comes to describe small-scale variability in air pollutants; b) these models might lack information on local sources of air pollution, therefore their correlation with measurements might be poor in some monitoring sites; c) the selection of which parameters to download requires expert knowledge in disciplines other than epidemiology and biostatistics, also because these models evolve rapidly over time; d) the processing of the variables, once downloaded, is not trivial, as it requires large computational capacity and good skills in statistical programming. As a result, the entire chain from data extraction to model building is time consuming and with no guarantee of substantial improvements compared with conventional GIS-based approaches.

Satellite data: the case of AOD

Satellite data are an extremely powerful source of information to describe air quality or land cover over large spatiotemporal domains. For this reason, it has become standard practice in modern air pollution modelling approaches to combine variables such as AOD, NDVI, LAN, OMI-based NO_x and O_3, land surface temperatures, and others with air pollutant measurements and GIS-based predictors. In the studies presented here the most relevant parameter has been AOD, therefore the discussion will focus on it.

In principle, AOD is the perfect candidate to capture PM variability over space and time. First, in studies I-III it was the only predictor, out of all those listed before, with the same spatial (1x1-km) and temporal (daily) resolution of the target domain. Second, it is directly linked to suspended particles because it is an indirect measure of them, although a columnar one. Third, it provides information on particles distribution in areas with no measurements. Fourth, it is freely available worldwide. Therefore, it shares most of the benefits already mentioned for spatial and spatiotemporal predictors. Unfortunately, the advantages end here, and the contribution of AOD in our spatiotemporal models was only marginal, for two main reasons:

low correlation with ground-level PM and large fraction of missing data. The correlation between co-located MAIAC AOD retrievals and PM measurements was below 0.20 both in Italy and in Sweden, suggesting a large discrepancy between the columnar measure and the ground-level concentrations. As a consequence, the relative importance of AOD in our spatiotemporal models was modest, showing the inherent limits of our mixed-effects and random forest approaches to calibrate columnar measures of aerosol scattering to ground level PM concentrations. In addition, the fraction of missing MAIAC AOD was ~ 60% in studies I and II and 80% in study III, a well-known problem of satellite retrievals at high altitudes such as those where Sweden is located, unexpected instead for Italy.

In conclusion, the huge amount of data collected in our studies I-III on air pollution monitoring, spatial predictors from official statistics and opensource geoportals, spatiotemporal outputs of regional atmospheric models, and satellite retrievals allowed us to build national models to predict daily mean concentrations of several air pollutants for each km^2 of the territory. The ability of such models to predict air pollution fields in areas with no data was undermined by the sparseness of the monitors and the quality of some of the input data. Future research should focus on the integration of air quality measurements from multiple sources, the use of AOD data from European satellites, and the definition of spatial predictors as a combination of standard variables available uniformly across the whole domain (as done in our studies) with more refined data on air pollution sources available at the local scale (e.g. traffic flows in cities).

5.1.2 Methodological considerations on exposure assessment

In addition to good data, the flexibility of the model used can make the difference between accurate and inaccurate predictions. This section will discuss the assumptions underlying our spatiotemporal models, how likely it is for those assumptions to hold, and how violations in them might have affected the resulting predictions and the health effects estimates. It should be emphasized that most of the following arguments can be generalized to any other exercise of air pollution exposure assessment.

The first assumption we have made is the one about the “generalizability” of the model, i.e. that the model we have trained on a limited set of observations can be generalized to the full spatiotemporal domain. In order for this to be true, the monitors should be representative of the entire study area, and their measurements should be able to capture the full set of air pollution sources. As previously discussed, we believe this was only partially true in our case studies. The monitors representing non-urban exposures were limited in Italy and very sparse in Sweden. We have tried to circumvent this problem by applying flexible multivariate models, such as mixed-effects models with random components by day, and machine learning methods, allowing for different weights in and out the main cities. We have also tried to design cross-validation strategies flexible enough to mimic the behavior of the prediction models on external receptor points. Nonetheless, we couldn’t prevent model uncertainty to be larger in remote areas, as previously shown in fig. 5.1. However, we are confident that the impact on the short-term health effects estimates obtained in studies IV and V was only marginal, as a small fraction of the population resided in such areas, contributing with a negligible amount of daily mortality or hospitalizations counts.

The second assumption we have made is on predictors being "representative" of the main emission sources as well as the main processes of air pollution formation and transport in a given location on a specific day. This is a key aspect because, if true, the weights estimated by our models for each covariate would account for most sources of variability in air pollutants' measurements, and would produce reliable predictions on external points. As previously noted, we couldn't collect data on real emission sources, but had to rely on proxies. Some of them (e.g. resident population, road network) have been extensively used in the literature because are highly correlated with air pollutants' measurements; others (land-cover variables, vegetation indexes, altitude) have less explanatory power because their main contribution is the characterization of areas with only few monitoring stations; finally, some parameters (such as ISA and LAN) have only marginally been used in previous applications, but were relevant in our applications, especially for predicting NO_2 and PM_{10} concentrations in Sweden (study III). As for the spatiotemporal covariates, we have included terms for the horizontal transportation patterns of air masses (wind components), the vertical distribution (height of the PBL), and the general meteorological conditions favoring or inhibiting chemical reactions among air pollutants (temperature, humidity, barometric pressure, etc.). These terms, despite their coarse spatial resolution, were extremely relevant in our spatiotemporal models because they captured a large fraction of the temporal air pollutants' variability, as demonstrated by their high ranks in terms of relative importance and the high temporal R^2 in left-out monitors.

The third assumption we have made is about model flexibility, i.e. ability of the proposed models to capture the complex interrelationships between the covariates, so to mimic the corresponding interactions between sources and meteorological processes. In study I we attempted to reach that goal by use of mixed-effects models. Here we incorporated random intercepts by day and random slopes of AOD-PM by day with the aim of capturing daily changes in the AOD-PM relationship plus daily residual variation in air pollutants unaccounted by the spatial and spatiotemporal covariates represented in the fixed effects. Unfortunately, this helped to improve model fitting of the temporal air pollution component, but was of little use on the spatial one. The random forest methodology chosen for studies II and III was better fit in capturing complex multivariate relationships between the covariates and the measured air pollutants' concentrations, without imposing specific functional forms in such relationships. In addition, the double strategy of random selection inherent the standard RF model at each iteration (two thirds of the observations and a subset of randomly chosen predictors) presumably allowed to estimate, for each covariate, different weights in cases when the same variable presented a different distribution across locations (e.g. between urban and non-urban areas). The random forest methodology has been recently compared to other machine-learning methodologies (Shtein et al. 2020), with very good results, although other researchers preferred alternative methods, such as extreme gradient boosting (Chen et al. 2019) and deep learning neural networks (Di et al. 2016).

In conclusion our methodological approaches, mixed-effects models in study I and random forests in studies II and III, allowed us to predict most of the air pollution variability in left-out monitors, both in space and in time. However, our results were not always optimal, as a combination of sparse monitored data, lack of predictors on key emission sources, and inherent ability of the models to capture temporal components of air pollution variability better than spatial ones. Future methodological research should focus on the application of "ensemble" techniques where multiple models, each with its own merits and limitations, are fit to the same data and their predictions are combined, in order to achieve better predictive power compared to the individual approaches.

5.2 EPIDEMIOLOGICAL ANALYSES

The predictions of daily air pollutants at high spatiotemporal resolution obtained under studies I-III have been used to estimate short-term effects on cardiovascular hospitalizations in Italy (study IV) and cause-specific mortality in the Stockholm county (study V). The next section will briefly summarize the main findings of the two studies, with a focus on the methodological choices and the main limitations of the adopted approaches. Then, a broader perspective will be outlined on the opportunity offered by novel spatiotemporal exposure modelling for evaluating short-term, and to a lesser extent long-term, health effects.

5.2.1 Short-term effects on daily mortality and morbidity

From concentrations to exposures

In both studies IV and V there has been a preliminary step of air pollution averaging to obtain estimates of daily exposures at the spatial units available for the epidemiological studies: municipality for Italy and SAMS for the Stockholm county. In the first case, we simply averaged the 1x1-km grid cells intersecting the municipalities, weighting each cell proportionally to the intersection area. In the second case, we attempted to estimate population-weighted exposure in each SAMS by further weighting each intersecting cell on the basis of the % urban cover in the cell, used as a proxy for population clustering. In other words, we gave more weight to the cells with more population, and less weight to those with few people or located in remote natural areas. This resulted in an increase in day-to-day variability in exposures, which was substantial for local-scale air pollutants such as NO_2 and $PM_{2.5}$ (fig. 4.7), and only marginal for more homogeneous ones such as PM_{10}, $PM_{2.5\text{-}10}$ and O_3 (details in study III). Whether this resulted in "better" health effects estimates remains unclear, and will be further discussed in the next section. To address this aspect, in study V we compared short-term association estimates obtained with our spatiotemporal exposures with those obtained using daily averages of urban background stations: we found slightly higher associations in the first case, exposure response functions very similar in the two cases, but standard errors smaller in the second case, suggesting that our spatiotemporal exposure assessment didn't increase statistical power but possibly reduced bias in the health effects estimation.

Spatially heterogeneous health effects

Both studies IV and V were aimed to investigate whether short-term associations between air pollutants and adverse health outcomes differed across space. In study IV we classified the 8,084 municipalities of Italy based on two different urbanization scores, and found comparable associations in major urban centers, smaller cities and rural areas. In study V we tried to compare effects between high-density and low-density SAMS, and provided association estimates for each of the 26 municipalities of the Stockholm county. We found a large variability in the point estimates of association, but the statistical power was very low, preventing us to detect statistically significant differences. In summary, we rejected the hypothesis of spatial heterogeneity in the short-term effects between air pollutants and daily mortality/morbidity in both studies. This is, in our view, an important result, because suggests the existence of harmful effects of air pollution even among populations living in rural and sub-urban areas, where concentrations are smaller and source profiles of air pollution differ substantially from those typical of the main conurbations. This is reflected by the exposure-response functions, which display non negligible effects at very low levels.

Study IV: time-series design

In study IV we have adopted a time-series design. First, we built daily time-series of CVD admission counts, PM concentrations and temporal confounders for each of the 8,084 Italian municipalities. Second, we stacked together data from all municipalities belonging to the same province. Third, we ran multivariate conditional Poisson regression models in each of the 110 provinces. Fourth, we meta-analyzed province-specific relative risks to obtain national estimates of associations. The main critical point in this strategy is probably the choice to analyze province-specific pooled data rather than the municipality-specific time-series. Doing so we have assumed that air pollution effect is the same across all the municipalities of the same province, and can be estimated with a single relative risk. Furthermore, the model assumes that confounding from time trends and meteorological factor is also common to all municipalities. This choice was operated as a compromise between the desire to estimate unbiased effects, and the complexity of analyzing thousands of time-series, the greatest majority of them non-informative because contributing with very few cases. Focusing on the first aspect, we acknowledge that we might have introduced some bias, possibly away from the null hypothesis of no effect, if the assumption of homogenous confounding was not true. Also, we are aware that an average estimate for the province might be little informative if the PM-CVD associations differed across municipalities of the same province. The analysis by urbanization level, however, helped in addressing both these aspects: for each province, only the municipalities with the same degree of urbanization were included in the same model, reducing the potential for residual confounding or heterogeneous spatial effects within strata.

Study V: case-crossover design

In study V we have adopted a different approach, the case-crossover design, because the spatial units were too small, and contributed individually with too few cases, to be analyzed with conventional time-series models. Based on the case-crossover paradigm, each deceased subject was attributed the air pollution exposure estimated for his/her SAMS on the day of death, and controls were chosen as the same days of the week (within the same month and year), for the same SAMS. Since controls were very close in time, and referred to the same small area, the potential for residual confounding was very limited. However, this came with the cost that contrasts in exposures were performed within the same spatial unit as well, potentially reducing the statistical power to detect significant small associations. This might be responsible for the larger confidence intervals compared to those we have estimated in the alternative approach of using averages from urban background monitors as daily exposures common to all individuals. The limited statistical power had also negative consequences in the investigation of the spatial heterogeneity in the health effects: we couldn't reject the null hypothesis of spatially homogeneous health effects because the study didn't have the required power to do otherwise.

In conclusion, we recognize the weaknesses of our study, which was inconclusive on one of the main hypotheses (presence of spatial heterogeneity in air pollution short-term effects) because of the small sample size and the reduced exposure contrasts within SAMS. However, the study was still able to document adverse effects of air pollutants in the whole population, especially during warm months. Future research should try to circumvent these problems by enlarging the sample size and replicating the same approach at the national level in Sweden, so to make good use of the full spatiotemporal exposure surfaces estimated in study III.

5.2.2 Opportunities of spatiotemporal air pollution exposure estimates in epidemiological research

Studies IV and V represent two examples of possible applications of spatiotemporal air pollution modelling in epidemiology, namely the investigation of short-term effects on mortality and morbidity outcomes across large geographical domains. We have previously highlighted the main limitations of the individual studies, and offered insights on the potential directions of future follow-up studies. Here, the purpose is to widen the spectrum of the desired epidemiological applications, focusing on the opportunities unraveled by exposure estimates available at fine spatiotemporal resolution. To do so, we will start from the standard paradigm of separating short-term and long-term health effects, to conclude with a possible unifying framework.

Future directions in short-term health effects studies

Needless to say, the main purpose of having spatiotemporal exposure models, rather than just spatial ones, is to investigate short-term effects. Remaining on the macroscales of studies IV and V, future research should move from the estimation of area-specific short-term effects to the investigation of whether and to what extent area-level characteristics (prevalence of chronic conditions, smoking habits, lifestyle, socio-economic status, proximity to healthcare facilities, etc.) are responsible for the spatial heterogeneity in the health effects. This would provide novel evidence on the interaction between individual and environmental risk factors, and inform policy makers on the areas of the territory, and the subgroups of the population, needing prior interventions. Moving to small-scale approaches, one opportunity offered by the availability of air pollutants' estimates at high spatiotemporal resolution is to explore spatial differences in the short-term health effects inside the urban areas, in order to identify districts or clusters of population especially vulnerable to the adverse effects of air pollutants. For example, it might be possible to investigate the potential interaction between daily air pollution exposure and residency in areas of the city characterized by the presence of other environmental stressors, such as high levels of road traffic noise, urban heat islands and distance from green spaces. Furthermore, if health data are available at the individual level for multiple points in time, as in panel studies with repeated measurements, concurrent spatiotemporal exposures would be crucial to disentangle within versus between-subject associations, shedding new light on the interplay between long-term and short-term effects in the same population.

Future directions in long-term health effects studies

It is more difficult to imagine applications of our spatiotemporal exposure estimates to investigate the long-term effects of air pollution, which wouldn't be feasible with alternative approaches, such as conventional LUR and dispersion models. One major advantage of spatiotemporal models is the availability of predictions for long periods of time, whereas LURs usually predict annual mean concentrations as a static map, while the outputs from dispersion models can be expensive to obtain for multiple years. An interesting study design, originating in econometrics and recently borrowed by environmental epidemiologists, is the difference-in-differences (D-D) approach (Card and Krueger 1994; Renzi et al. 2019; Wang et al. 2016). The most interesting feature of this design is the attempt to remove almost all potential candidates for confounding in the design stage, rather than by modelling. This is achieved by contrasting differences in exposures across time to differences in rates of mortality/diseases in the same populations, so that all those factors remaining stable in a population, or slowly varying over time, are automatically controlled for. Another advantage of the method is the simplicity of application, because it only requires annual mortality/morbidity rates for each study area, often available from official statistics, and simple multivariate Poisson models. The main limitations are the ecological approach and the limited statistical power, because the exposure contrast of interest is year-to-year variability in air pollution estimates, usually not very large.

A unifying framework for the joint evaluation of short- and long-term effects

After several decades of epidemiological investigations on the short-term and long-term health effects, it is today well recognized that air pollution is consistent with both, as it acts as a trigger of acute responses among susceptible individuals ("spilling of the glass") as well as a long-term risk factor contributing to chronic health deterioration ("filling of the glass"). While conventional study designs are forced to consider the two aspects as an unresolvable dichotomy, biologically speaking it makes much more sense to imagine them as extremes of a continuum, with future research needed to explore what lies in between. One of the causes of that dichotomy has been, historically, the lack of exposure data at the right spatial and temporal resolution. With the new advances in air pollution modelling, such gap has been finally filled, and new possibilities for epidemiological study designs open. The most promising one is, in my view, the use of prospective cohort data and time-varying survival models for the investigation of air pollution health effects at different averaging times, spanning from few days to multiple years.

6. CONCLUSIONS

The objective of this thesis, and of the five constituent papers, was to provide novel spatiotemporal exposure estimates of several air pollutants for two large geographical domains, and to investigate their short-term effects on mortality and morbidity outcomes. The main challenges in the exposure modelling and in the interpretation of epidemiological findings have been presented, and insights on possible future directions of research have been proposed.

The specific objectives of this work have been carefully addressed, and allowed to draw the following conclusions:

- Novel spatiotemporal exposure estimates have been produced on PM_{10}, $PM_{2.5}$ (Italy and Sweden), NO_2 and O_3 concentrations (Sweden only) at high spatial (1x1-km) and temporal (daily) resolution for long study periods (multiple years) and large geographical domains (two countries);
- Adverse short-term effects of particulate matter on daily cardiovascular admissions have been documented, with associations significant on specific outcomes such as heart failure and atrial fibrillation. Effects were highest at the lowest PM concentrations, also in semi-urban and rural municipalities;
- The association between daily PM and ozone with non-accidental mortality was slightly higher in more densely inhabited areas, but the study was underpowered to detect a significant spatial heterogeneity in the health effects.

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8. REFERENCES

Atkinson RW, Carey IM, Kent AJ, van Staa TP, Anderson HR, Cook DG. 2013. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 24:44–53; doi:10.1097/EDE.0b013e318276ccb8.

Basagana X, Aguilera I, Rivera M, Agis D, Foraster M, Marrugat J, et al. 2013. Measurement error in epidemiologic studies of air pollution based on land-use regression models. Am J Epidemiol 178:1342–1346; doi:10.1093/aje/kwt127.

Beaver S, Palazoglu A. 2009. Influence of synoptic and mesoscale meteorology on ozone pollution potential for San Joaquin Valley of California. Atmos Environ 43:1779–1788; doi:10.1016/j.atmosenv.2008.12.034.

Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, et al. 2008. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). Environ Health Perspect 116:196–202; doi:10.1289/ehp.10767.

Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B, et al. 2014. Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 383; doi:10.1016/S0140-6736(13)62158-3.

Biggeri A, Bellini P, Terracini B, Italian MISA Group. 2001. [Meta-analysis of the Italian studies on short-term effects of air pollution]. Epidemiol Prev 25: 1–71.

Breiman L. 2001. Random Forests. Mach Learn 45:5–32; doi:https://doi.org/10.1023/A:1010933404324.

Briggs DJ, Collins S, Elliott P, Fischer P, Kingham S, Lebret E, et al. 1997. Mapping urban air pollution using gis: A regression-based approach. Int J Geogr Inf Sci 11:699–718; doi:10.1080/136588197242158.

Card D, Krueger AB. 1994. Minimum wages and employment: a case study of the fast-food industry in New Jersey and Pennsylvania. Am Econ Rev 84: 772–793.

Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M, et al. 2013. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. Environ Health Perspect 121:324–331; doi:10.1289/ehp.1205862.

Chan SH, Van Hee VC, Bergen S, Szpiro AA, DeRoo LA, London SJ, et al. 2015. Long-Term Air Pollution Exposure and Blood Pressure in the Sister Study. Environ Health Perspect 123:951–8; doi:10.1289/ehp.1408125.

Chen H, Burnett RT, Copes R, Kwong JC, Villeneuve PJ, Goldberg MS, et al. 2016. Ambient Fine Particulate Matter and Mortality among Survivors of Myocardial Infarction: Population-Based Cohort Study. Environ Health Perspect 124:1421–8; doi:10.1289/EHP185.

Chen Z-Y, Zhang T-H, Zhang R, Zhu Z-M, Yang J, Chen P-Y, et al. 2019. Extreme gradient boosting model to estimate PM2.5 concentrations with missing-filled satellite data in China. Atmos Environ 202:180–189; doi:10.1016/j.atmosenv.2019.01.027.

Chi GC, Hajat A, Bird CE, Cullen MR, Griffin BA, Miller KA, et al. 2016. Individual and Neighborhood Socioeconomic Status and the Association between Air Pollution and Cardiovascular Disease. Environ Health Perspect 124:1840–1847; doi:10.1289/EHP199.

Crouse DL, Peters PA, Hystad P, Brook JR, van Donkelaar A, Martin R V, et al. 2015. Ambient PM2.5, O_3, and NO_2 Exposures and Associations with Mortality over 16 Years of Follow-Up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Health Perspect 123:1180–6; doi:10.1289/ehp.1409276.

Csavina J, Field J, Félix O, Corral-Avitia AY, Sáez AE, Betterton EA. 2014. Effect of wind speed and relative humidity on atmospheric dust concentrations in semi-arid climates. Sci Total Environ 487:82–90; doi:10.1016/j.scitotenv.2014.03.138.

Cutler A, Zhao G. 2001. Pert-perfect random tree ensembles. Comput Sci Stat 33: 490–497.

Dayan U, Levy I. 2005. The Influence of Meteorological Conditions and Atmospheric Circulation Types on PM10 and Visibility in Tel Aviv. J Appl Meteorol 44:606–619; doi:10.1175/JAM2232.1.

De Grove KC, Provoost S, Braun H, Blomme EE, Teufelberger AR, Krysko O, et al. 2018. IL-33 signalling contributes to pollutant-induced allergic airway inflammation. Clin Exp Allergy 48:1665–1675; doi:10.1111/cea.13261.

Dee DP, Uppala SM, Simmons AJ, Berrisford P, Poli P, Kobayashi S, et al. 2011. The ERA-Interim reanalysis: configuration and performance of the data assimilation system. Q J R Meteorol Soc 137:553–597;

doi:10.1002/qj.828.

Deiuliis JA, Kampfrath T, Zhong J, Oghumu S, Maiseyeu A, Chen LC, et al. 2012. Pulmonary T cell activation in response to chronic particulate air pollution. Am J Physiol Cell Mol Physiol 302:L399–L409; doi:10.1152/ajplung.00261.2011.

Demuzere M, Trigo RM, Vila-Guerau de Arellano J, van Lipzig NPM. 2009. The impact of weather and atmospheric circulation on O3 and PM10 levels at a rural mid-latitude site. Atmos Chem Phys 9:2695–2714; doi:10.5194/acp-9-2695-2009.

Di Q, Amini H, Shi L, Kloog I, Silvern R, Kelly J, et al. 2019. An ensemble-based model of PM2.5 concentration across the contiguous United States with high spatiotemporal resolution. Environ Int 130:104909; doi:10.1016/j.envint.2019.104909.

Di Q, Kloog I, Koutrakis P, Lyapustin A, Wang Y, Schwartz J. 2016. Assessing PM 2.5 Exposures with High Spatiotemporal Resolution across the Continental United States. Environ Sci Technol 50:4712–4721; doi:10.1021/acs.est.5b06121.

Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, et al. 1993. An Association between Air Pollution and Mortality in Six U.S. Cities. N Engl J Med 329:1753–1759; doi:10.1056/NEJM199312093292401.

Eeftens M, Tsai MY, Ampe C, Anwander B, Beelen R, Bellander T, et al. 2012. Spatial variation of PM2.5, PM10, PM2.5 absorbance and PMcoarse concentrations between and within 20 European study areas and the relationship with NO2 - Results of the ESCAPE project. Atmos Environ 62:303–317; doi:10.1016/j.atmosenv.2012.08.038.

Geurts P, Ernst D, Wehenkel L. 2006. Extremely randomized trees. Mach Learn 63:3–42; doi:10.1007/s10994-006-6226-1.

Goldman GT, Dominici F. 2019. Don’t abandon evidence and process on air pollution policy. Science (80-) 363:1398–1400; doi:10.1126/science.aaw9460.

Gryparis A, Paciorek CJ, Zeka A, Schwartz J, Coull BA. 2009. Measurement error caused by spatial misalignment in environmental epidemiology. Biostatistics 10:258–274; doi:10.1093/biostatistics/kxn033.

Hardy RJ, Thompson SG. 1996. A likelihood approach to Meta-Analysis with Random Effects. Stat Med 15:619–629; doi:10.1002/(SICI)1097-0258(19960330)15:6<619::AID-SIM188>3.0.CO;2-A.

Harkema JR, Keeler G, Wagner J, Morishita M, Timm E, Hotchkiss J, et al. 2004. Effects of concentrated ambient particles on normal and hypersecretory airways in rats. Res Rep Health Eff Inst 1–68; discussion 69-79.

Hatzakis A, Katsouyanni K, Kalandidi A, Day N, Trichopulous D. 1986. Short-Term Effects of Air Pollution on Mortality in Athens. Int J Epidemiol 15:73–81; doi:10.1093/ije/15.1.73.

Hu X, Belle JH, Meng X, Wildani A, Waller LA, Strickland MJ, et al. 2017. Estimating PM 2.5 Concentrations in the Conterminous United States Using the Random Forest Approach. Environ Sci Technol 51:6936–6944; doi:10.1021/acs.est.7b01210.

Katsouyanni K, Schwartz J, Spix C, Touloumi G, Zmirou D, Zanobetti A, et al. 1996. Short term effects of air pollution on health: a European approach using epidemiologic time series data: the APHEA protocol. 81ournal Epidemiol Community Heal 50:12–18; doi:10.1136/jech.50.Suppl_1.S12.

Kim BG, Lee PH, Lee SH, Kim YE, Shin MY, Kang Y, et al. 2016. Long-Term Effects of Diesel Exhaust Particles on Airway Inflammation and Remodeling in a Mouse Model. Allergy Asthma Immunol Res 8:246–56; doi:10.4168/aair.2016.8.3.246.

Korek M, Johansson C, Svensson N, Lind T, Beelen R, Hoek G, et al. 2017. Can dispersion modeling of air pollution be improved by land-use regression? An example from Stockholm, Sweden. J Expo Sci Environ Epidemiol 27:575–581; doi:10.1038/jes.2016.40.

Künzli N, Jerrett M, Garcia-Esteban R, Basagaña X, Beckermann B, Gilliland F, et al. 2010. Ambient air pollution and the progression of atherosclerosis in adults. PLoS One 5:e9096; doi:10.1371/journal.pone.0009096.

Künzli N, Jerrett M, Mack WJ, Beckerman B, LaBree L, Gilliland F, et al. 2005. Ambient air pollution and atherosclerosis in Los Angeles. Environ Health Perspect 113:201–206; doi:10.1289/ehp.7523.

Leong WC, Kelani RO, Ahmad Z. 2020. Prediction of air pollution index (API) using support vector machine (SVM). J Environ Chem Eng 8:103208; doi:10.1016/j.jece.2019.103208.

Liaw A, Wiener M. 2002. Classification and Regression by Random Forest. R News.

Logan W. 1953. Mortality in the London fog incident, 1952. Lancet 261:336–338; doi:10.1016/S0140-6736(53)91012-5.

Lumley T, Levy D. 2000. Bias in the case - crossover design: implications for studies of air pollution. Environmetrics 11:689–704; doi:10.1002/1099-095X(200011/12)11:6<689::AID-ENV439>3.0.CO;2-N.

Lyapustin A, Martonchik J, Wang Y, Laszlo I, Korkin S. 2011a. Multiangle implementation of atmospheric correction (MAIAC): 1. Radiative transfer basis and look-up tables. J Geophys Res 116:D03210; doi:10.1029/2010JD014985.

Lyapustin A, Wang Y, Korkin S, Huang D. 2018. MODIS Collection 6 MAIAC algorithm. Atmos Meas Tech 11:5741–5765; doi:10.5194/amt-11-5741-2018.

Lyapustin A, Wang Y, Laszlo I, Kahn R, Korkin S, Remer L, et al. 2011b. Multiangle implementation of atmospheric correction (MAIAC): 2. Aerosol algorithm. J Geophys Res 116:D03211; doi:10.1029/2010JD014986.

Maclure M. 1991. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 133:144–53; doi:10.1093/oxfordjournals.aje.a115853.

Mauad T, Rivero DHRF, de Oliveira RC, de Faria Coimbra Lichtenfels AJ, Guimarães ET, de Andre PA, et al. 2008. Chronic Exposure to Ambient Levels of Urban Particles Affects Mouse Lung Development. Am J Respir Crit Care Med 178:721–728; doi:10.1164/rccm.200803-436OC.

Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. 2007. Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women. N Engl J Med 356:447–458; doi:10.1056/NEJMoa054409.

Morishita M, Keeler GJ, Wagner JG, Marsik FJ, Timm EJ, Dvonch JT, et al. 2004. Pulmonary Retention of Particulate Matter is Associated with Airway Inflammation in Allergic Rats Exposed to Air Pollution in Urban Detroit. Inhal Toxicol 16:663–674; doi:10.1080/08958370490476550.

Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, et al. 2015. Expert position paper on air pollution and cardiovascular disease. Eur Heart J 36:83–93; doi:10.1093/eurheartj/ehu458.

Nieuwenhuijsen MJ. 2015. *Exposure Assessment in Environmental Epidemiology*. M.J. Nieuwenhuijsen, ed. Oxford University Press.

Novotny E V., Bechle MJ, Millet DB, Marshall JD. 2011. National Satellite-Based Land-Use Regression: NO 2 in the United States. Environ Sci Technol 45:4407–4414; doi:10.1021/es103578x.

Nyberg F, Gustavsson P, Järup L, Bellander T, Berglind N, Jakobsson R, et al. 2000. Urban Air Pollution and Lung Cancer in Stockholm. Epidemiology 11:487–495; doi:10.1097/00001648-200009000-00002.

Ostro B. 1984. A search for a threshold in the relationship of air pollution to mortality: A reanalysis of data on London winters. Environ Health Perspect VOL. 58:397–399; doi:10.2307/3429861.

Pey J, Querol X, Alastuey A, Forastiere F, Stafoggia M. 2013. African dust outbreaks over the Mediterranean Basin during 2001-2011: PM10 concentrations, phenomenology and trends, and its relation with synoptic and mesoscale meteorology. Atmos Chem Phys 13:1395–1410; doi:10.5194/acp-13-1395-2013.

Pope CA, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, et al. 1995. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151:669–74; doi:10.1164/ajrccm/151.3_Pt_1.669.

Pope CA, Turner MC, Burnett RT, Jerrett M, Gapstur SM, Diver WR, et al. 2015. Relationships between fine particulate air pollution, cardiometabolic disorders, and cardiovascular mortality. Circ Res 116:108–15; doi:10.1161/CIRCRESAHA.116.305060.

Prüss-Ustün A, Wolf J, Corvalàn C, Bos R, Neira M. 2016. Preventing disease through healthy environments: A global assessment of the environmental burden of disease. WHO, Geneva.

Raaschou-Nielsen O, Andersen ZJ, Jensen SS, Ketzel M, Sørensen M, Hansen J, et al. 2012. Traffic air pollution and mortality from cardiovascular disease and all causes: a Danish cohort study. Environ Health 11:60; doi:10.1186/1476-069X-11-60.

Renzi M, Forastiere F, Schwartz J, Davoli M, Michelozzi P, Stafoggia M. 2019. Long-Term PM10 Exposure and Cause-Specific Mortality in the Latium Region (Italy): A Difference-in-Differences Approach. Environ Health Perspect 127:067004; doi:10.1289/EHP3759.

Russo A, Lind PG, Raischel F, Trigo R, Mendes M. 2015. Neural network forecast of daily pollution concentration using optimal meteorological data at synoptic and local scales. Atmos Pollut Res 6:540–549; doi:10.5094/APR.2015.060.

Saldiva PHN, Clarke RW, Coull BA, Stearns RC, Lawrence J, Murthy GGK, et al. 2002. Lung Inflammation Induced by Concentrated Ambient Air Particles Is Related to Particle Composition. Am J Respir Crit Care Med 165:1610–1617; doi:10.1164/rccm.2106102.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. 2000. Fine Particulate Air Pollution and Mortality in 20 U.S. Cities, 1987–1994. N Engl J Med 343:1742–1749; doi:10.1056/NEJM200012143432401.

Schrenk HH, Heimann H, Clayton GD, Gafafer WM, Wexler H. 1949. Air pollution in Donora, Pa.: epidemiology of the unusual smog episode of October 1948: preliminary report. Public Health Bulletin (Wash D C) 306: 1–173.

Schwartz J, Marcus A. 1990. Morality and air pollution in London: a time series analysis. Am J Epidemiol 131:185–194; doi:10.1093/oxfordjournals.aje.a115473.

Shenfeld L. 1970. Meteorological aspects of air pollution control. Atmosphere (Basel) 8:3–13; doi:10.1080/00046973.1970.9676578.

Shtein A, Kloog I, Schwartz J, Silibello C, Michelozzi P, Gariazzo C, et al. 2020. Estimating Daily PM2.5 and PM10 over Italy Using an Ensemble Model. Environ Sci Technol 54:120–128; doi:10.1021/acs.est.9b04279.

Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, et al. 2018. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 392:1923–1994; doi:10.1016/S0140-6736(18)32225-6.

Turner MC, Jerrett M, Pope CA, Krewski D, Gapstur SM, Diver WR, et al. 2016. Long-Term Ozone Exposure and Mortality in a Large Prospective Study. Am J Respir Crit Care Med 193:1134–42; doi:10.1164/rccm.201508-1633OC.

U.S. Environmental Protection Agency. 2019. Integrated Science Assessment (ISA) for Particulate Matter (Final Report, 2019).

U.S. Environmental Protection Agency. 2009. Integrated science assessment for particulate matter.

Vedal S, Campen MJ, McDonald JD, Larson T V, Sampson PD, Sheppard L, et al. 2013. National Particle Component Toxicity (NPACT) initiative report on cardiovascular effects. Res Rep Health Eff Inst 5–8.

Vienneau D, de Hoogh K, Bechle MJ, Beelen R, van Donkelaar A, Martin R V., et al. 2013. Western European Land Use Regression Incorporating Satellite- and Ground-Based Measurements of NO 2 and PM 10. Environ Sci Technol 47:13555–13564; doi:10.1021/es403089q.

Wang Y, Kloog I, Coull BA, Kosheleva A, Zanobetti A, Schwartz JD. 2016. Estimating Causal Effects of Long-Term PM2.5 Exposure on Mortality in New Jersey. Environ Health Perspect 124:1182–8; doi:10.1289/ehp.1409671.

Yanosky JD, Paciorek CJ, Laden F, Hart JE, Puett RC, Liao D, et al. 2014. Spatio-temporal modeling of particulate air pollution in the conterminous United States using geographic and meteorological predictors. Environ Health 13:63; doi:10.1186/1476-069X-13-63.

Zhang H, Wang Y, Hu J, Ying Q, Hu XM. 2015. Relationships between meteorological parameters and criteria air pollutants in three megacities in China. Environ Res 140:242–254; doi:10.1016/j.envres.2015.04.004.

Zhang X, Staimer N, Gillen DL, Tjoa T, Schauer JJ, Shafer MM, et al. 2016a. Associations of oxidative stress and inflammatory biomarkers with chemically-characterized air pollutant exposures in an elderly cohort. Environ Res 150:306–319; doi:10.1016/j.envres.2016.06.019.

Zhang Z, Laden F, Forman JP, Hart JE. 2016b. Long-Term Exposure to Particulate Matter and Self-Reported Hypertension: A Prospective Analysis in the Nurses' Health Study. Environ Health Perspect 124:1414–20; doi:10.1289/EHP163.