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A longitudinal ecological study of seasonal influenza deaths in relation to climate conditions in the United States from 1999 through 2011

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ABSTRACT

Introduction: Influenza is an acute respiratory disease with significant annual global morbidity/mortality. Influenza transmission occurs in distinct seasonal patterns suggesting an importance of climate conditions on disease pathogenesis. This hypothesis-testing study evaluated microenvironment conditions within different demographic/geographical groups on seasonal influenza deaths in the United States.

Materials and methods: The United States Centers for Disease Control and Prevention (CDC) Wonder online computer interface was utilized to integrate and analyze potential correlations in data generated from 1999 through 2011 for climate conditions of mean daily sunlight (KJ/m^2), mean daily maximum air temperature (°C), mean daily minimum air temperature (°C), and mean daily precipitation (mm) from the North America Land Data Assimilation System (NLDAS) database and on influenza mortality (ICD-10 codes:J09, J10, or J11) from the Underlying Cause of Death database.

Results and discussion: Significant inverse correlations between the climate conditions of temperature, sunlight, and precipitation and seasonal influenza death rate were observed. Similar effects were observed among males and females, but when the data were separated by race and urbanization status significant differences were observed.

Conclusion: This study highlights key factors that can help shape public health policy to deal with seasonal influenza in the United States and beyond.

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Introduction

It was recently reported that the annual global burden of influenza during interpandemic years is about 1 billion clinical cases, about 3–5 million severe illnesses, and about 300,000–500,000 deaths [1]. In humans and animals, influenza is an acute respiratory disease that is caused by influenza virus A, influenza virus B, and influenza virus C. Influenza viruses belong to the Orthomyxoviridae family and have a negative sense RNA genome [2–4].

It is well-established that influenza transmission occurs in distinct seasonal patterns around the world. In temperate regions seasonal influenza occurs at peak incidence during late winter and early spring [5,6]. In tropical and subtropical regions peak influenza occurs during the rainy season each year [7,8]. As a result, it was described that the seasonality of influenza is related to biotic factors (viral determinants and host characteristics) and abiotic factors (environmental composition), and thus, a better understanding of these factors would help enable more effectiveness measures to be employed to deal with seasonal influenza [1].

The contiguous USA (48 states and the District of Columbia) offers a relatively unique backdrop of variability in climate to study the relationship between climate conditions and deaths from seasonal influenza. The driving forces between climate conditions in the contiguous USA are the consequence of differences in range of geographic features such as mountains and deserts, as well as significant differences in latitude [9]. The climate of the contiguous USA to the west of the 100th meridian is mainly semi-arid to arid, and the far southwestern USA is desert. The climate of the contiguous USA to the east of the 100th meridian in northern areas (locations > 40 north latitude) is humid continental, in the central and middle Atlantic coast regions it is humid temperate, in the Gulf and south Atlantic regions it is humid subtropical, and the southern tip of Florida is tropical. Alpine climates are found in the high-elevations of the Rocky Mountains, the Wasatch, and Bighorn mountain ranges, the Sierra Nevada, and the Cascade Range. A Mediterranean climate is found along the coast of California, and a cool temperate oceanic climate is found in the upper west coast areas of coastal Oregon and Washington.

The purpose of this longitudinal ecological study was to take advantage of the diverse climates in the contiguous USA to examine the potential correlation

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between different climate conditions and the death rate from seasonal influenza in the USA from 1999 through 2011. It is hypothesized, if there are potential correlations between climate conditions and the death rate from seasonal influenza that differences in microenvironment climate conditions will be of significant importance in mediating these effects in different demographic groups. This study will potentially provide information on important climate conditions that can help shape public health policy to deal with seasonal influenza in the USA and beyond.

Methods

This study employed the US Centers for Disease Control and Prevention (CDC) Wonder online computer interface to examine environmental and mortality databases [10].

Mortality data

The Underlying Cause of Death database was examined on the CDC Wonder online computer interface. The Underlying Cause of Death data are produced by the Mortality Statistics Branch, Division of Vital Statistics, National Center for Health Statistics (NCHS), US CDC, US Department of Health and Human Services (DHHS). The database is based on information from all death certificates filed in the fifty states and the District of Columbia. Deaths of nonresidents are excluded. Mortality data from death certificates are coded by the states and provided to the NCHS of the US CDC through the Vital Statistics Cooperative Program or coded by NCHS from copies of the original death certificates provided to NCHS by State registration offices.

The Underlying Cause of Death database was examined by time and location variables for deaths reported from 1999 through 2011 with a location in the contiguous 48 US states and the District of Columbia (excluding Alaska and Hawaii). The causes of death are classified in the Underlying Cause of Death database in accordance with the International Classification of Disease, Tenth Revision (ICD-10) codes and this study examined records coded with ICD-10 codes: J09.x (influenza due to identified avian influenza virus), J10.x (influenza due to identified influenza virus), or J11.x (influenza, virus not identified). In addition, in order to determine the rate of influenza deaths, general population estimates were utilized from Underlying Cause of Death database based upon population bridged-race estimates from the US Census Bureau estimates of US national, state, and county resident populations. Among the data examined, all sub-national data representing 0 to 9 deaths were suppressed and the corresponding denominator population figures were also suppressed.

The influenza-related death population and the general population estimates generated from analyzing the Underlying Cause of Death database were examined for detailed demographic information, including: gender, race, Census division, and urbanization. Table 1 summarizes the overall demographic breakdown of the populations examined.

Environmental data

The North America Land Data Assimilation System (NLDAS) database was examined on the CDC Wonder online computer interface. The data available from the NLDAS database are derived from the continental 48 US states and the District of Columbia (excluding Alaska and Hawaii) and provide detailed information on environmental measurements by location and time when the measurements were made. The NLDAS is a collaboration project among several groups: the National Oceanic and Atmospheric Administration (NOAA) National Centers for Environmental Prediction (NCEP) Environmental Modeling Center (EMC), the National Aeronautics and Space Administration (NASA) Goddard Space Flight Center (GSFC), Princeton University, the National Weather Service (NWS) Office of Hydrological Development (OHD), the University of Washington, and the NCEP Climate Prediction Center (CPC). The NLDAS Phase 2 (NLDAS-2) hourly forcing data used in this study were acquired as part of the mission of the NASA Earth Science Division. NLDAS-2 data are archived and distributed by the Goddard Earth Sciences (GES) Data and Information Services Center (DISC). In a study funded by the NASA Applied Sciences Program/Public Health Program, scientists at NASA Marshall Space Flight Center/Universities Space Research Association developed computer programs to process the NLDAS-2 hourly primary forcing files, extract the hourly air temperature, specific humidity, and atmospheric pressure data, and compute the daily maximum air temperature, minimum air temperature, and maximum heat index. They also identified in a Geographic Information System (GIS) the associated geographic locations of the centroids of the gridded NLDAS-2 dataset in terms of the counties and states they fall into so it can be aggregated to different geographic levels in the NLDAS database.

The NLDAS database was examined by time and location variables for the climate exposure variables of daily precipitation in millimeters (mm), daily air maximum and minimum temperature in degrees Celsius (°C), and daily sunlight in kilojoules per meter^2 (KJ/m^2) from 1999 through 2011. Table 2 summarizes the

Table 1. A demographic summary of the populations examined from 1999 through 2011.

Characteristic Examined	Influenza Deaths[a] ICD-10 codes: J09, J10, J11	Overall Population[a]	p-value[b]
Gender			< 0.0001
Males	7,049 (41.54%)	1,874,617,892 (49.11%)	
Females	9,920 (58.46%)	1,942,260,623 (50.89%)	
Race[c]			< 0.0001
Hispanic or Latino	1,224 (7.23%)	558,225,099 (14.62%)	
Black or African American	1,048 (6.19%)	484,357,169 (12.69%)	
White	14,210 (83.96%)	2,574,823,166 (67.46%)	
Asian or Pacific Islander	285 (1.68%)	169,073,816 (4.43%)	
American Indian or Alaska Native	159 (0.94%)	30,399,265 (0.8%)	
Census Division			< 0.0001
Division 1: new England (CT, RI, MA, VT, NH, ME)	1,018 (6%)	184,735,107 (4.84%)	
Division 2: Middle Atlantic (NY, PA, NJ)	1,683 (9.92%)	523,595,585 (13.72%)	
Division 3: East North Central (WI, IL, IN, MI, OH)	3,128 (18.43%)	596,408,598 (15.63%)	
Division 4: West North Central (ND, SD, NE, KS, MN, IA, MO)	2,499 (14.73%)	258,120,646 (6.76%)	
Division 5: South Atlantic (WV, MD, DE, DC, VA, NC, SC, GA, FL)	2,516 (14.83%)	728,208,137 (19.08%)	
Division 6: East South Central (KY, TN, MS, AL)	1,022 (6.02%)	230,170,336 (6.03%)	
Division 7: West South Central (TX, OK, AR, LA)	1,593 (9.39%)	439,868,805 (11.52%)	
Division 8: Mountain (NV, ID, UT, AZ, NM, CO, WY, MT)	1,427 (8.41%)	262,578,804 (6.88%)	
Division 9: Pacific (WA, OR, CA)	2,083 (12.27%)	593,292,497 (15.54%)	
2006 Urbanization			< 0.0001
Large Central Metro	3,360 (19.80%)	1,134,798,488 (29.73%)	
Large Fringe Metro	2,847 (16.78%)	924,688,394 (24.23%)	
Medium Metro	3,542 (20.87%)	750,229,439 (19.66%)	
Small Metro	2,017 (11.89%)	365,860,187 (9.58%)	
Micropolitan (non-metro)	2,670 (15.73%)	390,175,673 (10.22%)	
Noncore (non-metro)	2,533 (14.93%)	251,126,334 (6.58%)	

[a] The values were derived by adding the values for each year examined to calculate the cumulative numbers presented in the table.
[b] Determined using the χ^2 statistic.
[c] A total of 16,969 influenza deaths were identified, but 43 did not state Hispanic origin or not and were excluded from the table.

average climate exposures variables examined by Census division from 1999 through 2011.

Statistical analyses

In this study, the statistical package contained in StatsDirect (Version: 3.0.152) was utilized and in all statistical analyses a two-sided p-value < 0.05 was considered statistically significant. The null hypotheses for each of the statistical tests undertaken in this study were that there would be no differences between the groups examined or no correlation between the datasets examined.

The data were initially examined to determine if there were demographic differences among the seasonal influenza-related death population in comparison to the overall population examined. This included examination of potential differences in gender, race, Census division, and urbanization. The data were categorical variables, so a χ^2 statistic was employed. The data were then examined to determine the potential correlation between climate exposure variables and seasonal influenza-related deaths. Since, the data were continuous variables, the Spearman's rank correlation statistic was employed. The potential correlation between climate exposure variables and seasonal influenza-related deaths were examined by increasingly refining geographic and time variables. This included examining the data broken down by Census division, Census division by year, state, and state by year. Then, the potential correlation between climate exposure variables and seasonal influenza-related deaths were examined by breaking down the data by different demographic groups (i.e., gender, race, and urbanization) and holding time (1999 through 2011) and geographic (by state) variables constant.

Results

Table 1 reveals demographic characteristics examined among seasonal influenza death victims in comparison to the overall USA population. It was observed that there were significant differences in the distribution of gender, race, census division, and 2006 urbanization status among seasonal influenza death victims compared to the overall USA population. Among seasonal influenza death victims in comparison to the overall USA population, there

Table 2. A summary of the mean climate exposure for each census division from 1999 through 2011.

Census Division	Mean Daily Sunlight in KJ/m² (# of obs) [range]	Mean Daily Max Air Temperature in °C (# of obs) [range]	Mean Daily Min Air Temperature in °C (# of obs) [range]	Mean Daily Precipitation in mm (# of obs) [range]
Division 1: new England (CT, RI, MA, VT, NH, ME)	14,174.96 (5,787,812) [1,095.30 to 33,875.30]	10.97 (5,787,812) [−29.56 to 38.28]	3.07 (5,787,812) [−39.22 to 26.33]	3.34 (5,787,812) [0.00 to 215.00]
Division 2: Middle Atlantic (NY, PA, NJ)	14,307.90 (8,612,872) [1,151.50 to 33,935.20]	13.20 (8,612,872) [−26.39 to 40.44]	4.98 (8,612,872) [−34.94 to 27.33]	3.14 (8,612,872) [0.00 to 212.90]
Division 3: East North Central (WI, IL, IN, MI, OH)	14,771.15 (21,309,024) [940.50 to 33,921.90]	14.31 (21,309,024) [−24.28 to 45.94]	5.31 (21,309,024) [−37.50 to 29.28]	2.64 (21,309,024) [0.00 to 220.40]
Division 4: West North Central (ND, SD, NE, KS, MN, IA, MO)	15,295.92 (44,802,128) [921.80 to 32,297.50]	15.28 (44,802,128) [−30.78 to 48.22]	4.61 (44,802,128) [−41.44 to 30.61]	1.95 (44,802,128) [0.00 to 244.40]
Division 5: South Atlantic (WV, MD, DE, DC, VA, NC, SC, GA, FL)	17,151.67 (20,995,656) [1,562.80 to 39,461.40]	21.76 (20,995,656) [−17.56 to 42.94]	12.06 (20,995,656) [−23.72 to 30.17]	3.24 (20,995,656) [0.00 to 274.60]
Division 6: East South Central (KY, TN, MS, AL)	16,667.88 (14,039,836) [1,511.20 to 35,355.40]	21.69 (14,039,836) [−13.28 to 45.67]	11.43 (14,039,836) [−28.28 to 32.17]	3.57 (14,039,836) [0.00 to 257.50]
Division 7: West South Central (TX, OK, AR, LA)	18,113.12 (32,727,964) [1,629.00 to 36,062.70]	25.12 (32,727,964) [−15.11 to 47.61]	13.20 (32,727,964) [−22.94 to 32.50]	2.37 (32,727,964) [0.00 to 277.80]
Division 8: Mountain (NV, ID, UT, AZ, NM, CO, WY, MT)	17,299.97 (72,592,172) [993.40 to 33,959.80]	15.10 (72,592,172) [−32.17 to 49.61]	5.05 (72,592,172) [−39.06 to 37.28]	1.07 (72,592,172) [0.00 to 214.60]
Division 9: Pacific (WA, OR, CA)	17,371.03 (27,519,408) [963.60 to 38,703.70]	16.72 (27,519,408) [−24.06 to 51.22]	6.88 (27,519,408) [−31.56 to 37.67]	1.93 (27,519,408) [0.00 to 521.60]
Total	16,612.30 (248,386,872) [921.80 to 39,461.40]	17.34 (248,386,872) [−32.17 to 51.22]	7.17 (248,386,872) [−41.44 to 37.67]	2.08 (248,386,872) [0.00 to 521.60]

were significantly more females than males (male/female ratios = 1.4 vs 1.04). In addition, there were significantly less Hispanics or Latinos (7.23% vs 14.62%), Blacks or African Americans (6.19% vs 12.69%), Asians or Pacific Islanders (1.68% vs 4.43%) and significantly more Whites (83.96% vs 67.46%) when comparing seasonal influenza death victims to the overall USA population. It was also observed that seasonal influenza death victims in comparison to the overall USA population were significantly more common in rural areas (noncore (non-metro) = 14.93% vs 6.58% and micropolitan (non-metro) = 15.73% vs 10.22%) in comparison to large metropolitan areas (large central metro = 19.80% vs 29.73% and large fringe metro = 16.78% vs 24.23%).

Table 2 reveals the mean climate exposure variables for each census division from 1999 through 2011 examined in the study. It was observed based upon a total of 248,386,872 observations that the mean daily sunlight was 16,612.30 KJ/m², mean daily maximum air temperature was 17.34°C, the mean daily minimum temperature was 7.17°C, and the mean daily precipitation was 2.08 mm from 1999 through 2011 for the nine Census Divisions examined. There were significant differences between the different census divisions for mean daily sunlight, mean daily maximum air temperature, mean daily minimum temperature, and mean daily precipitation. Overall, the mean daily sunlight ranged from a low of 14,174.96 KJ/m² in Census Division 1 to a high of 18,113.12 KJ/m² in Census Division 7. Similarly, between Division 1 and Division 7 was the range of low to high mean daily maximum air temperatures (10.97°C–25.12°C) and mean daily minimum air temperatures (3.07°C–13.20°C). Finally, the low to high range of mean daily precipitation ranged from 1.07 mm in Census Division 8 to 3.57 mm in Census Division 6.

Table 3 summarizes the correlation between climate exposure variables and seasonal influenza death rate by examining increasingly broken down data by geographical location and time variables. It was observed that no significant correlations were observed between any of the climate exposure variables and seasonal influenza death rate when the data were analyzed by only Census Division. Subsequently, by further breaking down the data by Census Division and year, then by state, and by state and by year, revealed significant inverse correlations between more environmental exposure variables and seasonal influenza death rate. It was

Table 3. A summary of the correlation[a] between climate exposure variables and influenza death rate.

Breakdown of Data Examined (# of obs)	Mean Daily Sunlight in KJ/m^2 vs Influenza Death Rate	Mean Daily Max Air Temperature in °C vs Influenza Death Rate	Mean Daily Min Air Temperature in °C vs Influenza Death Rate	Mean Daily Precipitation in mm vs Influenza Death Rate
Census Division (n = 9)	Rho = −0.25 95% CI = −0.784 to 0.497 p = 0.4933	Rho = −0.317 95% CI = −0.810 to 0.44 p = 0.3853	Rho = −0.55 95% CI = −0.889 to 0.18 p = 0.1206	Rho = −0.167 95% CI = −0.748 to 0.559 p = 0.6436
Census Division by Year (n = 117)	***Rho = −0.203*** ***95% CI = −0.371 to −0.022*** ***p = 0.0285***	***Rho = −0.197*** ***95% CI = −0.366 to −0.0164*** ***p = 0.0331***	***Rho = −0.333*** ***95% CI = −0.485 to −0.161*** ***p = 0.0003***	Rho = 0.0143 95% CI = −0.195 to 0.168 p = 0.8783
State (n = 49)	***Rho = −0.498*** ***95% CI = −0.683 to −0.252*** ***p = 0.0003***	***Rho = −0.566*** ***95% CI = −0.731 to −0.339*** ***p < 0.001***	***Rho = −0.666*** ***95% CI = −0.798 to −0.473*** ***p < 0.001***	***Rho = −0.336*** ***95% CI = −0.564 to −0.60*** ***p = 0.0188***
State by Year (n = 422)	***Rho = −0.314*** ***95% CI = −0.398 to −0.226*** ***p < 0.0001***	***Rho = −0.402*** ***95% CI = −0.479 to −0.319*** ***p < 0.0001***	***Rho = −0.48*** ***95% CI = −0.55 to −0.403*** ***p < 0.0001***	***Rho = −0.193*** ***95% CI = −0.283 to −0.1*** ***p < 0.0001***

Note: Bold-Italics results are statistically significant.
[a] The Spearman's rank correlation statistic was employed

observed when the data were broken down by state or by state and by year that there were significant inverse correlations between the environmental exposure variables of mean daily sunlight, mean daily maximum air temperature, mean daily minimum air temperature, and precipitation. The ordering of inverse correlations from largest to smallest was as follows: mean daily minimum air temperature > mean daily maximum air temperature > mean daily sunlight > mean daily precipitation.

Table 4 reveals the correlation between climate exposure variables and seasonal influenza death rate by state for different demographic groups from 1999 through 2011. It was observed when the data were separated by gender that there were still significant inverse correlations between the climate exposure variables examined. The strength of the inverse correlations observed from largest to smallest for both males and females was as follows: mean daily minimum air temperature > mean daily maximum air temperature > mean daily sunlight > mean daily precipitation. It was also observed that when the data were separated by race that for each of the environmental exposure variables and seasonal influenza death rate there were significant inverse correlations observed for Whites. Whereas, among Hispanics or Latinos there was only a significant inverse correlation between mean daily precipitation and seasonal influenza death rate and among Blacks or African Americans there was no correlation between any of the climate exposure variables and influenza death rate. Finally, it was revealed that by examining urbanization as related to the correlation between climate exposure variables and seasonal influenza death rate that the lower the population density, the greater and more consistent the significant inverse correlation between climate exposure variables and seasonal influenza death rate. As a result, the least significant effects were observed for large central metro populations and the greatest significant effects were observed for small metro, micropolitan (non-metro), and noncore (non-metro) populations.

Discussion

The results of this epidemiological study provide new insights into the significant inverse correlation between variability in microenvironment climate conditions and the death rate from seasonal influenza in the contiguous USA. The specific climate conditions of temperature, sunlight, and precipitation were all significantly inversely correlated with the death rate from seasonal influenza, such that the lower the temperature, the lower the precipitation, or the lower the sun intensity, the higher the risk of death from seasonal influenza. It was further observed that when the data were examined by demographic features that both males and females revealed significant inverse relationships between the climate conditions examined and the death rate from seasonal influenza. By contrast, it was observed that among the different racial and urbanization groups examined, there were very significant differences in the relationship between climate conditions and death rate from seasonal influenza.

The results of this study are consistent with a number of previous ecological studies examining climate conditions and seasonal influenza epidemics across temperate climates. For example, investigators modeled the relationship between seasonal influenza epidemics in relation to climatic conditions in 78 locations from around the world.

Table 4. A summary of the correlation[a] between climate exposure variables and influenza death rate broken down by state from 1999 through 2011 for different demographic groups.

Breakdown of Data Examined (# of obs)	Mean Daily Sunlight in KJ/m[b] vs Influenza Death Rate	Mean Daily Max Air Temperature in °C vs Influenza Death Rate	Mean Daily Min Air Temperature in °C vs Influenza Death Rate	Mean Daily Precipitation in mm vs Influenza Death Rate
Gender				
Males (n = 48)	***Rho = −0.383 95% CI = −0.602 to −0.111 p = 0.0076***	***Rho = −0.504 95% CI = −0.689 to −0.257 p = 0.0003***	***Rho = −0.613 95% CI = −0.764 to −0.398 p < 0.0001***	***Rho = −0.440 95% CI = −0.644 to −0.178 p = 0.0019***
Females (n = 49)	***Rho = −0.543 95% CI = −0.715 to −0.308 p < 0.0001***	***Rho = −0.585 95% CI = −0.744 to −0.364 p < 0.0001***	***Rho = −0.677 95% CI = −0.805 to −0.489 p < 0.0001***	***Rho = −0.292 95% CI = −0.529 to −0.011 p = 0.0424***
Race[b]				
Hispanic or Latino (n = 19)	Rho = 0.453 95% CI = −0.002 to 0.752 p = 0.0523	Rho = 0.08 95% CI = −0.388 to 0.515 p = 0.7427	Rho = −0.051 95% CI = −0.494 to 0.413 p = 0.8372	***Rho = −0.802 95% CI = −0.921 to −0.547 p < 0.0001***
Black or African American (n = 28)	Rho = −0.153 95% CI = −0.498 to 0.233 p = 0.4345	Rho = −0.203 95% CI = −0.535 to 0.184 p = 0.3	Rho = −0.228 95% CI = −0.554 to 0.158 p = 0.2417	Rho = −0.337 95% CI = −0.631 to 0.041 p = 0.0793
White (n = 48)	***Rho = −0.515 95% CI = −0.697 to −0.27 p = 0.0002***	***Rho = −0.521 95% CI = −0.701 to −0.278 p = 0.0002***	***Rho = −0.622 95% CI = −0.77 to −0.41 p < 0.00001***	***Rho = −0.298 95% CI = −0.537 to −0.015 p = 0.0399***
2006 Urbanization				
Large Central Metro (n = 31)	Rho = −0.160 95% CI = −0.487 to 0.206 p = 0.3884	Rho = −0.352 95% CI = −0.628 to 0.003 p = 0.0528	***Rho = −0.396 95% CI = −0.658 to −0.048 p = 0.0284***	Rho = −0.195 95% CI = −0.514 to 0.171 p = 0.2914
Large Fringe Metro (n = 32)	***Rho = −0.356 95% CI = −0.627 to −0.009 p = 0.046***	***Rho = −0.417 95% CI = −0.669 to −0.080 p = 0.0183***	***Rho = −0.458 95% CI = −0.696 to −0.130 p = 0.009***	Rho = −0.147 95% CI = −0.417 to 0.213 p = 0.4217
Medium Metro (n = 40)	***Rho = −0.516 95% CI = −0.713 to −0.244 p = 0.0008***	***Rho = −0.457 95% CI = −0.673 to −0.17 p = 0.0033***	***Rho = −0.512 95% CI = −0.711 to 0.239 p = 0.0008***	Rho = −0.249 95% CI = −0.52 to 0.068 p = 0.1218
Small Metro (n = 39)	***Rho = −0.632 95% CI = −0.790 to −0.4 p < 0.00001***	***Rho = −0.759 95% CI = −0.867 to −0.528 p < 0.0001***	***Rho = −0.792 95% CI = −0.886 to −0.6.35 p < 0.0001***	***Rho = −0.407 95% CI = −0.640 to −0.105 p = 0.0106***
Micropolitan (non-metro) (n = 43)	***Rho = −0.627 95% CI = −0.780 to −0.402 p < 0.0001***	***Rho = −0.682 95% CI = −0.815 to −0.480 p < 0.0001***	***Rho = −0.748 95% CI = −0.856 to −0.578 p < 0.0001***	***Rho = −0.411 95% CI = −0.633 to −0.126 p = 0.0065***
Noncore (non-metro) (n = 41)	***Rho = −0.374 95% CI = −0.611 to −0.075 p = 0.0165***	***Rho = −0.586 95% CI = −0.757 to −0.340 p < 0.00001***	***Rho = −0.658 95% CI = −0.803 to −0.44 p < 0.0001***	***Rho = −0.560 95% CI = −0.740 to −0.305 p = 0.0002***

Note: Bold-Italics results are statistically significant.
[a] The Spearman's rank correlation statistic was employed.
[b] Analyses by Asian or Pacific Islander and American Indian or Alaska Native were not possible because there were too few influenza deaths by state. A total of 16,969 influenza deaths were identified, but 43 did not state Hispanic origin or not and were excluded from the table.

They observed in temperate climates that there were peaks in seasonal influenza epidemics during the months of lowest temperature, humidity, and solar radiation [11]. Similarly, other investigators examined in the temperate climate of France the relationship between the annual incidence rate of seasonal influenza and climate conditions in different regions in France [12]. They reported that the climate conditions associated with variations in temperature, humidity, and sunshine were significantly related to the weekly incidence rate of influenza within a single year. Finally, still other investigators examined climate conditions and influenza mortality data in the USA on a monthly basis from January 1973 to December 2002 among 359 urban counties [13]. They reported that the climate conditions of humidity and temperature were significantly associated with differences in seasonal influenza mortality.

The results of this study build upon and extend further the results reported in the aforementioned studies for several reasons. First, this study integrated several independent databases utilizing the CDC Wonder online computer interface. As a result, the ability for other investigators to access data examined in this study is simpler because of the CDC Wonder online computer interface. The CDC Wonder online computer interface provides a more comprehensive means to, in much greater detail, analyze the potential relationship between climate conditions and seasonal influenza death rate. The data analyzed in previous studies is generally not available to the public and the data collection methods utilized are fraught with many potential difficulties (i.e., individual weather stations, voluntary reporting of cases of influenza by healthcare providers, etc.). Second, the scale of climate differences examined is much larger than in previous studies. This study analyzed climate differences across multiple years and multiple geographic locations in the USA, where as the previous studies analyzed subsets of the population in the USA or the much small country of France. Third, this study also integrated demographic variables such as gender, race, and urbanization as part of the assessment of the correlation between climate conditions and the seasonal influenza death rate. None of the previously mentioned studies were able to undertake such analysis.

The results observed in this study are biologically plausible. It was previously suggested that temperature, solar radiation, and precipitation are known to significantly impact the transmissibility of influenza virus [1]. It was demonstrated in several laboratory experiments that cold and dry conditions are important in increasing influenza virus persistence in the air and increased transmission [14,15]. It was also described that inhibition of mechanical defenses of the respiratory mucosa and the immune system may be caused by the effects of the inhalation of cold air on nasal epithelium [16]. It was also suggested that solar radiation degrades influenza virus [1]. Finally, it was also described that solar radiation triggers robust seasonal vitamin D production in the skin, and because of vitamin D's known anti-infective/immune modulating properties, the consequence of vitamin D deficiency in winter months may mediate increased seasonal influenza epidemics [17].

In addition, while not the primary focus of the present study, it was observed that other factors such as gender, ethnicity, and urban/rural areas were found to be significantly related to the seasonal influenza death rate. It was specifically found that the death rate from seasonal influenza was significantly higher among males as compared to females. In addition, it was observed that the when examining the seasonal influenza death rate by race that relative to their general population percentage, Whites were significantly over represented, whereas Hispanics or Latinos, Blacks or African Americans, and Asians or Pacific Islanders were significantly under represented. Finally, it was observed that the seasonal influenza death rate was significantly higher in rural areas in comparison to large metropolitan areas. These results are consistent with a number of previous investigations examining demographic factors associated with influenza cases or deaths in temperate climates. For example, previous investigators examining ecological factors associated with pandemic influenza A (H1N1) hospitalization rates in the state of California revealed hospitalization rates were spatially dependent [18]. As another example, transmission of influenza A and B in a Pennsylvania school-based study population revealed that race was a significant mediating factor [19]. It would be worthwhile in future hypothesis-testing studies to more fully evaluate the biological mechanisms (e.g., genetic susceptibility, different social interactions, environmental exposures, etc) involved in potentially mediating the significant differences observed in demographic variables and the death rate from seasonal influenza.

Strengths/limitations

An important strength of this study is the overall study design employed to evaluate the potential correlation between climate conditions and the death rate from seasonal influenza. This study is apparently the first to integrate the independent Underlying Cause of Death and the NLDAS databases using the publically available CDC Wonder online computer interface. As a consequence, it was possible to examine on a longitudinal basis by geographic areas detailed population demographics (gender, race, urbanization) and medical outcomes (i.e., ICD-10 coding) from the Underlying Cause of Death database with detailed climate conditions from the NLDAS database. The complete independence of data collection methods, the multiple esteemed US government agencies involved in voluminous and detailed data acquisition and compiling, coupled with the ability to clearly and easily integrate the data from the two databases for the analyses undertaken in this study, strongly support the validity of the observations made in this study.

Another important strength of this study was the consistency of the inverse correlations observed between climate conditions and seasonal influenza death rate. It was found in every statistical analysis that the magnitude and the direction of the phenomena observed were consistent. This argues against the phenomena observed being the result of statistical chance. Importantly, it was also revealed that as the data were broken down further by geographical location and time variables that the magnitude and significance of the results observed increased. This, again, strongly suggests the validity of the correlations observed in this study.

A potential limitation of this study was that it employed an ecological study design. As such, it was not possible to examine the exact exposure history of each individual, and to determine a potential direct cause and effect relationship between climate conditions and seasonal influenza deaths. Despite this potential limitation, it was observed that as geographical location and time variables were further broken down, the more significant the observed phenomena became. This helps to support that the phenomena observed are genuine. In future studies, it would be worthwhile to further examine the consistency of the phenomena observed in this study, with more detailed records of climate exposure variables for each individual examined in the study to allow for a more direct cause and effect relationship to be determined.

Another potential limitation of this study was that only 16,969 seasonal influenza deaths were identified for examination in this study. As a consequence, as the seasonal influenza deaths were broken down further by location, time, and demographic variables the numbers became much smaller, and in some cases, it was not possible to analyze any numbers at all (i.e., the CDC Wonder online computer interface will not output results with numbers of sub-national data representing 0–9 deaths because of assurance of confidentiality concerns). The result of this limitation was a potential decreased statistical power to find potential correlations between environmental conditions and seasonal influenza death rates. Despite this limitation, given the breadth and the scope of the data examined, it did not significantly impact the ability of this study to find potential statistical correlations between environmental conditions and seasonal influenza death rates. It would be worthwhile in future studies to further explore the consistency of the phenomena observed in this study with other populations and other databases.

An additional potential limitation of this study was that only seasonal influenza deaths were examined. It was not possible from the data sources examined to evaluate the frequency of seasonal influenza cases. The examination of seasonal influenza cases is important because there are a larger number of seasonal influenza cases than deaths. As a result, seasonal influenza cases may allow for a more detailed analysis than the one undertaken in the present study. In addition, evaluation of seasonal influenza cases may help to examine the uncertainty of why seasonal influenza deaths are related to climate and other factors. Namely, it would help to determine whether more persons get seasonal influenza or a higher proportion of persons getting seasonal influenza die. It is recommended that future studies further explore this phenomenon.

It is also a possible limitation of this study that there were errors in identifying/recoding the true cause of death in the Underlying Cause of Death database and errors in recording/calculating the climate conditions analyzed in the NLDAS database. It is presumed that if such inaccuracies occurred in the data that they would have occurred with similar frequency among the different databases examined. Therefore, if such phenomena were present in the data examined, it would have reduced the statistical power of this study.

Conclusion

This longitudinal ecological study was the first to integrate data from the independent Underlying Cause of Death and NLDAS databases using the publically available CDC Wonder online computer interface. The results of this study revealed that diverse differences in microenvironment climate conditions in the contiguous USA were significantly inversely associated with the death rate from seasonal influenza from 1999 through 2011. This study also revealed for the first time that significant inverse correlations between microenvironment climate conditions and influenza death were significantly influenced by demographic factors such as gender, race, and urbanization. The methods developed and utilized in this study should be employed to evaluate the potential relationship between climate conditions and other human diseases. It is also hoped that future studies will further examine the phenomena observed in this study with other populations and databases.

Disclosure statement

Dr. Mark Geier and David Geier are directors of the Institute of Chronic Illnesses, Inc., and CoMeD, Inc. Neither the Institute of Chronic Illnesses, Inc., nor CoMeD, Inc., have any financial interest in the outcome of influenza. No other authors have a management or directorship position at the Institute of Chronic Illnesses, Inc., or CoMeD, Inc.

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