

Assessing the acute and chronic cardio-respiratory health impacts of ambient air pollution in China

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ABSTRACT

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Background: Ambient air pollution (AAP) exposure was estimated as contributing to 4.9 million deaths and 147 million disability-adjusted-life-years globally in 2017. The majority of this health burden (an estimated 91%) falls upon populations in low- and middle-income countries, particularly China. However, robust epidemiological evidence examining the cardio-respiratory health effects of AAP exposure remains limited in China relative to that of high-income countries.

Methods: A systematic review and meta-analysis were first performed synthesising evidence on cardio-respiratory health impacts of AAP exposure from low-and-middle-income countries (LMICs) exclusively, pooling risk estimates by pollutant, associated lag time (in days), and health outcome (cardiovascular and respiratory morbidity or mortality). The China Kadoorie Biobank (CKB) study, a large prospective cohort study of ~0.5 million Chinese adults (aged 30-79 years at baseline) was then utilised to examine the acute and chronic cardio-respiratory health impacts of AAP exposure. For acute cardio-respiratory impacts, both time-series and case-crossover analyses were employed, examining the percent excess risk (100 x [relative risk-1]) of first-time cardio-respiratory hospitalisations and readmissions, respectively, in the 219,020 participants located in five urban localities across years 2013-2016 (2010-2016 for Suzhou). Risk estimates of cardio-respiratory spells associated with AAP exposure were also pooled across all five urban regions collectively, by lag structure, cardio-respiratory spell type, and pollutant. For chronic cardio-respiratory

impacts, 53,002 participants located in the CKB region of Suzhou had AAP exposure assigned to their respective CKB baseline clinic locations for years (2013-2015) using localised spatiotemporal modelling. Cox proportional hazards models with time-dependent covariates were used to estimate hazard ratios (HR) of incident cardiovascular and respiratory disease associated with a 10μg increase per cubic metre in annual AAP levels.

Results: Eighty-five and sixty studies were identified examining the cardio-respiratory impacts of particulate matter (PM) and gaseous AAP exposure, respectively, in LMICs; the majority performed in the East Asia and Pacific region. Risk estimates varied by pollutant, health outcome, associated lag time and outcome but more significant risk estimates were observed for mortality versus morbidity. In CKB, 94,479 cardio-respiratory hospitalisation spells occurred in urban regions during the study period, including 65,168 (69%) readmissions. Daily AAP levels varied by region but consistent declines in sulphur dioxide (SO_2) and particulate matter (PM) were observed. Acute AAP exposure was associated with increased risk of cardio-respiratory spells in CKB participants for both first-time spells and readmissions with a minimal overall difference in risk by admission type, but some apparent risk differences by region. In pooled analysis, 100 μg/m^3 increase in carbon monoxide (CO) and 10 μg/m^3 increases in nitrogen dioxide (NO_2), PM_{10} and $PM_{2.5}$ were associated with first-time cardio-respiratory disease (percent excess risk = 5.65% [95% CI 0.84, 10.70] for CO and cardiovascular disease, 2.13% [0.75, 3.53] for NO_2 and stroke, and 0.92% [0.34, 1.49] and 0.66 [0.23,1.08] for $PM_{2.5}$ and PM_{10}, respectively, with respiratory disease). For cardio-respiratory impacts associated with long-term AAP exposure a 10 μg/m^3 increase in SO_2 was associated with a higher incidence of major cardiovascular disease (HR 1.07, [95% CI 1.02, 1.12]) and respiratory disease (1.11 [1.04, 1.19]), specifically chronic obstructive pulmonary disease (COPD) and pneumonia (1.24 [1.08, 1.44] and 1.12 [1.03, 1.23], respectively). Ozone (O_3) was associated with risk of major cardiovascular disease (1.02 [1.01, 1.03]) including all-type stroke, as well as ischaemic stroke specifically (1.04 [1.02, 1.05], 1.04

[1.02, 1.06], respectively). There were no differences in associated risk of cardio-respiratory disease across population subgroups examined.

Conclusions: In this adult Chinese population both acute and chronic exposure to AAP appeared associated with higher risk of incident cardio-respiratory disease. This suggests that current disease burden estimates which incorporate only mortality as an outcome are likely to underestimate the actual burden of AAP exposure in China.

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LIST OF ABBREVIATIONS

$\mu g/m^3$	Microgram per cubic metre
μm	Microgram
AAP	Ambient air pollution
ACF	Autocorrelation function
APPCL	Air pollution prevention and control law
BMI	Body mass index
CDC	Centres for disease control
CHD	Coronary heart disease
CI	Confidence interval
CKB	China Kadoorie Biobank
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
DALY	Disability-adjusted life year
DBP	Diastolic blood pressure
DLM	Distributed lag model
DOW	Day of the week
DSP	Disease surveillance point
EPA	Environmental Protection Agency
FEV_1	Forced expiratory volume
FVC	Forced vital capacity
GAM	Generalised additive model
GBD	Global burden of disease
GDP	Gross domestic products
GLM	Generalised linear model
HI	Health insurance
HIC	High-income country
HR	Hazard ratio
ICD	International classification of diseases
IER	Integrated exposure response
IHD	Ischaemic heart disease
IQR	Interquartile range
LC	Lung cancer
LLN	Lower limit of normal
LMIC	Low and middle-income countries

LRTI	Lower respiratory tract infection
LUR	Land use regression
MET	Metabolic equivalent of task
MG	Milligram
MG/m^3	Milligram per cubic metre
NCD	Non-communicable disease
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
O_2	Oxygen
O_3	Ozone
OR	Odds ratio
PACF	Partial autocorrelation function
$PM_{2.5}$	Particulate matter < 2.5 μm
PM_{10}	Particulate matter < 10 μm
PM	Particulate matter
PPM	Parts per million
RCC	Regional coordinating centre
RH	Relative humidity
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SO_2	Sulphur dioxide
TB	Tuberculosis
TIA	Transient ischaemic attack
TSP	Total suspended particles
URTI	Upper respiratory tract infection
VOC	Volatile organic compounds
WHO	World Health Organisation

CHAPTER 1. INTRODUCTION

1.1 Research context

It is estimated that 4.9 million deaths and 147 million disability-adjusted-life-years can be attributed to ambient (or outdoor) air pollution (AAP) and it was the fifth-ranking risk factor for global mortality in 2017. [2] The majority of this burden continues to come from low-and middle-income countries (LMICs), where an estimated 91% of attributable premature deaths occur. [3] LMICs have undergone rapid economic growth and industrial development over the past few decades but now face the greatest burden of AAP exposure. For example, in China, rapid industrialisation has resulted in drastic increases in AAP levels with an estimated 1.2 million deaths attributable to AAP exposure in 2017, the joint highest mortality burden alongside India. [2].

The adverse effect of AAP exposure on human health is not a recent discovery, with associations first documented over half a century ago. [4, 5] However, sustained increases in AAP levels, coupled with ageing populations and a rise in rates of non-communicable diseases (NCDs), has resulted in an intensified interest in understanding the true effects of AAP on health. Such interest coupled with the continued development of methodological techniques has led to a rise in documented associations between both acute and chronic AAP exposure and a multitude of adverse health effects across global settings. Such effects have been found to extend throughout the life course from adverse birth outcomes such as low birth weight and pre-term birth, [6, 7] to type-2 diabetes[8, 9] and even mental and neurodevelopmental disorders in later life, including Parkinson's Disease[10] and Dementia.[11]

However, given the nature of AAP exposure, the majority of documented health effects are those impacting the cardio-respiratory system with mounting substantial evidence on the relationship between AAP exposure and cardio-respiratory disease. As such, a causal link between certain components of AAP and cardio-respiratory disease is now supported by the

World Health Organisation (WHO), Global Burden of Disease (GBD) project and United States' (US) Environmental Protection Agency (EPA). AAP exposure is now estimated to account for 41% of global deaths from chronic obstructive pulmonary disease (COPD), 19% from lung cancer, 16% from ischaemic heart disease (IHD), 11% from stroke, and 35% from lower respiratory tract infection (LRTI). [12]

Paradoxically, however, research output is not proportional to AAP burden experienced within countries, and robust research from China on cardio-respiratory effects of AAP exposure is limited. Instead, the majority of robust evidence continues to emerge from high-income countries (HICs), particularly North America and Western Europe. This is exemplified in **Figure 1.1.** which shows integrated exposure-response functions at differing concentrations of particulate matter < 2.5 micrometres (μm) ($PM_{2.5}$), for IHD, stroke, COPD and lung cancer mortality, respectively. These IERs are used to calculate population attributable fractions and the subsequent disease burden attributable to $PM_{2.5}$ concentrations by both WHO[13] and GBD,[2] respectively, with the respective relative risk estimates for IER construction obtained from cohort studies across a range of $PM_{2.5}$ concentrations. However, given the scarcity of prospective evidence from China, mortality risks associated with very high $PM_{2.5}$ concentrations are obtained from studies of household air pollution, passive smoking and active smoking. This is despite these sources being more likely to differ in composition, exposure intensity, and toxicity. Effectively estimating the health burden of AAP exposure in China has therefore relied on extrapolations of risk from either studies performed in HICs with lower AAP levels or effect estimates derived from studies of household air pollution, passive smoking and active smoking, thus potentially underestimating the true associated disease burden of AAP exposure. [14]

Air pollution epidemiology is inherently challenging, and it encompasses a range of methodological issues not typically found in research of more traditional risk factors for health, issues that will be discussed throughout this thesis. However, given China's rapidly

ageing population,[15] accelerating non-communicable disease (NCD) prevalence, and potential dialling down of environmental targets amidst fears of a stagnating economy,[16, 17] the need for robust evidence to reliably estimate the adverse health effects including major cardio-respiratory diseases, associated with AAP exposure in China is now of pressing importance. The China Kadoorie Biobank (CKB), as the largest prospective observational study to date performed in China, represents a considerable previously unexplored resource to reliably begin to explore the health effects of AAP exposure in China.

1.2 Research aims and objectives

The overall research aim of this thesis was to investigate the associations of AAP exposure with both acute and chronic cardio-respiratory health effects using the CKB study. I planned to achieve the overall aim through measurable specific objectives as mentioned below:

- To summarise the documented evidence on the association between cardio-respiratory health effects of AAP exposure within LMICs exclusively (**Chapter 3**)
- To examine the associations between acute AAP exposure and cardio-respiratory health outcomes in CKB urban regions (**Chapter 5**)
- To examine the relationships between six major air pollutants, and risk of major cardio-respiratory endpoints in the CKB region of Suzhou (**Chapter 6**)

1.3 Outline of the thesis

Chapter 1: Provides an overview of this thesis. It outlines the context and significance of the research described in this thesis – the cardio-respiratory health effects of AAP exposure in China. It also describes the overall aim of this thesis, along with the chapter-specific objectives. It concludes by outlining the contents of this thesis by chapter.

Chapter 2: Further outlines the context and supporting background information of the research described in this thesis. It defines AAP, its different components and their respective sources. It then summarises the current state of AAP exposure in China. It also

provides a detailed background to the methodological approaches used in epidemiological studies to quantify both the acute and chronic health effects of AAP exposure alongside their respective difficulties. Finally, it critically reviews the main methods of AAP exposure classification used in studies and concludes by outlining the issue of exposure measurement error in studies of AAP exposure and health.

Chapter 3: Summarises the current evidence base regarding AAP exposure and cardio-respiratory health effects. To do so, it outlines the aims, methodology and results from a systematic review and meta-analysis investigating the cardio-respiratory effects of acute AAP exposure in LMICs exclusively. Sections of this chapter were published in *The Lancet Planetary Health* (17th December 2017 Vol. 1, Issue 9, Pages 368-280)[18] and *Environmental Health* (29th March 2018, Vol.17, Pages 1-41)[19]. This chapter then outlines and critically reviews the existing evidence base on the associations between chronic AAP exposure and cardio-respiratory disease in China specifically. It concludes by summarising the current state of the evidence base and highlighting existing gaps in research and knowledge.

Chapter 4: Provides the detailed methodology of the CKB study, the study population utilised in this thesis. Baseline socio-demographic, lifestyle characteristics and physical measurements of the study population are also presented.

Chapter 5: Examines the associations between acute AAP exposure and cardio-respiratory disease incidence in five CKB urban regions. It describes the re-classification of CKB health outcomes into the derived outcome variable of "spells" and their use to explore the associations between AAP exposures with both first-time cardio-respiratory hospitalisations and readmissions, respectively.

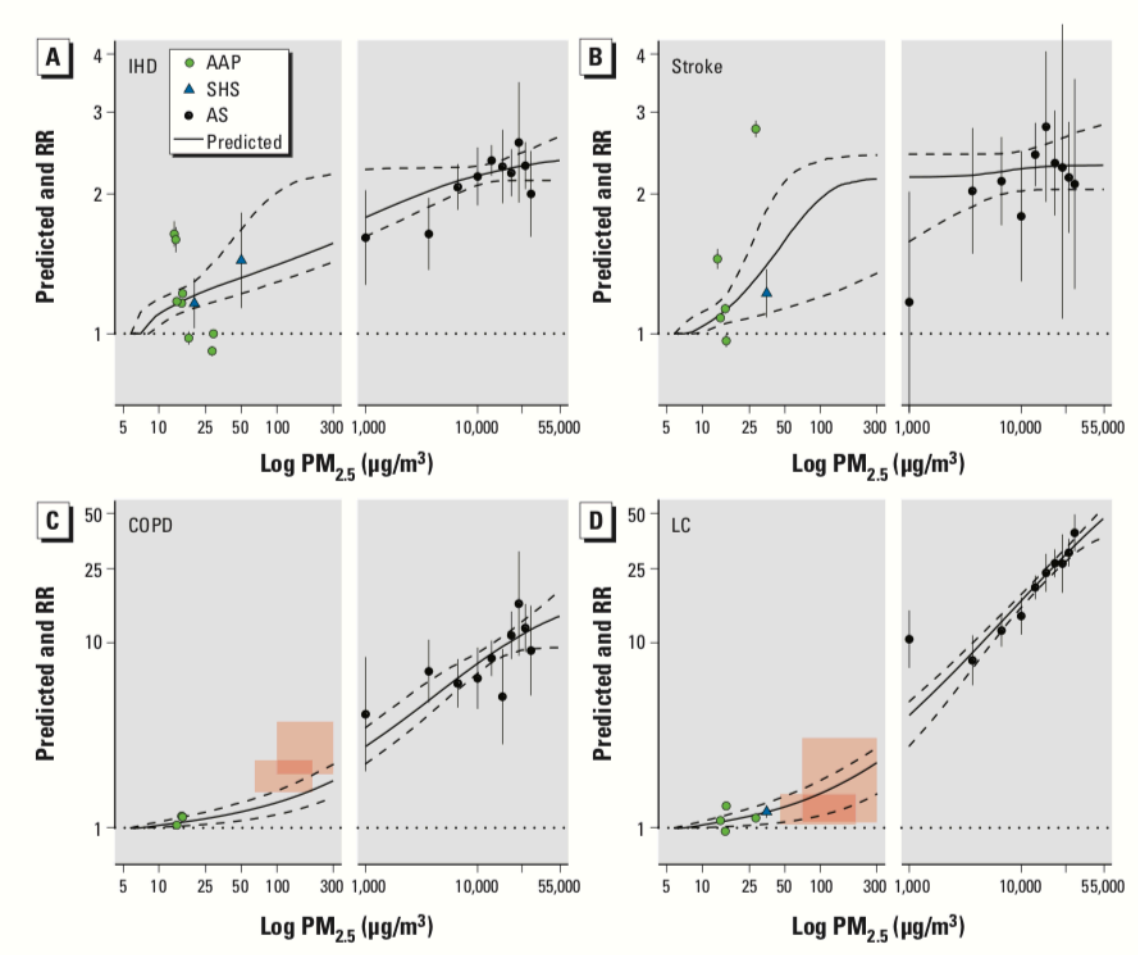
Chapter 6: Examines the associations between chronic AAP exposure assigned using a spatiotemporal model developed within CKB and major cardio-respiratory disease incidence in the CKB urban region of Suzhou. Specific outcomes include stroke (both ischaemic and haemorrhagic), IHD, COPD, and pneumonia.

Chapter 7: Summarises the main findings of this thesis, comparing them to the existing evidence described in Chapter 3, and it explores the overall strengths and limitations of the

research described in this thesis before outlining the relevant public health implications and concluding with the future research directions.

Figure 1.1 Integrated exposure response function for $PM_{2.5}$ exposure concentration and disease relative risk

Predicted values of integrated exposure response function (solid line) and 95% confidence intervals (dashed line) and type-specific relative risks (points) and 95% CIs (error bars) for IHD (A), stroke (B), COPD (C), and LC (D) mortality. Obtained from Burnett et al. [20]



CHAPTER 2. AIR POLLUTION EPIDEMIOLOGY

2.1 Ambient air pollution definitions and sources

Air pollution can be broadly defined as "the presence of a contaminant or pollutant substances in the air that does not disperse properly, and that interfere with human health or welfare or produce other harmful environmental effects". [21] While AAP can theoretically incorporate a huge number of potential substances which, if at high concentration would cause harm, in practice, it tends to consist of a group of pollutants classed by their physical properties, principally their composition and size. For this thesis, the six commonly examined pollutants are included. The definitions and sources of each of these pollutants are described below.

Particulate matter (PM_{10} and $PM_{2.5}$)

Airborne particulate matter (PM) synonymous with the dated regulatory measure of total suspended particulate (TSP) consists of an assortment of solid and/or liquid particles of varying sizes and chemical composition. PM can be further categorised into one of two groups based on size. Coarse or "inhalable particles" are the PM fraction consisting of particles with an aerodynamic diameter of <10 μm, (PM_{10}). The fine or "respirable" PM fraction contains those <2.5 μm ($PM_{2.5}$), and within this is ultrafine PM with particles less than 0.1 μm in size. PM can contain a wide range of chemical compounds, the exact type depending principally on the source.

Sources of primary PM (PM directly emitted into the atmosphere) can be both natural and anthropogenic. Primary natural sources include wildfires, mineral dust from arid regions, sea-spray, and resuspension of organic matter, with emission rates sensitive to climatic factors. Chemical constituents of naturally forming PM often include sodium chloride as well as mineral components such as aluminium, calcium and iron. The main primary anthropogenic source of PM is fossil fuel combustion but can also include agricultural

operations, construction activities, and resuspension of road dust into the air. Anthropogenic sources can be both mobile (vehicle emissions) and stationary (industry and power plants), with PM from anthropogenic sources typically containing elemental carbon (including black carbon), trace metals and minerals.

Secondary sources of PM include gases that following atmospheric reactions result in the formation of PM through nucleation. Such gaseous precursors include ammonia, volatile organic compounds (VOCs), sulphur dioxide, and nitrogen oxides. PM formed from secondary sources is often composed of sulphates, nitrates, organic compounds, and water and can also take longer to form than primary sourced PM travelling considerable geographic distances before PM formation occurs.

Nitrogen Dioxide (NO_2)

Nitrogen dioxide (NO_2) is a highly reactive gas toxic at high concentrations. NO_2 forms when nitic oxide (NO) reacts with other chemicals to form NO_2, with NO and NO_2 collectively known as NO_x. Primary sources of NO_x include stratospheric NO_x and lightning strikes, but the majority of NO_x sources are anthropogenic, principally vehicle exhausts and agriculture. NO_2 formation mainly occurs through the oxidation of nitric oxide (NO) by oxygen (O_2) in ambient air at very high temperatures, such as inside an internal combustion engine. The majority of NO_2 emissions (>90%) are released into the atmosphere during fossil fuel combustion. Secondary NO_2 can also be formed through the chemical reaction of NO and ozone (O_3) in the atmosphere.

Sulphur Dioxide (SO_2)

Sulphur dioxide (SO_2) is a gas formed during the combustion of sulphur-containing fuels. While natural primary sources of SO_2 do exist, volcanoes being a prominent example, an estimated 99% of SO_2 is from anthropogenic sources.[22] Sources chiefly include the processing of sulphur-containing material such as coal, oil and metal-containing ores

through industrial activities; SO_2 is also present in motor vehicle exhausts as a result of fuel combustion, although emissions from vehicles are less relative to industrial activity. Combustion of fossil fuels remains the single largest source of anthropogenic SO_2. [23]

Ozone (O_3)

Ozone (O_3) is a gas occurring naturally in the upper atmosphere (~6-30 miles above the earth's surface); however, in the lower atmosphere tropospheric or "ground-level ozone" is a secondary pollutant formed via the photochemical reactions of NOx, VOC and carbon monoxide (CO) with sunlight. The majority of O_3 precursors come from vehicle exhausts emissions, particularly during the morning hours, which then react photochemically over the course of the day, forming O_3 with concentrations often peaking in the mid-afternoon. O_3 formation is exacerbated on sunny days with reactions catalysed by heat and ultraviolet radiation, with O_3 distribution varying substantially due to climatic variability.

Carbon Monoxide (CO)

Carbon monoxide (CO) is emitted as a primary pollutant from incomplete combustion of carbon-containing fuels such as coal, wood, and natural gas, as well as petrol, kerosene and oil. The main sources of ambient CO are anthropogenic, principally vehicle exhausts where emissions are higher in inefficient cars, predominantly those without catalytic converters. Natural sources of CO also exist, including volcanoes, forest-fires and carbon releasing molecules, but these sources contribute less CO relative to anthropogenic sources.

2.2 Ambient air pollution in China

Following the widespread economic reform of 1978, China industrialised at a pace quicker than any developed country. With an 11-fold increase in gross domestic product (GDP) observed over the next four decades, [24] by 2010 China was the world's largest total energy consumer.[25] However, a lack of investment in energy-efficient technologies left energy

infrastructure underdeveloped and a reliance on fossil fuels within the country, particularly coal which remains China's primary source of energy, with China accounting for almost half of global coal consumption.[26] China's industrialisation was also coupled with increases in population size, numbers of motorised vehicle, and manufacturing output, leading to a dramatic rise in AAP at a national scale. While such industrialisation, population growth, and subsequent energy demand are prominent causes of Chinese AAP levels at the national scale, additional more localised contributory factors also exist. These include changing transport patterns, [27] widespread domestic use of solid fuels (particularly in more rural areas) [28] meteorological factors [29] changing land use and cover, [30] and the open burning of crop waste and biomass.[31]

A lack of regulation was also a major contributory factor to the excessive AAP levels in China. Although the first law on the protection and control of atmospheric pollution in China was implemented in 1987 (Air Pollution Protection and Control Law [APPCL]), revised in 1995, and again in 2000, it suffered from fragmented implementation, a lack of AAP monitoring capacity as a basic regulatory element, and judicial discretion. Similarly, while AAP guidelines have been present in China since 1982, [32] these were poorly adhered to. However, following widespread concerns surrounding AAP levels in China, AAP guidelines were revised, [33] with mandatory limits imposed for SO_2, NO_2, CO, O_3, PM_{10}, and $PM_{2.5}$. New policies were also designed to limit AAP levels in China including the Clean Air Action Plan (2013-2017). Renewed in 2017 this five-year action plan now contains specific targets for the reduction of SO_2, NO, and O_3 as well as a targeted increase in the annual numbers of days with "fairly good" air quality to at least 80%, and a decrease in highly polluted days by at least 25% compared with 2015.[34] This is in addition to the development of an established AAP monitoring network across the country. Concurrently, a major revision of the APPCL in 2016, also provided specific details for control of AAP caused by coal burning, industrial production, motor vehicles, dust, and agricultural activities as well as improved mechanisms for enforcement.[35]

As a result of these policies, recent declines are being observed in AAP levels across China, including a 50% decline in SO_2 concentrations reported across the most polluted Chinese provinces between 2005-2015 [36] as well as a declining annual national trend of -7.2% a year in $PM_{2.5}$ observed from 2013-2015 [37] with similar trends replicated in other studies.[38] Despite these declines strong spatial variation is still apparent across China in both concentration and composition of AAP as a result of varying emission intensity, meteorological conditions, and natural AAP sources. Overall, concentrations are higher in the North than in the South of China and concentrations of $PM_{2.5}$ highest in the densely populated urban clusters of the Beijing Tianjin Hebei region, and Pearl River Delta and Yangtze River Delta region shown in **Figure 2.1**.[1] Southern coastal regions of China have relatively lower AAP levels due to a lesser demand for fossil fuels and beneficial meteorological conditions. Even following such improvements, AAP exposure remains a major environmental and public health concern in China. Compared to other countries, improvements in absolute concentrations are relatively small. In 2018, China's air quality was ranked 177th out of 180 countries [39] with AAP in still the leading environmental threat to health in China. [40]

2.3 Measuring the health effects of air pollution

The earliest documented health effects of AAP exposure emerged following historically high episodes of AAP in HICs. These include the Meuse Valley episode of 1930 in Belgium, as well as Donora, Pennsylvania (1948), and London, United Kingdom (1952). During these peaks in AAP caused by high industrial pollution in combination with climatic factors, a higher number of excess deaths were noted. For example, in London, over 4000 more deaths than usual were recorded in a two week period surrounding the episode.[4] Since then, study methodologies used to examine the health effects of AAP exposure have advanced considerably with standardised study designs used to distinguish the health effects of acute and chronic AAP exposure, respectively. The most common methodologies used in epidemiological studies will now be outlined.

2.3.1 Acute health effects

Studies investigating acute-term health effects of AAP exposure are broadly based on methodologies from the aforementioned earliest AAP studies whereby expected counts of deaths within short time-periods were compared to AAP levels. However, study design methodologies have advanced considerably, with most commonly now utilising time-series and case-crossover analyses.

In time-series analysis, changes in AAP levels within short-time frames (usually a couple of days) are utilised to examine the effect of AAP on mortality and/or morbidity counts across an entire study population. For this, Poisson regression using generalised linear models (GLMs) or generalised additive models (GAMs) is used, with the unit of analysis the day itself rather than individual participants. The logarithm of expected morbidity/mortality rates for a given change in daily AAP concentration is then modelled with most time-series studies now incorporating rigorous statistical modelling techniques to control for potential confounders [41]. In this context, confounders are those variables known to affect both daily morbidity and/or mortality counts as well as daily pollution concentrations; this can include seasonality and long-term trends. Statistical modelling techniques including splines [42], LOESS functions [43] and Fourier terms [44] are typically incorporated to control for these in regression models. The advantage of time-series analysis is its ability to account for overdispersion in the data. However, a limitation of this analysis is that model specification may not be robust in controlling for potential temporal confounders, a commonly cited criticism with studies finding associations between AAP and mortality related to the selection of model specification [45].

The case-crossover analysis first described by Maclure [46] is a popular alternative study design to time-series analysis used in air pollution epidemiology. The case-crossover design is similar to a case-control study but with cases serving as their own controls. Log odds of

being a case are modelled given short-term AAP exposure calculated via conditional logistic regression. The choice of control times is an important consideration, bi-directional sampling of controls remains preferred, sampling symmetrically from times both before and after the case day of interest. If the case and control periods are relatively close together, this also controls for potential time-varying confounders. An advantage of case-crossover studies is that (should such data be available) AAP assignment can be conducted at the individual level as opposed to aggregate concentrations. However, unlike time-series analysis case-crossover analysis cannot typically account for overdispersion in the data.

Study methodologies investigating the acute health effects of AAP exposure have continued to advance further, for example to examine the effect of different lag structures of effect estimates using distributed lag models (DLMs) [47] as well as construction of exposure-response functions at specified concentrations.[48] Specific methodologies will be described further in **Chapter 5** of this thesis. While panel studies can also be used to examine the acute health effects of AAP exposure these are typically reserved for examining symptoms [49] as well as biological markers [50] in small study populations and will not be mentioned further in this thesis.

2.3.2 Chronic health effects

Cohort studies can capture the health effects of both acute and chronic AAP exposure but are typically regarded as studies to examine chronic exposure. To do so, "individual-level" measures of AAP exposure are required for participants ideally free of the disease of interest at baseline. Study participants are then followed prospectively over time, although retrospective cohort studies are also feasible. Individual-level AAP exposures are usually determined through a place of residence, with rates of disease in participants then compared between the exposed, and unexposed providing relative risk estimates most commonly for a 10 $\mu g/m^3$ increase in exposure.

2.3.3 Interpreting risk of AAP exposure

Regardless of whether mortality and/or morbidity is the health outcome of interest, the risk associated with AAP exposure can be interpreted in numerous ways as outlined by Kunzli et al. [51] from which the following groups have been adapted;

A) Increased risk of both chronic underlying diseases leading to increased frailty as well as the acute risk of disease amongst the frail
B) Increased risk of chronic underlying diseases leading to increased frailty but no acute risk relating to the timing of the disease event
C) No risk relating to underlying chronic disease, but acute exposure associated with increased risk of disease among those who are already frail
D) No risk of either underlying chronic disease, or risk relating to the timing of the disease event

The studies described above in **Section 2.3.1** used to examine the risk of acute health effects capture the risk presented in groups A and C only. However, should these be capturing predominantly A, the use of the term “acute” or “short-term” can be considered misleading, given some of these events may have developed through chronic AAP exposure. Studies examining chronic exposure described in **Section 2.3.2,** which use the cohort study design and rely on person-time can capture the full amount of time lost across the three kinds of cases (A, B and C). However, time lost from acute effects (A and C) cannot be disentangled from time lost due to pollution-induced frailty (B). This is exemplified in **Figure 2.2** adapted from a report by the UK Department of Health [52] and shows how risk associated with the respective terms of “chronic” and “acute” health effects cannot be fully distinguished.

Such discrepancy in the “type” of risk captured by each respective study design has been hypothesised as the reason for the larger risk estimates often observed in cohort studies of

chronic exposure relative to acute exposure studies with time-series and case-crossover designs.[51] Since "acute" exposure studies can capture risk from A and C only, while cohort studies can capture risk from A, B, and/or C, if studies are unbiased, and the effect of the different factors adjusted on in different models minimal, then having cohort study estimates larger than estimates from time-series studies is to be expected. Therefore, throughout this thesis although acute and chronic health effects are examined separately, it should be noted that these are unlikely to be as mutually exclusive as the research terminology typically suggests.

2.4. Quantifying Exposure

Exposure can be defined in the context of AAP as contact between an airborne pollutant and a surface of the human body.[53] Exposure requires a pollutant concentration in a particular place and the simultaneous presence of an individual in that specific place and time, with concentration not equating to exposure unless these two factors are both met.[53] Individual exposure technically encompasses the totality of air pollution, including household, ambient, and workplace exposure, however, the majority of epidemiological studies rely on mostly indoor and outdoor pollutant exposure and rarely in combination. For epidemiological studies examining the health effects of AAP, accurate exposure assignment to participants is vital to minimise bias and capture effects more reliably. The following section outlines the main methods used for AAP exposure assignment in epidemiological studies, highlighting specific examples from Chinese studies when relevant, and concludes by describing the issue of exposure measurement error.

2.4.1 Direct methods of AAP exposure measurement

Direct measurements of AAP quantify exposure while it is occurring, they typically utilise personal exposure measurements but can also include measures of biological markers or "biomarkers". Personal exposure measurement is considered the gold standard of air

pollution exposure measurements but also the most challenging requiring active and/or passive portable sampling devices ideally in conjunction with time-activity data (such as global position systems [GPS] and/or questionnaires). However, personal monitoring is unpractical and expensive for large epidemiological studies with their use often limited to smaller-scale pilot and panel studies within fixed micro-environments.[50, 54, 55] The use of biomarkers as exposure proxies capturing true inhaled dosage of AAP in participants has also been theorised. Although more commonly seen in studies of indoor air pollution given higher intensities of exposure and more controlled micro-environments, biomarkers have also been explored in assigning AAP exposure in Chinese study populations. [56] To date, no specific biomarker is deemed sufficiently precise to accurately reflect AAP exposure;[57] however, current contenders explored in experimental and observational studies include exhaled volatile organic compounds (VOCs) in blood and urine, [58] DNA adducts, [59] metabolites of pyrene, [60] urinary phenols, [61] and malondialdehyde.[62] Further limitations of using biomarkers of exposure include, difficulty in differentiating between cumulative exposure pathways and specific chemicals, lack of specificity with many biomarker parent chemicals also present in confounding activities such as cigarette smoking, and difficulties in collection and measurement limiting their use in large-scale epidemiological studies. Biomarkers have instead been suggested for use as part of an integrated exposure assessment approach complementing other methods such as personal monitoring and exposure modelling. [63]

2.4.2 Indirect methods of AAP exposure measurement

Indirect methods of AAP exposure measurement combine information about AAP levels at certain locations with information about the time spent in specific environments. However, the difficulty of obtaining information on all if any of the microenvironments where people spend their time limits the feasibility of indirect measurements. Most studies will instead sample only the outdoor community air microenvironment. The indirect approaches to AAP exposure measurements are outlined below.

2.4.2.1 Fixed-site monitors

The use of fixed-site monitors is arguably the most simplistic method of AAP exposure assignment where city/district-wide averages are treated as true exposure parameters for the study population. This approach is utilised in some of the earliest cohort studies examining chronic health effects [64, 65], as well as the majority of all Chinese cohort studies. [66-71] However, homogeneity in spatially averaged AAP exposure across study populations means that for cohort studies examining chronic health effects where spatial variability in exposure is required, health effects of AAP exposure can only be compared between relatively crude geographical areas. [64] For studies examining acute health effects where the exposure parameter of interest is acute temporal fluctuations in spatially averaged AAP levels, exposure measurements across fixed-site monitors are more appropriate, with the wide provision of regulatory AAP monitoring networks in China providing continuous real-time measurements particularly valuable to these studies. However, a lack of monitors in rural localities of China severely limits the applicability of this method to examine the health effects of AAP in rural areas. Instrument imprecision is also a possibility and limitation of this method, whether that be accidental malfunction or deliberate tampering. Fixed site exposure monitoring can also be supplemented, with other sources for example by using indoor-outdoor sampling**.** Since ~90% of time spent is indoors [72] relying solely on AAP levels has been criticised as a poor indicator of true pollutant exposures. [73] As personal monitoring is unfeasible in large epidemiological studies the use of a small number of well-chosen samples at indoor key locations to supplement AAP measurements has been suggested to provide a more reliable index of environmental conditions [74]. However, this has not yet been commonly explored in epidemiological studies in China.

2.4.2.2 Mobile air monitoring

Instruments strapped to portable means such as motor vehicles overcome some of the limitations of fixed-site monitors, including relative sparsity in distribution, and inability to capture high spatial resolution of pollutants within urban areas. However, mobile monitoring requires a lot of repeated temporal and spatial measurements and is unpractical for very large epidemiological studies.

2.4.2.3 Modelling air pollution exposure

Given the large study populations used in epidemiological studies of AAP exposure assigning personal exposure to all participants through direct methods is largely unfeasible and relying solely on fixed-site monitors (and even mobile monitors) is criticised for failing to capture the finer spatial resolution of pollutants. Exposure assessment modelling has therefore emerged as a common method of estimating AAP exposure with a variety of exposure assessment models developed, each of which will now be briefly described.

Proximity models are one of the most basic types of AAP exposure models used in epidemiological studies. The proximity of a receptor (study individual) to a pollution source is calculated to be used as the exposure parameter of interest. Residential proximity to roads has dominated epidemiological research, but these are also being combined with other factors such as road type, traffic flow, and road length [75, 76]. However in these models, none of the parameters influencing dispersion are considered, they also regard exposure as directly proportional to distance from the source only, and exposure misclassification is likely given the assumption of binary exposure designation usually though an arbitrary cut off (e.g. <100m from road is exposed and >100m from road is unexposed).

Geostatistical interpolation models such as inverse distance weighting, nearest neighbour analysis, and kriging have also been used in studies to generate AAP values from a specified number of points (measured AAP locations) at unmeasured localities. [77, 78] However, these techniques require high availability of monitoring data, often at greater

spatial resolution than seen for most countries monitoring networks. They also do not consider other environmental factors and can be limited when pollutants have high spatial variability across relatively small geographical areas.

Land-use regression (LUR) models advance the above geostatistical models to use measured pollutant concentrations in combination with predictor land-use and geographical covariates in estimating pollutant concentrations across unmeasured localities and are usually constructed within geographic information systems (GIS) using least-squares regression modelling. They are known to have a lower sampling effort than the aforementioned geostatistical models and a lower data requirement than dispersion models. [79] LUR models can account for smaller-scale variability in pollutant concentrations. However, numerous AAP sampling locations are still required to provide sufficient information on measured AAP variability. Accuracy of geographical covariates will also affect the accuracy of AAP estimates, and temporal discrepancy between geographic covariates and AAP levels may limit the model. Finally, LUR is used only over relatively small areas.

Air dispersion models incorporate emission data and meteorological data with numerical processing to yield concentrations of AAP dispersion properties over space and time. Basic information for each emission source is collected, and meteorological and topographical data are used to simulate physical dispersion processes. However, air dispersion models require assumptions on air dispersion patterns. Monitoring data is also often not available at sufficient spatiotemporal scales, and equipment and operation of the models can be high cost.

Hybrid models do not have an explicit definition, but can be broadly defined as a series of appropriate modelling tools which can be combined to describe different types of sources used to assign AAP exposure. [63] They combine differing exposure assessment methods including, personal monitoring methods, fixed-site monitoring, air dispersion modelling, and/or regional, urban and local models. Integration of personal and regional monitoring data

makes hybrid models capable of generating more accurate personal exposure assessment; however, personal monitoring is difficult to obtain, and integration of differing exposure models can also be challenging in limited resource scenarios. Hybrid models studying the health effects of AAP have been created in HICs predominantly. [80-82]

Spatiotemporal models have emerged as a flexible method to estimate AAP across unmeasured locations as well as times with observations viewed as realisations of a random function with spatiotemporal variability. Spatiotemporal models can also be described as "hybrid models" given they often use combinations of various geographical and satellite-based covariates. Spatiotemporal model complexity varies both in covariates included, (satellite remote sensing data, chemical transport models and land-use data are common), and in the spatial dimension, for example while GBD provided global coverage [83] others have been constructed solely for intraurban estimation. [84] Exact modelling techniques vary but can include Bayesian frameworks, [83, 85] neural networks [86] and machine learning methods. [87] Spatiotemporal models allow a more detailed temporal resolution (up to daily AAP levels) than spatial models such as LUR or interpolation and are thus useful in assigning temporally varying AAP exposure. However, model quality relies inherently on the quality of imputed data and depending on the modelling techniques they can also be computationally intensive limiting their use in epidemiological studies and have been predominantly seen epidemiological studies in HICs only. [88-90]

2.4.3 Exposure measurement error in epidemiological studies

All the exposure assignment methods outlined in **Section 2.4.1** (except personal monitoring) and **Section 2.4.2** represent only an approximation of true personal air pollution exposure from outdoor sources. This makes exposure measurement error unavoidable and a central concern in the relevant epidemiological studies. Measurement error can be broadly defined as any differences between a proxy measurement used and an individual's actual true exposure [91] and generally falls within either the Berkson or Classical error framework. Under

the Berkson error framework, we measure part of the true ambient AAP levels, which vary randomly about the AAP proxy measurement. While under the Classical error framework we measure the AAP proxy measurement which varies randomly about true ambient AAP levels. The exact details of Berkson versus Classical measurement error in AAP studies can be found in **Appendix A1** with most AAP exposure measurement errors combining elements of both. While Berkson measurement error typically leads to unbiased but more variable health effect estimates, Classical measurement error leads to biased estimates typically towards the null. That is under the classical measurement error framework; measurement error does not lead to spurious associations should there be no true association. [92]

Relevant examples of exposure measurement error in epidemiological AAP studies include: instrument error associated with ambient monitors (Classical error); differences between specific individual exposure and measured ambient concentration (Berkson error); and differences between measured population average over the study area with true individual ambient levels varying randomly about this population average measurement (Berkson error).

One such example is how several studies have found considerable differences between actual personal exposure and estimates based on central monitoring values,[93] however, it has been argued that for time-series studies where the number of events per day is calculated across study populations, the relevant exposure measure is the mean of personal exposures on that day, which is probably more tightly correlated with central station monitoring than individual exposures. [92]

As true exposure is almost always unknown, it's difficult to determine, and the exact effects of measurement error on estimated regression coefficients with the effects likely depending on study design, type of error, and the true relationship between exposure and health outcome variable.

2.5 Conclusion

This Chapter has outlined the relevant background in the field of air pollution epidemiology. It has defined AAP and the relevant pollutants of interest to this thesis, as well as describing AAP exposure in China including causes of, and trends in, AAP levels. It has also critically outlined the methodological approaches used to examine the health effects of AAP exposure including a brief critical review of AAP exposure classification methods. Finally, it concluded by briefly describing the issue of exposure measurement error relevant to epidemiological studies of AAP.

Figure 2.1 Spatial distributions of ten-year (2004-2013) $PM_{2.5}$ mean concentrations for all of China

(A) the Beijing-Tianjin metropolitan region (B), the Yangtze River delta (C), the Pearl River delta (D), and the Sichuan Basin (E). Obtained from Ma et al. [1]

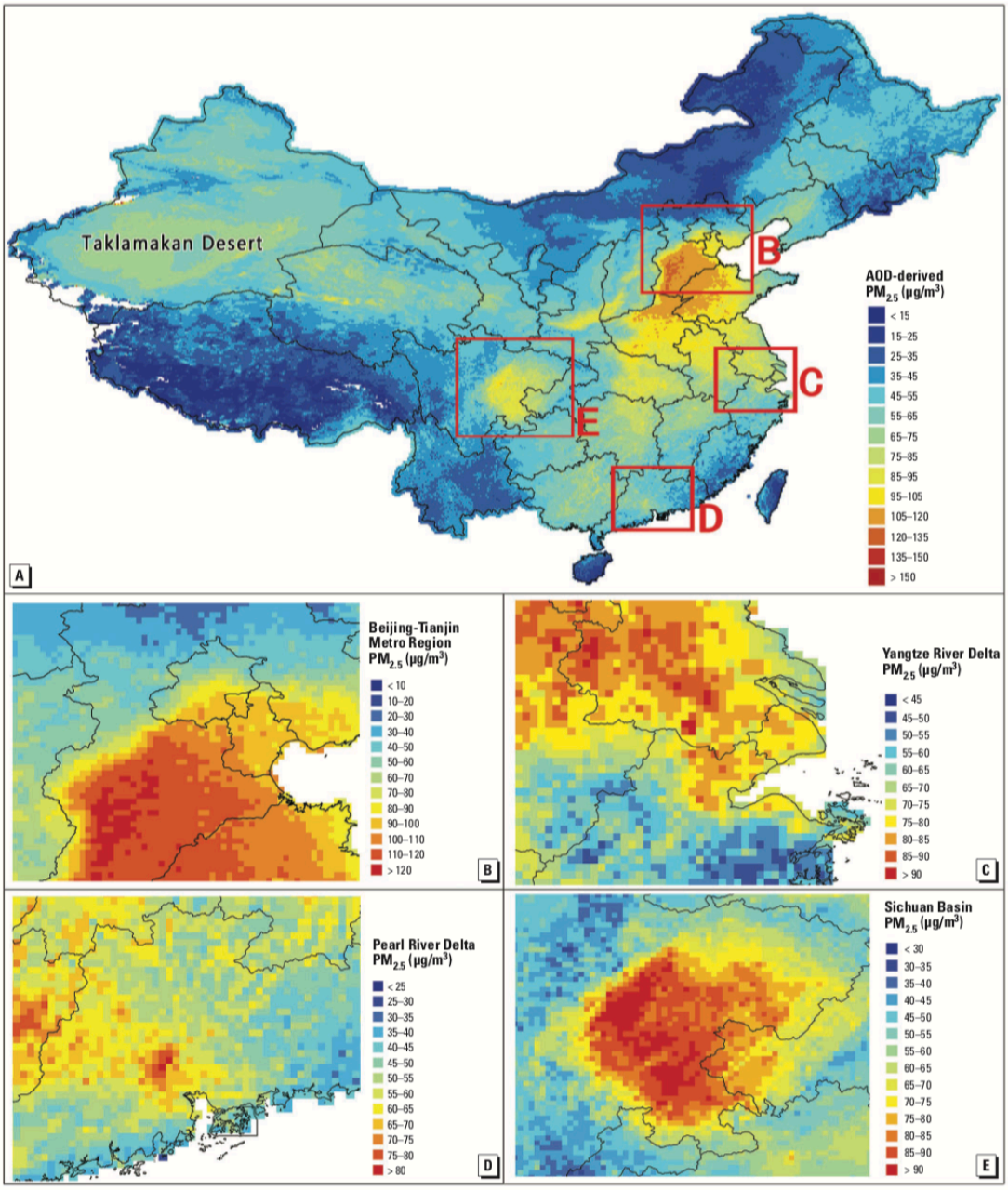
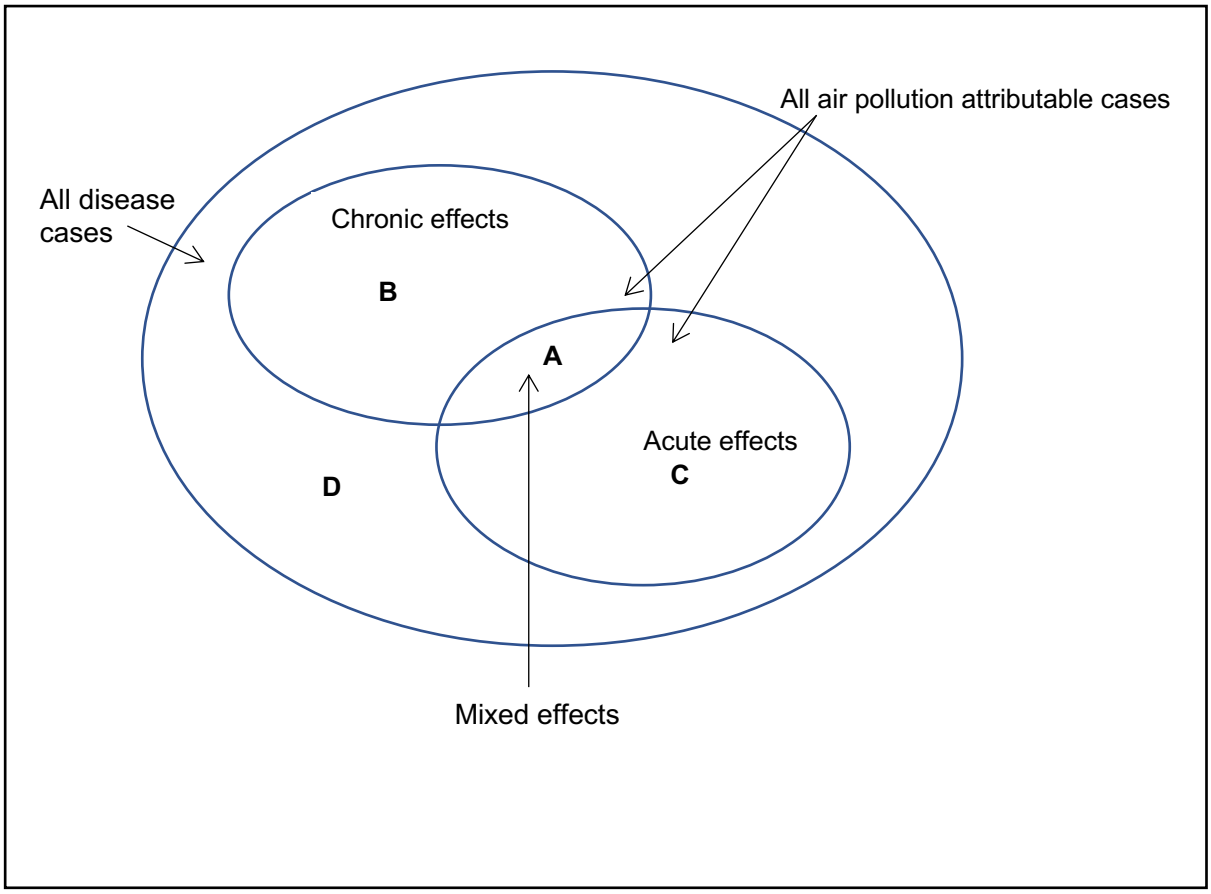


Figure 2.2 Illustration of disease cases attributable to air pollution in a population, adapted from a report from the UK Department of Health [52]

(A) Increased risk of both chronic underlying diseases leading to increased frailty as well as acute risk of disease amongst the frail; (B) Increased risk of chronic underlying diseases leading to increased frailty but no acute risk relating to timing of disease event; (C) No risk relating to underlying chronic disease, but acute exposure associated with increased risk of disease among those who are already frail; (D) No risk of either underlying chronic disease, or risk relating to the timing of the disease event. Circle sizes not reflective of relative effect.



CHAPTER 3. LITERATURE REVIEW

3.1 Introduction

As the topic of this thesis is ambient air pollution (AAP) in relation to cardio-respiratory health effects, this literature review collates, synthesises, and evaluates all available relevant evidence published in the English language on the topic. The subject matter of this literature review is divided into two sections examining the acute and chronic cardio-respiratory health impacts of AAP exposure, respectively.

3.2 Acute health effects

To synthesise available evidence on the acute health effects associated with AAP exposure, a systematic review and meta-analysis were performed. It examined the cardio-respiratory health effects of acute AAP exposure within low-and middle-income countries (LMICs) where evidence is known to be scarce relative to that in high-income countries (HICs). Results were published as two first-authored manuscripts, examining particulate and gaseous pollutants, respectively [18, 19] adhering to the distinction between particulate and gaseous pollutants seen within the literature. Correspondingly, the reporting of results and synthesis of the literature on acute health effects is also done separately for particulate and gaseous pollutants in this chapter.

3.2.1 Search methods

A systematic search was conducted in November 2016 using PubMed, Web of Science, Embase, LILACS, Global Health, and Proquest for studies published in the English language between database inception and November 2016, with search terms listed in **Appendix B1**. Hand searches were also performed by scanning bibliographies of the relevant scientific literature. Included studies analysed the cardio-respiratory (International Classification of Diseases, 9th [390-459/460-519] and 10th [I00-I99/J00-J99] revisions) health effects (both morbidity and mortality) of AAP (NO_x, SO_2, PM_{10}, $PM_{2.5}$, O_3, CO) exposure in adults (≥18

years). Studies had to be performed in LMICs as defined by the World Bank Classification [94]. Abstracts were then screened using the following pre-specified inclusion criteria; studies were required to (i) have attempted for one or more of the main confounding variables including season, meteorological trends, and existing health conditions; (ii) feature quantitatively measured cardiovascular/respiratory health outcomes; (iii) present effect estimates for the association between AAP and cardiovascular/respiratory outcomes in adults; (iv) have both AAP exposure and health outcomes recorded quantitatively; (v) have a study length of at least a year in duration; and finally, for practical reasons (vi) the study had to be published in English.

3.2.2 Meta-analysis methods

Data were extracted and stored in a Microsoft Access database, including study design, study population demographics, region, pollutant characteristics, sample size, type of cardio-respiratory events, exposure classification method, confounders addressed, analysis method, and generated risk estimates by pollutant, outcome and associated lag time (in days). Included studies were assessed for risk of bias. Since currently, there exists no standardised validated framework for assessing risk of bias in environmental epidemiology studies, risk of bias assessment was performed using a framework constructed a priori. This incorporated exposure assessment bias, detection bias, selection bias, and appropriate adjustment for confounders (for full risk of bias framework see **Appendix B2**). Due to expected heterogeneity in both pollutant and population characteristics across studies, estimates were pooled in meta-analysis using the random-effects model, as in other similar meta-analyses [95-99] using "metafor" package in R [100]. Pooled effect estimates were presented as percent excess relative risk ([RR-1] x 100) associated with a 10 μg/m^3 (1 part per million [ppm] for CO) increase in pollutant concentrations.

Estimates were pooled by pollutants, associated lag time (in days), and respective health outcomes (cardiovascular and respiratory morbidity or mortality). For this meta-analysis only

one estimate was included per city to ensure results were not biased by multiple inclusion of one heavily studied city. Where duplicate cities were presented for the same study periods, estimates were selected prioritising multi-city study estimates due to their often standardised and higher-quality methodologies. If city duplicates were still present the study with the lowest risk of exposure assessment bias was selected.

When study numbers were sufficient (≥2) estimates were pooled by specific cardiovascular and respiratory diseases, this included any of the main cardiovascular and respiratory diseases outlined in the PROSPERO protocol. [101] Where cause-specific cardiovascular and respiratory diseases were available, but their case numbers insufficient for pooling, these were pooled collectively as other respiratory disease (ICD-10: J00-J47), and heart disease (I05-I52), provided the health outcomes of interest were captured in these ICD-10 codes.

Multi-pollutant estimates were also pooled, as were estimates with studies assigned high risk of bias removed. Where study numbers permitted, pooling of estimates was also performed for individual LMIC regions separately. As it was anticipated this subgroup analysis would have fewer available risk estimates available for pooling than the main analysis, estimates were pooled for lags 0-3 inclusively (apart from region subgroups) generating sufficient numbers for meta-analysis.

Heterogeneity was assessed using the I^2 statistic, with percentages higher than 75% reflective of high levels of heterogeneity. [102] If high levels of heterogeneity persisted following subgroup analysis, meta-regression was used to determine potential sources of heterogeneity exploring study periods, and lag structure. Publication bias was determined by construction of funnel plots with trim and fill and quantified by Egger's tests.[103]

3.2.3 Search Results

A total of 2599 articles were identified through systematic searching; of these, 1055 duplicates were removed and the titles and abstracts of the remaining 1553 screened and assessed. Following the abstract screening, the full text of 257 articles were assessed for eligibility in meta-analysis. Of these, 91 and 64 articles on particulate ($PM_{2.5}$ and PM_{10}) and gaseous (NO_x, SO_2, O_3, CO) AAP, respectively, met the full inclusion criteria and provided sufficient information for meta-analysis were included. Following the exclusion of four identified cohort studies [66, 70, 104, 105] focusing on the chronic health effects of AAP exposure and two studies without reporting confidence intervals, 85 and 60 studies were included in meta-analyses for particulate, and gaseous, AAP respectively (**Figure 3.1**).

3.2.4 Particulate matter

Eighty-five articles describing the associations between particulate AAP exposure and cardio-respiratory mortality/morbidity were identified and included in meta-analyses (for a full summary of included articles, see **Appendix B3**). Of which, 72 used time-series analysis [106-178], 10 case-crossover [179-188], and 3 used a combination of both types of analysis [189-191]. The majority of included studies were performed in the East Asia and Pacific region (n=63), with most others from Latin America and Caribbean (n=16). Far fewer were performed in Europe and central Asia (n=2), the Middle East and North Africa (n=3) and sub-Saharan Africa (n=1).

3.2.4.1 Cardio-respiratory mortality

Fifty-six studies examined the associations between particulate AAP exposure and mortality, of these 39 reported on PM_{10} exposure, 11 on $PM_{2.5}$, and six reported estimates for both. Overall a 10 $\mu g/m^3$ increase in same-day (lag-0) PM_{10} and $PM_{2.5}$ appeared associated with 0.27% (95% CI, 0.11, 0.44), and 0.47% (0.34, 0.61) higher risk of cardiovascular mortality in meta-analyses (**Figure 3.2**). Estimates were slightly greater when using moving average lag

durations than single day (0.59% (0.25, 0.93), and 0.57% [0.10, 1.05] for 0-1-day PM_{10} and $PM_{2.5}$, respectively). Elevated risk of cardiovascular mortality was also observed when using the previous days concentration (lag-1) of both PM_{10} and $PM_{2.5}$ (0.40% [0.04, 0.76], and 0.39% [0.25, 0.52], respectively). Pooled estimates could be generated across a wider range of lag times for PM_{10} versus $PM_{2.5,}$ due to a greater number of identified articles analysing PM_{10}.

For respiratory mortality 10 $\mu g/m^3$ increases in same day concentrations of PM_{10} and $PM_{2.5}$ were associated with 0.56% (0.24, 0.87) and 0.57% (0.28, 0.86) higher risk, respectively. Associations between $PM_{2.5}$ and respiratory mortality were observed at a lag of 1-day as well as a 0-1-day lag (0.43% [0.27, 0.59], and 0.69% [0.45, 0.93]). Similarly, PM_{10} also demonstrated associations with respiratory mortality across a range of lag structures from same-day exposure up until a lag of 3-days, the greatest estimate observed at a moving average lag of 0-3 days (1.12% [0.78, 1.61]) (**Figure 3.2**). There appeared little difference in the magnitude of pooled risk estimates between PM_{10} and $PM_{2.5,}$ respectively as well as between cardiovascular and respiratory mortality.

For cause-specific cardio-respiratory disease mortality, significant associations were observed between PM_{10} and stroke (ICD-10: I60-I69) mortality in both East Asia and Pacific and Latin America and Caribbean regions, with greater risk observed in the later region (0.25% [0.20, 0.30] versus 1.06% [0.62, 1.49], respectively) (**Figure 3.3**). PM_{10} was also associated with mortality from heart disease (I05-I52) in East Asia and the Pacific region (0.46% [0.32, 0.60]). For cause-specific respiratory diseases acute PM_{10} exposure was associated with higher risk of COPD (ICD10:J41-J44), and other respiratory disease (J00-J47) mortality in the East Asia and Pacific region only (0.69% [0.09, 1.30] and 0.59% [0.14, 1.04], respectively). There were insufficient numbers of studies to allow pooling of estimates for $PM_{2.5}$ and cause-specific cardio-respiratory mortality.

When stratifying by region same day PM_{10} exposure was associated with cardiovascular mortality in the East Asia and Pacific region only (0.39% [0.17, 0.61]) (**Figure 3.4**). However, the number of studies examining other regions was low. When examining a 0-3-day lag a significant association was observed between PM_{10} and cardiovascular mortality in the Latin America and Caribbean region (0.63% [0.37, 0.88]) only. Unlike for cardiovascular mortality, greater risk of respiratory mortality was observed for PM_{10} exposure in Latin America and Caribbean versus East Asia and Pacific, across a range of lag dimensions. Although it was not feasible to pool estimates for $PM_{2.5}$ by region, it was possible to compare city-level estimates within the East Asia and Pacific region. The greatest estimates seemed to be in Guangzhou for cardiovascular mortality and Shanghai for respiratory, (1.33% [0.79, 1.87] and 0.63% [0.30, 0.96], respectively) (**Figure 3.5**). For PM_{10} and cardiovascular mortality the greatest effect was observed in Bangkok (1.58% [1.19, 1.97]), although a similarly sized estimate was also observed in Guangzhou (1.27% [0.89, 1.62]) (**Figure 3.6**). The greatest risk of respiratory mortality associated with PM_{10} exposure appeared in Sao Paulo (1.09 [0.81, 1.37]). The weakest pooled effect estimates for the association between PM_{10} and both cardiovascular and respiratory mortality appeared to be in Beijing (0.12% [0.05, 0.19], and 0.17% [0.05, 0.30]).

When pooling multi-pollutant estimates of PM_{10} which adjusted for additional pollutants, all associations between PM_{10} and respiratory mortality were attenuated to the null when adjusting for NO_x, SO_2, and O_3, (0.10% [-0.27, 0.46], 0.29% [-0.27, 0.85], and 0.53% [-0.09, 1.15], respectively). For cardiovascular mortality, adjustment for NOx and NOx plus SO_2 attenuated estimates to the null (**Figure 3.7**).

Pooled estimates were similar in both direction and magnitude following removal of those studies assigned high risk of bias only PM_{10} had a sufficient number of studies to do this. For respiratory mortality, removal of these studies tended to very slightly increase the magnitude of risk estimates (0.56% [0.24, 0.87] to 0.62% [0.27, 0.97], respectively for same-day PM_{10}).

For cardiovascular mortality there were minimal changes in pooled risk estimates (**Figure 3.8**).

Publication bias was evident for both PM_{10} and $PM_{2.5}$ and both cardiovascular and respiratory mortality (all p-values <0.01) although adjustment via trim and fill made little difference to pooled associations (**Appendix B4**).

3.2.4.2 Cardio-respiratory morbidity

Fewer articles examined particulate AAP and cardio-respiratory morbidity (n = 30) versus mortality (n = 55). No significant associations were observed between PM_{10} and cardiovascular morbidity; however, same-day PM_{10} was significantly associated with a 0.42% (95% CI, 0.16, 0.69) increase in respiratory morbidity. There were too few articles to examine $PM_{2.5}$ and cardiovascular morbidity, but a 10 $\mu g/m^3$ increase in same-day $PM_{2.5}$ was associated with 0.95% (0.04, 1.87) higher risk of respiratory morbidity (**Figure 3.2**).

For cause-specific cardiovascular disease morbidity, significant associations were observed between PM_{10} exposure and heart disease (I05-I52) morbidity in East Asia and Pacific region (0.17% [0.07, 0.27]) (**Figure 3.3**). However, both PM_{10} and $PM_{2.5}$ exposure had significantly negative associations with stroke morbidity in East Asia and Pacific (-0.08% [-0.13, -0.04] and -0.12% [-0.19, -0.05], respectively), hypothesised as potentially due to fewer individual surviving stroke in LMICs than developed countries,[192] PM particle numbers being more important than mass concentration,[193] or the elemental composition of PM having greater health effects than particle diameter.[194] Stratifying by region no significant associations were observed between PM_{10} and cardiovascular morbidity in either East Asia and Pacific or Latin America and Caribbean, although estimate numbers were low (2 and 4, respectively) (**Figure 3.4**). For pooled risk estimates of cardiovascular morbidity stratified by city, the only city presenting enough studies for pooling was Beijing, but no association was

observed between $PM_{2.5}$ or PM_{10} and cardiovascular morbidity in the region (**Figures 3.5 and 3.6**).

For respiratory morbidity, a 10 μg/m^3 increase in PM_{10} appeared associated with a 1.35% (0.18, 2.52) higher risk of COPD morbidity in Latin America and the Caribbean (**Figure 3.3**). When stratifying by city, both $PM_{2.5}$ and PM_{10} were similarly associated with higher respiratory morbidity in Beijing (0.74% [0.55, 0.93] and 0.70% [0.22, 1.18], respectively) (**Figures 3.5 and 3.6**). Too few estimates were available to stratify using multi-pollutant estimates. When removing studies assigned high risk of bias, the magnitude of risk estimates increased for PM_{10} and respiratory morbidity (0.42% [0.16, 0.69] to 0.53% [0.27, 0.78], respectively) (**Figure 3.8**). This was observed across all lag times, likely the result of removing studies with increased exposure measurement error, which under some assumptions leads to bias in estimates towards the null. However, for cardiovascular morbidity, there was a less consistent change in pooled risk estimates across lags.

Publication bias was present for PM_{10} and both respiratory and cardiovascular morbidity ($p<0.01$, $p<0.01$, respectively) but for $PM_{2.5}$ and respiratory morbidity only ($p=<0.01$ but adjustment via trim and fill made little change to pooled estimates (see **Appendix B4**). High levels of heterogeneity were also present in many pooled estimates. When this persisted following stratification by city, the sources were explored through meta-regression and determined to be associated with the pooling of effect estimates across differing lag-times and study periods.

3.2.4.3 Discussion

Both PM_{10} and $PM_{2.5}$ were associated with cardio-respiratory mortality and morbidity in LMICs with a larger magnitude of risk observed when using moving-average measures of PM versus single-day. This trend conforms to findings from other studies of acute health effects of AAP exposure in both HICs and LMICs regions [163, 195] and is potentially explained

by the grouping of health outcomes with varying onset times when using a moving-average lag structure. The large effect estimates for PM exposure and COPD morbidity in this study is unsurprising given the plethora of evidence supporting associations between PM (of both size fractions) and COPD (both development and exacerbation).[196-198] Relatively few articles were identified which examined $PM_{2.5}$ exposure and cardio-respiratory health outcomes. This is surprising given the considerable emphasis placed on $PM_{2.5}$ as a hazard relative to other pollutants in the evidence base from HICs [199, 200] and highlights the need for further research on the acute cardio-respiratory effects of $PM_{2.5}$ exposure in LMICs specifically.

Stratifying pooled estimates by region and city produced apparent spatial differences in the risk of both cardio-respiratory mortality and morbidity. This was exemplified by the apparent differences in pooled risk estimates when stratifying by region; for example same-day PM_{10} was associated with cardiovascular mortality in East Asia Pacific region only. Apparent geographic discrepancies in associated risk of cardio-respiratory disease were also observed within specific countries, the prominent example being China where the majority of studies were performed. In Guangzhou, risk of cardio-respiratory mortality associated with PM_{10} exposure appeared greater than in Shanghai and Beijing where PM levels are typically higher. A possible explanation for this within-country spatial variability in risk includes the flattening of the exposure-response curve at PM higher concentrations as hypothesised elsewhere. [201, 202] It may also potentially relate to the health care structure of Beijing where a high-quality health-care infrastructure and insurance system is available for permanent residents but not migrant workers. As such, a combination of a healthier population of permanent residents and under-reporting of adverse health among migrant workers might have resulted in smaller effect sizes.

3.2.5 Gaseous pollutants

Sixty studies examined associations between acute gaseous pollutants (NO_x, SO_2, O_3 and CO) exposure and cardio-respiratory health outcomes (**Appendix B5**). Fifty-three of these

were time-series analyses, [106, 107, 110, 112, 114, 115, 119, 120, 122-125, 128-130, 132, 134, 135, 139, 143, 144, 146, 148, 150, 152-157, 164, 167, 168, 170, 171, 173, 174, 176-178, 203-215] five case-crossover, [183, 184, 186, 216, 217] and two incorporated both study designs, [182, 191]Again, the majority of studies were performed in the East Asia and Pacific region (n=44); only 11 were from Latin America and Caribbean and far fewer from Middle East and North Africa (n=2), Europe (n=2) and sub-Saharan Africa (n=1). Cardio-respiratory mortality as an outcome was reported by more studies (n = 36) relative to morbidity (n = 24). Due to the limited number of articles in regions other than East Asia and the Pacific estimates were not pooled by pollutant and regions; instead the focus was on analysing estimates by city within East Asia and the Pacific region.

3.2.5.1 Cardio-respiratory mortality

For cardiovascular disease mortality 10 μg/m^3 increases in same-day NO_x, and SO_2 were associated with 0.92% (0.44, 1.39) and 0.50% (0.01, 1.00) higher risk of cardiovascular mortality, respectively (**Figure 3.9**). No significant associations were observed between same-day O_3 and cardiovascular mortality; however, there was a significant relationship when using moving average lags of O_3 (0.39% [0.07, 0.71], and 0.67% [0.23, 1.11], for 0-1- and 1-2-day lags respectively). Similarly, for NO_x and SO_2, greater estimates were also observed when using 0-1-day moving average lags versus single day however this trend did not persist at lags greater than 0-1 days. No significant associations were observed for CO, and cardiovascular mortality and the number of articles including CO was low (**Figure 3.10**).

For respiratory mortality a 10 μg/m^3 increase in NO_x and 1 ppm increase CO were both associated with mortality (0.70% [0.01, 1.40] and 3.08% [0.76, 5.40], respectively). As seen for cardiovascular mortality, greater associations were also observed using moving average measures, with both NO_x and SO_2 appearing associated with higher risk of respiratory mortality (2.20% and 1.09%, respectively at 0-1-day lag).

Only NO_x and SO_2 provided enough estimates for pooling by cause-specific cardiovascular disease mortality (**Figure 3.11**). Associations were observed for both NO_x and SO_2 and heart disease (ICD10: I00-I52) mortality in East Asia and Pacific region (1.52% [0.98, 2.06], and 1.31% [0.82, 1.81], for NO_x, and SO_2, respectively). NO_x and SO_2 were also associated with stroke mortality (1.01% [0.79, 1.24] and 0.64% [0.53, 0.76], respectively), however, due to limited numbers of articles by region, estimates were pooled across LMIC regions (East Asia and Latin America and Caribbean, inclusively). NO_x and SO_2 exposure were also associated with COPD mortality (1.81% [1.11, 2.51] and 1.68% [0.71, 2.64] respectively), and NO_x with respiratory disease mortality (J00-J47) (0.86% [0.34, 1.38]), all in the East Asia and Pacific region.

For pooled associations by city, NO_x was associated with cardiovascular mortality in all cities with the exception of Beijing (-0.02% [-0.53, 0.48]) (**Figure 3.12**). However, heterogeneity was particularly high for Beijing estimates (I^2 =91%), the source of which was identified to be associated with the pooling of study periods (p=0.005) and pollutant levels (p=0.004). SO_2 exposure was associated with cardiovascular mortality in two of the four cities identified (Shanghai and Wuhan), and no associations were observed for O_3. For respiratory mortality by city, NO_x was associated with 0.41% (0.11, 0.71) higher risk of respiratory mortality in Beijing, while SO_2 was significant in both Beijing and Guangzhou, (0.04%, [0.01, 0.06] and 1.35% [0.52, 2.17], respectively).

Pooling multi-pollutant estimates for cardiovascular disease resulted in slight attenuation of the effect estimate for NO_x; however, estimates remained significant (**Figure 3.13**). For SO_2 however, all associations with cardiovascular mortality were attenuated to null when adjusting for additional pollutants (the exception being O_3 which increased the observed association). For respiratory mortality, pooling multi-pollutant estimates also attenuated associations (again except O_3).

When articles assigned high risk of bias were removed estimates were slightly attenuated for both NO_x and SO_2 with cardiovascular disease but increased those at longer lags (**Figure 3.14**). For respiratory disease there was no change as none of the articles were assigned high risk of bias. Publication bias was found to be evident for NO_x and SO_2 with cardiovascular mortality only, using Egger's test ($p<0.01$, and $p<0.01$, respectively).

3.2.5.2 Cardio-respiratory morbidity

Fewer articles examined cardio-respiratory morbidity relative to mortality (24 vs. 36). No associations were observed between gaseous AAP exposure and cardiovascular morbidity (**Figure 3.9**). The exception was NO_x at a 0-1-day moving average lag, associated with 0.45% (0.05, 0.86) higher risk of cardiovascular morbidity. For respiratory morbidity both NOx at a 2-day lag (0.90% [0.46, 1.34]) and SO_2 at 0- and 0-1-day lags (0.73 [0.04, 1.42], 0.40% [0.19, 0.61]) appeared associated with higher risk.

For cause-specific cardiovascular disease NO_x was associated with both stroke (I60-I69) and heart disease (I00-I52) morbidity in East Asia and the Pacific region (0.95% [0.64, 1.26] and 1.08% [0.73, 1.43], respectively) (**Figure 3.11).** SO_2 estimates across multiple regions were combined for several cause-specific cardiovascular diseases, including heart disease morbidity (0.36% [0.19, 0.54] in both East Asia and Pacific as well as Latin America and Caribbean). Too few articles included O_3 and CO to examine their associations with cause-specific cardiovascular morbidity. For cause-specific respiratory disease morbidity again only NO_x and SO_2 provided sufficient estimates for meta-analysis with 0.91% (0.34, 1.49) and 1.64% (0.87, 2.40) higher risk of other respiratory (J00-J47) morbidity, respectively. NO_x also appeared associated with 2.48% (1.49, 3.46) higher risk of COPD morbidity.

When pooling estimates by city, only SO_2 was present in enough articles estimates to examine morbidity and a 10 $\mu g/m^3$ increase in SO_2 appeared associated with 0.50% (0.19, 0.82) higher risk of respiratory morbidity in Beijing (**Figure 3.12**). There were too few articles

assessing morbidity to examine how multi-pollutant models altered observed risk estimates. Removing studies assigned high-risk of bias resulted in little change in all pooled estimates (**Figure 3.14**).

Publication bias was evident for NO_x, and SO_2 with respiratory morbidity ($p = 0.017$, and $p = <0.01$, respectively) although trim and fill made little difference to pooled estimates (**Appendix B6**). No publication was observed for any gaseous pollutant and cardiovascular morbidity.

3.2.5.3 Discussion

More consistent pooled estimates were observed for gaseous AAP's association with mortality versus morbidity, as well as across moving-average lag structures. However, fewer studies examined the associations between gaseous AAP and morbidity in LMICs relative to mortality, particularly for O_3 and CO. The pooled estimates obtained in this analysis are similar to those seen in multi-city studies performed within LMIC regions; [207, 213] however, the majority of these aforementioned studies examine mortality only and further research is required which incorporates reliable estimates of morbidity. Results also differed from those seen in HICs, where smaller associations have been observed for NO_x [218] and cardio-respiratory mortality but larger estimates for CO, [219] a potential reason may include the limited number of LMIC studies including CO. Results from HICs located in close geographical proximity to LMIC regions such as Hong Kong, have similar results for mortality but greater risk estimates for morbidity than those seen here. [220] This is potentially due to greater uptake and availability of healthcare in these HICs as opposed to climatic or pollutant differences, which will be similar to nearby LMIC China.

3.2.6 Conclusions – acute health effects

Acute AAP exposure is associated with various cardio-respiratory outcomes within LMICs, but spatial variations are apparent. Although some of the results above from LMIC regions in

this study are similar in magnitude to those from HICs, they are not consistent enough to warrant extrapolation of the results from HICs into LMIC regions. Further research is required within LMICs exclusively to fully examine the health effects of AAP exposure on morbidity, particularly for gaseous AAP.

Following the systematic search undertaken in 2016, some further relevant studies have since been published on the cardio-respiratory health effects of short-term AAP exposure which this section will briefly summarise. In China, specifically, one research group have used time-series analysis to examine associations between short-term AAP exposure and daily cause-specific mortality in 272 Chinese cities with results published on individual pollutants resulting in several publications. The first of these found that $PM_{2.5}$ exposure (at a 0-2-day lag) was associated with 0.27% (95% CI 0.18, 0.36) greater risk of cardiovascular mortality [195], estimates similar in magnitude to those from the meta-analysis outlined in this chapter (0.23% [-0.02, 0.49]) which was restricted to LMICs only. They have also examined the association between short term CO concentrations and cardiovascular mortality across the same 272 cities finding a 1mg/m^3 increase in CO (lag 0-1) significantly associated with a 1.12% (0.42, 1.83) increase in cardiovascular disease mortality. [221] More recently in 2019 they examined short-term PM_{10} exposure and cause-specific mortality, finding PM_{10} significantly associated with higher risk of both cardiovascular (0.25% [0.13, 0.37]), and respiratory (0.26% [0.07, 0.46]) disease mortality. [222] A considerable strength of these studies is their size and likely national representativeness with 272 cities included in analysis covering all Chinese provinces. However, the study period itself was short (2013-2015), and only mortality was included as an outcome of interest.

Since 2016 two Chinese studies have looked at short-term AAP and stroke morbidity. [223] [224] The first of these examined hospital admissions for ischaemic stroke between 2013-2015 in 172 Chinese studies. [224] Unlike the studies above, which examined AAP exposure and mortality in China, this study incorporated morbidity as an outcome of interest and also

incorporated a greater number of pollutants in its analysis. Through time-series analysis it found in single pollutant models that 10 μg/m^3 increases in same-day PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3 and CO (1mg/m^3) were associated with 0.34% (0.20, 0.48), 1.37% (1.05, 1.70), 1.82% (1.45, 2.19), 0.01% (-0.14, 0.16) and 3.24% (2.05, 4.43), higher risk of stroke hospitalisation, respectively. Both SO_2 and NO_2 also remained associated with hospital admissions for ischaemic stroke in bi-pollutant models. Following this, in 2018, a smaller city-specific study also examined short term AAP exposure and stroke incidence, also finding both SO_2 and NO_2 associated with ischaemic stroke morbidity in Changzhou, China. [223] Similar to the meta-analysis described in this chapter they also found a greater effect using moving-average lags than single-day exposures.

Regarding other cardio-respiratory outcomes, a time-series study published in 2019 found short-term AAP exposure associated with a higher risk of COPD exacerbation in Beijing. This was following the implementation of the air pollution prevention and control action plan in 2013 and the subsequent decline AAP concentrations. [225] Interquartile range (IQR) increases in daily AAP concentrations were found to be significantly associated with risk of COPD exacerbations (2.90% [2.30, 3.50], 2.80% [2.10, 3.40], 1.80% [1.30, 2.20], 3.60% [2.80, 4.40], 1.90% [1.30, 2.40] and 2.70% [1.00, 4.40] for $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO and O_3, respectively). Although these recent publications do demonstrate an increase in the number of studies examining the associations between short-term AAP exposure and cardio-respiratory morbidity in China, morbidity as an outcome of interest, continues to be considerably under-researched relative to that of mortality.

3.3 Chronic health effects

Ten articles were identified which examined the chronic cardio-respiratory health effects of AAP exposure in China. [66, 67, 69, 70, 104, 105, 226-229] Of these four were identified through the systematic search strategy outlined above in **Section 2.2.1**, while a further six were

identified through a search performed in September 2018 to identify further studies from China only (search terms shown in **Appendix B7**). The details of each identified study can be found in **Table 3.1** and **Table 3.2**. Since fewer studies were found examining the chronic health effects (compared to acute health effects) of AAP exposure, the following section incorporates evidence on gaseous and particulate AAP inclusively. Where included articles reported health outcomes from causes additional to cardio-respiratory, these are included in **Table 3.1,** but the results not explicitly examined since they are not relevant to the aim of this thesis, which focuses exclusively on cardio-respiratory health effects.

3.3.1 Cardio-respiratory mortality

3.3.1.1 Prospective studies

Of the ten identified articles identified, seven were on cardio-respiratory mortality [66, 67, 69, 70, 104, 105, 226]. Three of these utilised pre-established prospective Chinese cohort studies, the China National Hypertension Survey [230] and Chinese Prospective Smoking Study [231], respectively.

China National Hypertension Survey Epidemiology Follow-up Study (1991-2000)

Established in 1991 with the principle aim of ascertaining hypertension prevalence across China, the China National Hypertension Survey [230] recruited 950,356 individuals aged ≥15 years selected from all 30 provinces in mainland China. In 1999/2000 a follow-up survey in 17 of the 30 provinces assessed vital status and disease outcomes in participants aged ≥40 years, with 169,871 individuals (83,533 men and 86,338 women) eligible for re-survey. [232] This subset of participants has since been used to examine the association of total suspended particulate (TSP), SO_2, and NO_x exposure, with cardio-respiratory mortality. [66] 70,947 urban participants were included (rural participants were excluded, given that there were no fixed site monitors available in rural areas) and AAP exposure (1991-1993 average) assigned to participants' area postal code from baseline address.

A 10 μg/m^3 increase in SO_2 exposure was associated with both cardiovascular and respiratory mortality (adjusted excess risk 3.2% [2.3, 4.0], and 3.2% [1.8, 4.7], respectively). NO_x and TSP were associated with cardiovascular mortality only (2.3% [0.6, 4.1], 0.9 [0.3, 1.5] respectively). Similarly, in multi-pollutant modelling effects of SO_2 exposure on, cardiovascular and respiratory mortality changed minimally, remaining statistically significant following adjustment for NOx and TSP. Associations of NOx with cardiovascular mortality were attenuated following adjustment for SO_2 or TSP. However, correlation coefficients were not reported between pollutants, and these results should be interpreted with caution, given the potential for multicollinearity. There was no significant effect modification by sex, smoking status, obesity, or education level although sizes of subgroups were small, potentially limiting power to detect any effect.

As the only identified prospective cohort study which includes gaseous AAP exposure this is an important study. However, it has significant limitations which include potential exposure measurement error from using fixed-site monitors only to assign exposure (as outlined in **Section 2.4.3** of this thesis). Secondly, TSP as an exposure metric cannot act as a truly valid proxy for PM given TSP is typically measuring larger particles (usually >10 μm but <50-100 μm), meaning the captured effects of NO_2 and SO_2 on cardio-respiratory mortality may, in fact, be reflective of PM effects at finer size fractions. Finally, there was no adjustment for household air pollution or passive smoke exposure, both relevant potential confounders in the relationship between chronic AAP exposure and cardio-respiratory mortality.

Chinese Prospective Smoking Study (1991-2006)

Two further articles used data from the Chinese Prospective Smoking study which included 224,064 males aged between 40-80 years recruited in 1990-91 from 45 areas chosen randomly from China's 145 disease surveillance points (DSPs), aimed to be nationally representative covering ~1% of China's population.

Zhou et al. examined associations between both PM_{10} and TSP and cardiovascular, and respiratory mortality, again with the restriction of urban participants only, leaving 71,431 males for inclusion. [233] AAP exposure was assigned by linking fixed-site monitoring data to participants' metropolitan area of residence at baseline with annual average TSP and PM_{10} concentrations estimated for years 1990-2006 (TSP in 1990-2000 and PM_{10} in 2001-2006). Incorporating both TSP and PM_{10} reflected changing Chinese air pollution monitoring policy, with TSP monitored between 1990-2000, replaced by PM after 2000. Significant associations were observed for a 10 $\mu g/m^3$ increase in TSP with cardiovascular disease mortality only (adjusted excess risk 1.0% [0.4%, 1.7%]), while PM_{10} was associated with both cardiovascular, and respiratory disease mortality (1.8% [0.8, 2.9], and 1.7% [0.3, 3.2], respectively). Stratified analysis was performed for PM_{10}, with little evidence of effect modification by smoking status, education and body mass index (BMI), however no formal test was performed to assess the significance of effect modification.

The common limitations above are still present in this study including exposure measurement error from the use of fixed-site monitors to assign exposure, and lack of adjustment for household air pollution and passive smoke exposure.

Yin et al. used the same cohort to examine $PM_{2.5}$ exposure and mortality, expanding causes of death to include cardiovascular, IHD, stroke, and COPD [69]. Follow-up time was the same as the study outlined above (1991-2006) however a greater number of deaths were included due to participants in both urban and rural areas being included in analysis (189,793 males). This was possible as $PM_{2.5}$ exposure was assigned using mean gridded values of satellite-based and chemical transport model estimates calibrated to available ground monitors. The continuous spatial surface of $PM_{2.5}$ at a 0.1°x 0.1° resolution (~11 x 11km at the equator) was based on mean concentrations between the years 2000-2005 assigned to all participants by baseline area of residence. This provided a wider range of exposure than in

previous studies [226], although it can be argued a 0.1° x 0.1° resolution will still not capture the finer scale spatial variation in $PM_{2.5}$ exposure.

Following adjustment for a range of individual and area-level confounders (see **Table 2.1**) a 10 μg/m^3 increase in $PM_{2.5}$ was significantly associated with all causes of death, with greatest risk observed for stroke mortality (adjusted hazard ratio, 1.14 [95% CI 1.13, 1.16]). The strength of associations between $PM_{2.5}$ exposure and mortality was greater than those in the previous study examining PM_{10} and TSP [226] which relied exclusively on fixed-site monitors for exposure assignment. Sensitivity analysis using differing years of exposure including, baseline exposure (1990) and average exposure from 1990-2005, gave similar effect estimates suggesting some degree of spatial homogeneity in $PM_{2.5}$ exposure during follow-up. However, it is also possible the 0.1°x 0.1° resolution may just not have captured finer spatial variability in PM exposure; thus, spatial homogeneity of exposure over time cannot be assumed.

This is the only identified cohort study that examines exposure-response relationships between AAP exposure and mortality. Estimated curves were similar across all causes of death and monotonic in shape with greater risk at higher concentrations and little change in risk below 20 μg/m^3. The observed effect estimates were also compared to those used for GBD 2015 [40], by combining respective estimates in a random-effects meta-analysis, as well as calculating effect estimates based on the age-specific (60-64 years) integrated exposure-response (IER) function between the 5^{th} and 95^{th} $PM_{2.5}$ percentile, reflecting the average age and exposure contrast within this cohort. Risk estimates from the study were found to be consistently higher than the corresponding IER estimates from GBD but similar to those from meta-analysis.

The use of satellite-based estimation of $PM_{2.5}$ exposure is particularly advantageous, likely reducing some exposure misclassification seen in studies relying solely on fixed-site

monitors. It also allowed the inclusion of both rural and urban-located individuals. However, including only males limits the wider generalisability of this study given the sex-based differences in mortality risk following AAP exposure which have been hypothesised and demonstrated in studies from both HIC [234, 235] and LMIC populations [162, 188]. Furthermore, the very high prevalence of active smoking in this male cohort (68.2%) potentially limits the generalisability of findings. A final limitation is that no additional pollutants were included, therefore, the degree to which $PM_{2.5}$ might be acting as a proxy for other unmeasured pollutants cannot be determined.

3.3.1.2 Retrospective cohort studies

Four of the seven articles examining cardio-respiratory mortality were based on two retrospective Chinese cohort studies. Unlike the aforementioned cohorts these retrospective cohorts were established specifically to examine associations between chronic AAP exposure and cardio-respiratory mortality.

Shenyang Retrospective Cohort (1998-2009)

In 2009 a population-based retrospective cohort study was performed across five urban districts of Shenyang with 12,584 individuals aged ≥25 years (in 1998) residing within 1 km of a fixed-site monitor (for at least 10 years). 9,941 residents (aged 35-103 years) completed the medical questionnaire, with chronic AAP exposure (annual averages as time-varying covariates) assigned to participants using their nearest fixed-site monitor. Two studies have since used to this cohort to examine associations between chronic AAP exposure and mortality, focusing on cardiovascular and cerebrovascular mortality [105], and respiratory mortality [104], respectively.

Zhang et al. found that for cardiovascular and cerebrovascular mortality significant associations were observed in both PM_{10} and NO_2 exposure, with the strength of association

greatest for NO_2 (adjusted hazard ratios 2.46 [2.31, 2.63], and 2.44 [2.27, 2.62] per 10 μg/m^3 increase for cardiovascular and cerebrovascular, respectively). No significant associations between SO_2 and mortality of any cause were observed within the cohort. These risk estimates obtained for PM_{10} and NO_2 exposure are considerably larger estimates than those seen in the other aforementioned Chinese studies as well as in prospective studies from Western populations [236, 237], however, the number of deaths included in this study was extremely small, (138 for cardiovascular and 118 for cerebrovascular, respectively). In stratified analysis, a slightly greater risk of mortality appeared in women, those with BMI <18.5 kg/m^2, and in smokers, however no formal tests of interaction were performed, and statistical power was likely to be limited due to even fewer deaths within subgroups.

Dong et al. then examined respiratory disease mortality, with both PM_{10} and NO_2 significantly associated with increased risk of mortality. Again, associations were observed for a 10ug/m^3 increase in NO_2 exposure (hazard ratios; 1.67 [1.60, 1.74]) and PM_{10} exposure (2.97 [2.69, 3.27]), and there was no significant association between SO_2 exposure and respiratory mortality. However, the number of respiratory deaths was extremely small (n=72), thus limiting any inference that can be obtained from this study on the relationship between chronic AAP exposure and respiratory disease mortality.

Northern China Retrospective Cohort (1998-2009)

A second retrospective cohort examined associations between chronic AAP exposure and cardio-respiratory mortality was performed across Northern China. This cohort larger than the aforementioned Shenyang cohort included 39,054 participants across four northern cities (Tianjin, Shenyang, Taiyuan, and Rizhao), encompassing a broader range of AAP levels. Again, individuals residing for at least 10 years within 1 km of fixed-site monitors were randomly selected, assigned annual mean AAP exposure estimates (used as a time-varying covariate) from their closest monitor.

The cohort has since been used in two studies that examine the associations between AAP exposure and cardiovascular [70], and respiratory and COPD mortality [67], respectively. For PM_{10} and cardiovascular mortality similar risk estimates were observed, as seen in the Shenyang cohort [105] (adjusted hazard ratios 1.23 [1.19, 1.26] vs 1.55 [1.51, 1.60], respectively). However, a wider range of cause-specific mortality was also included including ischaemic heart disease (IHD); dysrhythmia/heart failure/cardiac arrest; in addition to cardiovascular, and cerebrovascular disease mortality. PM_{10} was significantly associated with all the aforementioned causes of death, the greatest effect estimate reported for IHD (adjusted hazard ratio 1.37 [1.28, 1.47]). In stratified analysis statistically significant effect modification was observed with greater risk of mortality observed in those with higher education, higher income, those with occupational exposure, and in smokers for PM_{10} and both IHD and cardiovascular disease mortality**.**

Chen et al. used the same methodology as above to examine associations for PM_{10} and SO_2 with both respiratory disease and COPD mortality within the cohort [67]. Significant associations were observed for both PM_{10} and SO_2 exposure with respiratory and COPD mortality with greater risk observed for PM_{10} relative to SO_2 (1.46 [1.30, 1.64] vs 1.11 [1.02, 1.20], and 1.56 [1.36, 1.80] vs 1.15 [1.05, 1.25] for PM_{10}, versus SO_2 respectively and, for respiratory disease, and COPD mortality, respectively). In stratified analysis, stronger associations were observed in males, those with higher education, higher personal income, and in smokers, but no formal statistical tests of effect modification were performed.

In bi-pollutant models adjusting for SO_2 the strength of PM_{10} risk estimates increased (adjusted hazard ratios 1.82 [1.57, 2.12] and 1.90 [1.58, 2.27] for respiratory and COPD mortality, respectively), while for SO_2 adjusting for PM_{10} attenuated associations to the null (0.85 [0.72, 1.00] and 0.96 [0.82, 1.13], for respiratory and COPD mortality, respectively). However, the observed correlation between both pollutants was high (r=0.87); therefore, the construction of these models was arguably not plausible given such collinearity is known to

potentially bias regression coefficients. Furthermore, NO_2 which has been associated with respiratory mortality in numerous western studies was not included despite its inclusion in a similar study [238]on lung-cancer mortality for the same follow-up period and study population. Finally, as seen in the other retrospective cohort studies the number of deaths in the study was extremely low (67 and 46 across all regions for respiratory and COPD, respectively).

3.3.2 Cardio-respiratory morbidity

No articles examined the relationship between chronic exposure to AAP and cardio-respiratory morbidity in China by prospective study design. However, three Chinese cross-sectional studies were identified which examined chronic AAP exposure and prevalence of hypertension [227], cardiovascular disease [229], and COPD [228] respectively (**Table 3.2**).

The 33 Communities Chinese Health Study established in 2009 includes 24,485 individuals from 33 communities within three Chinese cities (Shenyang, Anshan, and Jinzhou), and has since been used to examine relationships between AAP exposure and both hypertension and cardiovascular disease prevalence.

To examine AAP exposure and hypertension prevalence, participants were assigned PM_{10}, SO_2, NO_2, and O_3 exposure (2006-2008 averages) from fixed-site monitors located <1-mile from their respective homes. IQR increases of PM_{10}, SO_2, NO_2, and O_3, exposure were significantly associated with hypertension prevalence (adjusted odds ratios, 1.12 [1.08, 1.16], 1.11 [1.04, 1.18], 1.09 [1.00, 1.20] and 1.13 [1.06, 1.20] for PM_{10}, SO_2, NO_2 and O_3, respectively). Hypertension was defined as average systolic blood pressure (SBP) ≥ 140mmHg or DBP ≥ 90 mmHg, and/or self-reported hypertensive medication consumption in the two weeks before the interview. In stratified analysis by sex, significant associations between AAP and hypertension prevalence were only found in males.

The same cohort was also utilised to examine the association of chronic PM_1 and $PM_{2.5}$ exposure with cardiovascular disease prevalence, defined as self-reported prior heart failure,

heart disease, or myocardial infarction, and/or stroke diagnosis [229]. Unlike the previous article, here PM_1 and $PM_{2.5}$ were assigned to community centroids through exposure modelling combining fixed-site monitoring data, satellite remote sensing, meteorology and land-use information at a 0.1°x 0.1°-degree spatial resolution. 10 $\mu g/m^3$ increases in PM (2008 average) were significantly associated with increased odds of cardiovascular disease prevalence (adjusted OR 1.12 [1.05, 1.20] and 1.06 [1.01, 1.11], for PM_1 and $PM_{2.5}$, respectively), with associations remaining consistent using differing multi-year averages of PM (2007-2008 and 2006-2008). Both age and sex were statistically significant effect modifiers in the relationship between PM_1 and cardiovascular disease, with higher associations observed in both males and the elderly.

For chronic AAP exposure and respiratory disease morbidity the only identified article was a cross-sectional study, including 5993 individuals from four cities in Guangdong. Participants were assigned annual average PM via portable gravimetric samplers placed at the spatial centroid of each participating cluster, the associations of PM_1 and $PM_{2.5}$ with COPD prevalence defined by spirometry (FEV_1:FVC <70%) and related lung function examined. [228]

$PM_{2.5}$ concentrations were associated with increased odds of COPD prevalence, with an adjusted OR of 2.42 (95% CI 1.42 to 4.12) for concentrations between >35 and ≤75 $\mu g/m^3$ and 2.53 (1.28 to 5.00) for >75 $\mu g/m^3$ relative to the reference concentration of ≤35 $\mu g/m^3$. PM_{10} had a similar but slightly weaker association with COPD prevalence. Both PM_{10} and $PM_{2.5}$ were also associated with adverse effects on lung function including significant reductions in both FEV_1 (-26 ml [-43, -9], and -14 ml [-22, -6], respectively) and FVC (-28 ml, [-49, -8], and -16 ml [-28, -4], respectively). In stratified analysis associations were only observed between PM and COPD prevalence in males and smokers, this is unsurprising given the considerable lower prevalence on COPD in females (4.1%) versus males (13.4%), and in non-smokers (4.4%) versus smokers (17.0%), in China. [239]

This was the only identified study on AAP and cardio-respiratory morbidity, which adjusted for second hand-smoke exposure and household air pollution (measured by "kitchen ventilation quality"). However, "kitchen ventilation quality", as a measure of household air pollution is a relatively crude exposure proxy, with household air pollution exposure in LMICs known to depend on a wide range of additional factors including household fuel-source[240] and burning techniques.[241]

3.3.3 Conclusions – chronic health effects

Evidence on the chronic health effects of AAP exposure and cardio-respiratory mortality in China has emerged from both prospective and retrospective cohort studies. Of the latter, all identified studies suffer from substantial limitations including high degrees of exposure measurement error from the assignment of AAP exposure to participants via solely fixed-site monitors; limited power due to few included deaths; and potential recall bias in both outcomes and included covariates due to the retrospective study design. Furthermore, these retrospective cohort studies did not control for the relevant potential confounders of household air pollution or second hand-smoke exposure.

Of the prospective studies identified only one assigned modelled exposure estimates not based solely on fixed-site monitors. However, this study included only $PM_{2.5}$ and at a relatively crude spatial resolution, potentially not capturing the smaller-scale spatial fluctuations in exposure required to effectively minimise exposure measurement error. This was also the only prospective study to control for passive smoking and household air pollution in estimates, and it included only males.

Besides, only one prospective cohort used by two studies [66, 226] allowed prior disease prevalence to be examined in participants but this was for hypertension and diabetes only. It therefore cannot be ascertained in any of the studies whether chronic AAP exposure was associated with mortality only in participants more susceptible given prevalence of prior

disease. Examining this remains important to strengthen the evidence base between AAP and cardio-respiratory mortality. Given these substantial limitations, the ability to draw any reliable inference on the association between chronic AAP exposure and cardio-respiratory mortality from these cohort studies is limited and more robust prospective evidence is needed.

Studies examining the chronic effects AAP exposure on cardio-respiratory morbidity in China are even more limited than for mortality with all identified articles cross-sectional in design, thus unable to examine the temporal relationship between AAP exposure and morbidity. None of the studies controlled for passive smoking and only one crudely adjusted for household air pollution with "kitchen ventilation".[228] Recall bias in both ascertained outcomes as well as included covariates is also possible in addition to exposure misclassification from the use of one fixed-site monitor per district, one ambient gravimetric sampler in community centroids, and spatially coarse satellite modelling, for the three studies, respectively.

As the above studies suffer from considerable limitations, more robust evidence is needed in China to assess the relationship between chronic AAP exposure and cardio-respiratory morbidity. While such associations have been documented in studies from Western populations, [242, 243] no prospective evidence currently exists in a Chinese population.

Following the literature search described above undertaken in September 2018, two prospective studies have recently been published examining the risk of cardio-respiratory morbidity associated with chronic AAP exposure in China. [244, 245] Both studies utilise the Prediction for Atherosclerotic Cardiovascular Disease Risk in China (China-PAR) project, which has been described in detail elsewhere. [246] In brief, it was carried out in 15 Chinese provinces and included four sub cohorts enrolled between 1992-2008 with AAP exposure then assigned using a 1x1km spatiotemporal model. The first of these AAP studies examined the association between chronic $PM_{2.5}$ exposure (characterised by quartiles of

exposure) and incident stroke (both overall and ischaemic and haemorrhagic subtypes, respectively). [244] For ~117,000 individuals and ~900,000 years of follow-up, a 10 μg/m^3 increase in $PM_{2.5}$ exposure was significantly associated with increased risk of all-type stroke incidence (adjusted hazard ratio 1.13, [95% CI 1.09, 1.17]). This study is the only study to date that has examined the association between AAP and stroke morbidity prospectively in China. The study's size and its use of a 1x1km spatiotemporal model to assign exposure are considerable strengths. However, similar to the prospective studies examining AAP exposure and mortality, it failed to adjust for the potential confounders of household air pollution, ambient temperature and second-hand smoke exposure. The authors also limit their analysis to only one pollutant of interest, making the construction of bi-pollutant models not possible.

The same China-PAR project has also been utilised to examine the risk of hypertension incidence associated with $PM_{2.5}$ exposure, finding a 10 μg/m^3 increase in $PM_{2.5}$ associated with increased risk of hypertension (adjusted hazard ratio 1.11, [1.05, 1,17]). However, this was in a smaller subset of the China-PAR project due to the exclusion of participants with recorded hypertension at baseline (~59,000 participants). This study did adjust for ambient temperature, but similar to the study described above, they did not adjust for household air pollution or second-hand smoke exposure and again limited the analysis to only one pollutant of interest. More evidence is needed to examine the chronic effects of AAP exposure on morbidity in China, ideally incorporating a greater number of air pollutants and adjusting for the potential confounders of household air pollution and second-hand smoke exposure.

3.4 Summary

This chapter has outlined and synthesised current available evidence on both the acute, and chronic, cardio-respiratory health effects of AAP exposure, across all LMICs, and within China, respectively. In doing so it presented the rationale, methodology, and results for a

systematic review and meta-analysis of acute cardio-respiratory mortality/morbidity associated with AAP exposure in LMICs.

Overall, acute increase in AAP exposure was associated with higher risk of adverse cardio-respiratory health effects, and risk estimates varied considerably by pollutants, health outcomes, associated lag times and region. The relevance of these varying factors in quantifying the health effects of acute AAP exposure demonstrates how extrapolation of generated risk estimates from HIC's into LMIC's is not suitable to effectively examine the health effects of acute AAP exposure. More regional-specific estimates are needed to examine the risks from acute AAP exposure in China, ideally including those less-studied pollutants (CO, O_3 and $PM_{2.5}$) and cardio-respiratory morbidity.

This chapter also evaluated existing evidence on chronic AAP exposure and the risk of cardio-respiratory mortality/morbidity in China. Far fewer studies were identified relative to that of acute health effects, and more robust evidence is needed. Prospective evidence is particularly limited, and potential bias from exposure misclassification a substantial limitation in the majority of all identified studies, which are also small in size, and frequently lacking adjustment of appropriate potential confounders. Finally, there are very few large-scale prospective studies on chronic AAP exposure concerning cardio-respiratory morbidity (needed to fully determine the burden of AAP exposure in China).

Table 3.1 Characteristics of studies examining long-term AAP exposure and cardio-respiratory mortality in China

Cohort (year established)	Geographical location(s)	Cause (number of deaths)	No. of participants	Exposure classification method	Pollutants included	Adjustment variables	Adjusted findings
Prospective							
China National Hypertension Survey (1991)	30 Chinese provinces	Cardiovascular (n=3013) Respiratory (n=921) Lung-cancer (n=624)	70,497	Fixed site monitors and geocoded addresses	TSP, SO_2 and NO_x	Age, sex, BMI, physical activity, education, smoking status (never/former/current), age started smoking, years smoked, cigarettes per day, alcohol intake, and hypertension status.	**Cardiovascular** * TSP (0.9 [0.3, 1.5]); SO_2 (3.2 [2.3, 4.0]); NOx (2.3 [0.6, 4.1]) **Respiratory** * TSP (0.3 [-0.5, 1.6]); SO_2 (3.2 [1.8,4.7]); NOx (2.6 [-0.2, 5.6]) **Lung-cancer** * TSP (1.1 [-0.1, 2.3]); SO_2 (4.2 [2.3, 6.2]); NOx (2.7 [-0.9, 6.5])
Chinese Prospective Smoking Study (1990/91)	25 Chinese cities	Cardiovascular (n=3869) Respiratory (n=2031) Lung cancer (n=817)	71,431	Fixed-site monitors linked to the metropolitan area of residence	TSP and PM_{10}	Age, BMI, physical activity, education, smoking status (never/former/current), amount smoked, age started to smoke, years smoked, alcohol intake, diabetes and hypertension status.	**Cardiovascular** † TSP (1.010 [1.004, 1.017]); PM_{10} (1.018 [1.008, 1.029]) **Respiratory** † TSP (0.998 [0.991, 1.006]) PM_{10} (1.017 [1.003, 1.032]) **Lung-cancer** † TSP (1.003 [0.998, 1.009], 1.010 [0.991, 1.030]) **All-cause** † TSP (1.004 [0.999, 1.010]), PM_{10} (1.016 [1.007, 1.026])
Chinese Prospective Smoking Study (1990/91)	45 Chinese areas	Non-accidental (50,022) Cardiovascular (n=18,859) COPD (n=11,989) Lung-cancer (n=2523) Stroke (n=11,301) IHD (n=3752)	189,793	11 x 11km satellite estimates for districts/counties obtained from GBD exposure model	$PM_{2.5}$	Individual level - age, marital status, education, smoking status (never/former/current), years of smoking, cigarettes per day, passive smoking, occupational exposure, alcohol drinking, units of alcohol per week, BMI, fresh fruit and vegetable consumption, household solid fuel use Area level - urban/rural, region and mean years of education	**Non-accidental** † (1.09 [1.08, 1.09]) **Cardiovascular** † (1.09 [1.08, 1.10]) **COPD** † (1.12 [1.10, 1.13]) **Lung cancer** † (1.12 [1.07, 1.14]) **Stroke** † (1.14 [1.13, 1.16]) **IHD**† (1.09 [1.06, 1.12])
Retrospective							
Shenyang Retrospective Cohort (2009)	Shenyang	Respiratory (n=72)	9,941	Participants selected 1 km from fixed-site monitors	PM_{10}, SO_2 and NO_2	Age, sex, BMI, education, smoking status (yes, no), number of cigarettes smoked per day, number of years smoking, personal income, occupational exposure, and physical activity	**PM_{10}** † (1.67 [1.60, 1.74) **SO_2** † (1.04 [0.97, 1.12]) **NO_2** † (2.97 [2.69, 3.27])
Shenyang Retrospective Cohort (2009)	Shenyang	Cardiovascular (n=138) Cerebrovascular (n=118)	9,941	Participants selected 1 km from fixed-site monitors	PM_{10}, SO_2 and NO_2	Age, sex, BMI, education, smoking status (yes, no), number of cigarettes smoked per day, number of years smoking, personal income, occupational exposure and physical activity	**Cardiovascular** † PM_{10} (1.55 [1.51, 1.60]); SO_2 (0.96 [0.92, 1.01]); NO_2 (2.46 [2.31, 2.63]) **Cerebrovascular** † PM_{10} (1.49 [1.45, 1.53]) SO_2 (0.95 [0.90, 1.00); NO_2 (2.44 [2.27, 2.62]) **All-cause** † PM_{10} (1.53 [1.50. 1.56]); SO_2 (0.95 [0.92, 0.99]); NO_2 (2.45 [2.34, 2.58])
Northern China retrospective cohort (2009)	Tianjin, Shenyang, Taiyuan, and Rizhao	All-cause (n=1435) Cardiovascular (n=677)	39,054	Participants selected 1 km from fixed-site monitors	PM_{10}	Age, sex, BMI, education, smoking status (never/former/current), personal income, occupational exposure, alcohol consumption, and physical activity, and vegetable and fruit consumption	**All-cause** † (1.24 [1.22, 1.27]) **Cardiovascular** † (1.23 [1.19, 1.26]) **IHD** †; (1.37 [1.28, 1.47]) **Dysrhythmias, heart failure, cardiac arrest** † (1.11 [1.05, 1.17]) **Cerebrovascular disease** † (1.23 [1.17, 1.28])
Northern China retrospective cohort (2009)	Tianjin, Shenyang, Taiyuan, and Rizhao	Respiratory (n=67) COPD (n=46)	39,054	Participants selected 1 km from fixed-site monitors	PM_{10} and SO_2	Age, sex, BMI, education, smoking status (never/former/current), personal income, occupational exposure, alcohol consumption, marital status, vegetable and fruit consumption and seafood and meat consumption	**Respiratory** † PM_{10} (1.46 [1.30, 1.64]) SO_2 (1.11 [1.02, 1.20]) **COPD** † PM_{10} (1.56 [1.36, 1.80]) SO_2 (1.15 [1.05, 1.25])

Abbreviations: COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; BMI, body mass index; NOx, nitrogen oxides; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; TSP, total suspended particles; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm * percent excess risk (95% CI) † hazard ratio (95% CI)

Table 3.2 Characteristics of studies examining long-term AAP exposure and cardio-respiratory morbidity in China

Study (years established)	Geographical location(s)	Outcome (number of events)	No. of participants	Exposure classification method	Pollutants included	Adjustment variables	Adjusted findings (OR [95% CI])
33 Communities Chinese Health Study (2009-2010)	14 cities in Liaoning province	Hypertension prevalence - defined as SBP ≥ 140 and DBP ≥90/ self-reported hypertensive medication prior to interview (n=8657)	24,845	Fixed-site monitors	PM_{10} SO_2 NO_2 O_3	Age, sex, ethnicity, education, income, smoking (yes/no), alcohol, exercise, dieting history, sugar consumption, family history of hypertension, and district	**PM_{10}** (1.12 [1.08, 1.16]) **SO_2** (1.11 [1.04, 1.18]) **NO_2**(1.09 [1.00, 1.20]) **O_3** (1.13 [1.06, 1.20])
33 Communities Chinese Health Study (2009)	14 cities in Liaoning province	CVD prevalence defined by self-reported heart failure, heart disease, myocardial infarction and/or stroke (n=1006)	24,845	Exposure modelling combining ground monitoring data, satellite remote sensing, meteorology, and land-use information at a 0.1 x0.1 resolution	$PM_{2.5}$ and PM_1	Age, sex, ethnicity, education, household income, smoking status (yes/no) physical activity and district-level gross domestic product.	**$PM_{2.5}$** (1.06 [1.01, 1.11]) **PM_1** (1.12 [1.05, 1.20])
National Science-Technology Support Plan Program (2012-2015)	Guangzhou, Shaoguan, Heyuan and Zhanjiang	COPD prevalence defined as FEV_1:FVC <70% diagnosed by spirometry examinations (n=521) COPD symptoms defined as one of the following symptoms lasting for more than 3 months and at least 2 years: dyspnoea, cough, sputum production, wheezing and chest tightness (n=1283) Other chronic pulmonary disease prevalence defined as asthma, chronic bronchitis, tuberculosis, bronchiectasis, interstitial lung disease, allergic rhinitis and allergic sinusitis (n=696)	5993	Portable ambient air sampler in centroids of sampling cluster	PM_{10} and $PM_{2.5}$	Age, sex education, smoking history (yes/no), history of childhood pneumonia, maternal smoking in pregnancy, maternal exposure to passive smoking in pregnancy, kitchen ventilation quality, passive smoking exposure, urban/rural distribution	**COPD prevalence** **$PM_{2.5}$** (2.42 (95% CI 1.42 to 4.12) for concentrations between >35 and ≤75 μg/m^3 2.53 (95% CI 1.42 to 4.12) for >75 μg/m^3) **PM_{10}** (2.44 (95% CI 1.45 to 4.12) for concentrations between >50 and ≤150 μg/m^3 **COPD symptoms** **$PM_{2.5}$** (1.46 (95% CI 1.13 to 1.18) for concentrations between >35 and ≤75 μg/m^3 1.29 (95% CI 0.89 to 1.86) for >75 μg/m^3) **PM_{10}** (1.45 [95% CI 1.13 to 1.86]) for concentrations between >50 and ≤150 μg/m^3 **Other chronic pulmonary diseases** **$PM_{2.5}$** (1.84 (95% CI 1.24 to 2.71) for concentrations between >35 and ≤75 μg/m^3 1.87 (95% CI 1.14 to 3.06) for >75 μg/m^3) **PM_{10}** (1.90 [95% CI 1.29 to 2.80]) for concentrations between >50 and ≤150 μg/m^3 **Lung function** PM_{10} and $PM_{2.5}$ FEV_1 (-26ml [-43, -9], and -14ml [-22, -6], respectively) PM_{10} and $PM_{2.5}$ FVC (-28ml, [-49, -8], and -16ml [-28, -4], respectively).

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; COPD, Chronic obstructive pulmonary disease; FEV_1, forced expiratory volume; FVC, forced vital capacity; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; O_3, ozone; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm

Figure 3.1 Results of the systematic search protocol

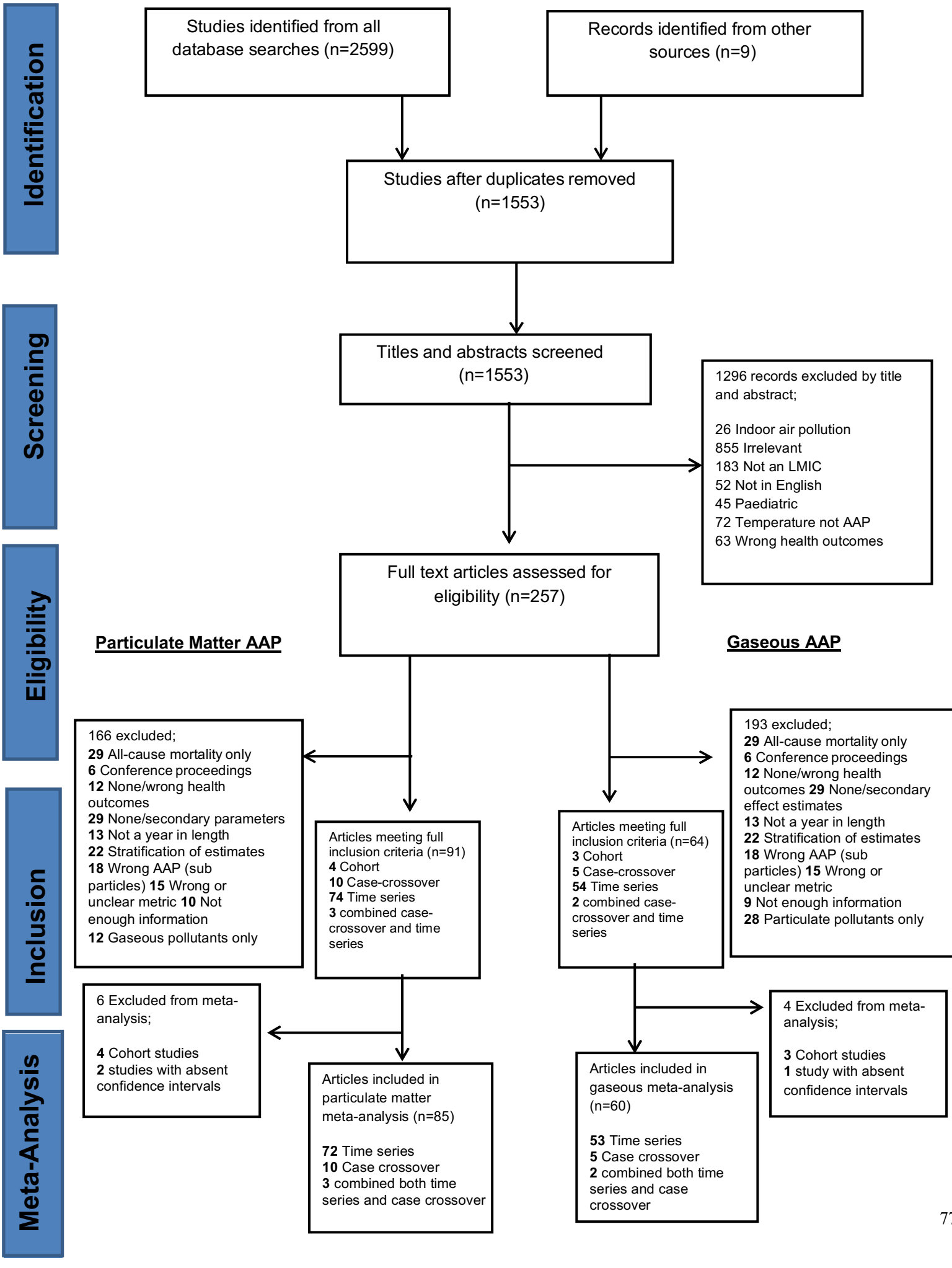
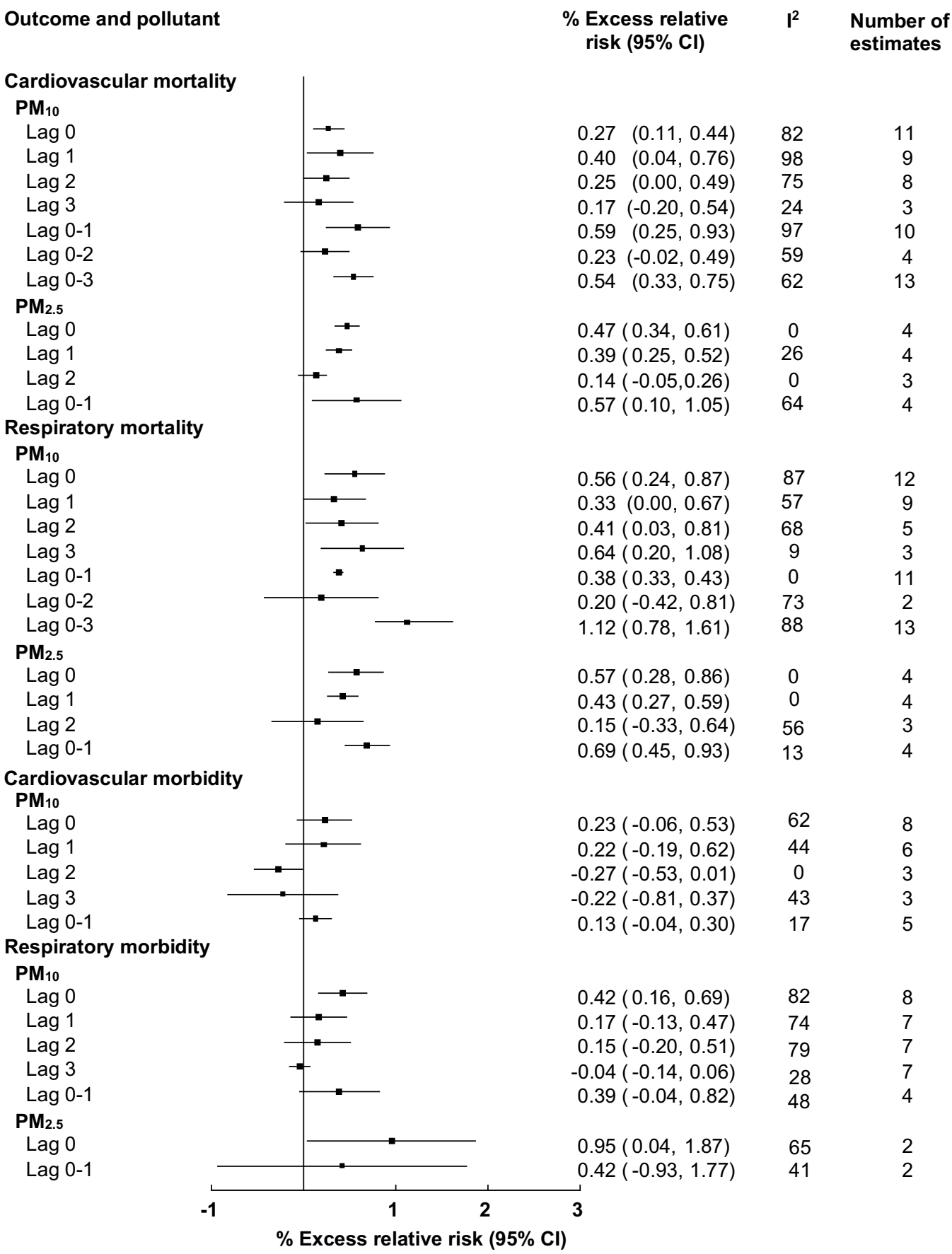


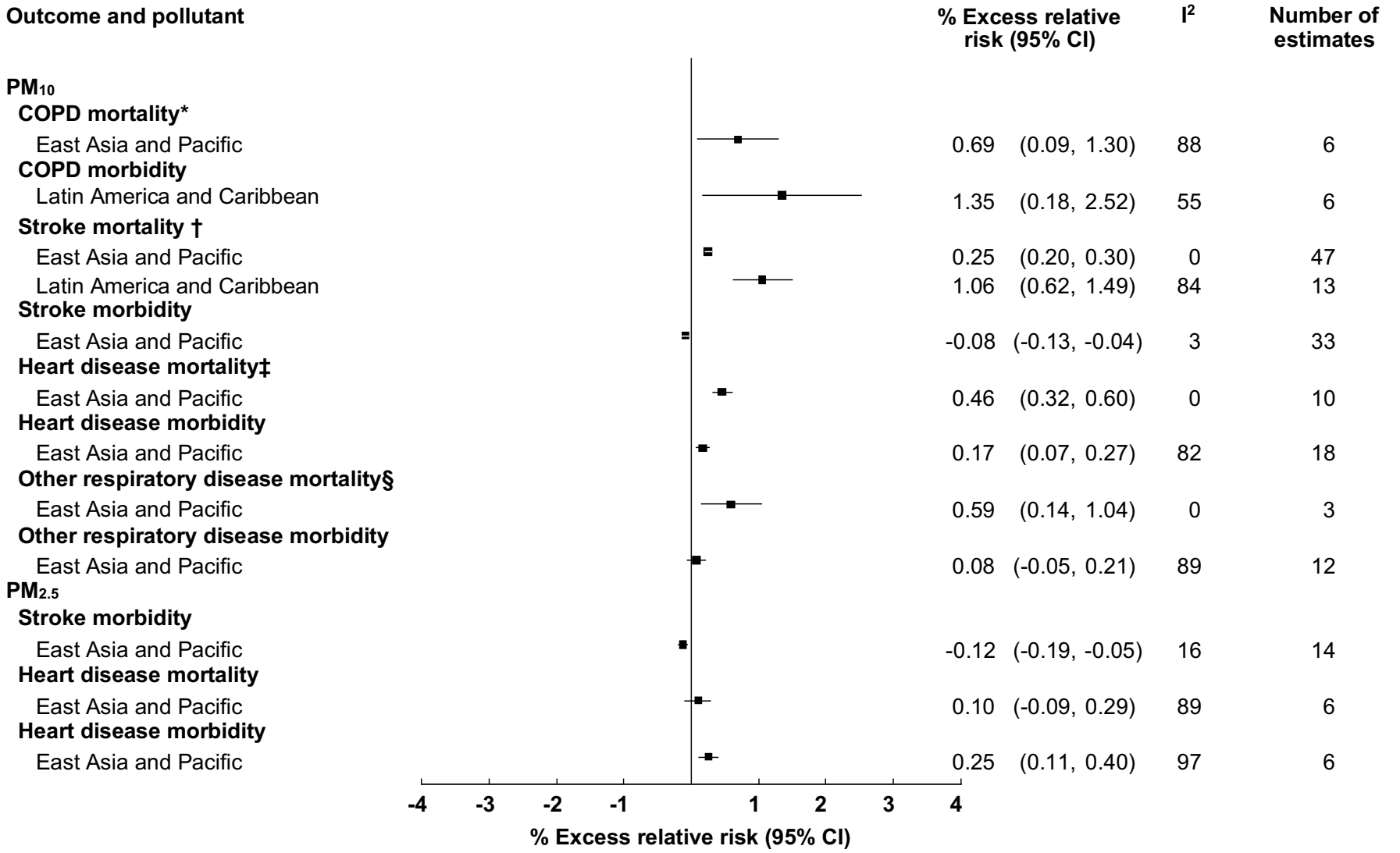
Figure 3.2 Pooled associations between particulate matter exposure and cardio-respiratory mortality/morbidity by outcome and lag time (days) in low-income and middle-income countries (LMICs)



*Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10μg/m^3 increase in particulate matter ambient air pollution from pooled study estimates

I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

Figure 3.3 Pooled associations between PM_{10}, $PM_{2.5}$ and mortality/morbidity by specific disease outcomes in low- and middle-income countries (LMICs)



Abbreviations: PM_{10}, particulate matter <10μm; $PM_{2.5}$, particulate matter <2.5μm; COPD, chronic obstructive pulmonary disease

Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10 $\mu g/m^3$ increase in particulate matter ambient air pollution from pooled study estimates pooled for lags 0-3 inclusively

* International Classification of Disease 10th Edition (ICD-10) J41-J44

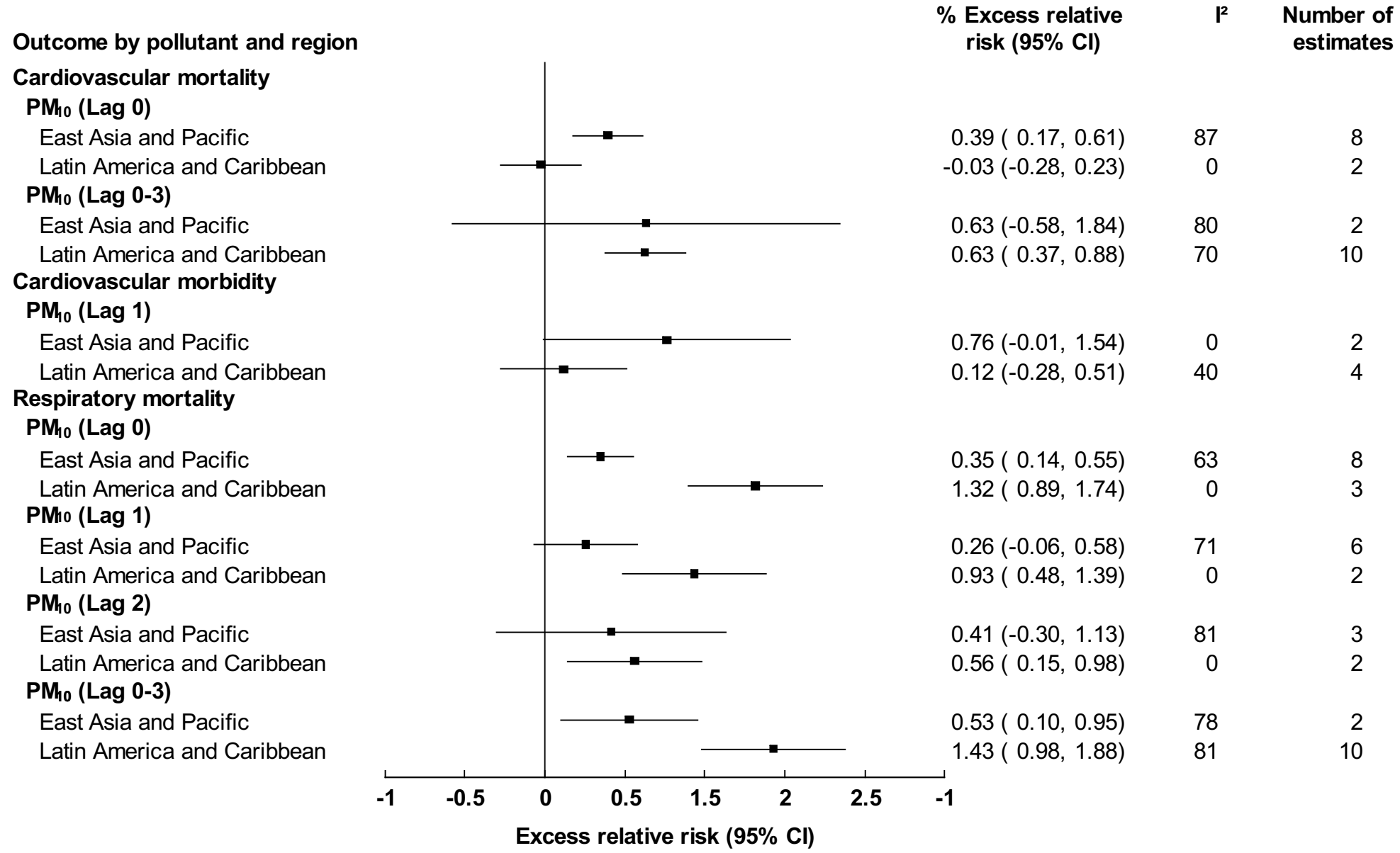
†ICD-10: I60-I69

‡ICD-10: I05-I52

§ICD-10: J00-J47

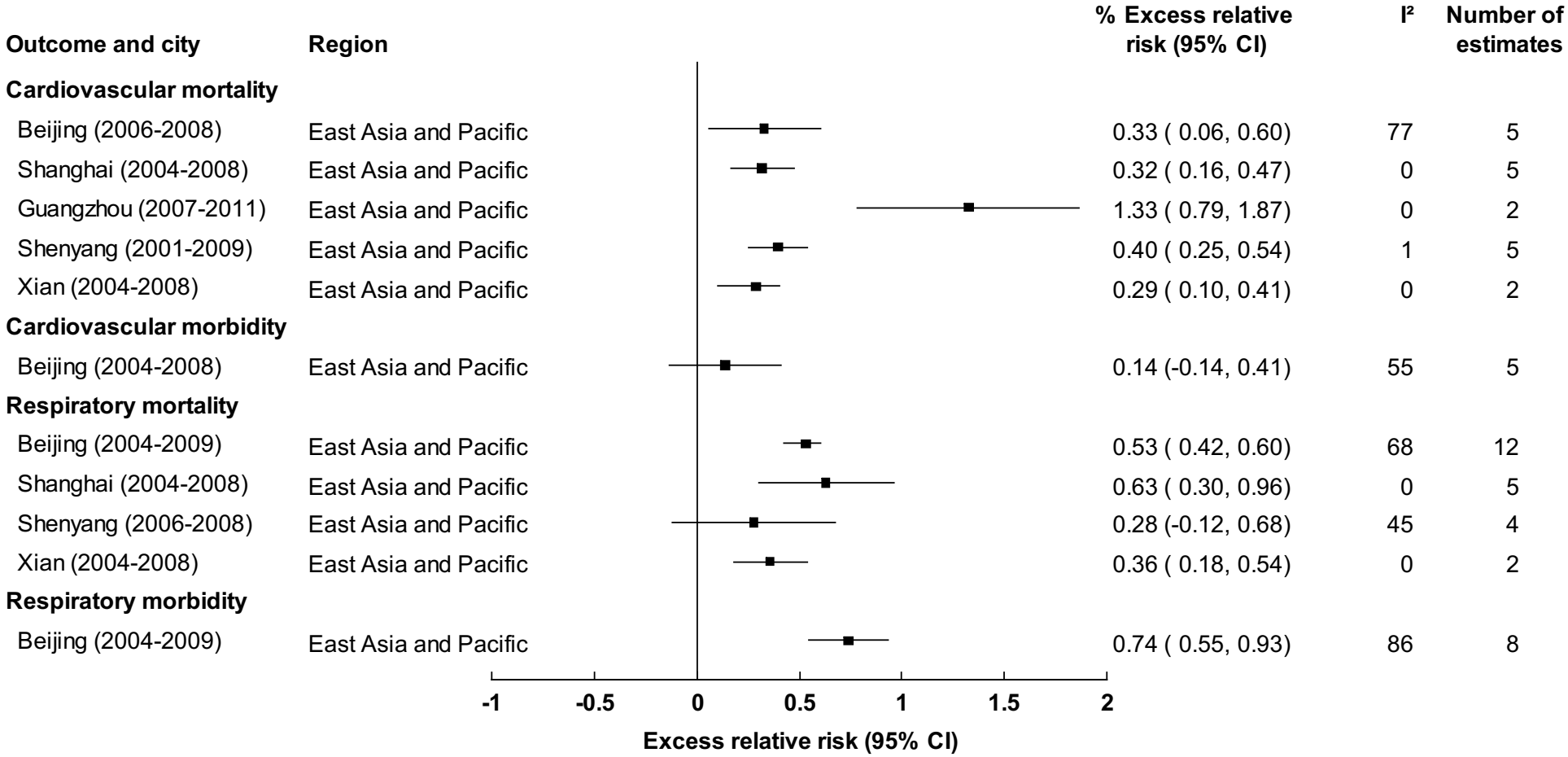
I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

Figure 3.4 Pooled associations between PM_{10} and mortality/morbidity by region in low- and middle-income countries (LMICs)



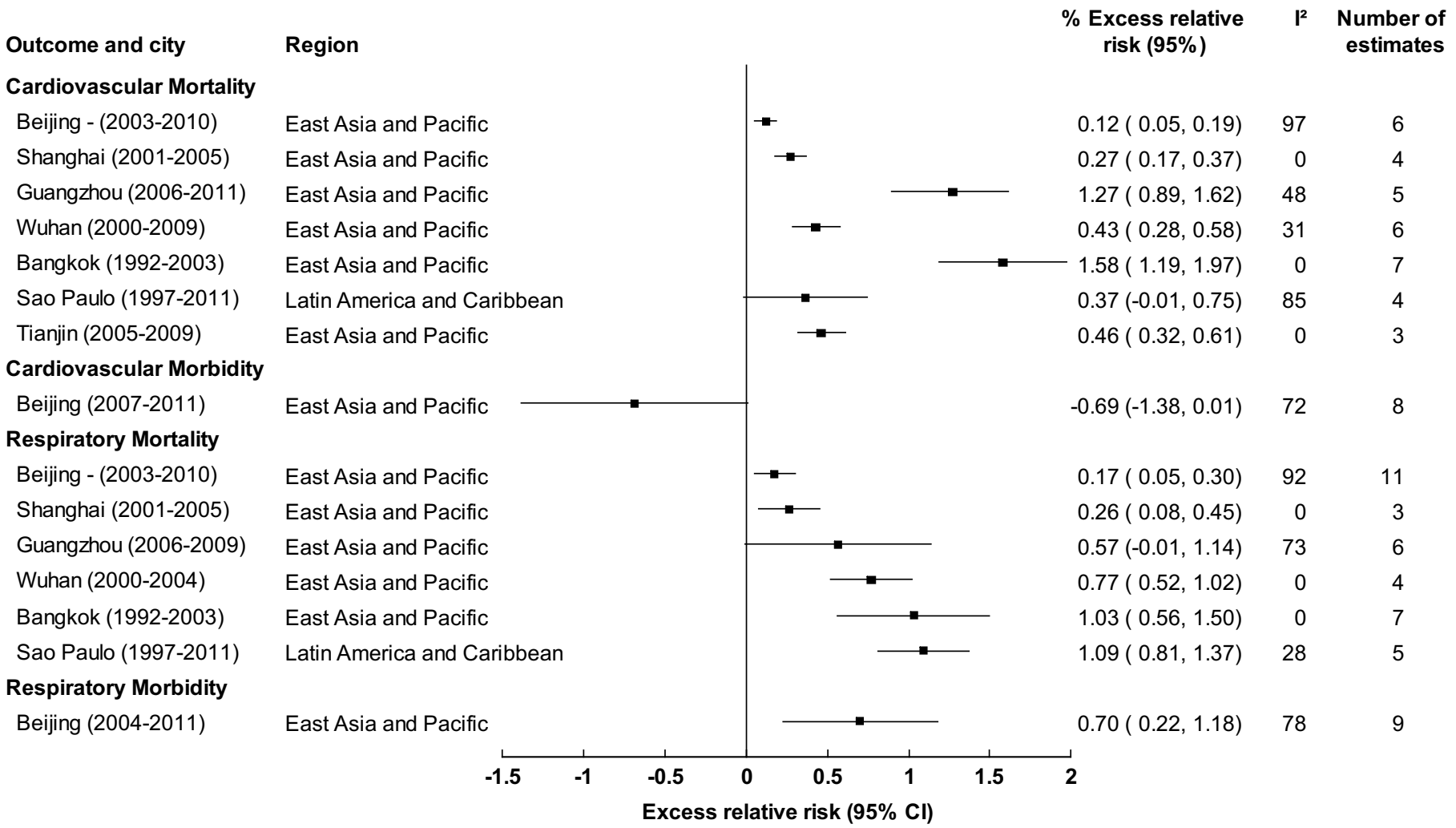
Abbreviations: PM_{10}, particulate matter <10 μm;
Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10 $\mu g/m^3$ increase in particulate matter ambient air pollution from pooled study estimates
I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

Figure 3.5 Pooled associations between $PM_{2.5}$ and cardio-respiratory mortality/morbidity stratified by city and respective study periods



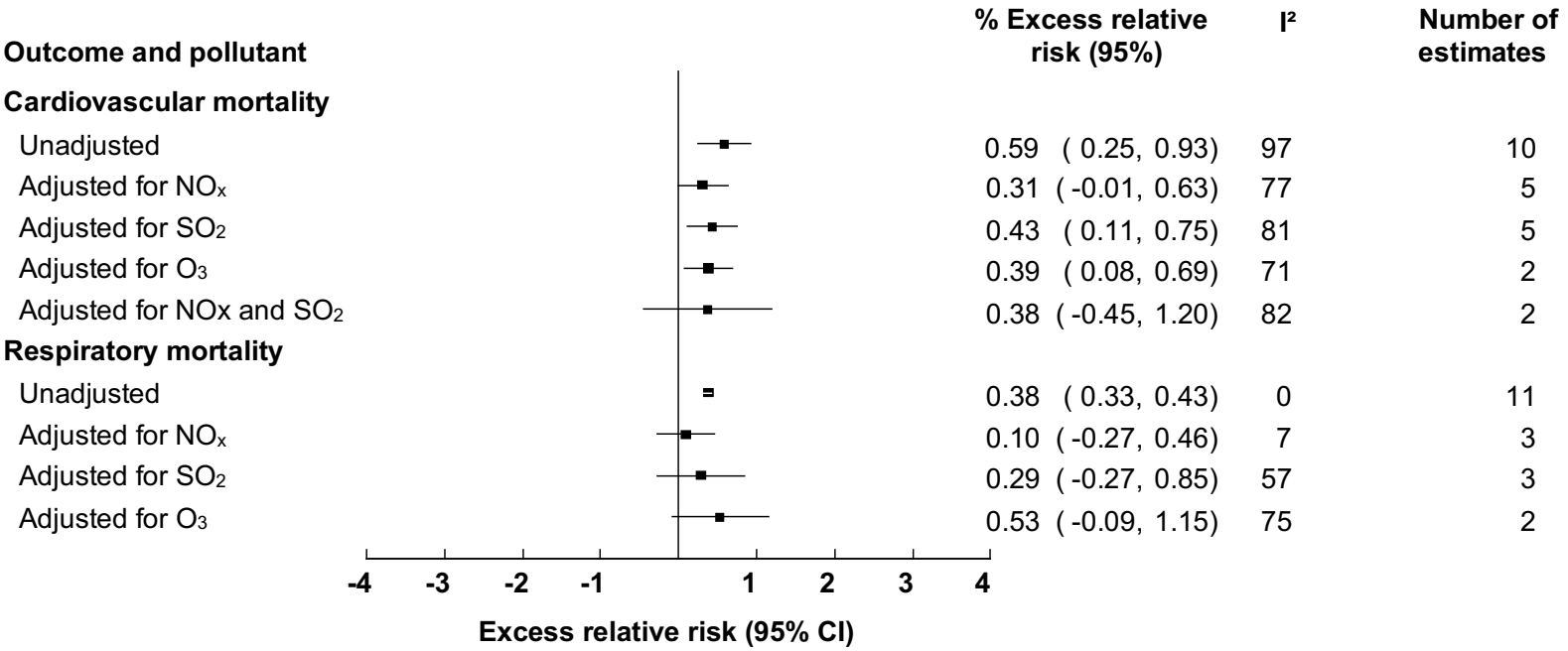
Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10 μg/m^3 increase in particulate matter ambient air pollution from pooled study estimates, pooled for lags 0-3 inclusively
I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

Figure 3.6 Pooled associations between PM_{10} and cardio-respiratory mortality/morbidity stratified by city and respective study periods



Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10 μg/m^3 increase in particulate matter ambient air pollution from pooled study estimates, pooled for lags 0-3 inclusively
I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

Figure 3.7 Pooled associations between PM_{10} and cardio-respiratory mortality/morbidity adjusted for additional pollutants

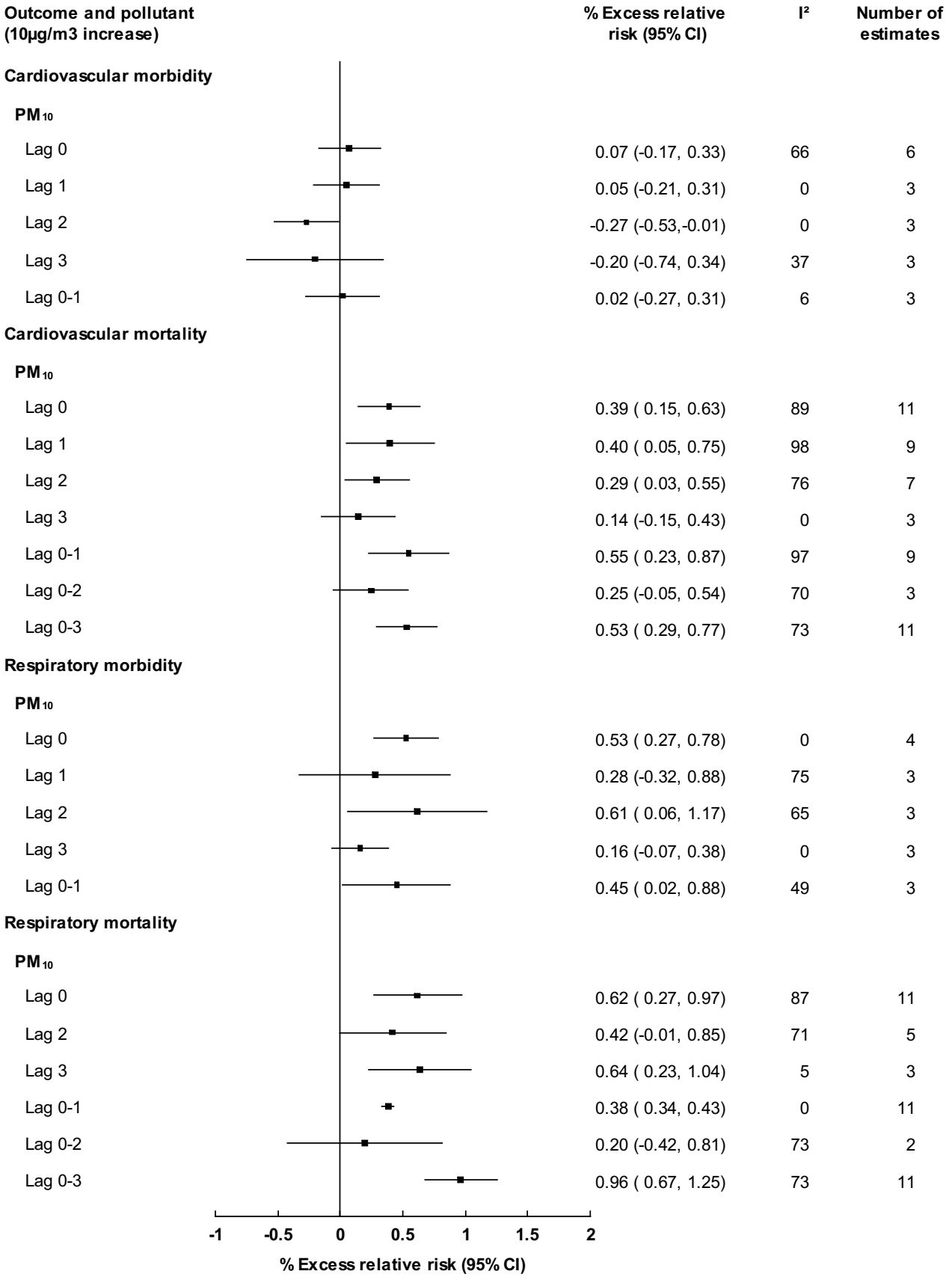


Abbreviations: NOx, nitrogen oxides; SO_2, sulphur dioxide; O_3, ozone

Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10 $\mu g/m^3$ increase in particulate matter ambient air pollution from pooled study estimates, pooled for lags 0-3 inclusively

I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

Figure 3.8 Pooled associations between PM_{10} and cardio-respiratory mortality/morbidity (with studies assigned high-risk of bias removed)

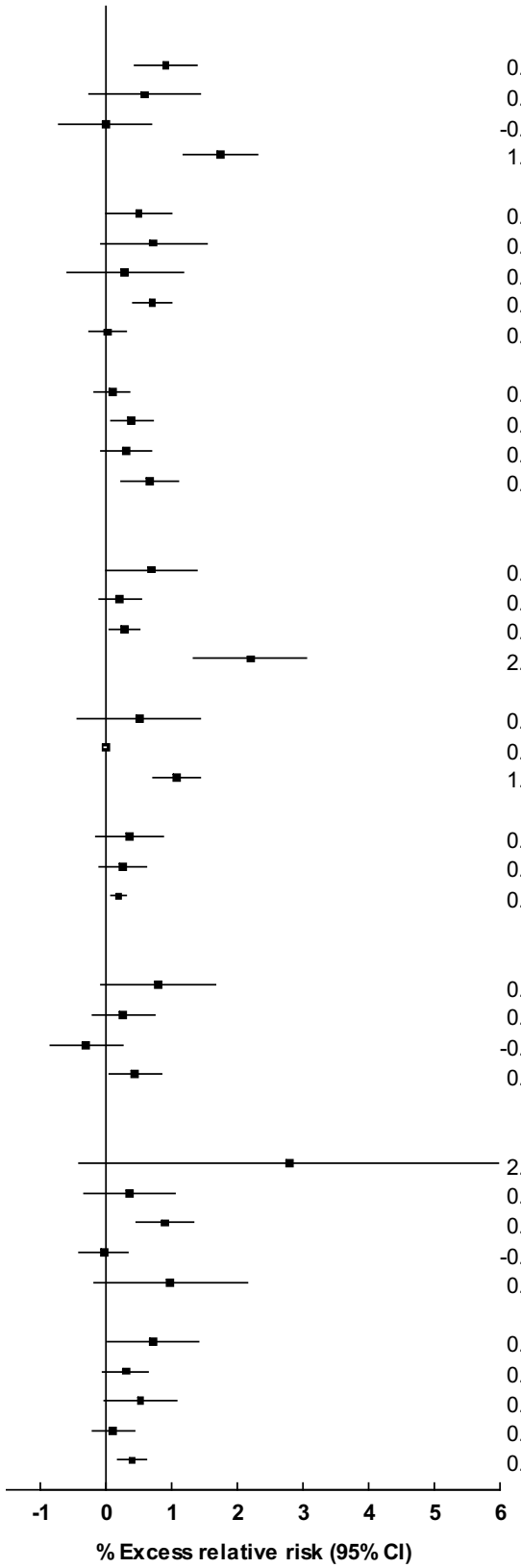


Abbreviations: PM_{10}, particulate matter <10µm; $PM_{2.5}$, particulate matter <2.5µm

Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10 $\mu g/m^3$ increase in particulate matter ambient air pollution from pooled study estimates

I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

Figure 3.9 Pooled associations between gaseous pollutant exposure and cardio-respiratory mortality/morbidity by outcome and lag time (days) in low-income and middle-income countries (LMICs)

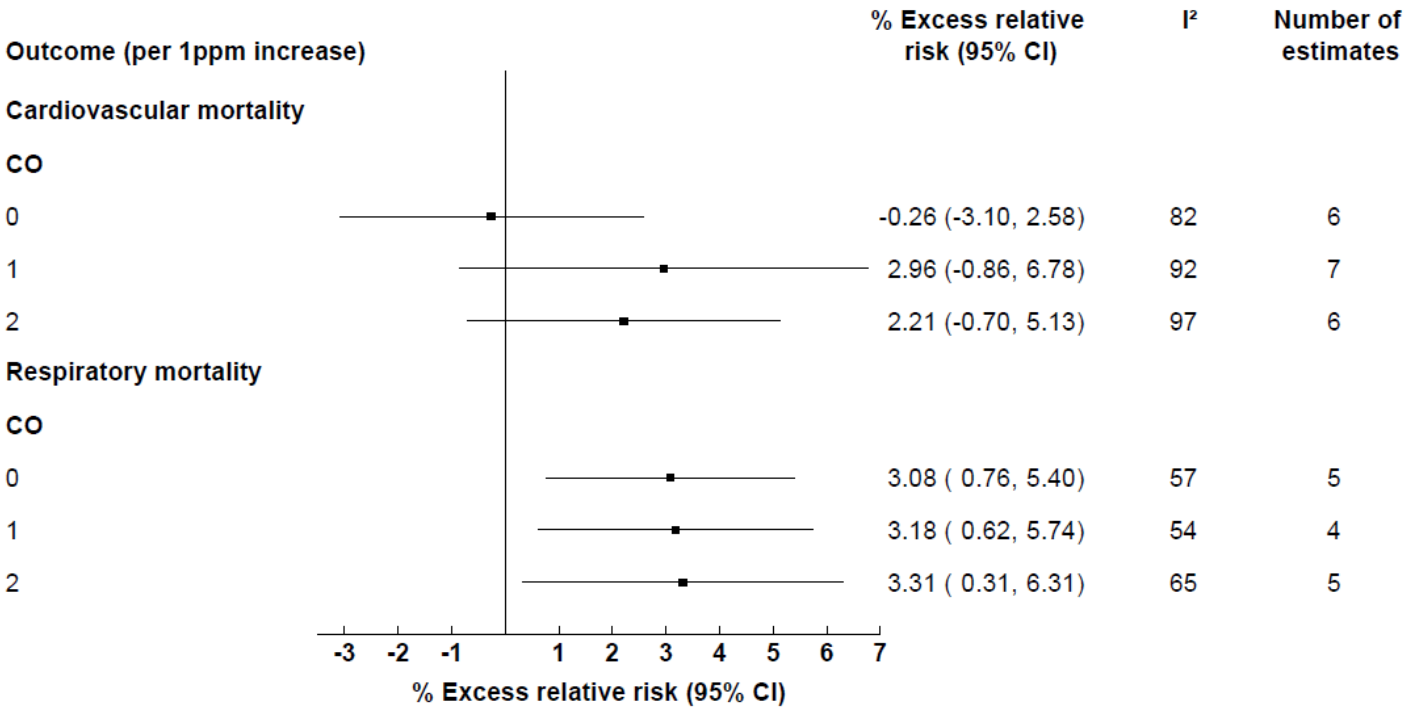


Outcome and pollutant ($10\ \mu g/m^3$ increase)	% Excess relative risk (95% CI)	I^2	Number of estimates
Cardiovascular mortality			
NO_x			
Lag 0	0.92 (0.44, 1.39)	83	8
Lag 1	0.59 (-0.26, 1.43)	87	5
Lag 2	-0.00 (-0.71, 0.70)	82	3
Lag 0-1	1.74 (1.19, 2.30)	86	18
SO_2			
Lag 0	0.50 (0.01, 1.00)	80	6
Lag 1	0.73 (-0.08, 1.55)	80	4
Lag 2	0.29 (-0.59, 1.17)	80	3
Lag 0-1	0.71 (0.41, 1.01)	87	18
Lag 0-2	0.04 (-0.24, 0.31)	8	2
O_3			
Lag 0	0.10 (-0.17, 0.37)	0	2
Lag 0-1	0.39 (0.07, 0.71)	52	5
Lag 0-3	0.32 (-0.06, 0.69)	96	7
Lag 1-2	0.67 (0.23, 1.11)	53	4
Respiratory mortality			
NO_x			
Lag 0	0.70 (0.01, 1.40)	82	7
Lag 1	0.22 (-0.10, 0.53)	44	6
Lag 2	0.29 (0.05, 0.52)	20	3
Lag 0-1	2.20 (1.34, 3.06)	78	17
SO_2			
Lag 0	0.51 (-0.43, 1.45)	62	4
Lag 1	0.00 (-0.01, 0.01)	0	3
Lag 0-1	1.09 (0.73, 1.44)	41	17
O_3			
Lag 0	0.36 (-0.16, 0.88)	0	2
Lag 0-1	0.26 (-0.09, 0.61)	0	6
Lag 0-3	0.19 (0.08, 0.31)	0	4
Cardiovascular morbidity			
NO_x			
Lag 0	0.79 (-0.08, 1.66)	51	5
Lag 1	0.27 (-0.21, 0.74)	35	4
Lag 2	-0.30 (-0.85, 0.25)	2	4
Lag 0-1	0.45 (0.05, 0.86)	0	4
Respiratory morbidity			
NO_x			
Lag 0	2.79 (-0.40, 5.98)	97	4
Lag 1	0.36 (-0.32, 1.04)	67	4
Lag 2	0.90 (0.46, 1.34)	16	3
Lag 3	-0.03 (-0.40, 0.34)	0	3
Lag 0-1	0.99 (-0.17, 2.15)	88	3
SO_2			
Lag 0	0.73 (0.04, 1.42)	80	4
Lag 1	0.30 (-0.03, 0.64)	37	5
Lag 2	0.53 (-0.01, 1.08)	61	4
Lag 3	0.11 (-0.21, 0.44)	4	4
Lag 0-1	0.40 (0.19, 0.61)	0	3

*Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10 $\mu g/m^3$ increase in particulate matter ambient air pollution from pooled study estimates

I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

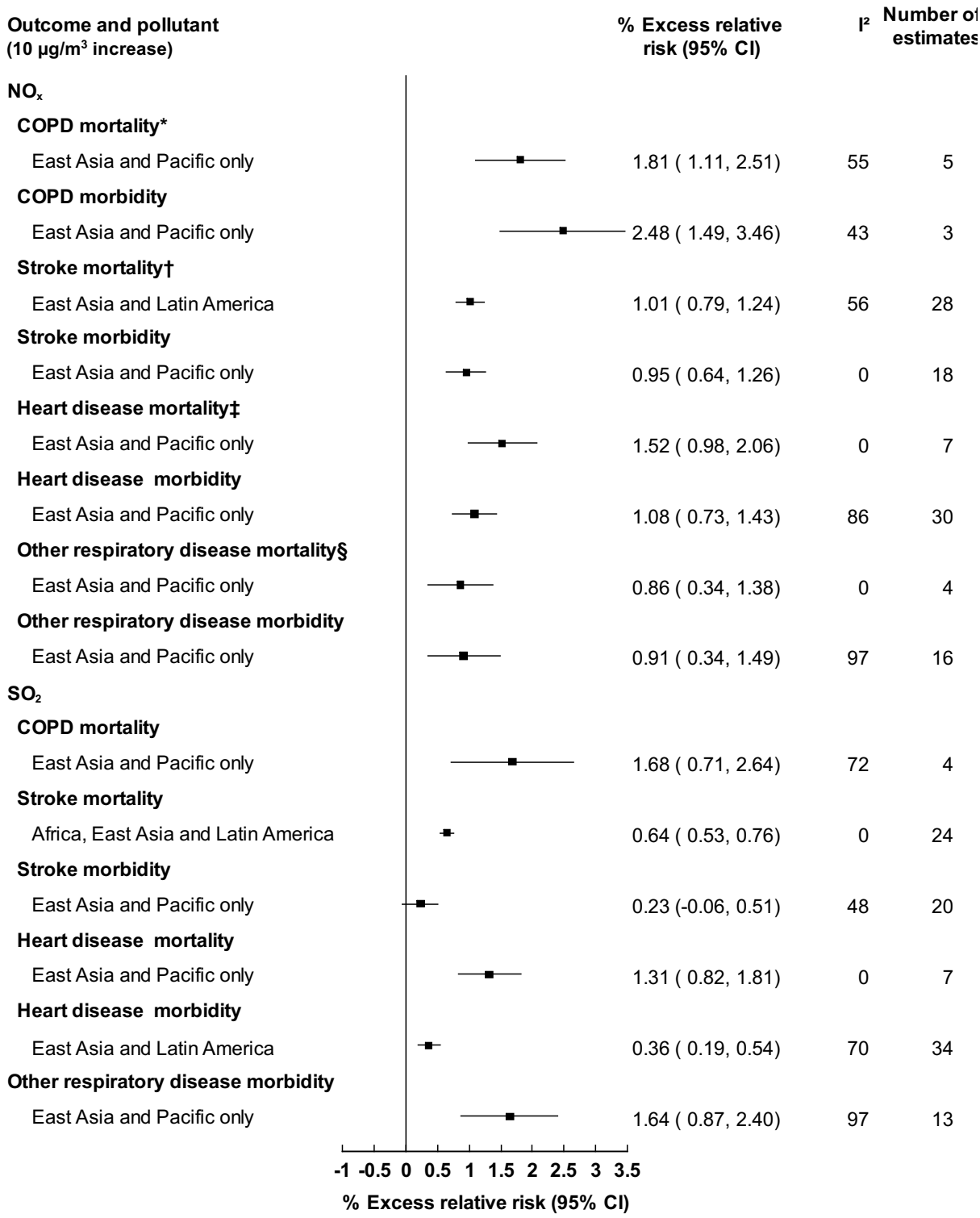
Figure 3.10 Pooled associations between carbon monoxide exposure and cardio-respiratory mortality/morbidity by outcome and lag time (days) in low-income and middle-income countries (LMICs)



*Estimates show percent excess relative risk of cardio-respiratory outcomes for a 1 parts-per million (ppm) increase in CO from pooled study estimates

I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

Figure 3.11 Pooled associations between gaseous pollutants and mortality/morbidity by specific disease outcomes in low- and middle-income countries (LMICs)



Abbreviations: NOx, nitrogen oxides; SO_2, sulphur dioxide; COPD, chronic obstructive pulmonary disease

Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10 µg/m^3 increase in particulate matter ambient air pollution from pooled study estimates, pooled for lags 0-3 inclusively

* International Classification of Disease 10th Edition (ICD-10) J41-J44

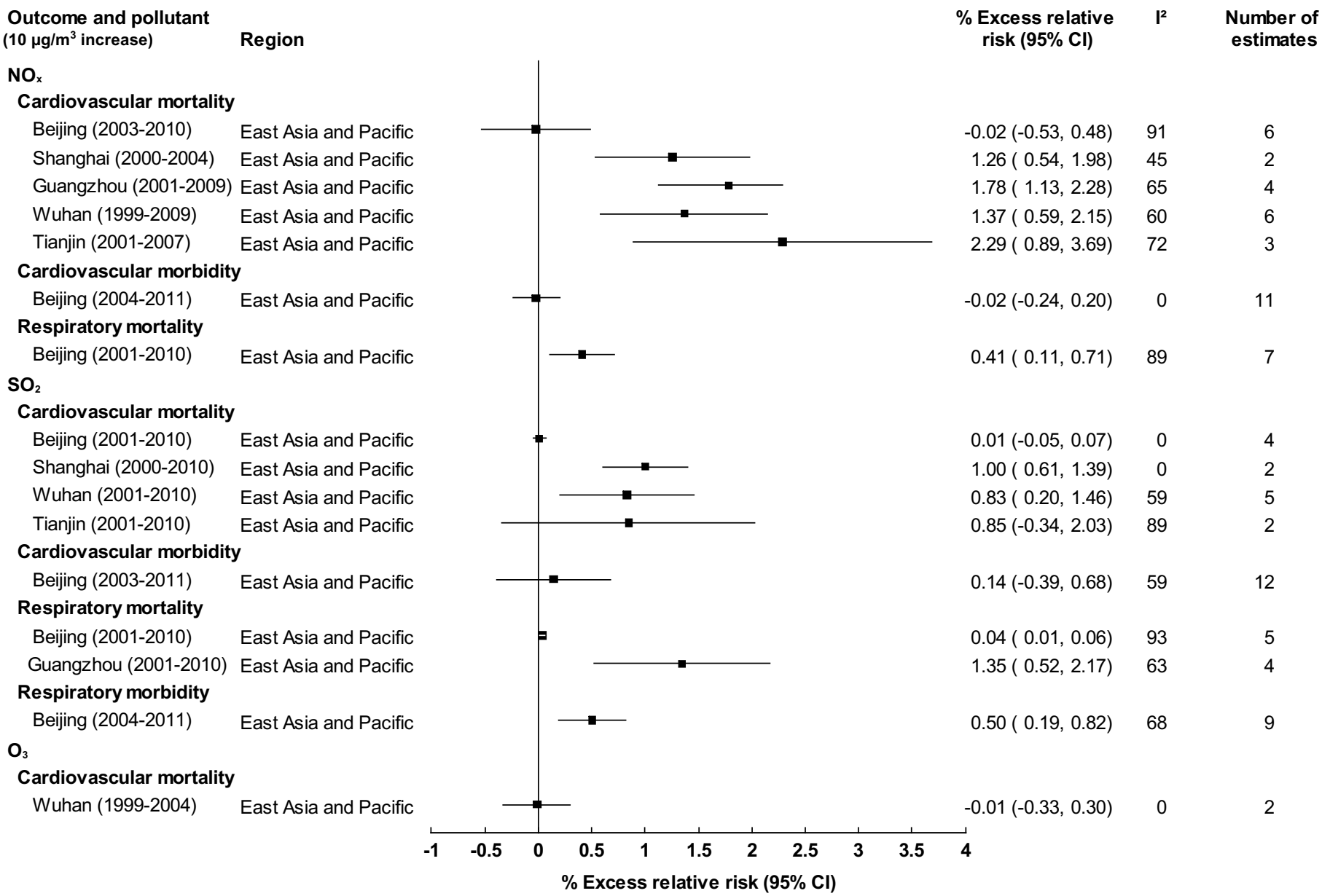
†ICD-10: I60-I69

‡ICD-10: I05-I52

§ICD-10: J00-J47

I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

Figure 3.12 Pooled associations between gaseous AAP and cardio-respiratory mortality/morbidity stratified by city and respective study periods

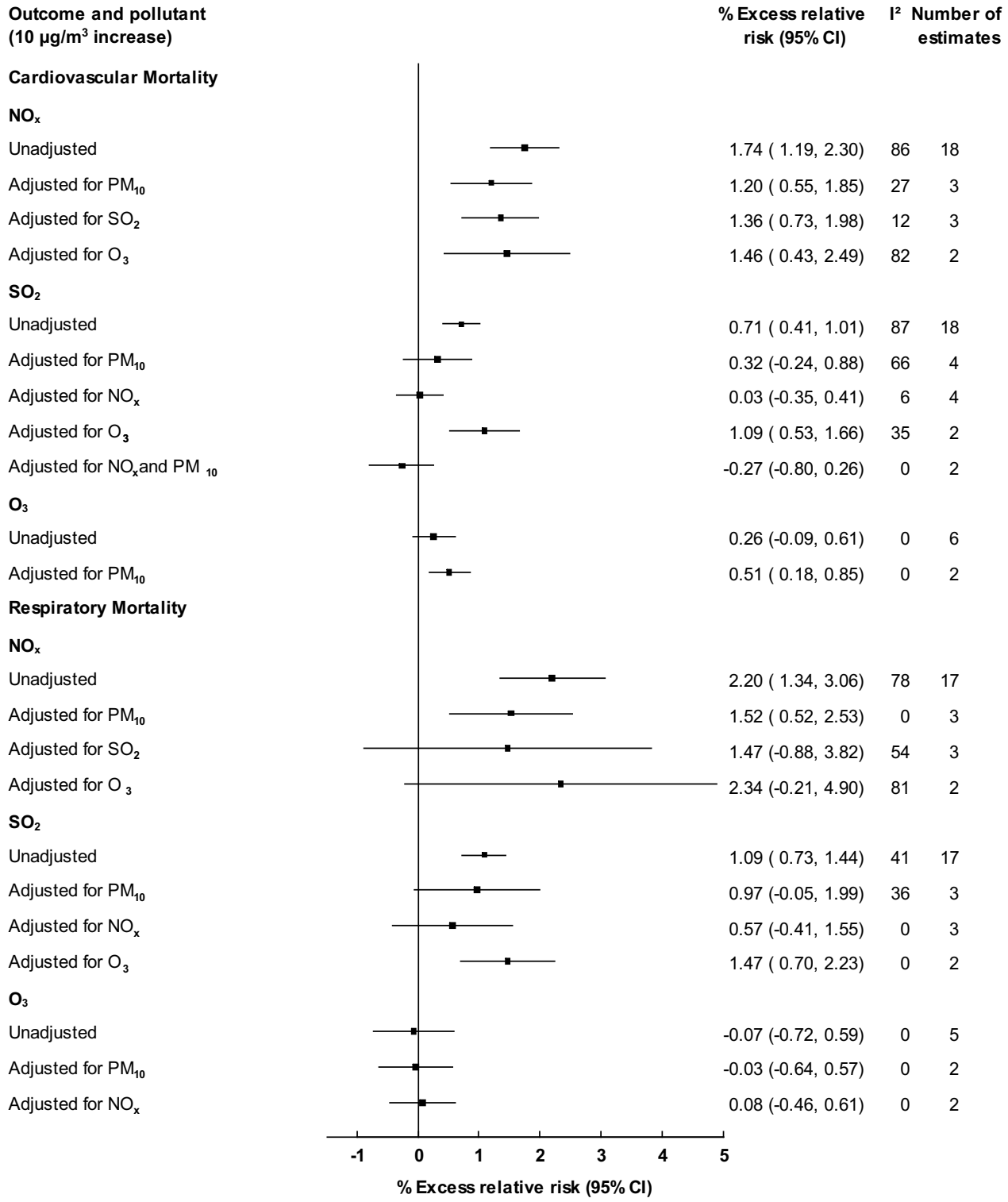


Abbreviations: NOx, nitrogen oxides; SO_2, sulphur dioxide; O_3, ozone

Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10 µg/m^3 increase in particulate matter ambient air pollution from pooled study estimates, pooled for lags 0-3 inclusively

I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

Figure 3.13 Pooled associations between gaseous AAP and cardio-respiratory mortality/morbidity adjusted for additional pollutants

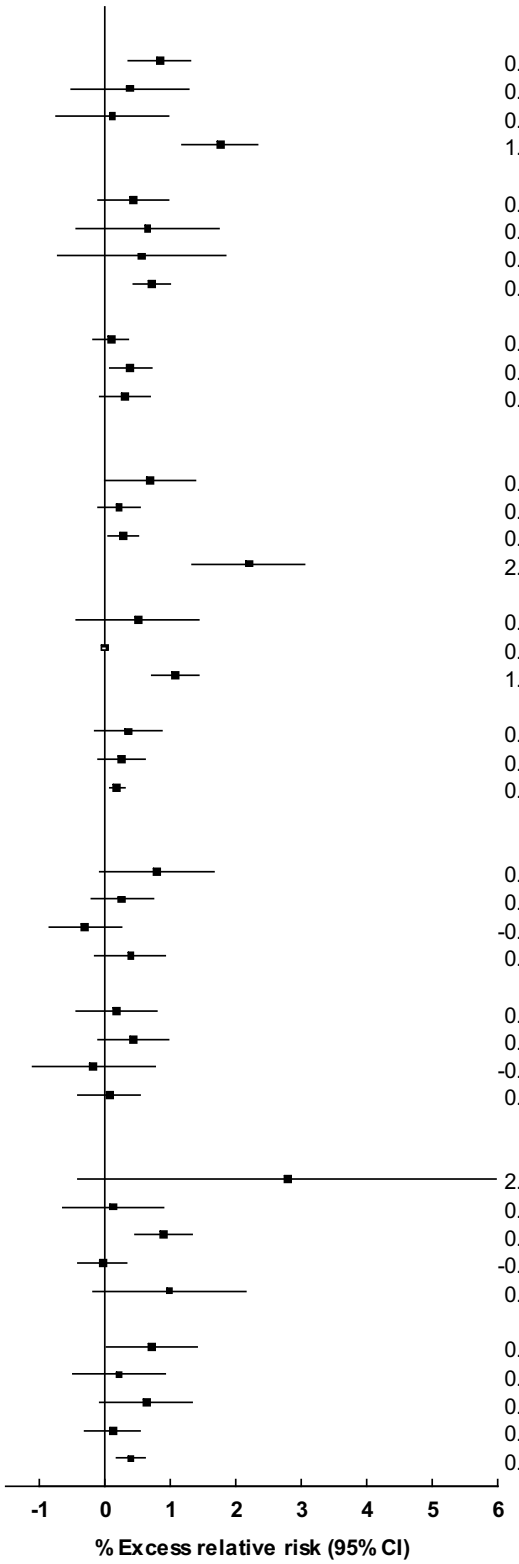


Abbreviations: NOx, nitrogen oxides; SO_2, sulphur dioxide; O_3, ozone; PM_{10}, particulate matter <10 µm

Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10 µg/m^3 increase gaseous AAP from pooled study estimates, pooled for lags 0-3 inclusively

I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

Figure 3.14 Pooled associations between gaseous AAP and cardio-respiratory mortality/morbidity (with studies assigned high-risk of bias removed)



Outcome and pollutant (10 µg/m³ increase)	% Excess relative risk (95% CI)	I²	Number of estimates
Cardiovascular mortality			
NO_x			
Lag 0	0.84 (0.36, 1.30)	84	7
Lag 1	0.39 (-0.51, 1.29)	89	4
Lag 2	0.12 (-0.74, 0.97)	91	2
Lag 0-1	1.78 (1.19, 2.34)	83	17
SO_2			
Lag 0	0.44 (-0.10, 0.98)	83	5
Lag 1	0.66 (-0.42, 1.74)	85	3
Lag 2	0.56 (-0.72, 1.84)	87	2
Lag 0-1	0.73 (0.45, 1.01)	75	17
O_3			
Lag 0	0.10 (-0.17, 0.37)	0	2
Lag 0-1	0.39 (0.07, 0.71)	52	5
Lag 0-3	0.32 (-0.06, 0.69)	96	6
Respiratory mortality			
NO_x			
Lag 0	0.70 (0.01, 1.40)	82	7
Lag 1	0.22 (-0.10, 0.53)	44	6
Lag 2	0.29 (0.05, 0.52)	20	3
Lag 0-1	2.20 (1.34, 3.06)	78	17
SO_2			
Lag 0	0.51 (-0.43, 1.45)	62	4
Lag 1	0.00 (-0.01, 0.01)	0	3
Lag 0-1	1.09 (0.73, 1.44)	41	17
O_3			
Lag 0	0.36 (-0.16, 0.88)	0	2
Lag 0-1	0.26 (-0.09, 0.61)	0	6
Lag 0-3	0.19 (0.08, 0.31)	0	4
Cardiovascular morbidity			
NO_x			
Lag 0	0.79 (-0.08, 1.66)	51	5
Lag 1	0.27 (-0.21, 0.74)	35	4
Lag 2	-0.30 (-0.85, 0.25)	2	4
Lag 0-1	0.40 (-0.15, 0.94)	0	3
SO_2			
Lag 0	0.18 (-0.43, 0.79)	70	6
Lag 1	0.44 (-0.10, 0.97)	24	4
Lag 2	-0.17 (-1.11, 0.77)	72	4
Lag 0-1	0.07 (-0.40, 0.55)	0	3
Respiratory morbidity			
NO_x			
Lag 0	2.79 (-0.40, 5.98)	97	4
Lag 1	0.14 (-0.64, 0.91)	66	3
Lag 2	0.90 (0.46, 1.34)	16	3
Lag 3	-0.03 (-0.40, 0.34)	0	3
Lag 0-1	0.99 (-0.17, 2.15)	88	3
SO_2			
Lag 0	0.73 (0.04, 1.42)	80	4
Lag 1	0.22 (-0.48, 0.92)	70	3
Lag 2	0.64 (-0.06, 1.33)	68	3
Lag 3	0.13 (-0.30, 0.55)	28	3
Lag 0-1	0.40 (0.19, 0.61)	0	3

*Estimates show percent excess relative risk of cardio-respiratory outcomes for a 10 µg/m³ increase in gaseous ambient air pollution from pooled study estimates

I^2 = percentage of variance in meta-analysis attributable to heterogeneity across studies

CHAPTER 4. THE CHINA KADOORIE BIOBANK STUDY

4.1. Background

The China Kadoorie Biobank (CKB), a collaboration between the Clinical Trials Service Unit and Epidemiological Studies Unit (CTSU) of Oxford University and the Chinese Academy of Medical Sciences, was set up with the principal aim of examining the aetiology of major chronic non-communicable diseases (NCDs) in China. While in Western countries mortality from common chronic diseases such as ischaemic heart disease (IHD), stroke and cancer is declining, in China the rapid epidemiological transition from infectious to NCDs coupled with the increasing prevalence of established risk factors including high rates of male smoking, decreased physical activity and changing diets has resulted in an increase in chronic NCDs with the disease burden anticipated to rise further. [247, 248] Although several prospective studies have been performed in China to examine the associations between various risk factors and outcomes, these are smaller, and are often restricted to the collection of data on specific outcomes and exposures [249, 250] and typically in study populations more restricted by geography [231, 251-253] or sex.[231]

CKB remains one of the largest prospective cohort studies in China to date, examining environmental, lifestyle, and genetic risk factors for disease. Located across ten diverse regions of China, CKB has a study population of ~0.5 million, a sample size potentially sufficient to detect even modest associations between relevant potential risk factors and disease. This makes it a particularly advantageous resource for studying AAP given the considerable uncertainty surrounding current risk estimates. Furthermore, the diversity of the CKB study population, availability of a wide range of individual-level covariates (both at baseline and at subsequent resurveys), and retrieval of extensive follow-up data, mean that CKB can effectively explore the interplay between environmental, lifestyle and genetic exposures.

4.2. Study design

CKB is a prospective study established in 2004 with just over 0.5 million males and females, collectively. Ten regions were selected to make up the study (**Figure 3.1**), five urban and five rural. These regions were selected to include diverse risk factors and diseases, but not to be representative of China as a whole. Regions were selected based on local disease patterns (for example the oesophageal cancer belt), exposure to certain risk factors, population stability, quality of death and disease registries, and local commitment and capacities of the region.

A multi-stage clustered random sampling scheme was employed, and within each region 100-150 administrative units (rural villages or urban residential communities) were selected for inclusion. Potential participants aged 35-74 years were identified via official residential records and invited to the survey. The final age range was then widened to 30-79 years to allow inclusion of survey respondents slightly outside the target age range. The whole process was coordinated by a team of medically trained staff from regional coordinating centres (RCCs). Ethics approval was obtained from Oxford University and Chinese Centre for Disease Control and Prevention (CDC) with further approvals from institutional research boards of local CDCs in each of the ten CKB regions.

The CKB study was designed to minimise selection bias limiting participation to the study by only age at baseline and ability to consent. However, as recently highlighted in the epidemiological literature and exemplified in similarly large prospective cohort studies (UK Biobank), biases from selection into a study, as well as attrition from a study, can lead to considerable differences between the study population and general population as a whole. [254] Although as mentioned, CKB was not designed to be nationally representative, recent epidemiological literature has also highlighted how such selection can induce collider bias introducing potentially spurious associations non-existent in the general population. [255] In this case, associations between an exposure and outcome may be equivalent to conditioning on those variables that led to participation in the study. Although unlikely to

affect the findings of this thesis given AAP exposure is unlikely to affect study participation, it remains an important consideration when using large observational studies. [255]

4.3. Baseline survey

Eligible participants were asked to bring national identity (ID) cards to the study assessment centre set up in their respective administrative units. Following participant registration and provision of informed consent to allow access to medical records and long-term blood storage, participants undertook interviewer-administered electronic questionnaires with duration of approximately 60-75 minutes. A total of 354 local staff took part in conducting the survey with 201 involved in baseline data collection. Extensive training was provided on data collection, use of the electronic questionnaire, the standard protocols involved for physical measurements, and on the use and maintenance of study equipment. All equipment underwent prior testing in a pilot study and was supplied centrally for all ten regions.

The administered questionnaires covered 10 sections collating information on general demographic characteristics; socioeconomic status; dietary and lifestyle habits (such as smoking, physical activity, and alcohol intake), exposure to smoking and household air pollution, personal and familial medical history (including current medication intake), sleep and mental status (via Composite International Diagnostic Inventory-short form [CIDI-SF]), and reproductive health, for females

Physical measurements were obtained including height, weight, hip and waist circumferences, bio-impedance, lung function (FEV_1, FVC), exhaled carbon monoxide, blood pressure and pulse rate using calibrated instruments with standard protocols. 10ml non-fasting venous blood samples were also obtained transferred on ice to a short-term storage facility before shipment to Beijing and Oxford for long-term storage. Certain biomarkers of inflammation, such as fibrinogen, interleukin-6 (IL-6), and C-reactive protein (CRP) have been collected, but only in a small subset of participants; thus blood-based biomarkers were not considered for use in this thesis.

All baseline surveys were completed in all ten regions by July 2008.

4.4. Quality control

Quality control included the use of regular central monitoring to assess recruitment rates, distribution of certain key variables, time delay with blood processing and consistency of data collected. Each member of staff involved in the survey across the ten regions received training on conducting the baseline survey, communication skills, practical use of study instruments, and the scientific rationale behind the study. Staff also received unique study identification numbers entered into study computers before data entry, allowing their entries to be identified and monitored by RCC staff if required. On-site monitoring was also performed with 6-monthly visits from the provincial CDC staff, and annual visits from both Beijing and Oxford staff.

4.5. Resurvey

Following the completion of baseline surveys, two resurveys, have been performed in 2008 and 2013-2014 in a subset of all surviving participants across all ten study regions, with 19,760 (response rate = 79.8%) and 24,996 (75.6%), participating, respectively. Of all CKB participants, 14,857 have participated in all three surveys. Resurveys collect the same data as at baseline as well as additional data to enhance and calibrate baseline data and to enable investigation into temporal trends in risk factor exposure.

4.6. Follow-up

Surviving CKB study participants are actively followed up for cause-specific mortality and morbidity using established surveillance systems. For incidence of stroke, IHD, diabetes and cancer, collection of data is performed via linkage with established disease registries in eight of the ten regions (Harbin, Suzhou, Liuzhou, Sichuan, Gansu, Henan, Zhejiang and Hunan). Further follow-up for incident cases of these diseases, plus for all additional causes of hospital admissions is done via health insurance (HI) claim databases which cover ~98% of

participants and are fully established in all ten regions, electronically linked to participants via their unique national ID.

For mortality cases, causes of death are obtained from China's Disease Surveillance Points (DSP) system, established by the Chinese government in the 1980s as part of their disease surveillance system to formulate health policies and strategies for preventing disease. Following its merge with the vital registration system in 2013 the DSP network provides a mortality surveillance system for the entire country. Following a participant's death, the death certificate is obtained by the regional CDC (where the RCC office is based) and coded (using ICD-10) by trained staff blinded to participant baseline information. A sample of death certificates is also cross-checked by CKB clinical staff, and if required, these are supplemented by reviewing participant medical records. For deaths not identified via this routine procedure, such as deaths without prior medical attention (<5%), causes of death are sought by reviewing hospital records or conducting verbal autopsies via a validated instrument before being sent to the regional CDC. Further validation is also undertaken by clinicians in the CKB National or International coordinating centres for stroke, IHD, COPD, cancer, and diabetes cases. This involves the uploading of medical records retrieved by regional CDCs to a secure study server and clinicians (blinded to participant baseline and resurvey information) reviewing and confirming or updating the recorded information.

For each CKB region, vital status of study participants is also monitored using official residential records enabling identification of participants lost to follow-up, for example those participants who have permanently moved out of the area.

4.7 Definitions and categorisation of baseline variables

Each participant's education level was categorised according to the highest level of education received; no formal education, primary school, middle school, high school, or further education (technical college or university).

Physical activity levels were expressed as metabolic equivalent of task (MET) hours/day, on average over the last year by each participant. MET values for each activity represent the ratio of energy expended per kilogram of body weight per hour during the activity to that expended when sitting quietly. Intensity and duration of different physical activities are combined into a single measure [256] with corresponding MET values assigned to each physical activity then multiplied by the hours per day the activity was performed. Each participant's total MET-hours per day reflect the sum of MET-hours per day for all activities combined, not including those from sedentary leisure time activities which are classified separately.

Participants' alcohol consumption was classified according to the frequency of usual consumption over the last year categorised as never/rarely, occasional, monthly or at least weekly. Those who drank alcohol at least weekly were further categorised according to the quantity of alcohol they reported consuming in a 'typical' week. Participants were also asked about their alcohol consumption before the last year: those who had drunk alcohol 'at least weekly' in the past but not over the last year were categorised as 'ex-weekly' drinkers; those who drank at least weekly over the last year who reported that their alcohol consumption had 'decreased a lot' compared with some years ago were classified as 'reduced- intake' drinkers. For this thesis, alcohol consumption was categorised as never, occasional, ex-regular/reduced and current regular.

For active smoking, participants were categorised as current smokers, never smokers, occasional smokers or ex-regular smokers. Passive smoking was defined as having lived with a smoker in the same house for at least six months, and was categorised as never, yes but not now or yes at present.

Regarding use of solid fuel, participants were asked to provide details on household air pollution exposure relating to cooking frequency, heating use and cookstove ventilation for up to their last three most recent residences in addition to the duration in each residence. For this thesis, solid fuel use was classified as the use of coal, or wood/charcoal for cooking

in participants who reported cooking on at least a monthly basis. For its use as an adjustment variable, household air pollution was derived from reported household solid fuel use (coal and biomass) and was classified from reported frequency and type of fuel used for cooking, the details of which can be found elsewhere.[257] In brief, participants who reported cooking at least on a monthly basis and who used heating in winter were asked subsequent questions on type of fuel use including: gas, electricity, coal, wood/charcoal, and other unspecified fuels, plus "central heating" if more than one was used only the most frequently used was recorded. Participants who cooked less than monthly were considered as non-cooking, and those who cooked weekly or more were further classified into two groups according to the primary cooking fuel (solid fuels versus clean fuels) used in the baseline residence. Similarly, those who used heating were categorised into two groups according to the primary heating fuel used. To approximate chronic exposure, the duration of continuous exposure to solid fuel for cooking or heating was calculated separately by aggregating the duration lived in consecutive residences during which solid fuels were primarily used. This resulted in the following categories of exposure; always clean fuels, switched from solid to clean fuels, always solid fuels, never cooked regularly and others (those with problematic recall information).

Self-reported disease history was in answer to the question "Has a doctor ever told you that you had the following disease?" and for this thesis included, ischaemic heart disease, hypertension, diabetes, stroke or transient ischaemic attack, emphysema/bronchitis, cancer, and tuberculosis.

Self-rated health was categorised by responses to the question, "how is your current general health status; excellent, good, fair or poor?" Family history of both stroke and myocardial infarction respectively was derived from each parent's disease history self-reported by participants. For this thesis participants were classified as having a family history of disease if they reported any prevalence of the respective disease in either their father and/or mother. Cardio-respiratory symptoms were self-reported at baseline, and for the purpose of this

thesis included, breathlessness, chest pain and chronic cough. Breathlessness and chest pain were classified using responses to the question if "you were walking on level ground with other people of the same age would you usually", "become short of breath", and "slow down due to chest discomfort" for breathlessness and chest pain, respectively. Chronic cough was defined as frequent coughing for ≥3 months during the past 12 months.

For physical measurements, body mass index (BMI) was calculated by dividing weight in kilograms by the square function of height in metres. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated as the mean of two recorded baseline measurements from frequently calibrated devices used on participants following five minutes rest. Lung function variables included forced expiratory volume (FEV_1) and forced vital capacity (FVC). These required each participant performing at least two successful forced expiratory manoeuvres instructed by a trained physician at baseline without a bronchodilator. To define airflow obstruction at baseline, the FEV_1: FVC ratio less than the lower limit of normal (LLN) was calculated using the Global Lung Initiative for East-Asians.[258]

For dietary variables baseline questionnaire asked participants their frequency of typical consumption over the previous year. Consumption of fresh fruit and vegetables were categorised as never/rarely, monthly, 1-3 days a week, 4-6 days per week. As 96.6% of participants reported daily consumption of fresh vegetables, consumption of preserved vegetables was instead used in this thesis, for which there was greater variability in consumption (26.4%, 5.9%, 22.8%, 24.2%, 20.8%, for daily, 4-6 days per week, 1-3 days per week, monthly and never/rarely, respectively).

4.8 Baseline characteristics of CKB study participants

A total of 512,891 participants were recruited to the study aged between 30-79 years (mean age, [standard deviation (SD) 51.5 [10.7] years) (**Table 4.1**), with more females relative to males in the cohort, 302,632 (59.0%), versus 210,259 (41.0%), respectively (CKB data release version 15). A slightly greater proportion of participants were from rural (55.9%)

regions compared to urban (44.1%). Participant numbers were also not evenly spread across the ten regions ranging from 29,689 (Haikou) to 63,357 (Henan). Regarding socio-demographic characteristics, only 21.0% of the study population were educated to at least high-school level, with a greater proportion in males (26.1%, versus 17.6% in females), and over half the population had an annual household income of less than 20,000 Yuan. The study population reported mean (SD) physical daily activity levels relating to household and leisure time, occupation, and commuting equivalent to 21.1 (13.9) metabolic equivalence of task (MET) hours per day.

There were substantial contrasts in the prevalence of active smoking by sex, with age and area-adjusted prevalence of current smoking 61.3% in males compared to only 2.4% in females. There were also large differences in alcohol consumption by sex, with males reporting much higher alcohol consumption, 33.1% of males reporting weekly alcohol drinking versus just 2.1% of females ($p<0.001$).

Less than half of the study population self-reported their current health as either “excellent” (17.6%) or “good” (28.1%), with a greater proportion of females self-reporting “poor” health relative to males (11.5%, versus 8.8%, respectively [$p<0.001$]). For the prevalence of self-reported health conditions, 11.6% of the population reported hypertension, 1.7% stroke or transient ischaemic attack (TIA), and 3% CHD. 3% of the population also reported prevalence of emphysema/bronchitis compared to only 0.5% for asthma. 16.4% of participants had reported family history of stroke and/or TIA, defined as self-reported prevalence of stroke and/or TIA in either their father and/or mother. Far fewer had such a family history of MI (2.8%). For prevalence of cardio-respiratory symptoms at baseline, 5.9% of the population reported feeling “short of breath when walking on level ground” with a greater proportion of these being females than males (6.9% versus 4.5% [$p<0.001$]). Significantly more females (3.8%) also reported prevalence of chest pain when walking on level ground than in males (2.4%) ($p<0.001$). However, males had higher prevalence of

chronic cough ≥ 3 months in duration than females (2.4 versus 3.8%, respectively [p<0.001]).

For physical measurements in the study population, mean BMI was 23.7 kg/m^2 (SD, 3.4), (23.5 kg/m^2 and 23.8 kg/m^2 in males and females, respectively, p<0.001) (**Table 4.2**). Mean (SD) systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the study population was 131.1 mmHg (21.3), and 77.8 mmHg (21.3), respectively. Regarding lung function, males had both higher mean FEV_1, and FVC measurements compared to females (2.61 litres [L] versus 1.91L, for FEV_1 and 3.10 L, versus 2.26 L, for FVC in males, versus females, respectively). However, a larger proportion of males had FEV1:FVC<0.70% (6.3% and 4.6%, for males and females, respectively, [p<0.001]) as well as greater proportions on FEV1:FVC< lower limit of normal (7.2% and 6.5%, in males and females, respectively, [p<0.001]).

4.9 Baseline characteristics of urban CKB study participants

Only participants from the urban CKB regions (Harbin, Qingdao, Liuzhou, Suzhou and Haikou) are included in this thesis. This is due to no data on AAP being available for the rural regions. 226,181 participants (mean age, [standard deviation (SD) 52.3 [10.9] years) were located across the five urban regions with numbers per region ranging from 29,687 (Haikou) to 57,555 (Harbin). Examining just the urban regions, a greater difference in the proportion of males versus females was observed than in the CKB population as a whole (40.4% males, 59.6% females, p<0.001) (**Table 4.3**). Over half of the population had an annual household income level of ≥20,000 Yuan (57.1%), and 35.8% of the population had an education level to at least high school. The proportion of males reaching this level was greater than in females (41.5% and 32.0%, respectively p<0.001). Mean (SD) reported MET-hours per day in urban CKB participants was 18.5 (12.6) and was higher in females (mean [SD] 19.30 [8.0]) than males (17.90 [5.9]) (p<0.001).

Again, there was a significant difference in the prevalence of active smoking by sex, with 54.9% of males reporting as regular smokers versus just 2.1% of females (p<0.001). However, females reported significantly higher prevalence of current exposure to passive smoking, compared to males (52.1% versus 13.5%, respectively, p<0.001). Regular alcohol consumption (defined as weekly alcohol drinking) was common in males (38.0%) but not females (2.1%).

Regarding self-reported health, 22.6% of the urban CKB population quantified their current health as “excellent”, and 23.4% as “good”. As in the entire CKB population, hypertension was the most commonly reported doctor-diagnosed chronic health condition, present in 13.8% of the population. Prevalence of other chronic conditions were lower (2.3%, 4.7%, 4.7%, 2.6%, and 0.8% for stroke, CHD, diabetes, emphysema/chronic bronchitis, and asthma, respectively). 18% of the urban population had family history of stroke/TIA and only 3.8% family history of MI. As also seen in the entire CKB population greater proportions of females in the urban CKB population reported being short of breath and experiencing chest pain when walking on level ground (5.0% and 3.1%, respectively), compared to males (3.3% and 2.0%, respectively) (p<0.001). However, males had a higher prevalence of chronic cough lasting ≥3 months in duration (4.5%, 1.9%, in males, and females, respectively, p<0.001).

In terms of physical measurements, the urban CKB population appeared to be less lean than the whole CKB population with 39% of urban participants having a BMI of ≥25.0 versus 32% in the whole CKB population. Males had significantly greater mean SBP and DBP (132.0 mmHg versus 127.5mmHG for SBP, and 79.5mmHg versus 75.8mmHG for DBP, in males and females, respectively) (**Table 3.4**). 3.9% of the population had an FEV_1: FVC<0.70%, and 4.9% FEV_1:FVC<lower limit of normal.

4.10 Summary

The CKB is one of the world’s largest prospective cohort studies and a valuable resource in both the detection of new and quantification of established risk factors for disease. The large

sample size, which is considerably greater than the previously described Chinese cohort studies which examined AAP, makes it particularly advantageous to examine relationships between AAP exposure and subsequent cardio-respiratory health effects with risk estimates that are typically modest. In addition to this, the availability of rich baseline data, and established cause-specific follow-up makes it possible to address numerous potential confounders and also examine a varied range of cause-specific disease, both incidence and mortality.

This chapter has presented the CKB study rationale, study procedures, survey implementation (both baseline and resurvey), and follow-up procedures used. It then presented the total and sex-specific distributions of socio-demographic and lifestyle factors, physical measurements and health-related characteristics in the population. The following chapter will examine the associations between acute AAP exposure and cardio-respiratory disease incidence in the five CKB urban regions

Table 4.1 Baseline characteristics in all CKB study participants by sex

Characteristic*	Males % (n=210,259)	Females % (n=302,632)	Total (n=512,891)
Age (years)†, %			
30-39	14.1	15.9	15.2
40-49	28.0	31.0	29.8
50-59	30.3	31.0	30.7
≥60	27.6	22.1	24.3
Mean ± SD	52.4 (10.9)	51.0 (10.5)	51.5 (10.7)
Education level, %			
No formal school	8.4	26.0	18.6
Primary school	32.4	31.7	32.2
Middle school	33.1	24.8	28.3
High school	18.0	13.2	15.1
College/ University	8.1	4.4	5.9
Annual household income (Yuan), %			
<10,000	26.0	29.7	28.2
10,000-19,000	28.4	29.5	29.1
20,000-34,999	25.2	24.3	24.7
≥35,000	20.3	16.4	18.0
Smoking category, %			
Never smoker	14.4	94.8	61.9
Occasional smoker	11.4	1.8	5.7
Ex-regular smoker	12.9	0.9	6.0
Smoker	61.3	2.4	26.4
Age started smoking, %			
<20	55.7	24.7	17.6
20-24	24.1	14.1	7.6
25-29	11.3	18.6	3.8
30-34	2.3	8.0	0.8
≥35	6.6	34.4	2.6
Passive smoking, %			
Never	36.1	16.4	24.5
Yes, but not now	42.6	23.9	31.3
Yes, at present	21.3	59.7	44.2
Physical activity (MET-hrs) ‡			
Mean ± SD	22.3 (15.3)	20.2 (12.8)	21.1 (13.9)
Alcohol consumption, %			
Never	20.0	63.6	45.9
Occasional/Ex-regular	35.5	32.5	33.6
Monthly	6.3	1.4	3.4
Reduced	4.9	0.4	2.3
Weekly	33.4	2.1	14.9
Self-rated health, %			
Excellent	20.2	15.9	17.6
Good	29.3	27.3	28.1
Fair	41.7	45.4	43.9
Poor	8.8	11.5	10.4
Household air pollution exposure, %			
Currently use wood/coal	49.2	51.6	36.1
Previously used wood/coal	71.1	75.4	44.5
Cooking frequency, %			
Daily	22.2	84.1	58.7
Weekly	17.4	7.8	11.8
Monthly	7.1	1.7	3.9
Never/Rarely	53.3	6.3	25.6
Self-reported health conditions§, %			
Hypertension	10.8	12.3	11.6
Stroke	2.2	1.4	1.7
Diabetes	2.9	3.4	3.2
TB	2.0	1.2	1.5
CHD	2.6	3.3	3.0
Asthma	0.6	0.5	0.5
Emphysema/Bronchitis	3.0	2.3	2.6
Family history of disease ¶, %			
Stroke	16.6	16.3	16.4
Myocardial infarction	2.8	2.8	2.8
Cardio-respiratory symptoms**, %			
Breathlessness	4.5	6.9	5.9
Chronic cough	5.8	2.5	3.8
Chest pain	2.4	3.8	3.2

* Means and percentages were standardised to the age and region area structure of the CKB population, where appropriate; †Adjusted for region only; ‡ MET-hrs, metabolic equivalent task hours/day; § TB: Tuberculosis, CHD: Coronary heart disease; ¶ Family history defined as baseline reported disease prevalence in mother and/or father; **Breathlessness defined as being short of breath when "walking on level ground with health people of the same age", chronic cough defined as "coughing frequently for ≥ 3 months" Two-sided p values were derived from Student's t test for continuous variables and X^2 test for categorical variables. All P values <0.05 except family history of MI (p=0.62)

Table 4.2 Baseline physical measurements in all CKB participants by sex

Characteristic*	Males % (n=210,259)	Females % (n=302,632)	Total (n=512,891)
Body mass index (kg/m^2), %			
<21.0	24.8	21.6	23.0
21.0-24.9	45.0	45.1	45.1
≥25.0	30.2	33.3	32.0
Mean (SD)	23.5 (3.2)	23.8 (3.5)	23.7 (3.4)
Systolic blood pressure (mmHg), %			
<120	28.0	36.0	33.0
120-139	41.6	30.4	37.5
≥140	5.4	5.6	29.5
Mean (SD)	132.3 (20.0)	130.4 (22.0)	131.1 (21.3)
Diastolic blood pressure (mmHg), %			
<80	56.5	64.8	61.4
80-89	28.2	24.2	25.8
>90	15.3	11.0	12.8
Mean (SD)	79.2 (11.4)	76.8 (10.9)	77.8 (11.2)
Lung function measurements, mean (SD)			
Pre-bronchodilator FEV_1, Litre†	2.61 (0.69)	1.91 (0.49)	2.20 (0.67)
Pre-bronchodilator FVC, Litre‡	3.10 (0.77)	2.26 (0.55)	2.61 (0.76)
Pre-bronchodilator FEV_1: FVC	0.84 (0.09)	0.85 (0.08)	0.84 (0.09)
Possible airflow obstruction, %			
FEV1: FVC <0.7	6.3	4.6	5.4
FEV1: FVC <lower limit of normal	7.2	6.5	6.9

*Means and percentages were standardised to the age and region area structure of the CKB population, where appropriate
† FEV; forced expiratory volume in 1 second
‡ FVC; forced vital capacity
Two-sided P values were derived from Student's t test for continuous variables and X^2 test for categorical variables. All p-values <0.05

Table 4.3 Baseline characteristics in all urban CKB study participants by sex

Characteristic*	Males % (n=91,354)	Females % (n=134,827)	Total (n=226,181)
Age (years)†, %			
30-39	13.5	13.1	13.3
40-49	28.5	30.3	29.6
50-59	29.1	30.7	30.1
≥60	28.9	25.8	27.0
Mean ± SD	52.7 ± 11.1	52.1 ± 10.7	52.3 ± 10.9
Education level, %			
No formal school	3.7	17.9	11.9
Primary school	19.2	20.4	20.1
Middle school	35.5	29.8	32.2
High school	25.5	22.9	24.0
College/ University	16.0	9.1	11.8
Annual household income (Yuan), %			
<10,000	10.9	15.5	13.6
10,000-19,000	27.8	30.2	29.3
20,000-34,999	32.6	31.3	31.8
≥35,000	28.8	23.0	25.3
Smoking category, %			
Never smoker	18.4	95.5	64.4
Occasional smoker	11.7	1.6	5.6
Ex-regular smoker	15	0.8	6.6
Current regular smoker	54.9	2.1	23.4
Age started smoking, %			
<20	53.0	23.1	15.5
20-24	25.5	13.3	7.5
25-29	12.8	20.5	4.0
30-34	2.3	7.8	0.8
≥35	6.5	35.3	2.4
Passive smoking, %			
Never	36.9	18.8	26.1
Yes, but not now	49.6	29.1	37.4
Yes, at present	13.5	52.1	36.6
Physical activity (MET-hrs) ‡			
Mean ± SD	17.85 ± 13.9	19.30 ± 11.7	18.45 ± 12.6
Alcohol consumption, %			
Never	15.2	61.3	42.9
Occasional/Ex-regular	35.1	34.1	34.4
Monthly	6.3	1.9	3.6
Reduced	5.3	0.3	2.4
Weekly	38.0	2.1	16.7
Self-rated health, %			
Excellent	25.4	20.7	22.6
Good	24.8	23.0	23.4
Fair	41.7	46.3	44.5
Poor	8.0	10.0	9.1
Household air pollution exposure, %			
Currently use wood/coal	9.0	9.4	6.0
Previously used wood/coal	44.8	49.5	34.6
Cooking frequency, %			
Daily	30.0	78.1	58.7
Weekly	24.8	12.1	17.3
Monthly	6.8	2.2	4.0
Never/Rarely	38.3	7.7	19.8
Self-reported health conditions §, %			
Hypertension	13.1	14.2	13.8
Stroke	3.0	1.9	2.3
Diabetes	4.6	4.7	4.7
TB	2.5	1.5	1.9
CHD	3.8	5.2	4.7
Asthma	1.0	1.0	0.8
Emphysema/Bronchitis	2.9	2.5	2.6
Family history of disease¶, %			
Stroke	17.9	18.2	18.0
Myocardial infarction	3.7	3.8	3.8
Cardio-respiratory symptom|, %**			
Breathlessness	3.3	5.0	4.3
Chronic cough	4.5	1.9	2.9
Chest pain	2.0	3.1	2.6

* Means and percentages were standardised to the age and region area structure of urban the CKB population, where appropriate; † Adjusted for region only; ‡ MET-hrs, metabolic equivalent task hours/day; § TB: Tuberculosis, CHD: Coronary heart disease; ¶ Family history defined as baseline reported disease prevalence in mother and/or father; **Breathlessness defined as being short of breath when "walking on level ground with health people of the same age", chronic cough defined as "coughing frequently for ≥ 3 months" Two-sided P values were derived from Student's t test for continuous variables and X^2 test for categorical variables. All p-values <0.05 except asthma (0.379) diabetes (0.836) and family history of MI (0.109)

Table 4.4 Baseline physical measurements in all urban CKB participants by sex

Characteristic*	Males % (n=91,354)	Females % (n=134,827)	Total (n=226,181)
Body mass index (kg/m^2), %			
<21.0	16.2	17.4	16.9
21.0-24.9	43.4	44.5	44.1
≥25.0	40.5	38.1	39.0
Mean (SD)	24.3 (3.3)	24.3 (3.5)	24.3 (3.4)
Systolic blood pressure (mmHg), %			
<120	29.2	42.2	37.0
120-139	40.2	32.2	35.4
≥140	30.7	25.6	27.6
Mean (SD)	132.04 (19.8)	127.52 (21.7)	129.30 (21.1)
Diastolic blood pressure (mmHg), %			
<80	55.7	68.4	63.3
80-89	28.3	22.1	24.6
≥90	16.0	9.5	12.1
Mean (SD)	79.5 (11.4)	75.8 (10.7)	77.32 (11.2)
Lung function measurements, mean (SD)			
Pre-bronchodilator FEV_1, Litre†	2.66 (0.68)	1.95 (0.48)	2.24 (0.66)
Pre-bronchodilator FVC, Litre†	3.09 (0.75)	2.27 (0.54)	2.60 (0.75)
Pre-bronchodilator FEV_1: FVC	0.86 (0.09)	0.86 (0.08)	0.86 (0.09)
Possible airflow obstruction, %			
FEV_1: FVC <0.7	4.4	3.5	3.9
FEV_1: FVC <lower limit of normal	4.7	4.9	4.9

*Means and percentages were standardised to the age and region area structure of the urban CKB population, where appropriate
† FEV; forced expiratory volume in 1 second
‡ FVC; forced vital capacity
Two-sided P values were derived from Student's t test for continuous variables and X^2 test for categorical variables. All p-values <0.05 (except FEV_1: FVC<lower limit of normal)

CHAPTER 5. ACUTE HEALTH EFFECTS

5.1 Introduction

As highlighted in **Chapter 3**, numerous studies performed in China have found associations between acute increases in AAP exposure and risk of both morbidity and mortality from major cardio-respiratory diseases. [195, 213, 221] However, the majority of these studies have focused solely on risk of cardio-respiratory mortality and research incorporating risk estimates for morbidity is relatively lacking. [18, 19] Furthermore, such studies although often large, are limited by their ecological study design, which makes examining the individual-level characteristics of participants affected largely unfeasible. No study to date in China has been able to examine the association between acute increases in AAP exposure and risk of cardio-respiratory hospitalisation by type of admission. In this thesis, 'type' of admission refers to either first-time hospital admissions or readmissions resulting from exacerbations of the pre-existing disease. Differentiating between these types of admission on an individual-level is required to determine whether increased AAP exposure is associated with adverse cardio-respiratory effects in healthy individuals, or merely in individuals with increased susceptibility due to pre-existing cardio-respiratory conditions.

While some studies have examined the effects of AAP on cardio-respiratory disease readmissions in high-income countries (HICs), [259-262] none to my knowledge have actively compared first-time disease events and readmissions in China where AAP levels are considerably higher than in HICs. Connecting AAP exposure to disease incidence in healthy individuals and not just in those with pre-existing disease challenges the idea that risk of cardio-respiratory disease from AAP exposure is only seen in the most vulnerable individuals and further validates its importance as a ubiquitous environmental risk to health. Identifying varying susceptibility to the health effects of AAP would also be advantageous for evidence-based policy and effective health protection strategies to mitigate the associated disease burden in China as well as potential identification of mechanisms of physiological assault. [263]

5.2 Aims

The study described in this Chapter, therefore, aimed to examine the associations between acute increases in AAP levels and risk of major cardio-respiratory hospitalisations by type of admission (first-time versus readmission events) within each urban CKB region as well as collectively across all regions. The secondary aims of this chapter included assessing the temporal trends of both AAP levels and cardio-respiratory hospitalisations in each region as well as examining variation in baseline socio-demographic and lifestyle characteristics in participants by type of admission for cardio-respiratory diseases.

5.3 Methods

Details of the CKB study design, general methodology, and study population have already been outlined in **Chapter 4** of this thesis. For the study described in this chapter, CKB participants in all urban regions (Harbin, Qingdao, Suzhou, Liuzhou and Haikou) were included for the study period 1st January 2013 (1st January 2010 for Suzhou) to 31st December 2016 corresponding to the availability of AAP data.

5.3.1 Environmental data

Data on daily concentrations (24-hr average) of nitrogen dioxide (NO_2), sulphur dioxide (SO_2), coarse and fine particulate matter (PM_{10}, $PM_{2.5}$), and carbon monoxide (CO) plus maximum mean 8-hr concentrations (10:00-18:00) of ozone (O_3) were obtained for each of the five CKB urban regions. Pollutant concentrations were recorded from fixed-site monitors contributing to the China National Air Pollution Monitoring System established as part of the Air Pollution Protection and Control Law (APPCL) [264] outlined in **Chapter 2**.

Pollutant data from monitors within each region were collated and averaged providing spatially averaged daily concentrations for each of the six pollutants and provided to this study by collaborators at Fudan University, Shanghai. The CKB regions of Harbin, Qingdao, Liuzhou, and Haikou had daily AAP levels for 2013-2015, while Suzhou data was available

from 2010-2016. Any missing daily pollutant concentrations were replaced with the respective pollutant's previous daily value (see **Appendix C1** for details of missing days).

Similarly, when measured pollutant values were implausibly high or low following comparison with the surrounding days, these were also replaced using the previous daily value (**Appendix C1**). However, the number of such values was small (n=1, for PM_{10} and O_3, respectively).

Daily mean values of temperature and relative humidity also spatially averaged across each region were obtained from the China Meteorological Data Service Centre again provided to this study by Fudan University for the corresponding period within each region. There were no missing values of meteorological measurements during the study period, and all recorded measurement values appeared plausible.

5.3.2 Outcome definitions and reclassification of CKB endpoints

As described in **Chapter 2**, studies examining the associated health effects of acute AAP exposure require a high degree of temporal accuracy in the recorded health outcomes of interest. As also previously outlined, CKB follow-up utilises national death registries, local disease registries and health insurance claims to capture cause-specific disease endpoints, reflective of the first recorded event of that respective disease since CKB baseline. To address the aims of the study in this Chapter, a new outcome variable was used as an alternative to the CKB "endpoints", this was required for two reasons. Firstly, it was essential to capture multiple occurrences of cardio-respiratory hospitalisation, thus allowing the relationship between AAP and hospital readmissions to be examined. Secondly, recorded cardiovascular and respiratory disease episodes may involve recording multiple subsequent cardio-respiratory health conditions in quick succession (for example hypertension detected following admission for another cardiovascular disease). Such disease sequelae are unlikely to be affected by AAP exposure but are rather detected through clinical investigation during hospitalisation. Therefore, for the purposes of this study a new outcome variable was

derived reclassifying data on all CKB hospital admissions of major cardio-respiratory disease into appropriate episodes referred to as hospitalisation “spells”.

Spells consisted of all hospital admissions of the same cardio-respiratory disease type with admission dates fewer than seven days apart (**Figure 5.1**), the rationale being that hospitalisations repeatedly occurring within seven days would likely be for the same condition. Multiple hospitalisations of the same major disease type with admission dates fewer than seven days apart were therefore counted as part of the same overall “spell” with the date of the first hospitalisation used as the admission date. Since construction of spells was based on major diseases of the same type, should an individual be admitted for major cardiovascular disease (ICD-10: I00-I99) and major respiratory disease (J00-J99) then subsequently detected, these were treated as two separate spells.

Previous studies on the adverse health effects of acute AAP exposure in China have typically separated mortality and morbidity events, respectively. However, because of the very low counts of mortality during the study periods (**Appendix C2**) derived spells represent both mortality and morbidity inclusively, the majority (~90%) representative of morbidity. Outpatient events were not included since these are likely predetermined in advance and thus unlikely to capture emerging cardio-respiratory disease on that day specifically. Spells with a duration longer than one year were removed as these were rather likely reflective of coding errors at the regional RCs or within the respective health insurance systems, and there was no clear systematic pattern in these spells.

Spells were generated for all major cardiovascular diseases (I00-I99), including all-type stroke (I60-I69), as well as all major respiratory diseases (J00-J99) for each urban CKB region. These were chosen due to their capacity for acute onset and their established relationship with AAP exposure documented in the surrounding evidence base. [265-268] Spells of chronic obstructive pulmonary disease (COPD) and ischaemic heart disease (IHD) were also constructed, but these were not included in the analysis due to very low event numbers for these diseases (**Appendix C3**), with small event counts known to severely limit the

power of both time-series and case-crossover analyses even if the study period is long. [269] Once spells were constructed these were then classified into first-time and readmissions by the CKB data team for use in this study; the details of this classification are shown in **Table 5.1**.

5.3.3 Participant exclusions

Given the ecological nature of the study designs used in this study, only participants who had died before the start of the study periods were excluded. This resulted in the exclusion of 2661, 1004, 642, 2253, and 601 participants in Harbin, Qingdao, Liuzhou, Suzhou, and Haikou, respectively, and left 219,020 participants across all five urban regions for inclusion in the analysis.

5.3.4 Statistical analysis

5.3.4.1 Descriptive analysis

Summary statistics were calculated by disease-specific spells for first-time, and readmissions, respectively, in each urban CKB region. Region-specific summary statistics, as well as Pearson correlation coefficients, were calculated for daily AAP levels plus meteorological values. To visually assess the presence of long-term trends and potential seasonality throughout the study periods time-series plots of daily AAP levels and spell counts were constructed for each region. All time-series plots had moving average smoothing filters applied to allow clearer interpretations of temporal patterns; the detailed methodology of this can be found in **Appendix C4.** To quantify long-term trends in AAP levels the percent change in annual mean AAP levels between the start and end of the study periods were calculated for each region. The proportion of days throughout the study period with recorded AAP levels exceeding air quality guidelines from both WHO[270] and China's national standards[33] were also calculated within each CKB region.

Finally, baseline socio-demographic, lifestyle characteristics and physical measurements of the study population were cross-tabulated by region as well as by cardio-respiratory

hospitalisation status adjusted for age, sex, and study region where appropriate using direct standardisation.

5.3.4.2 Statistical modelling

To investigate the associations between acute AAP exposure and risk of incident cardio-respiratory spells both time-series analysis, and case-crossover analyses, were carried out. As highlighted in **Chapter 2**, these are well-established study designs within the literature on the cardio-respiratory health effects of acute AAP exposure. Both designs rely principally on both daily fluctuations in AAP levels used to assess the short-term health effects of exposure. While in time-series analysis daily counts of the respective health outcome are utilised as the outcome of interest, in case-crossover analysis the unit of analysis is the individual rather than aggregated daily event counts.

In this study, both case-crossover and time-series analyses examined associations between acute fluctuations in AAP levels and risk of cardio-respiratory spells (by admission type) within each region. Both case-crossover and time-series analysis were used to ensure the robustness of generated risk estimates, with each design subject to limitations [271]. In this study, generated risk estimates were reported to be significant if they were so in both types of analysis. Risk estimates reported in the results section of this chapter were those generated in time-series analysis as these have more comparability to the surrounding evidence base with time-series analysis the more frequently utilised approach in the literature [18, 19]. Corresponding risk estimates from case-crossover analysis are shown in **Appendix C5**.

As both study designs use population-level measures of both daily AAP exposure and spell counts in analysis adjustment for individual-level confounders such as smoking is not required for either study design. Rather, potential confounders are those time-varying covariates potentially related to both daily cardio-respiratory spell counts and AAP levels and

include temperature, relative humidity, calendar time (reflective of seasonality and long-term trend), public holidays, and day of the week.

Detailed methodology for the time-series and case-crossover analyses used in this chapter will now be described in detail.

Time-series analysis

As daily cardio-respiratory spell counts are assumed to follow a Poisson distribution, Poisson regression models allowing for overdispersion were fitted to investigate whether acute fluctuations in AAP levels were associated with cardio-respiratory spells in each of the urban CKB regions. This utilised generalised additive models (GAMs), a flexible alternative to generalised linear models commonly used for time-series analysis for air pollution epidemiology [195, 266, 272, 273] due to their ability to relax the assumption of linearity in predictors. Instead, linear predictors $\eta=\sum_j \beta_j X_j$ are replaced by a function of smooth (and possibly non-linear) functions of form $\eta=\sum_j s_j(X_j)$ whereby the linear coefficients for covariates ($\beta_j X_j$) are replaced by polynomials typically smoothing splines or local regression (LOESS) functions denoted here as s. This facilitates adjustment for the potential non-linear confounding effects of the meteorological variables (temperature and relative humidity) as well as seasonality and long-term trends of both AAP and hospitalisations.

The Poisson regression model fitted is:

$$log[E(Yt)] = \alpha + b_1 X_{t\text{-}i} + s(lagged\ temperature, df = 6) + s(lagged\ relative\ humidity, df = 3) + s(calendar\ time, df = 7 * year) + b_2(DOW) + b_3(public\ holidays)$$

where $E(Yt)$ is the expected count of cardio-respiratory spells on day t; $X_{t\text{-}i}$ denotes the mean AAP levels on corresponding day *t* and at lag *i*; and s the cubic regression spline functions for both calendar time, and three-day moving average measures of daily mean temperature, and relative humidity. Since CKB is a closed cohort all models also incorporated the natural logarithm of persons at risk as an offset term. b_1 then represents the log relative risk of cardio-respiratory spells associated with a unit increase in the

pollutant of interest. Generated effect estimates were presented as percent excess risk ([Relative Risk-1] x 100) (95% confidence intervals) per 10 μg/m^3 increase in pollutant concentrations (100 μg/m^3 for CO due to the greater observed fluctuations in observed CO concentrations).

It was necessary to adjust for calendar time to account for potential unmeasured confounders, which vary with time. Examples include the seasonality of cardio-respiratory diseases, increased incidence of cardio-respiratory disease documented in China from late autumn to early spring [274, 275] potentially coinciding with higher measured AAP levels in winter months (except O_3). Cubic regression spline functions with seven degrees of freedom per year of study were applied to adjust for these. Seven degrees of freedom were chosen using a "fixed degrees of freedom approach" [41] and roughly equating to a two-month moving average, conforming to biological knowledge as well as the existing evidence base. [276, 277]

The relationship between ambient temperature and both cardio-respiratory disease incidence and mortality has also been well established in China. [42, 278, 279] With temperature a known correlate of AAP levels, controlling for potential confounding by temperature was essential in this study. To achieve this, a cubic regression spline function of daily temperature averaged across the previous three days was applied with six degrees of freedom. A lagged measure of temperature was chosen to account for the known delayed effects of temperature on cardio-respiratory disease [279, 280] and a three-day moving average lag found to be robust in controlling for the confounding effects of temperature. [281] To control for the potential confounding effects of relative humidity a cubic regression spline function of daily relative humidity averaged across the previous two days was applied with three degrees of freedom as in previous studies. [195, 268, 282] The greater number of degrees of freedom employed for temperature allowed for the known "j-shaped" non-linear curve between temperature and cardio-respiratory disease to be captured. [42, 283, 284].

As a day of the week effect in cardio-respiratory hospitalisations is common with fewer hospitalisation spells occurring on weekends relative to weekdays (see **Appendix C6**), a

derived categorical variable of day of the week was incorporated. Similarly, a derived indicator variable of Chinese public holidays was also incorporated adjusting for the potential confounding effect of public holidays where associations between AAP levels and hospitalisation spell counts could be confounded.

Following model construction, partial autocorrelation function (PACF) plots were constructed to assess the presence of any unwanted serial dependence in residuals (shown in **Appendix C7**). These showed remaining residual autocorrelation in the final models to be minimal.

Case-crossover analysis

The case-crossover study design is commonly used to examine the association between acute AAP exposure and adverse health outcomes. [285] Similar to a case-control study but with each subject acting as their own control, case-crossover analysis compares AAP levels at the time of an event (case period) to one or more periods when the event did not occur (control periods). Conditional logistic regression is used to estimate odds ratios of cardio-respiratory spells associated with AAP.

In this study, a time-stratified-case-crossover analysis was performed using 28-day strata thereby controlling for temporally varying covariates by design; a bi-directional sampling of control period was also applied to control for potential seasonal trends in pollutants. Temperature and relative humidity (averaged across the previous 3-days) were adjusted for. Case periods were matched to referent control periods by day of the week within the same 28 days strata to adjust for day of the week effects, and adjustment for public holidays made via inclusion of the indicator variable mentioned previously. As the case-crossover methodology relies on cases only, an offset term was not required.

Case-crossover effect estimates were presented as the percent increase in odds of hospitalisation spells associated with a 10 $\mu g/m^3$ increase in daily pollutant concentrations (100 $\mu g/m^3$ for CO). All case-crossover analysis was performed using the R package

"season", [286] which allows the fitting a time-stratified case–crossover to the regularly spaced time-series data for each region.

5.3.5 Pooled analysis

Estimates were pooled using a random-effects model with heterogeneity assessed using the I^2 statistic. [287] This examined risk of cardio-respiratory spells associated with AAP exposure across all five urban regions collectively, by lag structure, cardio-respiratory spell type, and pollutant and was performed for the effect estimates generated by time-series analysis and case-crossover analysis, respectively. Pooled estimates represent the percent excess risk of cardio-respiratory spells associated with a 10 $\mu g/m^3$ (100 $\mu g/m^3$ for CO) increase in pollutant concentrations across the five urban CKB regions, collectively.

5.3.6 Lag structures

Acute AAP exposure has been frequently associated with adverse cardio-respiratory health effects in China both on the concurrent day of exposure but also in the days following. [213, 223] To therefore account for the fact that AAP exposure may affect cardio-respiratory spell onset in a lagged fashion, both methodologies also incorporated lagged measures of daily AAP ranging from same-day (lag-0) exposure to a 3-day lag between exposure and spell onset. These lag dimensions were chosen in line with several large-scale studies performed both in HICs [268, 288] and China [289, 290] which suggest the strongest effect of AAP exposure on adverse cardio-respiratory health effects is on the same-day and previous days exposure with effect estimates tending to decrease at lags longer than two days. [182, 289, 290] However, lagged moving average measures of pollutants were also examined up to a lag of 4-days (0-3 day moving average).

To examine potential longer lag structures in the effects of AAP on cardio-respiratory spells, distributed lag models (DLMs) were also constructed up to a 7-day lag. DLMs are becoming a common methodology in environmental epidemiology as they can account for lagged differential effects of AAP exposure spread over multiple days while simultaneously

adjusting for the serial correlation in AAP between days, providing an adjusted conditional effect of lagged exposure. This is useful in allowing the examination of exposure-lag-response relationship between air pollution and cardio-respiratory spells, after controlling for potential confounders. A seven-day lag was chosen as some studies have found AAP exposure associated with delayed estimated effects for cardio-respiratory diseases [291] and others finding mortality effect estimates were larger when time scales longer than a few days were used. [47, 291] Full details of the DLM methodology are found in **Appendix C8** of this thesis**.**

5.3.7 Subgroup analysis

Associations of acute AAP exposure with risk of cardio-respiratory disease have been found to differ by age and sex. [132, 195] To examine this in this study, subgroup analysis was performed using the same time-series and case-crossover methodologies as in main analysis, stratifying spell counts by sex (males versus females) and age (CKB baseline ages of 60 years and over, versus under 60 years). The results can be found in **Appendices C9 and C10.** This was performed for cardiovascular and respiratory spells, respectively.

5.3.8 Sensitivity analysis

While other time-series studies occasionally explore using differing degrees of freedom through sensitivity analysis in adjustment for temporally varying covariates [277, 292] such sensitivity analysis was not performed in this study for two reasons. Firstly, initial exploratory analysis on CKB data found a minimal difference in risk estimates relating to the choice of degrees of freedom (see **Appendix C11**). Secondly, the use of case-crossover analysis as an alternate methodology and comparison of the results did in itself ensure sufficient robustness of the risk estimates.

To explore the stability of the associations of individual pollutants and when correlation coefficients were reasonable to do so, two-pollutant models were also fitted for both time-series and case-crossover analyses, using the same methodologies as in the main analysis.

Results from two-pollutant models can be found in **Appendix C12** Two-pollutant models were chosen over multi-pollutant models as the high correlations between pollutants would make interpretation of multi-pollutant models difficult. [293]

Finally, given the expected variation in AAP concentrations between CKB regions, risk estimates were also computed for an interquartile range (IQR) increase in AAP concentrations thereby allowing relative comparison of risk between both CKB regions and specific pollutants concentrations. Results for an IQR increase in AAP from time-series analysis are presented with results below by cardio-respiratory outcome while all results can be found in **Appendix C13** of this thesis for time-series analysis and case-crossover analysis, respectively.

5.4. Results

5.4.1. Descriptive results

Table 5.2 presents the summary statistics for daily AAP levels in each of the five CKB urban regions, respectively. There was considerable variability in pollutant concentrations between the five regions. PM_{10} concentrations were highest in the colder northern CKB regions of Harbin and Qingdao (104.8 μg/m^3, and 98.2 μg/m^3, respectively). The highest $PM_{2.5}$ concentrations were seen in Harbin (66.1 μg/m^3). For gaseous pollutants O_3 and CO concentrations were highest in Liuzhou (88.8 μg/m^3 and 1.1 mg/m^3, respectively), while concentrations of NO_2 were highest in Suzhou (54.4 μg/m^3). Haikou located in the far south of China had considerably lower AAP levels compared to the other regions as well as higher recorded temperature and relative humidity.

Moderate to high positive correlations were present between AAP levels (except O_3) in all regions (**Appendix C14**). All AAP levels (except O_3) also had moderate to strong inverse correlations with temperature in every region. Strong seasonal patterns were observed for all pollutant concentrations as shown in **Figure 5.2**, with greater concentrations of all pollutants (except O_3) recorded in winter months, regions with greater seasonal variability of

temperature and relative humidity had more pronounced seasonality in AAP levels (except O_3). Considerable declines in average annual levels of SO_2 and PM (both PM_{10} and $PM_{2.5}$) were observed in all regions throughout the study period, long-term temporal trends of other pollutants were more variable by region (**Tables 5.3 and 5.4**).

All CKB regions had days throughout the study period where AAP levels exceeded Chinese national guidelines. For $PM_{2.5}$ concentrations, this was, 28.6%, 18.6%, 23.8%, 18.9%, and 2.2% in Harbin, Qingdao, Suzhou, Liuzhou, and Haikou, respectively (**Appendix C15)**. Proportions of days exceeding WHO AAP guidelines were even higher with 74.5%, 78.5%, 84.1%, 84.0%, and 28.1% of days in Harbin, Qingdao, Suzhou, Liuzhou, and Haikou, respectively, exceeding WHO $PM_{2.5}$ guidelines (**Appendix C15).** $PM_{2.5}$ was the pollutant that exceeded Chinese national and WHO guidelines on the greatest number of days, likely due to more stringent guidelines compared to other pollutants.

94,479 cardio-respiratory (ICD-10 I00-I99, J00-J99) hospitalisation spells occurred across all five regions during the study period; this included 65,168 (69%) readmissions (**Table 5.5**). Among the 73,400 major cardiovascular disease spells, readmissions (n=54,692) were three times more frequent than first-time spells (n=18,708), while the 21,079 major respiratory disease spells were contributed by similar numbers of first-time (n=10,603) and readmission spells (n=10,476). Across all five regions, there were 31,759 all-type stroke spells, with more readmissions than first-time spells (18,660 versus 13,099, respectively). Few of all the cardio-respiratory spells were fatal cases (< 8%), and considerable variability was observed in mean daily spell counts by region. Counts of major cardiovascular disease spells were highest in Harbin (22.8) and lowest in Suzhou (2.9); stroke spells were also highest in Harbin (12.2) and lowest in Suzhou (1.1). Counts of major respiratory spells were also highest in Harbin (3.4) and lowest in Qingdao (1.4).

5.4.2. Temporal trends in spells

Figures 5.3-5.5 show time-series plots of daily counts of major cardio-respiratory spells by total, first-time and readmission spells, in each region, for cardiovascular, respiratory and stroke spells, respectively. For cardiovascular disease, seasonality in spells was evident in Harbin and Qingdao with greater daily spell counts in winter periods for both first-time spells and readmissions. In Haikou the opposite was observed with a drop in cardiovascular disease spell counts observed in winter months (for both first-time spells and readmissions). For the regions of Liuzhou and Suzhou less seasonality was observed for cardiovascular disease, spells; however, in Suzhou, an increasing trend in cardiovascular disease spell counts was observed. Similar temporal trends were observed for counts of all-type stroke as were seen for all major cardiovascular diseases across all regions (**Figure 5.3**). Seasonality was also evident for respiratory spell counts in Harbin, Qingdao and Suzhou with higher spell counts in winter months. Respiratory spells also showed an increasing long-term trend in these regions. Both Liuzhou and Haikou exhibited large peaks in respiratory spell counts in June 2015 and the winter of 2014, respectively. ICD-10 codes of all CKB hospitalisations were examined for these periods to see if these were reflective of influenza outbreaks within the regions. However, the majority of these disease cases were bronchitis and acute upper respiratory tract infections (**Appendix C15).**

5.4.3. Baseline characteristics by disease status

Table 5.6 presents the socio-demographic and lifestyle characteristics of participants cross-tabulated by cardio-respiratory spell status for all five regions collectively. Participants with readmission spells of either cardiovascular disease, all-type stroke, and respiratory disease were older, less physically active, and had poorer self-reported general health ($p<0.05$). **Table 5.7** cross-tabulates baseline physical measurement by spells status. Participants with readmissions had lower measures of mean FEV_1 and FVC at baseline compared to those with first-time spells ($p<0.05$).

In participants with recorded spells of major cardiovascular disease and all-type stroke specifically, a greater proportion of readmission participants had reported family histories of stroke, as well as a higher prevalence of breathlessness and chest pain at baseline compared to participants with first-time spells ($p<0.05$). Mean baseline measurements of body mass index (BMI), systolic and diastolic blood pressures (SBP, and DBP, respectively) were also greater for participants with readmissions versus first-time spells (all $p<0.05$). For all major respiratory diseases specifically, a greater proportion of participants with readmissions were ex-regular smokers compared to those with first-time spells (8.5% vs 6.6%, respectively). Readmission participants also reported lower prevalence of current and previous use of solid fuel for cooking than those with first-time spells ($p<0.05$). Prevalence of cardio-respiratory symptoms and possible airflow obstruction were also higher in participants with readmissions than first-time spells (all $p<0.05$).

5.4.4. Particulate matter exposure and risk of cardio-respiratory disease

5.4.4.1 Major cardiovascular disease

There were few significant associations between acute increases in PM exposure (both PM_{10} and $PM_{2.5)}$, and risk of cardiovascular disease spells in CKB regions (**Figure 5.6**). PM_{10} exposure in Qingdao was significantly associated with higher risk of cardiovascular disease spells and this was for first-time spells only (0.94% [95% CI: 0.17, 1.72], 1.27% [0.19, 2.35], 1.68% [0.50, 2.88], for lag-3, lag-0-2, and lag-0-3, respectively). Similarly, in Haikou, a 10 $\mu g/m^3$ increase in same-day PM_{10} was associated with 3.92% (1.12, 6.81) increase in first-time cardiovascular disease spells (**Figure 5.7**). $PM_{2.5}$ was also associated with risk of first-time cardiovascular disease spells in Haikou but only when using moving average measures of $PM_{2.5}$ (4.50% [0.65, 8.50], 4.61% [0.49, 8.90], 4.73% [0.43, 9.22], for lags 0-1, 0-2, and 0-3, respectively). For cardiovascular readmissions, the only association was in Suzhou for same-day $PM_{2.5}$ was associated with 1.10% (0.03, 2.19) higher risk.

Risk of cardiovascular spells associated with PM exposure was greater in all the examined CKB regions for an IQR increase in PM concentrations. In Qingdao, an IQR increase in PM_{10}

(65.3 μg/m^3) was associated with a 6.33% (1.12, 11.80), 8.56% (1.25, 16.40) and 11.52% (3.34, 20.35), higher risk of first-time cardiovascular spells for lag-3, lag-0-2, and lag-0-3, respectively. In Haikou, risk of first-time cardiovascular spells associated with an IQR increase in same-day PM_{10} (21.3 μg/m^3) was 8.55% (2.41, 15.07) (**Appendix C13 Figure C13.2**). Similarly, for $PM_{2.5}$, an IQR increase in Haikou (15.3 μg/m^3) was associated with 4.50% (0.65, 8.50), 4.61% (0.49, 8.90), 4.73% (0.43, 9.22), increased risk of first-time cardiovascular spells, for lags 0-1, 0-2, and 0-3, respectively. In Suzhou, an IQR increase (36.9 μg/m^3) in $PM_{2.5}$ was associated with 4.14% (0.11, 8.32) increased risk of cardiovascular readmissions (**Appendix C13 Figure C13.1**).

5.4.4.2 All-type stroke

PM exposure was associated with increased risk of stroke spells in the CKB region of Haikou only (**Figures 5.8 and 5.9**), with risk appearing slightly greater for first-time spells. PM_{10} and $PM_{2.5}$ at a 1-day lag were associated with 6.01% (2.63, 9.51) and 6.79% (2.63, 11.13) higher risk of first-time spells and 2.93% (0.02, 5.94) and 4.27% (0.70, 7.96) increased risk of readmissions, respectively. For IQR increases in $PM_{2.5}$ (15.3 μg/m^3) and PM_{10} (21.3 μg/m^3) in Haikou, an IQR increase at a 1-day lag were associated with 10.58% (4.06, 17.52) and 13.24% (5.68, 21.34) higher risk of first-time stroke spells, respectively. For stroke readmissions, IQR increases PM_{10} and $PM_{2.5}$ were associated with 6.60% (1.07, 12.44) and 6.36% (0.03, 13.07) higher risk of stroke readmissions in Haikou, respectively, (**Appendix C13 Figure C13.4)**.

5.4.4.3 Major respiratory disease spells

$PM_{2.5}$ was associated with risk of first-time respiratory spells in Suzhou at a 3-day lag (1.77% [0.60, 2.96]) (**Figure 5.10**). While PM_{10} was also associated with risk of first-time respiratory spells in Harbin and with smaller magnitude (0.64% [0.02, 1.26]). For readmission spells the only significant associations were in Suzhou, where same-day $PM_{2.5}$ associated with 1.79% (0.69, 2.90) increased risk of respiratory readmissions in Suzhou and risk appeared slightly greater when using moving average measures of $PM_{2.5}$ exposure, 2.16% (0.85, 3.48), 2.04%

(0.56, 3.56), and 2.20% (0.45, 4.04) for lags 0-1, 0-2, and 0-3, respectively. IQR increases in $PM_{2.5}$ (36.9 µg/m3) were associated with 6.70% (2.24, 11.35) higher risk of first-time respiratory spells in Suzhou. While in Harbin, an IQR increase in PM_{10} (74.4 µg/m^3) was associated with 4.89% (0.74, 9.06) higher risk of first-time respiratory spells. For respiratory readmissions, same-day $PM_{2.5}$ in Suzhou was associated with 6.77% (2.57, 11.13) higher risk for an IQR increase (36.9 µg/m^3) in exposure (**Appendix C13 Figure C13.5)**.

5.4.4.4 Two- pollutant models

The correlations between PM and other pollutants are presented in **Appendix C14**. Given the lower correlation coefficients between $PM_{2.5}$ and SO_2 relative to $PM_{2.5}$ and NO_2, two-pollutant models were created for $PM_{2.5}$ + SO_2 in each CKB region. When adjusting for SO_2, risk estimates observed between PM and cardiovascular, all-type stroke and respiratory spells remained similar (**Appendix C12 Figures C12.1 C11.2. and C12.3**). The exception to this was cardiovascular disease spells in Suzhou, where adjustment for SO_2 attenuated associations to null (**Figure C12.1**). For risk of first-time cardiovascular spells in Qingdao PM_{10} exposure remained significantly associated upon adjustment for SO_2 in both time-series and case-crossover analyses (1.15% [0.17, 2.14]).

5.4.5. Gaseous pollutant exposure and risk of cardio-respiratory disease

5.4.5.1 Major cardiovascular disease

Significant associations of similar magnitude were observed between gaseous AAP exposure and cardiovascular disease spells using both time-series (**Figures 5.6**) and case-crossover analysis (**Appendix C5**). However, risk varied by CKB region as well as by pollutant and spell type (first-time versus readmissions). In Qingdao, SO_2 exposure was positively associated with the risk of first-time cardiovascular disease spells (4.04% [95% CI 1.17, 7.01] at a 3-day lag) but not cardiovascular disease readmissions, with greater risk when using an IQR increase (20.9 µg/m^3) in SO_2 (8.64% [2.46, 15.21]). However, in Liuzhou, SO_2 was associated with an increase in major cardiovascular disease readmissions (3.06%

[0.11, 6.10]) only at a 2-day lag and not first-time spells (2.11% [-1.47, 5.81]). Similarly, in Suzhou, same-day SO_2, NO_2, and CO exposures, were all associated with cardiovascular disease readmission spells only (7.32% [4.24, 10.49], 2.88% [0.90, 4.89], and 15.08% [4.39, 26.85], respectively) with risk from SO_2 and CO exposure persisting across various lag dimensions. Risk of cardiovascular readmissions in Suzhou were also greater when using an IQR increase in same-day SO_2 (16.80 μg/m^3) , NO_2 (28.1 μg/m^3) and CO (400 μg/m^3), (12.60% [7.23, 18.24], 8.29% [2.55, 14.35] and 75.36% [18.77, 158.90], respectively). (**Appendix C13, Figure C13.1**)

In Haikou gaseous AAP was associated with both first-time cardiovascular disease spells and readmissions (**Figure 5.7).** A 10 μg/m^3 increase in NO_2 exposure at a 2-day lag was associated with 11.79% (2.79, 21.58) and 8.97% (3.05, 15.23) increased risk of first-time and readmission spells respectively. For an IQR increase in NO_2 (6.50 μg/m^3) this risk was lower (7.51% [1.80, 13.54], and 4.67% [1.00, 8.48], for first-time spells and readmissions, respectively). Same-day O_3 was associated with increases in both first-time cardiovascular disease spells and 2.80% [0.57, 5.08]) and readmissions in Haikou (3.01% [1.55, 4.50]), with greater risk magnitude for an IQR increase (10.80% [2.10, 20.23], and 11.72 [5.91, 17.86], respectively) (**Appendix C13, Figure C13.2**)

5.4.5.2 All-type stroke

Significant associations between gaseous AAP and first-time spells of all-type stroke were seen in Haikou and Qingdao where a 10 μg/m^3 increase in SO_2 was associated with a 39.13% (8.00, 79.24) and 4.39% (0.19, 8.76) increase in first-time stroke spells at a 1-day lag, respectively (**Figures 5.8 and 5.9**). For an IQR increase in SO_2, this risk was higher in Qingdao (9.39% [0.39, 19.19] for a 20.9 μg/m^3 increase) and lower in Haikou (8.97% [2.02, 16.38] for a 2.6 μg/m^3 increase). For stroke readmission spells in Haikou, NO_2 exposure was associated with increased risk across all moving lag dimensions peaking at with a 0-3-day lag with 18.59% [5.08, 33.83]. However, this risk was lower when using an IQR increase (6.5

μg/m^3) (11.72% [3.27, 20.85). Same-day O_3 was also associated with increased risk of stroke readmissions in Haikou (3.77% [1.45, 6.14]), with higher risk observed for an IQR increase (37.3 μg/m^3) (14.78% [5.50, 24.89]). Suzhou was the only other CKB region where gaseous AAP was associated with increased risk of stroke spells, and this was for readmissions only (27.69% [7.43, 51.76] and 6.10% [0.36, 12.18] for CO and SO_2 at a 1-day lag time) (**Figure 5.8**). For IQR increases in CO (400 μg/m^3) and SO_2 (16.80) in Suzhou, risk appeared higher at 165.85% (33.22, and 430.53) and 10.46% (0.6 21.3) (**Appendix C13, Figure C13.3**).

5.4.5.3 Major respiratory disease spells

NO_2 was associated with first-time respiratory spells in Suzhou (2.35% [0.18, 4.58], lag-3), and Liuzhou (5.44% [0.41, 10.73], at lag-0) (**Figures 5.10**), with greater observed risk for IQR increases in NO_2 (6.76% [0.50, 13.40] for a 28.1 μg/m^3 increase in Suzhou and 7.53% [0.56, 14.98 for a 13.70 μg/m^3 increase in Liuzhou) (**Appendix C13, Figure C13.5)**. In Haikou, same-day SO_2 was associated with risk of respiratory readmissions only, (29.31% [6.48, 57.02] for a 10 μg/m^3 increase and 6.92% [1.65, 12.45] for an IQR increase [2.6 μg/m^3]). CO was associated with a 17.11% (5.41, 30.11) increase in respiratory readmissions in Suzhou only for same-day exposure (88.09%, [23.46, 186.54] for an IQR increase of 400 μg/m^3).

5.4.5.4 Two- pollutant models

The results from the two pollutant models are shown in **Appendix C12.** SO_2 plus adjustment for $PM_{2.5}$ are shown in **Appendix C12 Figures C12.4 – C12.6**. The observed associations for SO_2 and cardiovascular disease spells in Qingdao and Liuzhou were attenuated to null upon adjustment for $PM_{2.5}$. However, in Suzhou the association between SO_2 and cardiovascular disease readmissions remained significant following adjustment for $PM_{2.5}$ (7.50% [4.02, 11.09]). For all-type stroke spells, the association previously observed between SO_2 and stroke spells in Haikou were fully attenuated to null upon adjustment for

$PM_{2.5}$. However, in Suzhou SO_2 remained a significant risk factor for stroke readmissions following adjustment for $PM_{2.5}$ (7.07% [0.62, 13.94]). The previously observed risk of SO_2 exposure with respiratory readmissions in Haikou was attenuated upon adjustment for $PM_{2.5}$ (23.86% [-8.11, 66.96]).

All associations between CO and cardiovascular disease were attenuated upon adjustment for SO_2 in all regions (**Appendix C12 Figure C12.7).** In Suzhou CO remained associated with stroke readmissions (22.53% [0.38, 49.59]) following adjustment for CO. However, following adjustment for SO_2, CO was no longer associated with respiratory readmissions in Suzhou.

5.4.6. Pooled results

Figures 5.12-5.14 show the pooled associations between acute AAP levels and cardio-respiratory spells across all five CKB urban regions. Only CO was associated with risk of major cardiovascular spells, with 5.65% (0.84, 10.70) increased risk of first-time spells only for a 100 μg/m^3 increase in same-day CO exposure consistent in both time-series and case-crossover analysis (**Figure 5.12**). For all-type strokes spells, NO_2 at both a 1-day lag and 0-1-day lag was associated with risk of first-time stroke spells (2.13% [0.75, 3.53], and 2.20% [0.63, 3.78], respectively). For respiratory hospitalisation spells, $PM_{2.5}$ and PM_{10} at 3-day lags were associated with 0.92% (0.34, 1.49) and 0.66% (0.23, 1.08) higher risk of first-time respiratory spells, respectively (**Figure 5.14**). There were no associations between AAP exposure of any kind and cardio-respiratory readmissions in pooled analysis.

5.4.7 Distributed lag models

The results from DLMs are shown in in **Appendix C17**. Upon visual inspection, generated risk estimates from DLMs appeared consistent with those generated using single-day and moving average concentrations in time-series and case-crossover analyses. However, certain associations were attenuated to null when using DLMs particularly those emerging from Haikou. Strong similarities between risk estimates from DLMs and time-series/case-

crossover analyses may be indicative of less serial correlation in the respective pollutant correlations than anticipated. A possible explanation for the attenuation of estimates in Haikou may relate to individual lag effects of AAP confounding each other in the standard time-series and case-crossover models in this region.

5.4.8 Subgroup analyses

Results from subgroup analysis stratified by age are found in **Appendix C9.** A total of 38,813 cardiovascular disease spells occurred in those aged 60 years and over at baseline; of these 6249, and 32,564 were first-time spells and readmissions, respectively. In participants aged less than 60 years at baseline 34,587, cardiovascular spells were recorded with 12,459, and 22,128 first-time and readmission spells, respectively. Acute AAP exposure was associated with risk of cardiovascular disease spells in both age groups but discrepancies in risk appeared between the two groups.

A greater number of significant associations were observed between acute AAP exposure and cardiovascular readmissions in participants aged 60 years and over versus those aged less than 60 years (**Appendix C9 Figures C9.1 and C9.2**). All pollutants (except CO) were associated with increased risk of cardiovascular disease readmissions in Liuzhou for those 60 years and over only (1.11% [0.28, 1.95], 1.59% [0.50, 2.69], 3.54% [0.83, 6.32], 4.17% [1.09, 7.34], and 1.47% [0.35, 2.61 for $PM_{10,}$ $PM_{2.5,}$ $SO_{2,}$ NO_2, and O_3, respectively]). Similarly, in Suzhou, NO_2 was associated with risk of first-time cardiovascular disease spells in those aged over 60 only (4.71% [0.14, 9.49]) as was $PM_{2.5}$ in Qingdao (2.94% [0.52, 5.43]). The exception to this was in Haikou where there were a greater number of significant associations between AAP exposure and cardiovascular disease spells in participants aged less than 60 years (**Appendix C9 Figure C9.3**).

There were significant risk estimates that remained consistent between both age groups. PM_{10} was associated with first-time cardiovascular disease spells in both age groups in Qingdao, however risk appeared to have a quicker onset in those aged 60 years and over

with 1.71% (0.91, 3.13), 1.50% (0.07, 2.96), increased risk of first-time cardiovascular disease spells at lags of 0 and-1 compared to 1.21% (0.32, 2.11) at a 3-day lag only in those aged under 60 (**Appendix C9 Figures C9.1 and C9.2**).

11,383 respiratory disease spells occurred in participants aged 60 years and over (4738 first-time, and 6645 readmissions), compared to 9696 spells in those under 60 years where a greater number of first-time spells were seen relative to readmissions (5865 versus 3831, respectively).

For first-time respiratory disease spells, in participants aged 60 years and over significant associations were observed in Suzhou for NO_2, PM_{10}, and $PM_{2.5}$ (3.70% [0.48, 7.02], 1.49% [0.39, 2.60], and 3.22 [1.55, 4.93], respectively) and Liuzhou for O_3 (3.45% [0.83, 6.14). For respiratory readmissions CO was also only associated with respiratory readmissions in those aged 60 years and over in Suzhou and Qingdao (**Appendix C9. Figure C9.4**). For those aged under 60 years significant associations for first-time respiratory spells were seen in Harbin for same-day NO_2 (4.80% [1.44, 8.27]) and Liuzhou for lag-1 O_3. For participants aged less than 60 years risk of respiratory readmissions appeared to be associated with PM_{10} in Suzhou (1.34% [0.02, 2.70]) and PM_{10} and SO_2 in Haikou (4.11% [0.27, 8.11] and 41.13% [7.83, 84.72]) (**Appendix C9. Figure C9.5**).

For subgroup analysis by age, the pooled results across all five regions are shown in **Appendix C9 Figure C9.7 and C9.8.** For major cardiovascular disease spells, the only significant associations were seen in those aged 60 years and over, where NO_2, SO_2, PM_{10} and $PM_{2.5}$ were all associated with increased risk of first-time spells (2.14% [1.55, 4.17], 2.61% [0.51, 4.75], 1.09% [0.10, 2.14], and 1.08% [0.14, 2.02]), respectively in time-series analysis. Similarly, for major cardiovascular disease readmission spells same-day NO_2 was associated with a 2.21% (0.48, 3.98) increase in risk in those aged 60 years and over only. For major respiratory spells the only significant pooled associations were observed in those aged 60 years and over for first-time spells was for lag-2 $PM_{2.5}$ and lag-3 PM_{10} which were associated 0.84% (0.01, 1.69) and 0.89% (0.30, 1.49) increased risk, respectively

(**Appendix C9 Figure C9.8**). There were no associations between acute AAP exposure and respiratory disease spells in those aged less than 60 years in pooled analysis (**Appendix C9 Figure C9.9**).

29,447 and 43,953 cardiovascular disease spells occurred in males, and females, respectively across the five regions (**Appendix C10 Tables C10.1 and C10.2**). Greater numbers of cardiovascular disease readmissions compared to first-time spells were observed in males and females (7329 versus 22,208, and 11,469 versus 32,484, respectively). For major cardiovascular disease spells in Qingdao, PM_{10} appeared to be associated with increased risk of first-time spells in males only (1.61% [0.30, 2.94]) (**Appendix C10 Figure C10.1**). However, for major cardiovascular disease spells, in Suzhou, PM_{10} and NO_2 appeared to be associated with increased risk of first-time cardiovascular spells in females only (1.25% [0.06, 2.45], 3.27% [0.05, 6.60]) (**Appendix C10 Figure C10.2**). In Haikou associations between AAP and cardiovascular disease spells were observed only in females (**Appendix C10 Figure C10.3).**

10,093 respiratory disease spells occurred in males and 10,986 in females. Acute AAP exposure appeared to be only associated with an increased risk of first-time respiratory spells in females (**Appendix C10 Figure C10.5**). For respiratory disease readmissions, $PM_{2.5}$ exposure in Suzhou was associated with increased risk of respiratory readmissions in both males and females (1.68% [0.26, 3.12], and 1.96% [0.25, 3.68], respectively). CO was only associated with respiratory readmissions in Suzhou males (22.17% [6.83, 39.71] for lag-0) and NO_2 with respiratory readmissions in Qingdao for females only (9.13% [1.82, 16.97] for lag-1). In Haikou SO_2 was associated with respiratory readmissions in females only, while PM_{10} and $PM_{2.5}$ appeared associated with respiratory readmissions in males (**Appendix C10 Figure C10.6**).

For pooled analyses by sex, CO was associated with increased risk of first-time cardiovascular disease across regions in males only, at a lag of 1 and 0-1 days (7.35% [0.56, 14.61], and 10.16% [0.20, 21.16], respectively). There were no pooled estimates

which remained significant in time-series and case-crossover analysis for AAP exposure and cardiovascular disease in females. However, in females, PM_{10} and $PM_{2.5}$ was associated with increased risk of first-time respiratory disease across regions at a 3-day lag (0.69% [0.10, 1.25] and 0.91% [0.20, 1.60]) **(Appendix C10 Figure C10.10).** CO was associated with respiratory readmissions in males (10.16% [0.15, 21.2] at a 0-1-day lag).

5.5 Discussion

5.5.1 Summary of main findings

In this study, the relationships between acute AAP exposure and risk of cardio-respiratory hospitalisations were explored using 219,020 Chinese adults located across five geographically varied Chinese localities. Cardio-respiratory hospitalisations were reclassified into the derived outcome variable of "spells" allowing the respective risk to be compared for first-time hospitalisations and readmissions in the same population. Compared to those with first-time cardio-respiratory spells, participants with cardio-respiratory readmission spells were older, less physically active, had poorer lung function, and higher prevalence of both cardio-respiratory diseases and symptoms at baseline.

Temporal trends in cardio-respiratory spells were evident both for first-time and readmission spells, but these did not appear consistent across regions. Northernmost CKB regions with greater temperature variability (Harbin, Qingdao and Suzhou) had high degrees of seasonality in recorded cardio-respiratory spells with higher spell counts during winter months. This trend was less evident in the Southern CKB regions (Haikou and Liuzhou). Longer-term temporal trends were also evident with increasing cardio-respiratory spell counts in regions; the greatest increase appeared in Suzhou likely due to the longer study period used in this region.

Acute AAP exposure was associated with increased risk of both cardiovascular (including all-type stroke) and respiratory spells with little consistent difference in magnitudes of generated risk estimates between first-time and readmission spells across regions. The one

exception to this was the region of Suzhou, where acute AAP exposure was overall more associated more with readmissions than first-time spells. On the whole, variability in the magnitude and consistency of risk estimates were observed between CKB regions. Potential explanations for this may include the differing pollutant concentrations (including peak concentrations as well as degree of variation) and compositions, [294, 295] participant characteristics, underlying health care practices, between regions. This heterogeneity is also a potential explanation for the relative absence of consistent risk estimates from pooled analysis, with only $PM_{2.5}$, CO and NO_2 associated with increased risk of cardio-respiratory spells, and for first-time spells only. Further explanation for the observed associations with first-time spells may surround the construction of the derived outcome variable of spells whereby readmissions were classified based on a repeat hospitalisation of the same major disease type. Therefore, participants with first-time spells may in fact have additional comorbid conditions that make them susceptible to the effects of AAP exposure.

When using two-pollutant models, significant effects were still observed between acute AAP exposure and risk of cardio-respiratory spells, but differences in specific pollutants remaining significant in two-pollutant models were apparent between regions. In Haikou, results from two-pollutant models suggested PM as the contributing pollutant associated with risk of stroke with associations remaining consistent upon adjustment for SO_2. However, in Suzhou, SO_2 remained significantly associated with cardiovascular disease and all-type stroke readmission spells following adjustment for $PM_{2.5}$, suggesting SO_2 may reflect the pollutant of concern in this region. This exemplifies how the acute effects of AAP exposure across CKB regions may be attributable to differing pollutants in that region and is unsurprising given differing pollutant concentrations, sources and composition throughout China in addition to the differing populations across regions.

Regarding the subgroups examined, in all regions (except Haikou), most associations between AAP exposure and cardiovascular spells were in those aged 60 years and over, a finding also seen in pooled analysis. This is a finding also supported within the existing

evidence base with age having been demonstrated a common effect modifier for the vulnerability of cardio-respiratory disease following AAP exposure[296] both in HICs[220] and LMICs[297] including China.[129] Explanations for this are principally hypothesised to involve increased frailty as a result of pre-existing health conditions (whether diagnosed or not) [298] as well as differing indoor/outdoor exposure patterns. [299] Risk between $PM_{2.5}$ and CO exposures with respiratory disease spells also appeared to vary between age groups only significant in those aged 60 years and over also conforming to the explanation above.

Differences in risk also appeared to be present by sex, particularly for respiratory disease where AAP was associated with first-time respiratory spells in females only, both within CKB regions (Harbin and Qingdao) and in pooled analysis across regions. This is a finding that has been observed in other studies performed in China [162, 188, 300], with possible explanations including increased biological susceptibility with females having smaller lung tissue and trachea exposed to the same magnitude of pollution, in addition to differences in dermal absorption and lung function between sexes [301] potentially influencing pollutant uptake, gas blood barrier permeability has also been found to differ by sex. [302] An additional explanation for this finding could also be the differing age distribution by sex in the study population (see **Table 4.3**).

5.5.2 Strengths and limitations

While studies examining the acute health effects of AAP exposure in China have typically had much larger sample sizes than seen in this study, [195, 221, 224] the predominant use of administrative datasets has meant that individual-level variables have seldom been incorporated. A principal strength of this study was its use of an established prospective cohort allowing the characteristics of individuals experiencing the events of interest to be examined. It also allowed the associations of acute AAP exposure with risk of both first-time hospitalisations, and readmissions, to be comparatively assessed. The incorporation of morbidity as an outcome of interest was an additional strength to this study, as highlighted in **Chapter 3** pollutant-related morbidity remains relatively under-researched in China

compared to mortality. A further considerable strength was the use of both time-series and case-crossover analyses as analytical methods, thereby improving the robustness of generated effect estimates with the majority of generated risk estimates consistent across both study designs.

There are, however, several limitations applicable to the study. Firstly, despite the considerable size of the CKB study it has mean daily hospitalisation counts considerably lower than other studies [195, 221, 224] therefore limited power due to a low number of daily spell counts is a sizable limitation. Whilst there has been little formal development in methodologies to assess power in time-series and case-crossover analyses [303], low daily counts are known to limit the credibility and power of time-series studies. [269, 303] This limitation of restricted power also prevented assessing additional potential effect modifiers available in the CKB baseline survey and which may exemplify differing effects of AAP exposure on population subgroups, effect modifiers such as socioeconomic status [304], and body composition. [305] Such effect modifiers may be of considerable importance in addition to that of hospitalisation type assessed both in this study as well as in studies performed outside of China. [259] [306]

While two-pollutant models were constructed in this study, observed collinearity in pollutant concentrations meant fitting multi-pollutant models was unfeasible. [307, 308] This is in addition to the potential biases arising from use of multi-pollutant models with differing levels of measurement error present for pollutants. [293] It is therefore likely as observed in the majority of studies examining the health effects of AAP exposure that the models incorporating a "single" pollutant as exposure are in fact a likely surrogate for a set of highly correlated pollutant exposures. [308] It is also inevitable that even when using bi-pollutant models only part of the total impact is captured.

Secondly, while GAMs remain a common choice for time-series analysis assessing the short-term health effects of AAP exposure, they have faced recent criticism regarding their use in epidemiological studies of AAP. Firstly, it has been found that when the relative risks

to be estimated are small, and at least two non-parametric smooth functions are included in the model, default convergence parameters used by GAMs may lead to biased estimates, overestimating the true parameter of interest. [309] Secondly, studies have also found that should "concurvity" (the equivalent of multicollinearity in generalised additive models) be present, then underestimation of the standard errors of parameters in GAMs can occur leading to significance tests with inflated type-1 error. [310] As a result of these findings, certain researchers have begun to favour alternative parametric smoothing functions instead, such as natural cubic splines, within a generalised linear model (GLM) framework. [311] Whilst it is possible these limitations of GAMs may have affected some results of this study, it is unlikely to impact the overall conclusions, particularly given the consistency between estimates generated by time-series analysis and case-crossover analysis.

The GAMs used in this study utilised a three-day moving average lag measure of daily temperature to control for the potential confounding effects of temperature on cardio-respiratory spells. Whilst this is a suitable lag choice to control for the short-term health effects of temperature, it's important to note that evidence has shown effect of adverse cold temperature on mortality/morbidity could be delayed for up to four weeks following exposure [312]. This would not be captured by the GAM model used in this study although the impact of such lagged temperature effects on risk estimates presented in this study are likely to be minimal.

The presence of AAP measurement error is a further limitation common to the majority of studies assessing the acute health effects of AAP exposure, as spatially aggregated measures of AAP exposure are likely unreflective of true exposures experienced by individuals. As highlighted in **Chapter 2,** this error likely consists of an unknown combination of both Classical and Berkson exposure measurement errors. Examples of these in this specific study may include, differences between true AAP levels and measurement of these via fixed-site monitors (Classical error), and differences between individual and population average exposures (Berkson error). While only Classical measurement error can introduce

bias (typically towards the null), Berkson measurement error can increase estimate variance. Since the exact amount of each can never be truly quantified, the majority of studies, including this one, will have an unknown combination of both. An additional limitation relates to those days with missing AAP data in the study period. While missing AAP concentration values were replaced with the previous day's concentration, should many consecutive days have missing values, this may be an unsuitable choice. A better imputation approach that minimises misclassification of AAP concentrations would have been estimating AAP values from other nearby monitors as done in other studies [313, 314]. While such approaches were not feasible in this study, given that the utilised AAP data was constructed in China, it's still a limitation of this study worth noting.

Finally, although superior to using the original CKB hospitalisation data (as shown in **Section 5.3.2**), utilisation of spells as a derived outcome of interest is also subject to several limitations. Firstly, readmissions were defined as a second-time occurrence of cardiovascular or respiratory disease, respectively; thus, individuals with existing comorbidities other than cardio-respiratory causes remained treated as first-time spells. Therefore, some individuals with first-time spells may, in fact, have other pre-existing diseases that result in increased susceptibility to AAP. This may be a substantial reason for the increased risk of first-time events versus readmissions in some regions. Secondly, as highlighted in **Chapter 4** CKB obtains hospitalisation data from established disease registries and health insurance databases, while mortality data are acquired from the Disease Surveillance Points network. Temporal discrepancies may be present between the true date of an individual's hospitalisation versus the date of recorded admission. This has the potential to bias risk estimates, particularly if such discrepancies are systematic in nature, e.g. through potential differences health insurance practices within regions.

5.5.3 Comparisons with the relevant literature

5.5.3.1. Particulate matter and cardio-respiratory disease

As highlighted in **Chapter 3** of this thesis, numerous studies performed in China have found consistent associations between acute exposure to both PM_{10} and $PM_{2.5}$ with adverse cardio-respiratory effects, the majority of which have focused exclusively on mortality, [114, 117, 127-132, 135, 136, 141, 142, 144, 150, 151, 157, 161, 167, 168, 170, 173, 180, 185, 188, 205, 206] and morbidity less frequently examined. [110, 115, 124, 134, 139, 155, 165, 166, 174, 177, 183, 217] Chinese studies with higher daily event counts than seen in this study have found both PM_{10} and $PM_{2.5}$ associated with increased risk of cardiovascular disease mortality [141, 173] with greater risk estimates often observed for $PM_{2.5}$ versus PM_{10}. [131, 141] This difference in risk has contributed to the hypothesis of $PM_{2.5}$ as the more harmful PM size fraction given its capacity to penetrate deeper into the alveolar-capillary membrane and infiltrate the cardiovascular system with greater ease compared to PM_{10}. [315] In this study, in the CKB region of Suzhou $PM_{2.5}$ was the only size fraction of PM exposure associated with readmissions of cardiovascular disease conforming to this hypothesis. However, in the region of Qingdao only PM_{10} was associated with first-time cardiovascular spells and not $PM_{2.5}$. Potential reasons for this could include compositional differences between PM_{10} and $PM_{2.5}$ in Qingdao, with studies also finding that mass alone is not always a good predictor of adverse health effects where compositional differences in PM are also present. [316]

Mechanistic pathways by which acute PM exposure has been linked to the onset of cardiovascular disease (including stroke) involves both the direct effects resulting from the translocation of fine particles into the bloodstream [317, 318] and indirect effects resulting from systemic inflammation [319] and subsequent oxidative stress. [320] Such PM-mediated effects are thought to include atherosclerotic plaque variability and thrombus formation [321] as well as increased vasoconstriction and autonomic nervous system variability documented through various toxicological studies. [322, 323] Experimental studies have also found nanoparticles (between 0.001 and 0.1 μm in size) reaching the trigeminal nerves, brainstem, and the hippocampus, [324] resulting in neurodegenerative pathology in-vivo [325, 326] leading to

increased stroke risk. It has been hypothesised that particulate matter has the greater impact on cardiovascular health than gaseous AAP as inhaled particles can contain a broad range of toxic particles, [327] many of which are toxic, with toxicity inversely related to size. [328]

Several large time-series and case-crossover studies have found consistent associations between PM exposure and cardiovascular morbidity both for PM_{10} [154, 169, 174, 177, 178, 184, 212] and $PM_{2.5}$. [154, 165, 182, 183] However, these findings are not unanimous, with other studies in China finding no such association. [115, 176] Hypothesised explanations for the lack of associations include misclassification of PM exposure relative to gaseous pollutants or PM exposure less representative of biologically relevant pollutant mixtures in certain study areas. [115] Overall, of those studies documenting associations between PM exposure and cardiovascular morbidity, these have found risk estimates of considerably smaller magnitude than observed in this study. For example, of the studies above, in a sample of ~57,000 hospitalisation episodes in Shanghai, the largest risk estimate was for same-day PM_{10} exposure and cardiac arrhythmia, where a 10 $\mu g/m^3$ increase associated with a 0.56% (0.42, 0.70) increase in hospitalisations. [177] Similarly, only one study to date has examined PM exposure in China and associated stroke hospitalisations exclusively, finding same-day $PM_{2.5}$ associated with 0.17% (0.02, 0.32) increased stroke risk in Beijing.[183] This is a much smaller estimate than observed in our study where 10 $\mu g/m^3$ increases in PM_{10} and $PM_{2.5}$ in Haikou were associated with 6.01% (2.63, 9.51) and 6.79% (2.63, 11.13), and 2.93% (0.02, 5.94) and 4.27% (0.70, 7.96) increased risk of first-time and readmission stroke spells, respectively. Possible explanations for the larger risk estimates observed in this study will be explored in detail at the end of this section.

Many studies have also found acute exposures to both PM_{10} and $PM_{2.5}$ associated with an increased risk of respiratory mortality in China. [111, 116, 131, 136, 137, 140, 150, 156, 157, 167, 168, 170, 173, 205] Similar to this study, evidence from multi-city studies in China has also demonstrated between city heterogeneity in risk estimates for PM exposures and respiratory disease mortality. For example, a study examining six cities in the Pearl-river Delta region of China

found significant associations in four of the six cities. [140] Similarly, a study examining acute PM_{10} exposure and COPD mortality in three Chinese regions (plus Hong Kong) found significant associations in only two regions and results attenuated upon controlling for SO_2. [144] Observed associations between PM exposure and respiratory disease mortality are far from unanimous [114, 129, 132, 138], for respiratory morbidity while both $PM_{2.5}$, [137, 166], and PM_{10} [124, 155, 174, 176] have been associated with increased risk, other studies have found no such association. [110, 115, 134]

Some of the results described in this chapter for respiratory disease risk were of similar size to those documented in previous studies examining acute PM exposure and respiratory morbidity. [137, 174] For example, a study in Beijing found a 10 μg/m^3 increase in $PM_{2.5}$ at a 3-day lag associated with 0.69% (0.55, 0.82) increased risk of respiratory disease admissions, similar to the 0.64% (0.04, 1.26%) observed in Harbin in this study. However, this finding is not consistent, as other risk estimates observed in this study were much larger than seen in other studies [124, 176] even studies with higher PM levels. [155, 166]

Acute PM exposure has been associated with free radical production and subsequent oxidative stress in lung cells[329] hypothesised as the primary mechanism for lung injury. Other hypothesised mechanisms include imbalances in intracellular calcium homeostasis [330] and inflammatory induced lung changes. [331] Acute PM exposure has also been frequently associated with impaired lung function (including reductions in both FEV_1 and FVC) both in healthy individuals as well as those with existing respiratory diseases [332-334]. These findings specifically support the findings of this study where $PM_{2.5}$ exposure was associated with increased risk of both first-time respiratory disease and readmissions in Suzhou.

5.5.3.2. Gaseous AAP and cardio-respiratory disease

Other studies from China have documented significant associations between acute gaseous AAP exposure and adverse cardio-respiratory outcomes including both mortality [114, 117, 129, 132, 144, 150, 170, 173, 180, 184, 186, 206, 207, 210, 213, 221, 335] and morbidity, [110, 124, 154, 155, 164, 174, 178, 182] again

with a greater number of studies examining the former. Studies examining morbidity have documented associations between gaseous AAP and increased risk of cardio-respiratory hospitalisations in China [115, 174, 212]. However, these studies have predominantly included NO_2 and SO_2, the effects of CO and O_3 on cardio-respiratory morbidity in China more under-researched.

Relative to PM exposure, the mechanisms by which acute exposure to gaseous AAP is thought to induce adverse cardio-respiratory effects remains uncertain given its inability to directly translocate into bloodstream. However, acute gaseous AAP exposure has been linked with induced activation of oxidant pathways [336], subsequent oxidative stress, [337, 338] and both systemic and localised inflammation. [339, 340] Toxicological and experimental studies have also found exposure to various gaseous pollutants associated with increased endothelial dysfunction [341, 342] as well as the promotion of cardiovascular sequelae. [343]

The evidence is not consistent for all pollutants. In China, several time-series studies have found associations for acute exposure to both SO_2, and NO_2, and risk of cardiovascular morbidity, [115, 154, 164, 174, 178] a number of these remained consistently associated with cardiovascular morbidity even following adjustment for PM. [115, 164, 178] Associations have been documented across a range of studied lag dimensions with significant findings ranging from the same-day and/or previous day only [177, 178] to a 7-day lag only[154] but are rarely consistent across the full range of lags studied, a possible explanation being differing temporality of disease onset in study populations. Contrastingly other studies have found no relationship between SO_2 or NO_2 and cardiovascular morbidity in China. [154, 176]

Only one study to my knowledge has examined the acute effects of CO exposure on cardiovascular disease morbidity in China.[344] It reported that a 1mg/m^3 increase in ambient CO was associated with 2.80% (2.20, 3.30) increased risk of cardiovascular disease hospitalisation in Beijing. Considering the larger increment used, this is a considerably smaller estimate than those generated in this study where 100 μg/m^3 increase in CO was

associated with 5.65% (0.84, 10.70) higher risk of first-time cardiovascular disease spells across regions. No studies to my knowledge in China have examined O_3 exposure and cardiovascular morbidity; however, several studies have found it associated with cardiovascular mortality in China.

For respiratory disease, acute gaseous pollutant exposure has been associated with oxidative stress, [336] bronchoconstriction and dyspnea, [345, 346] plus bronchial hyperreactivity, [347] with its documented capacity to damage and inflame the airway epithelium [348] with both NO_2 and SO_2 now classed as respiratory irritants [349] and NO_2 exposure also found to increase respiratory infection risk. [349, 350] In China specifically, studies have found both NO_2 and SO_2 associated with respiratory morbidity, for example, a time-series study performed in Shanghai found SO_2 exposure at a 3-day lag was associated with a 4.82% (4.58, 5.06) increase in outpatient visits for acute bronchitis [124]. Similarly, a time-series study in Beijing found same-day NO_2 associated with a 2.13% (1.07, 3.19) increase in hospitalisations of respiratory disease. [174]

No studies to my knowledge have examined the effects of O_3 and CO on respiratory morbidity; however large time-series studies have found, O_3 [157] and CO [156] to be associated with respiratory mortality in China along with SO_2 [170, 207] and NO_2. [129, 150] For CO exposure, a study performed in the Pearl River Delta region of China found a 0.5ppm increase in CO associated with 3.72% (1.71, 5.76) increased risk of respiratory mortality. The study outlined in this chapter found CO exposure associated with respiratory readmissions in the Suzhou region but with a higher excess risk (17.11% [5.41, 30.11). For O_3 the aforementioned study found it associated with a 0.87% (0.39, 1.36) increased risk of mortality across four Chinese cities, following adjustment for other pollutants [351]. This is in contrast to the study described in this chapter which found no associations between O_3 exposure and risk of respiratory disease morbidity.

There are several potential explanations for the greater magnitude of risk found in the study in this chapter than seen in the surrounding evidence base both for PM and gaseous pollutants. Firstly, CKB study populations likely consist of older individuals than in previous time-series and case-crossover studies which utilise entire populations not constrained within a closed cohort. This may have resulted in greater associated risk for CKB participants with greater adverse effects of AAP exposure documented in older ages both in China [129] and HICs. [220, 352]

Secondly, AAP levels in this study were lower than in the aforementioned studies examining AAP exposure and morbidity in China. [137, 166] This is likely because the majority of previous studies have been performed on either the Chinese "mega-cities" (typically Beijing and Shanghai) or large for nationwide multi-city studies. None to my knowledge have examined a small subset of smaller cities, with none of the regions included in this study described in the top 10 largest Chinese cities by population.[353] Furthermore, the study period for four of the five regions began immediately after implementation of China's "air pollution action plan" when PM concentrations, in particular, began to fall. It is therefore plausible for both these reasons individuals may be prompted to take fewer preventative measures against AAP exposures in the studied CKB regions, measures such as face masks, limiting time outside, and, personal air purifiers, all of which have been associated with some degree cardio-respiratory benefit in China. [354-356] With no minimum threshold identified for the adverse effects of AAP on mortality, potential reductions in (or total lack of) personal preventative measures may explain the increased risk in this study, particularly when coupled with the extreme peaks in pollutants still documented in all the studied CKB regions.
Finally, as discussed it is also possible that "concurvity", the equivalent of multicollinearity in GAMs could have led to underestimation of parameter variance and overstatement of association significance, [310]. However, given the consistency in observed pollutant coefficients between both time-series, case-crossover analysis this is unlikely. AAP

measurement error is also a likely possibility, but as highlighted in **Chapter 2**, this is more likely to result in a bias towards the null.

5.5.4 First-time spells versus readmissions

This study found acute AAP exposure was associated with increased risk of both first-time cardio-respiratory hospitalisations and readmissions, with little apparent difference in the magnitude of risk estimates between respective admission types. While it is possible that acute AAP exposure is associated with risk of equal magnitude in individuals with and without prior disease alternate explanations also remain a possibility. Firstly, as highlighted in **Section 5.3.2**, first-time spells were defined as a first-time occurrence of a cardiovascular or respiratory disease admission, respectively, therefore a participant with a first-time cardiovascular spell may have had prior comorbid conditions that increased their susceptibility to AAP exposure. This may also explain the greater number of significant risk estimates seen for participants aged 60 years and over who likely have a greater number of comorbidities than those under 60 years.

Secondly, individuals with existing cardio-respiratory disease prevalence may take increased personal precautions against AAP exposure; this could also potentially explain the associations observed in this study, where AAP exposure was associated with first-time spells only. Thirdly, as shown in **Table 5.6**, individuals with first-time cardio-respiratory spells reported greater levels of physical activity and lower prevalence of breathlessness and chest pain when walking. Therefore, individuals with first-time cardio-respiratory spells may be more mobile than those with readmissions who spend a greater amount of time indoors and less exposed to AAP. Finally, it is possible that the limitations outlined in **Section 5.5.2** may also be responsible.

5.6 Conclusions

In conclusion, this study observed temporal trends in both cardio-respiratory spells counts and AAP levels in all five urban regions of CKB particularly for PM and SO_2 concentrations,

which have declined across all regions. Significant differences in baseline socio-demographic and lifestyle characteristics in participants by type of admission for cardio-respiratory diseases were also observed. Acute exposure to AAP was associated with increased risk of both first-time and readmissions of cardio-respiratory diseases across five geographically diverse CKB regions. The magnitude of associated risk did not appear to differ drastically between first-time and readmissions of cardio-respiratory disease, suggestive that not only individuals with pre-existing diagnosed medical conditions are susceptible to the effects of gaseous AAP exposure in CKB. Although given the observed spatial variability the degree in which these findings can be extrapolated across China is arguable, it is at the very least suggestive policy to reduce AAP exposure may reduce risk of cardio-respiratory hospitalisation both in those with and without pre-existing disease. However, as highlighted in this chapter there are also alternative explanations for these findings and this study is subject to several major limitations. Further research is necessary with greater sample size, improved classification of admission type and improved exposure classification are required to further validate the findings of this study.

Table 5.1 Classification of cardio-respiratory spells into first-time spells and readmissions, respectively

Disease type (ICD-10)	First-time spells	Readmission spells
Major cardiovascular disease (I00-I99)	First-time cases of cardiovascular disease in participants with none of the following reported at CKB baseline; hypertension, ischaemic heart disease, and/or stroke/transient ischaemic attack (TIA).	Cardiovascular spells in participants with previously recorded cardiovascular spell during follow-up or a first-time spell in participants with any of the aforementioned diseases at CKB baseline
Major respiratory disease (J00-J99)	First-time cases of respiratory disease in participants with none of the following reported at CKB baseline; emphysema/bronchitis, asthma and/or tuberculosis.	Respiratory spells in participants with a previously recorded respiratory spell during follow-up or alternatively a first-time spell in participants with any of the aforementioned diseases at CKB baseline
All-type stroke (I60-I69)	First-time cases of all-type stroke disease in participants with no reported history of stroke TIA at CKB baseline	All-type stroke spells in participants with a previously recorded all-type stroke spell during follow-up or first-time spell in participants with reported history of stroke or TIA at CKB baseline

Abbreviations: ICD-10, International Classification of Diseases 10th edition

Table 5.2 AAP and meteorological summary statistics for the five urban CKB regions

	Harbin (2013-2016)				Qingdao (2013-2016)				Suzhou (2010-2016)				Liuzhou (2013-2016)				Haikou (2013-2016)			
	Mean	**Min**	**Max**	**IQR**	**Mean**	**Min**	**Max**	**IQR**	**Mean**	**Min**	**Max**	**IQR**	**Mean**	**Min**	**Max**	**IQR**	**Mean**	**Min**	**Max**	**IQR**
NO_2 ($\mu g/m^3$)	49.5	13.7	159.5	27.5	35.8	7.3	123.0	21.7	54.4	7.6	168.0	28.1	27.1	9.0	106.7	13.7	14.1	4.0	40.9	6.5
SO_2 ($\mu g/m^3$)	40.5	3.2	237.3	47.0	31.8	5.2	217.9	20.9	24.7	1.0	140.0	16.8	28.5	5.6	109.6	19.6	6.0	2.1	31.2	2.6
PM_{10} ($\mu g/m^3$)	98.2	16.1	931.6	74.5	104.8	19.3	454.7	65.3	80.0	2.0	678.0	54.0	81.7	16.7	310.4	59.3	40.3	9.0	166.9	21.3
$PM_{2.5}$ ($\mu g/m^3$)	66.1	7.8	758.7	58.5	52.3	6.6	311.0	37.1	53.5	1.0	323.3	36.9	56.8	9.9	253.4	43.0	22.4	3.6	131.3	15.3
CO (mg/m^3)	1.0	0.2	4.7	0.5	0.9	0.2	11.0	0.4	0.9	0.02	3.0	0.4	1.1	0.5	4.1	0.3	0.7	0.1	4.2	0.3
O_3 ($\mu g/m^3$)	57.7	9.1	184.5	35.7	88.0	11.26	244.9	51.6	56.3	2.0	220.9	41.3	88.8	0.1	222.0	51.8	60.3	9.4	190.3	37.3
Temp (°C)	5.4	-26.0	29.2	28.4	13.8	-11.1	30.7	16.4	17.2	-6.2	35.7	14.9	21.6	3.8	33.4	12.5	25.0	6.9	33.3	6.6
RH (%)	65.9	14.9	97.1	19.2	69.6	23.4	99.6	25.5	70.6	23.6	96.9	18.0	71.7	24.4	98.9	17.6	81.2	46.4	98.3	9.8

Abbreviations: IQR, interquartile range; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; CO, carbon monoxide; O_3, ozone; Temp, temperature (degrees Celsius); RH, relative humidity (%)

Table 5.3 Annual mean AAP levels by study year and percent change* throughout the study period in four of the five CKB regions

	Harbin					Qingdao					Liuzhou					Haikou				
	2013	2014	2015	2016	% change	2013	2014	2015	2016	% change	2013	2014	2015	2016	% change	2013	2014	2015	2016	% change
NO_2	53.5	52.9	49.4	42.3	-20.9	35.5	40.9	33.5	33.2	-6.5	40.3	30.1	23.7	24.1	-40.2	14.0	14.7	13.0	14.5	+3.6
SO_2	39.0	56.4	38.7	27.8	-28.7	45.3	33.4	27.5	21.7	-52.1	50.2	34.1	24.5	21.4	-57.4	6.6	6.0	5.3	5.9	-10.6
PM_{10}	106.9	109.5	102.6	74.0	-30.8	127.6	107.0	97.4	88.4	-30.7	128.8	94.6	70.9	67.7	-47.4	44.4	40.9	38.5	37.7	-15.1
$PM_{2.5}$	71.3	74.1	69.2	50.0	-29.9	58.0	55.5	51.1	44.8	-22.8	95.9	66.9	49.3	44.2	-53.9	25.1	22.8	21.3	20.6	-17.9
CO	0.96	0.86	1.0	1.2	+25.0	0.88	0.85	0.91	0.78	-11.4	1.01	1.07	1.07	1.05	+4.0	0.72	0.65	0.65	0.60	-16.7
O_3	43.6	64.9	60.6	61.2	+40.4	76.1	98.0	90.1	87.3	+14.7	113.0	97.1	85.6	77.8	-31.2	55.6	52.9	63.7	68.6	+23.4

All pollutants quantified in $\mu g/m^3$ (except CO in mg/m^3)
Abbreviations: IQR, interquartile range; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; CO, carbon monoxide; O_3, ozone.
*Percent changes calculated between first and last year of study period (2013 and 2016)

Table 5.4 Annual mean AAP levels by study year and percent change* throughout the study period in Suzhou

	Suzhou							
	2010	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**% change**
NO_2	64.3	63.1	55.5	43.5	50.1	43.5	49.6	-22.9
SO_2	33.1	33.0	24.2	23.1	21.3	23.1	16.7	-49.5
PM_{10}	99.6	109.1	75.2	57.5	66.1	57.5	73.4	-26.3
$PM_{2.5}$	53.4	51.8	51.8	52.4	60.6	52.4	46.2	-13.5
CO	0.85	0.91	0.84	0.80	0.87	0.80	0.94	+10.6
O_3	50.3	51.9	47.5	46.5	48.5	46.5	90.7	+80.3

All pollutants quantified in $\mu g/m^3$ (except CO in mg/m^3)
Abbreviations: IQR, interquartile range; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; CO, carbon monoxide; O_3, ozone
*Percent changes calculated between first and last year of study period (2010 and 2016)

Table 5.5 Frequencies of cardio-respiratory spells by spell type and region across five CKB urban regions (2013-2016*)

Summaries	Harbin (n=54,894)	Qingdao (n=34,503)	Suzhou (n=52,617)	Liuzhou (n=47,920)	Haikou (n=29,086)	Total (n=219,020)
Major cardiovascular disease (I00-I99†)						
Total	32,823	9793	7450	12,056	11,278	73,400
First-time	7134	2487	3039	3277	2771	18,708
Readmissions	25,689	7306	4411	8779	8507	54,692
Mean daily count	22.75	6.78	2.91	10.14	7.82	-
Max daily count	73	22	15	27	34	-
Fatal cases (%)	1268 (3.86)	410 (4.19)	664 (8.91)	715 (5.93)	632 (5.60)	3689 (5.03)
Major respiratory disease (J00-J99†)						
Total	4909	2082	6986	3902	3200	21,079
First-time	2629	1077	3360	1844	1693	10,603
Readmissions	2280	1005	3626	2058	1507	10,476
Mean daily count	3.40	1.44	2.73	3.28	2.22	-
Max daily count	13	9	17	14	17	-
Fatal cases (%)	287 (5.85)	51 (2.45)	108 (1.55)	180 (4.61)	108 (3.38)	734 (3.48)
All-type stroke (I60-I69†)						
Total	17,554	2124	2926	4548	4607	31,759
First-time	6578	910	1618	2125	1868	13,099
Readmissions	10,976	1214	1308	2423	2739	18,660
Mean daily count	12.16	1.47	1.14	3.83	3.19	-
Max daily count	43	11	7	12	14	-
Fatal cases (%)	571 (3.25)	109 (5.13)	282 (3.73)	350 (7.70)	313 (6.79)	1625 (5.12)

*Suzhou 2010-2016

† International Classification of Disease 10th edition

Table 5.6 Baseline characteristics of participants by cardio-respiratory spell type across all five urban CKB regions combined

Characteristics*	All major cardiovascular disease		All-type stroke		All major respiratory disease	
	First-time (n=18,709)	Readmission (n=25,086)	First-time (n=13,099)	Readmission (n=10,229)	First-time (n=10,603)	Readmission (n=5038)
Sex						
Male	39.0	39.2	41.9	49.5	40.9	39.3
Female	61.0	60.8	58.1	50.5	59.1	60.7
Age (years), mean (SD)	55.1 (10.3)	59.6 (9.4)	59.0 (10.1)	61.5 (9.3)	57.2 (10.8)	59.7 (9.9)
Education						
No formal school	12.4	11.4	12.4	12.9	14.0	13.0
Primary school	21.1	21.6	21.8	21.1	23.2	24.2
Middle school	31.5	32.0	31.7	33.6	30.8	30.9
High school or above	35.0	35.0	34.1	32.4	32.2	31.8
Passive smoking						
Never	26.0	27.6	25.8	26.2	24.2	26.0
Yes, but not now	36.6	35.5	37.2	36.4	38.0	35.6
Yes, at present	37.5	36.9	37.0	37.3	37.8	38.3
Smoking category						
Never smoker	63.6	64.3	63.9	63.8	62.9	63.3
Occasional smoker	5.3	5.0	5.1	4.6	5.1	5.0
Ex-regular smoker	6.4	8.0	6.5	7.0	6.6	8.5
Regular smoker	24.7	22.6	24.5	24.6	25.4	23.3
Physical activity (MET-hrs)						
<5	48.4	54.3	50.4	55.4	47.7	52.1
5-10	40.6	36.7	39.0	34.8	41.3	38.6
>10	11.0	9.0	10.6	9.9	11.0	9.3
Mean ± SD	18.5 (11.8)	17.0 (9.3)	18.1 (10.7)	16.5 (9.3)	18.5 (12.5)	17.5 (11.4)
Alcohol category						
Never	43.1	45.1	44.6	45.7	44.4	47.4
Occasional/monthly	36.0	33.0	33.9	32.5	34.9	32.3
Ex-regular/reduced intake	3.4	5.3	3.8	3.4	3.8	4.6
Current regular	17.5	16.6	17.7	18.4	16.9	15.7
Self-rated health						
Excellent	23.2	17.4	20.1	18.5	20.2	17.3
Good	23.5	18.9	21.6	18.7	21.3	17.0
Fair	44.6	49.4	47.4	46.7	47.1	48.4
Poor	8.7	14.4	10.9	16.0	11.4	17.2
Household air pollution						
Currently use wood/coal	9.5	5.5	8.4	8.1	13.3	10.2
Previously used wood/coal	49.0	47.2	48.2	48.7	51.8	51.3
Prior disease history						
CHD	-	10.35	5.4	7.0		
Hypertension	-	39.0	18.6	30.1	15.0	18.5
Diabetes	4.0	4.4	6.6	8.5		
Stroke	-	5.0	-	11.4	2.6	2.4
Emphysema/Bronchitis	2.8	3.2	2.6	2.6	-	13.5
TB	1.9	2.0	1.9	1.9	-	5.8
Family history of disease†						
Stroke	18.5	22.3	21.3	24.0	18.2	17.3
Myocardial infarction	4.2	5.2	4.9	4.0	3.7	4.5
Cardio-respiratory symptoms‡						
Breathlessness	4.1	8.5	5.5	7.6	5.3	12.0
Chronic cough	3.1	3.7	3.2	3.0	3.5	10.0
Chest pain	2.4	5.6	3.6	5.0	3.2	7.0

Abbreviations: MET, metabolic equivalent of tasks; TB, tuberculosis; CHD, coronary heart disease
*Apart from sex and age specific variables all other variables were standardised to the age sex and study area structure of the overall study population
‡ Family history defined as baseline reported disease prevalence in mother and/or father
‡ Breathlessness and chest pain defined as being “short of breath”, and “slowing down due to chest discomfort”, respectively, when “walking on level ground with health people of the same age”. Chronic cough defined as “coughing frequently for ≥3 months”

Table 5.7 Baseline physical measurements for participants by cardio-respiratory spell type across all five urban CKB regions combined

Characteristics*	All major cardiovascular disease		All-type stroke		All major respiratory disease	
	First-time (n=18,709)	Readmission (n=25,086)	First-time (n=13,099)	Readmission (n=10,229)	First-time (n=10,603)	Readmission (n=5038)
Body mass index (kg/m^2), %						
<21.0	2.6	1.9	2.2	2.1	4.1	6.7
21.0-24.9	57.4	47.4	54.1	49.0	57.8	57.0
≥25.0	40.0	50.7	43.7	48.9	38.1	36.3
Mean (SD)	24.4 (3.4)	25.2 (3.5)	24.7 (3.5)	25.2 (3.4)	24.2 (3.6)	24.3 (3.8)
Systolic blood pressure (mmHg), %						
<120	34.7	22.9	29.0	22.7	37.2	38.7
120-139	37.9	32.1	35.2	31.5	35.2	35.8
≥140	27.4	45.0	35.8	45.8	27.6	25.5
Mean (SD)	129.4 (20.2)	138.5 (23.1)	134.2 (22.8)	139.4 (23.3)	129.1 (21.8)	128.0 (21.2)
Diastolic blood pressure (mmHg), %						
<80	61.3	46.9	55.0	46.5	64.0	66.5
80-89	26.1	28.6	26.9	27.9	23.5	22.6
≥90	12.7	24.5	18.1	25.6	12.5	11.0
Mean (SD)	77.8 (11.0)	82.2 (12.1)	79.9 (11.7)	82.6 (12.4)	77.1 (11.1)	76.5 (10.8)
Lung function measurements, mean (SD)						
Pre-bronchodilator FEV_1†, Litre	2.23 (0.65)	2.17 (0.62)	2.20 (0.63)	2.14 (0.61)	2.17 (0.64)	1.94 (0.68)
Pre-bronchodilator FVC§, Litre	2.59 (0.73)	2.52 (0.69)	2.56 (0.71)	2.49 (0.68)	2.54 (0.72)	2.33 (0.74)
Pre-bronchodilator FEV_1: FVC	0.87 (0.08)	0.87 (0.09)	0.87 (0.08)	0.87 (0.08)	0.86 (0.09)	0.83 (0.12)
Possible airflow obstruction, %						
FEV1: FVC <0.7	3.2	2.8	2.6	2.4	5.6	12.8
FEV1: FVC <lower limit of normal	3.9	3.2	3.0	2.8	6.8	14.8

*Means and percentages standardised to the age and study area structure of the study population
Abbreviations: BMI; Body mass index, FEV; forced expiratory volume in one second, FVC; forced vital capacity, mmHg; millimetres of mercury

Figure 5.1 Example classification of CKB cardio-respiratory hospitalisations into first-time and readmission spells

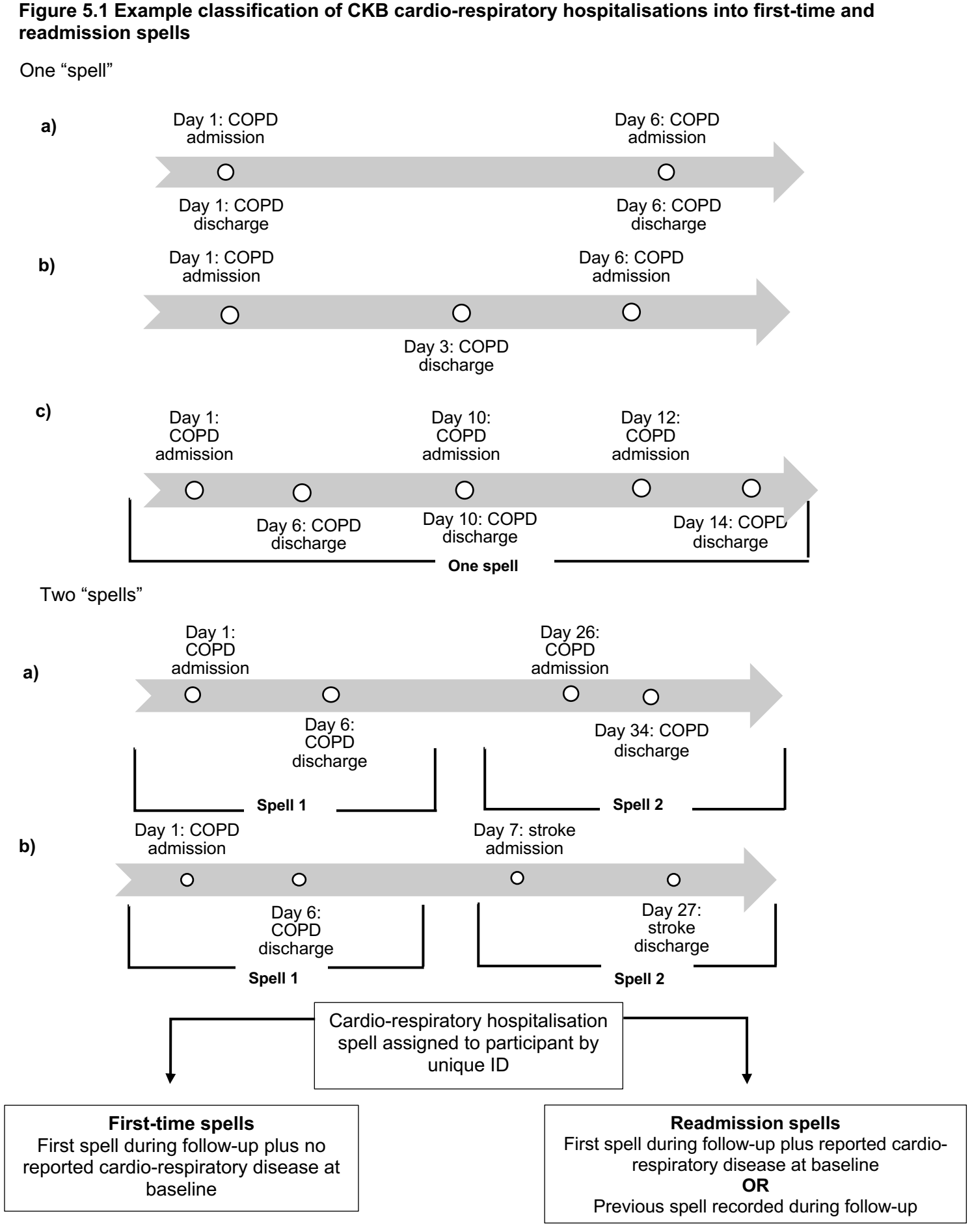
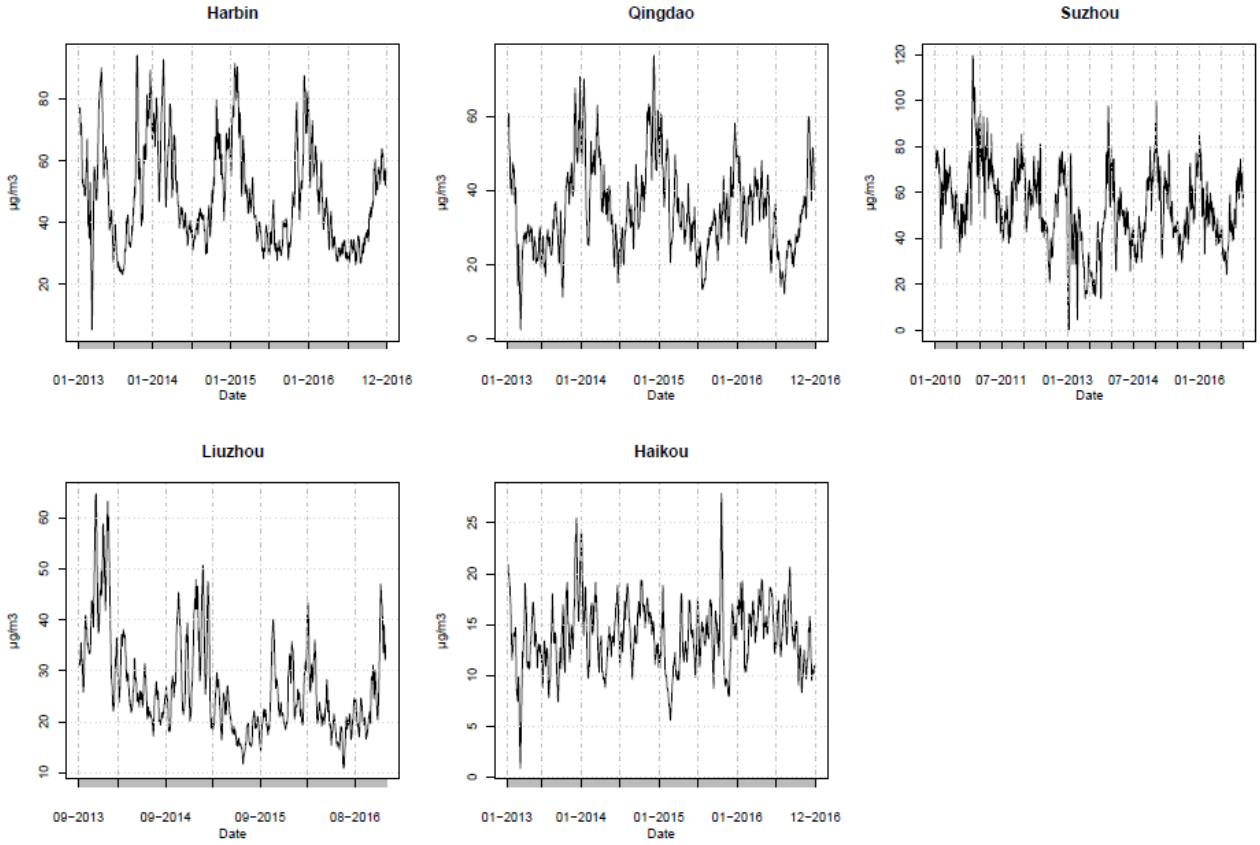
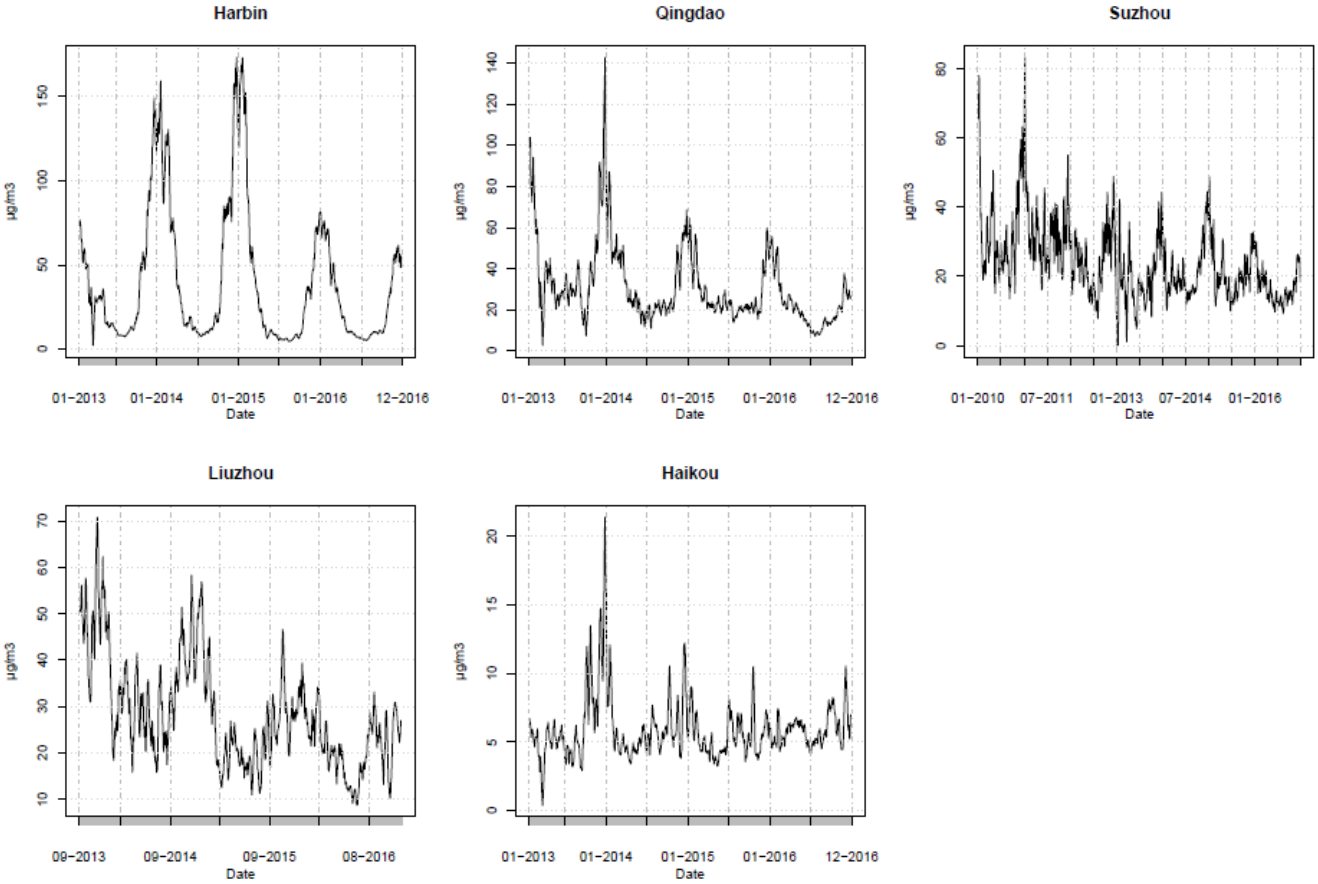


Figure 5.2 Time-series plots of daily AAP levels within each urban CKB region 2013-2016 (2010-2016 Suzhou)

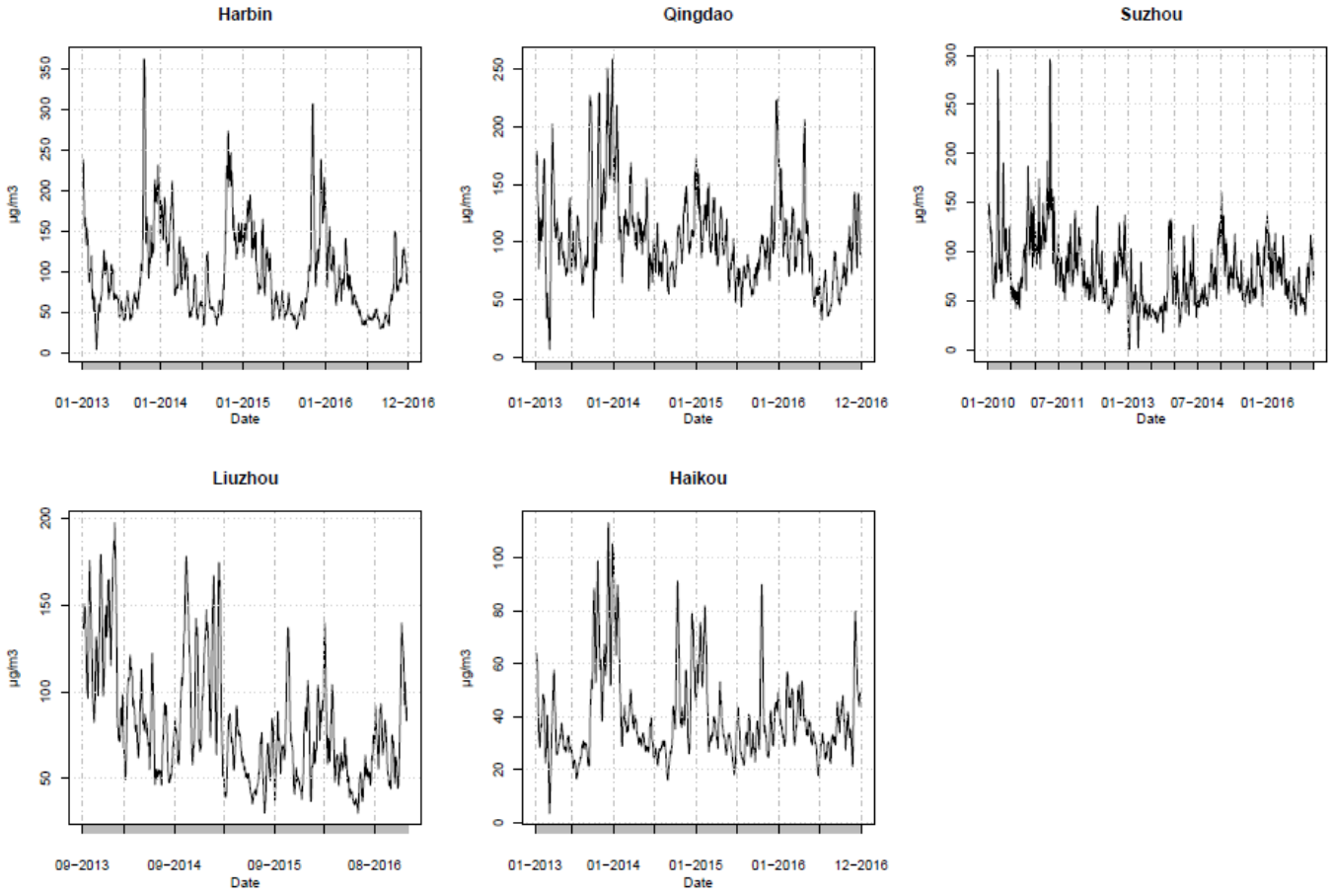
a) NO_2 (μg/m^3)



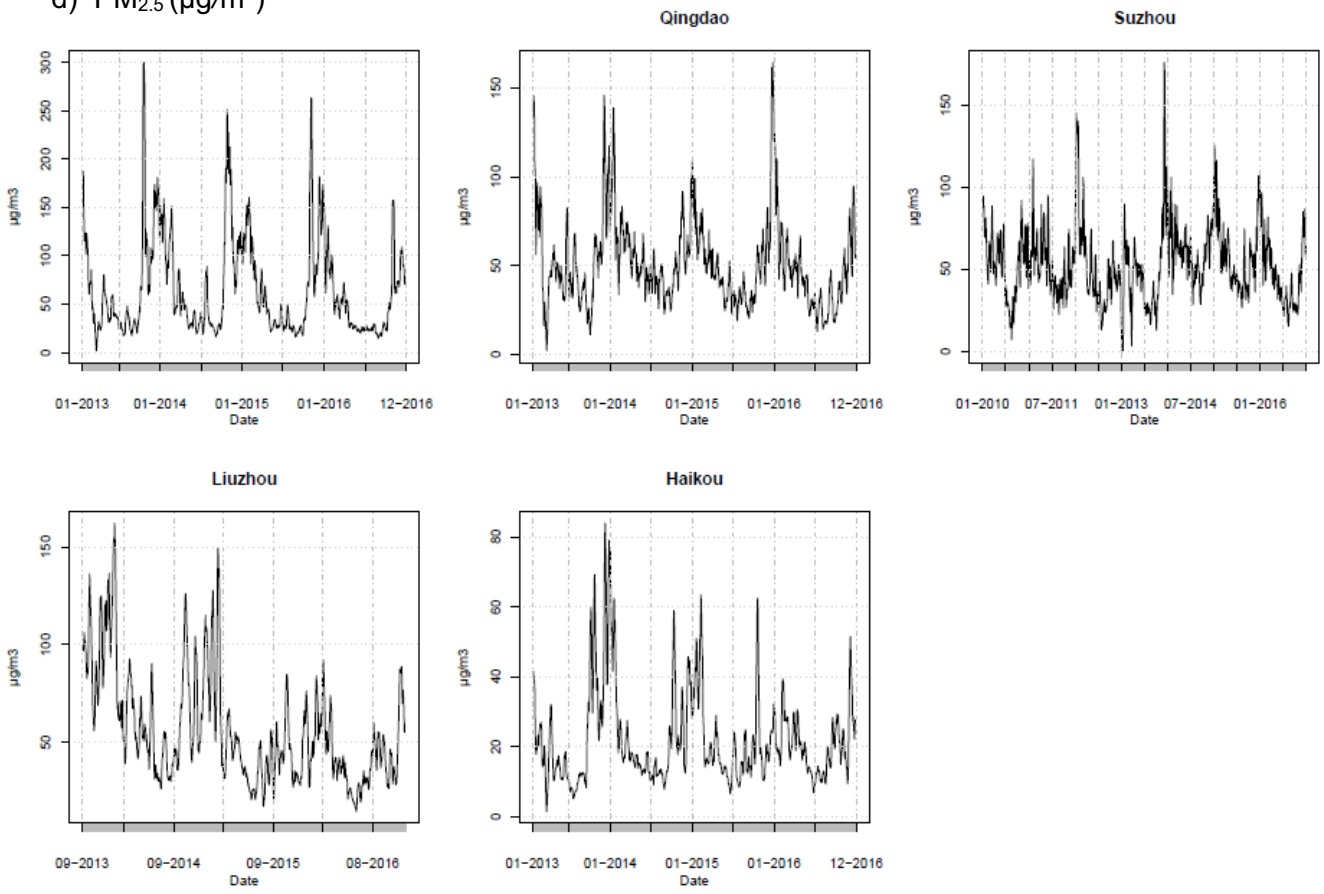
b) SO_2 (μg/m^3)



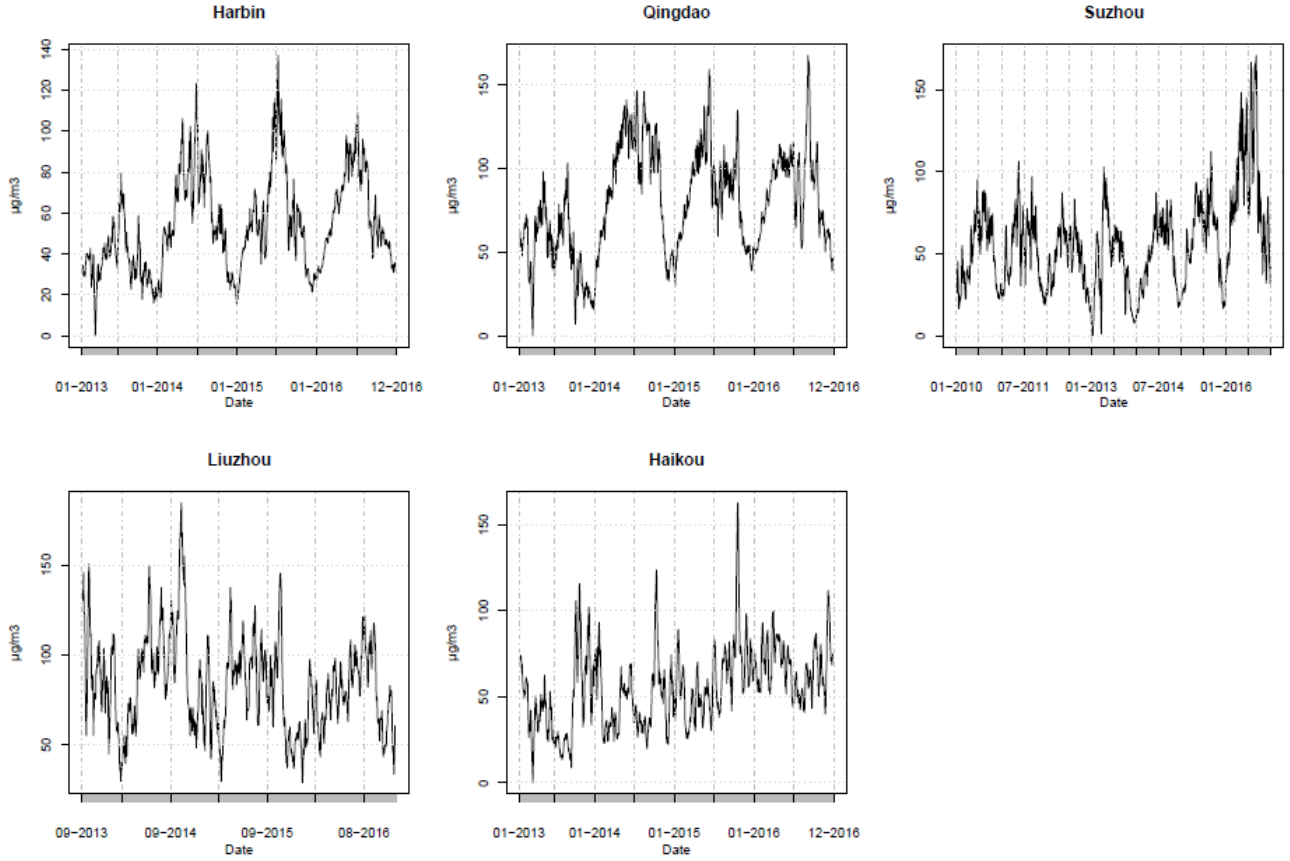
c) PM_{10} ($\mu g/m^3$)



d) $PM_{2.5}$ ($\mu g/m^3$)



e) O_3 (μg/m^3)



f) CO (mg/m3)

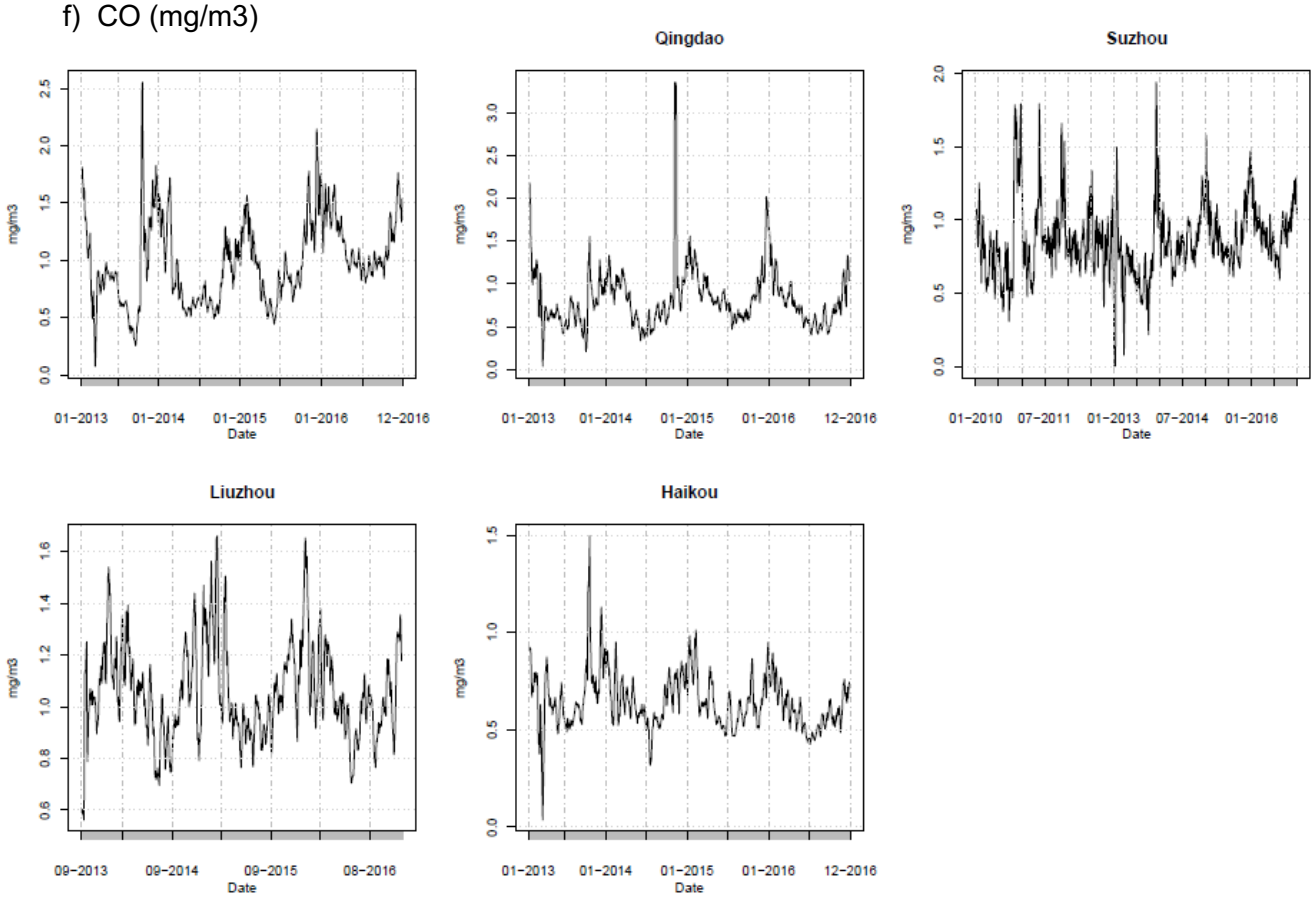


Figure 5.3 Time-series plots of all major cardiovascular disease spells by spell admission type in the five CKB urban regions

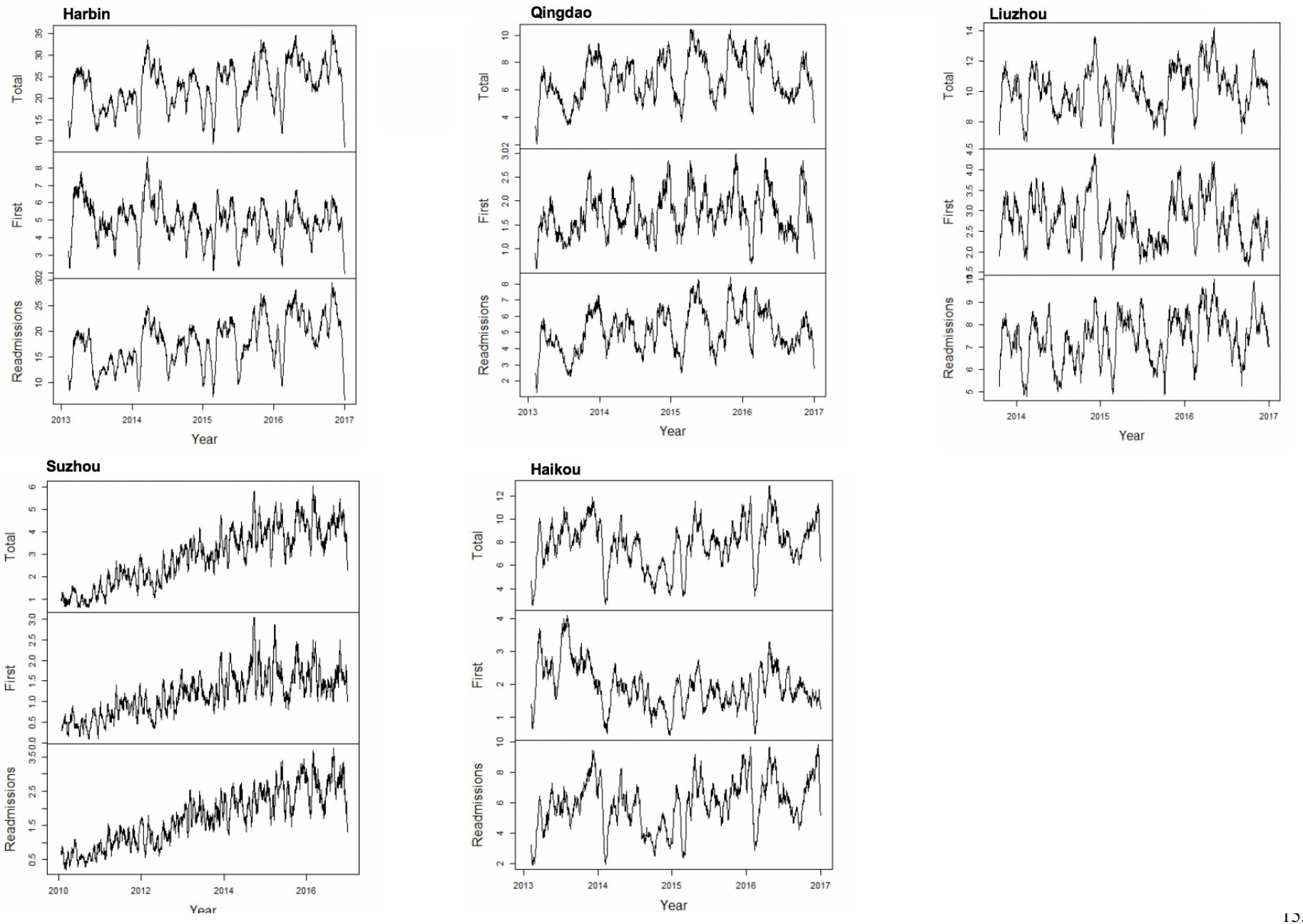


Figure 5.4 Time-series plots of all major respiratory disease spells by spell admission type in the five CKB urban regions

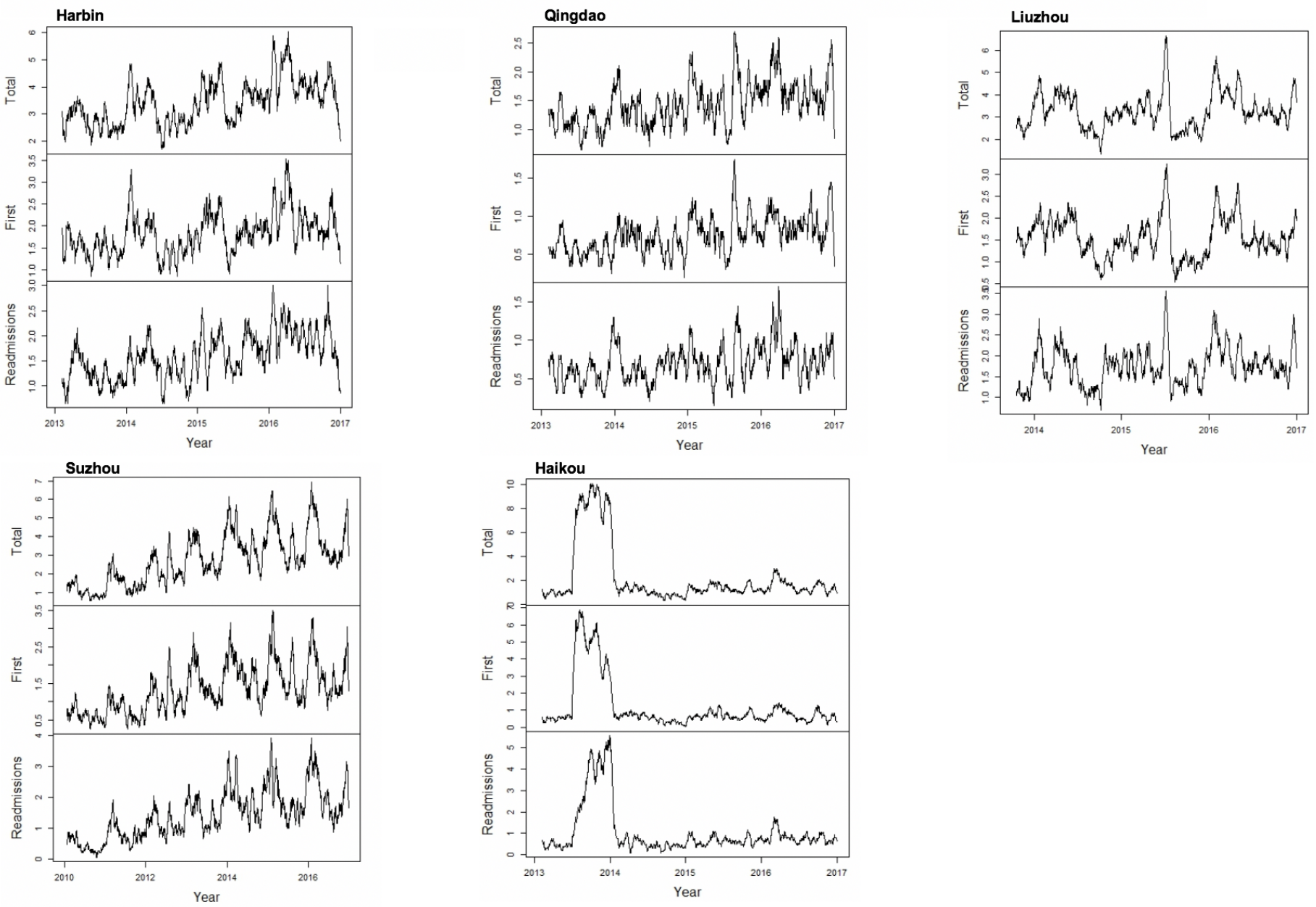


Figure 5.5 Time-series plots of all type stroke spells by spell admission type in the five CKB urban regions

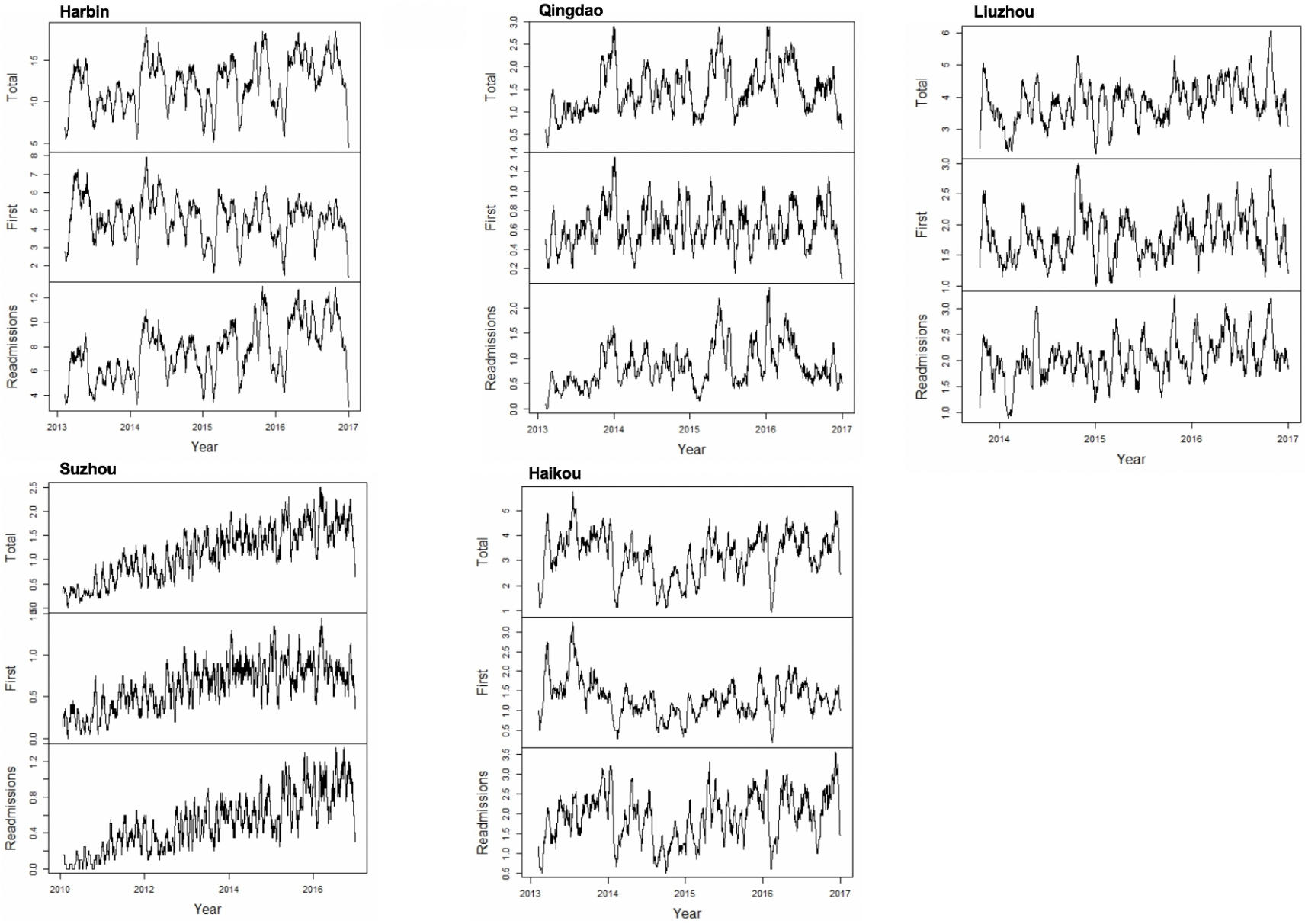
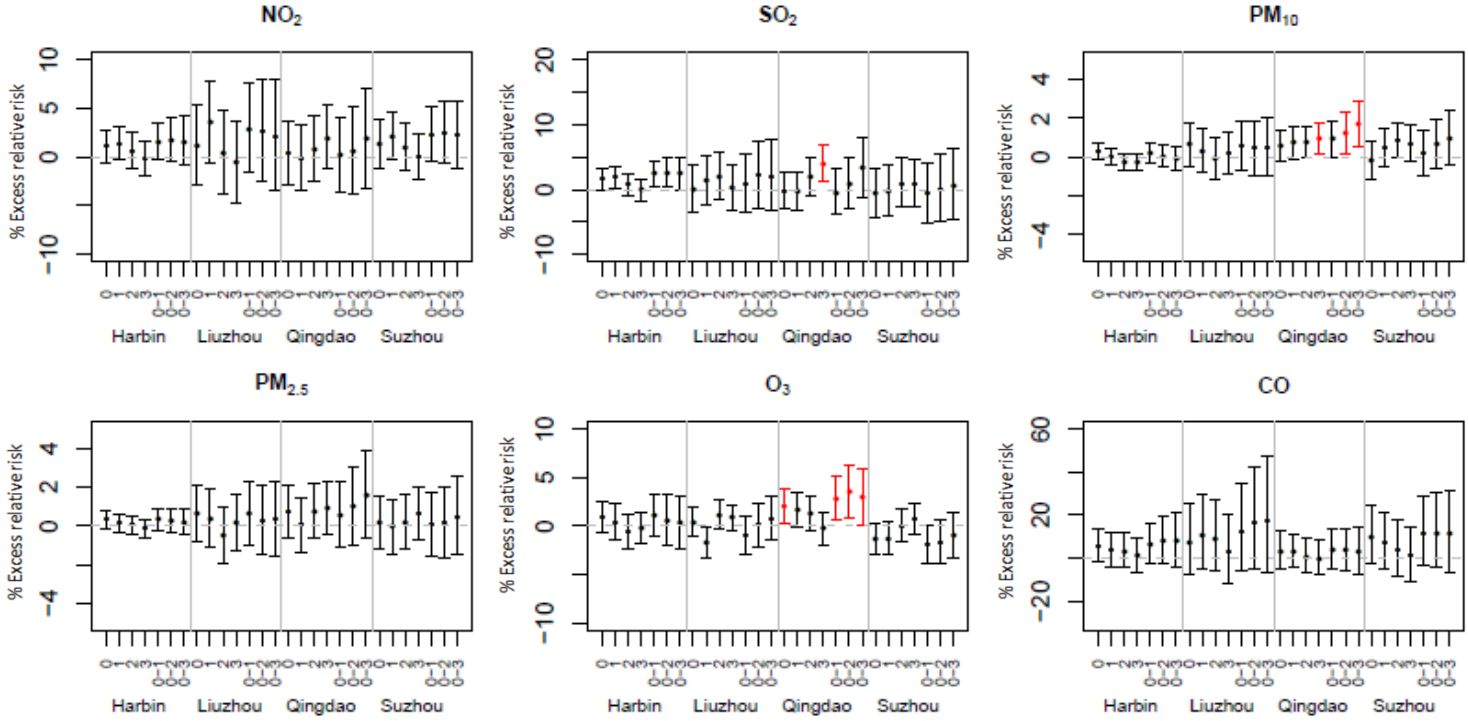
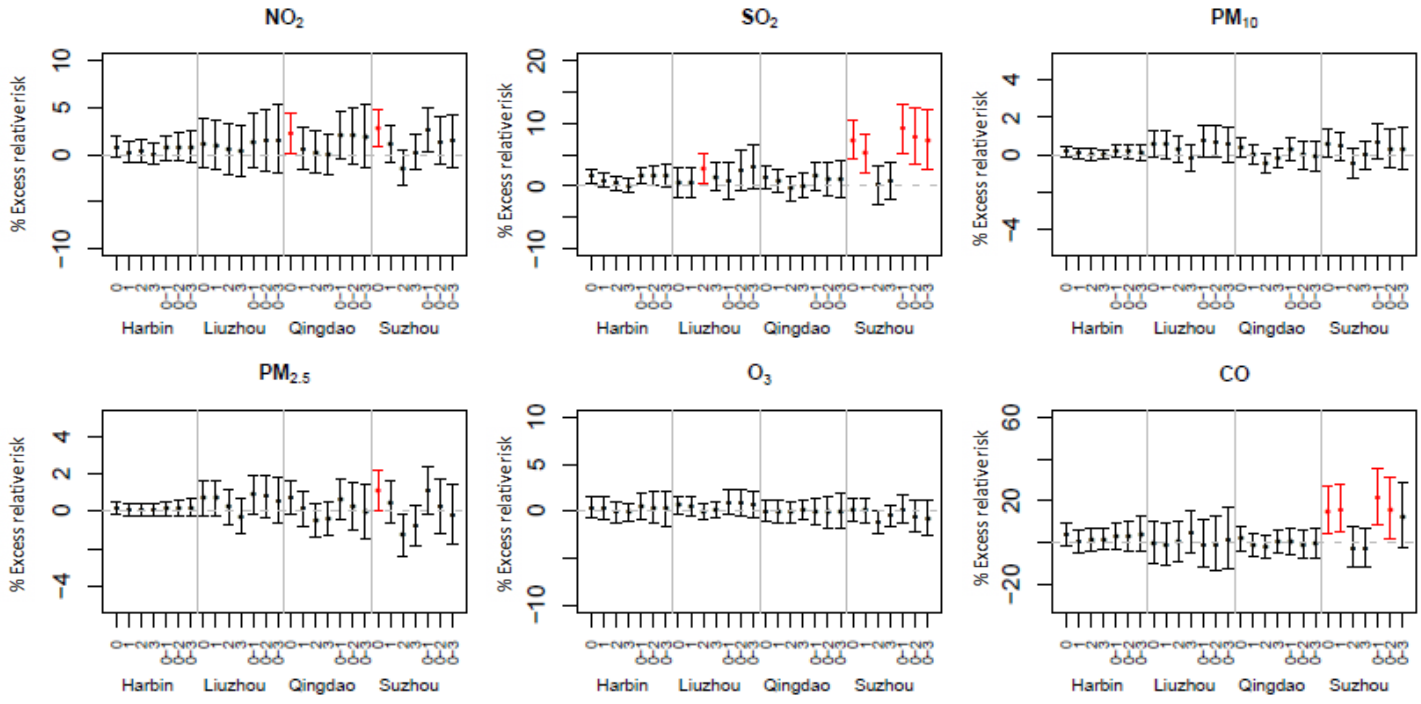


Figure 5.6 Percent excess risk of hospitalisation from major cardiovascular disease associated with a 10μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using time-series analysis**

a) First-time spells



b) Readmissions



*100 μg/m^3 for CO

**Suzhou (2010-2016)

p<0.05

Figure 5.7 Percent excess risk of hospitalisation from major cardiovascular disease associated with a 10μg/m^3* increase in AAP Haikou (2013-2016) using time-series analysis, and case-crossover analysis, respectively

a) Time-series analysis

b) Case-crossover analysis

*100 μg/m^3 for CO

p<0.05

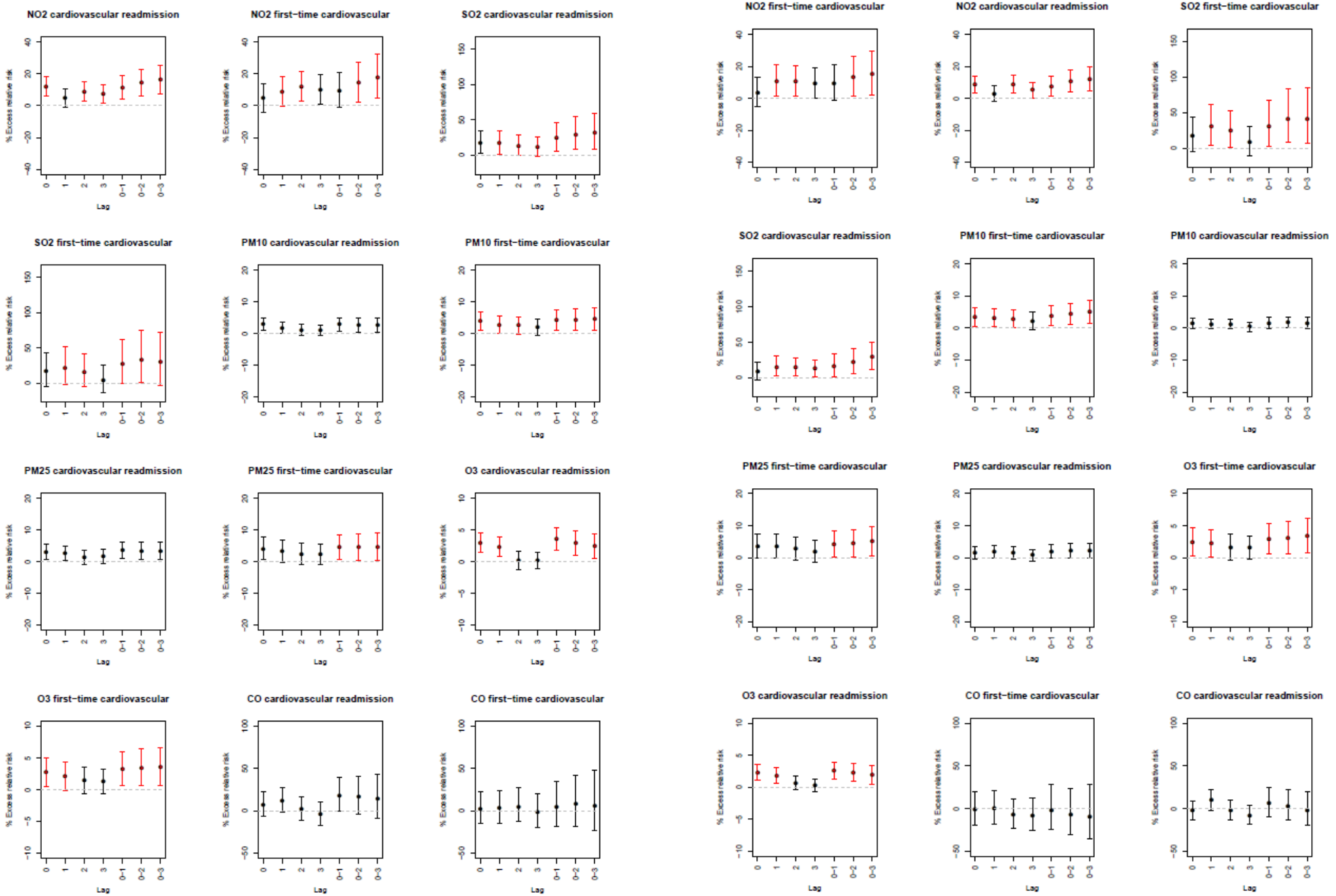
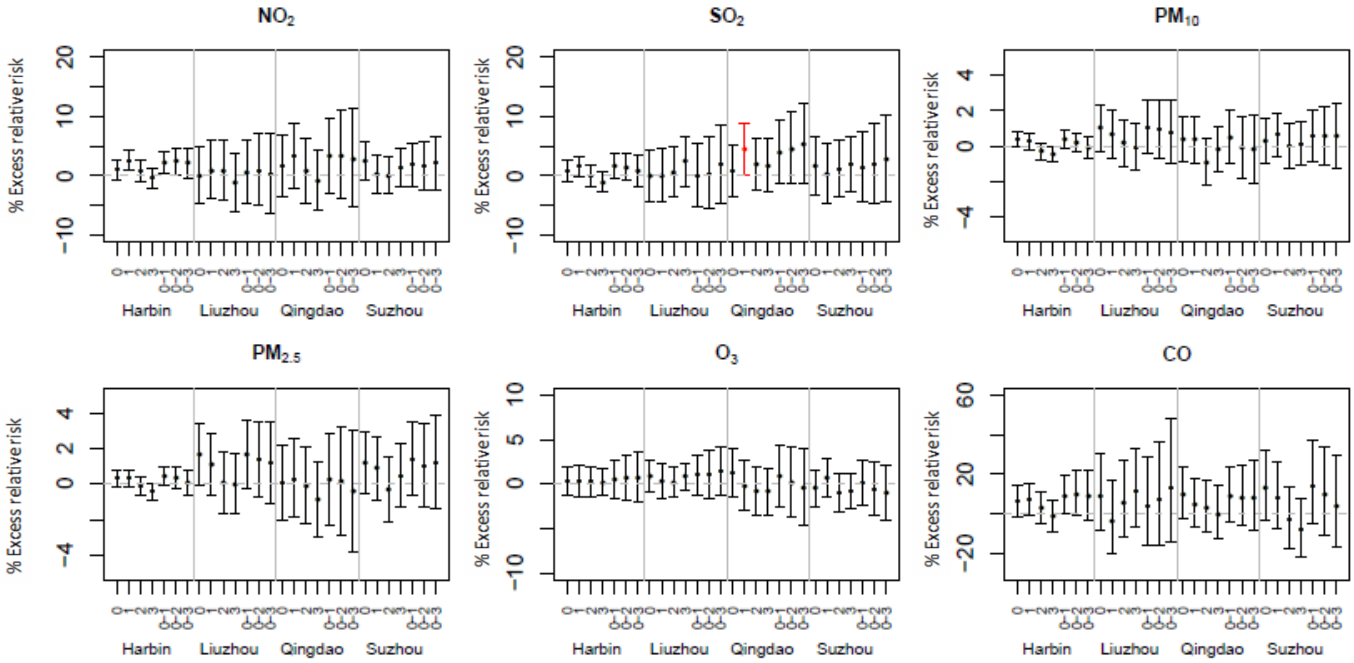
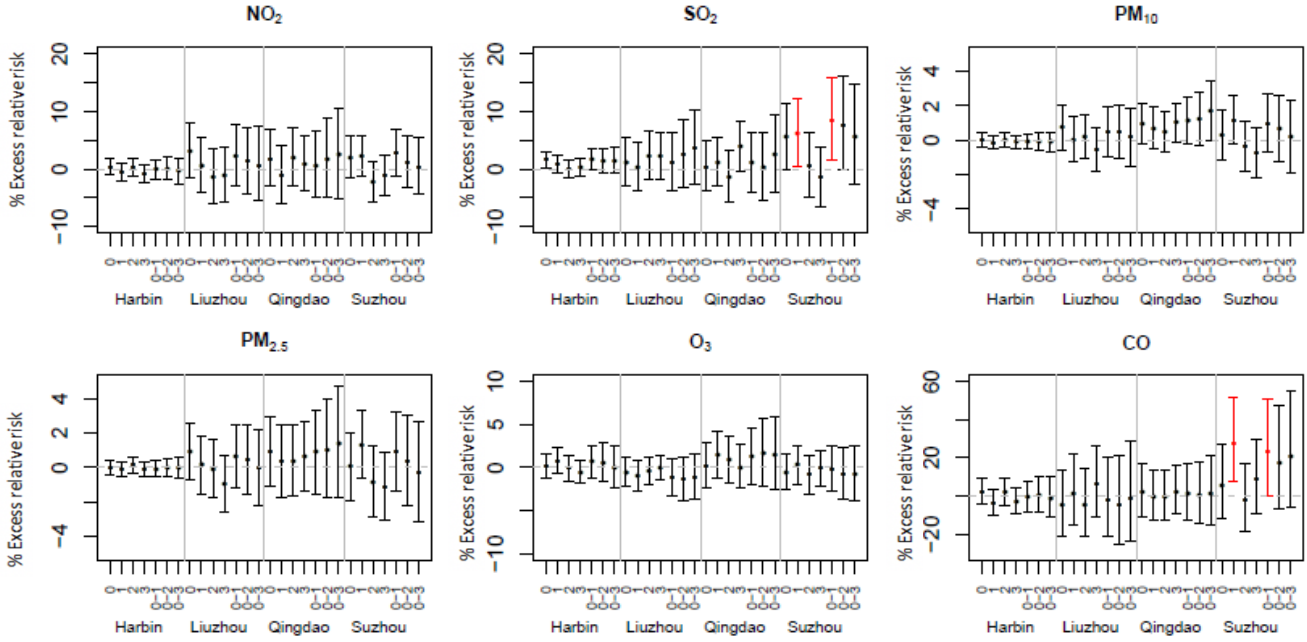


Figure 5.8 Percent excess risk of hospitalisation from all-type stroke associated with a 10μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using time-series analysis**

a) First-time spells



b) Readmissions



*100 μg/m^3 for CO

**Suzhou (2010-2016)

p<0.05

Figure 5.9 Percent excess risk of hospitalisation from all-type stroke associated with a 10μg/m^3* increase in AAP Haikou (2013-2016) using time-series analysis, and case-crossover analysis, respectively

*100 μg/m^3 for CO

p<0.05

a) Time-series analysis

b) Case-crossover analysis

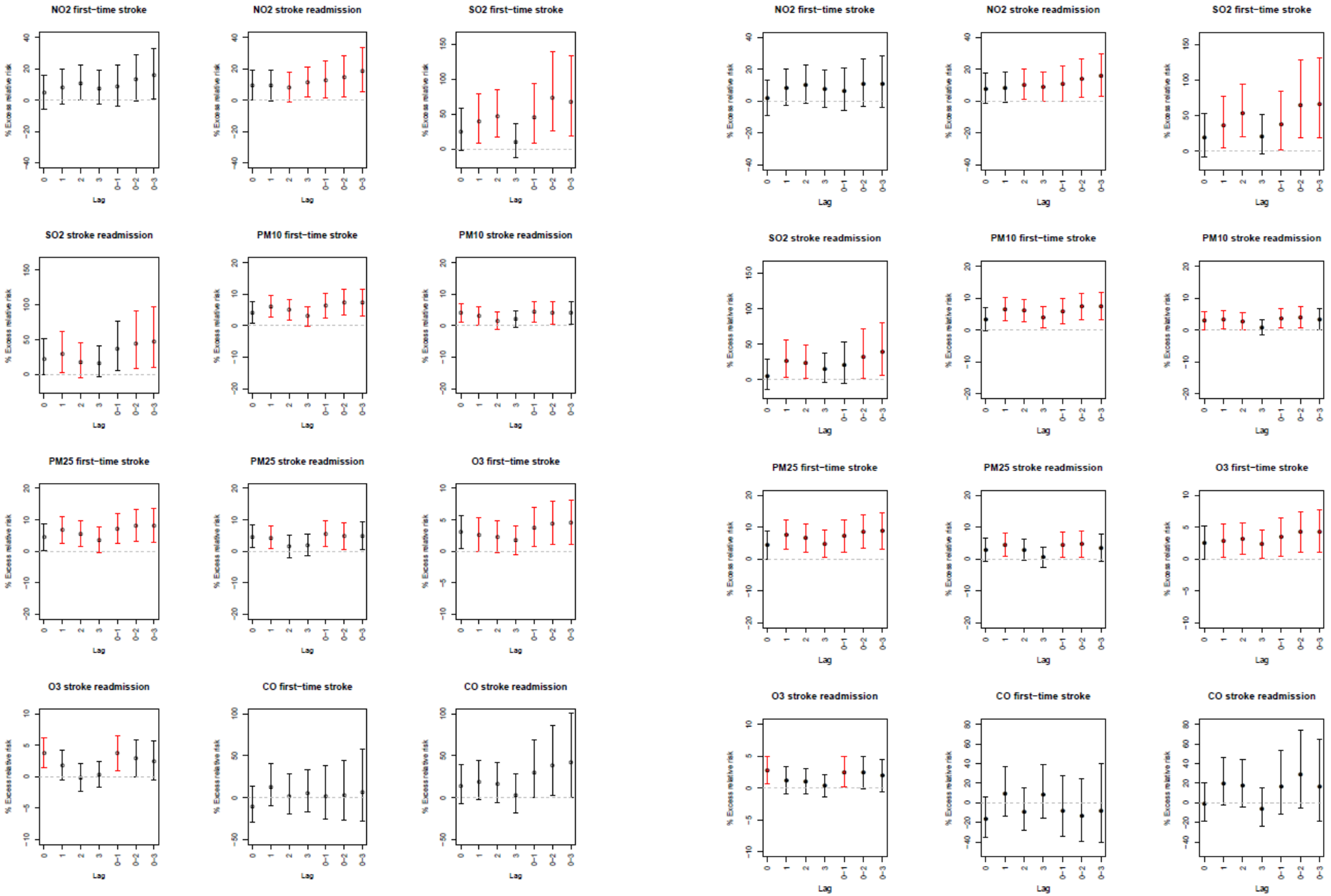
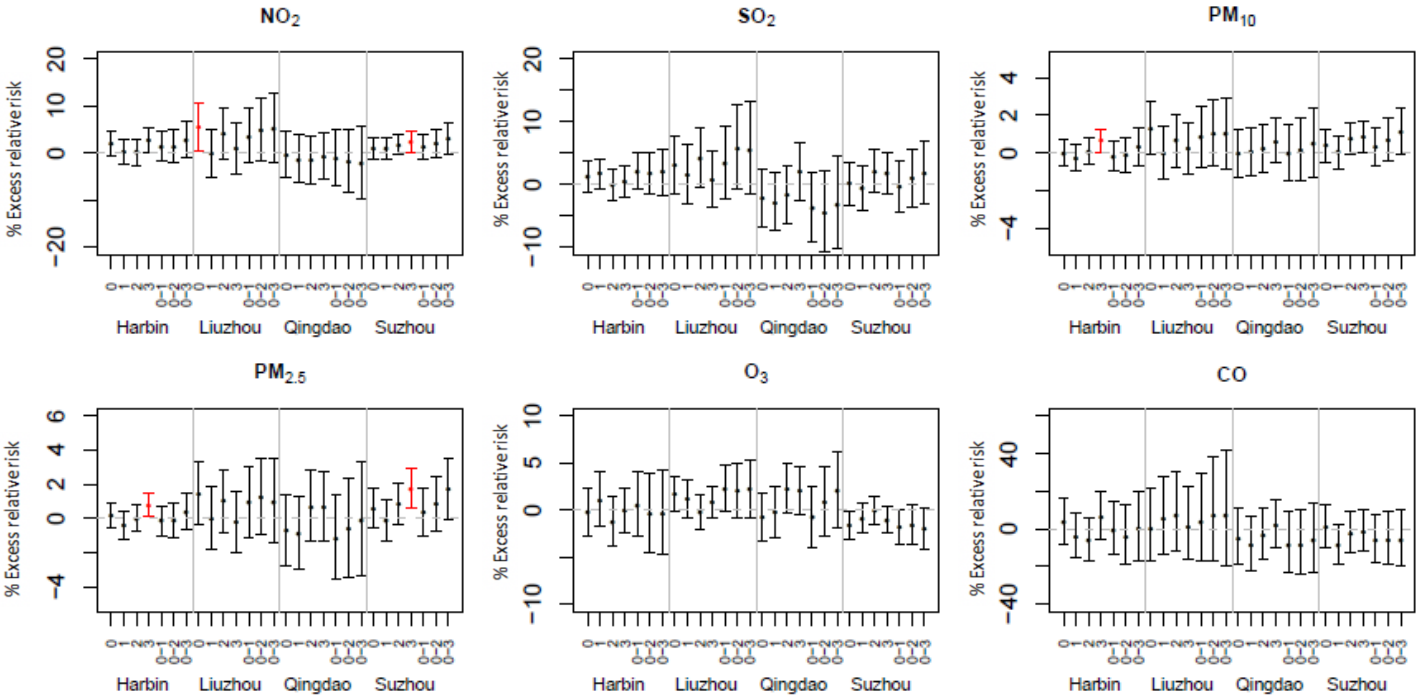
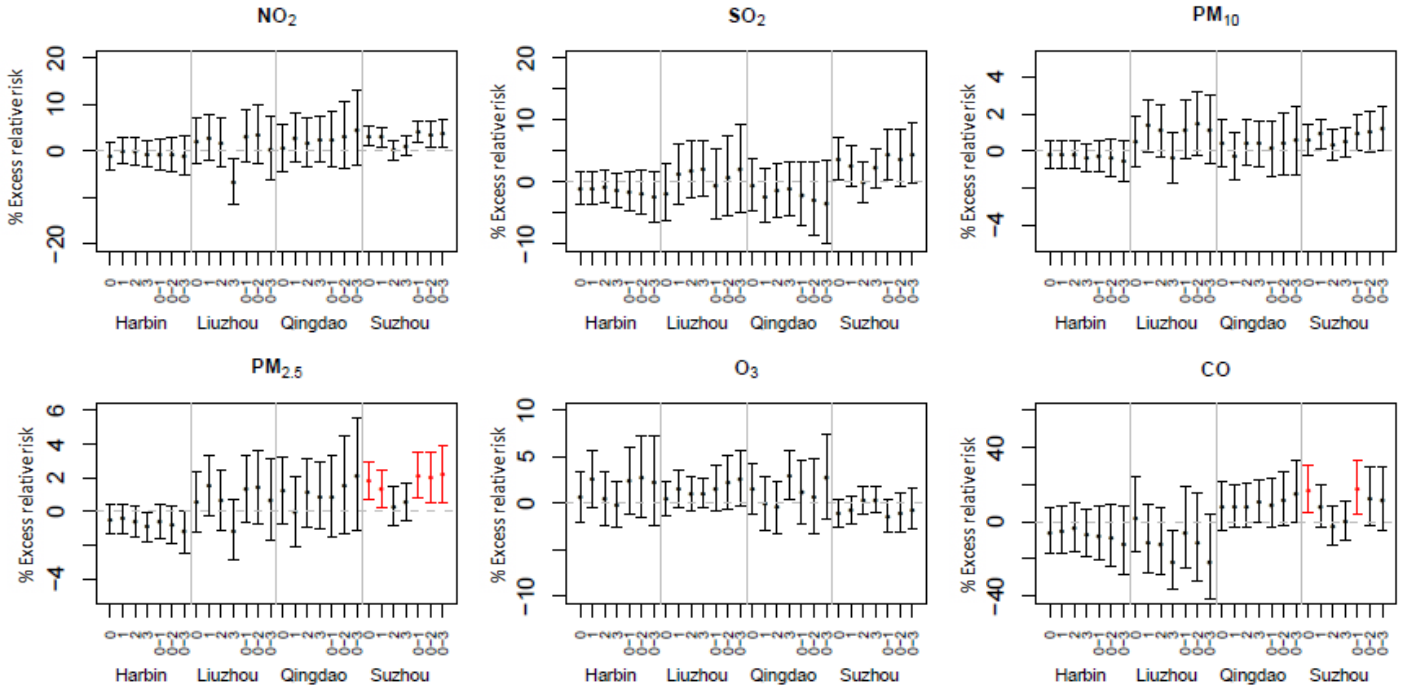


Figure 5.10 Percent excess risk of hospitalisation from major respiratory disease associated with a 10μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using time-series analysis**

a) First-time spells



b) Readmissions



*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05

Figure 5.11 Percent excess risk of hospitalisation from major respiratory disease associated with a 10μg/m^3* increase in AAP Haikou (2013-2016) using case-crossover analysis and time-series analysis, respectively

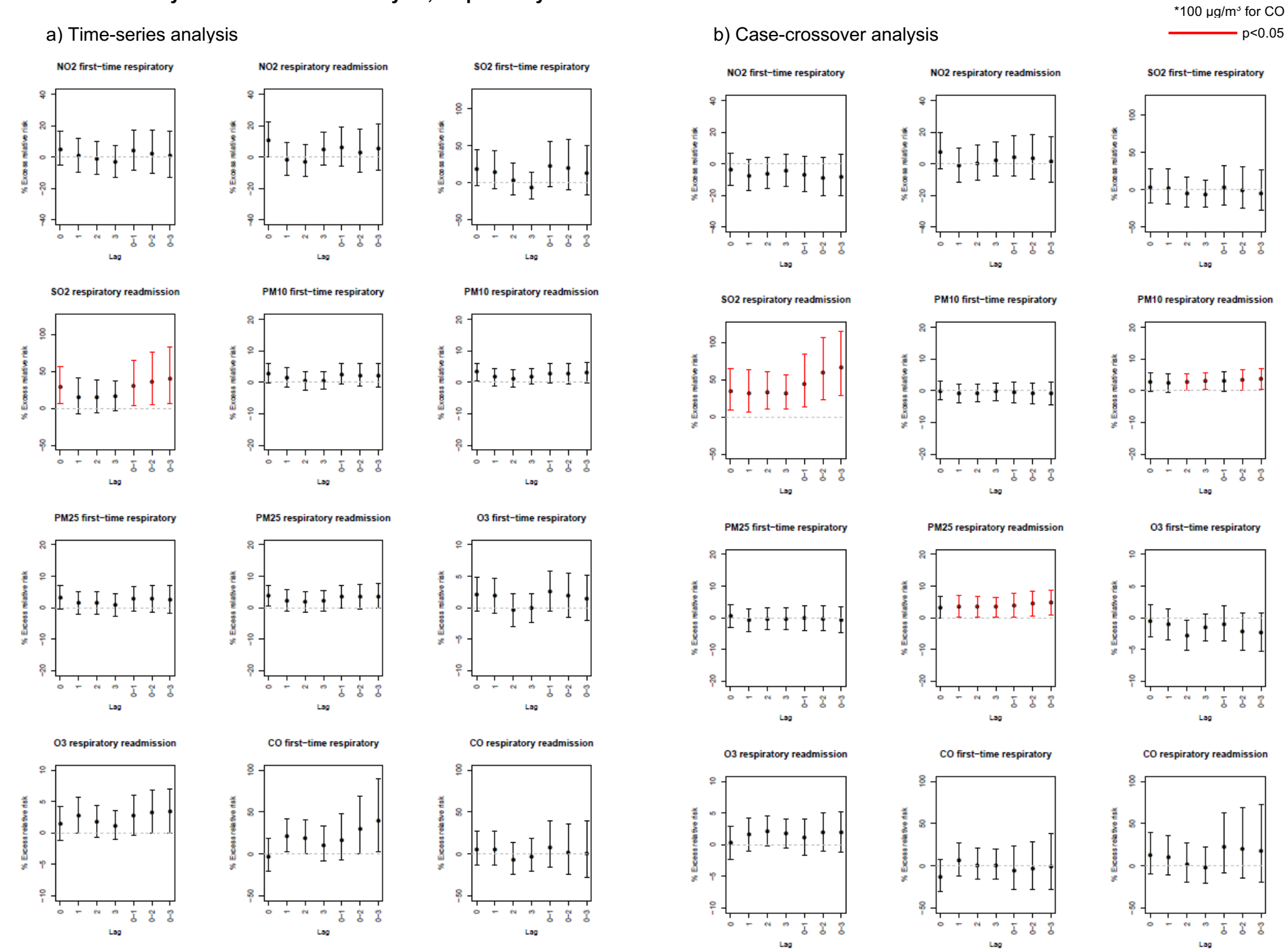
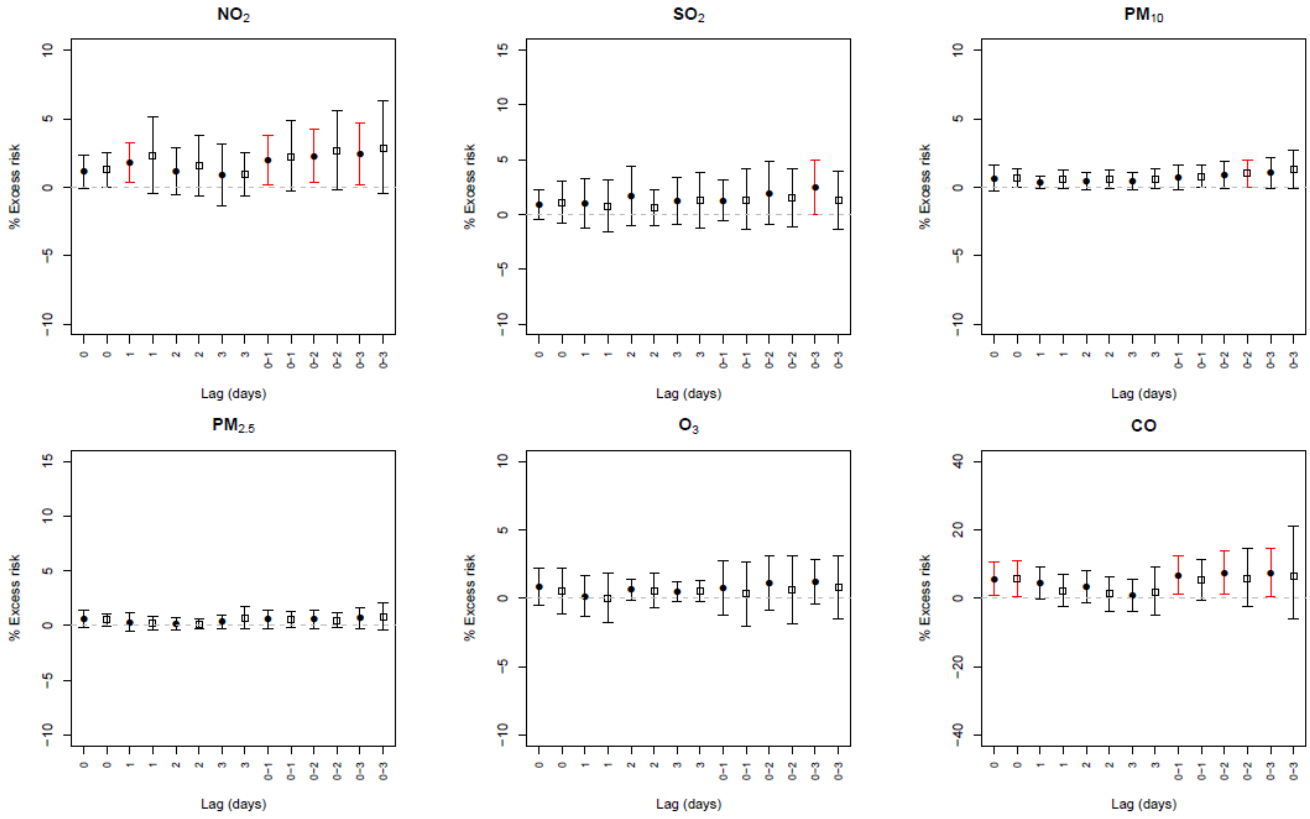
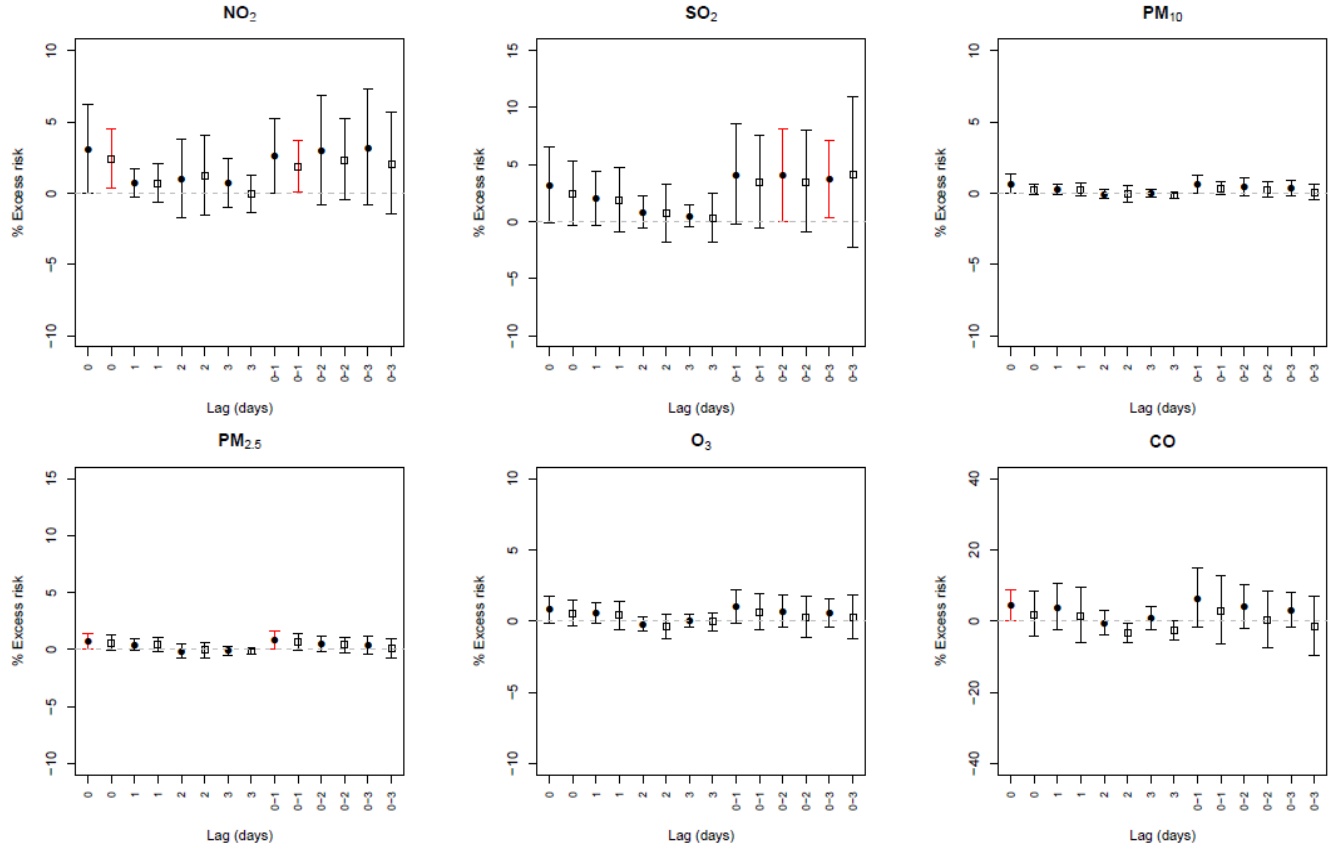


Figure 5.12 Pooled estimates for a 10 μg/m^3* increase in AAP and associated risk of cardiovascular disease spells across the five CKB urban regions (2013-2016)**

a) First-time spells



b) Readmissions



*100 μg/m^3 for CO

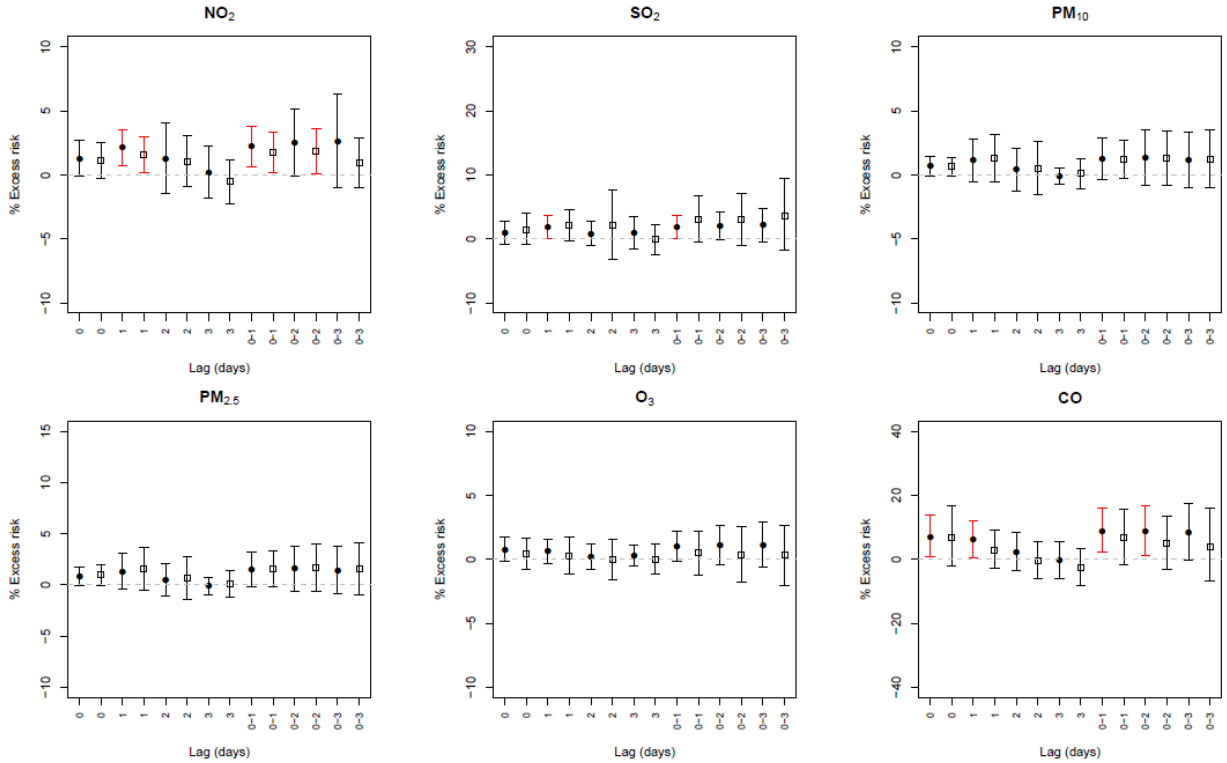
**Suzhou (2010-2016)

● Time−series □ Case−crossover

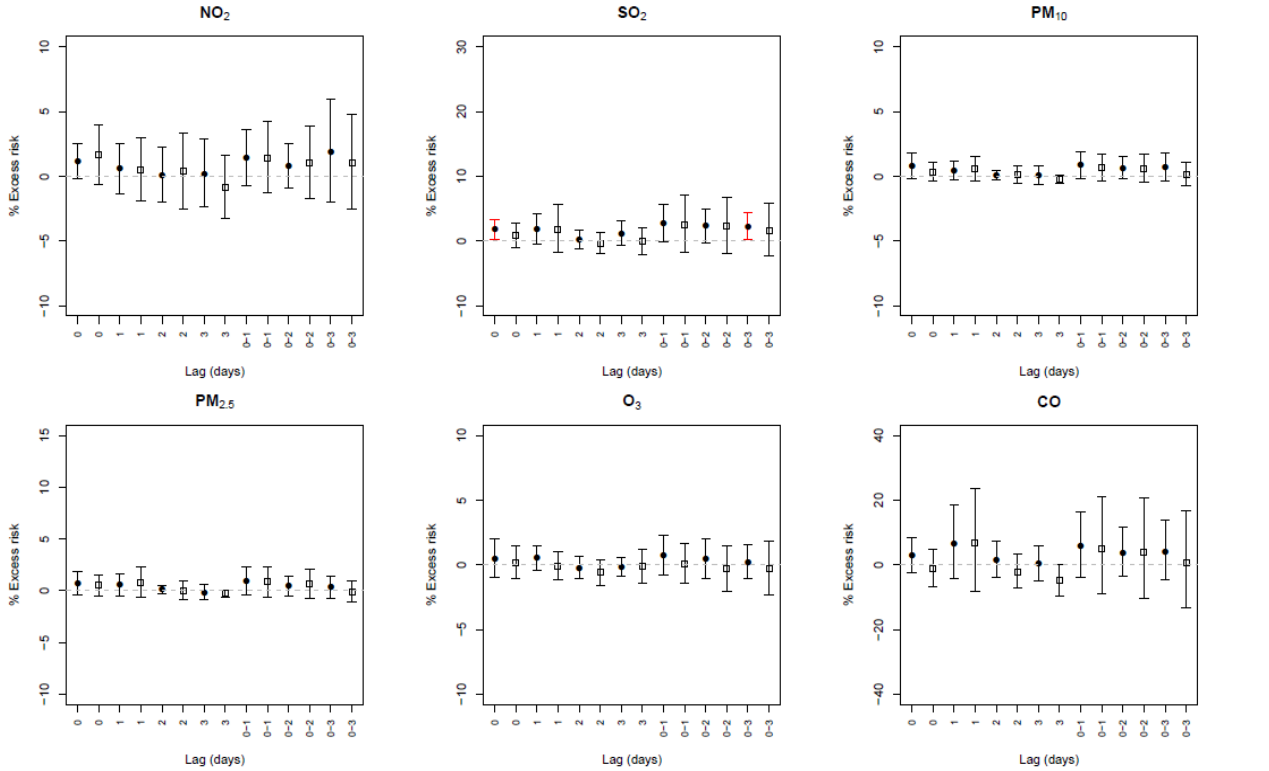
p<0.05

Figure 5.13 Pooled estimates for a 10 μg/m^3* increase in AAP and associated risk of all-type stroke spells across the five CKB urban regions (2013-2016)**

a) First-time spells



b) Readmissions

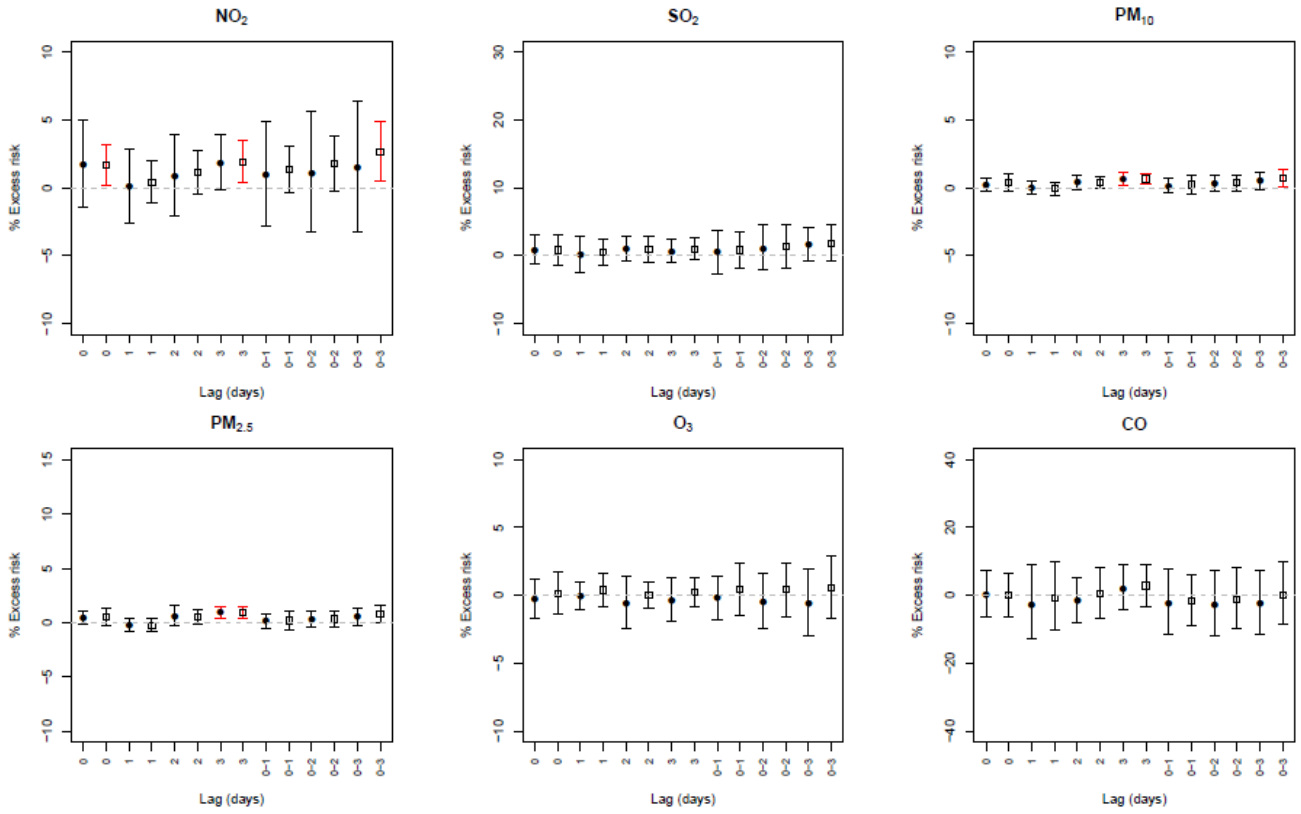


*100 μg/m^3 for CO

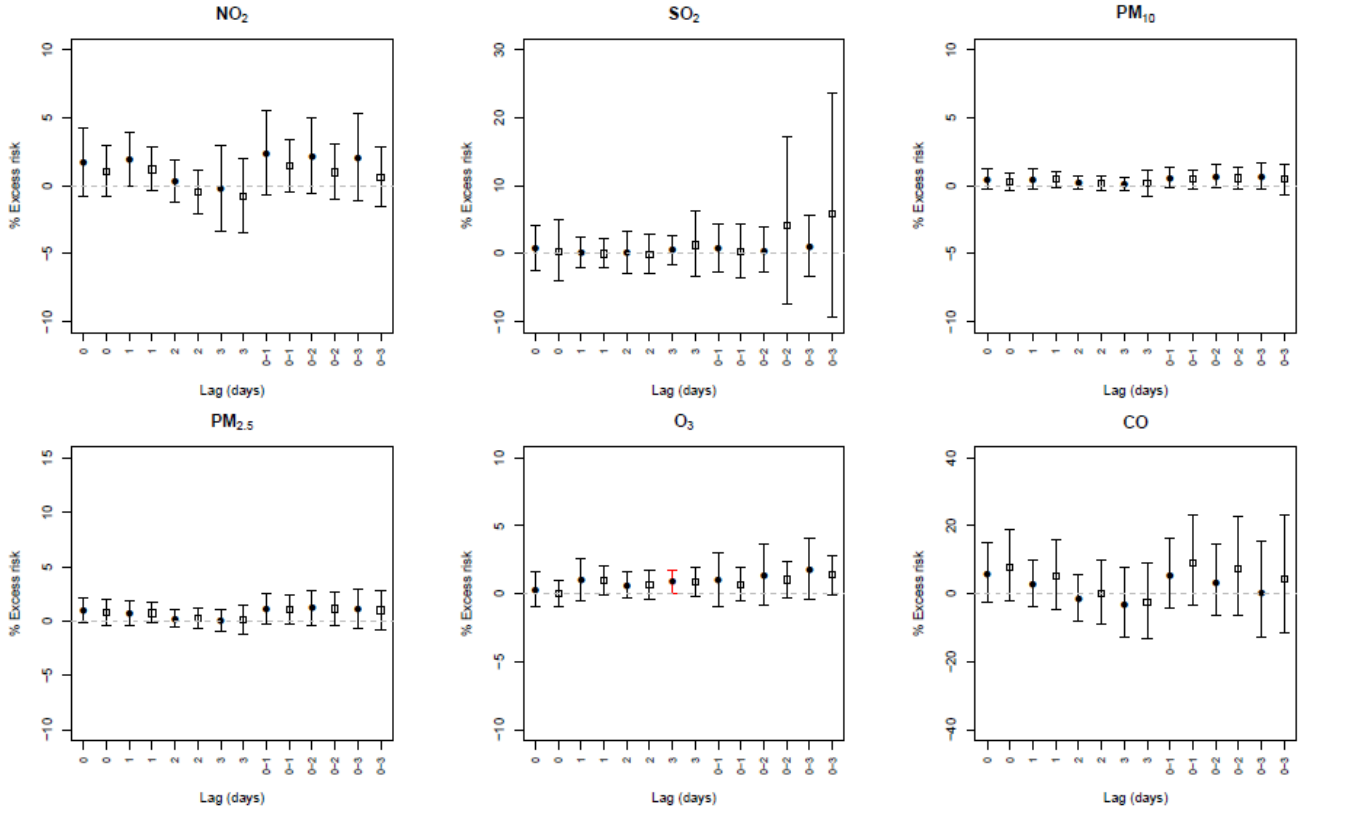
**Suzhou (2010-2016)

Figure 5.14 Pooled estimates for a 10 μg/m^3* increase in AAP and associated risk of respiratory disease spells across the five CKB urban regions (2013-2016*)

a) First-time spells



b) Readmissions



*100 μg/m^3 for CO

**Suzhou (2010-2016)

CHAPTER 6. CHRONIC HEALTH EFFECTS

6.1 Introduction

As highlighted in **Chapter 3.3**, evidence is now rapidly compiling which supports the association between chronic AAP exposure and adverse cardio-respiratory health outcomes in China. [66, 67, 69, 70, 104, 105, 226] However, to my knowledge, no prospective evidence currently exists from China on the association between chronic AAP exposure and risk of cardio-respiratory disease with the inclusion of morbidity as an outcome of interest. Given the prospective evidence base for chronic AAP exposure and increased risk of cardio-respiratory mortality (seen in both HICs and China), adverse effects on cardio-respiratory morbidity are at the least a plausible inference, with morbidity even hypothesised to more effectively capture the health effects of AAP compared to the more extreme and less immediate event of mortality. [357, 358] Quantifying pollution-related morbidity is important, not only because it is a likely precursor for pollution-related mortality, but also for its association with considerable estimated healthcare costs in China, costs much higher than those related to pollution-related mortality alone. [359] Without studies that incorporate both the mortality and morbidity effects of chronic AAP exposure in China, it's arguable that the disease burden of AAP exposure cannot be fully comprehended, leaving policy and health protection strategies designed to mitigate such burden without a fully comprehensive evidence base.

Furthermore, as described in **Chapter 3.3**, all current prospective evidence from China on the association between chronic AAP exposure and cardio-respiratory disease has used either fixed-site monitors, [66, 67, 70, 104, 105, 226] or satellite-based modelling, [69] to assign chronic AAP exposure to participants, often at relatively crude spatial and temporal resolutions. To my knowledge no study uses exposure assignment aiming to capture more localised variability in AAP levels. In addition, while fixed-site monitors are limited by their likelihood of substantial exposure misclassification, studies using satellite-based modelling in China have been limited to the examination of one pollutant, restricting the ability to examine multiple

pollutants of interest. Incorporating the effects of multiple pollutants is valuable as it allows (to some degree) the independent effects of pollutants on cardio-respiratory disease to be assessed. It also somewhat quantifies the consequences of complex air pollution exposures by providing risk estimates from pollutant mixtures closer to the complex pollutant exposures experienced by populations. However, in China, studies which have examined the effects of multiple pollutants, have used fixed-site monitors solely. [66]

The advantage of the CKB cohort over other studies in China is availability of detailed data on individual characteristics of participants. Many of the covariates available within CKB are representative of potential confounders neglected in previous studies on chronic AAP exposure and risk of cardio-respiratory diseases, such as second hand-smoking and household air pollution. By incorporating such covariates into the analysis, a more robust assessment of chronic AAP exposure on the risk of major cardio-respiratory diseases can be performed.

6.2. Aims

This chapter aimed to examine the relationship between all six criteria ambient air pollutants (NO_2, SO_2, PM_{10}, $PM_{2.5}$, O_3, and CO), and risk of major cardio-respiratory endpoints reflecting predominantly morbidity in a subset of the CKB study population using assigned exposure from spatiotemporal modelling and adjusting for a wide range of potential confounders. A secondary aim was to where possible fit additional multi-pollutant models to assess the stability of any observed pollutants' effects on the risk of major cardio-respiratory disease.

6.3. Methods

6.3.1 Study design and data collection

As described in **Chapter 4**, CKB recruited ~0.5 million participants aged 30-79 years at baseline across ten diverse regions of China. At baseline, electronic questionnaires

administered by trained professionals gathered information on socio-demographic and lifestyle characteristics with participants then followed up for cause-specific mortality and morbidity. To examine the associations between chronic exposure to six ambient air pollutants (NO_2, SO_2, PM_{10}, $PM_{2.5}$, O_3 and CO) and risk of major cardio-respiratory disease incidence, data on CKB participants from the city of Suzhou in Jiangsu province were used. Suzhou was the only CKB region in this study with available AAP data as of January 2019; with a spatially distributed network of fixed-site monitors. These monitors enabled the construction of a spatiotemporal AAP exposure model and assignment of spatially varying chronic AAP exposure concentrations to study participants.

6.3.2 Assignment of AAP exposure

All baseline CKB clinic locations were geocoded by CKB staff to be used as a proxy for participants' baseline residential addresses with each participant assumed to live roughly one kilometre (km) of their baseline clinic. In order to predict long-term concentrations of PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, and O_3 at each clinic location a localised spatiotemporal model was developed by CKB colleagues. Spatiotemporal models are now widely adopted within the air pollution literature due to their flexibility in modelling appropriate covariates, and incorporating both spatial and temporal dimensions into predictions. [360] To develop the spatiotemporal model daily measurements of PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, and O_3 for years 2013-2015 were collated from ten fixed-site monitors located across Suzhou (**Figure 6.1**). These were obtained for this study from collaborators at Fudan University, Shanghai. Measurements of daily meteorological variables for the same period were obtained from five fixed-site weather monitors located in Suzhou and the surrounding vicinity (**Figure 6.2**) from collaborators at the Chinese University of Hong Kong. Meteorological variables included daily averaged measures of ground temperature (degrees Celsius [°C]), wind-speed (metres/second [m/s]), relative humidity (%), and total precipitation (millimetres [mm]). A range of geographic data was also used for model construction, the details of which and source descriptions are shown in **Table 6.1.** In brief, they included the following variables

which were applied to both fixed-site monitor and clinic locations; distance to a major motorway/road network (in metres); total road length within a 1km buffer area (in metres); land-cover type (a binary variable reflecting “urban” or “non-urban”); and point altitude (in metres).

Full details on the development of the CKB spatiotemporal model can be found elsewhere.[361] In brief, it involved the use of latent Gaussian models and approximate Bayesian inference. Measured meteorological variables were first modelled as a Gaussian response to predict meteorological values at each pollution monitor and clinic location site. These predicted meteorological values were then included as hyperparameters along with the previously mentioned geographical variables into a spatiotemporal model for the prediction of pollutants. This model relied on the application of stochastic partial differential equations (SPDE) and approximate Bayesian inference to estimate parameters of pollutant exposure via Integrated Nested Laplace Approximation (INLA) using the R-INLA package. [362] The model predicted monthly pollutant concentrations at the 77 baseline clinic locations matched to 53,002 CKB participants in Suzhou. Monthly pollutant concentrations were averaged by year for each clinic location for use as the exposure variable to examine the association between chronic AAP exposure and risk of major cardio-respiratory disease incidence.

6.3.3 Outcome definitions and follow-up

As discussed in **Chapter 4.6**, CKB participants are followed up using electronic linkage with death and disease registries and the national health insurance system covering ~98% of the CKB population. For this study, all participants in Suzhou were followed up from 1st January 2013 to 31st December 2015 for cause-specific endpoints, representative of first-time disease cases since CKB baseline (2008). The endpoints of interest in this study were first-time cases of major cardiovascular disease (ICD-10: I00-I99), including all-type stroke (I60-I61, I63-I64, I69.0, I69.1, I69.3, I69.4), in addition to ischaemic stroke (I63) and intracerebral

haemorrhage (I61), ischaemic heart disease (IHD) (I20-I25), and other cardiovascular diseases (I00-I16, I27-I52, I62, I65-I89, I95-I99), respectively. For the analysis of respiratory diseases, endpoints of interest included first-time cases of major respiratory diseases (J00-J99), including chronic obstructive pulmonary disease (COPD) (J41-J44), pneumonia (J12-J18), and other respiratory diseases (J00-J06, J20-J22, J30-J40, J80-J86, J90-J96, J98-J99). All included endpoints incorporated both fatal and non-fatal events, but both cardiovascular and respiratory disease endpoints were predominantly non-fatal, 92.3% and 97.4% for cardiovascular and respiratory endpoints, respectively (**Appendix D1**). Full descriptions of these cardio-respiratory diseases contained within the respective endpoints can be found in **Table 6.2** and **Table 6.3**, respectively. Similarly, specific ICD-10 codes, and descriptions of disease cases captured within the endpoints "other cardiovascular diseases" and "other respiratory diseases" can be found in **Table 6.4**, along with their respective representations within the study population. Participants were followed until the event of interest or until censoring at the time of death, loss to follow-up, or the end-of follow up (31st December 2015), whichever occurred first.

6.3.4 Participant exclusions

For the study outlined in this Chapter specifically, one geocoded clinic located approximately 46 kilometres South-west of Suzhou **(Figure 6.3)** was excluded from analysis along with its associated participants (n=257). This was because the focus of this study was the effects of chronic AAP exposure within the more localised Suzhou area only, and the geographical location of this clinic made AAP exposure prediction difficult with the spatiotemporal model using covariates located predominantly within the central area Suzhou only. Following this exclusion, 53,002 participants across 77 geocoded clinics had AAP exposure assigned.

Participants with the disease outcome of interest recorded before the start of follow-up (1st January 2013) were also excluded, as these participants would be unable to experience the event of interest during follow-up. Participants with prior cancer reported at baseline or any

cancer incidence before the start of follow-up were also excluded given their susceptibility to cardio-respiratory disease as a comorbid condition. The term “baseline” here, and for the remainder of this chapter is referring to the CKB study baseline (~2008), and disease prevalence at baseline was assessed by the question “Has a doctor ever told you that you have the following disease?”.

Further exclusions were made according to specific disease outcomes under analysis and can be found in **Figure 6.4**. In brief, for the analysis of all major cardiovascular disease and other cardiovascular diseases, participants with baseline prevalence of stroke/transient ischaemic attack (TIA), and/or IHD were excluded. For the analysis of stroke (both all-type and ischaemic/haemorrhagic) participants with all-type stroke/TIA at baseline were excluded, while for analysis of IHD, participants with baseline IHD prevalence were excluded. For the analyses of all major respiratory diseases, those participants with prior asthma, tuberculosis, or emphysema/bronchitis were excluded.

6.3.5 Statistical analysis

6.3.5.1 Descriptive analysis

In addition to summary statistics of AAP levels, Pearson correlation coefficients were calculated for predicted mean AAP levels by clinic location both throughout the entire study period as well for each year, respectively, assessing correlations between concentrations. Temporal variability in AAP exposures was assessed by plotting both the annual and monthly predicted AAP levels by clinic location. Monthly AAP levels were also plotted alongside measured levels from the ten fixed-site monitors enabling comparison between measured and estimated levels of AAP. To quantify long-term temporal trends in pollutant levels, the average annual percentage change in mean AAP levels was calculated. To assess the spatial variability in pollutant levels across the 77 CKB clinics, clinics were

mapped with their respective predicted pollutant levels averaged for the entirety of follow-up (2013-2015).

Incidence rates throughout follow-up were calculated for each major cardio-respiratory disease outcome of interest. These rates were unadjusted since they were for descriptive purposes only, and not for inferring rates for a wider population.

Characteristics of the study population at CKB baseline (~2008) were cross-tabulated by sex and cardio-respiratory disease status described as means with standard deviations (SDs) or proportions by categories and were adjusted for age and sex where appropriate using direct standardisation, standardised to the age and sex distribution of all Suzhou CKB participants. Selected baseline characteristics included, age, sex, highest education (no formal education), active smoking status, passive smoke exposure of at least 6 months in duration, self-rated health, total physical activity (metabolic equivalent of task [MET-hours/day]), current and past solid fuel use for cooking, prevalence of doctor-diagnosed chronic cardio-respiratory diseases (including hypertension, stroke/TIA, diabetes, tuberculosis, IHD, and emphysema/bronchitis), family history of stroke and myocardial infarction, respectively, and prevalence of cardio-respiratory symptoms including, breathlessness, chronic cough, and chest pain.

Cross-tabulations of baseline physical measurements in the study population by sex and cardio-respiratory disease incidence were also done. These included body mass index (BMI) (kg/m^2), mean systolic (SBP) and diastolic (DBP) blood pressure (both mmHg), mean lung function measurements including pre-bronchodilator forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), ratio of FEV_1:FVC; and prevalence of possible airflow obstructions defined as FEV_1:FVC <0.7, and FEV_1:FVC, below the lower limit of normal based on age, sex, height, and ethnicity. Finally, mean (SD) pollutant exposures throughout

follow-up were calculated by sex and for those with and without the cardio-respiratory disease outcome of interest.

6.3.5.2 Prospective analysis

Cox proportional hazard models were fitted to investigate the relationships between chronic AAP exposure and disease endpoints with person-years calculated from the start of follow up (1st January 2013) to either the end of follow up (31st December 2015) or censoring/event date.

Participants' annually averaged pollutant exposures were entered into models as time-varying covariates with hazard ratios (HRs) and 95% confidence intervals (CIs) calculated for a 10 μg per cubic metre (m^3) increase in pollutant exposure. The exception to this was CO exposure, where a 100 $\mu g/m^3$ increase was used to match both the greater variability observed in CO exposure and the approach taken in other studies. All models included adjustment for age, sex, and clinic location by inclusion of a clustering term. The inclusion of a cluster term accounted for potential correlations in participant characteristics and disease outcomes within clinics by allowing these possible dependencies to be taken into account.

Similar to in **Chapter 5** of this thesis, hazard ratios were additionally computed for an IQR increase in pollutant concentrations, to enable comparison of risk between specific pollutant concentrations, these are presented in **Appendix D10**.

Further key potential confounders were determined based on the existing evidence base and were included in proportional hazard models irrespective of whether they changed risk estimates. For the analysis of major cardiovascular disease these included active smoking status (never, occasional, ex-regular, current regular), passive smoke exposure of at least 6 months in duration (never, previously, at present), self-rated health (excellent, good, fair, poor), BMI (kg/m^2, continuous), total physical activity (MET-hrs/day, continuous), alcohol

consumption (never, occasional/monthly, ex-regular/reduced intake, weekly regular), highest education level (no formal education, primary school, middle school, high school/college/university), solid fuel use (derived, defined by both the frequency and use of clean versus solid fuels for cooking, categorised as always clean fuels, solid to clean fuels, always solid fuels, never cooked regularly, and others), ambient mean annual temperature (degrees Celsius, continuous), and prior respiratory disease (derived, defined as incident major respiratory disease recorded prior to the cardiovascular disease outcome of interest, yes/no).

Additional potential confounders were entered using a stepwise relative change in estimate approach and were only included provided they changed the risk estimate for the association between AAP exposure and risk of cardio-respiratory disease. Given the smaller magnitude of risk estimates frequently observed in epidemiological studies of AAP exposure compared to more traditional epidemiological risk factors, a change in estimate was quantified as a change in the hazard ratio by at least 5%. [363] Additional potential confounders also had to be themselves associated with risk of major cardiovascular disease ($p<0.05$) and plausibly associated with both AAP exposure and cardiovascular disease. These included consumption of fresh fruit and preserved vegetables, respectively, (daily, 4-6 days per week, 1-3 days per week, monthly, never/rarely), current use of hypertensive medication (yes/no), and mean SBP (mmHg, continuous). Selected confounders remained the same for the analysis of each cardiovascular disease type and pollutant of interest to enable valid comparison between them.

For the analysis of major respiratory diseases key potential confounders remained the same as for cardiovascular disease including active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education level, solid fuel use, ambient mean annual temperature, and prior cardiovascular disease incidence (derived, defined as incident cardiovascular disease recorded prior to the

respiratory disease outcome of interest, yes/no). Additional potential confounders included the consumption of fresh fruit, and preserved vegetables, respectively, and current use of diabetes medication (yes/no). Again, selected confounders remained the same for analysis of each major respiratory disease type and pollutant of interest, enabling valid comparison to be made between them.

Where correlation coefficients were between 0 and +/-0.7, i.e. weak to moderate correlations, bi-pollutant models were fitted. Bi-pollutant models were chosen over multi-pollutant models as given the collinearity anticipated between co-pollutants modelling a large number of interrelated predictor variables would likely result in inflated variance and unstable risk estimates [307, 308]. Therefore, bi-pollutant models were used to attempt to assess the stability of effect for specific pollutant concentrations and their associations between AAP exposure and risk of cardio-respiratory disease incidence. Confounders in bi-pollutant models remained the same as for the single-pollutant models used in main analysis for cardiovascular and respiratory disease, respectively.

All statistical analysis was performed in R version 3.4.3 using packages “survival” [364] “DirectStandardisation”, [365] and “lubridate”, [366] with all analysis code written by myself. For the construction of forest plots a macro from an R package developed by colleagues in the Nuffield Department of Population Health was utilised.

6.3.6 Subgroup analyses

Where associations were observed between chronic AAP exposure and risk of major cardio-respiratory diseases, subgroup analyses were performed to assess factors that may modify the observed relationship. HRs were calculated by subgroups and chi-squared (X^2) tests for heterogeneity or trend (when subgroups could be arranged in a meaningful order) performed as appropriate using the coefficients and standard errors generated across subgroups. Subgroup analysis was performed for all major cardiovascular disease (I00-I99) and all

major respiratory disease (J00-J99) cases only, as these would have the greatest number of incident cases to facilitate meaningful stratification.

Subgroups of interest were identified a priori and based on both knowledge from the existing evidence base and those where numbers of disease outcomes would be sufficient following stratification. These included sex, age (categorised as <60, 60-69, and ≥70 years), education level (no formal education, primary school, middle school, and high school or above), active smoking status (never, ex-regular, occasional, current regular), passive smoke exposure of at least 6 months in duration (never, previously, at present), solid fuel use (always clean fuels, solid to clean fuels, always solid fuels, never cooked regularly, and others), BMI (categorised as <18.5, 18.5-25, and >25), self-rated health (excellent, good, fair, and poor), and prior respiratory disease incidence (for analysis of cardiovascular disease) or prior cardiovascular disease incidence (for analysis of respiratory disease). Included confounders remained the same as in main analysis for cardiovascular and respiratory disease, respectively.

6.3.7 Sensitivity analysis

To ensure the robustness of risk estimates for the association between AAP exposure and cardio-respiratory diseases, the relationship between AAP exposure and risk of incident certain infectious and parasitic diseases (A00-B99) was examined (see **Appendix D2**. for specific ICD-10 codes and respective descriptions of specific included infectious and parasitic diseases). These were chosen as there were a sufficient number of incident cases during follow-up (n=486) of which are unlikely associated with AAP exposure as known from the current evidence base on the relevant biological mechanisms of health effects associated with AAP exposure. [367, 368] The same key confounders were included as in the main analysis for cardio-respiratory diseases. Further potential confounders (including fresh fruit and preserved vegetable consumption, diabetes status, hypertension status, mean SBP and medication intake) were entered in a stepwise fashion and included only if they changed

the risk estimate of the strength of association, which none did**.** A lack of observed association between AAP exposure and risk of infectious and parasitic disease can be used to somewhat validate the robustness of findings observed for cardio-respiratory disease.

Finally, to compare the effect of differing temporal structures in AAP exposure on cardio-respiratory disease risk, associations were also examined using a monthly measure of AAP exposures as generated by the spatiotemporal model described in **Section 6.3.2.** For this, the same models were fitted as described above for each outcome, respectively. The exception to this was the adjustment for temperature where mean monthly ambient temperature was used in order to adjust for its known potential confounding effects.

6.4 Results

6.4.1 Pollutant concentrations

Summary statistics of predicted pollutant concentrations throughout the study period are shown in **Table 6.5.** Mean (SD) PM exposure across clinics during follow-up (2013-2015) was 84.88 $\mu g/m^3$ (24.68) and 75.04 $\mu g/m^3$ (24.27) for $PM_{10,}$ and $PM_{2.5}$, respectively. Mean (SD) concentrations of NO_2, SO_2, O_3 and CO were 68.65 $\mu g/m^3$ (37.32), 30.41 $\mu g/m^3$ (16.95), 97.60 $\mu g/m^3$ (36.38) and 0.61 mg/m^3 (0.22), respectively.

6.4.2 Pollutant correlations

Scatterplots and respective correlation coefficients for annual pollutant concentrations by clinic are shown in **Figure 6.5**. As expected, particulates PM_{10} and $PM_{2.5}$ exhibited a strong positive correlation with each other (r=0.81), as did NO_2 with $PM_{2.5}$ (r=0.74), NO_2 was less correlated with PM_{10} (r=0.34). NO_2, PM_{10}, and $PM_{2.5}$ exhibited negative correlations with O_3 (r=-0.54, r=-0.80, r=-0.81, respectively). SO_2 had weak correlations with other pollutant concentrations, the exception being CO with which it was negatively correlated (r=-0.61). CO was negatively correlated with all other pollutants except O_3 (r=0.01). Similar correlations to

those described above were observed in all pollutants when looking at each study year separately (**Appendix D3**), suggesting that while overall pollutant concentrations may have fallen throughout the study period, concentrations remained proportional to one another at the clinic level.

6.4.3 Temporal trends

Long-term trends in annual average AAP levels are shown by clinic in **Figure 6.6** and further quantified through the percentage change in mean concentrations across both clinics and fixed-site monitors shown in **Table 6.6**. Mean SO_2 concentrations fell by 39.9% and 38.3% throughout the study period across clinic locations and fixed-site monitors, respectively. PM_{10} and $PM_{2.5}$ concentrations also decreased throughout follow-up at both clinic locations (-22.1% and -21.9% for mean PM_{10} and $PM_{2.5}$, respectively) and fixed-site monitors, (-16.7% and -20.0% for mean PM_{10} and $PM_{2.5}$, respectively). Mean O_3 concentrations declined less, by -4.1% across clinics and -2.4% across monitoring sites. Mean NO_2 concentrations increased by 1.4% across clinic locations but across monitors a -1.2% increase in NO_2 was observed. Similarly, mean CO increased by 8.5% across clinic locations but declined by -0.3% across monitors. These observed variations in temporal trend between clinics and fixed-site monitors are potentially due to more localised variability in NO_2 and CO relative to the other more spatially homogenous pollutants.

For mean monthly AAP levels, temporal trends were similar between both estimated clinic concentrations and measured concentrations from fixed-site monitors (**Figure 6.7**). Predicted concentrations of pollutants at clinic locations were both greater and less than measured concentrations, with all measured concentrations captured within the ranges of prediction (except CO). In terms of seasonal variability in pollutants, PM, NO_2, SO_2 and CO had highest concentrations in winter and lowest during summer, while for O_3, the highest concentrations were observed in summer.

6.4.4 Spatial trends

AAP levels averaged for the entirety of follow-up are mapped by clinic location and pollutant type in **Figures 6.8-6.13**. There were no clear spatial patterns in AAP levels in their distribution by clinic location.

6.4.5 Baseline characteristics of the study population

Of the 53,002 included participants (30,758 females and 22,244 males), the mean (SD) age was 51.6 (10.4) years (**Table 6.7**). Only 37.6% of participants were educated to middle school or higher, with a greater proportion of males compared to females (49.7% versus 28.9%, respectively). Considerable sex- differences were present in smoking and alcohol consumption patterns. Age-adjusted prevalence of current regular smoking at baseline was 0.04% in female participants compared to 68.4% in males ($p<0.001$). Similarly, 40.9% of males consumed alcohol at baseline on a current regular (weekly) basis compared to only 0.6% of females ($p<0.001$).

29.0% of participants reported “excellent” general health compared to 10.4% who reported it as “poor”. Hypertension was the most prevalent chronic cardio-respiratory disease condition, present in 13.4% of participants, followed by emphysema/bronchitis present in 4.7%, while IHD was prevalent in only 1.1% of participants. 17.8% and 2.0% of participants reported a family history of stroke and MI, respectively. Regarding cardio-respiratory symptoms, 3.3% of participants reported feeling breathless when walking on level ground with prevalence greater in females than males (4.1%, 2.3%, respectively, $p<0.001$). Female participants also had a higher prevalence of self-reported chest pain when walking on level ground (2.3% versus 1.2% for females, and males, respectively, $p<0.001$). However, prevalence of chronic cough was greater in male participants than females (4.9% versus 2.4%) ($p<0.001$). 11.1% of all participants had possible airflow obstruction as defined by FEV_1: FVC < lower limit of normal (**Table 6.8**).

Mean PM exposure in participants was 84.6 μg/m^3 and 74.7 μg/m^3, for PM_{10} and $PM_{2.5}$, respectively, with exposure concentrations higher for males than females (85.4 μg/m^3 versus 84.0 μg/m^3, and 77.2 μg/m^3 versus 72.8 μg/m^3, for PM_{10} and $PM_{2.5}$, respectively, both $p<0.001$). For gaseous pollutants, mean exposure to NO_2 and SO_2 was 71.0 μg/m^3, and 32.2 μg/m^3, respectively, again with greater exposure concentrations in males than females (both $p<0.001$). Mean exposure to CO and O_3 was 0.54 mg/m^3 and 99.2 μg/m^3, respectively, with greater exposure concentrations of these pollutants in females than males (0.56 mg/m^3 versus 0.52 mg/m^3, and 100.9 μg/m^3 versus 96.8 μg/m^3, in females and males for CO and O_3, respectively, both $p<0.001$).

6.4.6 Baseline characteristics by cardiovascular disease incidence

For all major cardiovascular disease, the three-year study period included a total of 138,172 person-years of follow-up, (exact person-years varied by specific type of cardiovascular disease examined given slightly differing participant exclusion criteria). Throughout follow-up 2559 cases of incident major cardiovascular disease (ICD-10 I00-I99) were reported, these included 1051, 847, 178, 421, and 1601 cases of all-type stroke, ischaemic stroke, intracerebral haemorrhage, ischaemic heart disease, and other cardiovascular diseases, respectively. Of the 2559 major cardiovascular disease cases only 197 (~7.7%) were fatal (**Appendix D1**). Incidence rates of major cardiovascular disease by sex and age are shown in **Table 6.9**. Rates were higher in males than females except for other cardiovascular diseases, where rates were slightly greater in females than males (115.2/10,000 person-years and 108.9/10,000 person-years, respectively). Rates were also higher in older participants; for example, all-type stroke rates were 7.6/10,000 person-years in participants aged 30-39 years, versus 348.7/10,000 person-years in those aged >70 years.

Table 6.10 shows baseline participant characteristics by the incidence of major cardiovascular disease events during follow-up. Compared to those with no events, participants with incident cardiovascular disease incidence were older, with lower education

levels, less physically active, and a greater proportion reported “poor” general health. Greater proportions of participants with events were also ex-regular smokers and reported ex-regular/reduced consumption of alcohol compared to those without events.

Comparing participants with a cardiovascular disease event to those without, participants with events had higher prevalences of hypertension, emphysema/bronchitis and IHD at baseline (all $p<0.005$). Participants with cardiovascular disease events also had higher mean systolic and diastolic blood pressures and mean BMI compared to those without (all $p<0.05$) (except participants with intracerebral haemorrhage) (**Table 6.11**).

For mean AAP exposure, consistent differences were seen for O_3 exposure, which was significantly higher in participants with a cardiovascular disease event versus without (all $p<0.05$). Contrastingly, mean NO_2 and PM_{10} concentrations were higher in those without a cardiovascular disease event ($p<0.05$). Mean SO_2 concentrations were greater in those with cardiovascular disease events than without for all major cardiovascular disease, and all-type and ischaemic stroke. $PM_{2.5}$ concentrations were greater in those without a cardiovascular disease event except for ischaemic stroke.

6.4.7 AAP exposure and risk of cardiovascular diseases

6.4.7.1 Particulate matter

There were no associations between PM_{10} or $PM_{2.5}$ concentrations and increased risk of major cardiovascular disease incidence (**Figure 6.14)**. Instead, both PM_{10} and $PM_{2.5}$ appeared borderline associated with reduced risk of major cardiovascular disease (adjusted HRs of 0.97 [0.95, 0.99] and 0.97 [0.95, 0.99] for PM_{10} and $PM_{2.5}$ respectively). $PM_{2.5}$ specifically also appeared borderline associated with reduced risk of stroke, specifically ischaemic stroke (adjusted HRs of 0.94 [0.91, 0.98], and 0.94 [0.90, 0.98]).

6.4.7.2 Gaseous pollutants

Both SO_2 and O_3 exposure were associated with higher risk of incident cardiovascular disease, both major cardiovascular disease and other cardiovascular diseases (adjusted HRs of 1.07 [1.02, 1.12] and 1.02 [1.01, 1.03] for all major cardiovascular disease and 1.11 [1.04, 1.20] and 1.02 [1.01, 1.03] for other cardiovascular diseases) (**Figure 6.14**). O_3 specifically was also associated with risk of all-type and ischaemic stroke (adjusted HRs of 1.04 [1.02, 1.05] and 1.04 [1.02, 1.06], respectively). No other gaseous pollutant was associated with increased risk of major cardiovascular disease incidence and contrastingly NO_2 appeared borderline associated with reduced risk of stroke, both all-type and ischaemic (adjusted HRs of 0.98 [0.96, 1.00] and 0.97 [0.95, 0.99], respectively).

6.4.7.3 Bi-pollutant models

Following inspection of the correlations between pollutants the following bi-pollutant models were constructed; SO_2 + $PM_{2.5}$ (r=0.05); SO_2 + PM_{10} (r=-0.33); SO_2 + NO_2 (r=0.37); SO_2 + CO (r=-0.61); and SO_2 + O_3 (r=-0.37) with results from these shown in **Table 6.12**. Chronic SO_2 exposure remained associated with risk of major cardiovascular disease following mutual adjustment for all other pollutants, respectively (except adjustment for PM_{10} and O_3, respectively, which attenuated the association between SO_2 and all cardiovascular disease to borderline significant). The observed negative associations between $PM_{2.5}$ and PM_{10} with risk of major cardiovascular disease and stroke were no longer significant following adjustment for SO_2.

Bi-pollutant models were also constructed to assess the stability of the observed relationships between O_3 and cardiovascular disease, adjusting for the following pollutants; O_3 + NO_2 (r=-0.54); and O_3 + CO (r=0.01). O_3 exposure remained associated with increased risk of all major cardiovascular disease, all-type and ischaemic stroke and other cardiovascular diseases following adjustment for both NO_2 and CO **(Table 6.13).**

6.4.7.4 Subgroup analysis

For the observed associations between chronic AAP exposure and risk of all major cardiovascular disease **Table 6.14 and 6.15** show the adjusted HRs (95% CIs) stratified by selected characteristics at baseline. The observed risk of SO_2 exposure and O_3 exposures, respectively with cardiovascular disease did not appear to vary significantly by the population subgroups examined.

6.4.8 Baseline characteristics by respiratory disease incidence

During the three-year study period and a total 135,244 person-years of follow-up (again exact person-years varied by cause-specific respiratory disease examined given slightly differing participant exclusion criteria), there were 1763 cases of major respiratory disease (J00-J99), of which only 2.6% were fatal cases. Of the 1763 major respiratory disease endpoints, 329, 430, and 1323 were COPD, pneumonia, and other respiratory diseases, respectively. Major respiratory disease incidence rates by sex and age are shown in **Table 6.16**. Rates of every type of respiratory disease were higher in males than females. Rates were also higher in older-aged participants; for example, COPD rates ranged from 1.4/10,000 person-years in participants aged 30-39 years, to 173.0/10,000 person-years in those aged ≥70 years.

Baseline participant characteristics by the incidence of major respiratory disease are shown in **Table 6.17**. Compared to those without events, participants with recorded respiratory events were older, had lower education levels, lower levels of physical activity, and a greater proportion of participants reporting both current and previous solid-fuel use for cooking. Prevalence of current regular smoking was also greater in those with respiratory disease events than without (except those with other respiratory diseases). Baseline prevalence of self-reported hypertension, stroke, IHD, as well as breathlessness and chest pain was greater in participants with major respiratory disease events than those without. Chronic cough prevalence was also higher in those with respiratory disease events, except for

participants with COPD events. Unsurprisingly participants with respiratory events also had lower mean BMI, poorer lung function, and a higher prevalence of possible airflow obstruction compared to those without (**Table 6.18**).

Regarding mean AAP exposure during follow-up, except for pneumonia, average concentrations of $PM_{10,}$ NO_2 and CO were significantly greater in participants with a respiratory disease event than those without ($p<0.05$).

6.4.9 AAP exposure and risk of respiratory diseases

6.4.9.1 Particulate matter

Chronic $PM_{2.5}$ exposure was borderline associated with higher risk of other respiratory diseases incidence only (adjusted HR 1.04 [1.00, 1.09]) (**Figure 6.15**). Contrastingly, both PM_{10} and $PM_{2.5}$ exposures appeared negatively associated with pneumonia incidence (adjusted HRs of 0.94 [0.90, 0.98], and 0.94 [0.89, 1.00]).

6.4.9.2 Gaseous pollutants

Similar to the results for major cardiovascular disease incidence, only SO_2 and O_3 were associated with an increased risk of major respiratory diseases. SO_2 exposure was associated with increased risk of all major respiratory diseases (1.11 [1.04, 1.19]), COPD (1.24 [1.08, 1.44]), pneumonia (1.12 [1.03, 1.23), and other respiratory diseases (1.09 [1.01, 1.18]), respectively **(Figure 6.15).** O_3 exposure was associated with COPD and pneumonia incidence only (1.04 [1.00, 1.08]), and 1.04 [1.02, 1.06], respectively). Chronic CO exposure appeared negatively associated with incident COPD (0.90 [0.83, 0.97]).

6.4.9.3 Bi-pollutant models

Results from bi-pollutant models are shown in **Tables 6.19 and 6.20**. SO_2 exposure remained a statistically significant predictor for the incidence of all major respiratory

diseases with the exception of pneumonia, where adjustment for $PM_{2.5}$ attenuated the association to null. CO exposure was also no longer borderline significantly associated with reduced risk of COPD following adjustment for SO_2 (0.94 [0.86, 1.03]) (**Table 6.19**). O_3 remained a significant predictor of COPD and pneumonia risk following adjustment for NO_2, however adjustment for SO_2 attenuated the associations between O_3 and COPD to the null (**Table 6.20**).

6.4.9.4 Subgroup analysis

For chronic SO_2 exposure and risk of all major respiratory disease incidence results of subgroup analysis are shown in **Table 6.21**. The observed risk did not appear to vary significantly by the population subgroups examined.

6.4.10 Sensitivity analysis

Throughout the three years of follow-up there were 486 cases of infectious and parasitic diseases (A00-B99), the majority of which were unspecified infectious disease (B99), and unspecified infectious gastroenteritis and colitis (A09), full details of the ICD-10 codes and respective descriptions can be found in (**Appendix D2)**. Incidence rates of infectious and parasitic diseases were higher in older participants and were slightly higher in males (**Appendix D4)**. There were no significant associations between chronic exposure to any of the included pollutants and the risk of infectious and parasitic diseases (**Appendix D5).**

The results from monthly AAP exposure metrics are shown in **Appendix D6 and D7,** for cardiovascular and respiratory diseases, respectively. O_3 remained associated with risk of all-type and ischaemic stroke (adjusted HRs 1.03 [1.02, 1.05] and 1.03 [1.01, 1.05], respectively) when using monthly exposure measures. Monthly SO_2 exposure was also borderline associated with increased risk of both all-type and ischaemic stroke (adjusted HRs 1.06 [1.00, 1.12] and 1.08 [1.02, 1.14], respectively) but not with all major cardiovascular disease and other cardiovascular diseases as seen when using annual SO_2

exposure. For respiratory disease, monthly SO_2 exposure was associated with risk of all major respiratory diseases, including pneumonia (adjusted HRs 1.07 [1.03, 1.11], and 1.10 [1.02, 1.19]). O_3 and SO_2 were no longer associated with the risk of COPD when using monthly exposure.

6.5 Discussion

6.5.1 Summary of main findings

In this prospective cohort study of 53,002 Chinese individuals, associations between chronic AAP exposure and risk of incident major cardio-respiratory diseases were examined. Chronic AAP exposure was assigned to participants using a spatiotemporal model with a high spatial resolution. This is in contrast to previous studies using averaged AAP levels from fixed-site monitors or homogenous AAP levels assigned to all participants across a large spatial domain.

In participants without known prior history of cardiovascular disease, a 10 $\mu g/m^3$ increase in both chronic SO_2 and O_3 exposure, respectively, was associated with an elevated risk of all major cardiovascular disease incidence. Both SO_2 and O_3 also remained significant predictors of all major incident cardiovascular disease following adjustment for additional pollutants. For O_3, these additional pollutants included, SO_2, NO_2, and CO, respectively, while for SO_2, they included $PM_{2.5}$, NO_2, and CO, respectively. Interestingly, chronic particulate exposure was not associated with incident cardiovascular disease of any kind.

Regarding major respiratory disease, both chronic SO_2 and O_3 were associated with the incidence of major respiratory diseases. SO_2 exposure also remained a significant predictor of major respiratory disease incidence in bi-pollutant models adjusting for $PM_{2.5}$, PM_{10}, NO_2, CO and O_3, respectively. O_3 exposure remained borderline associated with major respiratory disease incidence following adjustment for NO_2 but not CO. Unsurprisingly, in sensitivity

analysis no associations were observed between chronic AAP of any kind and risk of infectious and parasitic diseases.

As one of the very few studies to also incorporate monthly measures of AAP exposure, these were also associated with risk of cardio-respiratory disease incidence and with some discrepancies in risk estimates when compared to the use of annual AAP exposure. Only monthly SO_2 was significantly associated with higher stroke risk, potentially due to the more acute nature of stroke onset with studies documenting acute increases in SO_2 associated with increased acute stroke risk in China [178, 224, 369]. Contrastingly, monthly AAP exposure was not significantly associated with all major cardiovascular disease and other cardiovascular disease as seen when using annual SO_2 exposure with a possible explanation being the wider range of diseases captured within these respective groupings potentially inclusive of those with longer latency in development. Only annual measures of O_3 and SO_2 were associated with increased COPD risk. This also could potentially be due to the longer latency period of COPD development. Residual confounding is also a possibility as although adjustment was made for monthly ambient temperature this was a crude average measure and, residual confounding in seasonality is still a potential explanation when using monthly AAP exposures.

6.5.2 Strengths and limitations

Before comparing results with those from the existing literature the strengths and limitations of the study will be discussed.

6.5.2.1 Selection of participants and confounding assessment

A principal strength of this study is its size; with 53,002 participants, it is to my knowledge, the largest study to date examining chronic AAP exposure and risk of incident cardio-respiratory disease in China. While larger prospective studies exist which examined chronic

AAP exposure and risk of cardio-respiratory mortality, [66, 69, 226] these used participants across larger geographic areas compared to the more localised spatial scale seen in this study. A further strength was the incorporation of a wide range of socio-demographic and lifestyle characteristics, in addition to the reported prevalence of doctor-diagnosed chronic conditions. A number of these were potential confounders not included in prior cohort studies on chronic AAP exposure and risk of cardio-respiratory disease in China, confounders such as household solid-fuel use, passive smoke exposure, and prior history of cardio-respiratory diseases. However, it is important to note that these were self-reported, and thus reporting biases, such as recall bias and social desirability bias, were possible.

Participants were invited from the general population to participate in the CKB study and were limited only by age at baseline and their ability to consent, therefore, selection bias, while a possibility, is unlikely to be an issue in this study. However, the "healthy volunteer effect" is always a possibility as discussed in **Section 4.2** of this thesis. Furthermore, covariates were for five years earlier than the beginning of exposure and follow-up of this study, therefore some of these characteristics of participants may have in the meantime changed which may lead to residual confounding. An example of this is the household fuel transition from solid to clean fuel use occurring between 2005-2015 in China following localised urban development and increased fuel accessibility across residential communities in China. [370] As a result of this transition, misclassification of solid fuel use may potentially influence participant susceptibility to cardio-respiratory disease and if related to AAP distribution could result in residual confounding.

6.5.2.2 Exposure assignment

A major strength of this study is its use of a localised spatiotemporal model to assign AAP exposure to participants. This allowed a higher degree of small-scale AAP exposure variability to be captured than in previous Chinese studies, thereby reducing exposure measurement error which has remained a substantial problem in epidemiological studies of

AAP [82, 371, 372]. It also addresses the call for studies with more robust exposure assessment in China [373]. The spatiotemporal model used for this study also enabled multiple pollutant exposures to be assigned to participants, facilitating the construction of bi-pollutant models.

However, a prominent limitation of this study is its use of baseline clinic location as a proxy for residential address. Although CKB participants are assumed to live roughly within one kilometre of their respective baseline clinic, this cannot be conclusively proven for all participants making exposure misclassification still a likely possibility. Furthermore, as historic residential AAP exposure could not be determined in this study, back-extrapolation of predicted exposures or cumulative estimation of lifelong exposures were not possible. Therefore, historical AAP exposure which likely plays an essential role in chronic disease development particularly for diseases with long latency periods including numerous cardio-respiratory diseases could not be determined. This limitation is worsened by the study's short-follow up period meaning it is unlikely that participants past AAP exposures potentially associated with cardio-respiratory disease development were fully captured in their assigned exposures. By examining CKB disease endpoints that predominantly capture morbidity with likely shorter latency time versus mortality may have somewhat overcome this issue, but it is still a major limitation to this study. To overcome the issue of the short follow up time, extrapolation of AAP levels to additional years of follow-up also could have been used to capture cardio-respiratory endpoints outside of the three-year study period, as seen in other studies.[69, 237] However, given the considerable chronic trends seen in AAP levels (particularly for $PM_{2.5}$), such extrapolation would be unlikely to capture participant exposure and was thus not performed.

Finally, as with all epidemiological studies of AAP exposure, the degree to which assigned AAP exposure represents true participant exposure remains imperfect. Individuals also spend roughly 90% of their time indoors [374] and exposure within microclimates while

travelling could not be determined in this study, likely contributing to errors in exposure measurements.

6.5.2.3 Outcome ascertainment

The inclusion of morbidity as an outcome of interest in this study is particularly important given a considerable portion of the burden relating to AAP exposure is likely captured by solely morbidity. Morbidity is also arguably more sensitive to AAP exposure than mortality, particularly for those diseases that do not lead to rapid death but rather the onset of chronic conditions such as many cardio-respiratory diseases. [375]

This study used established death and disease surveillance systems to capture the outcomes of interest. These are checked and validated by both CKB and NCC staff with an additional adjudication performed on several major diseases (cancer, IHD, stroke, COPD and diabetes). Here, events recorded in any of the data follow-up sources are retrieved and reviewed by clinicians at the CKB national or international coordinating centre blinded to baseline or resurvey data in order to confirm, or otherwise, disease events. However; misdiagnoses and under/over diagnoses are still always a possibility given discrepancies and variability in the operating of specific hospitals and health centres. Despite this, there is no reason to suspect that these would lead to a systematic bias nor should they be related to AAP exposure, exemplified by the lack of systematic difference in the geographic spread disease endpoints by clinic location (**Appendix D8**), meaning this potential bias unlikely affects the observed risk estimates in this study.

However, the concurrent capturing of cause-specific disease endpoints within CKB is a limitation as its possible endpoints may not reflect an incident cardio-respiratory disease affected by AAP exposure but rather a co-morbid condition detected following hospital admission for another disease. An example of this could be hypertension detected following

routine testing upon hospitalisation for another condition, and not truly associated with AAP exposures.

Finally, cohort studies of chronic AAP exposure also by design cannot effectively completely disentangle the true effects of acute AAP exposure from that of chronic exposure on risk of disease events [51]. Therefore, it's also possible that some of the effects of acute AAP exposure are captured within the generated risk estimates presented in this Chapter. This also perhaps explains some of the observed risks for SO_2 and incident cardio-respiratory diseases as acute SO_2 exposure was also associated with increased risk of cardio-respiratory disease incidence in Suzhou in **Chapter 5** of this thesis.

6.5.2.4 Adjustment for multiple testing

Throughout this chapter, a number of significance tests were performed assessing the associations between specific pollutants and cardio-respiratory outcomes. Although it is recommended in epidemiological studies to make suitable adjustments for multiple comparisons in order to prevent type I error [376] such adjustments for multiple testing are seldom performed in air pollution epidemiology [64, 377] and this was, on the whole an exploratory analysis as opposed to a confirmatory study with the goal of proving a predefined key hypothesis for decision making. [376] However, to the issue of multiple testing, a Bonferroni-corrected threshold can be applied by dividing 0.05 by the number of outcomes examined. In this case, 36 tests for cardiovascular outcomes (six pollutants and six cardiovascular outcomes) and 24 tests for respiratory outcomes (six pollutants and four respiratory outcomes) resulting in Bonferroni corrected p-values of 0.0014 and 0.002, respectively. The results from this chapter are shown with corresponding p-values in **Appendix D11** where the associations between O_3 and major cardiovascular disease, stroke and pneumonia as well as SO_2 and major respiratory disease remained significant at the corrected threshold. Additionally, since Bonferroni corrections may be overly

conservative due to correlated tests, p-values were also generated using the Benjamin-Hochberg procedure. [378]

6.5.3. Comparisons with the relevant literature

The findings of this chapter are now compared to existing prospective studies from China identified in the Literature Review of this thesis **(Table 2. 1)** as well as with the relevant prospective evidence from high-income countries (HICs), for particulate and gaseous AAP, respectively. Given the current scarcity of evidence on AAP exposure and non-fatal events exclusively, comparisons are also made with prospective studies examining cardio-respiratory mortality in China.

6.5.3.1 Particulate matter and major cardiovascular disease

Evidence is severely lacking on the association between chronic PM exposure and risk of incident cardiovascular disease in China. However, prospective evidence from HICs (particularly the USA and Western Europe) have shown consistent associations between PM exposure (at lower concentrations than seen in this study), and elevated risk of major cardiovascular disease and stroke incidence. [242, 379, 380] In China, three prospective studies have found chronic PM exposure associated with increased risk of cardiovascular mortality. [66, 69, 226] One of these studies assigned AAP exposure using a localised (5 x 5km) satellite exposure model and found significant associations between chronic $PM_{2.5}$ exposure and risk of cardiovascular mortality in addition to both stroke and IHD mortality, respectively. [69] Large-scale prospective studies from HICs have also found associations between chronic PM exposure and cardiovascular mortality, [64, 237, 381] including stroke [242, 380] and IHD [377] at observed PM concentrations lower than those in this study. Many of these studies also used methods of AAP exposure with an improved spatial resolution of exposures similar to this study. [382-386]

Along with evidence from epidemiological studies, several biological mechanisms by which PM exposure adversely affects the cardiovascular system have been identified through experimental and toxicological studies. As described in **Chapter 5,** these predominantly involve the inflammatory and haemostatic systems with PM able to translocate into the circulation [318] associated with the release of pulmonary derived proinflammatory mediators and perturbation of the autonomic nervous system (ANS). [265, 387] PM exposure has also been consistently associated with oxidative stress and systemic inflammation, [388, 389] as well as thrombosis and coagulatory changes to blood [390, 391] atherosclerosis, [392] heart-rate variability [322] and elevated blood pressure. [393, 394] Such PM-mediated subclinical effects are hypothesised to result in predisposition and both the instigation and progression of cardiovascular disease including IHD and stroke, particularly when combined with traditional cardiovascular risk factors. [265]

This accumulation of evidence has led to the conclusion by both the US Environmental Protection Agency (EPA) and UK Committee on the Medical Effects of Air Pollutants (COMEAP) that PM exposure is in some way causally associated with both cardiovascular mortality [395, 396] and morbidity. [396]

Therefore, the results outlined in this chapter study were surprising which found no significant associations between PM and increased risk of incident cardiovascular disease of any kind but rather a seemingly borderline protective effect between PM and all major cardiovascular disease likely the result of the limitations of this study as listed in **Section 6.5.2.** Further possible explanations for the lack of observed associations may include the declining PM exposure seen across all clinics throughout the study period, with similar PM reductions associated with declines in mortality and morbidity within a short time frame. [381, 397] In China specifically, significant declines in all-cause [398] and cardiovascular mortality, [399] as well as subclinical markers of inflammation [400] were observed following the implemented PM reductions during the 2008 Beijing Olympics where a 27% decline in PM was observed,

[401] similar to the decline observed in this study (21.9% decline in $PM_{2.5}$ across all clinic locations). It is plausible that this decline may have resulted in a reduction in the progression and development of PM-related cardiovascular disease.

An additional explanation for the lack of observed associations may relate to the composition of PM exposure in this study. Although the vast majority of epidemiological studies have focused solely on the mass concentration of PM, compositional differences also likely affect associated cardio-respiratory effects. [402, 403] Specific components of both fine and coarse PM have been found to be more strongly associated with cardio-respiratory mortality and morbidity than others, including elements such as sulphates and nitrates, from fossil-fuel combustion, [64, 65, 404] as well as elemental and organic carbon, nitrate, and trace components like nickel and arsenic. [200, 405] Similar research in China has also shown specific PM constituents (potassium, calcium, nitrate and sulphate) to be more associated with mortality than others (fluoride, sodium, magnesium, NO_2, and chlorides). [406] However, these studies are for acute exposure, with more research needed on the associations of chronic exposure to different PM composition with health outcomes. Nevertheless, it may be that the increased control of AAP emissions in China and observed decline in PM was coupled with a decline in PM components most associated with cardio-respiratory mortality and morbidity, potentially explaining the lack of observed associations between PM and incident cardiovascular disease in this study.

6.5.3.2 Gaseous pollutants and major cardiovascular disease

SO_2

Prior to this thesis, no prospective study had examined chronic SO_2 exposure and incident cardiovascular disease in China, and only one had examined SO_2 and cardiovascular mortality [66] and used fixed-site monitors to assign chronic exposure to participants finding associations between SO_2 exposure and cardiovascular mortality. The findings of this study on cardiovascular mortality are consistent with those outlined in this chapter, albeit slightly

weaker, potentially due to higher sensitivity of pollution-related morbidity relative to mortality, as already hypothesised in the literature. [358]

The overall evidence for the effects of gaseous pollutant exposure (including SO_2) on cardiovascular disease remains less conclusive relative to that of PM in both China and within HICs. However, prospective studies have found chronic SO_2 exposure associated with risk of cardiovascular disease mortality, [237, 377, 407] even after adjustment for $PM_{2.5}$ [408] consistent with the findings of this study. Experimental and toxicological studies have also shown SO_2 exposure capable of inducing oxidative damage in the heart and lungs of mice [409] as well as increased mitochondrial dysfunction.[410] In human studies, SO_2 exposure has been associated with reduced cardiac vagal control potentially increasing susceptibility to cardiac arrhythmia. [411] However, despite these associations, uncertainty remains surrounding the role of SO_2 and cardiovascular disease development with the majority of the evidence from studies on acute exposure. The effects of chronic SO_2 exposure on the cardiovascular system remains poorly understood and the associations are far from being regarded as causal, with SO_2 hypothesised to be a proxy for other pollutants. [412]

The study described in this Chapter found chronic SO_2 exposure associated with increased risk of other cardiovascular diseases of which 42.6% and 39.8% were hypertensive diseases and diseases of the veins, lymphatic system and lymph nodes, respectively (**Table 6.4**). While a recent meta-analysis found acute exposure to SO_2 associated with hypertension, only one other study has examined the association of chronic (3 year-averaged) SO_2 exposure and hypertension in China [227] and found a significant association with hypertension prevalence, although its use of a cross-sectional design limits the degree to which it can be accurately compared with the findings of this study.

The study outlined in this chapter also found that upon adjustment for PM_{10} and O_3, respectively the observed associations between chronic SO_2 exposure and all major

cardiovascular disease was attenuated to null. As studies that examine the chronic cardio-respiratory effects of SO_2 exposure are severely lacking, this finding cannot be compared in the context of the existing literature.

NO_2

Before this thesis, no prospective studies had examined the effects of chronic NO_2 exposure on incident cardiovascular disease in China. However, a prospective study from Rome had found chronic NO_2 exposure associated with cardiovascular disease incidence, including first-time IHD.[413] This finding is inconsistent with the findings of this Chapter which found no associations between chronic NO_2 exposure and risk of incident cardiovascular disease of any type. A possible explanation for this could be, as demonstrated in recent prospective studies chronic NO_2 exposure has been found to have more effect on fatal than non-fatal stroke risk, [242, 414, 415] with any-kind stroke making up 41.1% of cardiovascular disease cases in this study. Hypothesised reasons for this difference include reduced misclassification of fatal versus non-fatal events. [242] However, this is unlikely in CKB; as discussed in **Chapter 4**, cause-specific CKB disease endpoints are classified according to ICD-10 by trained staff of the DSP system and medical professionals in hospitals, respectively. An alternative hypothesis is that fatal cardiovascular events triggered by air pollution have specific biological mechanisms leading to higher severity and poorer prognosis [414] which may explain the lack of any observed association between NO_2 and incident cardiovascular disease found in this study where only ~7% of all incident major cardiovascular disease cases were fatal (**Appendix D1**). The seemingly protective association between NO_2 and ischaemic stroke found in this study is also unlikely, and potential explanations likely include, the limitations of this study outlined in **Section 6.5.2.**

In China, only one prospective study has examined the effects of NO_x on cardiovascular disease mortality using fixed-site monitors to assign exposure finding NO_x borderline associated with risk of cardiovascular mortality; [66] however, it did not adjust for covariates

such as household solid fuel use and passive smoke exposure. A recent meta-analysis of 15 studies in both HICs and LMICs, [95] found chronic NO_2 exposure weakly associated with risk of cardiovascular mortality; however, this attenuated to null when restricting to studies which adjusted for individual-level measures of BMI and smoking. Therefore, another explanation for the lack of association observed in this study may be the adjustment for a wide range of individual-level covariates such as household solid fuel use and passive smoke exposure not done in prior studies finding an association between NO_2 and cardiovascular disease.

O_3

To my knowledge, no prospective study has examined the association between chronic O_3 concentrations and risk of cardiovascular disease incidence nor mortality in China. While studies from HICs exist, they are limited. Most found no association between chronic O_3 exposure and cardiovascular disease mortality particularly following adjustment for co-pollutants [377, 416] and evidence on chronic O_3 exposure and cardiovascular disease mortality is still deemed inconclusive. [417, 418] Furthermore, the high collinearity often observed between O_3 and other pollutants in studies has meant it is difficult to obtain any reliable estimate for the independent effects of O_3. [377] This is limitation was in part addressed this study where it was possible to obtain risk estimates from bi-pollutant models. O_3 remained associated with risk of major cardiovascular disease following adjustment for NO_2, CO and SO_2. In China, O_3 has been linked with blood platelet activation and increased blood pressure [419] supporting the findings of this study although more research is required.

CO

The study described in this chapter found no associations between chronic exposure to CO and cardiovascular disease incidence. To my knowledge, no prospective study has examined chronic CO exposure and cardiovascular disease incidence nor mortality in China. However, a prospective study from South Korea did find chronic CO exposure to be associated with higher risk of both cardiovascular disease incidence and mortality [420]

however CO concentrations were strongly correlated with $PM_{2.5}$, in this study (r=0.93) and therefore this association may in fact be related to $PM_{2.5}$ exposure.

6.5.3.3 Particulate matter and major respiratory disease

Despite the respiratory system being the initial target of all AAP exposure, the exact mechanistic effects of chronic PM exposure on the respiratory system are not fully understood. [421] Hypothesised mechanisms are thought to involve adverse effects on lung cells, including oxidative stress, localised inflammation, cytotoxicity and epigenetic changes. [422-424] PM exposure has also been linked with decreases in pulmonary function both in studies performed in both China and HICs, but results are inconsistent [425, 426] and compared to the effects of acute PM exposure, the evidence on the association between chronic PM exposure and respiratory disease is less conclusive. [64, 427, 428] Therefore, the observed lack of associations seen in this study between chronic PM and major respiratory disease incidence is theoretically plausible, particularly given the observed decline in PM concentrations.

In China specifically, three prospective studies found significant associations between chronic $PM_{10,}$ $PM_{2.5}$ and TSP exposure (as a proxy for PM) and elevated risk of major respiratory disease mortality, [66, 69, 226] but only one adjusted for passive smoke exposure, and household air pollution .[69] Similarly, a recent prospective Taiwanese study found chronic $PM_{2.5}$ exposure assigned via a spatiotemporal model associated with increased risk of incident COPD. However, this study did not control for passive smoke exposure, nor household air pollution, both established risk factors for the development of COPD, making the validity of its findings questionable. Therefore, it is possible that the lack of observed association in this study between chronic PM exposure and incident respiratory disease is due to the adjustment of a wide range of individual-level covariates. Further possible explanations could involve the potential underdiagnoses of CKB COPD cases. Spirometry diagnosed COPD in China is rare, [429] and while the majority of CKB COPD cases are based

on substantiated clinical evidence (signs, symptoms, risk exposure, radiological examination or spirometry), very few used spirometry evidence to support diagnoses. It is therefore possible that milder forms of COPD may not have been accurately captured in the CKB endpoints. If such underdiagnoses were more common in participants from clinics with high PM exposure, the effects of chronic PM exposure on COPD could be diluted.

Given the lack of associations seen for PM exposure (particularly finer $PM_{2.5}$) and incident respiratory disease, the observed association was between chronic $PM_{2.5}$ exposure and other respiratory disease incidence is surprising given the composition of disease cases contained within this endpoint (see **Table 6.4**). Given the small risk estimate with borderline statistical significance observed the validity of the association is doubtful. Possible explanations may surround this study's limitations outlined in **Section 6.5.2** such as residual confounding.

6.5.3.4 Gaseous pollutants and major respiratory disease

SO_2

Evidence on the association between chronic SO_2 exposure and incident respiratory disease is lacking. Relatively few studies have investigated the toxicological effects of chronic exposure to SO_2 on the respiratory system, and prior to this thesis, no prospective study had examined chronic SO_2 exposure and incident respiratory disease in China. While comparable results have also been observed in large-prospective studies from HICs for SO_2 and respiratory mortality, [64, 237, 377, 430] only one prospective Chinese study has examined chronic SO_2 exposure and risk of respiratory disease mortality, and this found SO_2 exposure to be associated with 3.2% (1.8, 4.7) excess risk of respiratory mortality with risk estimates remaining consistent following adjustment for co-pollutants. This is consistent with the findings of the study outlined in this Chapter, which found chronic SO_2 exposure associated with major respiratory disease incidence with larger risk estimates than the aforementioned

Chinese study. Possible explanations for this difference could include discrepancy in risk between the effects of morbidity and mortality.

NO_2

Similar to the evidence surrounding SO_2, the evidence for NO_2 exposure and its association with incident respiratory disease is on the whole inconsistent. Experimental and toxicological studies have found NO_2 exposure associated with a wide range of adverse respiratory effects, including, reduced FEV_1: FVC ratios, epithelial injury and bronchoconstriction. [431-433] However, these are almost unanimously based on acute NO_2 exposure, and the respiratory health effects of chronic NO_2 exposure remains poorly understood. While some prospective studies from HICs have found chronic NO_2 exposure has been associated with incident respiratory disease including COPD [8] and asthma [434] others have found no such association. [427, 435]

However, a recent meta-analysis [95] of 13 cohort studies found a significant association between chronic NO_2 exposure and respiratory mortality, inconsistent with the results of the study described in this Chapter where no association between NO_2 exposure and incident major respiratory disease of any kind was observed. A possible explanation for this could be that the same meta-analysis found that when stratified by studies, which included an adjustment for individual-level covariates, associations were attenuated to the null. Therefore, adjustment for the wide-range of individual-level covariates in this study may explain the lack of association. Only one prospective cohort study in China examined NO_2 exposure and respiratory disease mortality [66], finding a significant association but failing to adjust for passive smoking or household air pollution and therefore, this may be overstating the size of the association between chronic NO_2 and respiratory mortality.

O_3

To my knowledge, no prospective studies in China have examined the effects of chronic O_3 exposure and risk of respiratory disease mortality nor incidence, and the effect of chronic O_3 exposure on adverse respiratory health remains relatively uncertain [417]. A large prospective cohort study from the USA did find that chronic to O_3 exposure was associated with increased risk of respiratory mortality robust following stratification by ambient temperature. [416] Similarly, experimental findings in animal and human studies have found O_3 exposure associated with airway inflammation reduced pulmonary function and gas exchange. [436] These findings are consistent with the results of this study which found chronic O_3 exposure associated with pneumonia and COPD incidence. They indicate that further research is required in China to confirm O_3 exposure as a risk factor for incident respiratory disease.

CO

To my knowledge, no other study has examined the effects of chronic CO exposure on respiratory disease incidence nor mortality in China and research is similarly limited from HICs making comparisons with the available literature difficult. While some experimental studies have found CO exposure associated with respiratory failure these were at concentrations comparable to active smoking and CO poisoning and thus not applicable to the concentrations observed in this study with much lower CO concentrations observed where evidence remains inconclusive. This study observed a significant inverse association between chronic CO exposure and risk of incident COPD. Given the lack of research surrounding the effects of chronic CO on incident COPD this could not be compared with existing evidence base. However, regarding biological plausibility of COPD this is unlikely to be true, but rather related to pollutant correlations as this association was attenuated to null following adjustment for SO_2.

6.5.4 Further potential explanations of findings

While several explanations for the findings of this study have been outlined above, these will now be fully discussed alongside further potential hypotheses. The lack of observed

associations seen for chronic $PM_{2.5}$ exposure and risk of incident major cardio-respiratory disease in this study is surprising given the existing evidence base. One explanation surrounds this study's short follow-up period (2013-2015) which may also encapsulate $PM_{2.5}$ with a "cleaner" composition following the implementation of APPCAP and subsequent decline in anthropogenic $PM_{2.5}$ in China [437]. Previous Chinese prospective studies had much longer follow-up durations covering periods prior to implementation of APPCAP where $PM_{2.5}$ levels were likely to be higher and potentially more toxic. [66, 69, 226]

Behavioural intervention is another potential explanation for the lack of associations, however, adjusting individual-level behaviour in response to AAP would be unlikely able to selectively reduce exposure to $PM_{2.5}$ but not SO_2 for which this study did observe a significant effect with incident cardio-respiratory disease. One hypothesis could surround the use of the increasingly popular face masks in China, which do not filter against gaseous AAP but are typically marketed as protecting against particulate matter, therefore, potentially reducing personal exposure to PM but not SO_2. However, a major limitation of such a hypothesis is that while some well-designed masks can filter against a limited degree of $PM_{2.5}$ components, they have been deemed inefficient in China [438].

A final potential explanation is the urbanisation of certain administrative districts of Suzhou containing CKB clinics between CKB baseline in 2008 and the follow-up period of this study (2013-2015), leading to increasing $PM_{2.5}$ concentrations but also potential improvements to participants' socio-economic status, clean fuel access, and healthcare availability. Therefore, $PM_{2.5}$ may appear to result in less adverse cardio-respiratory health impacts given the beneficial effect on health status associated with concurrent piecemeal urbanisation. Such an effect is unlikely to have been seen in previous studies in HICs, nor the previous prospective Chinese studies which assigned more spatially homogenous AAP exposure to participants. To examine this hypothesis, clinics were classified by whether they were likely to be in an urban or rural locality at CKB baseline (based on satellite imagery, see **Appendix**

D9.1). Stratified Cox regression models were then fitted allowing the baseline hazards to vary between these localities (originally urban clinics versus originally rural clinics) thereby testing this hypothesis. However, no differing effect of PM was observed in this analysis compared to the original models used in the main analysis, making the above hypothesis an unlikely explanation for the lack of observed associations (**Appendix D9.2**). Rather the lack of observed association most likely relates to the limitations of this study outlined in **Section 6.5.2** including exposure measurement error and very short-follow-up.

6.6 Conclusions

To conclude, in this study chronic AAP exposure was assigned to Chinese adults located in the city of Suzhou using a localised spatiotemporal model. Chronic AAP exposure was associated with increased risk of major cardio-respiratory diseases. The most robust associations were observed for chronic SO_2 and O_3 concentrations where observed associations remained significant while adjusting for co-pollutants following the construction of bi-pollutant models. No further associations were documented for AAP exposure (including PM) and increased risk of incident cardio-respiratory disease. This study suggests that SO_2 exposure can have adverse effects on cardio-respiratory health even at declining concentrations. However, further research is required to confirm this study's findings, ideally with much longer follow-up and assigned AAP levels at residential location, as these remain substantial limitations to this study.

Table 6.1 Descriptions of the geographical variables used for spatiotemporal model development to assign long-term ambient air pollution exposure to Suzhou participants in the China Kadoorie Biobank

Geographical variable	Data description	Units	Spatial resolution	Variables used in spatio-temporal model	Data source
OSM motorway road network	A shapefile of Suzhou's 2018 "motorway" road network, motorway roads are defined below (as by OSM[1]); 1. National Expressways 2. Provincial Expressways 3. Expressways connecting to an airport whose name contains "Expressway"	Kilometres (km)	NA	• Distance to nearest road • Total road length (km) in a 1km buffer surrounding each fixed-site monitor and clinic location	OpenStreetMap (2018) Available at: http://download.geofabrik.de/asia/china.html
OSM trunk road network	A shapefile of Suzhou's 2018 "trunk" road network, trunk roads are defined below (as by OSM[1]); 1. National highways 2. Elevated Roads or city expressways, which often contain the following words in their names (X环路, XX快速路, XX大道, XX高架), fully or partly elevated 3. Elevated roads connecting to a large public transport facility (e.g. airport or railway station)	Kilometres (km)	NA	• Distance to nearest road • Total road length (km) in a 1km buffer surrounding each fixed-site monitor and clinic location	OpenStreetMap (2018) Available at: http://download.geofabrik.de/asia/china.html
OSM primary road network	A shapefile of Suzhou's 2018 "primary" road network, primary roads are defined below (as by OSM[1]); 1. Provincial highways 2. Roads connecting several city/districts/towns collecting most inner-city traffic 3. Roads connecting to a large public transport facility 4. Roads connecting cities and counties	Kilometres (km)	NA	• Distance to nearest road • Total road length (km) in a 1km buffer surrounding each fixed-site monitor and clinic location	OpenStreetMap (2018) Available at: http://download.geofabrik.de/asia/china.html
OSM secondary road network	A shapefile of Suzhou's 2018 "secondary" road network, secondary roads are defined below (as by OSM[1]); 1. County-level highways 2. Roads connecting numerous residential, commercial, industrial areas, collecting most of the local traffic between urban areas. 3. Roads connecting to a public transport facility (e.g. airport or railway station) 4. Roads connecting counties and towns.	Kilometres (km)	NA	• Distance to nearest road • Total road length (km) in a 1km buffer surrounding each fixed-site monitor and clinic location	OpenStreetMap (2018) Available at: http://download.geofabrik.de/asia/china.html
Land cover data	TIFF file converted to raster shapefile of 37 varying land-cover classes for Suzhou (2015)	Categorical classes of land cover	300x300m	Class of land cover at fixed-site monitor and clinic locations	ESA – Medium Resolution Imaging Spectrometer (MERIS) satellite. Available at: http://maps.elie.ucl.ac.be/CCI/viewer/download.php
Elevation data	TIFF file converted to raster shapefile of elevation data for Suzhou (2015)	Metres	0.1°x0.1°	Calculated point altitude at fixed-site monitor and clinic locations	NASA - Global Digital Elevation Model (DEM) version 2 from ASTER remote sensing satellite. Available at: https://lpdaac.usgs.gov/dataset_discovery/aster/aster_products_table

[1] Open street map. 2019. Chinese tagging guidelines. [Online]. [11 March 2019]. Available from: https://wiki.openstreetmap.org/wiki/Chinese_tagging_guidelines

Abbreviations: TIFF, tagged image file format; ESA, European Space Agency; NASA, National Aeronautics and Space Administration; ASTER Advanced Spaceborne Thermal Emission and Reflection Radiometer

Table 6.2 Details of included cardiovascular endpoints, ICD-10 codes, descriptions and representation within the study population

Endpoint	ICD-10 descriptions and codes	% of total endpoints during follow-up*
All major cardiovascular diseases	All of those below (I00-I99)	100%
Stroke	Non-traumatic subarachnoid haemorrhage (I60), non-traumatic intracerebral haemorrhage (I61), cerebral infarction (I63) , stroke not specified as haemorrhage or infarction (I64), sequelae of cerebrovascular disease (I69), sequelae of intracerebral haemorrhage (I69.1), sequelae of cerebral infarction (I69.3), sequelae of stroke, not specified as haemorrhage or infarction (I69.4)	41.1%
Ischaemic stroke	Cerebral infarction (I63)	33.1%
Intracerebral haemorrhage	Non-traumatic intracerebral haemorrhage (I64)	6.96%
Ischaemic heart disease	Angina pectoris (I20), acute myocardial infarction (I21), subsequent ST elevation and non-ST elevation myocardial infarction (I22), certain current complications following ST elevation and non-ST elevation myocardial infarction (within the 28-day period; I23), other acute ischaemic heart diseases (I24), chronic ischaemic heart disease (I25)	16.5%
Other cardiovascular diseases	Acute rheumatic fever (I00-I02), chronic rheumatic heart diseases (I05-I09), hypertensive diseases (I10-I16), pulmonary heart disease and diseases of pulmonary circulation (I26-I28), other forms of heart disease (I30-I52), cerebrovascular diseases excluding stroke (I62, I65-I69), diseases of arteries, arterioles and capillaries (I70-I79), diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified except "other non-infective disorders of lymphatic vessels and lymph nodes (I80-I88), other and unspecified disorders of the circulatory system (I95-I99)	62.6%

* Will not equate to 100% as participants may have cause-specific cardiovascular endpoints coded as part of the same overall episode but only one endpoint will contribute to the endpoint “all cardiovascular diseases”

Table 6.3 Details of included respiratory endpoints, ICD-10 codes, descriptions and representation within the study population

Endpoint	ICD-10 descriptions and codes	% of total endpoints during follow-up*
All major respiratory diseases	All of those below (J00-J99)	100%
Chronic obstructive pulmonary disease (COPD)	Simple and mucopurulent chronic bronchitis (J41), unspecified chronic bronchitis (J42), emphysema (J43), other chronic obstructive pulmonary disease (J44)	18.7%
Pneumonia	Viral pneumonia, not elsewhere classified (J12), pneumonia due to Streptococcus pneumoniae (J13), pneumonia due to Haemophilus influenzae (J14), bacterial pneumonia not elsewhere classified (J15), pneumonia due to infectious organisms, not elsewhere classified (J16), pneumonia in diseases classified elsewhere (J17), pneumonia, organism unspecified (J18)	24.4%
Other respiratory diseases	All others including upper respiratory infection (J00-J06), other lower respiratory infection (J20-J22), bronchitis, not specified as acute or chronic (J40), other respiratory diseases principally affecting the interstitium (J80-J84), suppurative and necrotic conditions of the lower respiratory tract (J85-J86), other diseases of the pleura (J90-J94), intraoperative and post-operative complications of respiratory system (J95), respiratory failure not elsewhere classified (J96), other respiratory disorders (J98) respiratory disorders in diseases classified elsewhere (J99)	75.0%

* Will not equate to 100% as participants may have cause-specific respiratory endpoints coded as part of the same overall episode but only one endpoint will contribute to the endpoint “all respiratory diseases”

Table 6.4 ICD-10 codes contained within cardiovascular and respiratory endpoints classed as "other"

Endpoint	ICD-10 codes and descriptions	% of total endpoints during follow-up*
Other respiratory diseases (n=1323)	Bronchitis, not specified as acute or chronic (J40)	440 (33.3%)
	Other respiratory diseases including; diseases of bronchus, not elsewhere classified (J98.0), pulmonary collapse (J98.1), interstitial emphysema (J98.2), compensatory emphysema (J98.3); other disorders of lung (J98.4), diseases of mediastinum not elsewhere classified (J98.5), disorders of diaphragm (J98.6), other specified respiratory disorders (J98.8), respiratory disorder, unspecified (J98.9)	575 (43.5%)
	Other upper respiratory diseases including; vasomotor and allergic rhinitis (J30), chronic rhinitis, nasopharyngitis and pharyngitis (J31), chronic sinusitis (J32), nasal polyp (J33), other and unspecified disorders of nose and nasal sinuses (J34), chronic diseases of tonsils and adenoids (J35), peritonsillar abscess (J36), chronic laryngitis and laryngotracheitis (J37), disease of vocal cords and larynx, not elsewhere classified (J38) and others (J39)	141 (10.7%)
	All others including upper respiratory infection (J00-J06), other lower respiratory infection (J20-J22), other respiratory diseases principally affecting the interstitium (J80-J84), suppurative and necrotic conditions of the lower respiratory tract (J85-J86), other diseases of the pleura (J90-J94), intraoperative and post-operative complications of respiratory system (J95), respiratory failure not elsewhere classified (J96) respiratory disorders in diseases classified elsewhere (J99)	167 (12.6%)
Other cardiovascular diseases (n=1601)	Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified except "other non-infective disorders of lymphatic vessels and lymph nodes (I80-I88)	637 (39.8%)
	Hypertensive diseases (I10-I16)	682 (42.6%)
	Heart failure, complications and ill-defined descriptions of heart disease, and other heart disorders in diseases classified elsewhere (I50-I52)	143 (8.9%)
	All others including acute rheumatic fever (I00-I02), chronic rheumatic heart diseases (I05-I09), pulmonary heart disease and diseases of pulmonary circulation (I26-I28), other forms of heart disease (I30-I50), diseases of arteries, arterioles and capillaries (I70-I79),other and unspecified disorders of the circulatory system (I95-I99)	139 (8.7%)

*Percentages of each respective group of ICD codes contained within endpoints "other cardiovascular diseases" and "other respiratory diseases"

Table 6.5 Summary statistics of pollutant concentrations, Suzhou (2013-2015)

Pollutant (μg/m^3)	Mean* (SD)	Maximum†	Minimum†	IQR*
NO_2	68.65 (37.32)	270.44	23.45	35.14
SO_2	30.41 (16.95)	103.98	5.79	18.76
PM_{10}	84.88 (24.68)	166.39	44.93	23.79
$PM_{2.5}$	75.04 (24.27)	167.56	41.02	25.72
O_3	97.60 (36.38)	207.06	29.93	47.05
CO	0.61 (0.22)	1.15	0.07	0.34

Abbreviations: IQR, interquartile range; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm in size; $PM_{2.5}$, particulate matter <2.5 μm in size; O_3, ozone; CO, carbon monoxide
All pollutants quantified as μg/m^3(except CO quantified as mg/m^3)
*Average across entire region (all clinic locations)
† Clinic location specific

Table 6.6 Change in predicted pollutant concentrations during follow-up across all clinic locations and monitoring sites

Pollutant (μg/m^3)	2013	2015	% change
Clinic locations			
NO_2	68.39	69.37	+1.4
SO_2	38.65	23.21	-39.9
PM_{10}	91.87	71.55	-22.1
$PM_{2.5}$	83.59	65.25	-21.9
O_3	100.94	96.76	-4.1
CO	0.59	0.64	+8.5
Monitoring sites			
NO_2	51.50	50.29	-1.2
SO_2	30.62	18.89	-38.3
PM_{10}	95.16	79.31	-16.7
$PM_{2.5}$	69.53	55.61	-20.0
O_3	97.52	95.22	-2.4
CO	0.908	0.911	-0.3

Abbreviations NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm in size; $PM_{2.5}$, particulate matter <2.5 μm in size; O_3, ozone; CO, carbon monoxide
All pollutants quantified as μg/m^3(except CO quantified as mg/m^3)

Table 6.7 Baseline characteristics of Suzhou CKB study participants by sex

Characteristics*	Male % (n=22,244)	Female % (n=30,758)	Total % (n =53,002)
Age (years), mean (SD)	51.3 (10.3)	52.0 (10.4)	51.6 (10.4)
Education			
No formal school	10.4	44.7	30.0
Primary school	39.9	26.4	32.4
Middle school	36.2	21.9	27.9
High school and above	13.5	7.0	9.7
Smoking category			
Never smoker	7.8	99.1	60.8
Occasional smoker	10.7	0.5	4.7
Ex-regular smoker	13.1	0.01	5.6
Current regular smoker	68.4	0.04	28.9
Passive smoking			
Never	23.0	7.6	14.1
Yes, but not now	57.1	27.8	40.0
Yes, at present	19.9	64.5	46.0
Alcohol consumption			
Never	16.5	89.4	58.8
Occasional	31.7	9.7	18.9
Ex-regular/ reduced intake	11.0	0.4	4.9
Current regular	40.9	0.6	17.5
Self-rated health			
Excellent	33.0	26.1	29.0
Good	32.7	31.7	32.1
Fair	26.6	29.9	28.5
Poor	7.7	12.4	10.4
Physical activity (MET hour/d), mean (SD)	27.5 (16.1)	24.0 (14.3)	25.5 (15.2)
Household air pollution			
Currently cook using wood/coal	19.1	19.0	19.2
Previously cooked using wood/coal	72.5	66.8	72.9
Self-reported disease†			
Hypertension	12.8	13.9	13.4
Stroke	1.2	0.1	0.9
Diabetes	2.6	2.8	2.7
TB	1.7	0.1	1.1
CHD	1.0	1.1	1.1
Asthma	0.7	0.8	0.8
Emphysema/Bronchitis	4.7	4.6	4.7
Family history of disease‡			
Stroke	18.6	17.2	17.8
Myocardial infarction	2.0	2.1	2.0
Cardio-respiratory symptoms§			
Breathlessness	2.3	4.1	3.3
Chest pain	1.2	2.3	1.8
Chronic cough	4.9	2.4	3.4
AAP exposure (2013-2015) mean (SD)			
NO_2	76.1 (36.7)	67.2 (19.9)	71.0 (28.5)
SO_2	33.4 (17.0)	31.3 (15.0)	32.2 (15.9)
PM_{10}	85.4 (24.4)	84.0 (24.4)	84.6 (24.4)
$PM_{2.5}$	77.2 (23.3)	72.8 (18.6)	74.7 (20.8)
O_3	96.8 (38.6)	100.9 (36.9)	99.2 (37.7)
CO	0.52 (0.21)	0.56 (0.19)	0.54 (0.20)

Abbreviations: BMI: Body mass index; MET, metabolic equivalent of tasks; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm in size; $PM_{2.5}$, particulate matter <2.5 μm in size; O_3, ozone; CO, carbon monoxide. All pollutants quantified as $\mu g/m^3$(except CO quantified as mg/m^3)

*Apart from total and age specific variables all other variables are standardised to the age structure of the study population

† TB, Tuberculosis; CHD, coronary heart disease

‡ Family history defined as baseline reported disease prevalence in mother and/or father

§ Breathlessness defined as being short of breath when "walking on level ground with health people of the same age", chronic cough defined as "coughing frequently for ≥3 months"

Table 6.8 Physical measurements of Suzhou CKB participants by sex

Characteristics*	Males % (n=22.244)	Females % (n=30,758)	Total (n=53,002)
Body mass index (kg/m^2), %			
<21.0	17.6	18.0	17.9
21.0-24.9	46.5	46.4	46.5
≥25.0	35.9	35.6	35.6
Mean (SD)	24.0 (3.1)	24.1 (3.3)	24.0 (3.2)
Systolic blood pressure (mmHg), %			
<120	24.9	31.5	28.9
120-139	43.3	36.7	39.4
≥140	31.9	31.8	31.7
Mean (SD)	133.3 (19.0)	132.4 (21.1)	132.7 (20.3)
Diastolic blood pressure (mmHg), %			
<80	52.3	62.1	58.0
80-89	31.5	26.9	28.8
≥90	16.3	11.0	13.2
Mean (SD)	80.2 (10.7)	78.0 (9.9)	78.9 (10.3)
Lung function measurements, mean (SD)			
Pre-bronchodilator FEV_1, Litre †	2.62 (0.69)	1.90 (0.47)	2.20 (0.67)
Pre-bronchodilator FVC, Litre ‡	3.21 (0.74)	2.32 (0.54)	2.69 (0.77)
Pre-bronchodilator FEV_1:FVC	0.82 (0.09)	0.82 (0.08)	0.82 (0.08)
Possible airflow obstruction, %			
FEV1:FVC <0.7	9.3	7.2	8.1
FEV1:FVC <lower limit of normal	10.8	11.2	11.1

* Means and percentages standardised to the age structure of the study population
† FEV1: forced expiratory volume in 1 second.
‡ FVC: forced vital capacity.

Table 6.9 Cardiovascular disease incidence rates according to age and gender in Suzhou (2013-2015)

	All cardiovascular disease		All type stroke		Ischaemic stroke		Intracerebral haemorrhage		Ischaemic heart		Other cardiovascular diseases	
Characteristic	**No. of events**	**Rate**	**No. of events**	**Rate**	**No. of events**	**Rate**	**No. of events**	**Rate**	**No. of events**	**Rate**	**No. of events**	**Rate**
Gender												
Male	1100	193.6	489	82.4	374	62.8	106	62.8	196	32.9	639	108.9
Female	1459	179.3	562	66.0	473	55.4	72	55.4	225	26.4	962	115.2
Age (years)												
30-39	139	63.3	17	7.6	10	4.5	6	2.7	13	5.8	106	48.0
40-49	421	97.2	88	19.9	72	16.2	14	3.1	43	9.7	302	69.1
50-59	818	177.6	310	64.5	251	51.2	59	12.1	107	21.9	500	105.7
60-69	800	369.2	423	178.9	348	146.2	56	22.5	168	69.4	446	192.2
>70	381	737.4	213	348.7	166	268.4	43	63.9	90	141.5	247	417.6

Rates calculated per 10,000 person years

Table 6.10 Baseline characteristics of participants with and without major cardiovascular disease incidence, Suzhou (2013-2015)

Characteristics*	Endpoints											
	All cardiovascular disease		All-type stroke		Ischaemic stroke		Intracerebral haemorrhage		Ischaemic heart disease		Other cardiovascular diseases	
	Yes (n=2559)	No (n=45,173)	Yes (n=1051)	No (n=48,158)	Yes (n=847)	No (n=48,485)	Yes (n=178)	No (n=49,701)	Yes (n=421)	No (n=49,082)	Yes (n=1601)	No (n=47,104)
Sex												
Male	41.7	41.1	44.3	41.1	44.5	41.1	55.9	41.1	53.0	41.3	38.8	41.4
Female	58.3	58.9	55.7	58.9	55.5	58.9	44.1	58.9	57.0	58.7	61.2	58.6
Age (years), mean (SD)	57.8 (10.3)	50.3 (9.8)	61.4 (8.8)	50.7 (10.0)	61.5 (8.7)	50.8 (10.0)	60.4 (9.6)	51.0 (10.1)	61.0 (9.3)	50.9 (10.1)	57.0 (10.7)	50.7 (10.0)
Education												
No formal school	30.1	28.5	32.1	28.9	33.2	29.0	34.5	29.3	25.7	29.2	31.4	28.9
Primary school	33.4	32.3	33.9	32.2	34.3	32.2	31.0	32.2	40.0	32.3	31.9	32.3
Middle school	27.8	29.2	28.0	28.8	25.8	28.8	31.1	28.5	24.1	28.6	27.7	28.8
High school and above	8.7	10.0	6.0	10.1	6.7	10.0	3.4	10.0	10.2	9.9	9.0	10.0
Smoking category												
Never smoker	61.4	61.4	61.3	61.5	61.4	61.5	61.2	61.4	61.0	61.3	618	61.3
Occasional smoker	3.9	4.8	4.0	4.8	4.6	4.8	2.5	4.7	4.5	4.8	3.9	7.8
Ex regular smoker	6.1	4.9	6.0	5.1	5.7	5.1	6.0	5.2	5.9	5.2	6.4	5.0
Current regular smoker	28.5	28.9	28.7	28.7	28.3	28.7	30.4	28.7	28.6	28.8	28.0	28.9
Passive smoking												
Never	14.2	13.8	13.9	13.9	12.1	13.9	12.8	13.9	13.8	14.5	14.9	13.8
Yes, but not now	39.7	39.5	41.1	39.6	41.4	39.6	44.0	39.7	39.6	42.6	38.7	39.6
Yes, at present	46.1	46.8	44.9	46.6	46.5	46.5	43.2	46.5	46.6	42.9	46.3	46.6
Alcohol consumption												
Never	60.5	58.6	60.2	58.8	59.0	58.9	63.5	59.0	61.2	58.8	60.3	58.8
Occasional /(Monthly)	17.7	19.6	14.8	19.4	16.0	19.3	9.3	19.2	17.3	19.2	18.0	19.4
Ex-regular/ reduced intake	6.0	4.2	5.6	4.4	4.6	4.4	7.7	4.4	5.7	4.6	6.7	4.2
Current regular	15.8	17.6	19.4	17.4	20.4	17.4	19.5	17.4	15.8	17.4	15.0	17.6
Self-rated health												
Excellent	27.2	30.3	25.8	29.8	26.5	29.8	17.8	29.6	27.2	29.8	27.3	30.1
Good	29.0	32.7	31.4	32.4	28.8	32.4	34.3	32.3	32.7	32.4	28.2	32.6
Fair	29.6	28.0	28.1	28.3	31.4	28.3	37.1	28.4	25.1	28.2	30.3	28.1
Poor	14.3	9.0	14.7	9.5	13.3	9.5	10.8	9.7	15.0	9.6	14.3	9.2
MET hours/d, mean (SD)	25.3 (15.4)	26.3 (15.0)	24.6 (14.7)	26.1 (15.0)	24.0 (14.8)	26.0 (15.0)	23.4 (14.8)	25.9 (15.1)	23.6 (14.0)	26.0 (15.1)	26.1 (15.6)	26.6 (15.0)
Household air pollution												
Currently cook using wood/coal	19.5	18.1	17.0	18.2	16.5	18.2	24.0	18.3	18.2	18.3	21.1	18.1
Previously cooked using wood/coal	72.2	71.8	67.2	72.0	69.0	72.0	74.4	72.0	73.4	72.0	73.3	72.0
Self-reported disease †												
Hypertension	19.4	11.0	21.2	11.9	23.7	12.0	19.4	12.5	25.7	12.4	19.7	11.6
Stroke	-	-	-	-	-	-	-	-	15.3	7.5	-	-
TB	1.3	1.0	0.8	1.0	0.8	1.0	0.2	1.1	1.8	1.0	1.3	1.0
CHD	-	-	1.9	0.9	2.1	1.0	0.3	1.0	-	-	-	-
Asthma	0.7	0.7	0.6	0.7	0.2	0.7	0.4	0.7	0.3	0.7	0.7	0.7
Emphysema/Bronchitis	5.0	4.2	6.3	4.5	5.6	4.5	8.8	4.5	7.9	4.3	4.4	4.3
Family history of disease ‡												
Stroke	20.4	17.4	24.8	17.5	26.2	17.5	22.7	17.6	18.6	17.7	19.0	17.6
Myocardial infarction	2.5	2.0	2.8	2.0	3.9	2.0	1.9	2.0	3.8	2.0	2.2	2.0
Cardiorespiratory symptoms §												
Breathlessness	4.3	2.7	3.1	3.0	2.9	3.0	2.9	3.0	5.3	2.8	4.2	2.8
Chest pain	2.9	1.3	2.3	1.5	3.6	1.6	2.0	1.6	4.3	1.5	2.9	1.4
Chronic cough	3.6	3.2	3.3	3.3	2.1	3.3	5.9	3.3	5.2	3.3	3.1	3.3
Average AAP Exposure (2013-2015)												
NO_2	70.4 (29.3)	71.2 (28.6)	70.5 (26.6)	71.1 (28.6)	70.5 (26.8)	71.1 (28.6)	69.4 (29.0)	71.1 (28.6)	70.1 (28.6)	71.2 (28.7)	70.4 (29.6)	71.2 (28.6)
SO_2	32.9 (16.4)	32.2 (15.8)	32.8 (15.5)	32.3 (15.8)	33.5 (16.0)	32.2 (15.9)	31.4 (17.1)	32.2 (16.0)	31.5 (16.1)	32.3 (16.0)	32.4 (16.8)	32.3 (15.9)
PM_{10}	83.3 (24.2)	84.8 (20.9)	81.2 (24.5)	84.7 (24.4)	81.5 (24.4)	84.7 (24.5)	84.2 (27.2)	84.6 (24.4)	83.2 (23.8)	84.7 (24.4)	83.2 (25.0)	84.8 (24.4)
$PM_{2.5}$	73.9 (20.6)	74.9 (24.5)	74.8 (20.5)	71.9 (20.8)	72.0 (20.2)	74.7 (20.9)	72.9 (22.7)	74.7 (20.8)	72.7 (20.6)	74.7 (20.9)	74.2 (21.7)	74.9 (20.8)
O_3	101.8 (38.4)	98.9 (37.7)	104.0 (39.6)	99.1 (37.7)	104.7 (40.3)	99.1 (37.7)	101.1 (40.5)	99.1 (37.7)	99.9 (37.5)	99.1 (37.7)	101.0 (39.2)	98.9 (37.6)
CO	0.53 (0.20)	0.54 (0.20)	0.53 (0.19)	0.54 (0.20)	0.53 (0.19)	0.54 (0.20)	0.54 (0.18)	0.54 (0.2)	0.54 (0.19)	0.54 (0.20)	0.54 (0.2)	0.54 (0.2)

Abbreviations: BMI, Body mass index; MET, metabolic equivalent of tasks; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10; $PM_{2.5}$, particulate matter <2.5; O_3, ozone; CO, carbon monoxide. All pollutants quantified in $\mu g/m^3$ (except CO in mg/m^3) *Apart from total, sex and age specific variables all variables standardised to the age and sex structure of the study population † TB, Tuberculosis; CHD, coronary heart disease ‡ Family history defined as baseline reported disease prevalence in mother and/or father. § Breathlessness and chest pain defined as being "short of breath", and "slowing down due to chest discomfort", respectively, when "walking on level ground with health people of the same age". Chronic cough defined as "coughing frequently for ≥3 months
Two-sided P values derived from F-tests X^2 tests for continuous variables and categorical variables, respectively, all p values <0.05 (except family history of myocardial infarction and O_3 exposure).

Table 6.11 Baseline physical measurements for participants with and without major cardiovascular disease incidence, Suzhou (2013-2015)

Characteristics*	Endpoints											
	All cardiovascular disease		All-type stroke		Ischaemic stroke		Intracerebral haemorrhage		Ischaemic heart disease		Other cardiovascular diseases	
	Yes (n=2559)	No (n=45,173)	Yes (n=1051)	No (n=48,158)	Yes (n=847)	No (n=48,485)	Yes (n=178)	No (n=49,701)	Yes (n=421)	No (n=49,082	Yes (n=1601)	No (n=47,104)
Body mass index (kg/m^2), %												
<21.0	16.1	17.8	16.4	17.7	14.5	17.7	22.0	17.6	12.0	17.6	15.6	17.8
21.0-24.9	44.4	47.0	46.6	46.8	44.9	46.7	45.1	46.6	42.7	46.8	45.6	46.8
≥25.0	39.6	35.2	37.0	35.6	40.6	35.6	32.9	35.7	45.2	35.6	38.7	35.4
Mean (SD)	24.3 (3.4)	24.0 (3.2)	24.3 (3.4)	24.0 (3.2)	24.5 (3.4)	24.0 (3.2)	23.9 (2.9)	24.1 (3.2)	24.8 (3.6)	24.0 (3.2)	24.3 (3.3)	24.0 (3.2)
Systolic blood pressure (mmHg), %												
<120	23.4	30.4	20.0	29.8	19.9	29.8	18.1	29.4	25.8	29.5	23.5	29.9
120-139	36.9	40.3	40.3	40.0	39.8	39.9	36.6	39.7	33.9	39.7	35.5	40.0
≥140	39.7	29.4	39.6	30.0	40.4	30.3	45.2	30.8	40.4	30.8	41.0	30.1
Mean (SD)	136.5 (22.9)	131.5 (19.4)	138.2 (24.6)	131.9 (19.7)	138.5 (24.3)	132.0 (19.8)	140.8 (25.4)	132.2 (20.0)	137.3 (23.2)	132.2 (20.0)	137.0 (23.5)	131.9 (19.7)
Diastolic blood pressure (mmHg), %												
<80	49.4	59.2	50.8	58.8	49.9	58.7	42.1	58.4	47.2	58.3	48.6	58.8
80-89	31.6	28.4	30.8	28.6	30.2	28.6	39.4	28.7	31.8	28.7	31.8	28.5
≥90	19.0	12.4	18.4	12.7	19.9	12.7	18.5	12.9	21.0	13.0	19.5	12.7
Mean (SD)	80.9 (10.8)	78.7 (10.2)	81.1 (11.2)	78.7 (10.2)	81.4 (11.1)	78.7 (10.2)	81.7 (11.5)	78.8 (10.3)	81.1 (10.4)	78.9(10.3)	80.8 (11.1)	78.7 (10.2)

Abbreviations: BMI, Body mass index (calculated as weight in kilograms divided by height in meters squared); mmHg, millimetres of mercury

* Means and percentages were standardised to the age and sex structure of the study population

Table 6.12 Adjusted hazard ratios and 95% confidence intervals for cardiovascular disease incidence associated with a 10 μg/m^3 increase in SO_2 using bi-pollutant models, Suzhou (2013-2015)

Endpoint	Bi-pollutant model 1		Bi-pollutant model 2		Bi-pollutant model 3		Bi-pollutant model 4		Bi-pollutant model 5	
	SO_2 +	$PM_{2.5}$	SO_2 +	PM_{10}	SO_2 +	NO_2	SO_2 +	CO	SO_2 +	O_3
All major cardiovascular disease (n=2559)	1.06 (1.01, 1.11)	0.98 (0.96, 1.00)	1.05 (0.99, 1.11)	0.99 (0.96, 1.01)	1.07 (1.02, 1.12)	0.99 (0.98, 1.01)	1.07 (1.01, 1.13)	0.99 (0.96, 1.03)	1.04 (0.98, 1.10)	1.01 (1.00, 1.03)
All-type stroke (n=1051)	1.03 (0.95, 1.11)	0.95 (0.95, 1.11)	1.03 (0.93, 1.15)	0.98 (0.94, 1.03)	1.06 (0.98, 1.15)	0.98 (0.96, 1.00)	1.06 (0.97, 1.15)	0.99 (0.94, 1.04)	0.96 (0.88, 1.06)	1.04 (1.02, 1.06)
Ischaemic stroke (n=847)	1.03 (0.95, 1.12)	0.95 (0.91, 0.99)	1.05 (0.94, 1.17)	0.98 (0.94, 1.04)	1.07 (0.98, 1.16)	0.97 (0.95. 0.99)	1.07 (0.98, 1.16)	0.99 (0.94, 1.05)	0.96 (0.87, 1.07)	1.04 (1.02, 1.07)
Haemorrhagic stroke (n=178)	1.08 (0.90, 1.30)	0.98 (0.90, 1.04)	1.14 (0.93, 1.40)	1.02 (0.95, 1.11)	1.10 (0.91, 1.33)	1.01 (0.96, 1.05)	1.06 (0.86, 1.30)	0.95 (0.86, 1.06)	1.07 (0.89, 1.30)	1.01 (0.97, 1.05)
Ischaemic heart disease (n=421)	1.04 (0.95, 1.15)	0.99 (0.94, 1.05)	1.06 (0.93, 1.21)	1.00 (0.94, 1.07)	1.05 (0.96, 1.15)	0.99 (0.96, 1.03)	1.02 (0.93, 1.11)	0.95 (0.88, 1.03)	1.03 (0.91, 1.18)	1.01 (0.97, 1.05)
Other cardiovascular diseases (n=1601)	1.11 (1.03, 1.20)	1.00 (0.97, 1.03)	1.11 (1.03, 1.20)	1.00 (0.97, 1.03)	1.11 (1.04, 1.20)	1.00 (0.98 1.02)	1.12 (1.02, 1.22)	1.01 (0.95, 1.07)	1.11 (1.02, 1.21)	1.00 (0.99, 1.02)

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10; $PM_{2.5}$, particulate matter <2.5; O_3, ozone; CO, carbon monoxide.
All hazard ratios adjusted for age, sex, active and passive smoking, education level, alcohol consumption, mean body mass index, self-rated health, physical activity, solid fuel use, ambient temperature, hypertension medication, mean systolic blood pressure, consumption of fresh fruit, consumption of preserved vegetables, and prior respiratory disease incidence

Table 6.13 Adjusted hazard ratios and 95% confidence intervals for cardiovascular disease incidence associated with a 10 μg/m^3 increase in O_3 using bi-pollutant models, Suzhou (2013-2015)

Endpoint (n=)	Bi-pollutant model 1		Bi-pollutant model 2	
	O_3 +	NO_2 +	O_3 +	CO
All major cardiovascular disease (n=2559)	1.02 (1.01, 1.04)	1.01 (0.99, 1.03)	1.02 (1.01, 1.03)	0.98 (0.95, 1.02)
All-type stroke (n=1051)	1.04 (1.01, 1.06)	1.00 (0.97, 1.03)	1.03 (1.02, 1.05)	0.99 (0.95, 1.03)
Ischaemic stroke (n=847)	1.04 (1.01, 1.07)	1.00 (0.97, 1.03)	1.04 (1.02, 1.06)	0.99 (0.95, 1.04)
Haemorrhagic stroke (n=178)	1.04 (0.98, 1.10)	1.03 (0.98, 1.09)	1.02 (0.97, 1.06)	0.94 (0.86, 1.04)
Ischaemic heart disease (n=421)	1.01 (0.98, 1.05)	1.00 (0.95, 1.06)	1.01 (0.98, 1.04)	0.95 (0.88, 1.03)
Other cardiovascular disease (n=1601)	1.02 (1.00, 1.05)	1.01 (0.98, 1.04)	1.02 (1.00, 1.03)	0.99 (0.94, 1.04)

Abbreviations: NO_2, nitrogen dioxide; SO_2, O_3, ozone; CO, carbon monoxide.
All hazard ratios adjusted for age, sex, active and passive smoking, education level, alcohol consumption, mean body mass index, self-rated health, physical activity, solid fuel use, ambient temperature, hypertension medication, mean systolic blood pressure, consumption of fresh fruit, consumption of preserved vegetables, and prior respiratory disease incidence

Table 6.14 Adjusted hazard ratios for long-term SO_2 exposure and risk of all major cardiovascular disease stratified by subgroups of baseline characteristics

Characteristics	Number of subjects with disease endpoint	Hazard ratio (95% CI)
Sex		
Male	1100	1.07 (1.03, 1.12)
Female	1459	1.09 (1.01, 1.16)
Heterogeneity test p=0.78		
Age (years)		
<60	1463	1.06 (0.98, 1.14)
60-69	715	1.07 (0.98, 1.16)
≥70	381	1.10 (0.99, 1.21)
Trend test p=0.60		
Education		
No formal education	1067	1.11 (1.05, 1.17)
Primary school	829	1.05 (0.99, 1.13)
Middle school	466	1.01 (0.93, 1.11)
High school or above	197	1.14 (0.96, 1.35)
Trend test p=0.29		
Smoking status		
Never smoker	1548	1.08 (1.01, 1.16)
Ex-regular smoker	104	1.28 (1.06, 1.55)
Occasional smoker	217	1.04 (0.92, 1.18)
Regular smoker	690	1.05 (0.98, 1.13)
Heterogeneity test p=0.19		
Passive smoking		
Never	398	1.22 (1.09, 1.36)
Yes, but not now	1073	1.04 (0.97, 1.11)
Yes, at present	1088	1.07 (1.00, 1.14)
Heterogeneity test p=0.05		
Solid fuel use		
Always clean fuels	305	1.18 (1.06, 1.31)
Switched from solid to clean fuels	1174	1.08 (0.99, 1.18)
Always solid fuels	531	1.09 (1.01, 1.18)
Never cooked regularly	371	0.99 (0.90, 1.10)
Other	178	1.13 (0.94, 1.36)
Heterogeneity test p=0.25		
BMI		
<18.5	73	1.08 (0.84, 1.38)
18.5-25	1480	1.05 (0.99, 1.12)
>25	1006	1.11 (1.03, 1.19)
Trend test p=0.38		
Self-rated health		
Excellent	624	1.05 (0.96, 1.14)
Good	783	1.10 (1.02, 1.19)
Fair	776	1.03 (0.94, 1.12)
Poor	376	1.15 (1.00, 1.32)
Heterogeneity test p=0.44		
Prior respiratory endpoints		
Yes	254	1.11 (0.95, 1.29)
No	2305	1.07 (1.01, 1.13)
Heterogeneity test p=0.69		

Abbreviations: BMI; body mass index

Adjusted for (where appropriate) age, sex, active and passive smoking, education level, alcohol consumption, mean body mass index, self-rated health, physical activity, solid fuel use, ambient temperature, hypertension medication, mean systolic blood pressure, consumption of fresh fruit, consumption of preserved vegetables, and prior respiratory disease incidence

Table 6.15 Adjusted hazard ratios for long-term O_3 exposure and risk of all major cardiovascular disease stratified by subgroups of baseline characteristics

Characteristic	Number of subjects with disease endpoint	Hazard ratio (95% CI)
Sex		
Male	1100	1.02 (1.00, 1.03)
Female	1459	1.02 (1.01, 1.03)
Heterogeneity test p=0.70		
Age (years)		
<60	1463	1.02 (1.00, 1.03)
60-69	715	1.03 (1.00, 1.05)
>70	381	1.01 (0.99, 1.04)
Trend test p=0.92		
Education		
No formal education	1067	1.03 (1.02, 1.04)
Primary school	829	1.01 (0.99, 1.02)
Middle school	466	1.00 (0.97, 1.02)
High school or above	197	1.06 (1.02, 1.10)
Trend test p=0.60		
Smoking status		
Never smoker	1548	1.02 (1.01, 1.03)
Ex-regular smoker	104	1.05 (1.00, 1.10)
Occasional smoker	217	1.03 (1.00, 1.07)
Regular smoker	690	1.00 (0.99, 1.02)
Heterogeneity test p=0.12		
Passive smoking		
Never	398	1.04 (1.01, 1.08)
Yes, but not now	1073	1.00 (0.98, 1.03)
Yes, at present	1088	1.03 (1.01, 1.04)
Heterogeneity test p=0.08		
Solid fuel use		
Always clean fuels	305	1.02 (0.99, 1.05)
Switched from solid to clean fuels	1174	1.03 (1.01. 1.05)
Always solid fuels	531	1.01 (0.99, 1.03)
Never cooked regularly	371	1.01 (0.98, 1.04)
Other	178	1.03 (0.98, 1.08)
Heterogeneity test p=0.50		
BMI		
<18.5	73	1.00 (0.94, 1.07)
18.5-25	1480	1.02 (1.01, 1.04)
>25	1006	1.02 (1.01, 1.04)
Trend test p=0.85		
Self-rated health		
Excellent	624	1.03 (1.01, 1.05)
Good	783	1.02 (1.00, 1.03)
Fair	776	1.01 (0.98, 1.03)
Poor	376	1.04 (1.01, 1.07)
Heterogeneity test p=0.23		
Prior respiratory endpoints		
Yes	254	1.00 (0.97, 1.04)
No	2305	1.02 (1.01, 1.03)
Heterogeneity test p=0.40		

Abbreviations: BMI; body mass index

Adjusted for (where appropriate) age, sex, active and passive smoking, education level, alcohol consumption, mean body mass index, self-rated health, physical activity, solid fuel use, ambient temperature, hypertension medication, mean systolic blood pressure, consumption of fresh fruit, consumption of preserved vegetables, and prior respiratory disease incidence

Table 6.16 Respiratory disease incidence rates according to age and gender in Suzhou (2013-2015)

	All respiratory disease		COPD		Pneumonia		Other respiratory diseases	
Characteristic	**No. of events**	**Rate**	**No. of events**	**Rate**	**No. of events**	**Rate**	**No. of events**	**Rate**
Gender								
Male	777	140.1	181	31.6	167	29.2	593	105.7
Female	986	123.6	148	18.0	263	32.1	730	90.5
Age (years)								
30-39	101	47.5	3	1.4	26	12.1	79	37.0
40-49	322	76.9	20	4.7	87	20.4	242	57.4
50-59	559	123.9	65	13.9	134	28.9	425	93.3
60-69	544	252.2	138	60.6	118	15.9	404	183.0
≥70	237	439.2	103	173.0	65	108.9	173	306.9

Rates calculated per 10,000 person years
Abbreviations: COPD, chronic obstructive pulmonary disease

Table 6.17 Baseline characteristics of participants with and without major respiratory disease incidence, Suzhou (2013-2015)

Characteristics*	Endpoints							
	All respiratory disease		COPD		Pneumonia		Other respiratory disease	
	Yes (n=1763)	No (n=44,738)	Yes (n=329)	No (n=46,992)	Yes (n=430)	No (n=46,783)	Yes (n=1323)	No (n=45,451)
Sex								
Male	42.2	41.0	56.7	41.0	35.4	41.2	43.2	41.0
Female	57.8	59.0	43.3	59.0	64.6	58.8	56.8	59.0
Age, mean (SD)	57.2 (10.3)	50.5 (10.0)	64.1 (8.3)	50.8 (10.0)	56.8 (10.4)	50.8 (10.1)	57.0 (10.3)	50.6 (10.0)
Education								
No formal school	33.8	28.7	41.4	29.2	34.2	29.2	33.0	29.0
Primary school	33.9	32.1	32.0	32.2	33.4	32.2	34.2	32.1
Middle school	24.1	29.2	17.4	28.9	25.0	28.8	25.0	29.0
High school	7.1	8.1	4.2	7.9	6.9	7.9	6.9	8.0
College/university	1.1	1.9	5.0	1.8	0.5	1.9	0.9	1.9
Smoking category								
Never smoker	60.9	61.5	61.4	61.5	63.5	61.4	60.5	61.5
Occasional smoker	4.2	4.8	1.5	4.7	1.7	4.7	4.9	4.7
Ex regular smoker	5.5	4.7	3.3	4.8	5.3	4.8	5.5	4.7
Smoker	29.4	29.1	33.8	29.0	29.5	29.1	29.1	29.1
Passive smoking								
Never	13.9	13.8	11.9	13.8	14.8	13.8	13.5	13.8
Yes, but not now	40.2	39.6	30.6	39.6	43.3	39.6	39.5	39.6
Yes, at present	45.9	46.6	57.6	46.5	41.9	46.6	47.0	46.6
Self-rated health								
Excellent	27.2	30.6	24.0	30.4	24.9	30.4	27.8	30.5
Good	31.6	32.8	41.0	32.7	29.9	32.8	31.0	32.8
Fair	27.6	27.6	23.8	27.6	30.4	27.7	13.7	27.6
Poor	13.6	9.0	11.2	9.2	14.8	9.1	2.7	9.1
MET hours/day, mean (SD)	25.8 (15.1)	26.2 (15.0)	23.0 (13.7)	26.1 (15.1)	25.8 (15.0)	26.1 (15.1)	25.8 (15.2)	26.1 (15.0)
Household air pollution								
Currently cook using wood/coal	22.2	17.8	28.7	18.1	20.0	18.2	22.5	18.0
Previously cooked using wood/coal	75.5	72.0	81.4	72.2	80.1	72.2	73.91	72.1
Self-reported disease†								
Hypertension	14.0	12.5	15.1	12.7	14.5	12.6	14.3	12.5
Stroke	1.1	0.8	1.2	0.8	1.2	0.8	1.1	0.8
CHD	1.4	0.9	0.9	0.9	2.0	0.9	1.3	0.9
Family history of disease ‡								
Stroke	17.5	17.8	19.4	17.8	17.6	17.7	17.2	17.8
Myocardial infarction	2.1	2.0	0.2	2.0	2.4	2.0	2.1	2.0
Cardiorespiratory symptoms §								
Breathlessness	4.5	2.4	6.3	2.5	5.4	2.5	4.3	2.4
Chest pain	1.7	1.3	3.6	1.4	2.9	1.3	1.6	1.3
Chronic cough	3.2	2.5	1.8	2.5	3.5	2.5	3.2	2.5
Average AAP Exposure (2013-2015)								
NO_2	72.1 (30.7)	71.2 (28.4)	73.1 (32.4)	71.2 (28.6)	70.4 (25.6)	71.2 (28.6)	72.7 (32.5)	71.2 (28.4)
SO_2	31.1 (17.0)	32.4 (15.9)	27.1 (18.3)	32.3 (15.9)	33.1 (15.8)	32.4 (16.0)	31.1 (16.9)	32.3 (15.8)
PM_{10}	85.1 (26.5)	84.6 (24.2)	85.6 (30.3)	84.6 (24.3)	81.6 (24.2)	84.7 (24.3)	86.8 (27.8)	84.5 (24.2)
$PM_{2.5}$	76.0 (22.4)	74.7 (20.6)	77.5 (25.3)	74.7 (20.7)	74.2 (20.8)	74.8 (20.8)	77.4 (24.1)	74.6 (20.6)
O_3	97.9 (41.4)	99.2 (37.5)	89.7 (42.5)	88.1 (37.7)	103.9 (39.9)	99.1 (37.7)	96.0 (42.1)	99.2 (37.)
CO	0.55 (0.2)	0.54 (0.2)	0.55 (0.19)	0.54 (0.2)	0.53 (0.2)	0.54 (0.2)	0.55 (0.2)	0.54 (0.2)

Abbreviations: BMI, Body mass index; MET, metabolic equivalent of tasks; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10; $PM_{2.5}$, particulate matter <2.5; O_3, ozone; CO, carbon monoxide. All pollutants quantified in $\mu g/m^3$ (except CO in mg/m^3) *Apart from total, sex and age specific variables all variables standardised to the age and sex structure of the study population † TB, tuberculosis; CHD, coronary heart disease ‡ Family history defined as baseline reported disease prevalence in mother and/or father § Breathlessness and chest pain defined as being "short of breath", and "slowing down due to chest discomfort", respectively, when "walking on level ground with health people of the same age". Chronic cough defined as "coughing frequently for ≥3 months". Two-sided p-values derived from F-tests X^2 tests for continuous variables and categorical variables, respectively, all p values <0.005 (except family history of myocardial infarction and O_3 exposure).

Table 6.18 Baseline physical measurements for participants with and without major respiratory disease incidence, Suzhou (2013-2015)

Characteristics*	Endpoints							
	All respiratory disease		COPD		Pneumonia		Other respiratory	
	Yes (n=1763)	No (n=44,738)	Yes (n=329)	No (n=46,992)	Yes (n=430)	No (n=46,783)	Yes (n=1323)	No (n=45,451)
Body mass index (kg/m^2), %								
<21.0	21.0	17.0	25.1	17.2	20.4	17.3	21.4	17.1
21.0-24.9	45.1	47.0	49.9	46.8	47.9	46.8	43.8	46.9
≥25.0	33.9	33.9	25.0	36.0	31.7	35.9	34.8	36.0
Mean (SD)	23.8 (3.4)	24.1 (3.2)	22.9 (3.3)	24.1 (3.2)	23.8 (3.2)	24.1 (3.2)	23.9 (3.5)	24.1 (3.2)
Lung function measurements, mean (SD)								
Pre-bronchodilator FEV_1, Litre †	2.14 (0.7)	2.24 (0.65)	1.92 (0.64)	2.24 (0.65)	2.16 (0.64)	2.23 (0.65)	2.14 (0.66)	2.24 (0.65)
Pre-bronchodilator FVC, Litre ‡	2.65 (0.8)	2.74 (0.8)	2.50 (0.76)	2.73 (0.75)	2.65 (0.74)	3.49 (0.76)	2.65 (0.77)	2.73 (0.75)
Pre-bronchodilator FEV_1:FVC	0.81 (0.1)	0.83 (0.07)	0.79 (0.13)	0.82 (0.13)	0.82 (0.10)	0.82 (0.08)	0.81 (0.10)	0.83 (0.07)
Possible airflow obstruction, %								
FEV1:FVC <0.7	10.6	6.5	16.7	6.3	9.4	6.9	10.1	6.7
FEV1:FVC <lower limit of normal	13.3	9.7	20.8	9.9	11.9	10.0	12.7	9.8

Abbreviations: BMI, Body mass index (calculated as weight in kilograms divided by height in meters squared; COPD, chronic obstructive disease

* Means and percentages were standardised to the age and sex structure of the study population

† FEV1: forced expiratory volume in 1 second.

‡ FVC: forced vital capacity.

Table 6.19 Adjusted hazard ratios and 95% confidence intervals for respiratory disease incidence associated with a 10 μg/m^3 increase in SO_2 using bi-pollutant models, Suzhou (2013-2015)

Endpoint	Bi-pollutant model 1		Bi-pollutant model 2		Bi-pollutant model 3		Bi-pollutant model 4		Bi-pollutant model 5	
	SO_2 +	$PM_{2.5}$	SO_2 +	PM_{10}	SO_2 +	NO_2	SO_2 +	CO	SO_2 +	O_3
All respiratory disease (n=1763)	1.15 (1.08, 1.22)	1.04 (1.01, 1.07)	1.18 (1.09, 1.28)	1.04 (1.00, 1.08)	1.11 (1.04, 1.19)	1.02 (0.99, 1.04)	1.10 (1.02, 1.19)	0.98 (0.93, 1.04)	1.14 (1.06, 1.24)	0.99 (0.96, 1.01)
COPD (n=329)	1.29 (1.12, 1.49)	1.04 (0.95, 1.13)	1.27 (1.05, 1.54)	1.01 (0.92, 1.12)	1.25 (1.09, 1.43)	1.04 (0.98, 1.10)	1.19 (1.01, 1.40)	0.94 (0.86, 1.03)	1.27 (1.04, 1.54)	0.99 (0.94, 1.05)
Pneumonia (n=430)	1.09 (0.98, 1.21)	0.97 (0.91, 1.03)	1.01 (0.87, 1.17)	0.94 (0.88, 1.01)	1.11 (1.02, 1.22)	0.98 (0.94, 1.02)	1.09 (0.98, 1.21)	0.96 (0.88, 1.04)	1.04 (0.90, 1.20)	1.03 (0.99, 1.07)
Other respiratory disease (n=1323)	1.15 (1.07, 1.24)	1.07 (1.04, 1.10)	1.24 (1.15, 1.35)	1.08 (1.04, 1.12)	1.09 (1.01, 1.19)	1.03 (1.00, 1.06)	1.09 (1.00, 1.19)	1.00 (0.94, 1.06)	1.17 (1.07, 1.28)	0.97 (0.94, 1.00)

Hazard ratios calculated for a 10 μg/m^3 increase in pollutant exposure (except CO which used a 100 μg/m^3 increase).
Adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean temperature, prior cardiovascular disease, consumption of fresh fruit and preserved vegetables, respectively, use of diabetes medication

Table 6.20 Adjusted hazard ratios and 95% confidence intervals for respiratory disease incidence associated with a 10 μg/m^3 increase in O_3 using bi-pollutant models, Suzhou (2013-2015)

Endpoint (n=)	Bi-pollutant model 1		Bi-pollutant model 2	
	O_3 +	NO_2	O_3	CO
All respiratory disease (n=1763)	1.03 (1.00, 1.05)	1.04 (1.00, 1.07)	1.00 (0.99, 1.03)	0.97 (0.91, 1.02)
COPD (n=329)	1.07 (1.04, 1.11)	1.09 (1.02, 1.17)	1.02 (0.98, 1.07)	0.91 (0.83, 1.00)
Pneumonia (n=430)	1.04 (1.01, 1.07)	1.00 (0.95, 1.06)	1.03 (1.01, 1.05)	0.95 (0.89, 1.03)
Other respiratory disease (n=1323)	1.02 (0.99, 1.05)	1.04 (1.00, 1.08)	1.00 (0.97, 1.03)	0.97 (0.92, 1.04)

Hazard ratios calculated for a 10 μg/m^3 increase in pollutant exposure (except CO which used a 100 μg/m^3 increase).
Adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean temperature, prior cardiovascular disease, consumption of fresh fruit and preserved vegetables, respectively, use of diabetes medication

Table 6.21 Adjusted hazard ratios for long-term SO_2 exposure and risk of all major respiratory disease stratified by subgroups of baseline characteristics

Characteristic	Number of subjects with disease endpoint	Hazard ratio (95% CI)
Sex		
Male	776	1.15 (1.06, 1.24)
Female	987	1.07 (0.99, 1.16)
Heterogeneity test p=0.19		
Age (years)		
<60	1038	1.11 (1.02, 1.20)
60-69	488	1.16 (1.06, 1.27)
≥70	237	0.99 (0.86, 1.17)
Trend test p=0.54		
Education		
No formal education	801	1.09 (1.01, 1.18)
Primary school	575	1.13 (1.02, 1.25)
Middle school	281	1.13 (0.98, 1.29)
High school or above	106	1.27 (1.05, 1.54)
Trend test p=0.22		
Smoking status		
Never smoker	1035	1.07 (0.99, 1.15)
Ex-regular smoker	61	0.99 (0.74, 1.32)
Occasional	139	1.23 (1.03, 1.46)
Smoker	528	1.16 (1.06, 1.27)
Heterogeneity test p=0.31		
Passive smoking		
Never	268	1.12 (0.98, 1.29)
Yes, but not now	750	1.08 (1.00, 1.16)
Yes, at present	745	1.14 (1.04, 1.25)
Heterogeneity test p=0.60		
Solid fuel use		
Always clean fuels	173	1.29 (1.11, 1.50)
Switched from solid to clean fuels	781	1.07 (0.98, 1.18)
Always solid fuels	410	1.09 (0.99, 1.20)
Never cooked regularly	260	1.23 (1.08, 1.39)
Other	139	1.15 (0.96, 1.36)
Heterogeneity test p=0.17		
BMI		
<18.5	76	1.11 (0.86, 1.43)
18.5-25	1091	1.10 (1.03, 1.19)
>25	596	1.13 (1.02, 1.25)
Trend test p=0.74		
Self-rated health		
Excellent	441	1.20 (1.03, 1.31)
Good	580	1.14 (1.04, 1.24)
Fair	491	1.06 (0.97, 1.17)
Poor	251	0.99 (0.86, 1.15)
Heterogeneity test p=0.12		
Prior cardiovascular endpoints		
Yes	272	1.09 (0.96, 1.24)
No	1491	1.11 (1.04, 1.20)
Heterogeneity test p=0.80		

Abbreviations: BMI; body mass index

Adjusted for (where appropriate) age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean temperature, prior cardiovascular disease, consumption of fresh fruit and preserved vegetables, respectively, use of diabetes medication

Figure 6.1 Locations of fixed-site ambient pollutant monitors, Suzhou, Jiangsu province

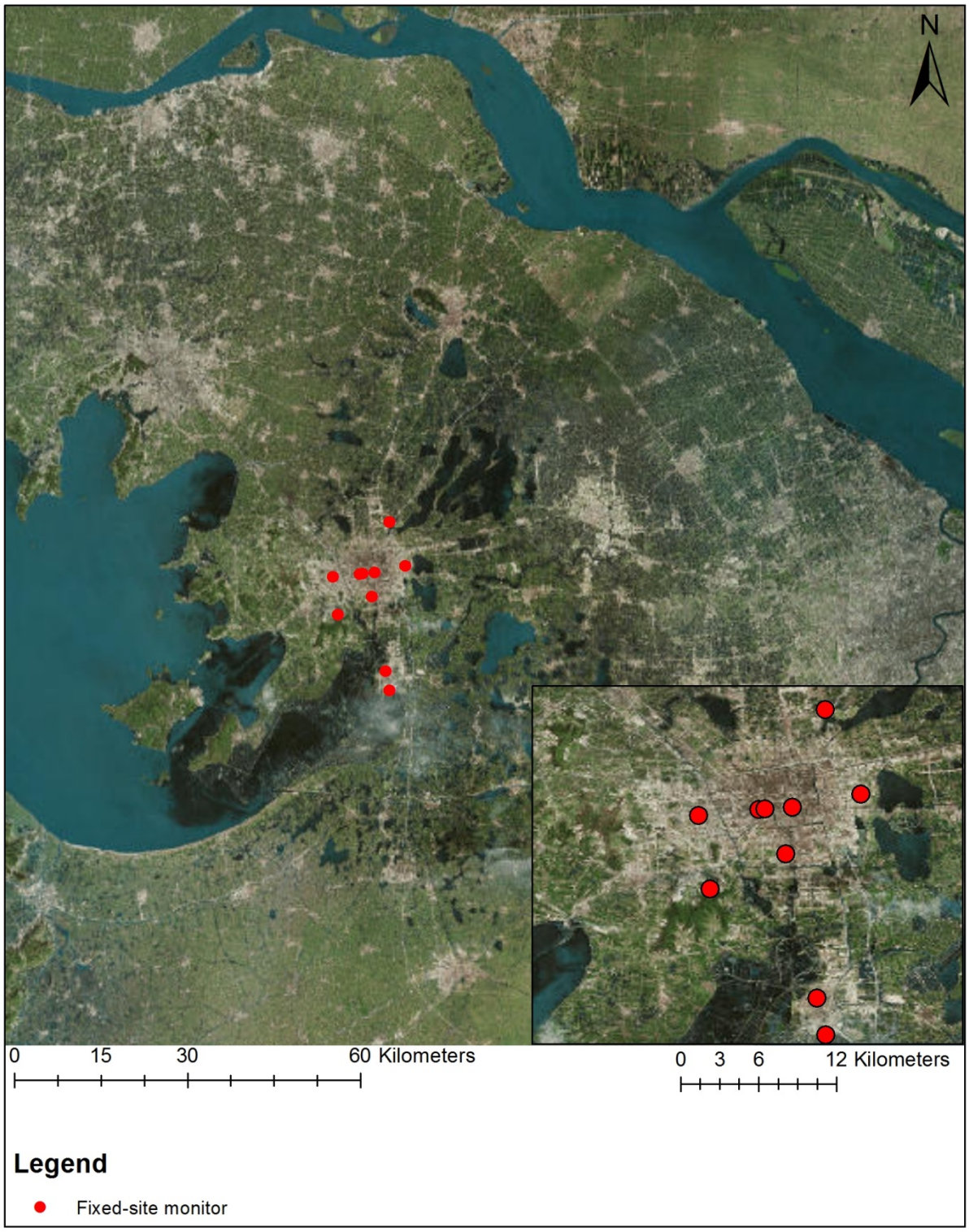


Figure 6.2 Locations of fixed-site weather monitors, Suzhou, Jiangsu province

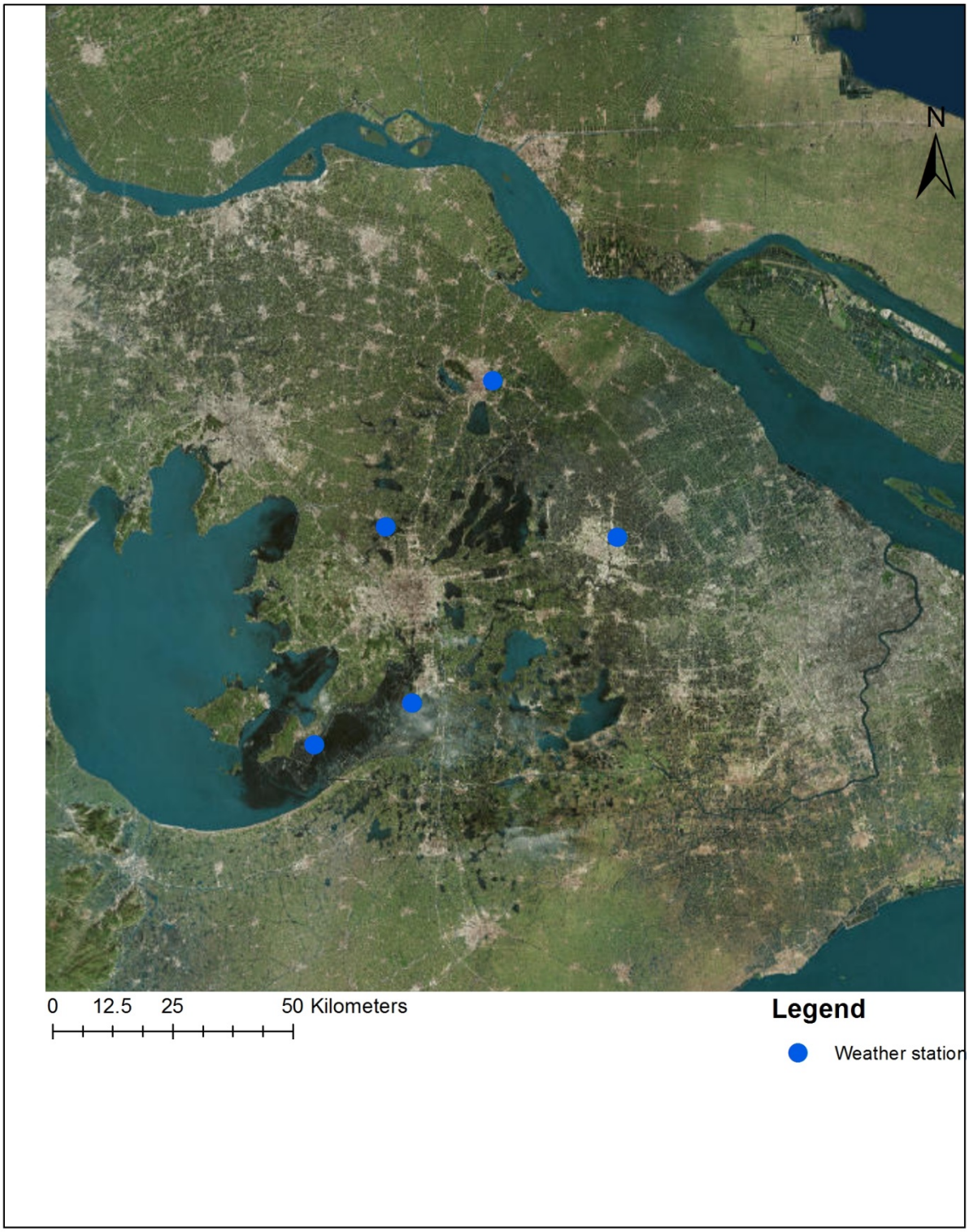


Figure 6.3 Locations of CKB baseline clinics including excluded clinic, Suzhou, Jiangsu province

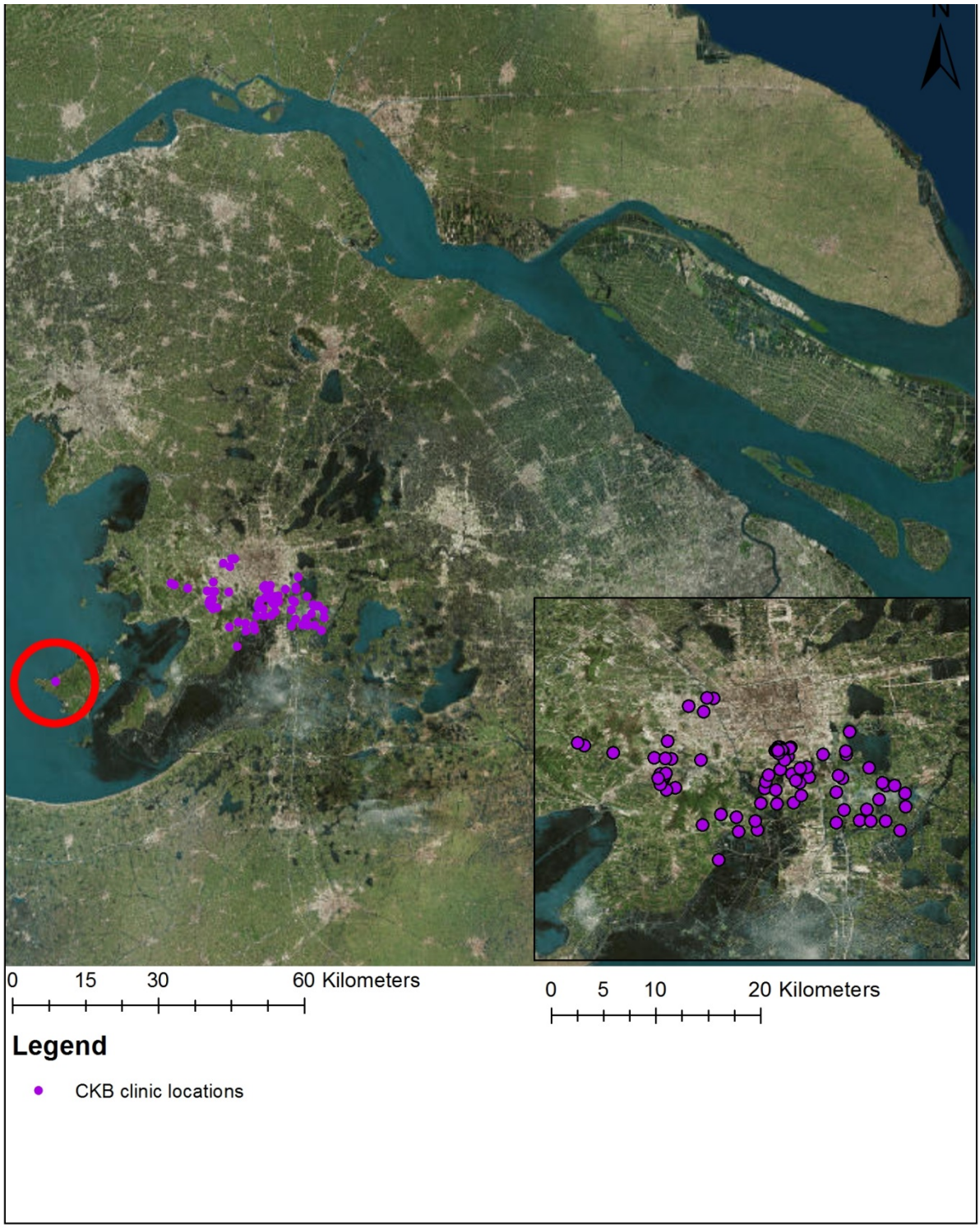
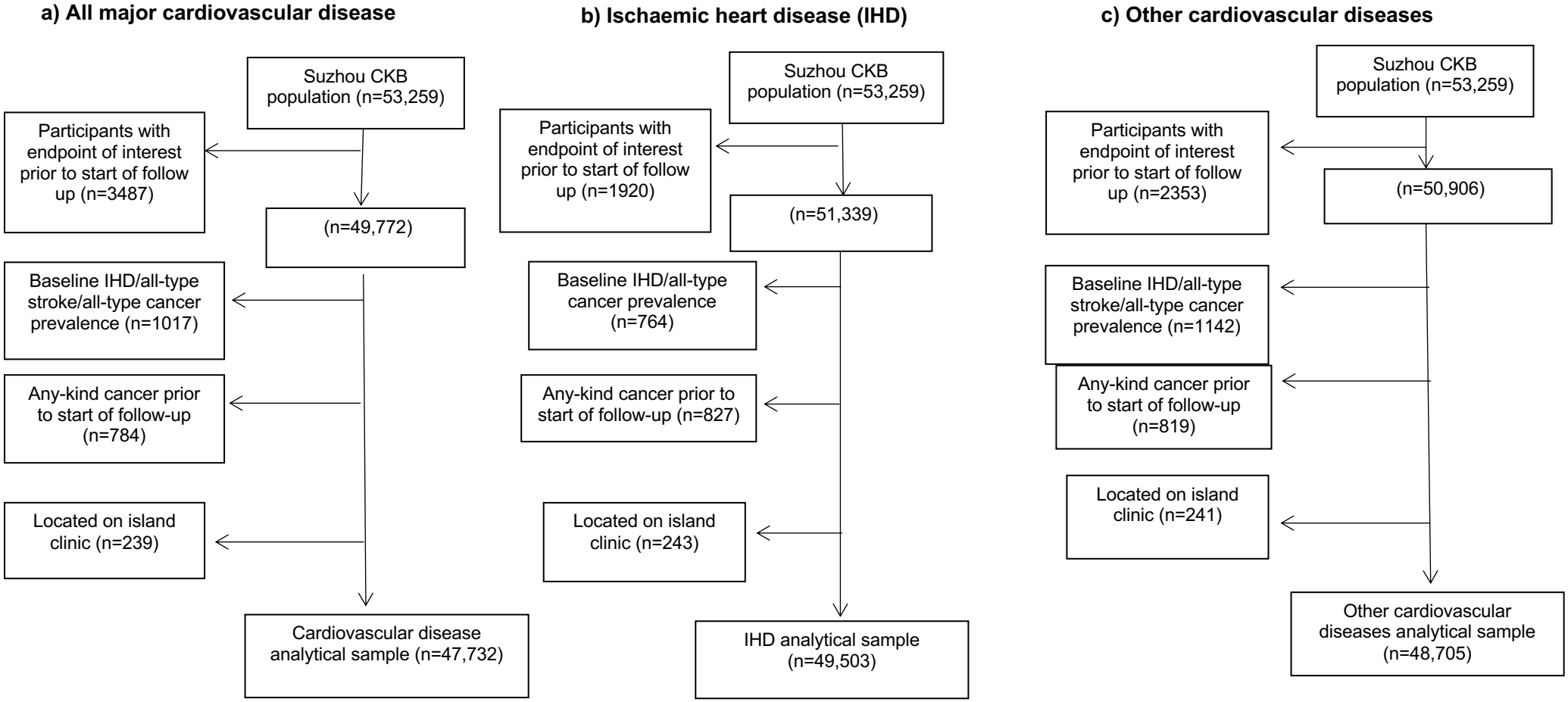
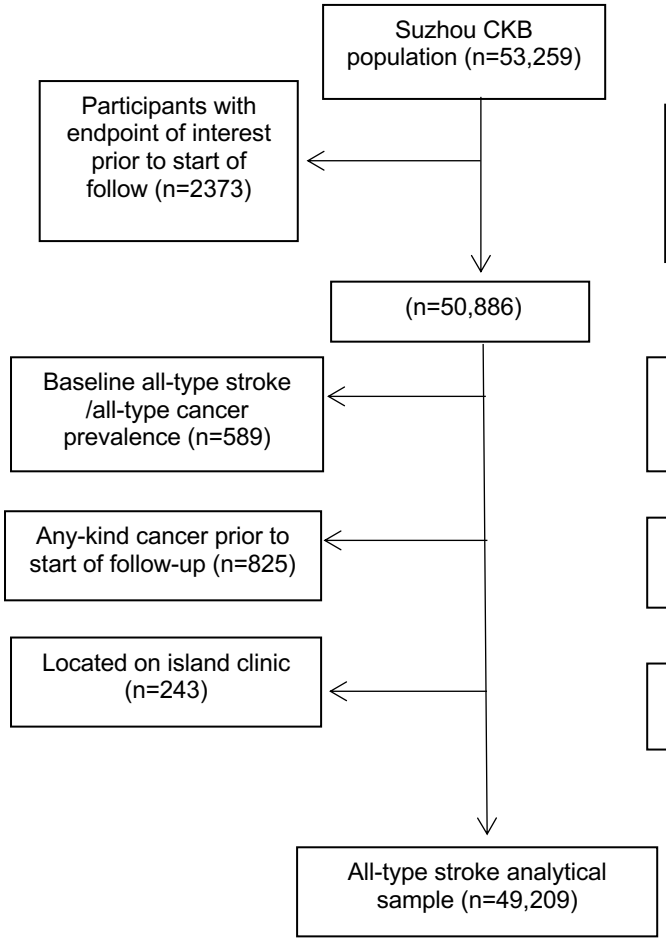


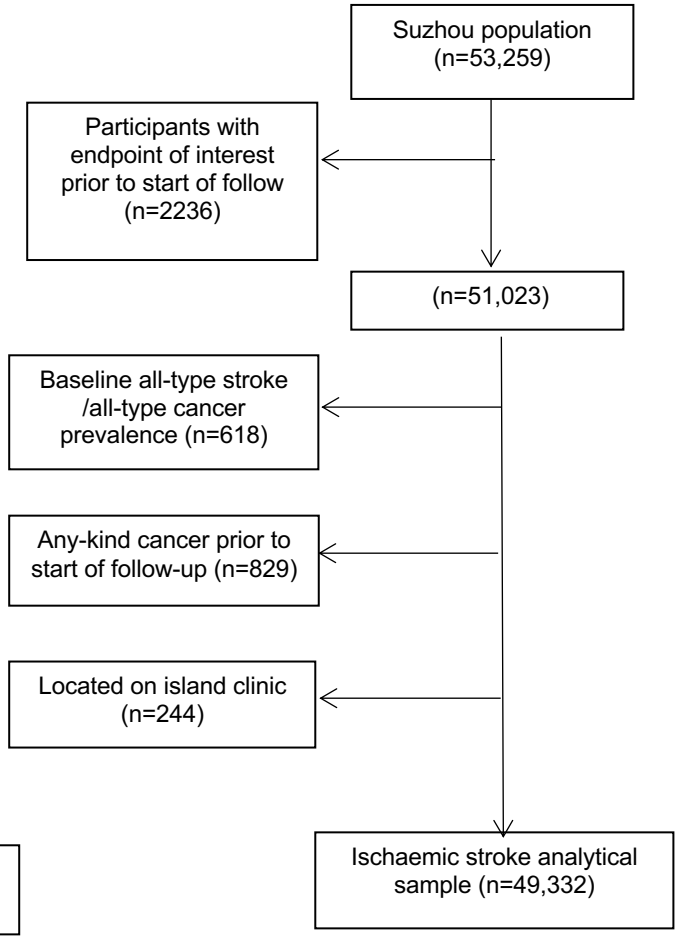
Figure 6.4 Participants exclusions



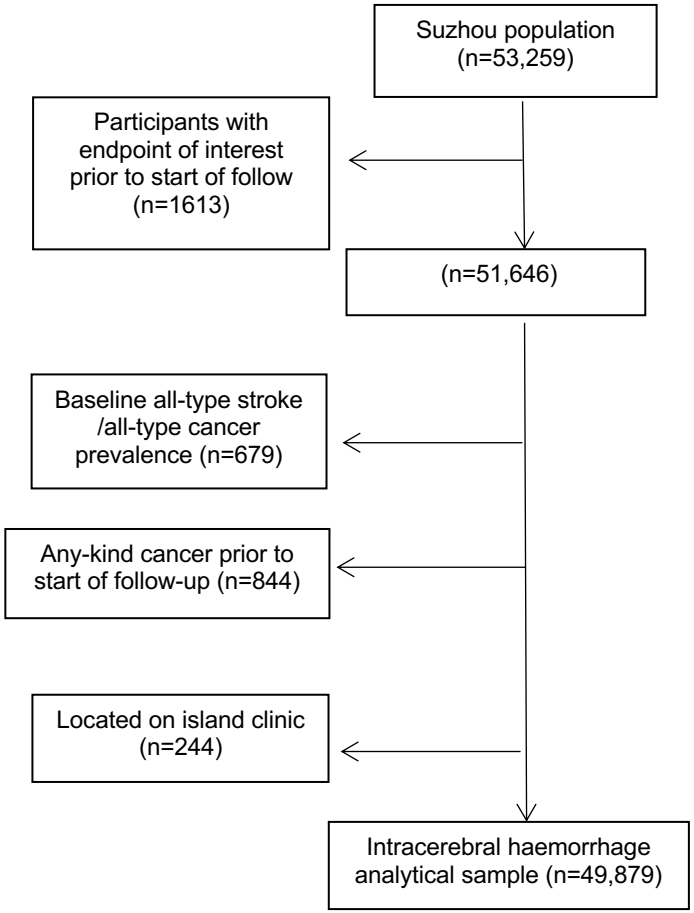
d) All-type stroke



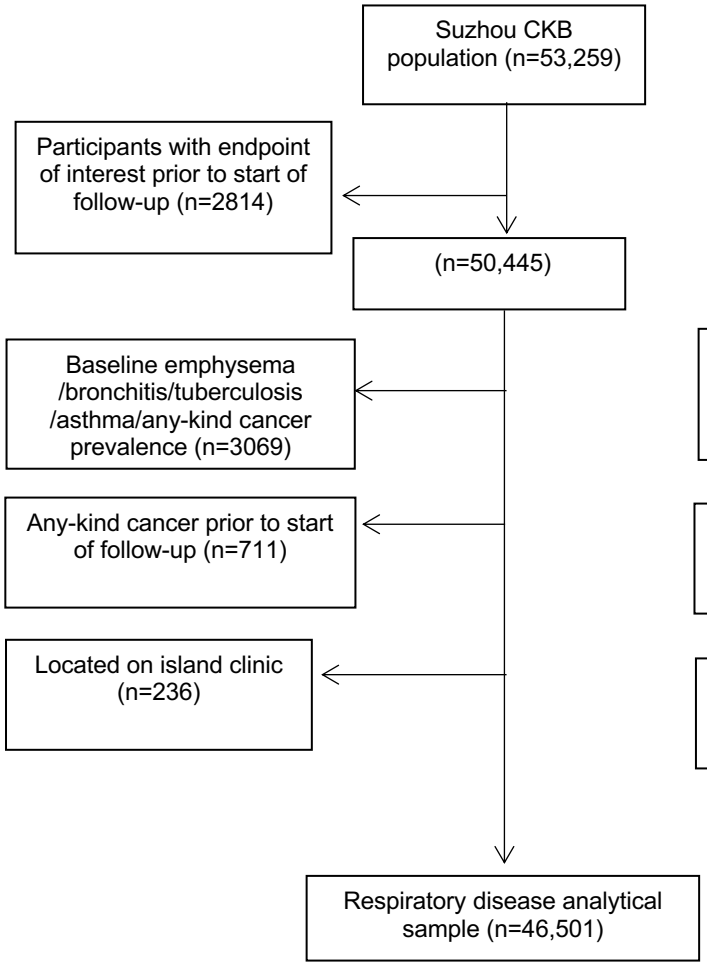
e) Ischaemic stroke



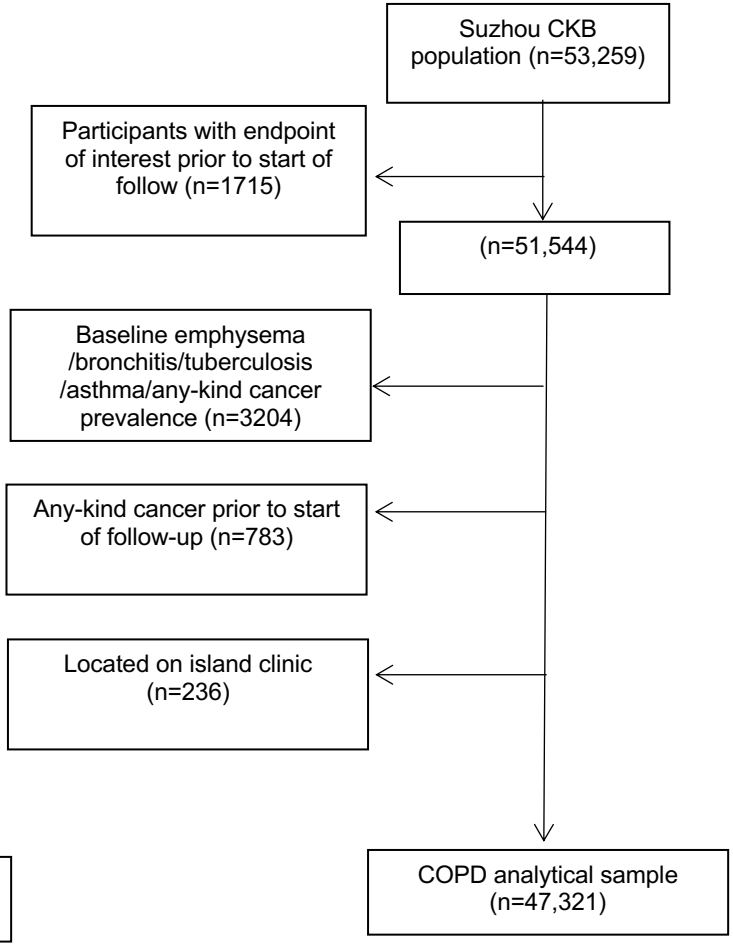
f) Intracerebral haemorrhage



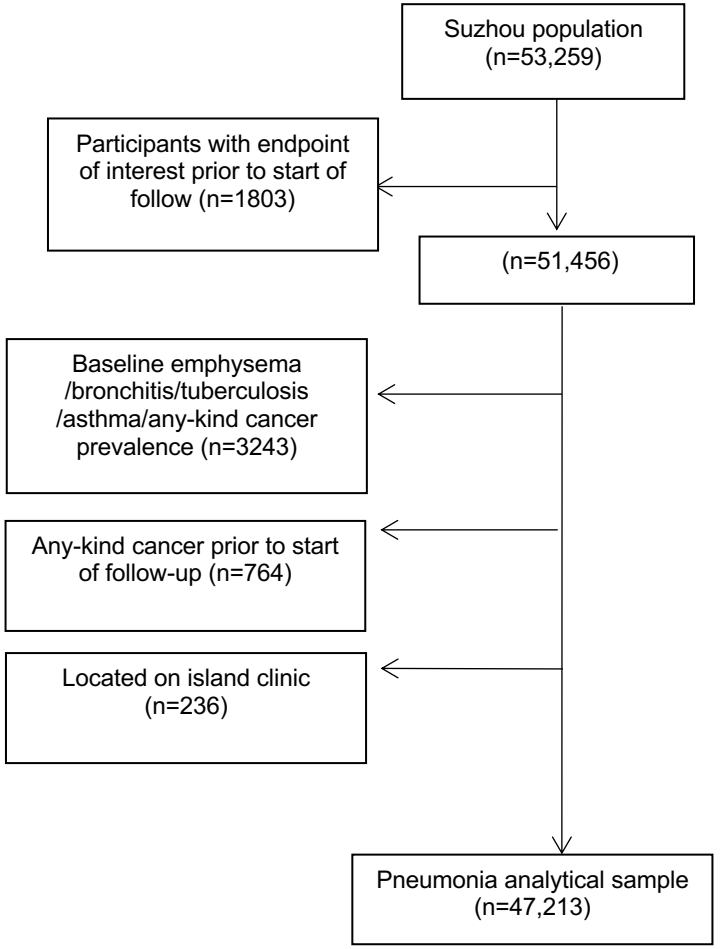
g) All major respiratory disease



h) Chronic obstructive pulmonary disease (COPD)



i) Pneumonia



j) Other respiratory diseases

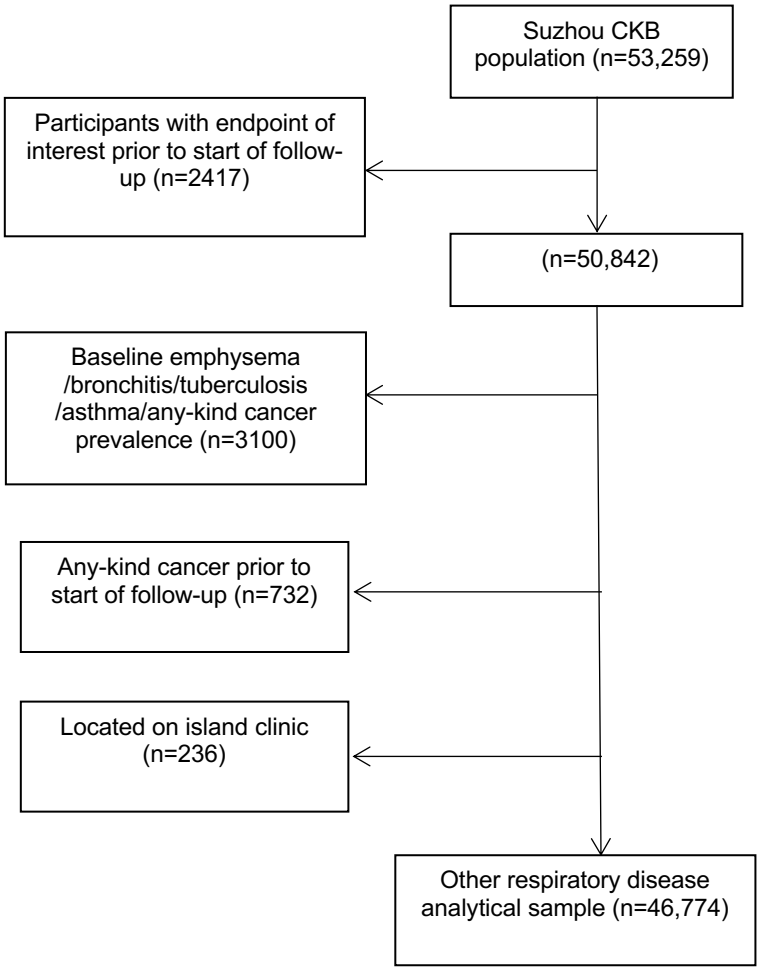
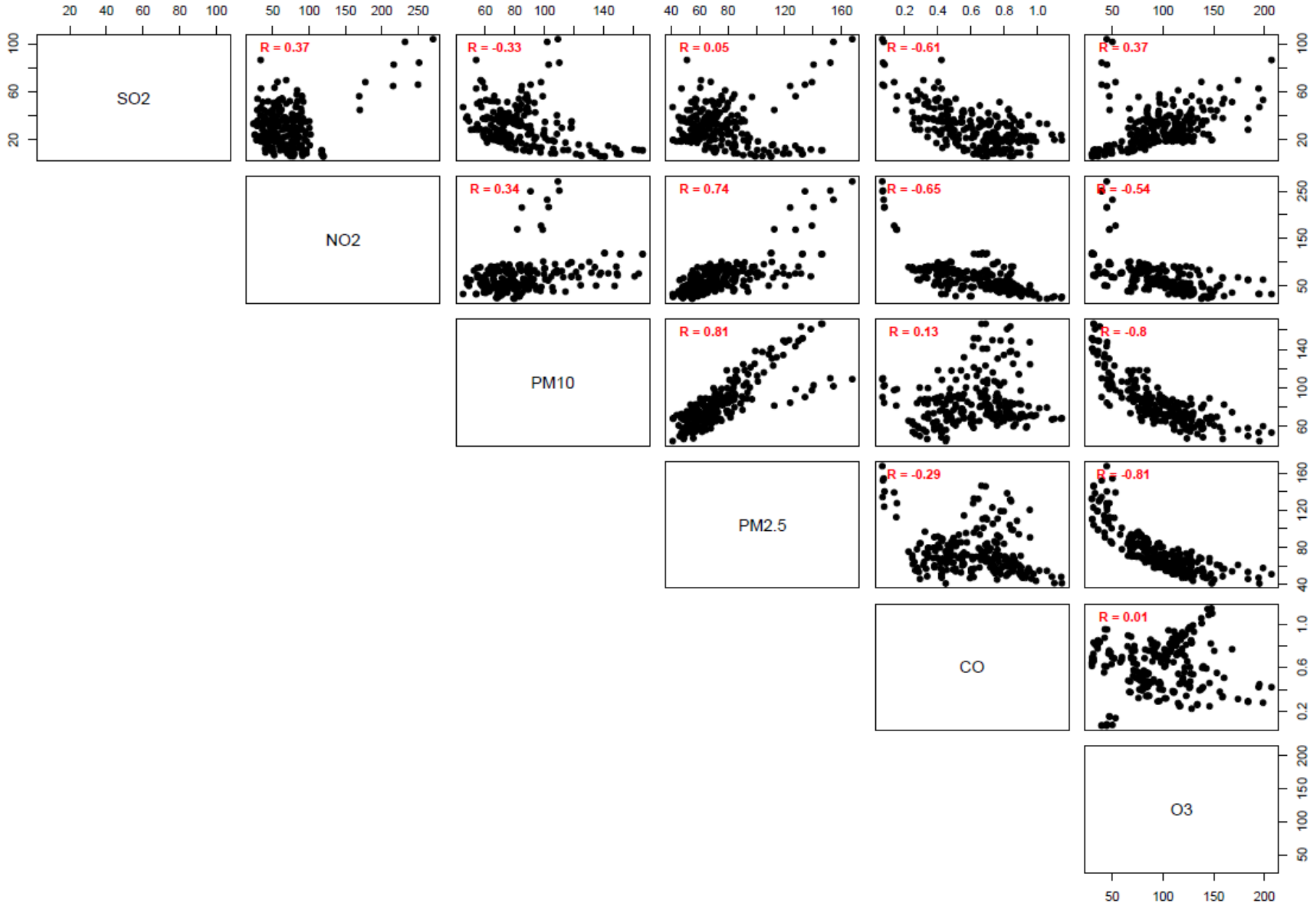
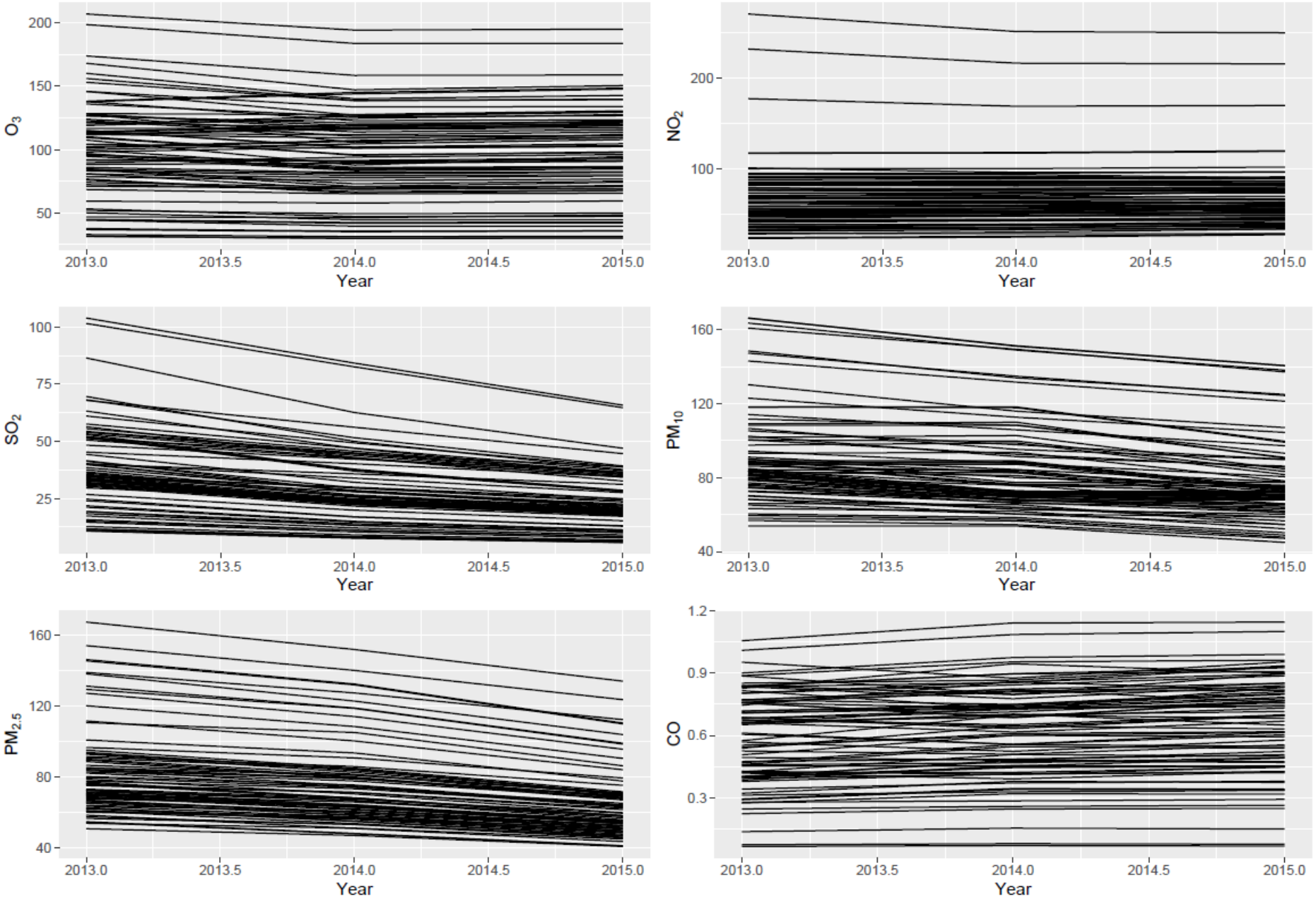


Figure 6.5 Scatterplots and Pearson Correlation coefficients between mean predicted pollutant concentrations by clinic location Suzhou (2013-2015)



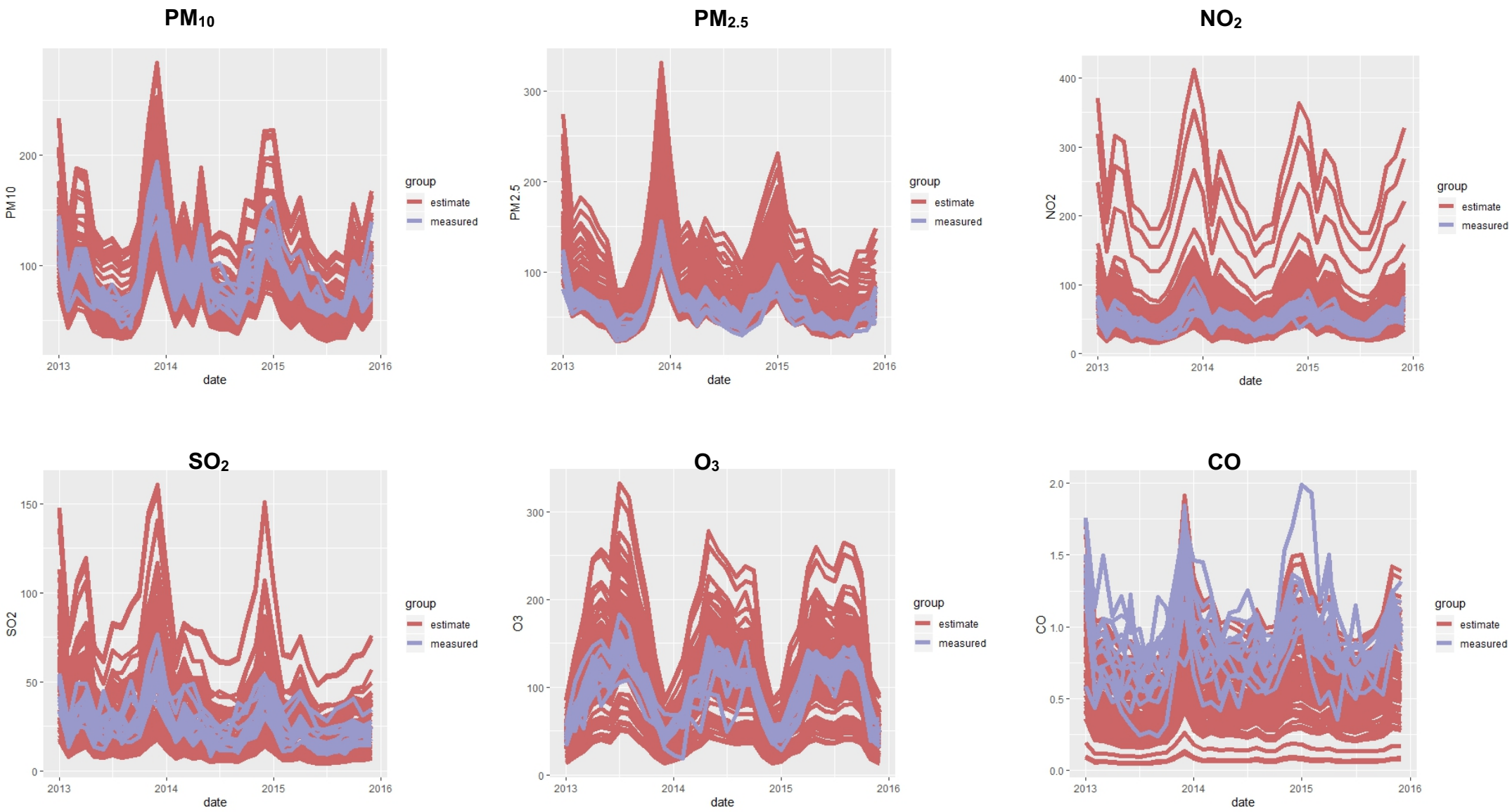
Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; O_3, ozone; CO, carbon monoxide. All pollutants measured in μg/m^3 except CO (mg/m^3)

Figure 6.6 Annual mean estimated pollutant concentrations by CKB clinic location, Suzhou (2013-2015)



Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; O_3, ozone; CO, carbon monoxide. All pollutants measured in $\mu g/m^3$ except CO (mg/m^3)

Figure 6.7 Estimated and measured monthly mean pollutant concentrations by CKB clinic location, and fixed-site monitors, respectively Suzhou (2013-2015)



Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; O_3, ozone; CO, carbon monoxide. All pollutants measured in $\mu g/m^3$ except CO (mg/m^3)

Figure 6.9 Average predicted NO_2 exposure by clinic location, Suzhou

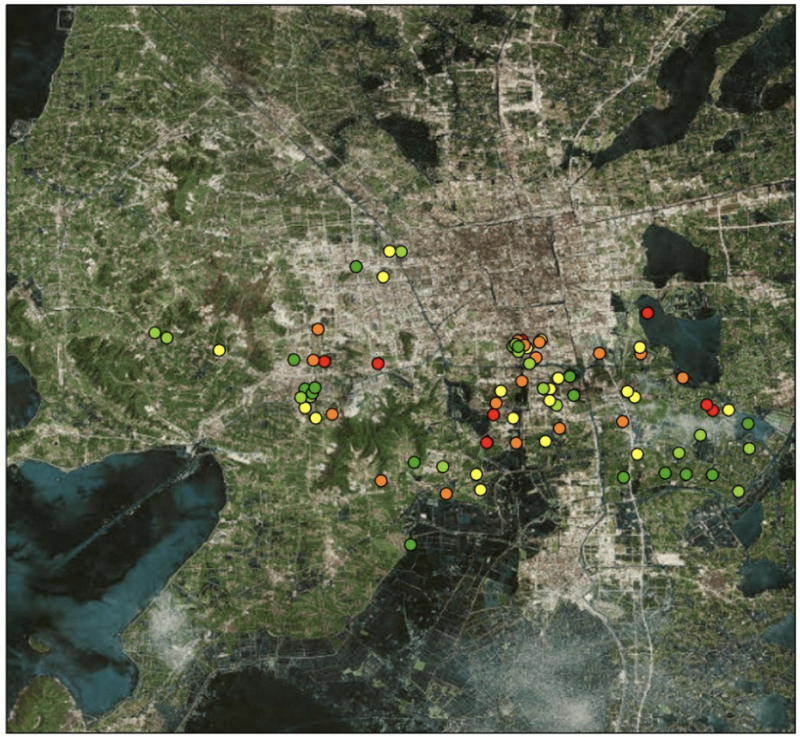


Figure 6.8 Average predicted SO_2 exposure by clinic location, Suzhou

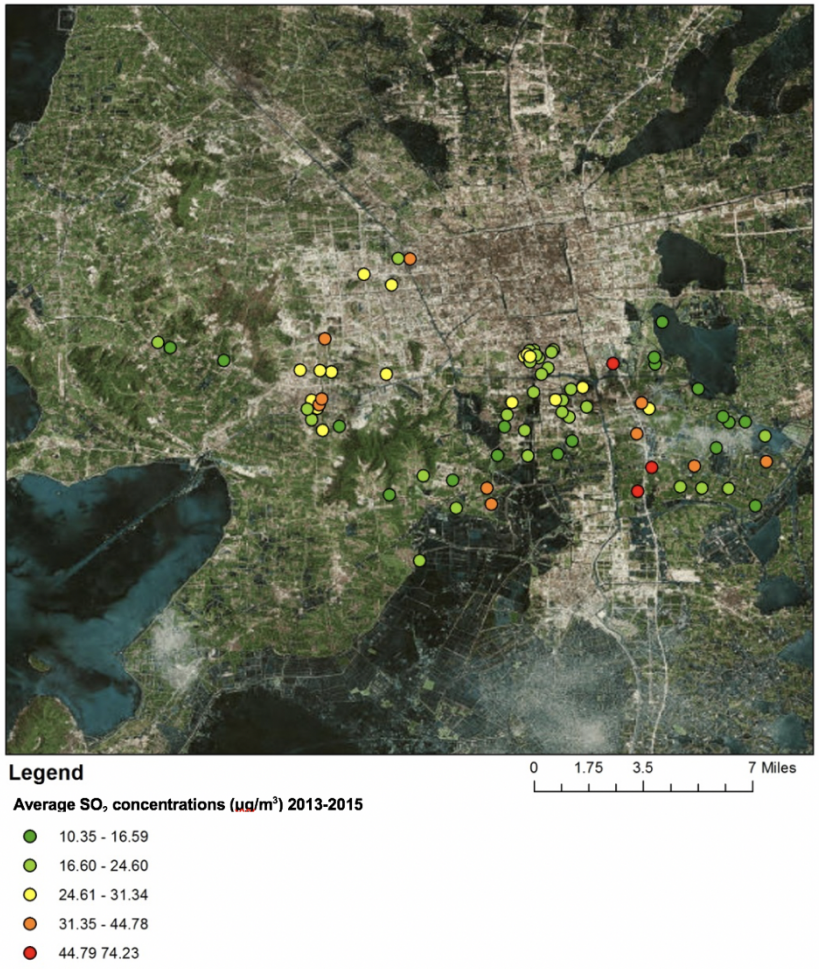


Figure 6.11 Average predicted PM_{10} exposure by clinic location, Suzhou

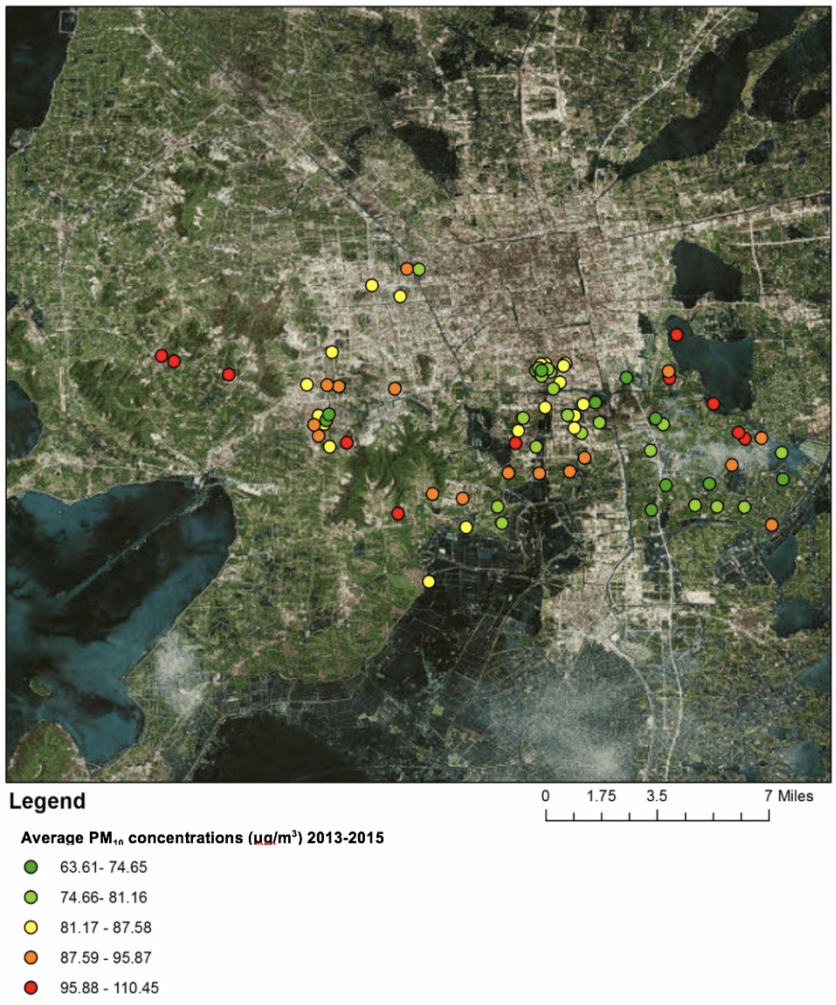


Figure 6.10 Average predicted $PM_{2.5}$ exposure by clinic location, Suzhou

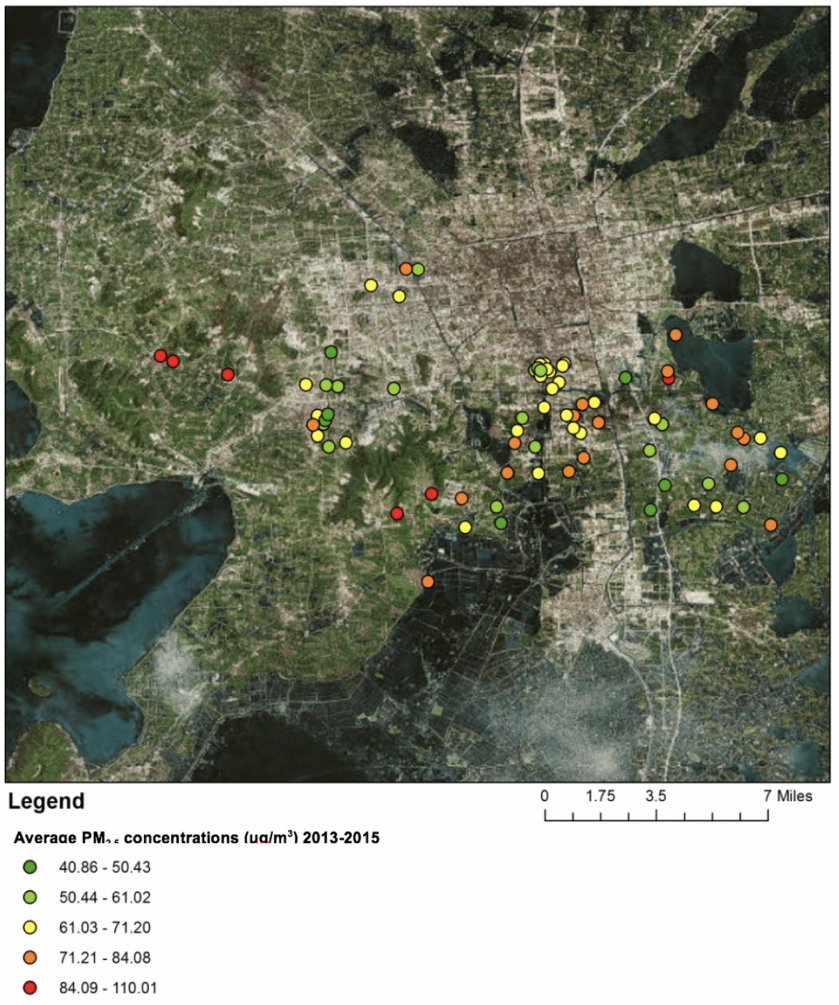


Figure 6.12 Average predicted CO exposure by clinic location, Suzhou

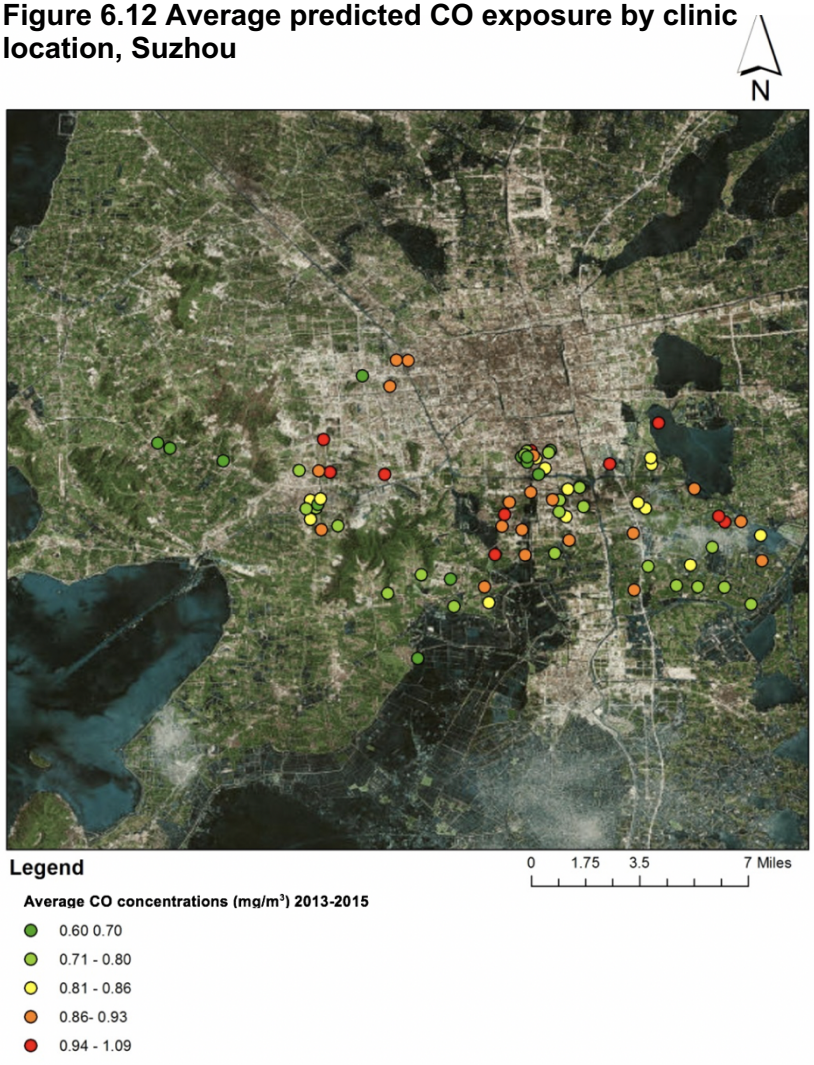


Figure 6.13 Average predicted O_3 exposure by clinic location, Suzhou

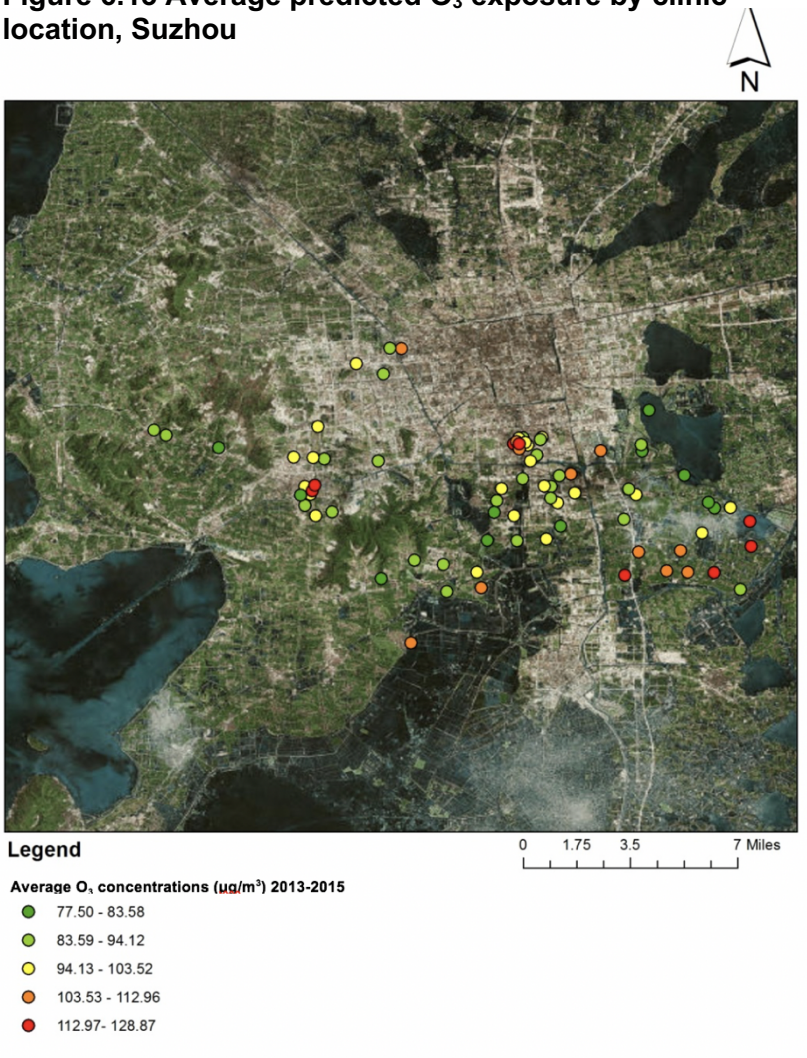
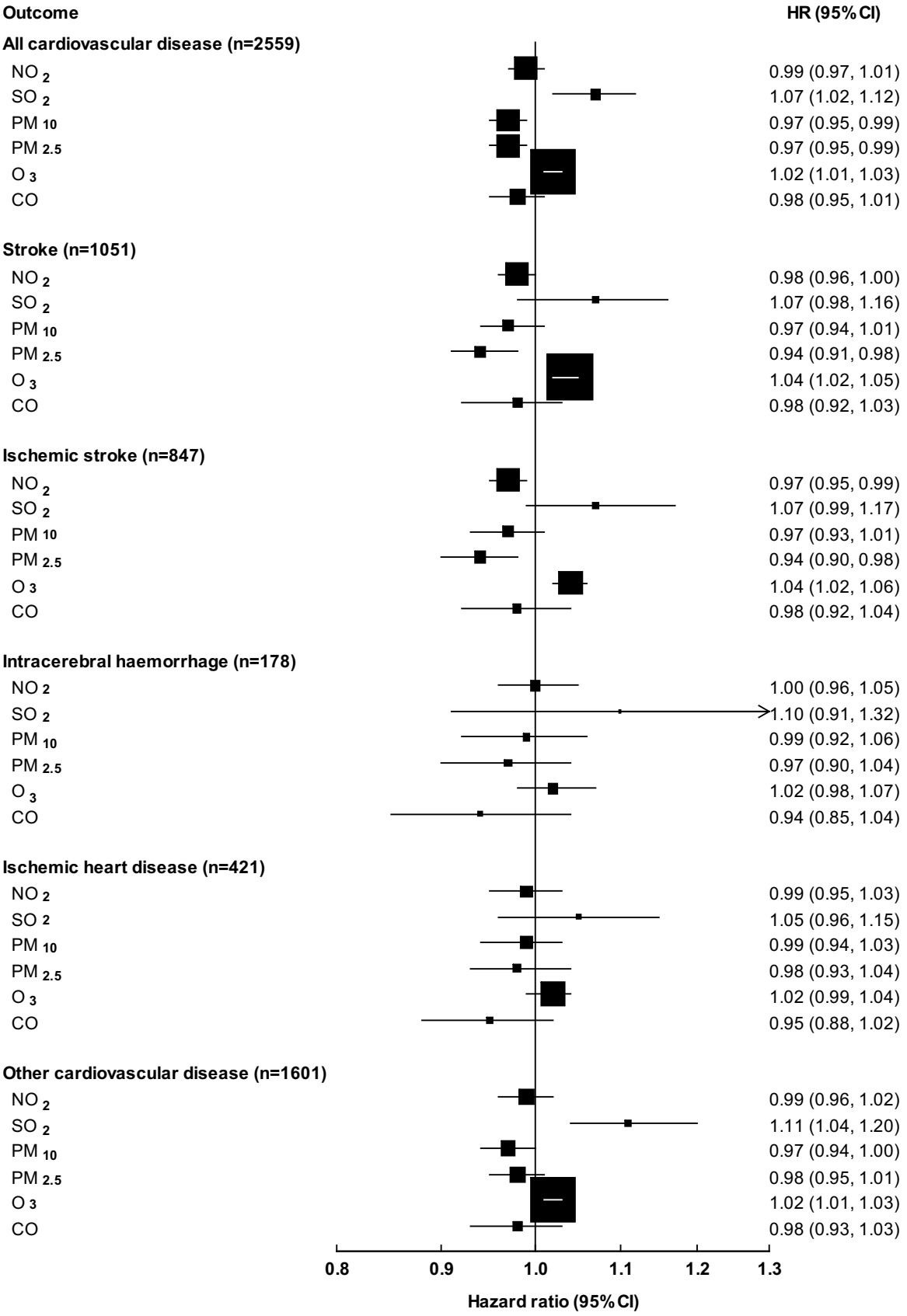


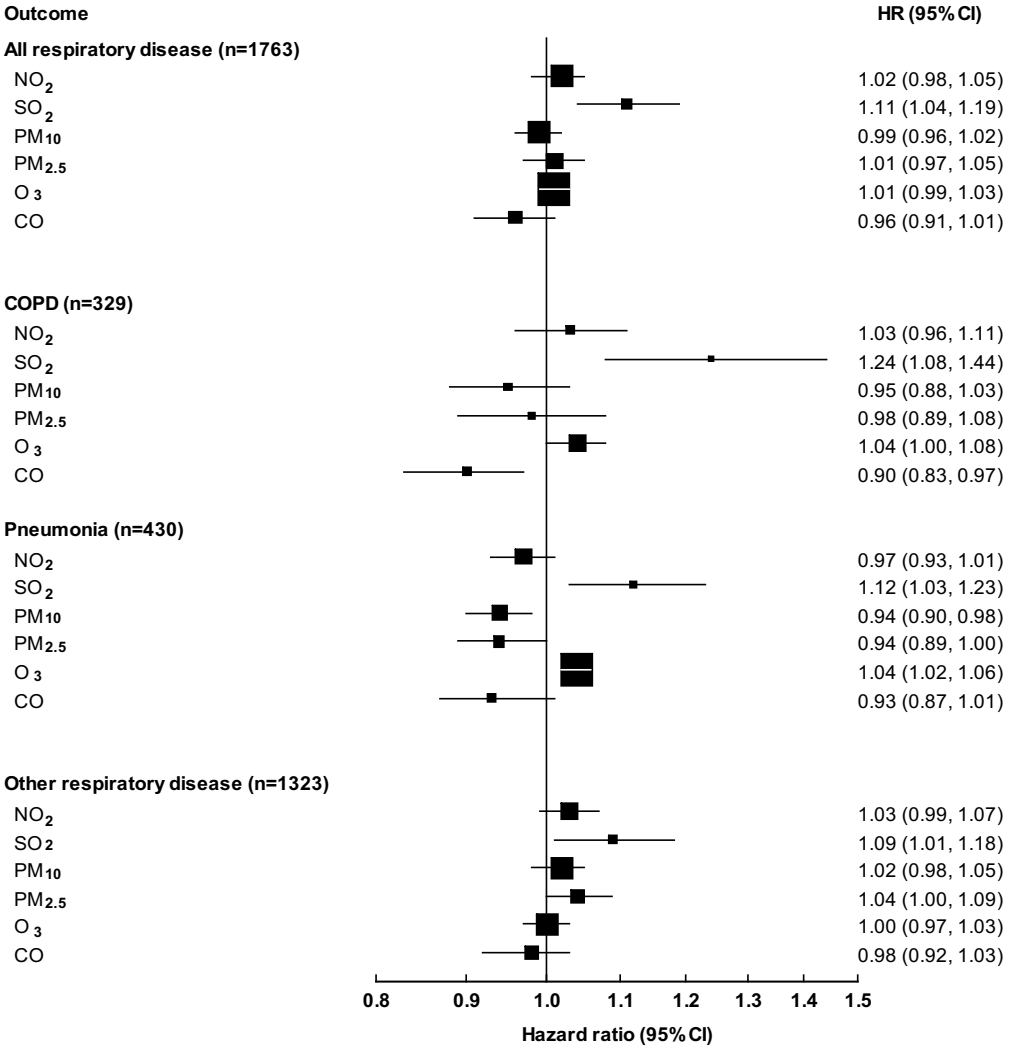
Figure 6.14 Adjusted hazard ratios for long-term AAP exposure and major cardiovascular disease risk



Hazard ratios calculated for a 10 μg/m^3 increase in pollutant exposure (except CO which used a 100 μg/m^3 increase*).* Adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean temperature, prior respiratory disease, consumption of fresh fruit and preserved vegetables, respectively, use of hypertensive medication, and mean SBP. Black boxes represent hazard ratios with size inversely proportional to variance of the log hazard ratio, and horizontal lines representing 95% confidence intervals (CIs)

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm*;* $PM_{2.5}$, particulate matter <2.5μm*;* O_3, ozone; CO, carbon monoxide.

Figure 6.15 Adjusted hazard ratios for long-term AAP exposure and major respiratory disease risk



Hazard ratios calculated for a 10 μg/m^3 increase in pollutant exposure (except CO which used a 100 μg/m^3 increase). Adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean temperature, prior cardiovascular disease, consumption of fresh fruit and preserved vegetables, respectively, use of diabetes medication. Black boxes represent hazard ratios with size inversely proportional to variance of the log hazard ratio, and horizontal lines representing 95% confidence intervals (CIs)

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10; $PM_{2.5}$, particulate matter <2.5; O_3, ozone; CO, carbon monoxide.

CHAPTER 7 DISCUSSION

7.1 Thesis overview

The aim of this thesis was to investigate both the acute and chronic associations of AAP exposure with cardio-respiratory health outcomes in China. **Chapters 1 and 2** reported on air pollution epidemiology and the importance of the topic in China, and on key methodological approaches and challenges to the field. **Chapter 3** provided a detailed review of existing peer-reviewed evidence on the cardio-respiratory health impacts of AAP exposure. A systematic review and meta-analyses of studies that reported on acute cardio-respiratory health effects of AAP within LMICs were carried out. **Chapter 3** also outlined results from an in-depth review of studies examining the chronic cardio-respiratory health effects associated with AAP exposure in China. **Chapter 4** provided details on the China Kadoorie Biobank (CKB) and the specific urban study population used in this thesis. **Chapter 5** reported on the findings in urban dwellers in CKB on the association between exposure to AAP and acute cardio-respiratory disease risk, examining both first-time hospitalisations and readmissions, respectively. The study described in **Chapter 6** attempted to investigate the chronic health effects of AAP exposure in CKB and in doing so, address the lack of studies examining AAP associated morbidity in the current evidence base. This chapter will now consolidate key findings of this thesis, the overall strengths and limitations will be discussed as well as the applicability of CKB as a study population with regard to the aims and objectives of this thesis. Finally, future research recommendations and public health implications will be discussed in the context of 21st-century epidemiology.

7.2 Key findings

7.2.1 Synthesis of the current evidence base

High AAP levels are recorded frequently in metropolitan areas around the world, particularly in LMICs. However, published findings from epidemiological research examining the associated cardio-respiratory health effects of AAP exposure do not reflect such growing

global ubiquity in distribution of AAP, with most studies, performed in HICs, despite 91% of AAP attributable deaths estimates to occur in LMICs [3]. The systematic review and meta-analysis presented in **Chapter 3** sought to address this by examining the risk of acute cardio-respiratory health effects associated with AAP exposure in LMICs specifically.

During the systematic review process, 85 and 60 studies were identified through systematic searching examining the acute effects of PM and gaseous pollutants respectively, the majority (74% and 73%, respectively) were from the East Asia and the Pacific region. Although participants living in major cities of South Asia and Africa are likely to be exposed to high AAP, fewer studies have been reported from these regions. These regions often lack AAP monitoring capacity. Findings from the systematic review and meta-analyses suggest observed risk estimates for the associations between short-term AAP exposure and cardio-respiratory health effects vary considerably by pollutant, health outcome, associated lag times and region.

Many studies from LMICs reported significant pooled associations for both $PM_{2.5}$ and PM_{10} and cardio-respiratory mortality and morbidity, particularly in East Asia and Pacific region. [111, 140, 163, 195] However, fewer studies examined $PM_{2.5}$ relative to PM_{10} despite $PM_{2.5}$ being hypothesised as the greater hazard to health with its smaller size and increased pathogenicity relative to PM_{10} due to high surface area to volume ratio. [439] This lack of research incorporating $PM_{2.5}$ measurements was likely due to delays until 2013 in the nationwide distribution of $PM_{2.5}$ monitors in China discussed **Section 2.2** [440] making studies before this time limited to Chinese megacities. [111, 131]

Moving average measures of AAP exposure (both particulate and gaseous) resulted in seemingly larger pooled risk estimates in the meta-analysis. This is a finding consistent with other studies both from HICs [266, 441] and LMICs including China [205, 442] where moving average measures are often associated with larger risk estimates for associated health effects than

single day measures. This variation in effect size is potentially due to moving average measures of AAP being able to capture associated health effects distributed over numerous days [443] [47] for example the net effect of a single hour of AAP spread over the succeeding 24 hours. It is particularly relevant as numerous toxicological studies have shown how effects of AAP exposure are distributed across days [444] and is applicable when many health outcomes of interest are broadly grouped such as cardiovascular disease where included diseases will have varying onset times.

Mortality was more commonly examined as an outcome of interest associated with AAP exposure in LMICs than morbidity, particularly for gaseous pollutants, where pooled estimates were more consistent for cardio-respiratory mortality versus morbidity. A likely explanation for this relates to data availability in LMICs, as while large administrative mortality datasets are available in certain LMICs such as the Chinese disease surveillance points system used for death registration and surveillance, [445] there remains a scarcity of morbidity data. Recently, utilisable morbidity datasets became available such as city-wide insurance datasets and hospital-specific databases, but are typically for particular city areas or hospitals and are therefore often utilised on a spatially piecemeal scale [155, 174, 176] limiting the ability for large multi-city studies as seen for AAP and mortality.[195] In this chapter, a justification for further research in LMICs incorporating morbidity as an outcome of interest was highlighted, followed by use of data from the CKB study in **Chapter 5** to answer some of the shortcomings of earlier studies with a lack of morbidity data, despite the fact CKB data is relatively small in size compared to data available for mortality time-series [195, 205] and case-crossover [185] studies.

Most studies were from China; however, where most identified studies were performed the strength of risk estimates in meta-analysis appeared to vary even down to the city level. PM appeared more strongly associated with cardiovascular mortality in Guangzhou versus Beijing with similar spatial variability seen for gaseous pollutants, and potential explanations

outlined in **Section 3.2.4.** The findings from meta-analysis on spatial variability in risk associated with AAP exposure are consistent with multi-city studies performed in both HICs [266, 446] and LMICs [163] as well as other meta-analyses. [447, 448] Epidemiological studies in China have also found detectable spatial differences even between city districts[175, 442] and urban-rural divides. [449] Hypothesised factors for such spatial variability in associated risk include the varying composition of air pollutants, insufficiency of protection and awareness, differing population structures and healthcare practices, factors likely to vary even more substantially between HIC and LMICs. These findings also therefore argue strongly against the extrapolation of risk estimates from HICs to LMICs and is unsuitable to robustly examine the associated health effects of acute AAP exposure in LMIC's (including China).

Regarding chronic cardio-respiratory health effects of AAP exposure in China, the systematic review in **Section 3.3** found severe lack of evidence from China on cardio-respiratory morbidity, as results reported so far are mostly from cross-sectional studies. This is despite calls for studies to include morbidity as an outcome of interest, as it is hypothesised as potentially more sensitive in capturing the health effects of AAP exposure [375] and providing a plausible and quantifiable link between AAP exposure and mortality. Without acknowledging morbidity associated with AAP exposure, the true associated burden of exposure in high concentration regions, including China, is unlikely to be fully comprehended. It also found that the vast majority of epidemiological studies in China have relied on spatially and temporally crude methods of AAP exposure classification principally fixed-site monitors with the more advanced exposure measurement methods seen in HICs seldom adopted by Chinese studies prompting the study in **Chapter 6** of this thesis.

7.2.2 Acute health effects

As shown in **Chapter 3** and outlined above, research incorporating cardio-respiratory morbidity as an outcome of interest when examining the acute cardio-respiratory effects of

AAP exposure in China is limited. Furthermore, the ecological study designs used have limited ability to explore individual characteristics of study participants. The aim of the analysis outlined in **Chapter 5** of this thesis was to examine acute AAP exposure and associated cardio-respiratory health outcomes in the CKB study. CKB data were analysed using both time-series and case-crossover approaches to examine the associated risk of first-time cardio-respiratory hospitalisations, as well as readmissions, and thus addressing the research gaps that existed before due to limited availability of morbidity data. Data from 219,020 participants located in urban CKB regions were utilised to investigate the association between AAP exposure and acute cardio-respiratory hospitalisations using the derived outcome variable of "spells" of which ~90% reflected morbidity events.

AAP levels varied by CKB region and frequently exceeded WHO daily $PM_{2.5}$ guideline values (except Haikou). Declining trends of SO_2 and PM concentrations were observed across all regions, likely due to the implementation of widespread national policy and targeted reductions of AAP in 2013, as discussed in **Section 2.2** of this thesis.

Participants with cardio-respiratory readmission spells were significantly older, less physically active, and had poorer self-reported general health. However, acute AAP exposure was associated with increased risk of cardio-respiratory spells in CKB participants for both first-time spells and readmissions with little overall difference in risk between the two types of admission. The exception to this was for participants in Suzhou where acute AAP exposure showed greater consistency with the risk of cardio-respiratory readmissions than first-time spells, particularly for PM and SO_2. Contrastingly, in pooled analysis across regions, acute AAP exposure was associated with increased risk of first-time cardio-respiratory spells only. Given the hypothesis that individuals with pre-existing health conditions would be more susceptible to increased severity of acute cardio-respiratory effects, [450, 451] these were unexpected findings with potential explanations detailed in **Section 5.5.1** of this thesis**.**

Apparent differences were observed in subgroup analyses by age and sex. Risk of cardiovascular spells following acute AAP exposure appeared greater in participants aged 60 years and over versus those under 60 years and risk of respiratory disease spells appeared greater in females than males. These results conform to hypothesised biological plausibility [302, 452] and findings from other studies, [132, 297] although for sex, results are more discordant. [453] No study to my knowledge has looked at these subgroups regarding morbidity by type of admission, adding increased value to this study, however, the validity and generalisability of these subgroup findings are debatable given the small sample size and limitations outlined in **Section 5.5.2**. While formal interaction tests may have improved power slightly, these were not performed in this thesis for several reasons. Firstly, the emphasis was placed on the overall patterns of consistencies and differences between groups rather than specific quantified differences. Secondly, given the issue of multiple testing, it was decided that the benefit formal tests of interaction would provide would likely be offset by the further increased number of statistical tests and increased probability of type-1 error, particularly given the very large number of statistical tests already performed. Finally, in time-series analysis fitting separate models allows a greater amount of model flexibility to be incorporated as smoothing functions can be applied separately to each subgroup model.

The observed variability in risk magnitude for acute AAP exposure and cardio-respiratory spells between CKB regions was also apparent and persisted following the construction of bi-pollutant models. In Suzhou, SO_2 remained significantly associated with stroke (all-subtypes) following adjustment for PM. In Haikou, the association between SO_2 and stroke was attenuated following adjustment for PM. Such variability in risk estimates between CKB regions was unsurprising given the differing pollutant concentrations and likely differences in pollutant composition, population characteristics and underlying health care practices and

providers. Collinearity between pollutant concentrations may also be an explanation with SO_2 and PM_{10} levels strongly correlated in Haikou (r=0.77) **(Appendix C12).**

Consistent with the findings of **Chapter 3** and the wider evidence base the magnitude of risk estimates appeared to be larger with the use of moving average lags similar to the findings of other studies as well as the meta-analysis outlined in **Chapter 3.** The results from DLMs were overall mostly consistent with those from time-series GAM models and case-crossover analysis. However, some significant risk estimates seen in time-series and case-crossover analyses were attenuated in DLM models. This is suggestive that the time-series and case-crossover analyses may be fitting simplistic models of the distribution of exposure-response over time and are confounded by adjacent lags. This was not explored further as the aims of this thesis did not include the exploration of lag structure effects.

7.2.3 Chronic health effects

While existing prospective evidence supports the association between AAP exposure and chronic cardio-respiratory health outcomes in China, the evidence base principally surrounds associated mortality risk only. As highlighted in **Section 3.3.2** of this thesis, cross-sectional evidence has shown tentative links between chronic AAP exposure and risk of cardio-respiratory morbidity, but reliable prospective evidence is severely lacking. Furthermore, in prospective studies in China, AAP exposure is largely estimated by averaging measurements from fixed-site monitors, thereby lacking the spatial resolution required to capture intra-urban contrasts and provide meaningful AAP estimates to study participants.

Global satellite-based AAP models do now provide exposure estimates for LMIC regions, such as the Data Integration Model for Air Quality (DIMAQ) which estimates $PM_{2.5}$ through the combination of fixed-site monitors, satellite retrievals of aerosol optical depth and chemical transport models. [83] However, such models typically examine one only pollutant (usually PM) and at spatial resolutions still unlikely to capture finer scale spatial variation in

exposures, thereby limiting their applicability to epidemiological studies. Satellite-based exposure models are also now emerging for China but remain in their infancy, focusing principally on the regional scale at a coarse spatial resolution. [454] Exposure models at the desired spatial resolution common to HICs [455] remain constrained in China by the availability of key input data, [456] and while such models are now being developed in China, they are yet to be commonly used in epidemiological studies and typically limited to one pollutant of interest. [457, 458] The study described in **Chapter 6** of this thesis aimed to address such limitations surrounding exposure measurement commonly seen in prospective Chinese studies. It used a localised spatiotemporal model of six criteria pollutants in a prospective study of 53,002 participants located in the CKB region of Suzhou.

Chronic SO_2 exposure was associated with statistically significant excess risk of both major cardiovascular and respiratory disease incidence, respectively. Chronic SO_2 exposure remained a significant predictor of both major cardiovascular and respiratory disease incidence in bi-pollutant models following adjustment for other pollutants of interest. This suggests SO_2 exposure remains a significant predictor of incident cardio-respiratory disease even at the declining concentrations throughout the study period (-39.9% from years 2013-2015). Although a lack of Chinese studies meant the observed associations between SO_2 exposure and incident cardio-respiratory disease could not be compared to the existing evidence base, some Chinese studies have found similar effects for mortality whereby SO_2 remained a significant predictor in bi-pollutant models. [66] Chronic O_3 exposure was also associated with risk of incident cardiovascular disease, specifically all-type and ischaemic stroke, again remaining a significant predictor in bi-pollutant models. O_3 also appeared associated with both COPD and pneumonia risk, but this risk was attenuated upon adjustment for SO_2. These findings suggest PM may not be the only pollutant of interest concerning cardio-respiratory disease risk. No differences were observed when comparing risk across subgroups potentially due to minimal exposure difference between subgroups,

particularly as AAP exposure was assigned to clinic location and not participant residential address, a substantial limitation of this study.

Contrastingly, comparing annual and monthly AAP exposures, monthly SO_2 exposure was no longer significantly associated with major cardiovascular disease but remained so with all-type and ischaemic stroke. The reason for this may be related to the acute onset of stroke versus other diseases captured within the grouping of major cardiovascular disease. Only annual O_3 and SO_2 exposures were associated with higher risk of COPD in the study population perhaps due to the latency of COPD in development or further residual confounding when using monthly exposure metrics such as the inclusion of crude adjustment for temperature. Given the emphasis on the distinction between acute and chronic health effects in the literature, [459, 460] few studies have looked at monthly AAP exposure most likely because it is unclear which of the two effects observed risk can then be classified as, meaning these findings could not be compared with existing studies.

All findings of the study were limited by its particularly short follow-up time (2013-2015) as well as the assignment of AAP exposure to participants baseline clinic location only. Further analysis is needed to explore the findings of this study further.

7.3 Strengths and limitations

7.3.1 Strengths

To my knowledge, this is the first systematic review and meta-analysis that examined the acute cardio-respiratory health effects of AAP exposure in LMICs exclusively **(Chapter 3)**. It explored associated cardio-respiratory health effects of AAP exposure from the regional to the city level within LMICs and effectively quantified the lack of studies examining cardio-respiratory morbidity as an outcome of interest as well as the lack of specific pollutants (CO, O_3 and $PM_{2.5}$) included in studies.

In **Chapter 4,** I provided the study methodology utilised in the CKB study, as well as highlighting CKB's comprehensive data availability and value as an unexplored resource concerning studying the cardio-respiratory health effects of AAP exposure in China. I made use of such data in **Chapter 5,** whereby ~219,000 participants located across the five CKB urban regions had cardio-respiratory hospitalisations classified by admission type. This enabled the only study to my knowledge which has examined the associations between acute AAP exposure and cardio-respiratory disease by type of admission, examining first-time events and readmissions, separately. This study outlined in **Chapter 5** also utilised both time-series and case-crossover study designs presenting estimates as significant as long as they remained so in both analysis types thereby showing the results as independent of the analytical approach used. DLMs were also constructed to explore further the lagged effects of acute AAP exposure providing an adjusted conditional effect of lagged AAP exposure and finding similar findings to that of standard time-series and case-crossover analyses.

The prospective study presented in **Chapter 6** then used a localised spatiotemporal model that assigned AAP exposure to CKB participants accounting for more small-scale variability of exposure than when relying solely on fixed-site monitor averages. Regarding outcome ascertainment, the inclusion of non-fatal cardio-respiratory events captured by hospitalisation and health insurance reimbursement records was a significant strength of this study. The abundance of reliably collected baseline characteristics and physical measurements in CKB was a further strength and allowed adjustment for a wide range of potential confounders previously neglected in studies of chronic AAP exposure in China such as household air pollution, passive smoking and prior disease incidence. Finally, the large size of the study population (53,002 participants) larger than other similar prospective studies China [67, 71] is a considerable strength and reduces the potential for bias by lack of representativeness.

7.3.2 Limitations

One of the most substantial limitations seen in this thesis, as well as the wider evidence base in general, surrounds the assignment of AAP exposure. This limitation is highlighted throughout this thesis from **Chapter 3,** whereby identified studies relied exclusively on fixed-site monitors to assign exposure, to the study in **Chapter 5,** which relied on fixed-site monitors only to assign exposure. As outlined in **Section 2.4.2.1,** this ignores smaller scale-spatial variability and likely results in some degree of both Berkson and Classical measurement error in epidemiological studies.

Although the prospective analysis in **Chapter 6** aimed to overcome this limitation utilising a more localised spatiotemporal model, this was still hindered by AAP exposure assigned to participants' baseline clinic location only with the residential location not available for CKB participants. Although it was presumed that participants live within 1km of their respective baseline clinic, the possibility for substantial exposure measurement error remains. Furthermore, the duration for which participants had resided at their baseline location was unknown and thus the degree to which assigned AAP values represent "chronic" exposure is debatable. A further substantial limitation of **Chapter 6** was its limited follow-up time, which was due to restricted years of AAP data availability. The majority of studies examining chronic health effects utilise much longer follow-up times thereby accounting for more historic AAP exposures, which given the latency time of developing numerous cardio-respiratory diseases may be of greater importance than recent exposures, particularly following the declines in AAP levels across China outlined in **Section 2.2** of this thesis.

Throughout this thesis, multiple significance tests have been performed, raising the issues of multiple testing and possible increased type-1 error. Therefore, the significance level used throughout this thesis is unlikely stringent enough to draw definitive conclusions from the analyses performed. Whilst this is a limitation of this thesis and could potentially result in some erroneous inferences, as previously stated in **Chapter 6** due to the exploratory nature

of the analysis conducted for this thesis, a greater emphasis was placed on estimates, the uncertainty around them and consistency between them rather than statistical significance. Furthermore, in **Chapter 5,** such tests will be correlated with each other due to the correlation between pollutants as well as between lag structures and regions, making any correction for multiple testing more challenging. Although a number of strategies used in genetic epidemiology could have been employed such as the false discovery rate [378] or Benjamini-Hochberg procedure which controls the false discovery rate under correlation of the p-values as utilised in **Chapter 6.** [461]

Regarding outcome ascertainment, there are limitations surrounding the classification methods used for constructing first-time and readmission spells of cardio-respiratory disease used in **Chapter 5** to assess the acute cardio-respiratory effects of AAP exposure. Firstly, classification of cardio-respiratory readmissions included previous hospitalisations since CKB baseline (~2008) only and hospitalisations prior to this time were not acknowledged, potentially misclassifying first-time spells and readmissions. Secondly, as outlined in **Section 5.3.2** the classification of readmissions relied on previous hospitalisations for only that disease outcome of interest; therefore, those with first-time spells may have been previously admitted for additional comorbid conditions (more so in the elderly) making them potentially still more susceptible to AAP. Thirdly, compared to existing time-series and case-crossover studies emerging from China, [124, 163, 164, 462] daily spell counts were far lower, likely limiting the power and subsequent applicability of findings, particularly for respiratory disease and all-type stroke. Finally, while health outcome recording is thorough in CKB as outlined in **Section 4.6**, possible temporal discrepancies between true hospitalisation events and date of recording is a potential limitation given the importance of temporal accuracy in both time-series and case-crossover studies.

The CKB study population is an invaluable resource for investigating both the established and emerging risk factors for a wide range of diverse diseases. However, as outlined in the

limitations above it does have some overall limitations in its overall applicability to AAP research, principally surrounding accurate AAP exposure assessment. Due to these limitations, the research outlined in this thesis is unable to conclude with certainty that both acute and chronic AAP exposure is associated with adverse cardio-respiratory health impacts in China. It is undoubtedly suggestive of such; however, the numerous limitations outlined above make it challenging to draw such objective conclusions from this research, specifically. Many of these limitations are not unique to the studies performed for this thesis but remain prevalent throughout the field of air pollution epidemiology. To overcome such uncertainty and frame AAP exposure as a risk factor with similar levels of certainty to the more traditional epidemiological risk factors for health, substantial changes are needed in future research, which will now be discussed.

7.4 Implications for future research

7.4.1 Exposure assessment

While studies utilising fixed-site monitors as proxies for exposure have been a valuable starting point in quantifying the cardio-respiratory health effects of AAP exposure in China, methods need to be updated. Accurate assignment of AAP exposure remains the greatest methodological challenge to be overcome in generating robust evidence for both the acute and chronic health effects of AAP exposure in China as well as LMICs more generally.

The study outlined in **Chapter 6** of this thesis attempted to address this utilising a localised spatiotemporal model to assign chronic AAP exposure. However, this model, as outlined in **Section 6.3.2**, was also likely limited to some degree by exposure measurement error and its application to CKB baseline clinic locations as opposed to residential address further limits applicability. The most valuable resource for prospective studies on AAP exposure is accurate AAP exposure for study participants with optimal spatial and temporal resolutions. That is accurate residential exposures for participants over prolonged study periods that

allow the latency of cardio-respiratory disease development to be accounted for and will provide substantial support for epidemiological studies in China.

The emphasised introduction of advanced satellite-based AAP models, application of small wearable sensors and incorporation of metabolomics into LMICs, particularly in China and India where the burden of AAP exposure is among the highest, will assist in facilitating such accurate residential exposures. While prospective cohort studies are emerging which apply enhanced satellite-based AAP models to participants in LMICs including China, [463, 464] are emerging, a more fundamental requirement surrounds the establishment of prospective cohorts designed specifically to examine AAP associated health impacts. Studies designed with this goal from inception would be beneficial in addressing the more complex data demands than seen in studies of more traditional risk factors for health. That is, to effectively generate evidence which overcomes the current limitations in existing research principally AAP exposure assessment, a shift is required from solely recycling existing cohort studies to developing contemporary studies designed to meet the substantial data demands required (predominantly surrounding exposure assignment) to successfully examine the health effects of AAP exposure in China. This requirement is exemplified by the use of the CKB study in this thesis where although CKB is one of the most detailed prospective cohorts globally with extensive data available at the highest calibre it still faces considerable limitations in its applicability to AAP epidemiology as outlined above in **Section 7.3.2.**

Finally, research should continue in China to examine the associated risk of AAP exposure for a wide range of pollutants, not just PM, which continues to dominate the evidence base.

Further exploration of the health effects associated with simultaneous and potentially synergistic exposure to multiple pollutants would also be beneficial. This may also facilitate the identification of the most harmful emission sources in China to inform regulatory policy. However, to achieve this, potential strategies to deal with the multicollinearity of pollutants

must be incorporated into studies, but the identification and application of such strategies still an ongoing area of research. Recent epidemiological studies have applied a range of potential strategies in to deal with the multicollinearity of pollutants examples including; additive main effects, [465] which utilises multi-pollutant or joint effect models with no interaction terms; principal component analysis, [466] which transforms a pollutant mixture into a smaller set of principle components used to represent pollutant concentrations; shrinkage based methods such as ridge regression [467] and least absolute shrinkage and selection operator regularization (LASSO),[467] which shrinks the coefficients of correlated pollutants towards zero; effect measure modification, [468] whereby differential effects are assessed by multipollutant joint effects or multiplicative interactive terms; [468] and Bayesian model averaging, [469] which averages the effect estimates across all possible models weighted by their posterior probabilities. However, a consensus on the most suitable approach to account for multicollinearity is yet to be reached, [470] leaving a considerable amount of uncertainty and likely preventing the widescale uptake of such methods. Further research is required to conclusively determine how to best deal with multicollinearity in epidemiological studies of AAP.

7.4.2 Disease outcomes

As highlighted throughout this thesis, there remains a considerable gap in the research on cardio-respiratory morbidity relative to mortality in China for both acute and chronic AAP exposure. While this thesis has contributed to this focusing predominantly on morbidity and examining first-time and readmissions, respectively, more evidence is needed ideally with longer follow-up times to accurately estimate the health burden. This is particularly important as chronic disease prevalence continues to rise in China with eight of the ten greatest causes of DALYs in China in 2017 NCDs [471] and an estimated 89% of deaths in China resulting from NCDs [472].

Regarding the acute health effects of AAP exposure, study sample sizes are ever-growing, [163, 221, 224] incorporating large nationwide administrative datasets of event counts, but in doing so, move further from inference to the individual level becoming increasingly susceptible to ecological fallacy. As highlighted in **Chapter 3** of this thesis, time-series and case-crossover studies from China have consistently found AAP exposure associated with acute cardio-respiratory mortality in general populations. Therefore, instead of further duplicating evidence, it is now also of interest to incorporate studies in LMICs closer to the individual level. While several time-series studies from China have examined mortality risk in pre-defined subgroups typically age and sex [224, 462, 473] few have begun to address this investigating additional effect modification at the level of the individual as seen in studies from HICs which have started to explore risk of mortality in individuals with pre-existing disease [298] and exacerbation of existing conditions. [259, 474] The study outlined in **Chapter 5** of this thesis examining both first-time spells and readmissions was a good starting point, but we need to go further ideally in larger study populations to look at readmissions, disease exacerbation and survival in individuals to identify potentially susceptible subgroups. This will assist in building the best evidence-based policy surrounding AAP exposure as well as effective health protection strategies.

Extending this to chronic health effects, well-designed cohort studies in sensitive populations, including the elderly, children and those with pre-existing diseases would also be beneficial. While the results from **Chapter 5** of this thesis as well as a host of time-series and case-crossover studies have begun to explore this for acute health impacts, little is known for chronic health impacts. The results in **Chapter 6** found no discrepancy in risk by the population characteristics examined, but sample sizes were small, follow-up short, and more research is needed to assess such variability reliably.

7.4.3 Quantification of bias

Throughout this thesis, the issues of exposure measurement error, selection bias and residual confounding have been discussed as likely limitations and sources of potential bias not just to the research described in this thesis throughout much of the air pollution epidemiology literature. Whilst the effect of certain types of bias on risk estimates has been studied, e.g. Classical measurement error resulting in biased estimates toward the null, quantification of the effects of other sources of bias is limited. Approaches such as regression calibration approaches have been explored in an attempt to correct for bias in estimation and inference resulting from exposure measurement error. However, such an approach often requires the collection of personal AAP measurements for validation [475]. While quantitative bias analysis has been briefly looked at within the AAP literature, [476] it would be advantageous for future studies to further incorporate this in order to quantify the direction, magnitude and uncertainty arising from such errors and determine their impact on study inference.

7.5 Public health implications

Regarding the acute cardio-respiratory health impacts of AAP exposure, a common narrative surrounds varying susceptibility of individuals to AAP exposure, with the predominant conclusion that those with pre-existing diseases are more susceptible. The findings of **Chapter 5** of this thesis suggest that not only individuals with pre-existing diagnosed medical conditions are susceptible to the effects of AAP exposure in China, but that risk may also extend to those free of the disease of interest. Therefore, policy to reduce AAP exposure may reduce the risk of cardio-respiratory hospitalisation both in those with and without pre-existing diseases. These results also suggest discrepancies in the associated risk of cardio-respiratory disease for the same pollutants by location. While widespread declines in AAP will always be a beneficial strategy in tackling AAP associated health impacts, in China this suggests targeted location-specific reductions in pollutants may also be useful, albeit problematic to enforce.

For chronic cardio-respiratory health impacts, this thesis examined one CKB region, making generalisability to other Chinese regions with likely differing pollutant concentrations composition and population characteristics debatable. However, given the associations documented between both SO_2 and O_3 with cardio-respiratory disease, it does suggest that regulatory policy focusing solely on PM concentrations in China will likely be insufficient in fully reducing the burden of associated cardio-respiratory disease.

As previously stated, AAP exposure was estimated to result in 4.9 million deaths in 2017 [2], 852,000 of these in China alone [12]. Such numbers placed AAP exposure as the fifth ranking risk factor for global mortality in 2017, [2] above that of high BMI, high LDL cholesterol and alcohol use. Regardless of the methodology used to obtain such quantified estimates of human life lost, their impact on raising public awareness surrounding AAP as well as subsequent policies for its reduction has been substantial. [477]

A decrease in AAP concentrations is always going to be beneficial, and the precautionary principle is without a doubt, the best approach to take in this scenario, with such declines in AAP also benefiting climate sustainability. However, policymakers should aim to familiarise themselves with the lack of epidemiological evidence on AAP exposure from certain regions, particularly LMICs. They must also continue to interpret such objective quantification of deaths attributable to AAP with a suitable degree of caution given the lack of epidemiological evidence and the reliance on broad assumptions used for their construction.

Furthermore, in light of both the results outlined in this thesis and surrounding evidence-base in general, the quantified similarity of risk between the health effects of AAP exposure and active cigarette smoking should also be avoided. Although crudely similar in their nature of exposure, accepting a similar health effect for active smoking and AAP negates the clear and substantial differences in the magnitude of their respective risk estimates for disease, [478]

the application of criteria for causal inference[479], and the numerous limitations surrounding epidemiological studies on AAP exposure as outlined in this thesis. Only when epidemiological studies on AAP exposure can adapt to overcome these substantial limitations can such comparisons even begin to be made.

7.6 Conclusions

This thesis found that in subsets of the CKB study population residing in urban localities, both acute and chronic AAP exposure appeared associated with an elevated risk of incident cardio-respiratory diseases. Acute AAP exposure was broadly associated with both first-time cardio-respiratory disease hospitalisations as well as readmissions with observed risk appearing to vary by pollutant and CKB region. Regarding chronic AAP exposure, the findings of this thesis suggest new evidence that long-term exposure to AAP principally SO_2 and O_3 is an important risk factor for both cardiovascular and respiratory disease incidence. Therefore, they suggest that current disease burden estimates focusing solely on mortality are likely underestimating the actual burden of AAP exposure in China. While documented associations in this thesis were subject to numerous limitations and remain purely suggestive of any causative effect between AAP exposure and cardio-respiratory disease in China, they have exemplified the feasibility and issues surrounding the use of a large established prospective cohort in addressing such associations.

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Assessing the acute and chronic cardio-respiratory health impacts of ambient air pollution in China

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Appendix A. Supplementary data to Chapter 2

Appendix A1. Measurement error in epidemiological studies of ambient air pollution, a summary of Berkson versus Classical components

The effects of measurement error in generalised linear models are broadly similar to the effects in the linear model [480, 481] Therefore, for simplicity, suppose we wish to examine the effect of $PM_{2.5}$ on hospital admissions on day t assuming the standard linear model:

$$Y_t = \alpha + b_t\, x_t + e_t$$

Whereby α and b are regression coefficients to be estimated and e residual error assumed independent of true exposure status denoted (x_t). Here $b_t\, x_t$ is the expected change in hospitalisations per unit change in true exposure status ($PM_{2.5}$).

Suppose instead of true exposure measures an imperfect surrogate measure of exposure (denoted W_t) is now used with the difference between x_t and W_t reflecting (non-differential) measurement error (denoted E). W_t is a surrogate when in the linear model setting with normally distributed random variables, W_t is not correlated with the disease model error ε

Measurement error can fall within two conceptual models:

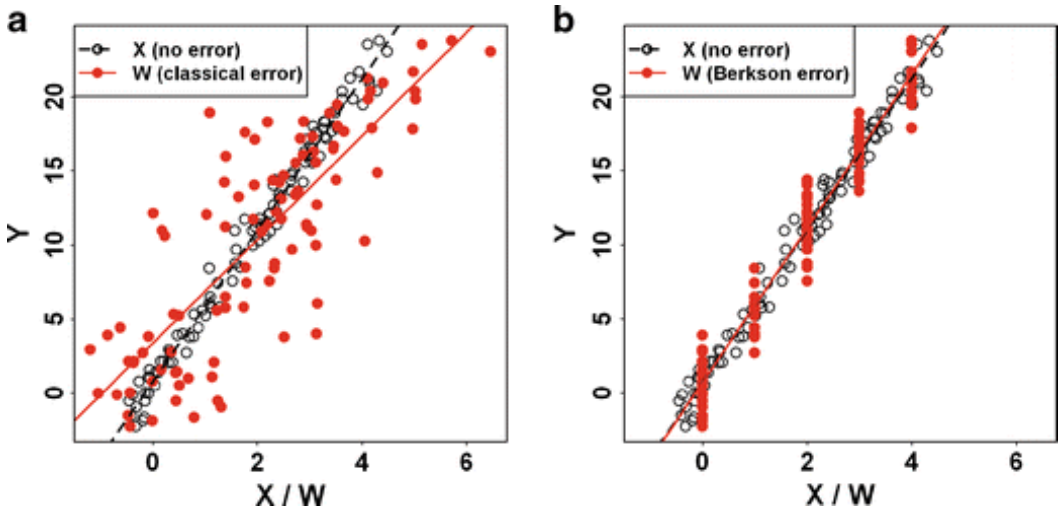
a) **Berkson measurement error** shown as: $x_t = W_t + E$

The Berkson measurement error scenario assumes that exposure measurement error E has a mean equal to zero and is independent of W_t. Under this scenario the surrogate measure W_t could represent AAP exposure that is shared by a group of participants whose individual exposure may vary due to time-activity patterns. In short, we measure only part of the true exposure. Should we regress Y_t on W_t instead of x_t this will not add bias to the regression coefficients assuming non-differential measurement error, however variance of the regression coefficients may increase.

b) **Classical measurement error** shown as: $W_t = x_t + E$

Classical measurement error assumes that random error in AAP measurement E has a mean equal to zero and as independent of x_t (as opposed to W_t in the Berkson error scenario). In short, we measure true exposure plus noise. Therefore, regressing Y_t on W_t can generate a biased estimate of $\beta_t\, x_t$ and in a simple linear regression $\beta_t\, W_t$ will be expected as attenuated relative to $\beta_t\, x_t$ (see **Figure A1**).

Figure A1 **Examples of a linear disease model relationship with the true exposure *X* overlaid with the empirical relationship given the mis-measured exposure *W*, measured with Classical (a) and Berkson (b) measurement error (adapted from Sheppard et al, 2011)**



Appendix B. Supplementary data for Chapter 3

Appendix B1. Systematic review search strategy

Utilised databases	PubMed EMBASE Web of Science Proquest Global Health LILACS

Search string; (PubMed, Embase, Web of Science, Proquest, Global Health)
(((((“Air pollution*” OR “nitrogen dioxide” OR “nitric oxide” OR “sulphur dioxide” OR “ozone” OR “particulate matter” OR “particulate” OR “carbon monoxide”) AND ((“time series” OR “timeseries” OR “time-series” OR “case crossover” OR “case control” OR “cohort” OR “cross sectional”))) AND ((“mortality” OR “death” OR “admission” OR “hospital admission” OR “emergency room” OR “accident & emergency”))) AND (“developing country” OR “Afghanistan” OR “Guinea” OR “Rwanda” OR “Benin” OR “Guinea-Bissau” OR ”Senegal” OR “Benin” OR “Guinea-Bissau” OR “Senegal” OR “Burkina Faso” OR “Haiti” OR “Sierra Leone” OR “Burundi” OR “Korea Dem. People’s Rep*” OR “Somalia” “Central African Republic” OR “Liberia” OR “South Sudan” OR “Chad” OR “Madagascar“ OR “Tanzania” OR “Comoros” OR “Malawi” OR “Togo” OR “Congo Dem. Rep” OR “Mali” OR “Uganda” OR “Eritrea” OR “Mozambique” OR “Zimbabwe” OR “Ethiopia” OR “Nepal” OR “Gambia” OR “Niger” OR “Armenia” OR “Kiribati” OR “Soloman Islands” OR “Bangladesh” OR “Kosovo” OR “Sri Lanka” OR “Bhutan” OR “Kyrgyz*” OR “Sudan” OR “Bolivia” OR “Lao” OR “Swaziland” OR “Cabo Verde” OR “Lesotho” OR “Syria*” OR “Cambodia” OR “Mauritania” OR “Tajikistan” OR “Cameroon” OR “Micronesia” OR “Timor-Leste” OR “Congo. Rep” OR “Moldova” OR “Tonga” OR “Cote d’Ivoire” OR “Mongolia” OR “Tunisia” OR “Dijibouti” OR “Morocco” OR “Ukraine” OR “Egypt, Arab Rep” OR “Myanmar” OR “Uzbekistan” OR “El Salvador” OR “Nicaragua” OR “Vanuatu” OR “Ghana” OR “Nigeria” OR “Vietnam” OR “Guatemala” OR “Pakistan” OR “West Bank and Gaza” OR “Honduras” OR “Papua New Guinea” OR “Yemen*” OR “India” OR “Philippines” OR “Zambia” OR “Indonesia“ OR “Samoa” OR “Kenya” OR “Sao Tome and Principe” OR “Albania” OR “Ecuador” OR “Montenegro” OR “Algeria” OR “Fiji” OR “Namibia” OR “American Samoa” OR “Gabon” OR “Palau” OR “Angola” OR “Georgia” OR “Panama” OR “Argentina” OR “Grenada” OR “Paraguay” OR “Azerbaijan” OR “Guyana” OR “Peru” OR “Belarus” OR “Iran, Islamic Rep” OR “Romania” OR “Belize” OR “Iraq” OR “Russia*” OR “Bosnia and Herzegovina” OR “Jamaica” OR “Serbia” OR “Botswana” OR “Jordan” OR “South Africa” OR “Brazil” OR “Kazakhstan” OR “St. Lucia” OR “Bulgaria” OR “Lebanon” OR “St Vincent and the Grenadines” OR “China” OR “Libya” OR “Suriname” OR “Colombia” OR “Macedonia” OR “Thailand” OR “Costa Rica” OR “Malaysia” OR “Turkey” OR “Cuba” OR “Maldives” OR “Turkmenistan” OR “Dominica” OR “Marshall Islands” OR “Tuvalu” OR “Dominican Republic” OR “Mauritius” OR “Venezuela” OR “Equatorial Guinea” OR “Mexico” OR “Africa” OR “Caribbean Region” OR “Central America” OR “Latin America” OR “South America” OR “Asia”))
Search string: (LILACS) – Curtailed search string due to smaller LMIC based database
(Air pollution OR nitrogen dioxide OR nitric oxide OR sulphur dioxide OR ozone OR particulate OR carbon monoxide) AND (mortality OR death OR admission OR emergency)

Appendix B2. Risk of bias assessment

All eligible studies were assessed to examine the risk of biases commonly seen in studies on ambient air pollution and health these include;

Detection Bias; studies with health outcomes objectively defined using clinical information or standardised death certification (ICD-9/10 coding) are defined as having low risk of detection bias.

Exposure Assessment Bias;

	Exposure Metric	**Risk of exposure assessment bias**
A	Exposure as a surrogate for air pollution (e.g. distance to road, personal recall)	High
A	Use of single fixed monitoring system	High
A	Use of multiple fixed monitoring systems	≥3 Moderate <3 High
B	Personal Exposure	Low
B	Chemical Transport/AOD Model	Moderate
B	Land Use Regression Model	Moderate
B	Other Satellite/Remote Sensing	Moderate

Combination of >2 of the above (providing at least one B measure) = low risk of bias

Adjustment of confounders; studies that have adjusted for at least 3 of the main confounding variables including, long-term trends, seasonality, weather, day of week, influenza epidemics, population characteristics and lifestyle factors (where study design allows) will be considered as having low risk of bias.

Bias from study publication date; older research studies inherently suffer with greater degree of biases, due to the lack of both AAP monitoring technology and health outcome data at times of completion. Thus, studies conducted prior to 1980 will be considered outdated with high level of bias assigned.

Selection Bias; studies that utilise populations with high susceptibility to health impacts of AAP for example all cases selected from hospitals or with an outdoor based occupation will be considered high risk of selection bias.

Following assessment for each included study, overall summary assessments of risk of bias both within and across studies will be assessed utilising the following table obtained from the Cochrane collaboration (see **Table B1**).

Table B1 Risk of bias overall assessment

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias.	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias.	Plausible bias that raises some doubt about the results.	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias.
High risk of bias.	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.

Appendix B3. Summary of included studies for meta-analysis examining particulate matter

Author	Year	Study design	Study Period	City	Region	Outcome	$PM_{2.5}$	PM_{10}	Risk of bias
Qian, Z.	2013	Case-crossover	2003-2008	Shanghai	East Asia and Pacific	M (CV)	No	Yes	Moderate
Ma, Y.	2011	Case-crossover	2006-2008	Shenyang	East Asia and Pacific	M (CV & R)	Yes	No	High
Xiang, H.	2013	Case-crossover	2006-2008	Wuhan	East Asia and Pacific	A (CV)	No	Yes	Moderate
Yang, C	2012	Case-crossover	2007-2009	Guangzhou	East Asia and Pacific	M (CV & R)	Yes	No	High
Liu, Y.	2015	Case-crossover	2006-2009	Anshan	East Asia and Pacific	M(CV)	Yes	No	Unclear
Chen, R.	2015	Case-crossover	2006-2009	Wuhan	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Bravo, M.	2016	Case-crossover	1996-2010	Sao Paulo	Latin America and Caribbean	M (CV & R)	No	Yes	Moderate
Huang, F.	2016	Case-crossover	2013-2014	Beijing	East Asia and Pacific	A (CV)	Yes	Yes	Moderate
Guo, Y.	2009	Case-crossover	2004-2006	Beijing	East Asia and Pacific	A (CV)	Yes	No	High
Escamilla-Cejudo, J. A	1999	Case-crossover	1995	Sao Paulo	Latin America and Caribbean	M (CV)	No	Yes	High
Capraz, O.	2016	Time-series	2007-2012	Istanbul	Europe and Central Asia	M (CV & R)	No	Yes	Moderate
Castillejos, M	2000	Time-series	1992-1995	Mexico City	Latin America and Caribbean	M (CV & R)	Yes	Yes	High
Chen, G	2008	Time-series	2001-2004	Shanghai	East Asia and Pacific	M (CV & R)	No	Yes	Moderate

Chen, R.	2010	Time-series	2005-2007	Multi-City	East Asia and Pacific	A (CV & R)	No	Yes	Moderate
Chen, R.	2011	Time-series	2006-2008	Beijing	East Asia and Pacific	M (CV & R)	Yes	No	Moderate
Chen, R	2013	Time-series	1996-2008	Multi-City	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Costa, A. F	2016	Time-series	2001-2011	Sao-Paulo	Latin America and Caribbean	M (CV & R)	No	Yes	Moderate
de Freitas	2016	Time-series	2001-2006	Vitoria	Latin America and Caribbean	A (CV)	No	Yes	Moderate
Diaz-Robles, L	2010	Time-series	2005-2007	Temuco and Pudahel	Latin America and Caribbean	M&A (CV & R)	No	Yes	Moderate
Gharehchachi, E.	2013	Time-series	2008-2010	Shiraz	Middle East and North Africa	A (CV & R)	No	Yes	High
Hosseinpoor, A. R	2005	Time-series	1996-2001	Tehran	Middle East and North Africa	A (CV)	No	Yes	Unclear
Huang, W.	2012	Time-series	2004-2008	Xi'an	East Asia and Pacific	M (CV & R)	Yes	No	High
Huang, W.	2009	Time-series	2004-2005	Shanghai	East Asia and Pacific	M (CV & R)	Yes	Yes	High
Kan, H.	2003	Time-series	2000-2001	Shanghai	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Kan, H.	2010	Time-series	2001-2004	Shanghai	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Kan, H.	2003	Time-series	2001-2002	Shanghai	East Asia and Pacific	M (CV)	No	Yes	Unclear
Kan, H.	2007	Time-series	2004-2005	Shanghai	East Asia and Pacific	M (CV & R)	Yes	Yes	High
Kan, H.	2008	Time-series	2001-2004	Shanghai	East Asia and Pacific	M (R)	No	Yes	Moderate
Li, G.X	2013	Time-series	2006-2009	Tianjin	East Asia and Pacific	M (CV & R)	No	Yes	Moderate

Li, P.	2013	Time-series	2004-2009	Beijing	East Asia and Pacific	M (R)	Yes	No	Moderate
Li, Y.	2015	Time-series	2005-2009	Beijing	East Asia and Pacific	M (CV & R)	Yes	No	High
Lin, H.	2016	Time-series	2013-2015	Multi-City	East Asia and Pacific	M (CV & R)	Yes	No	Moderate
Meng, X.	2013	Time-series	1996-2008	Multi-City	East Asia and Pacific	M (R)	No	Yes	Moderate
Nakhle, M.M	2015	Time-series	2012	Beirut	Middle East and North Africa	A (CV & R)	Yes	Yes	Unclear
Nascimento, L. F	2012	Time-series	2007-2008	San Jose dos Campos	Latin America and Caribbean	A (CV)	No	Yes	Unclear
Phung, D.	2016	Time-series	2004-2007	Ho Chi Minh City	East Asia and Pacific	A (CV & R)	No	Yes	Moderate
Qian, Z	2010	Time-series	2000-2004	Wuhan	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Qian, Z	2007	Time-series	2001-2004	Wuhan	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Romieu, I.	2012	Time-series	1997-2005	Multi-City	Latin America and Caribbean	M (CV & R)	No	Yes	Moderate
Stojic, S.S	2016	Time-series	2009-2014	Belgrade	Europe and Central Asia	M (CV & R)	No	Yes	Moderate
Tao, Y.	2012	Time-series	2006-2008	Multi-City	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Tong, L.	2014	Time-series	2008-2011	Tianjin	East Asia and Pacific	A (CV)	No	Yes	Unclear
Vichit-Vadakan, H.	2008	Time-series	1999-2003	Bangkok	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Wang, T.	2013	Time-series	2006-2010	Tianjin Binhai	East Asia and Pacific	M (CV)	No	Yes	Moderate
Wong, C.M	2008	Time-series	1999-2004	Multi-City	East Asia and Pacific	M (CV & R)	No	Yes	Moderate

Xie, J.	2014	Time-series	2010-2012	Shanghai	East Asia and Pacific	A (CV)	No	Yes	High
Xie, W.	2015	Time-series	2010-2012	Beijing	East Asia and Pacific	M&A (CV)	Yes	No	High
Xu, Q.	2013	Time-series	2013	Beijing	East Asia and Pacific	A (R)	Yes	No	Moderate
Ye, X	2016	Time-series	2001-2009	Shanghai	East Asia and Pacific	A (CV)	Yes	Yes	High
Yu, I.T. S	2012	Time-series	2006-2009	Guangzhou	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Zhang, F.	2011	Time-series	2003-2008	Beijing	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Zhang, Y.	2015	Time-series	2009-2011	Beijing	East Asia and Pacific	A (CV & R)	No	Yes	Moderate
Zhang, Z. L	2014	Time-series	2008-2011	Guangzhou	East Asia and Pacific	A (CV & R)	No	Yes	Moderate
Zeng, Q.	2015	Time-series	2007-2009	Wuhan	East Asia and Pacific	M (CV)	No	Yes	Moderate
Amancio, C. T	2014	Time-series	2005-2009	Sao Jose dos Campos	Latin America and Caribbean	M (CV)	No	Yes	High
Arbex, M. A	2009	Time-series	2001-2003	Sao Paulo	Latin America and Caribbean	A (R)	No	Yes	Moderate
Lin, H.	2016	Time-series	2009-2011	Guangzhou	East Asia and Pacific	M (CV)	Yes	Yes	High
Tao,Y.	2011	Time-series	2006-2008	Multi-City	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Tao, Y.	2014	Time-series	2001-2005	Lanzhou	East Asia and Pacific	A (R)	No	Yes	High
Cai, J.	2014	Time-series	2005-2011	Shanghai	East Asia and Pacific	A (R)	No	Yes	Moderate
Cao, J.	2012	Time-series	2004-2008	Xi’an	East Asia and Pacific	M (CV & R)	Yes	No	High

Leitte, A.M	2011	Time-series	2004-2006	Beijing	East Asia and Pacific	A (R)	No	Yes	High
Li, G.	2016	Time-series	2002-2006	Tianjin	East Asia and Pacific	M (CV)	No	Yes	Moderate
Mahiyuddin, W.R. W	2013	Time-series	2000-2006	Klang Valley	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Vanjanapoom, N.	2002	Time-series	1992-1997	Bangkok	East Asia and Pacific	M (CV & R)	No	Yes	High
Su, C.	2016	Time-series	2007-2008	Beijing	East Asia and Pacific	A (CV)	Yes	Yes	Moderate
Yang, Y.	2015	Time-series	2009-2010	Beijing	East Asia and Pacific	M (R)	No	Yes	Moderate
Zheng, S.	2013	Time-series	2001-2005	Lanzhou	East Asia and Pacific	A (CV)	No	Yes	Moderate
Lin, C.	2003	Time-series	1994-1995	Sao Paulo	Latin America and Caribbean	A (CV)	No	Yes	Moderate
Zahari, M.	2014	Time-series	2004-2009	Multi-City	East Asia and Pacific	A (R)	No	Yes	High
Lin, H.	2016	Time-series	2007-2011	Guangzhou	East Asia and Pacific	M (CV)	Yes	Yes	High
Yang, Y.	2013	Time-series	2009-2010	Beijing	East Asia and Pacific	M (CV & R)	No	Yes	Moderate
Zhang, Y.	2012	Time-series	2008-2009	Beijing	East Asia and Pacific	M (R)	No	Yes	Moderate
Wang, X.	2016	Time-series	2008-2009	Beijing	East Asia and Pacific	M (R)	No	Yes	Low
Nascimento, L.	2016	Time-series	2012	Volta Redonda	Latin America and Caribbean	A (R)	Yes	No	Moderate
Pudpong, N.	2008	Time-series	2002-2006	Muang Chiang Mai	East Asia and Pacific	A (CV & R)	Yes	Yes	High
Chen, R.	2013	Time-series	2001-2008	Multi-City	East Asia and Pacific	M (CV)	No	Yes	Moderate

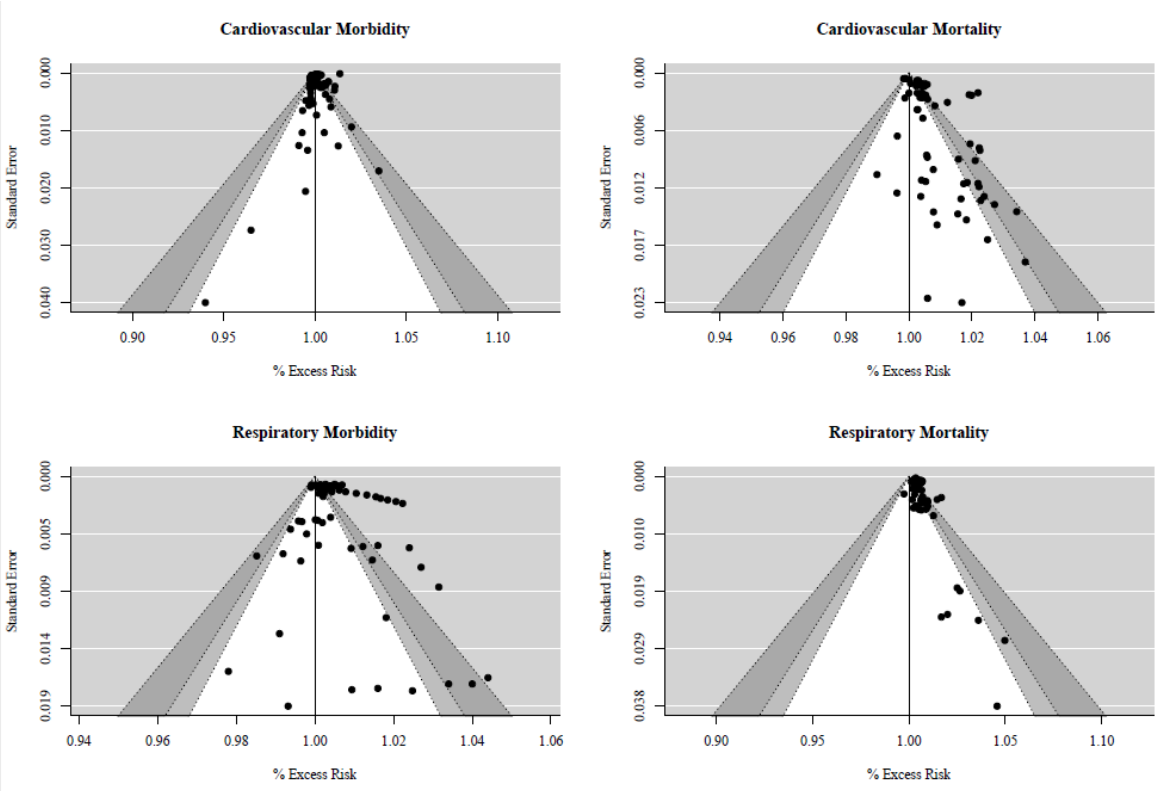
Borja-Aburto, V.	1998	Time-series	1993-1995	Mexico City	Latin America and Caribbean	M (CV & R)	Yes	No	High
Guo, L. J	2014	Time-series	2010-2011	Shanghai	East Asia and Pacific	A (R)	No	Yes	Moderate
Zhao, A.	2014	Time-series	2010-2011	Shanghai	East Asia and Pacific	A (R)	No	Yes	Moderate
Lee, H.	2015	Time-series	2001-2009	Multi-City	East Asia and Pacific	M (CV)	Yes	Yes	High
Blanco-Beccera, L.	2014	Time-series	1998-2006	Bogota	Latin America and Caribbean	M (CV & R)	No	Yes	Moderate
Gavinier, S	2014	Time-series	2007-2011	Sao Paulo	Latin America and Caribbean	A (CV)	No	Yes	High
Winchmann, J	2012	Both	2001-2006	Cape Town	Africa	M (CV & R)	No	Yes	High
Pinheiro, S	2014	Both	1998-2008	Sao Paulo	Latin America and Caribbean	M (CV & R)	No	Yes	Moderate
Guo, Y	2010	Both	2005-2007	Tianjin	East Asia and Pacific	M (CV)	No	Yes	Unclear

Abbreviations: M, mortality; A, admissions; CV, cardiovascular; R, respiratory; PM_{10}, particulate matter ≤10 μm; $PM_{2.5}$ particulate matter ≤ 2.5 μm

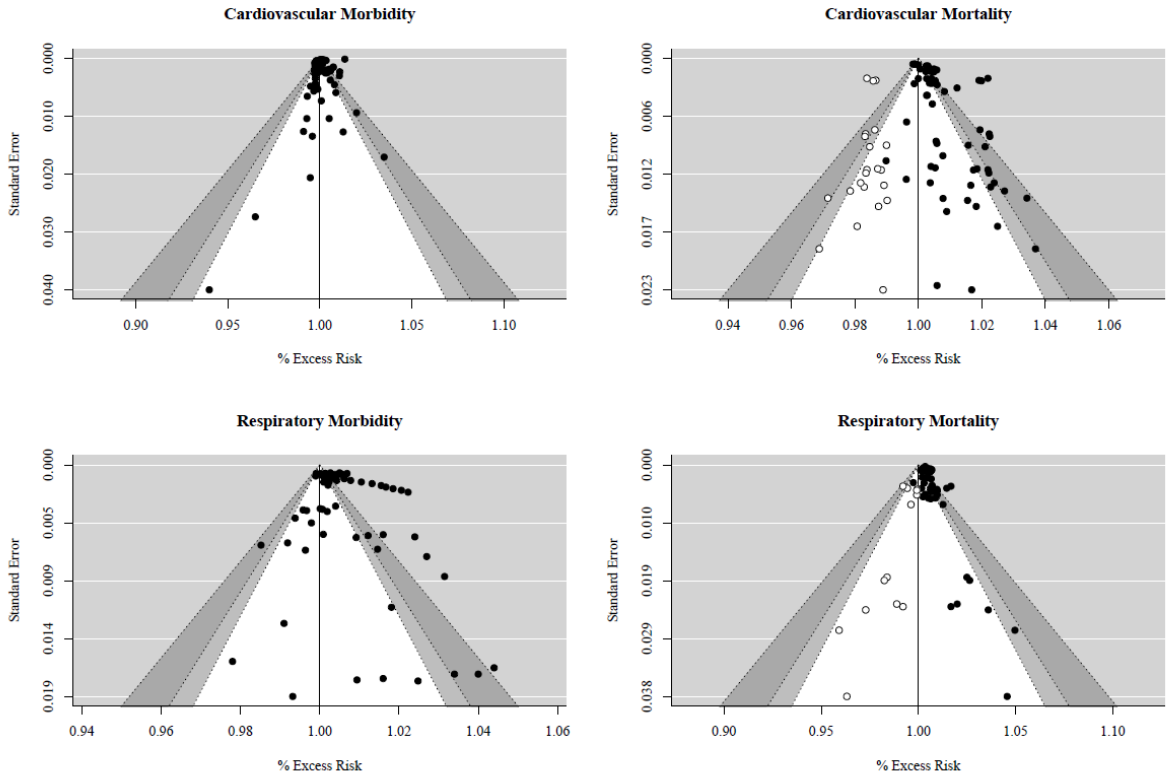
Appendix B4. Funnel plots with trim and fill, particulate matter

a) $PM_{2.5}$

Funnel plots

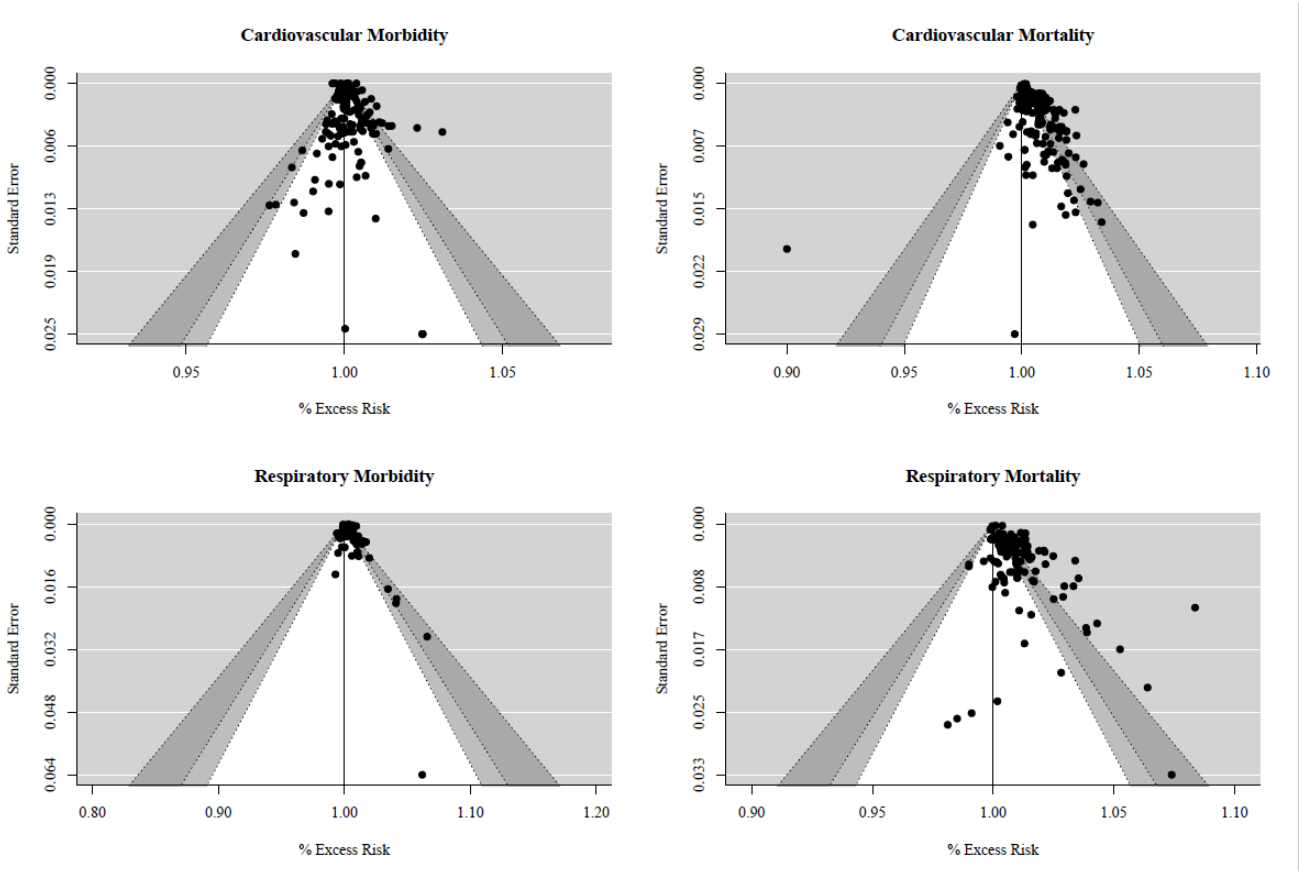


Funnel plots plus trim and fill

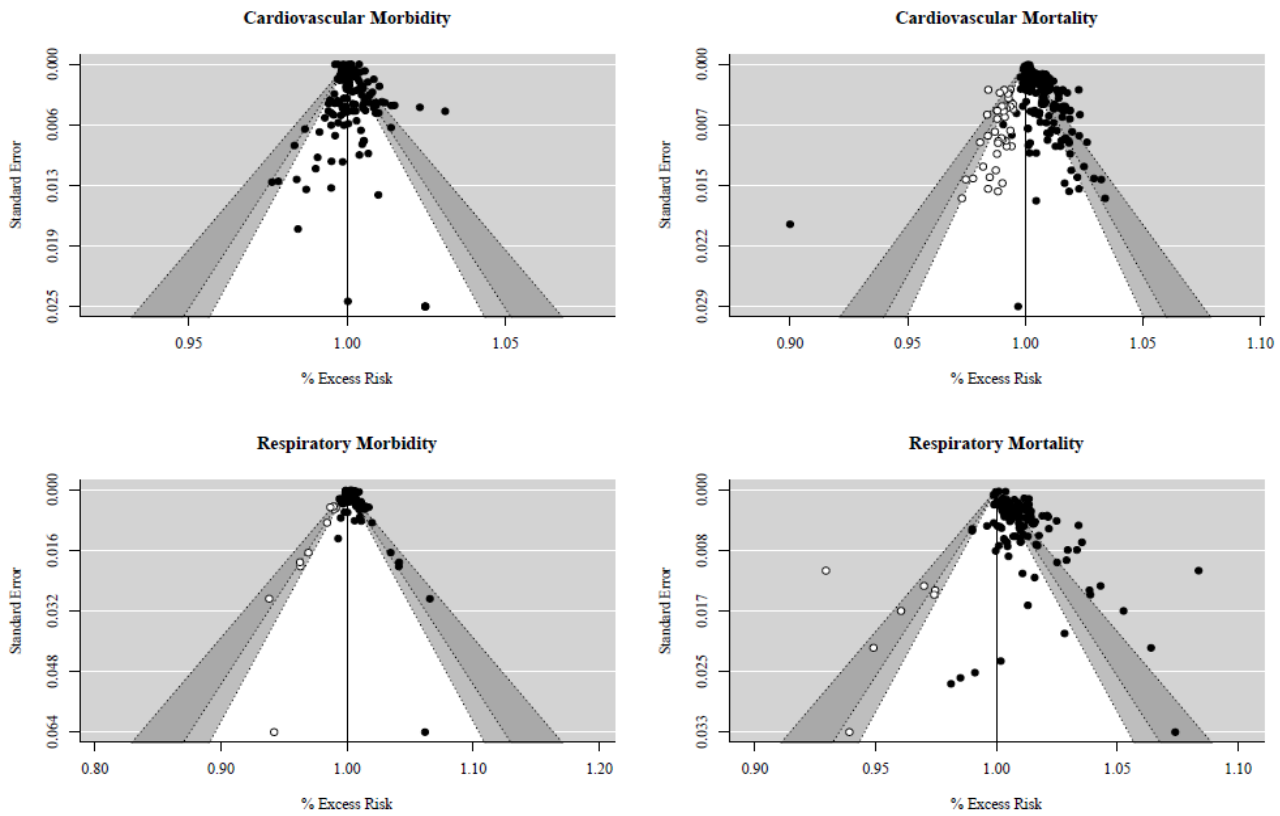


b) PM_{10}

Funnel plots



Funnel plots plus trim and fill



Appendix B5. Summary of included studies for meta-analysis examining gaseous pollutants

Author	Year	Study design	Study Period	City	Region	Outcome	SO_2	NOx	O_3	TSP	CO	Risk of bias
Qian, Z.	2013	Case-crossover	2003-2008	Shanghai	East Asia and Pacific	M(CV)	Yes	Yes	No	No	No	Moderate
Guo, Y.	2009	Case-crossover	2004-2006	Beijing	East Asia and Pacific	A (CV)	Yes	Yes	No	No	No	High
Xiang, H.	2013	Case-crossover	2006-2008	Wuhan	East Asia and Pacific	A (CV)	Yes	Yes	No	No	No	Moderate
Liu, Y.	2015	Case-crossover	2006-2009	Anshan	East Asia and Pacific	M(CV)	Yes	Yes	No	No	No	Unclear
Huang, F.	2016	Case-crossover	2013-2014	Beijing	East Asia and Pacific	A (CV)	No	Yes	No	No	Yes	Moderate
Abrutsky, R.	2012	Time-series	1996-2008	Buenos Aires	Latin America and Caribbean	M (CV)	No	No	No	No	Yes	Moderate
Capraz, O.	2016	Time-series	2007-2012	Istanbul	Europe and Central Asia	M (CV&R)	Yes	Yes	No	Yes	No	Moderate
Chen, G	2008	Time-series	2001-2004	Shanghai	East Asia and Pacific	M (CV&R)	Yes	Yes	No	No	No	Moderate
Chen, R.	2010	Time-series	2005-2007	Shanghai	East Asia and Pacific	A (CV&R)	Yes	No	Yes	Yes	No	Moderate
Chen, R.	2013	Time-series	1996-2008	Multi-City	East Asia and Pacific	M (CV&R)	Yes	Yes	No	No	No	Moderate
Costa, A.F.	2016	Time-series	2001-2011	Sao Paulo	Latin America and Caribbean	M (CV&R)	No	Yes	No	No	Yes	Moderate
de Freitas	2010	Time-series	2001-2006	Vitoria	Latin America and Caribbean	A (CV)	No	Yes	Yes	No	No	Moderate
Gharehchachi, E.	2013	Time-series	2008-2010	Shiraz	Middle East and North Africa	A (CV&R)	Yes	Yes	No	No	No	High
Hosseinpoor, A.R	2005	Time-series	1996-2001	Tehran	Middle East and North Africa	A (CV)	Yes	Yes	Yes	No	Yes	Unclear

Kan, H.	2003	Time-series	2000-2001	Shanghai	East Asia and Pacific	M (CV&R)	Yes	Yes	No	No	No	Moderate
Kan, H.	2010	Time-series	2001-2004	Shanghai	East Asia and Pacific	M (CV&R)	Yes	Yes	Yes	No	No	Moderate
Kan, H.	2003	Time-series	2001-2002	Shanghai	East Asia and Pacific	M (CV)	Yes	Yes	No	No	No	Unclear
Kan, H.	2008	Time-series	2001-2004	Shanghai	East Asia and Pacific	M (CV&R)	Yes	Yes	Yes	No	No	Moderate
Kan, H.	2010	Time-series	1999-2004	Multi-City	East Asia and Pacific	M (CV&R)	Yes	Yes	Yes	No	No	Moderate
Meng, X.	2013	Time-series	1996-2008*	Multi-City	East Asia and Pacific	M (R)	Yes	Yes	No	No	No	Moderate
Nascimento, L.F.	2012	Time-series	2007-2008	San Jose dos Campos	Latin America and Caribbean	A (C)	Yes	No	Yes	No	No	Unclear
Phung, D.	2016	Time-series	2004-2007	Ho Chi Minh City	East Asia and Pacific	A (CV&M)	Yes	Yes	Yes	No	No	Moderate
Qian, Z.	2010	Time-series	2000-2004	Wuhan	East Asia and Pacific	M (CV&R)	Yes	Yes	Yes	No	No	Moderate
Qian, Z.	2007	Time-series	2000-2004	Wuhan	East Asia and Pacific	M (CV&R)	Yes	Yes	Yes	No	No	Moderate
Romieu, I.	2012	Time-series	1997-2005	Multi-City	Latin America and Caribbean	M (CV&R)	No	No	Yes	No	No	Moderate
Stojic, S.S	2016	Time-series	2009-2014	Belgrade	Europe and Central Asia	M (CV&R)	Yes	Yes	No	No	No	Moderate
Tao, Y.	2012	Time-series	2006-2008	Multi-City	East Asia and Pacific	M (CV&R)	No	Yes	Yes	No	No	Moderate
Tong, L.	2014	Time-series	2008-2011	Tianjin	East Asia and Pacific	A (CV)	Yes	No	No	No	No	Unclear
Wong, C.M	2008	Time-series	1999-2004	Multi-City	East Asia and Pacific	M (CV&R)	Yes	Yes	No	No	No	Moderate

Xie, J.	2014	Time-series	2010-2012	Shanghai	East Asia and Pacific	A (CV)	Yes	Yes	No	No	No	High
Yu, I.T.S	2012	Time-series	2006-2009	Guangzhou	East Asia and Pacific	M (CV&R)	Yes	Yes	No	No	No	Moderate
Zhang, F.	2011	Time-series	2003-2008	Beijing	East Asia and Pacific	M (CV&R)	Yes	Yes	No	No	No	Moderate
Zhang, Y	2015	Time-series	2009-2011	Beijing	East Asia and Pacific	A (CV&R)	Yes	Yes	No	No	No	Moderate
Zhang, Y	2006	Time-series	2001-2004	Shanghai	East Asia and Pacific	M (CV&R)	No	No	Yes	No	No	Moderate
Zhang, Z.L	2014	Time-series	2008-2011	Guangzhou	East Asia and Pacific	A (CV&R)	Yes	Yes	No	No	No	Moderate
Amancio, C.T	2014	Time-series	2005-2009	San Jose dos Campos	Latin America and Caribbean	M (CV&R)	Yes	No	No	No	No	High
Arbex, M.A	2009	Time-series	2001-2003	Sao Paulo	Latin America and Caribbean	A (R)	Yes	No	No	No	Yes	Moderate
Tao, Y.	2011	Time-series	2006-2008	Multi-City	East Asia and Pacific	M (CV&R)	Yes	Yes	No	No	Yes	Moderate
Tao, Y.	2014	Time-series	2001-2005	Lanzhou	East Asia and Pacific	A (R)	Yes	Yes	No	No	No	High
Cai, J.	2014	Time-series	2005-2011	Shanghai	East Asia and Pacific	A (R)	Yes	Yes	No	No	No	Moderate
Leitte, A.M	2011	Time-series	2004-2006	Beijing	East Asia and Pacific	A (R)	Yes	Yes	No	No	No	High
Li, G.	2016	Time-series	2002-2006	Tianjin	East Asia and Pacific	M (CV)	Yes	Yes	No	No	No	Moderate
Mahiyuddin, W.R.V	2013	Time-series	2000-2006	Klang-Valley	East Asia and Pacific	M (CV&R)	No	Yes	Yes	No	No	Moderate
Su, C.	2016	Time-series	2007-2008	Beijing	East Asia and Pacific	A (CV &R)	Yes	Yes	No	No	No	Moderate

Yang, Y.	2015	Time-series	2009-2010	Beijing	East Asia and Pacific	M (R)	No	Yes	No	No	No	Moderate
Zheng, S.	2013	Time-series	2001-2005	Lanzhou	East Asia and Pacific	A (C)	Yes	Yes	No	No	No	Moderate
Yang, C.	2012	Time-series	2006-2008	Suzhou	East Asia and Pacific	M (CV&R)	No	No	Yes	No	No	Moderate
Lin, C.	2003	Time-series	1994-1995	Sao Paulo	Latin America and Caribbean	A (CV)	Yes	No	No	No	Yes	Moderate
Zahari, M.	2014	Time-series	2004-2009	Multi-City	East Asia and Pacific	A (R)	No	No	No	No	Yes	High
Yang, Y.	2013	Time-series	2009-2010	Beijing	East Asia and Pacific	M (CV&R)	No	Yes	No	No	No	Moderate
Sharovsky, R.	2004	Time-series	1996-1998	Sao Paulo	Latin America and Caribbean	M (R)	Yes	No	No	No	Yes	Moderate
Chen, R.	2012	Time-series	2001-2008	Multi-City	East Asia and Pacific	M (CV)	Yes	Yes	No	No	No	Moderate
Chen, R.	2012	Time-series	2001-2008	Multi-City	East Asia and Pacific	M (CV&R)	No	Yes	No	No	No	Moderate
Chen, R.	2012	Time-series	2001-2010	Multi-City	East Asia and Pacific	M (CV&R)	Yes	No	No	No	No	Moderate
Abrutsky, R.	2013	Time-series	2005-2009	Multi-City	Latin America and Caribbean	M (R)	No	No	No	No	Yes	Moderate
Guo, L.J	2014	Time-series	2010-2011	Shanghai	East Asia and Pacific	A (R)	Yes	Yes	No	No	No	Moderate
Zhao, A.	2014	Time-series	2010-2011	Shanghai	East Asia and Pacific	A (C)	Yes	Yes	No	No	No	Moderate
Gavinier, S.	2014	Time-series	2007-2011	Sao Paulo	Latin America and Caribbean	A (CV)	No	Yes	Yes	No	No	High
Winchmann, J	2012	Both	2001-2006	Cape Town	Africa	M (CV & R)	No	Yes	Yes	Yes	No	High

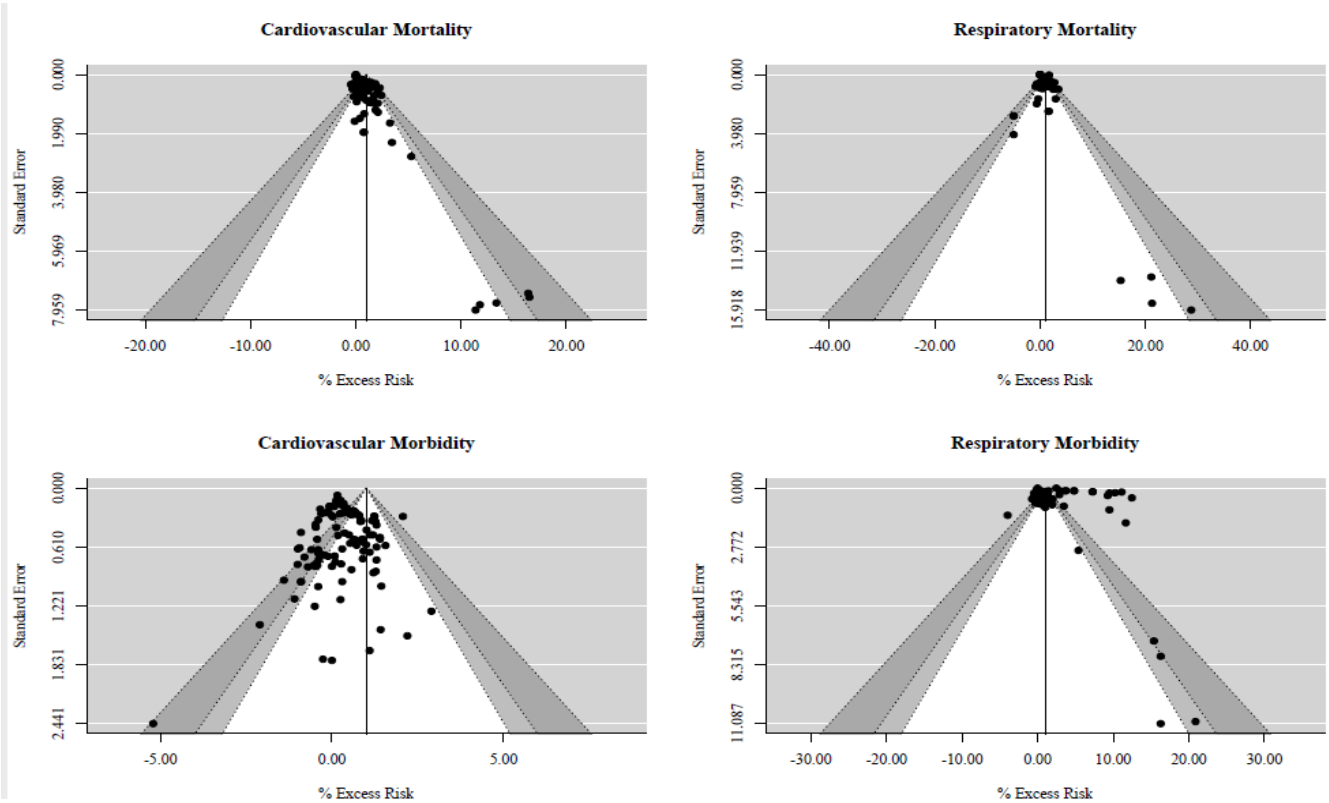
Guo, Y.	2010	Both	2005-2007	Tianjin	East Asia and Pacific	M (CV)	No	Yes	Yes	No	No	Unclear

Abbreviations: M, mortality; A, admissions; CV, cardiovascular; R, respiratory; NOx, nitrogen oxides; SO_2, sulphur dioxide; O_3, ozone; CO, carbon monoxide

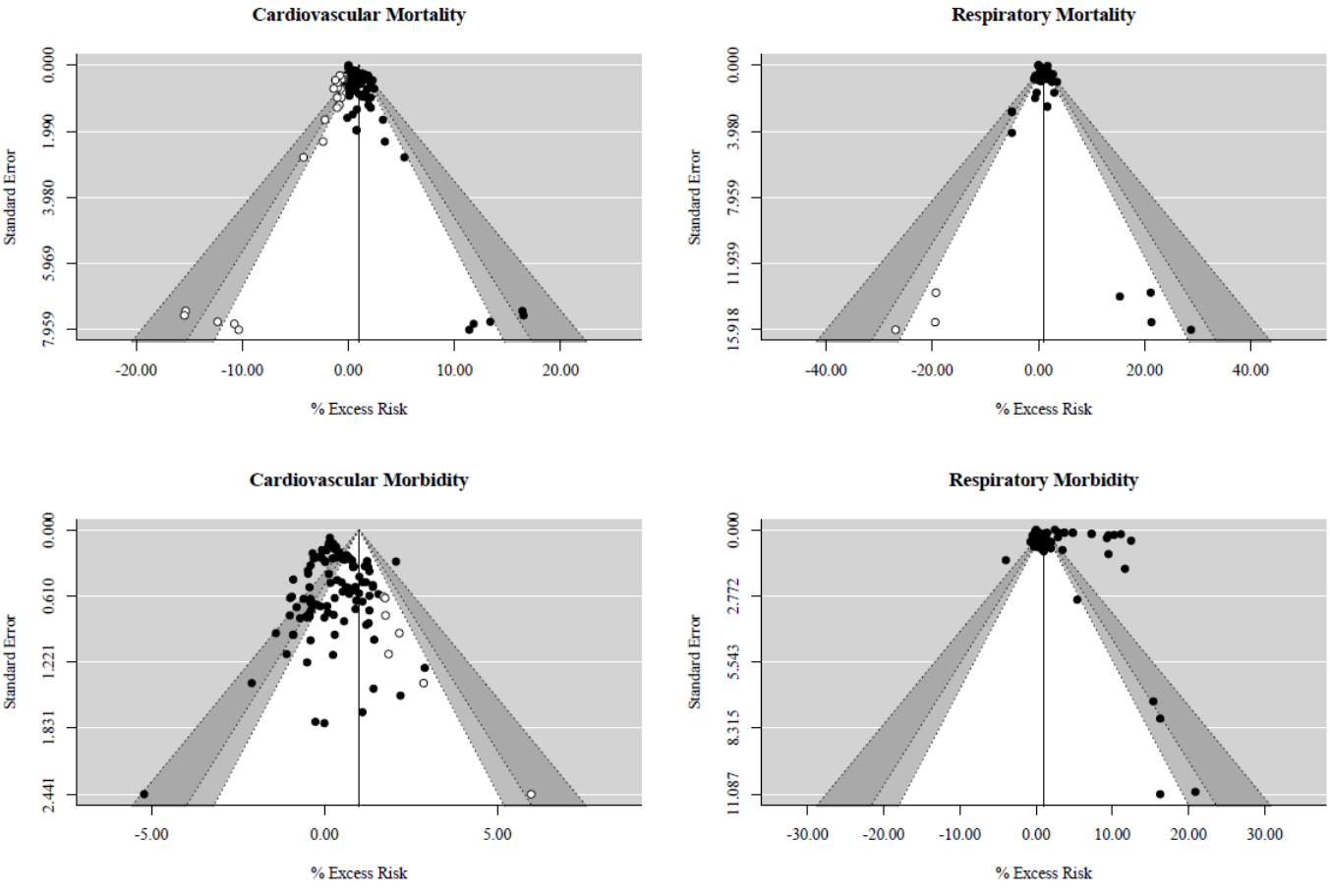
Appendix B6. Funnel plots with trim and fill, gaseous pollutants

a) SO_2

Funnel plots

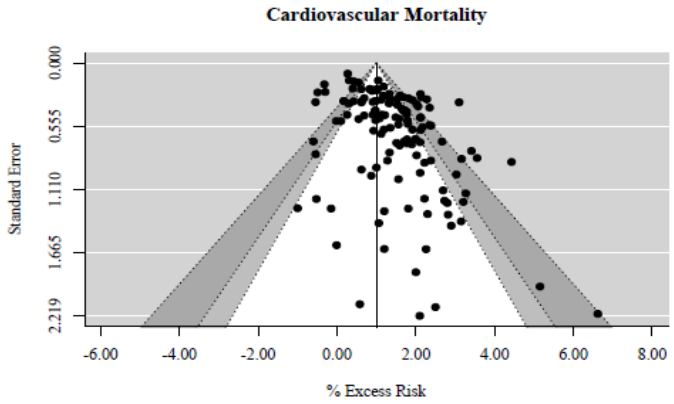


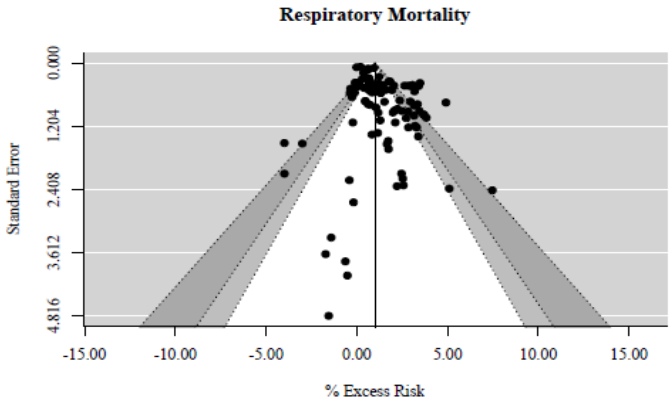
Funnel plots with trim and fill

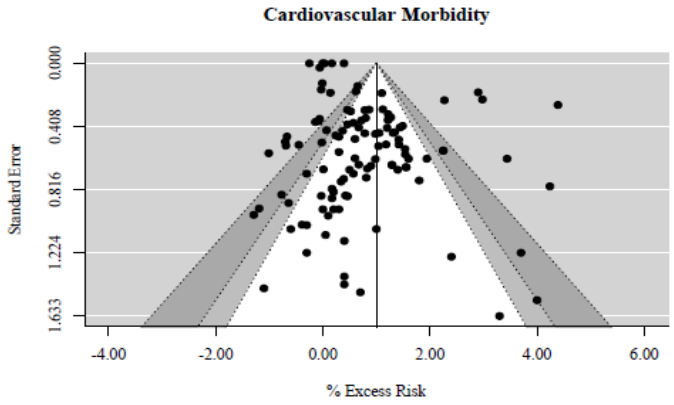


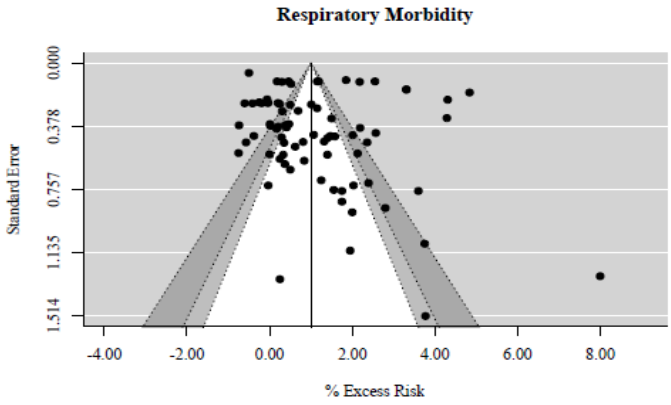
b) NO_2

Funnel plots

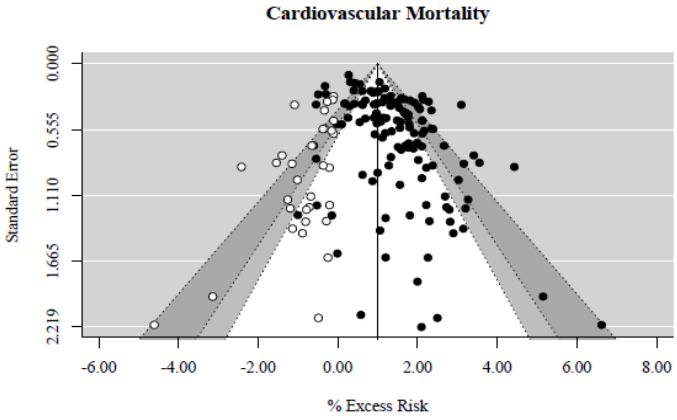


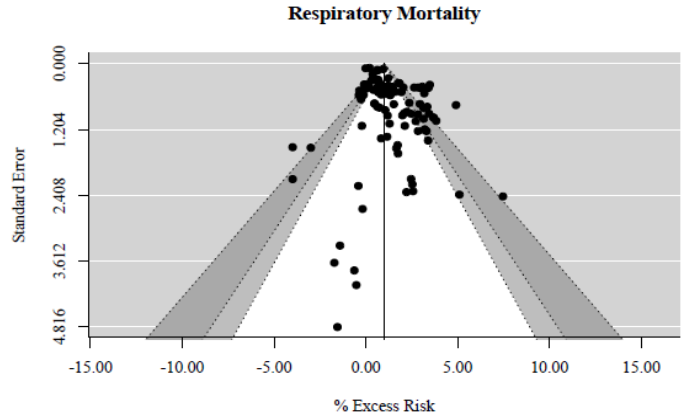


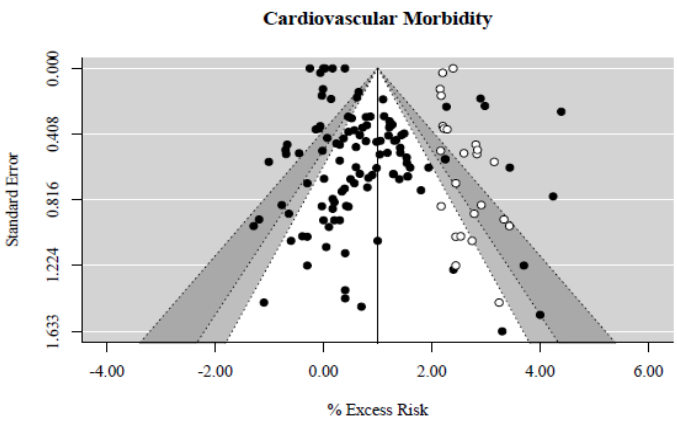


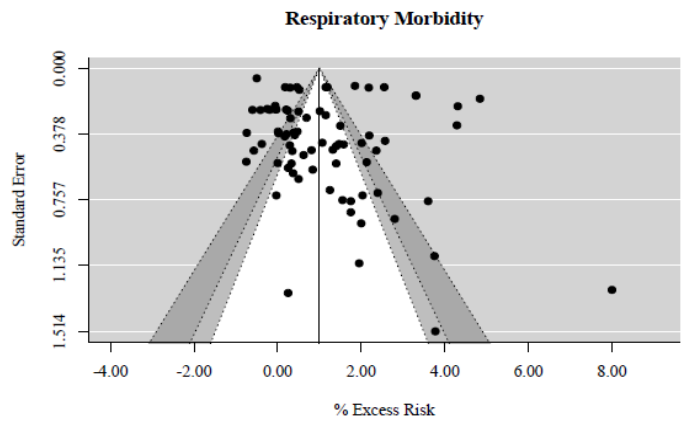


Funnel plots with trim and fill



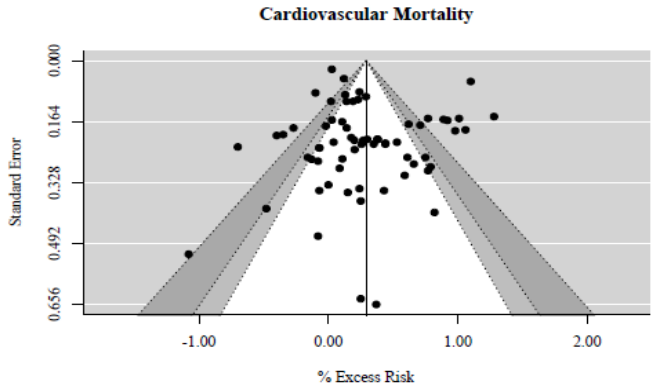


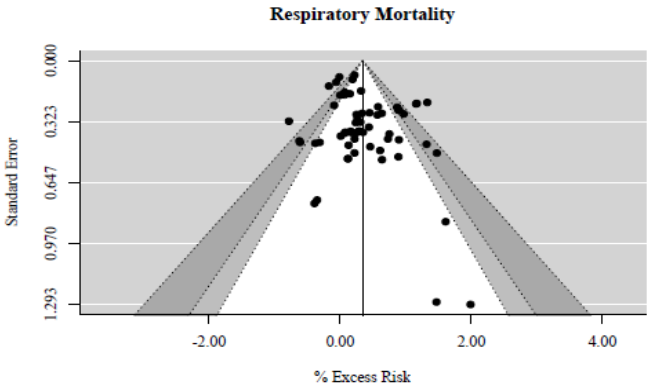


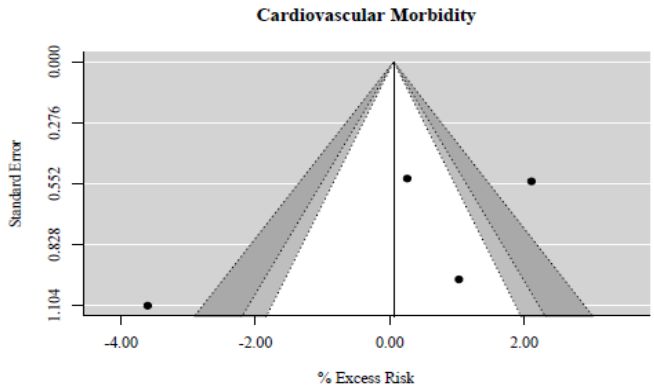


c) O_3

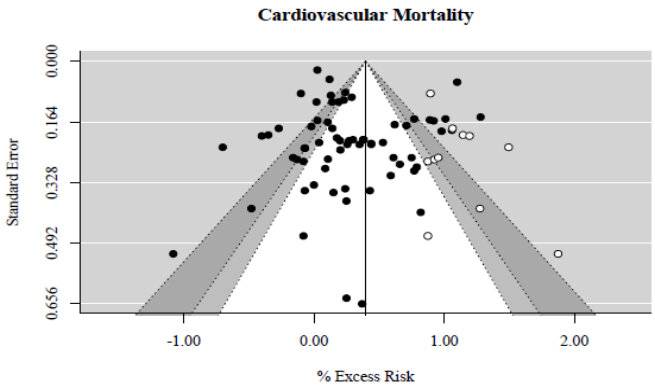
Funnel plots

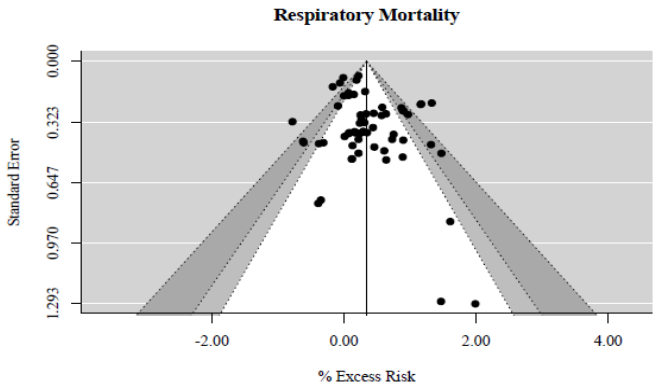


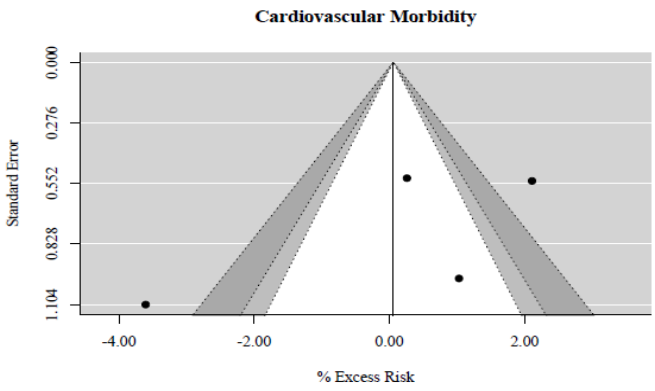




Funnel plots with trim and fill

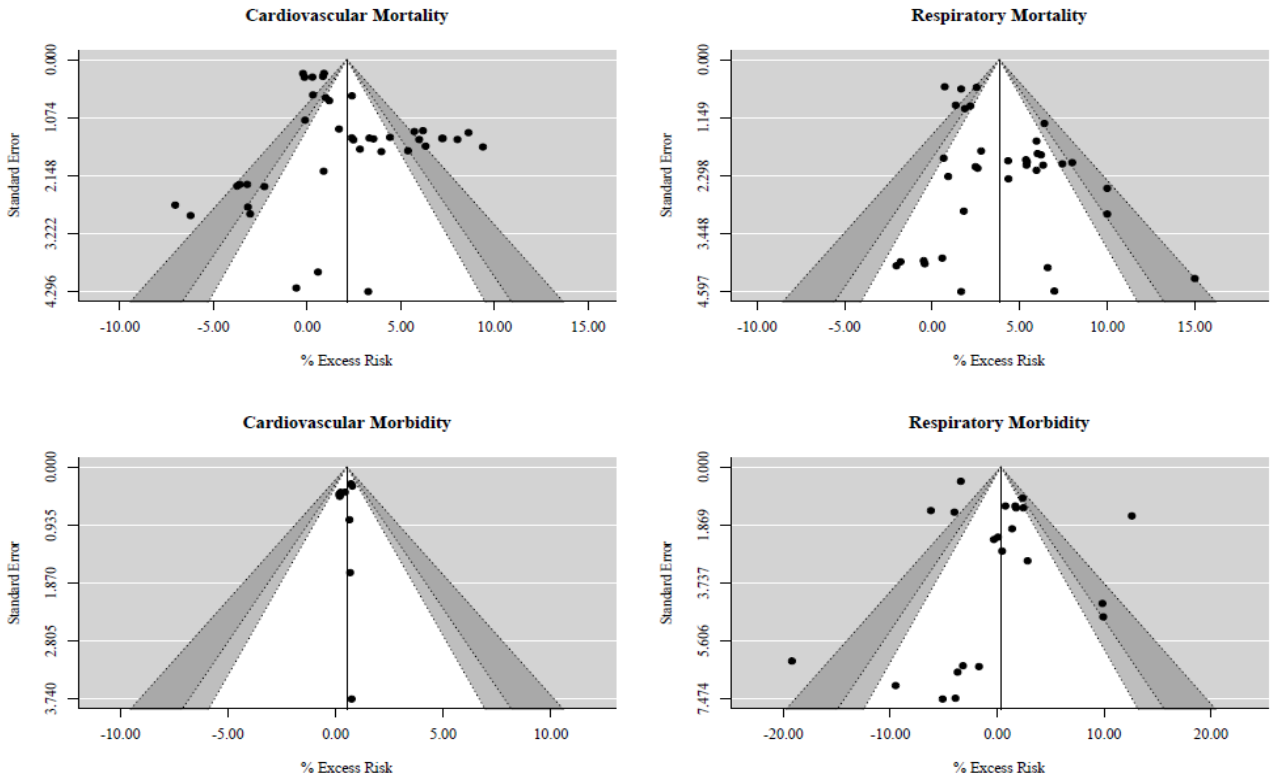




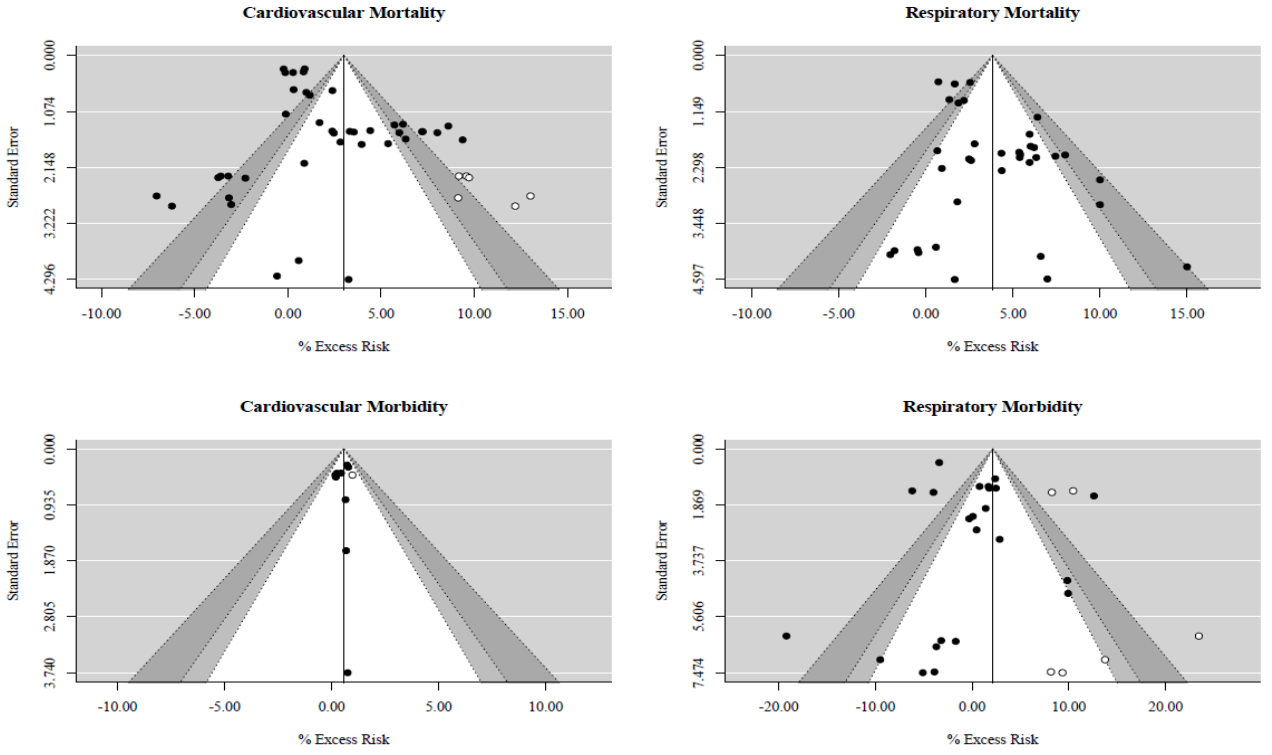


d) CO

Funnel plots



Funnel plots with trim and fill



Appendix B7. Search terms for studies examining chronic health effects

Exposure (combined with "OR")	Outcome (combined with "OR")	Setting (combined with "OR")
1. Nitrogen dioxide	1. Cardiovascular disease	1. China
2. Sulphur dioxide	2. Ischaemic heart disease	2. Asia
3. Sulphur dioxide	3. Coronary heart disease	
4. Ozone	4. Stroke	
5. Particulate matter	5. Hypertension	
6. Particulates	6. Blood pressure	
7. Carbon monoxide	7. Respiratory disease	
8. PM_{10}	8. Chronic obstructive pulmonary disease	
9. $PM_{2.5}$	9. COPD	
10. NO_2	10. Obstructive lung disease	
11. SO_2	11. Emphysema	
12. O3	12. Pneumonia	
13. CO	13. Bronchitis	
14. Ambient air pollution		
15. Outdoor air pollution		
16. Air pollution		

Terms combined with "AND" as below

Final search
(((((“particulate matter” OR “particulates” OR “nitrogen dioxide” OR “sulphur dioxide” OR “sulfur dioxide” OR “ozone” OR “carbon monoxide” OR “PM10” OR “PM2.5” OR “NO2” OR “ SO2” OR “O3” OR “CO” OR “ambient air pollution” OR “outdoor air pollution” OR air pollution”)) AND ((“cardiovascular disease” OR “ischemic heart disease” OR “coronary heart disease” OR “stroke” OR “blood pressure” OR “hypertension” OR “respiratory disease” OR “chronic obstructive pulmonary disease” OR “COPD” OR “obstructive lung disease” OR “emphysema” OR “pneumonia” OR “bronchitis”))) AND (“China” OR “Asia”)

Appendix C. Supplementary data for Chapter 5

Appendix C1. Missing days and implausible AAP measurements across the five CKB regions

Table C1.1 Missing days of AAP measurements by region and year of study

Region and pollutant	Missing days (n=)	% of total study period	Missing days by year of study				
			2010-2012	2013	2014	2015	2016
Ozone							
Harbin	104	7.2	-	54	29	17	4
Qingdao	151	10.5	-	108	22	17	4
Suzhou	43	1.7	-	38	1	-	4
Liuzhou	62	5.2	-	14	27	17	4
Haikou	121	8.4	-	70	30	17	4
All other pollutants*							
Harbin	15	1.0	-	13	1	1	-
Qingdao	15	1.5	-	20	1	1	-
Suzhou	39	1.5	-	38	1	-	-
Liuzhou	2	6.1	-	-	1	1	-
Haikou	15	1.0	-	13	1	1	-

* Nitrogen dioxide, sulphur dioxide, particulate matter<10 μm, particulate matter <2.5 μm, carbon monoxide

Table C1.2 Possible AAP measurement errors reflecting implausible AAP levels in Suzhou

Date	SO_2	NO_2	CO	PM_{10}	$PM_{2.5}$	O_3	Temp	RH
02/03/2012	31.00	58.00	1.046	66.00	39.00	18.00	6.60	85.30
03/03/2012	12.00	63.00	0.582	**1.00**	63.00	33.00	6.40	81.50
04/03/2012	22.00	66.00	1.105	50.00	86.00	18.00	7.50	91.30
02/05/2012	16.00	49.00	0.917	55.00	35.00	28.00	18.70	79.80
03/05/2012	28.00	118.00	1.035	255.00	102.00	**1.00**	21.70	63.00
04/05/2012	46.00	85.00	1.172	182.00	92.00	97.00	22.40	48.00

*Bold indicates implausible AAP value, replaced by previous day's concentration
Abbreviations: SO_2, sulphur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter<2.5 μm; O_3, ozone; Temp, temperature (degrees Celsius); RH, relative humidity (%)

Appendix C2. Counts and proportions* of fatal cardio-respiratory disease spells by region

Summaries	Harbin (n=54,894)	Qingdao (n=34,503)	Suzhou (n=52,617)	Liuzhou (n=47,920)	Haikou (n=29,086)	Total (n=219,020)
Fatal cases						
All major cardiovascular diseases (%)	1268 (3.86)	410 (4.19)	664 (8.91)	715 (5.93)	632 (5.60)	3689 (5.03)
All major respiratory diseases (%)	287 (5.85)	51 (2.45)	108 (1.55)	180 (4.61)	108 (3.38)	734 (3.48)
Any-type stroke (%)	571 (3.25)	109 (5.13)	282 (3.73)	350 (7.70)	313 (6.79)	1625 (5.12)

*Proportions of that cause-specific endpoint

Appendix C3. Frequencies of chronic obstructive disease (COPD) and ischaemic heart disease (IHD) spells, respectively across the five CKB urban regions (2013-2016*)

Summaries	Harbin (n=54,894)	Qingdao (n=34,503)	Suzhou (n=52,617)	Liuzhou (n=47,920)	Haikou (n=29,086)	Total (n=219,020)
COPD (J41-J44†)						
Total	1082	396	1608	1027	621	4734
First-time	515	151	580	315	265	1826
Readmissions	567	245	1028	712	356	2908
Mean daily count	0.75	0.27	0.63	0.86	0.43	-
Max daily count	5	3	6	6	6	-
Fatal cases (%)	124 (11.46)	16 (4.04)	66 (4.10)	49 (4.77)	65 (10.47)	320 (6.76)
IHD (I20-I25†)						
Total	11,667	4312	841	3630	1590	22,040
First-time	4059	1552	402	1469	792	8274
Readmissions	7608	2760	439	2161	798	13,766
Mean daily count	8.09	3.00	0.33	3.05	1.10	-
Max daily count	34	12	4	10	6	-
Fatal cases (%)	571 (4.89)	109 (2.53)	282 (33.53)	350 (9.64)	313 (19.69)	1625 (7.37)

*Suzhou 2010-2016

† International Classification of Diseases 10th edition

Appendix C4. Methodology for application of moving average filters in the time-series plots and analysis presented in this thesis

The moving average filter is a common approach used to smooth time-series data removing unwanted noise to better expose the signal of interest as well as highlight longer term trends or cycles. To calculate moving average values at time t, each value is calculated as the average of observations before and/or after t. The following specific methodologies were employed to calculate the moving averages used in the following respective parts of this thesis:

1. AAP time-series plots

   To apply moving average filters for use in the time-series plots **Figure 5.2,** the following approach was used to apply a 10-day moving average filter to each value using the "sma" function in the "smooth" R package. [482]

Table C4.1 Time-series data before moving average

Date	Lag 0 SO_2	Lag 0 NO_2	Lag 0 CO	Lag 0 PM_{10}	Lag 0 $PM_{2.5}$	Lag 0 O_3	Temperature
2010-01-01	55	103	1.100	189	108	10	4.6
2010-01-02	52	93	1.187	186	115	7	8.6
2010-01-03	38	66	0.705	126	72	6	7.9
2010-01-04	54	74	1.102	185	110	10	5.8
2010-01-05	79	55	1.213	115	78	11	-0.3
2010-01-06	70	67	0.955	103	69	19	1.5
2010-01-07	77	70	0.857	129	83	34	1.1
2010-01-08	99	88	1.290	126	80	54	2.0
2010-01-09	84	110	1.218	203	135	54	3.6
2010-01-10	49	61	1.117	129	95	54	5.9

Abbreviations; NO_2, Nitrogen dioxide; SO_2, sulphur dioxide, PM_{10}, particulate matter<10 µm; $PM_{2.5}$ particulate matter <2.5 µm; CO, carbon monoxide; O_3, ozone. All pollutants measured in µm/m^3 (except CO, mg/m^3)

The application of 10-day bi-directional moving average would result in the following time-series data;

Table C4.2. Time-series data following application of moving average filter

Date	Lag 0 SO_2	Lag 0 NO_2	Lag 0 CO	Lag 0 PM_{10}	Lag 0 $PM_{2.5}$	Lag 0 O_3	Temperature
2010-01-01	NA	NA	NA	NA	NA	NA	NA
2010-01-02	NA	NA	NA	NA	NA	NA	NA
2010-01-03	NA	NA	NA	NA	NA	NA	NA
2010-01-04	NA	NA	NA	NA	NA	NA	NA
2010-01-05	65.7	78.6	1.074	149.1	94.5	25.9	4.07
2010-01-06	66.6	73.8	1.073	144.0	93.8	30.3	3.90
2010-01-07	69.9	71.3	1.050	137.9	89.8	35.0	3.18
2010-01-08	72.3	70.5	1.036	137.0	87.7	39.8	2.24
2010-01-09	78.2	72.6	1.020	133.5	84.8	44.4	1.72
2010-01-10	77.6	75.1	1.009	140.2	87.8	45.4	2.01

Abbreviations; NO_2, Nitrogen dioxide; SO_2, sulphur dioxide, PM_{10}, particulate matter<10 µm; $PM_{2.5}$ particulate matter <2.5 µm; CO, carbon monoxide; O_3, ozone. All pollutants measured in µm/m^3 (except CO, mg/m^3)

2. Cardio-respiratory spell time-series plots

   The same methodology was used as above to apply moving average filters to spells counts in **Figures 5.3 to 5.5,** again using the created function and a bi-directional 10-day moving average lag

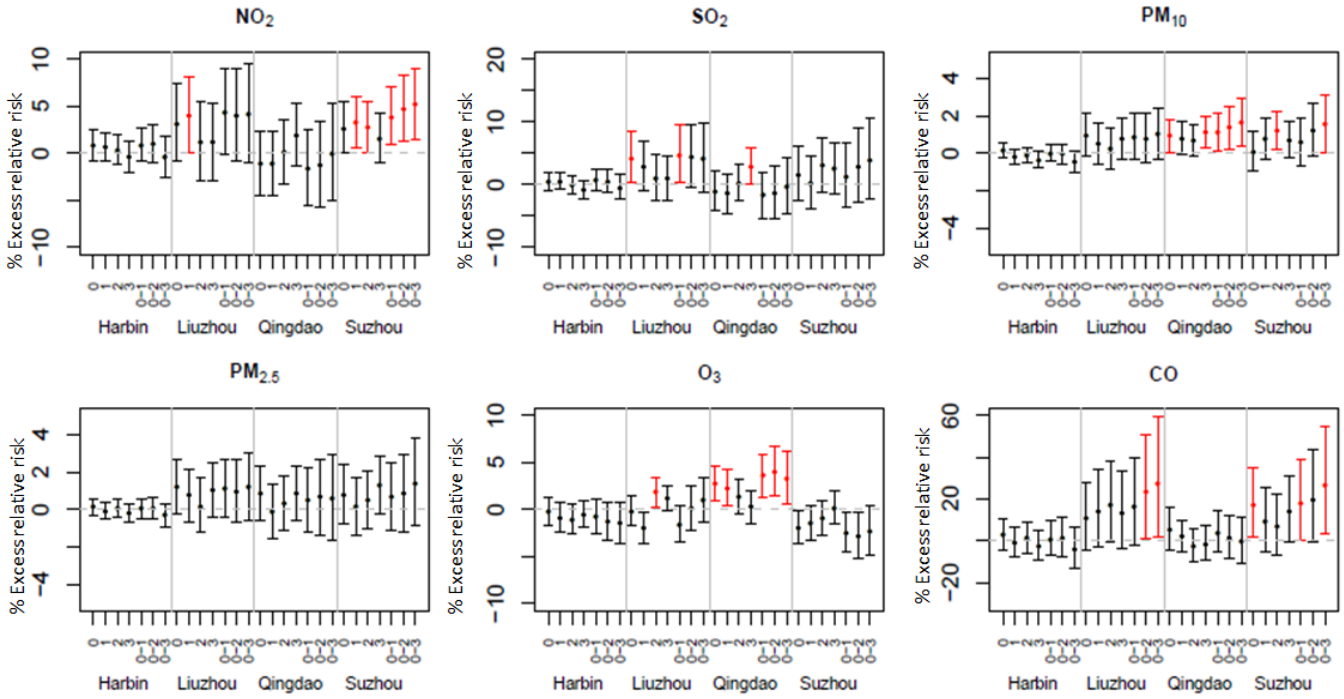
3. Moving average measures of lagged AAP used as exposures for time-series and case-crossover analyses

   Since moving average lagged measures of AAP are the moving average measures of previous exposure to AAP levels these took the average AAP levels from the previous days only, e.g. application of the moving average filter on the values “101, 103, 93, 89, 97, 65, 32” would become “NA, 102.0, 98.0, 91.0, 93.0, 81.0, 48.5”.

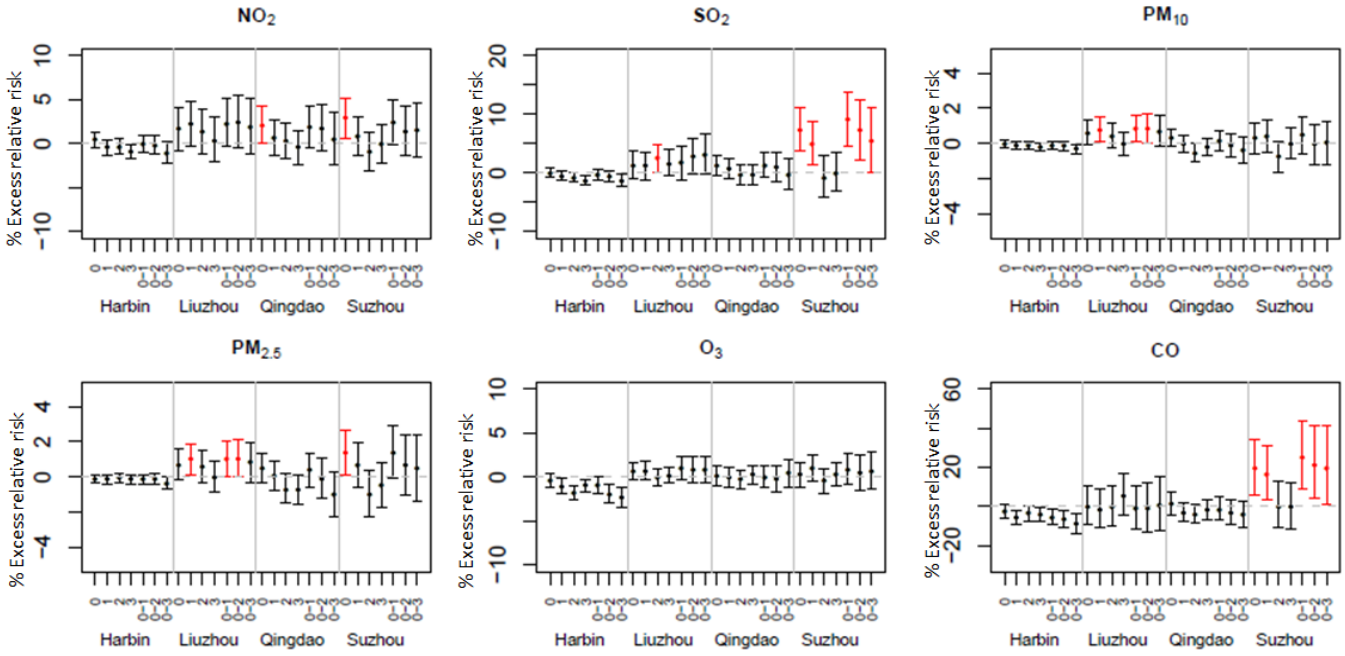
Appendix C5. Case-crossover results for the associations between acute AAP exposure and cardio-respiratory hospitalisations in the five CKB urban regions by admission type

Figure C5.1 Percent excess risk of hospitalisation for major cardiovascular disease associated with a 10μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using case- crossover analysis**

a) First-time spells

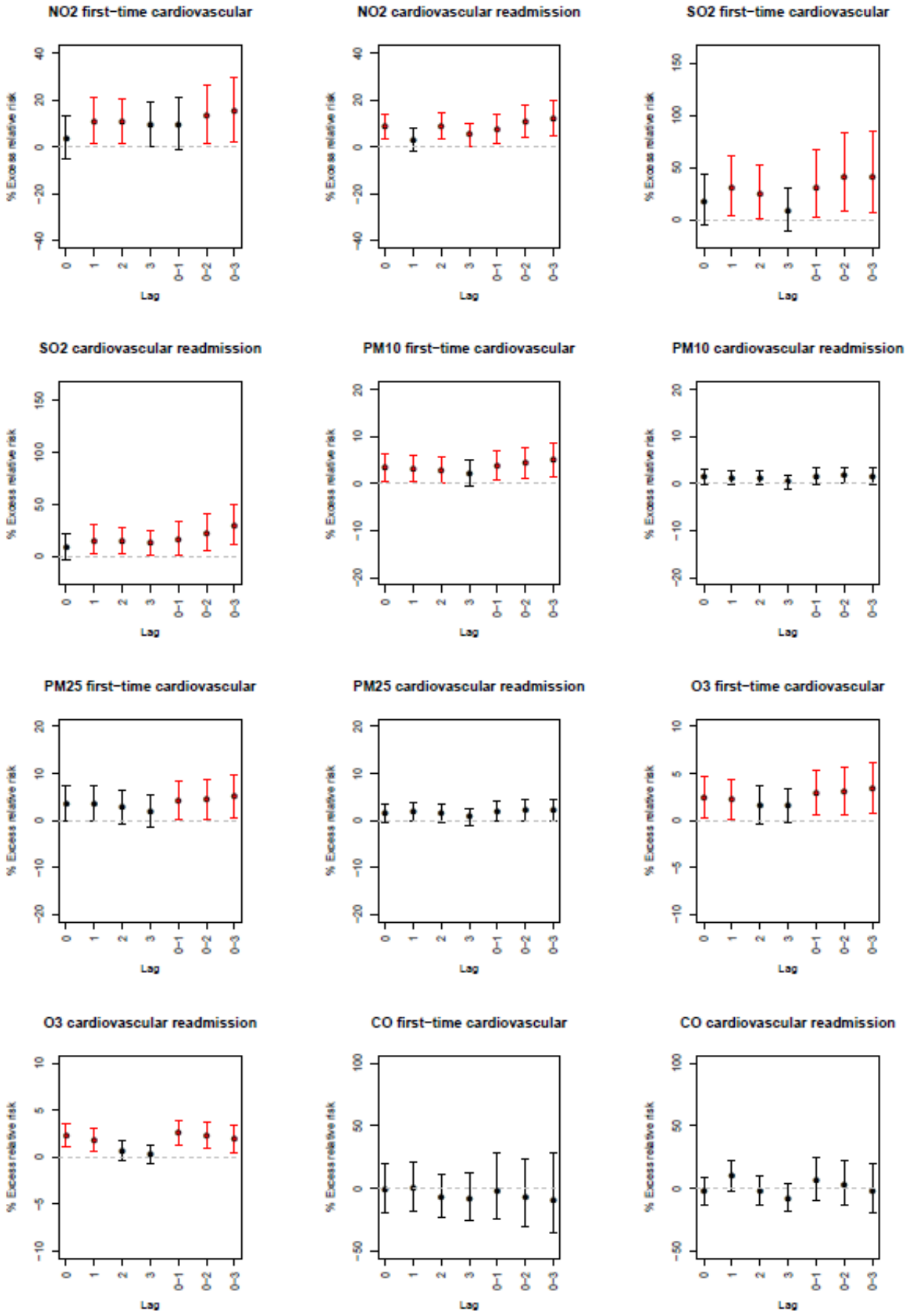


b) Readmissions



*100 μg/m^3 for CO
**Suzhou (2010-2016
p<0.05

Figure C5.2 Percent excess risk of hospitalisation for major cardiovascular disease associated with a 10 μg/m^3 increase* in AAP in Haikou (2013-2016) using case- crossover analysis

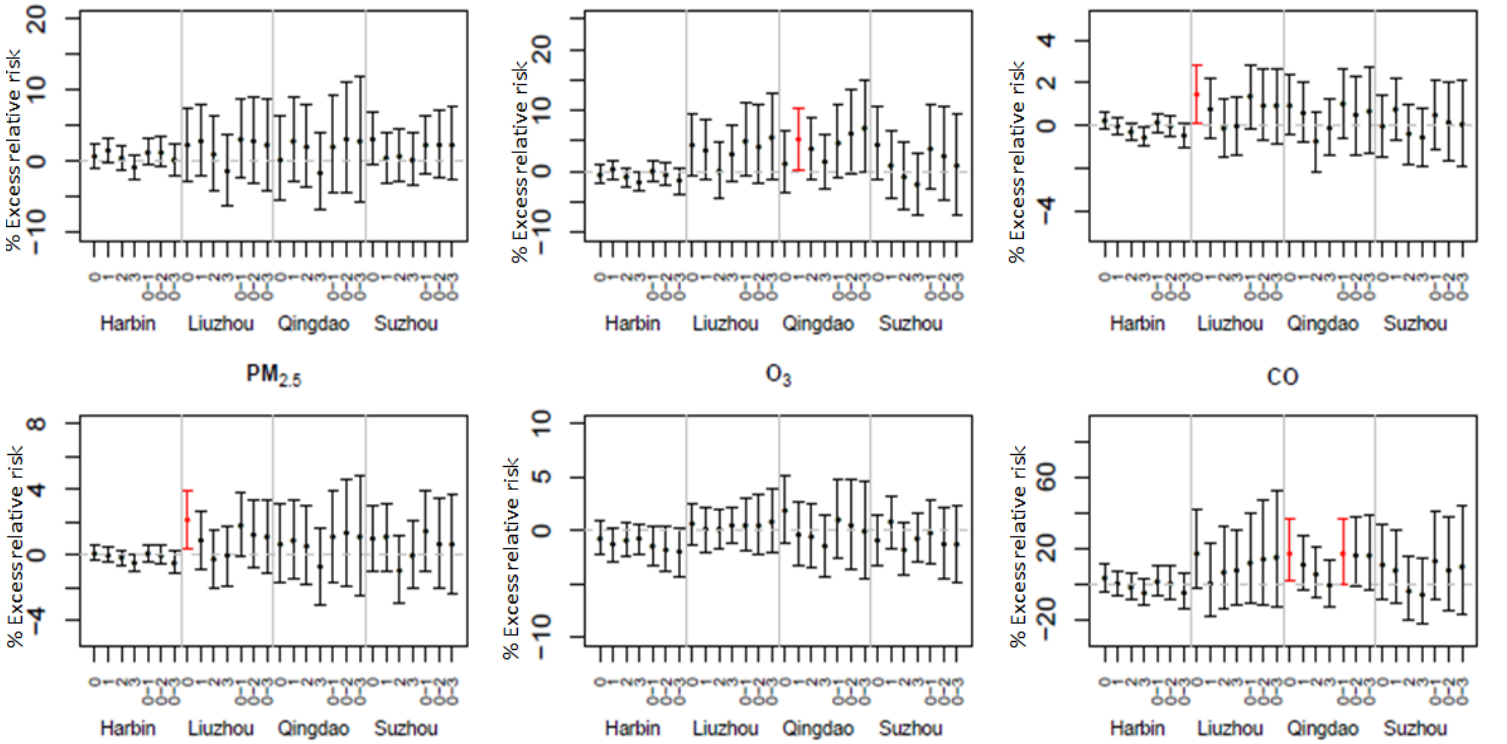


*100 μg/m^3 for CO

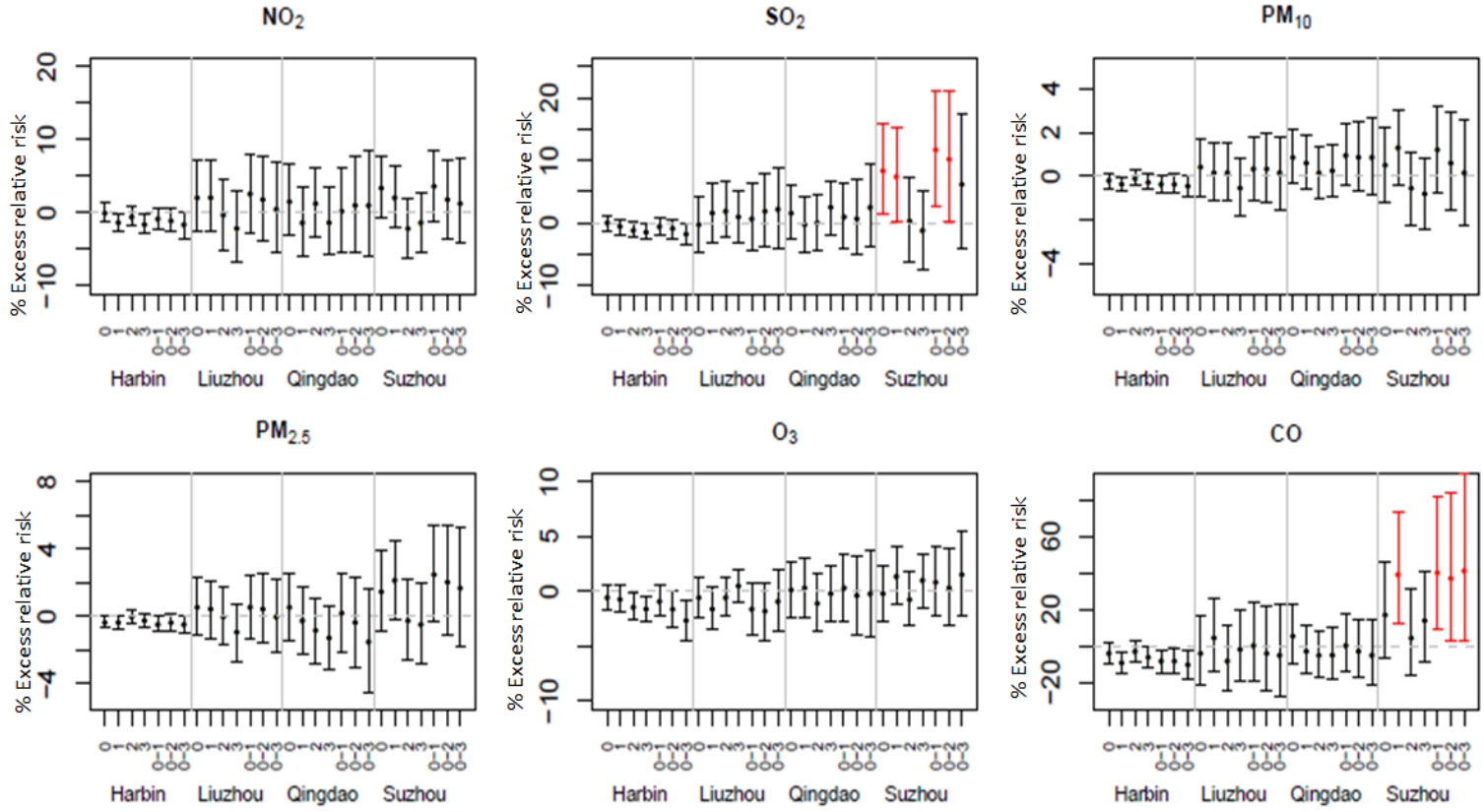
p<0.05

Figure C5.3 Percent excess risk of hospitalisation for all-type stroke associated with a 10 μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using case-crossover analysis**

a) First-time spells

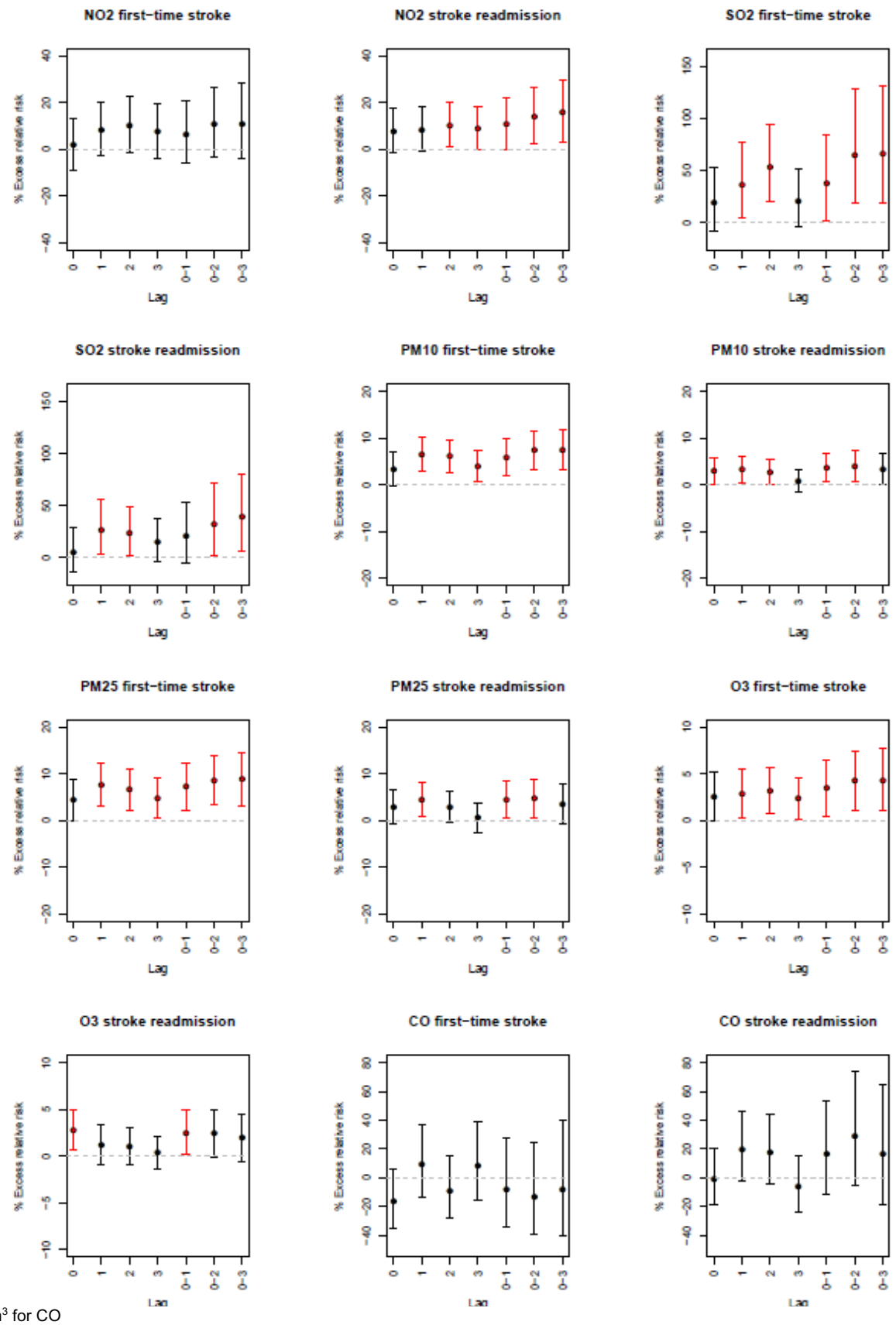


b) Readmissions



*100 μg/m^3 for CO
**Suzhou (2010-2016
p<0.05

Figure C5.4 Percent excess risk of hospitalisation for all-type stroke associated with a 10 μg/m^3 increase* in AAP in Haikou (2013-2016) using case- crossover analysis

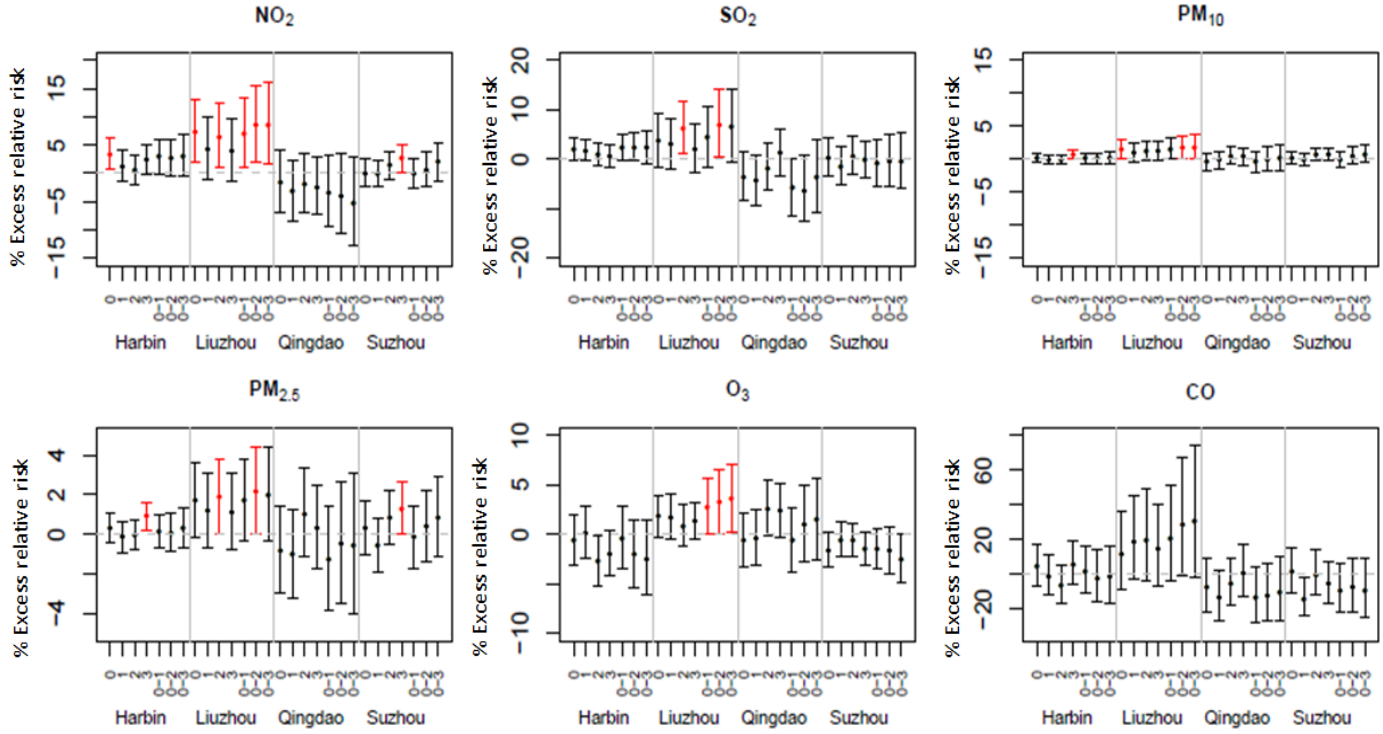


*100 μg/m^3 for CO

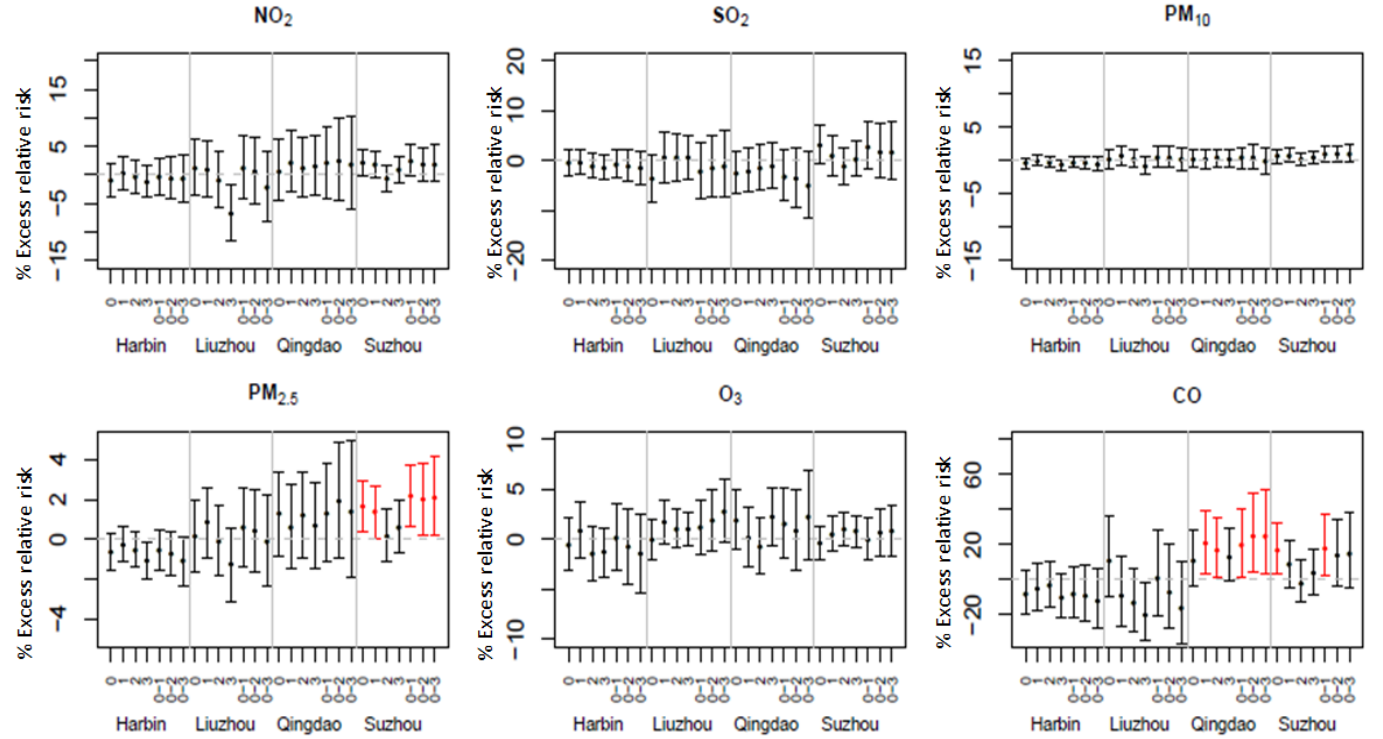
p<0.05

Figure C5.5 Percent excess risk of hospitalisation for major respiratory disease associated with a 10 μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using case-crossover analysis**

a) First-time spells

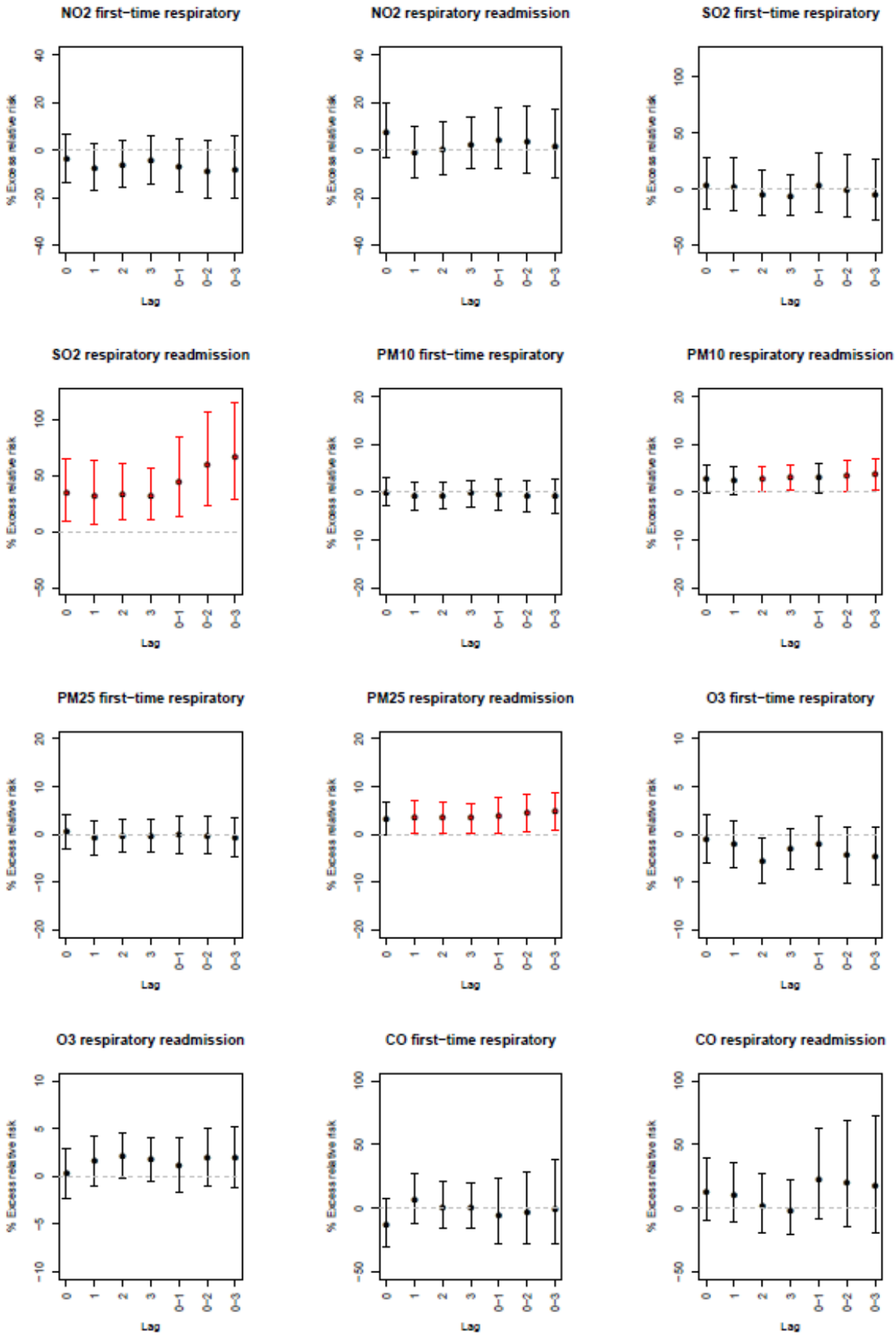


b) Readmissions



*100 μg/m^3 for CO
**Suzhou (2010-2016
p<0.05

Figure C5.6: Percent excess risk of hospitalisation for major respiratory disease associated with a 10 μg/m^3 increase in AAP in Haikou (2013-2016) using case- crossover analysis

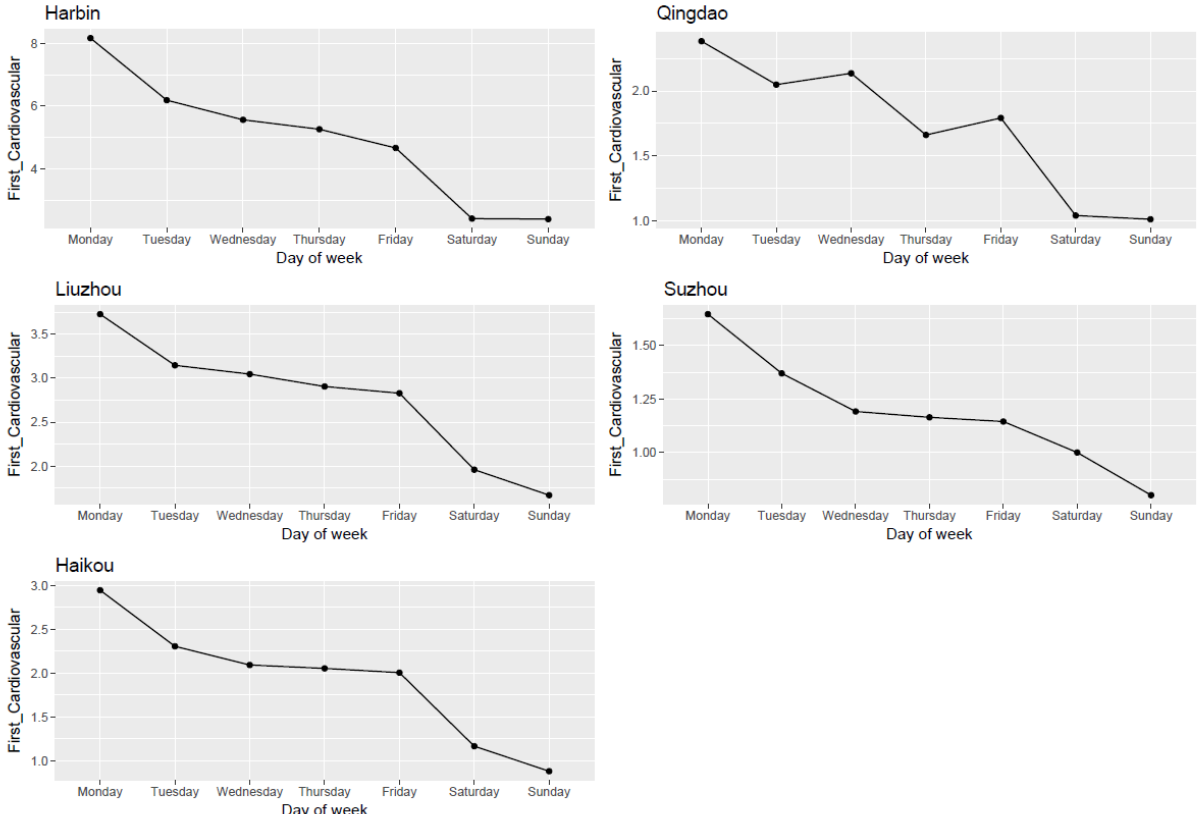


*100 μg/m^3 for CO

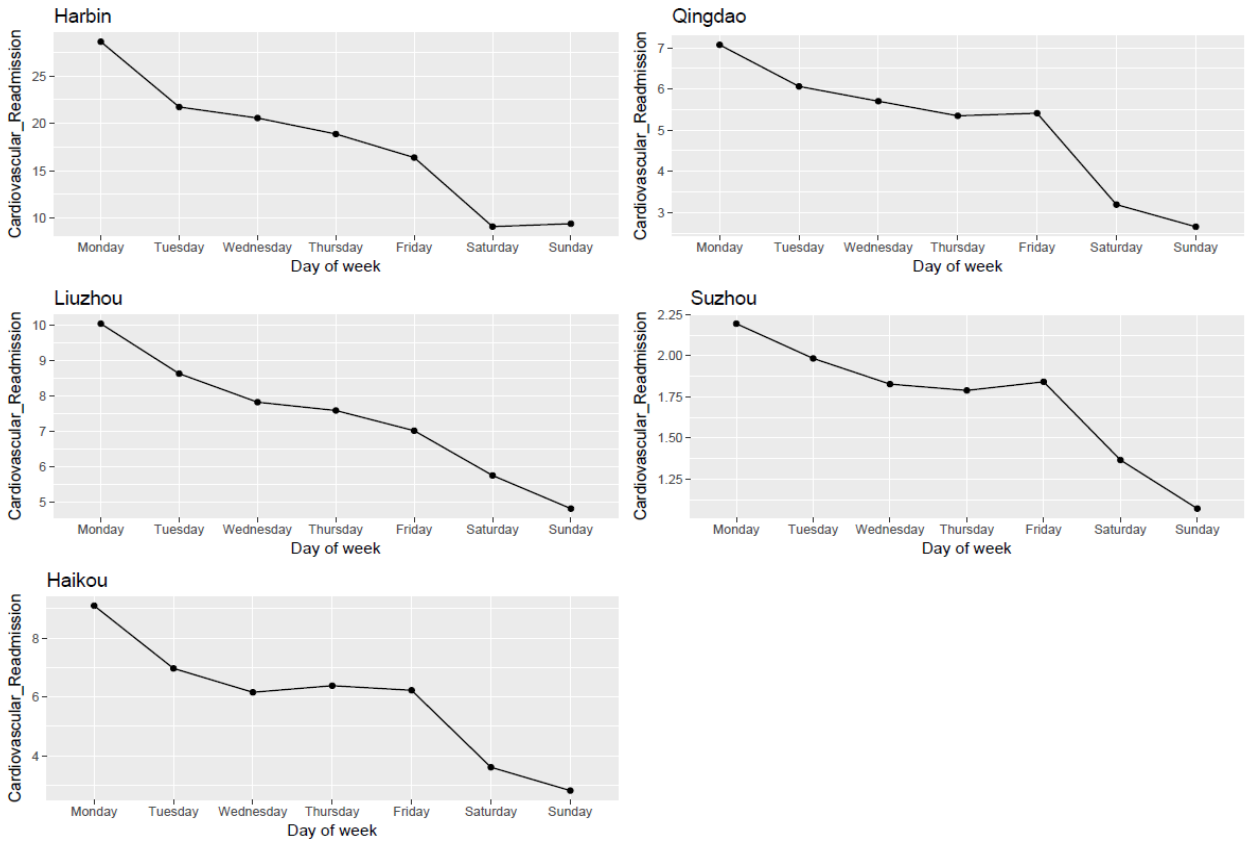
p<0.05

Appendix C6. Mean spells counts by day of the week each CKB urban region, by disease and admission-type, respectively

a) First-time cardiovascular spells

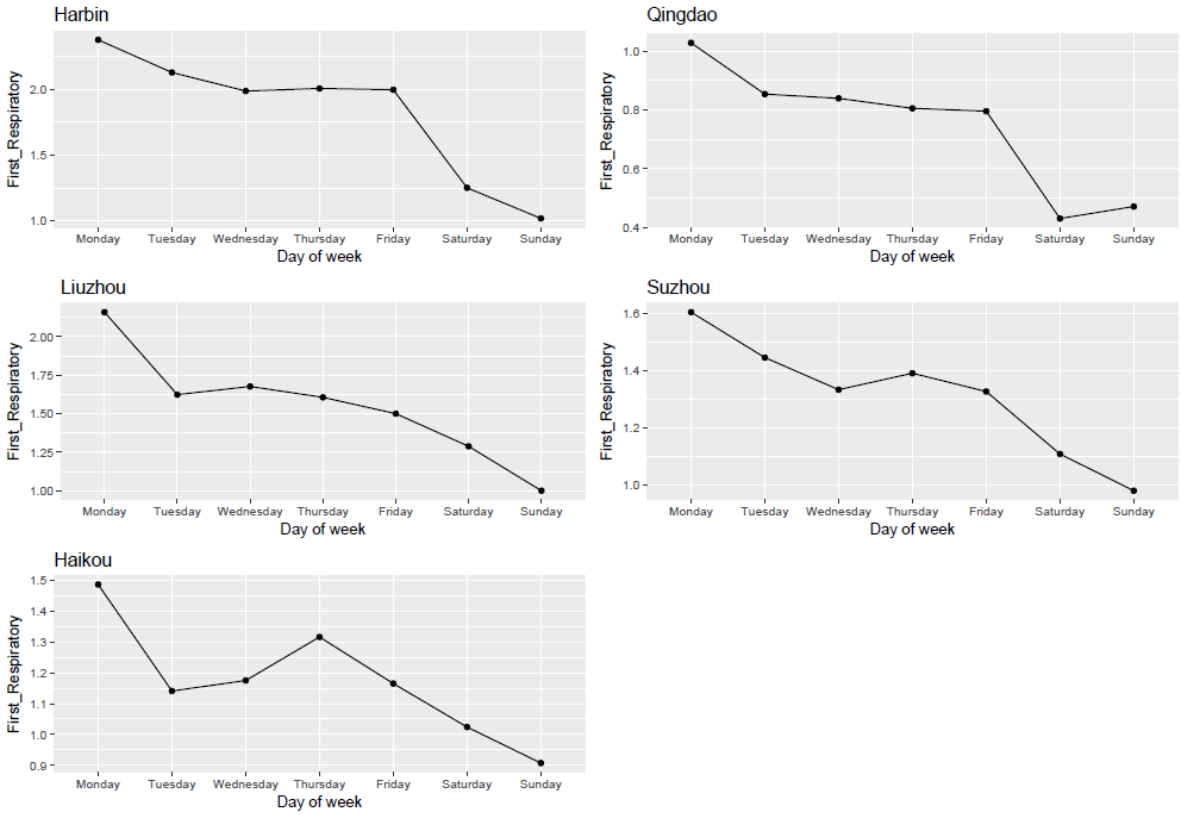


b) Cardiovascular readmissions

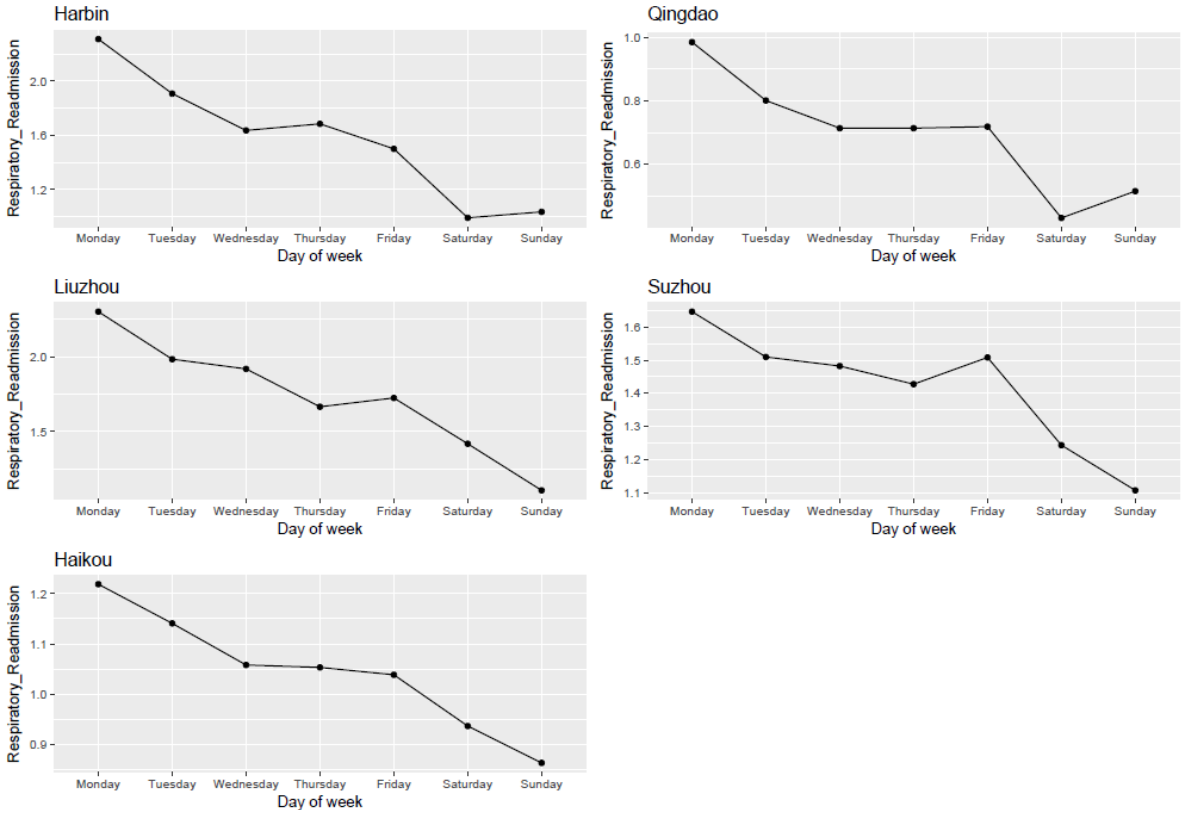


Appendix C6 Continued.

c) First-time respiratory spells

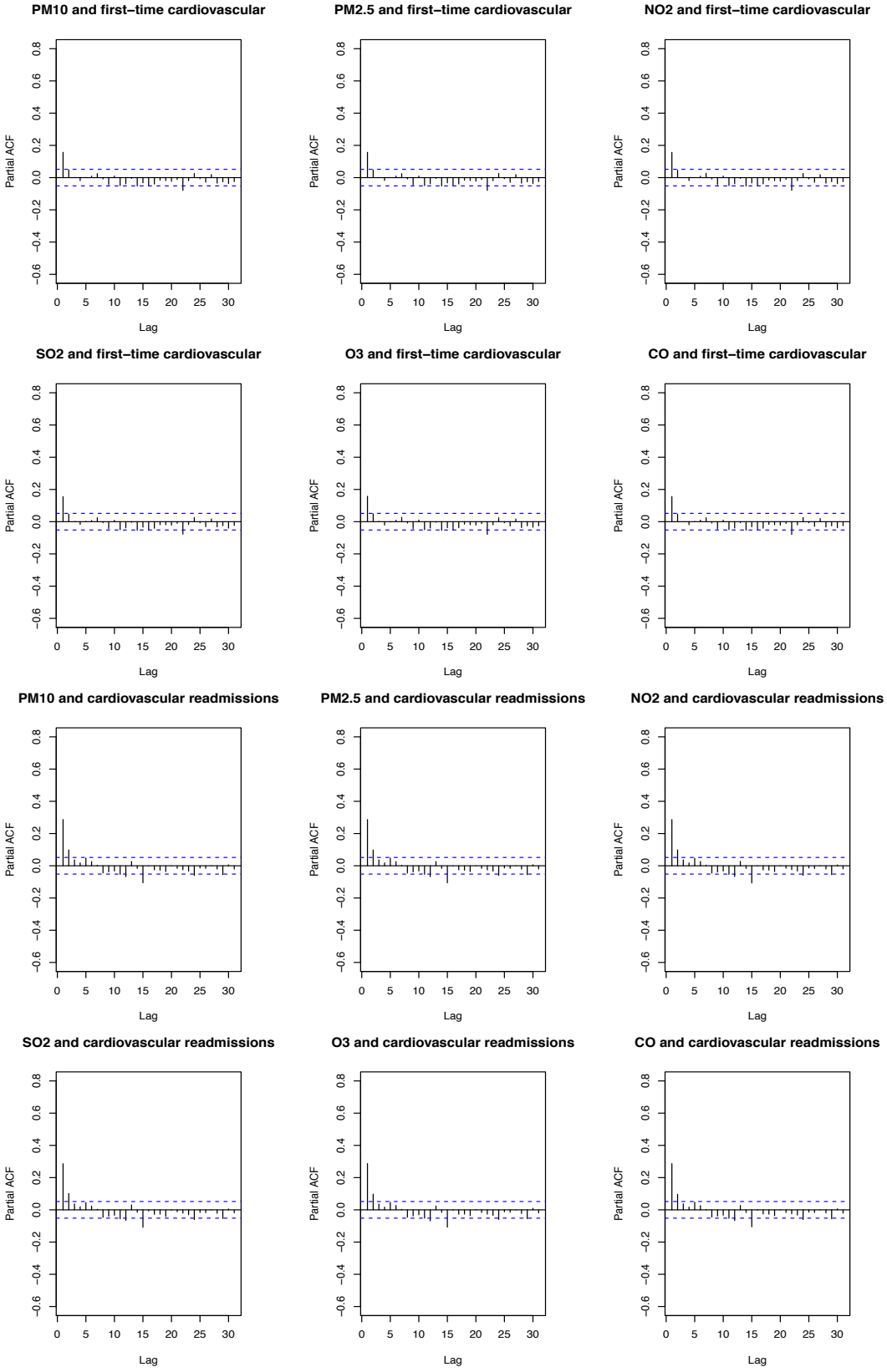


d) Respiratory readmission spells

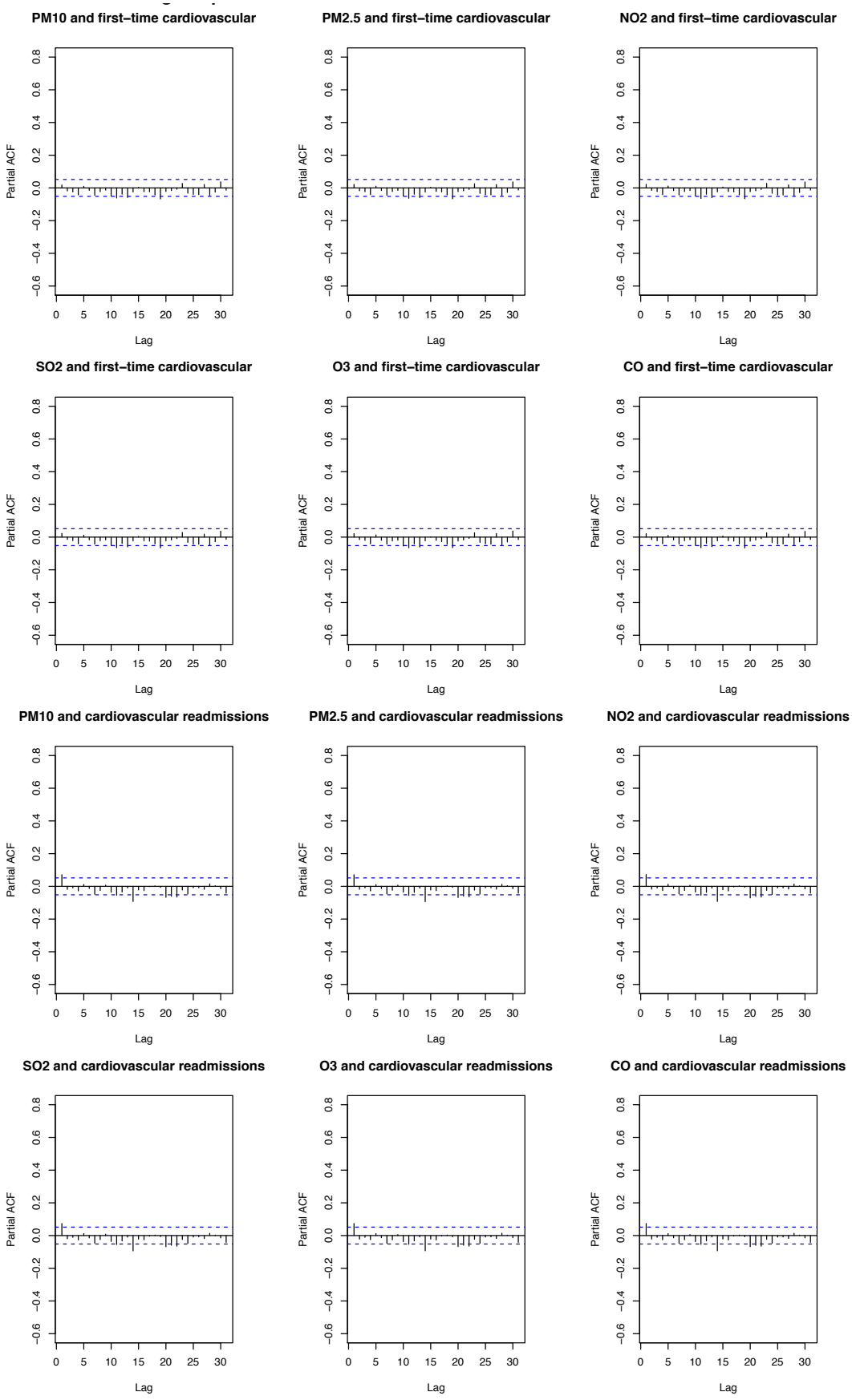


Appendix C7 Partial autocorrelation function plots of residuals in time-series analysis

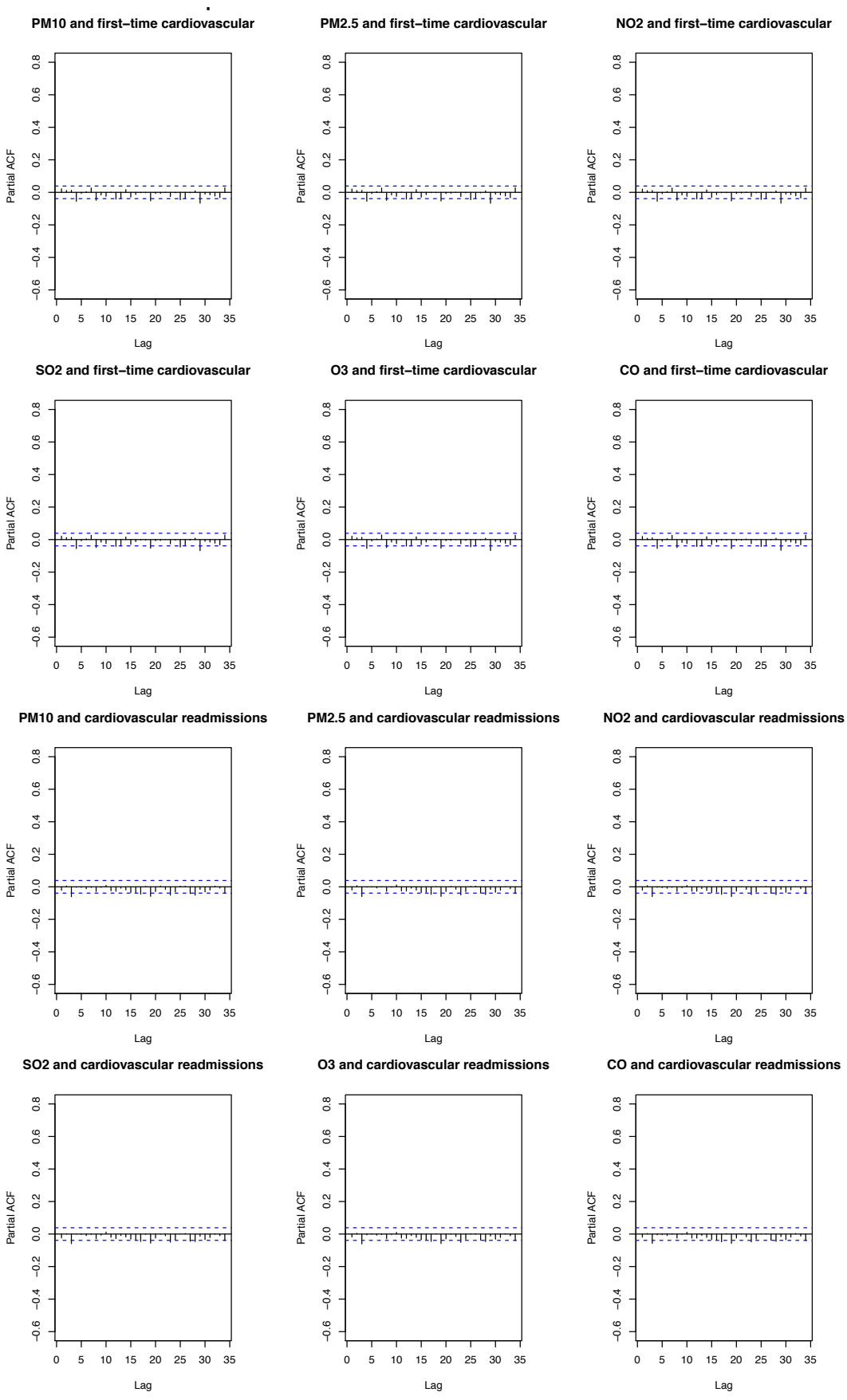
a) Harbin and cardiovascular disease spells



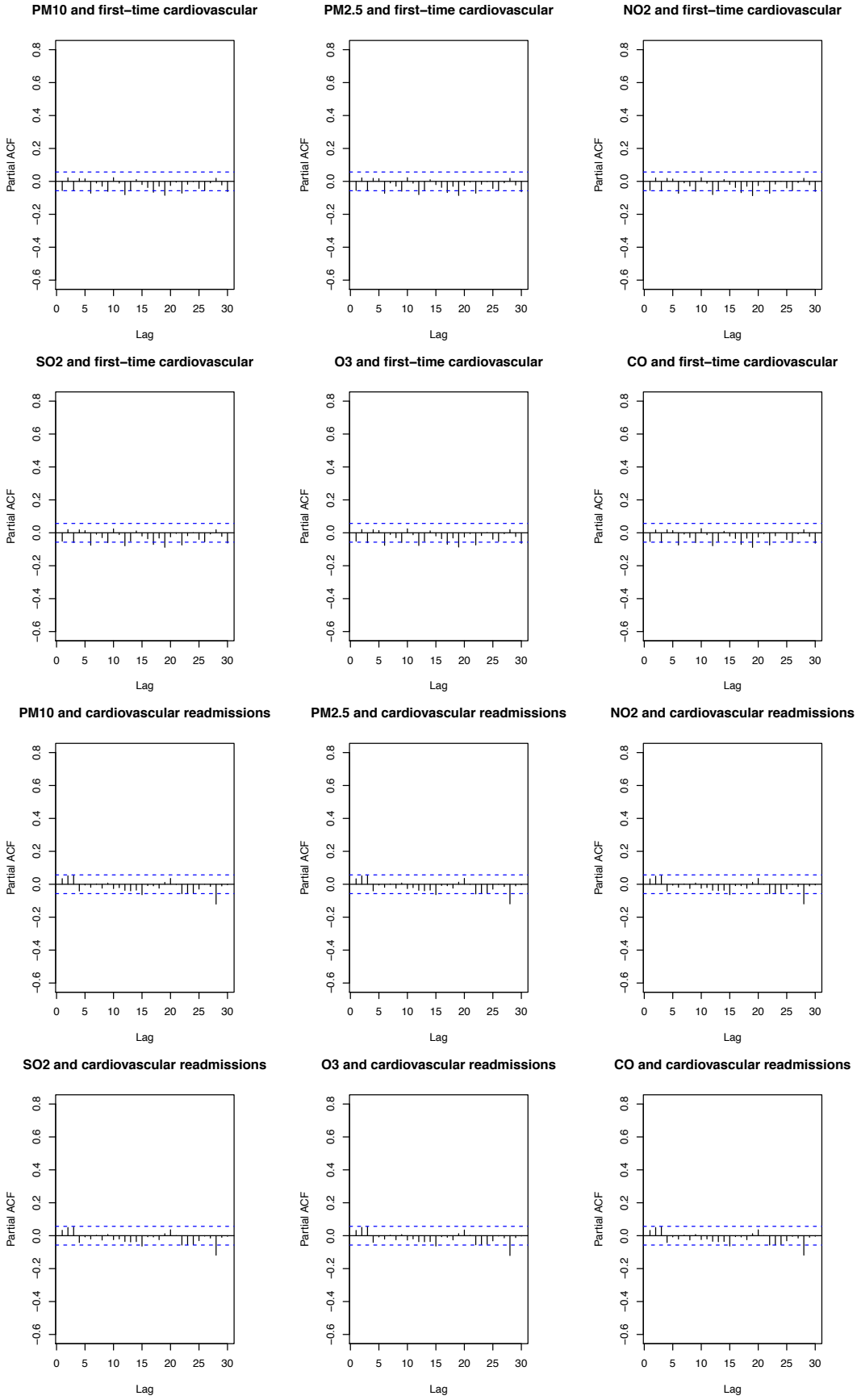
b) Qingdao and cardiovascular disease spells



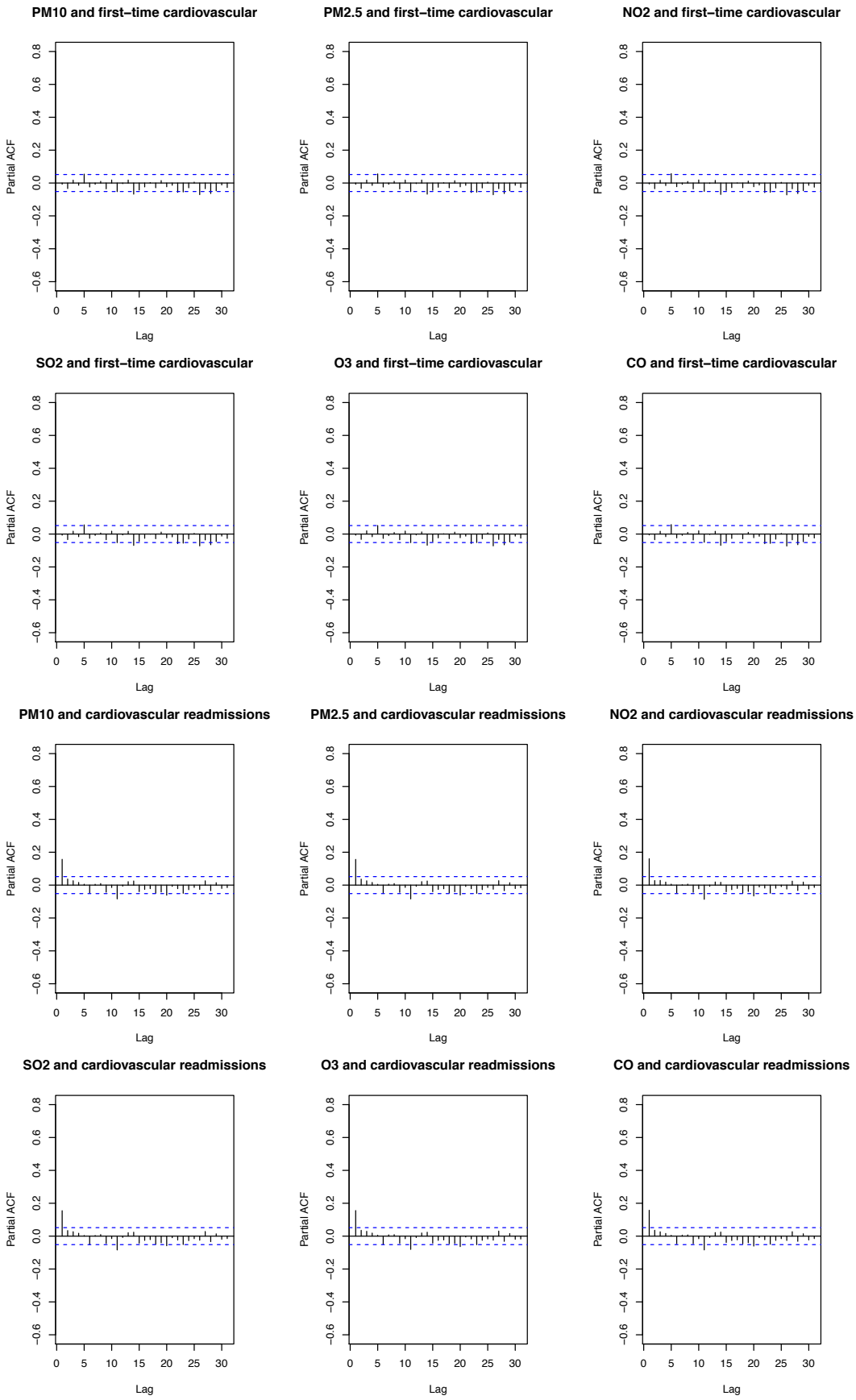
c) Suzhou and cardiovascular disease spells



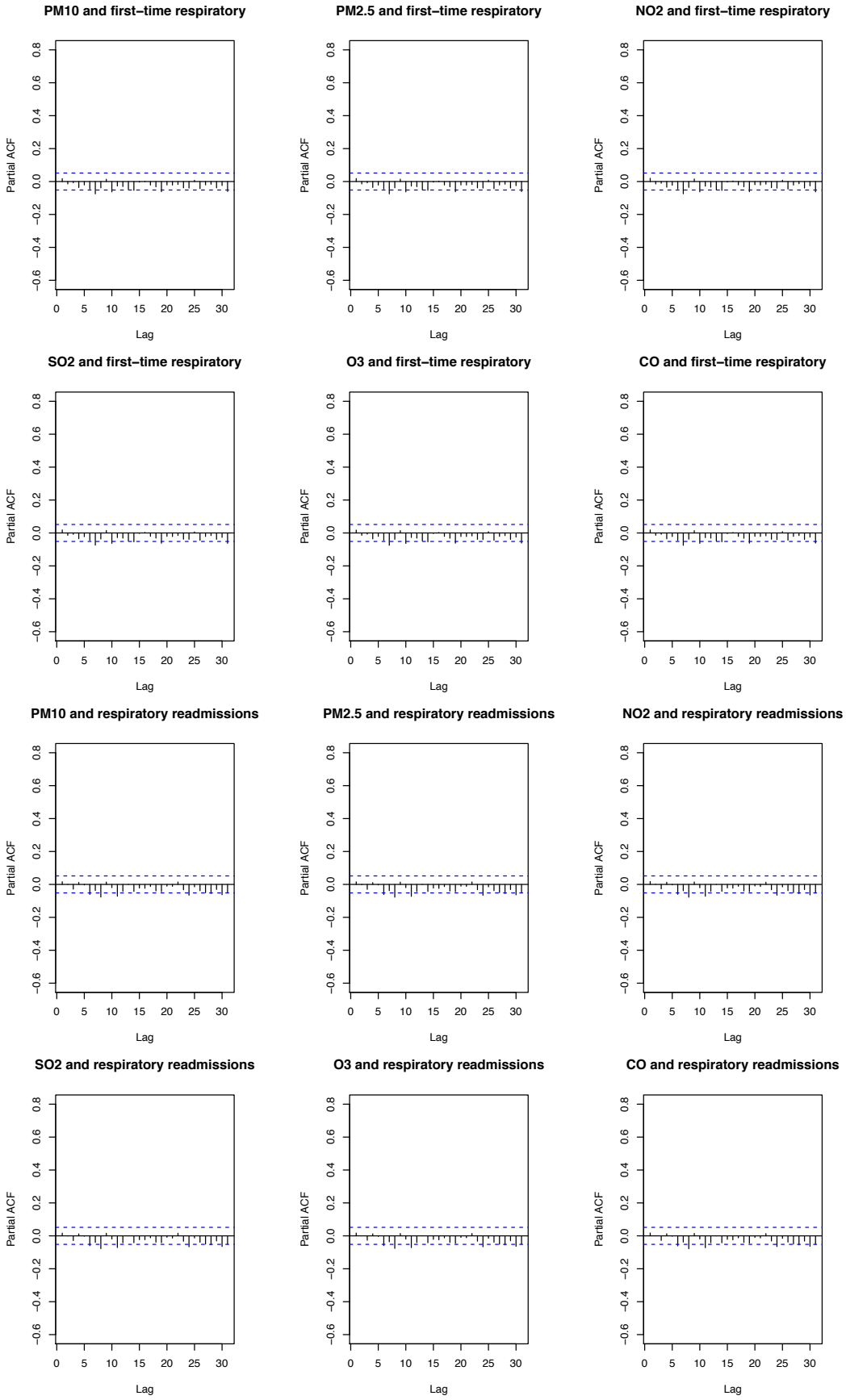
d) Liuzhou and cardiovascular disease spells



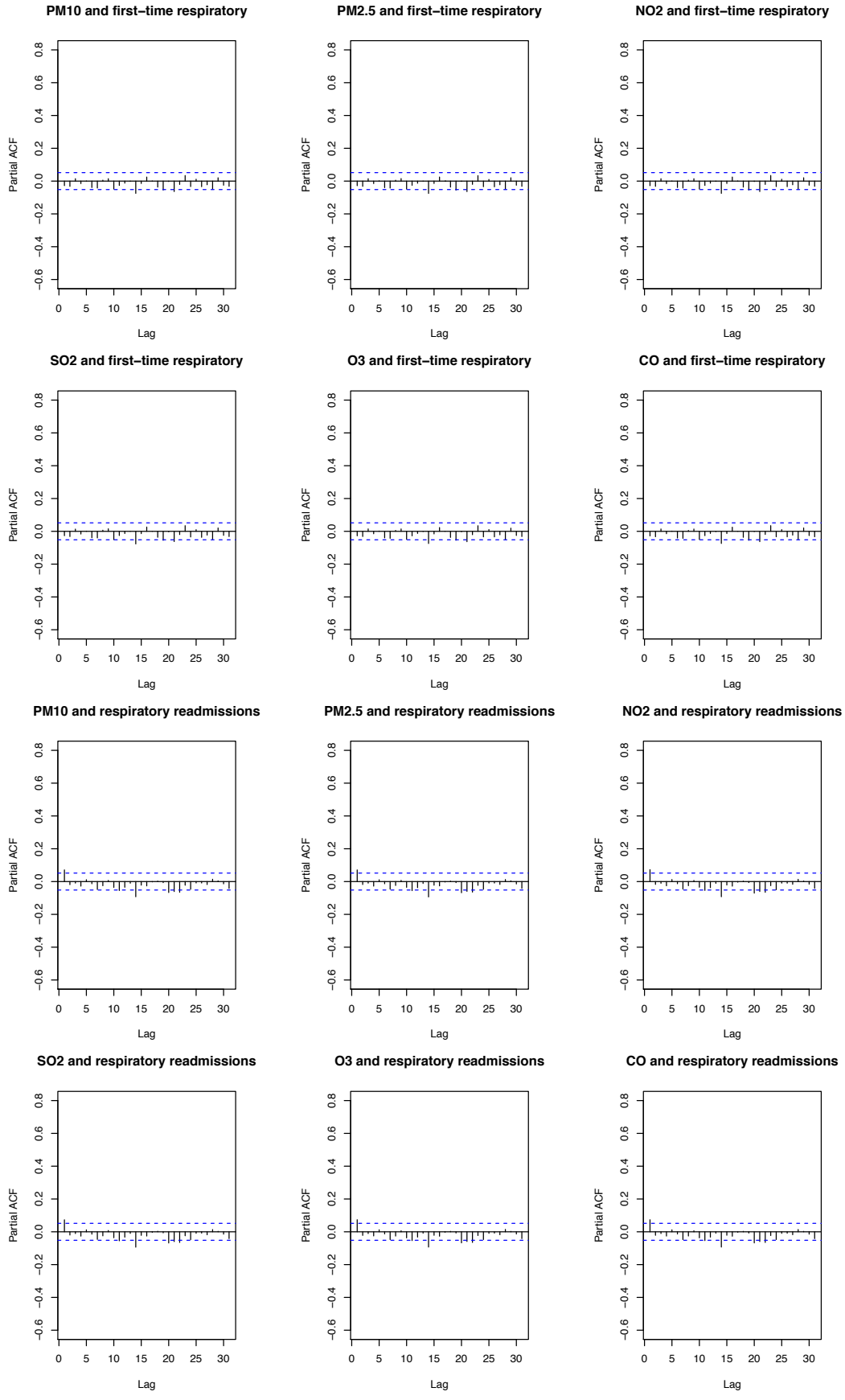
e) Haikou and cardiovascular disease spells



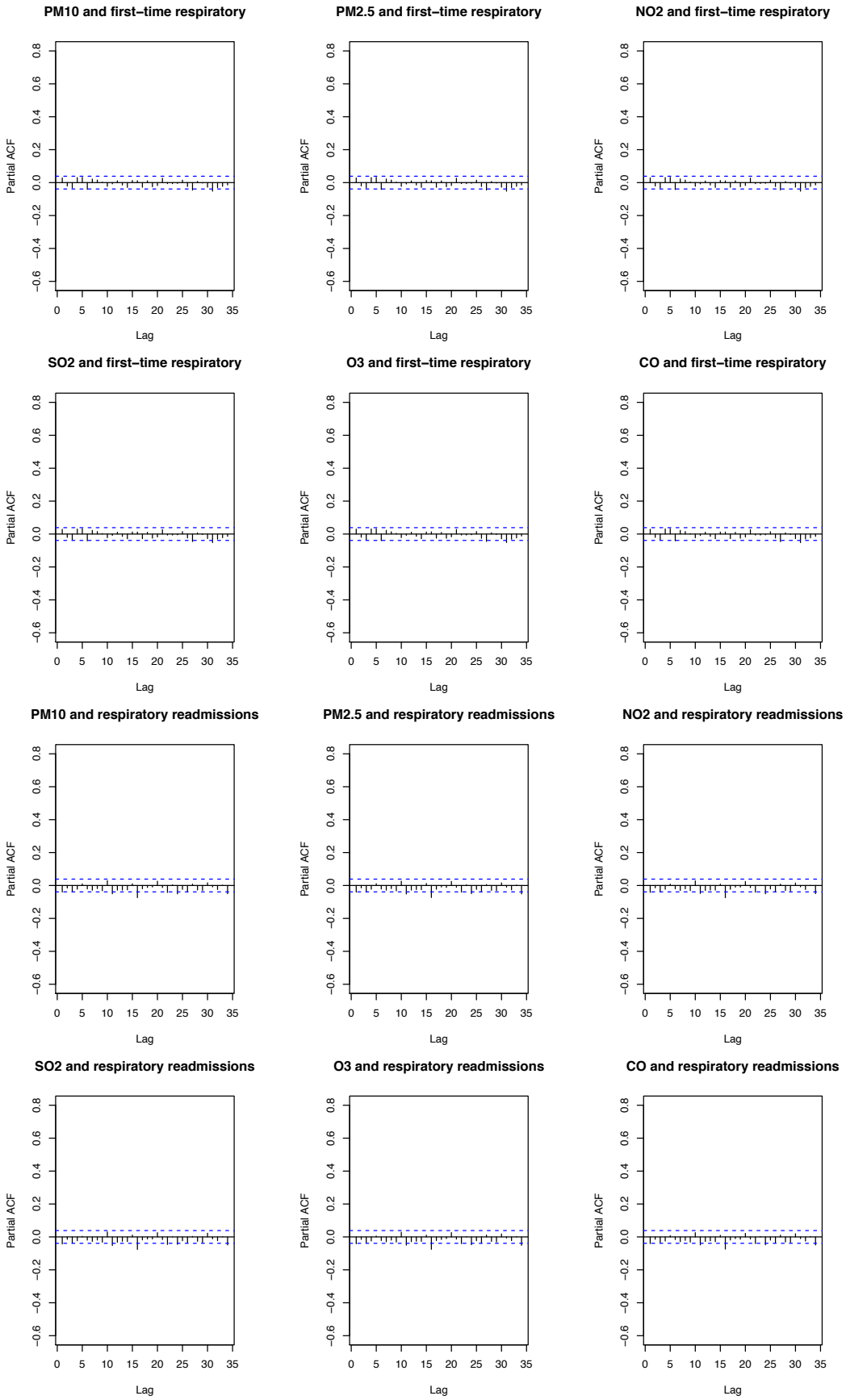
f) Harbin and respiratory disease spells



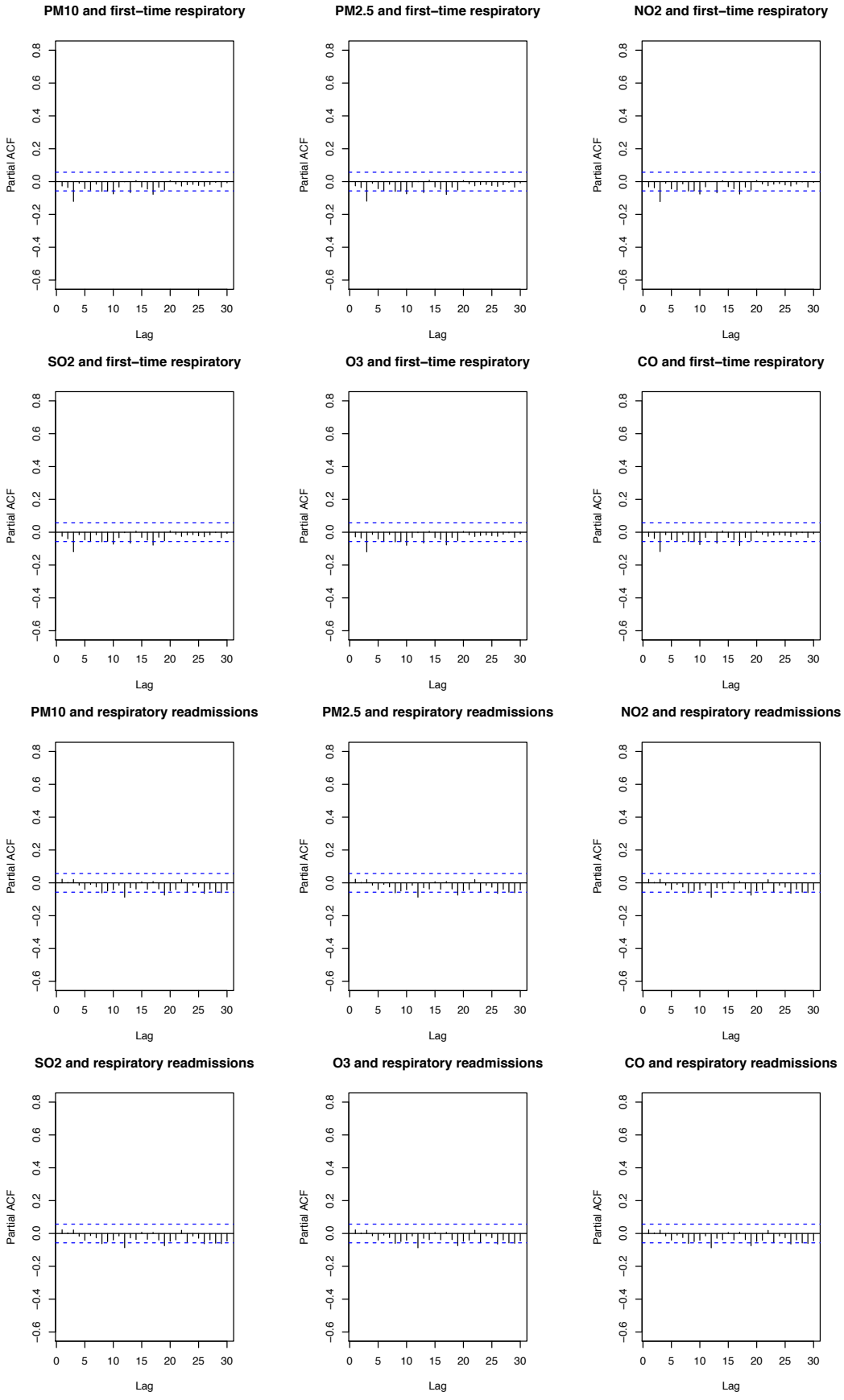
g) Qingdao and respiratory disease spells



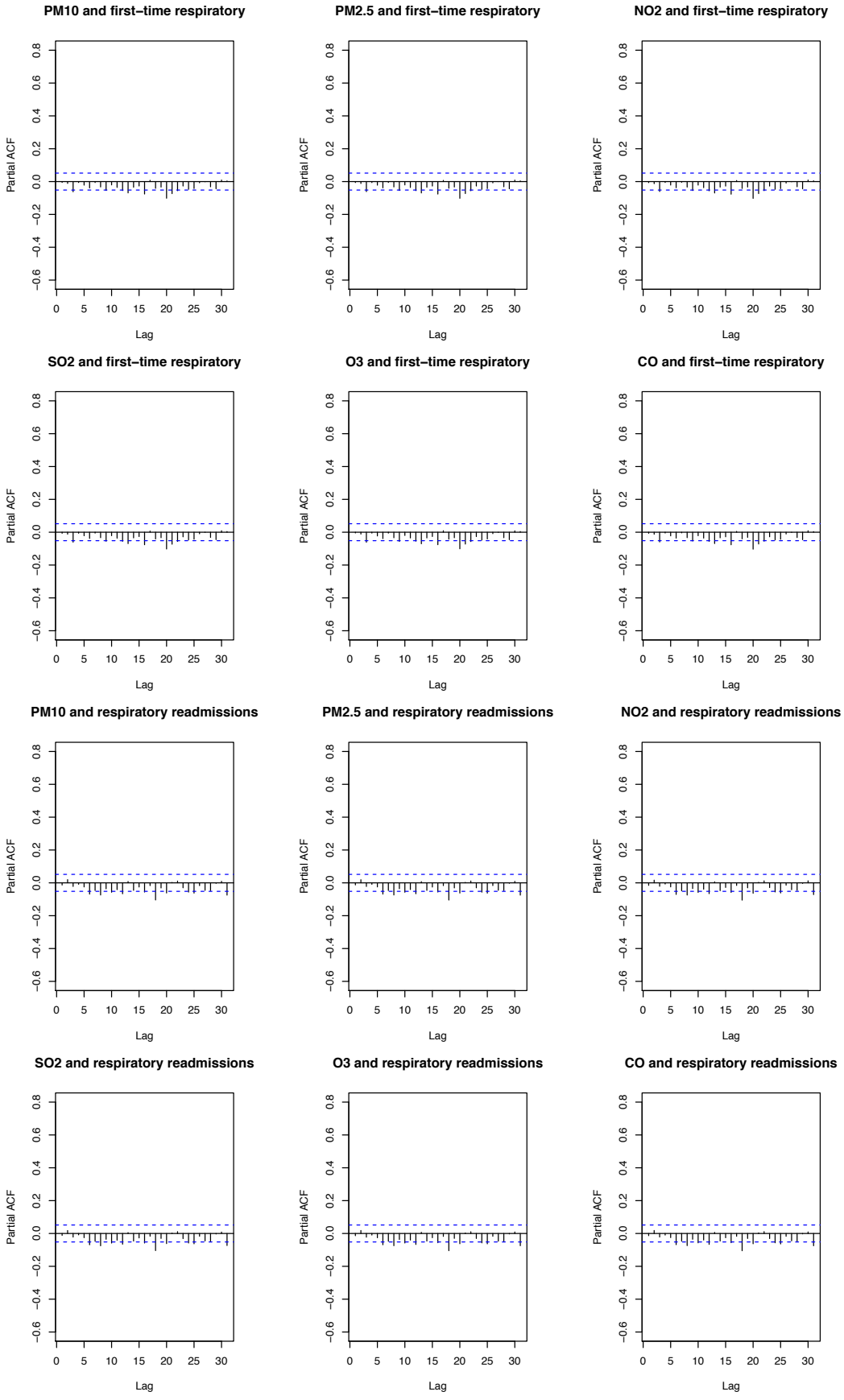
h) Suzhou and respiratory disease spells



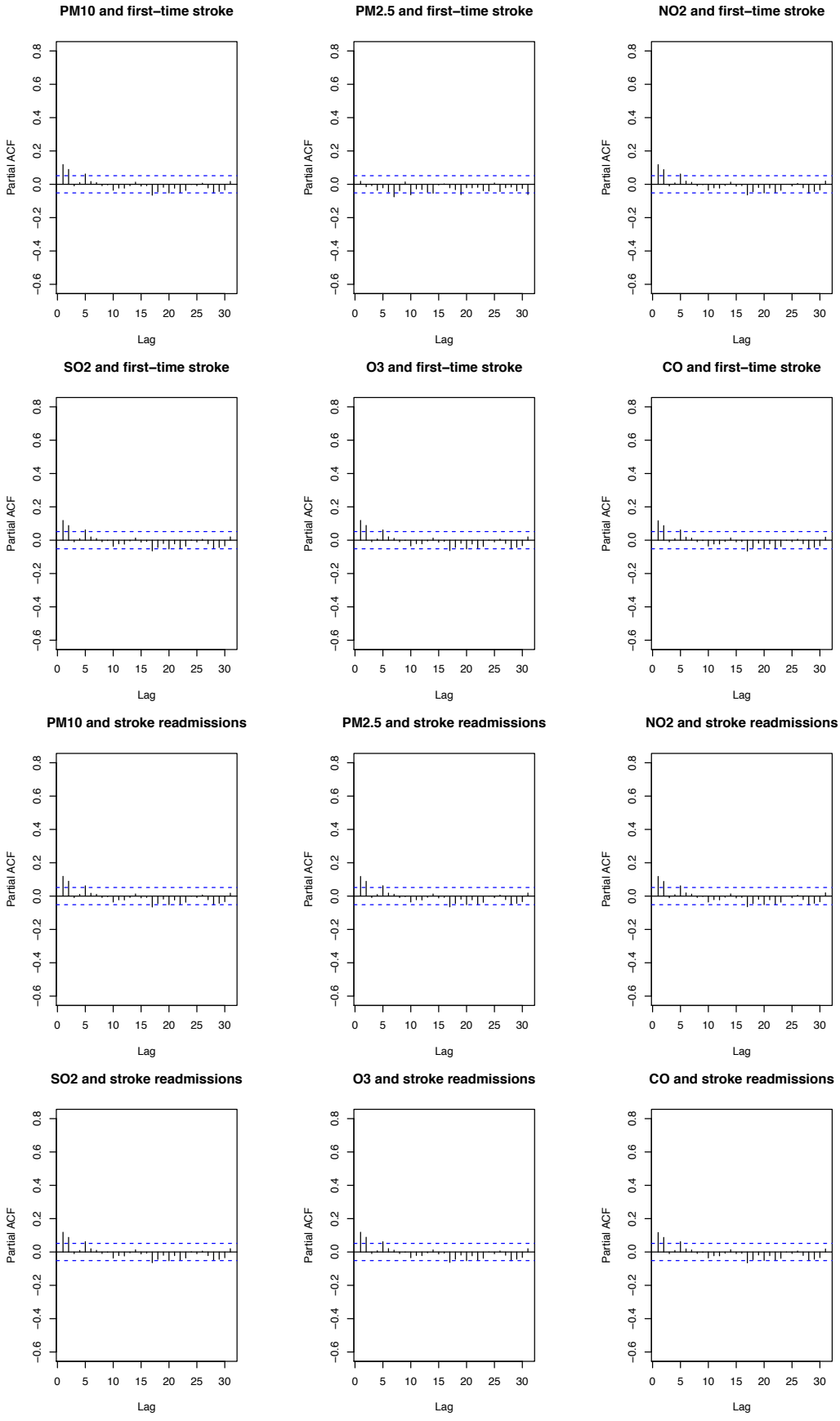
i) Liuzhou and respiratory disease spells



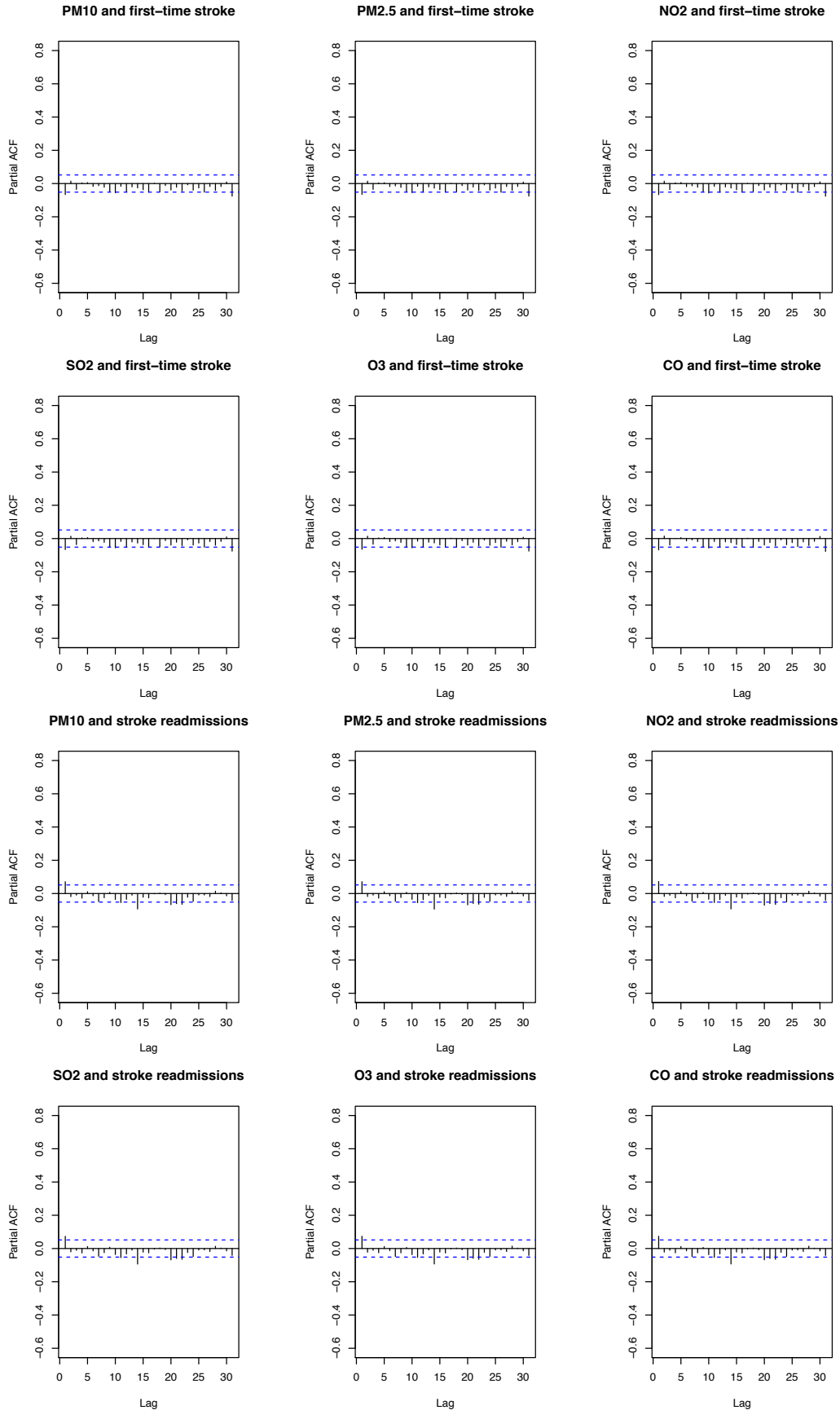
j) Haikou and respiratory disease spells



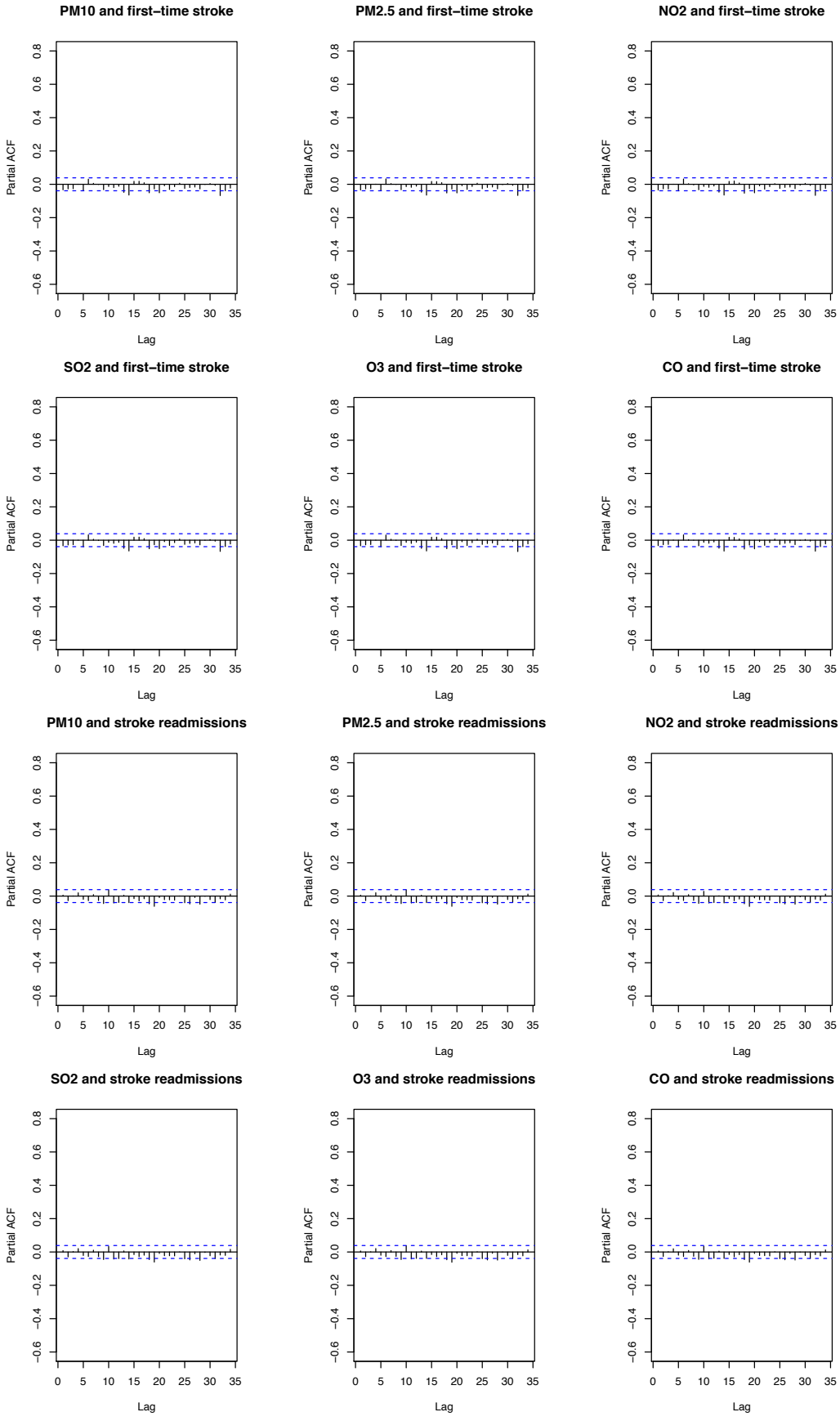
k) Harbin and all-type stroke spells



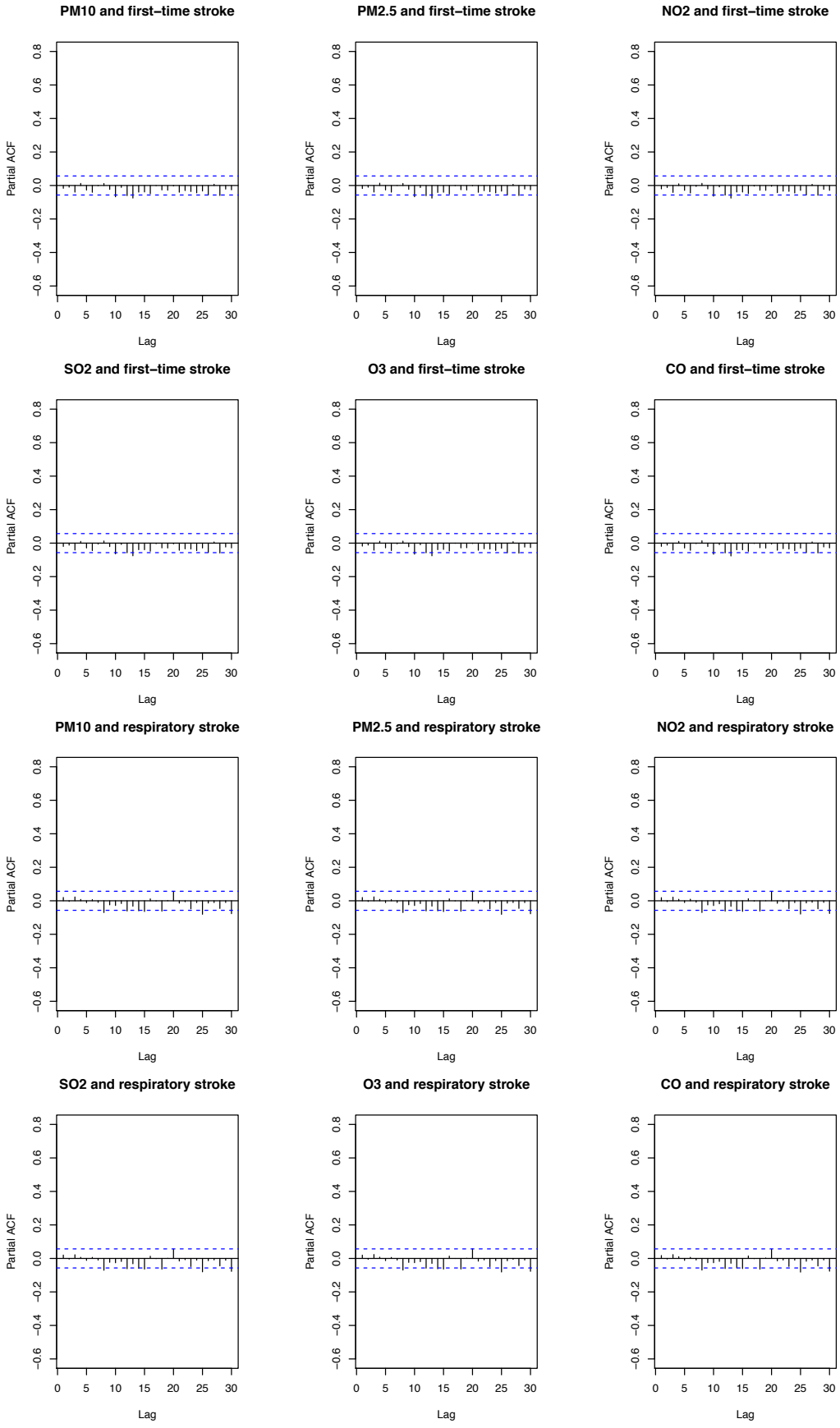
l) Qingdao and all-type stroke spells



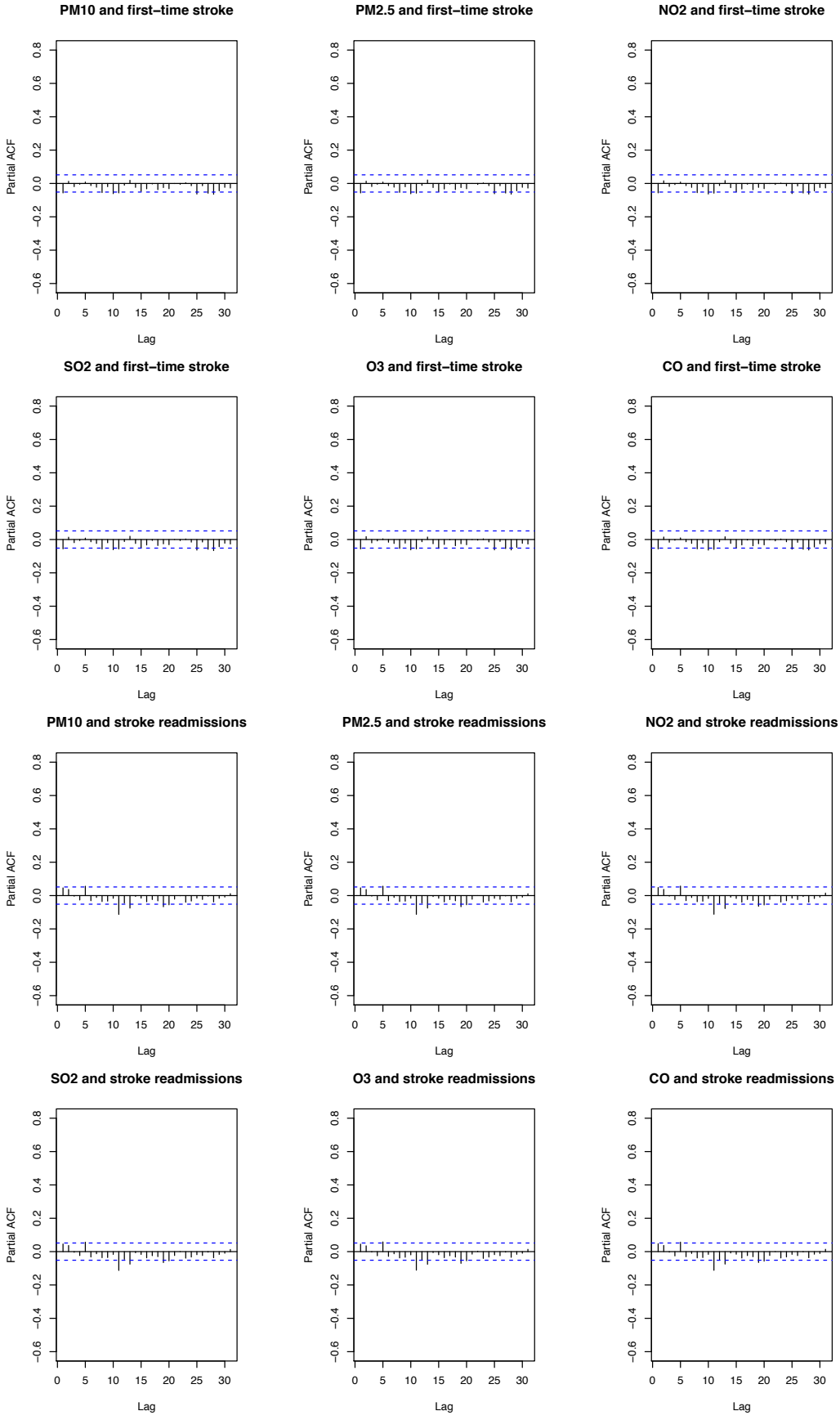
m) Suzhou and all-type stroke spells



n) Liuzhou and all-type stroke spells



o) Haikou and all-type stroke spells



Appendix C8 Distributed lag model methodology (adapted from Schwartz, 2000 [47] and Roberts, 2012 [483])

Supposing health outcomes occurring today depend on the "same-day" effect of today's ambient air pollution (AAP) concentrations but also the 1-day effect of yesterday's and the 2-day effect of the day before that etc. then the unconstrained distributed lag model is shown as:

$$Log[E(Y_t)] = \alpha + b_1 X_t + b_1 X_{t\text{-}q} + \varepsilon_t \qquad (1)$$

In this case $X_{t\text{-}q}$ reflects the respective pollutant concentration on q days before cardio-respiratory spell incidence. The overall effect of a 10 μg/m^3 increase pollutant concentration on a single day is thus its impact on that day plus its impact on subsequent days that is the sum of $b_{0+.....+}\, b_q$. However, as there will likely be substantial correlation in air pollution concentrations between days close together considerable collinearity would be introduced into this model, resulting in unstable estimates of b and thus, the risk estimates.

It is suggested to therefore constrain the vector of b_q's with the most common approach to constrain by lag number through fitting a polynomial function. The polynomial distributed lag model extends the unconstrained DLM shown in Equation 1 by constraining b_q's to be a polynomial function of the lag number as it is reasonable to assume that the effect of AAP on spells would be a smooth function of lag number.

The DLMs described in this thesis were constructed using the "dlnm" R package [484] with polynomials of degree 2 consistent with the surrounding literature. [47, 483] For the DLMs described in this thesis AAP levels lagged to for k=7 days were used, imposing the constraint that an increase in the pollutant concentration may only have an effect on incidence of cardio-respiratory spells for a lag up to 7-days. The same confounding variables were included in each DLM as in the main time-series analysis outlined in **Chapter 5.3.5.2**

Appendix C9. Subgroup analysis by age group

Table C9.1 Counts of cardio-respiratory spells by region in participants aged 60 years and over at CKB baseline

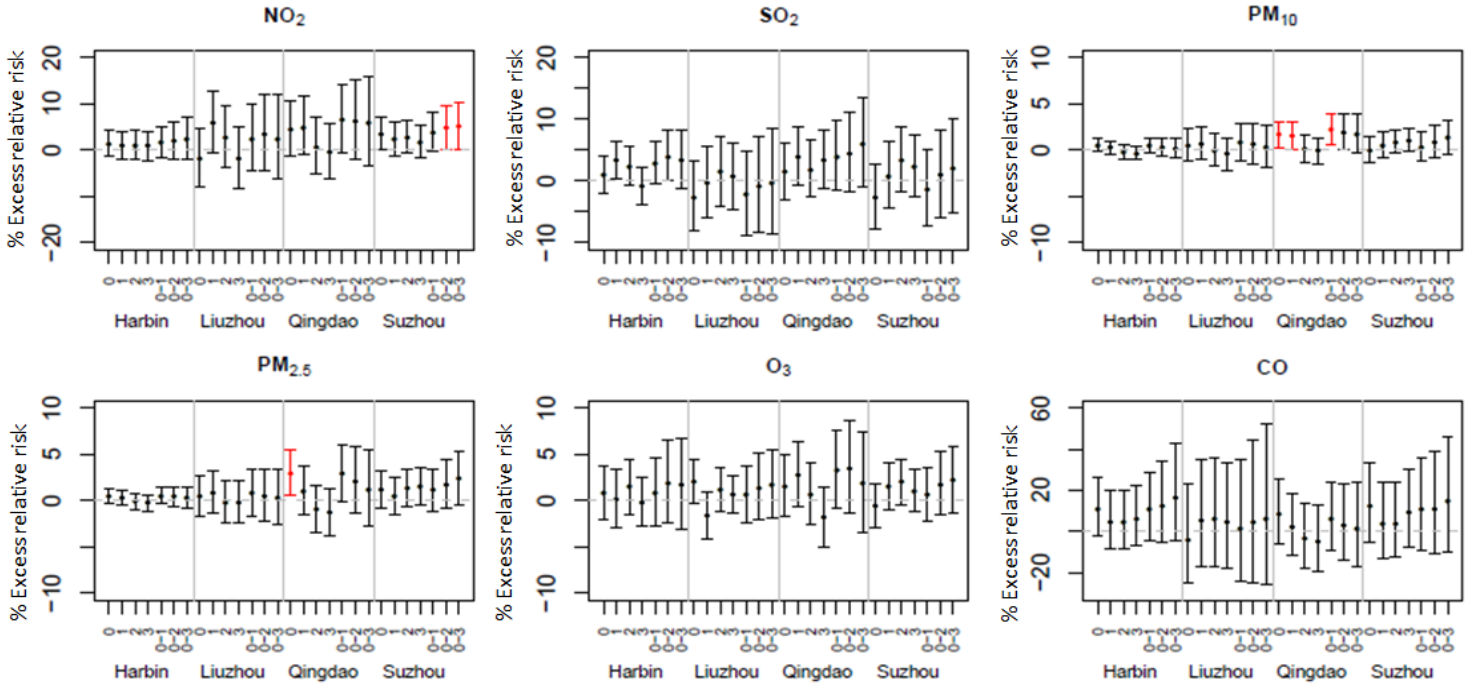
	CKB region and study populations					
	Harbin (n=15,712)	**Qingdao (n=6445)**	**Suzhou (n=12,234)**	**Liuzhou (n=13,201)**	**Haikou (n=8602)**	**Total (n=56,194)**
Major cardiovascular disease						
Total	16,541	4837	4249	6680	6506	38,813
First-time	2041	685	1228	1130	1165	6249
Readmissions	14,500	4152	3021	5550	5341	32564
Mean daily count	11.46	3.35	1.66	5.62	4.51	-
Major respiratory disease						
Total	2693	901	3840	2359	1590	11,383
First-time	1242	375	1486	950	685	4738
Readmissions	1451	526	2354	1409	905	6645
Mean daily count	1.87	0.62	1.50	1.98	1.10	-

Table C9.2 Counts of cardio-respiratory spells by region in participants aged less than 60 years at CKB baseline

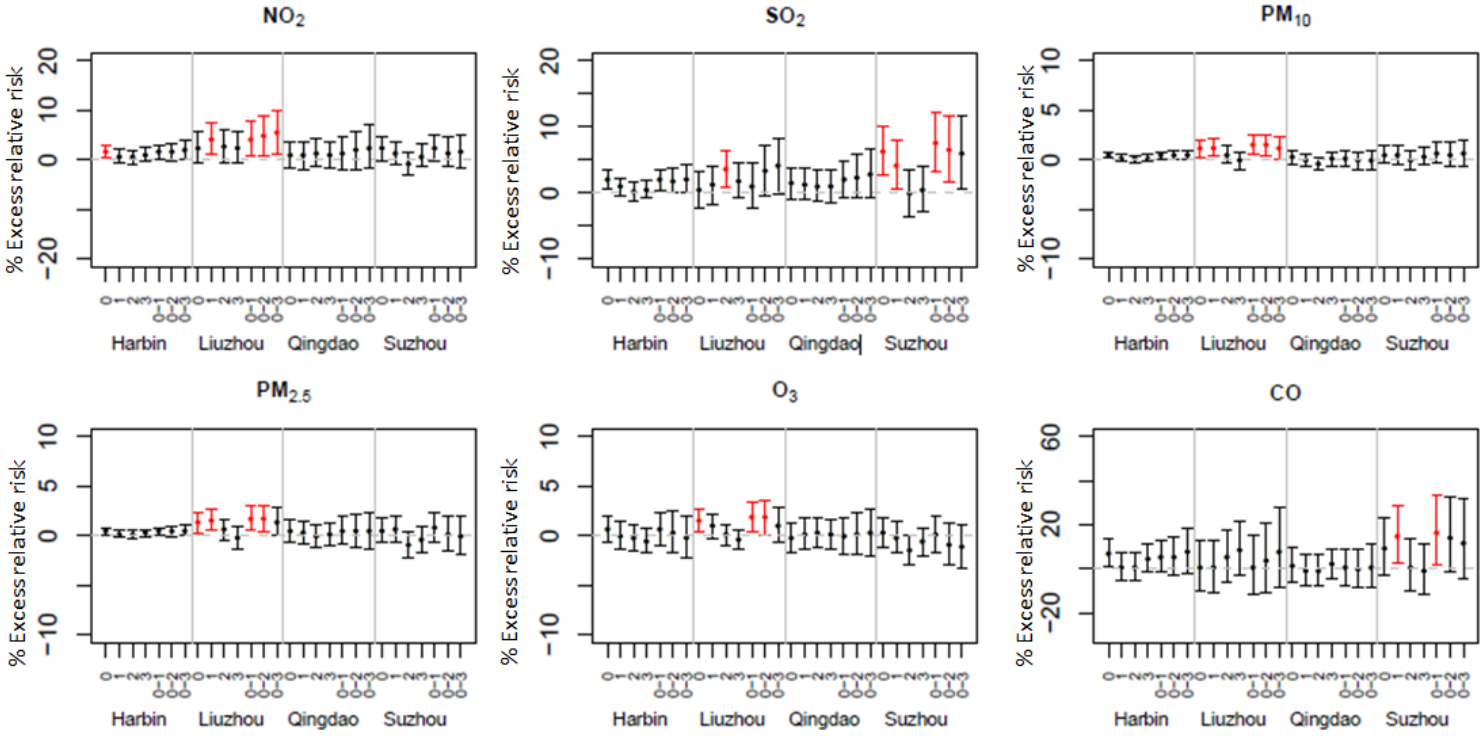
	CKB region and study populations					
	Harbin (n=39,182)	**Qingdao (n=28,058)**	**Suzhou (n=40,383)**	**Liuzhou (n=34,719)**	**Haikou (n=20,484)**	**Total (n=162,826)**
Major cardiovascular disease						
Total	16,282	4956	3201	5376	4772	34,587
First-time	5093	1802	1811	2147	1606	12,459
Readmissions	11,189	3154	1390	3229	3166	22,128
Mean daily count	11.28	3.43	1.25	4.52	3.31	-
Major respiratory disease						
Total	2216	1181	3146	1543	1610	9696
First-time	1387	702	1874	894	1008	5865
Readmissions	829	479	1272	649	602	3831
Mean daily count	1.12	0.82	1.23	1.30	1.12	-

Figure C9.1 Percent excess risk of hospitalisation for major cardiovascular disease associated with a 10 μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using time-series analysis in participants aged 60 years and over**

a) First-time spells



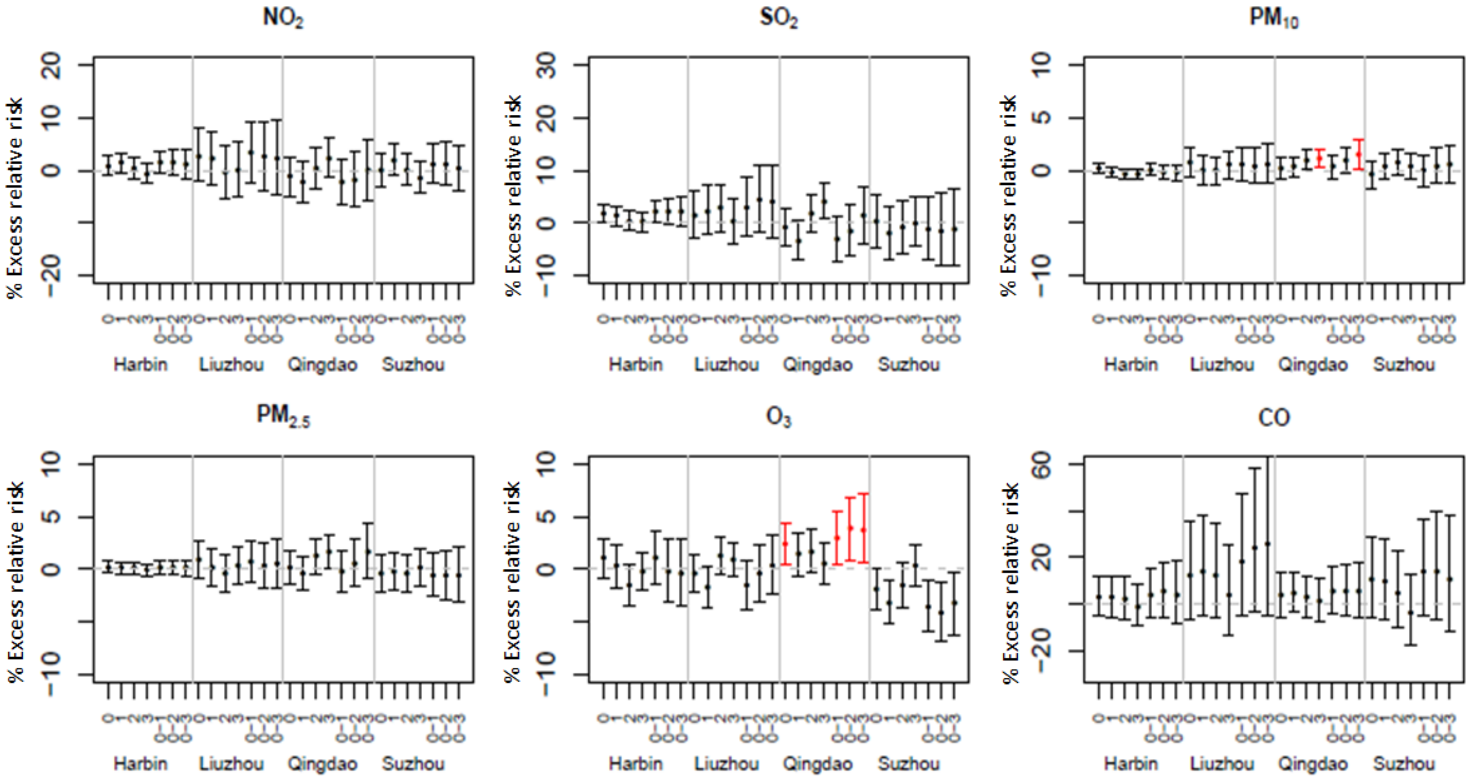
b) Readmissions



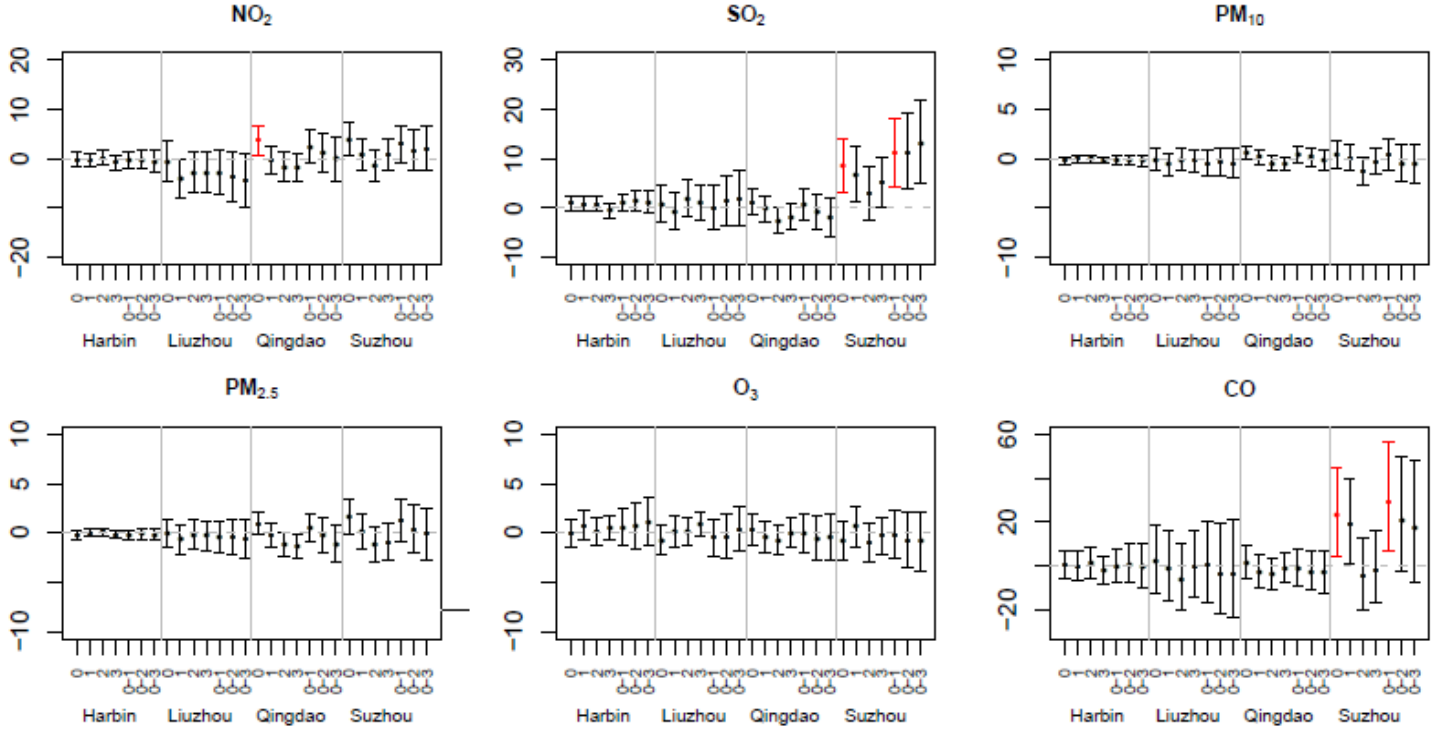
*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05 (in both time-series and case-crossover analysis)

Figure C9.2 Percent excess risk of hospitalisation for major cardiovascular disease associated with a 10 μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using time-series analysis in participants aged under 60 years**

a) First-time spells



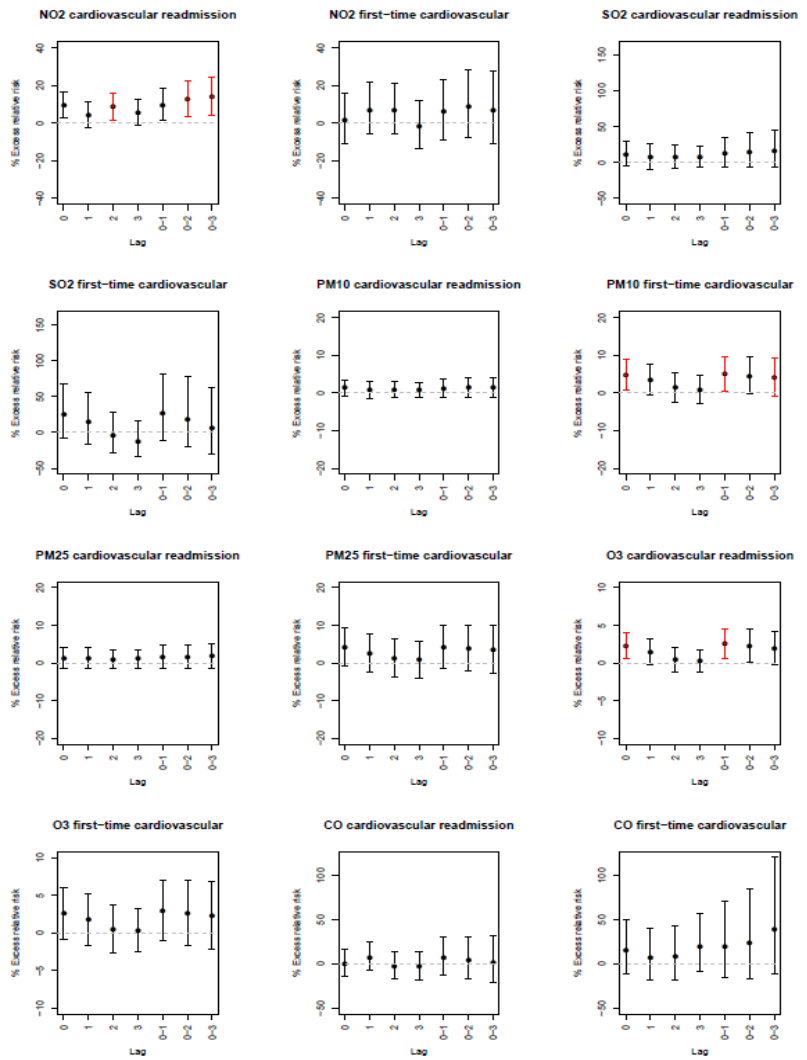
b) Readmissions



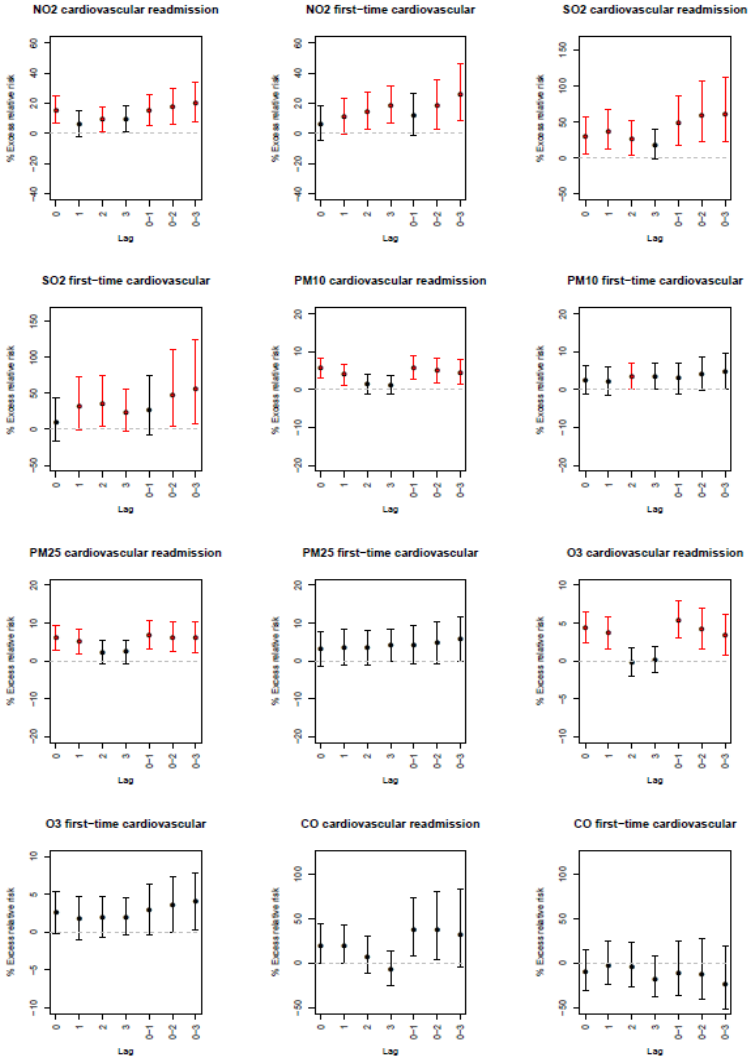
*100 μg/m^3 for CO
*Suzhou (2010-2016)
p<0.05 (in both time-series and case-crossover analysis)

Figure C9.3 Percent excess risk of hospitalisation for major cardiovascular disease associated with a 10 μg/m^3* increase in AAP Haikou (2013-2016) in those aged 60 years and over, and under 60 years, respectively using time-series analysis

a) 60 years and over



b) Under 60 years

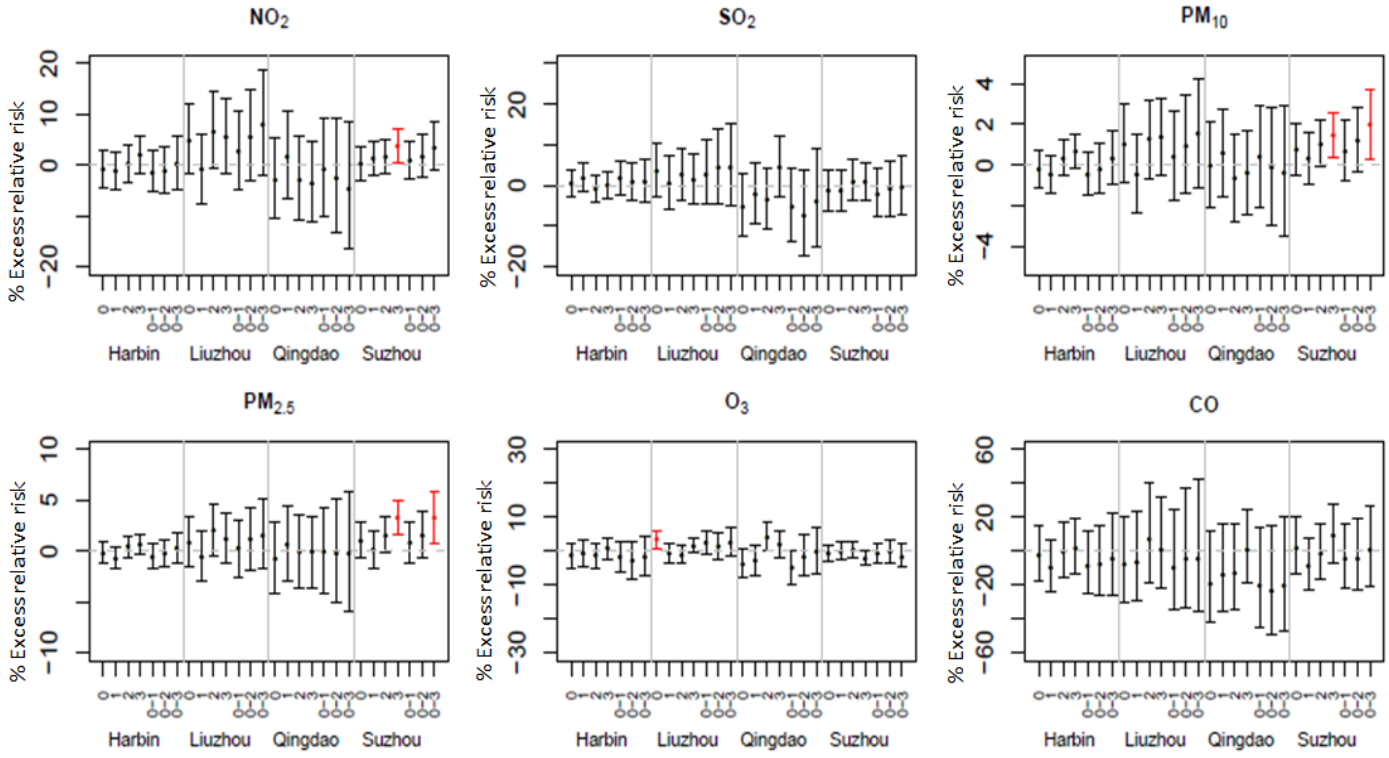


*100 μg/m^3 for CO

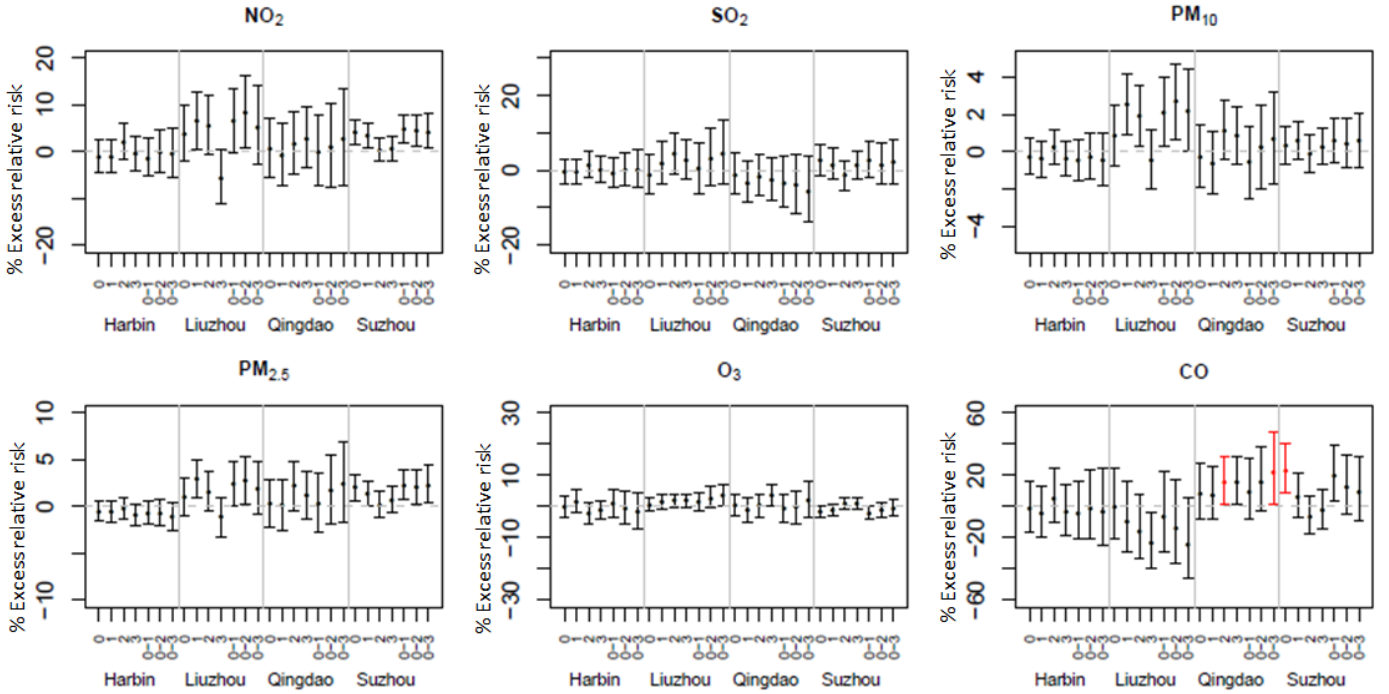
p<0.05 (in both time-series and case-crossover analysis)

Figure C9.4 Percent excess risk of hospitalisation for major respiratory disease associated with a 10 μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using time-series analysis in those aged 60 years and over**

a) First-time spells



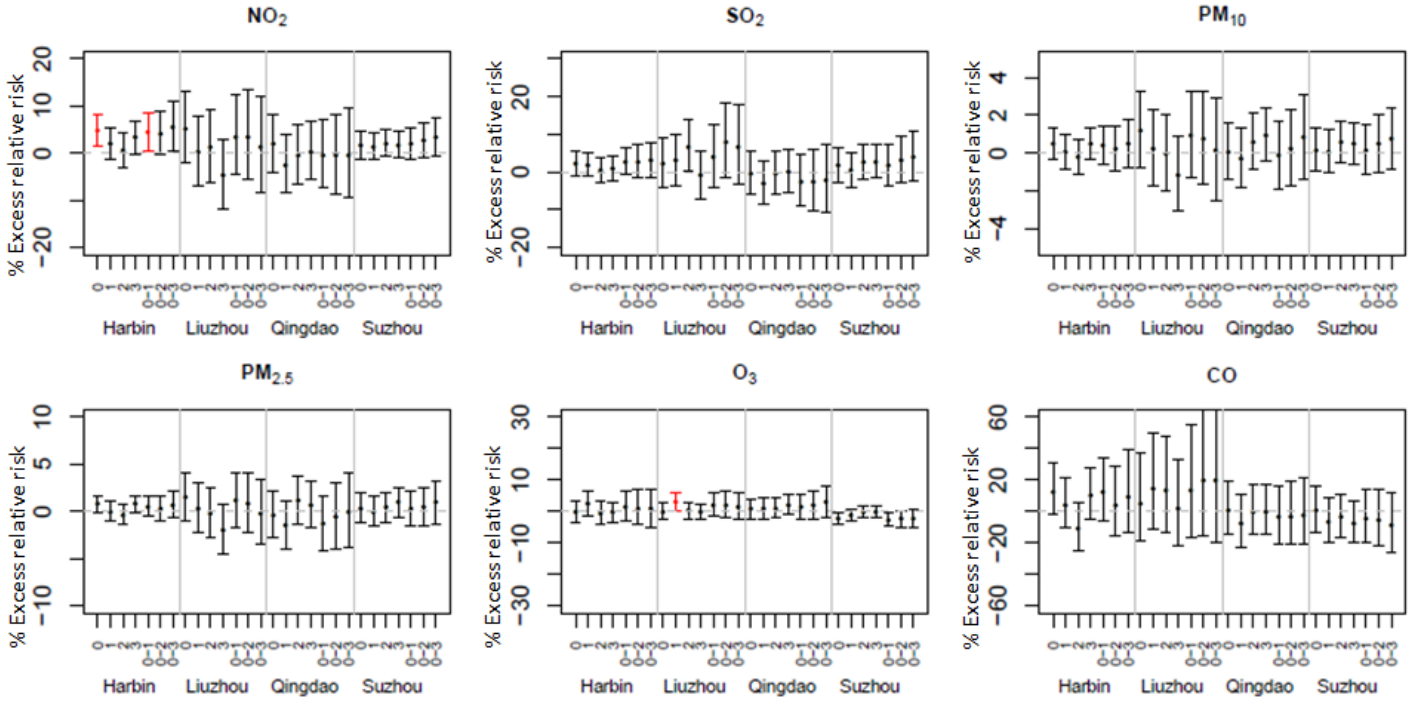
b) Readmissions



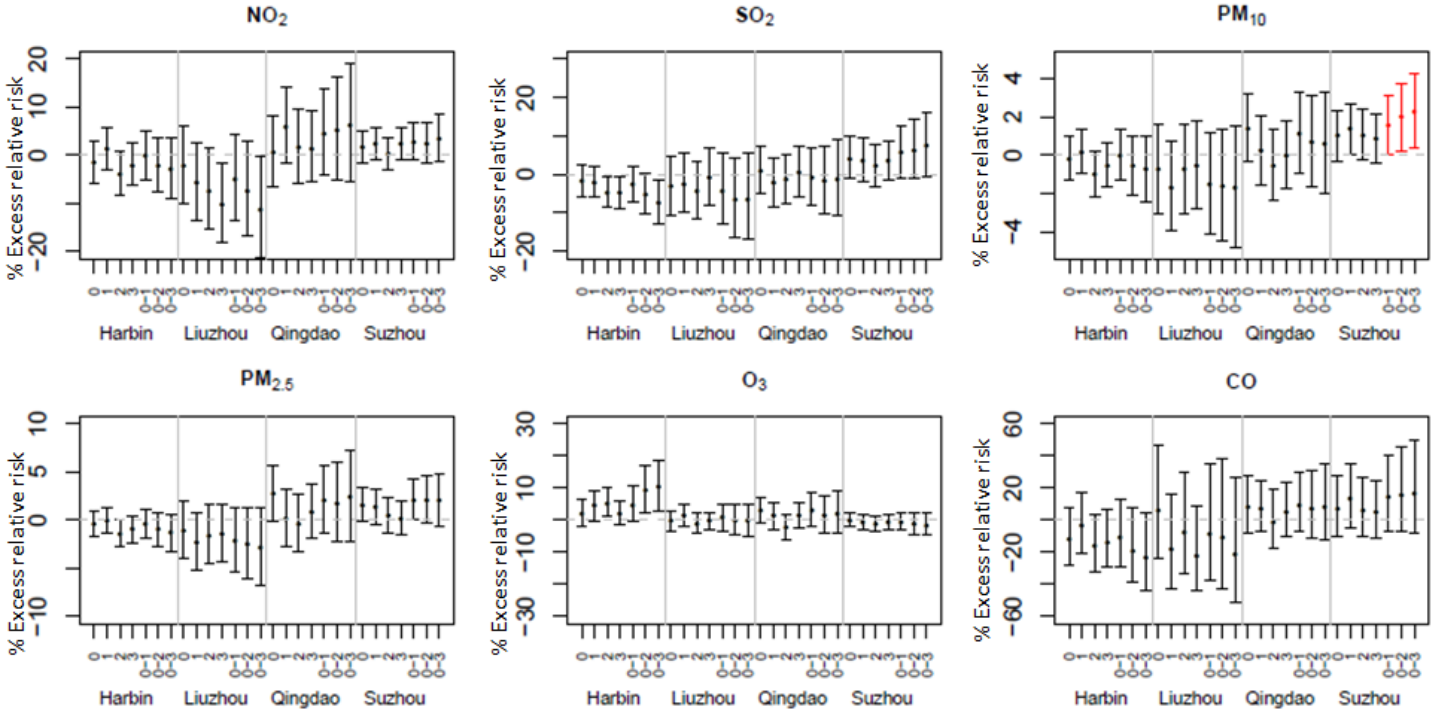
*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05 (in both time-series and case-crossover analysis)

Figure C9.5 Percent excess risk of hospitalisation for major respiratory disease associated with a 10 μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using time-series analysis in those aged under 60 years**

a) First-time spells



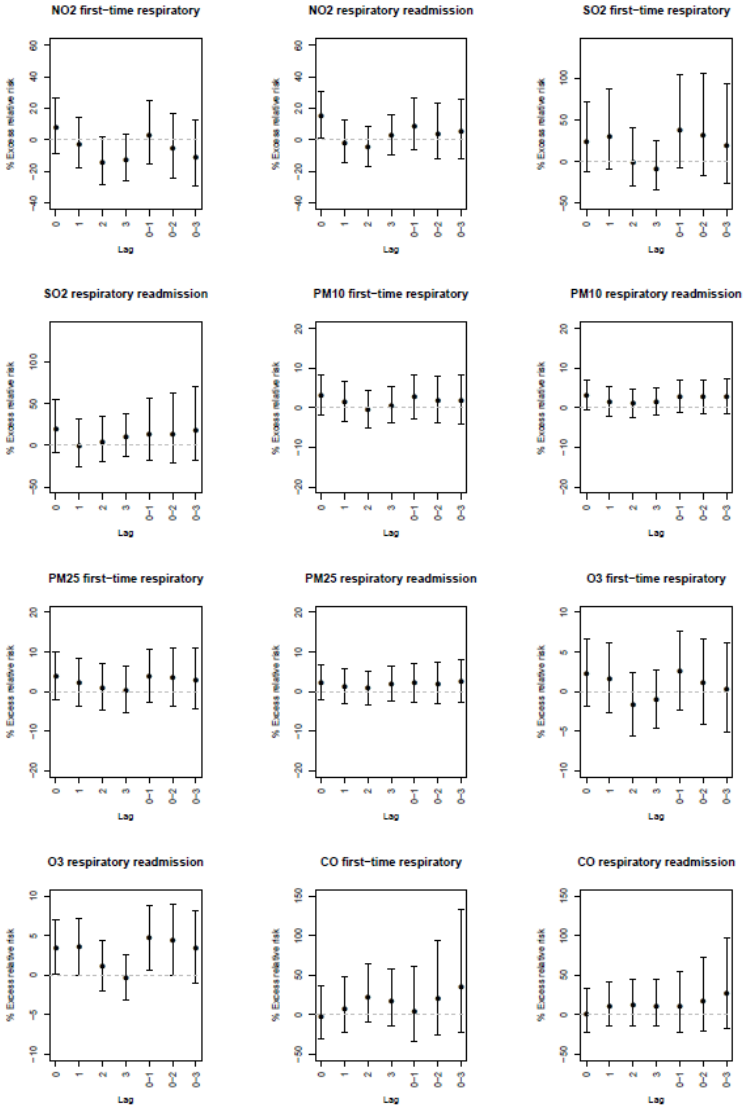
b) Readmissions



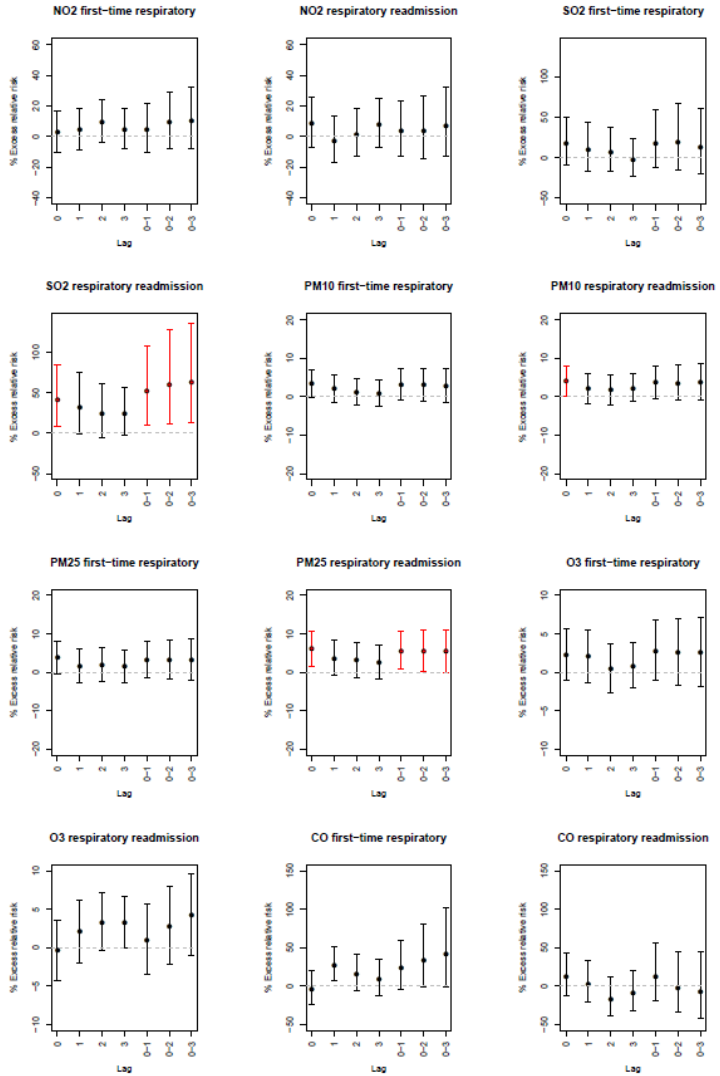
*100 μg/m^3 for CO
*Suzhou (2010-2016)
p<0.05 (in both time-series and case-crossover analysis)

Figure C9.6 Percent excess risk of hospitalisation for major respiratory disease associated with a 10 μg/m^3 increase* in AAP Haikou (2013-2016*) in those aged 60 years and over, and under 60 years, respectively

a) 60 years and over



b) Under 60 years

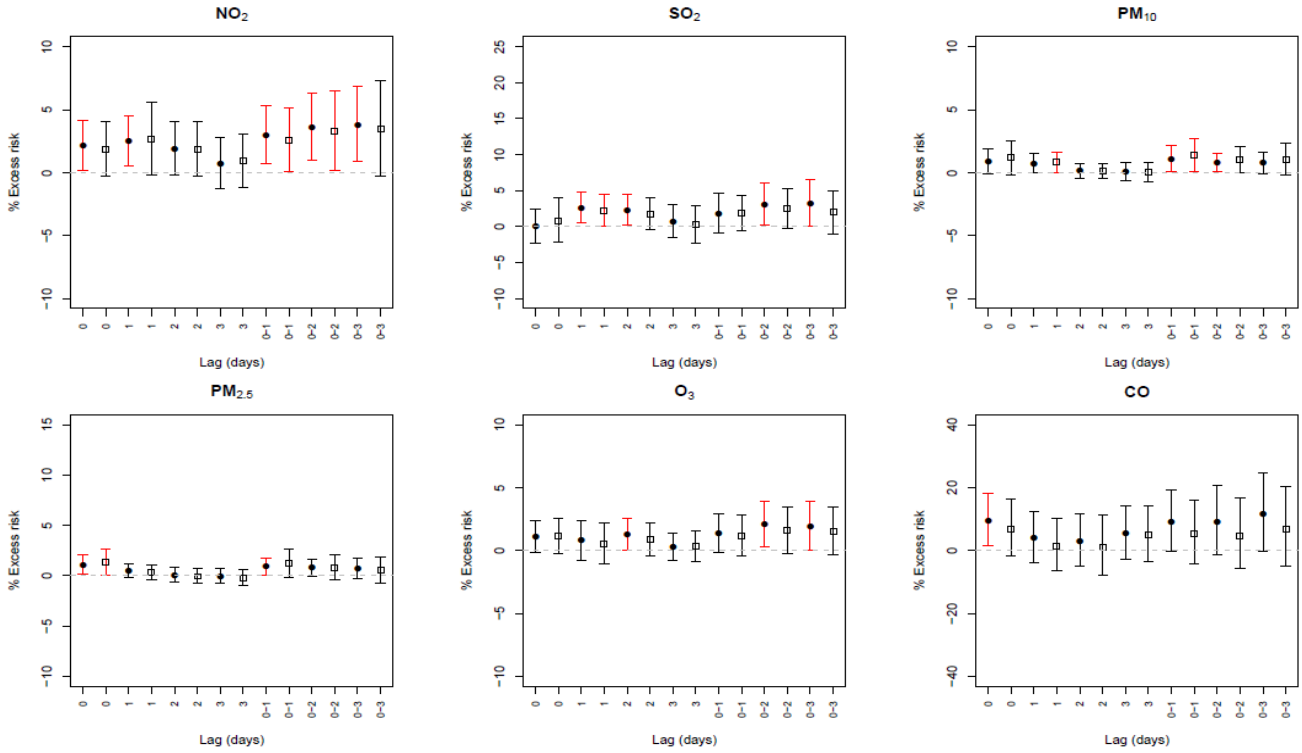


*100 μg/m^3 for CO

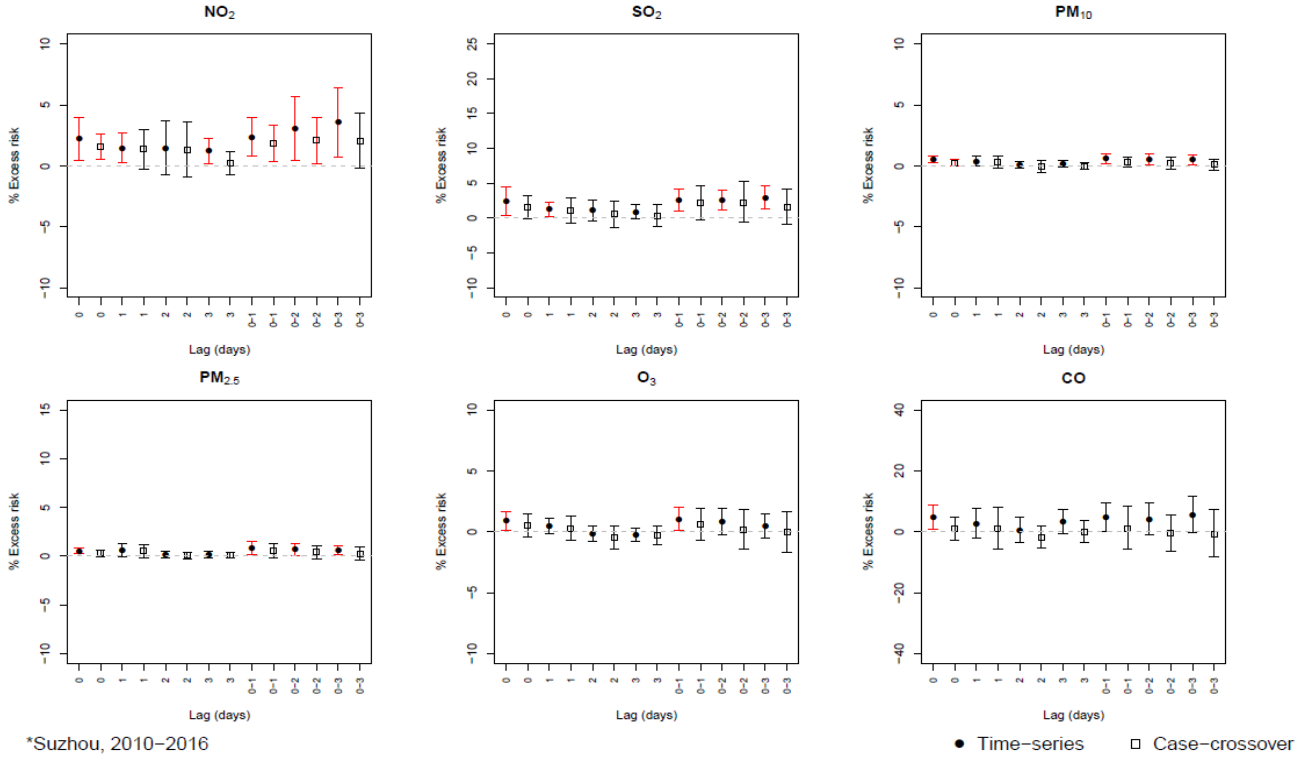
p<0.05 (in both time-series and case-crossover analysis)

Figure C9.7 Pooled estimates for a 10 μg/m^3 increase* in AAP and associated risk of major cardiovascular disease hospitalisation in those aged 60 years and over across the five CKB urban regions by spell type (2013-2016)**

a) First-time spells



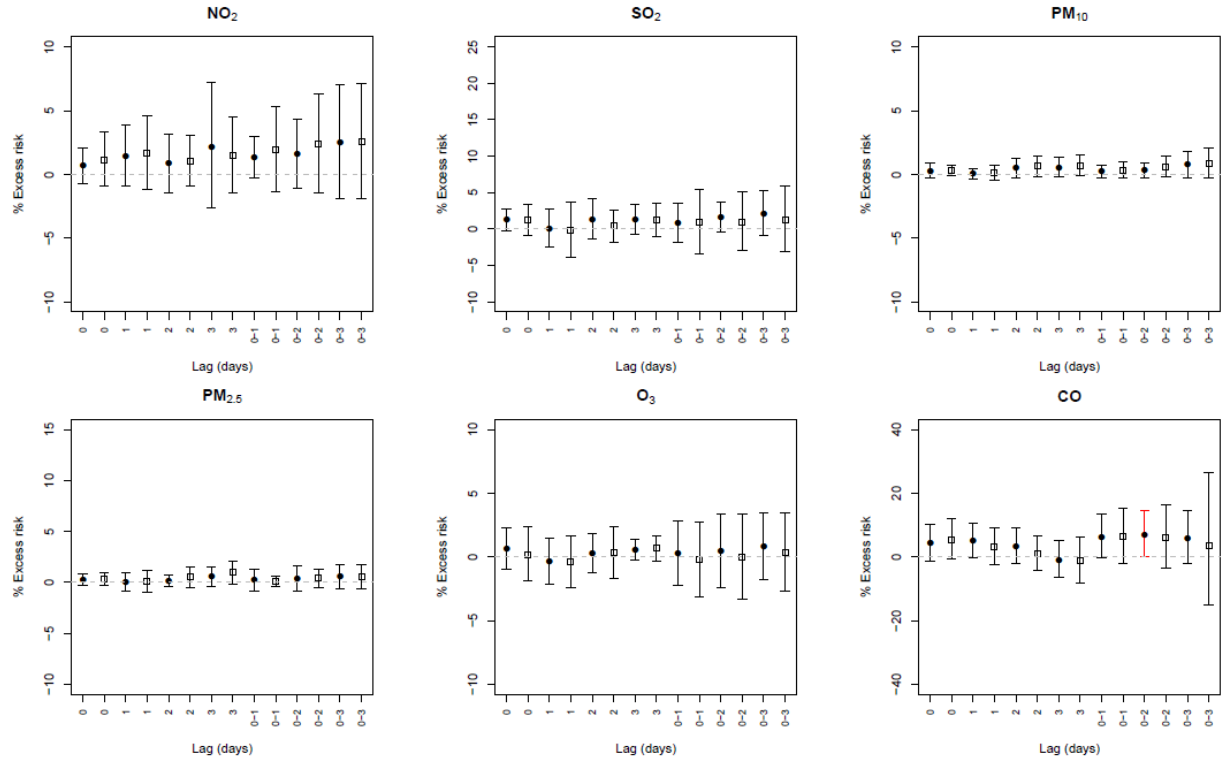
b) Readmissions



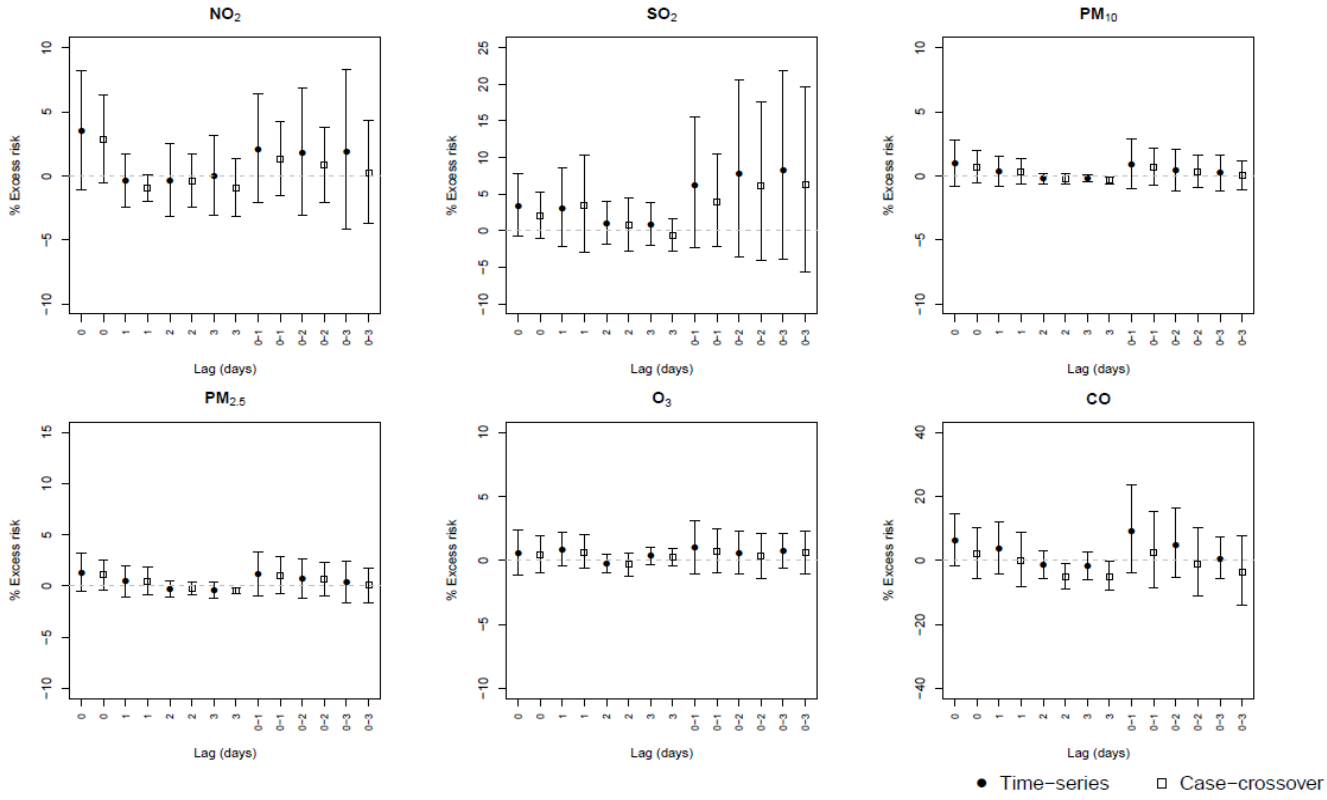
*100 μg/m^3 for CO
** Suzhou (2010-2015)
p<0.05

Figure C9.8 Pooled estimates for a 10 μg/m^3 increase* in AAP and associated risk of major cardiovascular disease hospitalisation in those aged under 60 years across the five CKB urban regions by spell type (2013-2016)**

a) First-time spells



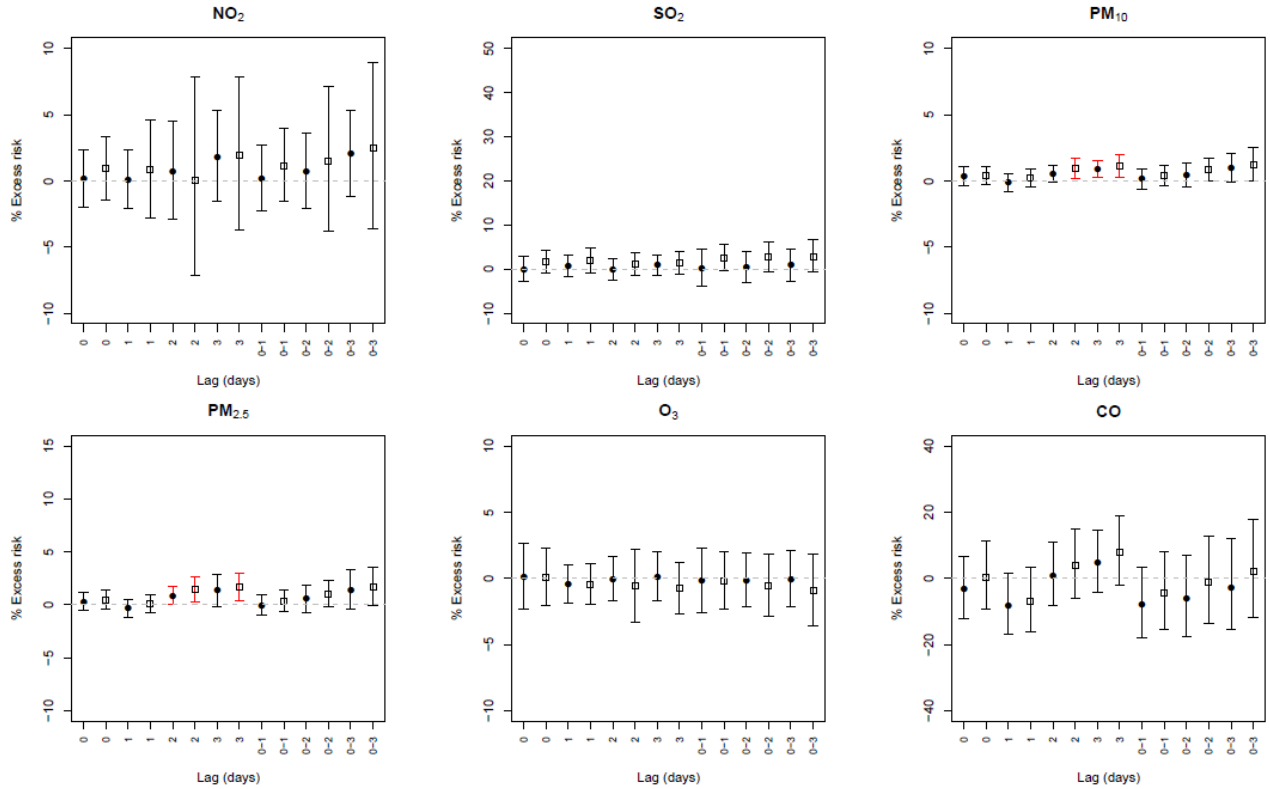
b) Readmissions



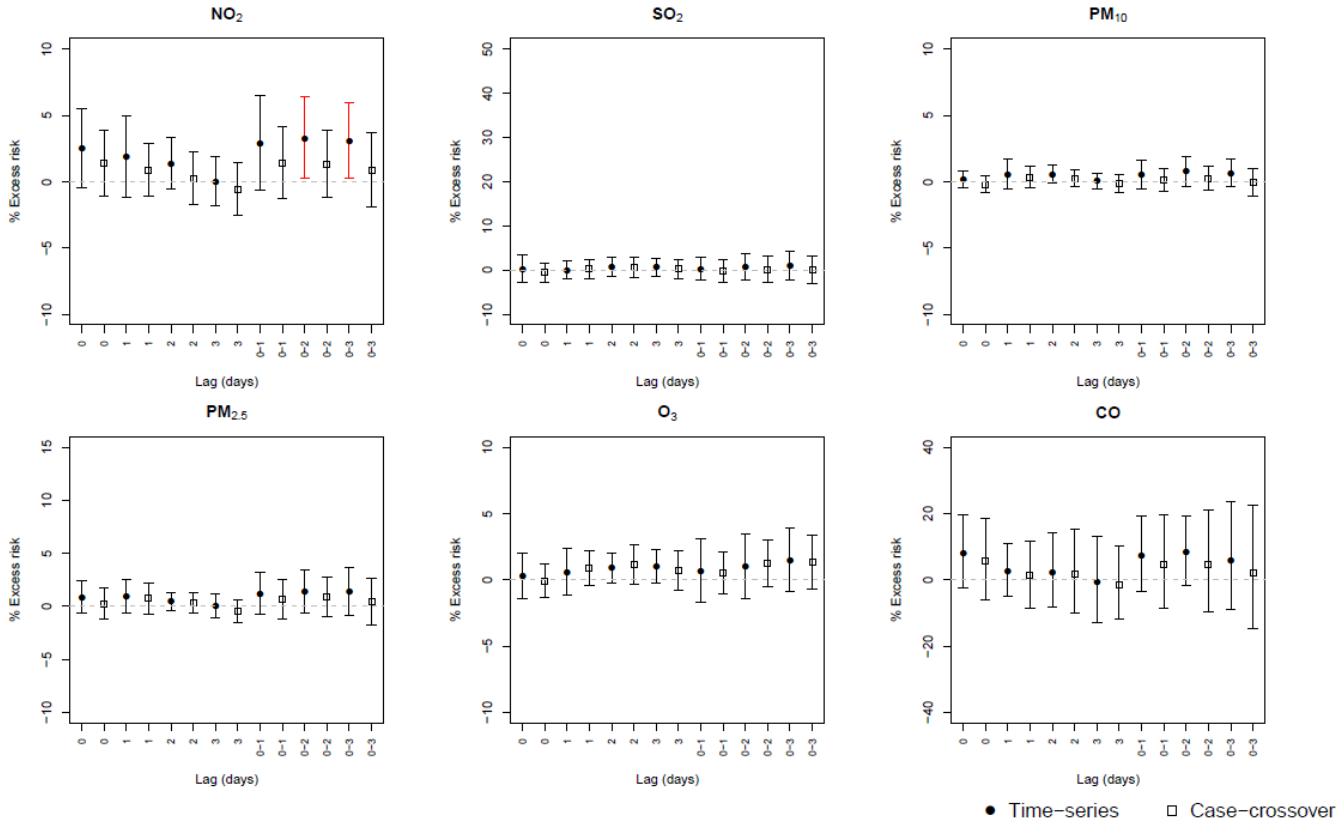
*100 μg/m^3 for CO
**Suzhou (2010-2015)
p<0.05

Figure C9.9 Pooled estimates for a 10 μg/m^3 increase* in AAP and associated risk of major respiratory disease spells in those aged 60 years and over across the five CKB urban regions (2013-2016)**

a) First-time spells



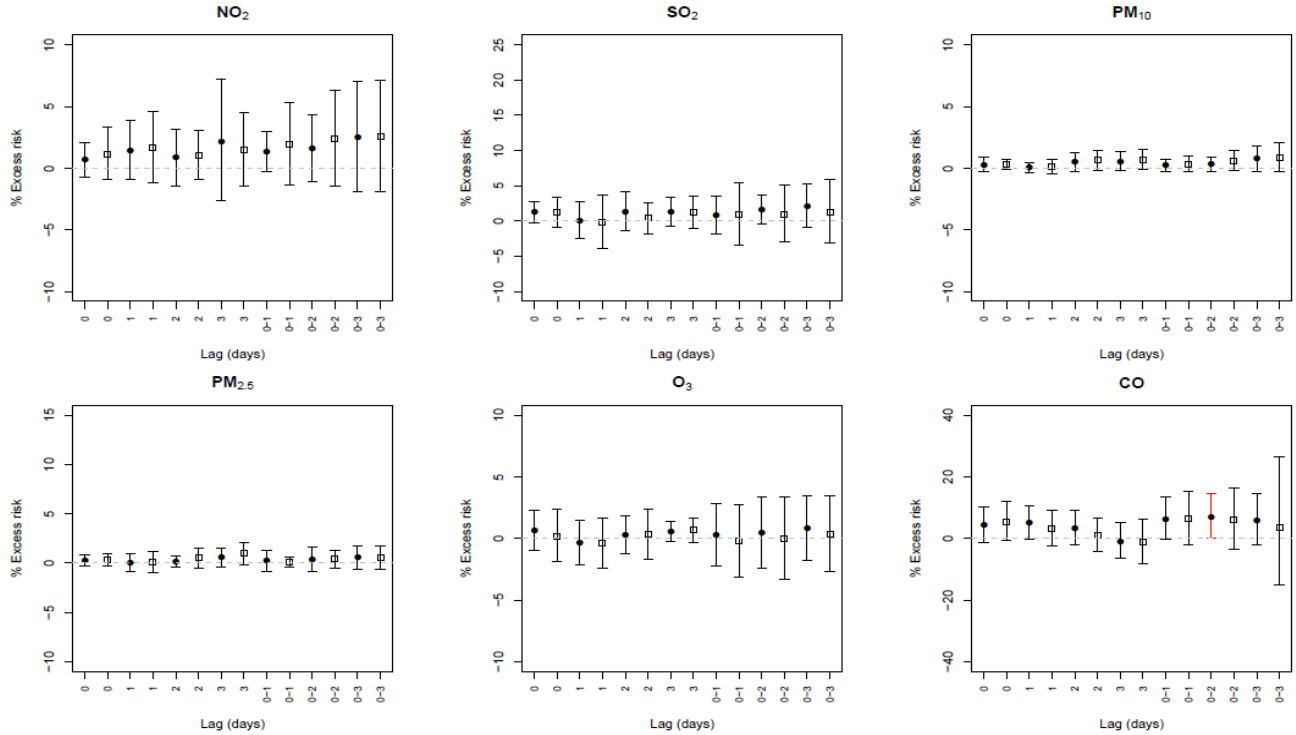
b) Readmissions



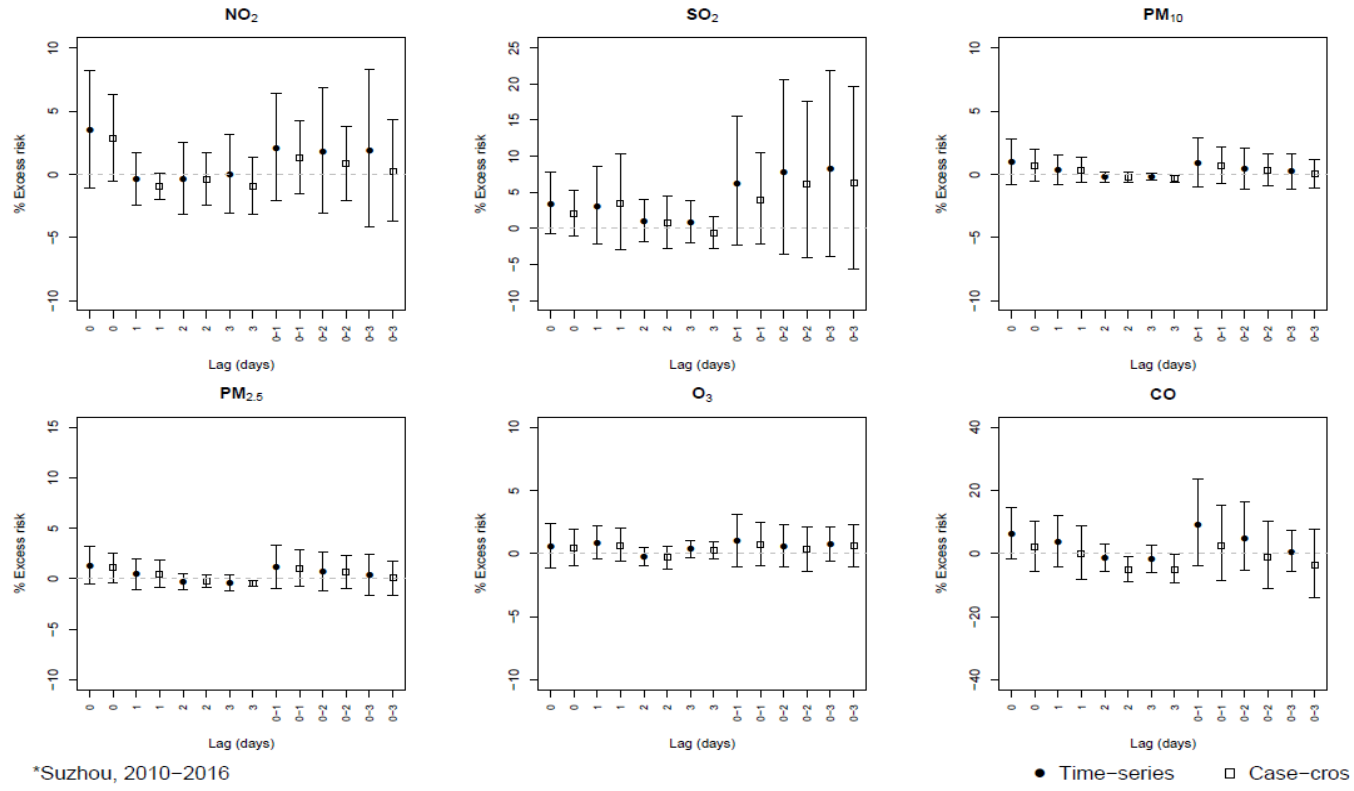
*100 μg/m^3 for CO
** Suzhou (2010-2016)
p<0.05

Figure C9.10 Pooled estimates for a 10 μg/m^3 increase* in AAP and associated risk of major respiratory disease spells in those under 60 years across the five CKB urban regions (2013-2016)**

a) First-time spells



b) Readmissions



*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05

Appendix C10. Subgroup analysis by sex

Table C10.1 Counts of cardio-respiratory spells by region in male CKB participants

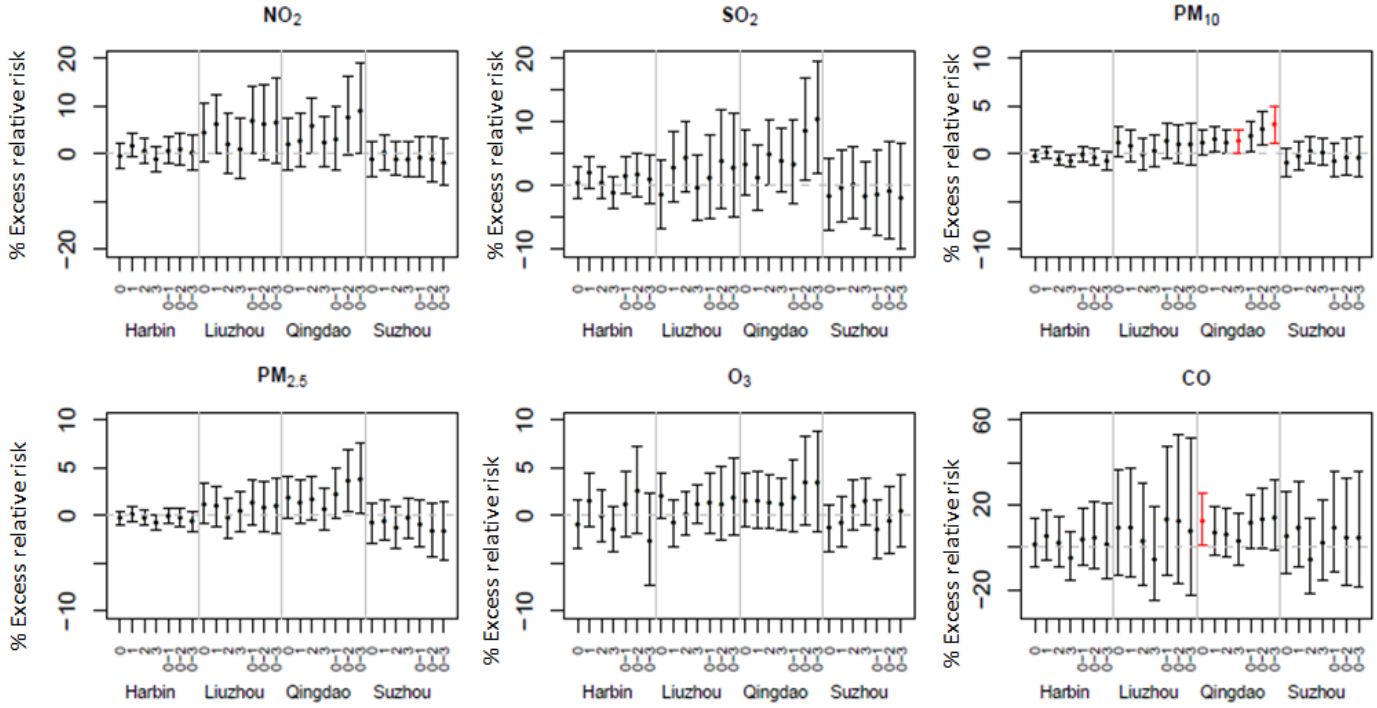
	CKB region and study populations					
	Harbin (n=21,732)	**Qingdao (n=15,024)**	**Suzhou (n=21,967)**	**Liuzhou (n=17,997)**	**Haikou (n=10,457)**	**Total (n=87,177)**
Major cardiovascular disease						
Total	13,025	3820	3244	5027	4331	29,447
First-time	2686	1050	1271	1242	990	7239
Readmissions	10,339	2770	1973	3785	3341	22,208
Mean daily count	9.02	2.65	1.27	4.22	3.00	-
Major respiratory disease						
Total	2159	992	3605	1997	1340	10,093
First-time	1076	474	1476	803	608	4437
Readmissions	1083	518	2129	1194	732	5656
Mean daily count	1.50	0.69	1.41	1.68	0.93	-

Table C10.2 Counts of cardio-respiratory spells by region in female CKB participants

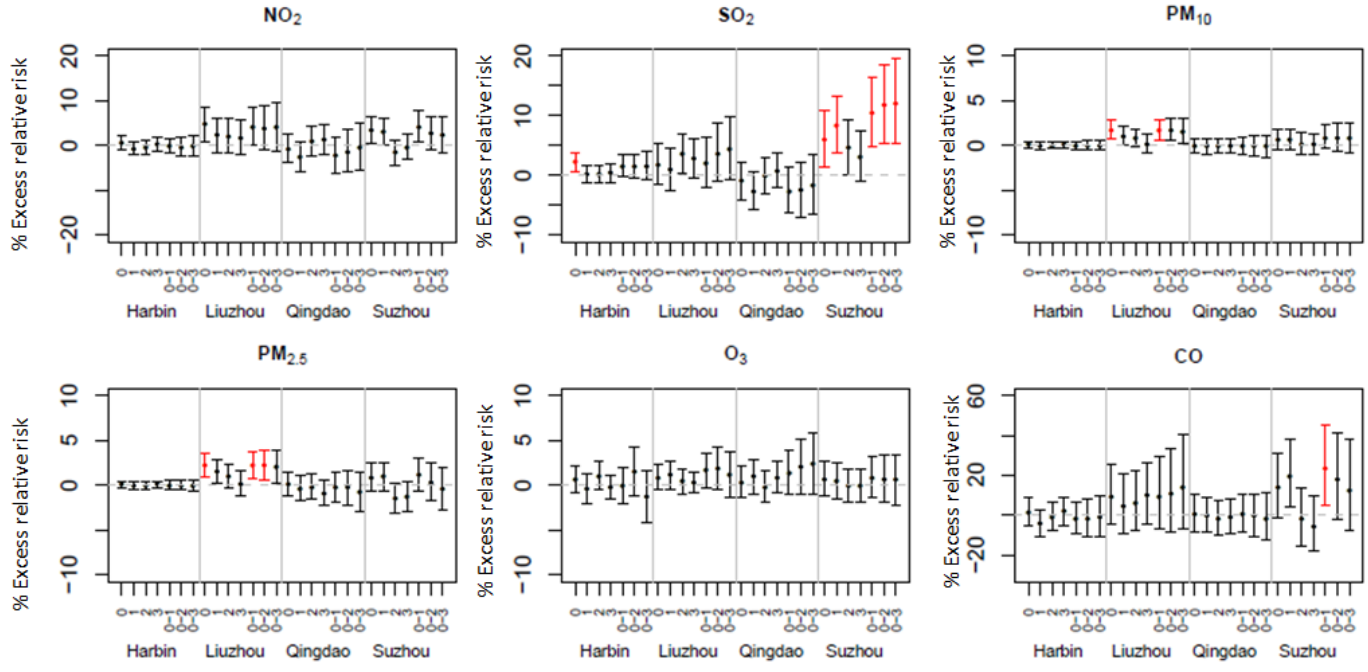
	CKB region and study populations					
	Harbin (n=33,162)	**Qingdao (n=19,479)**	**Suzhou (n=30,649)**	**Liuzhou (n=29,923)**	**Haikou (n=18,629)**	**Total (n=131,842)**
Major cardiovascular disease						
Total	19,798	5973	4206	7029	6947	43,953
First-time	4448	1437	1768	2035	1781	11,469
Readmissions	15,350	4536	2438	4994	5166	32,484
Mean daily count	13.72	4.14	1.64	5.91	4.81	-
Major respiratory disease						
Total	2750	1090	3381	1905	1860	10,986
First-time	1553	603	1884	1041	1085	6166
Readmissions	1197	487	1497	864	775	4820
Mean daily count	1.91	0.76	1.32	1.60	1.29	-

Figure C10.1 Percent excess risk of hospitalisation from major cardiovascular disease associated with a 10μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using time-series analysis in males**

a) First-time spells



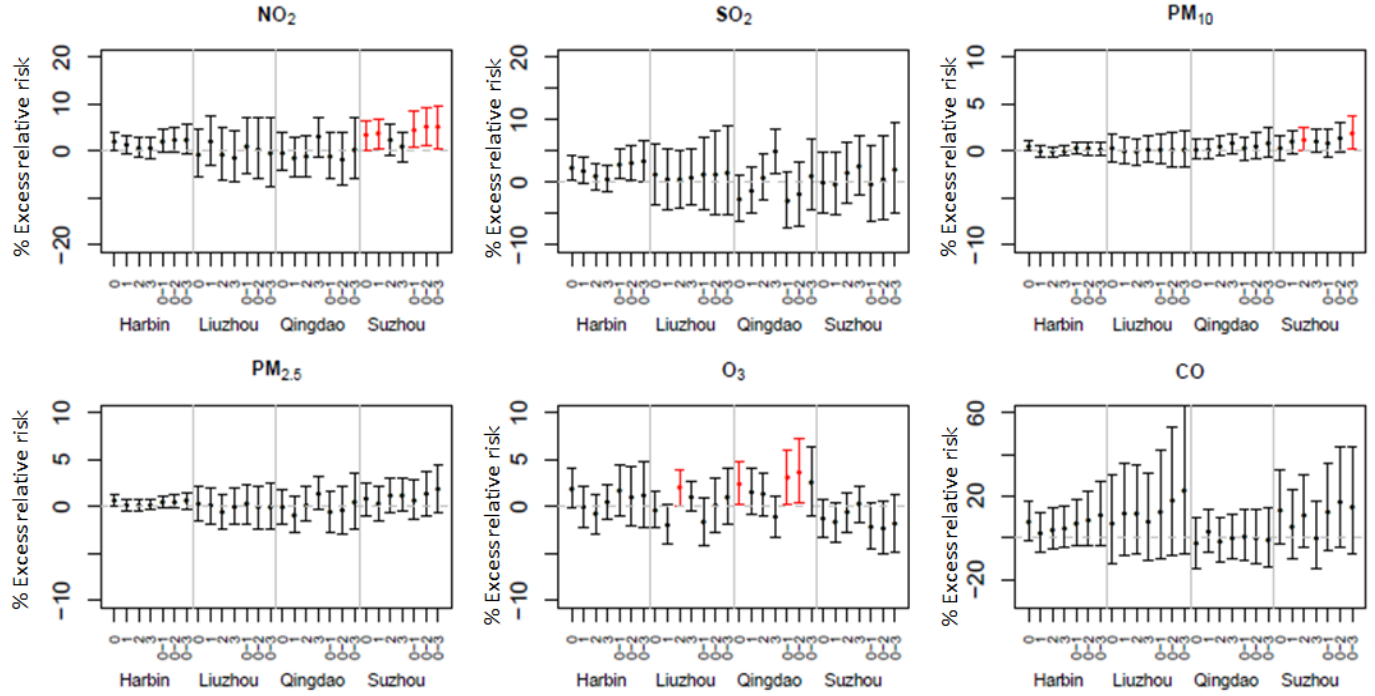
b) Readmissions



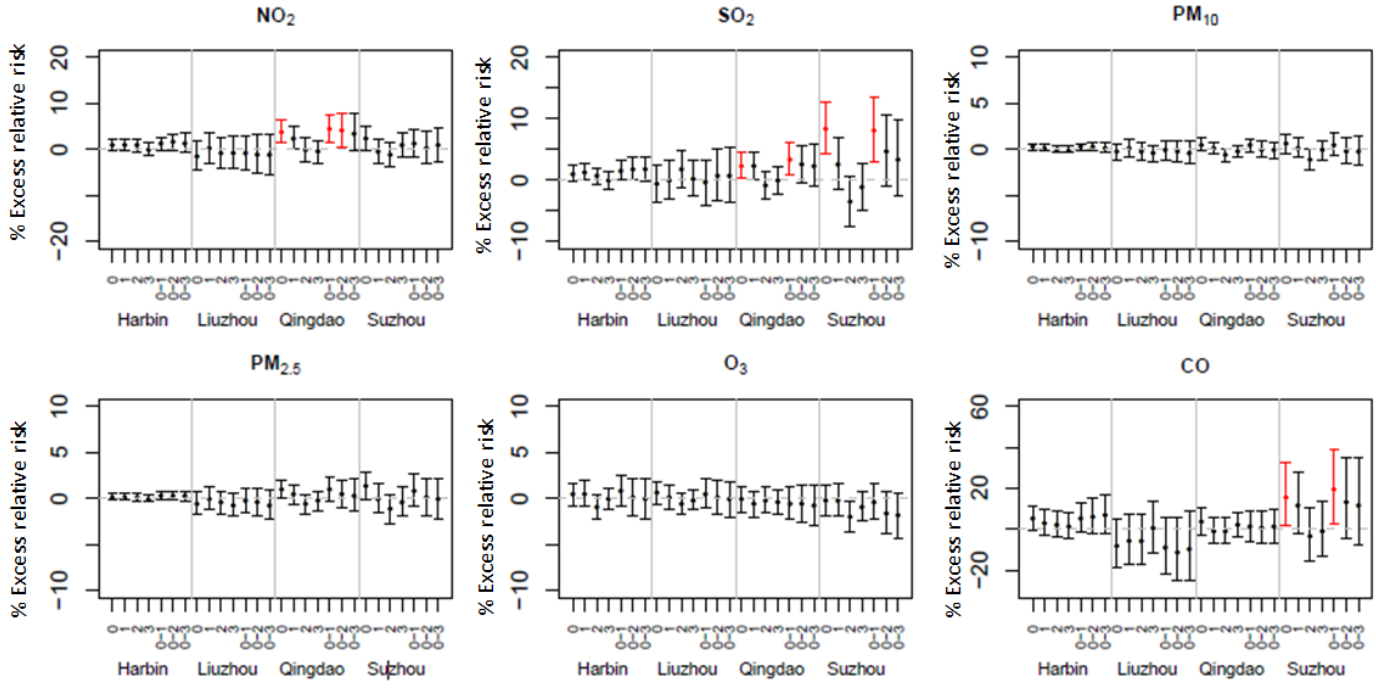
*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05 (in both time-series and case-crossover analysis)

Figure C10.2 Percent excess risk of hospitalisation from major cardiovascular disease associated with a 10μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using time-series analysis in females**

a) First-time spells



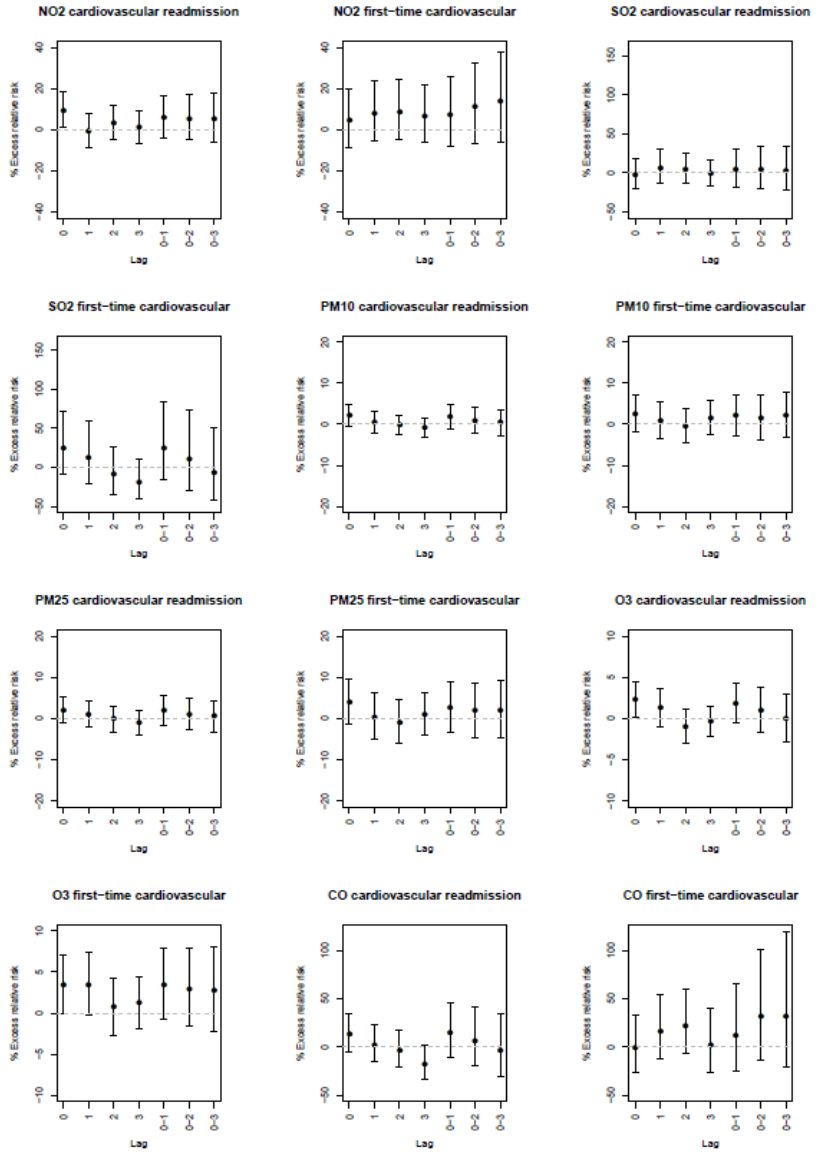
b) Readmissions



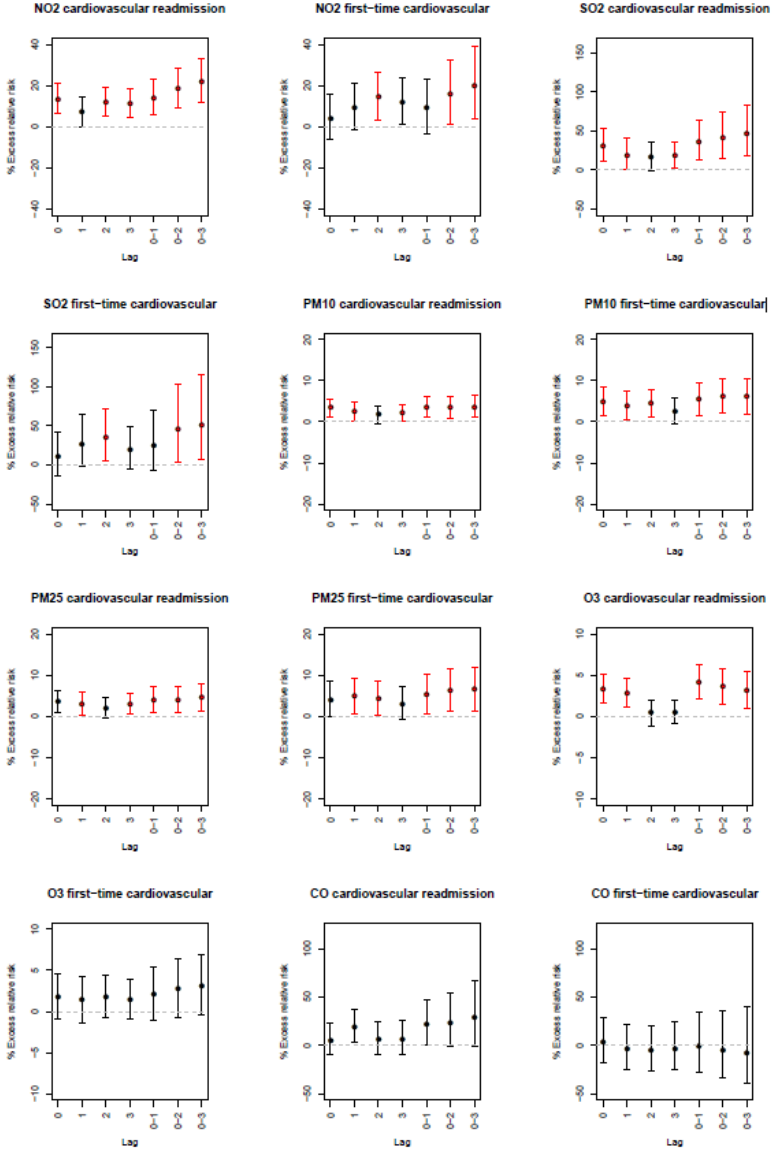
*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05 (in both time-series and case-crossover analysis)

Figure C10.3 Percent excess risk of hospitalisation from major cardiovascular disease associated with a 10μg/m^3 increase* in AAP Haikou (2013-2016) in males and females, respectively

a) Males



b) Females

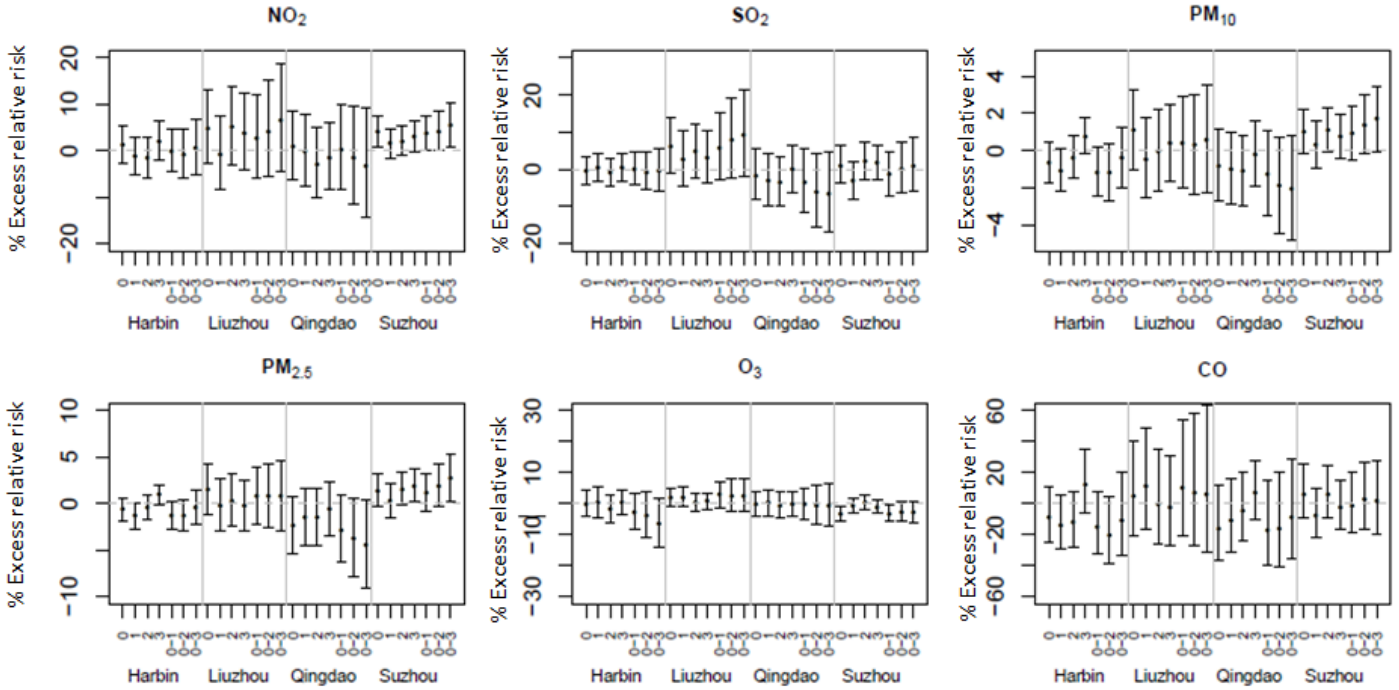


*100 μg/m^3 for CO

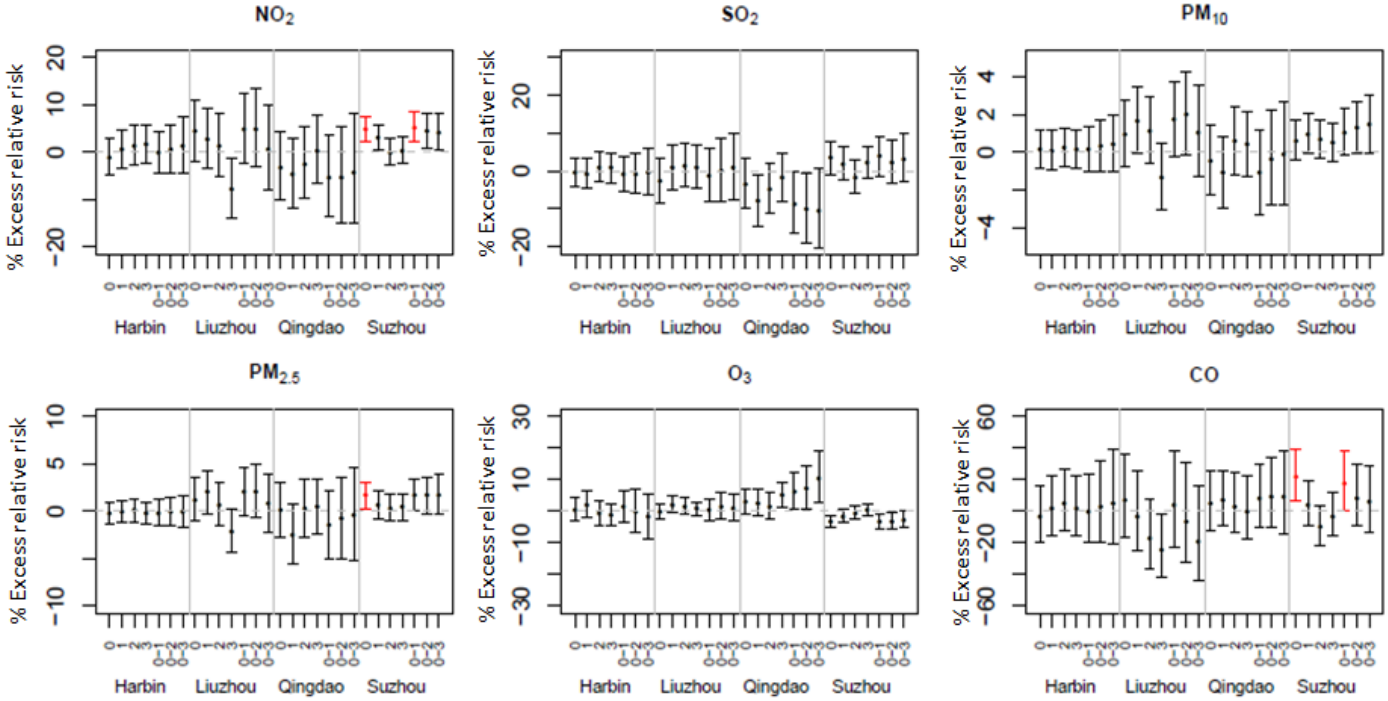
p<0.05 (in both time-series and case-crossover analysis)

Figure C10.4 Percent excess risk of hospitalisation from major respiratory disease associated with a 10μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using time-series analysis in men**

a) First-time spells



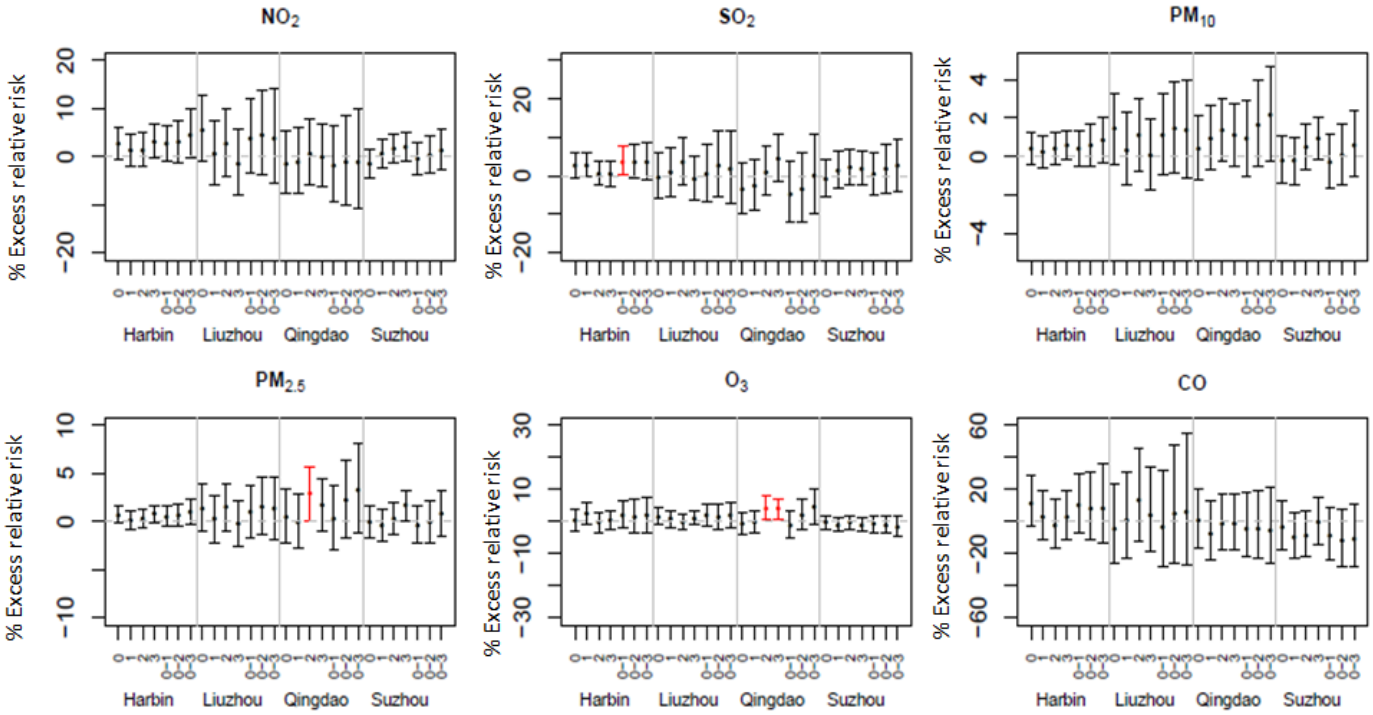
b) Readmissions



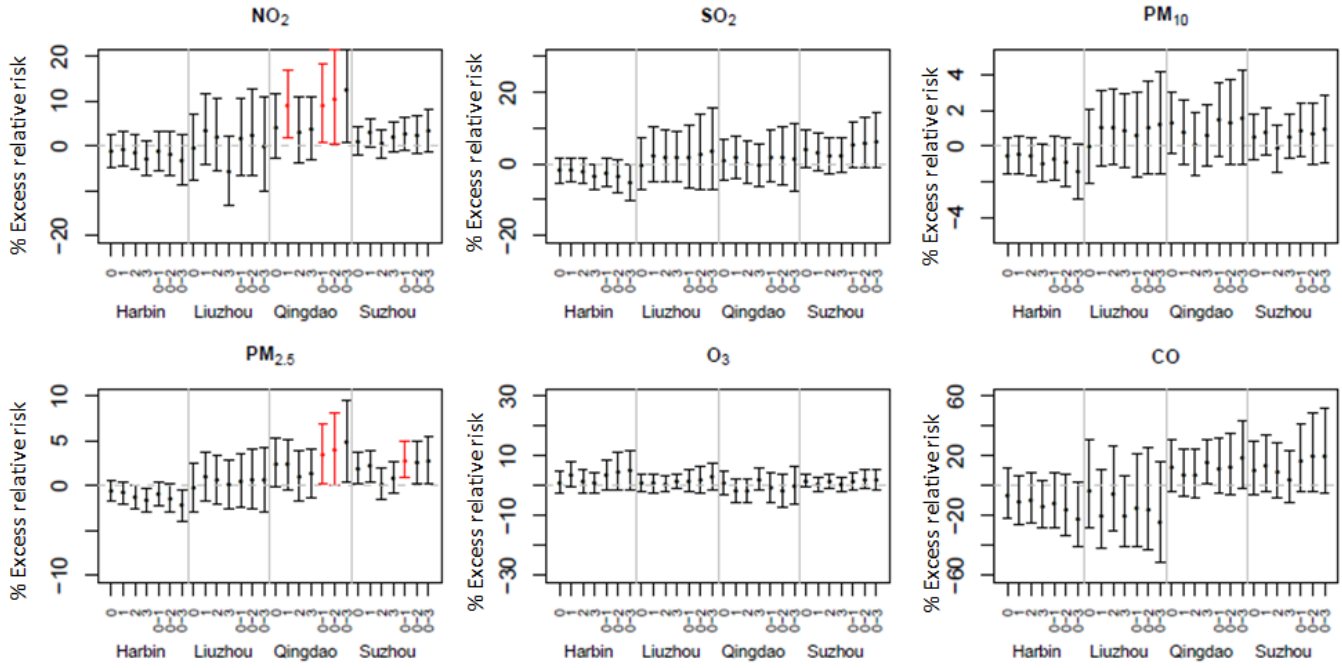
*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05 (in both time-series and case-crossover analysis)

Figure C10.5 Percent excess risk of hospitalisation from major respiratory disease associated with a 10 μg/m^3 increase* in AAP in four of the five CKB urban regions (2013-2016) using time-series analysis in women**

a) First-time spells



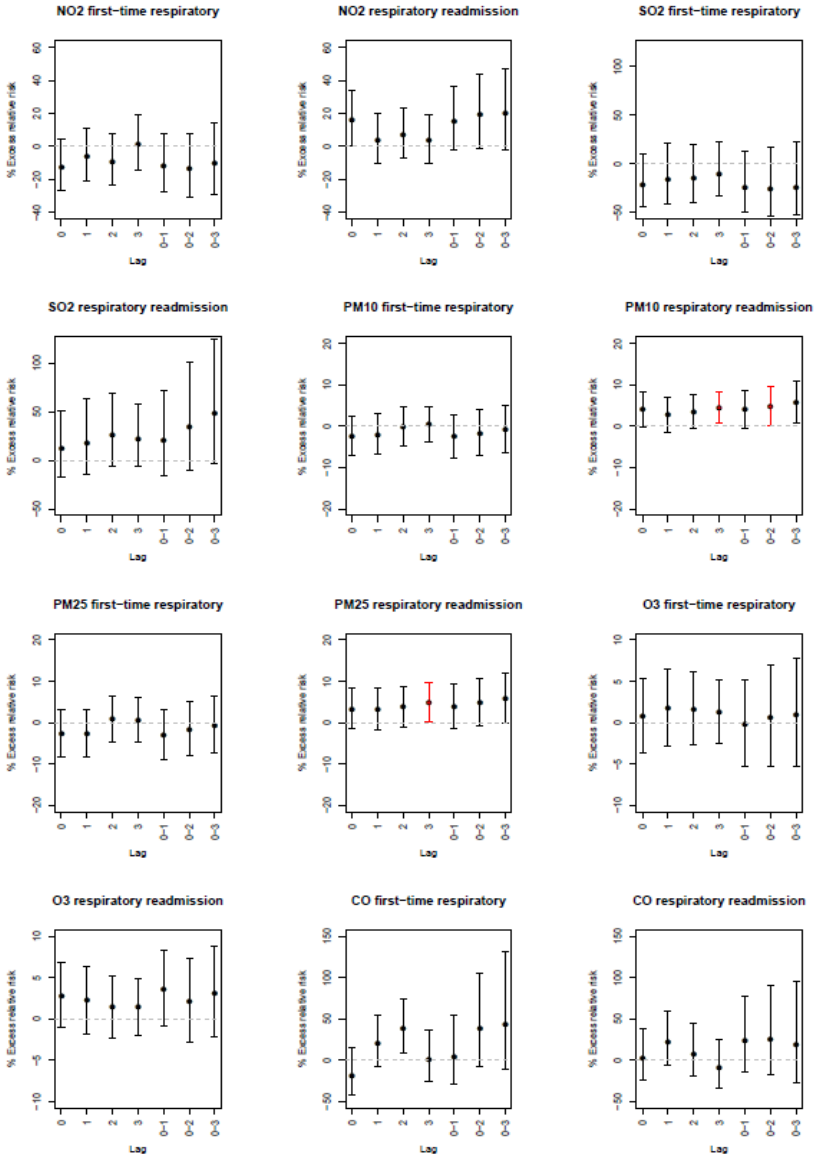
b) Readmissions



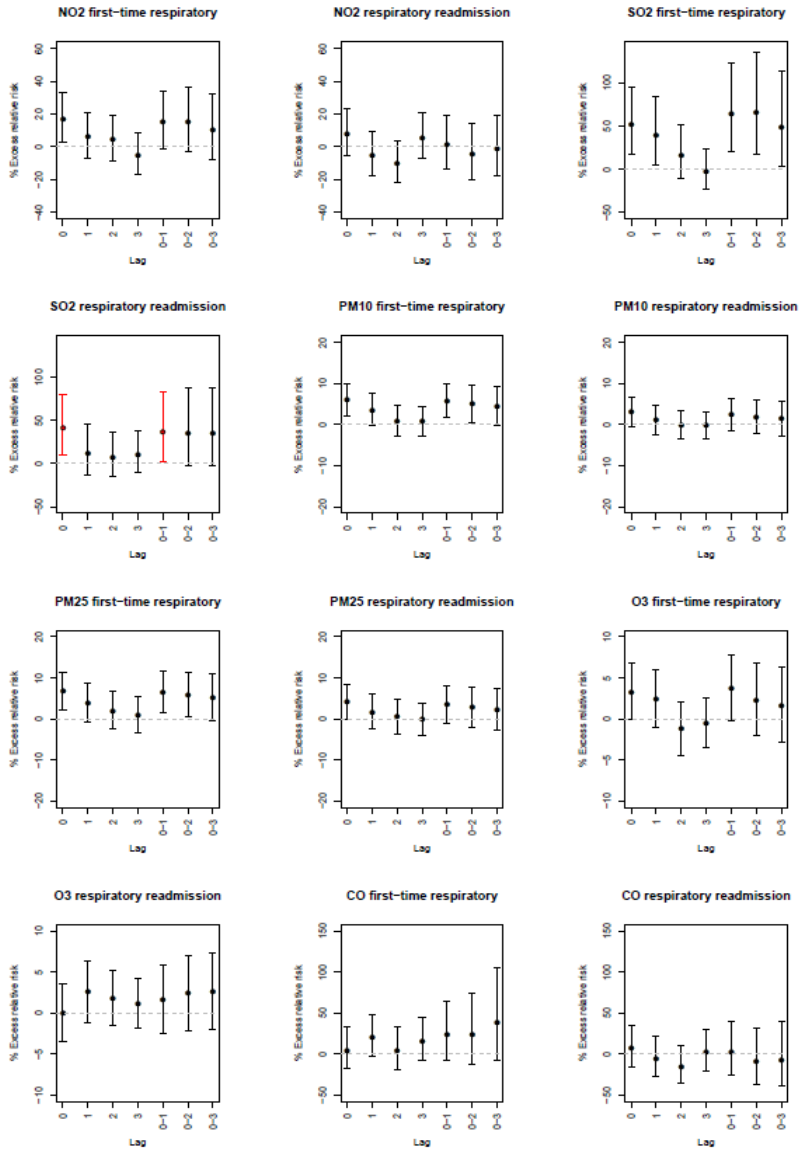
*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05 (in both time-series and case-crossover analysis)

Figure C10.6 Percent excess risk of hospitalisation from major respiratory disease associated with a 10 μg/m^3 increase* in AAP Haikou (2013-2016) in males and females, respectively

a) Males



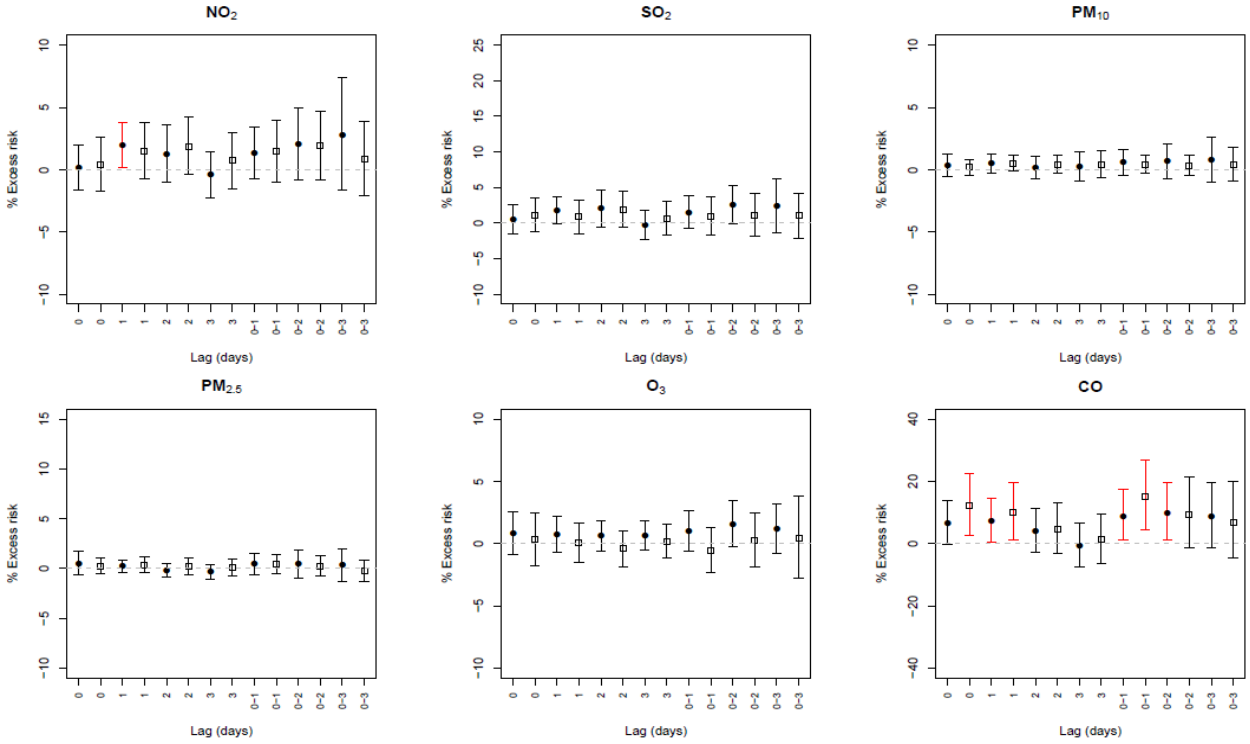
b) Females



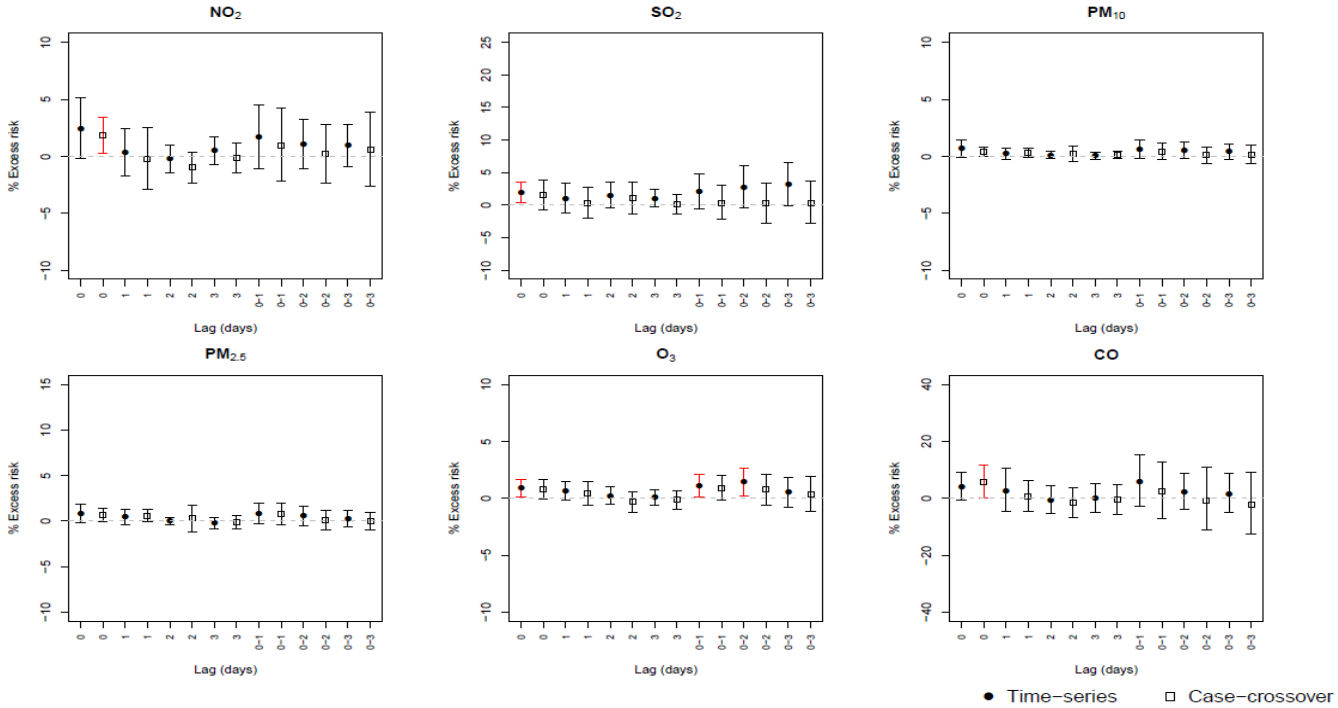
*100 μg/m^3 for CO — p<0.05 (in both time-series and case-crossover analysis)

Figure C10.7 Pooled estimates for a 10 μg/m^3 increase* in AAP and associated risk of cardiovascular disease spells in males across the five CKB urban regions (2013-2016)**

a) First-time spells



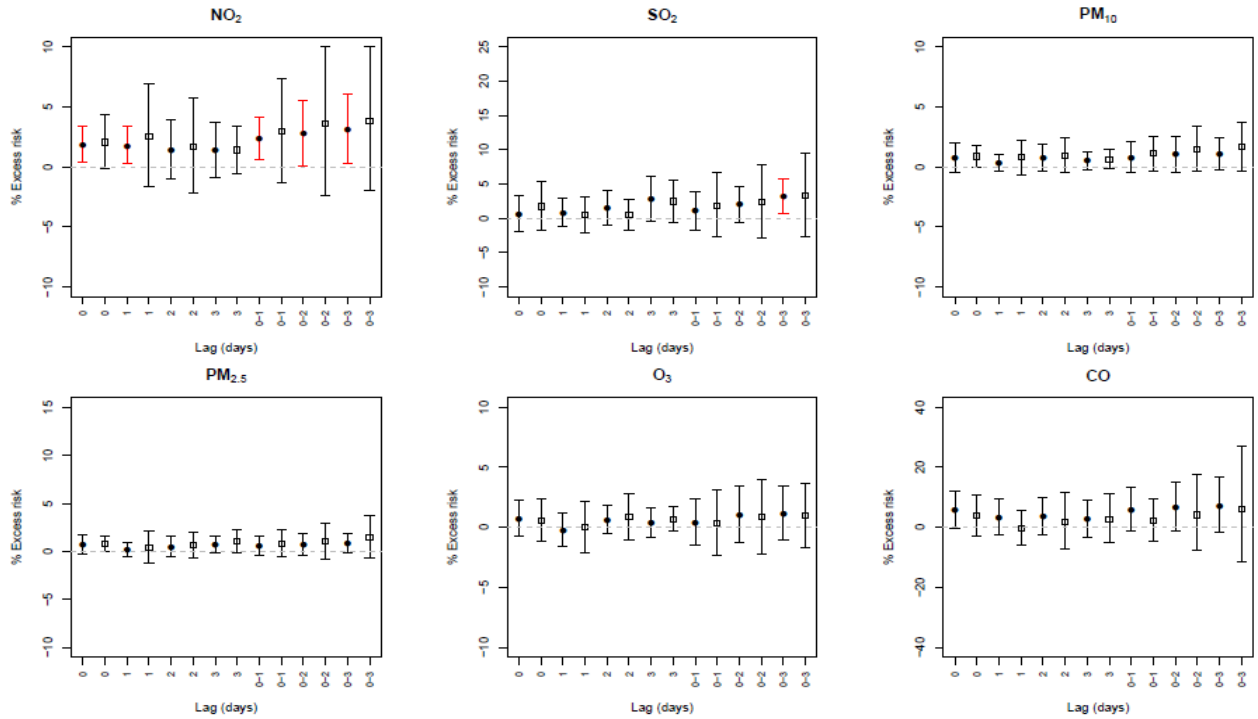
b) Readmissions



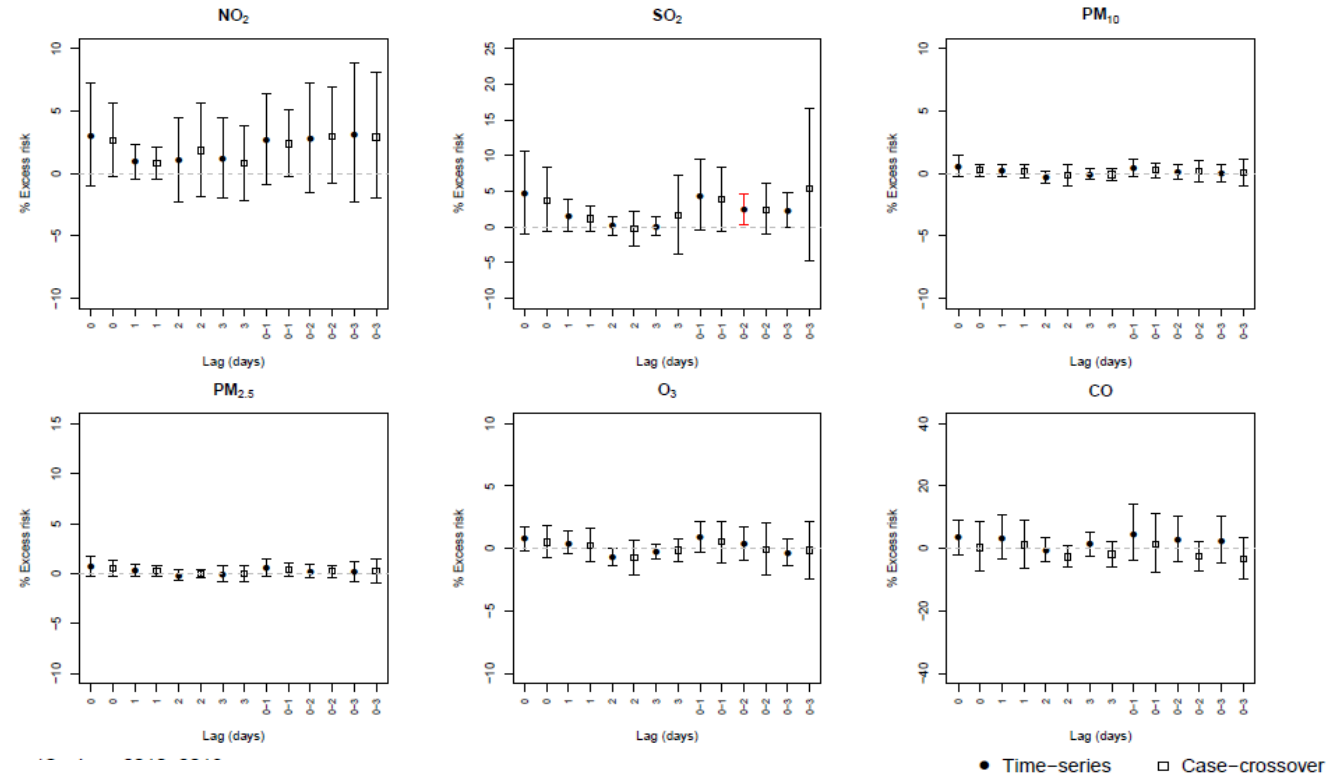
*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05

Figure C10.8 Pooled estimates for a 10 μg/m^3 increase* in AAP and associated risk of cardiovascular disease spells in females across the five CKB urban regions (2013-2016)**

a) First-time spells



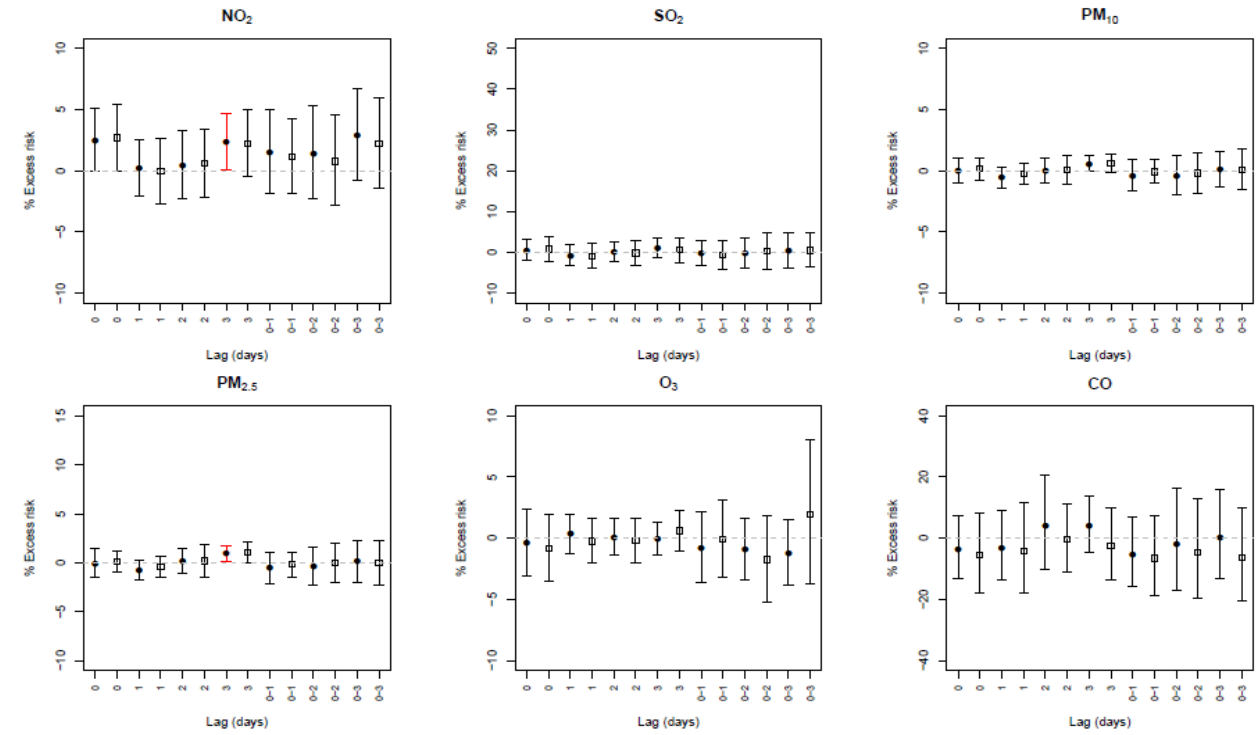
b) Readmissions



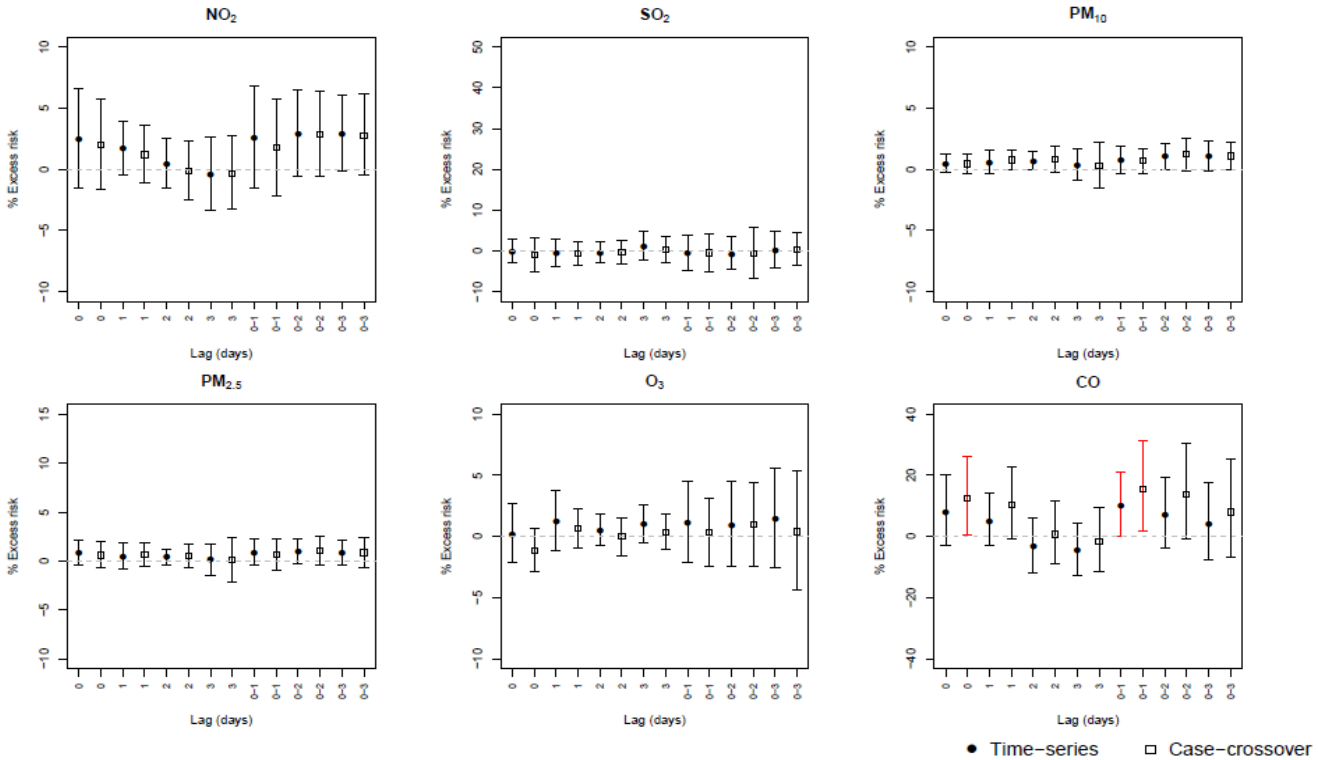
*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05

Figure C10.9 Pooled estimates for a 10 μg/m^3 increase* in AAP and associated risk of respiratory disease spells in males across the five CKB urban regions (2013-2016)**

a) First-time spells



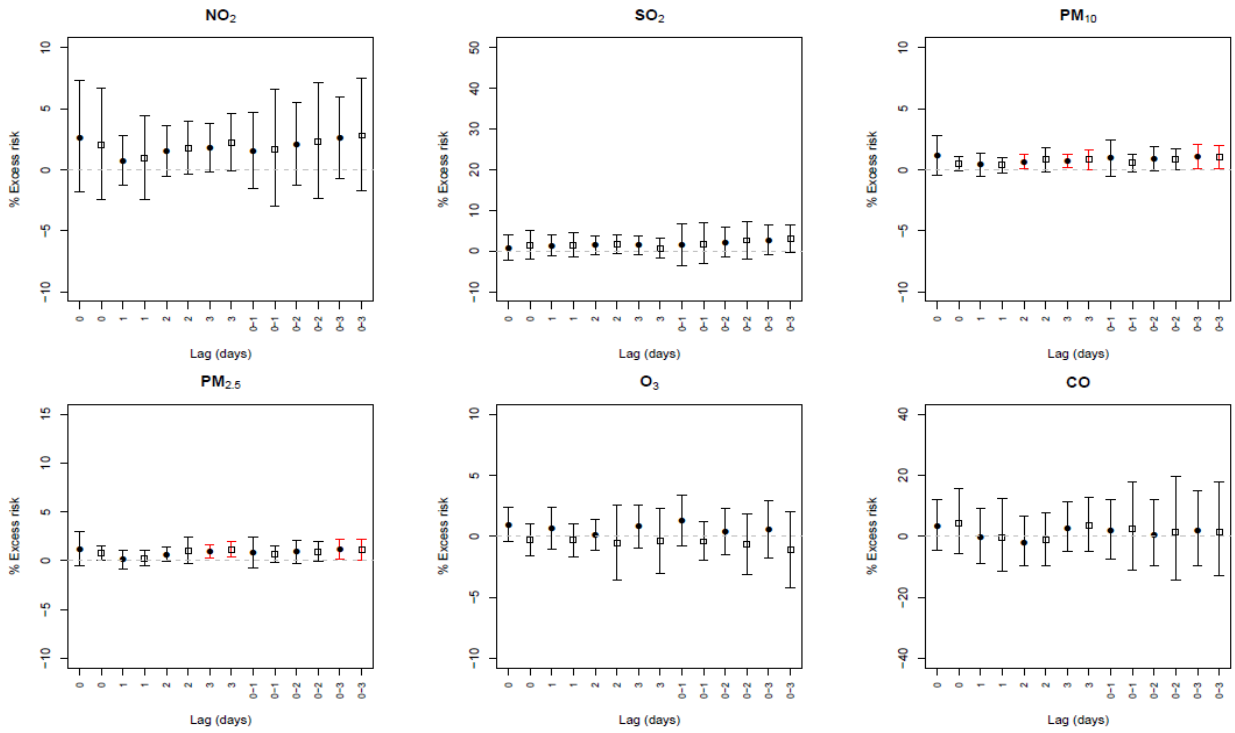
b) Readmissions



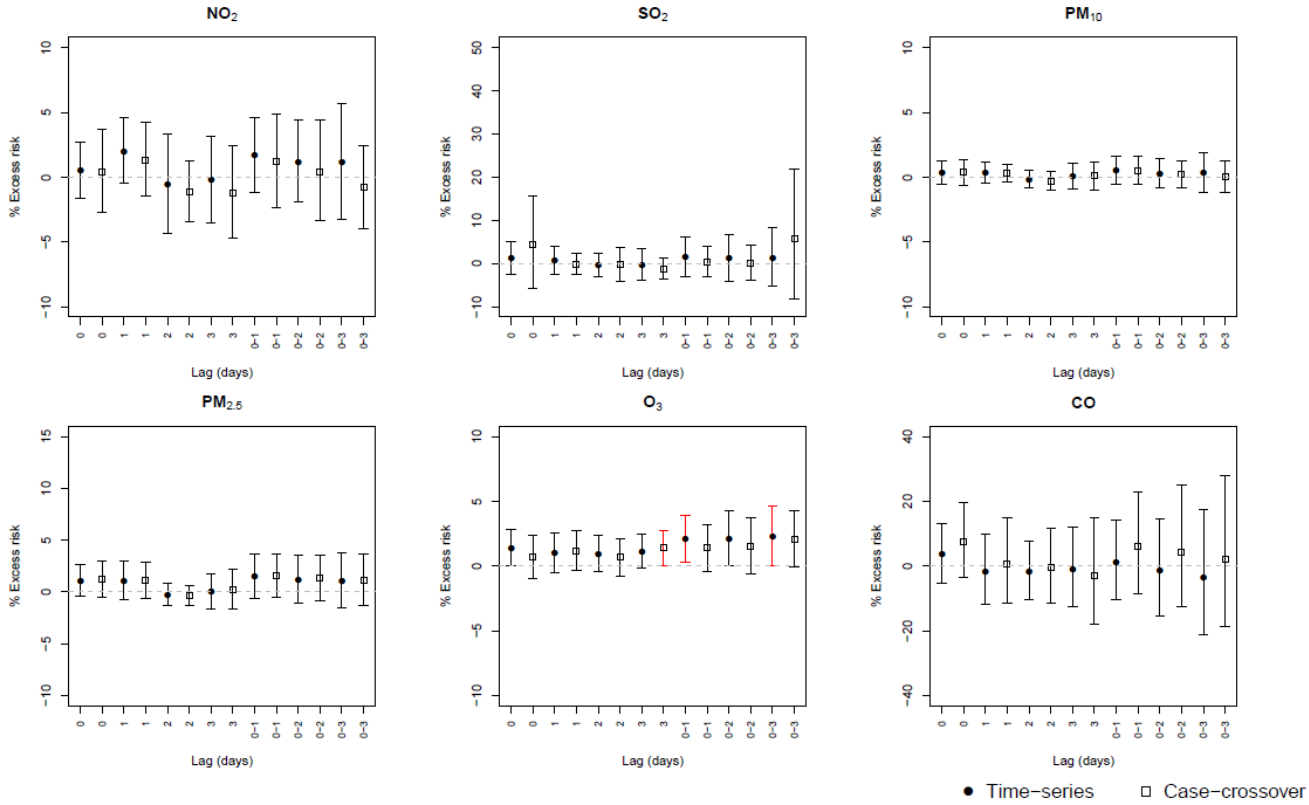
*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05

Figure C10.10 Pooled estimates for a 10 μg/m^3 increase* in AAP and associated risk of respiratory disease spells in females across the five CKB urban regions (2013-2016)**

a) First-time spells



b) Readmissions



*100 μg/m^3 for CO
**Suzhou (2010-2016)
p<0.05

Appendix C11. Percent excess risk (95% CIs) for short-term AAP exposure and cardiovascular readmissions spells in generalised additive models (GAMs) with differing degrees of freedom choice* and case-crossover analysis, respectively

Region, and pollutant	GAM-1†	GAM-2‡	GAM-3§	Case-crossover ¶
Harbin				
NO_2	0.79 (-0.34, 1.93)	0.97 (-0.15, 2.10)	0.68 (-0.46, 1.83)	0.43 (-0.42, 1.30)
SO_2	1.53 (0.40, 2.68)	1.63 (0.51, 2.76)	1.42 (0.27, 2.58)	0.03 (-0.74, 0.80)
PM_{10}	0.19 (-0.09, 0.47)	0.21 (-0.07, 0.49)	0.14 (-0.15, 0.42)	-0.03 (-0.24, 0.18)
$PM_{2.5}$	0.14 (-0.17, 0.46)	0.16 (-0.15, 0.47)	0.09 (-0.22, 0.41)	-0.10 (-0.34, 0.15)
O_3	0.38 (-0.71, 1.48)	0.27 (-0.82, 1.37)	0.53 (-0.60, 1.68)	-0.40 (-1.18, 0.40)
CO	3.64 (-1.46, 9.02)	3.07 (-1.93, 8.32)	3.02 (-2.09, 8.39)	-2.60 (-6.25, 1.17)
Qingdao				
NO_2	2.23 (0.12, 4.39)	2.38 (0.28, 4.53)	2.16 (0.05, 4.33)	2.12 (0.11, 4.18)
SO_2	1.31 (-0.54, 3.19)	1.44 (-0.37, 3.29)	1.21 (-0.65, 3.11)	1.18 (-0.60, 3.00)
PM_{10}	0.36 (-0.17, 0.89)	0.37 (-0.15, 0.90)	0.36 (-0.17, 0.89)	0.31 (-0.19, 0.82)
$PM_{2.5}$	0.72 (-0.16, 1.61)	0.72 (-0.16, 1.60)	0.69 (-0.19, 1.58)	0.51 (-0.32, 1.34)
O_3	0.02 (-1.12, 1.18)	-0.18 (-1.30, 0.95)	0.05 (-1.10, 1.20)	0.10 (-0.98, 1.20)
CO	1.75 (-4.03, 7.89)	1.28 (-4.42, 7.31)	1.43 (-4.41, 7.63)	1.35 (-4.32, 7.36)
Suzhou				
NO_2	2.88 (0.90, 4.89)	2.82 (0.88, 4.82)	2.79 (0.83, 4.80)	2.89 (0.65, 5.18)
SO_2	7.32 (4.24, 10.59)	7.17 (4.14, 10.29)	6.94 (3.84, 10.12)	7.40 (3.77, 11.17)
PM_{10}	0.62 (-0.15, 1.39)	0.55 (-0.20,1.32)	0.55 (-0.23, 1.33)	0.30 (-0.58, 1.19)
$PM_{2.5}$	1.10 (0.03, 2.19)	1.15 (0.09, 2.22)	1.12 (0.04, 2.20)	1.36 (0.11, 2.63)
O_3	0.19 (-1.04, 1.43)	0.11 (-1.11, 1.34)	0.32 (-0.91, 1.57)	0.23 (-1.18, 1.66)
CO	15.08 (4.39, 26.85)	15.52 (4.87, 27.27)	14.74 (3.75, 26.88)	19.23 (6.09, 34.01)
Liuzhou				
NO_2	1.24 (-1.30, 3.85)	0.90 (-1.60, 3.47)	0.95 (-1.59, 3.55)	1.63 (-0.81, 4.14)
SO_2	0.53 (-1.80, 2.90)	0.25 (-2.04, 2.58)	-0.03 (-2.35, 2.35)	1.31 (-1.10, 3.77)
PM_{10}	0.61 (-0.10, 1.32)	0.50 (-0.20, 1.21)	0.58 (-0.13, 1.30)	0.62 (-0.07, 1.30)
$PM_{2.5}$	0.69 (-0.23, 1.63)	0.57 (-0.34, 1.49)	0.70 (-0.23, 1.63)	0.72 (-0.17, 1.61)
O_3	0.65 (-0.30, 1.61)	0.52 (-0.42, 1.47)	0.54 (-0.41, 1.51)	0.61 (-0.37, 1.59)
CO	-0.51 (-9.81, 9.74)	-0.92 (-10.13, 9.23)	-2.05 (-11.24, 8.09)	0.01 (-9.27, 10.24)
Haikou				
NO_2	11.82 (5.79, 18.19)	16.99 (2.31, 33.78)	10.91 (4.90, 17.26)	8.57 (3.40, 14.00)
SO_2	17.39 (2.56, 14.37)	11.99 (6.02, 18.30)	15.82 (1.11, 32.66)	9.10 (-2.85, 22.52)
PM_{10}	2.91 (1.04, 4.82)	2.85 (0.98, 4.75)	2.58 (0.70, 4.49)	1.44 (-0.15, 3.05)
$PM_{2.5}$	3.08 (0.80, 4.20)	2.97 (0.69, 5.29)	2.65 (0.36, 4.99)	1.37 (-0.60, 3.39)
O_3	3.02 (1.55, 4.50)	2.63 (1.20, 4.09)	2.84 (1.38, 4.32)	2.29 (1.10, 3.50)
CO	2.91 (1.04, 4.82)	5.65 (-7.17, 20.25)	6.29 (-6.78, 21.20)	-2.75 (-13.32, 9.11)

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; O_3, ozone; CO, carbon monoxide

Column totals represent % excess risk for a 10 $\mu g/m^3$ increase in same-day (lag-0) AAP (100 μg/m3 for CO)

*Varying GAM models are representative of differing polynomial function choices adjusting for long-term trend and seasonality

†cubic regression spline with 7 degrees of freedom per year

‡cubic regression spline with 6 degrees of freedom per year

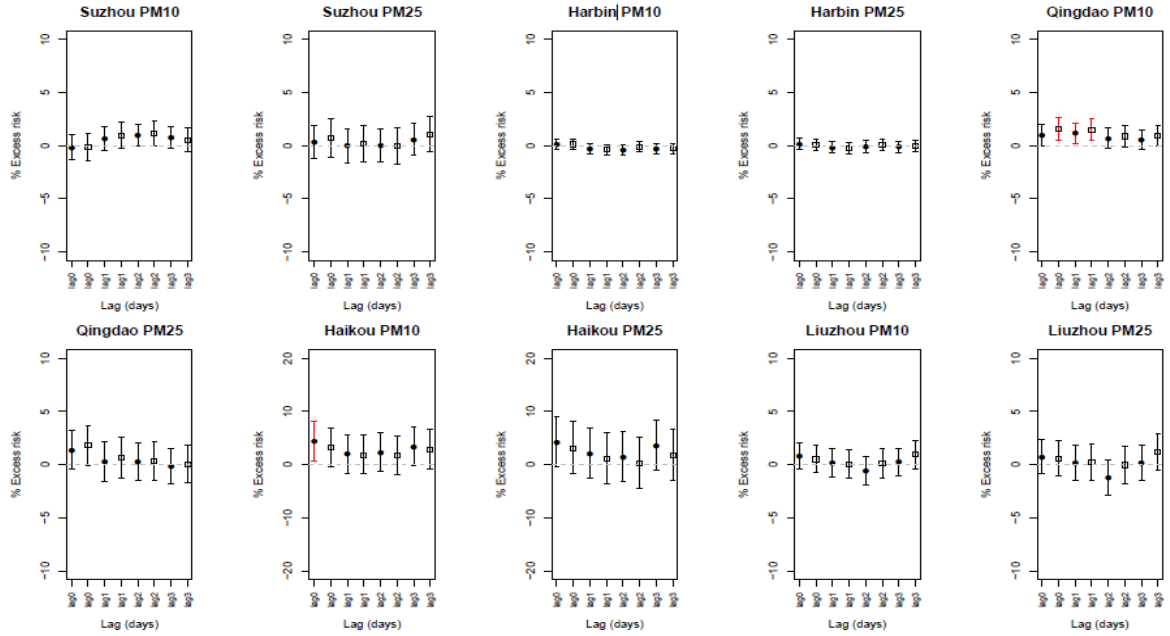
§cubic regression spline with 8 degrees of freedom per year

¶Time-stratified case-crossover analyses with 28-day strata using conditional logistic regression adjusted for temperature, relative humidity and matching by day of the week

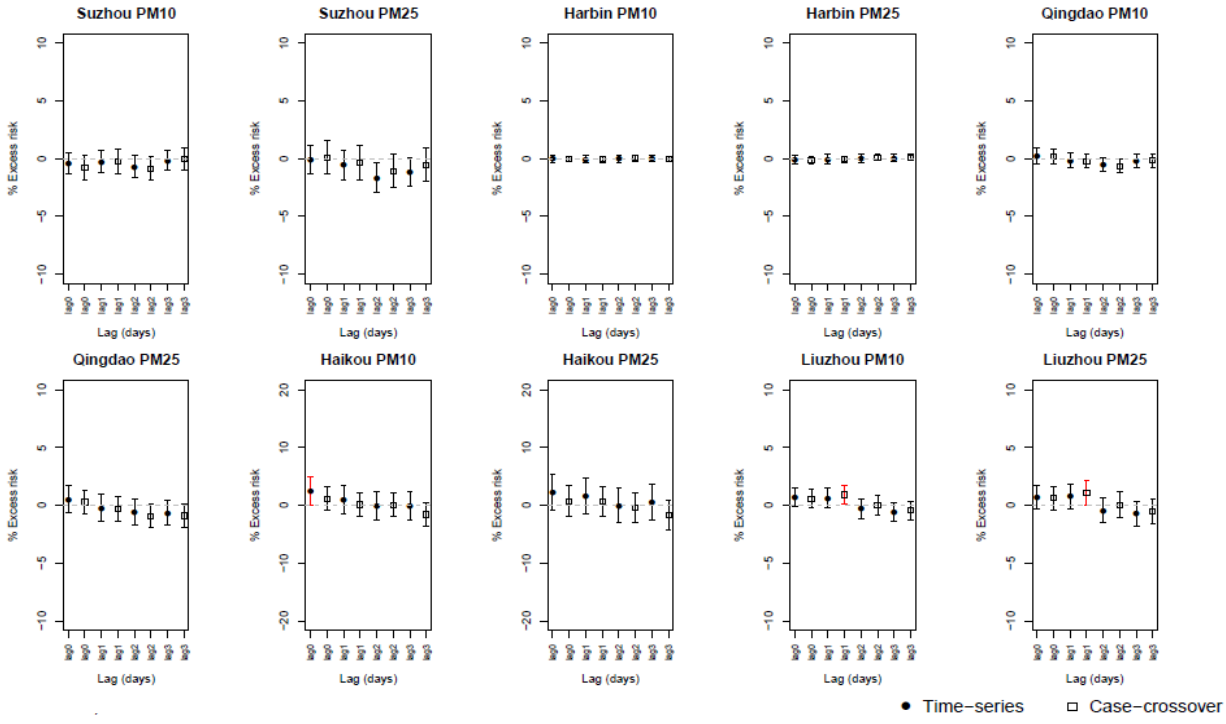
Appendix C12. Percent excess risk of cardio-respiratory hospitalisation spells associated with a 10 μg/m^3 increase in AAP in the five CKB urban regions in two pollutant models using both time-series and case-crossover analyses

Figure C12.1 Percent excess risk of cardiovascular spells associated with PM following adjustment for SO_2 in the five urban CKB regions (2013-2016*), respectively

a) First-time spells



b) Readmissions

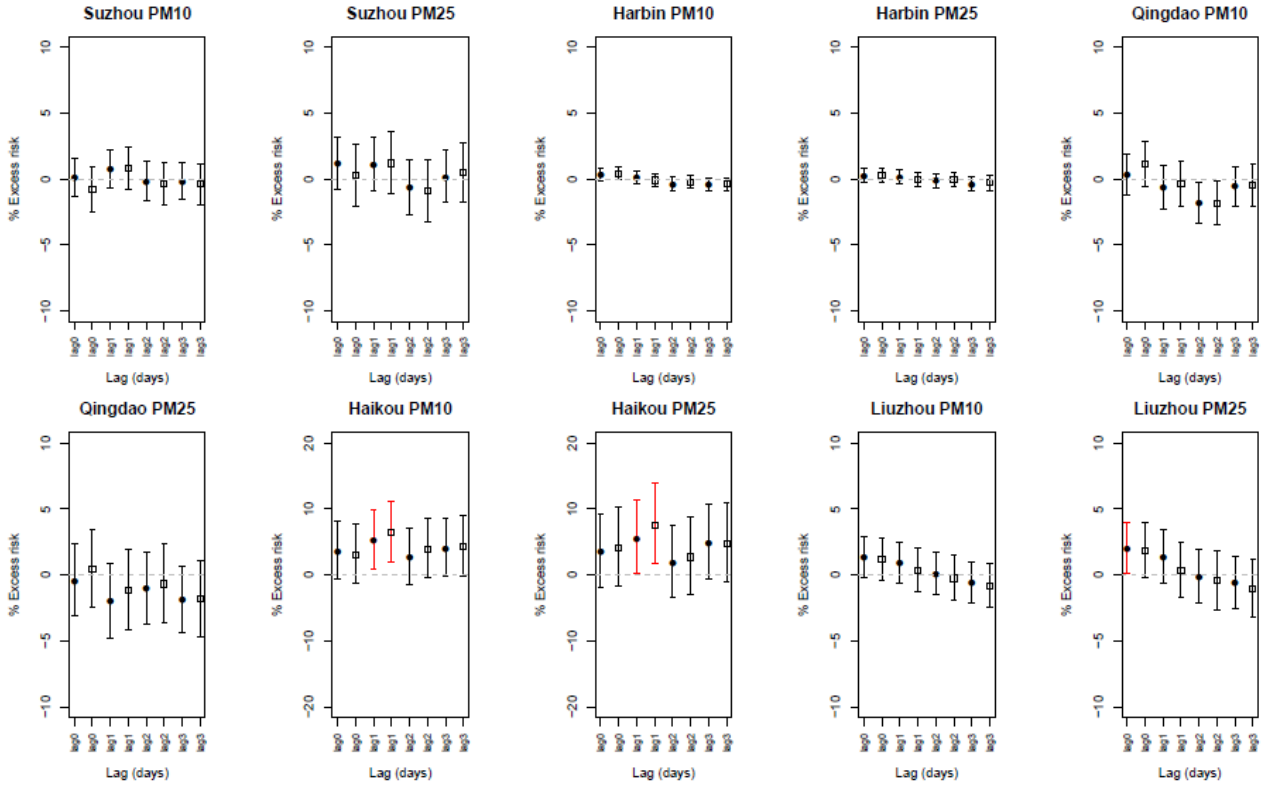


*Suzhou (2010-2016)

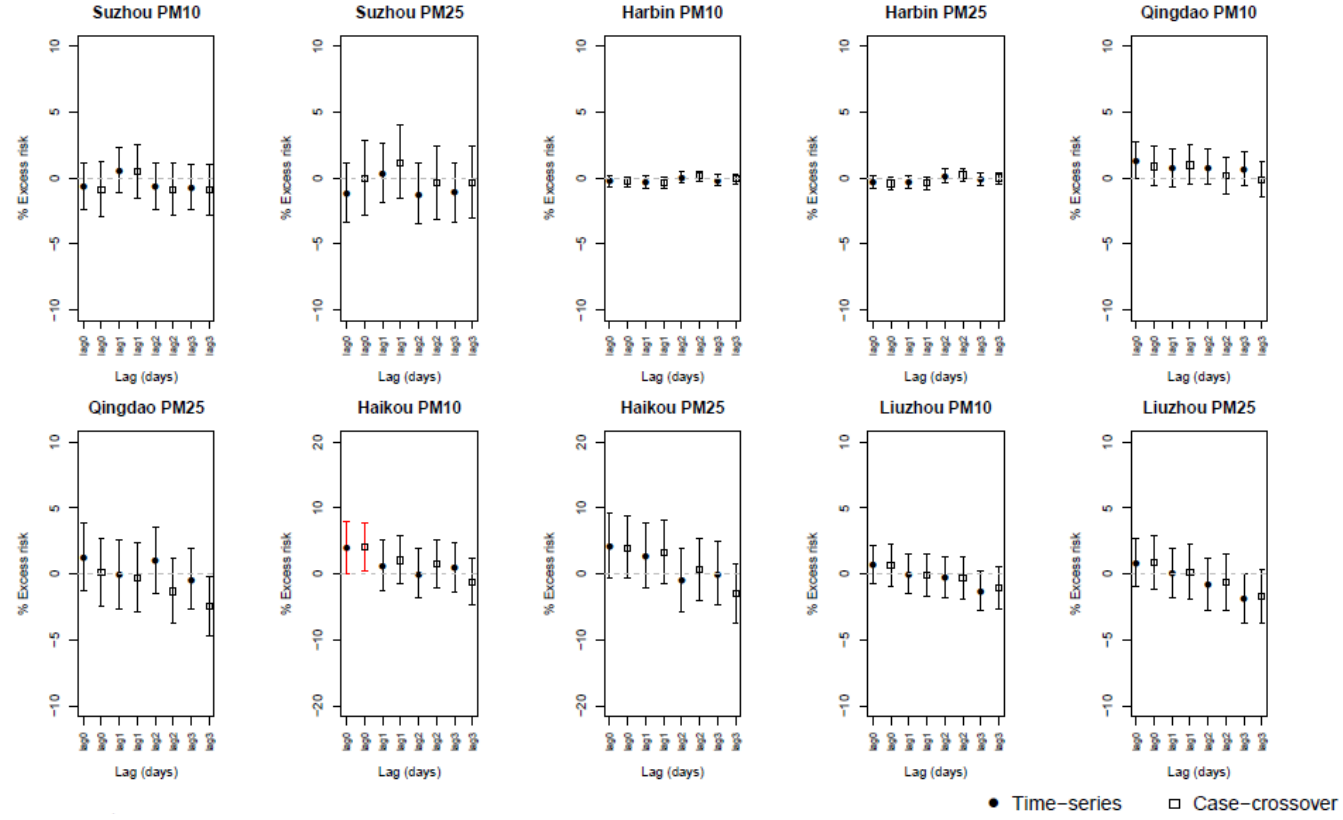
p<0.05

Figure C12.2. Percent excess risk of all-type stroke spells associated with PM following adjustment for SO_2 in the five urban CKB regions (2013-2016*), respectively

a) First-time spells



b) Readmissions

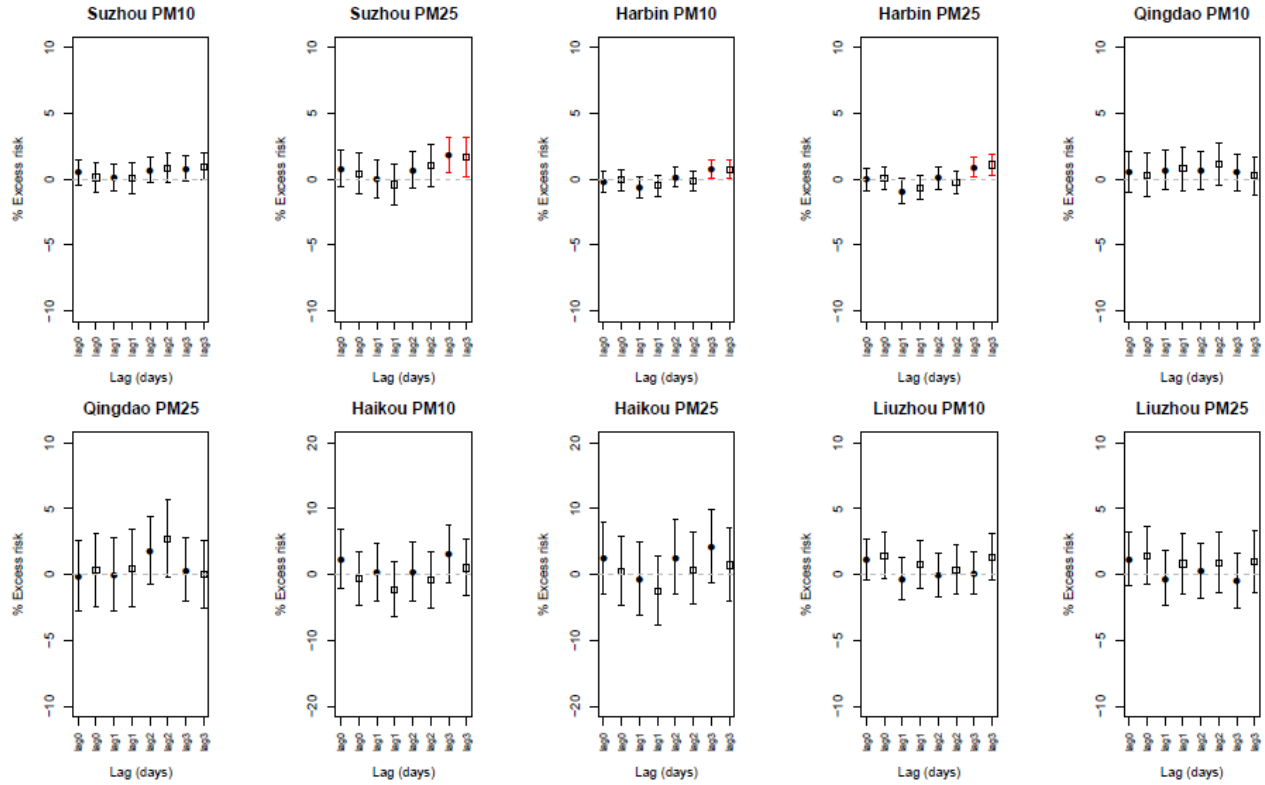


*Suzhou (2010-2016)

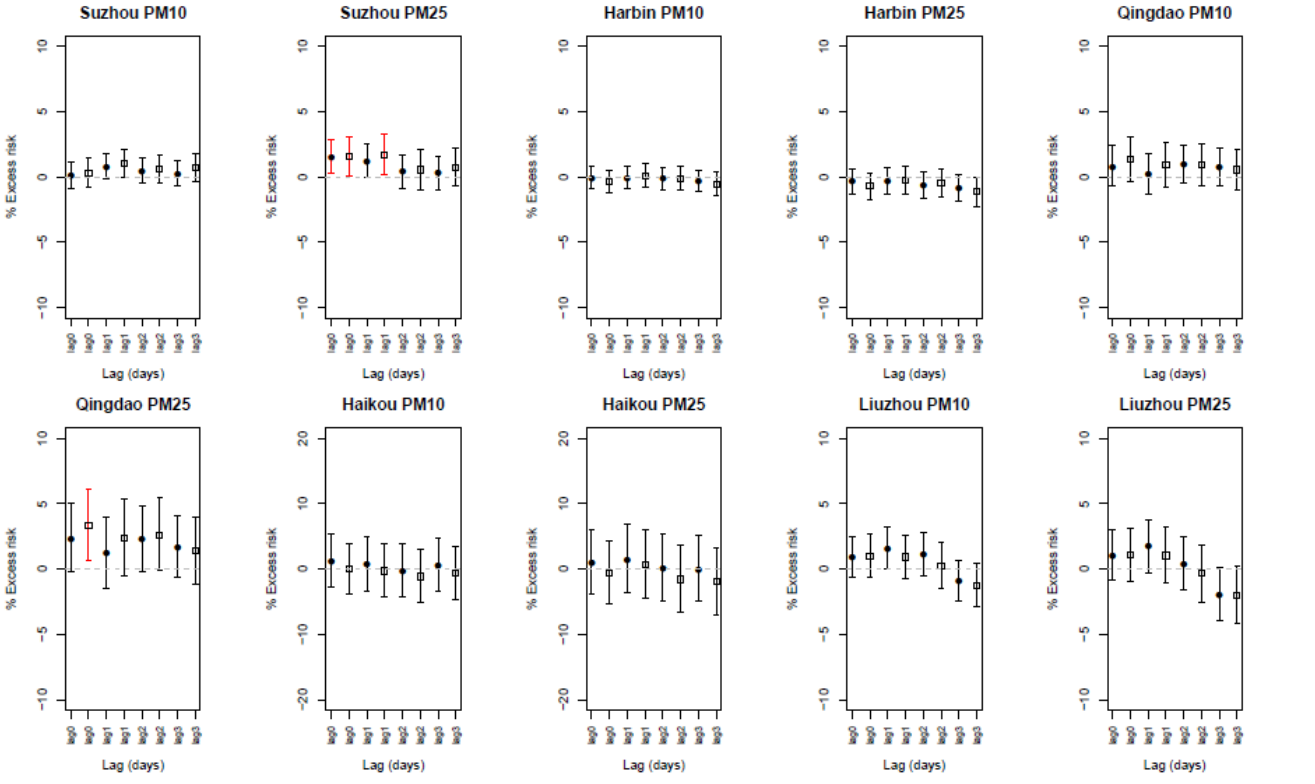
p<0.05

Figure C12.3 Percent excess risk of respiratory spells associated with PM following adjustment for SO_2 in the five urban CKB regions (2013-2016*), respectively

a) First-time spells



b) Readmissions

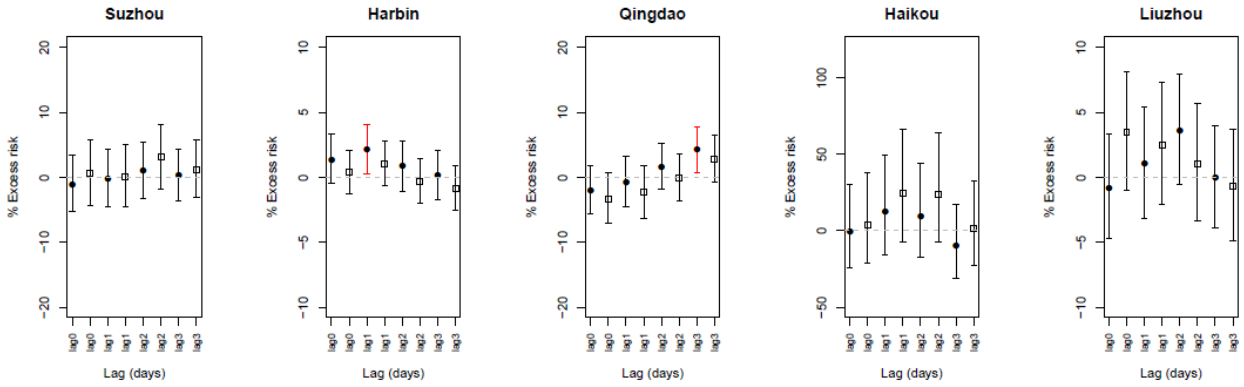


*Suzhou (2010-2016)

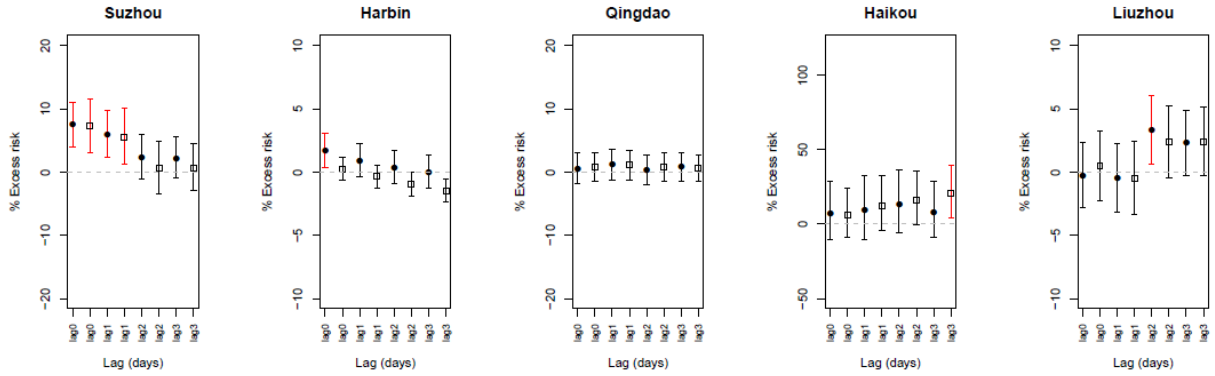
p<0.05

Figure C12.4 Percent excess risk of cardiovascular spells associated with SO_2 following adjustment for $PM_{2.5}$ in the five urban CKB regions (2013-2016*), respectively

a) First-time spells



b) Readmissions

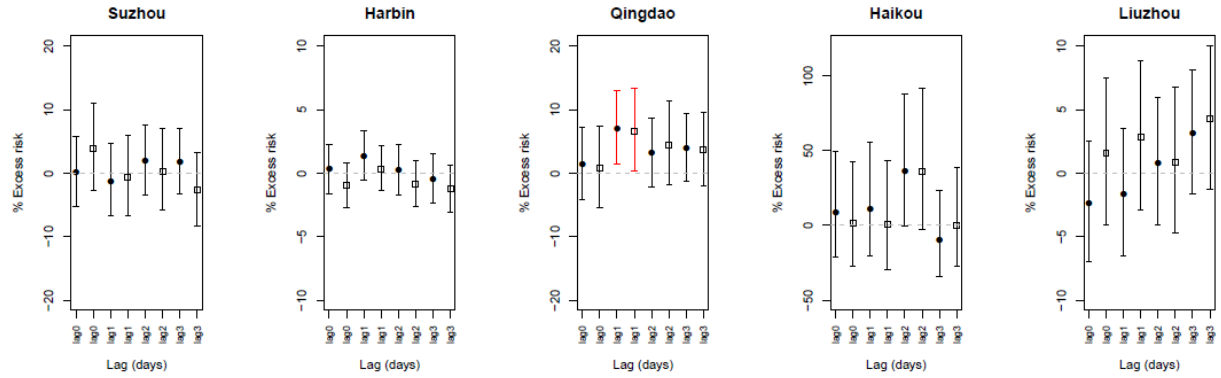


*Suzhou (2010-2016)

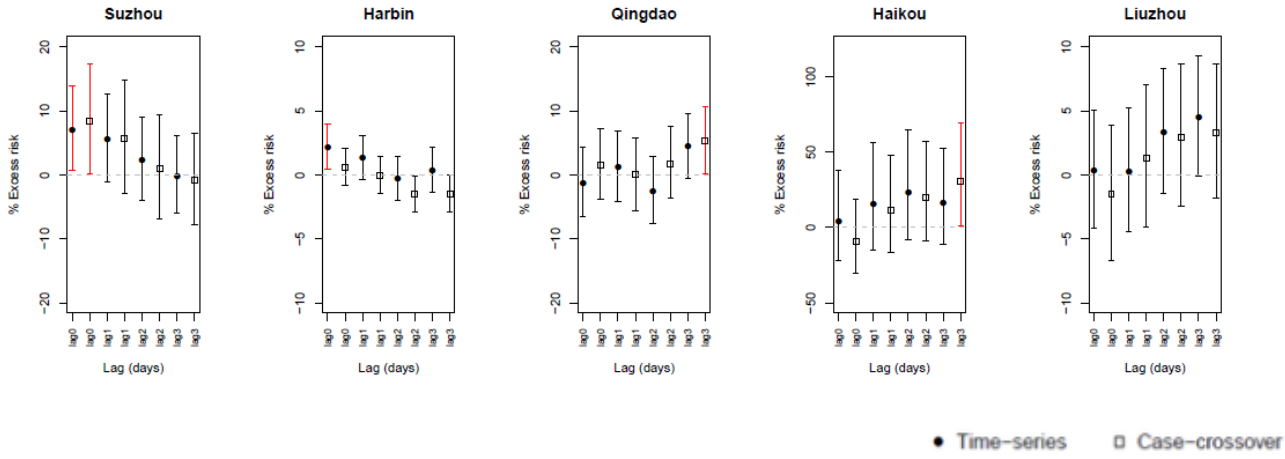
p<0.05

Figure C12.5 Percent excess risk of all-type stroke spells associated with SO_2 following adjustment for $PM_{2.5}$ in the five urban CKB regions (2013-2016*), respectively

a) First-time spells



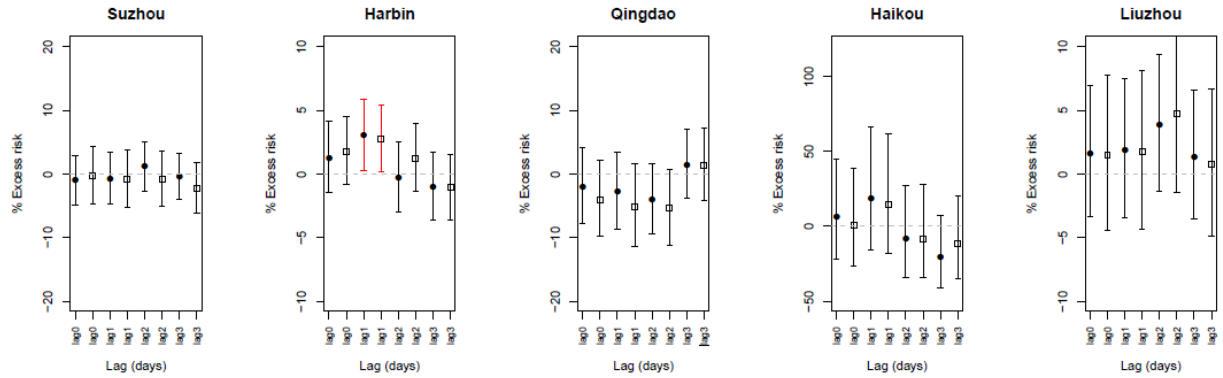
b) Readmissions



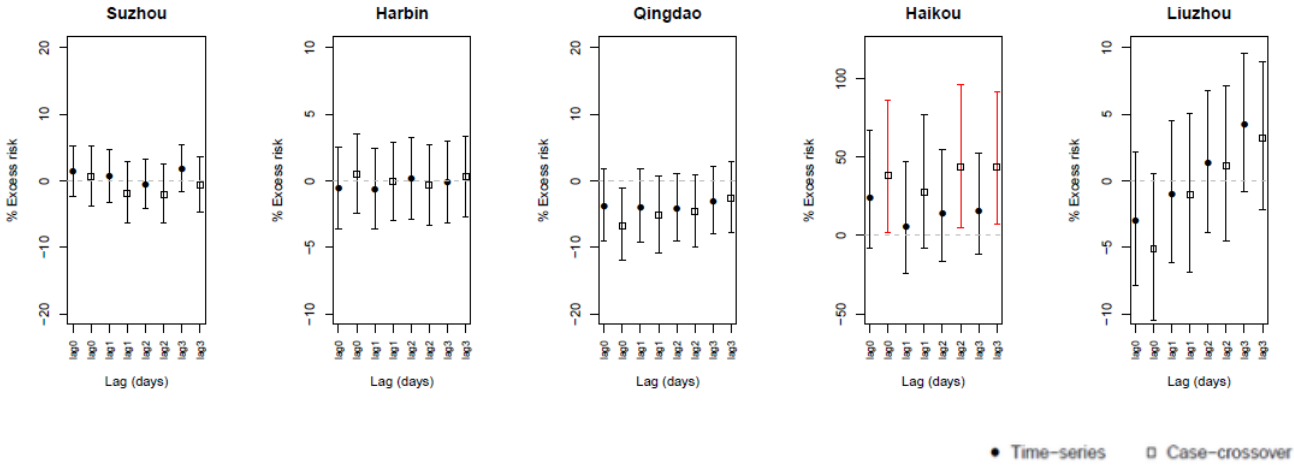
*Suzhou (2010-2016)
p<0.05

Figure C12.6 Percent excess risk of respiratory spells associated with SO_2 following adjustment for $PM_{2.5}$ in the five urban CKB regions (2013-2016*), respectively

a) First-time spells



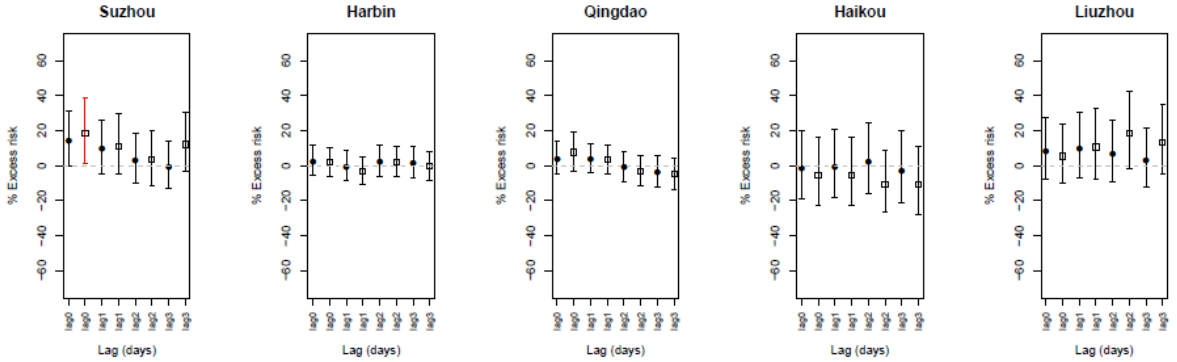
b) Readmissions



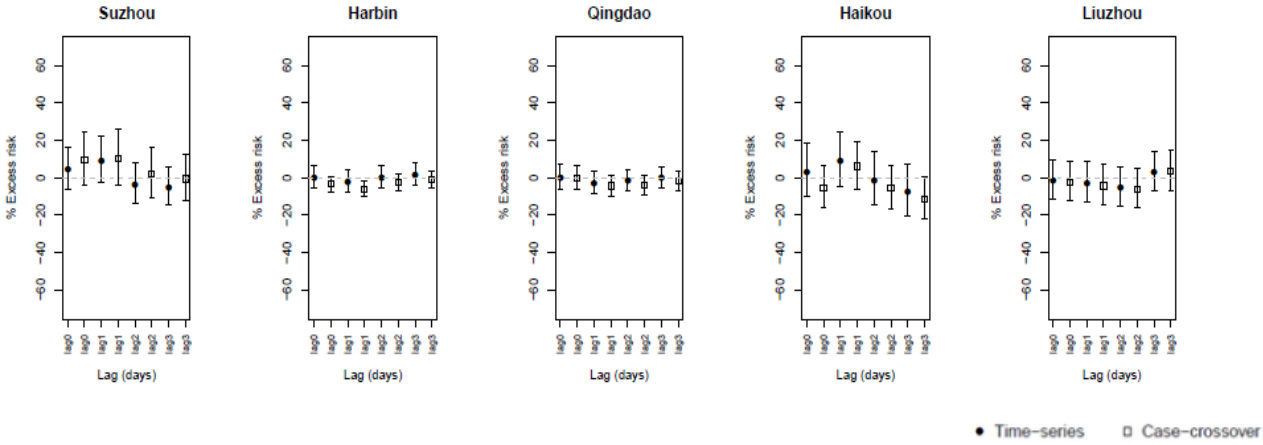
*Suzhou (2010-2016)
p<0.05

Figure C12.7 Percent excess risk of cardiovascular spells associated with a 100 μg/m^3 increase in CO following adjustment for SO_2 in the five urban CKB regions (2013-2016*), respectively

a) First-time spells



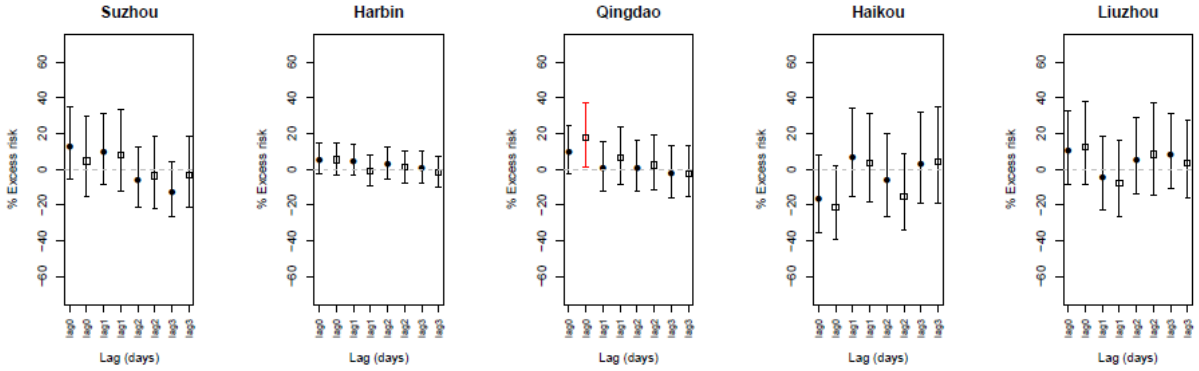
b) Readmissions



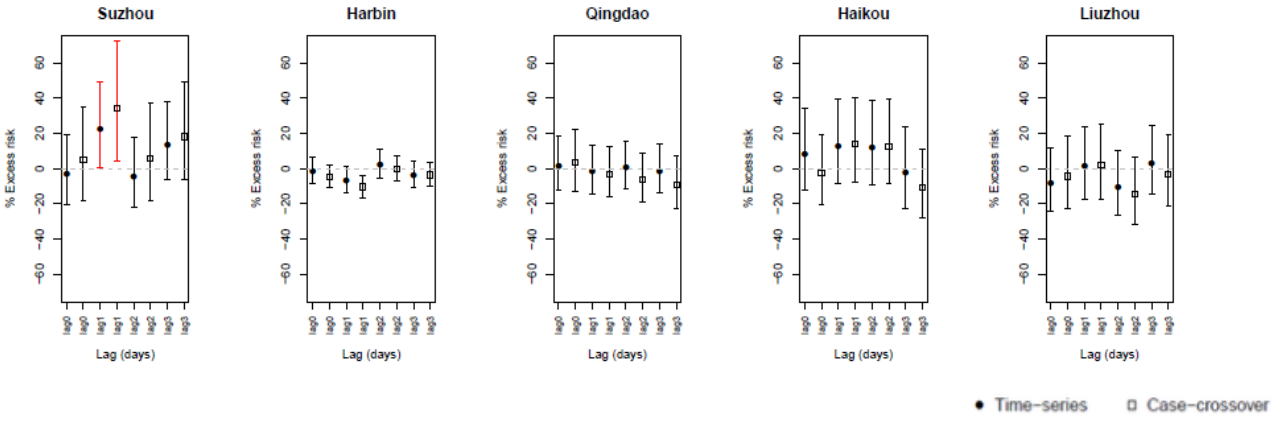
*Suzhou (2010-2016)
p<0.05

Figure C12.8. Percent excess risk of all-type stroke spells associated with a 100 μg/m^3 increase in CO following adjustment for SO_2 in the five urban CKB regions (2013-2016*), respectively

a) First-time spells



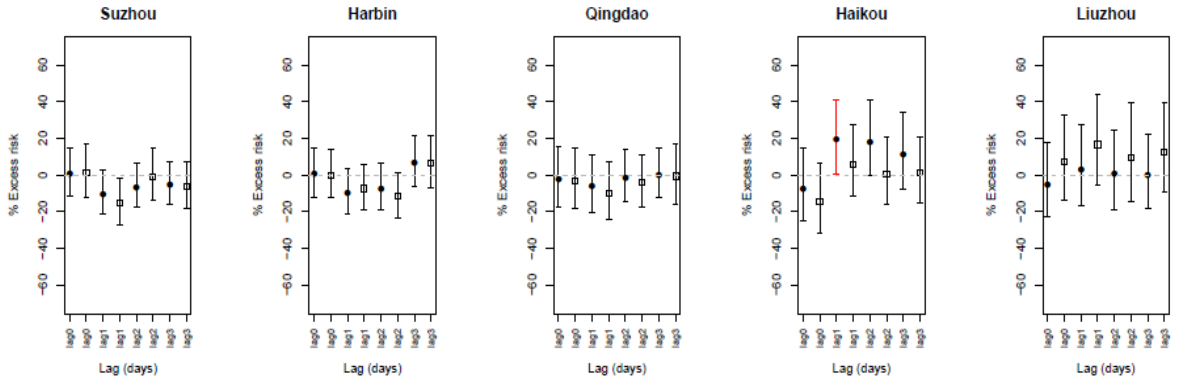
b) Readmissions



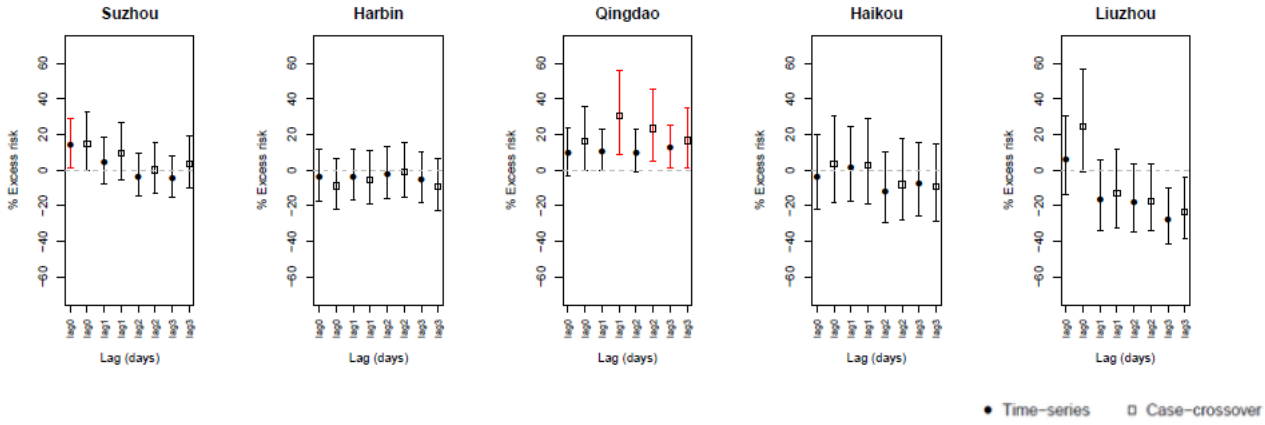
*Suzhou (2010-2016)
p<0.05

Figure C12.9 Percent excess risk of respiratory spells associated with a 100 μg/m3 increase in CO following adjustment for SO_2 in the five urban CKB regions (2013-2016*), respectively

a) First-time spells



b) Readmissions

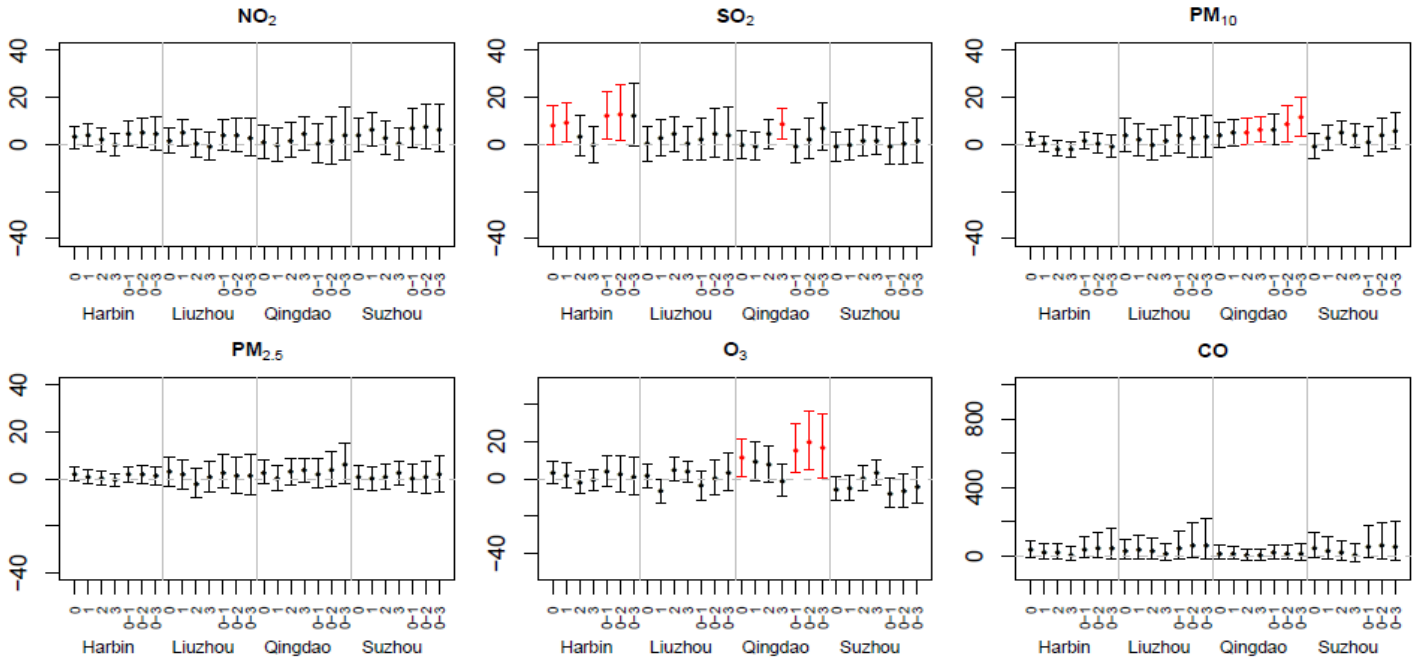


*Suzhou (2010-2016)
p<0.05

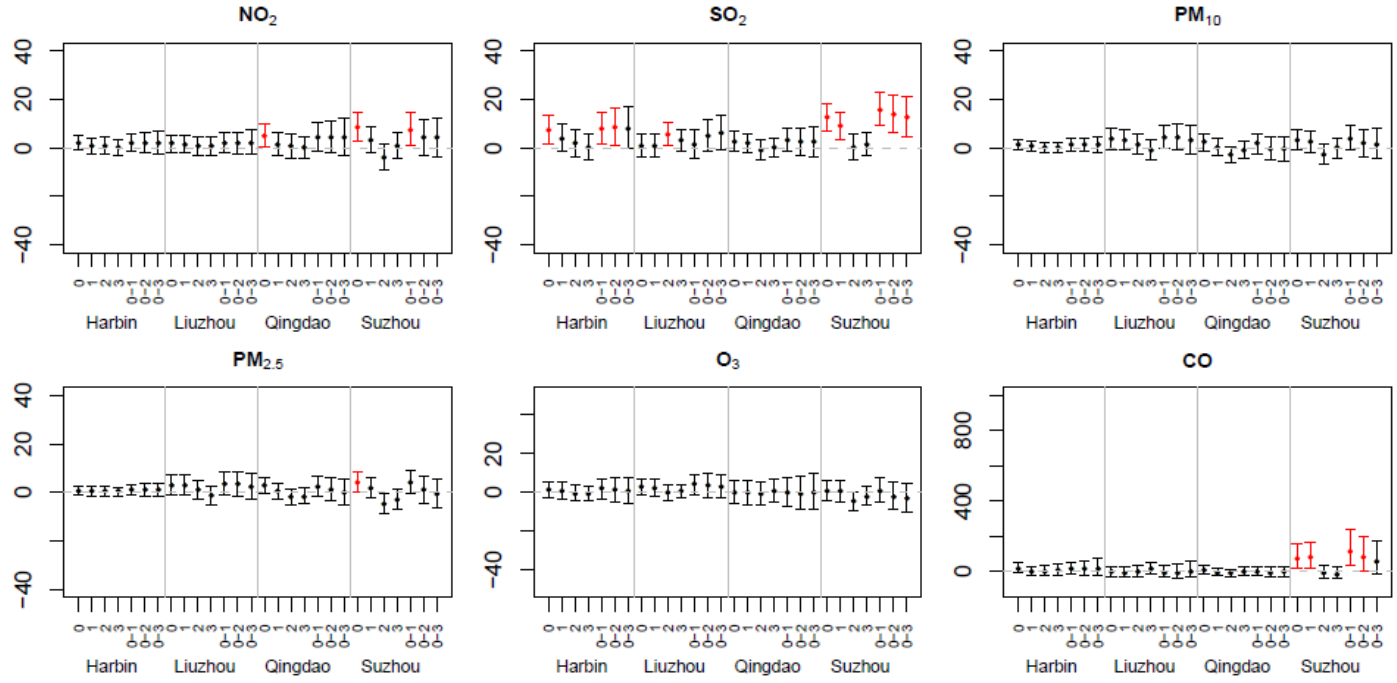
Appendix C13 Percent excess risk of cardio-respiratory hospitalisation spells associated with an interquartile range (IQR) increase in AAP concentrations

Figure C13.1 Percent excess risk of cardiovascular disease hospitalisation associated with an IQR increase in AAP in four of the five CKB regions (2013-2016*) using time-series analysis

a) First time spells



b) Readmissions

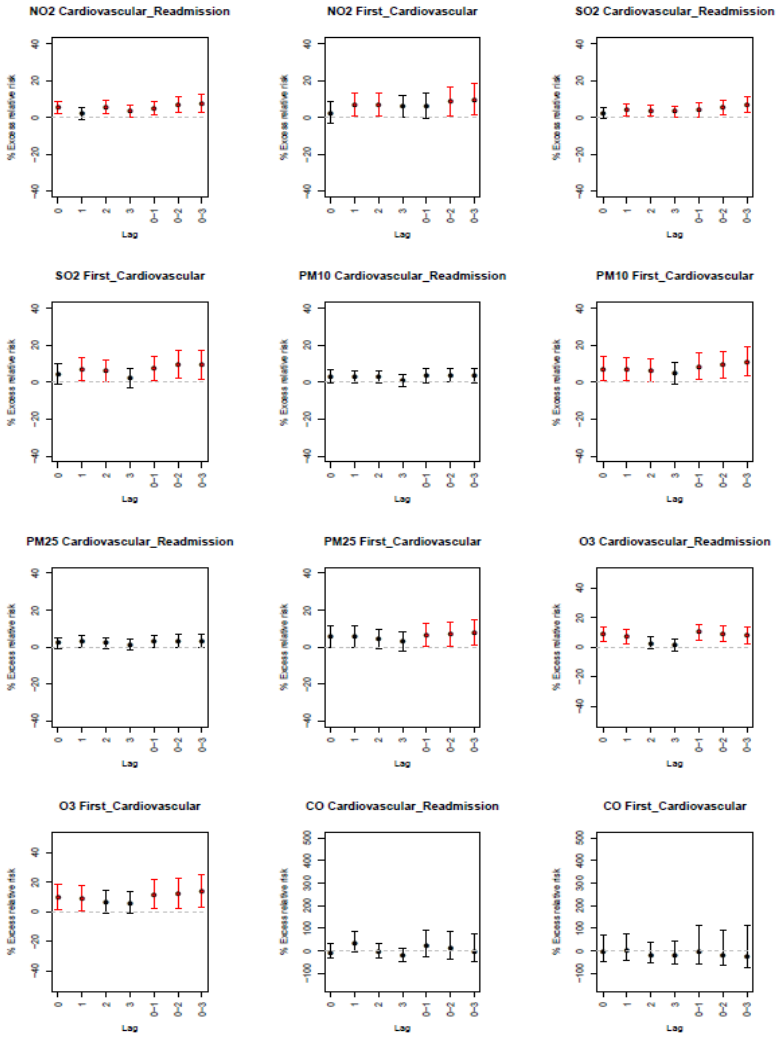


*Suzhou (2010-2016)

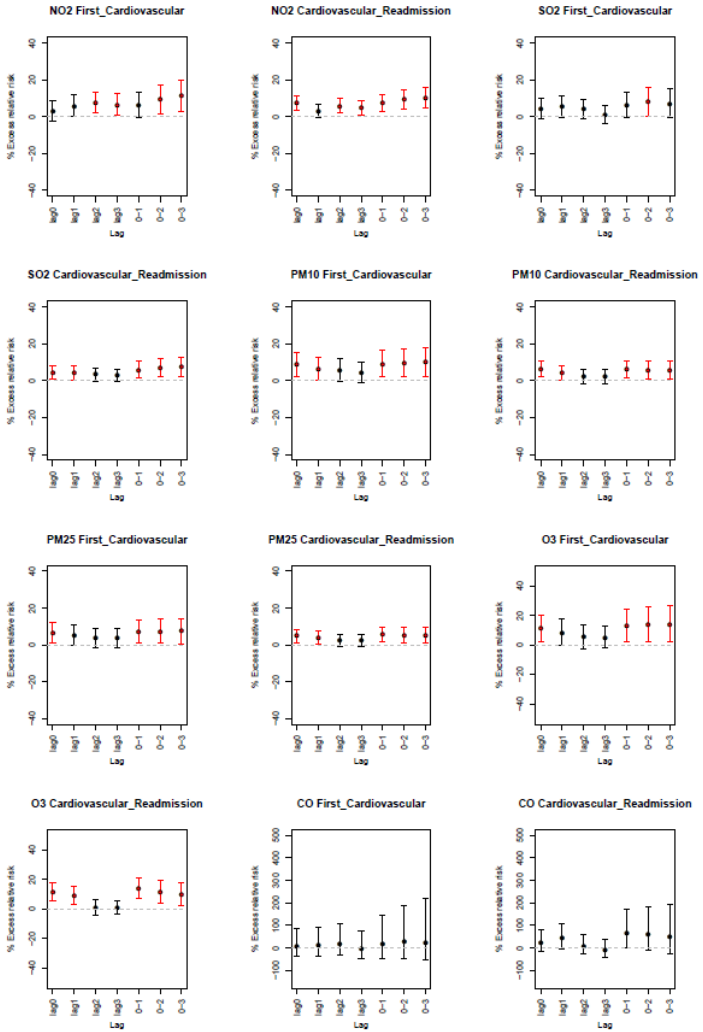
p<0.05

Figure C13.2 Percent excess risk of cardiovascular disease hospitalisation associated with an IQR increase in AAP in Haikou (2013-2016) using time-series and case-crossover analysis, respectively

a) Time-series



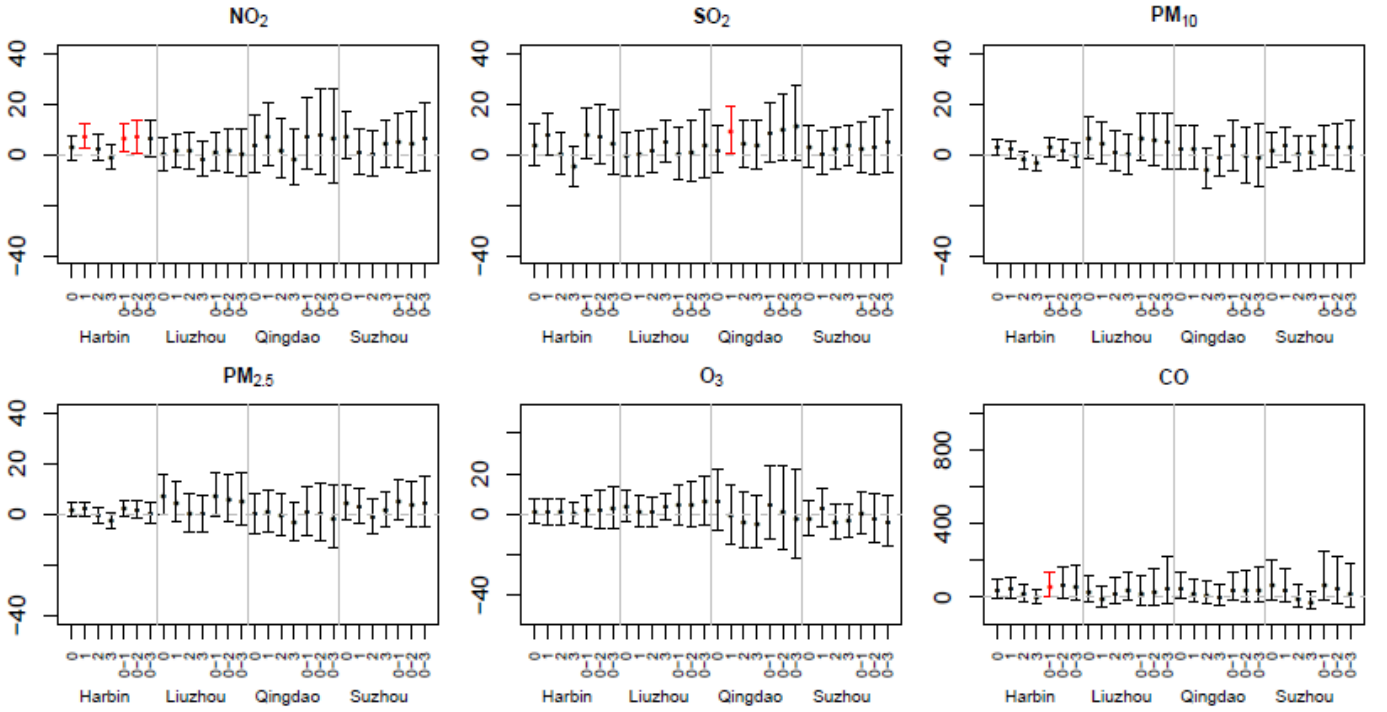
b) Case-crossover analysis



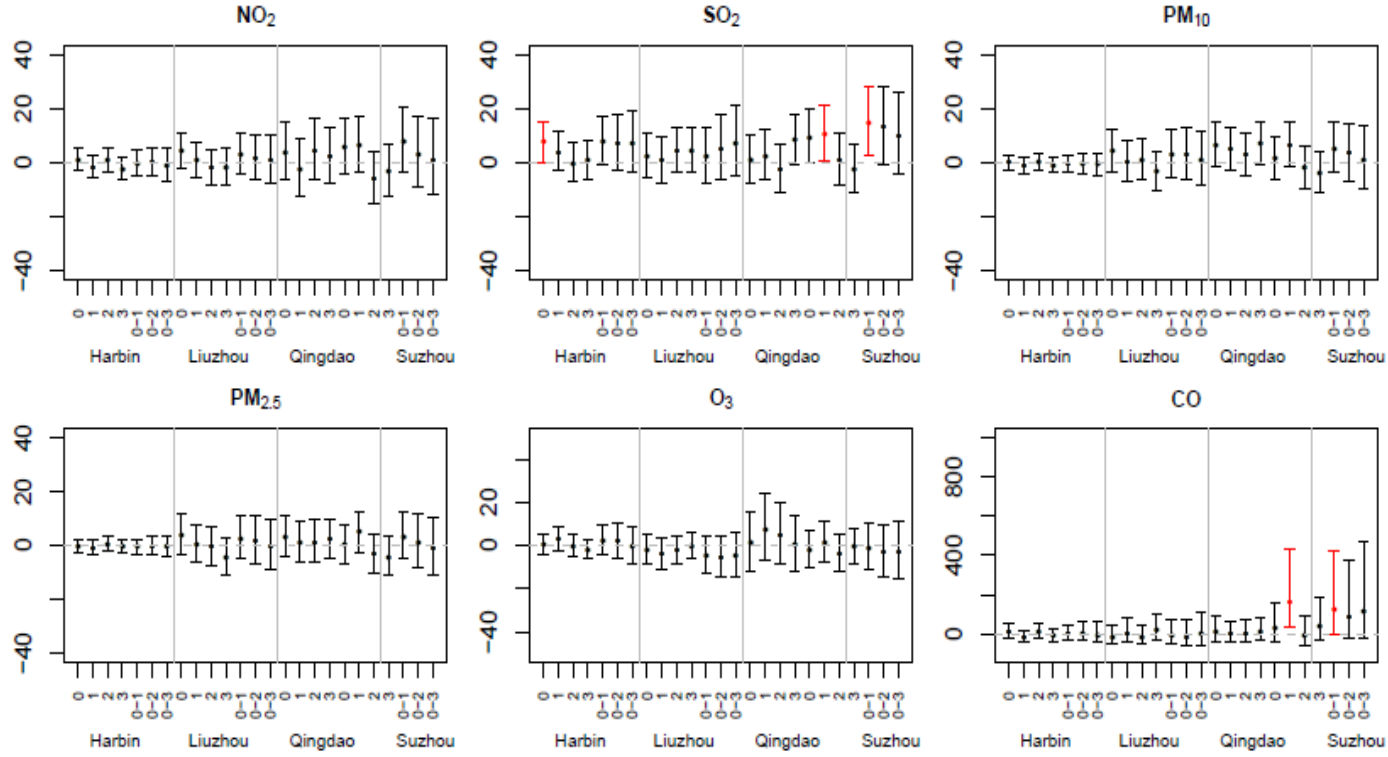
p<0.05

Figure C13.3 Percent excess risk of all-type stroke hospitalisation associated with an IQR increase in AAP in four of the five CKB regions (2013-2016*) using time-series analysis

a) First time spells



b) Readmissions

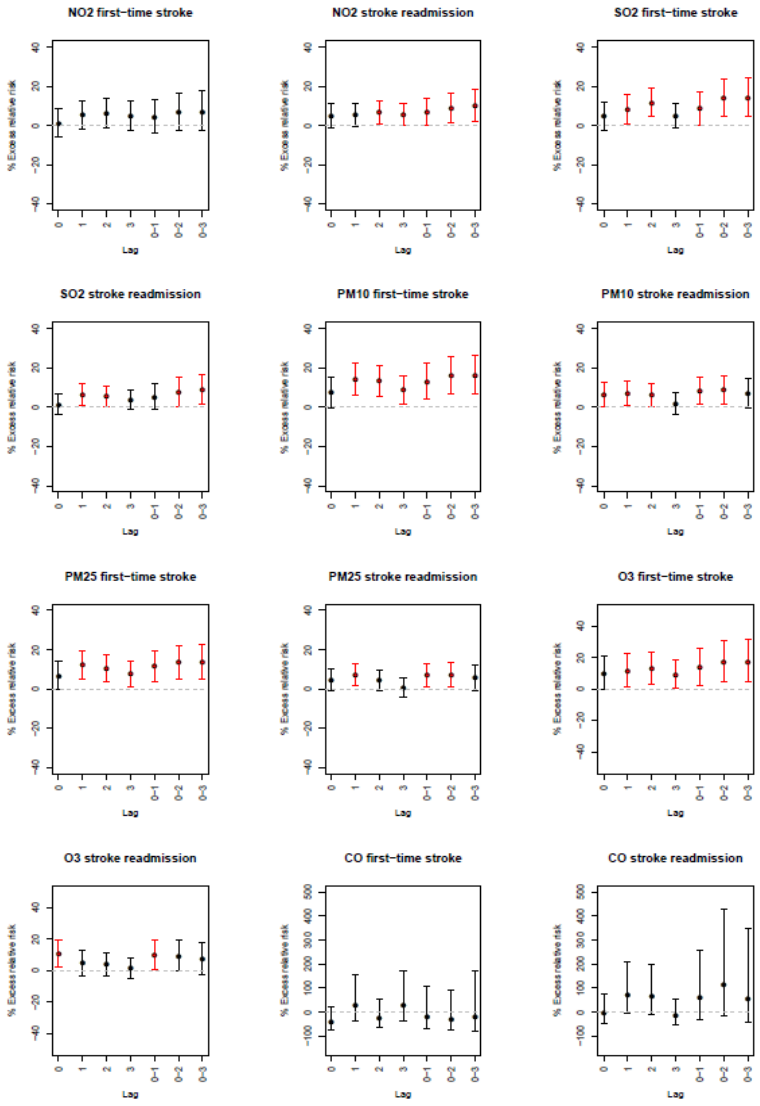


*Suzhou (2010-2016)

p<0.05

Figure C13.4 Percent excess risk of all-type stroke hospitalisation associated with an IQR increase in AAP in Haikou (2013-2016) using time-series and case-crossover analysis, respectively

a) Time-series analysis



p<0.05

b) Case-crossover analysis

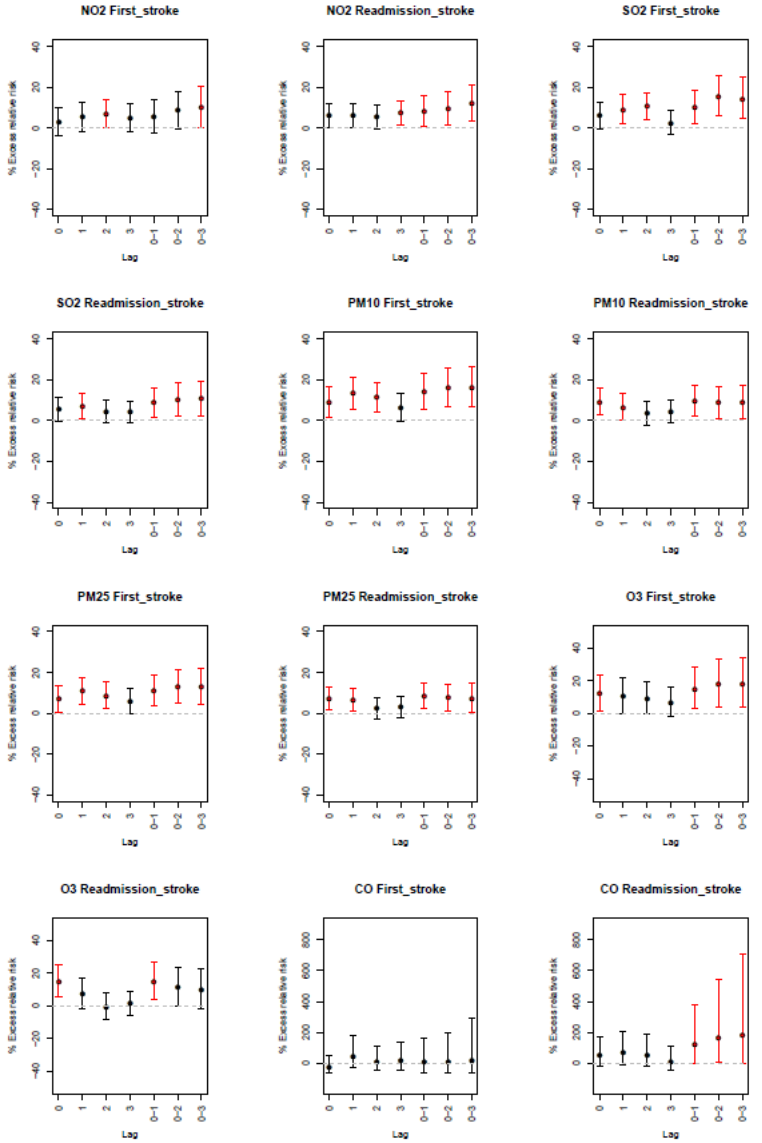
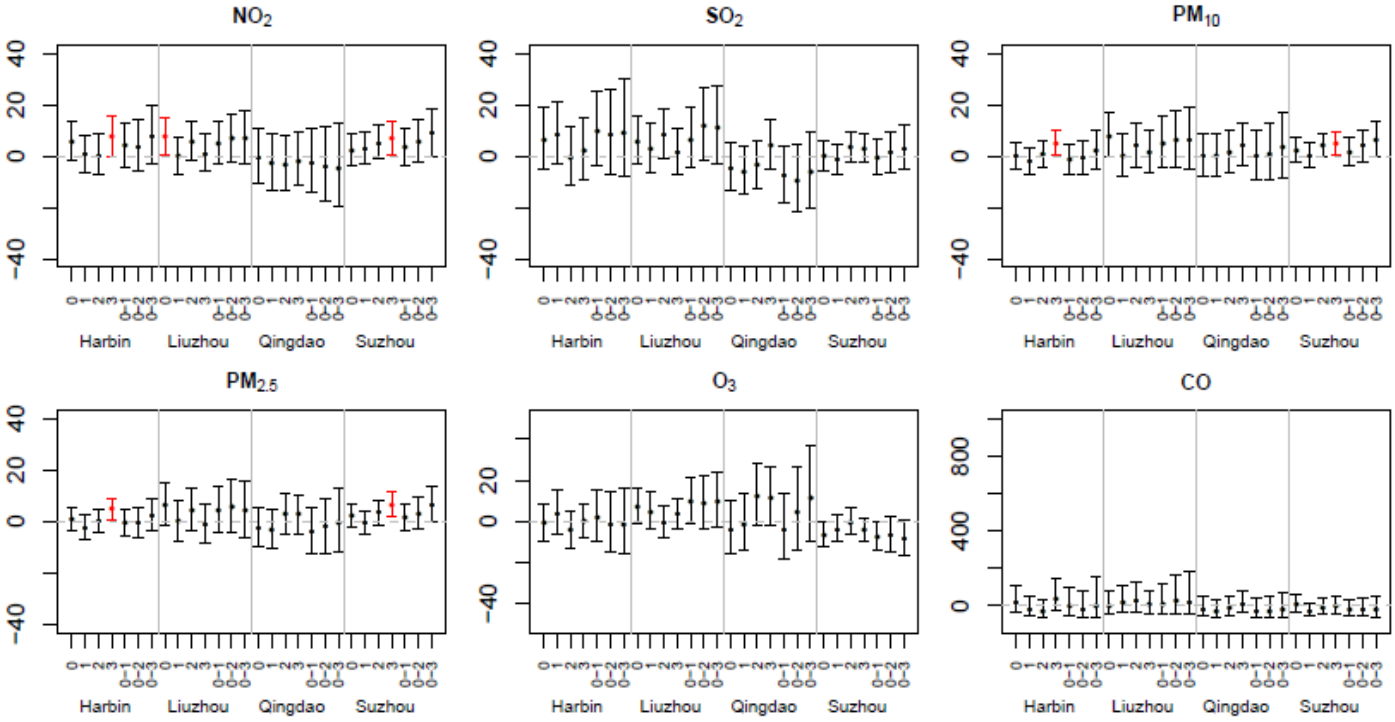
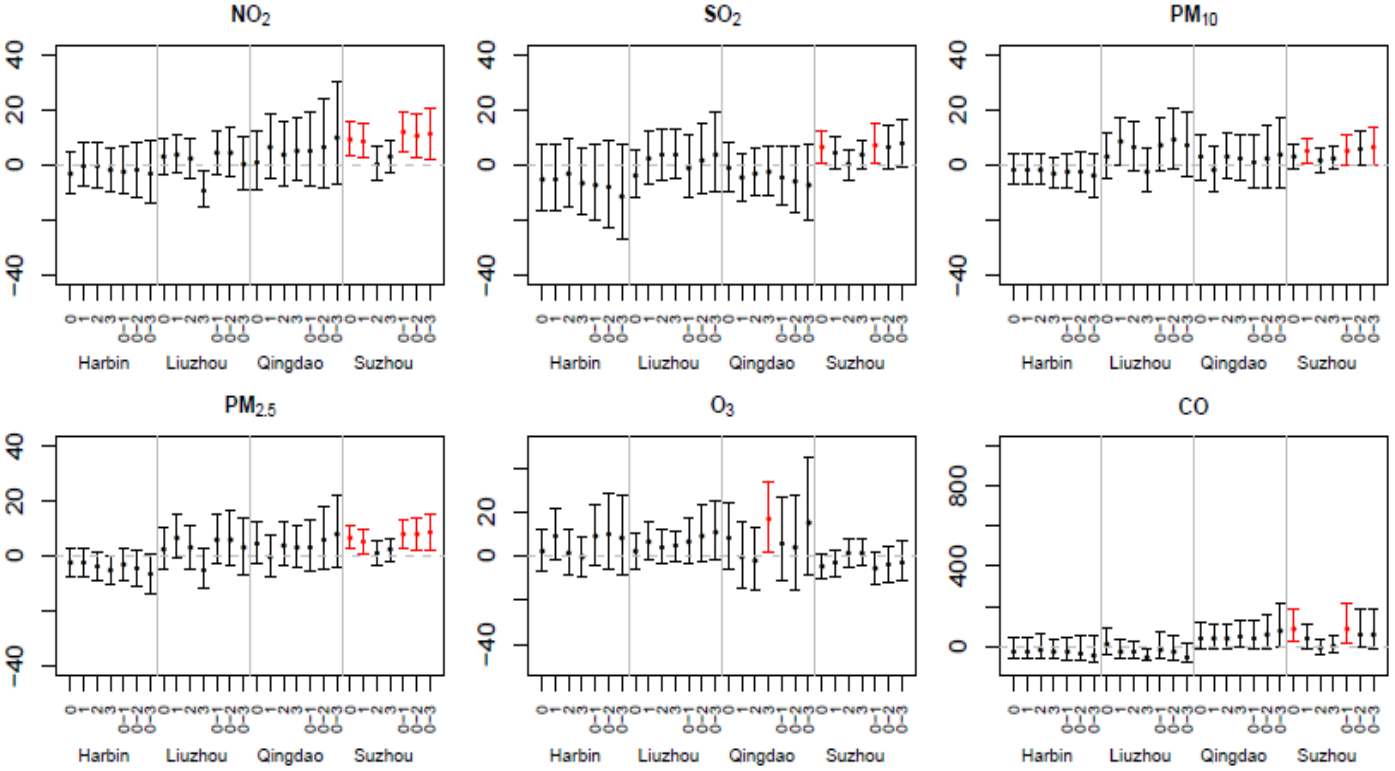


Figure C13.5 Percent excess risk of respiratory hospitalisation associated with an IQR increase in AAP in four of the five CKB regions (2013-2016*) using time-series analysis

a) First time spells



b) Readmissions

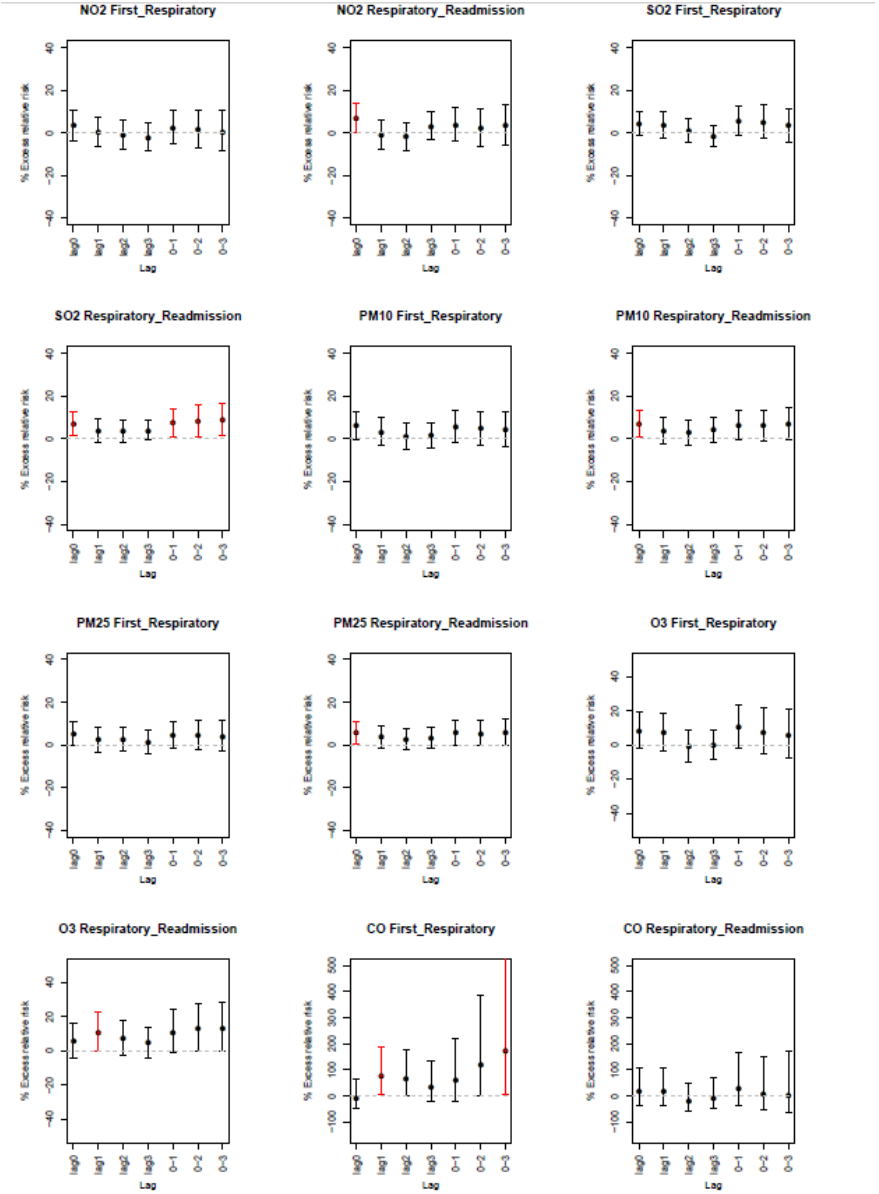


*Suzhou (2010-2016)

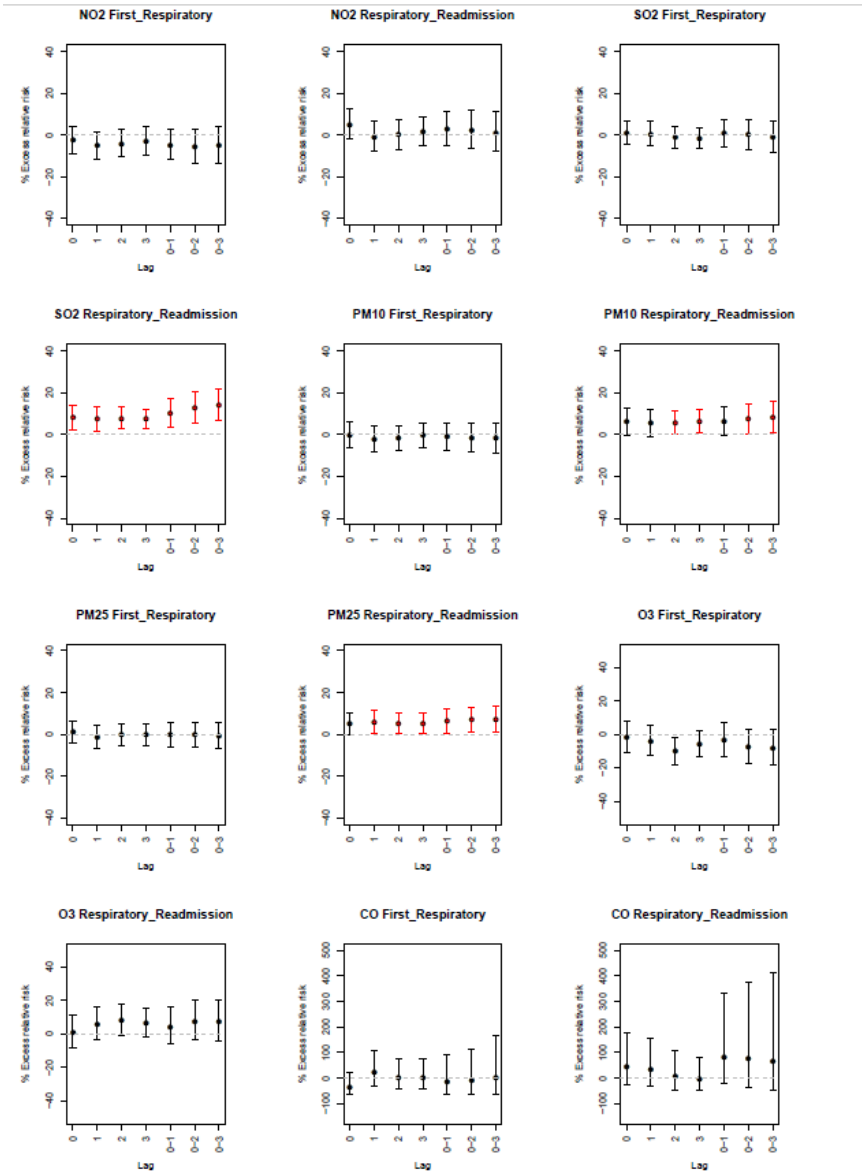
p<0.05

Figure C13.6 Percent excess risk of respiratory hospitalisation associated with an IQR increase in AAP in Haikou (2013-2016) using time-series and case-crossover analysis, respectively

a) Time-series analysis



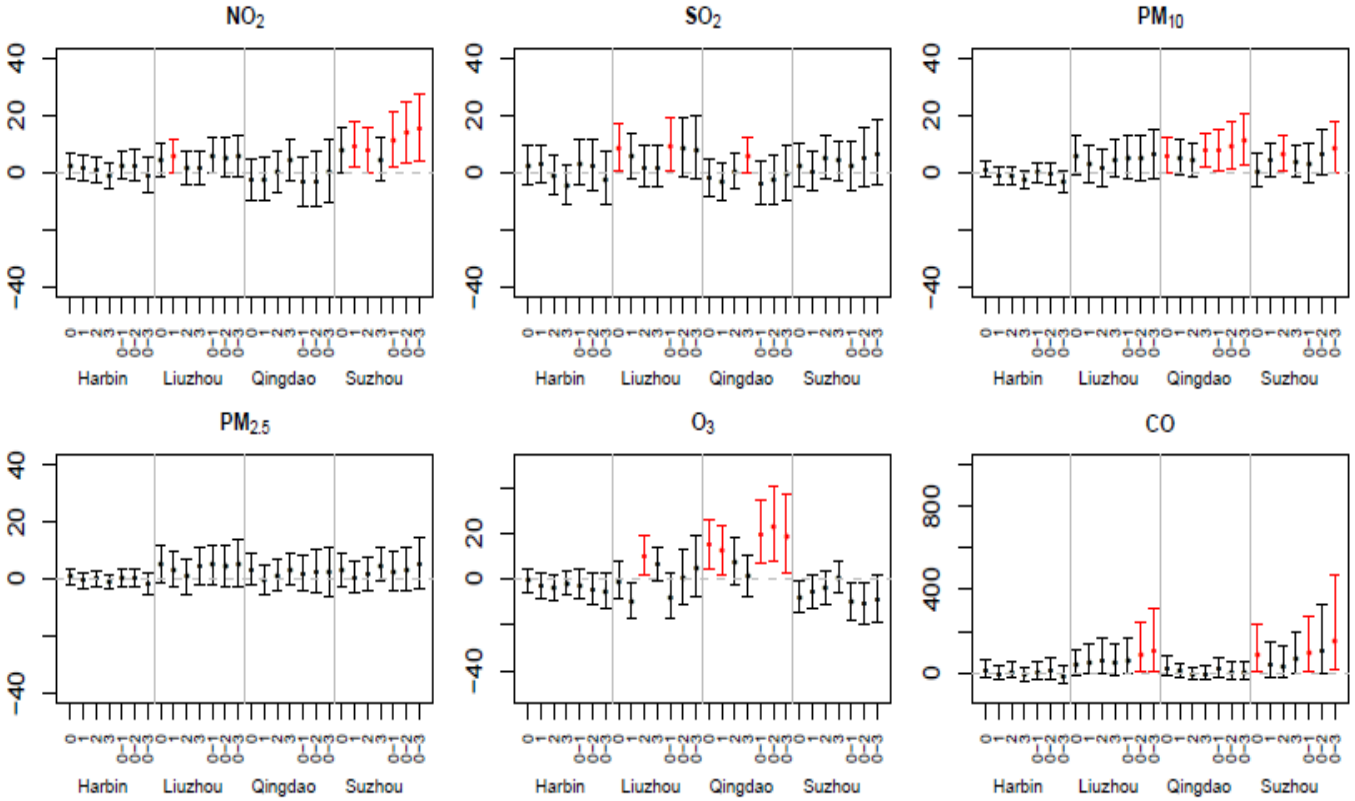
b) Case-crossover analysis



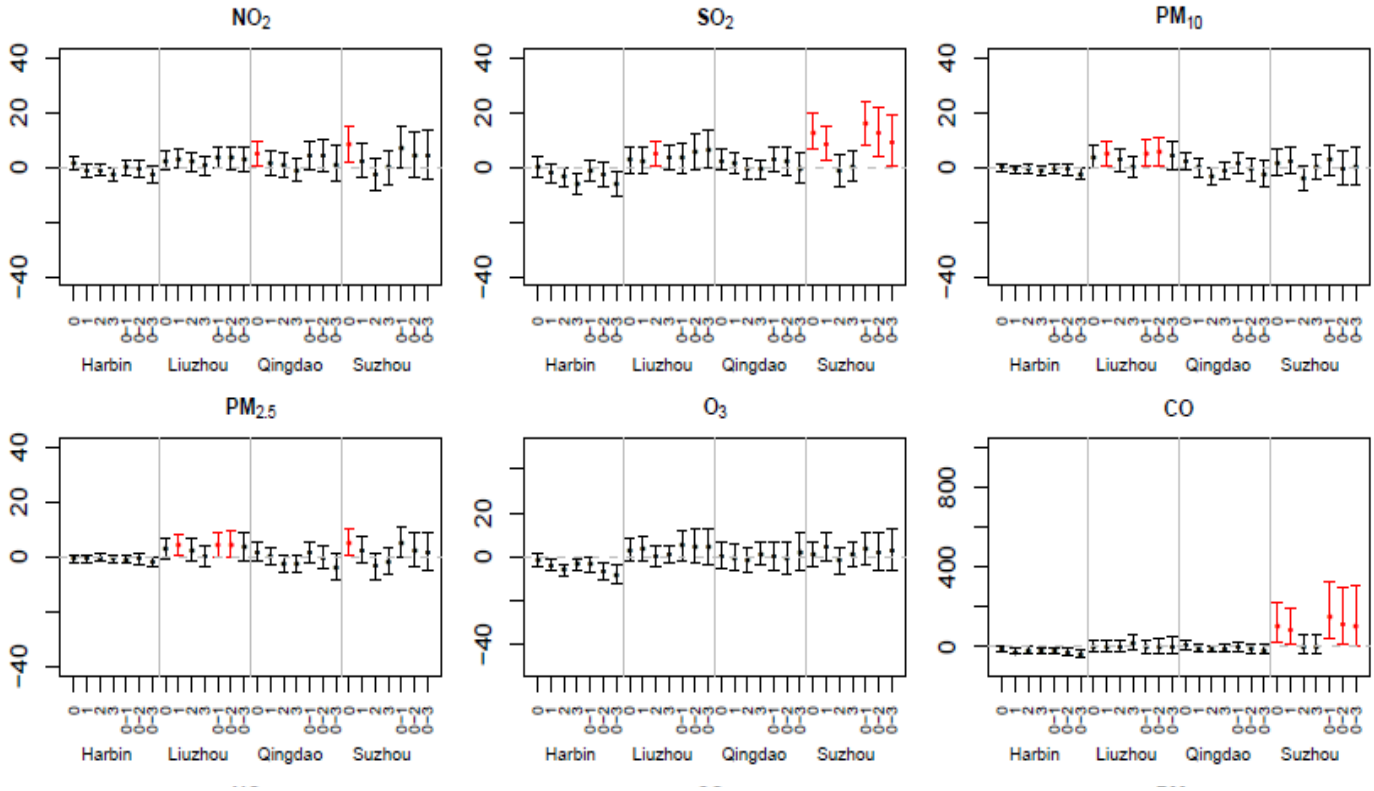
p<0.05

Figure C13.7 Percent excess risk of cardiovascular disease hospitalisation associated with an IQR increase in AAP in four of the five CKB regions using case-crossover analysis

a) First time spells



b) Readmissions

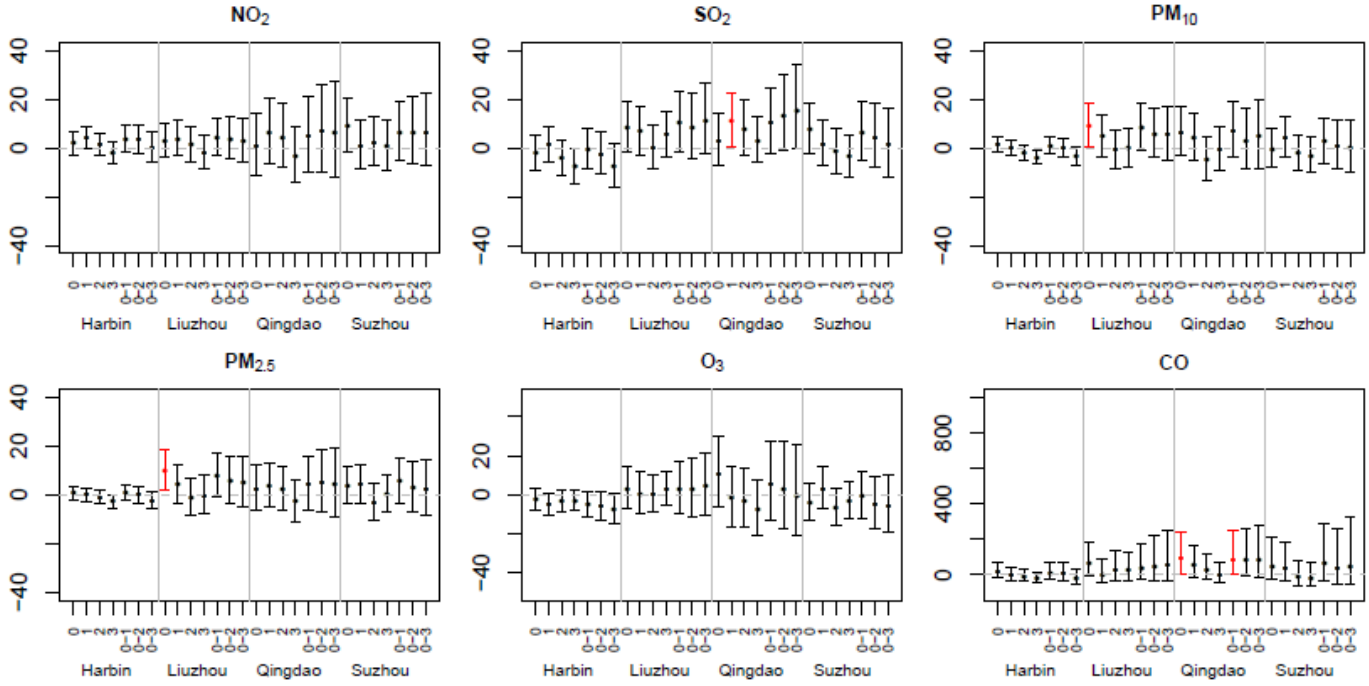


*Suzhou (2010-2016)

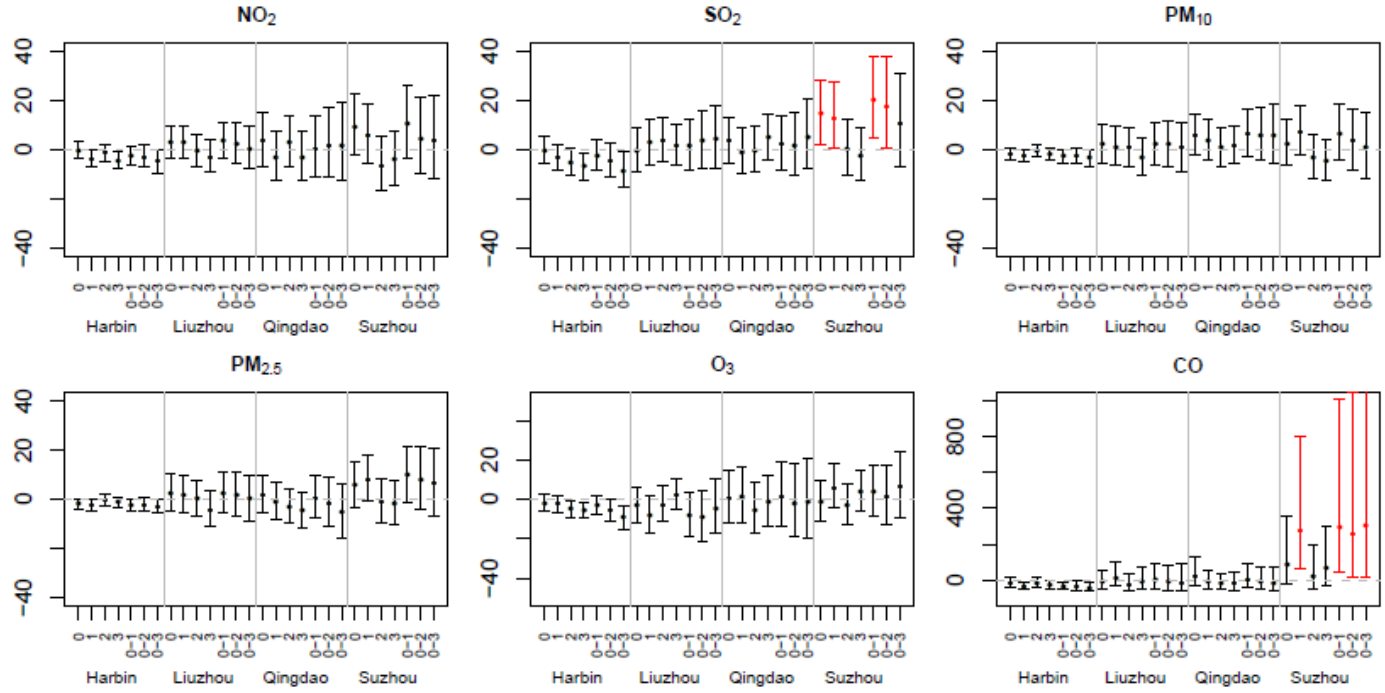
p<0.05

Figure C13.8 Percent excess risk of all-type stroke hospitalisation associated with an IQR increase in AAP in four of the five CKB regions using case-crossover analysis

a) First time spells



b) Readmissions

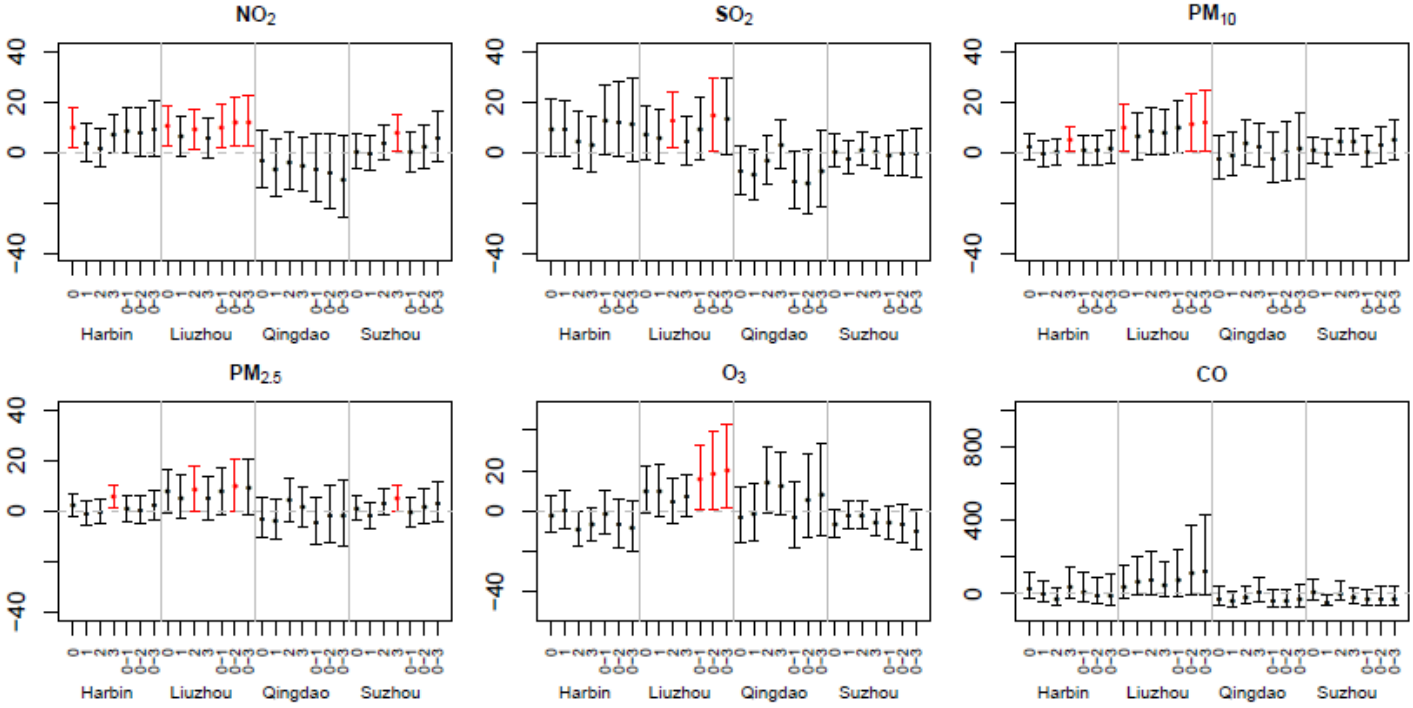


*Suzhou (2010-2016)

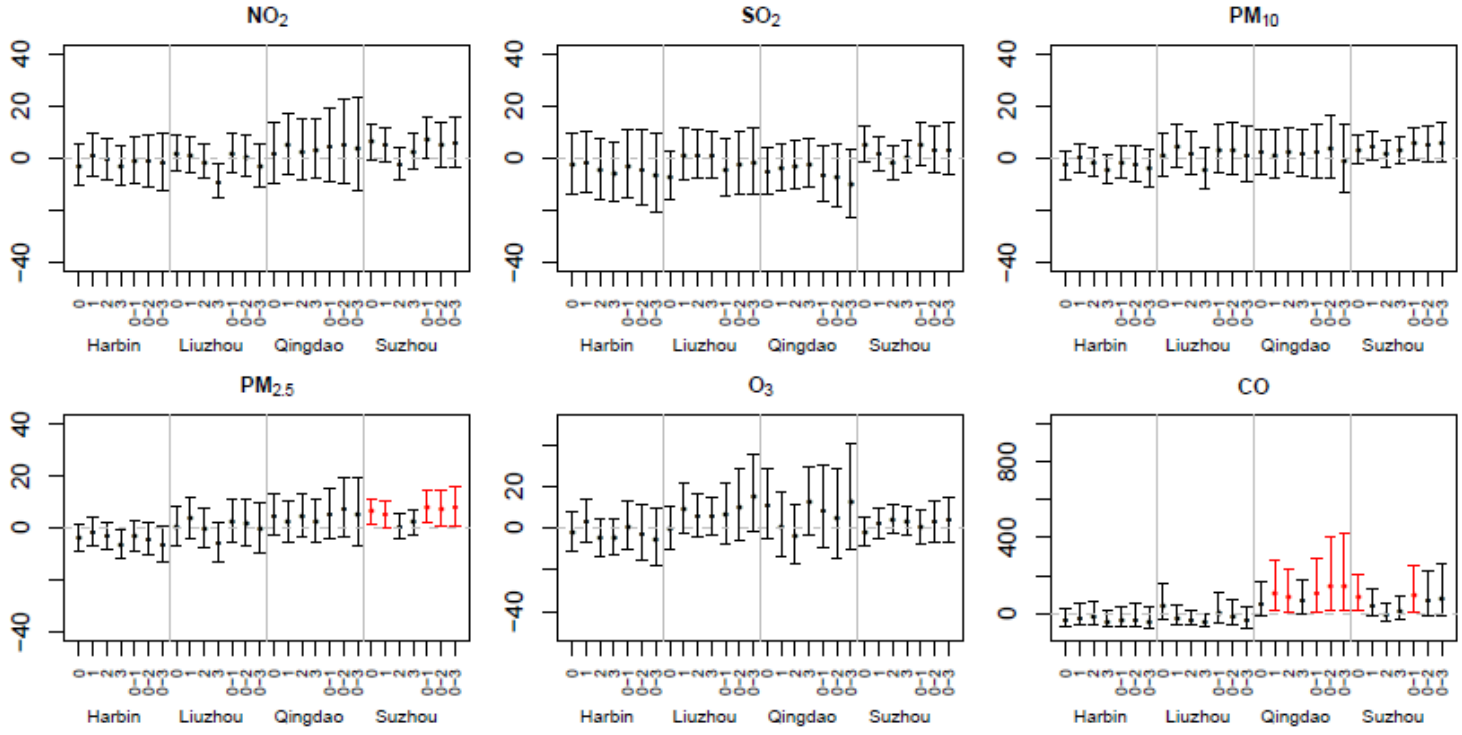
p<0.05

Figure C13.9 Percent excess risk of respiratory hospitalisation associated with an IQR increase in AAP in four of the five CKB regions using case-crossover analysis

a) First time spells



b) Readmissions



*Suzhou (2010-2016)

p<0.05

Appendix C14 Correlations between pollutants and meteorological variables in the five CKB urban regions

1). Harbin

		NO_2	SO_2	PM_{10}	$PM_{2.5}$	CO	O_3	Temperature (C)	Humidity (%)
NO_2	r	1.00	0.71	0.78	0.79	0.72	-0.30	-0.52	-0.01
	p-value	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.8357
SO_2	r		1.00	0.58	0.60	0.52	-0.44	-0.74	0.04
	p-value		-	<0.001	<0.001	<0.001	<0.001	<0.001	0.182
PM_{10}	r			1.00	0.95	0.74	-0.21	-0.40	-0.02
	p-value			-	<0.001	<0.001	<0.001	<0.001	0.383
$PM_{2.5}$	r				1.00	0.78	-0.25	-0.44	0.07
	p-value				-	<0.001	<0.001	<0.001	0.008
CO	r					1.00	-0.25	-0.51	0.18
	p-value					-	<0.001	<0.001	<0.001
O_3	r						1.00	0.63	-0.25
	p-value						-	<0.001	<0.001
Temperature	r							1.00	-0.03
(C)	p-value							-	0.143
Humidity	r								1.00
(%)	p-value								-

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; CO, carbon monoxide; O_3, ozone; Temp, temperature (degrees Celsius); RH, relative humidity (%)

2). Qingdao

		NO_2	SO_2	PM_{10}	$PM_{2.5}$	CO	O_3	Temperature (C)	Humidity (%)
NO_2	r	1.00	0.68	0.63	0.68	0.56	-0.23	-0.40	-0.40
	p-value	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
SO_2	r		1.00	0.62	0.68	0.48	-0.39	-0.53	-0.36
	p-value		-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PM_{10}	r			1.00	0.82	0.46	-0.12	-0.27	-0.23
	p-value			-	<0.001	<0.001	<0.001	<0.001	<0.001
$PM_{2.5}$	r				1.00	0.61	-0.19	-0.37	-0.06
	p-value				-	<0.001	<0.001	<0.001	0.0202
CO	r					1.00	-0.22	-0.38	-0.13
	p-value					-	<0.001	<0.001	<0.001
O_3	r						1.00	0.56	0.10
	p-value						-	<0.001	<0.001
Temperature	r							1.00	0.38
(C)	p-value							-	<0.001
Humidity	r								1.00
(%)	p-value								-

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; CO, carbon monoxide; O_3, ozone; Temp, temperature (degrees Celsius); RH, relative humidity (%)

3). Suzhou

		NO_2	SO_2	PM_{10}	$PM_{2.5}$	CO	O_3	Temperature (C)	Humidity (%)
NO_2	r	1.00	0.62	0.61	0.57	0.53	-0.32	-0.40	-0.18
	p-value	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
SO_2	r		1.00	0.54	0.43	0.38	-0.24	-0.34	-0.42
	p-value		-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PM_{10}	r			1.00	0.63	0.43	-0.04	-0.20	-0.35
	p-value			-	<0.001	<0.001	0.078	<0.001	<0.001
$PM_{2.5}$	r				1.00	0.57	-0.16	-0.37	-0.11
	p-value				-	<0.001	<0.001	<0.001	<0.001
CO	r					1.00	-0.17	-0.20	0.056
	p-value					-	<0.001	<0.001	0.004
O_3	r						1.00	0.46	-0.16
	p-value						-	<0.001	<0.001
Temperature	r							1.00	0.17
(C)	p-value							-	<0.001
Humidity	r								1.00
(%)	p-value								-

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; CO, carbon monoxide; O_3, ozone; Temp, temperature (degrees Celsius); RH, relative humidity (%)

4). Liuzhou

		NO_2	SO_2	PM_{10}	$PM_{2.5}$	CO	O_3	Temperature (C)	Humidity (%)
NO_2	r	1.00	0.63	0.85	0.82	0.51	0.19	-0.34	-0.21
	p-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
SO_2	r		1.00	0.65	0.64	0.32	0.28	-0.34	-0.41
	p-value			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PM_{10}	r			1.00	0.97	0.40	0.44	-0.18	-0.38
	p-value				<0.001	<0.001	<0.001	<0.001	<0.001
$PM_{2.5}$	r				1.00	0.47	0.34	-0.28	-0.31
	p-value					<0.001	<0.001	<0.001	<0.001
CO	r					1.00	-0.19	-0.37	0.23
	p-value						<0.001	<0.001	<0.001
O_3	r						1.00	0.44	-0.60
	p-value							<0.001	<0.001
Temperature	r							1.00	0.03
(C)	p-value								0.328
Humidity	r								1.00
(%)	p-value								

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; CO, carbon monoxide; O_3, ozone; Temp, temperature (degrees Celsius); RH, relative humidity (%)

5). Haikou

		NO_2	SO_2	PM_{10}	$PM_{2.5}$	CO	O_3	Temperature (C)	Humidity (%)
NO_2	r	1.00	0.41	0.35	0.34	0.22	0.27	-0.06	-0.06
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.033	0.02
SO_2	r		1.00	0.77	0.78	0.34	0.57	-0.32	-0.44
	p-value			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PM_{10}	r			1.00	0.96	0.46	0.66	-0.41	-0.34
	p-value			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
$PM_{2.5}$	r				1.00	0.49	0.62	-0.46	-0.27
	p-value					<0.001	<0.001	<0.001	<0.001
CO	r					1.00	0.24	-0.43	0.06
	p-value						<0.001	<0.001	0.032
O_3	r						1.00	-0.17	-0.45
	p-value							<0.001	<0.001
Temperature (C)	r							1.00	-0.23
	p-value								<0.001
Humidity (%)	r								1.00
	p-value								

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; CO, carbon monoxide; O_3, ozone; Temp, temperature (degrees Celsius); RH, relative humidity (%)

Appendix C15. Percentage of days exceeding national and international AAP guidelines throughout the study period in the five CKB regions

Table C15.1 Chinese air quality standards – GB 3095-2012[1]

Pollutant	annual limit	24hr limit
SO_2 (μg/m^3)	60	150
NO_2 (μg/m^3)	40	80
PM_{10} (μg/m^3)	70	150
$PM_{2.5}$ (μg/m^3)	35	75
O_3 (μg/m^3)	-	160
CO (mg/m^3)	-	4

*refers to "Class 2" limits – applied to all Chinese urban areas
[1]China MoE. Ambient air quality standard (GB 3095-2012). 2012

Table C15.2 % of days exceeding 24hr Chinese AAP guidelines in each CKB urban region throughout the study period (2013-2016*)

	Harbin	Qingdao	Liuzhou	Suzhou	Haikou
PM_{10}	3.7	17.5	10.5	8.3	0.21
$PM_{2.5}$	28.6	18.6	23.8	18.9	2.2
NO_2	9.8	2.1	0.3	11.3	0.0
SO_2	14.9	0.5	0	0.7	0.0
O_3	0.6	4.2	4.3	1.7	0.5
CO	0.8	0.5	0.1	0	0.1

*2010-2016 for Suzhou

Table C15.3 WHO 24hr air quality guidelines[2]

Pollutant	Limit
SO_2 (μg/m^3)	20
PM_{10} (μg/m^3)	50
$PM_{2.5}$ (μg/m^3)	25
O_3 (μg/m^3)	100

[2]World Health Organisation. Air quality guidelines. Global updated 2005. Particulate matter, ozone, nitrogen dioxide and sulfur dioxide

Table C15.4 % of days exceeding daily WHO guidelines in each CKB urban region throughout the study period (2013-2016*)

	Harbin	Qingdao	Liuzhou	Suzhou	Haikou
PM_{10}	71.5	87.9	98.4	69.3	22.3
$PM_{2.5}$	74.5	78.5	84.1	84.0	28.1
SO_2	52.8	64.1	67.3	50.8	0.5
O_3	8.8	34.2	0.1	9.8	9.3

*2010-2016 for Suzhou

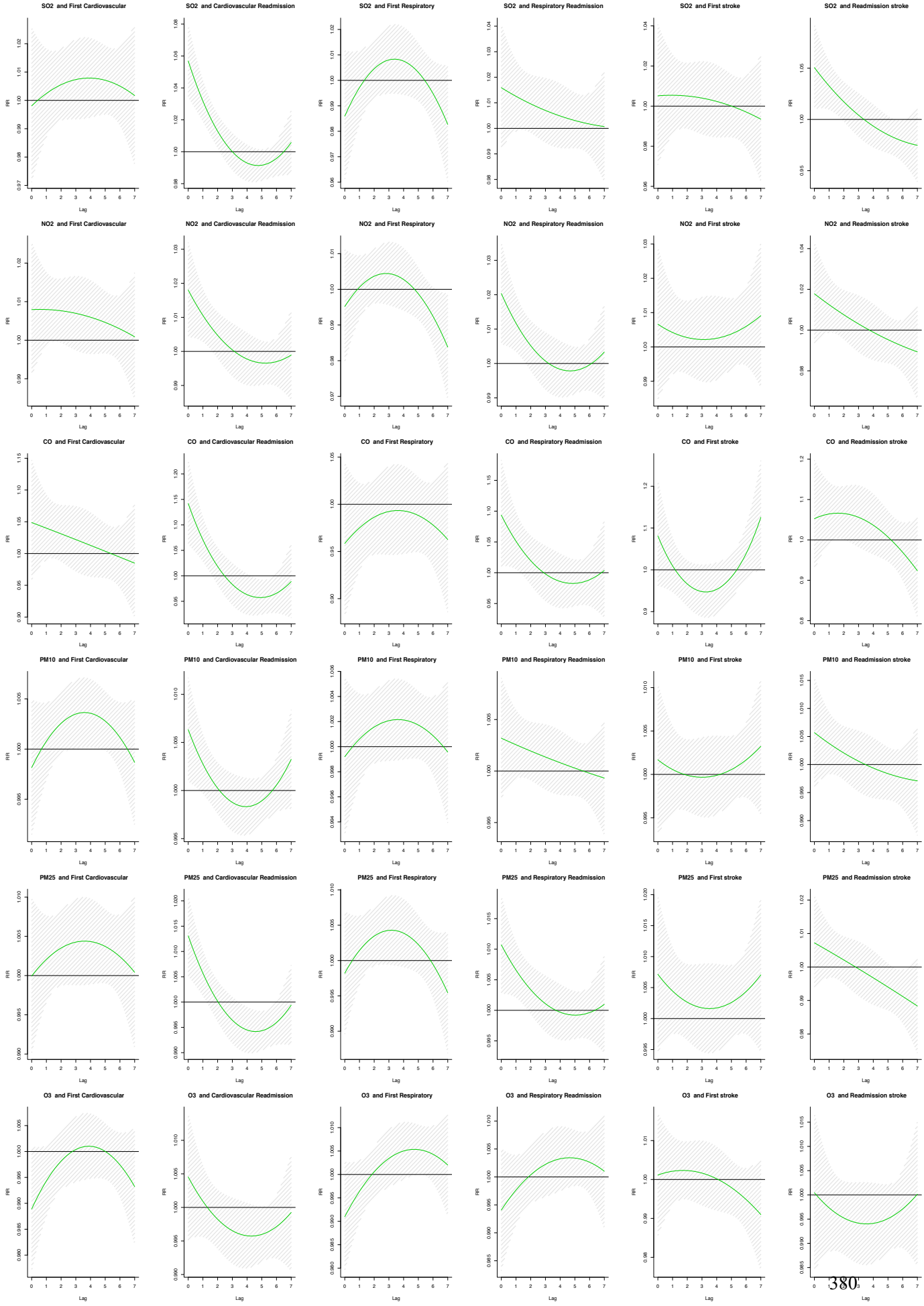
Appendix C16. ICD-10* codes and respective counts of respiratory hospitalisations flagged as abnormally high in time-series plots

ICD-10* descriptions and codes	Haikou (November 2013-January 2014)
Total respiratory hospitalisations (J00-J99)	1418 (100%)
Bronchitis not specified as acute or chronic (J40)	498 (35.1%)
Acute upper respiratory infection, unspecified (J06.90)	228 (16.1%)
Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia (J96.90)	156 (11.0%)
Disease of upper respiratory tract, unspecified (J39.90)	127 (9.0%)
Acute pharyngitis, unspecified (J02.90)	83 (5.9%)
Acute bronchitis, unspecified (J20.90)	33 (2.3%)
All others	293 (20.7%)
	Liuzhou (June-July 2015)
Total respiratory hospitalisations (J00-J99)	270 (100%)
Other disorders of lung (J98.414)	57 (21.1%)
Chronic obstructive pulmonary disease, unspecified (J44.9)	41 (15.2%)
Pneumonia, unspecified (J18.9)	41 (15.2%)
Acute bronchitis, unspecified (J20.9)	33 12.2(%)
Bronchitis not specified as acute or chronic (J40)	34 (12.6%)
All others	64 (23.7%)

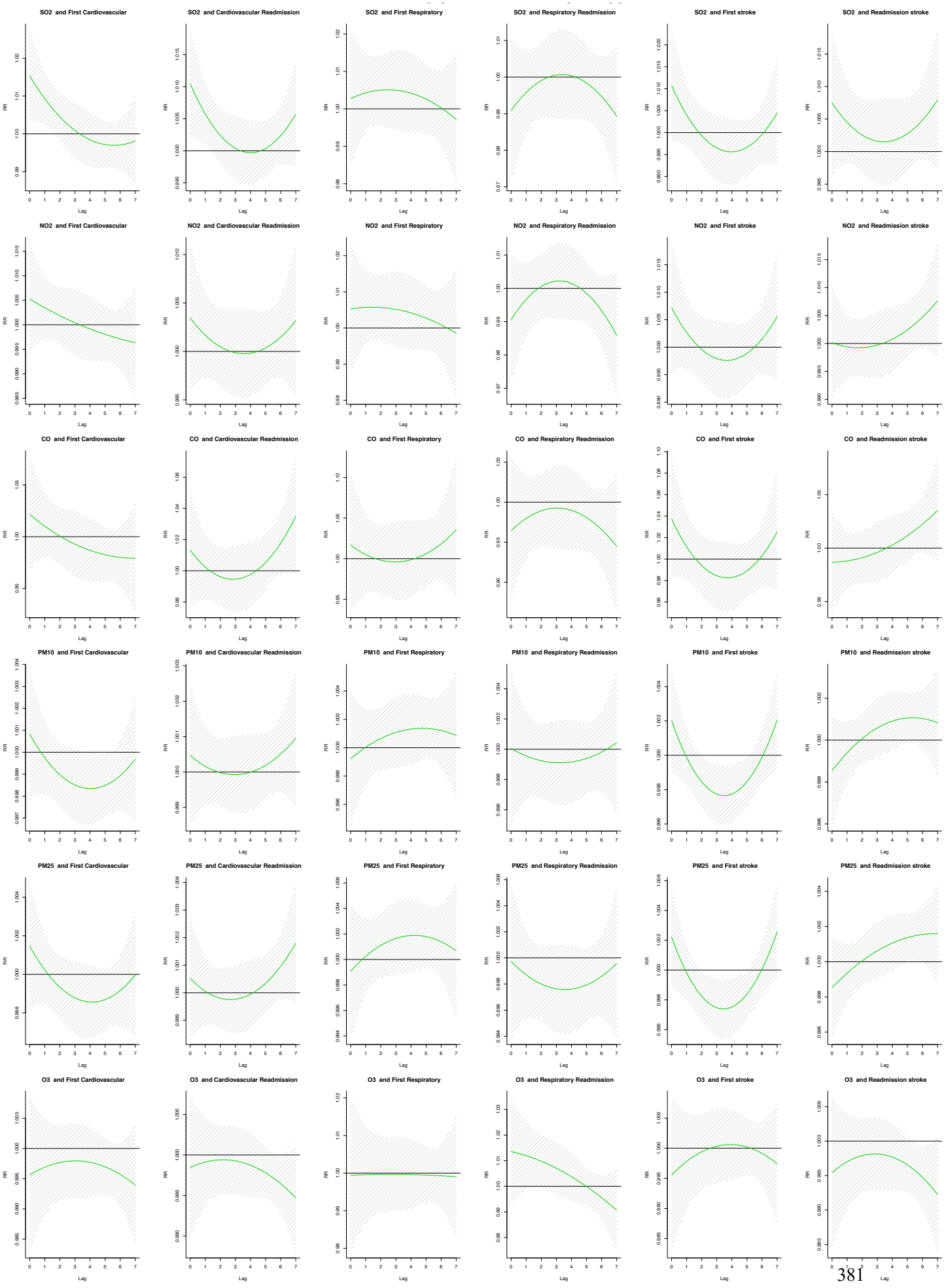
*International Classification of Disease, 10th Edition

Appendix C17. Distributed lag models for the associations between a 10 μg/m^3 increase in AAP and cardio-respiratory spells by pollutant and spell type

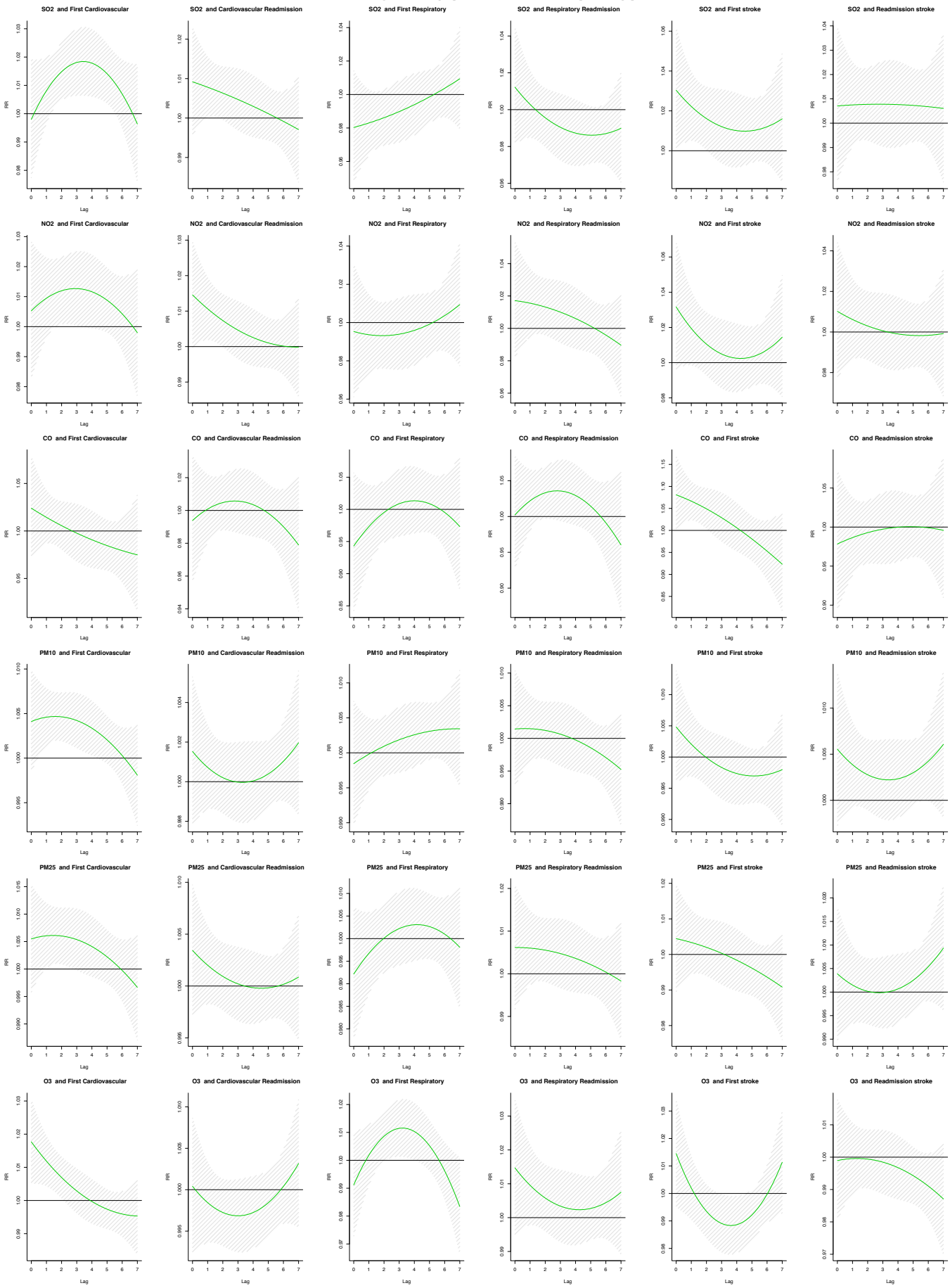
a) Suzhou



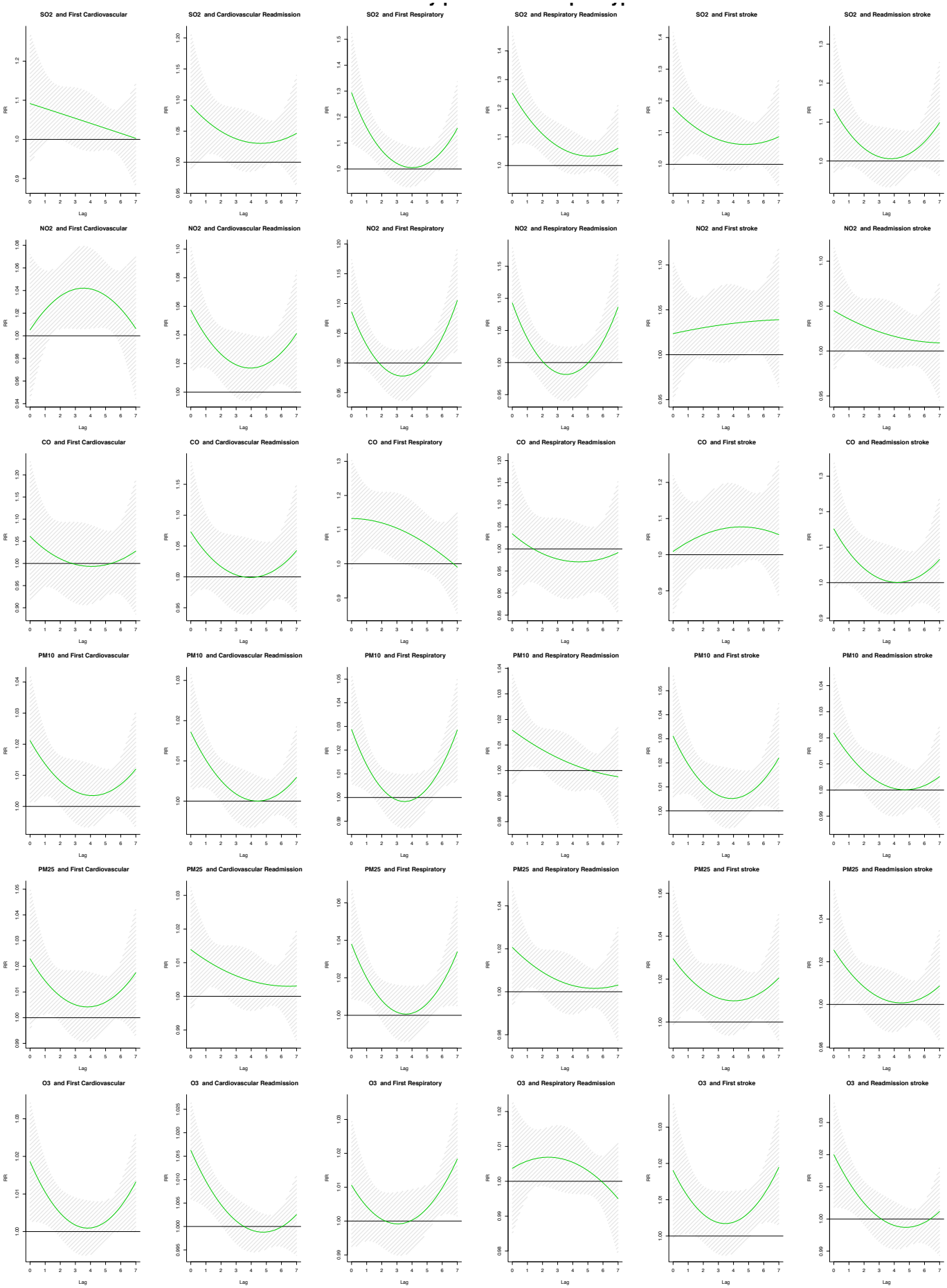
b) Harbin


SO2 and First Cardiovascular
SO2 and Cardiovascular Readmission
SO2 and First Respiratory
SO2 and Respiratory Readmission
SO2 and First stroke
SO2 and Readmission stroke
NO2 and First Cardiovascular
NO2 and Cardiovascular Readmission
NO2 and First Respiratory
NO2 and Respiratory Readmission
NO2 and First stroke
NO2 and Readmission stroke
CO and First Cardiovascular
CO and Cardiovascular Readmission
CO and First Respiratory
CO and Respiratory Readmission
CO and First stroke
CO and Readmission stroke
PM10 and First Cardiovascular
PM10 and Cardiovascular Readmission
PM10 and First Respiratory
PM10 and Respiratory Readmission
PM10 and First stroke
PM10 and Readmission stroke
PM25 and First Cardiovascular
PM25 and Cardiovascular Readmission
PM25 and First Respiratory
PM25 and Respiratory Readmission
PM25 and First stroke
PM25 and Readmission stroke
O3 and First Cardiovascular
O3 and Cardiovascular Readmission
O3 and First Respiratory
O3 and Respiratory Readmission
O3 and First stroke
O3 and Readmission stroke
RR
Lag

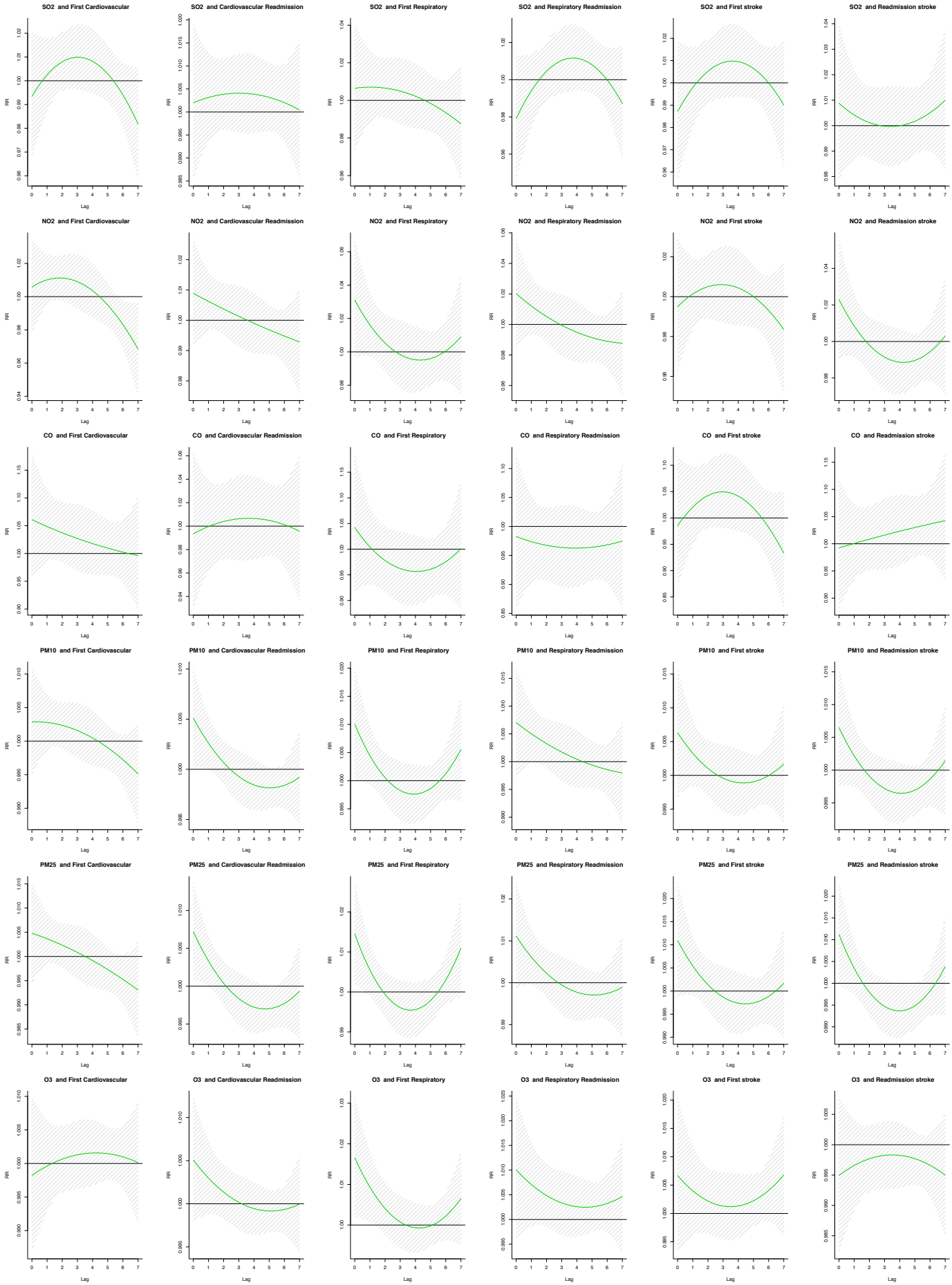
c) Qingdao


SO2 and First Cardiovascular
SO2 and Cardiovascular Readmission
SO2 and First Respiratory
SO2 and Respiratory Readmission
SO2 and First stroke
SO2 and Readmission stroke
NO2 and First Cardiovascular
NO2 and Cardiovascular Readmission
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NO2 and First stroke
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CO and First Cardiovascular
CO and Cardiovascular Readmission
CO and First Respiratory
CO and Respiratory Readmission
CO and First stroke
CO and Readmission stroke
PM10 and First Cardiovascular
PM10 and Cardiovascular Readmission
PM10 and First Respiratory
PM10 and Respiratory Readmission
PM10 and First stroke
PM10 and Readmission stroke
PM25 and First Cardiovascular
PM25 and Cardiovascular Readmission
PM25 and First Respiratory
PM25 and Respiratory Readmission
PM25 and First stroke
PM25 and Readmission stroke
O3 and First Cardiovascular
O3 and Cardiovascular Readmission
O3 and First Respiratory
O3 and Respiratory Readmission
O3 and First stroke
O3 and Readmission stroke
RR
Lag

d) Liuzhou


SO2 and First Cardiovascular
SO2 and Cardiovascular Readmission
SO2 and First Respiratory
SO2 and Respiratory Readmission
SO2 and First stroke
SO2 and Readmission stroke
NO2 and First Cardiovascular
NO2 and Cardiovascular Readmission
NO2 and First Respiratory
NO2 and Respiratory Readmission
NO2 and First stroke
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CO and First Cardiovascular
CO and Cardiovascular Readmission
CO and First Respiratory
CO and Respiratory Readmission
CO and First stroke
CO and Readmission stroke
PM10 and First Cardiovascular
PM10 and Cardiovascular Readmission
PM10 and First Respiratory
PM10 and Respiratory Readmission
PM10 and First stroke
PM10 and Readmission stroke
PM25 and First Cardiovascular
PM25 and Cardiovascular Readmission
PM25 and First Respiratory
PM25 and Respiratory Readmission
PM25 and First stroke
PM25 and Readmission stroke
O3 and First Cardiovascular
O3 and Cardiovascular Readmission
O3 and First Respiratory
O3 and Respiratory Readmission
O3 and First stroke
O3 and Readmission stroke
RR
Lag

e) Haikou


SO2 and First Cardiovascular
SO2 and Cardiovascular Readmission
SO2 and First Respiratory
SO2 and Respiratory Readmission
SO2 and First stroke
SO2 and Readmission stroke
NO2 and First Cardiovascular
NO2 and Cardiovascular Readmission
NO2 and First Respiratory
NO2 and Respiratory Readmission
NO2 and First stroke
NO2 and Readmission stroke
CO and First Cardiovascular
CO and Cardiovascular Readmission
CO and First Respiratory
CO and Respiratory Readmission
CO and First stroke
CO and Readmission stroke
PM10 and First Cardiovascular
PM10 and Cardiovascular Readmission
PM10 and First Respiratory
PM10 and Respiratory Readmission
PM10 and First stroke
PM10 and Readmission stroke
PM25 and First Cardiovascular
PM25 and Cardiovascular Readmission
PM25 and First Respiratory
PM25 and Respiratory Readmission
PM25 and First stroke
PM25 and Readmission stroke
O3 and First Cardiovascular
O3 and Cardiovascular Readmission
O3 and First Respiratory
O3 and Respiratory Readmission
O3 and First stroke
O3 and Readmission stroke
RR
Lag

Appendix D. Supplementary data for to Chapter 6

Appendix D1. Proportions of fatal cardio-respiratory endpoints within the Suzhou CKB study population (2013-2015)

Endpoint	Total number of endpoints	% of fatal endpoints
All cardiovascular disease	2559	7.7
All-type stroke	1051	8.6
Ischaemic stroke	847	1.9
Intracerebral haemorrhage	178	20.2
Ischaemic heart disease	421	6.4
Other cardiovascular diseases	1601	9.6
All respiratory disease	1763	2.6
Chronic obstructive pulmonary disease	329	6.7
Pneumonia	430	2.6
Other respiratory diseases	1323	2.2

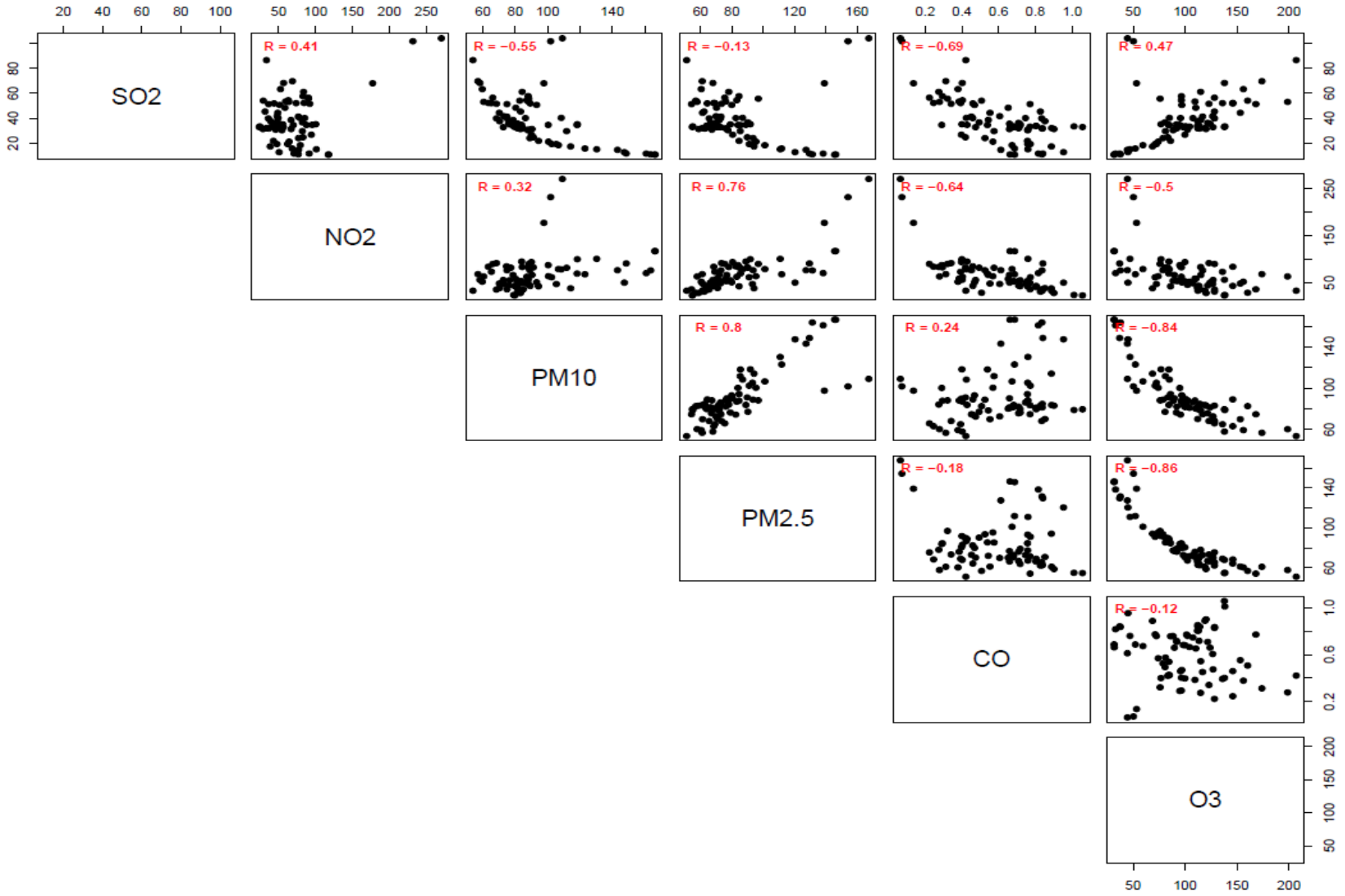
Appendix D2. Details of included infectious and parasitic diseases endpoints, ICD-10 codes, descriptions and representation within study population

Endpoint	ICD-10 codes and descriptions	% of total endpoints during follow-up
Certain infectious and parasitic diseases (n=486)	Unspecified infectious disease (B99)	192 (39.5%)
	Infectious gastroenteritis and colitis, unspecified (A09)	73 (15.0%)
	Tuberculosis (A15-A19)	50 (10.3%)
	Viral infections characterized by skin and mucous membrane lesions (B00-B09)	61 (12.6%)
	Other bacterial intestinal infections (A04)	29 (6.0%)
	Other bacterial diseases (A30-A49)	27 (5.6%)
	Others including, Helminthiases (B65-B83), viral hepatitis (B15-B19), mycoses (B35-B36), sequelae of infectious and parasitic diseases (B90-B94), other viral diseases (B25-B34), human immunodeficiency virus [HIV] disease (B20-B24)	54 (11.1%)

* will not equate to 100% as participants may have cause-specific respiratory endpoints coded as part of the same overall episode but only one endpoint will contribute to the endpoint "all infectious and parasitic diseases"

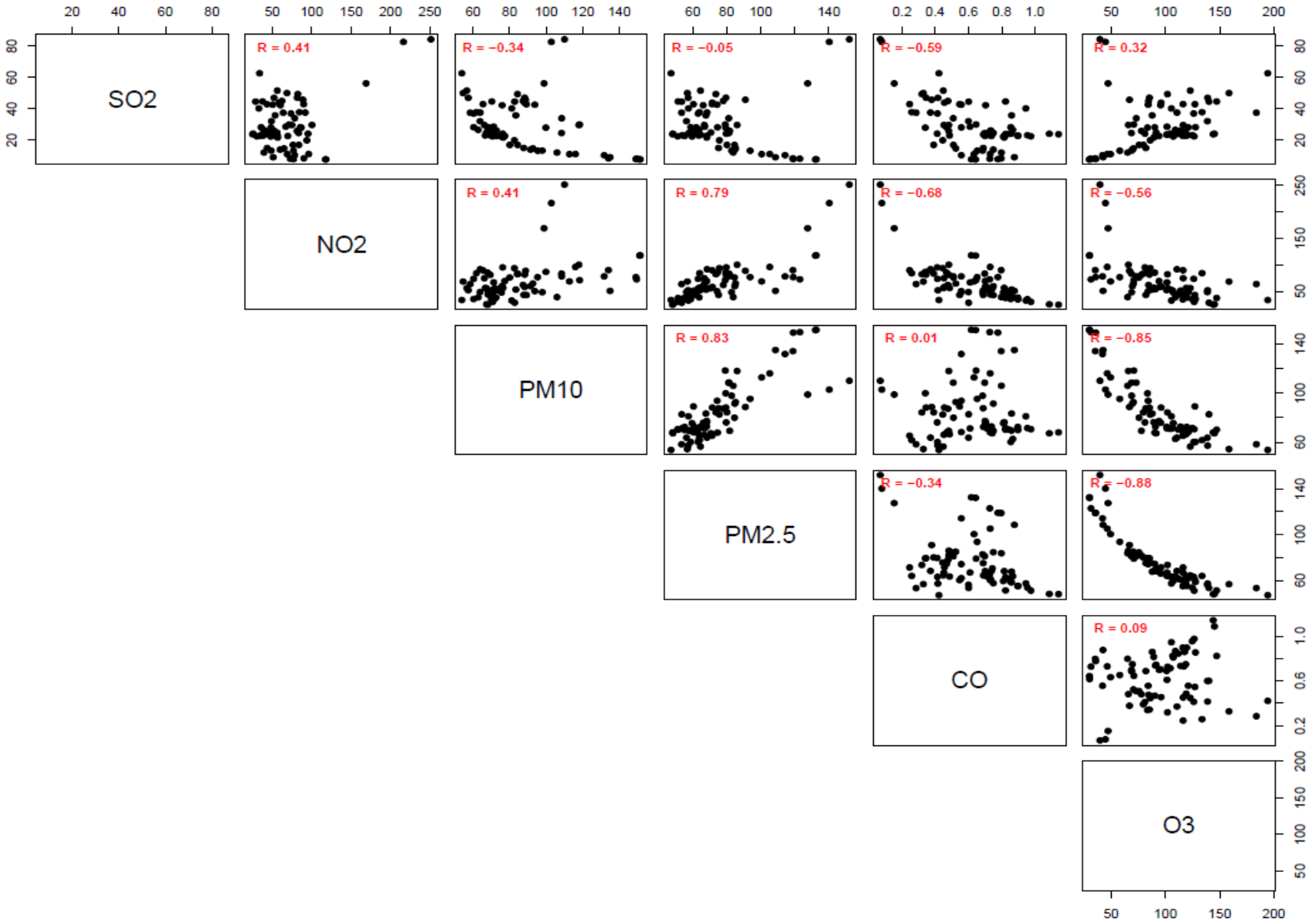
Appendix D3. Scatterplots and Pearson Correlation coefficients between mean predicted pollutant concentrations by clinic location for each year of follow-up respectively, Suzhou

a)2013



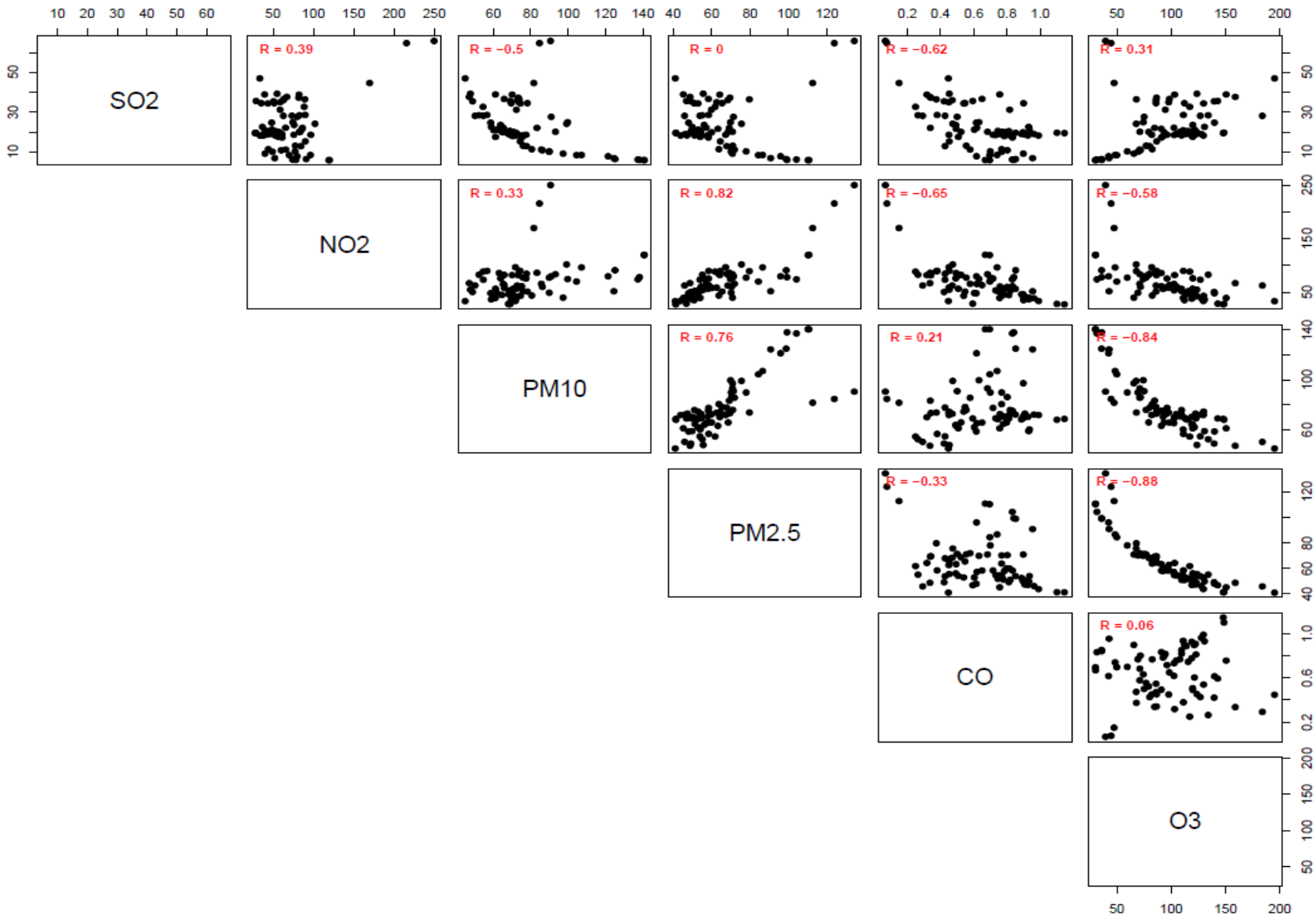
Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5 μm; O_3, ozone; CO, carbon monoxide. All pollutants measured in $\mu g/m^3$ except CO (mg/m^3)

b) 2014



Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 µm; $PM_{2.5}$, particulate matter <2.5 µm; O_3, ozone; CO, carbon monoxide. All pollutants measured in µg/m^3 except CO (mg/m^3)

c) 2015



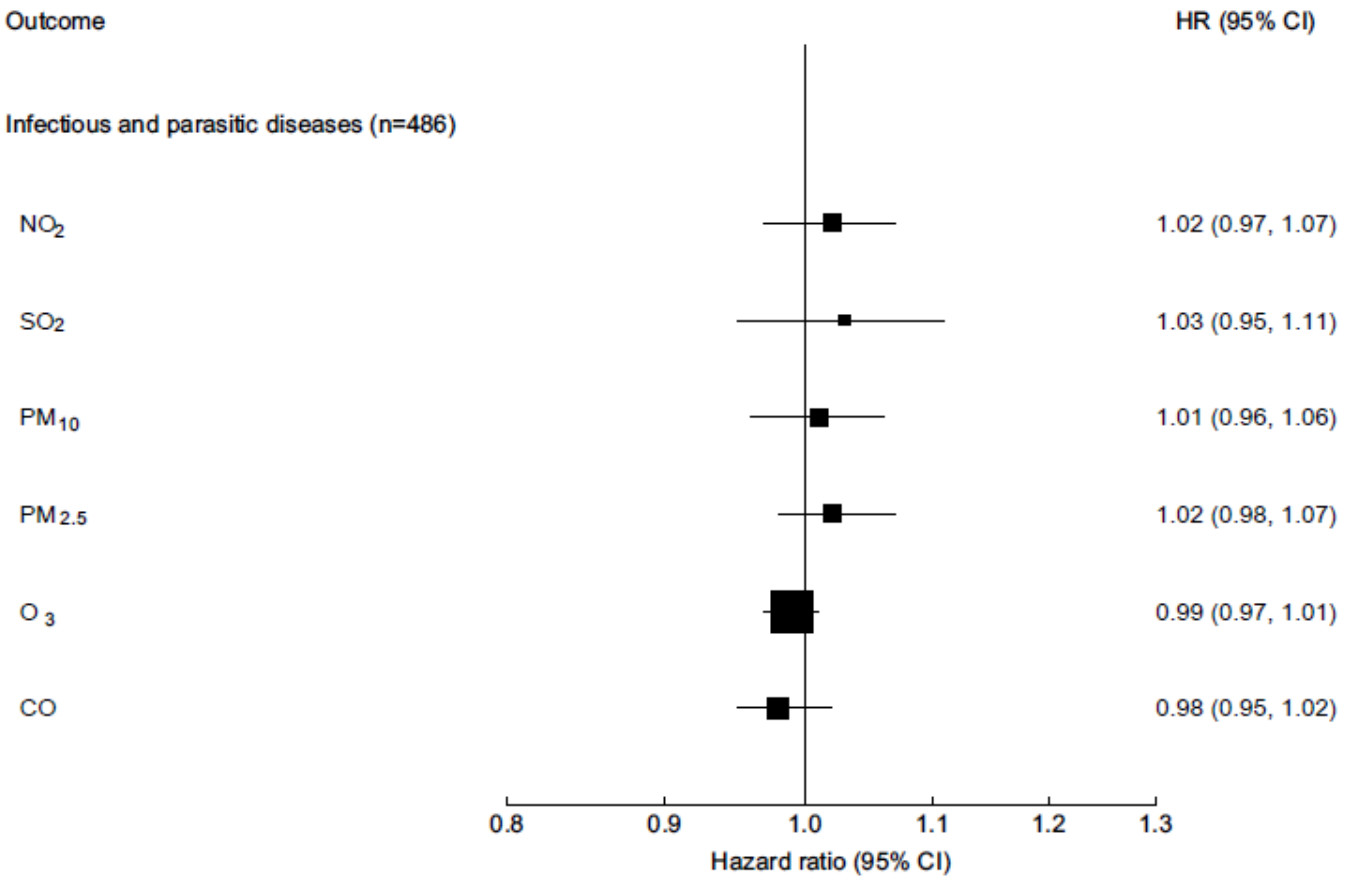
Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 µm; $PM_{2.5}$, particulate matter <2.5 µm; O_3, ozone; CO, carbon monoxide. All pollutants measured in $\mu g/m^3$ except CO (mg/m^3)

Appendix D4. Infectious and parasitic disease incidence rates according to age and gender in Suzhou (2013-2015)

	Infectious and parasitic disease	
Characteristic	**No. of events**	**Rate per 10,000 person years**
Gender		
Male	215	34.6
Female	271	30.6
Age (years)		
30-39	39	17.4
40-49	88	19.6
50-59	172	34.2
60-69	132	60.0
≥70	55	77.2

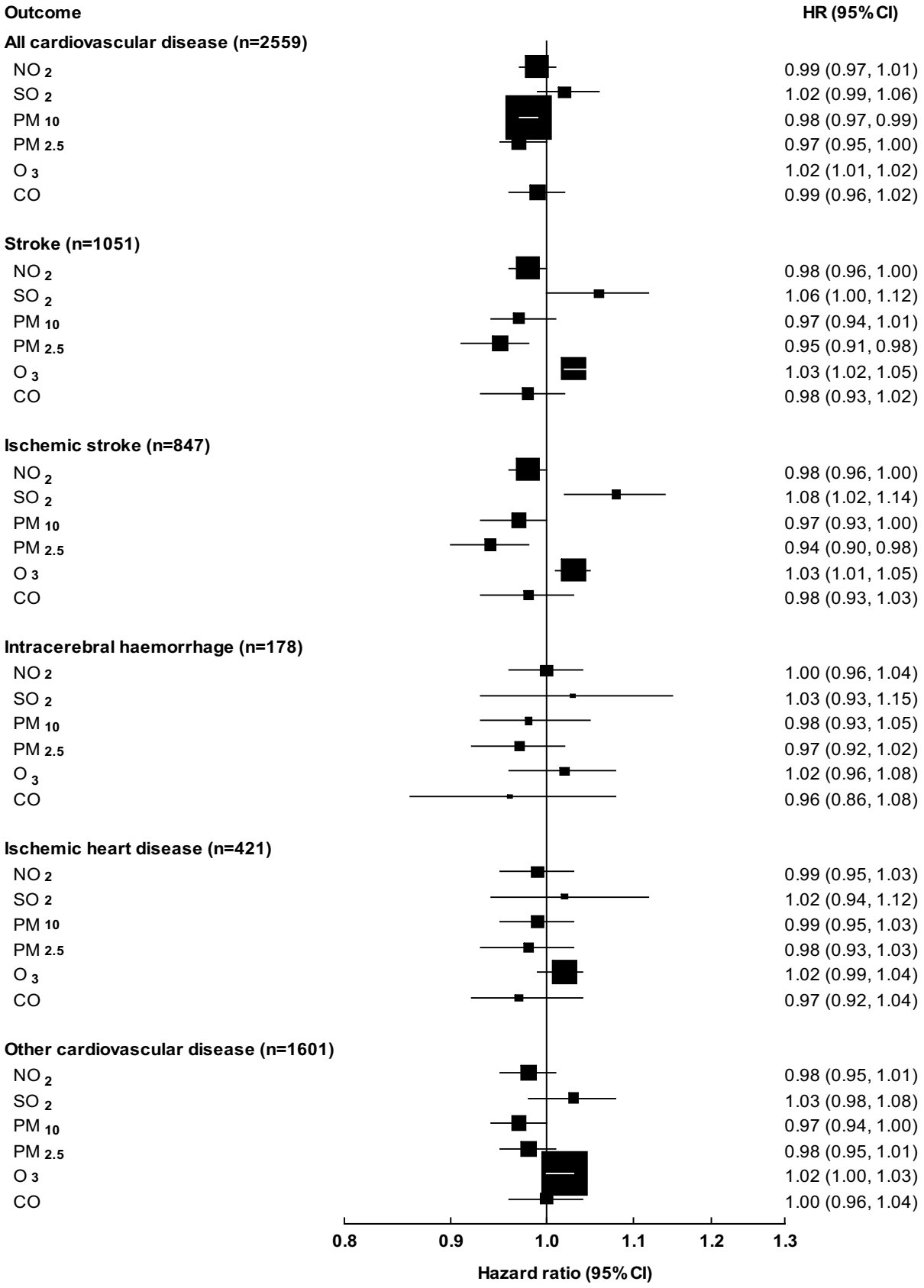
Per 10,000 person-years

Appendix D5. Adjusted hazard ratios for long-term AAP exposure and infectious and parasitic diseases used as negative control analysis



Hazard ratios calculated for a 10 μg/m^3 increase in pollutant exposure (except CO which used a 100 μg/m^3 increase) Hazard ratios were adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean temperature. Black boxes represent hazard ratios with size inversely proportional to variance of the log hazard ratio, and horizontal lines representing 95% confidence intervals (CIs)

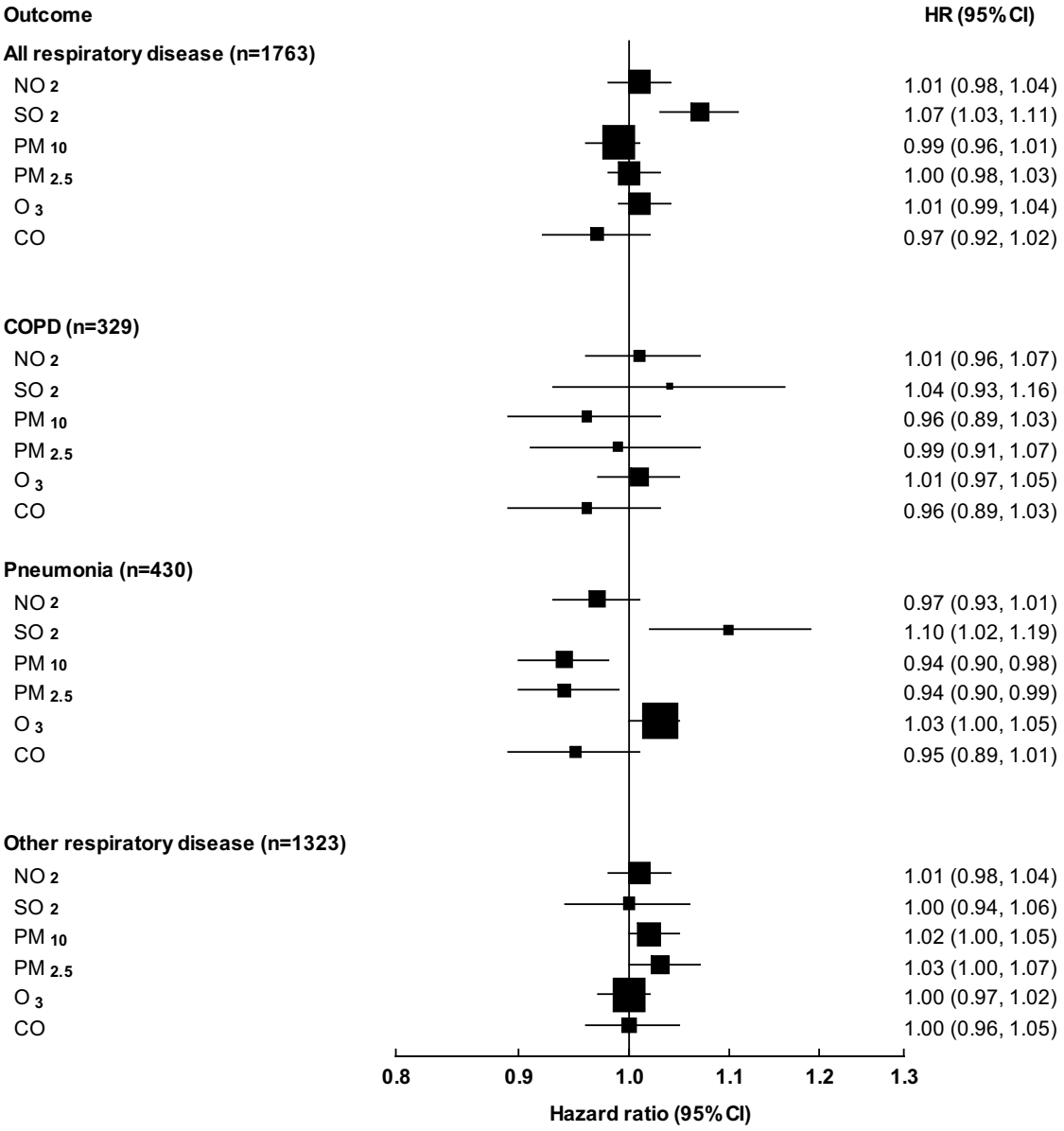
Appendix D6. Adjusted hazard ratios for monthly AAP exposure and major cardiovascular disease risk



Hazard ratios calculated for a 10 μg/m^3 increase in pollutant exposure (except CO which used a 100 μg/m^3 increase*)*. Adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean monthly temperature, prior respiratory disease, consumption of fresh fruit and preserved vegetables, respectively, use of hypertensive medication, and mean SBP. Black boxes represent hazard ratios with size inversely proportional to variance of the log hazard ratio, and horizontal lines representing 95% confidence intervals (CIs)

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10μm*;* $PM_{2.5}$, particulate matter <2.5μm*;* O_3, ozone; CO, carbon monoxide.

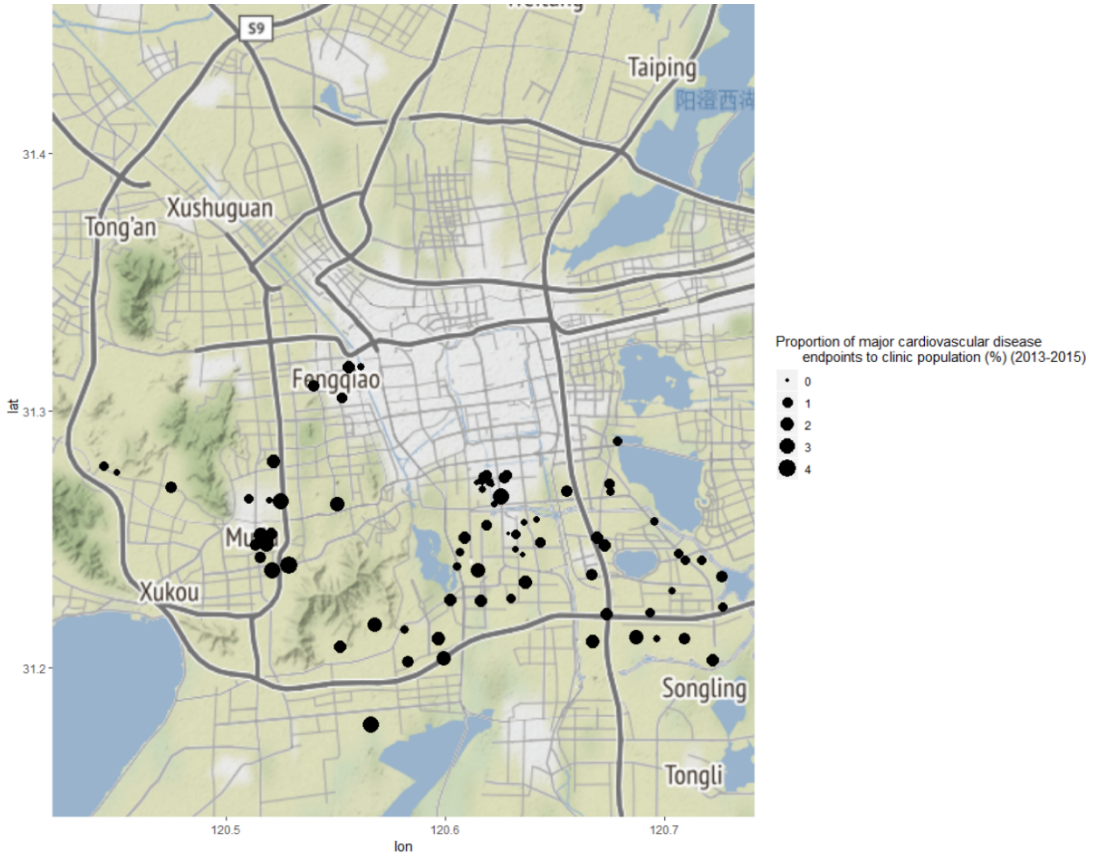
Appendix D7. Adjusted hazard ratios for monthly AAP exposure and major respiratory disease risk

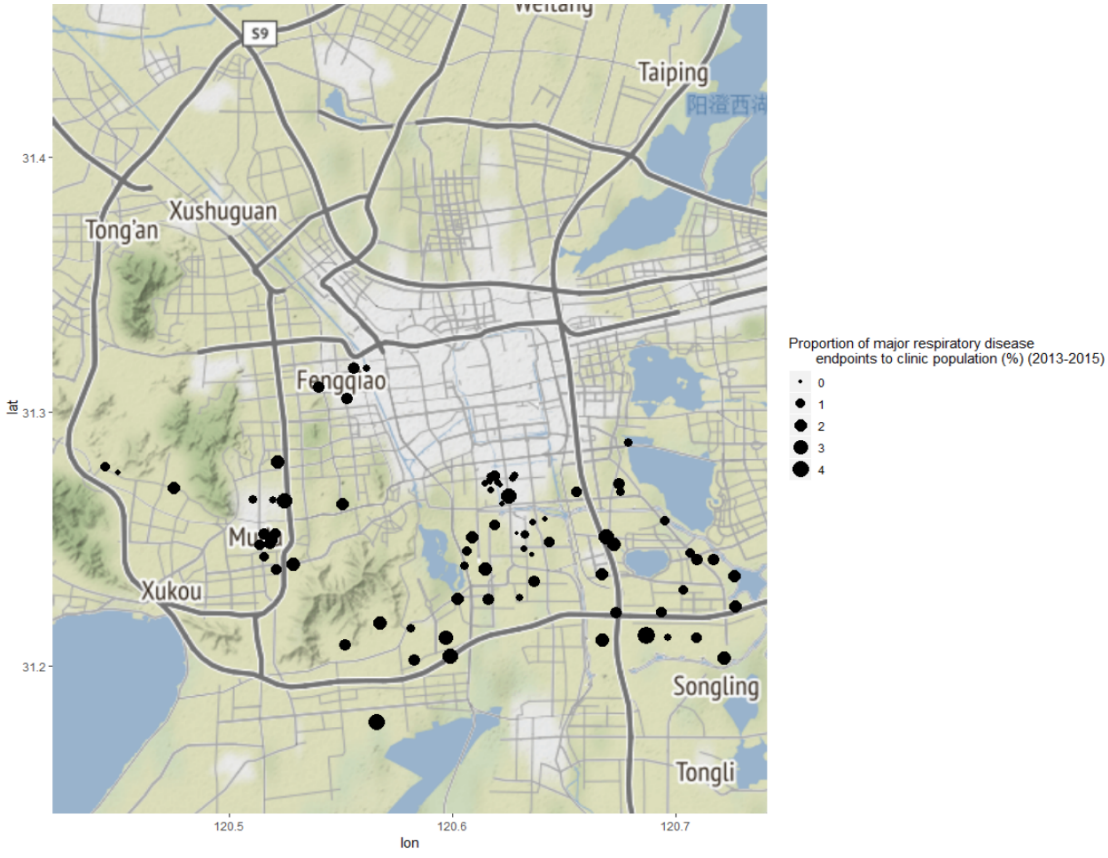


Hazard ratios calculated for a 10 μg/m^3 increase in pollutant exposure *(*except CO which used a 100 μg/m^3 increase*)*. Adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean monthly temperature, prior cardiovascular disease, consumption of fresh fruit and preserved vegetables, respectively, use of diabetes medication. Black boxes represent hazard ratios with size inversely proportional to variance of the log hazard ratio, and horizontal lines representing 95% confidence intervals (CIs)

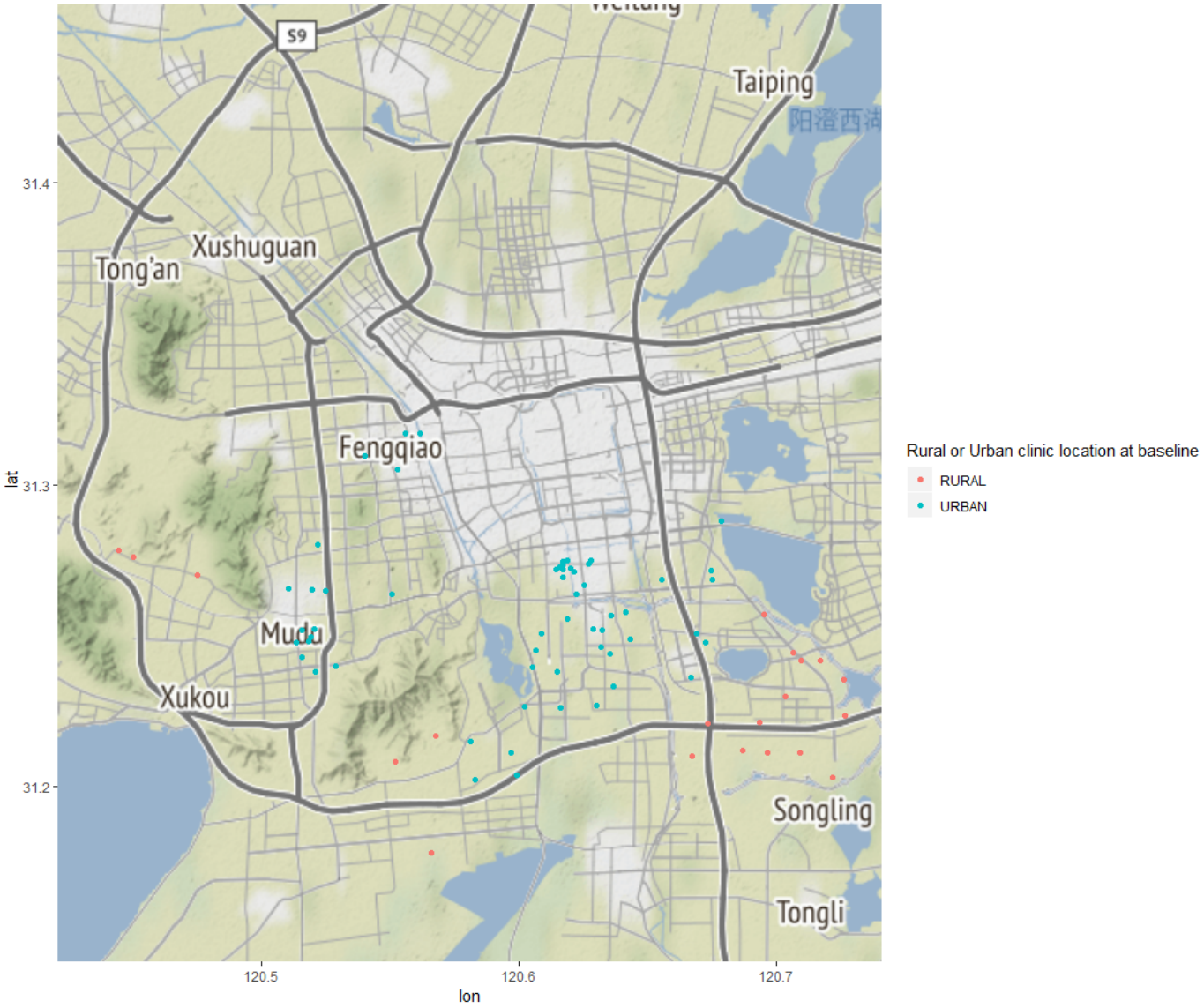
Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10; $PM_{2.5}$, particulate matter <2.5; O_3, ozone; CO, carbon monoxide.

Appendix D8. Spatial distribution of major cardiovascular and respiratory disease endpoints, respectively by CKB clinic location, Suzhou (2013-2015)





Appendix D9.1. Location of clinics classified as more urban or rural at the time of CKB baseline survey



Appendix D9.2 Adjusted hazard ratios from sensitivity analyses for long-term AAP exposure and all cardiovascular diseases (n=2559) with inclusion of a strata term allowing baseline hazard to vary between more urban and rural clinic locations

Pollutant	Hazard ratio (95% CI)
NO_2	0.99 (0.97, 1.01)
SO_2	1.07 (1.03, 1.12)
PM_{10}	0.96 (0.95, 0.98)
$PM_{2.5}$	0.95 (0.93, 0.98)
O_3	1.02 (1.01, 1.03)
CO	0.98 (0.94, 1.01)

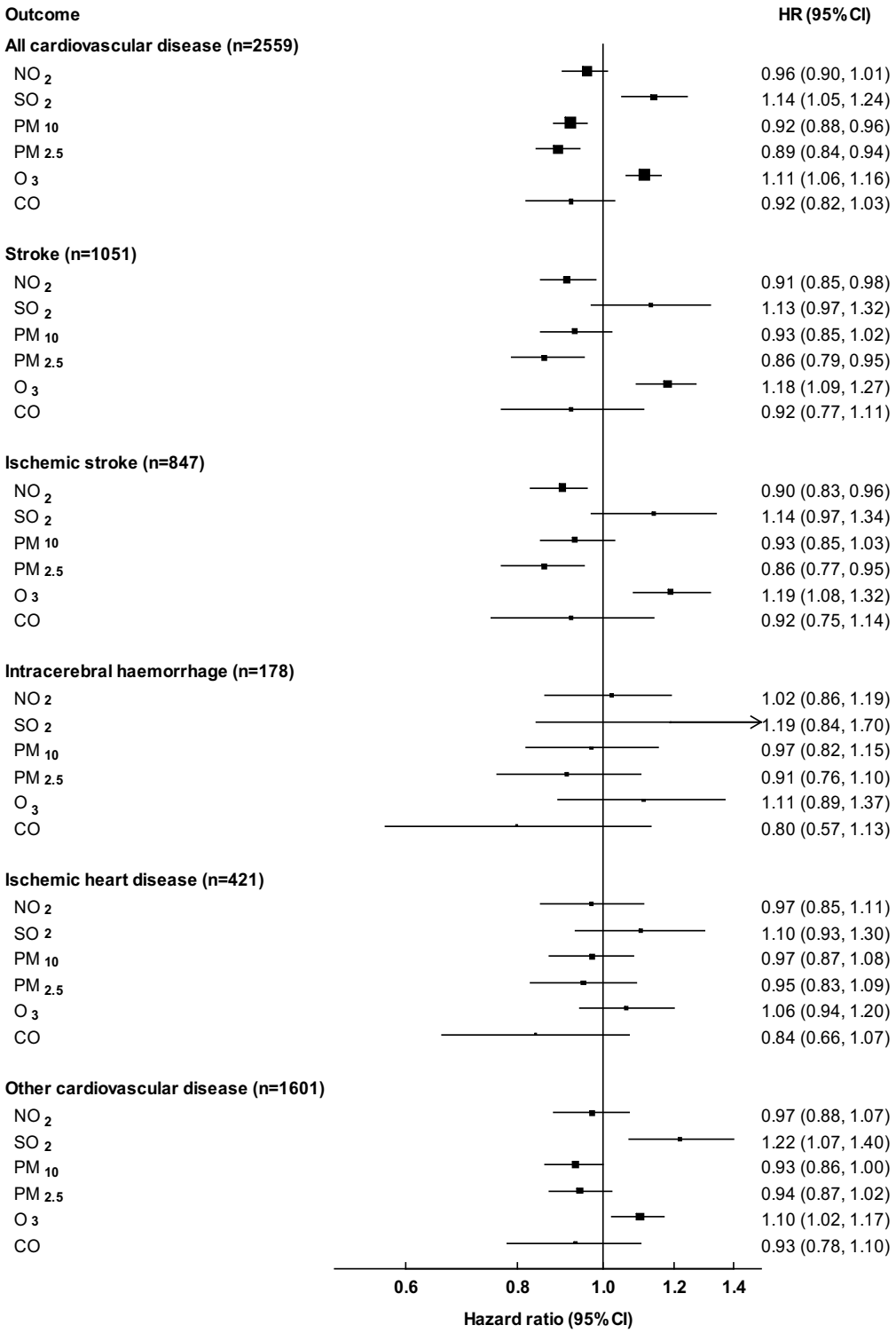
Hazard ratios adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean temperature, prior respiratory disease, consumption of fresh fruit and preserved vegetables, respectively, use of hypertensive medication, and mean SBP plus a strata term for urban vs. rural locality.
Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10; $PM_{2.5}$, particulate matter <2.5; O_3, ozone; CO, carbon monoxide

Appendix D9.3 Adjusted hazard ratios from sensitivity analyses showing long-term AAP exposure and all respiratory diseases (n=1763) with inclusion of a strata term allowing baseline hazard to vary between more urban and rural clinic locations

Pollutant	Hazard ratio (95% CI)
NO_2	1.01 (0.98, 1.03)
SO_2	1.11 (1.04, 1.15)
PM_{10}	0.97 (0.94, 1.00)
$PM_{2.5}$	0.98 (0.94, 1.01)
O_3	1.02 (1.00, 1.04)
CO	0.96 (0.91, 1.01)

Hazard ratios were adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean temperature, prior cardiovascular disease, consumption of fresh fruit and preserved vegetables, respectively, use of diabetes medication plus a strata term for baseline urban vs. rural locality.
Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10; $PM_{2.5}$, particulate matter <2.5; O_3, ozone; CO, carbon monoxide

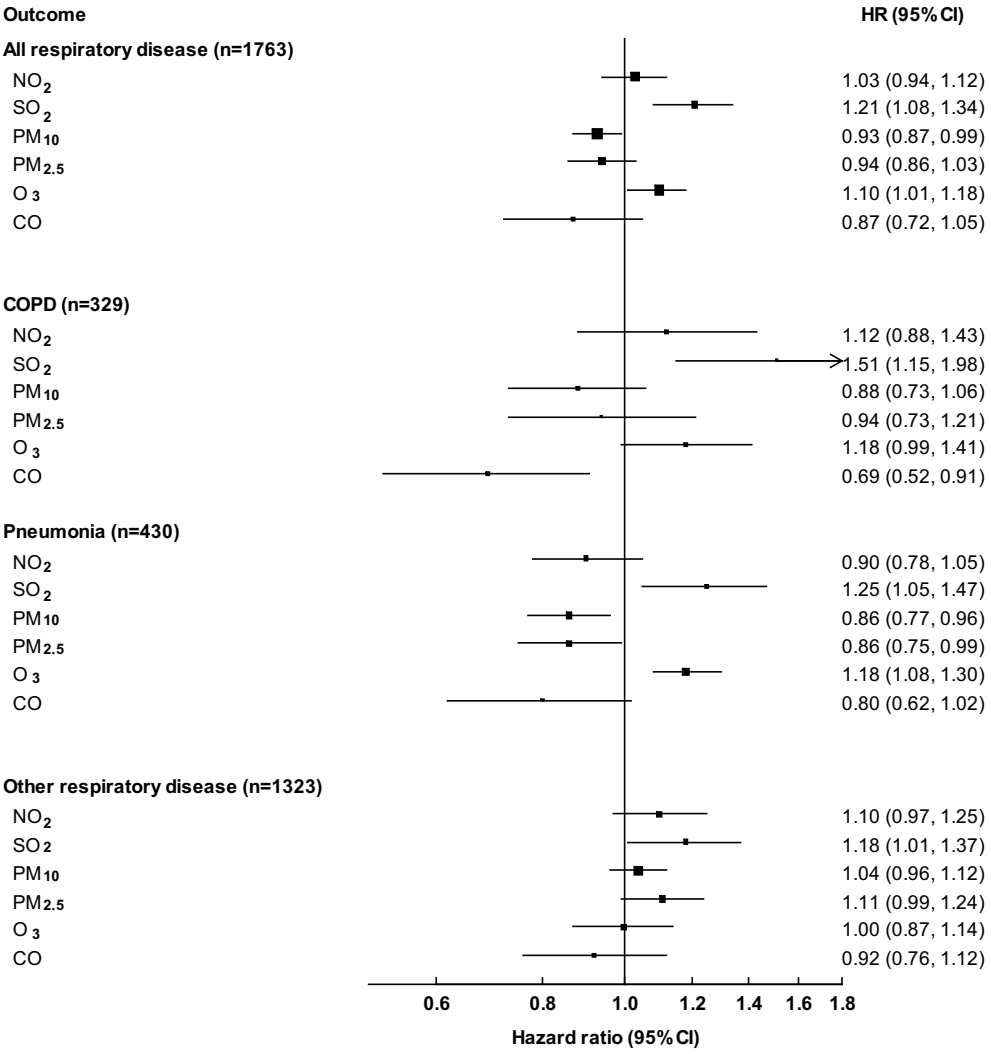
Appendix D10.1 Adjusted hazard ratios for an interquartile range (IQR) increase AAP exposure and major cardiovascular disease risk



Hazard ratios adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean monthly temperature, prior respiratory disease, consumption of fresh fruit and preserved vegetables, respectively, use of hypertensive medication, and mean SBP. Black boxes represent hazard ratios with size inversely proportional to variance of the log hazard ratio, and horizontal lines representing 95% confidence intervals (CIs)

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10μm; $PM_{2.5}$, particulate matter <2.5μm; O_3, ozone; CO, carbon monoxide.

Appendix D10.2 Adjusted hazard ratios for an interquartile range (IQR) increase AAP exposure and major respiratory disease risk



Hazard ratios adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean monthly temperature, prior cardiovascular disease, consumption of fresh fruit and preserved vegetables, respectively, use of diabetes medication. Black boxes represent hazard ratios with size inversely proportional to variance of the log hazard ratio, and horizontal lines representing 95% confidence intervals (CIs)

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10; $PM_{2.5}$, particulate matter <2.5; O_3, ozone; CO, carbon monoxide.

Appendix D11.1 Adjusted hazard ratios for long-term AAP exposure and major cardiovascular disease risk with corresponding p-values

Outcome and pollutant	Hazard ratio	p-value*	Benjamini-Hochberg corrected p-value**
All cardiovascular disease (n=2559)			
NO_2	0.99 (0.97,1.01)	0.30	0.47
SO_2	1.07 (1.02, 1.12)	0.003	0.015
PM_{10}	0.97 (0.95, 0.99)	0.01	0.036
$PM_{2.5}$	0.97 (0.95, 0.99)	0.012	0.039
O_3	1.02 (1.01, 1.03)	<0.001	0.012
CO	0.98 (0.95, 1.01)	0.16	0.288
Stroke (n=1051)			
NO_2	0.98 (0.96, 1.00)	0.015	0.045
SO_2	1.07 (0.98 1.16)	0.121	0.272
PM_{10}	0.97 (0.94 1.01)	0.113	0.271
$PM_{2.5}$	0.94 (0.91 0.98)	0.002	0.014
O_3	1.04 (1.02, 1.05)	<0.001	0.012
CO	0.98 (0.92, 1.03)	0.380	0.484
Ischemic stroke (n=847)			
NO_2	0.97 (0.95, 0.99)	0.002	0.014
SO_2	1.07 (0.99, 1.17)	0.106	0.271
PM_{10}	0.97 (0.93, 1.01)	0.153	0.288
$PM_{2.5}$	0.94 (0.90, 0.98)	0.004	0.018
O_3	1.04 (1.02, 1.06)	<0.001	0.012
CO	0.98 (0.92, 1.04)	0.45	0.540
Intracerebral haemorrhage (n=178)			
NO_2	1.00 (0.96, 1.05)	0.86	0.860
SO_2	1.10 (0.91, 1.32)	0.33	0.475
PM_{10}	0.99 (0.92, 1.06)	0.73	0.751
$PM_{2.5}$	0.97 (0.90, 1.04)	0.33	0.475
O_3	1.02 (0.98, 1.07)	0.36	0.480
CO	0.94 (0.85, 1.04)	0.2	0.343
Ischemic heart disease (n=421)			
NO_2	0.99 (0.95, 1.03)	0.68	0.720
SO_2	1.05 (0.96, 1.15)	0.26	0.425
PM_{10}	0.99 (0.94, 1.03)	0.60	0.655
$PM_{2.5}$	0.98 (0.93, 1.04)	0.49	0.569
O_3	1.02 (0.99, 1.04)	0.35	0.480
CO	0.95 (0.88, 1.02)	0.16	0.288
Other cardiovascular disease (n=1601)			
NO_2	0.99 (0.96, 1.02)	0.53	0.596
SO_2	1.11 (1.04, 1.20)	0.003	0.015
PM_{10}	0.97 (0.94, 1.00)	0.05	0.138
$PM_{2.5}$	0.98 (0.95, 1.01)	0.14	0.288
O_3	1.02 (1.01, 1.03)	0.008	0.032
CO	0.98 (0.93, 1.03)	0.39	0.484

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5μm; O_3, ozone; CO, carbon monoxide.
Hazard ratios calculated for a 10 μg/m^3 increase in pollutant exposure (except CO which used a 100 μg/m3 increase). Adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid fuel use, ambient mean temperature, prior respiratory disease, consumption of fresh fruit and preserved vegetables, respectively, use of hypertensive medication, and mean SBP

*p-value not adjusted for multiple testing. Bonferroni correction based on 36 tests would yield a threshold of 0.0014 (P=0.05/24)
** p-value adjusted for multiple testing using Benjamini-Hochberg (BH) procedure.

Appendix D11.2 Adjusted hazard ratios for long-term AAP exposure and major respiratory disease risk with corresponding p-values

Outcome and pollutant	Hazard ratio	p-value*	Benjamini-Hochberg corrected p-value**
All respiratory disease (n=1763)			
NO_2	1.02 (0.98, 1.05)	0.39	0.492
SO_2	1.11 (1.04, 1.19)	0.001	0.012
PM_{10}	0.99 (0.96, 1.02)	0.48	0.549
$PM_{2.5}$	1.01 (0.97, 1.05)	0.64	0.689
O_3	1.01 (0.99, 1.03)	0.27	0.405
CO	0.96 (0.91, 1.01)	0.13	0.260
COPD (n=329)			
NO_2	1.03 (0.96, 1.11)	0.36	0.480
SO_2	1.24 (1.08, 1.44)	0.003	0.024
PM_{10}	0.95 (0.88, 1.03)	0.19	0.304
$PM_{2.5}$	0.98 (0.89, 1.08)	0.66	0.689
O_3	1.04 (1.00, 1.08)	0.07	0.153
CO	0.90 (0.83, 0.97)	0.008	0.038
Pneumonia (n=430)			
NO_2	0.97 (0.93, 1.01)	0.18	0.304
SO_2	1.12 (1.03, 1.23)	0.011	0.044
PM_{10}	0.94 (0.90, 0.98)	0.005	0.030
$PM_{2.5}$	0.94 (0.89, 1.00)	0.04	0.120
O_3	1.04 (1.02, 1.06)	<0.001	0.012
CO	0.93 (0.87, 1.01)	0.07	0.153
Other respiratory disease (n=1323)			
NO_2	1.03 (0.99, 1.07)	0.15	0.277
SO_2	1.09 (1.01, 1.18)	0.035	0.120
PM_{10}	1.02 (0.98, 1.05)	0.35	0.480
$PM_{2.5}$	1.04 (1.00, 1.09)	0.07	0.153
O_3	1.00 (0.97, 1.03)	0.95	0.950
CO	0.98(0.92, 1.03)	0.41	0.492

Abbreviations: NO_2, nitrogen dioxide; SO_2, sulphur dioxide; PM_{10}, particulate matter <10 μm; $PM_{2.5}$, particulate matter <2.5μm; O_3, ozone; CO, carbon monoxide.
Hazard ratios calculated for a 10 μg/m^3 increase in pollutant exposure (except CO which used a 100 μg/m3 increase). Adjusted for age, sex, active smoking status, passive smoke exposure, self-rated health, BMI, total physical activity, alcohol consumption, highest education, solid-fuel use, ambient mean temperature, prior cardiovascular disease, consumption of fresh fruit and preserved vegetables, respectively, use of diabetes medication.

*p-value not adjusted for multiple testing. Bonferroni correction based on 24 tests would yield a threshold of 0.002 (P=0.05/24)
** p-value adjusted for multiple testing using Benjamini-Hochberg (BH) procedure.