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Guidance documents on measurements and modelling of novel air quality pollutants:

Modelling health effects of novel AQ parameters

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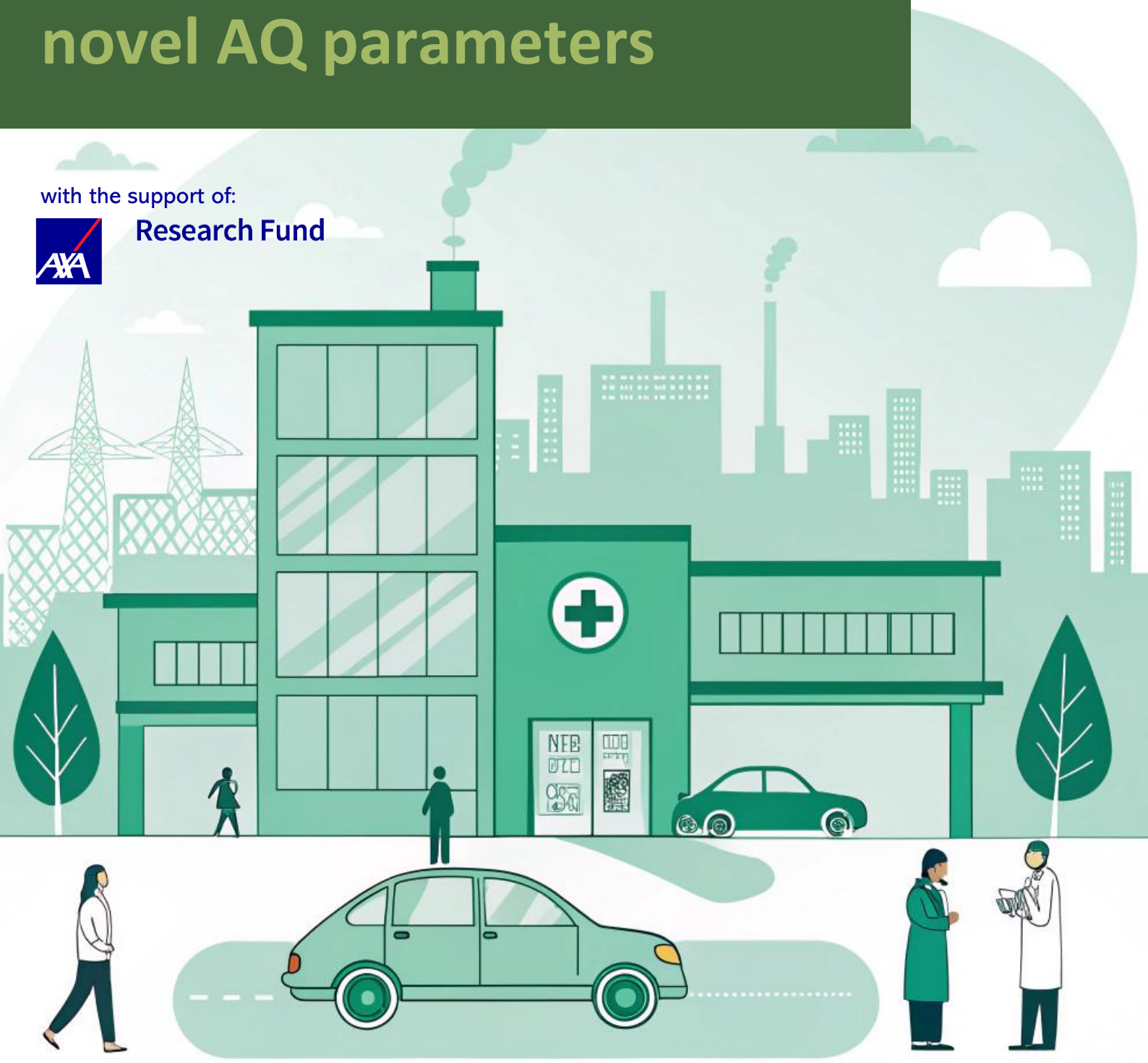

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Research Infrastructures Services Reinforcing Air Quality Monitoring Capacities in European Urban & Industrial AreaS (RI-URBANS)

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Abbreviations

ACTRIS	Aerosols, Clouds and Trace gases Research InfraStructure
AQ	Air quality
CEN	European Committee for Standardisation
dfs	Degrees of freedom
DLM	Distributed lag models
DLNM	Distributed lag nonlinear models
HE	Health effects
HIA	Health impact assessment
ICD	International classification of diseases
PACF	Partial Autocorrelation Function
PM	Particulate matter
$PM_{2.5}$	Mass concentration of particles <2.5 µm
PM_{10}	Mass concentration of particles <10 µm
PNC	Particle number concentrations
PNSD	Particle number size distribution
RI-URBANS	Research Infrastructures Services Reinforcing Air Quality Monitoring Capacities in European Urban & Industrial AreaS EU-project
RR	Relative risk
TSS	Time series studies
UFP	Ultrafine particles
WHO	World Health Organization

Chemical species

NO_2	Nitrogen dioxide
O_3	Ozone
SO_2	Sulphur dioxide

1. ABOUT THIS DOCUMENT

This document is connected to new European Air Quality Directive (NAQD). This document was prepared as part of "Research Infrastructures Services Reinforcing Air Quality Monitoring Capacities in European Urban & Industrial AreaS" (RI-URBANS) EU-project that connects the atmospheric observation expertise from Aerosols, Clouds and Trace gases Research InfraStructure Consortium, ACTRIS-ERIC with the urban AQ observation capacities of the regulatory AQMNs.

The NAQD underlines the importance of emerging pollutants for AQ and the well-being of the citizens. Particularly, novel pollutants such as ultrafine particles (UFP), UFP-number size distribution (PNSD), black carbon (BC) and elemental carbon (EC), as well as ammonia (NH3) and numerous volatile organic compounds (VOCs), and measurements of tracers of potential toxicity of PM (oxidative potential (OP) of particulate matter PM), are required or recommended to be monitored at both rural and urban supersites in order to support scientific understanding of their effects on health and the environment. For Member States whose territory is less than 10000 km_2, monitoring in supersites at urban locations would be sufficient as the levels measured could be considered as representative of the highest exposure of the population in the territory of such Member States.

To ensure that the information collected on air pollution is sufficiently representative and comparable across the European Union, it is important that standardised measurement techniques and common criteria for the number and location of measuring stations are used for the assessment of ambient AQ. The aim of this document on UFP and PNSD measurements (included as mandatory in urban supersites in the NAQD) is to facilitate upscaling of measurement techniques within the AQ monitoring networks (AQMNs).

In this Service Tool (ST) described here guides on the steps needed to conduct an epidemiological analysis linking novel air quality (AQ) metrics with health effects (HEs). Estimates of short-term associations between air pollution and health are usually based on studying the relationship between daily variations of air pollutant concentrations and daily counts of health outcomes such as mortality and/or morbidity (e.g. hospital admissions or hospital visits by various causes). This guidance document describes the different options that can be followed to conduct epidemiological studies, the data needs and the statistical methodologies than can be applied. Lastly, it illustrates, using the data compiled by the RI-URBANS project, the feasibility of implementing such analyses and the added value of the novel AQ metrics to determine HEs.

This is a RI-URBANS/ACTRIS guidance for this specific service tool that is part of the RI-URBANS deliverable D46 (D6.1, containing guidance for all service tools provided in the project) with the support for publication from AXA Research Fund to build up the final dissemination D55 (D7.6). Any dissemination of results must indicate that it reflects only the author's view and that the European Commission is not responsible for any use that may be made of the information it contains.

2. LINKING AIR POLLUTION CONCENTRATIONS AND HEALTH

There are several types of studies that can be used to link short-term exposure to air pollution with health effects (HEs). This guide focuses on two main types of studies that effectively use data from AQ Monitoring infrastructures in cities to draw conclusions on the HEs of different air pollutants. Thus, the methodology described here can be used to build a ST based on atmospheric international Research Infrastructures (such as ACTRIS, https://www.actris.eu/) and nationwide public AQ networks in conjunction with medical registries to address AQ challenges.

The two types of study described below address the estimation of the short-term HE of air pollution, i.e. those HEs that occur on the same day or a few days after an air pollution episode occurs. It is important to note that this methodology does not only estimate the effects of extreme episodes (i.e. days with very high levels of air pollution), but it also estimates effects of small changes in air pollution. These methods do not address, however, the estimation of effects of long-term exposure to air pollution, i.e. the effects of being chronically exposed (over years) to polluted air. The effects of long-term exposure to air pollution are generally more important than the short-term effects, but these often require other specific and costly epidemiological designs. The estimation of short-term effects can be done at a low cost based on existing infrastructures, and the results of these studies can provide timely and useful information on the harmfulness of different air pollutants. The studies on short-term effects usually detect the effects of air pollution on the most vulnerable groups of population.

Two main studies on short-term exposure effects will be described:

- **Time series studies (TSS)**. Such studies compare data from two time series: one of daily air pollution concentrations, and another of daily health indicators such as the daily number of deaths or the daily number of hospital admissions. If air pollution has an effect on mortality, one would expect to see a higher number of deaths on polluted days in comparison with clean days. Such studies are based on a single location, e.g. a city. TSS are used to investigate if an association exists and to quantify its magnitude. The data analysis requires complex methods that control for temporal and seasonal trends and time-varying potential confounders. In order to produce trustful estimates, TSS require a large number of cases, which can be achieved by conducting the study in large cities, by having long daily time series for several years, or by pooling data across cities.
- **Health impact assessment (HIA).** This technique uses existing knowledge on the relationship between air pollution and health to predict what is the expected effect in a target population, or to predict the health benefits in the target population under realistic assumptions (e.g. what would be the health benefits of reducing the levels of a certain air pollutant by 10%, or by not exceeding some recommended limits). Thus, HIA is not used to investigate if a relationship between pollution and health exists, but to predict the local health burden.

3. TIME SERIES ANALYSIS

3.1 Health data collection

3.1.1 Types of health data

Estimates of short-term associations between air pollution and health are usually based on studying the relationship between daily variations of air pollutant concentrations and daily counts of health outcomes such as mortality and/or morbidity (e.g.: hospital admissions or hospital visits by various causes). Common mortality and morbidity outcomes that are often associated with short-term air pollution changes are respiratory and cardiovascular diseases. Such studies are usually conducted at the city level.

Daily mortality and hospitalisation data (visits, emergency admissions, etc.) often originate from official registries and hospital reports and may include information such as cause of death, age, sex and the patient´s place of residence. This information can be used to evaluate the impacts of air

pollution on sensitive groups of population. For this purpose, health outcomes may be aggregated by age, sex or cause of death/admission.

Mortality causes and hospital admissions diagnosis are usually classified according to the International Classification of Diseases (ICD), developed by the World Health Organization (WHO) (https://icd.who.int/en).

3.1.2 Sources for health data

The most recommended sources for health data are national statistics offices and national/regional health agencies. Data from statistics offices and health agencies are often released with a lag time of months or years after collection. If very recent total daily mortality data is needed, burial services that have a wide coverage in the city may be used as a source, although this data is likely to lack information e.g., on cause of death, sex, age and place of residence of the deceased.

3.1.3 Issues affecting health data quality

An important issue for any data analysis is data quality. Health data records have the advantage of containing information of long periods and cover large populations (Baker and Nieuwenhuijsen, 2008) with little, if any, missing data gaps, as doctors register health incidents on a daily basis. However, other data quality issues may arise from these records:

- The **patients' place of residence** may be based on the information recorded by the primary health care system registration, which **may be outdated**. This issue may cause incorrect inclusion/or exclusion of patients in the researched geographic area.
- **Misdiagnosis** is in general another cause of health data quality issues. Misdiagnosis of the cause of death/hospitalisation will result in underestimation or overestimation of cause-specific daily counts and (random) noise in the daily count data (Baker and Nieuwenhuijsen, 2008)
- **ICD codes** have undergone **modifications** throughout the years, going from the 6th revision (1948) to the most recent 11th revision (2022). Diagnosis record errors may arise from the transition from one ICD revision to another. These transitions may also affect time series, when shifting from one version of ICD to the next.
- **Multiple hospital admissions** with the same diagnosis in a short time interval (e.g., days or weeks). Patients may return to the emergency room a few days or weeks after the first incident. While this emergency admission will be recorded twice by the hospital, the second hospitalisation may be caused by the same diagnosis as the first, and could be seen as a continuation of the same

event. One may avoid this "double counting" by excluding repeated hospitalisations with the same diagnosis within for instance one month apart from each other. This is only feasible when data on individuals can be accessed.

- **Misinterpretation of the data request**: authorities may misunderstand the health data request and include for instance emergency visits (patients leave on the same day) instead of only non-scheduled hospital admissions (overnight stays). To avoid misunderstandings, one should create a clear request, making sure to state any patient inclusions and exclusion rules adopted by the study.
- The **agencies/offices might have different methodologies** for collecting and storing the data. Therefore, they might not be collecting the exact same thing. E.g. different way of coding primary/secondary diagnosis, more vs. less detailed information (e.g. more specific ICD code vs general ICD groups), etc. One may be aware of these differences and take them into account in the discussion of the results.

3.1.4 Common challenges during health data collection

The following topics should be considered at the design phase of epidemiological time series studies:

- **Data suppression**: some health data providers may supress small numbers of health outcomes to minimise the risk of patient identification. For instance, days in which less than 5 people died of respiratory diseases may be replaced with a missing value (Not Available, NA). **Recommendation**: To avoid data suppression, one could request broader population groups by increasing for instance the age category range (e.g., from 0-74 years old instead of 0-10 years old) or completely removing aggregation categories such as age and sex from the analysis. Requesting data from large geographic regions instead of city level decreases the incidence of small numbers and consequently data suppression, at the price of the air pollution data collected being less representative of the entire population under study. Removing cause-specific outcomes from the analysis or choosing only large disease groups could also decrease data suppression, at the price of only being able to conduct less detailed analyses. One can deal statistically with suppressed data by using models for left-censored data or using techniques like multiple imputation. However, the percentage of data suppression should be kept small to obtain meaningful results.
- The **amount of suppressed data may be unknown** when making the request: authorities may require prepayment of the data before estimating the amount of suppressed information. In

those cases, only after the payment one will know if the data suits the purpose of the study. **Recommendation**: Request broad categories of data aggregation. Broader aggregations are less likely to contain small daily outcome numbers and therefore are less likely to be suppressed by the authorities. When data suppression is unavoidable, data imputation may be used to estimate missing values.

- **Expensive data**: the prices for health data can vary significantly among cities and from one authority to the next, ranging from zero to over several thousand euros. **Recommendation**: Search for official sources that provide health data for free. Alternatively, decreasing the level of details of the data request can decrease costs. For instance, reducing the period of analysis from 20 to 10 years or not requesting data aggregation by city, sex, or age may reduce the data processing time (statistician worked hours) and therefore, reduce the overall data costs. Detailed health data aggregation usually requires a longer processing time or a license, which significantly increases costs. In any case, project funding should be allocated for data purchasing accordingly.
- **Unavailable recent data**: health data providers may release data with a few years (often 1-2 years) of delay due to data collection and curation processes. **Recommendation**: Design the epidemiological study taking into consideration delays in data availability.
- **Data release waiting period**: weeks or months may pass from the time of data request to the time of data release, depending on the type of data, data aggregation, health authority and country. **Recommendation**: design the study expecting a waiting period of 1-6 months after data request for receiving the datasets. Health data requests should be sent at early stages of the project to avoid possible delays in data analysis.
- **Data access limitations (In-situs):** Some health data providers may have policies that restrict data access by foreign countries. In this case data access is usually allowed only in-situ with special permission. **Recommendation:** Reserve a budget for data acquisition travelling expenses, or alternatively, contact a colleague located in that particular country to access the data or carry out the data analysis in-situs.
- **Data license limitations**: Depending on the authority and how detailed is the request, health data may be granted through a data license application which may contain limitations such as: project usage (usage allowed only by projects mentioned in the license), expiration date and data combination with other datasets. The authority may also request that data released under an expiration date is destroyed upon expiration. **Recommendation**: Health data licenses and agreement rules should be followed to avoid penalties. It is recommended to create a catalogue

for each dataset to record data usage limitations such as license expiration date, usage by other projects, authority´s request for data destruction, etc.

An example of a health data catalogue is provided below In Table 1.

Table 1: *An example of a health data catalogue.*

	NAME OF THE CITY	
	MORTALITY	**HOSPITALISATION**
ID REQUEST		
DATE OF DATA		
DATE OF DATA ARRIVAL		
PERIOD		
AGE GROUPS		
SEX GROUPS		
CAUSES		
REGION		
INDIVIDUAL /		
SUPPRESSION		
PROVIDER		
CONTACT		
COST		
AGREEMENT END DATE		
NOTES		

3.2 Complementary data

Statistical models used for epidemiological time series studies should be adjusted to account for potential confounding variables and consequently reduce uncertainties from the modelled results. The model may be adjusted for measured and unmeasured variables such as the ones described below:

- **Long-term time trends and seasonality**: researchers often adjust models with flexible functions of time (e.g. splines), to control for seasonal and long-term trends. Splines can account for both long-term trends (e.g. a gradual decrease/or increase in mortality and air pollution levels) and seasonal patterns (e.g. increases in mortality and air pollution in winter). Splines offer enough flexibility to capture different seasonal patterns each year. The inclusion of splines of time in the model is a way to control for unobserved confounders that vary slowly over time and is an essential step in the analysis in order to obtain unbiased results.
- **Weather variables**: temperature and relative humidity are known confounders for air pollution-health associations. Temperature affects health outcomes in a non-linear manner, for instance increasing mortality during cold days in the winter and very warm days during summers

(Gasparrini et al., 2015), and often temperature covaries with time. The HEs of hot temperatures are often immediate (the most important effects are detected at lags 0 to 2), while the HEs of cold temperatures can be delayed several weeks. Other meteorological variables are associated with air pollution (e.g. wind) but the relationship with health is less obvious. Thus, it is not clear that they act as confounders and one may not need to adjust for them in the analysis. Meteorological data is often readily available from meteorological or AQ monitoring networks.

- **Bank holidays**: holidays influence air pollutant concentrations as people travel outside the city boundaries and fewer people need to reach the city to work. A decrease in the number of dwellers reduces pollution by decreasing, for instance, the number of vehicular emissions in the city. Similarly, health outcomes may also show a weekday dependence (Bates et al., 1990). This dependence may be caused by lower pollution levels in the city, or other weekend/holiday related factors like decreased number of health care workers resulting in increased mortality (Huang et al., 2019; Jahromi et al., 2019). Thus, analyses need to be adjusted for bank holidays and day of the week.
- **Other air pollutants**: other air pollutants may bias the time series analysis results. For example, imagine the case where one particular air pollution component is the only responsible for producing HEs. If one performs a time series analysis for another air pollution component that is correlated with the causal one, researchers may attribute a casual effect to the non-causal component. Weather affects multiple pollutants in the same way (e.g. low mixing height or stable atmosphere), and many air pollution components have the same source (e.g. combustion vehicles). These aspects lead to concentrations of several pollutants being highly correlated. For example, PM, NO_2 and SO_2 are known confounders (Bell et al., 2004) that show similar day-to-day variations, all affect health, and all influence PM concentrations by gas-to-particle secondary particle formation. Disentangling the HEs of different pollutants is one of the most challenging parts of the statistical analyses.
- **Influenza**: Influenza and respiratory infections are associated with mortality and explain significant part of the mortality peak in winter months (Peng et al., 2006). These influenza peaks may coincide with peaks of air pollution. Therefore, one needs to control for that in the analysis. When influenza data is unavailable, a proxy for influenza epidemics may be created by selecting weeks showing peaks in mortality/hospital admissions caused by respiratory diseases.

3.3 Required sample size

The short-term effects of air pollution are usually small in magnitude. For example, the HRAPIE project reports mortality increases of around 1% associated with a 10 µg/m3 increase in $PM_{2.5}$ concentrations (WHO, 2013). For hospital admissions, the estimates range from 0.5 to 2% for $PM_{2.5}$, and for incidence of asthma symptoms in children, estimates almost reach 3%. It is important to note that these cumulate over all days and everyone is exposed. Thus, they can represent an important burden. For example, in large cities, they may represent several hundred premature deaths per year.

In order to detect such small increases in mortality or hospital admissions, which are much smaller that the day-to-day variation in these variables, one needs big studies. Otherwise, studies do not have statistical power to detect such changes. In order to have 80% power to detect an increase of 1% in the health outcome, one may need around 100,000 deaths (summing all deaths in the period) (Armstrong et al. 2020). One can achieve the required number of deaths by studying large cities, by studying long time periods or by combining data from different cities. In order to detect increase in the health outcome of around 2%, the required number of events goes down to around 25,000.

3.4 Data analysis

Time series analysis of HEs of air pollution has a long tradition in the epidemiological literature. Although there are several potential methodologies to analyses such data, the most commonly used one is based **on quasi-Poisson regression models**. A very good introduction can be found in Bhaskaran et al. (2013). Peng and Dominci (2008) is also a good source for more advanced analyses. Those models are used to account for the fact that the response variable are counts and to account for over-dispersion in the data, which Poisson regression models cannot account for. The autocorrelation in the data is considered by using spline functions of time.

Delayed effects are considered by introducing into the model lagged versions of the pollutant series. Usually, the HEs of air pollution are found at very short lags, e.g. between lags 0 and 2. However, effects of up to 7 days are sometimes explored. If several lags of the pollutant series are introduced at the same time in the model, it will result in the so-called **distributed lag models (DLM).** As lagged versions of the pollutant series are highly correlated, the distributed lag model can be affected by collinearity problems. One way to solve this is to impose some (realistic) constraints. For example, that the estimated effects need to change smoothly over lag periods. In other words, that the effect

at lag 0 needs to be similar than that at lag 1, that the estimated effect at lag 1 needs to be similar than the estimated effects at lags 0 and 2, and so on. Such models are called constrained distributed lag models, and produce estimates that are less variable (and have narrower confidence intervals) in comparison with unconstrained models (Armstrong, 2006). Often, one constrains the estimated effect to vary smoothly over lags with a spline function. Recent advances also allow the estimation of nonlinear effects, leading to the framework of **distributed lag nonlinear models (DLNM)** that allow estimating nonlinear and delayed effects (Gasparrini et al., 2010; Gasparrini, 2011).

Multi-city studies are often conducted. Usually, each city is analysed separately, and results from the different cities are combined with univariate meta-analysis, when a single parameter needs to be combined (Borenstein et al., 2010; Katsouyanni et al., 2001), or with multivariate meta-analysis (Gasparrini and Armstrong, 2013), when one needs to combine several parameters (e.g., when estimating nonlinear curves).

Finally, a challenging issue is how to separate the **effects of multiple air pollutants**. This is still an area of active research, but some options are available. Often, it is useful to start by fitting single pollutant models separately for each pollutant, and proceeding in a second step by fitting two-pollutant models, as long as they are not very highly correlated. If the sample size is very large, one could even try to fit two-pollutant models with highly correlated pollutants. Then, one can try more sophisticated analyses to uncover more complex patterns.

The sections below provide a few more details on some of the issues mentioned in this section.

3.4.1 Single and Distributed lag models

The effects of air pollution on health may lag in time from a few days to a few weeks (Peng and Dominici 2008). For example, the mortality counts of today may result from the effects of yesterday´s pollution rather than today´s pollution. Thus, to accurately estimate the effects of air pollution on health, the lagged effect of air pollutants should be considered. The lag effect is often estimated by adding a lag term to the quasi-Poisson regression model, which is done by the use of single lag models or distributed lag models.

- **Single lag model**: assumes that an increase in exposure affects the outcome “l” days later (lag). This type of model considers lag days individually. That is, it uses one lag per model fit. This model has the advantage of being unaffected by missing days. However, it disregards the cumulative

effect of air pollution exposure several days previous to an event occurrence, and does not address confounding by other lags (Peng and Dominici 2008).

- **Distributed lag models (DLM)**: DLMs offer the advantage to evaluate the exposure-response association between pollutant and health outcome several days later, cumulatively (Gasparrini et al., 2010) and simultaneously. That is, it considers the cumulative of several lag days in only one model fit. One can actually obtain estimates for the effect of air pollution at one lag (adjusting for other lags) or for the cumulative effect of air pollution across all lags. Indeed, the effects of a peak of air pollution on mortality can be observed on the same day, on the day after, after two days, and so on, so the full effects of air pollution on mortality are the sum of those daily effects. Equivalently, using a backwards view, mortality today is an effect of the air pollution levels observed today, those observed yesterday, those observed two days ago, and so on. As disadvantages, DLMs require complete datasets (no missing days) (Peng and Dominici 2008). The latter limits the usage of DLM to variables that are either measured daily or variables that contain imputed data. Distributed lag models include highly correlated predictors (the lagged air pollution vectors) in the same model, and therefore results can have problems of collinearity. For example, the estimates can be quite variable, with even changes in direction of some estimated effects, and the confidence intervals can be very wide (Basagaña and Barrera-Gómez 2022). It can be a good practice to introduce some constraints to the model, for example that the estimated effects should vary smoothly over lags. In other words, that the effects of adjacent lags should be similar. With this, we try to avoid things like having a high estimation for lag 0, a very low one for lag 1, then again, a very high one for lag 2, and so on (wiggly estimates). This is often done by constraining groups of lags to have the same estimated, or by forcing the estimated effect of lags to vary smoothly according to a spline function. The mathematics behind this are complex, but luckily there is currently a package in the R software that facilitates fitting such models (DLMN package, (Gasparrini, 2011)). The package also allows estimating nonlinear associations within the framework of (constrained or unconstrained) distributed lag models, providing high flexibility. Useful reference to fit such models are available (Gasparrini et al., 2010; Gasparrini, 2011). A trade-off for the flexibility of distributed lag nonlinear models (DLNM) is the extra complexity introduced in the analyses, as many assumptions/decisions should be made on how to model the exposure-response and lag-response relationship (Peng and Dominici, 2008). The penalised framework for distributed lag nonlinear models facilitates some of the analysis's decisions (Gasparrini et al., 2017).

3.4.2 Adjustment methods for time trends

Both air pollution and health are often affected by time varying factors such as seasonality and long-term trends, which can confound the association between these variables. Adjustment for seasonality and time trends is an essential part of the analysis. There are several examples in which not adjusting for seasonality leads to wrong conclusions. For example, mortality is usually higher in winter, when concentrations of ozone are low, and lower in summer, when concentrations of ozone are high. The increased mortality in winter is due to respiratory infections and to other factors. A simple analysis linking mortality and ozone concentrations that does not account for such patterns would conclude that ozone is good for mortality (Bhaskaran et al., 2013).

Choosing the degree of adjustment for seasonality and time trends still generates some debate. Below, we describe some of the most common ways to control for time trends and seasonality.

3.4.2.1 Time stratified model (simple indicator variables)

One way to control seasonality and time trends is to stratify the data into different time scales (e.g., months, years, elapsed calendar months) and then input these functions of time in the regression model. For example, creating strata formed by groups of days from the same year, month and day of the week, and introducing these strata as adjustment variables in the regression model. While time stratified models can capture well long-term patterns, these fits can produce biologically unreasonable jumps from one interval to the next, in addition to requiring a large number of parameters (Bhaskaran et al., 2013).

3.4.2.2 Periodic functions (Fourier terms)

One can include in the model periodic functions of time such as Fourier terms (sine – cosine pairs), which are particularly useful for representing seasonality. These models generate fewer parameters and result in a smoother fit in comparison with the time stratified method, but they fail to capture year-to-year and non-seasonal variations (Bhaskaran et al., 2013).

3.4.2.3 Flexible spline functions

Flexible spline functions are smoothly jointed polynomial curves (often cubic) that can be used to represent trend and seasonality. These functions can be generated in a Poisson or quasi-Poisson model using as input a set of basis variables that are functions of the time variable. Although mathematically more complex, splines have the advantage of modelling trends and seasonality smoothly while still capturing variations between different years. Fitting spline models has become

easy with current statistical software. The use of splines to control for temporal trends has become the most commonly used method in environmental epidemiology studies.

The flexibility of the spline is controlled by the number of knots or the number of degrees of freedom (df), thus, carefully choosing the number of dfs that best fit the data is essential for removing time trend and seasonality without removing part of the short-term variation (Bhaskaran et al., 2013). The choice of df in the analysis is still the most complex part of controlling for time trends.

3.4.2.4 Deciding on spline smoothness levels

The smoothing function of time is used to remove the confounding effects of long-term trends and seasonality from the variable of interest. How smooth this function is allowed to be will define the amount of residual variation from which the association between exposure and health outcome will be estimated. The smoothness of the time function is determined by the number of degrees of freedom (dfs) and therefore, finding the optimum number df is crucial for an accurate association of air pollution and HEs.

The most common methods used for determining the best number of dfs of the time smoothing function are either empirical or data driven (Peng et al., 2006; Peng and Dominici 2008). The "empirical method" consists of choosing df based on previous experiments or published studies, while the data driven method consists on fitting the time smoothing function a number of times and choosing the number of dfs that best fits the data based on a particular evaluation criterion. For instance, the df that minimises the autocorrelation of the residuals (Peng et al., 2006). Some methods that have been recommended include:

- Fixing the number of degrees of freedom per year a priori (Perrakis et al., 2014). For example, 7 or 8 df per year have been suggested to be adequate for effectively removing the time trend of data without significantly removing short-term variations (Bhaskaran et al., 2013; Dominici et al., 2000).
- Find the df that minimise the absolute value of the sum of Partial Autocorrelation Function (PACF) over the number of lags (Peng et al., 2006; Perrakis et al., 2014).
- Find the df that best summarise the temporal pattern in the pollution series (Dominici et al., 2004; Peng et al., 2006), although one should not attempt to explain all the variability with a time function.

Whatever methods is chosen, it is a good practice to repeat the analyses with one or several other values for the df, to explore how sensitive are the results to the choice of df.

3.4.2.5 Adjustment methods for temperature

Temperature has a non-linear effect on mortality, as temperature increases may be both beneficial and detrimental to health depending on the season (Curriero et al., 2002). Due to the non-linear nature of the association between temperature and health outcomes, temperature effects may be modelled by adding one or two (cold and warm seasons) natural or cubic spline functions to the Poisson regression model (Armstrong 2006; Curriero et al., 2002; Rivas et al., 2021; Samoli et al., 2016; Stafoggia et al., 2017). The smoothness of the spline is controlled by the number of degrees of freedom. These functions can be used in a lagged manner to account for the delayed dependence of health outcomes on temperature. Effects of temperature can occur over long lags (e.g. up to 28 days). Thus, completely capturing the effect of temperature may need the use of very flexible cross bases. Including those complex temperature terms in a model of air pollution can introduce problems if datasets are not large enough.

3.4.2.6 Shape of exposure response function

The health impacts of PM are observed even in areas where PM concentrations are below regulatory limits (Liu et al., 2019). This fact implies that PM and health may have a nonlinear relationship, unlike previously thought. Knowing the correct shape of the exposure-response association between air pollution and health is important to create adequate air pollution mitigation strategies to protect human health (Samoli et al., 2005). Although some authors argue that the association between air pollutants and health outcomes is often considered linear (Devos et al., 2016; Kreienbrock, 2014), this shape of association may not be completely adequate for some pollutants (Pope et al., 2015). Samoli et al., (2005) investigated the shape of the exposure-response curve between PM_{10} and health outcomes in a multicity study using spline regression models and reported that linear models are adequate fit for the association. The most comprehensive analysis of time series studies, which includes 652 cities and almost 60 million deaths, showed that the relationships were quite linear, but with steeper slopes at lower PM concentrations (Liu et al., 2019). However, the association can be considered linear in many ranges of PM. Thus, researchers could explore the range of air pollution levels in their study and decide if linearity can be assumed. Assuming linearity facilitates the analysis and the interpretation of results. However, as mentioned above, techniques to estimate nonlinear associations are readily available, and one could fit those and let the data decide if the relationship is linear or not. It is also important to keep in mind that HIA is facilitated if linear (or other parametric forms) are available.

3.4.2.7 Single city vs meta-analysis

Associations between air pollution and health based on a single city may be considered unrepresentative and may not necessarily be observed in other cities with distinct characteristics such as population density, population age, air pollution sources, climatic conditions, etc. For this reason, studies often use a multi-city approaches over single site approach. Multisite approaches offer advantages, such as increased representativeness and potential for generalisation of the results, possibility to investigate causes for inter-site variations, or increased statistical power in comparison with the single site approaches (Basagaña et al., 2018). In multi-site studies, the overall exposure-health effect association can be obtained with a meta-analysis approach that aims to combine risk effects from several sites under a single statistical model framework. Essentially, meta-analysis computes a weighted average of the single-site effects, giving more weight to those sites with more precise estimates (usually those with the bigger sample size), and quantifies some measures of uncertainty in the results.

Meta-analysis may be done by either assuming fixed-effects or random-effects. In practice, many researchers choose a random-effects meta-analysis, thus allowing for heterogeneity of the results across sites. It is important to note that under a random-effect meta-analysis one can estimate from the data that there is no heterogeneity, thus effectively fitting a fixed-effects meta-analysis.

When one aims to combine a single estimate across sites (e.g. a relative risk from a single lag, or the combined effect across several lags), one can fit univariate meta-analyses. However, when one needs to combine several parameters per site (e.g. the effect at multiple lags, or a nonlinear effect represented by several parameters), one needs to use multivariate meta-analyses. There are several resources that illustrate how to conduct multivariate meta-analyses in the context of distributed lag nonlinear models (Gasparrini and Armstrong 2013).

3.4.2.8 Single vs multipollutant models

The air we breathe comprises a mixture of harmful gases and particles in solid and liquid states. The different pollutants often share temporal patterns as several of them share the same weather influences and sources (e.g. vehicles or industry). The day-to-day variation of air pollutant concentrations is primarily affected by environmental factors such as temperature, boundary layer height and relative humidity, as well as variations in emission sources. For these reasons, the concentration of several air pollutants may increase or decrease simultaneously with other pollutants, inducing a correlation among them. For example, total particle number and nitrogen

oxides are often correlated as they are both influenced by road traffic (Dos Santos-Juusela et al., 2013). This is a problem for inference, as if one finds an association between a pollutant and a health metric, the pollutant in question may not be the one causing the HEs, but one that is correlated with a pollutant causing the HEs (WHO, 2013). It can also be the case that several pollutants, or the mixture of them, is what is causing the HEs. Disentangling the HEs of different air pollutant is one of the more complex questions in air pollution epidemiology. In the case of time series analyses, these are observational studies in which certain pollutants almost always occur in conjunction, thus leaving a small variation to study what happens when one of the pollutants has high levels while other has low levels (such circumstances many never occur or occurs with very low frequency). This leads to high correlations that make it difficult to separate the different effects, unless huge datasets are available. When one wants to study several pollutants, the situation becomes worse. Ideally, a possible solution for this problem is to perform a multi-site study using highly contrasting sites as the different characteristics among sites may help the identification of potential confounding pollutants (Dominici et al., 2003). However, this is not always possible. Some statistical techniques have been proposed to analyse the effects of mixtures of highly correlated pollutants, but they are all limited by the amount of information of in the data (i.e. highly correlated pollutants provide limited information on the individual effect of each of the individual components).

It is recommended to start the study of multiple pollutants by fitting single pollutant models, i.e. models that only include one pollutant. Such models provide a first idea of potential associations present in the data, but the analyst should keep in mind that those models fail to consider the potential confounding effect of other air pollutants. Thus, when interpreting the results, analysts should always consider the possibility that the observed results are driven by a highly correlated pollutant, i.e. a pollutant that tends to have high levels at the same time that the pollutant in question. It is also recommended to study the correlation patterns between pollutants to have an idea of how they co-occur.

A second step often done in practice is to fit two-pollutant models (Chen et al., 2021; Liu et al., 2019). These can be done to see how the estimated effect of a main pollutant of interest changes after adjusting for other potentially harmful pollutant, or in general to see which of the pollutants still show an association while adjusting for the other. Sometimes, two pollutant models are restricted to pairs of pollutants that are not very highly correlated (Wang et al., 2020), assuming that for very highly correlated pollutants the effects are impossible to separate (with the available

sample size). Indeed, two-pollutant or multipollutant models often result in unstable estimates when handling highly correlated pollutants, so their results need to be interpreted with caution.

Apart from the issues explained above, another issue to consider is that different pollutants can be measured with different degrees of measurement error. Thus, it is possible that some regression coefficients are stronger than other simply because the particular pollutant was measured with less error than the others.

3.4.3 Issues when studying PM components

One of the challenges when studying the effect of PM components is that one or more particular constituents of PM may be highly correlated with total PM mass, for example, those that represent a large proportion of PM. In that case, the constituent may seem more strongly associated with the health outcome than other components simply because of its association with total PM (which is already associated with health) rather than because of its inherent toxicity (Mostofsky et al., 2012). Also, as mentioned above, many constituents may be driven by the same meteorological conditions, leading to high correlations between constituents. Constituents may also serve as tracers for a prevalent source. Thus, if one finds a health effect for a particular constituent, it may be interpreted as its own impact and also those of related constituents in the same source. In general, constituents are often emitted from several sources, and a single source emits several pollutants, so in practice it is very difficult to distinguish independent toxicities in an observational study (Mostofsky et al., 2012). Still, several complementary analyses can be fitted to assess for potential confounding by total PM mass. These include, as described in Mostofsky et al., (2012):

- **Adjusting the models for total PM mass**. This represents the effect of the constituent while holding the other constituents as constant. This approach has the risk of over-adjusting for factors that may be highly correlated with PM but that are also toxic.
- **Analysis using constituent residuals**: here, the analysis explores the effect of a specific constituent while holding total PM constant (i.e. it implies levels of other constituents are lower).
- **Analysis using PM residuals**. They explore the effect of PM independent of the impact of that specific constituent. E.g., what is the effect of increasing PM in days with similar value of the specific constituent.

In any case, results from analyses of different constituents should be interpreted with caution and guided by theoretical knowledge and results from experiments.

3.4.4 Ultrafine/Nanoparticles

Nanoparticles or ultrafine particles (UFP, usually defined as particles finer than 100 nm) are commonly measured in number concentrations (PNC) instead of the mass concentrations (PM) used for other aerosol fractions, such as $PM_{2.5}$ and PM_{10}. In general, UFP or PNC and coarser fractions of aerosols are poorly correlated, which indicates that they are not indicative of each other (de Jesus et al., 2019; Marconi et al., 2007).

It has to be considered that, in RI-URBANS, UFP are approached in WP1 by evaluating measurements of PNC size distributions (PNSD), PNC, and UFP. According to the European Committee for Standardization (CEN) and ACTRIS recommendations, PNSD should cover range of 10-800 nm. The PNSD datasets from 26 measurement sites have implemented measurement protocols starting with a particle size detection limit of 3 to 20 nm, depending of the site, and with a coarser one from 400 to 1000 nm.

Because 80-90 % of the total PNC (10-800 nm) is built up by the UFP fraction (<100 nm) (Baldauf et al., 2016; Hopke et al., 2022), we will use the terms PNC and UFP indistinctively. In any case, UFP concentrations are strongly dependent on the lower size limit that is being measured (i.e. higher concentrations should be expected when measuring PNC3-100 than when measuring PNC20-100), especially if studies also intend to evaluate the HEs of the nucleation mode particles (PNC<25 nm). The variation of the coarser size detection limit (i.e. 400 to 1000 nm) is less relevant in terms of comparing data, since the PNC in this size range accounts for a very low proportion of the total PNC. WP1 evaluated in detail all these differences and compiled PNC10-800 for most cases, but in a few of them it was PNC15-800 to PNC20-800. If multi-city studies are to be carried out, these are important parameters to consider. For comparability and meta-analyses, one approach could be to restrict the total size range to match the one that is covered in all the cities. That is, restricting the size range for the multi-city study to the common larger lower size cut and the lower larger size cut in all cities.

On the other hand, for evaluating HEs of the nucleation mode PNC10-25 in this study, datasets are excluded if the lower detection size is larger than 13 nm.

Moreover, UFP are known to show strong spatial heterogeneity (Puustinen et al., 2007), which may lead to exposure misclassification in epidemiological studies, particularly for the smallest particles, relying on a single monitoring station (which is often the case, as UFP are not a regulated pollutant and currently is only measured for research purposes). However, there are a number of studies reporting high temporal correlation of PNC across the city despite this known high spatial variability,

which indicates that using data from a single station might be a proper approach in time series analysis (Cyrys et al., 2008; Marconi et al., 2007; Puustinen et al., 2007).

3.4.5 Other strategies for multipollutant analysis

3.4.5.1 Factor analysis/source apportionment

Some studies use the component concentrations to estimate the daily concentrations coming from different sources (e.g., traffic, industry, natural sources, etc.). Factor analysis, positive matrix factorization or other techniques can be used for that (Amato et al., 2009). This has the advantage of having to estimate fewer parameters, as the number of sources is less than the number of constituents, and it may lead to more interpretable estimates, as results summarise all the effects of the constituents in one source. Moreover, focusing on the sources instead of in specific components facilitates the instauration and justification of policies for better AQ that target the most harmful sources.

With this analysis, one still needs to consider whether to adjust for total PM or not. One difficulty of the analysis of sources is that they tend to be different in different cities. For example, an industry source in one city may have a completely different source profile than in another city, if the types of industry present in each city are very different. This makes it difficult to combine results from multiple cities (Basagana et al., 2015; Mostofsky et al., 2012).

3.4.5.2 Clustering days

One can use clustering techniques to cluster days, i.e. to group days, according to the mixture of exposures observed in that day. Then, one studies the risk for the health event in each of the groups of days. These techniques evaluate the effect of having a specific mixture of pollutants, i.e. it does not evaluate the HEs of specific components but that of the overall mixture. In some situations, this can provide more realistic estimates as, as mentioned above, it if very difficult to separate the effects of the air pollution mixture. Several studies have used this technique (Ljungman et al., 2015; Pearce et al., 2018; Zanobetti et al., 2014). For example, they found that days with low mass concentrations, but high proportion of ultrafine particles resulted in elevated risk for some health outcomes (Ljungman et al., 2015), or that days that were warm and dry and with high levels of O_3 and $PM_{2.5}$ conferred some risks of other health outcomes (Pearce et al., 2018). This kind of approach also makes it difficult to combine results from different cities, as the clusters obtained in the different cities can be very different.

3.4.5.3 Hierarchical models

Hierarchical models often impose a structure in the data, e.g. specifying that pollutants of the same family or with similar chemical or toxicological properties should have similar health effect estimates. This results in estimated effects for each pollutant being shrunk towards the mean effect of the group, improving precision in estimation. Hierarchical models are often fitted with Bayesian techniques (Blangiardo et al., 2019), but non-Bayesian options have also been used (Suh et al., 2011). In some cases, such modelling can be quite complex, especially if one wants to include many features such as nonlinear or delayed effects, and it may require expertise in Bayesian statistics.

3.4.5.4 Other methods and final remarks

There are several other methods that have been suggested to estimate the effect of multiple pollutants. Here, we provide some references to reviews of such methods (Davalos et al., 2017; Oakes et al., 2014). Overall, analysts are encouraged to explore such methods and find the one that best fits their research question and data availability. However, as stressed above, disentangling the effects of multiple pollutants in observational studies is a complex problem, and all statistical methods are limited by the quality of information present in the data. Thus, it is recommended to do a complete analysis, starting by investigating the correlation between pollutants, following by fitting single pollutant models, then fitting two-pollutant models, and finally considering techniques for multipollutant models. Results from all these analyses should be analysed with caution, conducting several sensitivity analyses (e.g. trying to adjust for PM mass) and using available knowledge.

4. HEALTH IMPACT ASSESSMENT

Health impact assessment (HIA) is a technique that can be used to predict the potential health benefits and health impacts from a policy, program, activity or situation in a given population. In the case of short-term effects of air pollution, it could be used to assess, for example, how many deaths could be prevented if air pollution levels in a city did not exceed the limits recommended by WHO (or any other limit) any day of the year. Note that this technique can be used to illustrate the effects of air pollution in an area even when one does not have access to the time series of health data (e.g. the daily mortality series), or when the time series is too short to draw valid conclusions. This can be done provided that there is good evidence in the literature of the HEs of the particular pollutant

for which one wants to do the study. In particular, one needs an estimation of the relative risk of the pollutant, ideally coming from a meta-analysis of many studies, so that the relative risk (RR) is estimated with good precision and can be trusted. For example, the HRAPIE project provided the best available exposure–response functions for HIA of the effects of PM, O_3, and NO_2 (WHO, 2013). They provided estimates for both short-term and long-term exposure associations with health. However, this has an important scientific limitation for PM, BC and UFP, as it assumes that the RRs obtained elsewhere can be applied to a given city, country or region. This may not be correct if the physico-chemical patterns of particles, or the pollutants associated to BC, differ in different regions, and those properties lead to different health effects and RRs. In that case, using the average RRs of the place(s) where the RRs were obtained may lead to incorrect estimates.

4.1 Data needs

For the case of short-term associations, the HIA calculates the number of cases (e.g. mortality or hospital admission cases) attributable to air pollution in the baseline scenario, and compares it to the attributable number of cases in a counterfactual scenario. The data needed to conduct the HIA is the following:

- **Baseline exposure**. This is usually the present or past exposure, and one can use a daily time series of the specific pollutant under investigation to represent current exposure.
- **Air pollution levels in the counterfactual scenario**. The available time series can be modified to obtain that. For example, if the counterfactual scenario is one in which certain threshold is never exceeded, all days that exceed the threshold in the real series are replaced by the threshold. This way, the threshold is never exceeded in the modified series. Other types of scenarios could be envisioned, e.g. on in which the concentration of all days is reduced by 10%.
- **Size and profile demographics of the population exposed**. This may just be the population (total number) living in the particular area under study. In some cases, the population by sex and age ranges can also be used. The population can be considered to be the same in the current and counterfactual scenario, or it can be assumed to change.
- **Incidence rate of the health effect being studied**. For example, the underlying mortality rate in the population, in deaths per thousand people.
- **The risk estimates from exposure-response functions relating air pollution to the health effect** (e.g. mortality). This estimate comes from the epidemiological literature and ideally it should be an estimate based on the meta-analysis of several studies that appropriately summarises the

best available evidence for the association. There exist very good estimates of exposure-response functions for PM, NO_2 or O_3. For the case of nanoparticles or PM constituents, there is less evidence and the estimates available will be considered of less quality. In 2014, a WHO expert meeting concluded that it was premature to derive specific exposure-response functions for any PM component (WHO, 2014). However, estimates are available, and HIA exercises could be done as long as the limitations of the data are acknowledged.

4.2 Calculations

The predicted number of attributable cases (attributable number, AN) for a certain air pollutant (Poll), assuming the association is linear, can be calculated as $AN(Poll) = P*B*(1-1/RR(Poll))$, where P is the exposed population, B is the baseline population incidence of the given health effect, $RR(Poll) = \exp(\beta*Poll)$, Poll are the levels of the pollutant and β is obtained from the exposure response functions. Then, one can do the calculations for the baseline and counterfactual scenario to obtain the difference in the number of cases. In the context of a time series study, one can do the calculations for every day in the series and sum the number of cases throughout the study period. The following references provide examples of such HIA calculations (Holland et al., 2005; Izquierdo et al., 2020).

Uncertainty analysis is a key part of HIA. One can use different estimates of the exposure response functions, and use the confidence intervals of the exposure-response function estimates in simulation procedures to incorporate the uncertainty in the final estimates. Uncertainties in the disease burden, the pollution exposure level, response to the pollution and the counterfactual level of air pollution should also be incorporated. More details on the implementation of HIA studies can be found in the following reference (Holland et al., 2005).

5. ILLUSTRATION: PAN-EUROPEAN ANALYSIS OF HEALTH EFFECTS OF UFP-PNSD

Here, we present the experience of RI-URBANS, which illustrates how data from AQ Monitoring Networks can be used to evaluate the HEs of novel AQ metrics. RI-URBANS collected novel AQ metrics such as Nucleation, Aitken, Accumulation, UFP, BC or lung deposition surface area (LDSA), from different European cities. In addition, it contacted health agencies from different countries to

obtain daily mortality counts for the same periods. AQ and health data were combined and analysed using the time series methodology described above. The next sections provide more details. Results presented here are preliminary as they only include a sample of cities, but illustrate the feasibility of such analyses.

5.1 Data

Figure 1 shows the seven cities included in the present analysis, namely: Athens, Barcelona, Budapest, Madrid, Granada, Helsinki and Zurich. Table 2 shows the particle size range from each variable and their units.

***Figure 1**: Location of the station (Source: My maps – google map).*

***Table 2:** Description of the PM size segregated variables. PM: particulate matter; UFP: ultrafine particles.* *Upper limit of the size distribution is city-dependent (see Table 3).

Variable	Size range (nm)	Units
Nucleation	10-25	Particles/cm^3
Aitken	25-100	Particles/cm^3
UFP	10-100	Particles/cm^3
Accumulation	100-800*	Particles/cm^3
N25	25 – 800*	Particles/cm^3
Ntotal	10 – 800*	Particles/cm^3
PM2.5	≤ 2500	µg/m^3
PM10	≤ 10 000	µg/m^3

Table 3: *Description of stations, period, PNSD instrumentation and range, and data provider of mortality data from each city. Abbreviations: UB: urban background; SMPS: Scanning mobility particle Sizer; CPC; condensation particle counter; TDMPS: Twin differential mobility particle sizer; DMPS: Differential mobility sizer*

City (country)	Name of station (type)	Period	PNSD instrumentation	PNSD range (nm)	Mortality data provider
Athens (GR)	Thissio (UB)	2015-2019	SMPS TSI model 3034	10 – 470	Hellenic Statistical Authority (ELSTAT)
Barcelona (ES)	Palau Reial (UB)	2013-2019	SMPS TSI 3080 + CPC TSI 3772	12 – 478	Instituto Nacional de Estadística (INE)
Budapest (HU)	CAAG (UB)	2009 - 2019	Flow-switching DMPS + CPC TSI 3775	11 – 816	Hungarian Central Statistical Office (KSH)
Granada (ES)	UGR (UB)	2017 - 2019	SMPS TSI 3082 + CPC TSI 3772	11 – 496	Instituto Nacional de Estadística (INE)
Helsinki (FI)	Kumpula (UB)	2009 - 2019	TDMPS (Hauke-type DMA + CPC TSI 3025; Hauke-type DMA + CPC TSI 3010)	3 – 794	Statistics Finland (STAT.FI)
Madrid (ES)	CIEMAT (UB)	2009 - 2019	SMPS TSI 3080L + CPC TSI 3775	15 – 661	Instituto Nacional de Estadística (INE)
Zurich (CH)	Kaserne (UB)	2014 - 2019	SMPS TSI 3034 + Nafion aerosol dryer	17 - 478	Swiss Federal Statistical Office (BFS)

5.2 Statistical analyses

We modelled each city separately. Trends were accounted for using the combination of day of the week, month and year, using a time-stratified model estimated with conditional Poisson regression. Models were adjusted for temporal trends, temperature (cold and warm days), relative humidity, day of the week and holidays. Here, we examined the effects of pollutants at lags 0, 1 and 2 in separate models. Subsequently, we fitted 2-pollutant models including the different fractions and $PM_{2.5}$, to see if the associations changed. Results from the individual cities were combined using a random effects meta-analysis. Effect estimates were reported for an interquartile range increase in the pollutant.

5.3 Results, conclusions and recommendations

Results of the analyses are shown in Figures 2 and 3. All particle size modes were significantly associated with increasing effects on natural and cardiovascular mortality, except for the accumulation mode. The HEs of UFP (<100 nm) and PNC (total particle number concentrations, >10 nm) were similar in single pollutant models. One IQR increase in UFP (IQR: 3804 particles/cm3) and

PNC (IQR: 4528 particles/cm3) were associated with 0.83 [95% CI 0.18, 1.49] and 0.77% [95% CI 0,13; 1,41] increase in natural mortality, respectively, with a mean delay of 0 - 2 days after exposure (mean lags 0, 1 and 2). In two pollutant models, the HEs of the Nucleation, Aitken, UFP and PNC on natural mortality remained significant after adjusting for $PM_{2.5}$, evidencing an independent effect for UFP.

Our preliminary results indicate that the Nucleation, Aitken, UFP and the PNC particle size concentrations may increase mortality independently from larger PM fractions. This illustrates the feasibility of conducting such analyses and the added value of the novel AQ measurements in determining HEs.

Accordingly, RI-URBANS recommends measuring UFP and particle size distributions in urban areas to supply information for further epidemiological analyses and the development of AQ standards. The results obtained here were obtained without harmonisation of measurements, and HEs were evidenced, but harmonisation of these will results in a lower statistical noise in the analysis.

5.4 Acknowledgements

Spanish health data: primary health data provided by the Spanish Statistical Office (Instituto Nacional de Estadística, INE).

Athens mortality data: provided by the Hellenic Statistical Authority (ELSTAT).

Budapest health data: This work has been created with the use of daily mortality (Budapest_daily_mortality_A00_R99_19902020) data file, prepared upon individual request by the Hungarian Central Statistical Office (www.ksh.hu).

The degree of accuracy or reliability of the quantitative information presented here, the results and conclusions of the research are derived from the RI-URBANS own work on the datasets, and is the sole responsibility of the researchers.

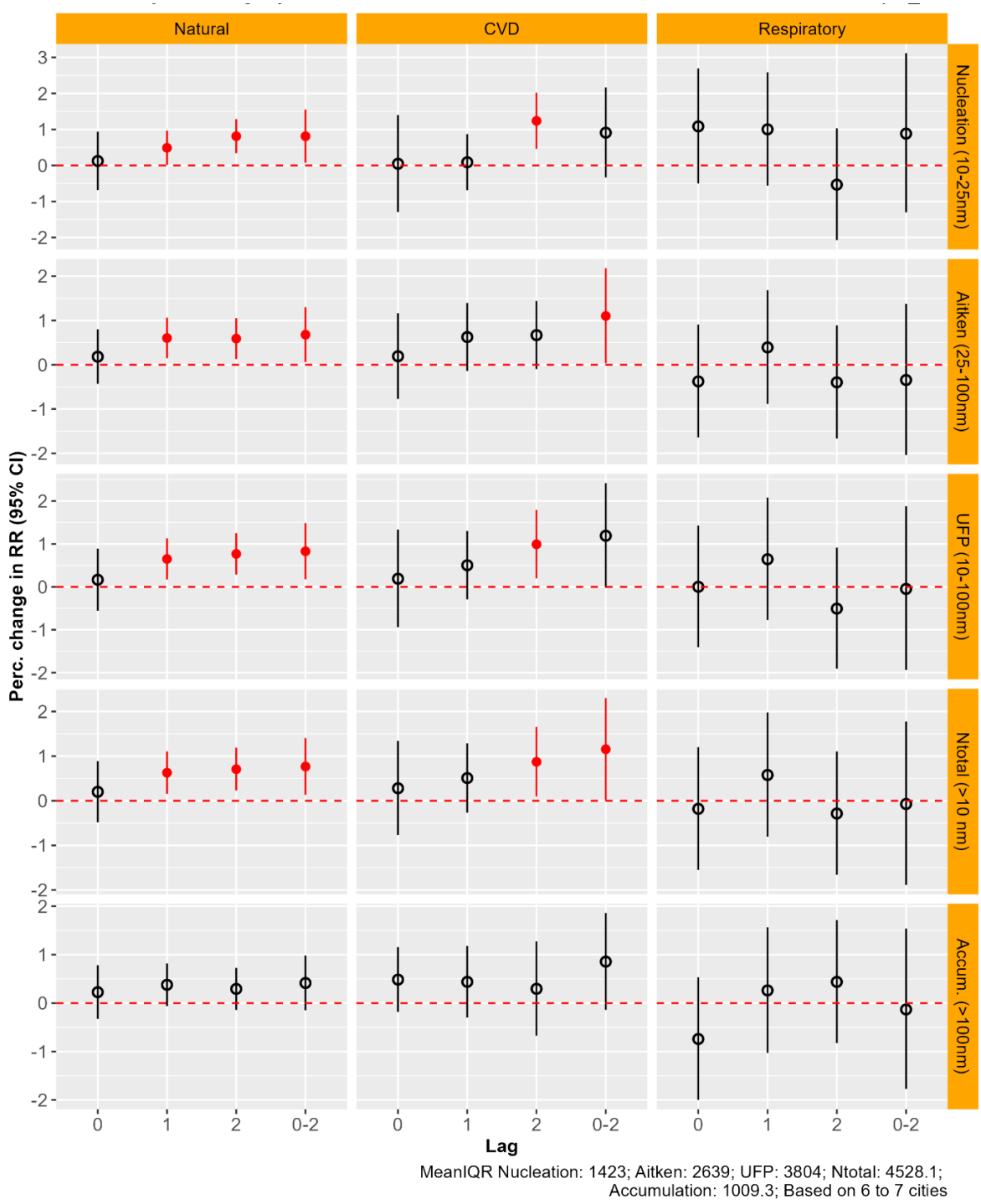

***Figure 2**: Meta-analysis from single pollutant models showing the effects of size segregated particle number concentrations on mortality by natural, cardiovascular diseases (CVD) and respiratory causes. Accum.: Accumulation mode. Results expressed as percentage increase in health effect per interquartile range (IQR) increase in exposure concentration.*

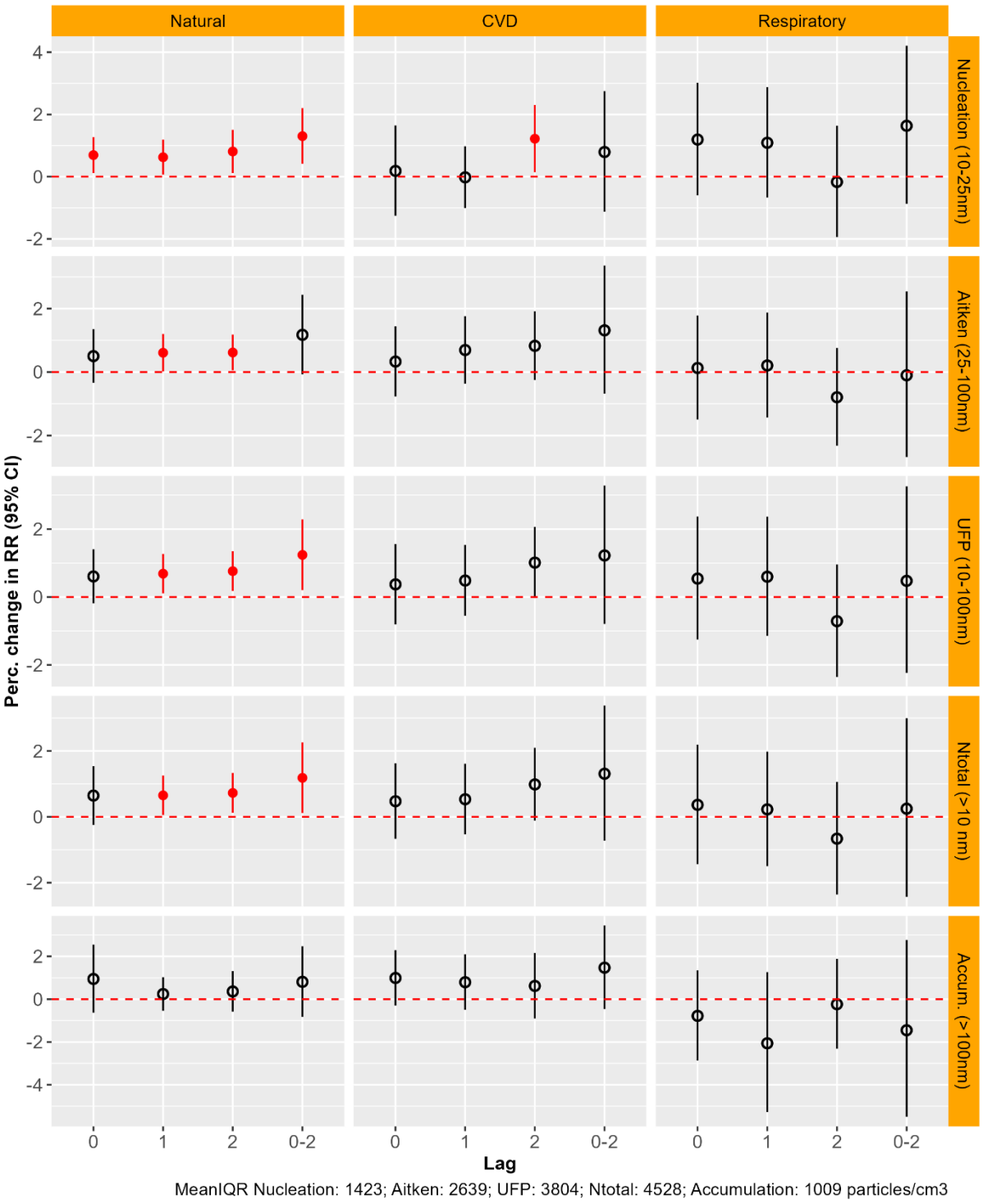

Figure 3: *Meta-analysis from two pollutant models adjusted for $PM_{2.5}$. Percentage increase in health effects per IQR increase in exposure concentration. Accum.: Accumulation mode.*

6. RECOMMENDATIONS

In terms of methodology for assessing the short-term health effects of air quality parameters, including novel metrics, we recommend:

- Use daily data and long-time series to evaluate the health effects of air pollution, as the size of the effect is small and large sample sizes are needed to capture them with precision. Combining results from multiple cities is also a good strategy, especially if small cities are involved.
- Models should control for seasonality to avoid biases, and they should explore different lags to capture delayed effects.
- When examining novel metrics, fitting two-pollutant models that include a more established health-damaging pollutant is recommended, to identify if the novel metric captures an independent effect.
- When studying nanoparticles in multi-city studies, the size range should be restricted so that all cities include the same range.

In terms of the preliminary analysis of novel metrics, we recommend:

- Nucleation, Aitken, UFP and the PNC particle size concentrations may increase mortality independently from larger PM fractions. Thus, nanoparticles should be regularly monitored in order to feed new research that could establish recommended levels to protect human health.

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