DAILY CHANGES AND SHORT-TERM EXPOSURE PATTERNS IN TIME SERIES STUDIES OF AIR POLLUTION AND ACUTE HEALTH EFFECTS

by

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ABSTRACT

This thesis investigated the effects of daily changes in exposure (delta) and short-term exposure patterns on the relationship between air pollution and health in time series studies. Using data from London and Hong Kong, delta was defined as the difference in particulate matter (PM_{10}) concentration between successive days. Short-term exposure pattern series were defined based on number of peaks in PM_{10} within rolling weekly blocks.

The mathematical equivalence of identifiable models for delta with conventional distributed lag model was derived and alternative model specifications were proposed. Measurement error and missing data exhibited more impact on delta than the absolute metrics in simulation studies. Evidence of association for delta PM_{10} with mortality was found only in Hong Kong which attenuated towards the null with more rigorous adjustment for weather.

The pattern analysis approach hypothesized, in addition to amount (dose) and duration of exposure, epidemiological studies ought to take patterns of exposure into account. However, convincing evidence was not found for the effect of short-term exposure patterns on mortality risk estimates both in London and Hong Kong. Refining the definition of exposure patterns and methodological improvements including analysing data from multiple cities are highly recommended in related studies in the future.

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THESIS LAYOUT

There are a total of six chapters in this thesis. The chapters are organised so that each can be read independently but as much effort has been made to maintain continuity and flow in moving from one chapter to the next. Thus, I acknowledge the occurrence of some inevitable repetitions of text when trying to balance between the two objectives.

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ABBREVIATIONS

APHENA	Air Pollution and Health: A European and North American Approach
APHEA	Air Pollution and Health: A European Approach
AIC	Akaike information criteria
CO	Carbon monoxide
COMEAP	Committee on the Medical Effects of Air Pollutants
df	Degrees of freedom
ΔPM_{10}	Delta PM_{10}
UDL	Unconstrained distributed lag
EU	European union
GAM	Generalized Additive Model
GLM	Generalized Linear Model
IOEM	Institute of Environmental and Occupational Medicine
IQR	Interquartile range
IRLS	Iteratively reweighted least squares
MCMC	Markov chain Monte Carlo
ML	Maximum Likelihood
MSE	mean square error
$\mu g/m^3$	Micrograms per cubic metre
μm	Micrometres
MC	Monte Carlo
NS	Natural splines
NO_2	Nitrogen dioxide
OR	Odds ratio
OLS	Ordinary Least Squares
NO_X	Oxides of nitrogen
O_3	Ozone
pdf	Probability density function
PM	Particulate matter
ppb	Parts per billion

ppm	Parts per million
PS	Penalised splines
PM_{10}	PM with aerodynamic diameter of less than 10 μm
$PM_{2.5}$	PM with aerodynamic diameter of less than 2.5 μm
$R\Delta PM_{10}$	Relative delta PM_{10}
RE	Relative efficiency
RH	Relative humidity
RR	Relative risk
SS	Smoothing splines
SD	Standard deviation
SO_2	Sulphur dioxide
UDL	Unconstrained distributed lag
UK	United Kingdom
US	United States
WHO	World Health Organisation

1. INTRODUCTION

1.1. Background

Air pollution has now become the largest environmental risk factor for global mortality. According to the World Health Organization (WHO), a staggering 3.7 million premature deaths in 2012 may be attributed to ambient air pollution around the world (WHO, 2014). This appears to be much larger than previously estimated figures (WHO, 2011). In the United Kingdom (UK) some 8100 deaths per year are estimated to be brought forward due particulate matter (PM) pollution alone and corresponding estimates for other pollutants only emphasize the importance of air pollution monitoring and control policies (COMEAP, 1998).

Consequently guidelines for air quality standards have been produced by international, regional and national authorities to minimize the burden of environmental health effects posed by different pollutants. These guidelines have also been updated from time to time in line with respective evidence indicating that even lower levels of some pollutants might have noticeable health effects (WHO, 2006, Anderson, 2009, WHO, 2013). Such progress is a result of improved understanding and advances in research methods over the last few decades.

Before the complex and diverse studies applied in the field today, there were some historical air pollution episodes in Europe and the United States (US) that marked the beginning of epidemiological investigation on health effects of air pollution; these have eventually led to the development of air quality related policy. The commonly cited episodes include Meuse Valley, Belgium (60 deaths, 1930), Donora, Pennsylvania (20 deaths, 1948) and the London fog (4000 deaths, 1952) the latter being the most catastrophic (Nemery et al., 2001, Brimblecombe, 1987, Anderson, 1999). Epidemiologists

and statisticians during those days depicted relationships between air pollution and health variables by simple graphical methods or comparison of mortality rates between different time periods (Carracedo-Martínez et al., 2010).

Since then a good number observational and experimental studies have been conducted taking advantage of advances in epidemiological and statistical methods. They investigated both acute and chronic effects of air pollution on human health providing evidence for decision making regarding air quality issues. These methodological developments include time series, cohort, case-crossover and panel study designs and have hugely benefited from improved computational capacity overtime (Dominici et al., 2003b, Rückerl et al., 2011). More recently, time series studies appear to be frequently used due to their relative ease and low cost (Anderson, 2009, Katsouyanni et al., 2009, Touloumi et al., 2004, Schwartz et al., 1996, Bhaskaran et al., 2013). The analytic methods to account for confounders that vary with time such as seasonality, long-term time trends and weather in time series studies have also undergone substantial improvement. Poisson generalized additive models (GAM) or generalized linear models (GLM) with smoothing functions for modelling nonlinear relationships of time and weather variables have become the standard in time series studies (Katsouyanni et al., 2009). A general form of such a model can be given as

$$Log(\mu_t) = Log[E(Y_t)] = \beta_0 + \beta P_{t-l} + \sum_{i=1}^{k} f_i\,(X_{ti}) \qquad (1.1)$$

where Y_t is the observed count of the relevant health outcome with expected count μ_t, effect estimate β represents the change in the logarithm of the population average health outcome (e.g. mortality or hospital admission counts) per unit change in pollutant P at lag l (P_{t-l}) and f_i represent a smooth function of covariate X_i to be included in the model

(Touloumi et al., 2006, Dominici, 2004). The model in 1.1 can easily be extended by adding more terms; for example we can incorporate indicator variables to account for day of the week effect and influenza epidemics as well as consider distributed lags in the model.

1.2. Rationale for the delta study

Time series studies of air pollution exposure and health outcomes such as mortality or hospital admissions as in model 1.1 above usually use simple day-to-day analyses sometimes with lagged approaches extending over some days or even weeks. However, from time to time alternative metrics for environmental exposures such as air pollution and temperature have been investigated based on different averaging times of exposure (Bell et al., 2005, Ostro et al., 2001, Delfino et al., 2002, Nastos et al., 2006, Darrow et al., 2011, Yang et al., 2012). This is an important issue as air quality guidelines are health based and if effect sizes are less accurate using current metrics then this would have a considerable influence on policy generation with respect to air quality. For example, Yang et al. (2012) compared three temporal metrics for ozone and reported stronger associations with mortality for maximum 8-hour average and 1-hour maximum concentrations than with 24-hour average concentrations. Conversely, Darrow et al. (2011) compared six different temporal metrics for four pollutants and concluded that similar results were obtained using the different metrics with few exceptions and favoured application of the present metrics used in setting air pollution guidelines by the US Environmental Protection Agency (EPA).

More formally, the purpose of exploring alternative metrics in such studies is to identify a biologically more relevant exposure measure which in turn could provide better risk estimates (Birnbaum, 2010, Darrow et al., 2011). Most of the metrics compared so far have

reflected mainly differences in averaging times or temporal variability, but differences in air pollution concentrations over successive days rather than or in addition to absolute concentrations could also be related to health outcomes. Conventional time series studies tell us the risk of death on any day with absolute levels of pollution concentration, say x+10 μg/m^3, is y% greater than on a day with pollution concentration of x μg/m^3. That is, there is no necessity for a temporal link between the two days; they can be consecutive days or many days apart. However, increases in pollution level over a short period of time may have larger health impact than a similar increase over a longer or extended period of time; i.e., sudden changes may result in more adverse effects than gradual changes from toxicology or physiology points of view.

This is an attractive argument biologically as the human body often responds to a change in stimulus or to the rate of change of stimulus; a good example is the way in which cutaneous pain receptors respond to stimulation (Burgess and Perl, 1967). However, there is to date very little published work using changes or rate of changes in exposure as alternative metrics in time series studies of air pollution, though a few studies have applied the change metrics for temperature (Guo et al., 2011, Nastos et al., 2006, Lin et al., 2013, Kim et al., 2014).

This approach to exposure metrics in the air pollution field had been proposed in a commentary before where the need to investigate for the effect of relative changes was pointed out (Ayres, 2007). It had also been highlighted that during the 1952 and 1990 air pollution episodes in London pollution levels were similar in relative terms but much lower during 1990 in absolute terms (Anderson, 2009). In an interesting article published recently in Science Dominici et al. (2014) asked "would a reduction in $PM_{2.5}$ from 12 to 10

μg/m^3 produce the same health benefits as a reduction from 14 to 12 μg/m^3)?" suggesting the need to investigate whether the same change in pollution from different baselines could have differential health effects. Hence one of the aims of this thesis was to explore the use of changes or rate of changes (delta exposures) in air pollution concentrations over successive days in time series studies of air pollution and health. This approach is referred to as the 'delta time series study' and is the topic of Chapter 3 and Chapter 4. However, while useful to study the effects of changes or rate of changes over a period of one day, such method may not be sufficient to examine the health effects of the dynamics or changes in air pollution levels over a period of more than one day but essentially small number of days. In order to study the effect of air pollution exposure patterns over small number of days, a method which involves identifying specific patterns in pollution exposure over a period of one week was proposed. The aim here was to compare the various pollution exposure patterns within a relatively short period of time with respect to the subsequent health effects. This approach is referred to as 'delta pattern analysis' and is the topic of Chapter 5.

1.3. Aims and objectives

The general aim of this thesis was to examine the association between air pollution and acute health effects taking into account changes in pollution concentrations between successive days as well as short-term exposure patterns over a period of one week.

The objective of the first part of the thesis (Chapter 2) was to provide an overview of methods in relation to the study of the health effects of air pollution.

The objective of the second part of the analysis (Chapter 3), 'delta time series methodological issues', was to examine statistical modelling and related issues in the delta time series approach.

The objective of the third part of the analysis (Chapter 4) was to present empirical results from application of delta time series approach for PM_{10} exposure and compare results using data from two different cities, London and Hong Kong.

The objective of the fourth part of the analysis (Chapter 5), 'delta pattern analysis', was to evaluate the effect of accounting for different PM_{10} pollution exposure patterns within one week window period on mortality risk estimates associated with air pollution.

Finally Chapter 6 presents an overall summary, discussion on potential limitations of the study, possible areas of focus for future work and concluding remarks.

1.4. Application of results

If there is evidence of effect from the delta time series and/or delta pattern analysis approaches, then further investigations could look into how to use the results to inform mechanistic explanations for the relationship between air pollution and adverse health effects. Moreover, it could be expected that, such results would influence the risk estimates of acute health effects of air pollution which are used for setting standards. The methods developed may also be applied in similar biomedical research where data from a time series are analysed.

To sum up, this thesis presents methodological work proposing alternative ways of incorporating the short-term dynamics of exposures in order to evaluate their effect on health risk estimation in air pollution studies. This is demonstrated using data on daily

PM_{10} concentration and daily mortality from London and Hong Kong. If the results between the two cities were in agreement, then the observed association would be less likely to have occurred by chance. On the other hand, if the results were different, then it would be likely that the underlying differences in the characteristics of the cities could have influenced the health risk estimates. Some of the factors which could lead to such differential effects include weather, background average daily air pollution concentration, socio-economic and demographic patterns. A summary of such characteristics for London and Hong Kong extracted from Wong et al. (2002) is provided in Tables 1.1 and 1.2 of Appendix A.

2. STUDYING HEALTH EFFECTS OF AIR POLLUTION

Some important tools for the study of air pollution and health are presented in this chapter. The topics covered include basic definitions, criteria pollutants, air quality guidelines and monitoring, outline of commonly studied health effects and an overview of epidemiological and statistical methodologies in air pollution studies. Finally, issues related to exposure metrics, multi-pollutant models, bias from ecologic design and measurement error in air pollution studies are outlined. Some references (literature) for further discussion on each section are provided as relevant.

2.1. Air pollution

In simple terms air pollution refers to the presence of higher levels of any substance than there should normally be in the indoor or outdoor environment. More formally, air pollution refers to the presence of certain gaseous or particulate compounds above a certain level specified in the international or national air quality guidelines which are set up to lessen public health risk. This is not the same as contamination which is merely the presence of chemicals with no known environmental harm (Harrison, 2001).

2.1.1. Major pollutants and sources

The major pollutants listed out in the UK's Air Quality Strategy document published in 2007 included particulate matter (PM) with aerodynamic diameter of less than 10 (PM_{10}) and 2.5 ($PM_{2.5}$) μm, Oxides of nitrogen (NO_X), Ozone (O_3), Sulphur dioxide (SO_2), Carbon monoxide (CO), Lead (Pb), Polycyclic aromatic hydrocarbons (PAHs), Benzene, 1,3-butadiene and Ammonia (Defra, 2007). Similarly the US EPA refers to the first six as 'criteria' pollutants to be included in their National Ambient Air Quality Standards (United States Environmental Protection Agency). This selection is primarily based on the significance of adverse effect to public health posed by each of the pollutants.

Air pollution may occur due to natural causes such as wild fires and volcanic eruptions but anthropogenic sources are the main target of air pollution control policies. Emissions from motor vehicles and the combustion of fossil fuels by industries and power stations contribute a large proportion to ambient air pollution from human activities. Burning of solid fuels (mostly in the form of biomass) is the major source for indoor pollutants and of particular concern in developing countries (Wilkinson et al., 2009, Kurmi et al., 2012).

2.1.2. Monitoring and standards

In general, air quality measurements are taken across several sites in both rural and urban areas particularly in the developed world. These monitoring sites provide relatively high frequency background air pollution concentrations on an hourly or sub hourly basis. For example, the UK Automatic Urban and Rural Network (AURN) comprises of a total of 178 monitoring sites which produce measurements of several pollutants as frequently as every quarter of an hour (Defra, 2014). In air pollution studies, temporal averages from one or more monitoring stations are usually considered to represent daily exposure concentrations. Another way to assign exposure levels at a specific location and time involves building models which take into account various spatial and temporal factors such as traffic density and weather. Land use regression (LUR) models are very popular in this regard (Jerrett et al., 2005, Hoek et al., 2008). Recently, organizations such as the European Space Agency and the National Aeronautics and Space Administration (NASA) have been working to provide complementary air pollution data at finer spatial resolutions in 'near-real time' for some pollutants using satellite measurements (Duncan et al., 2014, van Donkelaar et al., 2010).

In order to protect human health international and national authorities set standards for air quality. Monitoring bodies use these standards to control for concentration levels of the major pollutants in the ambient air from their monitoring sites. Table 2.1 shows a general WHO guideline for five major pollutants (WHO, 2006).

Table 2.1: Worldwide guidelines for major pollutants in µg/m ^{3} (WHO 2005)

Pollutant	**Mean concentration**				
	Annual	**24-hour**	**8-hour**	**1-hour**	**10-minute**
$PM_{2.5}$	10	25	-	-	-
PM_{10}	20	50	-	-	-
O_3	-	-	100	-	-
NO_2	40	-	-	200	-
SO_2	-	20	-	-	500
CO[§]	-	-	10	30	-

[§]Based on WHO guidelines published in 2000 (WHO 2000)

A recent WHO project, "Review of evidence on health aspects of air pollution – REVIHAAP", reviewed the accumulating air pollution epidemiology literature; the review concluded supporting the scientific basis of the 2005 WHO guidelines as well as confirming the benefit of revising the guideline (WHO, 2013). It should, however, be noted that there are variations in guidelines (Table 2.2) based on country (Boyd, 2006) or approaches used to set the standards (Maynard RL, personal communication).

Table 2.2: Regional comparison of air quality standards and guidelines

Pollutant	WHO	EU	Australia	US	Canada
Ozone 8 hour, ppb	50	60	80	80	65
Fine particulate 24 hour, $\mu g/m^3$	25	50	25	65	30
Sulphur dioxide 24 hour, ppb	8	48	80	140	115
Nitrogen dioxide Annual, ppb	21	21	30	53	53
Carbon monoxide 8 hour, ppm	9	9	9	9	13

Source: Boyd DR, The Air We Breathe: An International Comparison of Air Quality Standards and Guidelines, 2006.

2.2. Health effects of air pollution

In earlier studies, it was thought that adverse health effects of air pollution were primarily associated with respiratory problems for example bronchitis (Committee on the Medical Effects of Air Pollutants, 2006). This was because the mechanism by which air pollution harms human health was not intuitive for other important health effects such as cardiovascular diseases (Anderson, 2009). Eventually, studies begun to propose potential mechanisms and showed evidence particularly for cardiovascular related mortality and morbidity (Seaton et al., 1995, Poloniecki et al., 1997, Seaton et al., 1999, Pope, 2000). A number of possible biological mechanisms have been proposed to explain how exposure to air pollution results in adverse health outcomes; the 'oxidative stress' and the 'multifactorial' concepts are two explanations among others and details can be found elsewhere (Ayres et al., 2010, Anderson, 2009).

Air pollution is associated with both acute and chronic health effects. Acute effects are due to variations in air pollution exposure over a relatively shorter time scale (hours to days of exposure). They include transient physiological changes in the respiratory functions (which are reversible), asthma attacks, hospital admissions and mortality mainly due to respiratory and cardiovascular causes (Harrison, 2001, Walters et al., 1994, Katsouyanni et al., 1997). Chronic effects are due to cumulative exposure to air pollution over a longer time scale

(years of exposure). Associations that have been reported include lung cancer, reduced lung growth or function and mortality (Dockery et al., 1993, Pope et al., 2002, Elliott et al., 2007, Committee on the Medical Effects of Air Pollutants, 2009). Estimating the total public health burden of disease related to air pollution has been a challenging task but methodological improvements have continued (COMEAP, 1998, Cohen et al., 2005, Burnett et al., 2014).

2.3. Statistical and epidemiological methods

Both experimental and observational studies have been applied to investigate the association between air pollution and human health. Experiments can be conducted in vitro to expose tissues or using controlled chambers to expose human subjects to a potential toxicant for a short period of time usually for a couple of hours (Harrison, 2001, Ayres et al., 2010). The outcomes of interest could be disease symptoms or biomarker responses (McCreanor et al., 2007, Bleck et al., 2010, HEI Review Panel on Ultrafine Particles, 2013). Experimental studies could provide insights into mechanistic relationships and short-term exposure effects in specified subpopulations of interest. It is, however, not practical to examine longer term exposure effects and is difficult to simulate real world exposure patterns in most settings. Reports from experimental studies on health effects of air pollution have not always been consistent (Cassee et al., 2013, HEI Review Panel on Ultrafine Particles, 2013).

As controlled random allocation of realistic levels air pollution exposure is not feasible in experimental investigations, the so called ‘natural’ or ‘quasi’ experiments have been exploited. In a natural or quasi experimental study, an intervention or policy beyond the investigator’s control produces variation in exposure levels and the ensuing difference in

health outcomes are examined (Craig et al., 2012). There are a limited number of such interventions which have been used in quasi-experimental studies including the closure of a steel mill in Utah (1986), coal bans in Dublin (1990), restriction on sulphur content of fuel in Hong Kong (1990), the congestion charging scheme in London (2003) and the strict air pollution regulations by the Chinese government for the Beijing Olympic (2008). These studies have demonstrated convincing evidence on the health benefits of a reduction in air pollution concentrations (Pope, 1989, Clancy et al., 2002, Hedley et al., 2002, Tonne et al., 2008, He et al., 2015).

Epidemiologic (observational) studies, on the other hand, are extensively used to examine both short-term (hours to days of exposure) and long-term (years of exposure) health effects of air pollution. In subsequent sections, some of the epidemiologic study methods are outlined for both short-term (including episode, case-crossover, time series and panel studies) and long-term (including cohort and cross-sectional studies) effects. More emphasis is put on the time series study design as the thesis is based on application of this method. Therefore, relatively extensive details are provided on historical development of the method from applications in econometrics to environmental epidemiology, relevant model specification issues and estimation of parameters.

2.3.1. Short-term effects

2.3.1.1. Episode studies

According to Anderson (1999) an air pollution episode is ‘a short-term increase in ambient air pollution which is greater than would be normally expected as part of day-to-day variation’; such episodes could result in large increases in morbidity and mortality and sometimes are considered as ‘environmental disasters’. These studies rely on comparison

of health outcomes prior, during and after the occurrence of an air pollution episode (Pope, 2000). Thus a key element in the analysis of effects of episodes is to define a method for determining a control exposure period in order to estimate the occurrence of adverse health effects of interest in the absence of an air pollution episode. This will then be compared with the health effect estimates during the episode so that the relative increase will be evaluated. Some of the control methods that have been used include: period just before the episode, equivalent dates in adjacent years, post episode period and geographical control populations (Anderson, 1999).

While air pollution episode studies tend to have less rigour for confounding control and limited power to detect effects, historical episodes have demonstrated remarkably that air pollution at extreme levels can lead to substantial increases in mortality and morbidity (Anderson, 1999, Pope, 2000). The air pollution episodes in Meuse Valley, Belgium (about 60 deaths, 1930), Donora, Pennsylvania (about 18 deaths, 1948) and the London fog (about 4000 deaths, 1952) have played an important role in explaining short-term health effects of air pollution and for the subsequent public attention drawn towards air quality issues (Firket, 1936, Schrenk, 1950, Brimblecombe, 1987, Anderson, 1999). Other noticeable episodes have occurred later but with comparatively lower magnitude in most cases (Wichmann et al., 1989, Hoek and Brunekreef, 1993, Anderson et al., 1995).

Recently, air pollution episodes related to anthropogenic sources are less common but occasional episodes from natural causes such as dust storms pose risk to public health. Such episodes have occurred in several parts of the world including Australia (Merrifield et al., 2013), Asia (Higashisaka et al., 2014), Europe (Mallone et al., 2011) and North

America (Grineski et al., 2011) which are geographically prone to dust storms or whenever dust is carried into by strong wind.

2.3.1.2. Case-crossover studies

The case-crossover design was introduced by Maclure (1991) and has been widely applied in air pollution studies (Lee and Schwartz, 1999, Sunyer et al., 2000, Pope et al., 2006, Bedada et al., 2012, Bhaskaran et al., 2011, Maclure, 1991). It is particularly useful for estimating the risk of a rare acute outcome associated with short-term exposure, such as air pollution. In case-crossover design each case acts as their own control and like case-control studies (Breslow and Day, 1980) the distribution of exposure is compared between 'cases' and 'controls'. That is, exposure at the time just prior to the event (case or index time) is compared with a set of 'control' or 'referent' times that represent the expected distribution of exposure for non-event follow-up times. The design helps primarily to control confounding by subject-specific factors which do not change overtime such as ethnicity and gender.

However, ability to control for time-dependent variables depends on the method used for selection of referent times (Janes et al., 2005). For example, Bateson and Schwartz suggested that confounding of exposure by seasonal patterns could be controlled by design in the case-crossover approach by choosing control days close to event days (Bateson and Schwartz, 1999, Bateson and Schwartz, 2001). Yet, Janes et al (2005) recommend the time-stratified case-crossover design for avoiding time–trend bias and potential gain in power. In this design, referent days can be restricted to the same weekday, month and year as the event day (Janes et al., 2005). The case-crossover analysis is carried out using conditional logistic regression providing odds ratios (ORs) as effect estimates. The design

had been questioned on the grounds of efficiency and difficulty to easily allow for over-dispersion but some of these issues have been addressed exploiting its equivalence with time series method (Armstrong and Gasparrini, 2011, Lu et al., 2008).

2.3.1.3. Panel studies

In a panel study design, data are collected repeatedly on a cohort of individuals over multiple occasions. The design is particularly useful when interest is to examine changes in repeated measurements of the outcome over time in relation to exposure. It has been used in air pollution studies mainly to assess effect acute air pollution exposure on various morbidity outcomes (Roemer et al., 1998, Huang et al., 2012). Data from panel studies are usually analysed using multi-level regression (mixed model) approach when the response is Gaussian. Other alternative statistical models for analysis of such data include generalized estimating equations (GEE), generalized linear mixed models (GLMM) and generalized additive mixed models (GAMM) (Liang and Zeger, 1986, Breslow and Clayton, 1993, Lin and Zhang, 1999). The latter is useful to model data with a multi-level or spatial structure allowing incorporation of flexible non-linear relationships for some covariates as necessary.

2.3.1.4. Time series studies

A- Background to time series analysis

A time series is a sequence of observations or measurements taken over time. Each measurement or observation in the series could be an accumulation of a quantity continuously for a given duration. Examples include daily rainfall and electrocardiogram (ECG) traces from a patient. Alternatively, in a discrete time series observations are made at distinct, usually regular, time intervals. The time intervals could be relatively short (e.g.

magnetic resonance imaging (MRI) scans of the brain every second) or relatively long (e.g. daily exchange rates between Pound Sterling and US dollar).

In general, observations in a time series tend to show serial dependence over time which is sometimes referred to as autocorrelation or serial correlation. Basic statistical methods are not suited for the analysis of such data. This is because the methods fundamentally assume observations in a set of data are realizations of mutually independent random variables (Diggle, 1990, Zeger et al., 2006). Time series analysis is the methodology that deals with the complexity induced by the serial correlation in a systematic way.

Time series analysis methods for biomedical data were historically developed from applications in econometrics where the main focus was forecasting future values of quantities, for example annual gross domestic product (GDP) of a country or daily returns from an asset such as stocks. The two common features in a time series data are trend and seasonality. The former refers to the long-term tendency to increase or decrease over time. The latter refers to the systematic or periodic shorter term patterns, for example variations within the course of each year in an air pollution time series. Time series analysis methods usually aim to filter out these features in subsequent models for forecasting and estimation of parameters of interest. By filtering out the trend and seasonality attributes from the data one hopes to obtain a stationary series, a series where the mean is constant over time and the autocovariance between any two time points does not depend on the actual time points but rather the time lag between them (Diggle, 1990).

In univariate time series analysis, the auto regressive integrated moving average (ARIMA) model as introduced in Box and Jenkins is more common (Box and Jenkins, 1970). An

ARIMA model is a generalization of the ARMA model where differencing the series becomes an essential aspect, i.e., taking the difference between observations at different lags in order to achieve a stationary series. The vector autoregressive moving average (VARMA) and vector autoregressive (VAR) models are applied to fit multivariate time series models investigating relationships between two or more variables of interest (Reinsel, 1993, Lütkepohl, 1993, Johansen, 1995). Bayesian time series models have also become popular in forecasting applications as they allow integrating uncertainty in model parameters in a more flexible way (Pole et al., 1994). Another important extension to the Box-Jenkins approach (linear) is the development of non-linear time series models (Tong, 2002). Machine learning or statistical learning techniques have also been applied in time series forecasting. Classification and regression trees (CART) and nearest-neighbour classifiers are examples of machine learning applications where the data determine the form of the predictive relationship in the series unlike simple regression methods where the form is somehow pre specified (Hastie et al., 2009).

B- Time series in air pollution and health studies

In the previous section, some key methods and related references have been outlined in relation to one of the objectives of time series analysis which is forecasting. These methods have been widely applied in econometrics, finance, meteorology and engineering. Application of time series methods in the study of the health effects of air pollution is relatively recent. However, the primary interest here is parameter estimation in order to describe relationships between variables (rather than forecasting future values). In earlier air pollution studies, investigators were limited to explaining relationships between air pollution and health by simple graphical methods or comparison of mortality rates at different time periods for example before and during an air pollution episode (Carracedo-

Martínez et al., 2010). The marked health effects during severe episodes like the 1952 London fog alerted authorities and led to routine collection of data on pollutants (Black Smoke and SO_2) and health outcomes (daily counts of mortality and hospital admissions) for monitoring purposes (Anderson, 1999). As the routine data accumulated over time and computational capacity to implement complex statistical models improved, time series regression methods became extensively entertained in air pollution studies. By the early 1990s time series studies started to dominate the air pollution epidemiology literature as making use of routinely collected monitoring data provided a cheaper alternative (Schwartz et al., 1996, Touloumi et al., 2004, Katsouyanni et al., 2009, Anderson, 2009).

Time series methods can also provide considerable power for detecting short-term health effects of air pollution. The power depends on the length of the series and average number of daily events as the method evaluates associations between daily variations in number of health events and daily variations in air pollution exposure (Bhaskaran et al., 2013, Winquist et al., 2012). Time series regression is a frequently applied method in estimating such short-term effects and a brief account of the methodology is outlined below based on daily mortality as the outcome and daily air pollution level as the exposure.

Outcome distribution

Daily mortality counts are the most commonly studied health outcomes in air pollution studies (Anderson, 2009, Rückerl et al., 2011). The daily counts are small relative to the general population. The Poisson process could represent the underlying generating mechanism for the daily counts. For a Poisson model with expected daily mortality counts μ, the probability of y daily counts is given by

$$P(Y = y \mid \mu) = \frac{\mu^y}{y!} e^{-\mu}, \qquad y=0,1,2,3,\ldots. \tag{2.1}$$

with variance of Y equal to its expected value, μ.

An important assumption in a Poisson model such as given in (2.1) is the underlying mortality rate or risk is constant (i.e., staionarity of the series). However for the daily mortality series, the expected value μ may appear to vary with time due to time varying predictors of mortality in addition to the main exposure interest, air pollution concentrations. Long-term time trends, seasonality, weather, calendar days and epidemics like influenza are some examples that could affect the expected daily mortality counts with time. It is worth noting that while other individual risk factors such as smoking and diet can affect mortality in general, their effect on the expected daily mortality counts (μ) is assumed to be negligible. This is fair because the model is set up in such a way that the unit of analysis is based on days and the distribution of such individual factors does not change much from one day to another. To reiterate, controlling for factors that change with time is more important under the proposed model.

Relative risk model

Given that the outcome of interest is daily mortality count with the above mentioned properties, a Poisson regression model would be appropriate to study their association with daily air pollution concentrations taking into account potential time varying confounders. Such a relative risk model can be represented in the generalized linear models (GLM) (McCullagh and Nelder, 1989) framework for exponential family distribution as follows:

Response distribution: $Y_t \sim \text{Poisson}(\mu_t)$, $E(Y_t) = \mu_t$ (2.2)

Linear predictor: $\eta_t = \beta_0 + \beta_1 X_{t1} + ... + \beta_p X_{tp}$

Link function: $\log(\mu_t) = \eta_t$

where Y_t is mortality count on day t, μ_t expected number counts on day t, $X_{t1}, ..., X_{tp}$ are time varying predictors of mortality counts, $\beta_1, ..., \beta_p$ are unknown coefficients of the predictors.

Daily mortality counts and air pollution series exhibit serial dependence due to seasonality, weather and long-term time trends. Data are in general available for some of the potential confounders including temperature, relative humidity and epidemics such as influenza which can be adjusted for directly in the above model. But control of seasonality and long-term trends requires indirect strategies that involve adjusting for the time itself. Methods based on stratifying by time and fitting periodic functions using sine and cosine functions of time itself can be considered to capture seasonal patterns but may not be adequate (Bhaskaran et al., 2013). A more common strategy in the literature is to use a smooth function of time in the model (Dominici, 2004, Peng et al., 2006, Touloumi et al., 2006). Thus the linear predictor in the above model can be extended as follows:

$$\log(\mu_t) = \beta_0 + \beta_1 X_{t1} + ... + \beta_p X_{tp} + f(t; \lambda) \quad (2.3)$$

where f is a smooth function of time and λ is the smoothing parameter which controls how rough or smooth f should be.

Smoothing functions

The smooth function f is usually represented using flexible regression splines such as penalized splines. This representation of the linear predictor by adding smooth terms leads to what is known as generalized additive modelling (GAM) (Hastie and Tibshirani, 1990).

GAMs are sometimes referred to as semi-parametric models because they allow to incorporate both strictly parametric specification for some covariates as well as a more flexible specification (using smooth functions) with no detailed parametric representation for other covariates (Wood, 2006, Peng and Dominici, 2008). In general, flexibility is achieved by fitting spline functions of time by dividing the time period into subintervals and fitting, usually, a cubic polynomial in each interval. The resulting curves are then joined smoothly at the end of each subinterval (which is known as a knot). When both the smoothing function (*f)* and its second derivative are continuous over the entire series and *f* is restricted to be linear at both extremes of the series, then *f* is referred to as 'natural cubic spline'. The smoothness of a natural spline depends on the number knots (or alternatively on the number of df allowed for *f*); larger knots result in rough or 'wiggly' fit and fewer knots result in a smoother fit.

Another common alternative method of smoothing is a penalized regression spline. This method is based on a compromise between minimizing both bias and variance. This is aimed to be achieved by adding a roughness penalty term to the usual residual sum of squares minimization (least squares) objective. That is, the aim is shifted towards minimizing the penalised sum of squares

$$\sum_{i=1}^{n}\{Y_i - f(x_i)\}^2 + \lambda\int_a^b \{f''(u)\}^2\, du$$

instead of just the usual least squares

$$\sum_{i=1}^{n}\{Y_i - f(x_i)\}^2$$

for any twice differentiable function *f* on the interval [a, b] and a smoothing parameter λ.

Other smoothing methods that have been considered in the literature include locally weighted regression smoothing (lowess), kernel smoothing and moving average (median) smoothing but will not be explored further here (Speckman, 1988, Schwartz et al., 1996, Wong et al., 2002).

Parameter estimation

Literature that provide detailed derivation of parameter estimates for model (2.3) can be found elsewhere (Dominici et al., 2004, Wood, 2006, Peng et al., 2006) and an example taken from Peng et al. (2006) is attached in Appendix B. The derivation, which uses iteratively reweighted least squares (IRLS) method, is given for both natural splines (NS) and penalised splines (PS) smoothing approaches. Sensitivity analyses have shown that the amount of smoothing would have more consequences on the resulting model fit than the method of smoothing used, for example NS versus PS (Katsouyanni et al., 2009, Touloumi et al., 2006). Thus choosing the smoothing parameter requires considerable attention and there are two general approaches to this problem. The first, including generalized cross validation (GCV) and Akaike information criteria (AIC) values (Akaike, 1974), is a data driven approach (Schwartz et al., 1996, Wood, 2006). A second approach is to use a specific df based on *a priori* information on biological grounds or previous studies (Schwartz et al., 1996, Katsouyanni et al., 2009).

Other model extensions

For the Poisson regression model given in (2.3) above, an important assumption is equality of the variance and the mean. But in practice the variance could be greater than the theoretical value implied by the estimated mean for count data. Overdispersion is the term used to refer to this phenomenon and its presence in the data may result in smaller model

based estimates for variances (standard errors). A common (quasi-likelihood) approach to deal with overdispersion is to rescale the standard errors using for example a scale parameter estimated by dividing the Pearson chi-square statistic with the residual df (McCullagh and Nelder, 1989). Another approach would be to use a more suitable distribution than the Poisson, for example, the Negative binomial distribution (Zewotir and Ramroop, 2009, Hammami et al., 2013). For daily mortality count data, some authors have reported that overdispersion is modest (Jordan et al., 1997, Peng and Dominici, 2008).

Air pollution on a single day could be related to health on a concurrent or a lagged day as well as distributed over a number of days. Thus the single lag model representation in model (2.3) can be extended to include distributed lags of interest. The distributed lag models have also been used as a method to support the argument against the 'harvesting only' effect of air pollution (Bell et al., 2004). Under the harvesting (mortality displacement) theory, only a group of very frail individuals' mortality is associated with air pollution. In other words air pollution studies are picking up signals from the frail persons who would have died in a few days' time anyway (Zeger et al., 1999). In the second Air Pollution and Health: A European Approach (APHEA 2) study investigators used a distributed lag model (of up to 40 days delay) for examining association of mortality and PM_{10} and argued that short-term air pollution effects are not principally due to harvesting only (Zanobetti et al., 2002).

Modern time series studies are based on data from several locations, for example, cities, countries or regions. Compared to single location studies, multi-location studies increase power for detection of air pollution effects across locations. They also allow assessment of heterogeneity in a formal way. While theoretically conceivable to specify a single multi-

level model for data with such structure, in practice it is avoided. Instead multi-location time series studies apply a two-stage approach; first relative risk estimates are obtained using models such as presented in (2.3) above for each location and the individual estimates are then combined using meta-regression techniques (Katsouyanni et al., 1997, Touloumi et al., 2004). Two-stage Bayesian hierarchical modelling framework has also been successfully applied for combining estimates across locations in air pollution studies (Dominici et al., 2000a, Huang et al., 2005, Katsouyanni et al., 2009). This approach allows investigation of posterior estimates for the true location specific relative risks. Assessing the posterior distribution of the between-location variance also helps to better understand the level of heterogeneity compared to a point estimate of the variance. Posterior distributions can be estimated using Markov chain Monte Carlo (MCMC) methods (Tierney, 1994, Gilks et al., 1996, Peng and Dominici, 2008).

After fitting any statistical model, checking the model in light of the underlying assumptions is the next important step. Plots for residual and fitted values over time are useful diagnostic tools. These are helpful for checking outliers, temporal patterns that remain in the model and to compare models which better pick up seasonal patterns (Schwartz et al., 1996, Bhaskaran et al., 2013). Model checking becomes even more crucial for time series models in air pollution studies as there are several decisions to be made with respect to selection of the method and amount of smoothing, lag choice and confounder model to name but a few. In general, whether or not such decisions have considerable influence on relative risk estimates should always be checked in sensitivity analyses (Bhaskaran et al., 2013, Katsouyanni et al., 2009, Schwartz et al., 1996).

Implementation

Time series studies are one of the most frequently applied methods in the study of short-term health effects of air pollution and subsequent setting of air quality standards (Anderson et al., 2007, Bhaskaran et al., 2013, Bell et al., 2004). They have been implemented using GLMs with parametric splines, for example, natural cubic splines (Katsouyanni et al., 2009) or GAMs with non-parametric splines, for example, smoothing splines (Dominici et al., 2003b). The models are based on linear (with no threshold assumption) as this has been shown to be the case for particulate matter pollution effects (Schwartz et al., 2001, Samoli et al., 2005, Anderson, 2009, Vedal et al., 2003).

A number of statistical software programmes can fit both the GLMs and GAMs but the R software seems the most popular in air pollution studies. The GAM package by Hastie and the MGCV package by Wood are two of the commonly used packages to fit GAMs in the R environment (Hastie, 2013, Wood, 2014).

The Air Pollution and Health: A European and North American Approach (APHENA) study can be considered as one of the 'state-of-the-art' time series studies (Katsouyanni et al., 2009). This international study presented rich data from several cities in Europe and North America. It also provided a methodological guideline based on several sensitivity analyses and experiences of experts from the two continents. Hence, the time series methodology in this thesis is mostly adapted from the APHENA study protocol with additional sensitivity analyses as deemed necessary.

2.3.2. Long-term effects

2.3.2.1. Cohort studies

In a cohort study a group of individuals with some shared characteristics or experience are identified and each cohort member followed up over a period of time or until an event of interest (e.g. mortality or morbidity) occurs. Then the rate of occurrence of the event is compared between groups of cohort members classified by different exposure levels (e.g. exposed versus unexposed or for a unit increase in average exposure concentration). When data are collected in this way (prospectively) after the study has been set up, it is referred to as a prospective cohort study. Alternatively retrospective cohort studies can be set up using pre-existing data on events and exposure which had been collected over a certain period of time in the past.

The health effects of long-term air pollution exposure are usually investigated in cohort studies. Although the aim of conducting cohort studies is to estimate long-term effects, this is not necessarily discernible from those of short-term effects. That is health outcomes observed in a cohort study may be due to chronic as well as acute exposures combined (Dockery et al., 1993, Künzli et al., 2001, Krewski et al., 2005). The outcome of interest could be similar to those studied in short-term effects (all-cause or cause specific mortality and/or morbidity). However, exposure is assigned based on some cumulative measure (e.g. annual average concentrations) and ensuring exposure variation heavily relies on variability between different locations, i.e., spatial variability. The common statistical tool used to analyse air pollution cohort studies is the Cox proportional hazards model (Cox, 1972). In addition to estimating long-term effects, such modelling approach allows control for potential confounding by individual level factors including but not limited to smoking, demographic and socio-economic variables.

Some cohort studies in the US and UK have found comparable associations between particulate matter pollution and adverse health effects. Earlier, the Harvard Six Cities study reported the adjusted rate ratio between the most and least polluted cities for fine particles as 1.26 (95% CI: 1.08, 1.47) for all-cause mortality (Dockery et al., 1993). And later, the American Cancer Society (ACS) study reported an adjusted relative risk ratio of 1.17 (95% CI: 1.09, 1.26) for the same outcome and exposure (Pope et al., 1995); an extended reanalysis of the ACS has been published in 2009 providing consistent evidence on the adverse health effects of fine particles (Krewski et al., 2009). A study on an English and Welsh cohort also reported an adjusted hazard ratio (HR) for all-cause mortality of 1.20 (95% CI: 1.04, 1.38) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ (Tonne and Wilkinson, 2013). In relation to air pollution associated morbidity outcomes, a large English cohort study reported an adjusted hazard ratio of 1.06 (95% CI: 1.01–1.11) for incidence of heart failure per an interquartile range change in PM_{10} (Atkinson et al., 2013). The study did not find evidence of association for other cardiovascular outcomes in contrast to some previous studies (Miller et al., 2007, Puett et al., 2009).

2.3.2.2. Cross-sectional studies

Cross-sectional study designs have also been used to study long-term effects in earlier (Pope, 2000) as well as more recent (Elliott et al., 2007, Forbes et al., 2009, Berhane et al., 2011) air pollution studies. Briefly, a cross-sectional study can be applied for example to compare annual mortality rates (adjusted say for age and sex) between different locations based on their annual mean air pollution levels; this is easily facilitated by fitting regression models.

2.4. Other common issues in air pollution studies

A detailed discussion on important methodological issues in the study of health effects of air pollution was provided by Berhane et al. (2004) albeit in the context of long-term effects. Most of the issues raised, however, apply to short-term health effect studies and still remain active areas of research. In relation to the issues of exposure metrics for particulate matter pollution, the aim is to find a biologically relevant metrics and this has been looked at in two ways. One focused on investigation of various temporal averaging times (Darrow et al., 2011) while another explored specific components and their source apportionment (e.g. primary versus non-primary) in terms of their relative importance in predicting health outcomes (Atkinson et al., 2014).

The development of multi-pollutant approach may facilitate determination of the relative importance of pollutants or sources and estimation of the overall health effects in relation to a complex pollutant mixture. This in turn is hoped to shape regulation policies into a multi-pollutant framework where standards for several pollutants could be set simultaneously (Dominici et al., 2010). However, fitting multi-pollutant models poses challenges because of non-trivial amount of correlation between pollutants, potential interaction between them and the relatively small health effects that need to be detected to name but a few (Tolbert et al., 2007). Despite this, health effects of particulate pollution have been shown to persist in multi-pollutant models although with reduced effect estimates and at times weaker evidence compared to single pollutant models (Le Tertre et al., 2002, Samet et al., 2000, Tolbert et al., 2007, Bhaskaran et al., 2011). Recent studies have been developing a more comprehensive approach to multi-pollutant metrics, where a summary reflecting the composition and relative importance of the pollution mixture can

be used in epidemiological models (Oakes et al., 2014, Sun et al., 2013, Vedal and Kaufman, 2011).

Ecological bias is another common issue related to the design of epidemiological time series studies. This can be regarded as the bias due to differences in regression lines between models based on daily aggregated data and that of individual data from which the aggregated data was compiled (Berhane et al., 2004). The impact of such ecological bias on risk estimates has been shown to be negligible at least for particulate pollution in the presence of reasonable spatial homogeneity among monitors from which air pollution exposure measurements were taken (Shaddick et al., 2013).

Another recurring issue in epidemiological studies of the health effects of air pollution is exposure measurement error. In general classical measurement error results in biased (towards the null) effect estimates in regression while such bias is not expected for Berkson type error (Armstrong, 1998). Uncertainty is inevitable with regard to how well daily air pollution measurements represent the mean daily exposure for a given population or over a given geographical location and effect of measurement error has been a subject of considerable research (Zeger et al., 2000, Dominici et al., 2000b, Sheppard et al., 2005, Goldman et al., 2011, Szpiro and Paciorek, 2013, Dionisio et al., 2014). Studies have suggested that measurement error in air pollution attenuates health effect estimates particularly for data from a single monitoring station; however such attenuation tends to be little if any as the number of monitoring stations (to calculate average exposure) over the geographical region of interest increases (Sheppard et al., 2005, Butland et al., 2013).

2.5. Summary

Following marked air pollution episodes such as the 1952 London smog, earlier episode studies provided compelling evidence for a causal link between air pollution and mortality and morbidity with larger effect sizes. Such a large effect was observed at very high levels of pollution, i.e., higher doses. More recently, evidence from time series studies and case-crossover studies indicate significant albeit small adverse health effects at the current relatively much lower pollution levels, i.e., lower doses. Together, the studies and associated results so far reflect two important aspects of exposure: the amount (dose) of exposure and the duration of exposure. This thesis hypothesised that, in addition to the amount (dose) and the duration of exposure, the pattern in which exposure was experienced and/or the rate at which exposure dose was changing could be important in determining health effects. Subsequent chapters present some theoretical and empirical results based on investigation of the proposed hypothesis in the context of time series modelling framework.

3. STATISTICAL ISSUES IN RELATION TO USING CHANGES IN AIR POLLUTION EXPOSURE BETWEEN SUCCESSIVE DAYS AS EXPOSURE METRIC IN TIME SERIES STUDIES

3.1. Exposure metrics in air pollution studies

In environmental epidemiology, exposure metrics simply refers to the summary variable used to characterise exposure for a certain pollutant. Various temporal metrics have been considered in epidemiologic time series studies of air pollution and acute health effects. These metrics in most cases are averages calculated over some relevant time period presumed to be related with the health effect of interest. Suppose $X = \{x_1, x_2, x_3, ...x_n\}$ represent n measurements taken in a day and assume they are given in ascending order with minimum and maximum at x_1 and x_n respectively. For example, if air pollution is measured every quarter of an hour in a city background monitor then there will be n=24x4=96 measurements per day. Thus, a typical approach to calculate an exposure metrics on day t would be to take the average of the measurements throughout the day as:

$$X_t = \frac{\sum_{i=1}^{n} x_i}{n} \qquad (3.1)$$

Particulate matter pollution is an example represented by such daily (24-hour) average metrics. For other pollutants, running mean concentrations are preferred than the daily (24-hour) average exposure. Carbon monoxide and ozone metrics, for example, are based on daily 8 hour running means (Defra, 2007). It is then usually hypothesized that variability in exposure concentrations across days (X_t) may be important to explain the variations in daily health outcomes. Beyond such standards, some studies have considered sub daily temporal metrics for the criteria air pollutants and investigated the effects of hourly variations in exposure (Bhaskaran et al., 2011). The selection of the best exposure metrics for a pollutant mainly depends on its biological relevance and good representation of average population exposure; i.e., more strongly correlated with average population exposure compared to other metrics (Birnbaum, 2010, Darrow et al., 2011).

In addition to daily variations in absolute concentrations, variations in daily changes in exposure concentrations between successive days had also been proposed to have potential effects on health (Ayres, 2007). This hypothesis is primarily based on biological grounds that physiological systems respond to changes or rate of changes of a stimulus. It has been investigated in a time series study of temperature and mortality (Guo et al., 2011) and cross-sectional study of temperature and asthma admissions (Nastos et al., 2006) elsewhere and Chapter 4 will examine this for particulate pollution. The present chapter provides an overview of some statistical modelling and other issues related to using the change or rate of change metrics for PM_{10} in time series modelling context which have not been addressed previously. This will be supplemented by three simulation studies in relation to the main topics covered in the chapter, namely investigation of measurement error, comparison of models based on alternative change metrics and the impact of missing data handling methods on properties of risk estimates.

3.2. Definition and properties of the change metrics

3.2.1. Definition

The change metric, *delta PM_{10}* (ΔPM_{10}), was defined as the change in mean absolute PM_{10} concentrations between successive days as shown in equation 3.2.

$$\Delta P_t = P_t - P_{t-1} \qquad (3.2)$$

where P_t and P_{t-1} represent PM_{10} concentrations on day t and previous day t-1 respectively.

3.2.2. Measurement error and statistical properties

Measurement errors are commonly classified in the environmental epidemiology literature as classical and Berkson types (Zeger et al., 2000). Measurement error in air pollution can arise due to, for example, imprecision of measuring devices and location of monitoring

stations. Risk estimates will be affected differently depending on the error type present (Goldman et al., 2011). In classical type error the individual measurements vary around the true exposure with expectation equal to the true value. In Berkson type error a group of subjects is assigned the same average (proxy) value and true exposures vary around this proxy with expectation equal to this group value (Armstrong, 1998). Exposure measurement error (for continuous variables) or misclassification (for categorical variables) has been shown to result in biased risk estimates if classical type and reduced power whether classical or Berkson in epidemiological studies (Armstrong, 1998, Sorahan and Gilthorpe, 1994, Goldman et al., 2011, Butland et al., 2013). Zeger et al. (2000) argued that air pollution measurements could be prone to mixture of both classical and Berkson errors with the latter being predominant.

This section demonstrates the impact of pure classical measurement error on the mean and variance properties of the absolute and delta PM_{10} metrics. Such comparison would be useful for example if the delta metrics were to be considered as an alternative to the absolute metrics.

Errors in exposure measurements may comprise random as well as systematic component as shown below in equations 3.3 and 3.4 respectively:

$$P_{observed} = P_{true} + \varepsilon \tag{3.3}$$

$$P_{observed} = P_{true} + \theta + \varepsilon \tag{3.4}$$

where $P_{observed}$ is the observed exposure with some measurement error ε or $\theta + \varepsilon$, P_{true} is the true exposure and θ is the amount of systematic error; and the true exposure is

uncorrelated with the random error ε and $\varepsilon \sim N(0,\sigma_\varepsilon^2)$ under the classical measurement error framework.

Systematic errors, in general, bias the expected value but do not affect variance estimate of measurements. In the case of this study, unlike the absolute metrics, systematic error would have no influence on the expectation of delta as the bias cancels out when differences between consecutive absolute concentrations are taken. On the other hand, one would expect the variance of delta to depend on the first-order autocorrelation of the "true" absolute metric series irrespective of whether systematic and/or random measurement error present. This is because delta is defined as the difference between two random variables namely lag 0 and lag 1 of pollution exposure. These properties are summarised in Table 3.1 using notations $P=P_{observed}$ and $P^*=P_{true}$ for observed and true ambient air pollution concentrations respectively.

Table 3.1: Properties of absolute and delta metrics in the presence of random and systematic error

Model	**Expected value**	**Variance**
Absolute metrics		
1. $P = P^* + \varepsilon$	$E(P) = E(P^*)$	$V(P) = V(P^*) + V(\varepsilon)$
2. $P = P^* + \theta + \varepsilon$	$E(P) = E(P^*) + \theta$	$V(P) = V(P^*) + V(\varepsilon)$
Delta metrics on day t (for both 1 and 2)		
$\Delta P_t = (P_t^* - P_{t-1}^*) + (\varepsilon_t - \varepsilon_{t-1})$	$E(\Delta P_t) = E(P_t^* - P_{t-1}^*) = 0$	$V(\Delta P_t) = V(P_t^* - P_{t-1}^*) + V(\varepsilon_t - \varepsilon_{t-1})$

And the first-order autocorrelation $\rho(1)$ can be calculated as

$$\rho(1) = \gamma(1) \Big/ \gamma(0)$$

where $\gamma(1) = E[(P_t^* - E(\mathrm{P}_t^*))(P_{t-1}^* - E(\mathrm{P}_t^*))]$ is the first-order auto-covariance and $\gamma(0) = E[(P_t^* - E(\mathrm{P}_t^*))^2]$ is the variance.

The results above imply that application of the delta metrics as well as interpretation of risk estimates from it should be looked at cautiously in light of the potential effect of measurement error. These theoretical arguments are also supported by an empirical study using simulation and the results are presented in Appendix C (Simulation study I).

This section merely raised the issue of measurement error in the context of application of the delta metrics and highlighted the potential impact on the descriptive properties of the metrics. A full treatment of the issue would extend the present analysis by adding autocorrelation in the errors, including classical and Berkson type errors with the ensuing implications on properties of risk estimates and study power as well as developing appropriate adjustment methods where bias is detected.

3.3. Patterns, correlations and interpretation for delta and absolute metrics

3.3.1. Differences in patterns and correlations

As the new delta metrics are defined based on simple algebraic subtraction of consecutive pollutant values, it might give the impression that both the original and new metrics should have similar patterns over time. This may not be the case, however, as the two quantities differ in how they represent exposure. To make this point clearer, 24 daily observations for pollution levels (say for PM) were generated and the corresponding delta PM values were calculated. The data were simulated artificially so that they represent the possible pattern

combinations in a series. The patterns of absolute and delta PM measures are explored under four scenarios (over a period of time):

A. increasing PM levels (increment not constant from day to day)
B. decreasing PM levels (decline not constant from day to day)
C. constant increment of PM from day to day over a period of time
D. constant decline from day to day over a period of time

In order to understand the similarities and/or differences between the patterns of the absolute and delta metrics, it will be useful to explore through each of the above four cases by plotting the data series. The ranges for the four cases A, B, C and D can be seen by referring to Figure 3.1 below. The correlation between PM and delta PM was not strong at 0.29 (Table 3.3). In all cases, declines in absolute PM from one day to the next are marked by corresponding negative delta PM values.

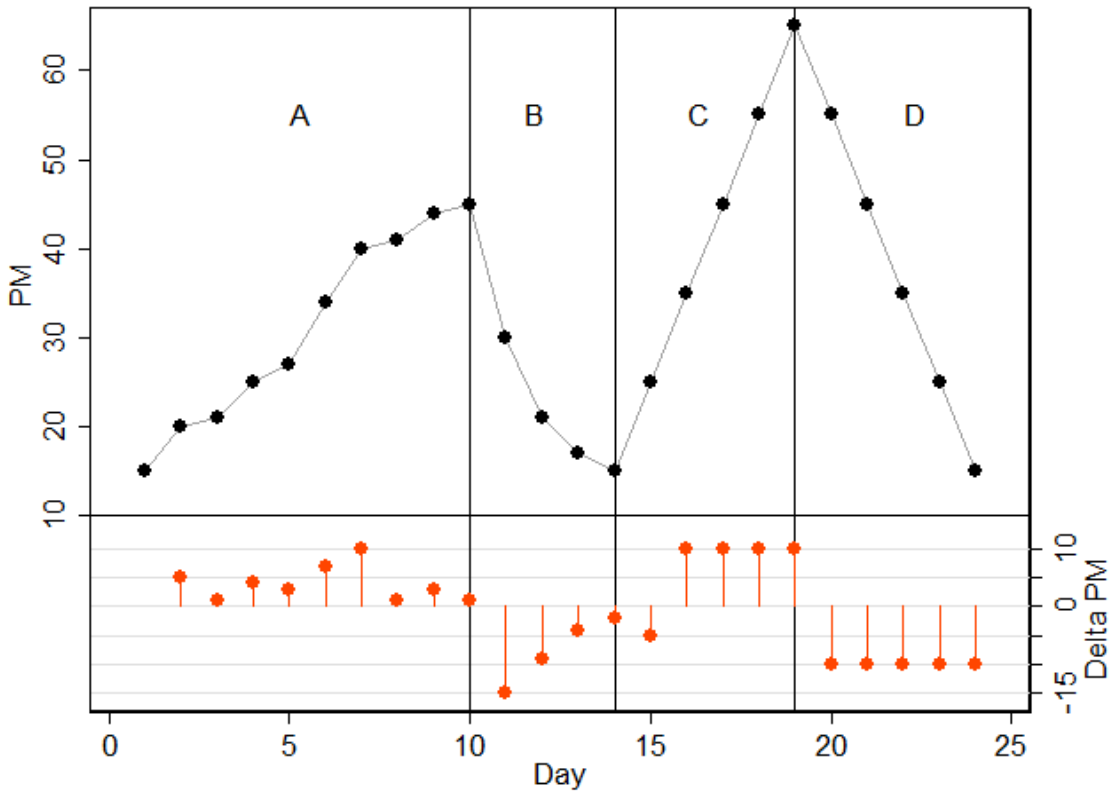
Case A: Delta PM values indicated changing patterns (increments and decrements) although the absolute PM levels were consistently increasing over the given period.

Case B: Delta PM values showed increasing patterns although the absolute PM levels were declining consistently over the given period.

Case C: Absolute PM levels were set to increase by a fixed amount (10 units) from day to day which resulted in constant delta PM values.

Case D: Absolute PM levels were set to decrease by a fixed amount (10 units) from day to day which again resulted in constant delta PM values albeit negative.

Figure 3.1: Possible pattern relationships between PM and delta PM for simulated data

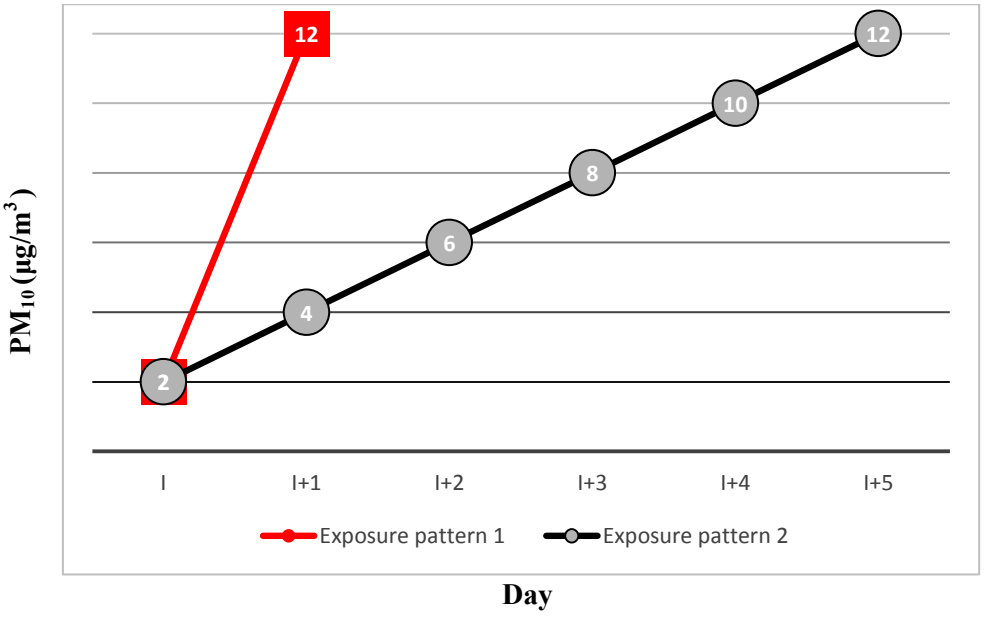


It is clear (from simple observation of Figure 3.1 above for example) that delta PM should not be expected to show similar patterns with the absolute PM measurements. Perhaps they are measuring different aspects of exposure to PM pollution. This could be explained by using some analogy between the definitions of delta and velocity. Velocity is defined as the rate of change of displacement ($V=S_2-S_1/T_2-T_1$ where V is velocity S, is displacement and T is time) while delta in our case is the change in pollution level per day. If we consider the change in time as one unit in the former case, then it is clear that delta and absolute measurements differ in similar way velocities and displacements differ. Hence, delta could be defined as the rate of change of pollution exposure per day.

3.3.2. Interpretation

Risk estimates for the absolute metrics from a time series analysis are usually reported as percentage increases in adverse health outcome of interest per unit increase in pollution concentration. On the other hand, the corresponding risk estimates for delta should be interpreted as percentage increases in health risk per unit increase in the *change* or *rate of change* of pollution. The fact that delta can potentially measure something the absolute metric doesn't is discussed using Figure 3.2. Consider two exposure scenarios where pollution increased from 2 to 12 μg/m^3 in one day (illustrated as exposure pattern 1) and over six days by 2 μg/m^3 each day (illustrated as exposure pattern 2). A conventional time series model based on absolute metrics relates both scenarios with the same relative risk, i.e., the relative risk per 10 μg/m^3 (12-2=10 μg/m^3) remains the same. The corresponding rates of changes were 10 and 2 μg/m^3 per day under exposure patterns 1 and 2 respectively. Thus supplementing the conventional metric based model with delta could help to assess the possible health effects of such changes or rate of changes in air pollution.

Figure 3.2: Exposure pattern scenarios over the course of six days



3.4. Modelling options for delta and the identification problem

Often the short-term health effects of absolute PM_{10} are studied using a Poisson generalized additive model (GAM) in the time series framework; for some health outcome Y and pollutant P at single lag *l* on day t, such model can be given as

$$\mathrm{Log}[\mathrm{E}(\mathrm{Y}_t)] = \alpha + \beta \mathrm{P}_{t-l} + \sum_{i=1}^{k} \mathrm{f}_i(\mathrm{X}_{ti}) \qquad (3.5)$$

where $f_i(X_{ti})$ represent smooth functions of confounders (X_{ti}), α is the intercept and β is the log relative risk of the outcome per unit increase in P (Hastie and Tibshirani, 1986, Dominici et al., 2002, Katsouyanni et al., 2009).

Hence, an intuitive model to study the effect of change controlling for absolute measure from which the change was calculated would be:

$$\eta_t = \beta_1^0 \mathrm{P}_t + \beta_2^0 \mathrm{P}_{t-1} + \beta_3^0 \Delta \mathrm{P}_t + \ldots \qquad (3.6)$$

where $\eta_t = \mathrm{Log}[\mathrm{E}(\mathrm{Y}_t)]$, $\Delta \mathrm{P}_t = \mathrm{P}_t - \mathrm{P}_{t-1}$, t=2, 3, 4..., N and ignoring intercepts and confounders.

Nevertheless, P_t , P_{t-1} and ΔP_t are in general collinear and the model is non-identifiable; despite being intuitive to specify it appears to be an overparmetrised one. In a non-identifiable model, different model structures result in equivalent observations. According to Casella and Berger "a parameter θ for a family of distributions $\{f(x \mid \theta) : \theta \in \Theta\}$ is identifiable if distinct values of θ correspond to distinct pdfs. That is, if $\theta \neq \theta'$, then $f(x \mid \theta)$ is not the same function of *x* as $f(x \mid \theta')$" (Casella and Berger, 2002). The parameter θ in this definition can also be a vector (of parameters).

Expanding and rearranging model 3.6 as shown below indicates it can equivalently be modelled using only two parameters say β_1 and β_2 implying redundancy of the third coefficient β_3^0.

$$\begin{aligned}\eta_t &= \beta_1^0 \, P_t + \beta_2^0 \, P_{t\text{-}1} + \beta_3^0 \Delta P_t + \ldots \\ &= \beta_1^0 \, P_t + \beta_2^0 \, P_{t\text{-}1} + \beta_3^0 (P_t - P_{t\text{-}1}) + \ldots \\ &= (\beta_1^0 + \beta_3^0) P_t + (\beta_2^0 - \beta_3^{'0}) P_{t\text{-}1} + \ldots \\ &= \beta_1 P_t + \beta_2 P_{t\text{-}1} + \ldots\end{aligned}$$

3.5. Simple identifiable models for delta

Depending on the aim of the study model 3.5 can be adapted to model effect of the change metrics as follows:

$$\eta_t = \beta \Delta P_t + \ldots \quad (3.7)$$

$$\eta_t = \beta_1^{'} P_t + \beta_2^{'} \Delta P_t + \ldots \quad (3.8)$$

$$\eta_t = \beta_1^{''} \Delta P_t + \beta_2^{''} P_{t\text{-}1} + \ldots \quad (3.9)$$

$$\eta_t = \beta_1^{'''} ((P_t + P_{t\text{-}1})/2) + \beta_2^{'''} \Delta P_t + \ldots \quad (3.10)$$

where $\eta_t = \text{Log}[E(Y_t)]$, $\Delta P_t = P_t - P_{t-1}$, t=2,3,...,N and ignoring intercepts and confounders.

These specifications can be obtained by constraining model 3.6 such that $\beta_1^0 = \beta_2^0 = 0$ for (3.7), $\beta_2^0 = 0$ for (3.8), $\beta_1^0 = 0$ for (3.9) and $\beta_1^0 = \beta_2^0$ for (3.10).

The first model 3.7 can be used to study the single effect of delta without controlling for any absolute metric. Models 3.8, 3.9 and 3.10 can be used to study the effect of delta that is in addition to the current, lagged and average exposures respectively.

3.6. Implications of delta models in time series context

Although models 3.7-3.10 above enable estimation of delta effects, models 3.8-3.10 are apparently equivalent. The merit of these models thus relies on their convenience for biological interpretation rather than mathematical novelty. The latter is not an added value of the delta models because all their parameters can be obtained from a conventional unconstrained distributed lag (UDL) model as described in the next section.

3.6.1. Equivalence of the delta models with UDL model

Let P_t represent pollution on day t, P_{t-1} pollution on the previous day and Y_t the count on day t for the health outcome of interest. A conventional unconstrained distributed lag (UDL) model with lags 0 and 1 for the pollutant P (ignoring terms not in P_t or $P_{t-1)}$ can be specified as

$$\eta_t = \beta_1 P_t + \beta_2 P_{t-1} + ... \qquad (3.11)$$

Now the delta models given above in 3.8-3.10 can be expanded as follows (ignoring terms not in P_t, P_{t-1} or ΔP_t):

$$\begin{aligned} \eta_t &= \beta_1' P_t + \beta_2' \Delta P_t + ... \\ &= \beta_1' P_t + \beta_2' (P_t - P_{t-1}) + ... \\ &= (\beta_1' + \beta_2') P_t + (-\beta_2') P_{t-1} + ... \end{aligned} \qquad \text{for (3.8)}$$

$$\begin{aligned} \eta_t &= \beta_1'' \Delta P_t + \beta_2'' P_{t-1} + ... \\ &= \beta_1'' (P_t - P_{t-1}) + \beta_2'' P_{t-1} + ... \\ &= \beta_1'' P_t + (\beta_2'' - \beta_1'') P_{t-1} + ... \end{aligned} \qquad \text{for (3.9)}$$

$$\eta_t = \beta_1'''((P_t + P_{t-1})/2) + \beta_2'''\Delta P_t + \ldots$$
$$= \frac{\beta_1'''}{2} P_t + \frac{\beta_1'''}{2} P_{t-1} + \beta_2'''(P_t - P_{t-1}) + \ldots$$
$$= (\frac{\beta_1'''}{2} + \beta_2''')P_t + (\frac{\beta_1'''}{2} - \beta_2''')P_{t-1} + \ldots \quad \text{for (3.10)}$$

Therefore equivalence of models 3.8, 3.9 and 3.10 with 3.11 can then be established if

$$\beta_1 = \beta_1' + \beta_2' \text{ and } \beta_2 = (-\beta_2') \tag{3.12}$$

$$\beta_1 = \beta_1'' \text{ and } \beta_2 = (\beta_2'' - \beta_1'') \tag{3.13}$$

$$\beta_1 = \left(\frac{\beta_1'''}{2} + \beta_2'''\right) \text{and } \beta_2 = \left(\frac{\beta_1'''}{2} - \beta_2'''\right) \tag{3.14}$$

3.6.2. Equivalence between delta models

Equivalence between models that include delta in addition to the absolute metrics at lags 0, 1, and their average (i.e., average of lags 0-1) easily follows from rearranging 3.12, 3.13 and 3.14 shown above.

There are of course other potential models (other than 3.7-3.10) that could be considered but these were proposed on the grounds of model parsimony and ease of interpretation. Potential alternative specifications for delta and their implications are discussed in the next section supplemented by a simulation study when relevant.

3.7. Alternative specifications for identifiable delta models

In section 3.5 above simple models to assess the relationship between the change metrics and a health outcome of interest were proposed. And in section 3.6 it was established that the conventional UDL model and those models involving delta in addition to lags 0, 1 or average of lags 0 and 1 are basically equivalent. A few further options could however be explored in order to obtain alternative delta metrics which can perhaps break such equivalence and hence achieve distinct delta models that could provide relatively better description of the data. Some alternative specifications for delta which can help to achieve this objective include

1. substituting delta with its absolute value
2. setting negative delta values to 0, i.e., taking maximum(delta, 0)
3. using a relative measure of delta instead of the absolute delta

in the models proposed previously (3.8-3.10) or adding these alternative delta metrics in model (3.11). Hence, the resulting models can be summarised as shown below in 3.15-3.18.

$$\eta_t = \beta_1^{(1)} P_t + \beta_2^{(1)} P_{t-1} + \beta_3^{(1)} |\Delta P_t| + ... \quad (3.15)$$

$$\eta_t = \beta_1^{(2)} P_{t-1} + \beta_2^{(2)} |\Delta P_t| + ... \quad (3.16)$$

$$\eta_t = \beta_1^{(3)} P_{t-1} + \beta_2^{(3)} Max(\Delta P_t, 0) + ... \quad (3.17)$$

$$\eta_t = \beta_1^{(4)} P_{t-1} + \beta_2^{(4)} R\Delta P_t + ... \quad (3.18)$$

where $\eta_t = \text{Log}[E(Y_t)]$, $|\Delta P_t|$ is the absolute value of delta, $Max(\Delta P_t, 0)$ is the maximum of delta and zero and $R\Delta P_t$ (relative delta) measures the relative change in pollution and was defined as:

$$R\Delta P_t = \Delta P_t / P_{t-1} \qquad (3.19)$$

The above metrics and related models could then be appraised based on description of (a) ease of interpretation of parameter estimates (b) how well they represent the pattern of or correlate with the original change metrics (c) likely degree of collinearity and model parsimony (d) relative model fit.

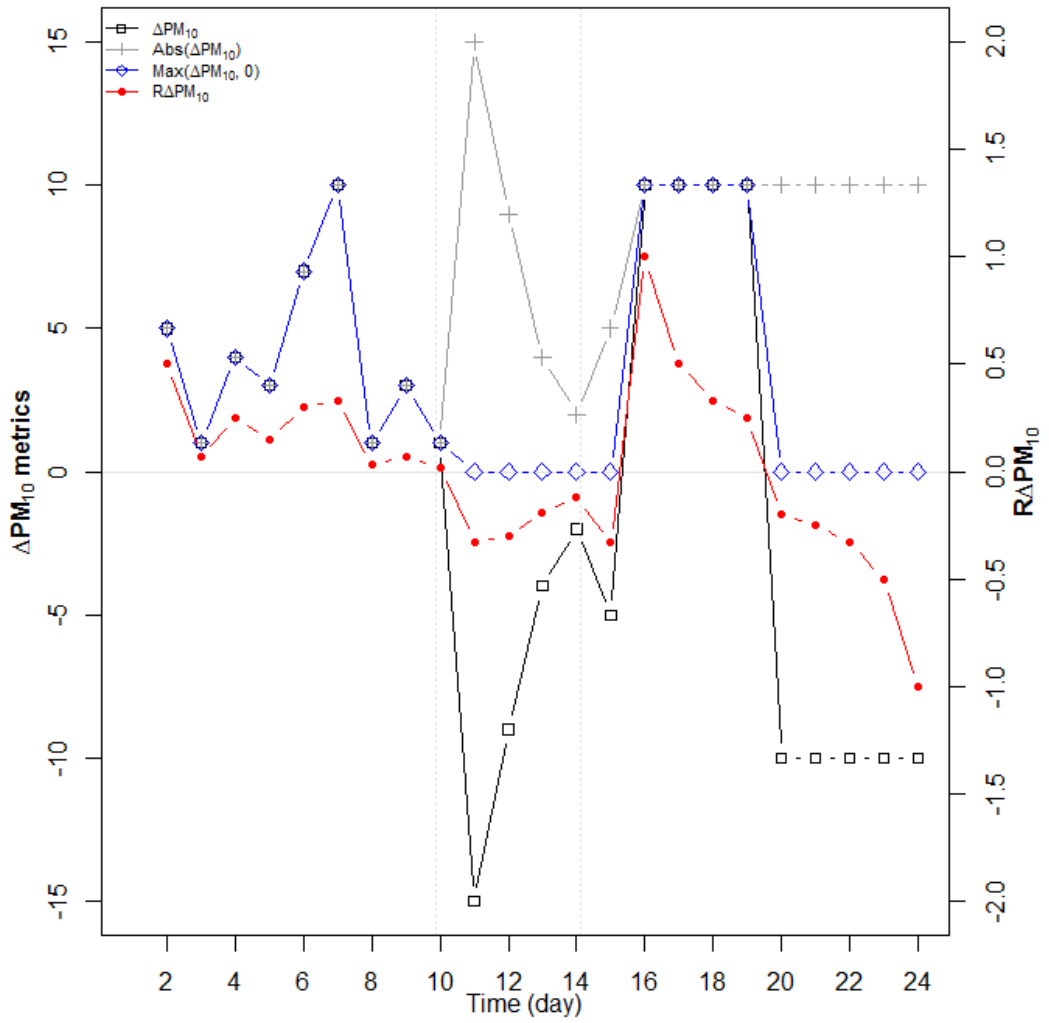
a) Ease of interpretation

Although the absolute value and maximum metrics are mathematically fine to work with, they are less intuitive to interpret in comparison to delta. Unlike delta, they are restricted to non-negative values and relative risks always relate to a unit increase between two days having non-negative values for the change metrics. This is, however, not an issue for the relative delta metrics in model 3.18 which retains the sign of the original change metrics.

b) Correlation with the original change metrics

The artificially generated data presented in section 3.3.1 were used again to visually investigate possible relationships between patterns of delta and the three alternative metrics proposed. Figure 3.3 shows that not all delta patterns are reflected by the absolute and maximum metrics when delta is less than zero while the relative delta seems to perform comparatively better in capturing those patterns.

Figure 3.3: Comparison of the patterns of alternative metrics for identifiable delta models



c) Model parsimony and collinearity

Some degree of collinearity is expected in all the models as delta is correlated with the absolute metrics (Table 3.2). Yet, compared to models with two metrics, collinearity has more substantial implication in the three metrics model. The worst case scenario in this regard occurred when modelling $P_{t,}$ P_{t-1} and ΔP_t as shown in 3.6 where one of the three parameters was effectively redundant (due to perfect multi-collinearity). The degree of collinearity for this as well as for other combinations of absolute and delta metrics can be investigated using the variance inflation factor (VIF) and condition number. Table 3.2

shows models for the various metrics combinations are within the rule of thumb cut off (10 for example) for both VIF and condition number (Chen et al., 2003) except for model 3.6 which included lag 0, lag 1 and delta.

Table 3.2: Simple collinearity diagnostics between combinations of PM_{10} and alternative delta metrics for simulated data

Variable	VIF	Sqrt (VIF)	Tolerance	R^2	Condition number
PM_{10}	-2.55e+15	−	≈0[§]	1.0000	
Lag1 PM_{10}	-2.55e+15	−	≈0	1.0000	−
ΔPM_{10}	-8.83e+14	−	≈0	1.0000	
PM_{10}	3.25	1.80	0.3076	0.6924	
Lag1 PM_{10}	3.60	1.90	0.2779	0.7221	3.5736
$\lvert\Delta PM_{10}\rvert$	1.20	1.10	0.8335	0.1665	
PM_{10}	3.17	1.78	0.3159	0.6841	3.2510
Lag1 PM_{10}	3.17	1.78	0.3159	0.6841	
Lag1 PM_{10}	1.17	1.08	0.8560	0.1440	1.4911
$\lvert\Delta PM_{10}\rvert$	1.17	1.08	0.8560	0.1440	
Lag1 PM_{10}	1.12	1.06	0.8967	0.1033	1.3955
$R\Delta PM_{10}$	1.12	1.06	0.8967	0.1033	
Lag1 PM_{10}	1.09	1.05	0.9136	0.0864	1.3538
ΔPM_{10}	1.09	1.05	0.9136	0.0864	
Lag1 PM_{10}	1.01	1.01	0.9884	0.0116	1.1144
Max (ΔPM_{10}, 0)	1.01	1.01	0.9884	0.0116	

[§]Approximately zero but with negative sign

Although replacing ΔP_t in 3.6 with its absolute value $|\Delta P_t|$ led to an identifiable model as shown in 3.15, it would still be the least favoured compared to the rest two metric models due to the relatively stronger correlation present between $|\Delta PM_{10}|$ and lag 1 PM_{10} (Table 3.3) as well as if model parsimony is to be considered.

Table 3.3: Correlation between PM_{10} and alternative delta metrics[§] for simulated data

	ΔPM_{10}	$\lvert\Delta PM_{10}\rvert$	Max (ΔPM_{10}, 0)	$R\Delta PM_{10}$	PM_{10}
ΔPM_{10}	1				
$\lvert\Delta PM_{10}\rvert$	-0.25	1			
Max (ΔPM_{10}, 0)	0.88	0.24	1		
$R\Delta PM_{10}$	0.92	-0.14	0.85	1	
PM_{10}	0.29	0.23	0.41	0.22	1
Lag1 PM_{10}	-0.29	0.38	-0.12	-0.32	0.83

[§]All metrics measured in $\mu g/m^3$ except relative delta which has no unit

d) Model fit

Finally, daily time series data from Hong Kong spanning the period 2002-2008 were used in order to determine the best fitting model among the proposed alternatives. That is, whether any of the alternative delta metrics presented in 3.15-3.18 fitted the data better than the relatively simpler delta models in 3.9 or 3.11 was checked in Poisson generalized additive models controlling for temperature, time trends and seasonality. The outcome of interest here was non-accidental mortality and relative risks, standard errors and AIC values were estimated for each of the models fitted. Descriptive statistics of the PM_{10} metrics investigated for the Hong Kong data are given in Table 3.4 and a summary of the results from the fitted GAM models is presented in Table 3.5. Compared to the reference model 3.11, model 3.16 was the most inferior with change in AIC about 2.2. Nevertheless, the difference in AIC values among the remaining models was not remarkable (change in AIC ranging between -1.6 and 0.5). A further simulation study based on the same data provided more or less similar conclusions (more details on the simulation procedure and results in Appendix C, Simulation study II).

Table 3.4: Summary of PM_{10} and delta metrics for Hong Kong (2002-2008)

Metric[§]	Mean (SD)	Minimum	Maximum	Median	IQR
PM_{10}	54.5 (28.7)	12.0	208.0	48.6	41.6 (30.7, 72.3)
ΔPM_{10}	-0.04 (20.4)	-125.4	115.2	0.1	19.0 (-9.5, 9.5)
$\lvert\Delta PM_{10}\rvert$	14.1 (14.7)	0.003	125.4	9.5	16.8 (3.5, 20.3)
Max (ΔPM_{10}, 0)	7.0 (12.6)	0.0	115.2	0.1	9.5 (0.0, 9.5)
$R\Delta PM_{10}$	0.06 (0.4)	-0.9	3.1	0.003	0.4 (-0.2, 0.2)

[§]All metrics measured in $\mu g/m^3$ except relative delta which has no unit

Overall, based on the descriptive and empirical comparisons (a)-(d) above, the relative delta may be preferable among the proposed alternative metrics in similar time series studies where the aim is investigating health effects of changes or rate of changes in exposure. This not only helps to get around the model identfiability problem but also amends the problem of equal weighting given to different baseline absolute pollution concentrations. For example, changes from 30 to 60 units and 40 to 70 units will both have a delta value of 30 units. However, in relative terms the rate of change compares as 100% versus 57%. In addition, the relative delta measure is fairly intuitive to interpret, showed very strong correlation with delta and provided reasonably similar model fit compared to other alternative metric models.

Table 3.5: Model comparison for various delta metrics based on AIC values with log RR (SE) estimates for non-accidental mortality per IQR increase in respective metric for Hong Kong

Model	Change in AIC[§]	Lag1 PM_{10}	ΔPM_{10}	Abs(ΔPM_{10})	Max(ΔPM_{10}, 0)	RΔPM_{10}
3.11	Reference	0.01271 (0.00466)	--	--	--	--
3.9	0.0	0.02401 (0.00412)	0.00516 (0.00213)	--	--	--
3.15	0.5	0.01166 (0.00472)	--	0.00295 (0.00269)	--	--
3.16	2.2	0.01699 (0.00398)	--	0.00413 (0.00264)	--	--
3.17	-1.6	0.02102 (0.00374)	--	--	0.00418 (0.00158)	--
3.18	0.0	0.02292 (0.00397)	--	--	--	0.0052 (0.0022)

[§]Calculated by subtracting AIC value of the reference model (3.11) from each model's respective AIC

3.8. Handling missing data in delta metrics

Analysis in the presence of non-trivial amount of missing data generally leads to reduction in power and precision and may result in biased estimates (Little and Rubin, 2002, Carpenter and Kenward, 2008, Janssen et al., 2010, Jackson et al., 2010). In time series studies of air pollution and health, the exposure data quite often come with some level of missing measurements. Thus, investigators attempt to impute the missing data according to some procedure and imputation methods continue to be an active research area in air pollution epidemiology (Katsouyanni et al., 2001, Plaia and Bondì, 2006, Junger and Ponce de Leon, 2015). However, when the missing rate in a data set is small, air pollution studies tend to carry out the analysis on the observed data set excluding missing measurements (Touloumi et al., 2004, Bhaskaran et al., 2011).

In the context of delta metrics, the number of missing values could reach up to double as much as those for absolute metric in a specific data set. Let N_A and N_D represent number of missing observations for the absolute and delta metrics respectively, then N_D is always greater than or equal to N_A (that is $N_D \geq N_A$, and maximum of $N_D=2N_A$). Hence, imputation of missing absolute concentration values will become a more crucial step for analysis involving the delta metrics than the absolute metrics.

Thus, a simulation study was conducted in order to compare two missing data handling methods namely excluding versus imputing missing observations. The imputation procedure that was considered for this analysis was taken from the APHENA study (Katsouyanni et al., 2009). The method computes missing data taking into account temporal and spatial averages (if data from a number of monitoring stations are available).

The simulation was based on daily time series data from Hong Kong which had complete PM_{10} measurements for the period 2002-2008 (2557 days). Using this data, first the following model was fitted:

$$\text{Log}[P_t] = \alpha + \beta \,\text{Log}(P_{t-1}) + \sum_{i=1}^{k} f_i(X_{ti}) \qquad (3.20)$$

where t is day of observation, $\text{Log}(P_t)$ and $\text{Log}(P_{t-1})$ represent PM_{10} concentrations at lags 0 and 1 respectively on the log scale, α is the intercept, β is the regression coefficient, $f_i(X_{ti})$ represent smooth functions of confounders (X_{ti}) which included temperature with 3 degrees of freedom (df), long-term time trends and seasonality with 4 df per year.

Then, model predicted mean for PM_{10} on each day and the corresponding standard deviation of residuals were computed. Next, PM_{10} data series was generated from a log-normal distribution based on the model predicted mean and standard deviation for the first monitoring station. Data for six additional monitoring stations were also generated in order to conform to the APHENA imputation method and one of the six stations was set to have larger average pollution. The procedure was repeated 1000 times and hence obtaining 1000 time series data sets (each 2557 days long) for seven monitoring stations. After this, missing rates of 3%, 5%, 10%, 30% and 50% were randomly introduced to each simulated data set for the first monitoring station while the missing rate for the rest six stations was kept at 3%. A second data series was then created for the first monitoring station by replacing the missing observations based on the APHENA imputation method which uses temporal and spatial averages from the other six stations. Finally, Poisson GAM model (equation 3.21 below) was fitted to each data set from the first station to estimate coefficients for lag 1 and delta PM_{10} after excluding the missing data as well as using the

imputed data set (more details on the simulation procedure in Appendix C, Simulation study III).

$$\text{Log}[E(Y_t)] = \alpha + \beta_1 \Delta P_t + \beta_2 P_{t-1} + \sum_{i=1}^{k} f_i(X_{ti}) \quad (3.21)$$

where t is day of observation, ΔP_t and P_{t-1} represent delta and lag 1 PM_{10} concentrations respectively, α is the intercept, β_1 and β_2 are the regression coefficients and $f_i(X_{ti})$ represent smooth functions of confounders (X_{ti}) which include temperature with 3 degrees of freedom (df), long-term time trends and seasonality with 8 df per year and day of the week.

The results from each model (β_1 and β_2) were saved and summarised using their average, SD, bias, relative bias, MSE and relative efficiency. The corresponding estimates from Hong Kong which had complete PM_{10} data were assumed as the "true" values for calculating bias. The aim again was to investigate the extent of missing data which could lead to potentially large bias and compare the performance of the APHENA imputation method against excluding missing data.

A summary of the results from this simulation study is presented in Table 3.6. When the missing rate was small (≤10% for example), excluding missing observations had little impact on mean square error (MSE) estimates for both lag 1 and delta PM_{10} coefficients. The MSE estimates almost doubled as the proportion of missing data increased, for example, from 10% to 30%. This was driven mainly by increases in the variance of coefficients as the respective increase in bias was relatively small.

Likewise, the MSE for the imputation based estimates was little affected by small proportion of missing data (≤10% for example) while higher rates led to increased MSE estimates. However, unlike the analysis excluding missing data, the increase in MSE was

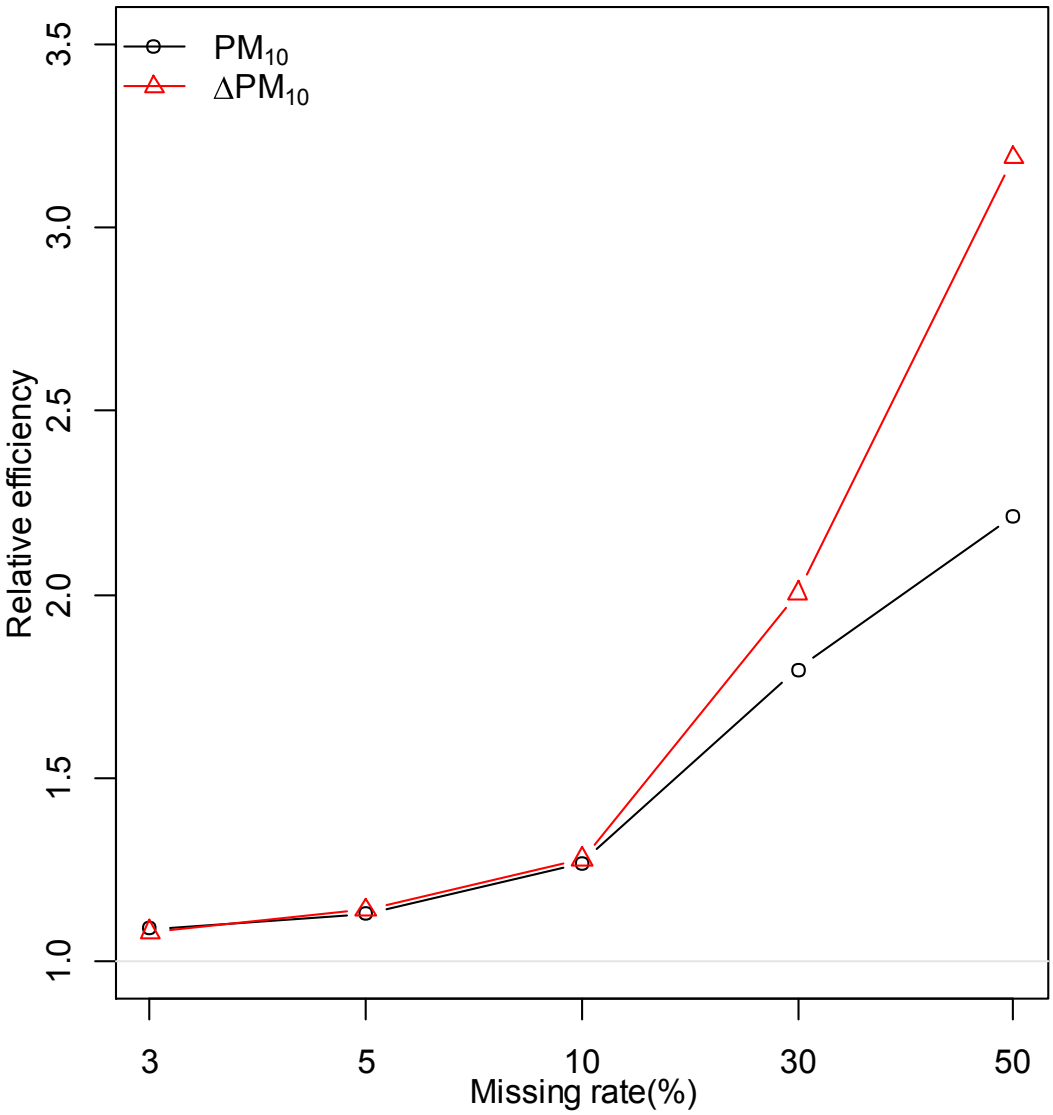
mainly driven by larger bias in coefficient estimates while the increase in variance was relatively small.

Comparison of the two methods for handling missing data, excluding versus imputation, shows that there is substantial gain in relative efficiency using the imputation approach (see Table 3.6 and Figure 3.4). This is true for each rate of missing data considered in the simulation study.

Table 3.6: Comparison of missing data handling methods in a simulation study for estimating log RRs per IQR increase for Lag1 PM_{10} and Delta PM_{10}

	Parameters									
	Lag 1 PM_{10} ("true" value=0.020363)					**Delta PM_{10}** ("true" value=0.004210)				
	Missing rate (%)									
	3	5	10	30	50	3	5	10	30	50
A) Excluding missing (Ex)										
$\hat{\beta}_{Ex}$	0.020396	0.020272	0.020366	0.019952	0.019748	0.004222	0.004178	0.004219	0.004126	0.004114
Bias	0.000033	-0.000092	0.000002	-0.000412	-0.000616	0.000012	-0.000032	0.000009	-0.000085	-0.000096
Relative bias	0.001622	-0.004510	0.000101	-0.020225	-0.030226	0.002840	-0.007610	0.002096	-0.020080	-0.022830
SD	0.004493	0.004568	0.004975	0.006863	0.010608	0.001650	0.001713	0.001833	0.002467	0.003731
MSE	0.000020	0.000021	0.000025	0.000047	0.000113	0.000003	0.000003	0.000003	0.000006	0.000014
B) APHENA imputed (Ap)										
$\hat{\beta}_{Ap}$	0.020678	0.020781	0.021288	0.023344	0.026120	0.004281	0.004291	0.004404	0.004822	0.005368
Bias	0.000314	0.000418	0.000924	0.002981	0.005757	0.000071	0.000081	0.000193	0.000611	0.001158
Relative bias	0.015426	0.020519	0.045381	0.146371	0.282709	0.016770	0.019210	0.045895	0.145145	0.274987
SD	0.004288	0.004273	0.004315	0.004177	0.004222	0.001585	0.001602	0.001608	0.001633	0.001740
MSE	0.000018	0.000018	0.000019	0.000026	0.000051	0.000003	0.000003	0.000003	0.000003	0.000004
Relative efficiency										
$MSE(\hat{\beta}_{Ex}) \big/ MSE(\hat{\beta}_{Ap})$	1.092043	1.132763	1.270871	1.794950	2.215162	1.082175	1.141285	1.280182	2.004307	3.188856

Figure 3.4: Relative efficiency (RE) of estimates for coefficients of Lag 1 and delta PM_{10} excluding versus imputing missing data. RE=MSE[excluding]/MSE[imputing]



3.9. Summary and conclusion

In this chapter some issues in relation to the properties and modelling of the change metrics (delta) for PM_{10} were discussed. It was highlighted using a simulation study that measurement error could have more severe impact on the delta metrics than the absolute metrics as reflected by larger variance of the former with increasing measurement error. The mathematical equivalence of potential identifiable models for delta with UDL model was shown and alternative identifiable models for delta were proposed. The alternative metrics were compared based on description of their properties in relation to the original change metrics as well as the relative model fit using a simulation study. The comparison indicated that the relative delta metrics would be preferred among the alternatives for delta in the evaluation of effects of changes or rate of changes. Finally, the impact of missing data was investigated using simulation. In particular, analysis excluding missing data and imputation based on the APHENA study procedure (Katsouyanni et al., 2009) were compared. The results showed that the relative efficiency of the imputation was much better than analysis excluding the missing observations. Therefore, imputation of missing data should be an important step particularly for models using the delta metrics.

4. CHANGES IN AIR POLLUTION BETWEEN SUCCESSIVE DAYS AND MORTALITY: A TIME SERIES STUDY

4.1. Introduction

Time series studies of short-term exposure to ambient air pollution have reported adverse associations with health including death and emergency admission to hospital (Anderson et al., 2007, Wong et al., 2002, Schwartz, 1994, Bell et al., 2013). Such studies correlate daily concentrations of pollution with daily counts of health events. A variety of daily metrics to characterise pollutant exposure including 24-hour averages and maximum hourly concentrations (Bell et al., 2005, Ostro et al., 2001, Delfino et al., 2002) have been investigated as well as the possibility that pollutant exposure has a concurrent or a delayed effect on health, by studying exposures lagged by one or more days (Katsouyanni et al., 1996, Hoek et al., 2001, Janssen et al., 2013). Others have considered combinations of these lagged measures assuming unconstrained or constrained distributed lag models (Schwartz, 2000a, Braga et al., 2001, Samoli et al., 2013). The purpose of exploring alternative pollutant metrics in such studies is to identify the most relevant exposure measure so that risk estimates are correctly quantified (Birnbaum, 2010, Darrow et al., 2011).

Time series studies in environmental epidemiology quantify the change in risk of a health outcome associated with a given increment in pollutant exposure; the interpretations of such risk estimates do not necessarily take account of the temporal order of the exposures or the change or rate of change of the pollutant concentrations on a day-to-day basis. The latter may be biologically relevant since the human body often responds to a change or to the rate of change of a stimulus; a good example being the way in which cutaneous pain receptors respond to stimulation (Burgess and Perl, 1967). It is thus hypothesised that differences, absolute or relative, in air pollution concentrations across successive days may

be a useful exposure metric for exploring short-term health effects of air pollution. That is, an increase of 10 μg/m^3, for example, in pollutant concentrations occurring between one day and the next would have a greater impact on health than the same increment occurring gradually over a number of days. This hypothesis, the *delta* hypothesis, has been proposed before (Ayres, 2007) and is yet to be evaluated in air pollution epidemiology although its equivalent has been examined in time series studies of temperature (Guo et al., 2011, Nastos et al., 2006, Lin et al., 2013, Ebi et al., 2004, Kyobutungi et al., 2005, Kim et al., 2014). In a similar argument, Dominici et al. have recently called for investigation of whether or not the health benefits of reducing air pollution say from "14 to 12" μg/m^3 and "12 to 10" μg/m^3 would be the same (Dominici et al., 2014). Hence, this study investigated the association of changes between successive daily measurements of PM_{10} and daily mortality in London and Hong Kong. It is argued that if results from both cities (which have different weather, air pollution profile, lifestyle, health indicators, etc.) were in agreement, then associations observed if any could potentially be considered causal (Wong et al., 2002).

4.2. Methods

4.2.1. Data

Detailed description of the data and sources for London and Hong Kong are provided elsewhere (Atkinson et al., 2010, Wong et al., 2008). Briefly, for London daily 24-hour average concentrations of PM_{10} measured at an urban background monitoring station (North Kensington) were obtained from the United Kingdom air quality archive (UK-AIR) managed by the Department for Environment, Food and Rural Affairs (DEFRA). Corresponding measures of daily average temperature were obtained from the British Atmospheric Data Centre. Daily mortality data for all non-accidental, cardiovascular and respiratory causes were obtained from the Office for National Statistics (ONS) and the daily data covered the period 1st January 2000 to 31st December 2005.

Similarly, for Hong Kong PM_{10} concentrations (24-hour average) and weather data were obtained from the Environmental Protection Department, Hong Kong. Daily mortality data for all non-accidental, cardiovascular and respiratory causes were obtained from the Census and Statistics Department, Hong Kong. The daily data were collected for the period 1st January 2002 to 31st December 2008.

4.2.2. Defining "delta"

A new metric, *delta* PM_{10} (ΔP_t), was defined as the change in mean absolute PM_{10} concentrations (referred to as just PM_{10}) between consecutive days (equation 4.1 below).

$$\Delta P_t = P_t - P_{t-1} \qquad (4.1)$$

The change relative to the absolute concentration was also quantified defining a second metric, *relative delta PM_{10} ($R\Delta P_t$)* by dividing the value of *delta PM_{10}* by the lag 1 PM_{10} concentration (equation 4.2 below).

$$R\Delta P_t = \Delta P_t \Big/ P_{t-1} \tag{4.2}$$

where P_t and P_{t-1} represent PM_{10} concentrations on day t and previous day t-1 respectively.

4.2.3. Statistical methods

The proposed delta metrics are based on simple algebraic manipulation of the existing absolute PM_{10} measures. Thus, conventional Poisson generalized additive models (GAMs) were applied to study their association with daily mortality counts. A generic form of such models for health outcome Y and pollutant P at single lag *l* on day t can be given as follows:

$$\text{Log}[E(Y_t)] = \alpha + \beta P_{t-l} + \sum_{i=1}^{k} f_i(X_{ti}) \tag{4.3}$$

where $f_i(X_{ti})$ represent smooth functions of confounders (X_{ti}) which include temperature with 3 degrees of freedom (df), long-term time trends and seasonality with 8 df per year and day of the week (Hastie and Tibshirani, 1986, Dominici et al., 2002, Katsouyanni et al., 2009). Based on this the following two time series models were proposed to evaluate the health effects of air pollution under a change paradigm for exposure metrics:

$$\text{Log}[E(Y_t)] = \beta \Delta P_t + \ldots \qquad \textit{delta effect only} \tag{4.4}$$

$$\text{Log}[E(Y_t)] = \beta_1' \Delta P_t + \beta_2' P_{t-1} + \ldots \qquad \textit{additional effect to the lagged value} \tag{4.5}$$

where ΔP_t is as defined in equation (4.1) above, t=2, 3, 4..., N and ignoring intercepts and confounders.

However, after algebraic analysis as shown in Chapter 3, model (4.5) appears to be equivalent with the conventional unconstrained distributed lag 1 model:

$$\text{Log}[\text{E}(\text{Y}_t)] = \beta_1 \text{P}_t + \beta_2 \text{P}_{t-1} + ... \quad (4.6)$$

This means that given the parameters of one of the models (4.5) or (4.6), one can easily compute the parameters of the other model, i.e., they are alternative parameterisations but with possibly different interpretations. The merit of the delta metrics lies in the convenience to directly evaluate responses to changes in exposure between consecutive days. In fact, the models remain equivalent if P_{t-1} in (4.5) was replaced with either P_t or $(P_t + P_{t-1})/2$.

Models (4.4-4.5) were fitted to both delta and relative delta PM_{10} but algebraic equivalence of models (4.5) with (4.6) could be established only for delta PM_{10}. For comparison purposes, a conventional lag 1 model (4.7) below was also fitted:

$$\text{Log}[\text{E}(\text{Y}_t)] = \alpha_1' \text{P}_{t-1} + ... \quad (4.7)$$

Although the approach for this analysis was guided by an *a priori* specified protocol which was mostly based on the APHENA study (Katsouyanni et al., 2009), it is always important to check whether the results would be affected by alternative specifications (Bhaskaran et al., 2013). Therefore, associations of the three exposure metrics (absolute PM_{10}, delta and relative delta PM_{10}) with mortality were explored at single lags of 0-6 and averages of lags 0-1, 0-2, ..., 0-6 in order to assess the sensitivity of results to lag choice. In addition, whether a non-linear modelling approach could better describe associations of the delta metrics with mortality was examined (both on a continuous scale as well as after categorising delta into three groups). Interaction effects of the delta metrics (delta and

relative delta PM_{10}) with that of absolute PM_{10} at lag 1 were also checked. Furthermore, the impact of restricting the analysis to days with positive deltas only was investigated; the aim here was assessing the effect of sampling based on days with air pollution increases as intuitively only pollution increases are expected to have effect on health. Finally, sensitivity of results to choice of df for smoothing time and temperature was checked over the range 2-14 dfs. Residual plots were used to check for any remaining patterns in the data and other model anomalies. Model comparisons were based on AIC values. All analyses were performed using the R statistical package (R Core Team, 2012). Results are presented as percentage changes in mortality for an interquartile range (IQR) increase in PM_{10} metric unless otherwise stated and all hypotheses tests are based on 5% significance level.

4.2.4. Summary of study protocol

This section outlines briefly the health outcomes, exposure variables and different aspects of the modelling approach in the study. The latter involved *a priori* specification of smoothing parameters for the GAMs and the determination of confounders to be included. This was guided by the literature and the final study protocol described below was taken mostly from the APHENA study (Katsouyanni et al., 2009) which can be regarded as one of the most credible time series studies of air pollution and health.

4.2.4.1. Outcome and exposure

Mortality: Daily counts of deaths for people who resided and died in London and Hong Kong of non-accidental (ICD-10 Chapters A–R), cardiovascular (ICD-10 Chapter I) and respiratory (ICD-10 Chapter J) causes for all ages. For Hong Kong, ICD-9 codes 001–799, 390–459 and 460–519 were also included for non-accidental, cardiovascular and respiratory mortality respectively.

Exposure: Absolute PM_{10} (24-hour average) and corresponding delta PM_{10} and relative delta PM_{10} were the exposures of interest. The definition for the delta metrics is as given in equations (4.1) and (4.2) above.

4.2.4.2. Model specification

Exposure lags: Models are based on lag 0 for delta PM_{10} and lag 1 for absolute PM_{10} as these are commonly used exposure lags in the literature (Katsouyanni et al., 2009, Guo et al., 2011).

Smoothing: Smoothing splines were applied for fitting smooth functions of calendar time and temperature.

Missing values: Missing data could have more serious implication in the delta than conventional models as the number of missing observations could easily double in the delta approach. This is because our new metrics depend on the differences of exposure between successive days. Hence, missing data for PM_{10} were handled by adapting the APHENA (Katsouyanni et al., 2009) protocol as detailed below. A missing observation on day *i* of year *k* from monitoring station j was replaced by a weighted average of the values of the other monitoring stations as follows:

$$\hat{x}_{ijk} = \bar{x}_{i.k}\left(\bar{x}_{.jk} / \bar{x}_{..k}\right) \qquad (4.8)$$

where $\bar{x}_{i.k}$ is the mean value on day *i* of year *k* among all monitors reporting, $\bar{x}_{.jk}$ is the mean value for monitor *j* in year *k* and $\bar{x}_{..k}$ is the overall mean level in year *k*.

Degrees of freedom for seasonality: The use of 8 *df per* year has been adopted in this time series study.

Covariates in the model: A smooth term for lag 0 temperature with 3 df was included and dummy variables were entered to control for day of the week effects. Models were not controlled for influenza and relative humidity; the effect of the latter was however investigated in a sensitivity analysis.

4.2.4.3. Non-linear exposure-response relationships

GAMs were fitted with smoothed delta and relative delta PM_{10} for 2-14 df in order to assess whether such models provided a better fit than the linear approach.

4.2.4.4. Categorised delta metrics

Each delta metric was grouped into 3 categories. Delta PM_{10} values were categorised as <0, 0-10 and ≥ 10 $\mu g/m^3$ and relative delta PM_{10} values as <0, 0-0.1 and ≥ 0.1.

4.3. Results

4.3.1. Summary for the time series data

Table 4.1 presents some descriptive statistics for daily mortality, PM_{10}, delta PM_{10} and relative delta PM_{10} concentrations. PM_{10} concentrations in Hong Kong were more than double those in London; the median (IQR) levels were 23 (18.7, 29.8) and 48.6 (30.7, 72.3) $\mu g/m^3$ for London and Hong Kong respectively. The corresponding delta PM_{10} and relative delta PM_{10} concentrations were 0.7 (-4.9, 5.4) $\mu g/m^3$ and 0.03 (-0.19, 0.25) for London and 0.11 (-9.48, 9.5) $\mu g/m^3$ and 0.003 (-0.17, 0.22) for Hong Kong respectively. Daily mortality rates were in general lower in Hong Kong; the median daily number of deaths from non-accidental, cardiovascular and respiratory causes was 145, 54 and 22 in London and 95, 26 and 18 in Hong Kong respectively. Compared to the warm season (April-September), mortality and pollution concentrations were somewhat higher for the cold season (October-March) in both cities. There were 65 missing observations (about 3%) for PM_{10} in London which were imputed according to the procedure described in the study protocol above (equation 4.8).

A strong seasonal pattern with slightly declining trend was observed for mortality in both cities over the respective study periods while such a trend was less obvious for the three exposure metrics considered for PM_{10} in this study (Figure 4.1).

Table 4.1: Summary of number of daily deaths and PM_{10} metrics for London (2000-2005) and Hong Kong (2002-2008)

	Full data					By season[a], Mean (SD)	
Variable	**Mean (SD)**	**Minimum**	**Maximum**	**Median**	**IQR (25^{th}, 75^{th} Percentiles)**	**Cold**	**Warm**
London							
Daily mortality							
Non-accidental	147.3 (22)	96	302	145	26 (133, 159)	157.6 (22.1)	137.1 (16.5)
Cardiovascular	54.6 (10.4)	27	116	54	13 (48, 61)	58.7 (9.9)	50.5 (9.1)
Respiratory	23.1 (9.9)	6	139	22	10 (17, 27)	27 (11.6)	19.3 (5.7)
Daily pollutant metrics and weather							
PM_{10} ($\mu g/m^3$)	25.7 (10.7)	5.8	98.1	23	11.1 (18.7, 29.8)	26 (11.1)	25.5 (10.2)
Delta PM_{10} ($\mu g/m^3$)	0.02 (9.5)	-63.3	43.9	0.7	10.3 (-4.9, 5.4)	0.03 (10.2)	-0.01 (8.6)
Relative delta PM_{10}[b]	0.06 (0.37)	-0.82	2.5	0.03	0.4 (-0.2, 0.3)	0.1 (0.4)	0.05 (0.3)
Temperature (°C)	12.4(5.4)	-0.2	29.3	12.1	8.1 (8.4, 16.5)	8.6 (3.7)	16.1 (4.1)
Dew point (°C)	6.8 (4.8)	-6.5	18	7	6.9 (3.4, 10.3)	4.3 (4.1)	9.2(4.1)
Hong Kong							
Daily mortality							
Non-accidental	96 (14.7)	55	161	95	19 (86, 105)	100.7 (15.7)	91.2 (11.9)
Cardiovascular	26.6 (6.7)	7	56	26	9 (22, 31)	29.1 (7)	24.1 (5.4)
Respiratory	18.4 (5.8)	5	52	18	8 (14, 22)	19.5 (6.2)	17.4 (5.3)
Daily pollutant metrics and weather							
PM_{10} ($\mu g/m^3$)	54.5 (28.7)	12	208	48.6	41.6 (30.7, 72.3)	68.1 (27)	40.8 (23.3)
Delta PM_{10} ($\mu g/m^3$)	-0.04 (20.4)	-125.4	115.2	0.11	18.9 (-9.48, 9.5)	-0.1 (22.4)	0.1 (18.2)
Relative delta PM_{10}	0.06 (0.4)	-0.87	3.1	0.003	0.4 (-0.2, 0.22)	0.1 (0.4)	0.1 (0.4)
Temperature (°C)	23.51 (5)	8.2	31.8	24.9	8.2 (19.5, 27.7)	19.9 (4.1)	27.1 (2.5)
Humidity (%)	78.1 (10.2)	31	98	79	12 (73, 85)	74.8 (11.6)	81.4 (7.2)

[a]Season: Warm (April-September), Cold (October-March)
[b]Relative delta has no unit

Figure 4.1: Patterns of PM_{10} ($\mu g/m^3$), Delta PM_{10} ($\mu g/m^3$), Relative delta PM_{10} and non-accidental mortality

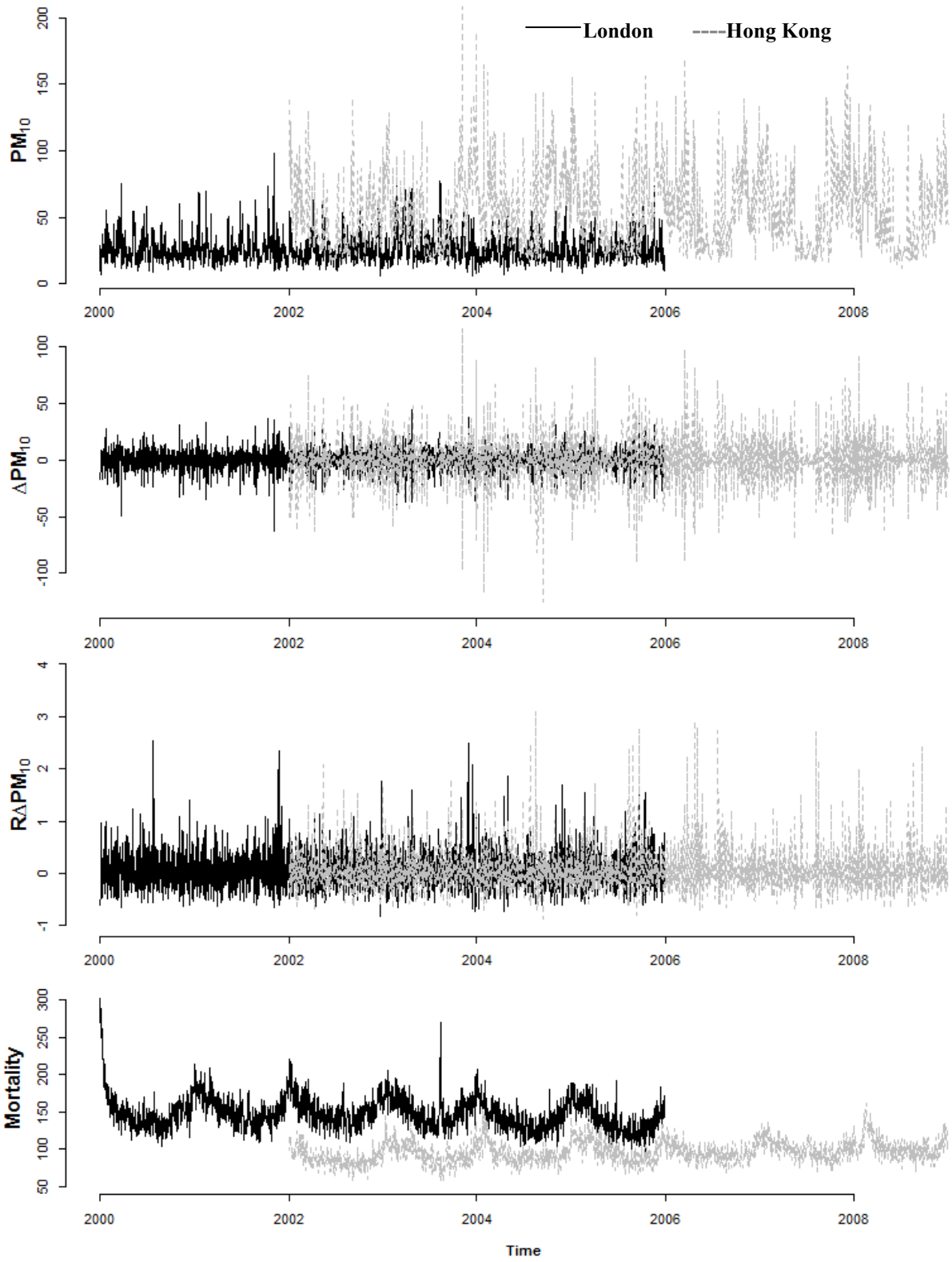


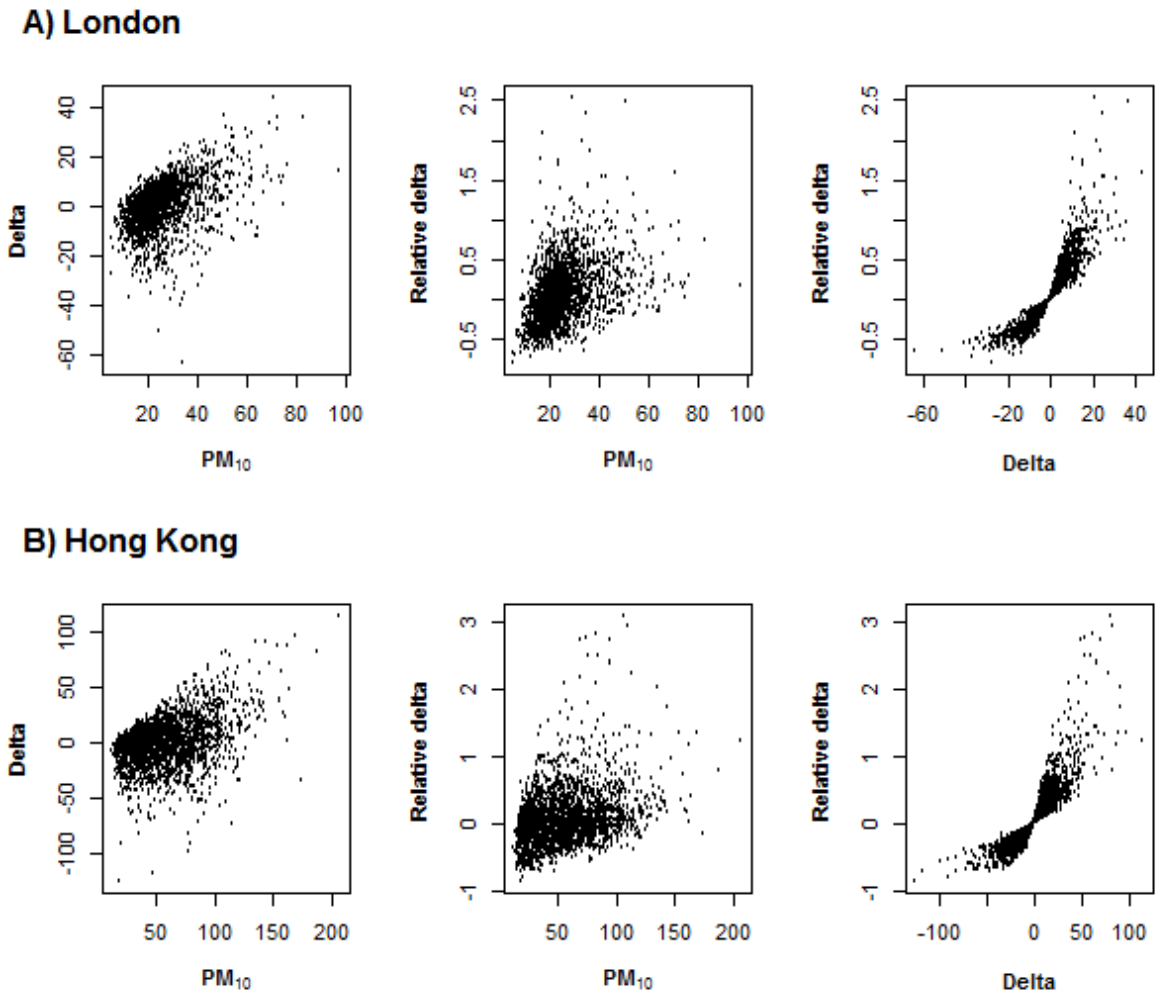
Table 4.2 and Figure 4.2 display the correlations between the three PM_{10} metrics. There was a strong correlation between delta and relative delta measures; the Spearman correlation coefficient was 0.98 in London and 0.97 in Hong Kong. However, both showed moderate negative correlations with absolute PM_{10} at lag 1 with coefficient -0.4 for London and -0.3 for Hong Kong (Table 4.2). Autocorrelation and partial autocorrelation functions for all variables as well as the respective cross-correlations are presented in appendix D, Figure 4.9, Figure 4.10 and Figure 4.11.

Table 4.2: Spearman correlation coefficient for non-accidental mortality and the various PM_{10} metrics

	Non-accidental mortality	PM_{10}	Lag1 PM_{10}	ΔPM_{10}	$R\Delta PM_{10}$	Temperature
London						
$PM_{10}(\mu g/m^3)$	0.15					
Lag1 $PM_{10}(\mu g/m^3)$	0.18	0.52				
$\Delta PM_{10}(\mu g/m^3)$	-0.01	0.49	-0.4			
$R\Delta PM_{10}$[§]	-0.02	0.48	-0.44	0.98		
Temperature (°C)	-0.5	0.11	0.14	-0.03	-0.04	
Dew point (°C)	-0.41	0.04	0.14	-0.11	-0.11	0.89
Hong Kong						
$PM_{10}(\mu g/m^3)$	0.24					
Lag1 $PM_{10}(\mu g/m^3)$	0.24	0.79				
$\Delta PM_{10}(\mu g/m^3)$	-0.003	0.29	-0.3			
$R\Delta PM_{10}$	-0.003	0.29	-0.31	0.97		
Temperature (°C)	-0.44	-0.47	-0.48	0.01	0.01	
Humidity (%)	-0.1	-0.5	-0.4	-0.14	-0.14	0.12

[§]Relative delta has no unit

Figure 4.2: Scatter plots showing correlation between PM_{10} ($\mu g/m^3$), Delta ($\mu g/m^3$) and Relative delta



4.3.2. Non-accidental mortality

Table 4.3 presents the percentage increase in mortality for an IQR increase in the respective PM_{10} metric. In Hong Kong, the conventional lag 1 PM_{10} metric showed significant association with non-accidental mortality as expected with percentage increase of 1.97 (95% CI: 1.23, 2.73). However, there was little evidence of association for delta and relative delta PM_{10} in the single metric models with percentage increases in mortality of -0.04 (95% CI: -0.41, 0.33) and 0.04 (95% CI: -0.35, 0.43) respectively. Likewise, in London the conventional lag 1 PM_{10} metric showed significant association with non-accidental mortality with percentage increase 0.91 (95% CI: 0.50, 1.32). However, the associations for delta -0.59 (95% CI: -1.01, -0.16) and relative delta -0.59 (95% CI: -1.01, -0.16) appeared to be negative.

In Hong Kong, after controlling for lag 1 PM_{10}, estimates for percentage increase in mortality for an IQR increase in delta and relative delta PM_{10} were similar: 0.51 (95% CI: 0.1, 0.92) and 0.51 (95% CI: 0.09, 0.93) respectively. Lag 1 PM_{10} effects themselves increased from 1.97 (95% CI: 1.23, 2.73) to 2.44 (95% CI: 1.61, 3.28) and 2.31 (95% CI: 1.48, 3.15) after controlling for delta and relative delta respectively. However, these associations were not seen in the London data.

4.3.3. Cardiovascular mortality

For both cities there was no evidence of association for delta and relative delta PM_{10} with cardiovascular mortality in the single metric models (Table 4.3). After controlling for lag 1 PM_{10}, the percentage increases in cardiovascular mortality for an IQR increase in delta and relative delta PM_{10} were similar in Hong Kong at 1.12 (95% CI: 0.3, 1.95) and 1.18 (95% CI: 0.37, 2.0) respectively. Lag 1 PM_{10} effects increased from 2.36 (95% CI: 0.95, 3.79) to

3.43 (95% CI: 1.84, 5.04) and 3.21 (95% CI: 1.71, 4.74) after controlling for delta and relative delta respectively. Nevertheless, these associations were not present in the London data (Table 4.3).

4.3.4. Respiratory mortality

In general, there was little evidence of association for delta and relative delta PM_{10} with respiratory mortality both in the single metric models and after controlling for lag 1 PM_{10} for both cities (Table 4.3). The exception was where a negative association appeared in London for delta PM_{10} with an estimated percentage increase of -1.26 (95% CI: -2.28, -0.23).

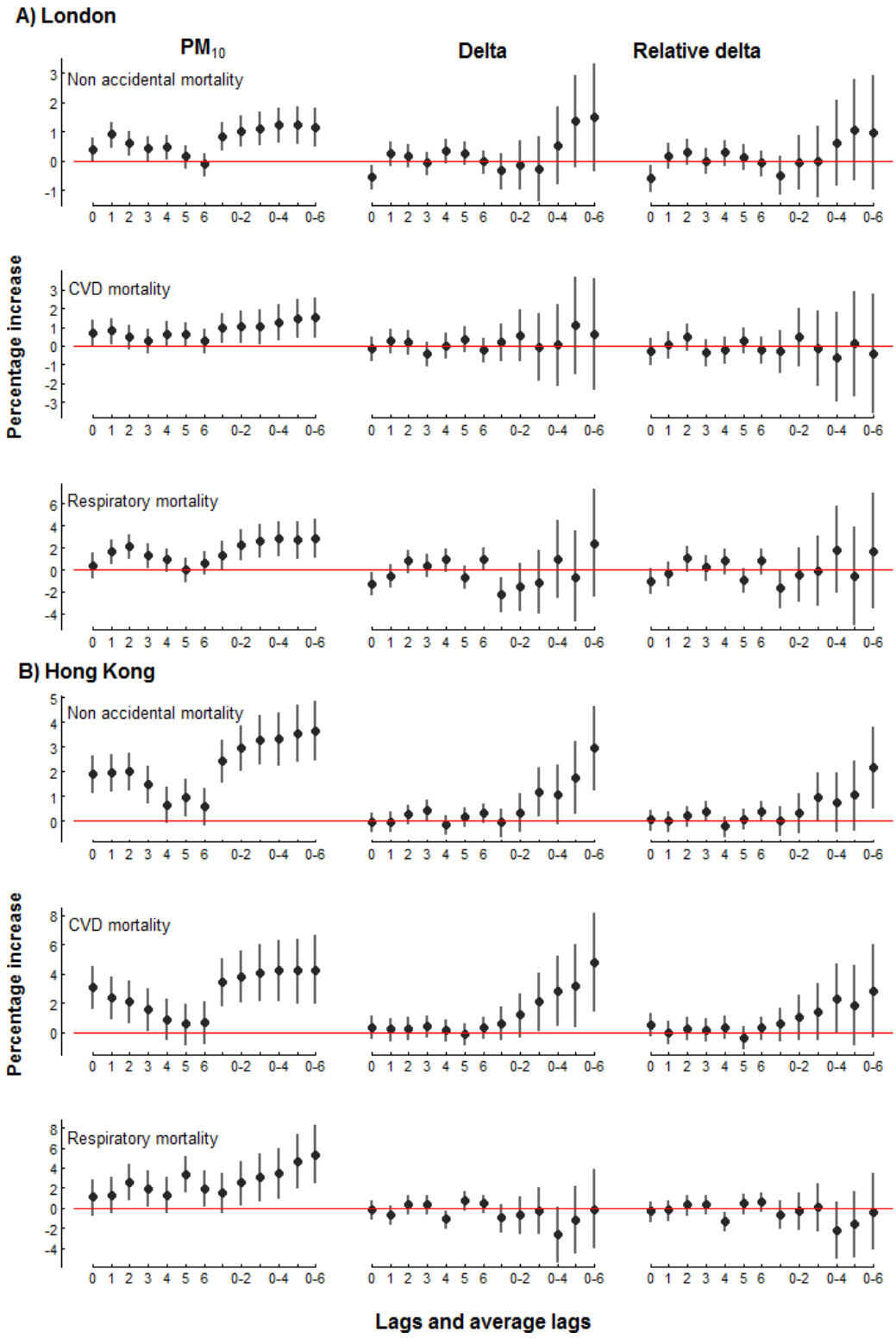
Table 4.3: Percentage increase (95% CI) in mortality per IQR increase in PM_{10} metric by cause of death

London	**Non-accidental**	**Cardiovascular**	**Respiratory**
Conventional metrics (PM_{10}, $\mu g/m^3$)			
Lag1 PM_{10}	0.91(0.5, 1.32)	0.81(0.13, 1.48)	1.63(0.55, 2.73)
Delta metrics (ΔPM_{10}, $\mu g/m^3$)			
ΔPM_{10}	-0.54(-0.93, -0.15)	-0.14(-0.78, 0.5)	-1.26(-2.28, -0.23)
Lag1 PM_{10} +ΔPM_{10}	0.83(0.37, 1.3) + -0.14(-0.58, 0.3)	0.98(0.22, 1.74) + 0.32(-0.41, 1.06)	1.29(0.05, 2.54) + -0.65(-1.82, 0.55)
Relative delta metrics ($R\Delta PM_{10}$, no units**)**			
$R\Delta PM_{10}$	-0.59(-1.01, -0.16)	-0.31(-1.01, 0.4)	-1.03(-2.14, 0.1)
Lag1 PM_{10} + $R\Delta PM_{10}$	0.82(0.37, 1.27) + -0.21(-0.68, 0.26)	0.84(0.11, 1.58) + 0.08(-0.69, 0.85)	1.48(0.28, 2.69) + -0.35(-1.59, 0.91)
Hong Kong			
Conventional metrics (PM_{10}, $\mu g/m^3$)			
Lag1 PM_{10}	1.97(1.23, 2.73)	2.36(0.95, 3.79)	0.88(-0.92, 2.7)
Delta metrics (ΔPM_{10}, $\mu g/m^3$)			
ΔPM_{10}	-0.04(-0.41, 0.33)	0.36(-0.34, 1.07)	-0.34(-1.22, 0.55)
Lag1 PM_{10} +ΔPM_{10}	2.44(1.61, 3.28) + 0.51(0.1, 0.92)	3.43(1.84, 5.04) + 1.12(0.3, 1.95)	0.67(-1.44, 2.82) + -0.17(-1.2, 0.87)
Relative delta metrics ($R\Delta PM_{10}$, no units**)**			
$R\Delta PM_{10}$	0.04(-0.35, 0.43)	0.52(-0.24, 1.29)	-0.55(-1.48, 0.39)
Lag1 PM_{10} + $R\Delta PM_{10}$	2.31(1.48, 3.15) + 0.51(0.09, 0.93)	3.21(1.71, 4.74) + 1.18(0.37, 2)	0.5(-1.45, 2.49) + -0.44(-1.45, 0.58)

4.3.5. Sensitivity to the choice of lag

Figure 4.3 below shows the percentage increase estimates for all the three metrics for each of the single lags 0-6 and the corresponding average lags (from 0-1 to 0-6 days). In general, there were considerable and consistent effects for the conventional PM_{10} metric at various lags and for all the mortality outcomes in both cities (although some lags, for example, lags 5 and 6, did not show significant association and percentage increase estimates were elevated in average lag models with increasing lag number). With respect to the delta metrics, there was similarity in terms of effect of delta and relative delta PM_{10} on mortality in the single lag and average lag models. In most cases, there was little evidence of association of the delta metrics with mortality at the various lags considered. The exceptions include delta and relative delta PM_{10} for non-accidental mortality at lag 0, delta PM_{10} for respiratory mortality at lag 0 and average of lags 0-1 in London and for averaging over longer lags in Hong Kong.

Figure 4.3: Association of PM_{10} metrics for single and average lags (from 0-1 to 0-6 days) with mortality



4.3.6. Non-linear relationship for single lag models

Potential non-linear relationships were examined using GAM models with 2-14 df for delta and relative delta metrics in the study (Appendix D: Figures 4.9 and 4.10 for London and Figures 4.11 and 4.12 for Hong Kong). These non-linear models did not provide any material improvement over their linear counterparts based on AIC values (Appendix D: Table 4.7). A further sensitivity analysis was conducted by restricting the data to days with positive deltas only (i.e., for days with air pollution increases as intuitively only pollution increases are expected to have an effect). Overall, conclusions were similar to those based on the full dataset. For example, the exposure-response relationship using GAMs with 3 df smooth for the absolute and delta PM_{10} metrics are presented in Appendix D: Figures 4.13 (full data set) and 4.14 (positive deltas only) for London and Figures 4.15 (full data set) and 4.16 (positive deltas only) for Hong Kong.

4.3.7. Categorised delta metrics

Categorization of the delta metrics did not provide any clear insights with respect to associations with mortality for any of the causes. For London, percentage increase estimates for both delta and relative delta were not significant compared to the respective reference categories (Table 4.4). In Hong Kong, some differences were observed for non-accidental and cardiovascular mortality but not for respiratory mortality (Table 4.4). Overall, compared to models based on the continuous scale delta metrics, categorized delta metrics did not provide material improvement on model fit based on AIC values (Appendix D: Table 4.7).

Table 4.4: Percentage increase (95% CI) in mortality after categorizing the delta metrics

Variable[§]	Group	Non-accidental	Cardiovascular	Respiratory
London				
ΔPM_{10}	<0	Reference	Reference	Reference
	0-10	0.28(-0.52, 1.08)	0.90(-0.42, 2.24)	0.81(-1.33, 3.00)
	≥10	-0.85(-2.04, 0.35)	0.28(-1.68, 2.29)	-1.32(-4.45, 1.90)
Lag1 PM_{10}	-	0.08(0.04, 0.12)	0.09(0.02, 0.15)	0.16(0.05, 0.26)
$R\Delta PM_{10}$	<0	Reference	Reference	Reference
	0-0.1	-0.09(-1.22, 1.06)	0.69(-1.18, 2.59)	1.56(-1.50, 4.72)
	≥0.1	0.07(-0.74, 0.89)	0.79(-0.55, 2.15)	-0.08(-2.24, 2.12)
Lag1 PM_{10}	-	0.08(0.04, 0.12)	0.09(0.02, 0.15)	0.15(0.04, 0.25)
Hong Kong				
ΔPM_{10}	<0	Reference	Reference	Reference
	0-10	0.79 (-0.24, 1.82)	2.11 (0.12, 4.14)	0.74 (-1.65, 3.19)
	≥10	1.31 (0.27, 2.37)	3.37 (1.33, 5.46)	-2.14 (-4.49, 0.27)
Lag1 PM_{10}	-	0.05 (0.04, 0.07)	0.08 (0.04, 0.11)	0.03 (-0.02, 0.07)
$R\Delta PM_{10}$	<0	Reference	Reference	Reference
	0-0.1	1.02 (-0.23, 2.29)	1.09 (-1.3, 3.54)	0.78 (-2.12, 3.76)
	≥0.1	1.06 (0.12, 2)	3.44 (1.61, 5.31)	-1.3 (-3.43, 0.87)
Lag1 PM_{10}	-	0.05 (0.04, 0.07)	0.08 (0.04, 0.11)	0.02 (-0.02, 0.07)

[§] PM_{10} and ΔPM_{10} measured in $\mu g/m^3$ while $R\Delta PM_{10}$ has no unit

4.3.8. Interaction

In general, there was no evidence of an interaction effect of delta and conventional metrics (lag 1 PM_{10}) on mortality from all causes as well as from specific causes in both London and Hong Kong (Table 4.5). This is without reading too much into the apparently borderline significant results for non-accidental and cardiovascular mortality in London for which the interaction term was very small.

Table 4.5: Interaction effects of delta and absolute metrics on mortality[a]

Variable[b]	Non-accidental	Cardiovascular	Respiratory
London			
Lag1 PM_{10}	0.08 (0.04, 0.13)	0.1 (0.03, 0.17)	0.12 (0.004, 0.23)
ΔPM_{10}	-0.09 (-0.18, -0.002)	-0.1 (-0.24, 0.05)	-0.1 (-0.33, 0.14)
ΔPM_{10}*Lag1 PM_{10}	0.002 (0, 0.004)	0.004 (0, 0.01)	0.001 (-0.01, 0.01)
Lag1 PM_{10}	0.08 (0.03, 0.12)	0.09 (0.02, 0.16)	0.12 (0.003, 0.23)
$R\Delta PM_{10}$	-0.73 (-2.87, 1.41)	-1.95 (-5.48, 1.58)	2.09 (-3.56, 7.73)
$R\Delta PM_{10}$*Lag1 PM_{10}	0.01 (-0.08, 0.1)	0.1 (-0.04, 0.24)	-0.14 (-0.37, 0.1)
Hong Kong			
Lag1 PM_{10}	0.06 (0.04, 0.08)	0.08 (0.04, 0.12)	0.04 (-0.004, 0.09)
ΔPM_{10}	0.04 (-0.003, 0.09)	0.08 (-0.01, 0.17)	-0.05 (-0.16, 0.06)
ΔPM_{10}*Lag1 PM_{10}	-0.0002 (-0.001, 0.0003)	-0.0003 (-0.001, 0.001)	0.001 (-0.0004, 0.002)
Lag1 PM_{10}	0.06 (0.04, 0.08)	0.08 (0.04, 0.12)	0.04 (-0.01, 0.08)
$R\Delta PM_{10}$	0.52 (-1.53, 2.58)	1.67 (-2.29, 5.63)	-2.42 (-7.22, 2.38)
$R\Delta PM_{10}$*Lag1 PM_{10}	0.02 (-0.02, 0.06)	0.03 (-0.05, 0.11)	0.05 (-0.05, 0.15)

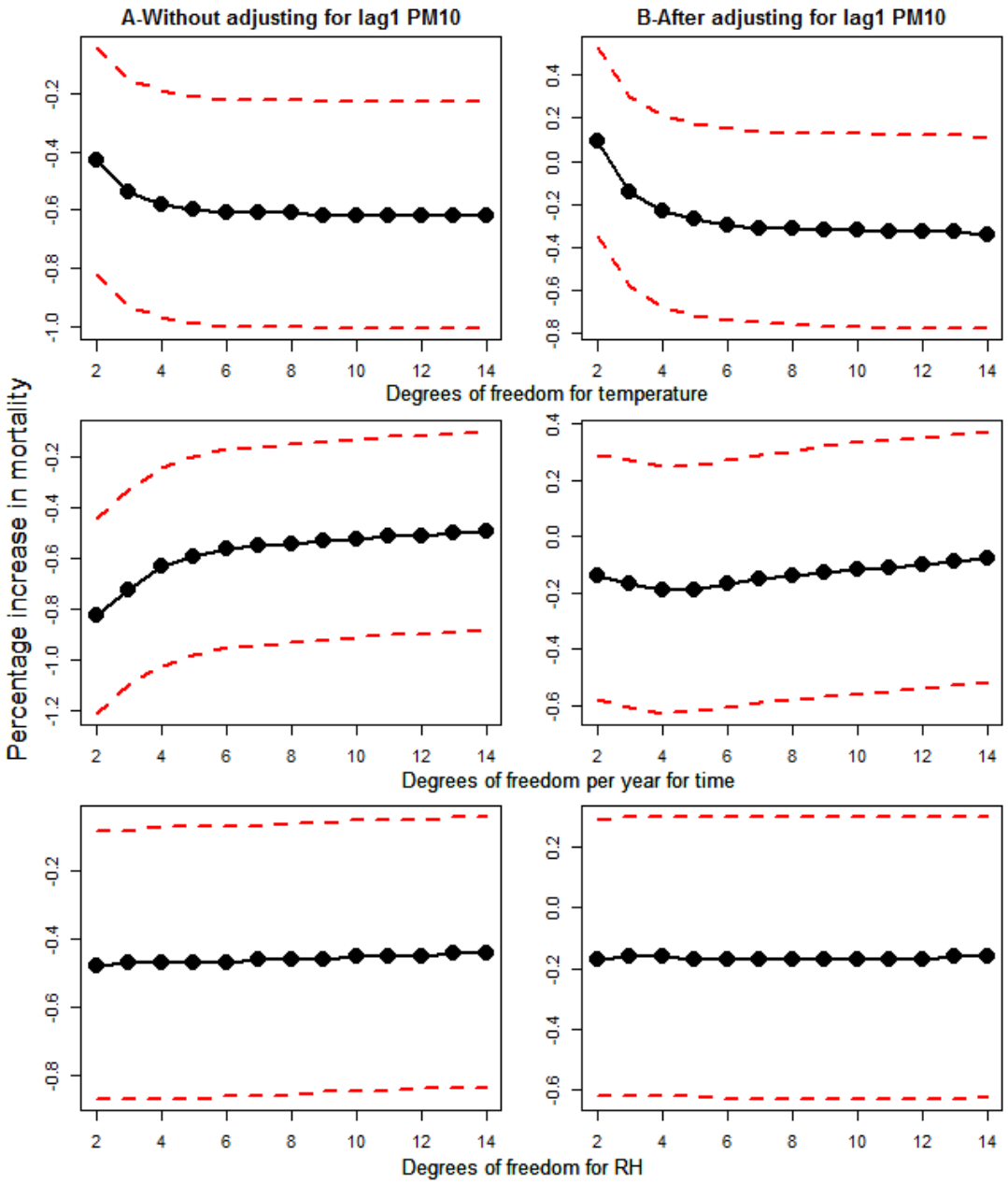
[a]Results are provided as100*Log RR

[b]PM_{10} and ΔPM_{10} measured in $\mu g/m^3$ while $R\Delta PM_{10}$ has no unit

4.3.9. Sensitivity to df choice for time, temperature and relative humidity

In London, percentage increase estimates for delta PM_{10} both with and without controlling for lag 1 PM_{10} appeared to converge after approximately 4 df smoothing for temperature (Figure 4.4, first panel). For calendar time, such convergence was less obvious over the range of 2-14 dfs investigated (Figure 4.4, second panel). However, overall conclusions are more or less similar at least qualitatively with that of *a priori* chosen dfs (3 df for temperature and 8 df per year for calendar time). Furthermore, adjusting for relative humidity had little impact on estimated percentage increases in mortality and this appeared to be true irrespective of the amount of smoothing (df) used for relative humidity (Figure 4.4, third panel).

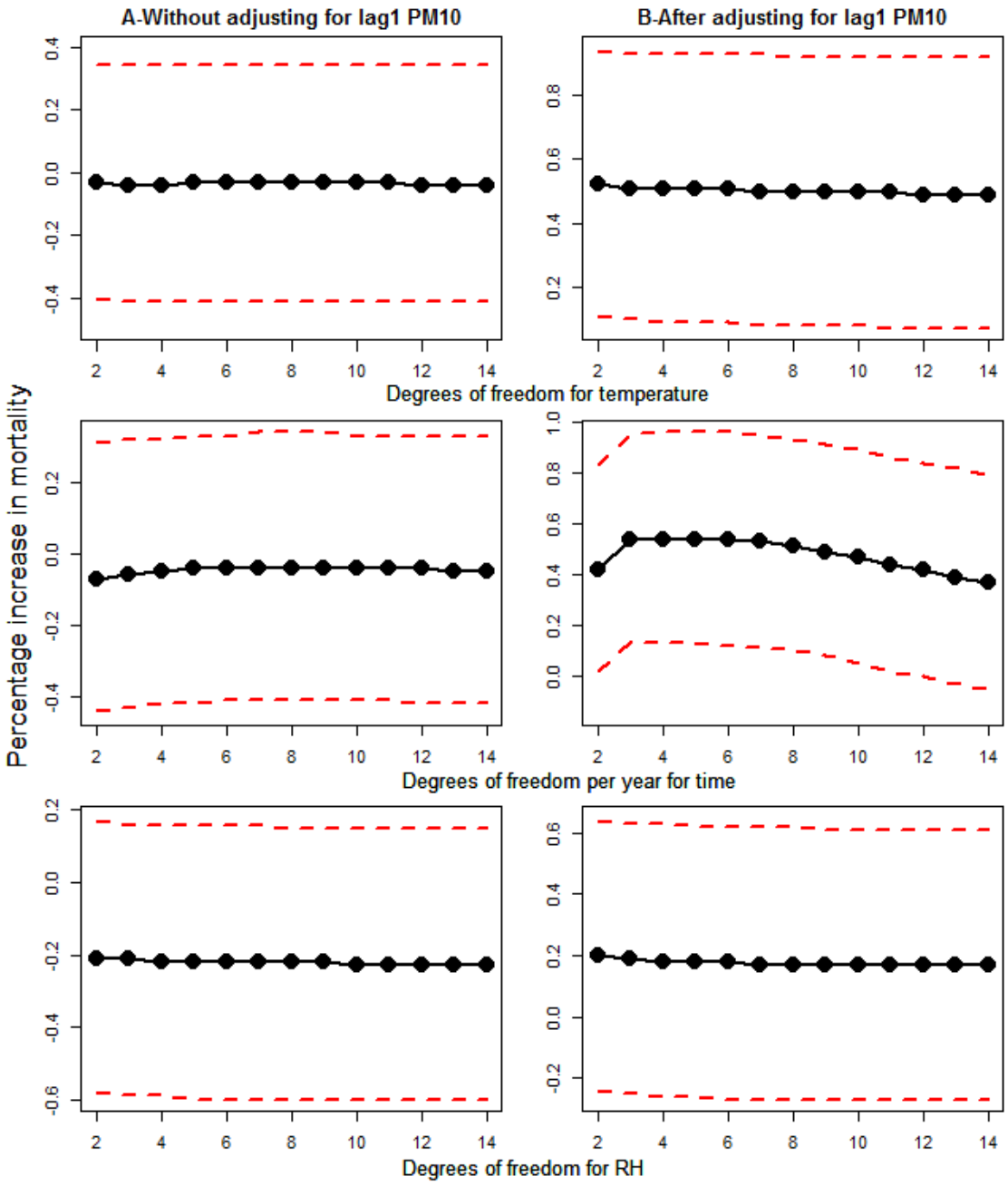
Figure 4.4: Percentage increase (with 95% CI) in non-accidental mortality per IQR increase in delta PM_{10} controlling for temperature, calendar time and relative humidity (RH) at 2-14 df, London



In Hong Kong, the amount of smoothing for calendar time appeared to matter more than that of temperature (Figure 4.5, first and second panels). Moreover, controlling for relative humidity tended to attenuate relative risk estimates towards the null (Figure 4.5, third

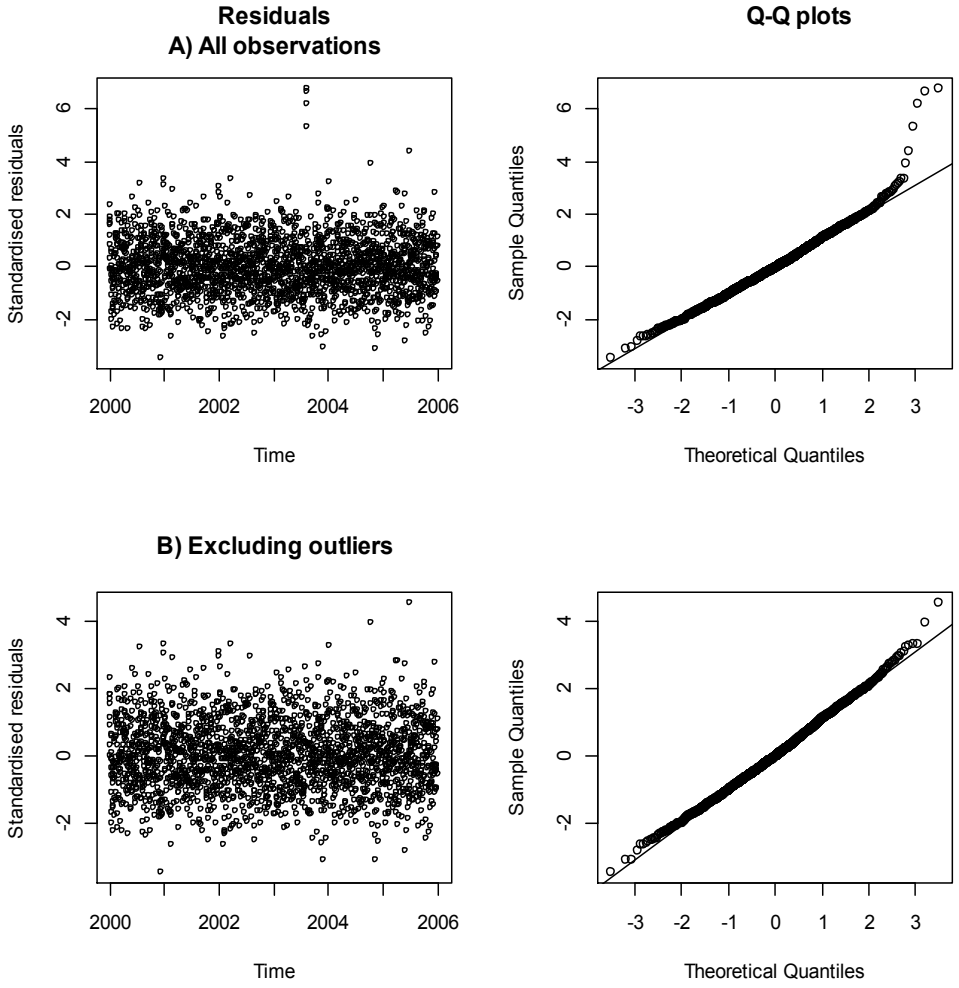
panel). However, similar to London, relative risk estimates were not affected much by the amount of smoothing for relative humidity.

Figure 4.5: Percentage increase (with 95% CI) in non-accidental mortality per IQR increase in delta PM_{10} controlling for temperature, calendar time and relative humidity (RH) at 2-14 df, Hong Kong



As shown in Figure 4.6, there were a few extreme observations in London mainly during August 2003. These excessive mortality counts were probably the consequence of the extreme temperature during the 2003 heat wave episode in London (Kovats et al., 2006). Excluding those outlying data points from the models substantially attenuated risk estimates towards the null as presented in Table 4.6. Moreover, the conventional lag 1 PM_{10} metrics was no longer significantly associated with cardiovascular and respiratory mortality after removing the outliers. Otherwise, in terms of statistical significance, the results were not much different qualitatively from those based on the full data set. Hence, the overall conclusions from this study will be based on analyses on the full dataset.

Figure 4.6: Residuals and q-q plots before and after excluding outliers, London



For the Hong Kong data set, there were no such obvious outlying observations in both models with and without controlling for relative humidity (Figure 4.7).

Figure 4.7: Residuals and q-q plots before and after controlling for RH, Hong Kong

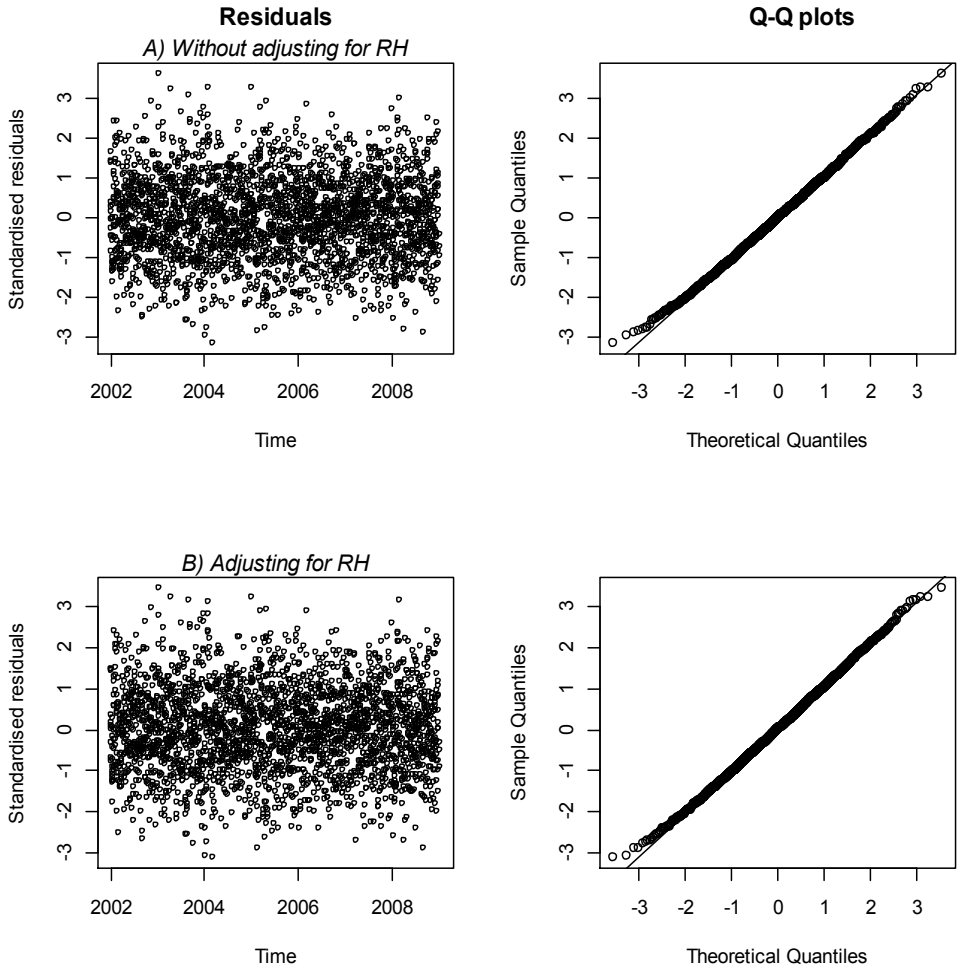
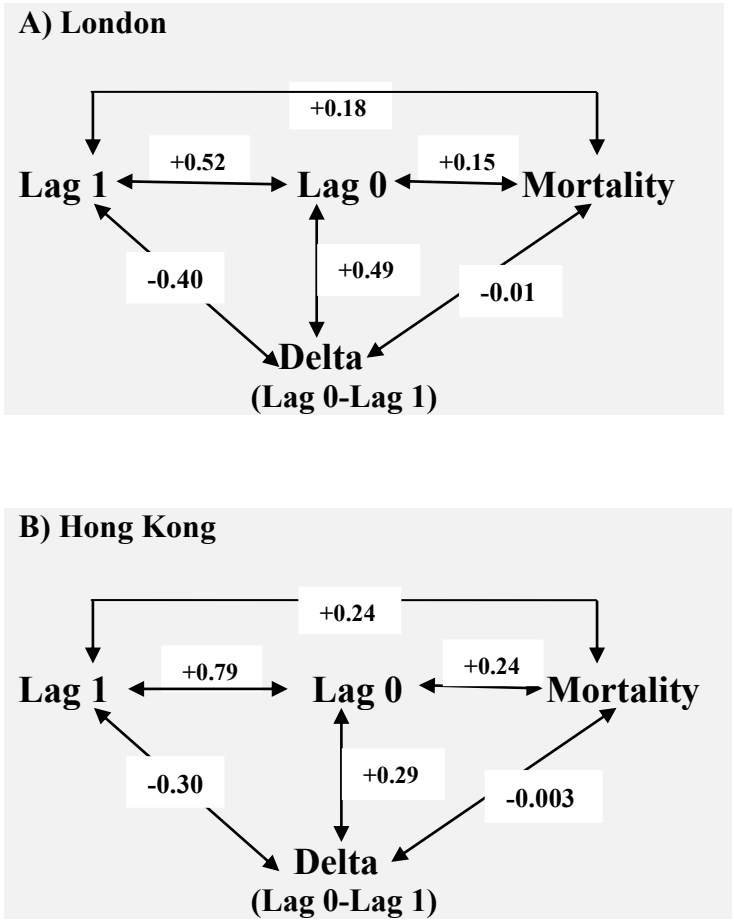


Table 4.6: Percentage increase (95% CI) in mortality per IQR increase in PM_{10} metric by cause of death after excluding outliers in London

London	**Non-accidental**	**Cardiovascular**	**Respiratory**
Conventional metrics (PM_{10}, $\mu g/m^3$)			
Lag1 PM_{10}	0.54(0 .13, 0.95)	0.36(-0.31, 1.03)	0.94(-0.14, 2.03)
Delta metrics (ΔPM_{10}, $\mu g/m^3$)			
ΔPM_{10}	-0.47(-0.86, -0.08)	-0.07(-0.71, 0.57)	-1.08(-2.10, -0.05)
Lag1 PM_{10} +ΔPM_{10}	0.39(-0.08, 0.85) + -0.29(-0.73, 0.16)	0.43(-0.33, 1.2) + 0.14(-0.59, 0.87)	0.49(-0.75, 1.75)+-0.85(-2.03, 0.35)
Relative delta metrics ($R\Delta PM_{10}$, no units**)**			
$R\Delta PM_{10}$	-0.54(-0.96, -0.12)	-0.25(-0.94, 0.45)	-0.90(-2.0, 0.22)
Lag1 PM_{10} + $R\Delta PM_{10}$	0.38(-0.07, 0.84)+ -0.36(-0.83, 0.11)	0.31(-0.13, 0.77)+ -0.11(-0.88, 0.67)	0.69(-0.51, 1.91)+-0.58 (-1.82, 0.67)

It was reported above that both delta and relative delta showed negative associations with cause-specific mortality in single metric models. Some of those associations became positive after adjusting for lag 1 PM_{10} particularly in Hong Kong. Figure 4.8 below illustrates the interrelationship between mortality and the various PM_{10} metrics. For both London and Hong Kong, delta showed negative correlation with lag 1 PM_{10} and mortality which themselves were positively correlated. This could be a possible reason for the observed difference in the coefficients of delta before and after adjusting for lag 1 PM_{10}.

Figure 4.8: Schematics for interrelationships between non-accidental mortality, delta, lag 0 and lag 1 PM_{10} using pairwise correlation coefficients



4.4. Discussion

This study proposed two alternative metrics for PM_{10} based on changes of the 24 hour mean concentrations over successive days. The first, delta PM_{10}, is merely the difference in absolute PM_{10} concentrations between successive days whereas the second, relative delta PM_{10}, is computed by dividing delta PM_{10} on a given day by the respective lag 1 PM_{10} concentration. Consequently, it is equally valid to refer to both these change metrics (delta) as rate of change metrics since they measure the extent of changes in pollution concentrations over a period of one day.

In theory, the delta approach to exposure metrics could help to directly evaluate the effect of change or rate of change in pollution over a period of one day in time series models. This is not the same as the conventional metric models where risk estimates are per unit increase in the exposure between any two days in the series whereas risk estimates from the delta metrics are per unit increase in the change or the rate of change in exposure (from one day to the next). Hence, the interpretation of delta parameters is different from those of absolute metric parameters in time series models. Though the interpretations are not equivalent, the parameter estimates for the delta PM_{10} models can be computed directly from the conventional unconstrained distributed lag model parameters (of lags 0 and 1).

In this study, the conventional PM_{10} metrics at lag 1 showed consistent positive association with mortality in both Hong Kong and London (except for respiratory deaths in Hong Kong) which is in agreement with previous time series studies (Katsouyanni et al., 2009, Peng et al., 2006, Samet et al., 2000). Contrary to the proposed hypothesis (*a priori* expectation) both delta and relative delta showed negative associations with cause-specific mortality particularly in single metric models. This could be due to a relatively stronger

negative correlation of delta and relative delta with lag 1 PM_{10} which is positively related with mortality, i.e., the relationship could have been confounded by lag 1 as illustrated in Figure 4.8. In addition to attenuation of risk estimates, presence of measurement error in a covariate may also transfer part or all of the effect to another correlated covariate in the model if the latter had much lower measurement error (Zidek et al., 1996, Zeger et al., 2000, Thomas, 2014).

There have been very few studies investigating associations of daily changes in exposure with health outcomes of interest and none have considered PM_{10} pollution exposure. For example, Guo et al. (2011) and Nastos et al. (2006) studied daily changes in temperature in relation to daily mortality series and childhood asthma admissions respectively. The latter applied Pearson's χ^2 test and multivariate methods after categorizing the daily changes into quintiles and reported that overall such metrics did not show any association except for changes in minimum temperature. On the other hand, Guo et al. (2011) used the change metrics in time series models and considered delta both on a continuous scale as well as after categorizing into three groups. They reported significant associations of large changes (whether negative or positive) with increased mortality.

Unlike the results from temperature studies, this study suggested that illustrating delta effects would be more complex in time series studies of air pollution where only increases are expected to have an adverse effect in a linear fashion (Katsouyanni et al., 2009, Samet et al., 2000, Le Tertre et al., 2002, Dominici et al., 2003b). For temperature, J-, U-, or V-shaped relationships have been reported (Armstrong, 2006, Braga et al., 2002, Armstrong et al., 2011) and, as shown by Guo et al. (2011), both negative and positive extremes in delta metrics could be related to health outcomes in a consistent direction. However,

relative delta measures were not considered in previous studies. For example, a change from 10 to 20 units (100% change) would be considered the same as a change from 40 to 50 units (25% change); in addition, the equivalence of delta models with conventional unconstrained distributed lag models was not recognised.

The findings from this study (which did not suggest much effect of daily changes on their own) could give an impression of agreement with previous studies which analysed exposure at various time scales and reported stronger effects for long-term exposures than for short-term exposures like delta (Dominici et al., 2003a, Schwartz, 2000b, Valari et al., 2011). Nevertheless, such comparisons cannot be considered direct and could be inappropriate due to the different approaches used in exposure classification. While the delta metrics could provide a convenient interpretation biologically, the inconsistency of results between London and Hong Kong is not straightforward to explain. It could perhaps be related to the difference in average baseline PM_{10} concentrations (26 $\mu g/m^3$ in London and 54 $\mu g/m^3$ in Hong Kong). The more pronounced delta effect observed in Hong Kong could be indicating that large increases in delta PM_{10} would have severe impact on daily mortality as the average PM_{10} concentration in Hong Kong was more than double compared to London over the respective study periods.

Limitations of the absolute metrics are expected to be more or less reflected on delta. Issues like exposure measurement error could have more impact on delta than the absolute metrics as variability in delta could generally be larger as shown in Chapter 3. The estimates for the delta metrics were also less precise and were inconsistent between London and Hong Kong. In addition, only PM_{10} exposures were investigated using data from two cities and rate of changes over a period of one day. Future studies could extend

the time period for rate of change measures and include other air pollutants, preferably using a multi-city framework.

Overall, there was some evidence for an effect of the delta metrics when used together with lag 1 PM_{10} in Hong Kong though this was much less convincing for London; also controlling for delta, in general, resulted in increased lag 1 PM_{10} effect estimates with some exceptions for London and respiratory mortality. If these associations could be shown consistently in further studies, this would support the hypothesis based on biological precedent that changes or rate of changes in exposure are important in determining the effect of particulate pollution on health; and that this can be explored by using the delta approach. This in turn could influence air quality guidelines as controlling for rate of changes of pollution would become important. However, the delta metrics alone does not seem to explain variations in mortality sufficiently.

5. THE EFFECT OF SHORT-TERM EXPOSURE PATTERNS ON THE RELATIONSHIP BETWEEN AIR POLLUTION AND MORTALITY IN TIME SERIES STUDIES

5.1. Introduction

Several epidemiologic studies have demonstrated convincing evidence of the adverse health effects of air pollution mainly from cardiovascular and respiratory causes (Atkinson et al., 1999, Samet et al., 2000, Anderson et al., 2007, Katsouyanni et al., 2009). Most of the evidence on short-term effects of air pollution comes from studies using times series models (Anderson et al., 2001, Bell et al., 2004). Such studies model the relationship between daily pollutant concentrations and the daily number of health events in a study population. Without any loss of generality consider daily mortality and PM_{10}. Both measures are time series, being measured daily over the years. Deaths exhibit serial dependence arising from time dependent risk factors such as weather and seasonality. Pollution measures are usually serially correlated because of factors related to the sources and weather.

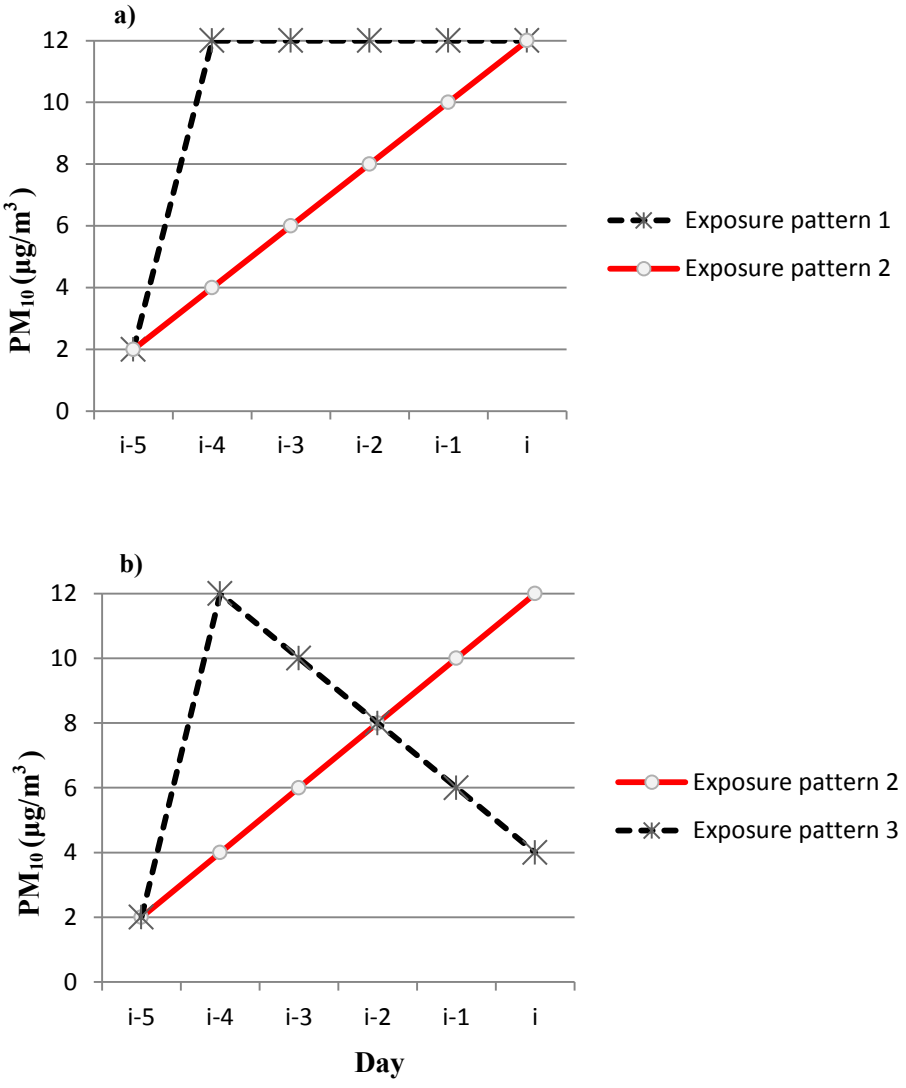
Conventional epidemiologic time series studies do not utilize the serial dependence in the model specification. Indeed, the goal is usually to control for seasonality to remove serial correlation in the health time series. The resulting regression model relates risk of death to PM_{10} concentration on a log scale. So, for example, when a 10 $\mu g/m^3$ increment in PM_{10} is associated with a 1% increase in mortality (RR=1.01) the interpretation will be as follows: on a day when the PM_{10} concentration is, say 12 $\mu g/m^3$, the risk of death is increased by 1% compared to a day when the concentration is 2 $\mu g/m^3$. There is no requirement for the two days to be sequential, i.e., the relationship ignores time sequence.

Now consider the following two exposure pattern scenarios:

I) on day *i-5* PM_{10} was 2 µg/m^3. On day *i*-4 PM_{10} was 12 µg/m^3 and remained constant (at 12 µg/m^3) on days *i*-3 to *i* (Exposure pattern 1, Figure 5.1a).

II) on day *i-5* PM_{10} was 2 µg/m^3. On day *i* PM_{10} was 12 µg/m^3. Assume the pollution increased by 2 µg/m^3 per day over the five days (Exposure pattern 2, Figure 5.1a).

Figure 5.1: Exposure pattern scenarios over the course of six days with a) unequal and b) equal cumulative exposure levels



A conventional time series study cannot answer the question 'would the health effects of the changes in PM_{10} (from 2 to 12 μg/m^3) for the two scenarios presented in Figure 5.1a (one incremental over a period of five days and the other all in one go over one day) be the same?' as it cannot differentiate the two exposure patterns.

However, the comparison of the two scenarios as framed above is arguably unfair since the cumulative exposures were not the same. Perhaps a better comparison would be as presented in Figure 5.1b (where the cumulative exposure under the two scenarios is the same, i.e., 2+4+6+8+10+12=42 μg/m^3).

The aim of this study was thus to investigate the impact of accounting for such short-term patterns of air pollution exposure on mortality risk estimates in time series studies.

5.2. Methods

5.2.1. Data

The same data sets as described in Chapter 4 from London (2000-2005) and Hong Kong (2002-2008) were analysed for this study. In brief, daily data on 24-hour average concentrations of PM_{10}, weather and mortality from respiratory (ICD-10 Chapter J), cardiovascular (ICD-10 Chapter I) and all non-accidental (ICD-10 Chapters A–R) causes were collected from both cities. Further detailed description of the data collection for London (Atkinson et al., 2010) and Hong Kong (Wong et al., 2002) can be found elsewhere.

5.2.2. Defining exposure patterns

First '*delta* PM_{10}' values were computed as the change in mean absolute PM_{10} concentrations between consecutive days as described in Chapter 4. Then three ways of defining and searching specific exposure patterns were proposed. Figure 5.2 would be useful to guide the characterization of patterns in this manner (an example with reference to this Figure is provided in the next section). The definitions were based on the following characteristics of exposure patterns within a given (short) period of time:

1. Number of peaks for PM_{10}
2. Number of positive values of delta PM_{10}
3. Number of peaks for delta PM_{10}

For this study one week period was used as the definitive study window. Two approaches were considered to explore PM_{10}—mortality relationships taking into account these exposure patterns.

The first approach involved grouping the data into blocks of non-overlapping weeks starting on the 1st day of the time series and then identification of specific patterns within each week and corresponding mortality measures. This process transformed the daily time series to weekly aggregated data series and was mainly used for exploratory analysis (referred to as the weekly approach).

The second approach, which is the primary aim of this analysis, involved identifying similar exposure patterns as above except that it generated pattern data for blocks of seven days starting with each day rather than considering sequential non-overlapping seven day periods (referred to as the daily approach). This generated much more data and did not impose artificial decisions on the starting point for the analysis.

5.2.3. Pattern identification

5.2.3.1. The weekly approach

This approach is summarised as follows for each of the three cases (for which an example is given using Figure 5.2 below).

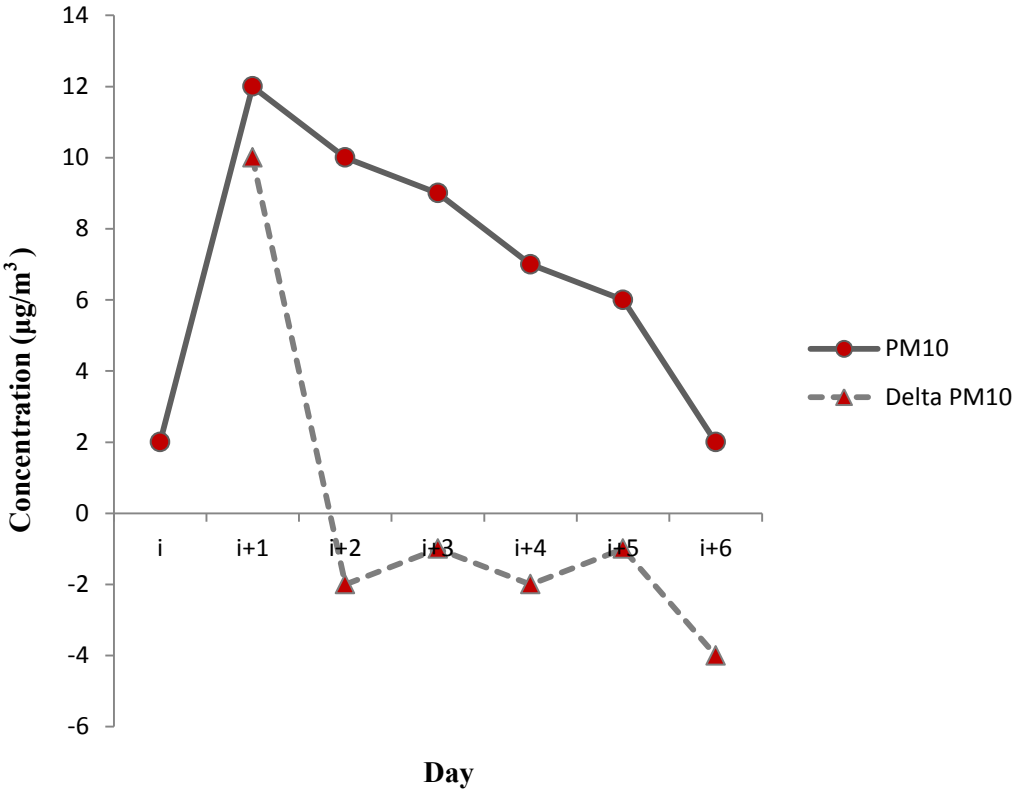
Case 1-The number of peaks of PM_{10} in each block; the range for the number of peaks of PM_{10} will be between 0 and 3.

Case 2-The number of positive delta PM_{10} values in each block; the range for the number of positive delta values will be between 0 and 7.

Case 3-The number of peaks of delta PM_{10} in each block; the range for the number of delta peaks will be between 0 and 3.

Data were grouped into sequential blocks of seven days starting on the 1st day of the data series. Then exposure patterns were identified for each of the three cases by counting the number of occurrences within each block. For example, in the hypothetical data presented in Figure 5.2, there was only one peak for PM_{10}, one positive delta PM_{10} (i.e., one increase in PM_{10}) and two peaks for delta PM_{10} over the six day period window. This corresponds to exposure pattern 3 in Figure 5.1b presented above.

Figure 5.2: Exposure patterns of absolute PM_{10} and delta PM_{10} based on hypothetical data over a six day period



5.2.3.2. The daily approach

For the daily approach, the above procedure was extended by identifying the pattern data for each block in the same way, but specifying the definition of a block as the seven day period starting on each day of the time series in turn.

5.2.3.3. Outcome measure

For both approaches mortality at the end of each block (the day following each seven day window) was used as the outcome measure.

5.2.4. Additional sensitivity analyses

a) Tolerance for pattern search

The above procedure for pattern identification was set up based on simple comparison of three data points for detection of each peak or based on the criteria delta>0 for number of positive delta with no minimum criteria on the magnitude of differences. Thus, a supplementary sensitivity analysis was conducted by searching patterns in the same way as described above, but with a tolerance of one standard deviation for each comparison in searching peaks for PM_{10} and delta. For number of positive delta this would count patterns with delta>SD rather than delta>0.

b) Cumulative exposure effect

A further sensitivity analysis was also performed using the average of the cumulative PM_{10} concentrations over the previous week (i.e., for lags 0-6) instead of lag 1 PM_{10}. The aim of this analysis was to check whether any observed pattern effects were artefacts of the cumulative exposure over the week on which patterns were defined.

5.2.5. Statistical analysis

Poisson generalized additive models (GAMs) were used to examine whether the defined exposure patterns could influence pollution—mortality relationships. Models were adjusted for potential confounding by temperature, long-term time trends and seasonality and day of the week effects (Dominici et al., 2002, Hastie and Tibshirani, 1986, Katsouyanni et al., 2009).

More specifically, the interaction between PM_{10} at lag 1 and the three exposure patterns was modelled using model 5.1 as given below:

$$\mathrm{Log}[\mathrm{E}(\mathrm{Y_t})] = \alpha + \beta P_{t-1} + \lambda E_t + \theta(E_t * P_{t-1}) + \sum_{i=1}^{k} f_i(X_{ti}) \qquad (5.1)$$

where t is day of observation,Y is mortality count, P_{t-1} is PM_{10} at lag 1, E is exposure pattern (categorical variable), E*P interaction terms for exposure pattern and PM_{10} at lag 1, α is the intercept, β is log relative risk (RR) associated with PM_{10} at lag 1, λ and θ are vectors of coefficients for categories of E and E*P respectively, $f_i(X_{ti})$ represent smooth functions of confounders (X_{ti}) which included temperature with 3 degrees of freedom (df), long-term time trends and seasonality with 8 df per year and day of the week. Choice of modelling approach and smoothing parameters is mostly guided by the APHENA study protocol as detailed in Chapter 4 (Katsouyanni et al., 2009). Stratified relative risks were calculated from model (5.1) using daily patterns data (daily patterns approach) whereas the weekly pattern data were used for descriptive purposes only. All the analyses were performed using the R statistical package (R Core Team, 2012).

5.3. Results

Detailed descriptive statistics for the data sets used for this study can be found in Chapter 4. In brief, PM_{10} data were acquired for a total of 2192 days (delta PM_{10} values on 2191 days) in London and 2557 days (delta PM_{10} values on 2556 days) in Hong Kong over the study period of six and seven years respectively. For the daily exposure pattern data, the total number of days was further reduced from 2191 to 2184 in London and from 2556 to 2549 in Hong Kong as the first daily pattern observation was only available on the ninth day; in other words the first seven observations were omitted. The median absolute PM_{10} and delta PM_{10} concentrations were 23 $\mu g/m^3$ and 0.7 $\mu g/m^3$ in London and 48.6 $\mu g/m^3$ and 0.11 $\mu g/m^3$ in Hong Kong respectively. The medians for daily number of mortality counts from non-accidental, cardiovascular and respiratory causes were 145, 54 and 22 respectively in London while rates were lower in Hong Kong with corresponding daily mortality of 95, 26 and 18 (Chapter 4, Table 4.1). There was a moderate correlation (0.49 in London and 0.29 in Hong Kong) between delta and absolute PM_{10} measurements (Chapter 4, Table 4.2).

5.3.1. Weekly pattern analysis

A summary of the weekly pattern data is given in Table 5.1. For London, the daily time series data resulted in 312 non-overlapping blocks used for exploring the weekly patterns. For absolute PM_{10}, one peak (50.6%) and two peaks (42.6%) per week were most common, whereas for delta, two peaks were most common (61.9%) followed by single peak (32.1%). About 71% of the blocks had three or four number of positive deltas per week with four positives the most frequent (40.7%). The average mortality per pattern level was highest (162) for three peaks per week for absolute PM_{10} peaks, being lower for

weeks with fewer peaks. Such a trend was not seen for delta peaks and the number of positive delta values. The highest average mortality was observed for the lowest categories (0 for number of delta peaks and 1 for number of positives delta); nevertheless these categories occurred rarely (Table 5.1).

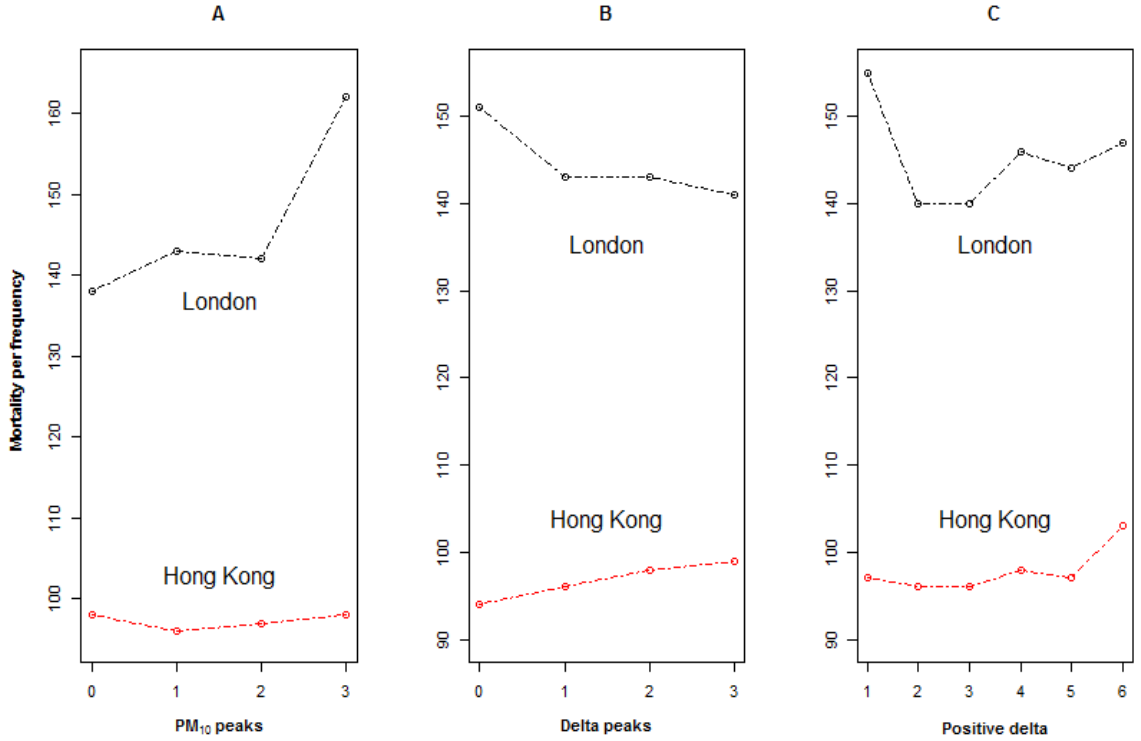
Table 5.1: Pattern frequency and mortality[§] measures per each pattern level for weekly pattern data

	London			Hong Kong		
Pattern metric	**Frequency (%)**	**Total mortality**	**Mortality per frequency**	**Frequency (%)**	**Total mortality**	**Mortality per frequency**
PM_{10} peaks						
0	11 (3.5)	1516	138	22 (6)	2152	98
1	158 (50.6)	22575	143	205 (56.3)	19654	96
2	133 (42.6)	18939	142	125 (34.3)	12330	97
3	10 (3.2)	1623	162	12 (3.3)	1177	98
Delta peaks						
0	3 (1)	453	151	9 (2.5)	844	94
1	100 (32.1)	14347	143	134 (36.8)	12826	96
2	193 (61.9)	27593	143	200 (54.9)	19560	98
3	16 (5.1)	2260	141	21 (5.8)	2083	99
Number of positive delta						
1	1 (0.3)	155	155	9 (2.5)	875	97
2	32 (10.3)	4486	140	52 (14.3)	4976	96
3	92 (29.5)	12835	140	121 (33.2)	11670	96
4	127 (40.7)	18520	146	115 (31.6)	11244	98
5	50 (16)	7192	144	58 (15.9)	5620	97
6	10 (3.2)	1465	147	9 (2.5)	928	103

[§]Based on daily non-accidental mortality on the day just after the end of the exposure week for pattern identification

In Hong Kong the time series data resulted in 364 non-overlapping blocks of weeks and the distribution of pattern data was more or less similar to that of London. However, there was less variation in average mortality per pattern level and the highest mortality, 103, was observed for the six positive deltas per week group (Table 5.1). In both cities, the average mortality per pattern level showed an increasing trend with increasing pattern levels except for delta PM_{10} in London (Figure 5.3).

Figure 5.3: Short-term exposure patterns and average non-accidental mortality per pattern frequency based on weekly pattern data (A) Number of PM_{10} peaks (B) Number of delta peaks (C) Number of positive delta



5.3.2. Daily rolling pattern analysis

5.3.2.1. PM_{10} peaks

The distribution of daily patterns and corresponding mortality measures are summarised in Table 5.2. In London, weeks with a single absolute PM_{10} peak were most common (54.3%) followed by two peaks per week (38.6%). Average mortality per pattern level was highest for three peaks per week compared to weeks with fewer peaks. There was no variation in average mortality for weeks with peaks between zero and two. In Hong Kong, PM_{10} peaks had similar distribution with that of London (single and double peaks per week were about 55.1% and 34.6% respectively) but showed little variation in average mortality between pattern levels (Table 5.2).

Table 5.2: Summary of pattern frequency and mortality[§] per each pattern level for daily pattern data

Pattern metric	Frequency (%)	Non-accidental		Cardiovascular		Respiratory	
		Total mortality	Mortality/ frequency	Total mortality	Mortality/ frequency	Total mortality	Mortality/ frequency
PM_{10} peaks			**London**				
0	109 (5.0)	16069	147	5959	55	2320	21
1	1185 (54.3)	173539	147	64391	54	26572	22
2	844 (38.6)	124072	147	46043	55	19744	23
3	46 (2.1)	7020	153	2608	57	1163	25
Delta peaks							
0	24 (1.1)	3517	147	1368	57	480	20
1	833 (38.1)	122560	147	45575	55	18957	23
2	1234 (56.5)	180858	147	67020	54	28110	23
3	93 (4.3)	13765	148	5038	54	2252	24
Number of positive delta							
0	1 (0.05)	172	172	72	72	32	32
1	12 (0.6)	1660	138	592	49	246	21
2	206 (9.4)	29185	142	10721	52	4422	22
3	669 (30.6)	96880	145	35989	54	14981	23
4	865 (39.6)	128564	149	47696	55	20097	23
5	369 (16.9)	55109	149	20534	56	8623	23
6	62 (2.8)	9130	147	3397	55	1398	23
PM_{10} peaks			**Hong Kong**				
0	221 (8.7)	21301	96	6016	27	4065	18
1	1404 (55.1)	133462	95	36986	26	25253	18
2	881 (34.6)	85489	97	23546	27	16781	19
3	43 (1.7)	4219	98	1197	28	830	19
Delta peaks							
0	51 (2.0)	4777	94	1297	25	905	18
1	990 (38.8)	94036	95	25985	26	17757	18
2	1402 (55.0)	135251	96	37535	27	26199	19
3	106 (4.2)	10407	98	2928	28	2068	20
Number of positive delta							
0	3 (0.1)	299	100	79	26	61	20
1	53 (2.1)	5091	96	1427	27	1010	19
2	361 (14.2)	33533	93	9200	25	6291	17
3	887 (34.8)	85214	96	23568	27	16495	19
4	782 (30.7)	75526	97	20848	27	14509	19
5	384 (15.1)	37148	97	10448	27	7134	19
6	76 (3.0)	7378	97	2113	28	1368	18
7	3 (0.1)	282	94	62	21	61	20

[§]Based on daily cause specific mortality on the day just after the end of the exposure week for pattern identification

In London, mortality risk from each cause was highest for the 3 peaks per week group. The percentage increases per 10 μg/m^3 increase in PM_{10} at lag 1 were 6.46 (95% CI: 3.55, 9.45) for non-accidental, 7.65 (95% CI: 2.86, 12.65) for cardiovascular and 9.95 (95% CI: 1.70, 18.86) for respiratory mortality. These were much larger compared to the estimates without adjusting for any patterns; 0.82 (95% CI: 0.45, 1.18) for non-accidental, 0.73 (95% CI: 0.12, 1.33) for cardiovascular and 1.47 (95% CI: 0.49, 2.46) for respiratory mortality (Table 5.3). There was an increasing tendency of the relative risk with increasing number of PM_{10} peaks per week (Figure 5.4). However, similar effects were not replicated for Hong Kong in terms of statistical significance. Yet, the percentage increase estimates in the three peaks per week group 0.74 (95% CI: -0.47, 1.97) and 2.05 (95% CI: -0.69, 4.86) for non-accidental and respiratory mortality were still considerably greater than the corresponding conventional estimates, 0.47 (95% CI: 0.29, 0.64) and 0.32 (95% CI: -0.09, 0.73) respectively.

5.3.2.2. Delta PM_{10} peaks

In London, double peaks per week were most common (56.5%) followed by a single peak per week (38.1%). The average mortality per pattern level was more or less the same (between 147 and 148) at all levels of delta peaks (Table 5.2). Hong Kong had comparable distribution of delta peaks with London; double (55.0%) and single (38.8%) peaks per week were most common. Average mortality per pattern level for delta peaks was also comparable with that of PM_{10} peaks and did not seem to vary hugely between levels of delta peaks (Table 5.2).

In London, the highest mortality risk was for the three delta peaks per week group similar to the observation for absolute PM_{10} peaks. For three delta peaks per week group, the percentage changes in non-accidental, cardiovascular and respiratory mortality per 10 $\mu g/m^3$ increase in PM_{10} at lag 1 were 2.28 (95% CI: 0.81, 3.78), 1.88 (95% CI: -0.55, 4.38) and 5.95 (95% CI: 1.82, 10.25) respectively. These were also greater than the respective percentage increase estimates obtained without adjusting for delta peaks (Table 5.3, Figure 5.4). However, such relationships with delta peaks were not seen in Hong Kong (Table 5.3, Figure 5.4).

Table 5.3: Stratified percentage increases (95% CI) in mortality per 10 μg/m^3 increase in PM_{10}

Pattern	Non-accidental	Cardiovascular	Respiratory
London			
PM_{10} peaks			
0	0.57 (-0.59, 1.75)	0.24 (-1.65, 2.18)	1.89 (-1.25, 5.13)
1	0.35 (-0.11, 0.81)	0.11 (-0.65, 0.87)	0.7 (-0.53, 1.95)
2	1.73 (1.05, 2.41)	2.01 (0.89, 3.14)	3.69 (1.84, 5.56)
3	6.46 (3.55, 9.45)	7.65 (2.86, 12.65)	9.95 (1.7, 18.86)
Delta peaks			
0	1.55 (-0.81, 3.96)	2.8 (-1.15, 6.92)	1.16 (-4.94, 7.65)
1	0.81 (0.25, 1.38)	1.2 (0.27, 2.14)	0.47 (-1.03, 1.99)
2	0.71 (0.23, 1.2)	0.22 (-0.56, 1.01)	1.98 (0.69, 3.29)
3	2.28 (0.81, 3.78)	1.88 (-0.55, 4.38)	5.95 (1.82, 10.25)
Number of positive delta			
0-2	0.42 (-1.46, 2.33)	-1.95 (-4.94, 1.14)	3.25 (-1.97, 8.74)
3	-0.19 (-1.1, 0.74)	-0.4 (-1.9, 1.12)	0.78 (-1.63, 3.25)
4	1.81 (1.21, 2.41)	1.73 (0.75, 2.72)	3.87 (2.24, 5.53)
5-6	1.81 (1.17, 2.45)	1.73 (0.68, 2.79)	3.87 (2.13, 5.64)
Unadjusted			
	0.82 (0.45, 1.18)	0.73 (0.12, 1.33)	1.47 (0.49, 2.46)
Hong Kong			
PM_{10} peaks			
0	0.41 (0.03, 0.8)	0.83 (0.08, 1.58)	-0.28 (-1.17, 0.61)
1	0.48 (0.26, 0.7)	0.35 (-0.07, 0.77)	0.67 (0.16, 1.18)
2	0.42 (0.11, 0.73)	0.52 (-0.07, 1.12)	0.03 (-0.69, 0.76)
3	0.74 (-0.47, 1.97)	-0.03 (-2.31, 2.3)	2.05 (-0.69, 4.86)
Delta peaks			
0	0.01 (-0.73, 0.75)	0.32 (-1.1, 1.77)	-1.51 (-3.22, 0.23)
1	0.5 (0.26, 0.74)	0.66 (0.19, 1.12)	0.62 (0.05, 1.18)
2	0.46 (0.24, 0.69)	0.48 (0.04, 0.92)	0.35 (-0.18, 0.88)
3	0.43 (-0.28, 1.14)	0.58 (-0.78, 1.95)	-1.11 (-2.71, 0.52)
Number of positive delta			
0-2	0.26 (-0.22, 0.75)	0.34 (-0.6, 1.29)	0.1 (-1.04, 1.24)
3	0.52 (0.23, 0.82)	0.49 (-0.08, 1.06)	0.71 (0.02, 1.4)
4	0.21 (-0.08, 0.51)	-0.05 (-0.61, 0.51)	0.27 (-0.41, 0.95)
5-6	0.42 (0.09, 0.74)	0.67 (0.05, 1.29)	-0.3 (-1.04, 0.45)
Unadjusted			
	0.47 (0.29, 0.64)	0.57 (0.23, 0.9)	0.32 (-0.09, 0.73)

5.3.2.3. Number of positive delta values

In London, about 71% of the weeks had three or four positive deltas with four positives the most frequent (nearly 40%). The highest mortality count per pattern frequency (172 deaths) was observed for weeks in which the number of positive delta values was zero but this occurred only once. If we disregarded this observation, then there would be more or less increasing trend of mortality counts as the number of positive deltas increased (Table 5.2). Likewise, three (34.8%) and four (30.7%) positive deltas were more common in Hong Kong. Compared to London, average mortality per pattern varied little in Hong Kong and the highest average mortality per pattern observed for zero positive deltas which occurred very rarely (Table 5.2).

Like the previous two pattern metrics, weeks with larger number of positive deltas (greater than or equal to four positive deltas per week) resulted in higher mortality risk estimates in London. For the group with more five or more positive deltas, the percentage changes in non-accidental, cardiovascular and respiratory mortality per 10 $\mu g/m^3$ increase in PM_{10} at lag 1 were 1.81 (95% CI: 1.17 to 2.45), 1.73 (95% CI: 0.68 to 2.79) and 3.87 (95% CI: 2.13 to 5.64) respectively. Again, these were greater than the respective unadjusted estimates (Table 5.3, Figure 5.4). Such effect of number of positive deltas on relative risk estimates was not apparent for Hong Kong (Table 5.3, Figure 5.4).

Figure 5.4: Percentage increases in mortality per 10 μg/m^3 increase in PM_{10} stratified by exposure patterns (A) Unadjusted for any pattern (B) Number of positive delta (C) Number of PM_{10} peaks and (D) Number of delta peaks

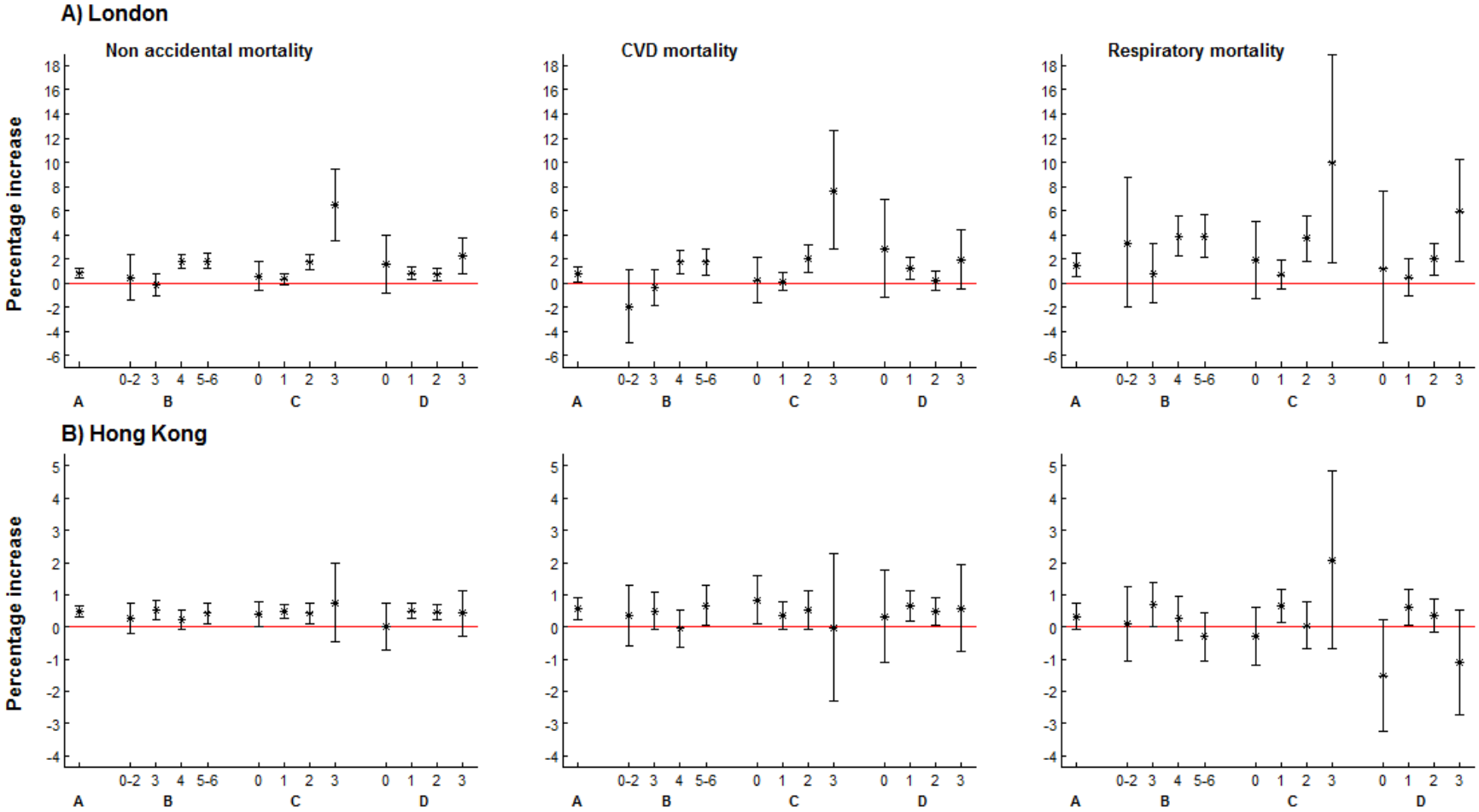


Table 5.4 presents estimates for percentage increases in mortality from each cause per 10 μg/m^3 increase in lag 1 PM_{10} after adjusting for relative humidity in Hong Kong. Overall, the additional control for relative humidity attenuated effect estimates but resulted in little change with respect to significance of pattern effects. The attenuation of excess risk estimate was also observed for the unadjusted model.

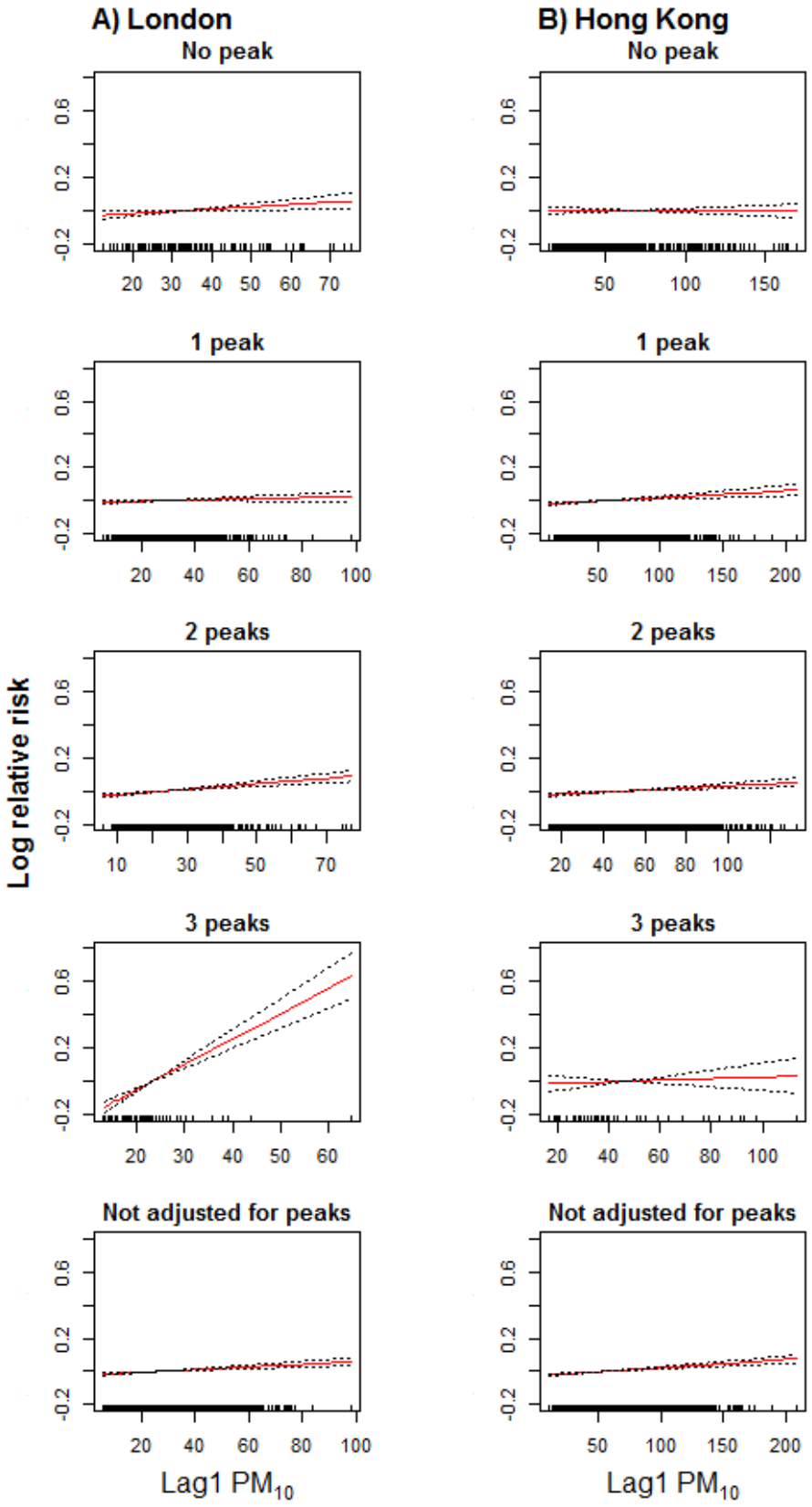
Table 5.4: Stratified percentage increases (95% CI) in mortality per 10 μg/m^3 increase in PM_{10} after additional control for RH in Hong Kong

Pattern	Non-accidental	Cardiovascular	Respiratory
PM_{10} peaks			
0	0.34 (-0.05, 0.73)	0.71 (-0.04, 1.46)	-0.32 (-1.21, 0.57)
1	0.34 (0.11, 0.57)	0.12 (-0.31, 0.56)	0.57 (0.04, 1.1)
2	0.26 (-0.06, 0.58)	0.26 (-0.35, 0.88)	-0.11 (-0.85, 0.63)
3	0.55 (-0.67, 1.78)	-0.37 (-2.65, 1.97)	1.92 (-0.83, 4.74)
Delta peaks			
0	-0.02 (-0.76, 0.72)	0.26 (-1.17, 1.71)	-1.46 (-3.17, 0.28)
1	0.39 (0.14, 0.63)	0.47 (0, 0.95)	0.53 (-0.04, 1.11)
2	0.31 (0.07, 0.55)	0.23 (-0.23, 0.69)	0.22 (-0.33, 0.77)
3	0.26 (-0.45, 0.98)	0.31 (-1.05, 1.69)	-1.28 (-2.89, 0.36)
Number of positive delta			
0-2	0.16 (-0.33, 0.65)	0.17 (-0.77, 1.13)	0.01 (-1.13, 1.16)
3	0.39 (0.09, 0.69)	0.29 (-0.29, 0.87)	0.58 (-0.12, 1.29)
4	0.08 (-0.22, 0.37)	-0.27 (-0.84, 0.3)	0.17 (-0.52, 0.87)
5-6	0.3 (-0.02, 0.63)	0.49 (-0.13, 1.12)	-0.36 (-1.12, 0.39)
Unadjusted			
	0.33 (0.15, 0.51)	0.35 (0, 0.71)	0.21 (-0.23, 0.64)

5.3.3. Exposure-response relationship in pattern analysis models

Figure 5.5 shows the exposure-response relationship between non-accidental mortality and PM_{10} at lag 1 stratified by number of PM_{10} peaks as well as for the model not adjusted for any pattern. In London, the highest responses appear to be driven by weeks with two or three peaks while the unadjusted model seems to reflect responses only for weeks with zero or one peak in PM_{10}. However, for Hong Kong the unadjusted and stratified responses were fairly similar.

Figure 5.5: Exposure-response relationship between non accidental mortality and PM_{10} at lag 1 stratified by number of PM_{10} peaks



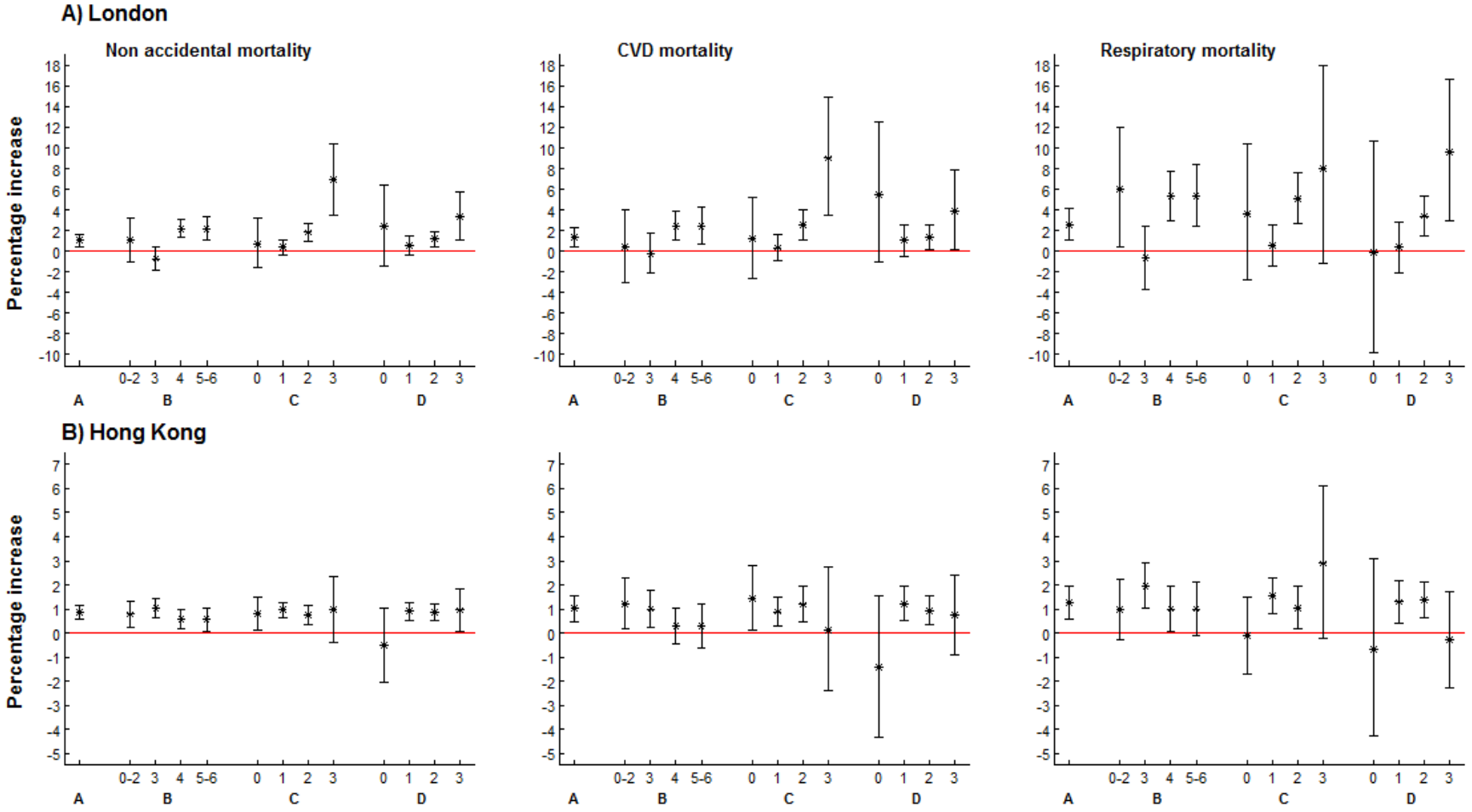
5.3.4. Average cumulative exposure

The estimates for the percentage increase in mortality related to the average cumulative PM_{10} concentration for lags 0-6 are presented in Table 5.5. Compared to estimates for lag 1 PM_{10}, the estimates for average cumulative PM_{10} effects were generally elevated for both London and Hong Kong. The elevation in excess risk estimates was observed in both unadjusted and pattern adjusted models. Nevertheless, the overall qualitative conclusions were little affected whether lag 1 or average cumulative was used as the PM_{10} metric (i.e., in terms of the relationship between PM_{10} and mortality taking into account each of the three exposure patterns). There was also a remarkable increasing trend of excess mortality risk estimates with increasing number of positive deltas, PM_{10} peaks and delta peaks in London but not in Hong Kong (Figure 5.6).

Table 5.5: Stratified percentage increases (95% CI) in mortality per 10 μg/m^3 increase in average cumulative PM_{10} exposure (lags 0-6)

Pattern	Non-accidental	Cardiovascular	Respiratory
London			
PM_{10} peaks			
0	0.72 (-1.64, 3.15)	1.18 (-2.71, 5.22)	3.58 (-2.83, 10.42)
1	0.37 (-0.36, 1.12)	0.34 (-0.88, 1.57)	0.53 (-1.41, 2.51)
2	1.82 (0.93, 2.71)	2.56 (1.1, 4.04)	5.09 (2.66, 7.58)
3	6.89 (3.53, 10.36)	9.01 (3.42, 14.89)	7.99 (-1.16, 17.98)
Delta peaks			
0	2.42 (-1.43, 6.41)	5.51 (-1.09, 12.55)	-0.11 (-9.84, 10.67)
1	0.51 (-0.41, 1.43)	1.07 (-0.45, 2.61)	0.37 (-2.05, 2.85)
2	1.18 (0.46, 1.91)	1.31 (0.12, 2.5)	3.41 (1.46, 5.39)
3	3.39 (1.06, 5.78)	3.92 (0.1, 7.88)	9.6 (3.01, 16.6)
Number of positive delta			
0-2	1.05 (-1.06, 3.21)	0.44 (-2.98, 3.99)	6.05 (0.45, 11.95)
3	-0.72 (-1.86, 0.44)	-0.22 (-2.11, 1.7)	-0.65 (-3.65, 2.43)
4	2.19 (1.33, 3.06)	2.46 (1.04, 3.9)	5.37 (2.98, 7.8)
5-6	2.19 (1.12, 3.28)	2.46 (0.69, 4.27)	5.37 (2.46, 8.36)
Unadjusted			
	1.04 (0.45, 1.62)	1.37 (0.43, 2.32)	2.59 (1.05, 4.15)
Hong Kong			
PM_{10} peaks			
0	0.8 (0.11, 1.5)	1.43 (0.11, 2.78)	-0.12 (-1.7, 1.49)
1	0.96 (0.64, 1.28)	0.89 (0.27, 1.5)	1.55 (0.81, 2.31)
2	0.74 (0.36, 1.12)	1.18 (0.45, 1.92)	1.05 (0.16, 1.95)
3	0.98 (-0.38, 2.35)	0.14 (-2.39, 2.73)	2.89 (-0.24, 6.12)
Delta peaks			
0	-0.53 (-2.06, 1.03)	-1.42 (-4.32, 1.56)	-0.66 (-4.27, 3.09)
1	0.9 (0.53, 1.26)	1.22 (0.51, 1.93)	1.29 (0.43, 2.16)
2	0.87 (0.54, 1.19)	0.94 (0.32, 1.56)	1.37 (0.63, 2.12)
3	0.95 (0.08, 1.83)	0.74 (-0.91, 2.42)	-0.28 (-2.26, 1.74)
Number of positive delta			
0-2	0.78 (0.25, 1.32)	1.22 (0.2, 2.26)	0.97 (-0.27, 2.23)
3	1.03 (0.64, 1.43)	1 (0.25, 1.76)	1.96 (1.03, 2.89)
4	0.57 (0.18, 0.96)	0.28 (-0.47, 1.03)	1 (0.09, 1.92)
5-6	0.57 (0.09, 1.05)	0.28 (-0.63, 1.2)	1 (-0.12, 2.13)
Unadjusted			
	0.87 (0.59, 1.15)	1.01 (0.47, 1.55)	1.25 (0.6, 1.92)

Figure 5.6: Percentage increases in mortality per 10 μg/m^3 increase in average cumulative PM_{10} (lags0-6) stratified by exposure patterns (A) Unadjusted for any pattern (B) Number of positive delta (C) Number of PM_{10} peaks and (D) Number of delta peaks



5.3.5. Other cut offs for pattern definition

Both summary of pattern distribution and related excess risk estimates for patterns defined with one standard deviation (SD) tolerance are presented in Table 5.6. Compared to the original definition, the results based on one SD tolerance did not have three PM_{10} peaks per week as well as greater than four positive deltas in both cities. Furthermore, the frequency of some pattern levels was severely diminished. For example, the frequency of two PM_{10} peaks decreased from 38.6% and 34.6% to 0.5% in London and Hong Kong respectively (Table 5.2 and Table 5.6).

In London, single peaks for $PM_{10,}$ double peaks for delta and four positive deltas per week resulted in much greater percentage increase in mortality from each cause compared to the corresponding unadjusted estimates. The percentage increase (95% CI) in non-accidental, cardiovascular and respiratory mortality per 10 $\mu g/m^3$ increase in PM_{10} at lag 1 were 3.07 (2.18, 3.97), 4.23 (2.74, 5.74) and 4.7 (2.25, 7.2) respectively for single PM_{10} peaks, 4.68 (3.37, 6), 4.33 (2.21, 6.49) and 8.47 (4.82, 12.25) respectively for two delta peaks and 3.0 (1.13, 4.9), 3.43 (0.33, 6.62) and 5.4 (0.39, 10.66) respectively for four positive deltas per week. Such large effects were not observed in Hong Kong (Table 5.6).

Table 5.6: Summary of pattern distribution and related percentage increase in mortality per10 μg/m^3 increase in lag1 PM_{10} based on pattern definition with ±SD tolerance

Pattern	Frequency (%)	Percentage increase (95 % CI)		
		Non-accidental	Cardiovascular	Respiratory
PM_{10} peaks		**London**		
0	1869 (85.6)	0.43 (0.04, 0.83)	0.12 (-0.52, 0.76)	1 (-0.04, 2.06)
1	305 (14)	3.07 (2.18, 3.97)	4.23 (2.74, 5.74)	4.7 (2.25, 7.2)
2	10 (0.5)	0.87 (-3.63, 5.57)	-1.1 (-8.3, 6.67)	-0.84 (-12.51, 12.4)
Delta peaks				
0	1314 (60.2)	0.39 (-0.09, 0.88)	0.28 (-0.52, 1.09)	0.67 (-0.63, 1.98)
1	735 (33.7)	0.79 (0.24, 1.34)	0.75 (-0.16, 1.67)	1.47 (-0.02, 2.98)
2	130 (6)	4.68 (3.37, 6)	4.33 (2.21, 6.49)	8.47 (4.82, 12.25)
3	5 (0.2)	-1.7 (-12.03, 9.83)	-3.28 (-18.93, 15.4)	6.43 (-18.36, 38.75)
Number of positive delta				
0	859 (39.3)	0.97 (-0.07, 2.02)	1.66 (-0.06, 3.41)	0.54 (-2.23, 3.38)
1	871 (39.9)	0.92 (0.28, 1.57)	0.61 (-0.45, 1.67)	1.9 (0.19, 3.65)
2	378 (17.3)	0.49 (-0.19, 1.17)	-0.33 (-1.43, 0.79)	0.69 (-1.07, 2.48)
3	62 (2.8)	1.96 (0.78, 3.15)	2.21 (0.27, 4.19)	3.67 (0.5, 6.94)
4	14 (0.6)	3.0 (1.13, 4.9)	3.43 (0.33, 6.62)	5.4 (0.39, 10.66)
PM_{10} peaks		**Hong Kong**		
0	2256 (88.5)	0.44 (0.25, 0.62)	0.61 (0.25, 0.96)	0.23 (-0.2, 0.66)
1	281 (11.0)	0.59 (0.16, 1.03)	0.26 (-0.56, 1.1)	0.98 (-0.05, 2.02)
2	13 (0.5)	1.28 (-1.58, 4.23)	-0.41 (-5.59, 5.06)	-3.09 (-9.34, 3.6)
Delta peaks				
0	1619 (63.5)	0.4 (0.19, 0.62)	0.65 (0.24, 1.06)	0.29 (-0.21, 0.79)
1	769 (30.2)	0.52 (0.24, 0.8)	0.44 (-0.1, 0.97)	0.43 (-0.22, 1.08)
2	157 (6.1)	0.61 (0, 1.22)	0.32 (-0.84, 1.48)	0.02 (-1.39, 1.45)
3	4 (0.2)	4.47 (-0.67, 9.88)	4.77 (-4.79, 15.28)	3.57 (-8.14, 16.77)
Number of positive delta				
0	1023 (40.1)	0.19 (-0.22, 0.62)	0.54 (-0.27, 1.35)	-0.18 (-1.15, 0.81)
1	1012 (39.7)	0.57 (0.29, 0.84)	0.59 (0.06, 1.12)	0.74 (0.09, 1.39)
2	415 (16.3)	0.34 (0, 0.68)	0.3 (-0.36, 0.96)	0.2 (-0.6, 1.01)
3	86 (3.4)	-0.03 (-0.65, 0.58)	0.61 (-0.57, 1.81)	-1.6 (-3.02, -0.16)
4	13 (0.5)	0.78 (-0.86, 2.45)	-1.32 (-4.37, 1.82)	-0.42 (-4.16, 3.46)

Results based on further grouping of each pattern metric (defined using one SD tolerance) into binary categories are presented in Table 5.7. In London, weeks with 1-2 PM_{10} peaks were associated with 2.99 (95% CI: 2.12, 3.86), 4.02 (95% CI: 2.58, 5.47) and 4.47 (95% CI: 2.12, 6.88) percent increases in non-accidental, cardiovascular and respiratory mortality per 10 $\mu g/m^3$ increase in PM_{10} at lag 1 respectively. Likewise, 1-3 delta peaks per week were associated with 1.42 (95% CI: 0.91, 1.93), 1.35 (95% CI: 0.51, 2.2) and 2.61 (95% CI: 1.24, 4.01) percent increases in non-accidental, cardiovascular and respiratory mortality per 10 $\mu g/m^3$ increase in PM_{10} at lag 1 respectively. Positive deltas (weeks with 3-4 number of positive deltas) were also associated with relatively larger mortality risks with percentage increases of 2.42 (95% CI: 1.41, 3.44), 2.82 (95% CI: 1.15, 4.52) and 4.18 (95% CI: 1.41, 7.03) for non-accidental, cardiovascular and respiratory mortality respectively. In general, these large effects were not replicated for Hong Kong.

Table 5.7: Summary of pattern distribution based on binary categories and related percentage increase in mortality per 10 μg/m^3 increase in lag1 PM_{10}

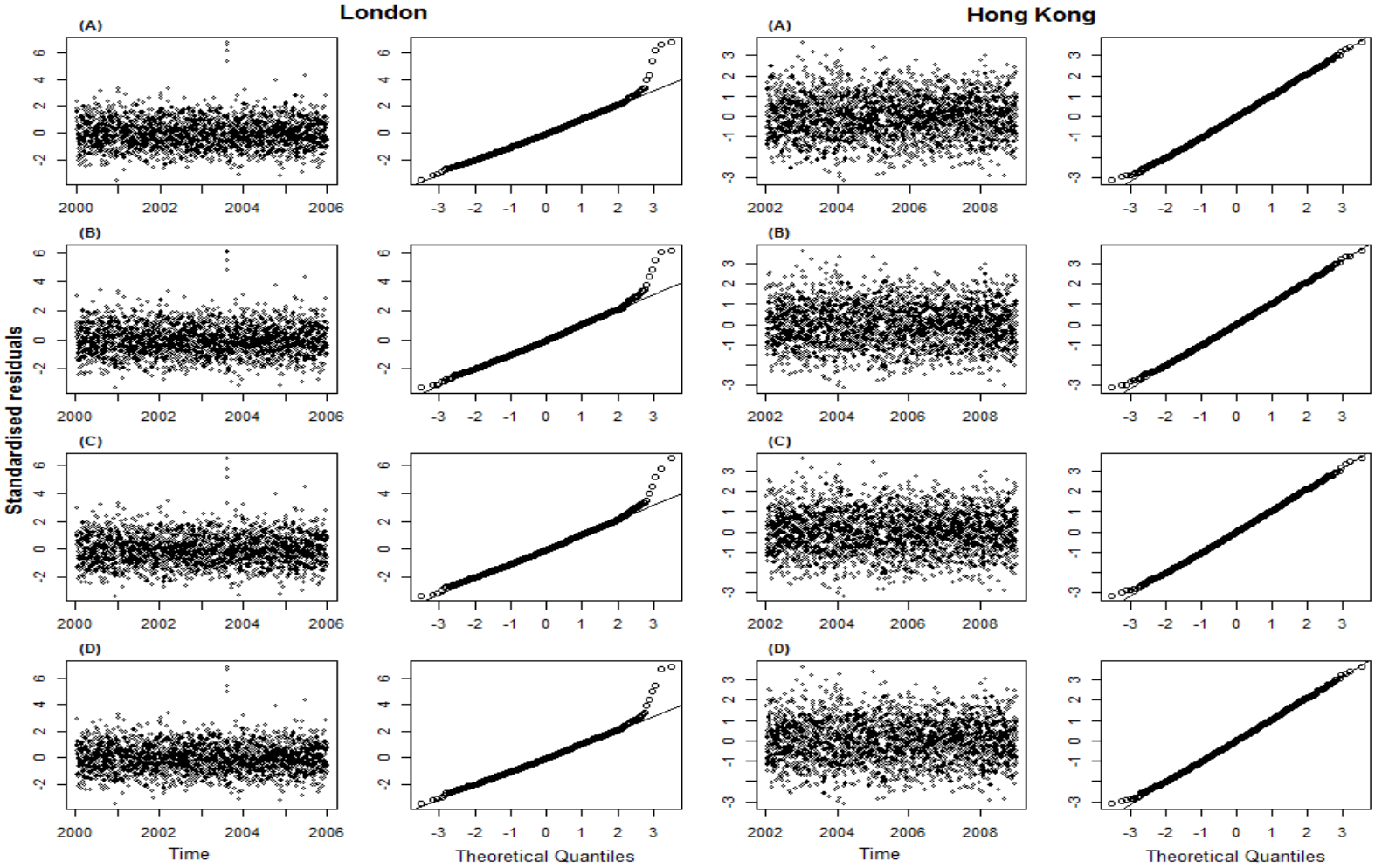
Pattern[§]	Frequency (%)	Excess risk (95 % CI)		
		Non-accidental	Cardiovascular	Respiratory
PM_{10} peaks		**London**		
0	1869 (85.6)	0.43 (0.04, 0.83)	0.12 (-0.53, 0.76)	1 (-0.04, 2.06)
1-2	315 (14.0)	2.99 (2.12, 3.86)	4.02 (2.58, 5.47)	4.47 (2.12, 6.88)
Delta peaks				
0	1314 (60.2)	0.38 (-0.11, 0.86)	0.26 (-0.53, 1.07)	0.64 (-0.65, 1.94)
1-3	870 (39.8)	1.42 (0.91, 1.93)	1.35 (0.51, 2.2)	2.61 (1.24, 4.01)
Number of positive delta				
0-2	2108 (96.5)	0.55 (0.15, 0.96)	0.24 (-0.43, 0.91)	0.96 (-0.12, 2.05)
3-4	76 (3.5)	2.42 (1.41, 3.44)	2.82 (1.15, 4.52)	4.18 (1.41, 7.03)
PM_{10} peaks		**Hong Kong**		
0	2256 (88.5)	0.44 (0.25, 0.62)	0.61 (0.25, 0.96)	0.22 (-0.2, 0.65)
1-2	293 (11.5)	0.62 (0.19, 1.04)	0.23 (-0.56, 1.04)	0.93 (-0.05, 1.92)
Delta peaks				
0	1619 (63.5)	0.41 (0.19, 0.62)	0.65 (0.24, 1.07)	0.29 (-0.21, 0.8)
1-3	930 (36.5)	0.53 (0.28, 0.79)	0.44 (-0.05, 0.92)	0.33 (-0.26, 0.93)
Number of positive delta				
0-2	2450 (96.1)	0.47 (0.28, 0.66)	0.46 (0.1, 0.82)	0.51 (0.07, 0.95)
3-4	99 (3.9)	0.03 (-0.55, 0.62)	0.33 (-0.78, 1.47)	-1.42 (-2.75, -0.08)

[§]Pattern definition with ±SD tolerance

5.3.6. Model diagnostics

Figure 5.7 shows residuals over time and q-q plots for non-accidental mortality based on the models fitted for each pattern model, namely number of positive delta, number of PM_{10} peaks and number of delta peaks as well as for the unadjusted model. Any clear model anomaly is not apparent for Hong Kong but a few extreme observations are noticed for London particularly clustered towards the end of 2003.

Figure 5.7: Residuals and Q-Q plots for unadjusted and pattern adjusted models for non-accidental mortality and lag 1 PM_{10} A) Unadjusted for any pattern B) Number of positive delta C) Number of PM_{10} peaks D) Number of delta peaks



The percentage increase estimates for mortality from each cause after excluding the six outlying observations in London are presented in Table 5.8 and in Figure 5.8. It appeared that excluding the six observations attenuated most risk estimates towards the null and largely with no significant association between mortality and PM_{10} after taking exposure patterns into account. This was also true for the conventional estimates which did not adjust for any patterns. However, for non-accidental mortality the association remained significant even after excluding outlying data points; the percentage increase per 10 $\mu g/m^3$ increase in PM_{10} at lag 1 was 0.49 (0.13, 0.86) and much lower compared to the estimate based on the full data set which was 0.82 (0.45, 1.18) as shown in Table 5.8 and Table 5.3. The residuals from the models based on the data excluding the outliers did not show any obvious model anomaly (Figure 5.9). Hence, the overall conclusions of this study will be based on the final analyses which did not include the outlying observations.

Table 5.8: Stratified percentage increases (95% CI) in mortality per 10 $\mu g/m^3$ increase in PM_{10} after excluding outliers in London

Pattern	Non-accidental	Cardiovascular	Respiratory
	London		
PM_{10} peaks			
0	0.56 (-0.6, 1.73)	0.23 (-1.67, 2.16)	1.85 (-1.25, 5.04)
1	0.34 (-0.12, 0.8)	0.1 (-0.65, 0.86)	0.7 (-0.53, 1.93)
2	0.66 (-0.04, 1.36)	0.74 (-0.4, 1.9)	1.55 (-0.31, 3.45)
3	-0.47 (-3.93, 3.12)	-2.32 (-7.84, 3.53)	4.91 (-4.23, 14.93)
Delta peaks			
0	1.38 (-0.91, 3.72)	2.57 (-1.3, 6.58)	0.84 (-4.75, 6.76)
1	0.86 (0.3, 1.43)	1.27 (0.34, 2.21)	0.52 (-0.98, 2.04)
2	0.29 (-0.2, 0.77)	-0.39 (-1.18, 0.4)	1.32 (0.03, 2.63)
3	0.32 (-1.29, 1.96)	0.1 (-2.55, 2.82)	1.59 (-2.75, 6.12)
Number of positive delta			
0-2	0.42 (-1.47, 2.34)	-1.95 (-4.96, 1.17)	3.23 (-1.98, 8.72)
3	-0.11 (-1.02, 0.82)	-0.29 (-1.79, 1.23)	0.89 (-1.51, 3.36)
4	0.83 (0.22, 1.45)	0.5 (-0.5, 1.5)	2.11 (0.47, 3.78)
5-6	0.83 (0.2, 1.47)	0.5 (-0.54, 1.54)	2.11 (0.41, 3.84)
Unadjusted			
	0.49 (0.13, 0.86)	0.33 (-0.27, 0.93)	0.85 (-0.12, 1.83)

Figure 5.8: Percentage increase in mortality per 10 µg/m^3 increase in PM_{10} after excluding outliers in London stratified by exposure patterns (A) Unadjusted for any pattern (B) Number of positive delta (C) Number of PM_{10} peaks and (D) Number of delta peaks

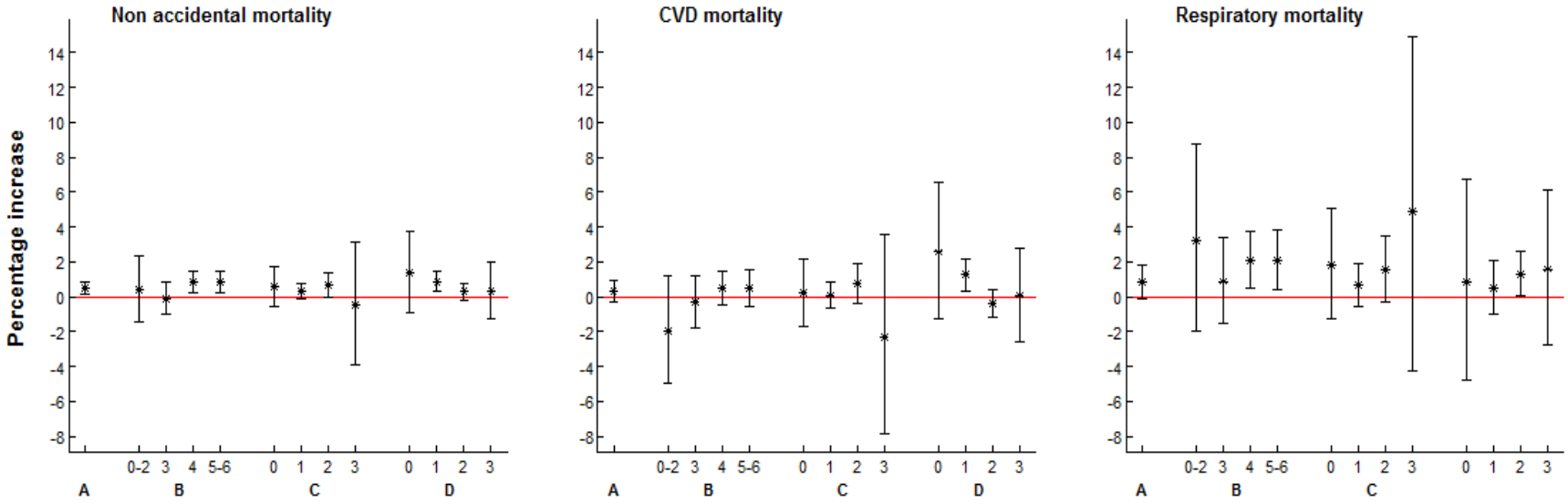
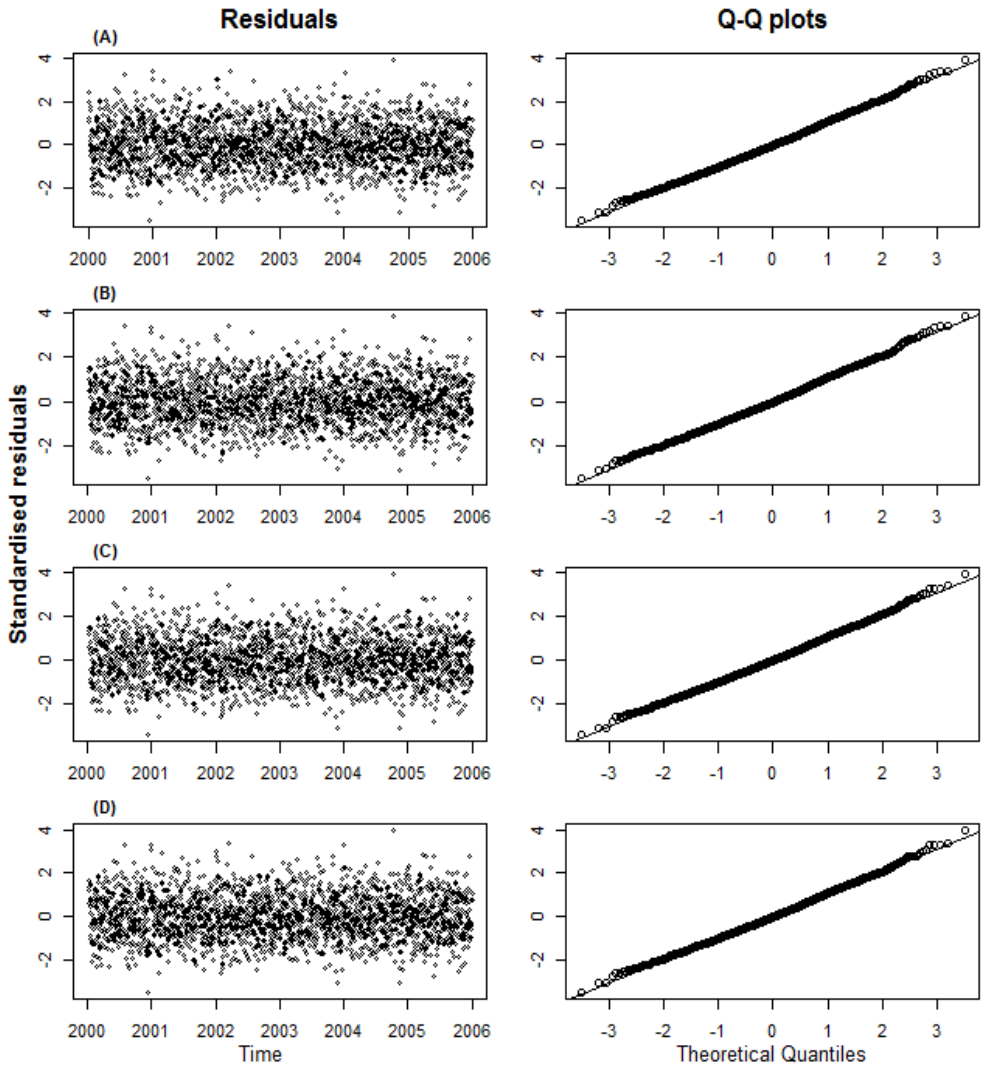


Figure 5.9: Residuals and Q-Q plots for unadjusted and pattern adjusted models for non-accidental mortality and lag 1 PM_{10} after excluding outliers in London A) Unadjusted for any pattern B) Number of positive delta C) Number of PM_{10} peaks D) Number of delta peaks



Comparison of pattern adjusted models with the conventional unadjusted model using AIC for non-accidental, cardiovascular and respiratory mortality is given in the Appendix E, Table 5.12. Compared to the conventional unadjusted models, pattern adjusted models showed a better fit in London for PM_{10} peaks and number of positive delta whereas delta peaks showed inferior model fit. Adjusting for patterns didn't provide improved model fit in Hong Kong.

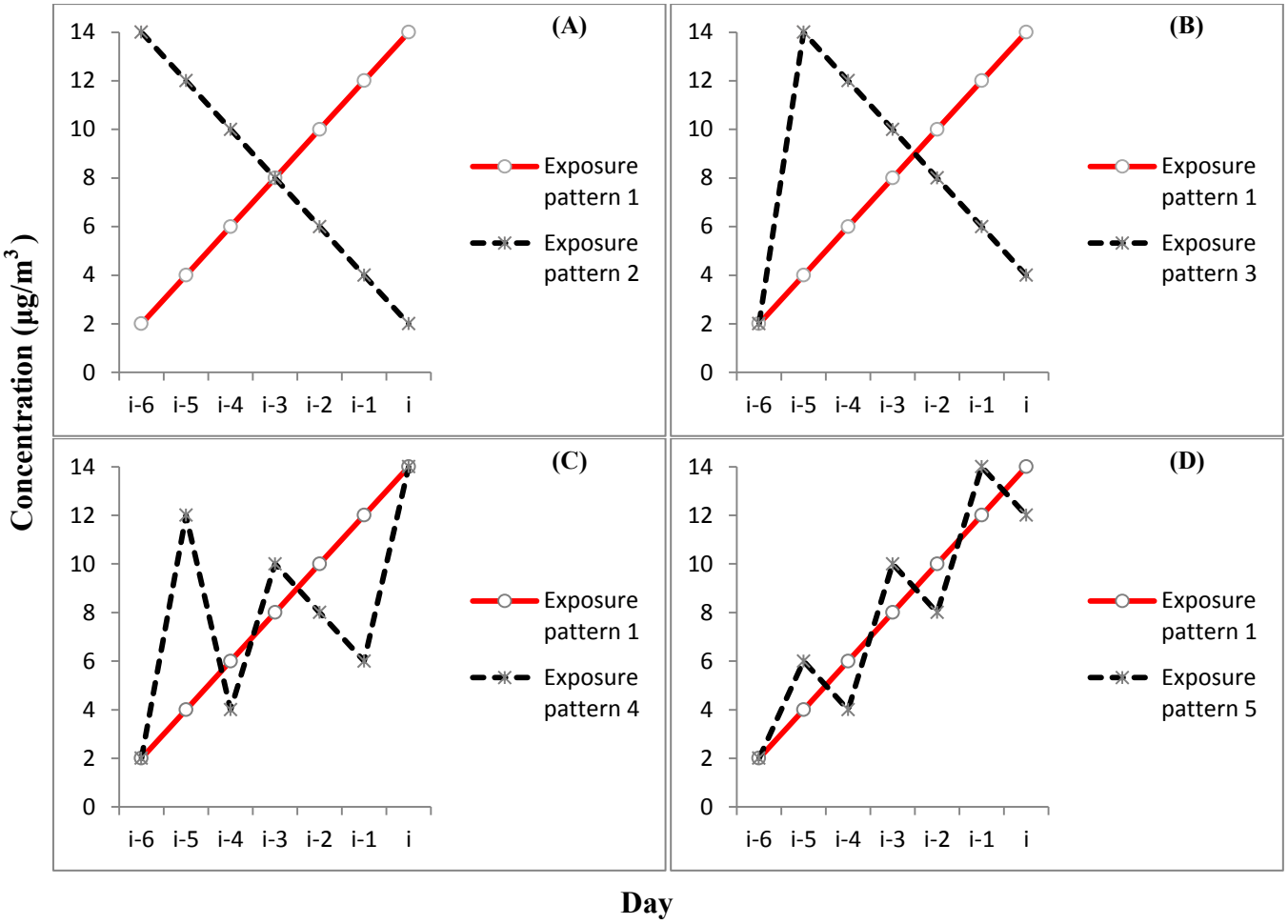
5.3.7. Exposure variability and number of peaks

In general, weeks with higher number of PM_{10} peaks over a relatively longer period could potentially reflect relatively static or less volatile pollution concentration patterns compared to strictly increasing or decreasing pollution patterns. This, however, is not necessarily true particularly in the context of this study for which exposure patterns are defined over periods of weekly windows. To clarify this, consider the small data set presented in Table 5.9. The same set of observations, say for PM_{10} concentrations in $\mu g/m^3$, were used to generate various pollution exposure patterns (patterns 1 to 5) and thus keeping the mean and variance from each scenario the same. Patterns 1 and 2 represent strictly increasing and decreasing pollution trends respectively and hence the number of peaks is zero. Patterns 3, 4 and 5 represent a week with 1, 2 and 3 PM_{10} peaks respectively (Figure 5.10). These data show that the variance or volatility can remain the same under all the possible exposure patterns, i.e., the variance was the same when the number of peaks per week ranged from zero (the minimum) to three (the maximum).

Table 5.9: Data showing exposure patterns with various number of peaks per week for the same mean and variance

Day	Pattern 1	Pattern 2	Pattern 3	Pattern 4	Pattern 5
i-6	2	14	2	2	2
i-5	4	12	14	12	6
i-4	6	10	12	4	4
i-3	8	8	10	10	10
i-2	10	6	8	8	8
i-1	12	4	6	6	14
i	14	2	4	14	12
Mean	8	8	8	8	8
SD	4.3	4.3	4.3	4.3	4.3
Peaks/week	0	0	1	2	3

Figure 5.10: Exposure patterns over a weekly window with (A) zero (B) one (C) two and (D) three peaks for the same cumulative exposure and equal variance



5.4. Discussion

The approach adopted in this study was to define some selected patterns of exposure and determine whether these affected the effect sizes in terms of risk of mortality during a given time period. The best way to address this issue would be to identify all such distinct exposure patterns present in a data set and check whether or not health effects vary by exposure pattern. However, such a blanket approach would result in too many comparisons and several patterns would appear only rarely (Appendix E: Tables 5.8-5.11, Figure 5.10).

Consequently, it became necessary to resort to characterising exposure patterns by picking the relatively obvious features: (a) number of increases in PM_{10} concentration from the previous day over a defined period (in this case seven days), i.e., the number of positive delta PM_{10} values, (b) number of peaks for PM_{10} and (c) number of peaks for delta PM_{10} over a seven day time period. This approach is not the same as a distributed lag analysis where the main aim is to study the cumulative effect of exposure over the course of several days. In fact, the previous example presented in Figure 5.1b clarifies this distinction by comparing two different exposure patterns for which the cumulative exposure over the few days considered was the same. The analyses based on average cumulative exposure also helped to highlight that any observed pattern effect would not be an artefact of variations in particulate pollution over the entire week on which patterns were defined.

If the findings for exposure pattern effects were significant, then their implications with respect to estimation of public health risk as well as control in relation to air pollution would be important. The former would be affected by exposure patterns since it was hypothesized that larger number of peaks and positive changes per week would result in higher risks; for example, the larger number of PM_{10} peaks (≥ 2) occurred in about 40% of

the 7-day blocks in the London dataset. For the latter, again if pattern effects were significant, excess risk in mortality could possibly be reduced by minimizing the number of increases or peaks in air pollution over the given period of time, for example, through short-term policy interventions. Such control could be applied prospectively by forecasting possible exposure patterns and related health risk estimates but a better understanding of the meteorological factors governing the appearance of these "peaky" weeks would inform on how better to reduce exposures.

The importance of considering such patterns of air pollution exposure that are relevant to health including number of peak exposures had been highlighted earlier (Künzli et al., 2001) but not yet addressed in a similar epidemiological time series framework as in this study. Exploring the issue of exposure pattern in epidemiological studies appeared to be relatively more common for occupational exposure where studies examined peak exposure or number days with peak exposure over a given period of time in relation to health (Zuskin and Valic, 1973, Virji et al., 2011, Richter et al., 2012). In the air pollution epidemiology literature, Pope (Pope, 1989) reported substantial increase in respiratory hospital admissions for months with peak particulate pollution for both adults and children. But this cannot be compared with the current study directly as it looked at the effect of higher average exposures over longer time periods (a month) rather than the shorter term patterns such as number of peaks per week as considered in this study.

The study findings would also be interesting from mechanistic point of view had they been significant. The effects of particulate pollution are believed to be mediated through the generation of an inflammatory response in the airways and release of pro-inflammatory cytokines and free radicals (Pope, 2000, Valavanidis et al., 2013). In this regard, a number

of human and animal laboratory studies have investigated the effects of repeated and/or peak exposure to certain air pollutants (Sandström et al., 1992a, Sandström et al., 1992b, Blomberg et al., 1999, Bardet et al., 2014, Mukae et al., 2001, Mazzoli-Rocha et al., 2014).

Sandström et al. (1992a, 1992b) reported adverse effects on bronchoalveolar lymphocytes and immune defence after repeated short-term exposures to moderate concentrations of NO_2. Blomberg et al. (1999) concluded that NO_2 is a proinflammatory pollutant with repeated exposure after finding a significant reduction in neutrophils in the bronchial epithelium, with the bronchial wash and myeloperoxidase neutrophil content increasing by twofold and 1.5-fold respectively.

Bardet et al. (2014) observed a decrease in the interleukin-8 (IL8) production after repeated exposure of epithelial cells (3 times) to formaldehyde (a gaseous indoor pollutant); no change was observed in markers of cell damage after single or double exposure. Likewise, another study on human bronchial epithelial cells has shown that the IL8 release in response to tumour necrosis factor-α (TNFα) at 72 hours nearly doubled when low dose TNFα was applied as a split dose separated by 48 hours compared to a single dose and nearly tripled compared to constant dose (Sapey E, personal communication). There was also an increase in IL8 output at a higher dose with a separated dose although the increase was less marked in percentage terms (Appendix E: Figure 5.11).

Mukae et al. (2001) examined the bone marrow in relation to repeated PM_{10} exposure in their animal study reporting increased systemic inflammatory responses which they suppose could be related to cardiopulmonary diseases. Another animal study by Mazzoli-Rocha et al. (2014) also reported adverse effects on pulmonarymechanics, lung histology

and greater macrophage inflow to the lung with repeated exposure to traffic and biomass particles.

However, most of the laboratory studies understandably examined relatively higher concentrations of pollutants whereas ambient concentrations of PM_{10} considered in this epidemiological study were much lower. This could be a possible reason for the discrepancy between the laboratory studies and the present study for which the findings were mostly negative.

Other studies have looked at exposure with respect to time scale decomposition with the aim to address the issue of "harvesting or mortality displacement" in air pollution epidemiology (Schimmel and Murawski, 1976, Zeger et al., 1999). The studies reported increased mortality risk from air pollution over medium to longer time scales than shorter time scales using time and frequency domain as well as wavelet analyses methods and concluded that not all air pollution associated mortality is due to harvesting (Dominici et al., 2003a, Kelsall et al., 1999, Schwartz, 2000b, Valari et al., 2011, Zeger et al., 1999).

In the context of this study, while evidence against harvesting over a period of more than one week cannot be provided, any harvesting effect over a period of less than one week may not be consistent with the findings. This is particularly supported by the larger effects observed for the average cumulative exposure in comparison to lag 1 PM_{10} in pattern adjusted models. The approach in this study could, however, be explored further to investigate harvesting by extending the time window used for exposure pattern definition.

Similar investigations in the future would benefit from addressing some of the limitations noted in the present study. Like most time series studies in air pollution epidemiology,

exposure measurement error could affect the risk estimates as discussed in chapter 3. The observed attenuation of the effect estimates towards the null after excluding some extreme observations in London also made interpretation of the study results complicated. This is because equivalent attenuation was observed for the conventional estimate (ignoring patterns) for which an effect would be expected. A multi-location study would highly desirable as it increases power and allows investigation of heterogeneity formally. Another limitation of the study was that definition of exposure patterns was solely based on the number of peaks and positive increases in pollution; the definition didn't include information on the magnitude of increases or peaks in exposure. The analysis using one standard deviation tolerance for pattern definition helped to explore sensitivity to magnitude of pattern metrics and generally provided similar qualitative conclusion with respect to effect of patterns on mortality. However, extensions to this study could focus on methods of incorporating actual magnitude information as well as on extending the approach to examining presence of non-linear effects perhaps in a distributed lag framework (Gasparrini et al., 2010). The latter could be more challenging in terms of statistical modelling but any effect of exposure patterns in a distributed lag model would provide stronger evidence on the importance of such patterns. The distribution of 'all possible' exposure patterns and their relationship with mortality could also be investigated using larger datasets from multiple cities perhaps with differing mean daily exposures.

In conclusion, the findings from this study suggested little effect of exposure patterns (represented by number of positive delta, PM_{10} peaks and delta peaks) on the association between PM_{10} and mortality (for all non-accidental, cardiovascular and respiratory causes). Refining the definition of exposure patterns and methodological improvements are highly recommended in related studies in the future.

6. SUMMARY, LIMITATIONS AND CONCLUDING REMARKS

The aim of this research was to investigate the effects of changes and exposure patterns on the relationship between health and air pollution. Thus, a simple change metrics (delta) was defined and potential alternative metrics were presented in Chapter 3. Then, delta and one of the alternatives proposed, relative delta, were applied in an empirical study using data from London and Hong Kong in Chapter 4. This approach was then extended in Chapter 5 by considering exposure patterns over a period of one week (as opposed to the delta approach which looked only at daily changes in exposure). The sections below present a summary of the material in each chapter, an overview of limitations of the research and some concluding remarks.

6.1. Overall summary

Methodological issues in relation to the properties and modelling of the change (delta) metrics for the delta time series approach were discussed in Chapter 3. It was highlighted that measurement error could have a more severe impact on the delta metrics than the absolute metrics as reflected by larger variance of the former with increasing measurement error. The mathematical equivalence of potential identifiable models for delta with a distributed lag model (of lags 0 and 1) was shown and alternative identifiable models for delta were proposed. The alternative metrics were compared based on description of their properties in relation to the original change metrics as well as their relative model fit using time series data from Hong Kong. The comparison indicated that the relative delta metrics would be preferred among the alternatives for delta in the evaluation of effects of changes or rate of changes. Finally, the impact of missing data was investigated using simulation. Particularly, analyses excluding missing data and imputation using the APHENA (Katsouyanni et al., 2009) study method were compared. The results showed that the

relative efficiency of the imputation based risk estimates was much better than analyses excluding the missing observations.

The delta time series study evaluated the effect of changes or rates of changes in PM_{10} on the mortality–PM_{10} relationship. Delta and relative delta were computed using data from London and Hong Kong. Poisson GAMs were applied to study associations of delta and relative delta PM_{10} with mortality and to examine the effect of controlling for delta metrics in conventional metric models, i.e., absolute PM_{10} at lag 1. The percentage increase in mortality for an interquartile range increase in delta PM_{10} was 0.51 (95% CI: 0.10, 0.92) for non-accidental and 1.12 (95% CI: 0.30, 1.95) for cardiovascular mortality after controlling for lag 1 PM_{10} in Hong Kong. Lag 1 PM_{10} effects increased from 1.97 (95% CI: 1.23, 2.73) to 2.44 (95% CI: 1.61, 3.28) for non-accidental and from 2.36 (95% CI: 0.95, 3.79) to 3.43 (95% CI: 1.84, 5.04) for cardiovascular mortality after controlling for delta PM_{10}. However, similar results could not be replicated for London where the effect of both delta metrics was not consistent with expectations.

The pattern analysis approach extended delta time series study by considering exposure patterns over longer periods (one week). Using the same data from London and Hong Kong, exposure patterns were defined on each day by counting number of (a) Positive changes (delta) in PM_{10} over successive days, (b) PM_{10} peaks and (c) Delta peaks for the week just before the mortality day. Again Poisson GAMs were used to study the mortality–PM_{10} relationship taking into account exposure patterns in the previous week in addition to the usual confounders including time trends, seasonality, day of the week and temperature. In London, inclusion or exclusion of a few outlying observations had substantial impact on risk estimates and led to different conclusions. Mortality risk from

each cause was highest for the 3 peaks per week group. For example, in the 3 peaks per week group, the percentage increases per 10 μg/m^3 increase in PM_{10} at lag 1 were 6.46 (95% CI: 3.55, 9.45) for non-accidental, 7.65 (95% CI: 2.86, 12.65) for cardiovascular and 9.95 (95% CI: 1.70, 18.86) for respiratory mortality based on the full data set. The results dramatically changed to null when outliers were excluded; the corresponding percentage increases were -0.47 (-3.93, 3.12) non-accidental, 2.32 (-7.84, 3.53) for cardiovascular and 4.91 (-4.23, 14.93) for respiratory mortality. The results from the latter analyses were more consistent with those from Hong Kong. Yet, for Hong Kong, the percentage increase estimates in the three peaks per week group 0.74 (95% CI: -0.47, 1.97) and 2.05 (95% CI: -0.69, 4.86) for non-accidental and respiratory mortality were still much greater than the corresponding conventional estimates, 0.47 (95% CI: 0.29, 0.64) and 0.32 (95% CI: -0.09, 0.73) respectively. Results were qualitatively similar for the other pattern metrics.

6.2. Limitations and further work

Investigating whether changes or rate of changes in exposure and short-term exposure patterns could have an impact on the air pollution–mortality relationship is important; this is because if they do then it would have implication both on policy and potential mechanistic explanations (Dominici et al., 2014). However, applying the change metrics (delta) in conventional time series models was not necessarily straightforward. First, evaluating the effect of delta by directly incorporating into conventional distributed lag (DL) model was problematic as this led to an unidentifiable model. A reasonable next step was to replace delta by one of the alternative metrics (absolute value, maximum or relative delta) as proposed in Chapter 3. Though such models could be identifiable, the concern on potential multicollinearity remained a drawback. Hence, the final suggestion was to

assume the coefficient of lag 0 in the model to be zero. It was shown, using data from Hong Kong, that both the former and the latter approach provided fairly comparable model fits based on AIC values. Although this is a reasonable approach as a first attempt to study delta for air pollution exposure, it could be extended and its theoretical implications explored further in a distributed lag modelling framework in future studies. Moreover, the potential effect of concurvity (Ramsay et al., 2003), the non-linear equivalent of multicollinearity, was not examined in this study.

Another limitation of the delta metrics was sensitivity to the impact of measurement error; the results presented in Chapter 3 showed that the variance of delta gets much larger with increasing measurement error variance. Hence statistical power in subsequent empirical studies using the delta metrics could decrease with increasing measurement error. Furthermore, estimates for delta metrics coefficients would also be less efficient under substantial amount of missing data as shown in the simulation study (Chapter 3). Though this is in general true for any exposure metric including the absolute measurements, the rate of missing data is generally higher for the delta metrics than the absolute measurements indicating imputation should perhaps be an essential part of analyses involving the delta metrics.

Working with the delta metrics appears to be relatively more convenient when applied to temperature exposure than air pollution. This is because both extreme increases (positive delta) and decreases (negative delta) in temperature are associated positively with adverse health effects through somewhat U shaped or similar functions (McMichael et al., 2008, Ma et al., 2014, Armstrong, 2006). Guo et al. (2011) and Lin et al. (2013), for example, have successfully showed delta effects for temperature in time series studies. On the other

hand, only increases in air pollution are associated positively with adverse health outcomes in a linear function thus making the comprehension of negative delta values less intuitive. Nevertheless, this does not necessarily mean modelling delta is mathematically more complex for air pollution exposure than for temperature.

The empirical results from the delta time series approach using data from London and Hong Kong need to be interpreted with caution. Associations observed in any epidemiological study are generally scrutinised in light of confounding, selection and information bias as well as chance. On top of this, making a consistent overall conclusion based on this study only appeared to be difficult given lack of agreement between London and Hong Kong results obtained following an *a priori* specified study protocol. Both delta and relative delta showed association with mortality in Hong Kong but not in London. Measurement error could be one possible explanation for the lack of evidence of association in London as discussed previously. On the other hand, the association observed in Hong Kong could as well be affected by residual confounding or chance alone could be the explanation for the observed association though very unlikely. Given the results from several sensitivity analyses conducted, residual confounding seems to have played a part for the observed association in Hong Kong while results from London remained consistent in the corresponding sensitivity analyses.

More or less similar caution applies to interpretation of the results from the pattern analysis approach. Ironically, remarkable pattern effects were observed in London but only due to a few extreme observations. Removing those outlying data points largely reduced pattern effects to null which was consistent with the findings in Hong Kong. Given the way exposure patterns were defined, perhaps potential influence of distributed lag (DL) effects

should be taken in to account. In order to get more insight on this issue, a sensitivity analysis using average cumulative PM_{10} exposure rather than lag 1 PM_{10} was conducted and the conclusions for both London and Hong Kong were little affected. Yet it would be an interesting extension to this study if pattern effects could be demonstrated in the DL modelling framework. A major challenge would be to find signal strong enough to be picked up by patterns after including DLs.

The pattern identification procedure was based on some selected characteristics of the exposure patterns over rolling blocks of weeks and may not necessarily represent all possible patterns in the entire data set. Obtaining the distribution of all possible patterns requires a very large data series in order to guarantee reasonable frequency for each pattern. As an alternative method, future investigations could also explore potential application of multivariate methods like principal component analysis in order to group similar patterns together.

Bias from missing data is unlikely to be a concern in both delta time series and pattern analysis because only London had a small proportion of missing data (about 3%) which was imputed using the APHENA method (Katsouyanni et al., 2009). Finally, only PM_{10} was considered to develop the methodology for delta time series and pattern analysis approaches in the thesis. This is fairly reasonable as PM_{10} is a major pollutant for which relatively more consistent associations have been established with mortality and morbidity (Pope and Dockery, 2006, Bell et al., 2013, Berhane et al., 2011). Comparable results would probably be expected for $PM_{2.5}$ due to its high degree of correlation with PM_{10} (Atkinson et al., 2010) but this needs to be extended to other pollutants once the

methodology is well developed and some of the limitations highlighted above are somehow resolved.

To sum up, this study can be a good base for a further extended research on effects of changes or rate of changes in exposure and patterns of exposure in order to obtain more robust conclusions. Based on the discussions above, taking into account the following issues could be beneficial in future studies:

I. Study power and heterogeneity: Setting up a multi-location study either through exploring present collaborative research projects or establishing new ones in Europe, North America, Asia and elsewhere if possible.

II. Methodological research: This can be looked at in terms of modelling and design aspects. Improvements on modelling issues include exploring the applicability of distributed lag models and developing a more comprehensive study protocol for multi-location studies. The set of all possible exposure patterns that could occur over a time period of interest may be explored in a relatively long series and needs to be summarised using multivariate statistical methods. On the other hand, the ecologic time series design can be supplemented by studies in vitro and in vivo. Pollutants other than PM_{10} can be included both in single as well as multi-pollutant models and PM_{10} exposure can also be examined with respect to toxicity of its components.

6.3. Concluding remarks

1. The change metrics (delta) showed larger variance than the absolute metrics in the presence of non-trivial measurement error. Thus, the delta metrics may not be a suitable proxy for the absolute metrics and regression estimates could be biased (at least for classical error). Among the alternative metrics proposed for identifiable delta models, relative delta is recommended in similar studies. Although it did not substantially improve model fit compared to the other metrics, relative delta provided additional information by capturing relative changes and had the strongest correlation with delta. Missing rates could generally be larger for the delta than the absolute metrics reaching up to double in the worst case scenario. Efficiency of risk estimates in the presence of missing data decreased with increasing missing rate as shown in the simulation study. Hence imputation of missing data would be a crucial first step for analyses involving the delta metrics.

2. Following an *a priori* specified study protocol for the delta time series approach, evidence of association for delta and relative delta PM_{10} with mortality was found in Hong Kong but not in London controlling for lag 1 PM_{10} in addition to the usual confounders. This implies while delta metrics could provide a convenient interpretation biologically, further investigations are needed to explore the reasons for geographical discrepancies in risk estimates. However, in sensitivity analysis with more rigorous adjustment for weather, the observed association in Hong Kong attenuated towards the null. The study thus reaffirms the importance of sensitivity analysis in time series studies of the health effects of air pollution and could be used as a basis to develop a more comprehensive study protocol for similar studies.

3. The main hypothesis in relation to the exposure pattern analysis was, in addition to amount (dose) and duration of exposure, epidemiological studies ought to take patterns of exposure into account. However, convincing evidence was not found for the effect of short-term exposure patterns on mortality risk estimates in London (after removing outliers) and Hong Kong. Refining the definition of exposure patterns and methodological improvements including analysis of data from multiple cities are highly recommended in related studies in the future.

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8. APPENDICES

APPENDIX A: Supplementary materials for Chapter 1

Summary of background demographic, health, and environmental data for London and Hong Kong is presented below in the tables 1 and 2 extracted from the paper by Wong et al. (2002).

Table 1.1: Comparison of environmental factors of Hong Kong and London

Environmental factor	Hong Kong	London
Population (millions)	6.2 (1995)[a]	6.9 (1992)[b]
Area (km^2)	1,092	1,580
Climate	Subtropical, with rain and tropical cyclones in the summer months	Maritime, with mild winters and temperate summers
Mean January/July temperatures (°C)	16/29	3/23
Rainfall	224 cm, most falling in the summer months	58 cm, evenly distributed through the year
Topography	Peninsula with offshore islands	Estuarine river basin
Lifestyle		
Smoking rates (≥ 15 years of age)	Male 26.7%; female 3.1%[c]	Male 28%; female 27%[d]
Regular alcohol consumers	Male 20.0%; female 2.0%[e]	Male 27%; female 11%[d]
Health care system	Primary care services provided mainly by private sector (85%) Hospital services provided mainly by public sector (86%)	National Health Service
Median size of private dwellings	40.0–69.9 m^2[a]	85 m^2[f]
GDP per capita (with adjustment for purchasing power parity)	U.S. $20,458[g]	U.S. $20,890[g]
Leading causes of death	(1996 data)[h] 1. Malignant neoplasms, 31.3% 2. Heart diseases, 15.8% 3. Cerebrovascular disease, 10.7% 4. Pneumonia (all forms), 10.6% 5. Injury and poisoning, 5.1%	(1996 data)[i] 1. Circulatory diseases, 42.6% 2. Malignant neoplasms, 25.0% 3. Respiratory diseases, 15.9% 4. Digestive diseases, 3.6% 5. Injury and poisoning, 2.9%

GDP, gross domestic product.
[a]Data from the Hong Kong Annual Digest of Statistics (*17*). [b]Data from the Office of Population and Censuses Surveys (*18*). [c]Data from the Census and Statistics Department (*19*). [d]Data from Statistics on Smoking: England, 1976 to 1996 (*20*). [e]Data from Janus et al. (*21*); alcohol consumption at least once per week (25–74 years of age). [f]Data from the Office of National Statistics (*22*). [g]Data from Asia Week (*23*). [h]Department of Health. Department of Health Annual Report (*24*). [i]Data from the Office of National Statistics (*25*).

Table 1.2: Comparison of selected health and air pollution statistics between Hong Kong and London

Health variable	Hong Kong	London
Population < 15/> 65 years of age (%)	18.9/10.0 (1996)[a]	18.8/13.9 (1992)[b]
Infant mortality rate (per 1,000 live births)	4.0	7.2
Age-standardized mortality[c] (per 1,000 population)		
From all causes	3.7	4.5
From respiratory diseases	0.7	0.5
From cardiovascular diseases	0.9	1.9
Emergency admissions for respiratory disease		
Respiratory (% of all causes)	10.0 (1996)	5.1 (1992/1993)
Age standardized rate[c] (per 1,000 population)	12.9	8.0 (1992–1994)
Age distribution (%)		
0–14 years	33	35
15–64 years	22	26
≥ 65 years	45	39
Subcategories (%)		
Lower respiratory infections (ICD-9 466, 480–487)	23	22
Asthma (ICD-9 493)	13	25
COPD (ICD-9 490–496, excluding 493)	24	15
Emergency admissions for cardiovascular disease		
Cardiovascular (% of all causes)	7.6 (1996)	5.9 (1992/1993)
Age standardized rate (per 1,000 population)	5.8	5.5 (1992–1994)
Age distribution (%)		
0–14 years	2	0
15–64 years	37	32
≥ 65 years	61	68
Subcategories (%)		
Stroke (ICD-9 430–438)	22	19
Cardiac (ICD-9 390–429)	63	70
[Ischemic heart disease (ICD-9 410–414)]	37	30
[Arrhythmias (ICD-9 427)]	20	9
[Cardiac failure (ICD-9 428)]	22	18
Sources of pollutant emissions	(1997)[d] (TSP including PM_{10})	(1997)[e]
PM_{10} (%)		
Traffic (vehicle, marine vessel, aircraft)	61	83
Industry	6	11
Power generation (and heating for London)	33	6
NO_x (%)		
Traffic (vehicle, marine vessel, aircraft)	41	83
Industry	8	5
Power generation (and heating for London)	45	13
SO_2 (%)		
Traffic (vehicle, marine vessel, aircraft)	14	28
Industry	21	34
Power generation (and heating for London)	65	38

TSP, total suspended particulate.
[a]Data from the Hong Kong Department of Health (*24*).[b]Data from the Office of Population and Censuses Surveys (*18*). [c]The standard population was adopted from Segi (*26*). [d]Data from the Planning, Environment and Lands Bureau (*27*). [e]Data from the London Research Centre (*28*).

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APPENDIX B: Supplementary materials for Chapter 2

Parameter estimation

This section presents methods for estimation of parameters (βs) as outlined in Peng *et al.* (2006). First the linear predictor given in Chapter 2 (model 2.3)

$$\log(\mu_t) = \beta_0 + \beta_1 X_{t1} + ... + \beta_p X_{tp} + f(t;\lambda) \qquad 2.3$$

where f is a smooth function of time and λ is the smoothing parameter which controls how rough or smooth f should be can be written using matrix notation to facilitate the derivation:

$$\mathrm{Y} \sim \mathrm{Poisson}(\mu)$$

$$\log(\mu) = \mathrm{X}\beta + \mathrm{f} \qquad 2.4$$

where $\mathrm{Y}=Y_1 \ldots Y_n$, f is a smooth function evaluated at t=1,…,n and X is an nx(p+1) design matrix containing a column of ones.

For a given nxd spline basis matrix B, the model in (3) above can be written as

$$\log(\mu) = \mathrm{X}\beta + \mathrm{B}\alpha \qquad 2.5$$

where α is a vector of coefficients (of length d).

The natural spline (NS) model is fit using iteratively reweighted least squares (IRLS) as follows. Suppose W is an nxn diagonal weight matrix, z is the working response from the last iteration of the IRLS algorithm and $\mathrm{X}^*=[\mathrm{X} \mid \mathrm{B}]$ the full design matrix, then the parameter estimates will be

$$\begin{bmatrix} \hat{\beta}_{ns} \\ \hat{\alpha} \end{bmatrix} = \left(\mathrm{X}^{*'}\mathrm{W}\mathrm{X}^{*}\right)^{-1}\mathrm{X}^{*'}\mathrm{W}\mathrm{z} \qquad 2.6$$

In the case of penalised splines (PS), a smoother matrix (S) for **f** needs to be computed first. For a given smoothing parameter λ and a symmetric fixed penalty matrix H, this will be

$$S = B\left(\mathrm{B}'\mathrm{B} + \lambda \mathrm{H}\right)^{-1}\mathrm{B}' \qquad 2.7$$

And the estimate for the coefficient will be

$$\hat{\beta}_{ps} = \left(\mathrm{X}'\mathrm{W}(\mathrm{I}-\mathrm{S})\mathrm{X}\right)^{-1}\mathrm{X}'\mathrm{W}(\mathrm{I}-\mathrm{S})\mathrm{z} \qquad 2.8$$

Reference

Peng RD, Dominici F, Louis TA. 2006. Model choice in time series studies of air pollution and mortality. Journal of the Royal Statistical Society: Series A (Statistics in Society) 169(2): 179-203.

APPENDIX C: Supplementary materials for Chapter 3

Methods and additional results for simulation studies

1. Simulation study I

1.1. Aims and objectives

The aim of the first simulation study was to compare the statistical properties of the absolute and delta metrics in the presence of systematic and random measurement error. More specifically, the objective of the Monte Carlo (MC) simulation was to compare mean and variance properties of absolute and delta PM_{10} metrics for different levels of measurement error variance assuming observed data on PM_{10} (log transformed) as the "true" exposure. The simulation study was set up using data on PM_{10} from Hong Kong for the period 2002-2008 as the "true" exposure. The simulated data for the observed exposure was assumed to contain pure classical measurement error. The simulation procedure can be considered as a simplified version of that showed in Goldman et al. (2011) but with two major modifications; instead of calculating error variance, a range of values for the variance were assessed and no autocorrelation was assumed for errors. Daily observed absolute PM_{10} series were generated by adding random error to the "true" exposure assuming log-normal distribution. The results are summarised in Table 3.7 for the mean estimates and in Table 3.8 for the SD estimates for a range of random measurement error variances as well as with and without systematic error. This will support the theoretical/analytical results presented in Table 3.1.

1.2. Simulation procedures

a) The measurement error models under random error only (3.20) and with both random and systematic error (3.21) together with the corresponding model for delta are given below.

$$X_{observed} = X_{true} + \varepsilon \qquad 3.20$$

$$X_{observed} = X_{true} + \theta + \varepsilon \qquad 3.21$$

$$\begin{aligned} \Delta X^{T}_{observed} &= X^{T}_{observed} - X^{T\text{-}1}_{observed} \\ &= X^{T}_{true} - X^{T\text{-}1}_{true} + \varepsilon^{T} - \varepsilon^{T\text{-}1} \end{aligned} \qquad 3.22$$

where $X_{observed}$ is the observed exposure with some measurement error ε, X_{true} is the true exposure, θ is the amount of bias and $\Delta X^{T}_{observed}$ is delta at time T; the true exposure is uncorrelated with ε and $\varepsilon \sim N(0,\sigma_e^2)$.

b) The measurement error variances (σ_e^2) compared were 0.0001, 0.01, 0.25, 1, 2.25, 3.61, 4 and 6.25 (hence the corresponding SDs will be 0.01, 0.1, 0.5, 1, 1.5, 1.9, 2 and 2.5 respectively).

c) The systematic error value (θ) was set at 3.

d) The number of simulations performed for each scenario was 1000.

e) Daily time series data on PM_{10} from Hong Kong for the period 2002-2008 were used as the "true" exposure after log transformation. Hence the observed data were simulated by adding systematic and/or random measurement error (with different levels of error variance) to this "true" distribution.

f) The function rnorm() in R was used to generate each data set from a normal distribution (on the log scale).

g) The results from each MC simulation were saved in a spreadsheet and summarised using the mean, SD, bias and relative bias.

h) The summary from the above step (g) was used to compare the absolute and delta metrics, i.e., to assess the respective bias and variance.

1.3. Results

In the absence of systematic error, the expected value (mean) estimates were little affected by measurement error level (ε) for both absolute and delta metrics. Introducing systematic error induced bias in the mean estimate for absolute metrics by the same amount as the systematic error, in this case by three, whereas it had no influence on the delta metrics as expected (Table 3.7).

The bias in the SD estimates increased as the measurement error variance (sigma) increased for both the absolute and delta metrics. In agreement with the theoretical results presented in Table 3.1, systematic error had no influence on the SD estimates and the delta metrics generally had larger SD than the absolute metrics (Table 3.8). Moreover, the inflation of SD estimates with increasing measurement error was substantially greater for the delta metrics as shown in Figure 3.5. These results imply that application of the delta metrics as well as interpretation of risk estimates from it should be looked at cautiously in light of the potential effect of measurement error.

Table 3.7: Summary of results from simulation study for the estimate of the mean

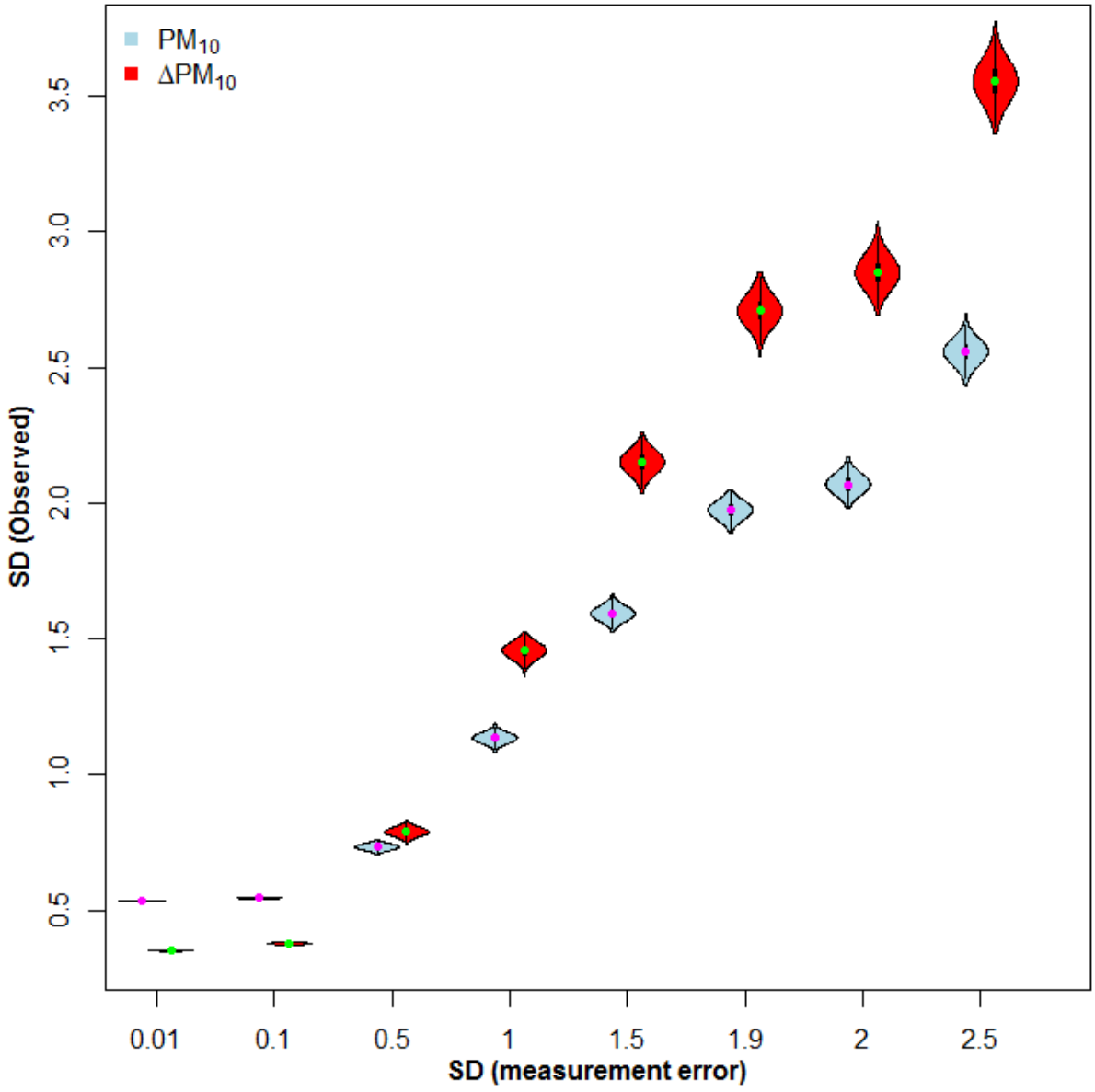
Metric	Systematic error	"True" mean	Sigma	MC mean	MC bias	MC relative bias*
PM	0	3.8586	0.01	3.8586	0.0000§	0.0000
			0.10	3.8587	0.0001	0.0000
			0.50	3.8587	0.0001	0.0000
			1.00	3.8592	0.0006	0.0001
			1.50	3.8591	0.0005	0.0001
			1.90	3.8591	0.0005	0.0001
			2.00	3.8563	-0.0023	-0.0006
			2.50	3.8578	-0.0008	-0.0002
	3	3.8586	0.01	6.8586	3.0000	0.7775
			0.10	6.8587	3.0001	0.7775
			0.50	6.8587	3.0001	0.7775
			1.00	6.8592	3.0006	0.7776
			1.50	6.8591	3.0005	0.7776
			1.90	6.8591	3.0005	0.7776
			2.00	6.8563	2.9977	0.7769
			2.50	6.8578	2.9992	0.7773
Delta	0	-0.0005	0.01	-0.0005	0.0000	-0.0003
			0.10	-0.0005	0.0000	0.0071
			0.50	-0.0005	0.0000	0.0079
			1.00	-0.0005	0.0000	0.0417
			1.50	-0.0005	0.0000	-0.0026
			1.90	-0.0005	0.0000	0.0782
			2.00	-0.0004	0.0000	-0.0160
			2.50	-0.0005	0.0000	0.0791
	3	-0.0005	0.01	-0.0005	0.0000	-0.0003
			0.10	-0.0005	0.0000	0.0071
			0.50	-0.0005	0.0000	0.0079
			1.00	-0.0005	0.0000	0.0417
			1.50	-0.0005	0.0000	-0.0026
			1.90	-0.0005	0.0000	0.0782
			2.00	-0.0004	0.0000	-0.0160
			2.50	-0.0005	0.0000	0.0791

*MC relative bias=MC bias/True value
§Value<0.0001

Table 3.8: Summary of results from simulation study for the estimate of the SD

Metric	Systematic error	"True" SD	Sigma	MC mean	MC bias	MC relative bias
PM	0	0.5356	0.01	0.5357	0.0001	0.0002
			0.10	0.5448	0.0092	0.0172
			0.50	0.7325	0.1969	0.3675
			1.00	1.1343	0.5987	1.1177
			1.50	1.5926	1.0570	1.9734
			1.90	1.9732	1.4376	2.6839
			2.00	2.0699	1.5343	2.8645
			2.50	2.5564	2.0208	3.7728
	3	0.5356	0.01	0.5357	0.0001	0.0002
			0.10	0.5448	0.0092	0.0172
			0.50	0.7325	0.1969	0.3675
			1.00	1.1343	0.5987	1.1177
			1.50	1.5926	1.0570	1.9734
			1.90	1.9732	1.4376	2.6839
			2.00	2.0699	1.5343	2.8645
			2.50	2.5564	2.0208	3.7728
Delta	0	0.3494	0.01	0.3497	0.0003	0.0009
			0.10	0.3770	0.0276	0.0791
			0.50	0.7887	0.4393	1.2572
			1.00	1.4561	1.1067	3.1675
			1.50	2.1504	1.8010	5.1548
			1.90	2.7087	2.3593	6.7525
			2.00	2.8502	2.5008	7.1575
			2.50	3.5531	3.2037	9.1692
	3	0.3494	0.01	0.3497	0.0003	0.0009
			0.10	0.3770	0.0276	0.0791
			0.50	0.7887	0.4393	1.2572
			1.00	1.4561	1.1067	3.1675
			1.50	2.1504	1.8010	5.1548
			1.90	2.7087	2.3593	6.7525
			2.00	2.8502	2.5008	7.1575
			2.50	3.5531	3.2037	9.1692

Figure 3.6: MC estimates of SD for "observed" PM_{10} and ΔPM_{10} data for different levels of measurement error variance; plots show kernel density on both sides of a box plot (circles at the centre of each plot are medians)



2. Simulation study II

2.1. Aims and objectives

The second simulation study in this thesis aimed to determine the performance of some of the proposed models relative to the conventional distributed lag model and check whether any of the alternative delta metrics in 3.15-3.18 fitted the data better than the relatively simpler delta model in 3.9. The results are summarised in Table 3.9.

2.2. Simulation procedures

a) The models to be compared as given in Chapter 3 included

$$\eta_t = \beta_1^{''}\Delta P_t + \beta_2^{''} P_{t-1} + ... \quad (3.9)$$

$$\eta_t = \beta_1 P_t + \beta_2 P_{t-1} + ... \quad (3.11)$$

$$\eta_t = \beta_1^{(1)} P_t + \beta_2^{(1)} P_{t-1} + \beta_3^{(1)} |\Delta P_t| + ... \quad (3.15)$$

$$\eta_t = \beta_1^{(2)} P_{t-1} + \beta_2^{(2)} |\Delta P_t| + ... \quad (3.16)$$

$$\eta_t = \beta_1^{(3)} P_{t-1} + \beta_2^{(3)} Max(\Delta P_t, 0) + ... \quad (3.17)$$

$$\eta_t = \beta_1^{(4)} P_{t-1} + \beta_2^{(4)} R\Delta P_t + ... \quad (3.18)$$

b) Model performance was assessed using AIC values.

c) The number of simulations performed for each scenario was 10000.

d) The simulation used time series data from Hong Kong for the period 2002-2008. Daily mortality series were generated based on predicted values from a Poisson generalized additive model with lag1 PM_{10} and delta PM_{10} concentrations in addition to controlling for temperature, day of the week, time trends and seasonality.

e) The function rpois() in R was used to generate each data set from a Poisson distribution.

f) Similar models as in (d) above were fitted to the simulated data for each of the models in (a) using one of the alternative metrics for delta as appropriate.

g) Relative risks, standard errors and AIC values for each model from each simulation were then saved in a spreadsheet and summarised using their average.

h) Finally the difference in average AIC values between the reference model (3.11) and the remaining models was calculated.

i) The results from (g) and (h) were tabulated and used to assess the relative performance among the proposed delta metrics.

Table 3.9: Model comparison for various delta metrics based on AIC values with log RR (SE) estimates for non-accidental mortality per IQR increase in respective metric using simulated data for Hong Kong

Model	Change in AIC[§]	Lag1 PM_{10}	ΔPM_{10}	Abs(ΔPM_{10})	Max(ΔPM_{10}, 0)	RΔPM_{10}
3.11	Reference	0.01373 (0.00458)	--	--	--	--
3.9	0.0	0.02579 (0.00416)	0.00551 (0.00209)	--	--	--
3.15	1.0	0.01373 (0.00458)	--	-0.00034 (0.00269)	--	--
3.16	6.5	0.01997 (0.00416)	--	0.00101 (0.00269)	--	--
3.17	2.0	0.02205 (0.00374)	--	--	0.00342 (0.00162)	--
3.18	2.1	0.02415 (0.00416)	--	--	--	0.00479 (0.00220)

[§]Calculated by subtracting AIC value of the reference model (3.11) from each model's respective AIC

3. Simulation study III

3.1. Aims and objectives

The aim of the last simulation study thesis aimed to compare two missing data handling methods namely excluding versus imputing missing observations. Specifically, the objective was to investigate the extent of missing data which could lead to potentially large bias and compare the performance of the APHENA imputation method against excluding missing data from analyses of such data.

3.2. Simulation procedures

a) In the APHENA study missing observation on day *i* of year *k* from monitoring station *j* was replaced by an average weighted by the values of the temporal average from the station as well as other monitoring stations as given in the study protocol (equation 4.8) presented in Chapter 4:

$$\hat{x}_{ijk} = \bar{x}_{i.k}\left(\bar{x}_{.jk} / \bar{x}_{..k}\right)$$

where is $\bar{x}_{i.k}$ the mean value on day *i* of year *k* among all monitors reporting, $\bar{x}_{.jk}$ is the mean value for monitor *j* in year *k* and $\bar{x}_{..k}$ is the overall mean level in year *k*.

b) Data were generated for a single monitoring station of interest as well as six additional monitors to be used for the APHENA imputation method. In addition one station was set to have higher average pollution levels than the rest.

c) Each simulated data set for PM_{10} was generated from a log-normal distribution with model predicted mean and standard deviation; the model predictors used for log PM_{10} were lag 1 PM_{10} (log scale) and smooth functions of temperature and time.

d) The simulation was based on daily time series data from Hong Kong for the period 2002-2008 which had complete PM_{10} data.

e) Missing rates of 3%, 5%, 10%, 30% and 50% were randomly introduced to each simulated data for the monitoring station of interest.

f) For the rest six monitoring stations the proportion of missing data was set to only 3%.

g) The number of simulations performed for each scenario was 1000.

h) The function rnorm() in R was used to generate each data set from a normal distribution (on the log scale).

i) For analyses using the imputed data sets, the missing observations in (d) above for the monitoring station of interest were replaced according to the procedure in (a).

j) Poisson GAM models were fitted to each data set both before and after imputation to estimate RR estimates for lag 1 and delta PM_{10}.

k) The results from each model (RRs) were saved in a spreadsheet and summarised using their average, SD, bias, relative bias, MSE and relative efficiency. The RR estimates from Hong Kong which had complete PM_{10} data was assumed as the "true" value for calculating bias.

4. Additional results from simulation studies

Figure 3.6: Boxplots for MC estimates of the mean for "observed" PM_{10} and ΔPM_{10} data at different levels of measurement error variance

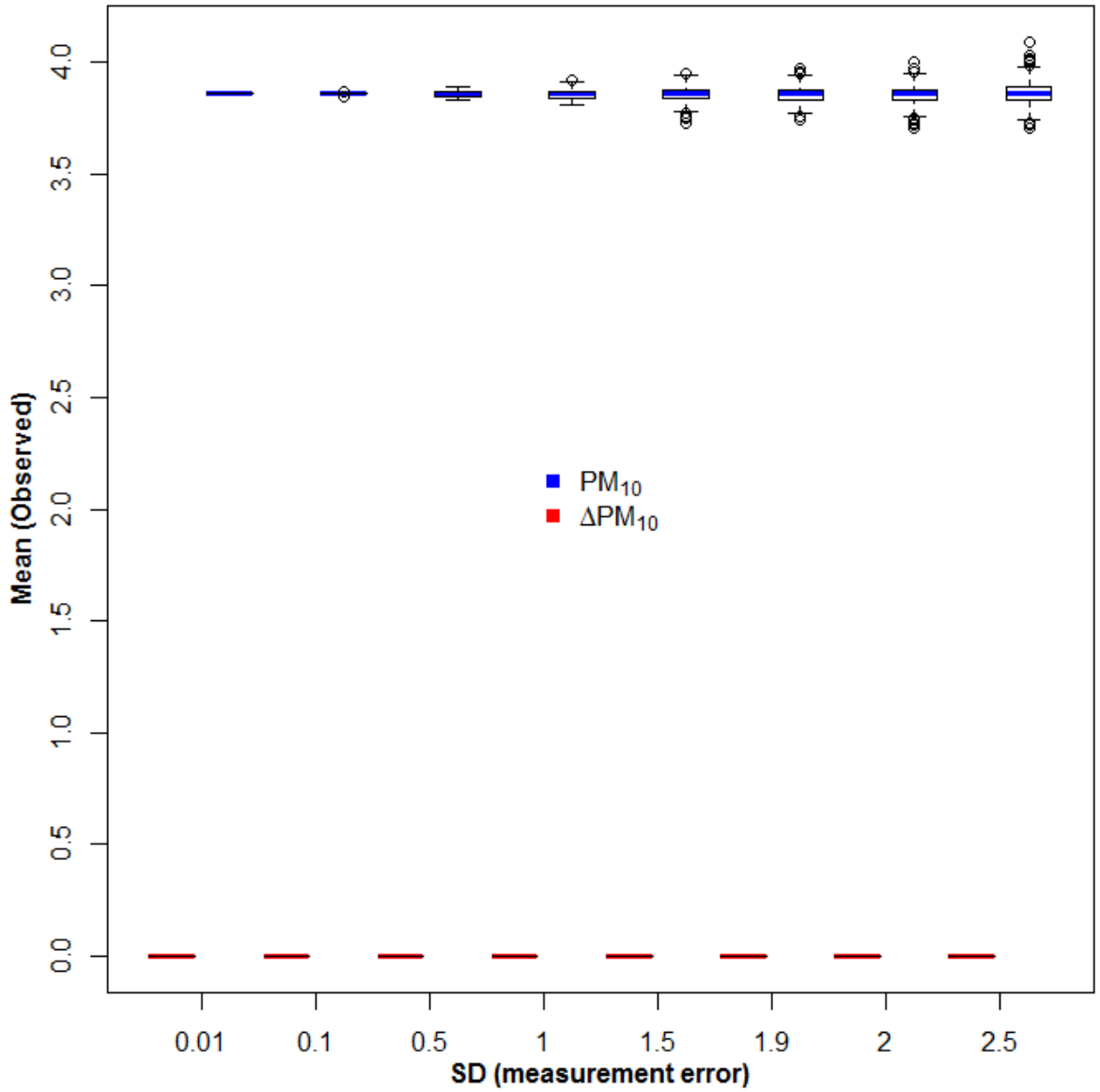


Figure 3.7: Boxplots for MC estimates of the SD for "observed" PM_{10} and ΔPM_{10} data at different levels of measurement error variance

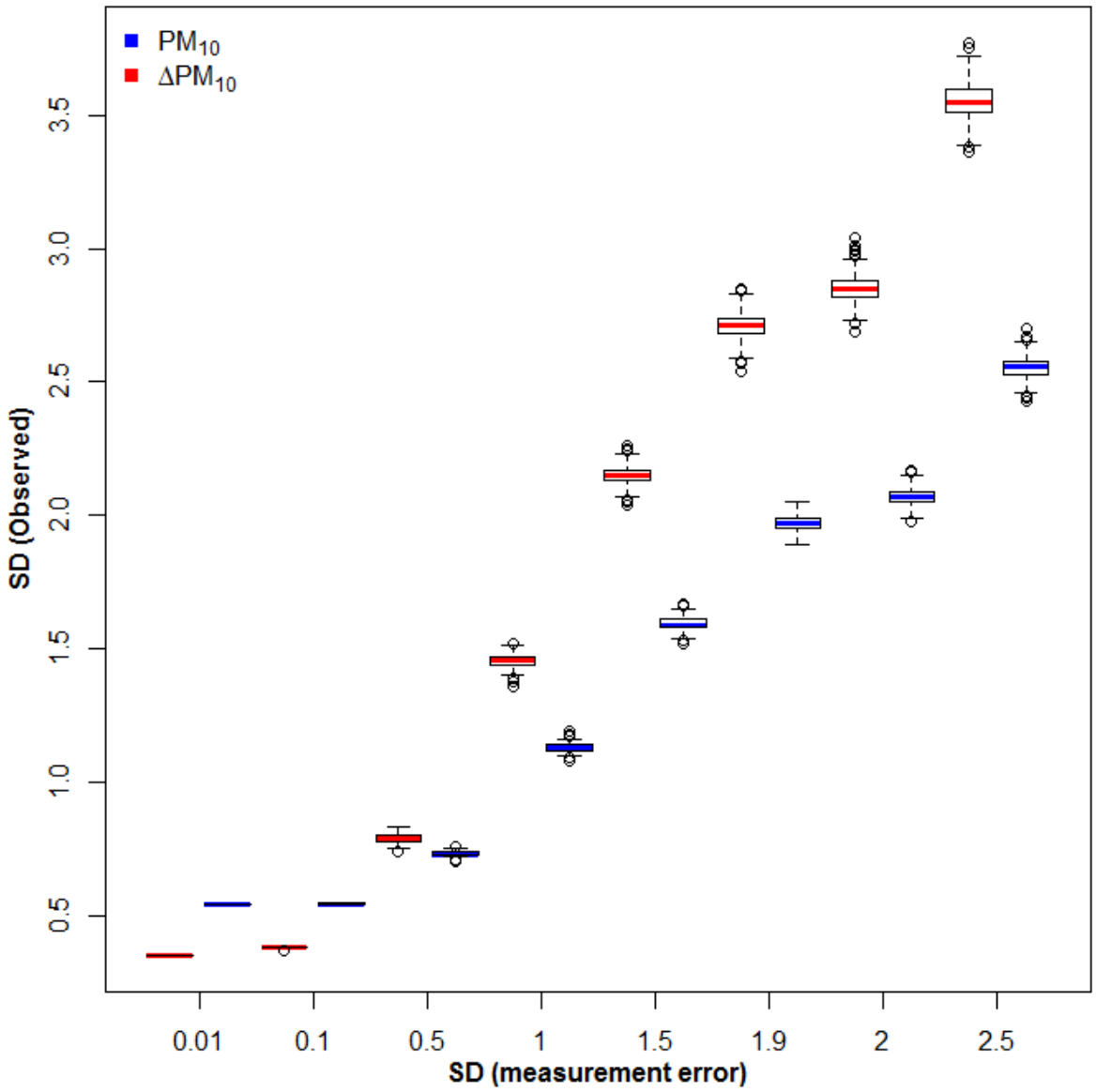


Figure 3.8: Boxplots for model comparison of alternative delta metrics using the change in AIC relative to the UDL mode in MC simulations

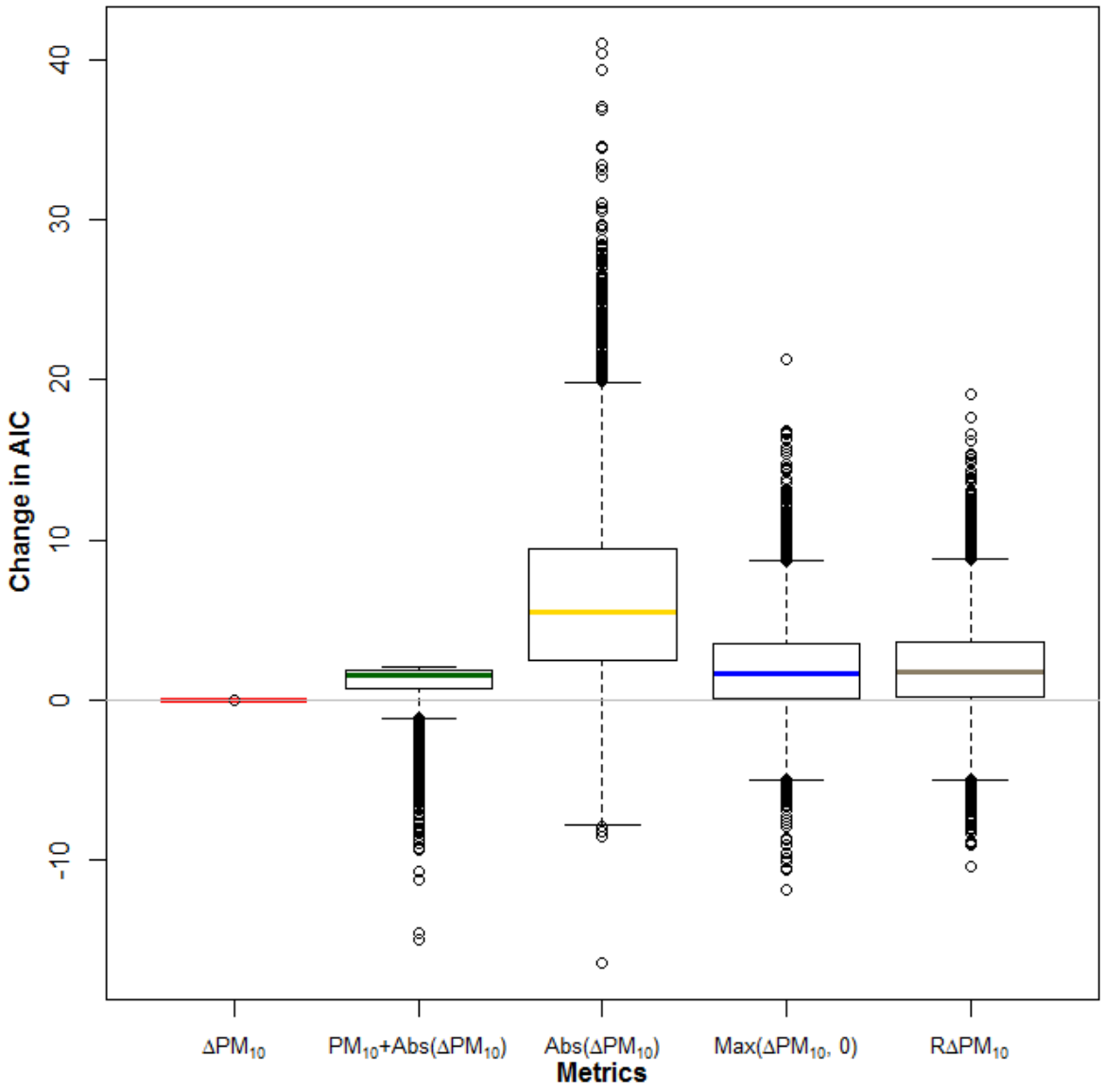


Figure 3.9: Boxplots for MC estimates of the RR associated with lag 1 PM_{10} and for different rates of missing data

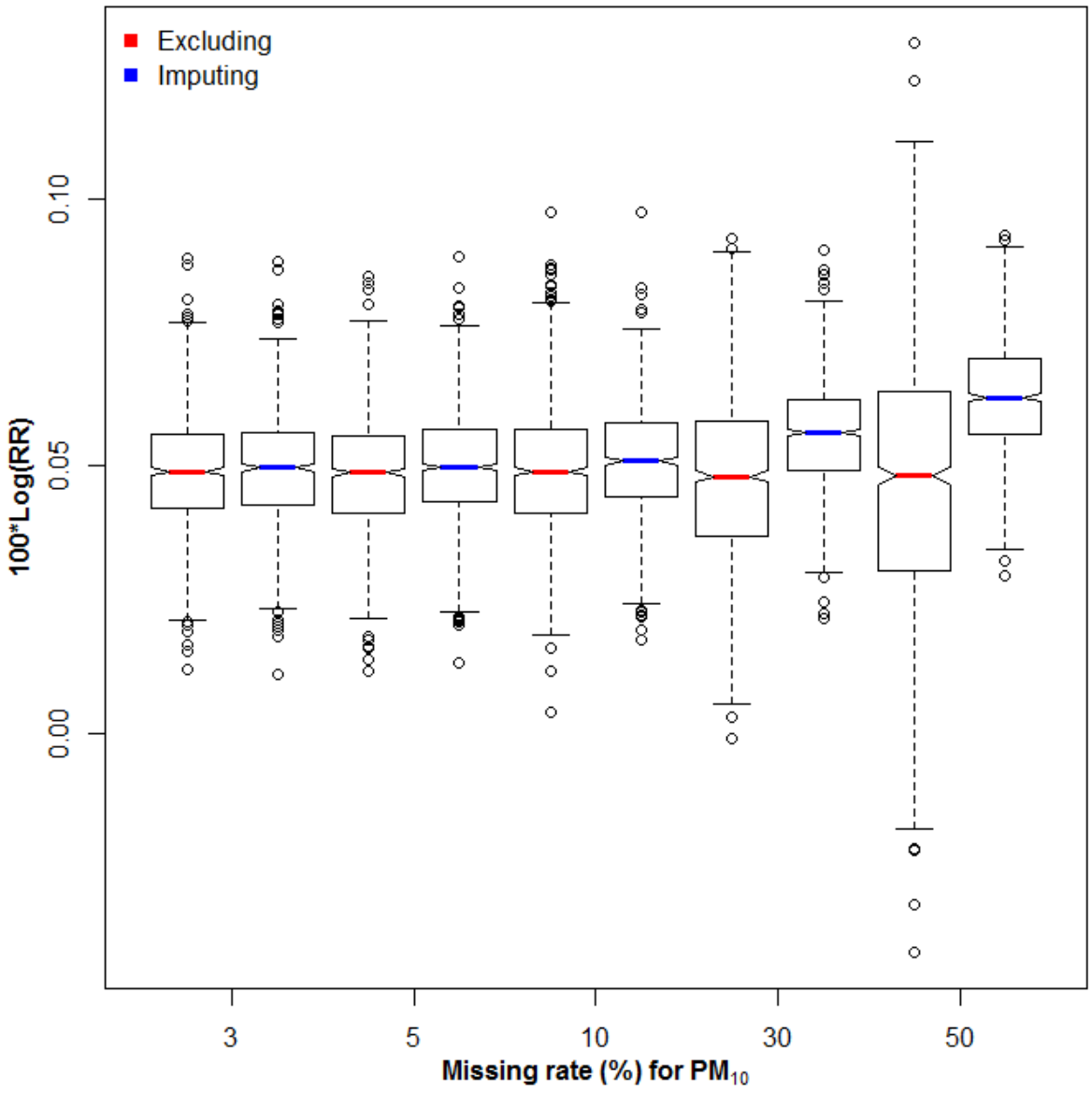
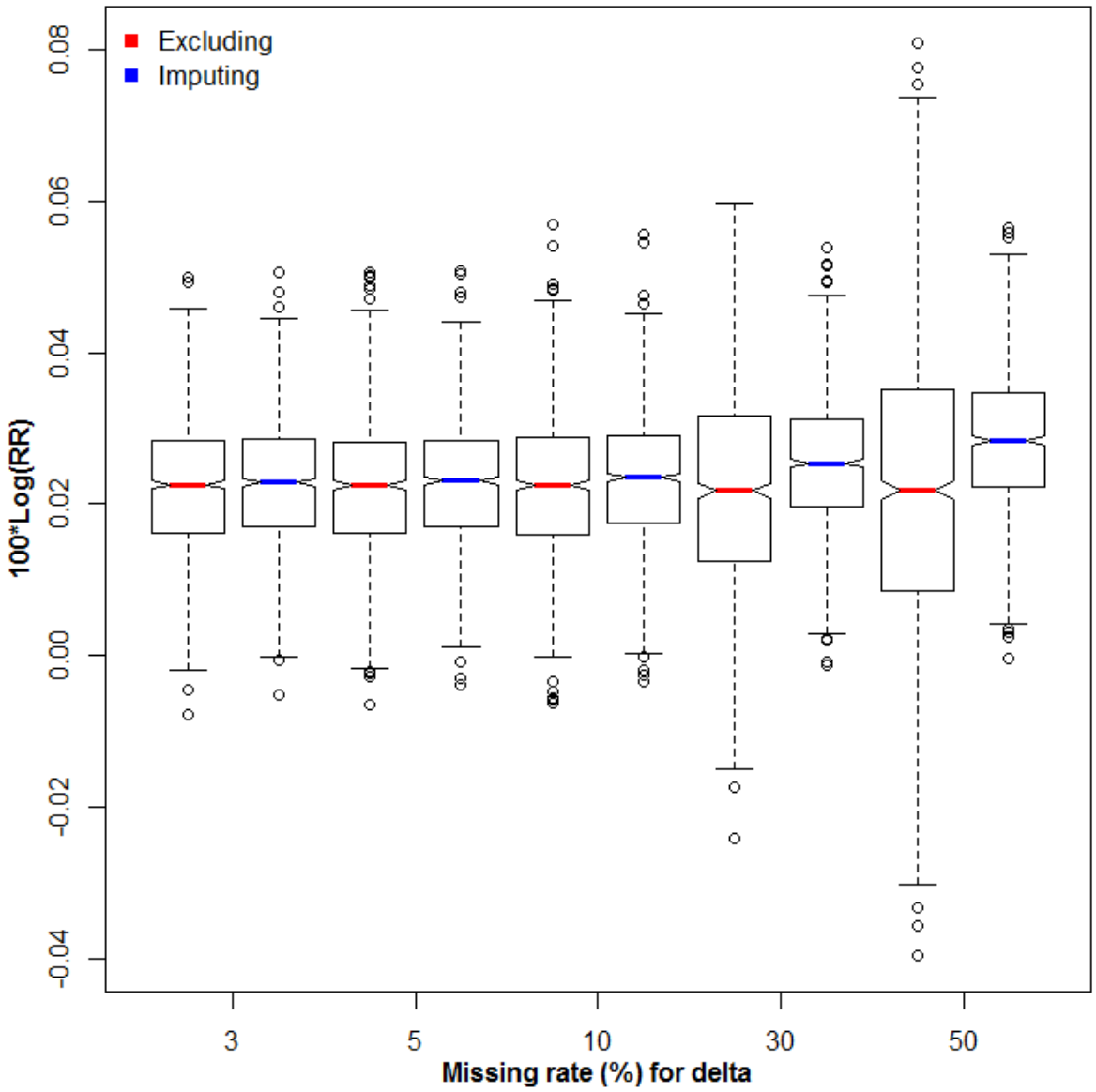


Figure 3.10: Boxplots for MC estimates of the RR associated with ΔPM_{10} and for different rates of missing data



APPENDIX D: Supplementary materials for Chapter 4

1-Model comparison using AIC values

Table 4.7: Comparison of model fits with the reference[§] model by mortality causes. Change in AIC calculated by subtracting the AIC value of the respective reference model from each model under consideration

	London			Hong Kong		
Non-linear delta models with df smoothing						
df	**change in AIC**			**change in AIC**		
	Non-accidental	**Cardiovascular**	**Respiratory**	**Non-accidental**	**Cardiovascular**	**Respiratory**
2	-0.43	-0.03	0.86	-0.94	0.65	0.02
3	-0.94	0.44	0.86	-1.36	1.29	-0.64
4	-1.47	1.07	0.61	-1.35	2.23	-1.64
5	-1.44	1.98	0.79	-0.98	3.14	-2.41
6	-0.88	3.10	1.48	-0.23	3.85	-2.61
7	-0.07	4.33	2.49	0.76	4.36	-2.34
8	0.75	5.56	3.66	1.86	4.78	-1.82
9	1.45	6.75	4.87	2.97	5.21	-1.20
10	2.02	7.89	6.06	4.05	5.76	-0.57
11	2.49	9.01	7.18	5.07	6.46	0.03
12	2.92	10.12	8.20	6.02	7.33	0.60
13	3.36	11.24	9.13	6.93	8.35	1.16
Models based on categorical delta						
	-0.52	0.98	1.86	0.91	-2.04	-2.86

[§]The reference model corresponds to the conventional distributed lag model as specified in Chapter 3 (model 3.11)

2- Cross-correlations, autocorrelation (ACF) and partial autocorrelation functions (PACF) for all variables in London and Hong Kong time series

Figure 4.9: ACF and PACF for all variables in A) London and B) Hong Kong

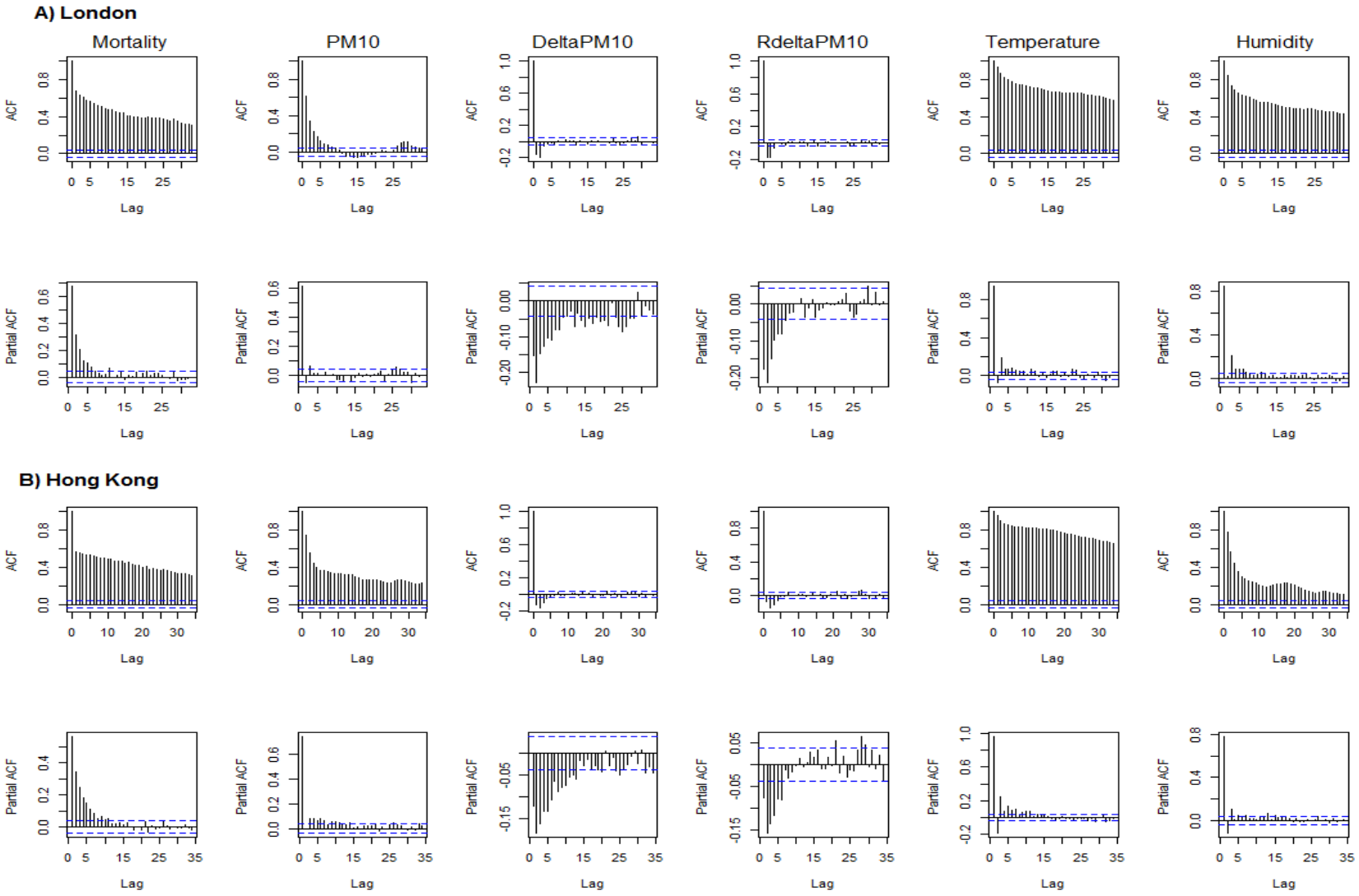


Figure 4.10: Cross-correlations among all variables in London

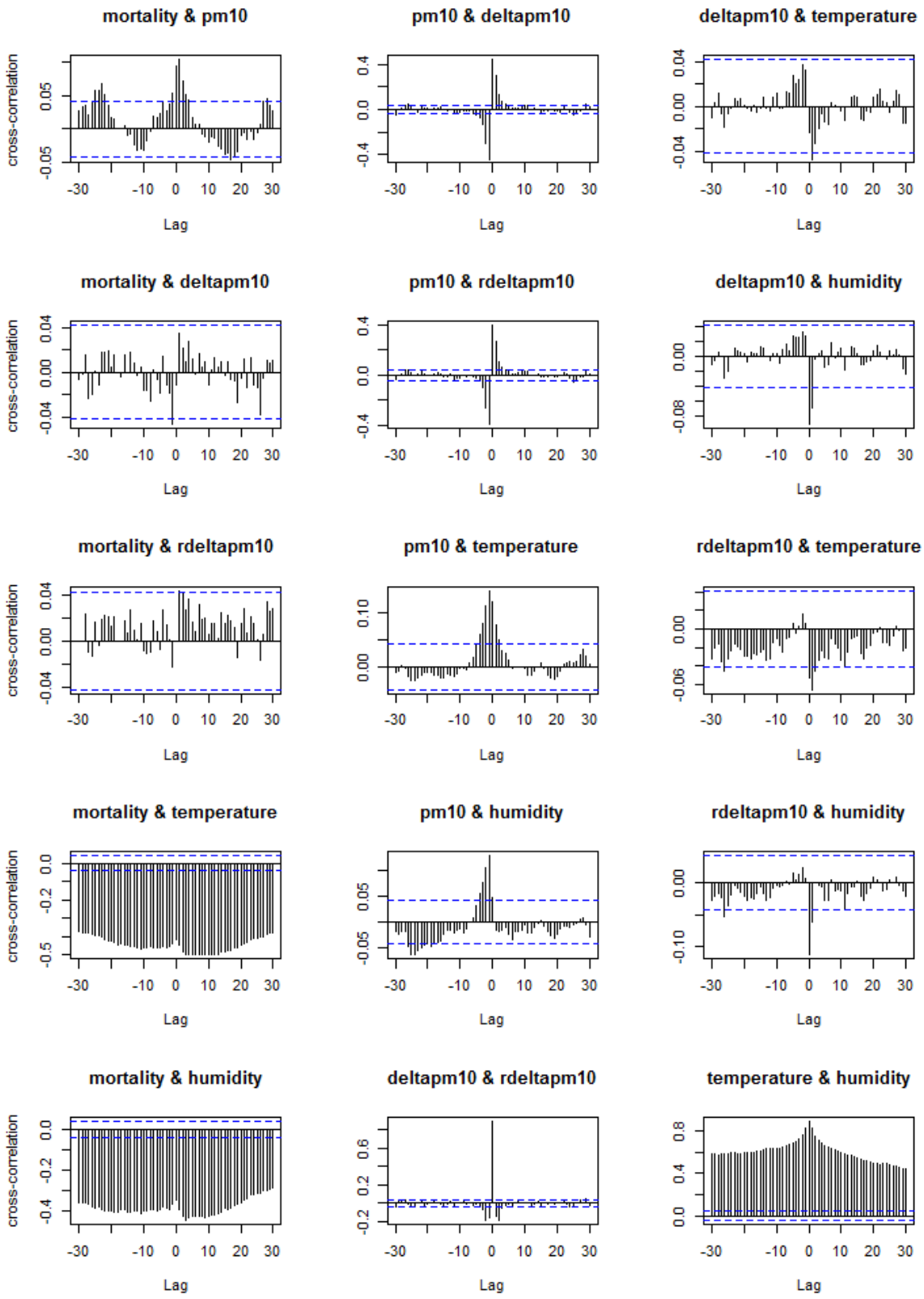
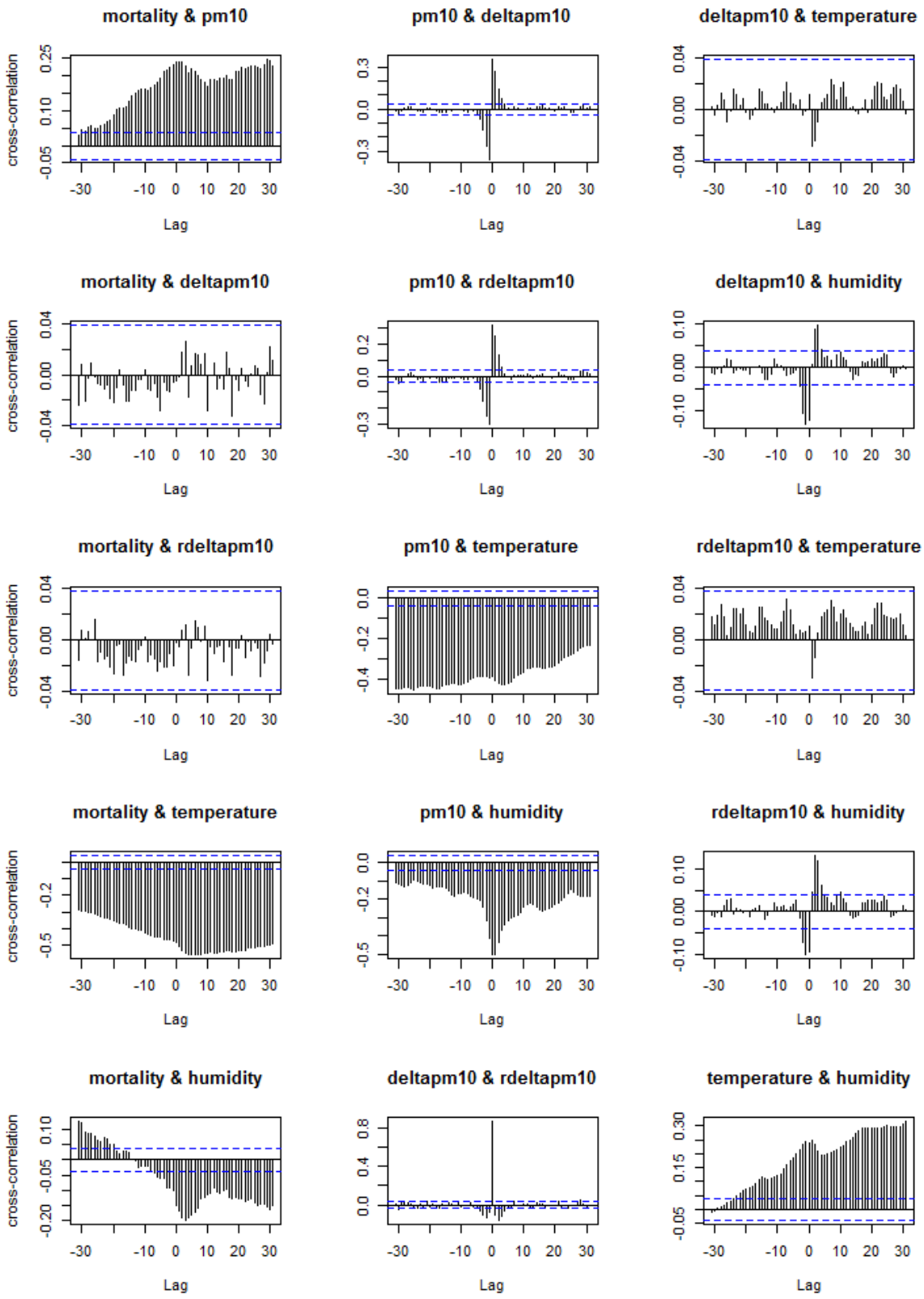


Figure 4.11: Cross-correlations among all variables in Hong Kong



3-Plots for non-linear exposure-response relationships

Figure 4.12: Non-linear exposure-response relationship between non-accidental mortality and Delta, London (df on each panel)

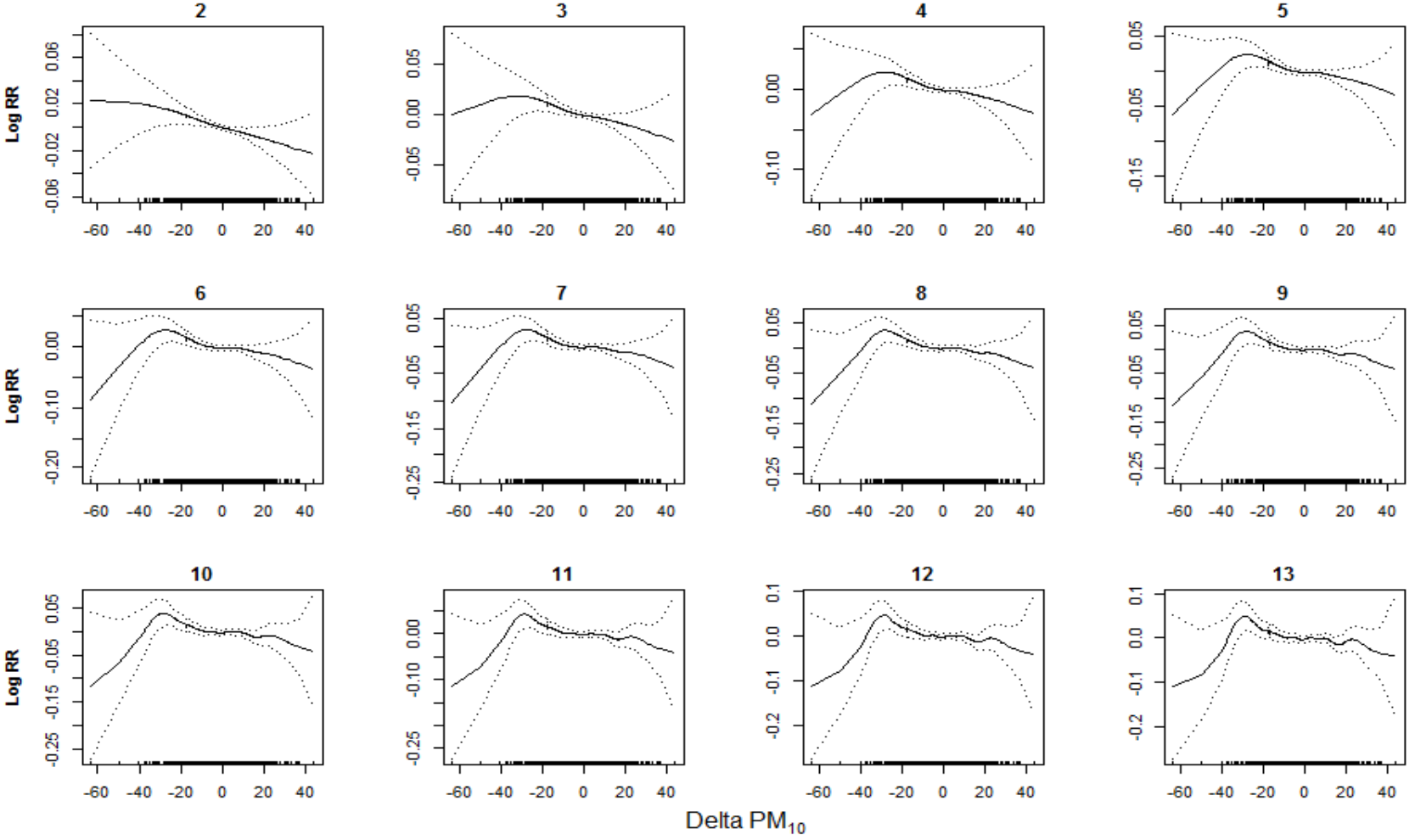


Figure 4.13: Non-linear exposure-response relationship between non-accidental mortality and Relative delta, London (df on each panel)

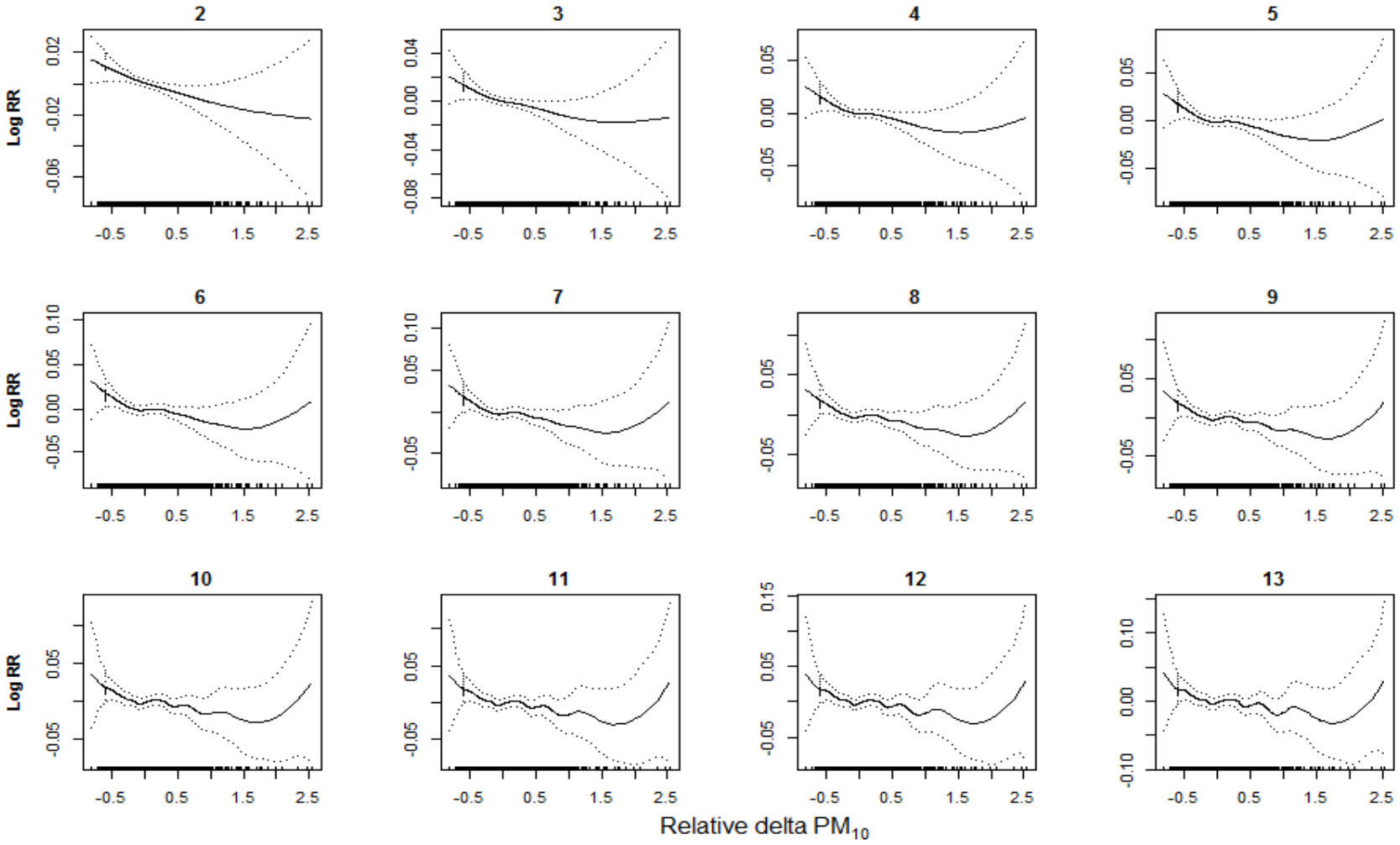


Figure 4.14: Non-linear exposure-response relationship between non-accidental mortality and Delta, Hong Kong (df on each panel)

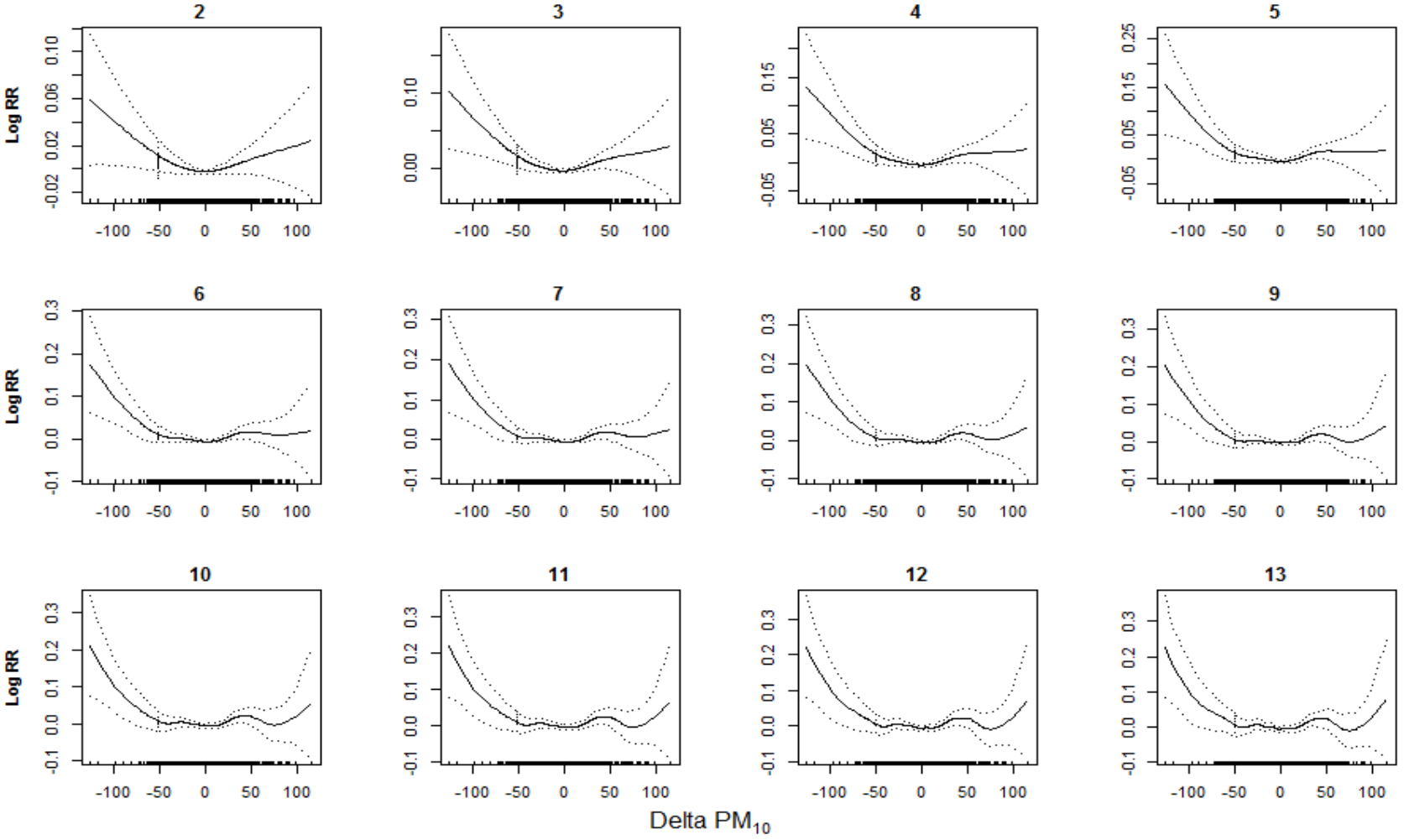


Figure 4.15: Non-linear exposure-response relationship between non-accidental mortality and Relative delta, Hong Kong (df on each panel)

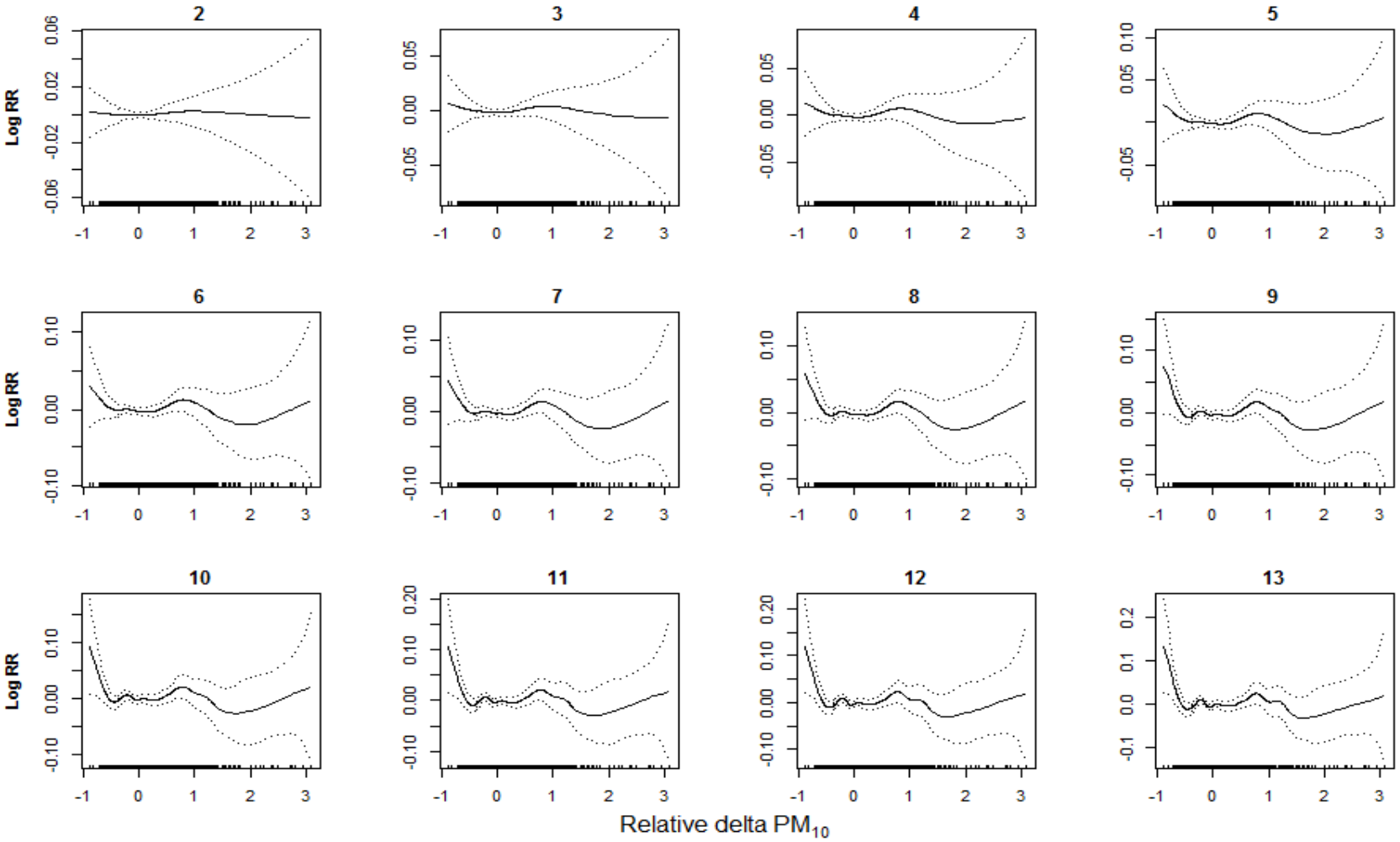


Figure 4.16: Non-linear exposure-response relationship between PM_{10} metrics and mortality for 3 df smooth, London (Full data set)

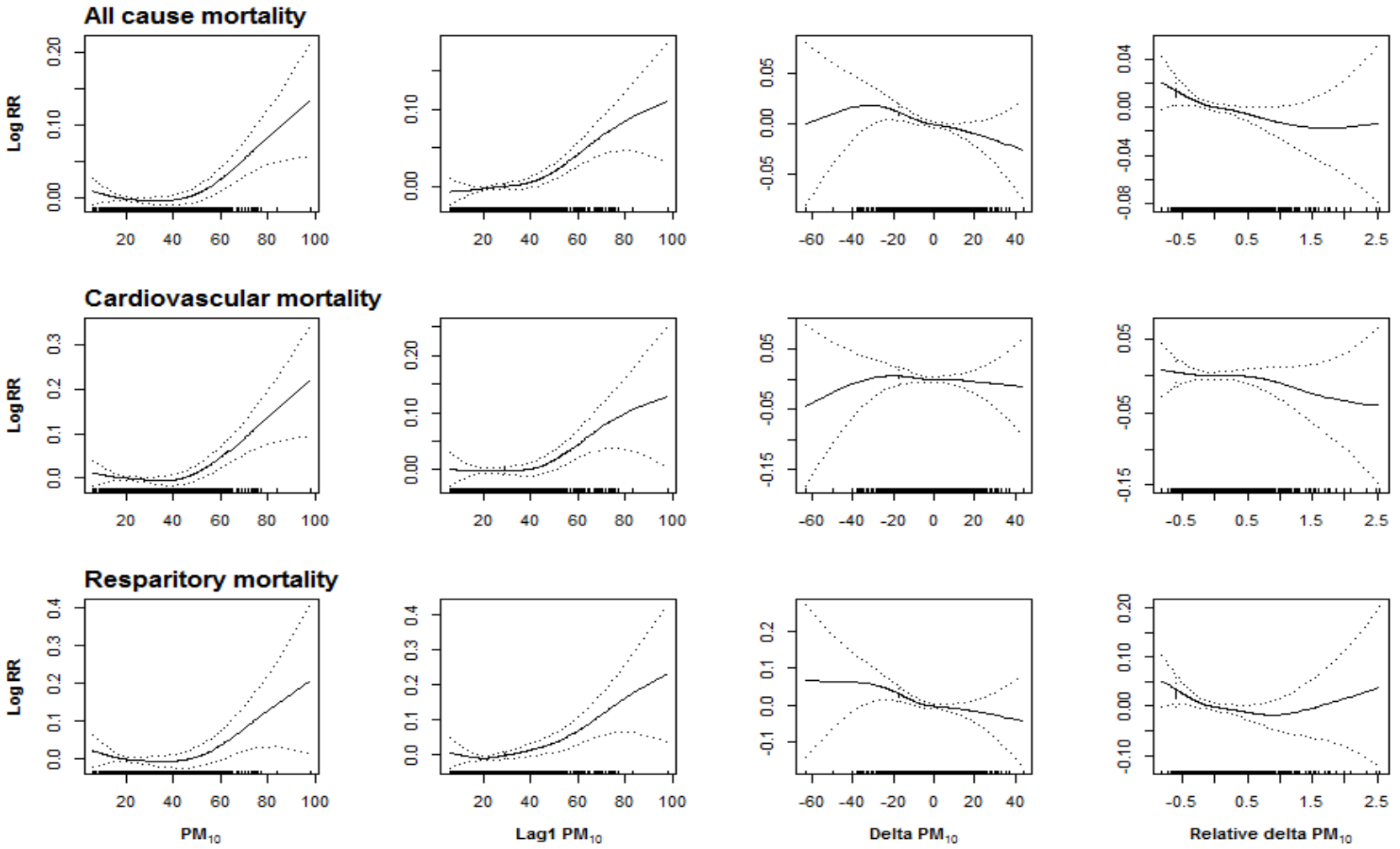


Figure 4.17: Non-linear exposure-response relationship between PM_{10} metrics and mortality for 3 df smooth, London (Positive deltas only)

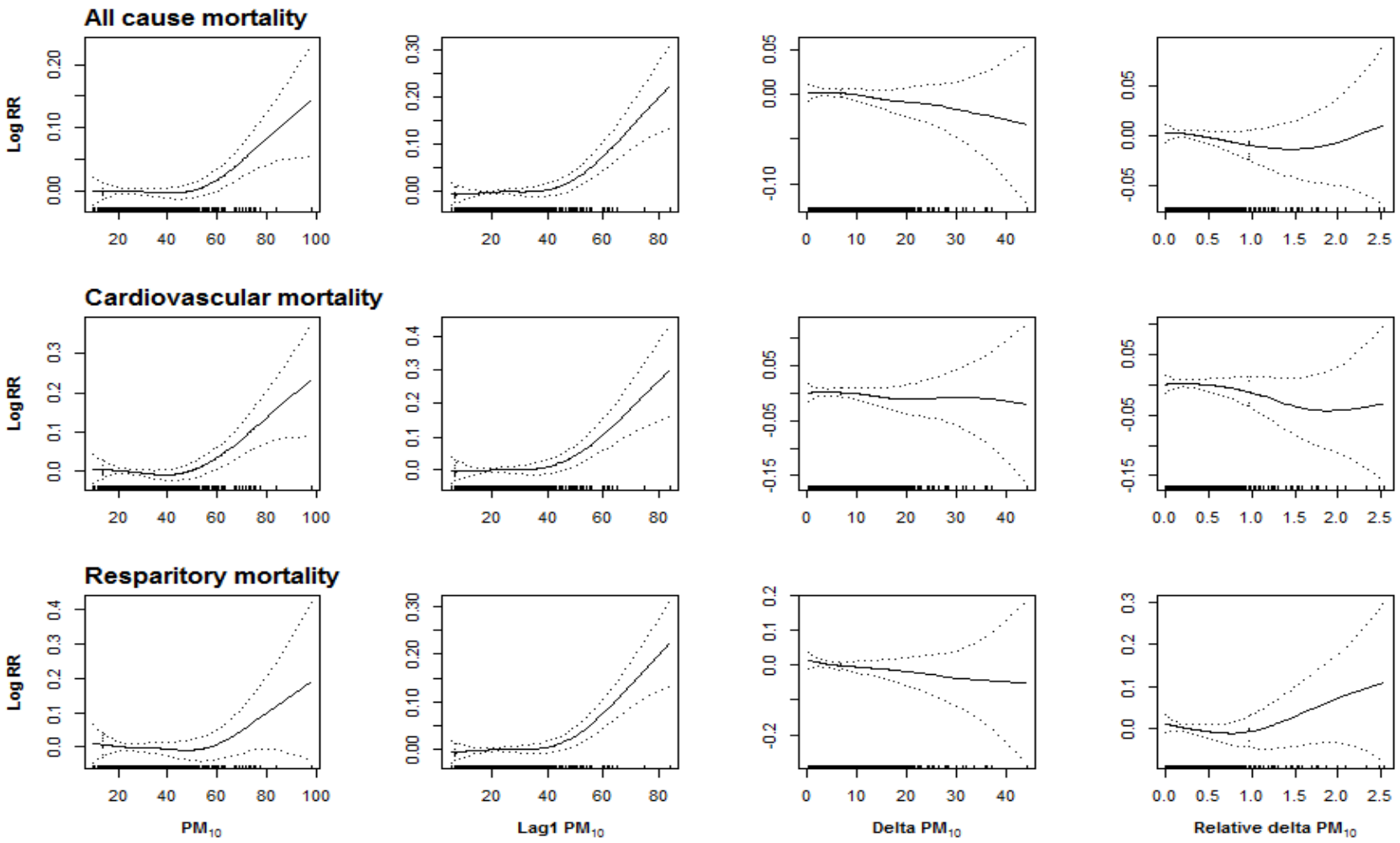


Figure 4.18: Non-linear exposure-response relationship between PM_{10} metrics and mortality for 3 df smooth, Hong Kong (Full data set)

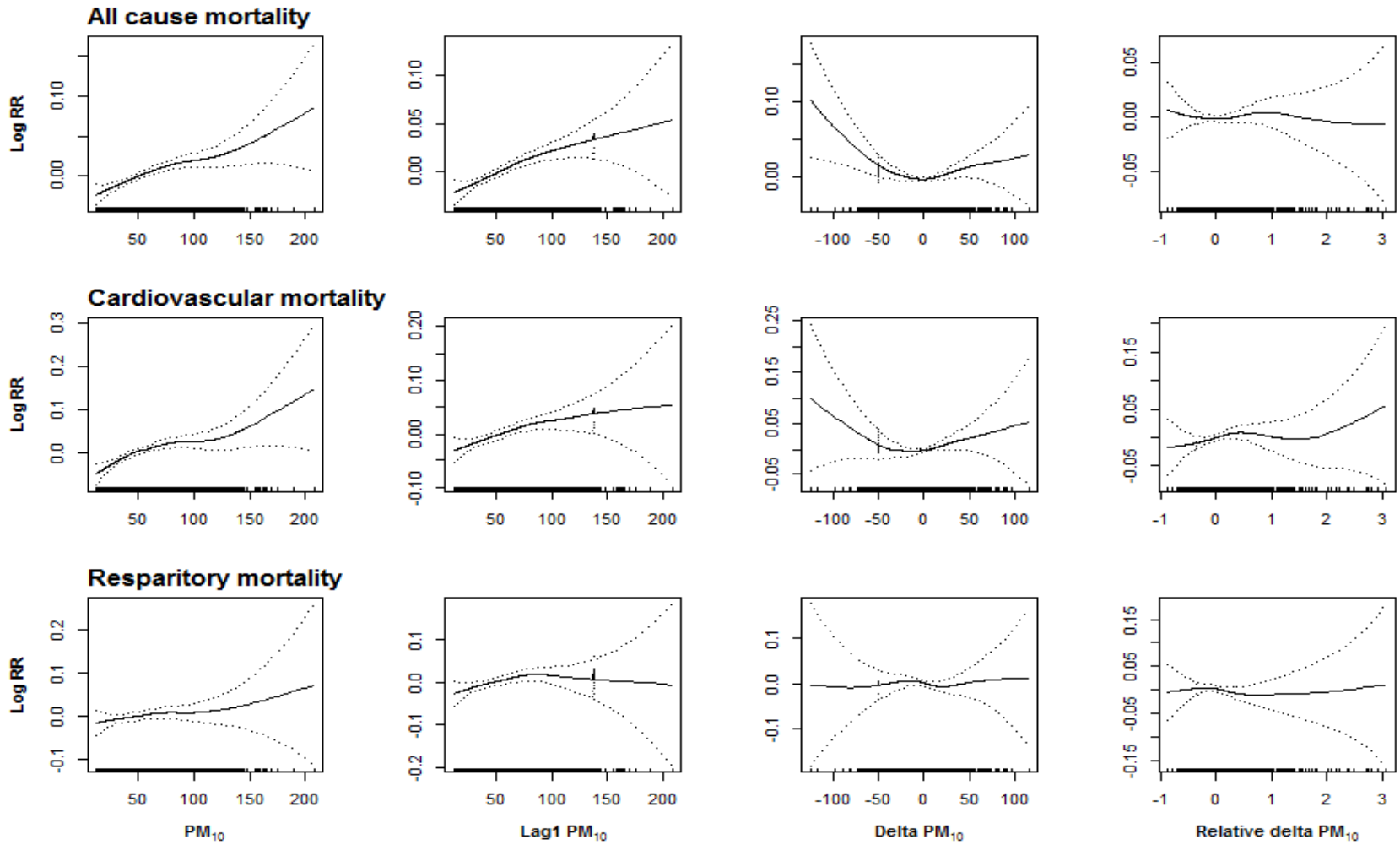
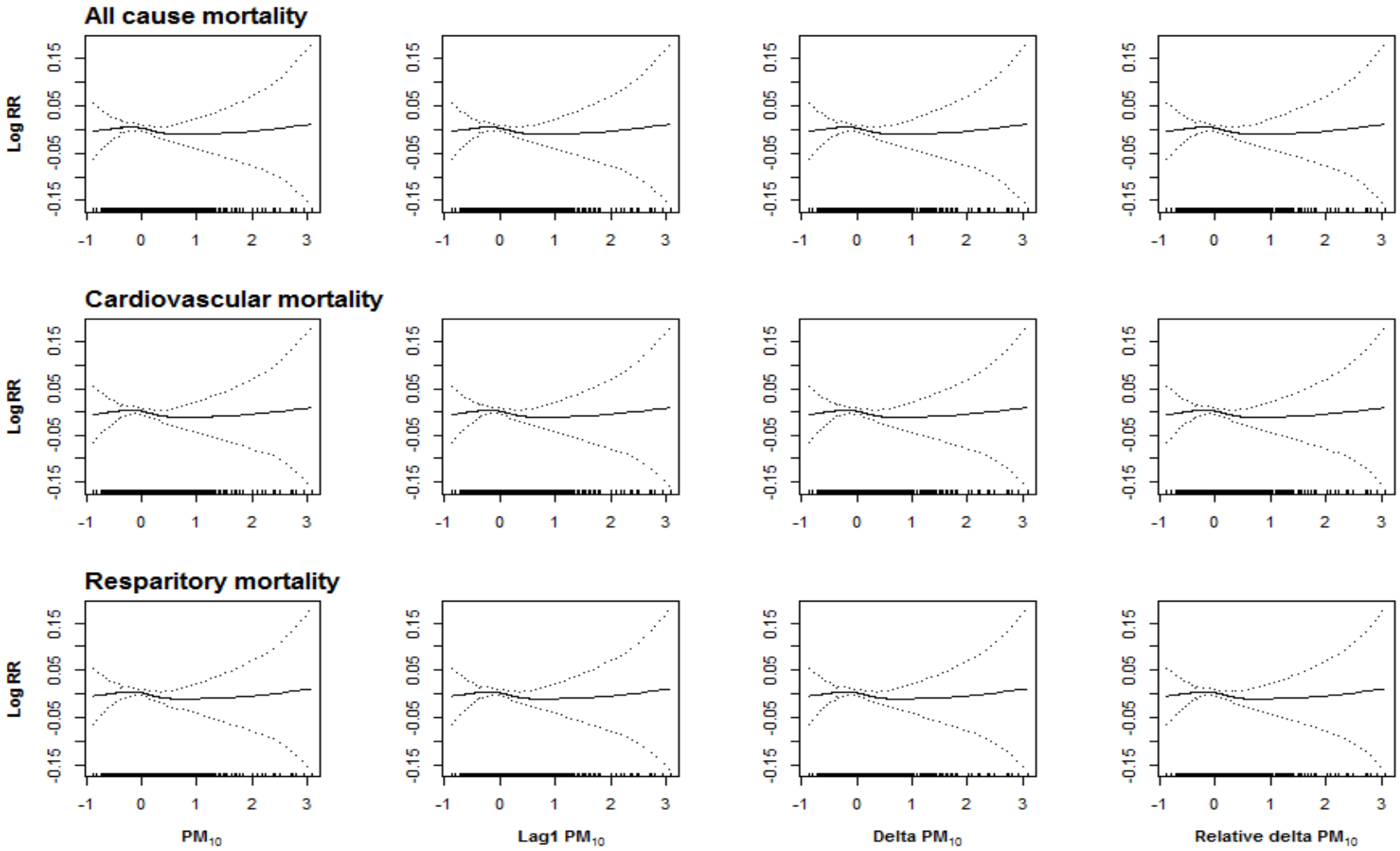


Figure 4.19: Non-linear exposure-response relationship between PM_{10} metrics and mortality for 3 df smooth, Hong Kong (for positive deltas)



APPENDIX E: Supplementary materials for Chapter 5

1. More on exposure pattern definition and results

Some of the questions the exposure pattern analysis approach could answer included

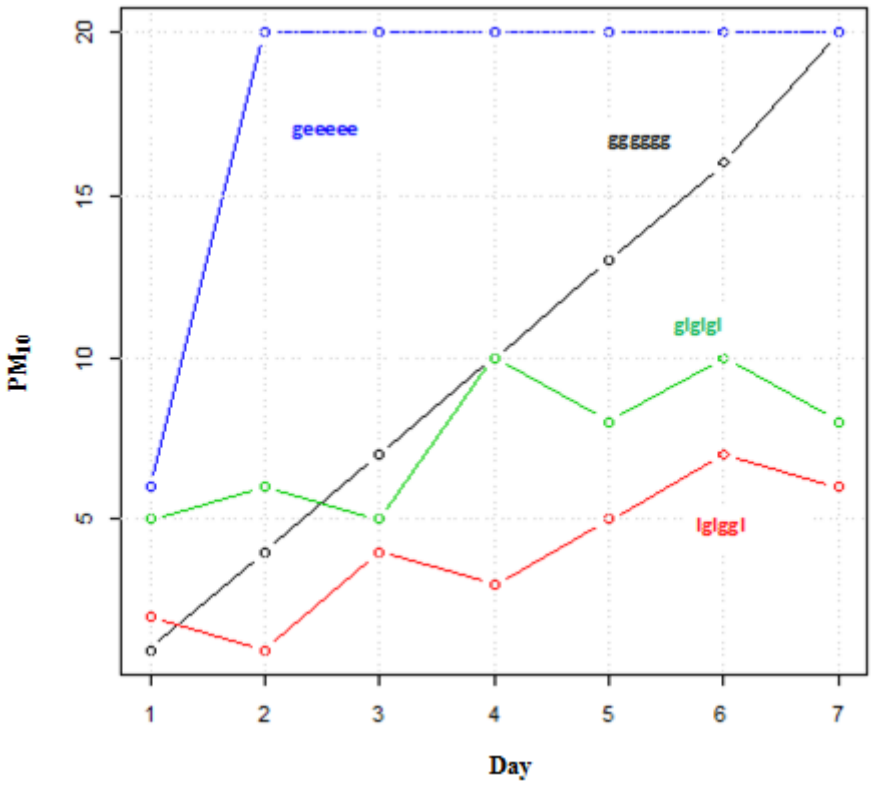
- Which patterns were more frequent?
- Which ones resulted in more deaths compared to others?
- Could accounting for exposure patterns affect air pollution risk estimates?
- Were differences if any significant?

In order to answer the above questions the following three approaches can be considered for defining and searching exposure patterns over rolling blocks of weeks:

1. specific patterns based on number of positive delta
2. specific patterns based on number of peaks of delta and absolute PM_{10}
3. all possible patterns present in the data

In Chapter 5 of the thesis approaches (1) and (2) were applied and corresponding results presented. And the last (3) is recommended for future pursuit using large dataset. In this supplementary material results found in attempt to find all possible patterns in one of the data sets analysed (London 2000-2005) are presented. This was achieved by identifying patterns based on pairwise comparison of neighbouring delta and absolute PM_{10} values within each block (result would be either of one is equal, less or greater than the other). The comparison was also repeated with tolerance of ±SD. An example of a sample of the possible patterns is illustrated below in Figure 5.10.

Figure 5.10: Sample patterns within a week block



The corresponding outcome measures could be

- Mortality at the end of each block (the next day just after the week window)
- Total mortality for the whole week following the exposure week window
- Average daily mortality for the week following the exposure week window

The data generated in this way showed that there were 59 and 69 distinct patterns for delta and absolute PM_{10} respectively. This can be summarised with respect to patterns with highest frequency (table 5.8) and by those patterns which gave rise to largest mortality counts per pattern (table 5.9).

Table 5.8: Summary of all distinct patterns present in the data-by most frequent

Exposure	Pattern	Frequency (F)	Total Mortality (M)	M/F	Weekly total M	Weekly M/F	Average M/Day	Average Temp/F
Delta PM_{10} *(frequency≥10)*								
28	gllglg	17	2311	136	17123	1007	144	14
11	gglggl	16	2302	144	16876	1055	151	12
23	glglgl	16	2260	141	16732	1046	149	11
12	gglglg	13	1878	144	13401	1031	147	12
21	glggll	13	1855	143	13470	1036	148	11
20	glgglg	12	1718	143	12498	1042	149	11
27	gllggl	12	1790	149	12589	1049	150	12
46	lgllgl	11	1647	150	11385	1035	148	11
13	gglgll	10	1373	137	10075	1008	144	12
42	lglggl	10	1409	141	10311	1031	147	12
43	lglglg	10	1409	141	10067	1007	144	14
Absolute PM_{10} *(frequency≥8)*								
18	ggllgl	15	2093	140	15127	1008	144	14
17	ggllgg	14	2077	148	14430	1031	147	12
12	gglggl	12	1807	151	13345	1112	159	7
6	ggggll	12	1671	139	12404	1034	148	10
28	glglgl	10	1623	162	11555	1156	165	12
24	glgggl	10	1373	137	10114	1011	144	14
8	ggglgl	9	1375	153	9322	1036	148	11
40	lggggl	8	1303	163	8923	1115	159	12
41	lggglg	8	1222	153	8341	1043	149	14

g: greater, l: less, e: equal
Temp: Temperature

Table 5.9: Summary of all distinct patterns present in the data-by highest mortality (top 10 counts per pattern)

Exposure	Pattern	Frequency (F)	Total Mortality (M)	M/F	Weekly total M	Weekly M/F	Average M/Day	Average Temp/F
Delta PM_{10}								
5	ggggll	1	210	210	1359	1359	194	2
54	llglgl	6	1017	170	6881	1147	164	16
9	gggllll	3	511	170	3569	1190	170	10
45	lgllgg	2	337	168	2228	1114	159	9
59	llllgg	1	168	168	1060	1060	151	10
16	gglllg	4	665	166	4485	1121	160	8
7	ggglgl	4	653	163	4220	1055	151	13
50	llgggl	1	161	161	1080	1080	154	7
29	gllgll	4	612	153	4167	1042	149	11
10	glggg	1	153	153	1225	1225	175	8
Absolute PM_{10}								
1	egglgl	1	196	196	1215	1215	174	1
15	ggllel	1	177	177	1172	1172	167	15
40	lggggl	8	1303	163	8923	1115	159	40
21	glegll	1	163	163	1123	1123	160	21
28	glglgl	10	1623	162	11555	1156	165	28
31	gllegg	1	162	162	1025	1025	146	31
39	gllllll	1	159	159	1163	1163	166	39
43	lgglgg	4	632	158	4601	1150	164	43
63	llglll	2	314	157	2261	1130	162	63
26	glggll	4	621	155	4455	1114	159	26

g: greater, l: less, e: equal
Temp: Temperature

When the pattern search was repeated with a tolerance of ±SD, the number of distinct patterns increased to 168 and 87 for delta and absolute PM_{10} as compared to the previous 59 and 69 patterns respectively. The corresponding results are summarised with respect to patterns with highest frequency (table 5.10) and by those patterns which gave rise to largest mortality counts per pattern (table 5.11).

Therefore, this is not suitable for a formal statistical analysis given the number of comparisons possible and the small frequency of several patterns.

Table 5.10: Summary of all distinct patterns present in the data-by most frequent and ±SD tolerance

Exposure	Pattern	Frequency (F)	Total Mortality (M)	M/F	Weekly total M	Weekly M/F	Average M/Day	Average Temp/F
Delta PM_{10} *(frequency≥5)*								
1	eeeeee	26	3591	138	25957	998	143	13
3	eeeeel	12	1738	145	12141	1012	145	13
83	geeeee	10	1460	146	10335	1034	148	11
8	eeeelg	6	863	144	6334	1056	151	10
93	geelgl	5	869	174	6033	1207	172	7
2	eeeeeg	5	778	156	5495	1099	157	8
119	gleeee	5	669	134	5003	1001	143	14
Absolute PM_{10} *(frequency≥5)*								
1	eeeeee	114	16056	141	115463	1013	145	13
2	eeeeeg	10	1452	145	10286	1029	147	11
44	eleeee	9	1303	145	9453	1050	150	10
63	geleee	9	1255	139	9145	1016	145	15
3	eeeeel	9	1239	138	9275	1031	147	12
7	eeeele	8	1145	143	8587	1073	153	10
29	egeeee	8	1110	139	7740	968	138	16
25	eeleee	7	1057	151	7451	1064	152	10
4	eeeege	7	1024	146	7221	1032	147	13
39	egleee	6	871	145	6390	1065	152	11
8	eeegee	6	820	137	6191	1032	147	11
76	leeeee	5	837	167	5570	1114	159	11
12	eeegle	5	789	158	5528	1106	158	9
17	eegeee	5	694	139	4612	922	132	16

g: greater, l: less, e: equal
Temp: Temperature

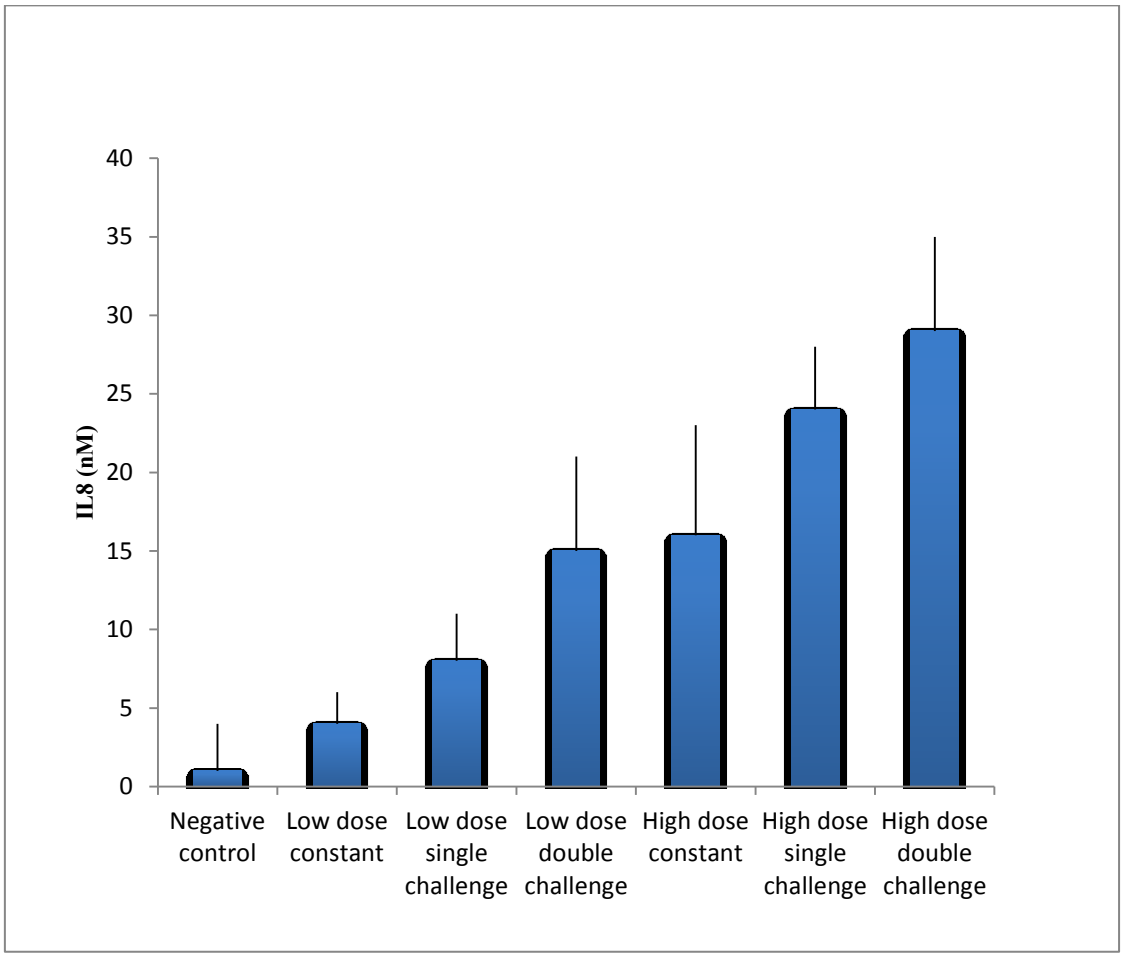
Table 5.11: Summary of all distinct patterns present in the data-by highest mortality (top 10 counts per pattern) and ±SD tolerance

Exposure	Pattern	Frequency (F)	Total Mortality (M)	M/F	Weekly total M	Weekly M/F	Average M/Day	Average Temp/F
Delta PM_{10}								
77	elglgl	1	270	270	1468	1468	210	25
42	egeeel	1	210	210	1359	1359	194	2
108	ggeeee	2	396	198	2611	1306	186	9
166	lglgel	1	194	194	1128	1128	161	8
117	gglgel	1	189	189	1301	1301	186	3
104	gelgel	1	185	185	1223	1223	175	6
54	eglgee	1	183	183	1230	1230	176	5
94	geellg	1	182	182	1134	1134	162	10
122	gleege	1	182	182	1128	1128	161	8
111	ggelge	1	180	180	1204	1204	172	7
Absolute PM_{10}								
61	gegegl	1	270	270	1468	1468	210	25
41	eglegl	1	194	194	1128	1128	161	8
70	ggglgl	1	192	192	1289	1289	184	2
21	eeglee	2	363	182	2264	1132	162	9
36	egelle	1	182	182	1134	1134	162	10
43	egllel	1	177	177	1172	1172	167	8
16	eeelge	3	519	173	3475	1158	165	8
35	egelee	1	173	173	1053	1053	150	8
71	ggleee	2	342	171	2374	1187	170	4
68	ggeele	1	169	169	1208	1208	173	5

g: greater, l: less, e: equal
Temp: Temperature

2. Exposure patterns and responses from *in vitro* experiment[§]

Figure 5.11: Comparison of inflammatory responses (IL8) of bronchial epithelial cells 72 hours after exposure to inflammatory insults (TNFα) with different patterns. Average exposures were the same under low dose scenarios and high dose scenarios compared over the 72 hour period



[§]From Sapey E, Personal communication

3. Model comparison using AIC values

Table 5.12: Comparison of pattern adjusted models with the conventional unadjusted model by mortality causes. Change in AIC calculated by subtracting the AIC value of pattern adjusted model from the respective AIC value of the unadjusted model

Pattern	London			Hong Kong		
	change in AIC			change in AIC		
	Non-accidental	**Cardiovascular**	**Respiratory**	**Non-accidental**	**Cardiovascular**	**Respiratory**
PM_{10} peaks						
	13.86	2.75	1.21	-8.84	-3.76	-0.39
Delta peaks						
	-5.26	-0.97	0	-10.75	-10.92	-2.32
Number of positive delta						
	13.46	-1.68	9.13	-2.71	-1.29	-4.66

APPENDIX F: Publications from this thesis

Nuredin I Mohammed, KB Hubert Lam, Richard W Atkinson, Ross Anderson, Chit Ming Wong, Jon G Ayres (2015). Exploring daily changes in air pollution as a new exposure metric: Application to time-series studies of short-term health effects (submitted).

Nuredin I Mohammed, KB Hubert Lam, Richard W Atkinson, Ross Anderson, Chit Ming Wong, Elizabeth Sapey, Jon G Ayres (2015). Repeated short-term peaks of PM_{10} exposure have a greater effect on mortality: a new approach to time series analysis (in preparation).

Nuredin I Mohammed, KB Hubert Lam, Richard W Atkinson, Ben Armstrong, Ross Anderson, Chit Ming Wong, Jon G Ayres (2015). Statistical issues related to using changes in air pollution exposure between successive days as exposure metric in time-series studies of short-term health effects: the delta study (in preparation).