



ORIGINAL RESEARCH

Impact of Temperature Relative Humidity and Absolute Humidity on the Incidence of Hospitalizations for Lower Respiratory Tract Infections Due to Influenza, Rhinovirus, and Respiratory Syncytial Virus: Results from Community-Acquired Pneumonia Organization (CAPO) International Cohort Study

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Abstract

Background: Transmissibility of several etiologies of lower respiratory tract infections (LRTI) may vary based on outdoor climate factors. The objective of this study was to evaluate the impact of outdoor temperature, relative humidity, and absolute humidity on the incidence of hospitalizations for lower respiratory tract infections due to influenza, rhinovirus, and respiratory syncytial virus (RSV).

Methods: This was a secondary analysis of an ancillary study of the Community Acquired Pneumonia Organization (CAPO) database. Respiratory viruses were detected using the Luminex xTAG respiratory viral panel. Climate factors were obtained from the National Weather Service. Adjusted Poisson regression models with robust error variance were used to model the incidence of hospitalization with a LRTI due to: 1) influenza, 2) rhinovirus, and 3) RSV (A and/or B), separately.

Results: A total of 467 hospitalized patients with LRTI were included in the study; 135 (29%) with influenza, 41 (9%) with rhinovirus, and 27 (6%) with RSV (20 RSV A, 7 RSV B). The average, minimum, and maximum absolute humidity and temperature variables were associated with hospitalization due to influenza LRTI, while the relative humidity variables were not. None of the climate variables were associated with hospitalization due to rhinovirus or RSV.

Conclusions: This study suggests that outdoor absolute humidity and temperature are associated with hospitalizations due to influenza LRTIs, but not with LRTIs due to rhinovirus or RSV. Understanding factors contributing to the transmission of respiratory viruses may assist in the prediction of future outbreaks and facilitate the development of transmission prevention interventions.

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1 Introduction

Lower respiratory tract infections are the third leading cause of death worldwide¹. Data suggest that influenza and other respiratory viruses are major causes of many of these infections^{2,3}.

Several of these pathogens are transmitted from person to person or from the environment to person, but a clear understanding of the transmission dynamics of influenza and other respiratory viruses is still evolving. Due to this, predicting transmission and epidemics of these viruses is challenging⁴. Climate factors such as temperature, relative humidity and absolute humidity have been shown to impact the transmission of respiratory viruses. However, the influence of each of these factors is still controversial. Some studies suggest that low humidity increases viral stability and transmission of influenza^{5,6} and respiratory syncytial virus (RSV)⁷. Lowen and colleagues have also documented varied

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transmission efficiencies of influenza viruses at different temperatures and relative humidities⁸. Conversely, other studies suggest that high humidity may increase the stability of rhinovirus and adenovirus, favoring transmission⁹. Most of the data related to climate factors and transmission dynamics of respiratory viruses has been generated from basic science research, ecological studies, and passive disease surveillance (e.g. viral specimens obtained for clinical practice).

The Community-Acquired Pneumonia Organization (CAPO) cohort study is a multicenter, international study of adult hospitalized patients with lower respiratory tract infections (LRTIs), which began in 2001. The database for the CAPO study contains information on over 15,000 patients with CAP from over 40 countries. As part of this ancillary study, consecutive hospitalized patients with LRTIs from all nine adult acute care hospitals in Louisville, KY during three consecutive influenza seasons were enrolled. Each of these patients underwent active surveillance for 12 respiratory viruses upon admission. Combining this dataset with data from the National Weather Service allowed us the unique opportunity to evaluate the role of climate factors at the patient level using active respiratory virus surveillance.

The objective of this study was to evaluate the impact of outdoor temperature, relative humidity, and absolute humidity on the incidence of hospitalizations for lower respiratory tract infections due to influenza, rhinovirus, and RSV.

2 Methods

2.1 Study Design

This was a secondary analysis of the CAPO database. As mentioned previously, this ancillary study of CAPO was a 3-year, prospective study, enrolling consecutive adult hospitalized patients with lower respiratory tract infections (LRTIs) due to influenza during three consecutive influenza seasons. Consecutive adult hospitalized patients with a diagnosis of LRTI were evaluated prospectively from 4 adult hospitals in Louisville, Kentucky during the influenza season 2010/2011, from 8 hospitals during the 2011/2012 season, and in all 9 adult care hospitals in Louisville, Kentucky, during the influenza season 2012/2013. After informed consent was obtained, a nasopharyngeal swab was obtained from each patient for respiratory virus detection. The normal climate of Louisville is classified as a warm, humid, and temperate, with average temperatures during the influenza season of approximately 30°F, and average precipitation of 3-4 inches per month during the same season.

2.2 Inclusion Criteria

Consecutive adult patients with the diagnosis of a lower respiratory tract infection were approached by a study coordinator for inclusion in the study. Upon signing of the consent form, the patient was enrolled and prospectively followed. Over 95% of the residents of Louisville, KY sought care in these nine hospitals under study during the third year of the study (Kentucky Hospital Association, unpublished data), therefore only patients from the third year (2012/2013 influenza season) were included in the

present analysis.

2.3 Exclusion Criteria

Patients with more than one respiratory virus identified from the nasopharyngeal swab were excluded from the analysis.

2.4 Human Subjects Protection

Institutional Review Board approval was obtained at all participating CAPO institutions prior to data collection.

2.5 Study Definitions

Lower respiratory tract infection (LRTI) was defined as a one sign of acute infection (e.g. subjective/objective fever and/or chills) and 2 new respiratory symptoms (e.g. cough, shortness of breath, change in sputum production).

LRTI was further stratified as community-acquired pneumonia (CAP), acute exacerbation of chronic obstructive pulmonary disease (AE-COPD), or acute bronchitis (AB).

Community-Acquired Pneumonia (CAP) was defined as the presence of a new pulmonary infiltrate on chest radiograph at the time of hospitalization that was associated with at least one of the following three criteria:

1. New or increased cough
2. An abnormal temperature ($< 35.6^{\circ}\text{C}$ or $> 37^{\circ}\text{C}$)
3. Leukocytosis, leukopenia, or left shift

Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AE-COPD) was defined as the lack of pulmonary infiltrate on chest radiograph at the time of hospitalization that was associated with at least one of the above three criteria PLUS a history of COPD.

Acute Bronchitis (AB) was defined as the lack of pulmonary infiltrate on chest radiograph at the time of hospitalization that was associated with at least one of the above three criteria, without a history of COPD.

Influenza LRTI was defined if the patient had a Luminex xTAG respiratory viral panel positive for any influenza virus via nasopharyngeal swab.

Respiratory syncytial virus LRTI was defined if the patient had a Luminex xTAG respiratory viral panel positive for any respiratory syncytial virus via nasopharyngeal swab.

Rhinovirus LRTI was defined if the patient had a Luminex xTAG respiratory viral panel positive for rhinovirus via nasopharyngeal swab.

Date of Acquisition of LRTI: To calculate the incidence of each virus by week, the following formula was used: $([\text{date of admission to the hospital}] - ([\text{number of days with respiratory symptoms prior to hospitalization}] + 1))$. This formula allowed us to approximate the date of acquisition of the etiology of LRTI.

Table 1 Baseline Patient Characteristics and Climate Data Of Those With And Without Influenza Lower Respiratory Tract Infections

Variable	Influenza n=135	No Influenza n=332	P-Value
Age, Median (IQR)	64 (19.5)	63 (20.2)	0.254
Male Gender, n (%)	79 (59)	186 (56)	0.680
COPD, n (%)	66 (49)	194 (58)	0.065
Diabetes, n (%)	48 (36)	123 (37)	0.832
Obese (BMI ≥30kg/m ²), n (%)	53 (39)	149 (45)	0.259
Risk Factors for Healthcare-Associated Pneumonia (HCAP), n (%)	38 (28)	126 (38)	0.054
Congestive Heart Failure, n (%)	27 (20)	102 (31)	0.022
Liver Disease, n (%)	6 (4)	21 (6)	0.517
Cancer, n (%)	16 (12)	29 (9)	0.303
Renal Disease, n (%)	25 (19)	64 (19)	0.897
Days with Respiratory Symptoms Prior to Hospitalization, Median (IQR)	3 (4)	4 (5)	0.209
Average Absolute Humidity the Day Before Symptom Onset, Median (IQR)	4.1 (1.6)	4.3 (1.8)	0.010
Average Relative Humidity the Day Before Symptom Onset, Median (IQR)	70.9 (9.1)	70.9 (9.2)	0.367
Average Temperature the Day Before Symptom Onset, Median (IQR)	3.3 (4.5)	3.8 (3.8)	0.003

Table 2 Baseline Patient Characteristics and Climate Data Of Those With And Without Rhinovirus Lower Respiratory Tract Infections

Variable	Rhinovirus n=41	No Rhinovirus n=426	P-Value
Age, Median (IQR)	64 (22)	63 (20.8)	0.822
Male Gender, n (%)	25 (61)	240 (56)	0.623
COPD, n (%)	23 (56)	237 (56)	1.000
Diabetes, n (%)	11 (27)	160 (38)	0.234
Obese (BMI ≥30kg/m ²), n (%)	16 (39)	186 (44)	0.622
Risk Factors for Healthcare-Associated Pneumonia (HCAP), n (%)	11 (27)	153 (36)	0.305
Congestive Heart Failure, n (%)	7 (17)	122 (29)	0.143
Liver Disease, n (%)	3 (7)	24 (6)	0.722
Cancer, n (%)	8 (20)	37 (9)	0.045
Renal Disease, n (%)	6 (15)	83 (19)	0.537
Days with Respiratory Symptoms Prior to Hospitalization, Median (IQR)	4 (5)	4 (5)	0.784
Average Absolute Humidity the Day Before Symptom Onset, Median (IQR)	4.3 (1.4)	4.3 (1.8)	0.680
Average Relative Humidity the Day Before Symptom Onset, Median (IQR)	69 (9.1)	70.9 (9.3)	0.970
Average Temperature the Day Before Symptom Onset, Median (IQR)	3.8 (3.8)	3.8 (4.2)	0.612

2.6 Study Variables

Predictor Variable - The primary predictor variables for the present study were as follows: 1) average absolute humidity per week, 2) minimum absolute humidity per week, 3) maximum absolute humidity per week, 4) average relative humidity per week, 5) minimum relative humidity per week, 6) maximum relative humidity per week, 7) average temperature (degrees Celsius) per week, 8) minimum temperature (degrees Celsius) per week, and 9) maximum temperature (degrees Celsius) per week. Data were gathered from the national weather service, and the absolute humidity in grams/meters³ was calculated with the following formula (T =temperature in degrees Celsius, rh = percent relative humidity):

$$(6.112 \times e^{(17.67 \times T)/(T+243.5)} \times 2.1674 \times rh) \setminus (273.15 + T)$$

Each of these variables was assigned to a particular patient based on the formula described above for the date of acquisition of LRTI.

Confounding Variables - We evaluated the following potentially confounding variables: age, gender, obesity, risk factors for HCAP, the number of days with respiratory symptoms prior to hospitalization, as well as a history of: COPD, liver disease, renal disease, diabetes, congestive heart failure, and cancer.

Quality Control/Data Management Plan - Trained study coordinators or research associates collected data both from patient interviews/questionnaires, and from medical records. All data were collected on a paper case report form and were subsequently entered into an online case report form. The online system included validators to limit data entry error. Once the case was

entered, trained study coordinators and research associates examined each case for abnormal data. Any queries were sent back to the coordinator collecting data for remedy. Once all queries were answered, the data were corrected and finally entered into the online database.

2.7 Statistical Analysis

Categorical variables were expressed as frequencies and percentages and were compared between those with and without influenza, with and without rhinovirus, and with and without RSV using Chi-squared or Fisher's exact tests. Continuous variables were expressed as medians and interquartile ranges or means and standard deviations and were compared between groups using the Mann-Whitney U test or the student's t-test. P-values ≤0.05 were considered statistically significant in all analyses unless otherwise specified.

Poisson regression models with robust error variance were used to model the incidence of hospitalization with a LRTI due to either: 1) influenza, 2) rhinovirus, and 3) respiratory syncytial virus (A and/or B), separately¹⁰. For each of those three outcomes, nine separate models were run, using each of the nine predictor variables listed in the *Study Variables* section. All models were adjusted for the confounding variables described previously.

P-values of ≤0.05 were considered statistically significant, and R v3.0 was used for all analyses.

Table 3 Baseline Patient Characteristics and Climate Data Of Those With And Without Respiratory Syncytial Virus Lower Respiratory Tract Infections

Variable	Respiratory Syncytial Virus n=27	No Respiratory Syncytial Virus n=440	P-Value
Age, Median (IQR)	60 (17)	63 (21)	0.824
Male Gender, n (%)	19 (70)	246 (56)	0.164
COPD, n (%)	16 (59)	244 (55)	0.842
Diabetes, n (%)	9 (33)	162 (37)	0.838
Obese (BMI ≥ 30kg/m ²), n (%)	14 (52)	188 (43)	0.425
Risk Factors for Healthcare-Associated Pneumonia (HCAP), n (%)	9 (33)	155 (35)	1.000
Congestive Heart Failure, n (%)	13 (48)	116 (26)	0.024
Liver Disease, n (%)	1 (4)	26 (6)	1.000
Cancer, n (%)	0 (0)	45 (10)	0.095
Renal Disease, n (%)	6 (22)	83 (19)	0.619
Days with Respiratory Symptoms Prior to Hospitalization, Median (IQR)	4 (2.5)	4 (5)	0.379
Average Absolute Humidity the Day Before Symptom Onset, Median (IQR)	4.1 (1.9)	4.3 (1.8)	0.824
Average Relative Humidity the Day Before Symptom Onset, Median (IQR)	70.9 (14.2)	70.9 (9.3)	0.686
Average Temperature the Day Before Symptom Onset, Median (IQR)	3.3 (3.4)	3.8 (3.8)	0.307

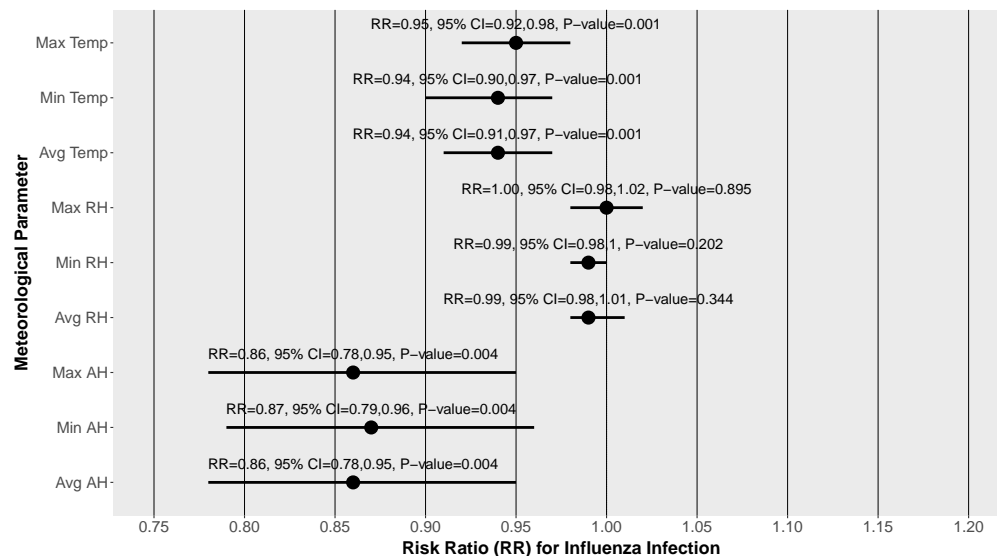


Fig. 1 Adjusted impact of climate factors on hospitalizations due to influenza virus lower respiratory tract infections (Avg = average; Min = minimum; Max = maximum; AH = absolute humidity; RH = relative humidity; Temp = temperature in degrees Celsius)

3 Results

A total of 467 hospitalized patients with LRTI were included in the study, 293 with CAP, 126 with AECOPD, and 48 with AB. A total of 135 (29%) patients had influenza, 41 (9%) had rhinovirus, and 27 (6%) had RSV (20 RSV A, 7 RSV B). Baseline patient characteristics and baseline climate data on the day before symptom onset of hospitalized patients with and without LRTIs due to influenza, rhinovirus, and RSV can be found in **Tables 1, 2, and 3**, respectively.

During the three seasons, the average weekly absolute humidity was 4.7 grams/m³ (min=2.3 grams/m³; max=9.2 grams/m³), the average weekly relative humidity was 71.1% (min=42.3%; max=85.7%), and the average weekly temperature was 4.3°C (min=-2.3°C ; max=12.7°C).

The adjusted impact of each of the nine climate factors for influenza infection, rhinovirus infection, and RSV infection can be seen in **Figures 1, 2, and 3**, respectively. The average, minimum, and maximum absolute humidity and temperature variables were

associated with hospitalization due to influenza LRTI, while the relative humidity variables were not. Correlations between each of the nine climate factors and the weekly influenza incidence rates are depicted in **Figure 4**. None of the nine predictor variables were associated with hospitalization due to rhinovirus or RSV.

4 Discussion

This study suggests that absolute humidity and temperature on the day before symptom onset are associated with hospitalizations due to influenza LRTIs, but not with LRTIs due to rhinovirus or respiratory syncytial virus during the influenza season. Furthermore, the relative humidity on the day before symptom onset was not associated with hospitalizations due to any of the etiologies evaluated. Although temperature was associated with influenza LRTIs, the protective effects were small compared to those related to relative humidity.

The relationships between climate factors and respiratory virus infection incidence are documented in the literature but most

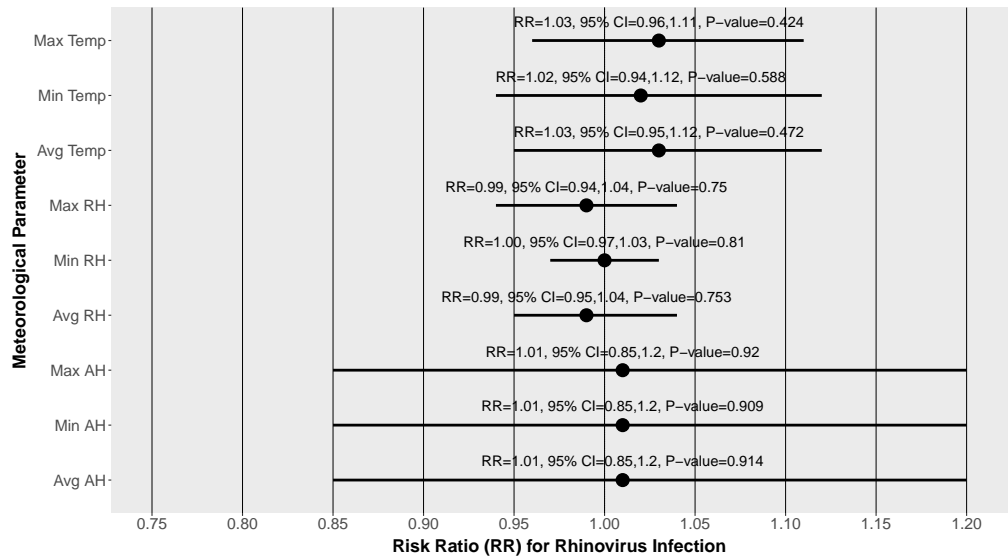


Fig. 2 Adjusted impact of climate factors on hospitalizations due to rhinovirus lower respiratory tract infections (Avg = average; Min = minimum; Max = maximum; AH = absolute humidity; RH = relative humidity; Temp = temperature in degrees Celsius)

published studies are somewhat limited in their methods and scope^{5,11-43}. For example, there are no true incidence studies evaluating this correlation enrolling all hospitalized patients with lower respiratory tract infections in a defined population during a defined time period in the literature. Available clinical data do suggest that influenza virus infections are related to absolute humidity²⁹, relative humidity⁴⁴, and temperature⁴⁵. Interestingly, contact transmission of the influenza virus, but not aerosol transmission, may be facilitated in times of high temperature⁴⁶ and in the presence of high humidity Rhinovirus has been shown to survive more readily in aerosols as well as on surfaces in the presence of high relative humidity^{9,47}. Since droplet and contact are known modes of transmission of this organism, it has been suggested that high humidity may prevent the virus from desiccating thereby prolonging survival on environmental surfaces and subsequently facilitating transmission.⁶ Increases in the incidence of RSV infections have been correlated with both low and high relative humidity levels^{48,49}. However, rainfall has been associated with RSV incidence in multiple studies, both negatively and positively^{7,50-54}.

Various theories behind the association between climate factors and the incidence of respiratory viruses have been proposed. Most of the theories have focused on the low temperature/humidity correlations with influenza virus^{8,42}. Both inter-host factors such as viral stability changes, respiratory droplet size, and airflow, as well as host factors such as respiratory secretion production and composition, viral clearance, seasonal nutrition changes, ultraviolet light, and socio-behavioral changes (e.g. close indoor contact) have been described as potential mechanisms^{8,55}. Our results suggest that host factors, including socio-behavioral factors may not be primary drivers of respiratory viral epidemics during winter seasons. The climate certainly influences droplet size, host and socio-behavioral factors, but if those

factors were related to respiratory viral transmission, similar patterns of association between climate factors and different viruses should be seen. Since only the influenza virus was associated with climate factors, our data suggest that absolute humidity and temperature may affect influenza virus stability, pathogenesis or virulence.

This study has a number of limitations. First, we did not account for indoor climate, which may be different than outdoor climate and could modify viral survival and transmission during the winter months. Second, although we made an attempt to define the date of infection with each virus, it is possible that we have not accurately defined this date, leading to misclassification of climate factors to each patient. Third, we had a relatively small sample size, which makes it difficult to make accurate assessments. Since we enrolled patients only during the influenza season, it is possible that we missed a number of cases of viral lower respiratory tract infections. For example, RSV and rhinovirus may have been circulating at different times of the year leading to biased estimates during the winter season. It is also possible that some patients were misclassified as not having an LRTI due to one of these viruses due to the diagnostic technique used. It is possible that patients arriving to the hospital may already have reduce their respiratory virus to an undetectable level, resulting in misclassification. Finally, since this study was ecological in nature, it is not possible to confirm that each patient was truly exposed to a particular temperature or humidity level, particularly indoor temperature and humidity values, where an individual may spend the majority of their day. Another limitation of this study is the fact that there are no accepted gold standard definitions of any of the LRTIs we evaluated. Because of this, we may have misclassified patients based on various definitions. Due to the relatively small sample size, we were not able to evaluate differences among the three influenza seasons. This could possibly induce bias in the re-

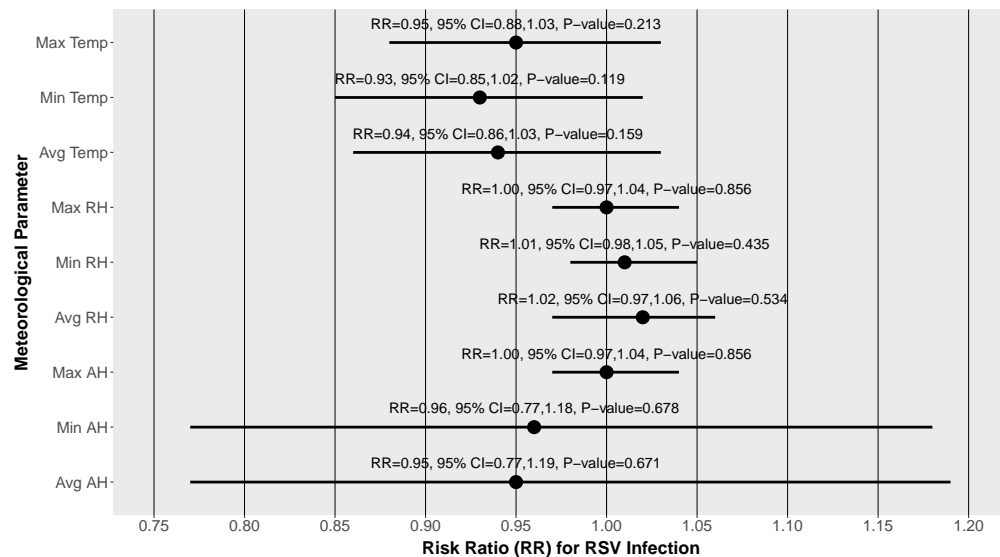


Fig. 3 Adjusted impact of climate factors on hospitalizations due to respiratory syncytial virus lower respiratory tract infections (Avg = average; Min = minimum; Max = maximum; AH = absolute humidity; RH = relative humidity; Temp = temperature in degrees Celsius)

sults. We were also not able to evaluate the role of asthma and/or use of inhaled corticosteroids in COPD patients. This may bias the results due to residual confounding.

The major strength of this study is that it is a population-based incidence study of nearly all residents of Louisville, Kentucky requiring hospitalization for a LRTI using active respiratory virus surveillance. Most prior studies largely relied on a patient sample or passive surveillance and attempted to correlate population based climate data with the patient sample. Since we were able to enroll nearly all hospitalized patients with lower respiratory tract infections in Louisville, we are able to reduce the bias inherent in some other studies.

Future studies may consider the both the role of the outdoor and indoor climate on the incidence of respiratory virus infections. The indoor climate, humidity in particular, has been suggested as an important factor in respiratory virus transmission⁵⁶. Combining the indoor and outdoor temperature may facilitate the development of more robust predictive models for respiratory virus infections. Furthermore, results of these studies may lead to the development of climate modification interventions to limit viral transmission. Finally, there is a need to further elucidate the mechanisms behind the correlation between low absolute humidity and the pathogenesis and/or virulence of the influenza virus but not other respiratory viruses.

In conclusion, this study adds to the body of evidence that the outdoor climate factors, particularly absolute humidity, are associated with influenza incidence. However, we were not able to demonstrate any impact of climate on the incidence of rhinovirus or respiratory syncytial virus. Understanding factors contributing to the transmission of respiratory viruses may assist in the prediction of future outbreaks and facilitate the development of novel interventions for preventing respiratory viral transmission.

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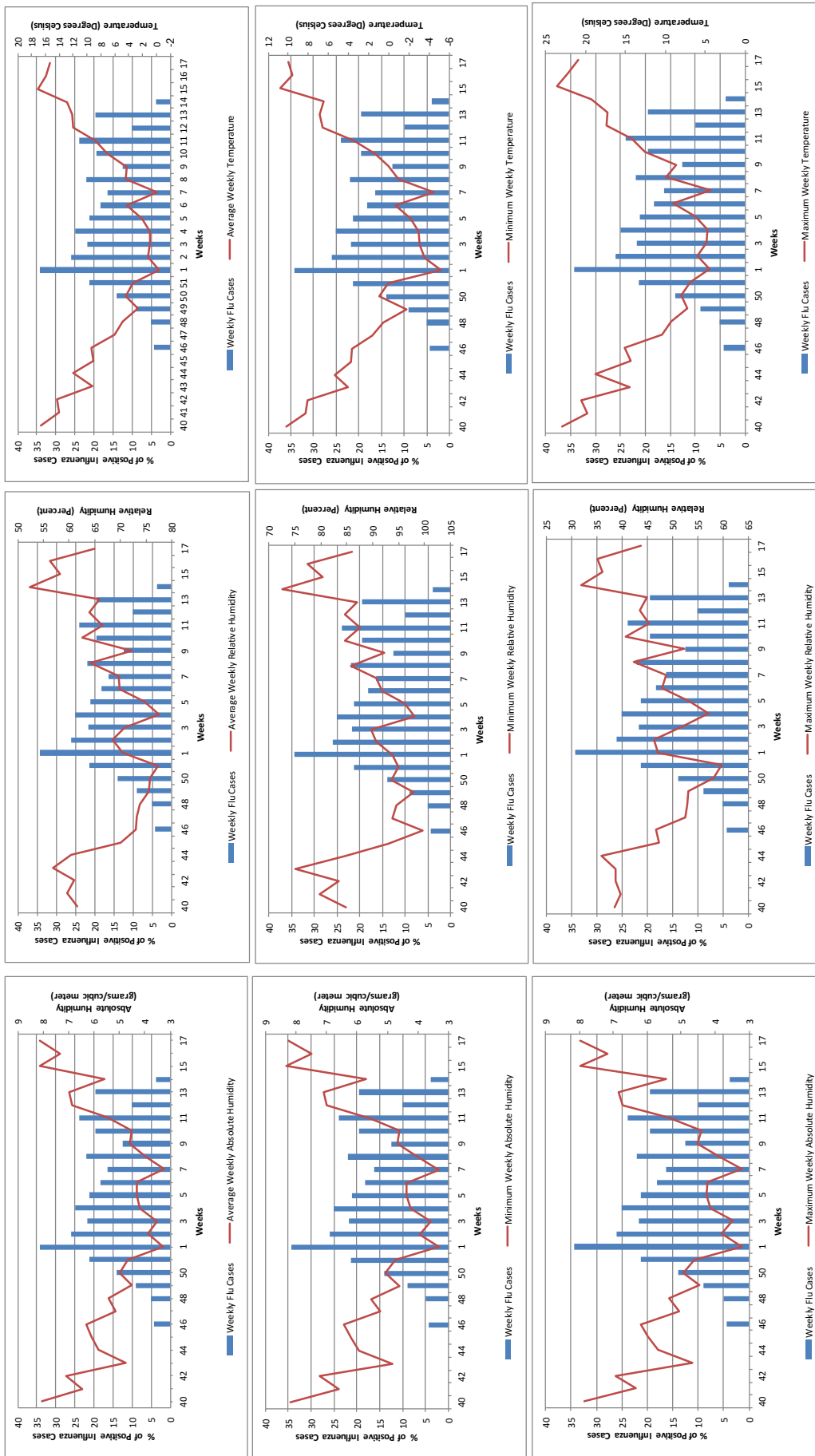


Fig. 4 Depiction of the correlation between nine climate variables and the weekly influenza incidence rate

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