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The Effects of Air Pollution on Asthma Hospital Admissions in Adelaide, South Australia, 2003–2013: Time-Series and Case-crossover Analyses

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Summary of the "take home" message: Daily variation in asthma hospitalisation is associated with air pollution, and the association differs across seasons and age groups.

Abstract

Background: Air pollution can have adverse health effects on asthma sufferers, but the effects vary with geographic, environmental and population characteristics. There has been no long time series study in Australia to quantify the effects of environmental factors including pollen on asthma hospitalisations.

Objectives: This study aimed to assess the seasonal impact of air pollutants and aeroallergens on the risk of asthma hospital admissions for adults and children in Adelaide, South Australia.

Methods: Data on hospital admissions, meteorological conditions, air quality and pollen counts for the period 2003–2013 were sourced. Time series analysis and case-crossover analysis were used to assess the short-term effects of air pollution on asthma hospitalisations. For the time series analysis, generalized log-linear quasi-Poisson and negative binomial regressions were used to assess the relationships, controlling for seasonality and long-term trends using flexible spline functions. For the case-crossover analysis, conditional logistic regression was used to compute the effect estimates with time-stratified referent selection strategies.

Results: A total of 36,024 asthma admissions were considered. Findings indicated that the largest effects on asthma admissions related to $PM_{2.5}$, NO_2, PM_{10} and pollen were found in the cool season for children (0–17 years), with the five-day cumulative effects of 30.2% (95% CI: 13.4–49.6%), 12.5% (95% CI: 6.6–18.7%), 8.3% (95% CI: 2.5–14.4%) and 4.2% (95% CI: 2.2–6.1%) increases in risk of asthma hospital admissions per 10 unit increments, respectively. The largest effect for ozone was found in the warm season for children with the

five-day cumulative effect of an 11.7% (95% CI: 5.8–17.9%) increase in risk of asthma hospital admissions per 10 ppb increment in ozone level.

Conclusion: Findings suggest that children are more vulnerable and the associations between exposure to air pollutants and asthma hospitalisations tended to be stronger in the cool season compared to the warm season, with the exception of ozone. This study has important public health implications, and provides valuable evidence for the development of policies for asthma management.

Introduction

Asthma is a common condition, affecting one in ten Australians, and has been chosen as one of the nine national health priority areas in Australia [1]. Most of the major studies on respiratory health effects of air pollutants have emerged from the Northern Hemisphere, with fewer investigations from Australia where air quality, population exposures and climatic conditions are likely to differ. The findings from a multi-city study assessing the air pollution effects on respiratory hospital admissions including 7 cities in Australia and New Zealand indicated that the air pollution effects differed among those cities [2]. There is evidence that many environmental factors are associated with the development and exacerbation of asthma, including allergens, airborne irritants, weather conditions and indoor conditions [3,4].

It has been well documented that exposure to air pollutants such as nitrogen dioxide (NO_2), ozone and particulate matter (PM) has adverse effects on the immune system, airway responsiveness and asthma exacerbations [5-7]. Outdoor airborne pollutants can be released from a variety of sources including mobile and stationary sources. The most common sources of air pollution in Australia are emissions from motor vehicles, industrial production, home heating sources and bushfires [8,9]. In addition, drought-related dust storms can occasionally cause extreme pollution events [10]. Sensitisation and exposure to aeroallergens such as pollens have also been reported as major triggers of asthma exacerbations [11].

The location for this study was Adelaide, the capital of South Australia (SA), which lies between the boundaries of latitude 34º55´ S and longitude 138º35´ E and has unique and variable climatic conditions with hot summers, mild winters and low annual average rainfall. South Australia is known as the driest state in the driest continent on earth. To the best of our knowledge, there has been no previous study of the short-term effects of air pollution and

aeroallergens such as pollen on asthma hospitalisations in Adelaide. Moreover, there has been no long time series study in Australia to quantify the effects of environmental factors including pollen on asthma hospitalisations. Considering the high burden of asthma in Australia, and the relative lack of studies examining the association with air quality, there is a need for further evidence to inform the development of public health strategies to prevent the detrimental effects of air pollutants and aeroallergens in Australian populations. Furthermore, it is important to identify impacts on both children and adults, as the adverse health effects of exposure to air pollutants might vary across different life stages such as childhood and adulthood. The aim of this study was to assess the effects of air pollution and pollen on asthma hospitalisations in Adelaide. To provide robust conclusions, time series analysis and case-crossover (CCO) analysis were both applied and the results compared.

Materials and Methods

Hospital data: Data relating to asthma hospital admissions in Adelaide during the 10-year period from 1 July 2003 to 30 June 2013 were sourced from the SA Department of Health together with information on date of admission, daily counts of asthma hospital admissions and age groups (aggregated as 0–17 years and 18+ years). Asthma admissions were based on the diagnostic codes in accordance with the International Classification of Disease (ICD) 10th version (ICD-10) coding system. The daily counts of asthma hospital admissions include asthma (ICD-10, J45) and status asthmaticus (ICD-10, J46). Australia has a very strict quality assurance procedure to maintain the hospital data at the highest standard. In accordance with the National Health Information Agreement, all states and territories are mandated to provide an annual submission to the Australian Institute of Health and Welfare (AIHW) of all admitted activity information for the states.

Air pollution data: Air pollution data for the study period were obtained from the Environment Protection Authority (EPA) monitoring site located at Netley, a suburb in the Western Region of the Adelaide airshed. Quality checks were made on the air quality data to ensure the validity of the data for the analysis. The site is located 5 kilometers west of the city centre, which is located centrally in the Adelaide metropolitan area, where the northern most suburb is 40-45 kilometers north of the central business district (CBD), and the southern most suburb is 40 kilometers south of the CBD. Daily maximum one-hour average concentrations of NO_2 and ozone, and daily average PM_{10} and $PM_{2.5}$ concentrations were considered.

Pollen data: Pollen grain data were obtained from the Asthma Foundation (SA) and the Adelaide aerobiology laboratory. Pollen grains were collected using the Hirst automatic volumetric spore trap sampling method [12] . Particles that adhered to the Vaseline-coated

sampling slides were analysed to determine the number of grains per cubic meter of air sampled in a 24-hour period. The daily levels were calculated for tree pollen including *Ash tree, Birch, Cypress, Eucalyptus, Fruit tree, Olive tree, Pinus, Plane tree, She-Oak, and Wattle;* weed pollen including *Chenopodiaceae, Compositae, Plantain, Polygonaceae, and Salvation Jane;* and grass pollen. Daily total pollen counts were calculated in number of grains/m^3.

Meteorological data: Meteorological data for the study period were obtained from the Australian Bureau of Meteorology, Kent Town station (station code 23090), situated centrally in metropolitan Adelaide. Data included daily average ambient temperature and daily average relative humidity based on synoptic observations.

Statistical analysis

In the literature, time series analysis is the most commonly used statistical methodology for assessing the effects of air pollution on health outcomes [13] . CCO analysis has also been used as an alternative analytical approach to control for seasonal confounding by design [14-16] . There remains debate as to which technique is preferable for evaluating time series data as each has its own advantages and disadvantages and as a result, both are applied in this study. For the time series analysis, generalized log-linear quasi-Poisson regressions were used to assess the relationships between exposure of primary interest and outcomes, controlling for seasonality, potential confounders and long-term trends using splines. Briefly, log-linear generalized linear models (GLMs) were fitted with spline functions for time, and natural cubic splines for temperature and humidity to assess the effects of air pollutants on hospital admissions for asthma. The optimal degrees of freedom (*df*) for the seasonality and trend component were selected by minimising the serial correlation in the residual via the

partial autocorrelation function (PACF) [17,18] . The optimal *df* for weather variables (i.e. temperature and relative humidity) was selected by minimising the Akaike Information Criterion (AIC).

Single-pollutant distributed lag (DL) models included one pollutant or pollen at a time with a lag structure of lag days 0–4 and were adjusted for potential confounding factors such as day of the week, holidays (school holidays and public holidays) and weather variables (temperature and humidity). The lag structure was optimized and lag days 0–4 were selected in this study. To control for seasonality and long-term trends, a smooth function for time based on splines with 4 *df*/year was included in the models. Weather variables were considered as non-linear and were controlled by using natural cubic splines with optimal *df* (i.e. 4 *df* for temperature and humidity). Wald tests were used to assess the overall effects and non-linearity. To model the effects of mean temperature, three lag periods i.e. lag days 0-1, 2-7 and 8-14 were used. For humidity, the average relative humidity of the current and previous four days was used (i.e. lag days 0-4). The log-linear GLM equation for a single-pollutant DL model can be expressed as follows:

$$logE(Y_t) = \sum_{\ell=0}^{4} \beta_\ell Z_{t-\ell} + DOW + SchH + PubH + bs(Time, 4\,df/yr) + ns(Temp, 4df) + ns(RH, 4df)$$

where, $E(Y_t)$ represents the expected number of daily asthma hospital admissions at day t; β_ℓ represents the coefficient for air pollutants (log relative rate) for lag ℓ; $Z_{t-\ell}$ represents levels of air pollutants for day t at lag ℓ; DOW represents an indicator variable for day of the week; $SchH$ represents an indicator variable for school holiday; $PubH$ represents an indicator variable for public holiday; $bs(Time, 4\,df/yr)$ represents the spline functions for time with 4 *df*/year; $ns(Temp, 4df)$ represents the natural cubic spline function for temperature with 4 *df*, and $ns(RH, 4df)$ represents the natural cubic spline function for humidity with 4 *df*. The

cumulative effect (also known as overall effect or net effect) of an exposure over 5 lag days was estimated (i.e. cumulative effect=$\sum_{\ell=0}^{4}\beta_{\ell}$).

Multi-pollutant DL models included multiple air pollutants (i.e. NO_2, ozone, $PM_{2.5}$) and pollen in the model and adjusted for other factors using the same approaches as those for single-pollutant DL models. Since there is high collinearity between PM_{10} and $PM_{2.5}$ with pairwise Pearson correlation coefficient of 0.70, this would lead to instability in effect estimates in the multivariate regression analysis [19] . The use of $PM_{2.5}$ rather than PM_{10} levels as air quality indicators has been widely accepted and recommended in the World Health Organization air quality guidelines [20] . Thus, the multi-pollutant DL models were built with multiple air pollutants (i.e. NO_2, ozone, $PM_{2.5}$) and pollen.

For the CCO analysis, conditional logistic regression (CLR) was used to compute the effect estimates of air pollutants and pollen with time-stratified and symmetric bidirectional referent selection strategies [21] . The effects of temperature and humidity were incorporated using natural cubic splines. The main CCO analyses were conducted using the time-stratified referent selection strategy (CCO-TS) with a stratum length of 28 days and an exclusion period of 2 days either side of the case day [2]. As a sensitivity analysis, the CCO analysis was performed using the symmetric bidirectional (CCO-SBI) referent selection strategy. Effect modification by age group (i.e. children: 0–17 years; adults: 18+ years) and season (i.e. cool season: April to September; warm season: October to March) was also examined.

A variety of sensitivity analyses were carried out to test the robustness of the effect estimates for both time series and CCO analyses. A sensitivity analysis for the time series analysis involved use of the negative binomial regression approach in place of the quasi-Poisson

regression for handling overdispersion [22] . In the final model for time series analysis, lagged deviance residuals were added to the model when significant early residual autocorrelation was observed. A sensitivity analysis for the CCO analysis was conducted using SBI referent selection strategy with referents 7 and 14 days before and after the case day. A final sensitivity analysis for both time series and CCO analyses involved the use of a 5-day moving average (MA) models in place of the DL models with lag days 0–4.

In addition, to recover information from the 10.4% of observations with missing air pollution or pollen levels on one or more than one variables, a multiple imputation procedure with five imputations was used to handle the missing data for the main analyses, and the complete-case analysis using the dataset without imputations was conducted as a sensitivity analysis. Multivariate imputation was conducted with the common approach of assuming that all variables in the final model follow a multivariate normal distribution.

A series of plots including time series plots, residual plots and PACF plots were used to check the model fit for the time series analyses. All statistical procedures were undertaken using Stata statistical software version 13.1 [23] . The study was qualified as negligible risk research and exempt from the ethical review of the Human Research Ethics Committee of the University of Adelaide as we did not use any personal data in the study.

Results

Summary of exposure measures and asthma events

The summary statistics of asthma hospital admissions and environmental variables in Adelaide, Australia, 2003–2013 are presented in Table 1. There was a total of 36,024 asthma hospital admissions recorded during the study period. Of the total asthma hospital admissions, 59.6% (21,462 counts) were children aged 0–17 years, and 40.4% (14,562 counts) were adults aged 18+ years. The peak of daily counts of asthma hospital admissions usually occurred in winter, and sometimes also occurred in late autumn or late summer. There were a total of 3,653 observations (i.e. days) including 388 (10.4%) with missing data on one or more than one exposure variables (i.e. air pollutants and pollen). The percentage of missing data for ozone, NO_2, pollen, PM_{10} and $PM_{2.5}$ was 0.9%, 1.0%, 2.5%, 3.8% and 4.1%, respectively.

Association of asthma admissions with air pollutants from time-series analyses

The results for selection of lag structure indicated that there was little evidence of pollution effects at lags longer than 4 days (see Figure 1). The estimated cumulative effects of single-pollutant and multi-pollutant DL models are presented in Table 2. Findings from single-pollutant DL models indicated that estimated cumulative effects over 5 days for both age groups combined were significantly associated with every 10 unit increase in the air pollutants assessed. The estimated cumulative effects were 21.2% (95% CI: 12.2–30.8%), 8.0% (95% CI: 3.9–12.2%), 7.6% (95% CI: 4.4–10.9%), 3.4% (95% CI: 0.5–6.4%), and 1.5% (95% CI: 0.6–2.4%) for $PM_{2.5}$, ozone, NO_2, PM_{10} and pollen, respectively. However, 10 unit increments of air pollutants/pollen are equivalent to 3.50 standard deviations of $PM_{2.5}$, 1.26 standard deviations of ozone, 1.04 standard deviations of NO_2, 0.99 standard deviations of PM_{10} and 0.20 standard deviations of pollen, respectively. Thus, the effect size measured

by every 10 unit increment is not relative to the spread of the pollutants/pollen, and not comparable between pollutants/pollen. Generally, data suggested positive and statistically significant associations between the exposures and asthma hospital admissions for both age groups combined, children and adults, apart from the non-significant effects of PM_{10} and pollen on asthma hospital admissions for adults. In addition, the CCO–TS analyses yielded similar results (see Table 2), which provided veracity for the time series analyses.

The results of the multi-pollutant models indicated that an increase in the risk of asthma hospital admissions over 5 days for both age groups combined was associated with every 10 unit increase in $PM_{2.5}$, ozone, NO_2 and pollen. The estimated cumulative effects were 11.1% (95% CI: 2.1–21.0%), 5.5% (95% CI: 1.5–9.7%), 5.0% (95% CI: 1.6–8.6%) and 1.0% (95% CI: 0.1–1.9%) for $PM_{2.5}$, ozone, NO_2 and pollen, respectively. Generally, data from the multi-pollutant DL models suggested positive and statistically significant associations between air pollutants/pollen and daily asthma hospital admissions for both age groups combined and children alone, except for the non-significant ozone effect on asthma hospital admissions for children. In contrast, evidence of environmental effects on asthma hospital admissions for adults was very weak, with the exception of good evidence of ozone effect on asthma hospitalisations for adults (P-value=0.028). In comparison with the effect estimates from the single-pollutant DL models, the effect estimates of air pollutants or pollen from these multi-pollutant DL models were moved towards the null, suggesting (as expected) that the estimated effects of environmental factors from the single-pollutant DL models were confounded by each other.

Effect modification by age group and season

The air pollution effects on daily asthma hospitalisations in children were stronger than those in adults (Table 2). Results from the DL models with CCO-TS design stratified by season (see Table 3) indicated associations between exposure to air pollutants and asthma hospital admissions tended to be stronger for $PM_{2.5}$, NO_2, PM_{10} and pollen in the cool season than in the warm season. In contrast, there was evidence of significant positive associations between ozone concentrations and asthma hospitalisations during the warm season, whereas ozone associations in the cool season were negative but non-significant.

Modeling weather effects as flexible curves

The results from the single-pollutant ($PM_{2.5}$) DL models suggested that the overall effects of temperature and humidity were statistically significant for children (see Figure 2). The curve can be viewed as the weather effects in relative risk across the temperature range with specific lag days. For example, for children at lag days 8–14, at the range of 10–15 ºC, the curve was nearly flat suggesting a negligible temperature effect; whereas at the range of 15–25 ºC, for every one unit (ºC) increase in temperature the risk of asthma hospitalisations tended to reduce. However, at the range of 27–35 ºC, the risk of asthma hospitalisations slightly increased with the increasing temperature. The confidence intervals in the regions of lower and extreme higher temperatures were wide, reflecting the limited number of days on which these extremes of temperature occurred, and the departure from the reference temperature. There was a decrease in the risk of asthma hospitalisations of children observed at lower relative humidity and a slight increase at higher relative humidity. Overall, weather effects on asthma hospitalisations were more likely to be significant for children compared to those for adults (Figure 2).

Sensitivity analyses and model checking

The results for sensitivity analyses are presented in the supplementary file. For time series analyses, effect estimates for air pollutants and pollen did not appear to be sensitive to the use of the negative binomial regression approach in place of the quasi-Poisson regression approach for handling overdispersion (see Table S1); and the adjustment for residual autocorrelation appeared to have little effect on the point estimates for the air pollutant and pollen effects (see Figure S1). The results of time series analyses using the dataset without imputation are presented in Table S2. For CCO analysis, the selection of referent schemes between CCO-TS and CCO-SBI influenced the estimates for the health effects of air pollution and pollen (see Table S3). The CCO-TS analysis generally yielded equivalent estimates compared with time series regression. For both the time series analysis and CCO analysis, using the DL models and moving average models yielded similar estimates for the air pollution and pollen effects (see Table 2).

In addition, the time series plot with observed and fitted values of asthma hospital admissions, the residual plot and the PACF plot from the multi-pollutant DL model are presented in Figures S2- S4, respectively. These plots suggested that the model provided a good description of the data and fitted the data well. The seasonality and long-term trends were well controlled. No significant residual autocorrelation was seen in the final model.

Discussion

To the best of our knowledge, this is the first long time series study in Australia to quantify the effects of environmental factors including pollen on asthma hospitalisations. Previous studies have been short time series studies, for instance examining the non-linear associations between grass pollen and asthma hospitalisations or emergency department (ED) visits in Melbourne within a selected season in one year [24,25] . In general, the air pollutants and pollen investigated were all found to have adverse effects on daily hospital admissions for asthma in Adelaide, but the associations markedly differed in age groups (i.e. children and adults) and seasons (i.e. cool and warm seasons). Importantly, this study also found that children were more susceptible to the increasing levels of air pollutants/pollen. In season-specific analyses, associations were often stronger in the cool season, apart from those for ozone, which were weaker.

There was little evidence for first-order interactions between air pollutants and pollen. In addition, the point estimates obtained from multi-pollutant models were generally attenuated compared to those derived from single-pollutant models. Methodologically speaking, the estimated effects from time series analysis and CCO analysis were comparable when the seasonality and long-term trends were adequately controlled for. Previous studies have also showed the equivalence of CCO analyses and time series analyses by utilising health outcome data [14,16,26,27] and simulated data [13,28,29] .

Comparison with other studies

$PM_{2.5}$: In the present study, $PM_{2.5}$ exhibited positive estimated effects of 30.2% (95% CI: 13.4–49.6%), 24.0% (95% CI: 11.6–37.8%) and 15.6% (95% CI: -1.8–36.0%) increases in risk of asthma hospital admissions per 10 $\mu g/m^3$ increment of $PM_{2.5}$ from single-pollutant DL

models in the cool season for children, both age groups combined and adults, respectively. This finding is consistent with many other studies that have demonstrated significant associations between $PM_{2.5}$ and asthma hospital admissions [5,30,31] . However, lack of consistency was also seen in the effect of $PM_{2.5}$ on asthma admissions. For instance, a multi-city study in Canada found no significant association between exposure to $PM_{2.5}$ and asthma admissions [32] . In this study, $PM_{2.5}$ was associated with substantially greater effects than PM_{10}. The results supported the findings from previous studies that $PM_{2.5}$ is linked to more adverse effects than larger particles PM_{10} [33-35] . Fine particles in the size range of $PM_{2.5}$ have a much greater probability of reaching the small airways and the alveoli of the lung, while the larger particles PM_{5-10} can only reach the proximal airways where they are eliminated by mucociliary clearance if the airway mucosa is intact [36-38] . Moreover, fine particles ($PM_{2.5}$) provide a greater surface area and hence potentially larger concentrations of inhaled air pollutants per unit mass [39,40] . The use of $PM_{2.5}$ rather than PM_{10} levels as air quality indicators has been widely accepted and recommended in the World Health Organisation air quality guidelines [20] .

NO_2: We found the largest effect associated with NO_2 was a 12.5% (95% CI: 6.6–18.7%) increase in risk of asthma hospital admissions per 10 ppb increment in NO_2 from the single-pollutant DL model in the cool season for children. This large estimated effect of NO_2 is in agreement with several studies of air pollution and asthma hospitalisations [41-44] . For example, the effect size of the NO_2 association found in this study was comparable to that found in a study from Alberta (Canada), in which there was an OR_{IQR}=1.09 (95% CI: 1.03–1.15) (IQR=13.5 ppb) for asthma ED visits among children (5–14 years) [44] . A meta-analysis of atmospheric NO_2 exposure in relation to asthma in children aged 0–18 years including 12 observational studies consisting of six cohort, one case-control, and five cross-sectional studies,

and representing 7 countries reported similar findings to the present study – i.e. a 13.5% (95% CI: 1.031–1.251) increase in asthma incidence was associated with a 10 ppb elevation in NO_2 concentration [45] .

PM_{10}: In the cool season, the largest effect associated with PM_{10} was an 8.3% (95% CI: 2.5–14.4%) increase in the risk of asthma hospital admissions per 10 $\mu g/m^3$ increment of PM_{10} for children, while 6.7% (95% CI: 2.3–11.2%) and 4.3% (95% CI: -2.2–11.1%) were observed for both age groups combined and adults, respectively. The estimated effect for PM_{10} in this study is consistent with many other epidemiological studies that found significant associations between PM_{10} and hospital admissions or ED visits for respiratory diseases [46,47] . A recent systematic review and meta-analysis using 36 studies published during the period 1990–2008 to assess the PM_{10} effect on respiratory health of asthmatic children provided strong evidence for an effect of PM_{10} as an aggravating factor for asthma symptom episodes in children [48] .

Ozone: The largest effect associated with ozone was an 11.7% (95% CI: 5.8–17.9%) increase in the risk of asthma hospital admissions for children per 10 ppb increase in ozone concentration from the single-pollutant DL model in the warm season, while 11.6% (95% CI: 4.3–19.5%) and 12.3% (95% CI: 5.0–20.0%) increases in risks were observed using the multi-pollutant DL and MA models, respectively. These findings are consistent with many single-city studies reporting associations between levels of ozone and hospital admissions for asthma [44,49,50] , however, other studies have reported no association or inconsistent results between ozone and asthma hospitalisations [51-53] or had mixed results for different seasons or age groups [41,54,55] . A meta-analysis was conducted with 96 peer-reviewed published articles in English from 1990 to 2008 to analyse the ozone effect on respiratory

hospital admissions [56] . The study reported that significant associations with ozone were observed for asthma hospital admissions for both age groups combined, whereas asthma hospital admissions were not significantly associated with ozone levels for children or adults (15–64 years) [56] .

Pollen: A unique aspect of this work was the investigation of the effects of aeroallergens on asthma in Australia, which has been largely overlooked in respiratory research. The largest effect associated with pollen was a 4.2% (95% CI: 2.2–6.1%) increase in risk of asthma hospital admissions per 10 grains/m^3 increment of pollen, found in the cool season for children. Our results are consistent with other studies, which found that pollen counts were significantly associated with asthma hospital admissions and asthma morbidity [57-59] . A time series analysis assessing different types of allergenic pollen and asthma hospital emergencies in metropolitan Madrid (Spain), for the period 1995–1998, found statistically significant associations between pollen levels and asthma related emergencies, independent of the effect of air pollutants [57] . Recently, a CCO analysis assessing the effect of pollen on asthma hospital admissions in Spain, for the period 1995–2007, reported that daily average pollen levels were associated with a slight to moderate increase in asthma hospital admissions, and daily maximum pollen levels were positively associated with a much more dramatic increase in asthma hospital admissions [60] . It has been previously reported that components of air pollutants interacted with inhalant allergens carried by pollen grains [61,62] . However, little evidence of significant interaction effects between air pollutants and pollen was found in the present study, consistent with other studies [41,63] . Some previous studies have found no significant association between pollen levels and hospital admissions or ED visits for asthma [43,64,65] . There may be several reasons for the lack of consistency with our findings, including geographical differences in the allergen levels, the prevalence of atopy and bronchial

responsiveness in different populations, and the clinical and pathological nature of asthma [41,66] . Additionally, there are many different types of aeroallergens that are influenced by seasonality and location and some are too large to penetrate into the small airways [67] .

Weather effects: The present study adds to knowledge about the effects of weather and seasonality on asthma risks for children and adults. For example, the humidity effects in the warm season were stronger than that in the cool season regardless of age groups. The extremes of lower and higher humidity at lag days 0–4 were associated with a higher risk of asthma hospitalisation. This could be potentially explained by low humidity allowing the release of pollen from anthers favouring dispersion and transport phases, while spore release is generally favoured by high levels of humidity [68,69] . In general, weather effects were stronger for children compared with adults. It is possible that children are more vulnerable to adverse effects of weather conditions due to their under-developed capacity for physiological adaptations to weather [70] . In general, the influence of weather on asthma is still poorly understood and while studies have found that high ambient temperatures induced the risk of children's asthmatic symptoms [71] , in the present study, the adverse effect of high temperature has not been observed, which could possibly due to the limited number of days with high temperature.

Age group: Overall, the air pollution effects on daily asthma hospitalisations in children were stronger than those in adults. This may be because children's immune systems and lungs are not fully developed; and children breathe more air per unit body weight and are typically more active in the open air than adults. Furthermore, peripheral airways in children are anatomically smaller than those in adults so that inflammation can result in proportionally greater airway obstruction [72-74] . It is also possible that adults use their medication more appropriately to

address their symptoms before they become severe, while children may be more likely to need hospital intervention for their symptoms. The fact that effects in children were more likely to be statistically significant might also be due to the relatively larger sample size of asthma hospitalisations in children ($n = 21462$) compared to that in adults ($n = 14562$). However, the effect of sample size could be negligible as the numbers of asthma hospitalisations in children and adults were quite large.

Season: Our finding that the associations with several exposures (i.e. NO_2, PM_{10}, $PM_{2.5}$ and pollen) were stronger during the cool season than those in the warm season is consistent with previous studies [75,76] . However, many other studies have shown different seasonal patterns of air pollutant effects (e.g. [42,43,77]). The underlying mechanism for these apparent seasonal differences is unclear. There are a number of potential reasons for the seasonal differences observed in the present study. Firstly, the stronger associations observed in the cool season could likely arise from winter temperature inversions, when cold air becomes trapped at the earth's surface beneath a layer of warmer air. Temperature inversions can result in stagnant air masses and the accumulation of air pollutants [78] , and have been shown to be associated with increased rates of ED visits for asthma as independent risk factors [79] . Secondly, the higher prevalence of respiratory infections and the cooler air during winter may sensitise children to the allergenic effects of pollutants and pollen. Thirdly, the sources of these air pollutants could be different between the cool and warm seasons. For example, the pollen types in the cool season may be more allergenic than those in the warm season. Furthermore, it could be potentially related to the nonlinear dose-response functions. For example, in general, the levels of NO_2 were higher during the winter months compared to those in summer months, and the higher levels of NO_2 during the cool season may be on a steeper part of the dose-response curve. In addition, there may also be

personal behavioural differences (e.g. air conditioning use, time spent outdoors and activity levels) that affect personal pollutant exposure levels.

Comparison of the estimated effects of air pollutants and pollen with those reported in the existing literature was difficult because the studies differed in many respects, including analytic methods, statistical power, pollutants assessed, metrics of the pollutants, disease coding systems and age ranges reported. The inconsistent results for air pollution effects on asthma hospital admissions and respiratory health might be attributed to many factors, such as study population characteristics, geographic conditions, and local environments.

Public health implications and recommendations

Findings from the present study have implications for public health policies, and particularly for policymakers in the State health department and those concerned with air quality in the State. We have shown a greater vulnerability to increasing levels of air pollution for children, and the larger effect estimates were found in children for all air pollutants compared to those for adults. Thus, it would be appropriate that any air quality warning systems should be directed particularly to vulnerable people, including children under the age of 18 years with asthma.

This study provides evidence to suggest that exposure to air pollutants and asthma hospitalisations tends to be stronger in the cool season compared to the warm season, with the exception of ozone. We would recommend that for individuals with asthma, in particular children and in the cool season, the risks of exercising outdoors when air pollutants including particulate matter and NO_2 levels are high should be considered, with close attention to medication use. A reduction in the health impact will also require strategies to limit the

production of these pollutants, for example by promoting the use of active and public transport options. Defining the areas of greatest exposure within the urban environment will also be important, so that strategies to minimise exposure can be targeted to these areas. For example, the use of outdoor recreation facilities could be discouraged during peak traffic times, or the location of playgrounds and schools adjacent to major roads considered in future urban planning.

Exposure to pollen allergens in the cool season was significantly associated with higher asthma hospital admissions in children with a large effect size in relative to the spread of pollen, i.e. a 21.2% (95% CI: 11.1–30.8%) increase in risk of asthma hospitalisations with one standard deviation increment of pollen. Recommendations for the reduction of pollen allergen exposure for children during the pollen season may include taking appropriate steps to reduce exposure and the vigilant use of medications on high pollen or pollution days in cool seasons.

Strengths and limitations of the study

The study has several strengths. Firstly, this was a comprehensive investigation of the effects of air pollution on the risk of hospital admissions for asthma; and one of the few studies to take pollen into account, and to examine interactions between air pollution and pollen levels. The study provided new evidence of adverse effects of exposure to air pollution and pollen on daily asthma hospital admissions in Adelaide using a large dataset spanning the period of 2003–2013. The study included comparison of the effects on children and adults. Secondly, two commonly used approaches in air pollution epidemiology, namely time series analysis and CCO analysis, were applied and compared in this study, with both approaches producing

similar results. In each analysis there was comprehensive adjustment for potential confounders, and controlling for seasonality and long-term trends.

Our study has some limitations. Firstly, daily aggregated data of asthma hospitalisations with no individual level information were used in the present study. For this reason, we cannot rule out the possibility of misclassification of control days in the CCO analysis, which would occur if a case was re-admitted for asthma within the 28 control day stratum. According to nation-wide data for asthma hospital re-admissions, a small proportion (<5%) of individuals having additional hospital re-admissions within 28 days would violate the assumption for the CCO-TS design with a stratum length of 28 days [80] . Secondly, as in other similar studies in this field, the data on air pollution, pollen and meteorological variables were measured at only one fixed monitoring station, and it was assumed that they adequately represented the exposure for the population. Exposure measurement error, or misclassification, is inherent in all large environmental epidemiologic studies of air pollution health effects and the extent of this measurement error may vary by pollutant, with the primary pollutants (e.g. those from traffic emissions) tending to have more measurement error than the secondary pollutants (e.g. ozone) [81,82] . Finally, data from only one city was used in the present study, and caution should be used in the generalizability of the findings of this study to other cities or populations.

Much remains to be studied to explore the effects of air pollution and aeroallergens on asthma, using the combination of biological, genetic/genomic, epidemiological and clinical approaches. However, public health approaches to reduce exposure to air pollution should continue to be implemented. For instance, some public preventive measures can be considered including encouraging policies to promote access to non-polluting and sustainable sources of energy, reducing utilisation of fossil fuels, controlling motor vehicle emissions,

improving public transport systems, reducing private vehicular traffic, better urban planning, and planting non-allergic trees in cities.

Conclusions

The study was carried out to assess the short-term effects of air pollution, pollen and weather variables on daily asthma hospital admissions in Adelaide, the capital city of South Australia. The findings from time-series and CCO analyses have shown strong evidence to suggest adverse effects of the studied air pollutants and pollen on daily asthma hospital admissions in Adelaide. Air pollution effects differed between age groups and seasons. Findings from this study also importantly suggest that children were more vulnerable to the increasing levels of air pollution and pollen; and that associations between exposure to air pollutants and asthma hospital admissions tended to be stronger in the cool season compared to those in the warm season, with the exception of ozone.

Our findings were robust to a variety of sensitivity analyses, and were generally in good agreement with the existing knowledge. Replication studies in other cities should be undertaken to confirm the findings and to provide greater opportunity for interpretation and comparison. The study has important public health implications, and provides valuable evidence for the development of environmental health policy for asthma prevention, particularly in children.

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Conflict of interest

The authors have no conflict of interest to declare.

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Figure legends

Figure 1: Estimated relative risk using single-pollutant distributed lag models for both age groups combined with lag days 0–7.

Figure 2: Estimated risk of asthma relative to mean temperature and mean humidity for children [2(a)] and adults [2(b)] from the single-pollutant ($PM_{2.5}$) distributed lag models.

Tables

Table 1: Summary statistics of asthma hospital admissions and environmental variables in Adelaide

Variables	Daily mean	SD[a]	Percentile					IQR[a]	N[a]
			Min[a]	p25	p50	p75	Max[a]		
Admissions for children	5.88	3.42	0.00	3.00	5.00	8.00	26.00	5.00	3653
Admissions for adults	3.99	2.36	0.00	2.00	4.00	5.00	15.00	3.00	3653
Admissions for all ages	9.86	4.46	0.00	7.00	10.00	13.00	30.00	6.00	3653
NO_2 (ppb)	19.40	9.57	0.00	12.00	21.00	26.83	103.00	14.83	3616
Ozone (ppb)	28.86	7.92	2.00	24.00	28.00	32.00	105.00	8.00	3619
PM_{10} ($\mu g/m^3$)	18.46	10.09	1.00	12.30	16.50	21.70	125.90	9.40	3515
$PM_{2.5}$ ($\mu g/m^3$)	7.79	2.86	1.60	5.90	7.27	9.10	61.20	3.20	3502
Pollen (grains/m^3)	73.68	50.53	0.00	33.00	66.00	104.00	316.00	71.00	3563
Temperature (ºC)	17.29	5.64	6.70	12.80	16.40	20.70	38.70	7.90	3653
Relative humidity (%)	58.80	16.91	7.62	48.12	60.00	71.50	95.12	23.38	3653

[a] IQR: Interquartile range; Min: minimum; Max: maximum; N: number of observations; SD: standard deviation; p25: 25th percentile; p50: median; p75: 75th percentile.
All ages: both age groups combined.

Table 2: Comparison of estimated cumulative effects (IRRs or ORs) and 95% CIs between time series regressions (TSR) and CCO analyses with TS referent scheme (CCO-TS)

Age group	Model	Variable	TSR			CCO-TS		
			IRR	(95% CI)	P	OR	(95% CI)	P
All ages	SPDLM	NO_2	**1.076**	**(1.044, 1.109)**	**<0.001**	**1.077**	**(1.046, 1.109)**	**<0.001**
		Ozone	**1.080**	**(1.039, 1.122)**	**<0.001**	**1.067**	**(1.029, 1.107)**	**<0.001**
		PM_{10}	**1.034**	**(1.005, 1.064)**	**0.020**	**1.035**	**(1.007, 1.064)**	**0.013**
		$PM_{2.5}$	**1.212**	**(1.122, 1.308)**	**<0.001**	**1.229**	**(1.139, 1.327)**	**<0.001**
		Pollen	**1.015**	**(1.006, 1.024)**	**0.001**	**1.012**	**(1.003, 1.021)**	**0.012**
	MPDLM	NO_2	**1.050**	**(1.016, 1.086)**	**0.004**	**1.049**	**(1.016, 1.084)**	**0.004**
		Ozone	**1.055**	**(1.015, 1.097)**	**0.007**	**1.042**	**(1.001, 1.085)**	**0.044**
		$PM_{2.5}$	**1.111**	**(1.021, 1.210)**	**0.015**	**1.142**	**(1.050, 1.243)**	**0.002**
		Pollen	**1.010**	**(1.001, 1.019)**	**0.029**	1.007	(0.998, 1.017)	0.125
	MPMAM	NO_2	**1.055**	**(1.021, 1.090)**	**0.001**	**1.047**	**(1.014, 1.080)**	**0.005**
		Ozone	**1.052**	**(1.012, 1.093)**	**0.010**	**1.044**	**(1.003, 1.085)**	**0.033**
		$PM_{2.5}$	**1.110**	**(1.021, 1.207)**	**0.015**	**1.147**	**(1.055, 1.246)**	**0.001**
		Pollen	**1.013**	**(1.004, 1.022)**	**0.005**	1.009	(1.000, 1.018)	0.063
Children	SPDLM	NO_2	**1.099**	**(1.057, 1.144)**	**<0.001**	**1.118**	**(1.077, 1.162)**	**<0.001**
		Ozone	**1.070**	**(1.018, 1.125)**	**0.007**	**1.074**	**(1.025, 1.124)**	**0.003**
		PM_{10}	**1.057**	**(1.019, 1.097)**	**0.003**	**1.048**	**(1.012, 1.086)**	**0.008**
		$PM_{2.5}$	**1.271**	**(1.150, 1.404)**	**<0.001**	**1.284**	**(1.165, 1.416)**	**<0.001**
		Pollen	**1.022**	**(1.010, 1.034)**	**<0.001**	**1.017**	**(1.005, 1.029)**	**0.007**
	MPDLM	NO_2	**1.063**	**(1.018, 1.110)**	**0.006**	**1.081**	**(1.037, 1.128)**	**<0.001**
		Ozone	1.036	(0.985, 1.090)	0.174	1.037	(0.985, 1.092)	0.164
		$PM_{2.5}$	**1.135**	**(1.016, 1.268)**	**0.025**	**1.144**	**(1.026, 1.275)**	**0.015**
		Pollen	**1.016**	**(1.004, 1.028)**	**0.007**	1.011	(0.999, 1.023)	0.080
	MPMAM	NO_2	**1.074**	**(1.030, 1.121)**	**0.001**	**1.082**	**(1.038, 1.127)**	**<0.001**
		Ozone	1.040	(0.990, 1.093)	0.121	1.045	(0.993, 1.098)	0.089
		$PM_{2.5}$	**1.147**	**(1.028, 1.279)**	**0.014**	**1.162**	**(1.044, 1.293)**	**0.006**
		Pollen	**1.021**	**(1.009, 1.033)**	**0.001**	**1.013**	**(1.001, 1.025)**	**0.034**
Adults	SPDLM	NO_2	**1.048**	**(1.004, 1.095)**	**0.033**	1.019	(0.973, 1.067)	0.429
		Ozone	**1.078**	**(1.019, 1.141)**	**0.009**	1.059	(0.999, 1.123)	0.052
		PM_{10}	0.997	(0.956, 1.040)	0.893	1.016	(0.973, 1.061)	0.470
		$PM_{2.5}$	**1.125**	**(1.005, 1.260)**	**0.041**	**1.149**	**(1.017, 1.297)**	**0.025**
		Pollen	1.005	(0.992, 1.018)	0.459	1.005	(0.991, 1.020)	0.490
	MPDLM	NO_2	1.039	(0.990, 1.090)	0.123	1.003	(0.953, 1.055)	0.918
		Ozone	**1.067**	**(1.007, 1.130)**	**0.028**	1.053	(0.987, 1.123)	0.116
		$PM_{2.5}$	1.073	(0.947, 1.217)	0.269	1.140	(0.997, 1.303)	0.055
		Pollen	1.001	(0.988, 1.015)	0.840	1.002	(0.988, 1.017)	0.744
	MPMAM	NO_2	1.033	(0.985, 1.082)	0.185	0.995	(0.946, 1.046)	0.833
		Ozone	1.058	(1.000, 1.120)	0.051	1.044	(0.980, 1.112)	0.181
		$PM_{2.5}$	1.057	(0.934, 1.197)	0.383	1.125	(0.986, 1.285)	0.081
		Pollen	1.002	(0.989, 1.015)	0.781	1.003	(0.988, 1.017)	0.719

All ages: both age groups combined;
IRR/OR: Incidence rate ratio/Odds ratio in relation to a 10 unit increment in the respective pollutants; 95% CI: 95% confidence interval; P: P-value; Var: predictor variable;
SPDLM: Single-pollutant distributed lag model; MPDLM: Multi-pollutant distributed lag model;
MPMAM: Multi-pollutant moving average model;
Bold: The estimated IRRs or ORs for air pollutants and pollen are statistically significant (P-value<0.05).

Table 3: Estimated cumulative effects for air pollutants and pollen from distributed lag models with CCO-TS design

	CCO-TS (cool season)			CCO-TS (warm season)		
	OR	(95% CI)	P	OR	(95% CI)	P
Single-pollutant DL models						
All ages						
NO_2	**1.091**	**(1.048, 1.136)**	**<0.001**	**1.056**	**(1.008, 1.105)**	**0.021**
Ozone	0.980	(0.912, 1.053)	0.582	**1.100**	**(1.053, 1.148)**	**<0.001**
PM_{10}	**1.067**	**(1.023, 1.112)**	**0.002**	0.999	(0.961, 1.037)	0.944
$PM_{2.5}$	**1.240**	**(1.116, 1.378)**	**<0.001**	**1.187**	**(1.054, 1.337)**	**0.005**
Pollen	**1.025**	**(1.010, 1.040)**	**0.001**	0.998	(0.985, 1.011)	0.744
Children						
NO_2	**1.125**	**(1.066, 1.187)**	**<0.001**	**1.110**	**(1.048, 1.176)**	**<0.001**
Ozone	0.973	(0.885, 1.070)	0.575	**1.117**	**(1.058, 1.179)**	**<0.001**
PM_{10}	**1.083**	**(1.025, 1.144)**	**0.004**	1.011	(0.964, 1.060)	0.664
$PM_{2.5}$	**1.302**	**(1.134, 1.496)**	**<0.001**	**1.221**	**(1.053, 1.416)**	**0.008**
Pollen	**1.042**	**(1.022, 1.061)**	**<0.001**	0.999	(0.983, 1.016)	0.934
Adults						
NO_2	1.048	(0.985, 1.115)	0.135	0.970	(0.899, 1.045)	0.421
Ozone	0.989	(0.885, 1.105)	0.848	1.072	(0.999, 1.150)	0.055
PM_{10}	1.043	(0.978, 1.111)	0.199	0.980	(0.920, 1.043)	0.523
$PM_{2.5}$	1.156	(0.982, 1.360)	0.081	1.116	(0.914, 1.363)	0.281
Pollen	1.003	(0.982, 1.025)	0.773	0.996	(0.975, 1.018)	0.734
Multi-pollutant DL model						
All ages						
NO_2	1.046	(0.997, 1.099)	0.067	1.014	(0.964, 1.067)	0.585
Ozone	0.942	(0.873, 1.016)	0.119	**1.110**	**(1.052, 1.171)**	**<0.001**
$PM_{2.5}$	**1.139**	**(1.006, 1.290)**	**0.041**	1.071	(0.942, 1.217)	0.297
Pollen	**1.022**	**(1.008, 1.037)**	**0.003**	0.995	(0.982, 1.009)	0.499
Children						
NO_2	1.064	(0.997, 1.134)	0.061	1.059	(0.994, 1.129)	0.077
Ozone	0.916	(0.829, 1.012)	0.083	**1.116**	**(1.043, 1.195)**	**0.001**
$PM_{2.5}$	1.147	(0.973, 1.352)	0.102	1.056	(0.899, 1.241)	0.506
Pollen	**1.039**	**(1.020, 1.059)**	**<0.001**	0.996	(0.979, 1.013)	0.630
Adults						
NO_2	1.028	(0.955, 1.107)	0.468	0.942	(0.866, 1.023)	0.157
Ozone	0.980	(0.872, 1.102)	0.741	**1.104**	**(1.011, 1.205)**	**0.028**
$PM_{2.5}$	1.122	(0.927, 1.357)	0.238	1.080	(0.874, 1.336)	0.477
Pollen	1.001	(0.979, 1.023)	0.964	0.996	(0.975, 1.018)	0.741

All ages: both age groups combined;
CCO-TS: Case-crossover design with time-stratified referent scheme;
Bold: The estimated ORs for air pollutants and pollen are statistically significant (P-values<0.05).

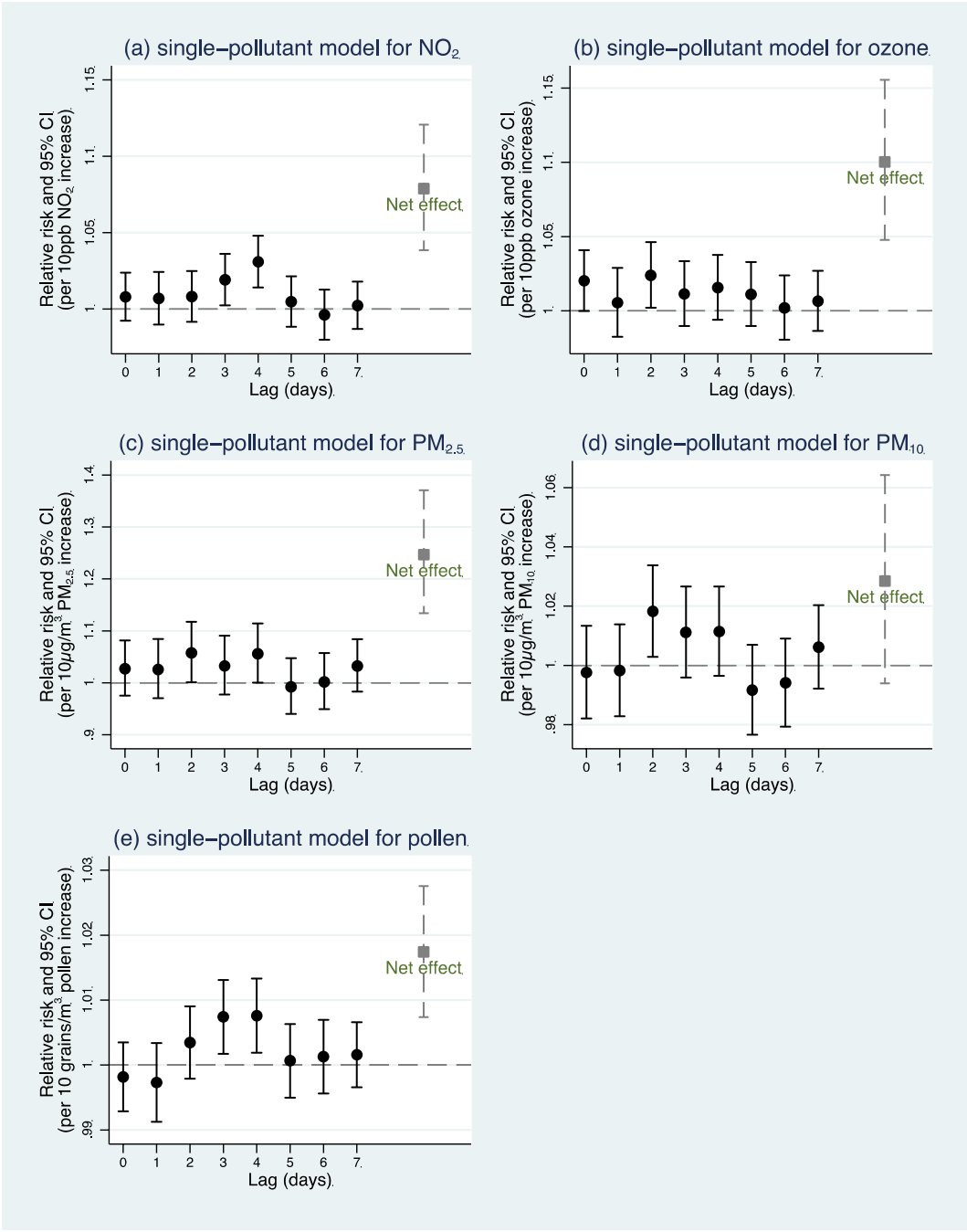

Figure 1: Estimated relative risk using single-pollutant distributed lag models for both age groups combined with lag days 0–7.

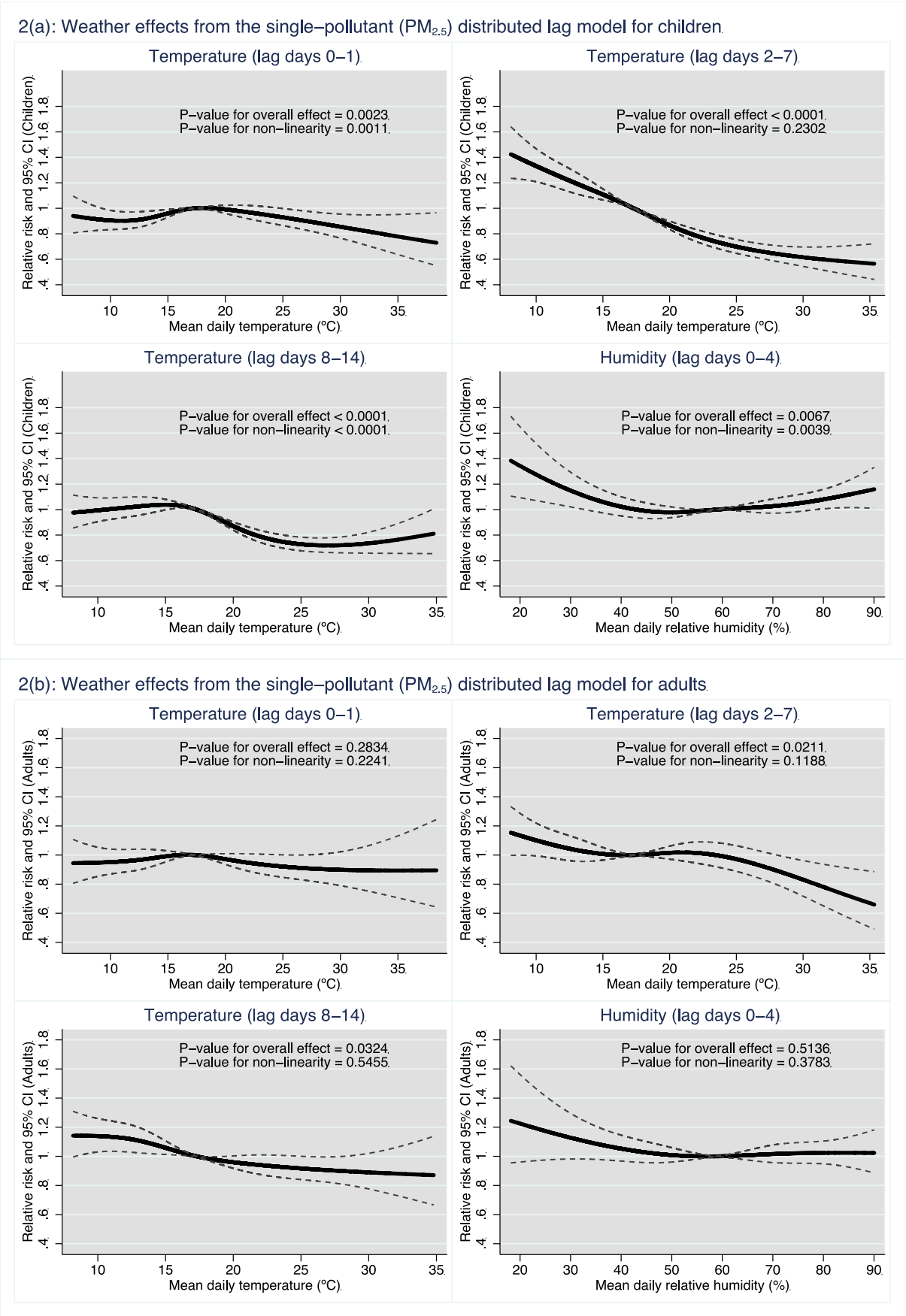

Figure 2: Estimated risk of asthma relative to mean temperature and mean humidity for children [2(a)] and adults [2(b)] from the single-pollutant ($PM_{2.5}$) distributed lag models.