The Impact of PM2.5 on Severe Asthma Exacerbation

Whitney Chiu[1#], Shufan Wang,[1#]

[1]Dalla Lana School of Public Health, University of Toronto, Toronto, Canada, M5G 1X5

#WC and SW contributed equally.

Abstract

Background: Asthma has become a global public health concern with more than 300 million people being affected worldwide and is a disease especially prevalent in children. Asthmatic patients may experience severe exacerbation episodes which requires hospitalization and attributes to a substantial proportion of the annual healthcare expenditures. In recent years, researchers have identified a link between fine particulate matter (PM2.5), a component of ambient air pollutant, and asthma incidence. However, it is unclear whether PM2.5 is also associated with the risk of severe asthma exacerbations.

Objective: The goal of our study is to examine the relationship between PM2.5 density and asthma related ED visits. We will also be assessing potential effect modification of age on the relationship between air pollution exposure and severe asthma exacerbation.

Methods: We used the Moran's I to examine global and local patterns of spatial correlation. OLS models were constructed to assess the association between PM2.5 concentration and asthma related ED visits in children and adults. We adopted the forward model building strategy to select for possible confounding variables.

Results: Spatial correlation and autocorrelation were not observed at both global and local level. The results from the adjusted OLS and spatial lag model suggested that PM2.5 concentration was not a significant predictor of asthma related ED visits in both children and adults.

Conclusion: Air pollution did not seem to be associated with severe asthma exacerbation. The difference in ED visits observed across California may be a result of differential SES level and other health indicators.

Introduction

In the recent decades, *asthma* has become a worldwide public health concern with an estimated 339 million people being affected and is the most prevalent chronic disease among children [1, 2]. Asthma is a non-communicable respiratory disease characterized by chronic airway inflammation leading to constriction and its symptoms include coughing, wheezing and shortness of breath [1, 2]. More recently, researchers have suggested that asthma is actually composed of a group of diseases, each with its own risk factors and etiology [3]. However, despite the increased understanding of asthma, no cure has been identified for the disease, but it can be managed through a combination of quick acting and long-term control medications [4].

Patients with asthma may often experience exacerbation, which are periods of worsened disease symptoms and can be classified into mild, moderate or severe [5]. The more severe forms often requiring hospitalization and are associated with increased morbidity and mortality, making asthma one of the most expensive diseases to treat [5, 6]. The annual financial burden of asthma in the US is estimated to be $80 billion, accounting for both medical expenditure and missed productivity [7]. Those with severe exacerbations corresponds to a substantial proportion of the burden as each episode costs approximately $2,040 to treat and contributes to many missed workdays and schooldays [6]. Thus, there is an urgent need to identify preventative methods to alleviate the burden of asthma on society.

There have been many risk factors identified for asthma, with the most prominent ones are cigarette smoke and other irritant exposures, allergies, obesity and physical activity [8-12]. As well, asthma is much more prevalent in children who are male and adults who are female, leading experts to believe age and sex are also important determinants of asthma risk [13, 14]. However, with the recent trend in climate change, researchers have been interested in examining the relationship between ambient air pollution and risk for asthma [15]. One of the main components of air pollution is fine particulate matter (PM2.5), which may be composed of sulfates, nitrates, ammonia, black carbon and mineral dust [16]. Its small size allows it to penetrate deeply into the lung and can irritate the alveolar wall, jeopardizing lung function [17]. Studies have identified associations between PM2.5 with a number of respiratory conditions, including lung cancer, chronic obstructive pulmonary disease as well as asthma [17-19]. However, it is still unclear whether PM2.5 is responsible for asthma exacerbation, especially in those with more severe episodes.

Thus, the aim of our study is to understand whether air pollution is related to severe asthma exacerbation by analyzing the associations between the annual PM2.5 concentration and asthma related emergency department (ED) visits in California. As well, due to the high prevalence of asthma in children, we would also like to assess whether there is effect modification by age on the relationship of air pollution and asthma exacerbation.

Methods

Study Design and Data sources

Our study examined cross-sectional county-based exposure and outcome data in the state of California from 2014. Concentration of fine particulate matter was obtained from the National Environmental Public Health Tracking Network, where the county daily average concentration (measured in $\mu g/m^3$) was provided. Asthma related ED visits were collected from the Emergency Department and Ambulatory Surgery Database. Patients asthma as their principal diagnosis for their ED visit, according to the ICD-9-CM code, were included. The county-based asthma ED visits were calculated as per 10,000 overall population, per 10,000 children (<18 years old) or per 10,000 adults (>18 years old).

To control for possible confounding, county based demographic data (population age, sex, race, education and childhood poverty, unemployment and social associations) were obtained from the American Census, American Community Survey and the Bureau of Labor Statistics. Variables on health behaviours and clinical care (adult smoking, adult diabetes, adult obesity, adult physical inactivity, health insurance) were accessed from the Behavioral Risk Factor Surveillance System, CDC Diabetes Interactive Atlas and Small Area Health Insurance Estimates. All demographic and health related variables were measured as a proportion.

Statistical Analysis

Descriptive analyses were done using R version 3.5.1. Baseline characteristics encompassing demographic, health indicators, air pollution and asthma ED rates were calculated as mean$\pm$standard deviation. Spatial distribution of PM2.5 concentrations, asthma related ED rates in children, adults and the overall population were mapped using ArcGIS Pro. Preliminary spatial analyses including univariate, bivariate, and local Moran's I as well as regression analysis were conducted using GeoDa.

Preliminary spatial analyses

To determine the global and local spatial clustering patterns of our main exposure and outcome between each county in California, preliminary analysis was conducted before the fitting regression models to our data. A spatial weight using first order queen's contiguity matrix was specified. Univariate Moran's I were calculated to assess global spatial autocorrelation for the exposure and the outcomes individually. Bivariate Moran's I were assessed to determine whether there is spatial dependence between the our main predictor and outcomes. We examined PM2.5 in relation to asthma ED rates in children, adults, and overall population. Moran scatter plots were presented to visualize the effects. Since global Moran's I does not give information on location clusters, the local univariate Moran's I and the LISA cluster map were further constructed to identify hot spots, cold spots and spatial outliers. Statistical significance were assessed using the randomization approach with 999 permutations.

Regression analyses

Ordinary linear regression was used to examine the association between PM2.5 and asthma ED rates in children and adults. Due to the different spatial pattern of adult and

child asthma ED visits in relation to PM2.5, we kept outcome stratified by age. Two ordinary linear regression models were constructed to further determine whether a spatial lag or spatial error model would be appropriate.

The two final multivariable model for children and adult asthma ED rates was determined separately by, first testing a selection of potential confounders in univariate models. Variables that have a p-value greater than 0.25 were excluded. Preliminary multivariable models were then built with the main predictor of PM2.5 level and covariates that were tested significant in the univariate analyses at the <0.25 level. The final multivariate model was determined by using backward model selection. Variables that were not significant based on the p-value cut-off of 0.05 and did not change >10% of the beta estimates were eliminated from the models. Finally, in the two final models, percent of non-Hispanic black, percent of children in poverty, and number of membership associations per 10,000 population were included in the children asthma ED rate model, while prevalence of diabetes in adults >20 years old, percent of adults that are current smokers, and percent of population >16 years old unemployed but seeking work were included in the adult asthma ED rate model as covariates. The spatial lag model was tested significant and was used in the final child model. However, neither spatial lag nor spatial error model was applicable to the adult model.

Missing Data

There were no missing data in the co-variables, however, there were several counties with missing values for asthma related ED rates. The frequencies of missing data in the outcome variables were relatively low (≤7%). Although these counties had to be excluded from analysis, it should not have a huge influence on the overall results.

Results

Population baseline and descriptive statistics

The baseline characteristics of the study population were presented in **Table 1**. The average median age between the counties was around 40 years old and were composed of a majority of adults that are non-Hispanic Whites. There was an average of 23% of children living in poverty, 9% of unemployment and 7 social associations per 10,000 population across the state. The prevalence of diabetes, obesity, smoking, and heavy drinking were 8.67%, 24.24%, 18.22% and 13.34% respectively. The average density of PM2.5 was 10.14 $\mu g/m^3$. The asthma related ED visit in the total population was 51.65 per 10,000 population, but the rate was observed to be higher among children.

The spatial distribution of PM2.5 concentration is presented in **Figure 1**. The highest concentration of fine particulate matter was found in central and southern California and lower concentrations along the east and west border of the state. The overall asthma related ED rates were presented in **Figure 2**. Childhood asthma related ED rates were observed to be higher in central and southern California (**Figure 4**), however, ED visits in adults tend to be higher in the norther border (**Figure 3**).

Preliminary spatial analyses

The univariate Moran's I for asthma ED rate in children was significant, indicating that the child asthma ED rate between counties in California are spatially autocorrelated with a clustering pattern (**Figure 5.** Moran's I= 0.258, p= 0.004). However, both asthma ED rates in adults and in overall population were not significantly different from complete spatial randomness. PM2.5 level also had a significantly positive Moran's I, indicating aggregation of similar PM2.5 level across counties (**Figure 8.** Moran's I= 0.405, p= 0.001).

The bivariate Moran's I were significant between PM2.5 and asthma ED rates in children and adults separately. Child asthma ED rates showed a significant aggregated spatial pattern in relation to PM2.5 (**Figure 9.** Moran's I= 0.232, p= 0.002); however, adult asthma ED rates showed a dispersed pattern with boarder line significance (**Figure 10**. Moran's I= -0.086, p= 0.056). The LISA map of local Moran's I showed a cold spot of PM2.5 level around the north eastern counties in California. No significant hot spots or cold spots were identified regarding child and adult asthma ED rates. Still, a spatial outlier with low child and adult asthma ED rates surrounding San Joaquin county was observed.

Regression analyses

Table 3 presented the ordinary linear regression results. PM2.5 level was not associated with adult asthma ED rates, adjusting for diabetes prevalence, current smokers, and unemployment. Results of spatial lag model in **Table 4** showed that PM2.5 level was also not associated with child asthma ED rates, adjusting for children in poverty, race of non-Hispanic black, and family and social support (number of membership associations per 10,000 population). The spatial lag effect of child asthma ED rate suggested that counties of higher child asthma ED rates would predict an increased likelihood of similar events in neighboring counties. The use of spatial lag model enabled us to adjust for the confounding effect of spatial autocorrelation within the outcome variable in the relationship between PM2.5 and child asthma ED rate. The spatial dependence of asthma ED rates in children across countries no longer existed after fitting the spatial lag model.

Discussion

In our study, based on cross-sectional county-based data in the state of California in 2014, we found that PM2.5 level was not related to either children or adult asthma exacerbation. However, there were certain limitations in our study. First, with only the annual average of PM2.5 level, we were not able to account for fluctuations of air quality during the day or a specific time of the year, since extreme values are likely to have been averaged out. Therefore, the aggregated PM2.5 data may not accurately depict the exposure which the individual patients may have experienced. Second, un-measured and unadjusted confounding factors could be another reason that lead to the insignificant association between PM2.5 level and asthma ED rate. Independent risk factors of asthma such as environmental tobacco smoking, occupational exposures, and family history were not adjusted for due to data unavailability. Third, despite having tried to replace variables that measure similar concepts and drop some covariates that appeared to be collinear, a certain degree of multicollinearity was still observed in the

OLS model for adult asthma ED rates. Finally, due to the cross-sectional nature of our study, we were not able to capture the temporality between the main exposure and outcomes.

One of the biggest strengths in our study was the incorporation of complete demographic, social and other health related variables to model the risk of severe asthma exacerbation. Behavioral variables such as physical inactivity and alcohol drinking were used to control for poor healthy decisions in adults; number of membership associations and percent of children in poverty were included as a proxy to measure people in lower socioeconomic status who are more likely to make poor healthcare decisions. As well, the relatively diverse population of California makes our results more generalizable and may also help formulate public health decisions in other regions. Appropriate model selection was another strength of our study. Based on model diagnostics, first, the linear regression assumption including normality of residuals and homoskedasticity was met in the adult asthma ED rate model; second, spatial dependence of child asthma ED rate has been attenuated after the lag model was applied, indicating that the spatial autocorrelation of the outcome has been properly adjusted for. The result of the likelihood ratio test was also non-significant, meaning that a higher order model was not required.

Our findings of overall poor health and low socioeconomic status are associated with asthma ED rates have been noted in other studies [20-22]. Directing resources to counties that have a higher poverty rate could possibly enable patients to better control for asthma exacerbation and prevent further ED visits. Prospective studies should focus on working with individual level data to capture a more accurate estimates of PM2.5 exposure from everyday activities, in addition to the baseline exposure indicated by the value of the air quality detectors. Effect modification of both age and sex should be further explored since they are important determinants of asthma risk [23]. Future research is needed to assess reasons of the spatial outlier around San Joaquin to understand other factors that potentially influence asthma ED rates in both children and adults as well.

Conclusion

Annual PM 2.5 level was not associated with asthma exacerbation in the state of California at county level. Therefore, based on our data, differential level in PM2.5 may not be the key factor for underlying variability in asthma ED rates in both children and adults. However, significant differences in prevalence of diabetes and smoking in adults may explain the spatial variation in adult asthma ED rate, while higher asthma ED rate in children across counties in California may be explained by significant differences in social economic status.

Appendix
Table 1

Variables	Mean ±SD
Population	669008±1467
Median age	39.46±6.47
Proportion of females	49.52±2.22
Proportion of children (<18)	22.51±4.21
Proportion of senior (>65)	15.97±4.80
Proportion of adults (18-65)	61.52±3.31
Proportion of non-Hispanic Black	3.05±3.02
Proportion of non-Hispanic White	55.22±19.62
Proportion of Hispanic	29.85±17.75
Proportion of Asians	7.49±8.28
Proportion with some college education	59.61±10.09
Proportion of Child living in poverty	22.51±7.33
Number of Social Associations per 10,000 population	6.96±2.37
Proportion of unemployment	8.88±3.24
Prevalence of diabetes in adults	8.67±1.07
Proportion of adults with BMI >30kg/m2	24.24±3.56
Proportion of adults reporting heavy/binge drinking	18.22±1.35
Proportion current adult smokers	13.34±1.81
Average daily density of PM2.5	10.14±2.90
Rate of asthma related ED visits per 10,000 population	51.65±15.72
Rate of asthma related ED visits per 10,000 children	77.45±27.25
Rate of asthma related ED visits per 10,000 adults	43.23±14.69

Table 1 presents baseline characteristics of the various counties in California.

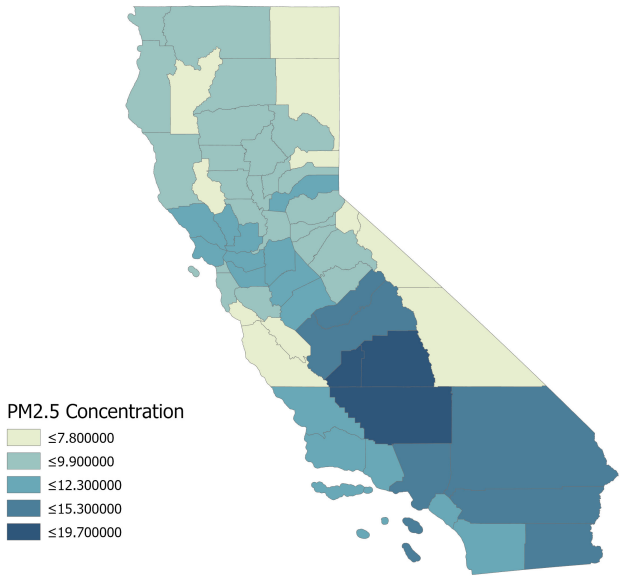


Figure 1 Presents the concentration of PM2.5 in the various counties of California

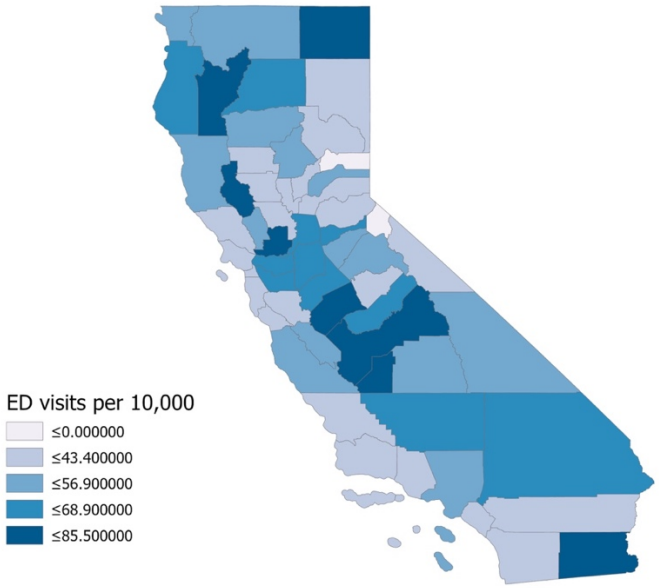


Figure 2 presents the spatial distribution of asthma related ED visits per 10,000 persons in California.

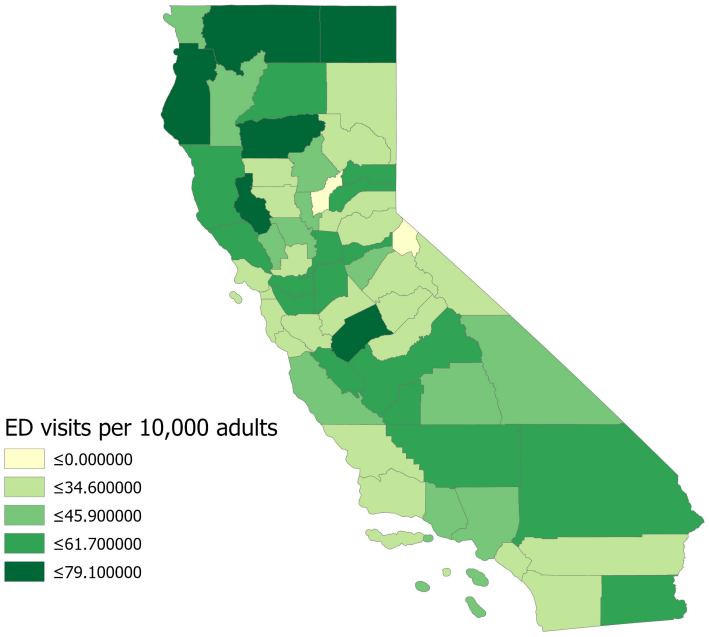


Figure 3 presents the spatial distribution of asthma related ED visits per 10,000 adults (>18 years old) in California.

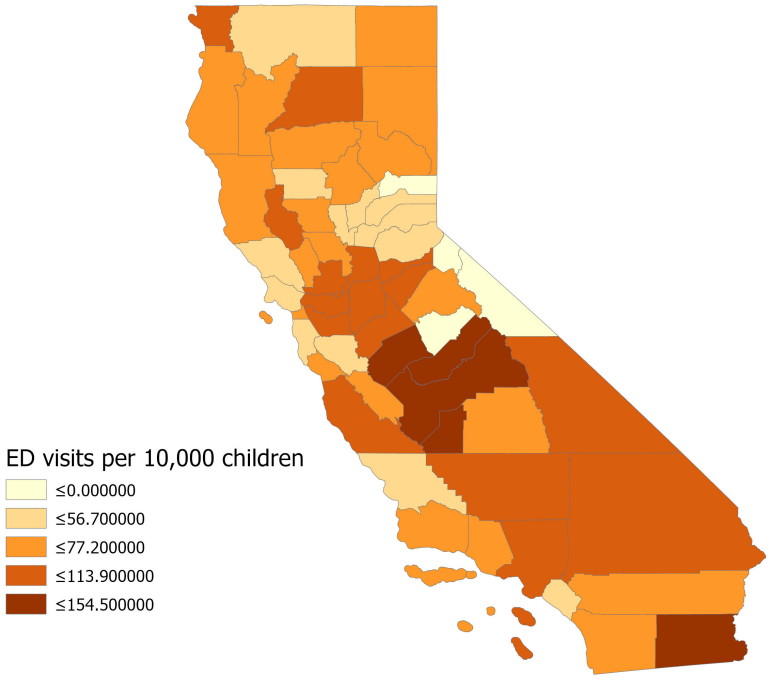
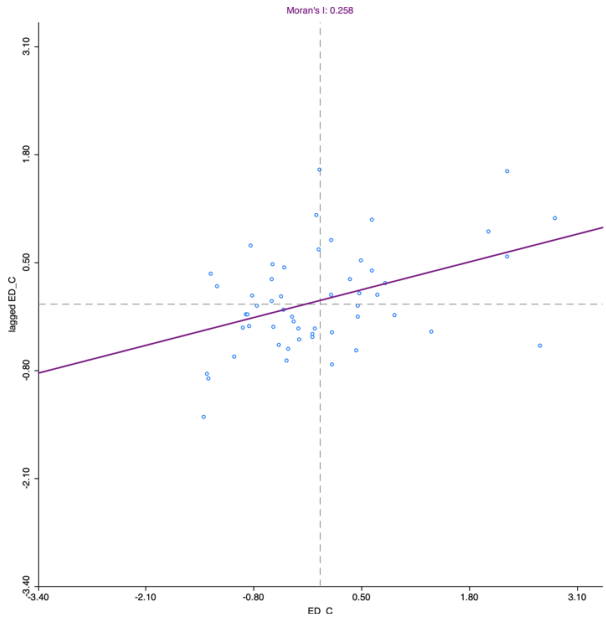


Figure 4 presents the spatial distribution of asthma related ED visits per 10,000 children (<18 years old) in California.

Univariate Moran's I scatter plot



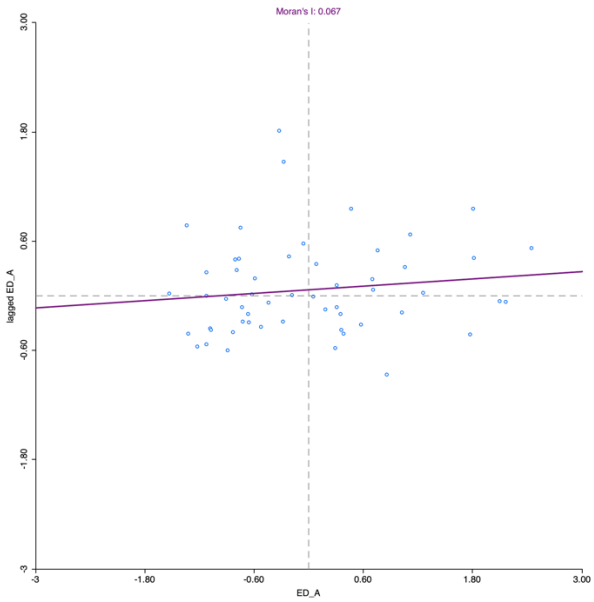
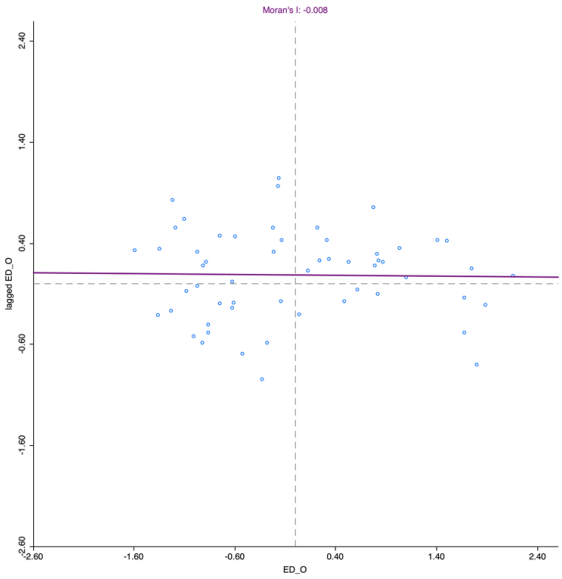


Figure 5 (Left) presents the univariate Moran's I for asthma ED rates in children, **I= 0.258, p= 0.004.**
Figure 6 (Right) presents the univariate Moran's I for asthma ED rates in adults, I= 0.067, p= 0.172.



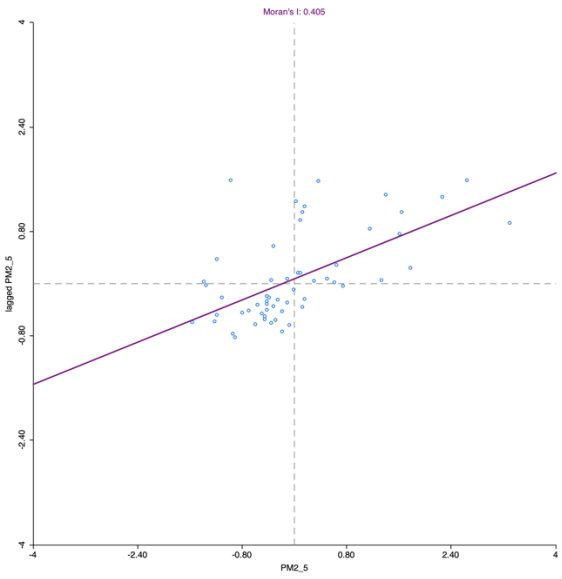
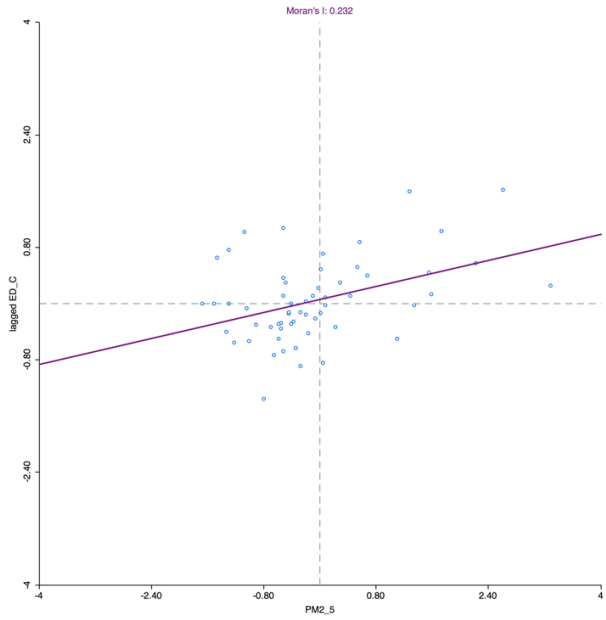


Figure 7 (Left) presents the univariate Moran's I for asthma ED rates in overall population, I= -0.008, p= 0.438.
Figure 8 (Right) presents the univariate Moran's I for PM2.5 level, **I= 0.405, p= 0.001.**

Bivariate Moran's I scatter plot



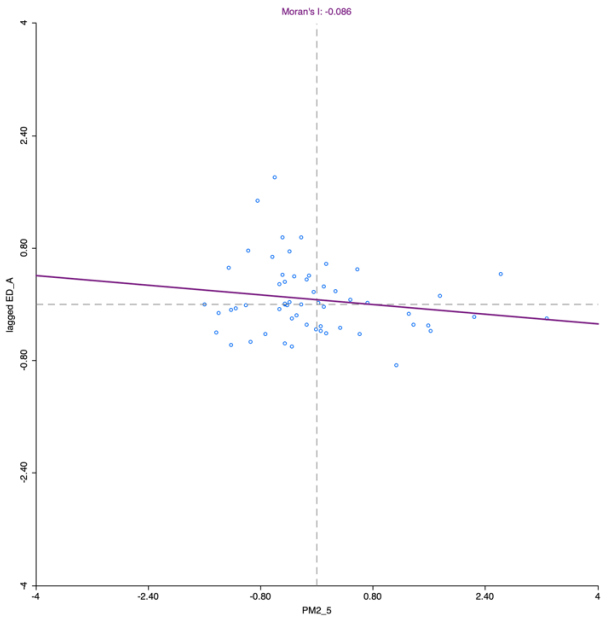


Figure 9 (Left) presents the bivariate Moran's I for PM2.5 and asthma ED rate in children, **I= 0.232, p= 0.002.**

Figure 10 (Right) presents the bivariate Moran's I for PM2.5 and asthma ED rate in adults, I= -0.086, p= 0.056.

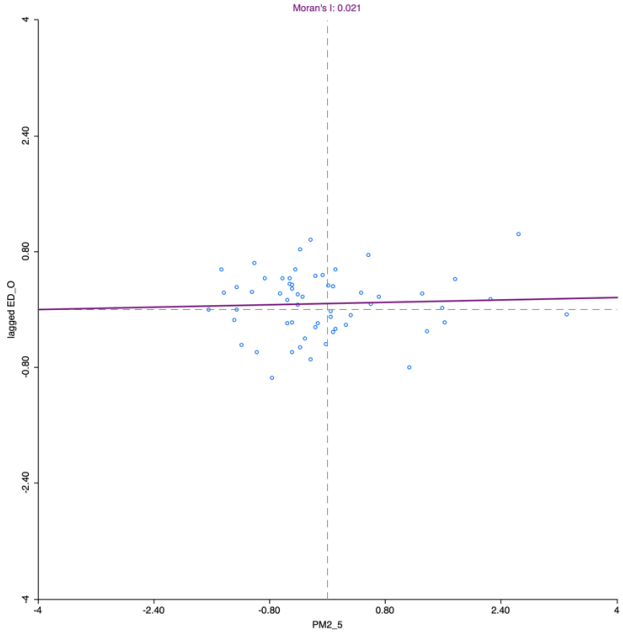
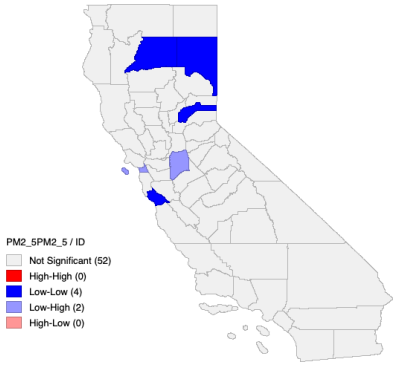


Figure 11 presents the bivariate Moran's I for PM2.5 and asthma ED rate in overall population, I= 0.021, p= 0.347.

Local indicator of Spatial Association (LISA) Cluster maps



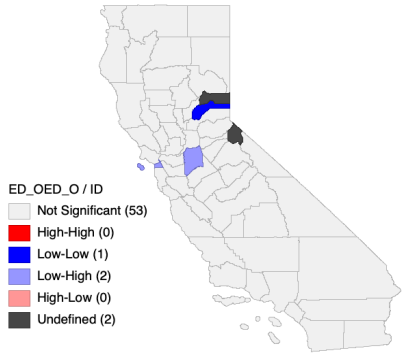
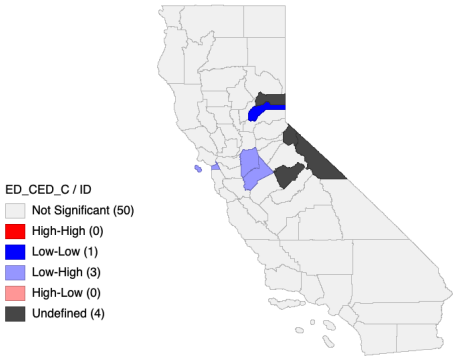


Figure 12 (Left) presents the LISA cluster map for PM2.5 level.
Figure 13 (Right) presents the LISA cluster map for asthma ED visits in overall population.



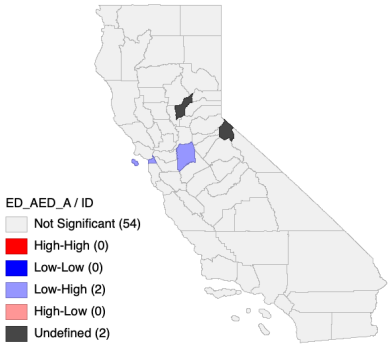


Figure 14 (Left) presents the LISA cluster map for asthma ED visits in children.
Figure 15 (Right) presents the LISA cluster map for asthma ED visits in adults.

Regression tables

REGRESSION

SUMMARY OF OUTPUT: ORDINARY LEAST SQUARES ESTIMATION

Data set	: asthma		
Dependent Variable	: ED_C	Number of Observations	: 54
Mean dependent var	: 77.4481	Number of Variables	: 5
S.D. dependent var	: 26.9955	Degrees of Freedom	: 49
R-squared	: 0.509420	F-statistic	: 12.7204
Adjusted R-squared	: 0.469372	Prob(F-statistic)	: 3.56546e-07
Sum squared residual	: 19305.8	Log likelihood	: -235.36
Sigma-square	: 393.996	Akaike info criterion	: 480.721
S.E. of regression	: 19.8493	Schwarz criterion	: 490.666
Sigma-square ML	: 357.515		
S.E of regression ML	: 18.9081		

Variable	Coefficient	Std.Error	t-Statistic	Probability
CONSTANT	16.7639	17.1874	0.975362	0.33417
PM2_5	1.33567	1.15376	1.15766	0.25261
Black	2.92858	1.0029	2.9201	0.00528
Pov_C	1.8452	0.409751	4.50322	0.00004
Support	-0.623093	1.21333	-0.51354	0.60988

REGRESSION DIAGNOSTICS
MULTICOLLINEARITY CONDITION NUMBER 15.478863
TEST ON NORMALITY OF ERRORS

TEST	DF	VALUE	PROB
Jarque-Bera	2	1.5471	0.46137

DIAGNOSTICS FOR HETEROSKEDASTICITY
RANDOM COEFFICIENTS

TEST	DF	VALUE	PROB
Breusch-Pagan test	4	16.0989	0.00289
Koenker-Bassett test	4	12.7271	0.01269

DIAGNOSTICS FOR SPATIAL DEPENDENCE
FOR WEIGHT MATRIX : queen
(row-standardized weights)

TEST	MI/DF	VALUE	PROB
Moran's I (error)	0.1287	1.9574	0.05030
Lagrange Multiplier (lag)	1	5.3824	0.02034
Robust LM (lag)	1	4.1678	0.04120
Lagrange Multiplier (error)	1	1.9768	0.15973
Robust LM (error)	1	0.7621	0.38267
Lagrange Multiplier (SARMA)	2	6.1445	0.04632

========== END OF REPORT ==========

REGRESSION

SUMMARY OF OUTPUT: ORDINARY LEAST SQUARES ESTIMATION

Data set	: asthma		
Dependent Variable	: ED_A	Number of Observations	: 53
Mean dependent var	: 43.5604	Number of Variables	: 6
S.D. dependent var	: 14.7916	Degrees of Freedom	: 47
R-squared	: 0.291128	F-statistic	: 3.86051
Adjusted R-squared	: 0.215716	Prob(F-statistic)	: 0.0051768
Sum squared residual	: 8220.04	Log likelihood	: -208.871
Sigma-square	: 174.894	Akaike info criterion	: 429.742
S.E. of regression	: 13.2248	Schwarz criterion	: 441.563
Sigma-square ML	: 155.095		
S.E of regression ML	: 12.4537		

Variable	Coefficient	Std.Error	t-Statistic	Probability
CONSTANT	-33.2466	20.8861	-1.59181	0.11813
PM2_5	-0.429577	0.754286	-0.569515	0.57172
Black	0.0368582	0.673542	0.054723	0.95659
Unemply	-0.165931	0.716374	-0.231627	0.81784
Diabets	4.74237	1.94139	2.44277	0.01839
Smoke_A	3.13914	1.21099	2.59221	0.01267

REGRESSION DIAGNOSTICS
MULTICOLLINEARITY CONDITION NUMBER 33.680572
TEST ON NORMALITY OF ERRORS

TEST	DF	VALUE	PROB
Jarque-Bera	2	2.3283	0.31218

DIAGNOSTICS FOR HETEROSKEDASTICITY
RANDOM COEFFICIENTS

TEST	DF	VALUE	PROB
Breusch-Pagan test	5	8.6106	0.12564
Koenker-Bassett test	5	17.1815	0.00417

DIAGNOSTICS FOR SPATIAL DEPENDENCE
FOR WEIGHT MATRIX : queen
(row-standardized weights)

TEST	MI/DF	VALUE	PROB
Moran's I (error)	-0.0915	-0.6014	0.54758
Lagrange Multiplier (lag)	1	0.7160	0.39746
Robust LM (lag)	1	0.0062	0.93724
Lagrange Multiplier (error)	1	0.9402	0.33224
Robust LM (error)	1	0.2304	0.63125
Lagrange Multiplier (SARMA)	2	0.9464	0.62302

========== END OF REPORT ==========

Table 2 (Left) presents ordinary linear regression results, testing the association between asthma ED rates in children and PM2.5 level.
Table 3 (Right) presents ordinary linear regression results, testing the association between asthma ED rates in adults and PM2.5 level.

```
REGRESSION
----------
SUMMARY OF OUTPUT: SPATIAL LAG MODEL - MAXIMUM LIKELIHOOD ESTIMATION
Data set            : asthma
Spatial Weight      : queen
Dependent Variable  :        ED_C  Number of Observations:   53
Mean dependent var  :     78.1434  Number of Variables   :    6
S.D. dependent var  :     26.7658  Degrees of Freedom    :   47
Lag coeff.   (Rho)  :    0.250108

R-squared           :    0.588627  Log likelihood        :   -226.276
Sq. Correlation     : -            Akaike info criterion :    464.551
Sigma-square        :     294.711  Schwarz criterion     :    476.373
S.E of regression   :     17.1671

------------------------------------------------------------------------------
       Variable       Coefficient     Std.Error       z-value    Probability
------------------------------------------------------------------------------
           W_ED_C      0.250108       0.141467        1.76796      0.07707
         CONSTANT       5.65608        16.9642       0.333413      0.73882
            PM2_5      0.427618        1.05008       0.407226      0.68384
            Pov C        1.9434       0.359259        5.40947      0.00000
          Support     -0.787994        1.05969      -0.743611      0.45711
            Black       3.09444       0.874405         3.5389      0.00040
------------------------------------------------------------------------------

REGRESSION DIAGNOSTICS
DIAGNOSTICS FOR HETEROSKEDASTICITY
RANDOM COEFFICIENTS
TEST                                    DF       VALUE         PROB
Breusch-Pagan test                      4         20.0931      0.00048

DIAGNOSTICS FOR SPATIAL DEPENDENCE
SPATIAL LAG DEPENDENCE FOR WEIGHT MATRIX : queen
TEST                                    DF       VALUE         PROB
Likelihood Ratio Test                   1          2.9155      0.08773
============================== END OF REPORT ==============================
```

Table 4 presents the spatial lag model testing the association between asthma ED rates in adults and PM2.5 level.

References

1. *Asthma*. [Webpage] 2019 [cited 2019 December 18]; Available from: https://www.who.int/news-room/q-a-detail/asthma.
2. *The Global Asthma Report 2018*. 2018.
3. Pavord, I.D., et al., *After asthma: redefining airways diseases.* Lancet, 2018. **391**(10118): p. 350-400.
4. National, A.E. and P. Prevention, *Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007.* The Journal of allergy and clinical immunology, 2007. **120**(5 Suppl): p. S94.
5. Dougherty, R.H. and J.V. Fahy, *Acute exacerbations of asthma: epidemiology, biology and the exacerbation-prone phenotype.* Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology, 2009. **39**(2): p. 193-202.
6. Suruki, R.Y., et al., *The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA.* BMC Pulm Med, 2017. **17**(1): p. 74.
7. Nurmagambetov, T., R. Kuwahara, and P. Garbe, *The economic burden of asthma in the United States, 2008–2013.* Annals of the American Thoracic Society, 2018. **15**(3): p. 348-356.
8. Beuther, D.A. and E.R. Sutherland, *Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies.* American journal of respiratory and critical care medicine, 2007. **175**(7): p. 661-666.
9. Mitchell, E., et al., *The association between BMI, vigorous physical activity and television viewing and the risk of symptoms of asthma, rhinoconjunctivitis and eczema in children and adolescents: ISAAC Phase Three.* Clinical & Experimental Allergy, 2013. **43**(1): p. 73-84.
10. Weinmayr, G., et al., *Atopic sensitization and the international variation of asthma symptom prevalence in children.* American journal of respiratory and critical care medicine, 2007. **176**(6): p. 565-574.
11. Mitchell, E.A., et al., *The association between tobacco and the risk of asthma, rhinoconjunctivitis and eczema in children and adolescents: analyses from Phase Three of the ISAAC programme.* Thorax, 2012. **67**(11): p. 941-949.
12. Malo, J.-L. and M. Chan-Yeung, *Asthma in the workplace: a Canadian contribution and perspective.* Canadian respiratory journal, 2007. **14**(7): p. 407-413.
13. Martinez, F.D., et al., *Asthma and wheezing in the first six years of life.* New England Journal of Medicine, 1995. **332**(3): p. 133-138.
14. Melgert, B.N., et al., *Are there reasons why adult asthma is more common in females?* Current allergy and asthma reports, 2007. **7**(2): p. 143-150.
15. Guarnieri, M. and J.R. Balmes, *Outdoor air pollution and asthma.* Lancet (London, England), 2014. **383**(9928): p. 1581-1592.
16. *Air Pollution*. [Webpage] 2018 [cited 2019 December 16]; Available from: https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health.
17. Xing, Y.-F., et al., *The impact of PM2.5 on the human respiratory system.* Journal of thoracic disease, 2016. **8**(1): p. E69-E74.
18. Pope, C.A., 3rd, et al., *Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution.* JAMA, 2002. **287**(9): p. 1132-1141.

19. Zhao, J., et al., *Role of PM(2.5) in the development and progression of COPD and its mechanisms.* Respiratory research, 2019. **20**(1): p. 120-120.
20. Bacon, S.L., et al., *Individual-level socioeconomic status is associated with worse asthma morbidity in patients with asthma.* Respir Res, 2009. **10**(1): p. 125.
21. Basagana, X., et al., *Socioeconomic status and asthma prevalence in young adults: the European Community Respiratory Health Survey.* Am J Epidemiol, 2004. **160**(2): p. 178-88.
22. Uphoff, E., et al., *A systematic review of socioeconomic position in relation to asthma and allergic diseases.* Eur Respir J, 2015. **46**(2): p. 364-74.
23. Skobeloff, E.M., et al., *The influence of age and sex on asthma admissions.* Jama, 1992. **268**(24): p. 3437-40.

Shufan Wang
Dalla Lana School of Public Health, University of Toronto
155 College St, Toronto, ON, M5T 3M7

December 16, 2019

Dr. Jonathan A. Bernstein,
Professor of Medicine
Director of Clinical Research
University of Cincinnati, Department of Internal Medicine
Cincinnati, OH

Dear Dr. Bernstein

We wish to submit our original research paper “The Impact of PM2.5 on Severe Asthma Exacerbation” to the Journal of Asthma. This article was written by myself and my colleague Whitney Chiu. Due to the high prevalence of asthma and the high cost of exacerbation related hospitalization cost, there presents an urgent need to understand risk factors associated with severe asthma exacerbation. Air pollutant has been previously implicated in the development of asthma, and recently, there is a concern with how elevated fine particulate matter levels may trigger severe exacerbation episodes. Out study aims to entangle the associations between PM2.5 and asthma related ED visits in California and also to examine whether there is effect modification by age on the main relationship.

In our paper, we found that PM2.5 was actually not significantly associated with severe asthma exacerbation rates but social economic status was found to be a consistent predictor of asthma related ED rates. One of the biggest strengths in our study was the incorporation of complete demographic, social and other health related variables to better model the risk of severe asthma exacerbation. As well, the relatively diverse population of California makes the results more generalizable and may help formulate public health decisions in other regions.

We think that our study has a great fit with the Journal of Asthma because there is high alignment in terms of the research aim. Further, our manuscript only contains original work and has not been published or under consideration elsewhere. All authors have approved the manuscript for submission and the authors have no conflicts of interest to disclose.

Please address all correspondence concerning this manuscript to me at shufan.wang@mail.utoronto.ca.

Thank you for your consideration of this manuscript,

Sincerely,
Shufan Wang