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Using Syndromic Surveillance to Assess the Impact of Environmental Factors on Asthma- and COPD- Related ED Visits in Douglas County, Nebraska

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Abstract

BACKGROUND: Asthma and chronic obstructive pulmonary disease (COPD) are chronic diseases associated with health disparities in Douglas County, Nebraska and in the United States. Currently there is a lack of information describing the impact of environmental factors in Nebraska on the burden of emergency department (ED) visits or hospitalizations related to these chronic respiratory (CR) diseases. The aim of this study was to determine if there is an association between the numbers of seasonal viral respiratory (SVR)- related ED visits, outdoor air pollutants, aeroallergens, or meteorological factors on the number of CR- related ED visits in Douglas County, Nebraska.

METHODS: We analyzed electronic health record (EHR) data from 8 of 9 hospitals in Douglas County, NE for ED visits from February 28, 2016 to December 29, 2018. Syndromic surveillance definitions were used to identify CR- and SVR- related ED visits in EHR ED data. Aeroallergen, outdoor air pollutant and temperature data were obtained. Descriptive statistics were performed on EHR and environmental data. Negative binomial models were used to determine the association between the number of CR- related weekly ED visits and the environmental factors of interest. These models were stratified to account for possible cofounding effect of patient age and season. Patient age was stratified into 3 age groups: < 18 yrs., 18-39 yrs., ≥ 40 yrs.

RESULTS: Significant associations were observed between the number of CR- related weekly ED visits and the weekly number of SVR-related ED visits, mean weed pollen counts, mean mold spore counts, mean minimum temperature, mean carbon monoxide levels and mean fine particulate matter ($PM_{2.5}$) levels. Discrepancies in significant associations between the CR- related weekly ED visits and the environmental variables were observed after stratifying the model by season and age groups. For instance, SVR-related weekly ED visits were significantly associated with an increase in CR-related weekly ED visits among the < 18 yrs. and 18 to 39 yrs. age groups in the summer, the ≥ 40 yrs. age group in the fall, and the 18 to 39 yrs. and the ≥ 40 yrs. age groups in the winter. Minimum temperature was significantly associated with the increase in CR- related weekly ED visits among the < 18 yrs. and 18 to 39 yrs. age groups in the fall. Significant associations with an increase in CR- related weekly ED visits were also observed for $PM_{2.5}$ among the 18 to 39 yrs. and ≥ 40 yrs. age groups in the spring, and the < 18 yrs. and ≥ 40 yrs. age groups in the fall. Weed pollen and mold spores were also significantly associated with an increase in CR- related weekly ED visits. While significant associations were observed for weed pollen during the summer among the < 18 yrs. age group, significant associations were observed for mold spores among all age groups during spring, and among the ≥ 40 yrs. age group during summer. Carbon monoxide was associated with a decrease in CR-related weekly ED visits for the 18 to 39 yrs. age group in the fall.

CONCLUSIONS: Results of this study indicate the association between environmental factors and CR-related ED visits in Douglas County, Nebraska could be affected by not only by SVR disease cycles, temperature and other environmental factors, but also by age. Additional analyses may be needed to further explore these associations.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are chronic diseases associated with health disparities in Douglas County NE, as well as statewide (Douglas County Health Department [DCHD], 2007; Nebraska Department of Health and Human Services [NDHHS], 2001; NDHHS, 2015; NDHHS, 2016; Office of Disease Prevention and Health Promotion [ODPHP], 2016; Professional Research Consultants, Inc.[PRC], 2015). According to the NDHHS, in 2014 the overall asthma mortality rate in Nebraska was slightly higher than the overall National asthma mortality rate. The report also indicates a higher age-adjusted mortality rate due to COPD in Nebraska from 2011 to 2014 than the rate in the United States. Significant health disparities were reported among American Indians, and low income Nebraska residents for both asthma and COPD. Asthma was also a significant health disparity among African Americans, (NDHHS, 2016). Moreover, results of a 2007 asthma report suggest that asthma was a more serious threat in Douglas and Sarpy Counties than in the rest of Nebraska, or the United States (DCHD, 2007). This report also indicates an evident health disparity among racial groups in Douglas County when comparing rates of self-reported asthma across the United States. In addition, results by geographic region within Douglas County suggest that the highest average asthma- related death rates occurred on the east side of 42nd Street, the highest rates of asthma related hospital discharges occurred in the east-northeast, east-southeast and west-northeast regions, and the highest number of asthma-related ED visits occurred in the east-northeast region (DCHD, 2007). A more recent report indicated higher overall mortality rates in Douglas County than the overall National rates for COPD from 2011 to 2013. COPD was reported as a relevant health disparity in Douglas County among African Americans

(PRC, 2015). These reports may indicate that socio-demographic or environmental factors (or both), may have contributed to the higher asthma- related morbidity and mortality observed in these regions.

Both asthma and COPD can affect health care use, quality of life, productivity, and even result in death (Brzezińska-Pawłowska, Rydzewska, Łuczyńska, Majkowska-Wojciechowska, Kowalski & Makowska, 2016; Guarascio, Ray, Finch, & Self, 2013; Nurmagambetov, Kuwahara, & Garbe, 2018; Sears, 2008; Teach *et al*., 2015). Moreover, these two chronic respiratory diseases represent significant costs in health care resources to the Unites States (Guarascio *et al.*, 2013; Nurmagambetov *et al*., 2018). Although both asthma and COPD are obstructive pulmonary diseases and share many similarities, these chronic diseases have different etiology, symptoms, type of airway inflammation, inflammatory cells, mediators, consequences of inflammation, response to therapy, onset age and course (Cukic, Lovre, Dragisic, & Ustamujic, 2012). For instance, while asthma usually starts at a young age, COPD onset starts in patients 40 years or older (Cukic, *et al*., 2012; Shavelle *et al*., 2009).

Asthma and COPD are both characterized by an underlying airway inflammation and episodic exacerbations (Brzezińska-Pawłowska *et al*., 2016; Guarascio *et al*., 2013; Fireman, 2003; Silverman, Stevenson, & Hastings, 2003). Various studies suggest that there is an association between the number of these exacerbations and a long-term decline in lung function (Bai, Vonk, Postma, & Boezen, 2007; Donaldson, Seemungal, Bhowmik, & Wedzicha 2002; as cited in Brzezińska-Pawłowska *et al*., 2016). Some of the exacerbation triggers include air pollution (e.g., particulate matter, ozone, sulfur dioxide, nitric oxide, and carbon monoxide), aeroallergens (e.g., mold and pollen), viral upper respiratory infections, and weather conditions such as cold air (Brzezińska-Pawłowska *et al*., 2016; Cirera *et al*., 2012; Fireman, 2003; Ho *et al*., 2007; Ko *et al*., 2007; Liao, Hsieh, & Chio, 2011; Samoli, Nastos, Paliatsos, Katsouyanni, & Priftis, 2011; Singh, Singh, Singh, Daya, & Singh, 2017; Teach *et al*., 2015; Wang & Chau, 2013; Williams, Sternthal, & Wright, 2009). Recurrent exacerbations may indicate significant comorbidities, severe disease, or poor compliance with disease management strategies (Sears, 2008; Takemura *et al*., 2011). Exacerbations can occur any time during the year, however seasonal patterns are well documented and are mainly influenced by viral respiratory infections or environmental factors (Brzezińska-Pawłowska *et al*., 2016; Goodman *et al.*, 2017; Jenkins, *et al.*, 2012; Sears, 2008; Teach *et al.*, 2015).

Although seasonality is observed for both asthma and COPD exacerbations, there are differences between these two chronic respiratory diseases in the factors affecting these exacerbations. According to epidemiological and clinical studies, the seasonal patterns of asthma exacerbations vary according to the patients' age. Children frequently experience asthma exacerbations after returning to school during the fall due to respiratory viral infections, and the possible synergistic interaction between allergen sensitization and respiratory viral infections. On the other hand, older adults frequently experience asthma and COPD exacerbations during the winter (Sears, 2008; Sears & Johnston, 2007; Johnston, 2007). Hence, a better understanding of risk factors for exacerbations is needed in order to implement effective prevention strategies to decrease morbidity and mortality associated with asthma and COPD (Sears, 2008; Williams *et al.*, 2009).

The aim of this study was to address the gaps in knowledge regarding the effects of age, seasonal infectious respiratory diseases, temperature, aeroallergens and outdoor air pollutants on the incidence of asthma and COPD- related ED visits in Douglas County, Nebraska. We hypothesize that there is an association between the number of asthma- and COPD- related weekly ED visits in Douglas County and seasonal viral respiratory (SVR)-related ED visits or environmental factors. We also hypothesize that these associations are affected by seasonal trends in the levels of these environmental factors and by age group. Currently there is no published information describing the impact of environmental factors in Nebraska on the burden of ED visits or hospitalizations related to these chronic respiratory diseases. Therefore, this information could help develop prevention strategies, as well as inform interventions.

Methods

Ethics Statement

Only existing de-identified EHR ED data was used for this study, and no personal identifier information (PII) was recorded during the study. Therefore, this study was exempt from institutional review board approval and did not require consent from patients, or from parents or guardians on behalf of children (UNMC, 2016).

Data sources

For this retrospective database study we used EHR ED data to study the association between the number of SVR- related ED visits, levels of outdoor air pollutants, aeroallergen counts, and temperature on the number of asthma- and COPD- related ED visits in Douglas County, Nebraska during the February 28, 2016 to December 29, 2018 period.

1. Hospital data

Outcome variable. Syndromic surveillance EHR data from ED visits at eight of nine hospitals located in Douglas County, NE was extracted from the Nebraska Department of Health and Human services Syndromic Surveillance System database for the period of February 28, 2016 to December 29, 2018. From these electronic health records we used the reported visit date, hospital identifier, chief complaint, clinical impression, list of International Classification of Diseases, 9th Revision (ICD-9) and 10th revisions (ICD-10) discharge diagnostic codes, as well as the patients' age, race and ethnicity to process and analyze the data. The reported visit date was used to create the ED visit *week* variable. Weeks were identified by using the Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report (MMWR) categories (CDC, n.d.). The reported patient age was used to create 2 age group stratifications: 1) all age groups (0-4 yrs., 5-14 yrs., 15-19 yrs., 20-24 yrs., 25-34 yrs., 35-64 yrs., and ≥65 yrs.); and 2) children vs. pre COPD onset age adults vs. COPD onset age and older adults (< 18 yrs., 18-39 yrs., 40 + yrs.). Patient's race and ethnicity were used to create the *race-ethnicity* variable with the categories *Black-Non Hispanic*, *White-Non Hispanic*, *Other-Non Hispanic*, and *Any Race-Hispanic*. Search terms in the reported chief complaint, clinical impression, and the list of ICD-9 and ICD-10 discharge diagnostic codes in these electronic health records were used to classify the ED visits as related to chronic respiratory (CR) diseases (asthma or COPD). Nebraska's version of the Electronic Surveillance System for the Early Notification of Community-based Epidemics (ESSENCE) software was used to identify CR-related ED visits (CDC, 2016). This classification definition was adapted from CDC's National Syndromic Surveillance Program (NSSP) ESSENCE Asthma Chief Complaint and Discharge Diagnosis Category (CDC, 2019) and used to determine the weekly number of ED visits related to CR by MMWR week (Table 1).

Explanatory variable. ED visits by MMWR week related to SVR diseases (influenza, adenovirus or respiratory syncytial virus) were identified from syndromic surveillance EHR data by using ESSENCE. Similar to the CR syndromic surveillance definition, the SVR definition contained search terms used to query the reported chief complaint and clinical impression, and ICD-9 and ICD-10 codes to search the discharge diagnostic code list of each electronic health record (Table 1). This definition was adapted from CDC's NSSP ESSENCE Influenza Like Illness v1 Chief Complaint and Discharge Diagnosis Category (CDC, 2019).

2. Environmental data

Explanatory variables. Aeroallergen, outdoor air pollution and temperature data were obtained for the MMWR week 9-2016 to 52-2018 period. Pollen and mold spore daily counts were obtained from the American Academy of Allergy Asthma & Immunology (AAAAI) National Allergy Bureau (NAB) certified reporting station in Bellevue, NE (American Academy of Allergy, Asthma & Immunology [AAAAI], 2019). Missing values were imputed by assigning to the days with missing counts the counts of the previous days, for up to 3 days. Count values from subsequent days were assigned when more than 3 days of data were missing (Gleason, Bielory & Fagliano, 2014; Goodman *et al.*, 2017). Variables were created for mean counts by MMWR week for grass pollen, tree pollen, ragweed pollen, weed pollen and mold spores by calculating the weekly average for each pollen and mold spore type. Outdoor air quality and temperature data was obtained from the Environmental Protection Agency (EPA) Air Quality System API (Environmental Protection Agency [EPA], 2015). The dataset consisted of Air Quality Index (AQI), hourly data for fine particulate matter ($PM_{2.5}$), carbon monoxide (CO), ozone (O_3) and sulfate dioxide (SO_2), and daily maximum and minimum temperature from 8 monitoring station sites in Douglas County, NE during the MMWR week 9-2016 to 52-2018 period. Temperature units were converted from Celsius to Fahrenheit (°F). Mean values by MMWR week were calculated from these outdoor air pollutant values to create the analysis variables (Goodman *et al.*, 2017).

Statistical Methods

Descriptive analyses. Descriptive analyses including mean, median, standard deviation, minimum and maximum were performed for number of CR- related ED visits by MMWR week, SVR- related ED visits by MMWR week, mean weekly pollen and mold spore daily counts, mean weekly daily temperature and mean hourly outdoor air pollutant levels. Tree pollen weekly mean count values were transformed by dividing by 10 and mold spore values by dividing by 1,000. In addition, the percent of all ED visits related to CR or SVR was calculated, and the CR- related ED visits stratified by patient's sex, age and race/ethnicity groups. Histograms and normal probability plots were used to assess if outdoor air pollutant and temperature values were normally distributed. Scatterplots of the number of CR- related ED visits by MMWR week vs. mean daily minimum temperature and mean daily maximum temperature were used to explore the relationship between the outcome variable and temperature. Charts of values by MMWR week were plotted for outcome and explanatory variables to determine if there were trend differences by season.

Generalized linear models. Generalized linear models (GLMs) were used to determine the association between the number of CR- related weekly ED visits and the environmental factors of interest (Chan *et* *al*., 2015; Rappold *et al.*, 2011; Yang *et al.*, 2011). The outcome variable analyzed was the number of CR-related ED visit counts by MMWR week. The explanatory variables were the number of SVR- related ED visits by MMWR week, and the means by MMWR week for pollen (i.e., grass, tree, weed pollen), mold spore daily counts, maximum daily temperature, minimum daily temperature, and hourly outdoor air pollutant levels (i.e., $PM_{2.5}$, CO, O_3 and SO_2) in Douglas County, NE. Univariate Poisson and Negative Binomial regression models with log link were used to select significant variables to be included in the multivariable model. The log of the total weekly ED visits was used as an offset to adjust for weekly fluctuation in ED volume. We used the Scale Deviance and Pearson Chi-Square criteria for assessing goodness of fit to evaluate whether either Poisson or Negative Binomial regression models were suitable for the analysis. The model was adjusted for seasonality to account for differences by season. Possible interaction with season was determined for each environmental variable, and the final multivariable model stratified by season if interaction was observed. Patterns of temporal variation were compared by fitting separate GLM models for winter, spring, summer and fall (Mathes, Ito, & Matte, 2011; Teach *et al*., 2015). The final multivariable models were fitted by backward elimination of variables that are least significantly associated with the outcome. In order to stay in the model variables should have a p-value <0.05. Stratification of the model was used to account for the possible confounding effect of patient age. Separate models were fit by age group including: < 18 yrs., 18-39 yrs., and ≥40 yrs. Each pollen and mold variable was only included in the model for the season where the particular aeroallergen was present for most of the season weeks (Brzezińska-Pawłowska *et al*., 2016). An alpha level of 0.05 was used to determine statistical significance. All analyses were done by using SAS software version 9.4 of the SAS system for Windows, Copyright (c) 2002-2012 by SAS Institute Inc.

Results

Descriptive analyses. A description of the ED visits during MMWR weeks 9-2016 to 52-2018 (February 28, 2016 to December 29, 2018), including percent of all ED visits that were CR- related, percent of all ED visits that were SVR- related, and the stratification of CR- related ED visits by patient demographics is provided in Table 2. The proportion of all ED visits related to CR diseases was 3%, and the proportion related to SVR diseases was 4%. The highest proportion of CR- related ED visits was observed among females, and those in the ≥40 yrs. and 35-64 yrs. age groups. Results of the descriptive analyses for the outcome variable, CR- related ED visits, are shown in Fig. 1. A seasonality pattern was observed when comparing the yearly trends of CR- related ED visits by MMWR weeks, with a spike in the number of weekly visits during late summer and early fall (MMWR weeks 33-45), and during early winter (MMWR weeks 51-53). Seasonality was also observed for the yearly trends of the number of SVR- related ED visits (Fig.2). In this case a smaller spike was observed during late summer (MMWR weeks 33-45), and a larger one during the winter (MMWR weeks 51-11).

Descriptive analysis results for aeroallergens, outdoor air pollutants and temperature are summarized in Table 3 and Figs. 3-5. Tree pollen and mold spore weekly mean counts were approximately 10 and 1,000 times higher respectively than the values for grass, weed and ragweed (Table 3 and Figs. 3-4). Therefore, tree pollen weekly mean counts values were transformed by dividing by 10 and mold spore values by dividing by 1,000. Time series showing the seasonal patterns of pollen and mold spore values are shown in Figs. 3-4. While tree and grass pollen count spikes were observed during the spring, weed pollen count spikes were observed during late summer and early fall. Mold spores count spikes were observed from late spring through early fall. The yearly trend of mean outdoor air pollutant levels by MMWR week is shown in Fig. 5. Seasonality patterns were observed for carbon monoxide and ozone, with the lowest levels of carbon monoxide during the summer and the lowest for ozone during the fall. Table 3 shows the descriptive analysis results for the outdoor air pollutant hourly values. The descriptive analysis results for the weekly mean values are shown in Fig. 5. The similarity between the mean and median values for each outdoor air pollutant and temperature value indicate these values follow symmetric distribution. Both the histograms and the normal probability plots indicate the outdoor air pollutant and temperature values are normally distributed (data not shown). A scatter plot of the mean temperature values by MMWR week vs. the number of CR- related weekly ED visits indicates a negative correlation between temperature and the outcome (Fig. 6).

Generalized linear models. Results of the Scale Deviance and Pearson Chi-Square criteria for assessing goodness of fit indicate over-dispersion for most of the univariate models. Table 4 indicates the parameter estimates obtained from these univariate models. Most of the significant variables were selected to be included in the multivariable models. However, the parameter estimates for ragweed pollen and maximum temperature were not included in the multivariable models due to collinearity with weed pollen and minimum temperature, respectively. Results of the Scale Deviance and Pearson Chi-Square criteria for assessing goodness of fit indicate over-dispersion for the multivariable models. Hence, the negative binomial regression model was more appropriate in this case.

Next, the models were then stratified by season since significant interactions were observed between season and most of the explanatory variables. Models were also stratified by age group. The final multivariable models fitted by backward elimination are shown below.

Models stratified by season:

(1) Spring

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 PM2.5_t + \beta_2\ MinT_t + \beta_3\ Mold\_trnsf_t$$

(2) Summer

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 SVR_t$$

(3) Fall

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 SVR_t + \beta_2 CO_t$$

(4) Winter

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 SVR_t$$

Models stratified by season and age group:

(1) Spring, < 18 yrs.

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1\ MinT_t + \beta_2\ Mold\_trnsf_t$$

(2) Summer, < 18 yrs.

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 SVR_t + \beta_2\ WPollen_t$$

(3) Fall, < 18 yrs.

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 PM2.5_t + \beta_2\ MinT_t + \beta_3\ Mold\_trnsf_t$$

(4) Spring, 18 to 39 yrs.

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 PM2.5_t + \beta_2\ MinT_t + \beta_3\ Mold\_trnsf_t$$

(5) Summer, 18 to 39 yrs.

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 SVR_t$$

(6) Fall, 18 to 39 yrs.

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 CO_t + \beta_2\ MinT_t + \beta_3\ Mold\_trnsf_t$$

(7) Winter, 18 to 39 yrs.

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 SVR_t$$

(8) Spring, ≥40 yrs.

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 PM2.5_t + \beta_2\ MinT_t + \beta_3\ Mold\_trnsf_t$$

(9) Summer, ≥40 yrs.

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1\ Mold\_trnsf_t$$

(10) Fall, ≥40 yrs.

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 SVR_t + \beta_2 PM2.5_t$$

(11) Winter, ≥40 yrs.

$$Log\ (E\ (y_t)) = \alpha_t + \beta_1 SVR_t$$

Where,

y = Number of chronic respiratory- related ED visits at week t

SVR = Number of seasonal viral respiratory- related ED visits at week t

CO = Mean CO (ppb/hour) at week t

PM2.5 = Mean PM2.5 (µg/m^3 per hour) at week t

MinT = Mean minimum temperature (°F) at week t

WPollen = Mean daily weed pollen counts (per m^3 of air/ day) at week t

Mold_trnsf = Mean daily mold spore counts (per m^3 of air/ day) / 1000 at week t

Results of these Negative Binomial models indicate differences in significant associations between the outcome and explanatory variables by season (Table 5). Mold, $PM_{2.5}$ and minimum temperature were significantly associated with an increase in CR- related ED visits during the spring. The risk of a CR- related ED visit increased by 0.6% for every 1000 unit increase in mold, and by 2% for every 1 unit increase in $PM_{2.5}$. For every 1 degree °F increase in minimum temperature, the risk of a CR- related ED visit decreased by 1%. On the other hand SVR- related ED visits were significantly associated with the increase of CR- related ED visits in summer, fall and winter. For every 1 unit increase in SVR- related ED visits, the risk of a CR- related ED visit increased by 0.5%, 0.1% and 0.07% during the summer, fall and winter respectively. Differences in significant associations between the outcome variable and explanatory variables were also observed after stratifying the model by season and age group (Tables 6 and 7). Age-adjusted relative risk (RR) values are shown in Table 7. The stratification by season and age group indicate significant associations between mold spores, and the increase of CR- related ED visits for all age groups during spring with RR ranging from 1.0002 to 1.0148. Significant associations were observed between $PM_{2.5}$ levels and the increase of CR- related ED visits for the 18 to 39 yrs. and the ≥ 40 yrs. age groups during spring with RR ranging from 1.0074 to 1.0617. On the other hand, minimum temperature was significantly associated with the decrease of CR- related ED visits among the < 18 yrs. and the 18 to 39 yrs. age groups during spring with RR ranging from 0.9716 to 0.9963. During the summer, significant associations were observed between SVR- related ED visits and the increase of CR- related ED visits among those in the < 18 yrs. and the 18 to 39 yrs. age groups with RR ranging from 1.0011 to 1.0340. Weed pollen and mold spores were significantly associated with the increase of CR-related ED visits during summer among the < 18 yrs. (RR = 1.0025, 95% CI: 1.0016-1.0034, p-value < 0.0001), and ≥ 40 yrs. age groups (RR = 1.0030, 95% CI: 1.0002-1.0058, p-value = 0.0345) respectively. During the fall, SVR- related ED visits were significantly associated with the increase of CR- related ED visits among those in the ≥ 40 yrs. age group with RR ranging from 1.0011 to 1.0135. Significant associations between mold spores and a decrease of CR- related ED visits were observed among the < 18 yrs. and the 18 to 39 yrs. age groups during fall with RR ranging from 0.9913 to 0.9994. Carbon monoxide was also significantly associated with a decrease of CR- related ED visits during the fall for the 18 to 39 yrs. age group with RR ranging from 0.0599-0.4517. Significant associations were observed between $PM_{2.5}$ and the increase of CR- related ED visits during the fall among those in the < 18 yrs. age group with RR ranging from 1.0090 to 1.0551. However, $PM_{2.5}$ was associated with the decrease of CR- related ED visits among those in the ≥ 40 yrs. age group with RR ranging from 0.9630 to 0.9927. During the winter, SVR- related ED visits were significantly associated with the increase of CR- related ED visits among those in the 18 to 39 yrs. and ≥ 40 yrs. age groups with RR ranging from 1.0012 to 1.0054.

Discussion

Spikes in the number of SVR- related ED visits observed during late summer (MMWR weeks 33-45) and during the winter (MMWR weeks 51-11) correspond to the cycles of COPD and asthma exacerbations previously described by Sears and Johnston (Sears, 2008; Sears & Johnston, 2007; Johnston, 2007). According to Johnston, most of asthma and COPD exacerbations in children and adults are associated with seasonal viral respiratory diseases. Therefore, these cycles are affected by variations in the timing of appearance of each type of respiratory virus (e.g., influenza and respiratory syncytial virus [RSV]). For instance, the observed spike in asthma exacerbation- related ED visits during late summer and early fall was mostly associated with rhinovirus infection in children at the beginning of the school year (Johnston, 2007). In older adults a spike in both asthma- and COPD- related ED visits is observed during winter. However, this cycle seems to be independent from the timing of seasonal respiratory viruses and the factors associated to the spike in asthma- and COPD- related ED visits and could be associated with cooler temperatures (Jenkins *et al*., 2012; Johnston, 2007). The negative correlation observed between temperature and the outcome in the scatter plot of the mean temperature values by MMWR week vs. the number of CR- related weekly ED visits (Fig. 6) is consistent with other studies that indicate that lower temperatures have a negative impact on asthma and COPD exacerbations (Brzezińska-Pawłowska *et al*., 2016; Jenkins *et al*., 2012; Johnston, 2007; Sears, 2008; Sears & Johnston, 2007).

Negative binomial model results indicate significant associations between the weekly number of SVR- related ED visits and the increase in weekly CR- related ED visits among those in the < 18 yrs. and 18 to 39 yrs. age groups in the summer, those in the ≥ 40 yrs. age group in the fall, and those in the 18 to 39 yrs. and ≥ 40 yrs. age groups in the winter. Results also indicate that minimum temperature is significantly associated with the increase in weekly CR- related ED visits among those in the < 18 yrs. and 18 to 39 yrs. age groups in the fall, but not among those in the ≥ 40 yrs. age group. Significant associations between $PM_{2.5}$ levels and an increase in weekly CR- related ED visits were observed among those in the 18 to 39 yrs. and the ≥ 40 yrs. age groups in the spring, and those in the < 18 yrs. age group in the fall. The association between $PM_{2.5}$ and the outcome during spring and fall may be due to a possible interaction between particulate matter and temperature, where lower temperatures help to keep $PM_{2.5}$

longer in the air (Hsu, Hwang, Kinney, & Lin, 2017). Further analysis may be needed to determine possible factors related to $PM_{2.5}$ or mold spores and the negative association with weekly CR- related ED visits during the fall. The significant association between CO and the decrease of CR- related ED visits during the fall for the 18 to 39 yrs. age group could be the effect of the potential anti-inflammatory effect of lower concentrations of carbon monoxide in ambient air (Tian *et al.*, 2014). Although some epidemiological studies have reported positive associations between ambient CO and asthma- and COPD- related ED visits and hospitalizations, other studies indicate a decrease in hospital admissions associated to the exposure to ambient CO (Castner, Guo & Yin, 2018; Tian *et al.*, 2014; Yang, *et al.*, 2005). Recent clinical and experimental studies indicate that possible anti-inflammatory effects of CO, including the decreased risk of respiratory tract infections, could be beneficial on COPD exacerbations (Motterlini & Otterbein, 2010; Tian *et al.*, 2013; Tian *et al.*, 2014). However, spatial variability is an important factor when assessing the effect of CO exposure since the ambient concentration of this pollutant can rapidly decrease with distance (US EPA, 2010). Additional analyses may help to address the possible spatial variability of ambient CO (e.g., combustion, traffic) and its correlation of with other combustion related pollutants (US EPA, 2010). The differences observed between age groups could be due to effect modification by age (Alhanti *et al.*, 2016). Several studies indicate a relationship between the seasonal patterns of CR exacerbations and the patients' age (Alhanti *et al*., 2016; Johnston, 2007; Sears, 2008; Sears & Johnston, 2007; Silverman, 2003). Children are more susceptible to asthma exacerbations than adults due to the underdevelopment of their immune and pulmonary system, and because of higher levels of exposure to ambient air pollutants (Bateson & Schwartz, 2008; Salvi, 2007). Conversely, COPD onset age is 40 years or older and it is most common among smokers (Cukic, *et al*., 2012; Shavelle *et al*., 2009). Overall, similar to previous reports, results of this study suggest that the seasonal pattern of asthma and COPD exacerbations may be influenced not only by SVR disease cycles, temperature and other environmental factors, but also by age (Brzezińska-Pawłowska *et al*., 2016; Jenkins *et al*., 2012; Johnston, 2007).

Some of the limitations associated to this study include the possible effect modification of socio-demographic factors which was not determined. Therefore, additional analyses are needed to determine the possible effect modification by sex, race/ethnicity, and socioeconomic status on the association between environmental factors and CR- related ED visits. In addition, the presence of only one National Allergy Bureau certified pollen monitoring station may not be sufficient to accurately determine the effect of aeroallergens on CR- related ED visits in Douglas County, Nebraska. Another limitation of the study was having both asthma and COPD combined within the CR syndromic ESSENCE definition. In this study we included the ≥ 40 yrs. age group as an indicator of possible COPD- related visits. Separate asthma and COPD syndromic ESSENCE definitions will be needed for a more accurate assessment of the effects of environmental factors on ED visits related to each of these chronic respiratory diseases. Moreover, the time component was too complex to adjust beyond adding the total weekly ED visits as offset. However, the offset only provides a baseline rate. A possible approach could be to analyze correlated data over time with a random effect for emergency department. Another option could be the use of generalized additive regression models with a cubic spline function of time to adjust for temporal trends (Goodman *et al.*, 2014).

Conclusions

Overall, results of this study indicate that asthma and COPD exacerbation-related ED visits from these eight hospitals may be influenced by seasonal respiratory viruses, weed pollen, mold spores, and cool temperatures. Results also indicate interaction with season and a possible cofounding effect of patient age. Therefore, the association between environmental factors and CR- related ED visits in Douglas County, Nebraska could be affected by both the seasonal variation in the levels of these factors and differences in exposure by age group. Additional analyses are needed to further explore these associations.

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Figures and Tables

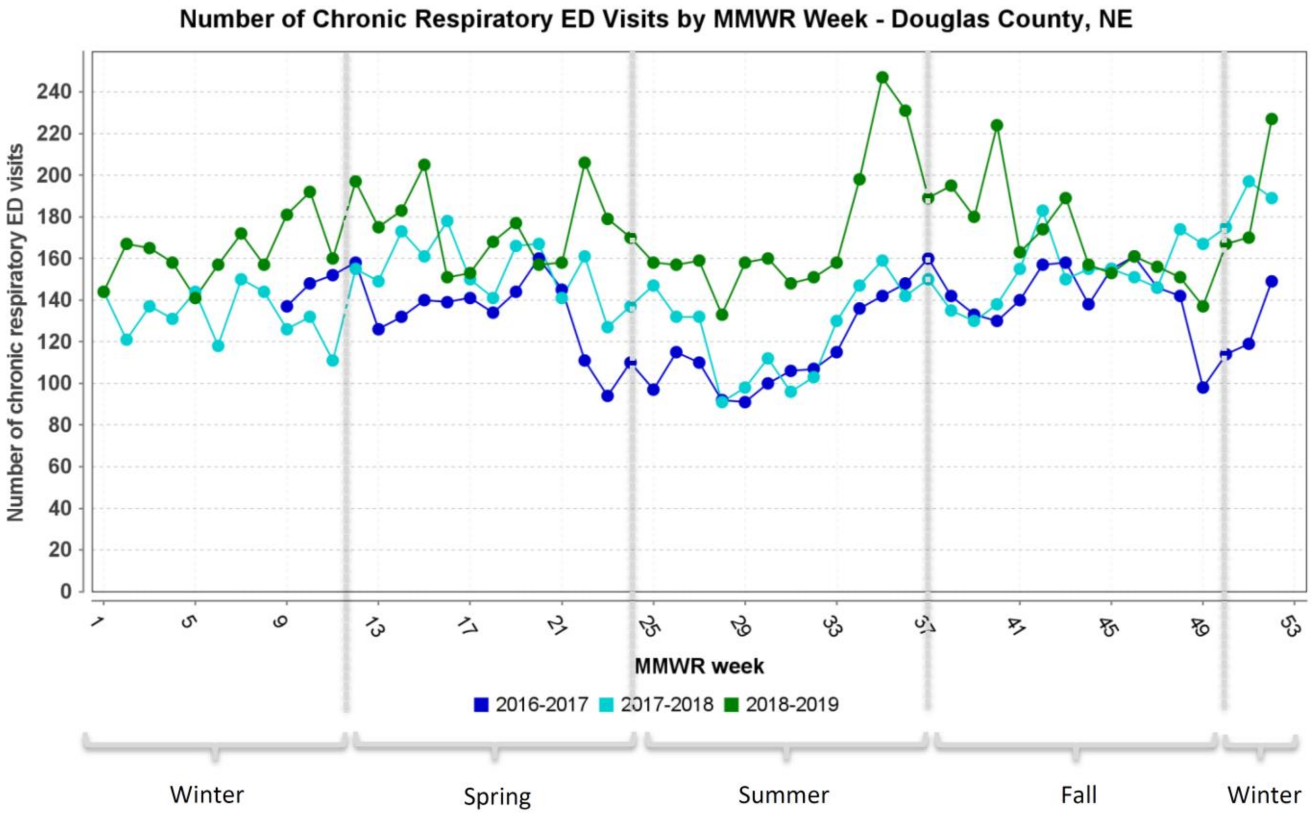
Table 1. Description of syndromic surveillance definitions

	Inclusion terms		Exclusion terms	
Definition	**Search Terms**	**Discharge Diagnosis Codes**	**Search Terms**	**Discharge Diagnosis Codes**
CR	asthma, bronchospasm, COPD, reactive airway disease	ICD9-CM: 493, 491, 492, 496 ICD10-CM: J44.0, J44.1, J44.9, J45	not asthma, not COPD	
SVR	fever and (cough or sore throat); RSV, adenovirus, influenza	Influenza ICD9-CM: 487.0, 487.1, 487.8, 488.01, 488.11, 488.81, 488.09, 488.19, 488.89 ICD10-CM: J09, J10, J11	denies fever, denies cough, denies sore throat, stomach flu, flu/influenza shot, flu/influenza vaccine	ICD10-CM: A08.4
		Adenovirus ICD9-CM: 079.0, 480.0 ICD10-CM: J12.0, B34.0, B97.0		ICD9-CM: 077.3 ICD10-CM: B30.1
		Respiratory syncytial virus (RSV) ICD9-CM: 079.6 ICD10-CM: J12.1, J20.5, J21.0, B97.4		

Table 2. Number of CR and SVR- related ED visits in Douglas County, NE during MMWR weeks 9-2016 to 52-2018

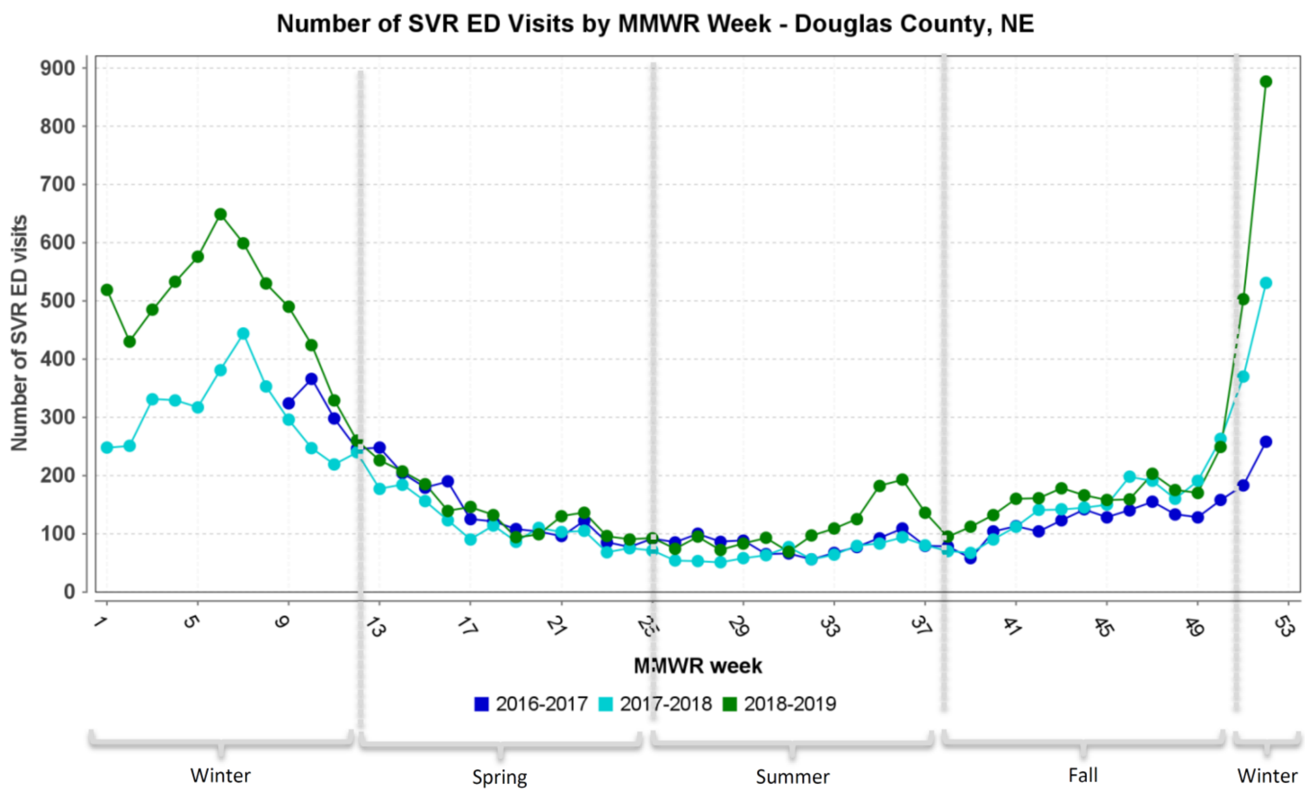
Characteristic	Total number of visits	% *
All ED visits	703859	
CR-related ED visits	24485	3*
Sex		
Female	14313	58
Male	10171	42
Age Groups		
Age <18 years	5269	21
Age 18-39 years	5090	21
Age ≥40 years	14127	58
All Age Groups		
Age 0-4 years	1902	8%
Age 5-14 years	2827	12%
Age 15-19 years	946	4%
Age 20-24 years	1255	5%
Age 25-34 years	2537	10%
Age 35-64 years	7858	32%
Age ≥65 years	7160	29%
Race		
Black-Non Hispanic	3348	15
White-Non Hispanic	15988	72
Other-Non Hispanic	1211	5
Any Race-Hispanic	1379	6
SVR- related ED visits	28384	4*

* The number of all ED visits was used as denominator to calculate the percent of chronic respiratory- related, as well as the seasonal viral respiratory- related ED visits. All other percentages where calculated by using the total number of chronic respiratory- related ED visits as denominator.



Chronic respiratory (CR)- related ED visits descriptive statistics						
	N	Mean	Std. Dev.	Minimum	Maximum	Median
CR- related ED visits by MMWR week - All	148	165	38	94	258	159
CR- related ED visits by MMWR week - Winter	31	178	44	115	258	161
CR- related ED visits by MMWR week - Spring	39	172	38	94	254	160
CR- related ED visits by MMWR week - Summer	39	150	37	95	248	148
CR- related ED visits by MMWR week - Fall	39	165	28	103	226	161

Figure 1. Outcome variable: Number of CR- related ED visits by MMWR week. Seasons indicated by the following MMWR week periods: Winter = wks. 51-11, Spring = wks. 12-24, Summer = wks. 25-37 and Fall = wks. 38-50; N = total number of weeks



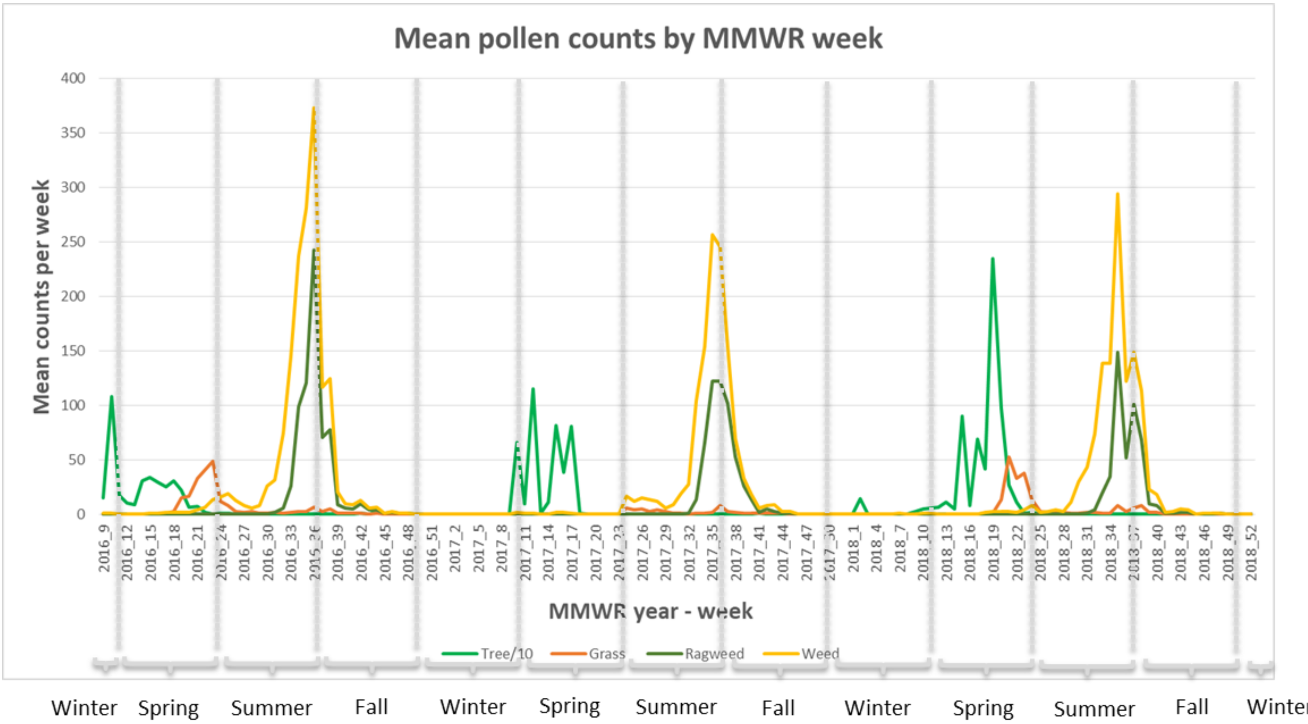
Seasonal viral respiratory (SVR)- related ED visits descriptive statistics						
	N	Mean	Std. Dev.	Minimum	Maximum	Median
SVR- related ED visits by MMWR week - All	148	192	155	52	874	136
SVR- related ED visits by MMWR week - Winter	31	437	169	183	874	384
SVR- related ED visits by MMWR week - Spring	39	145	58	74	300	124
SVR- related ED visits by MMWR week - Summer	39	88	31	52	193	84
SVR- related ED visits by MMWR week - Fall	39	148	47	58	292	146

Figure 2. Explanatory variable descriptive analysis: Number of SVR- related ED visits by MMWR week. Seasons indicated by the following MMWR week periods: Winter = wks. 51-11, Spring = wks. 12-24, Summer = wks. 25-37 and Fall = wks. 38-50; N = total number of weeks

Table 3. Descriptive statistics of aeroallergens, outdoor air pollutants and temperature variables in Douglas County, NE during MMWR weeks 9-2016 to 52-2018

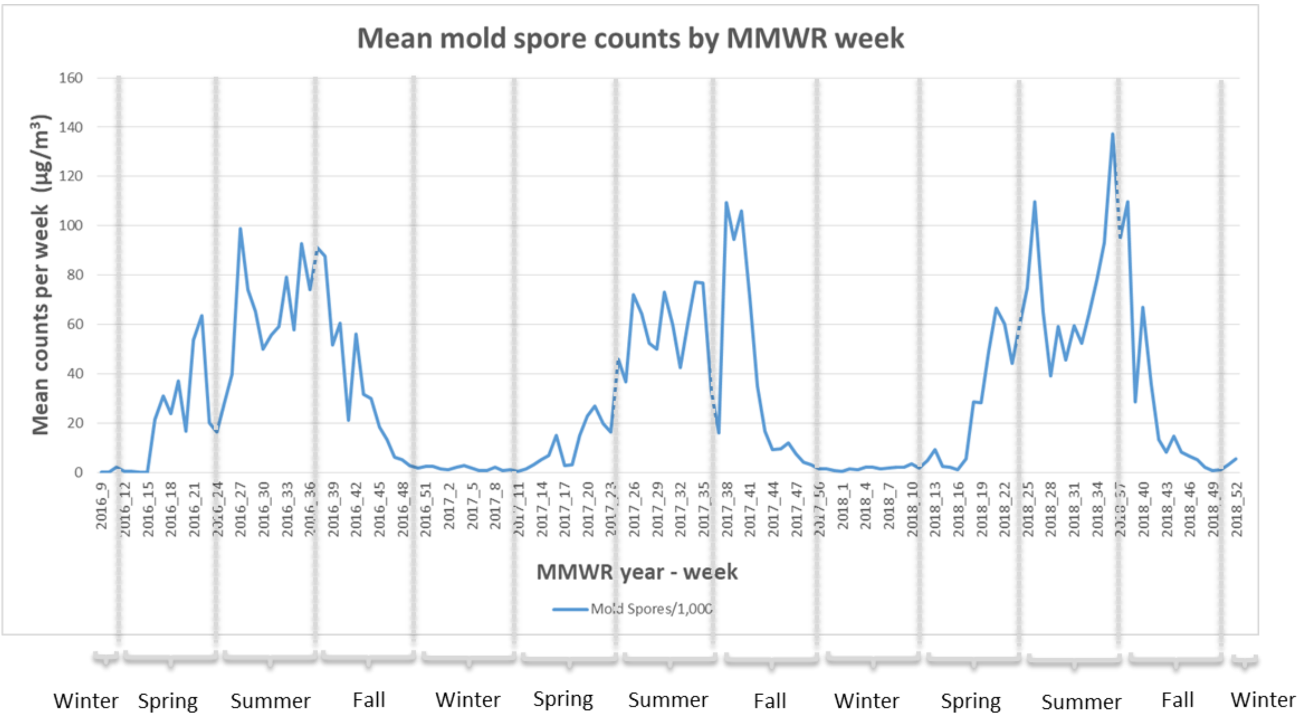
Characteristic	N	Mean	S.D.	Min.	Max.	Median
Aeroallergens (counts per m^3 of air/ day)						
Pollen Combined	1038	126	402	0	6337	11
Grass	1038	3	10	0	161	0
Trees	1038	95	401	0	6334	0
Weed	1038	27	73	0	682	1
Ragweed	1038	11	41	0	519	0
Mold	1038	31056	38485	0	257154	13870
Outdoor Air Pollutants						
CO (ppm/ hour)	48829	0.29	0.20	-0.20	2.10	0.20
O_3 (ppm/ hour)	56453	0.03	0.01	0.00	0.08	0.03
$PM_{2.5}$ (µg/m^3 per hour)	23322	8.58	6.91	-8.00	384.00	8.00
SO_2 (ppb/ hour)	64121	0.67	2.89	-1.90	105.00	0.10
Temperature						
Maximum Temperature (°F, 24 hours)	804	66.12	21.73	5.36	118.94	68.90
Minimum Temperature (°F, 24 hours)	804	44.83	19.95	-9.22	82.22	45.86

N = Total number of weeks
S.D. = Standard deviation
µg/m^3 = Micrograms/cubic meter
ppb = Parts per billion
ppm = Parts per million



Weekly mean pollen counts descriptive statistics						
	N	Mean	Std. Dev.	Minimum	Maximum	Median
Tree (counts per m^3 of air/ day) / 10	148	10	28	0	235	0
Grass (counts per m^3 of air/ day)	148	3	9	0	53	0
Ragweed (counts per m^3 of air/ day)	148	11	34	0	243	0
Weed (counts per m^3 of air/ day)	148	27	64	0	373	2

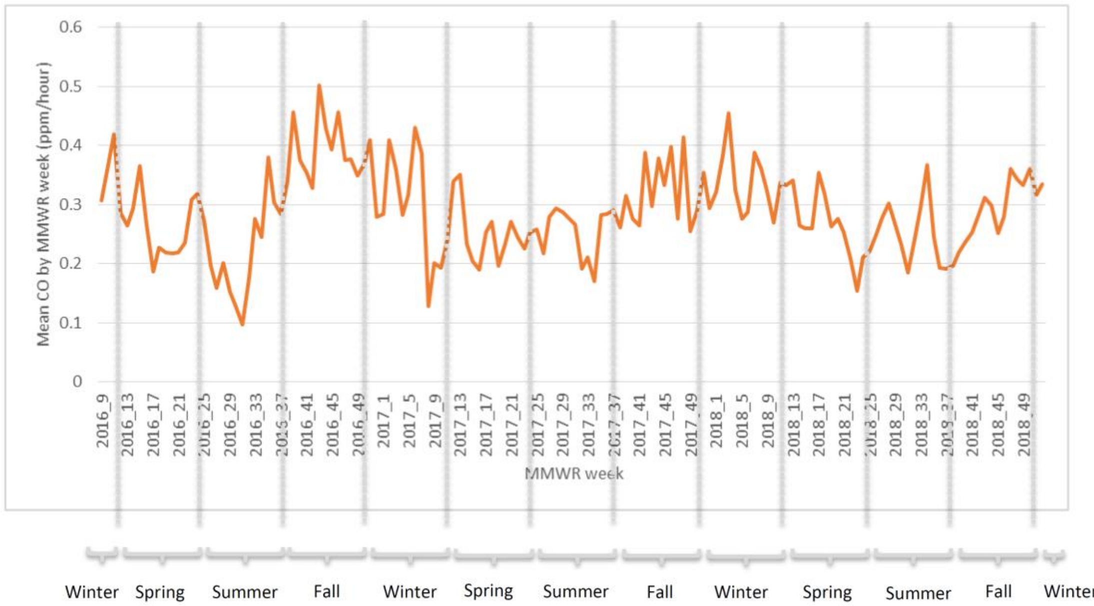
Figure 3. Explanatory variable descriptive analysis: Mean pollen counts by MMWR week. Seasons indicated by the following MMWR week periods: Winter = wks. 51-11, Spring = wks. 12-24, Summer = wks. 25-37 and Fall = wks. 38-50; N = total number of weeks



Weekly mean mold spore counts descriptive statistics						
	N	**Mean**	**Std. Dev.**	**Minimum**	**Maximum**	**Median**
Mold (counts per m^3 of air/ day) /1,000	148	31	33	0	137	17

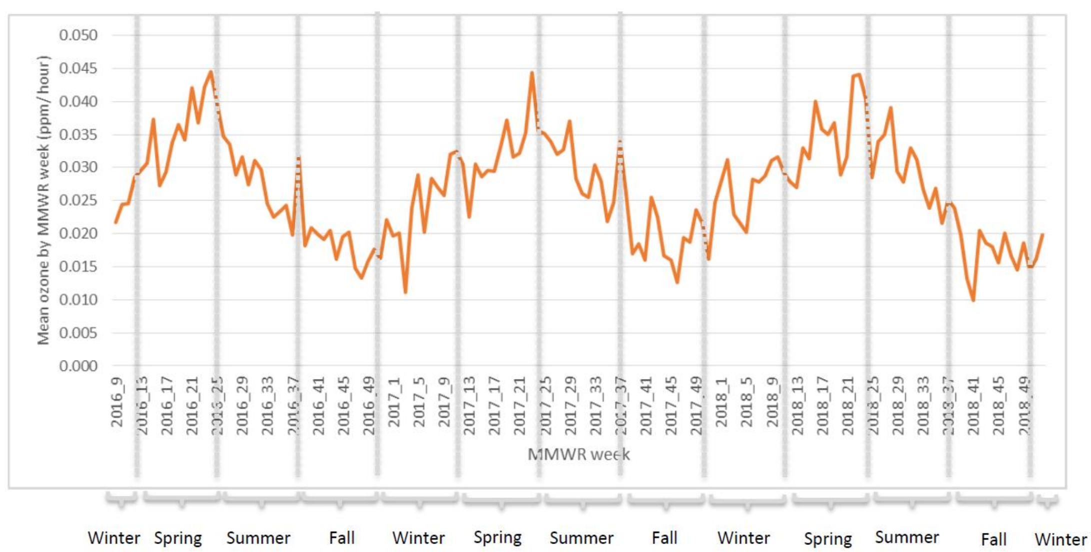
Figure 4. Explanatory variable descriptive analysis: Mean mold spore counts by MMWR week. Seasons indicated by the following MMWR week periods: Winter = wks. 51-11, Spring = wks. 12-24, Summer = wks. 25-37 and Fall = wks. 38-50; N = total number of weeks

a)



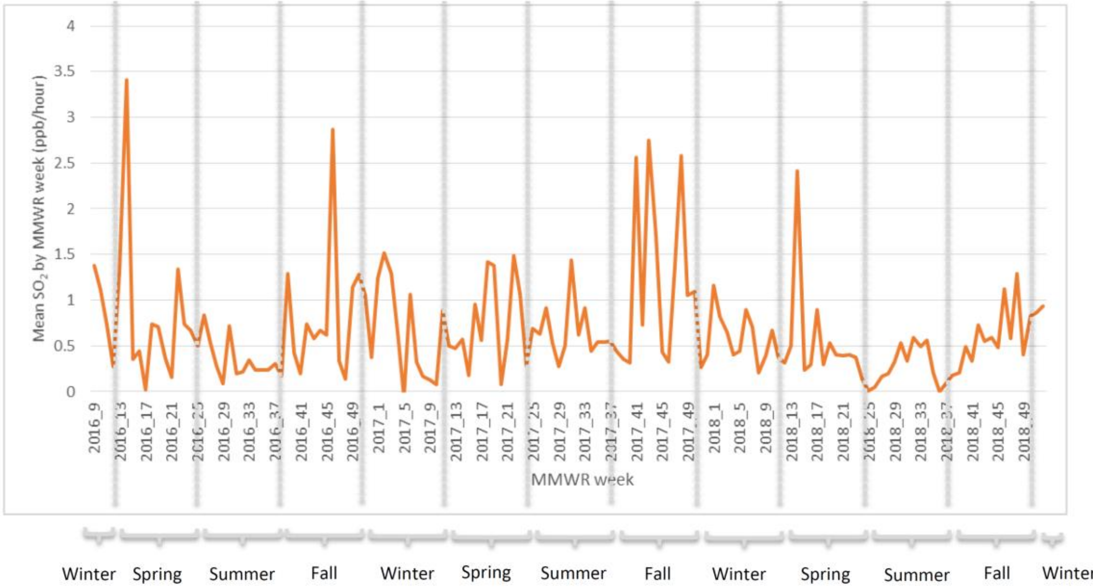
Carbon Monoxide (CO) Descriptive Statistics						
	N	Mean	Std. Dev.	Minimum	Maximum	Median
CO (ppm/hour) weekly mean	148	0.288	0.074	0.097	0.501	0.281

b)



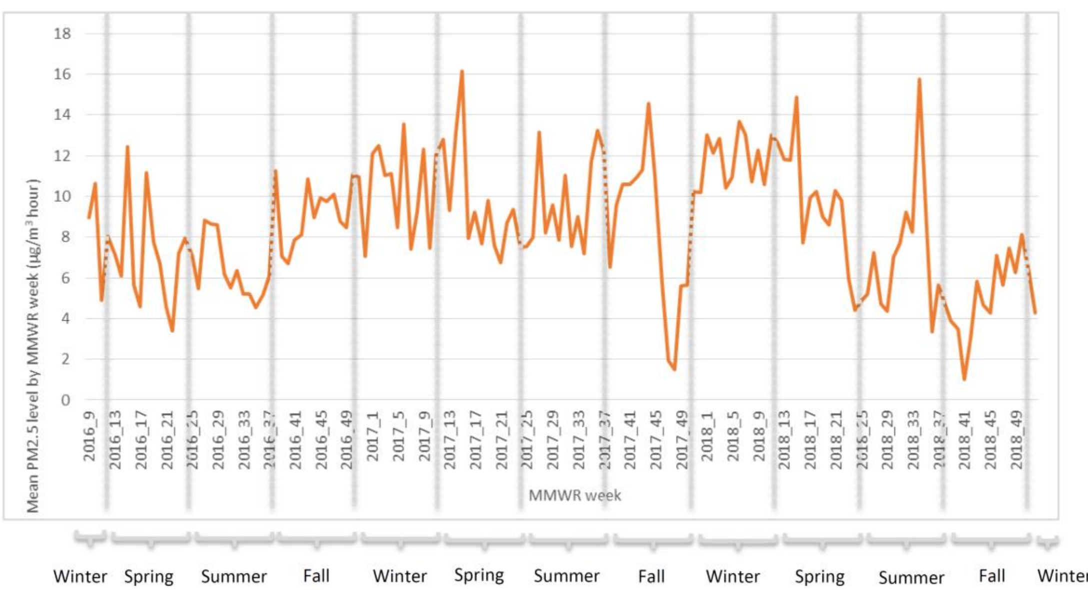
Ozone (O_3) Descriptive Statistics						
	N	Mean	Std. Dev.	Minimum	Maximum	Median
O_3 (ppm/hour) weekly mean	148	0.027	0.008	0.01	0.044	0.027

c)



Sulfate Dioxide (SO_2) Descriptive Statistics						
	N	**Mean**	**Std. Dev.**	**Minimum**	**Maximum**	**Median**
SO_2 (ppb/hour) weekly mean	148	0.67	0.579	-0.064	3.412	0.53

d)



PM $_{2.5}$ Descriptive Statistics						
	N	**Mean**	**Std. Dev.**	**Minimum**	**Maximum**	**Median**
PM $_{2.5}$ (μg/m^3 per hour) weekly mean	148	0.67	0.579	-0.064	3.412	0.53

Figure 5. Explanatory variable descriptive analysis: Mean outdoor air pollutant levels by MMWR week. a) Carbon monoxide, b) ozone, c) sulfate dioxide, d) PM $_{2.5}$. Seasons indicated by the following MMWR week periods: Winter = wks. 51-11, Spring = wks. 12-24, Summer = wks. 25-37 and Fall = wks. 38-50; N = total number of weeks

a) b)

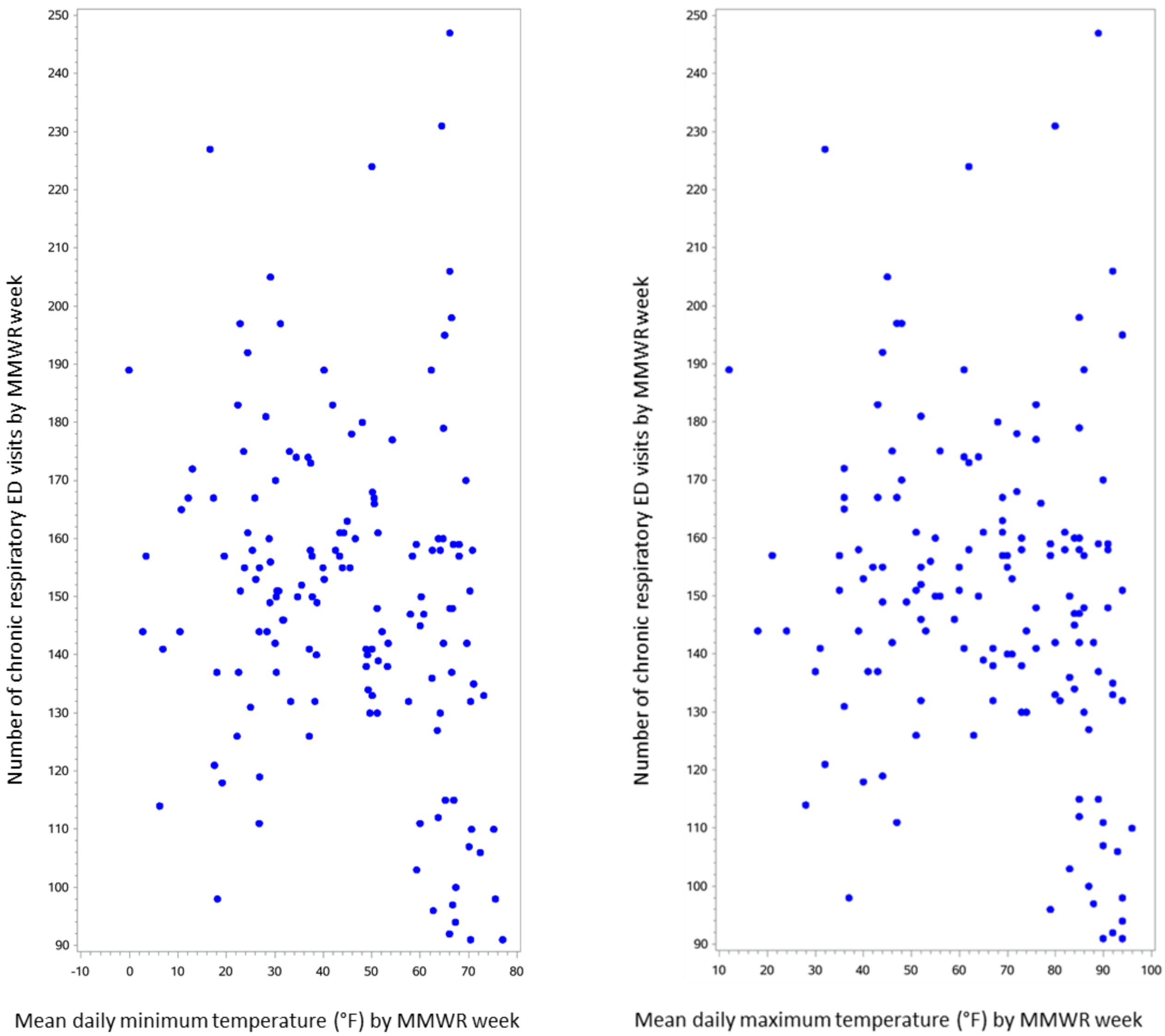


Figure 6. Explanatory variable descriptive analysis: Scatter plot of mean temperature values by MMWR week. a) Mean daily minimum temperature (°F), b) Mean daily maximum temperature (°F).

Table 4. Univariate parameter estimates adjusted by season for CR- related ED visits in Douglas County, NE during MMWR weeks 9-2016 to 52-2018

	Log-link Negative Binomial		
Variable	**β**	**95% C.I.**	**p-value**
Spring			
SVR- related ED visits (per MMWR week)	0.0007	(-0.0001, 0.0016)	0.0893
Aeroallergens			
Grass pollen (counts per m^3 air/ day)	-0.0024	(-0.0057, 0.0009)	0.1595
Tree pollen (counts per m^3 air/ day), 10 unit increase	0.0008	(-0.0002, 0.0019)	0.1324
Mold spores (counts per m^3 air/ day), 1000 unit increase	-0.0001	(-0.0026, 0.0024)	0.9093
Outdoor Air Pollutants			
CO (ppm/hour)	-0.4410	(-1.4232, 0.5412)	0.3789
Ozone (ppm/hour)	-6.1072	(-15.3001, 3.0857)	0.1929
$PM_{2.5}$ (µg/m^3 per hour)	0.0238	(0.0076, 0.0399)	0.0039
SO_2 (ppb/ hour)	-0.0606	(-0.1363, 0.0150)	0.1162
Temperature			
Minimum Temperature (°F, 24 hours)	-0.0046	(-0.0084, -0.0009)	0.0155
Summer			
SVR- related ED visits (per MMWR week)	0.0045	(0.0030, 0.0059)	< 0.0001
Aeroallergens			
Weed pollen (counts per m^3 air/ day)	0.0008	(0.0002, 0.0014)	0.0083
Mold spores (counts per m^3 air/ day), 1000 unit increase	0.0038	(0.0014, 0.0061)	0.0018
Outdoor Air Pollutants			
CO (ppm/hour)	0.8586	(-0.2027, 1.9199)	0.1128
Ozone (ppm/hour)	-14.0118	(-26.2940, -1.7297)	0.0254
$PM_{2.5}$ (µg/m^3 per hour)	0.0023	(-0.0201, 0.0246)	0.8421
SO_2 (ppb/ hour)	-0.2245	(-0.4338, -0.0151)	0.0356
Temperature			
Minimum Temperature (°F, 24 hours)	-0.0118	(-0.0247, 0.0012)	0.0762
Fall			
SVR- related ED visits (per MMWR week)	0.0010	(0.0002, 0.0019)	0.0175
Aeroallergens			
Mold spores (counts per m^3 air/ day), 1000 unit increase	-0.0002	(-0.0015, 0.0010)	0.7087
Outdoor Air Pollutants			
CO (ppm/hour)	-0.8388	(-1.3913, -0.2862)	0.0029
Ozone (ppm/hour)	1.6053	(-8.8558, 12.0663)	0.7636
$PM_{2.5}$ (µg/m^3 per hour)	-0.0185	(-0.0306, -0.0064)	0.0028
SO_2 (ppb/ hour)	0.0043	(-0.0539, 0.0625)	0.8854
Temperature			
Minimum Temperature (°F, 24 hours)	0.0005	(-0.0026, 0.0035)	0.7617

Winter			
SVR- related ED visits (per MMWR week)	0.0007	(0.0004, 0.0009)	< 0.0001
Outdoor Air Pollutants			
CO (ppm/hour)	0.4040	(-0.4089, 1.2169)	0.3300
Ozone (ppm/hour)	5.7893	(-4.7252, 16.3037)	0.2805
$PM_{2.5}$ (µg/m^3 per hour)	0.0032	(-0.0199, 0.0263)	0.7867
SO_2 (ppb/ hour)	-0.1155	(-0.2536, 0.0227)	0.1014
Temperature			
Minimum Temperature (°F, 24 hours)	-0.0062	(-0.0111, -0.0013)	0.0126

Table 5. Significant parameter estimates and relative risk by season for CR- related ED visits in Douglas County, NE during MMWR weeks 9-2016 to 52-2018

	Log-link Negative Binomial						
Variable	**β**	**95% C.I.**		**p-value**	**R.R.**	**95% C.I.**	
Spring							
Aeroallergens							
Mold spores (counts per m^3 air/ day), 1000 unit increase	0.0064	0.0034	0.0095	< 0.0001	1.0064	1.0034	1.0095
Outdoor Air Pollutants							
$PM_{2.5}$ (µg/m^3 per hour)	0.0232	0.0078	0.0386	0.0031	1.0235	1.0078	1.0394
Temperature							
Minimum Temperature (°F, 24 hours)	-0.0102	-0.0152	-0.0052	< 0.0001	0.9899	0.9849	0.9948
Summer							
SVR- related ED visits (per MMWR week)	0.0045	0.0030	0.0059	< 0.0001	1.0045	1.0030	1.0059
Fall							
SVR- related ED visits (per MMWR week)	0.0010	0.0002	0.0017	0.0117	1.0010	1.0002	1.0017
Outdoor Air Pollutants							
CO (ppm/hour)	-0.8107	-1.3240	-0.2974	0.0020	0.4445	0.2661	0.7427
Winter							
SVR- related ED visits (per MMWR week)	0.0007	0.0004	0.0009	< 0.0001	1.0007	1.0004	1.0009

Table 6. Significant parameter estimates by season and age group for CR- related ED visits in Douglas County, NE during MMWR weeks 9-2016 to 52-2018

Variable	< 18 yrs.				18 to 39 yrs.				≥ 40 yrs.			
	β	**95% C.I.**		**p-value**	**β**	**95% C.I.**		**p-value**	**β**	**95% C.I.**		**p-value**
Spring												
Aeroallergens												
Mold spores (counts per m^3 air/ day) , 1000 unit increase	0.0066	0.0007	-0.0125	0.0280	0.0102	0.0057	0.0147	< 0.0001	0.0035	0.0002	0.0068	0.0374
Outdoor Air Pollutants												
$PM_{2.5}$ (µg/m^3 per hour)					0.0374	0.0149	0.0599	0.0011	0.0241	0.0074	0.0408	0.0047
Temperature												
Minimum Temperature (°F, 24 hours)	-0.0191	-0.0288	-0.0093	0.0001	-0.0112	-0.0187	-0.0037	0.0035	-0.0054	-0.0107	0.0000	0.0484
Summer												
SVR- related ED visits (per MMWR week)	0.0044	0.0011	0.0077	0.0093	0.0203	0.0072	0.0334	0.0025				
Aeroallergens												
Weed pollen (counts per m^3 air/ day)	0.0025	0.0016	0.0034	< 0.0001								
Mold spores (counts per m^3 air/ day), 1000 unit increase									0.0030	0.0002	0.0058	0.0345
Fall												
SVR-related ED visits (per MMWR week)									0.0073	0.0011	0.0134	0.0208
Aeroallergens												
Mold spores (counts per m^3 air/ day), 1000 unit increase	-0.0048	-0.0087	-0.0009	0.0170	-0.0045	-0.0084	-0.0006	0.0226				
Outdoor Air Pollutants												
CO (ppm/hour)					-1.8049	-2.8151	-0.7947	0.0005				
$PM_{2.5}$ (µg/m^3 per hour)	0.0313	0.0090	0.0536	0.0059					-0.0225	-0.0377	-0.0073	0.0038
Temperature												
Minimum Temperature (°F, 24 hours)	0.0143	0.0051	0.0236	0.0023	0.0098	0.0009	0.0188	0.0309				
Winter												
SVR- related ED visits (per MMWR week)					0.0033	0.0012	0.0054	0.0020	0.0027	0.0017	0.0037	< 0.0001

Table 7. Relative risks by season and age group for CR- related ED visits in Douglas County, NE during MMWR weeks 9-2016 to 52-2018

Variable	< 18yrs.				18 to 39 yrs.				≥ 40 yrs.			
	R.R.	**95% C.I.**		**p-value**	***R.R.***	**95% C.I.**		**p-value**	***R.R.***	**95% C.I.**		**p-value**
Spring												
Aeroallergens												
Mold spores (counts per m^3 air/ day), 1000 unit increase	1.0066	1.0007	0.9876	0.0280	1.0103	1.0057	1.0148	< 0.0001	1.0035	1.0002	1.0068	0.0374
Outdoor Air Pollutants												
$PM_{2.5}$ (µg/m^3 per hour)					1.0381	1.0150	1.0617	0.0011	1.0244	1.0074	1.0416	0.0047
Temperature												
Minimum Temperature (°F, 24 hours)	0.9811	0.9716	0.9907	0.0001	0.9889	0.9815	0.9963	0.0035	0.9946	0.9894	1.0000	0.0484
Summer												
SVR- related ED visits (per MMWR week)	1.0044	1.0011	1.0077	0.0093	1.0205	1.0072	1.0340	0.0025				
Aeroallergens												
Weed pollen (counts per m^3 air/ day)	1.0025	1.0016	1.0034	< 0.0001								
Mold spores (counts per m^3 air/ day), 1000 unit increase									1.0030	1.0002	1.0058	0.0345
Fall												
SVR- related ED visits (per MMWR week)									1.0073	1.0011	1.0135	0.0208
Aeroallergens												
Mold spores (counts per m^3 air/ day), 1000 unit increase	0.9952	0.9913	0.9991	0.0170	0.9955	0.9916	0.9994	0.0226				
Outdoor Air Pollutants												
CO (ppm/hour)					0.1645	0.0599	0.4517	0.0005				
$PM_{2.5}$ (µg/m^3 per hour)	1.0318	1.0090	1.0551	0.0059					0.9778	0.9630	0.9927	0.0038
Temperature												
Minimum Temperature (°F, 24 hours)	1.0144	1.0051	1.0239	0.0023	1.0098	1.0009	1.0190	0.0309				
Winter												
SVR- related ED visits (per MMWR week)					1.0033	1.0012	1.0054	0.0020	1.0027	1.0017	1.0037	< 0.0001