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Ozone pollution and asthma emergency department visits in the Central Valley, California, USA, during June to September of 2015: a time-stratified case-crossover analysis

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Ozone Pollution and Asthma Emergency Department Visits in the Central Valley, California, USA, During June to September of 2015: A Time-Stratified Case-Crossover Analysis

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Abstract

Objective: The San Joaquin Valley (SJV) exceeds the state and national standards for ozone (O_3). This study investigates whether short term exposure to O_3 is associated with asthma emergency department (ED) visits. *Methods:* We identified 1101 ED visits in June-September of 2015 in SJV, California, who lived within 15 km of active air monitors. Conditional logistic regression models were used to obtain the odds ratio (OR) and 95% confidence interval (CI) associated with an interquartile (IQR) increase in ozone. We explored potential effect modification by sex (female, and male), race (White, Black, and Hispanic), age (2-5, 6-18, 19-40, 41-64 and >= 65), and by county (Merced, Madera, Kings, Fresno and Kern). *Results:* An interquartile range (18.1 ppb) increase in O_3 exposure three days before an asthma attack (lag 3) was associate with a 6.6% [OR: 1.066 (95% CI: 1.032, 1.082)] increase in the odds of having an asthma ED visit. The overall ORs differed across age groups and races/ethnicities, with strongest for children aged 6–18 years [OR: 1.219 (95% CI: 1.159, 1.280)] and adults 19-40 years [OR: 1.102 (95% CI: 1.053, 1.154)], and Blacks [OR: 1.159 (95% CI: 1.088, 1.236)], respectively. O_3 exposure was not positively associated with asthma ED visits for Whites while it was for other underrepresented groups. Fresno had the highest number of asthma ED visits and positive association among all five counties. *Conclusion:* We found that O_3 exposure is associated with asthma ED visits in the SJV.

Keywords: Asthma attacks; air pollution; ozone exposure; conditional logistic regression; San Joaquin Valley, California

Introduction

Anthropogenic activities have resulted in the release of different air pollutants contributing to respiratory diseases globally [1]. The San Joaquin Valley (SJV), located in California experiences some of the highest levels of air pollution in the USA, particularly for ozone (O_3) [2]. Air pollution in this area is due to anthropogenic-rooted pollution sources, including vast areas of farming lands, heavy truck traffic on I-5 and Highway 99 (i. e. intra-state highways), and industrial sources; and wildfires happening in this area [2]. The effect of pollution from these resources are amplified by topography and meteorological patterns (i. e. recurring high pressure systems during summer time that leads to stagnation, wind patterns that carry ozone precursors from the Bay area and northern California, and China) that concentrate pollutants in densely populated areas in SJV [2]. Consequently, a significant number of people in this region suffer from cardiorespiratory diseases including asthma which could be exacerbated by air pollutants [3].

Asthma, a complex and heterogenous chronic non-communicable disease characterized by recurrent attacks of breathlessness and wheezing, varies in severity and frequency from person to person [4]. In addition, asthma is under-diagnosed and under-treated, and is considered a substantial medical and financial burden to those affected [4-6]. Epidemiological studies have reported positive associations between air pollutants and asthma attacks, especially among children ≤ 17 years old, and Blacks [7-14]. Meng YY. et al. (2010) found that the prevalence of asthma ED visits was more among children, Latino and Blacks who live in areas with high concentrations of O_3 in the SJV [3]. Malig et al. (2016) found that short term exposure to O_3 was positively associated with ED visits for asthma [15]. Studies on animals (i. e. infant monkeys) showed that exposing the monkeys to O_3 results in having fewer airway generations, hyperplastic bronchiolar epithelium, and altered smooth muscle in terminal and respiratory bronchioles in the studied animals [16]. Although the SJV is known for its poor air quality and high prevalence of respiratory diseases, the number of epidemiological studies focusing on the association between short term exposure to O_3 pollutants and asthma attacks in this region is limited.

In this study, the association between short term exposure to O_3 and asthma ED visits in SJV from June to September of 2015 in SJV is investigated using time-stratified case-crossover analysis. We also analyzed the potential effect modification of sex (female, and male), race (Whites, Blacks, and Hispanics), age (i. e. 2-5, 6-18, 19-40, 41-64 and >= 65), and county (Merced, Madera, Kings, Fresno, Kern). Furthermore, we performed a county-based analysis of O_3 association with asthma ED visits to investigate patterns in association with location.

Material and Methods

Data and Participants

All the asthma ED visit data for the SJV were obtained from California's Office of Statewide Health Planning and Development (OSHPD). The dataset contains information on individual patient records including patient's ZIP code, sex, birthdate, principal language, service date, diagnoses, cause of injury, treatments/procedures, and expected source of payment are submitted every three months by EDs to OSHPD. ED visits due to asthma attacks identified by the International Classification of Diseases, 9th Revision (ICD-9) codes were used to select cases for analysis. Multiple visits by a single person cannot be identified because the data is not linked by person longitudinally due to the lack of access to social security number; therefore, each valid observation was taken as an independent observation.

Study Design

The time-stratified case-crossover design is an alternative to conventional time series regression for analyzing associations between short-term air pollution exposure and the risk of an acute adverse health event [15-17]. In this design, the hazard period (i.e. the day of asthma ED admission) is compared to other referent days. The design, which we applied in this study, is to compare the exposures of individual patients during the hazard period (i.e. the day of asthma ED admission) to their exposures on up to 3 or 4 referent days (i. e. depending on the day of week and length of month) occurring on the same day of the week during the same month. Because each individual serves as his/her own control, there is limited confounding by factors that do not vary within a month. The simple lag models, up to 6 days before the event days, and cumulative lag models were used to study the acute effect of O_3 on the occurrence of asthma. Specifically, in the simple lag model, we used the concentration of the day before the event (lag 1), two days before the event (lag 2) and up to six days before the event (lag 6). The cumulative lag model used the mean concentration of the pollutant in the day of the event and the previous day was used as lag 0-1, and 7 days mean concentration of the pollutant as lag 0-6.

Exposure Assessment

Figure 1 indicates the study area. Air pollution data were collected from 18 active sampling stations during the warm season (June-September) of 2015.

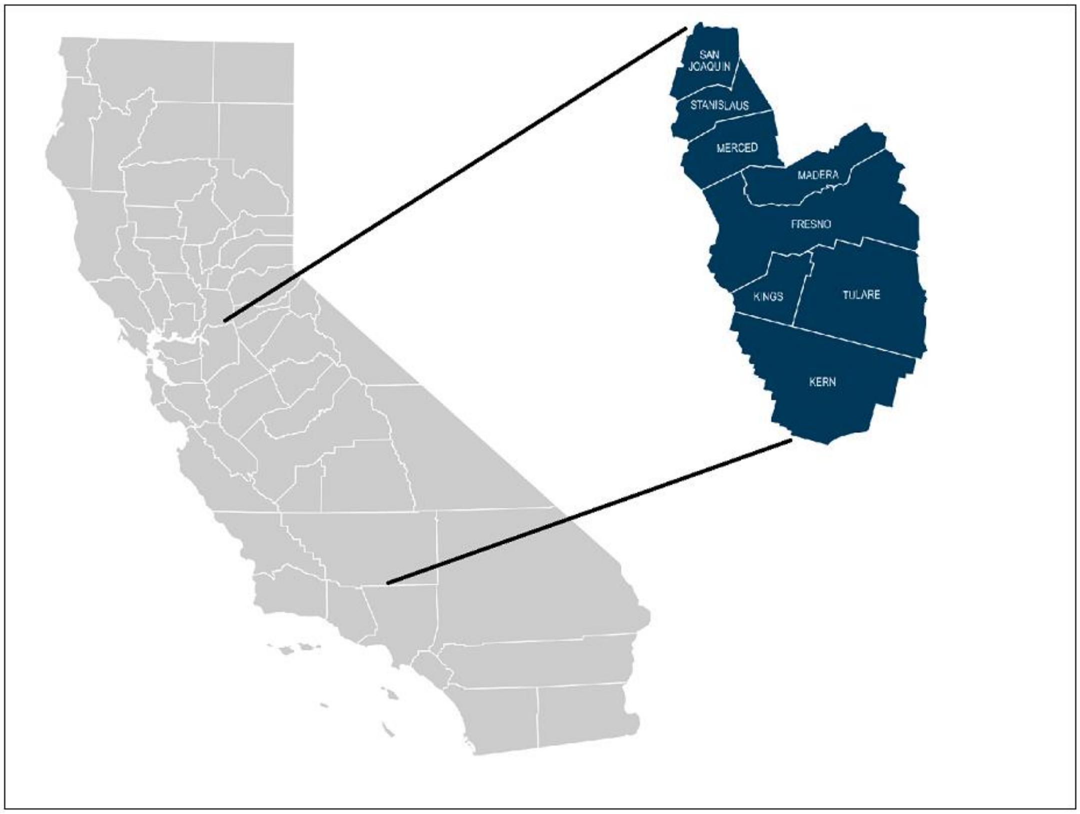

Figure 1. The study area (San Joaquin Valley, California, USA) during June to September of 2015

We conducted analyses specific to warm season (June-September) visits, since the ozone levels are generally higher due to increased sunlight catalyzing its formation [7, 15]. And, it has been suggested that there is a strong inverse correlation between surface O_3 and fine particles from traffic sources which might confound or conceal the real effects of O_3 [18]; hence, we assumed that ambient measurements in warm season, when people spend more time outdoors, may represent the actual average population exposure better. In this study, daily-average values were collected for NO_2, $PM_{2.5}$, and CO. O_3 concentration is the maximum daily 8-hr average. Temperature is the mean daily degrees Celsius (C^o). Among all the meteorological factors, we used temperature since this factor is a potential confounding factor. the single site representative of zip code area is limited by localized meteorological impacts that may impact the single monitor. We controlled for temperature via restricted cubic spline (RCS) with 3 degrees of freedom (3 d.f.). Appendix B (Figure B. 1) indicates restricted cubic spline from conditional logistic regression with temperature as the predictor and asthma ED visit as the outcome.

Air pollution exposures were assigned to the patients' ZIP code of residence given that the center of the ZIP code be located within 15 km of the sampling station. The radius selected here is based on previous studies including variation in elevation of the area [15]. Elevation in the SJV is generally uniform in the high density urban areas of the valley floor and begins to increase into the Sierra Nevada on the more rural eastern area; hence, 15 km radius was selected. Geographical assignment was performed using QGIS V. 2.14.20. In this regard, 82 ZIP codes were covered in this study.

Statistical Analysis

ICD-9 code 493 for asthma related visits (National Center for Health Statistics, 2011) was used to select patient records (date of visit, principal diagnosis, residential ZIP code, age, race/ethnicity, and sex). After analyzing the number of patients visiting ED in the eight counties of the SJV, few patients visited ED in Stanislaus, San Joaquin, and Tulare counties. Thus, our research focused on the other five counties (Merced, Madera, Kings, Fresno and Kern) with higher ED visits. To account any bias resulting from removing the three mentioned counties from the study, we conducted a sensitivity analysis including these three counties to the model.

Conditional logistic regression models were used to estimate the association between O_3 and the odds of an asthma ED visit. We controlled for temperature via restricted cubic spline (Spline (T)), $PM_{2.5}$, NO_2 and CO during the same exposure window. The time-stratified case-crossover analysis using conditional logistic regression can be written as follows [19]:

$$
\begin{aligned}
l_c(\beta) = \sum_{k=1}^{n} Y_k \times \{ &\left(\beta_1 \times O_{3_{(k-l)1}}\right) + \left(\beta_2 \times PM_{2.5_{(k-l)1}}\right) + \left(\beta_3 \times NO_{2_{(k-l)1}}\right) \\
&+ \left(\beta_4 \times CO_{(k-l)1}\right) + (\beta_* \times spline\left(T_{(k-l)1}\right)) \\
&- \log\left[\sum_{j=2}^{5} exp \left(\left(\beta_1 \times O_{3_{(k-l)j}}\right) + (\beta_2 \times PM_{2.5_{(k-l)j}}) + \left(\beta_3 \times NO_{2_{(k-l)j}}\right)\right.\right. \\
&\left.\left. + \left(\beta_4 \times CO_{(k-l)j}\right) + (\beta_* \times spline\left(T_{(k-l)j}\right))\right)\right]\}
\end{aligned}
$$

Y_k is daily counts of asthma events on k-th day;

$\left(O_{3_{(k-l)1}}\right), \left(PM_{2.5_{(k-l)1}}\right), \left(NO_{2_{(k-l)1}}\right), \left(CO_{(k-l)1}\right), and \left(spline\left(T_{(k-l)1}\right)\right)$ stand for the covariates for the case (i. e. control day or the day that an individual visited the ED;

$\left(O_{3_{(k-l)j}}\right), (PM_{2.5_{(k-l)j}}), \left(NO_{2_{(k-l)j}}\right), \left(CO_{(k-l)j}\right), and \ (spline\left(T_{(k-l)j}\right))$ are covariates for the three or four matched controls;

l is the number of days before the event day (*l = 1, 2, 3, 4, 5, and 6 days before the event day);* Consequently, the matched control days are shifted by *l day* as well ($(k-l)j$);

$\beta = \beta_1, \beta_2, \beta_3, \beta_4$ refers to the coefficient for each covariate; and, β_* represents two coefficients of variables provided by restricted cubic spline (RCS). Noted that RCS with k-knots (i. e. 3 knots in our study) provides $k-1$ variables (i. e. the linear variable itself and $k-2$ cubic variables). For further details about RCS and its application for continuous variables, we encourage readers to read [20].

The reported odds ratios (OR) and 95% confidence intervals (CI) are based on an inter-quartile range (IQR) increase of O_3. Potential effect modifications were evaluated by stratifying models for age (2-5, 6-18, 19-40, 41-64, and >=65), race/ethnicity, including White (Non-Hispanic White), Black (Non-Hispanic Black), and Hispanic, and sex (female, and male). In this study, we analyzed the association between O_3 and asthma ED visits by stratifying for counties (Merced, Madera, Kings, Fresno and Kern). Two pollutant models were developed. In a single pollutant model, we only investigate the association between O3 and asthma ED visits controlling for temperature (Spline (T)). However, in the multi-pollutant model, we control for the concomitant presence of other air pollutants (PM2.5, NO2 and CO) and temperature (Spline (T)). All analyses were performed using STATA V. 14 (College Station, TX).

Results

Descriptive Analysis of the Hospital Data

Table 1 indicates the demographic characteristics of the cases in this study. There were 1101 asthma visits to EDs within the study area in the summer (June to September) of 2015. O_3 concentrations are high in the SJV compared to other regions in the USA manifesting in 1000 cases of asthma ED visits in the 5 counties.

Table 1. Characteristics of asthma ED visits from June to September of 2015 in SJV, California, USA (n=1101)

Characteristics	Total # of Patients	Percent (%)
Sex		
Female	601	54.5
Male	500	45.5
Race		
White	351	31.8
Black	174	15.8
Hispanic	573	52.0
Age		
2-5	131	11.8
6-18	298	27.0
19-40	371	33.6
41-64	239	21.7
>=65	62	5.6
Total Population	1101	100

54.5% percent of the study population was female. In addition, 31.8%, 15.8%, and 52%were found to be White, Black, and Hispanic, respectively. The mean age for the population in this study was 27.0 years; furthermore, 11.8%, 27%, 33.6%, 21.7% and 5.6% of the population in this study are between the age of 2 and 5 years old, 6 and 18 years old, 19 and 40 years old, 41 and 64 years old, and 65 or more years old, respectively. The demographic characteristics of the cases in each county is shown in Appendix A (Table A. 1). As shown in the table, Fresno county with 524 and Kings county with 63 recorded the highest and lowest counties with asthma ED visits, respectively, in SJV in June-September 2015.

Descriptive Analysis of the Air Pollutants

Table 2 describe the daily mean concentrations of $PM_{2.5}$, CO, NO_2, temperature as well as the 8-hr maximum daily average of O_3 for the sampling stations in the summer of 2015.

Table 2. The distribution of air pollutants in five counties (Merced, Madera, Kings, Fresno and Kern) in the SJV during the warm season (June to September) of 2015

				Percentile				
Pollutant	Mean	SD	Minimum	25	50	75	Maximum	IQRs
O_3 (ppb)	50.7	12.6	15.2	41.1	49.2	59.2	94.5	18.1
$PM_{2.5}$ (μg/m^3)	10.8	5.5	.7	7.2	10.0	13.0	62.1	5.7
CO (ppb)	224.0	89.0	100.0	158.3	204.1	266.2	525	107.7
NO_2 (ppb)	7.3	4.9	0.0	3.4	6.0	9.5	27.4	6.0
Temperature Cº	22.5	3.7	5.2	22.9	25.4	17.9	34.2	5.0

Abbreviations: SD, Standard Deviation; O_3 (8-hr maximum average); $PM_{2.5}$, Particulate matter with diameter of less than 2.5 (daily-average); CO, Carbon monoxide (daily-average); NO_2, Nitrogen dioxide (daily-average); IQRs, Inter-quartile ranges

As shown in Table 2, the mean 8-hr maximum concentration of O_3 is 50.7 ppb. The federal standard threshold for O_3 is 70 ppb (4th highest daily maximum 8-hr). During this study, the largest exceedances of the federal standard level occurred at Kern County (104 times during the study) followed by Fresno County (56 times). The 8-hr federal standard was exceeded 203 times in the SJV during this study. This is important since the SJV experiences some of the highest levels of ozone in USA (2). The linear relationship between the independent variables was also tested, since it is necessary for these variables to have a linear relationship before performing conditional logistic regression analysis. In order to analyze the collinearity between temperature and other variables (i.e. temperature has comparatively high correlation with other variables), we tried to predict temperature using other variables (O_3, $PM_{2.5}$, CO, and NO_2) applying a linear regression model.

Single-Pollutant and Multi-Pollutant Model

Table 3 indicates the association between air pollutants and asthma ED admission during the warm season (June-September) of 2015 for the single-pollutant and multi-pollutant model. We found that O_3 is associate with asthma ED visits in SJV during June-September of 2015. Based on the results, an IQR (18 ppb) increase in O_3 exposure at lag 1, lag 3 and lag 0-6 is associated with 2.5% [OR: 1.025 (95% CI: 1.001, 1.050)], 5.5% [OR: 1.055 (95% CI: 1.030, 1.080)], and 1.4% [OR: 1.014 (95% CI: 1.001, 1.035)] increase in the odds of having an asthma ED visit, respectively.

Table 3. The association between O_3 and asthma ED visits in SJV June-September of 2015

	Single-Pollutant Model		***Multi-Pollutant Model***							
Single and cumulative lags	O_3 (ppb)		Adjusting for $PM_{2.5}$ (μg/m^3)		Adjusting for NO_2 (ppb)		Adjusting for CO (ppb)		Adjust for all	
	OR	**95% CI**	OR	**95% CI**	OR	**95% CI**	OR	**95% CI**	OR	**95% CI**
Lag 0	0.970	0.948, 0.994	0.951[a]	0.928, 0.975	0.979	0.956, 1.004	0.980	0.958, 1.004	0.956	0.932, 0.980
Lag 1	1.027[b]	1.001, 1.050	0.989	0.964, 1.015	1.031[b]	1.007, 1.058	1.029[b]	1.005, 1.056	1.034[b]	1.011, 1.062
Lag 2	1.010	0.988, 1.038	0.986	0.963, 1.011	1.016	0.993, 1.042	1.016	0.993, 1.042	0.988	0.965, 1.016
Lag 3	1.052[a]	1.021, 1.072	1.044[a]	1.018, 1.070	1.075[a]	1.049, 1.101	1.070[a]	1.045, 1.097	1.066[a]	1.032, 1.082
Lag 4	1.015	0.990, 1.040	0.995	0.970, 1.022	1.016	0.993, 1.042	1.020	0.996, 1.046	1.000	0.975, 1.027
Lag 5	1.001	0.976, 1.026	0.971[b]	0.947, 0.998	1.004	0.979, 1.029	1.005	0.980, 1.031	0.975	0.949, 1.002
Lag 6	1.003	0.978, 1.029	0.996	0.971, 1.024	1.009	0.982, 1.035	1.004	0.977, 1.029	0.998	0.971, 1.026
Lag 0-1	0.981	0.957, 1.005	0.949[a]	0.925, 0.973	0.989	0.964, 1.015	0.987	0.963, 1.013	0.951	0.927, 0.977
Lag 0-6	1.014[b]	1.001, 1.035	0.984	0.956, 1.011	1.016	0.989, 1.044	1.016	0.989, 1.044	1.006	0.963, 1.018

Abbreviations: CI, confidence interval; OR, odds ratio

[a] Statistically significant (*P* <0.01)

[b] Statistically significant (*P* <0.05)

As shown in the table for the multi-pollutant model, it was found that the association between O_3 at lag 3 and asthma ED visits increased slightly when we controlled for concomitantly present pollutants. Controlling for $PM_{2.5}$, CO, and NO_2, it was found that an 18.1 ppb increase of 8-hr maximum average daily O_3 exposure is associated with 6.6% [OR: 1.066 (95% CI: 1.032, 1.082)] increase in the odds of having an asthma ED visits. We could not find any positive association at lag 0 and lag 0-1 for the multi-pollutant model; by controlling for $PM_{2.5}$, CO, and NO_2, an 18.1 ppb increase in O_3 exposure at lag 0 is associated with 4.4% [OR: 0.956 (95% CI: 1.032, 1.082)] decrease in the odds of having an asthma ED visits. Thereafter, we kept all concomitantly present pollutants in the model to have a better understanding of the association of O_3 exposure and asthma ED visits in SJV during the summer of 2015.

Stratification by Sex, Age, Race/Ethnicity

Figure 2 shows the odds ratios per IQR increase in O_3 controlled for CO, $PM_{2.5}$, and NO_2 and adjusted for temperature by simple lag and cumulative lag models for asthma ED visits during June to September of 2015 in SJV with stratification by sex. For O_3, we found that an IQR increase in the O_3 concentration at three days before the event day (lag 3) is associated with 6.6% [OR: 1.066 (95% CI: 1.028, 1.106)] increase in the odds of having an asthma ED visit among females. We found negative association between O_3 and asthma ED visit among males at lag 1 and lag 0-1.

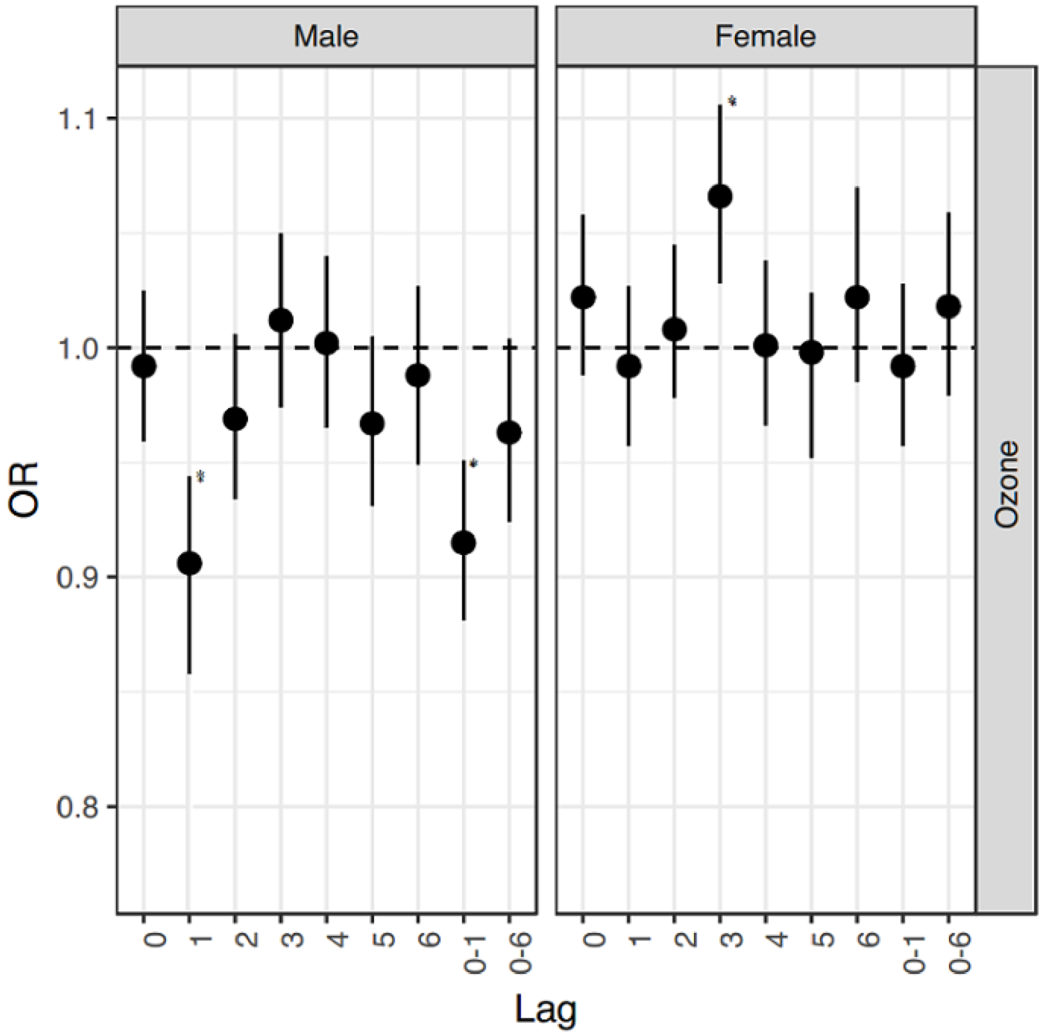

Figure 2. Odds ratio (95% CI) per IQR increase in O_3 (18.1 ppb) controlled for $PM_{2.5}$, NO_2, CO, and temperature by simple lag model (i. e. Lag 0 = same-day exposure, lag 1 = exposure 1 day prior, etc.), and cumulative lag (i. e. Lag 0-1 = mean of lag 0 and lag 1, lag 0-6= mean of lags 0 through 7) for asthma ED visits during June to September of 2015 in SJV, stratifying for sex (i. e. male, and female); the statistically significant findings are shown by * in the figure

Figure 3 shows the odds ratios per IQR variation in O_3 controlled for CO, $PM_{2.5}$, and NO_2, and adjusted for temperature by simple lag and cumulative lag models for asthma ED visits during June to September of 2015 in SJV with stratification by race/ethnicity (White, Black, and Hispanic).

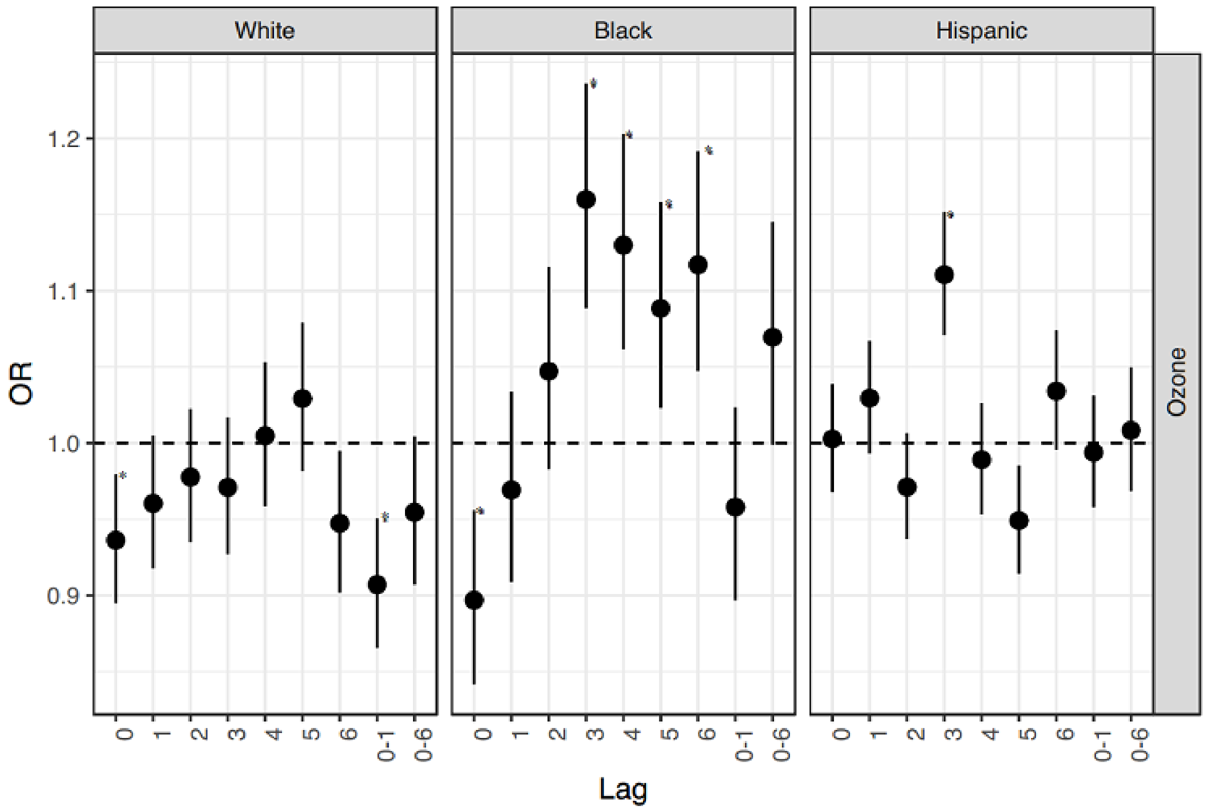

Figure 3. Odds ratio (95% CI) per IQR increase in O_3 (18.1 ppb) controlled for $PM_{2.5}$, NO_2, CO, and temperature by simple lag model (i. e. Lag 0 = same-day exposure, lag 1 = exposure 1 day prior, etc.), and cumulative lag (i. e. Lag 0-1 = mean of lag 0 and lag 1, lag 0-6= mean of lags 0 through 7) for asthma ED visits during June to September of 2015 in SJV, stratifying for race (i. e. White, Black, and Hispanic); the statistically significant findings are shown by * in the figure

Based on the results, we found that O_3 is positively associated with asthma ED visits among Black and Hispanic. The IQR of 18.1 ppb increase in the O_3 exposure at lag 3 (i. e. three days before the event day) is associated with 15.9% [OR: 1.159 (95% CI: 1.088, 1.236)] and 11% [OR: 1.110 (95% CI: 1.070, 1.151)] increase in the odds of having an asthma ED visits among Blacks and Hispanics, respectively. It is noteworthy that we did not find positive association between O_3 and ED visits among Whites. However, at lag 0 and lag 0-1, we found negative association between O_3 and asthma ED visits among Whites.

Figure 4 shows the odds ratios per IQR increase in O_3 controlled for CO, $PM_{2.5}$, and NO_2, and adjusting for temperature by simple lag and cumulative lag models for asthma ED visits during June to September of 2015 in SJV with stratification by age (2-5, 6-18, 19-40, 41-64 and >= 65).

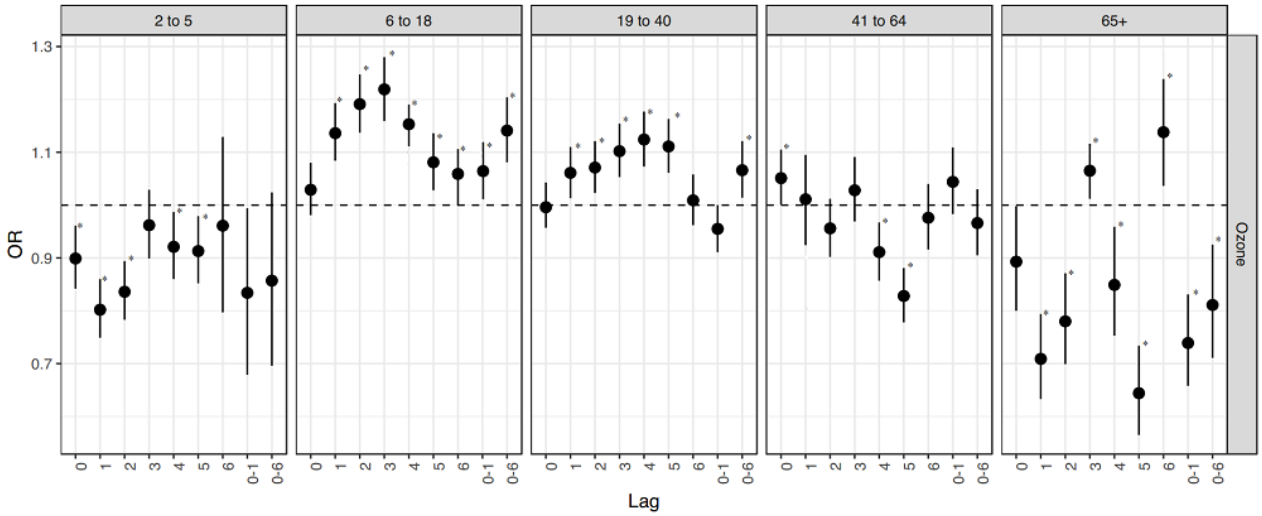

Figure 4. Odds ratio (95% CI) per IQR increase in O_3 (18.1 ppb) controlled for $PM_{2.5}$, NO_2, CO, and temperature by simple lag model (i. e. Lag 0 = same-day exposure, lag 1 = exposure 1 day prior, etc.), and cumulative lag (i. e. Lag 0-1 = mean of lag 0 and lag 1, lag 0-6= mean of lags 0 through 7) for asthma ED visits during June to September of 2015 in SJV, stratifying for age (i. e. 2-5, 6-18, 19-40, 41-64 and >= 65); the statistically significant findings are shown by * in the figure

We found that the association between asthma ED visits among children (2-5 years of age) and O_3 is inverse. We also found that O_3 is positively associated with asthma ED visit among those aged between 6 and 18 years old. We found that 18.1 ppb increase in O_3 exposure at lag 3 is associated with 21.9% [OR: 1.219 (95% CI: 1.159, 1.280)] increase in the odds of having an asthma ED visits among those who aged between 6 and 18. Based on the results, we also found that an IQR increase in O_3 exposure at lag 4 is associate with 12.4% [OR: 1.124 (95% CI: 1.073, 1.177)] increase in the odds of having an asthma ED visits among those who aged between 19 and 40. For 65 and older, we found that an IQR increase in O_3 exposure at lag 6 is associated with 13.8% [OR: 1.138 (95% CI: 1.006, 1.266)] increase the odds of having an the asthma ED visits.

Stratification by county

Table 4 indicates the county-based association between O_3 and Asthma ED visits in SJV during June-September of 2015.

Table 4. County-based association between O_3 and Asthma ED visits in SJV during June-September of 2015

Single and cumulative lags	**Fresno**		**Kern**		**Merced**		**Kings**		**Madera**	
	OR	**95% CI**	OR	**95% CI**	OR	**95% CI**	OR	**95% CI**	OR	**95% CI**
Lag 0	0.900	0.843, 0.978	1.054[b]	1.015, 1.124	1.055[a]	1.033, 1.079	0.871	0.543, 1.398	0.547	0.328, 0.800
Lag 1	0.889	0.770, 0.908	1.051	0.994, 1.133	0.800	0.600, 1.066	1.108	0.651, 1.886	0.887	0.691, 1.139
Lag 2	0.846	0.797, 0.899	1.070	0.991, 1.154	0.353	0.204, 0.541	1.389	0.787, 2.450	0.720	0.549, 0.945
Lag 3	1.120[a]	1.048, 1.186	1.051	1.000, 1.105	0.416	0.211, 0.656	0.997	0.579, 1.719	0.510	0.396, 0.658
Lag 4	0.791	0.635, 0.945	1.081	0.994, 1.154	0.914	0.704, 1.186	1.181	0.671, 2.079	0.866	0.653, 1.149
Lag 5	0.822	0.790, 0.918	1.038	0.940, 1.120	0.975	0.747, 1.274	1.471	0.811, 2.668	0.402	0.181, 0.676
Lag 6	1.145[a]	1.060, 1.220	0.999	0.919, 1.073	0.544	0.317, 0.809	0.645	0.385, 1.081	0.304	0.201, 0.521
Lag 0-1	0.765	0.714, 0.826	0.870	0.606, 1.105	0.825	0.623, 1.093	1.000	0.598, 1.672	0.645	0.494, 0.840
Lag 0-6	0.902	0.841, 0.968	1.030	0.947, 1.121	0.642	0.372, 0.975	1.054	0.590, 1.884	0.489	0.348, 0.686

Abbreviations: CI, confidence interval; OR, odds ratio

[a] Statistically significant (P <0.01)

[b] Statistically significant (P <0.05)

As shown in the table, an IQR increase in O_3 exposure at lag 0 is associated with 5.4% [OR: 1.054 (95% CI: 1.015, 1.124)] and 5.5% [OR: 1.054 (95% CI: 1.033, 1.079)] increase the odds of having an asthma ED visits in Kern and Merced counties, respectively. We also found that an IQR increase in O_3 exposure at lag 6 is associated with 14.5% [OR: 1.145 (95% CI: 1.060, 1.220)] increase the odds of having an asthma ED visits in Fresno county, which is larger than those of Kern and Merced Counties.

Sensitivity Analysis

One of the concerns in this study was the probable bias imposed by removing the three counties of Stanislaus, San Joaquin, and Tulare which had few asthma ED visits. As shown in Appendix C (Table C. 1), the difference in the ORs (%) of the ORs obtained for eight county analysis and five county analysis is not more than 3 %. It indicates that removing these three counties from the study had negligible effect on the main result of this study.

Discussion

In this time-stratified case-crossover study, we investigated the association between short term exposure to O_3 and asthma ED visits from June to September of 2015 in SJV, California, USA. California experienced the highest concentration of O_3 in the USA in 2015. EPA reports from nationwide network of monitoring sites indicates that the west region of the USA in 2015 experienced the highest concentration of O_3 with mean concentration of 74 ppb, in comparison with Northwest (63 ppb), Southwest (69 ppb), South (69 ppb), Southeast (62 ppb), Northeast (69 ppb), Upper-Midweast (65 ppb), Central (65 ppb), and West North Central (60 ppb) of the USA [21]. Our findings suggest that increase in O_3 exposure increased the odds of asthma ED visits in SJV during specific lags and these associations varied depending on race, sex, age and counties. The positive association between O_3 and asthma ED visits were observed mostly at lag 0, lag 3, and lag 6.

In the single and multi-pollutant models, we found that O_3 may have positive association with asthma ED visits in SJV during June to September of 2015. Our findings are in agreement with some existing studies on this topic while are conflicting with others. In a systematic meta-analysis of multi-community asthma prevalence studies by Anderson et al. (2013), it was concluded that there was no significant association between O_3 and asthma attacks [22]. In a study by Laurent et al. (2008) on the association between ambient air pollution estimated in small geographic areas and asthma attacks in Strasbourg, France, in 2000–2005, no significant association was found between O_3 and asthma attacks [23]. In a study conducted by Ding et al. (2016) on the assessment of the effects of pollutants on asthmatic children in Chongqing, China, no association between O_3 and triggering hospital visits for asthma in children was found [11]. However, there have been studies showing a statistically significant association between O_3 and asthma attacks [15, 24]. The reason for this difference could be due to lower levels of O_3 concentration in studies that found no associations [25]. To test this speculation, we further analyzed the association between O_3 and asthma ED visits by stratifying for counties. In the present study, the concentration of O_3 during the summer of 2015 was between 15.3 to 94.5 ppb. We investigated the number of times each county exceeded the standard level of 70 ppb (California and National Standard thresholds); the results showed that Fresno, Kern, Kings, Madera and Merced counties exceeded this standard level by 56, 104, 13, 21, and 31 times, respectively. O_3 has a positive association with asthma ED visits at the counties (Fresno, Kern and Merced) where the highest number of exceedances were recorded.

In studies that reported no association between O_3 and asthma ED visits (22-23), especially in the systematic meta-analysis study conducted by Anderson et al. (2013), the analysis are based on the annual analysis of the association between O_3 and asthma attacks; while, in studies that the association is reported to be positive [15, 26], the concentration of this pollutant differs significantly from warm to cold season. In a study by Wendt JK, et al., (2014), the association between asthma attack and O_3 exposure was significant in warm season only, and not in cold season [27]. Another reason for this could be due to the negative correlation of O_3 and particulate matter, especially in cold season, which can conceal or confound the real effect of O_3.

In this study, we tested whether patients' characteristics could modify the effect of air pollutants on the asthma ED visits. The results showed that sex is not a modifier; the association between O_3 exposure and asthma ED visits at lag 3 was positive and significant for females, and not males. In previous studies, sex was not found as a significant modifier [11, 26]. A possible explanation for these findings may be due to the effect of O_3 on the respiratory system damage that is common to both sexes such as inflammation [28].

We found positive association between O_3 and asthma ED visits among Black and Hispanic. Our results show that there is a delayed lag between exposure to O_3 and asthma ED visits among Blacks and Hispanics, which could not be observed through models focusing on the day of the exposure and/or the day before that. It also indicates that Blacks visit ED three to six days after the exposure, implying that the effect of exposure lasted longer among them. In a study by Alhanti et al. (2016) on short-term relationships between asthma emergency department visits and ambient O_3, CO, NO_2, SO_2, and $PM_{2.5}$, it was found that non-white racial groups are more vulnerable to short term increase of O_3 [29]. Table A.1 in Appendix A indicates the characteristics of asthma ED visits in

June to September of 2015 in SJV, California, USA with stratification by county. We found that a large number of Blacks (40% of the total population of Blacks in this study from all counties) were residents of Kern county where the highest OR for O_3 was recorded, as shown in table 4. There are several epidemiological studies showing the association between O_3 exposure and asthma ED visits among Black and Hispanic [26, 30]. Wendt JK, et al., (2014) reported that the highest estimated odds ratio observed in Blacks [OR:1.08 (95% CI, 1.03, 1.13)] and the lowest odds ratio observed in Whites [OR:1.01 (95% CI, 0.93, 1.10)] during the warm season [27].

As mentioned in previous studies [31-33], racial and ethnic minorities could be more prone to asthma exacerbation when they are exposed to asthma triggers disproportionally. Effects of ethnicity might be confounded with those effects associated with low socioeconomic status. Factors such as social inequalities in racial minorities, socioeconomic status (i. e. differences in exposures related to places of residence, types of employment, and social behaviors) or differing vulnerability from pre-existing medical conditions, health-related behaviors, and higher stress can explain the positive association among Blacks and Hispanics [15, 31]. Furthermore, previous research supports that human biologic variation has influence in asthmatics, supporting the differences encountered between races [34].

The response of each age group (2-5, 6-18, 19-40, 41-64 and >= 65) to the exposure to O_3 was assessed. We could not find a positive association between O_3 and asthma ED visits among children 2 to 5 years old. We speculate that children 2 to 5 years old spend most of their times inside the buildings, resulting for them to be less exposed to the ambient O_3 pollution, especially in the warm seasons. Observing asthma ED visits in this age group could be due to viral respiratory tract infections (i. e. caused mainly by rhinovirus), as reported in previous studies [35]. In previous studies, it is shown that the association between O_3 and asthma hospitalization and ED visits differ among different age groups; and, they could not find any effect among children [25]. We found that asthma ED visits among those who were 6 to 18 years old are more associated with O_3 exposure at Lag 1 to lag 3, with the highest association at lag 3 and after that the association seems to shrink but still positively significant; however, the association among 19 to 40 years old increased in strength gradually from lag 1 to lag 4, with the highest association at lag 4. It can be implied that children 6 to 18 years respond faster to the exposure than adults 19 to 40 years old. In previous studies, the strongest association between O_3 exposure and asthma ED visits is reported to be among 5 to 18 years old [29, 36-37]. In a study conducted by Silverman R. A and Ito K (2010), they reported that the association between asthma hospitalization and O_3 exposure is stronger among children 6 to 18 years old and adults 19 to 49 years old [36]. In addition, the associations in these two age groups are seen beyond the lag 0 and 1 days in that study, which is similar to the results of our study. This pattern was also seen by Wendt JK, et al. (2014) [27].

The differences encountered among different age groups may be due to structural and immunological characteristics that differ with as individuals aging processes [38]. It should be noted that lung surface area per unit of body weight is larger in children than adults, and under normal breathing, breathe considerably more air per unit of body weight than adults (i. e. with the highest rates in the youngest children) [39]. Since children spend more time outside, particularly in the afternoon and in summertime when concentrations of O_3 are typically higher, or at bus stops or traveling to school in the morning when traffic pollutants are at their maximum, they are more exposed to O_3 pollution [40]. The socioeconomic status of the families of children can play an important role in children having asthma ED visits. In other words, asthmatic children of families with low socioeconomic status are reported to have greater exposure to outdoor air pollution and greater susceptibility to the effects of pollutants than do children from families of high socioeconomic status [41-42]. Neighborhood characteristics, including increased levels of crime, less green space, or poor food access, and stress, and diet might contribute to this susceptibility too [43].

In this study, we observed the association between O_3 exposure and asthma ED visits to have a delayed lag, especially for Blacks, children 6 to 18 years and adults 19 to 40 years. It indicates that the effect of a specific exposure event is not limited to the period when it is observed, but it is delayed in time. For future studies, this pattern should be addressed by applying the distributed non-linear lag modeling. Recognizing areas of high pollution (e. g. SJV) and including questionnaires at physicians' offices regarding residency in highly polluted areas, may aid sensitive populations to minimize risk of exposure. Even more, physicians may be able to provide a better assessment of the asthmatic triggers and more individualized advice on how to prevent asthmatic exacerbations due to air pollution.

Limitations

There was potential for exposure misclassification (i. e. poor correlation between the O_3 levels measured at fixed sites and personal exposure), since the air pollution exposures were assigned to the patients' ZIP code of residence given that the center of the ZIP code be located within 15 km of the sampling station. Therefore, some of the ZIP codes at the edge of the 15 km are not fully within the defined radius, resulting in having some patients who are living further than 15 km to the sampling station.

There was also potential for misclassification of asthma cases when only using the first diagnosis code, rather than the first 2-3. In previous studies, it has been shown that [44] other conditions (e. g. infection) may exacerbate asthma and using the primary billing code would exclude such visits. However, using the other diagnosing codes (i. e. second and third diagnosing codes for asthma) may sacrifice specificity in capturing asthma ED visits; in other words, there are ED cases (e. g. sprains and fractures) which are non-related visits with a secondary diagnosis of asthma.

Conclusion

This study investigated the association between short term exposure to O_3 and asthma ED visits during June to September of 2015 in the San Joaquin Valley, California, USA, using a time-stratified case-crossover design. We found that O_3 is associated with asthma ED visits in SJV. We found that females were more affected to O_3. Also, a positive association between Asthma ED visits and O_3 exposure among Black and Hispanics was found. Furthermore, the association between O_3 exposure and asthma ED visits among those who were between 6 to 18 years old was stronger than those found for the other age groups in this study. The county-based analysis showed that the association between O_3 exposure and asthma ED visits is positive in Fresno, Kern and Merced and not in Kings and Madera Counties. These results merit further investigation.

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Appendix C

Table C. 1. Sensitivity analysis of the association between O_3 and asthma ED visits in SJV in June-September of 2015: the difference (%) in the ORs of five and eight county analysis

Single and cumulative lags in multi-pollutant analysis	[d] ***Five County analysis***		[e] ***Eight County analysis***		[c] **Difference in OR (%)**
	O_3 (ppb)		O_3 (ppb)		
	OR	**95% CI**	OR	**95% CI**	

Lag 0	0.956	0.932, 0.980	0.980	0.940, 1.018	2.4
Lag 1	1.034[b]	1.011, 1.062	1.028[b]	1.008, 1.051	-0.6
Lag 2	0.988	0.965, 1.016	0.999	0.945, 1.054	1.1
Lag 3	1.066[a]	1.032, 1.082	1.059[a]	1.030, 1.087	-0.7
Lag 4	1.000	0.975, 1.027	1.005	0.970, 1.034	0.5
Lag 5	0.975	0.949, 1.002	0.984	0.946, 1.024	0.9
Lag 6	0.998	0.971, 1.026	0.990	0.964, 1.020	-0.8
Lag 0-1	0.951	0.927, 0.977	0.981	0.930, 1.029	3
Lag 0-6	1.006	0.963, 1.018	1.010	0.954, 1.056	0.4

Abbreviations: CI, confidence interval; OR, odds ratio

[a] Statistically significant (P <0.01)

[b] Statistically significant (P <0.05)

[c] Difference in OR (%) = (OR (Eight county analysis) - OR (Five county analysis)) × 100

[d] Five county analysis: Merced, Madera, Kings, Fresno and Kern

[e] Eight county analysis: Merced, Madera, Kings, Fresno, Kern, Stanislaus, San Joaquin, and Tulare