Absolute Humidity, Temperature, and Influenza Mortality: 30 Years of County-Level Evidence from the United States

Author 1: Alan I. Barreca (corresponding author)

Title and affiliation
- Assistant Professor
- Department of Economics, Tulane University

Degrees
- PhD in Economics, University of California, Davis
- MA in Economics, University of California, Davis
- BS in Economics, Santa Clara University

Contact details
- Office: 504-252-0258
- Fax: 504.865.5869
- Email: abarreca@tulane.edu

Full address

Alan Barreca
206 Tilton Hall
Tulane University
New Orleans, LA 70118

Author 2: Jay P. Shimshack

Title and affiliation
- Associate Professor
- Department of Economics, Tulane University

Degrees
- PhD in Agricultural and Resource Economics, University of California, Berkeley
- MS in Agricultural and Resource Economics, University of California, Berkeley
- BS in Business Marketing and Management, Cornell University

Contact details
- Office: 504.862.8353
- Fax: 504.865.5869
- Email: jshimsh@tulane.edu

Acknowledgements

Author affiliations: Department of Economics, Tulane University, New Orleans, Louisiana (Alan Barreca and Jay Shimshack). The authors thank Nick Sanders, Charles Stoecker, and the participants at the 2011 Western Economic Association conference for providing helpful comments. This work not supported by external grants. Conflicts of interest: none declared.

Running head

Absolute Humidity, Temperature, and Influenza

Absolute Humidity, Temperature, and Influenza Mortality: 30 Years of County-Level Evidence from the United States

ABSTRACT: Recent research exploring associations between environmental factors and influenza outcomes has devoted substantial attention to the role of absolute humidity. Yet, the existing literature provides very little quantitative epidemiological evidence on the relationships between absolute humidity, other weather variables, and influenza outcomes in human populations. The present study helps fill this gap by analyzing longitudinal weather and influenza mortality data, observed every month between January 1973 and December 2002, for each of 359 urban US counties. A flexible regression model simultaneously explores fully nonlinear relationships between absolute humidity and influenza outcomes, and temperature and influenza outcomes. Results indicate that absolute humidity is an especially critical determinant of observed human influenza mortality, even after controlling for temperature. There are important non-linear relationships; humidity levels below approximately 6 grams of water vapor per kilogram of air are associated with increases in influenza mortality. Model predictions suggest that approximately half of the average seasonal differences in US influenza mortality can be explained by seasonal differences in absolute humidity alone. Temperature modestly influences influenza mortality as well, although results are less robust.

KEYWORDS: disease susceptibility; disease transmission, infectious; humidity; temperature; influenza, human; mortality; virus survival

ABBREVIATIONS: C, Celsius; CI, Confidence interval; F, Fahrenheit; g/kg, Grams of water vapor per kilogram of air; ICD, International Classification of Diseases; mm, Millimeters; SIR, Susceptible infected recovered; US, United States.

WORD COUNTS: Abstract – 178 words; Text – 3,489 words

Absolute Humidity, Temperature, and Influenza Mortality: 30 Years of County-Level Evidence from the United States

Estimates suggest that influenza causes between 1,700 and 59,000 deaths annually in the United States (1-6). Total morbidity from influenza is poorly understood, but also represents a significant public health threat. Despite the widespread prevalence, mechanisms driving influenza host susceptibility, disease transmission, and virus survival remain controversial (7,8).

Observers have long suspected that environmental factors are among the key determinants of influenza incidence, primarily because outbreaks exhibit pronounced seasonal and geographic patterns. Early experimental studies found that solar insolation reduces influenza virus survival (9-11). More recent related investigations showed that increased vitamin D levels may enhance host immunity (12-14). Other work found that low relative humidity and low temperature favor influenza virus survival and disease transmission (15-18). Cold temperatures and precipitation may also cause susceptible individuals to move indoors, thereby increasing disease transmission (19,20).

Of late, the literature exploring environmental determinants of influenza has devoted substantial attention to absolute humidity. In contrast to relative humidity, which is a function of water vapor and temperature, absolute measures of humidity isolate the water vapor content in a mass (or parcel) of air. A reevaluation of an experimental study involving guinea pigs found that low absolute humidity is better than low relative humidity at predicting influenza transmission (21-22). Recent epidemiologic evidence, using aggregate state-level data from the United States, showed that anomalous drops in absolute humidity predict the onset of human influenza outbreaks as measured by excess mortality (23). Emerging simulation evidence on pandemic outbreaks is further supportive of a link between declines in absolute humidity and enhanced disease transmission or virus survival (8).

Despite recent advances, the literature provides little quantitative epidemiological evidence on the simultaneous relationships between absolute humidity, other weather variables, and influenza outcomes in human populations. This paper helps fill that gap. The present study analyzes longitudinal weather and influenza data, observed every month between January 1973 and December 2002, for each of 359 urban US counties. The aim is to understand the simultaneous impacts of absolute humidity and temperature on influenza mortality.

The authors believe this analysis makes several contributions. First, the data permit the first large-scale ecologic analysis of the impact of absolute humidity and other weather conditions on human influenza mortality. Second, weather data observed at the county-level reduce misclassification errors that may plague data observed at larger geographic scales like states or nations. Third, the study's statistical methods control for numerous possible confounders, reducing the possibility that observed weather-influenza links are driven by omitted factors independently associated with both environmental factors and influenza. Fourth, the analysis considers temperature and humidity simultaneously, allowing the researchers to separately assess: (a) the effects of humidity holding other weather conditions constant, and (b) the effects of temperature holding other weather conditions constant. Since temperature and absolute humidity are naturally related (7,23), models that individually examine temperature or humidity will inaccurately estimate their respective effects on influenza morbidity and mortality.

MATERIALS AND METHODS

Influenza Mortality Data

Mortality data were obtained from the National Center of Health Statistics' Multiple Causes of Death files. All deaths with an International Classification of Diseases (ICD) code associated with "influenza" for a primary or secondary cause were categorized as influenza mortality (24,25). Dushoff et al. (6) showed that these multiple-cause influenza classifications are significantly more robust than single underlying-cause classifications alone. For each county and month, mortality rates per 100,000 individuals were calculated by dividing the total influenza death counts by the estimated population in 100,000s. Population data for each county-year were obtained from the National Cancer Institute's Surveillance Epidemiology and End Results series.

It is likely that influenza mortality rates are measured with error. Influenza deaths are not always corroborated virologically, and deaths due to influenza may be attributed to other respiratory and circulatory diseases (6,26). ICD coding practices changed in 1979 and 1999. ICD coding may vary across seasons, and misclassifications may be more prevalent in summer months. ICD coding may also vary systematically across locations due to differences in age profiles, availability of virus surveillance, and other factors.

Weather Data

Weather data were obtained from the National Climatic Data Center's Global Summary of the Day files. The weather data are organized by station and day. Daily mean temperatures were reported in degrees Fahrenheit (°F). Daily specific humidity, a common measure of absolute humidity, in grams of water vapor per kilogram of air (g/kg) was calculated from daily dew point and atmospheric pressure data following standard meteorological formulas (27,28). Daily total precipitation was obtained in inches. All station-days missing absolute humidity were dropped (0.4% of all station days) and all station-days missing precipitation were dropped (3.0% of all station days). Stations missing more than half of the absolute humidity and/or precipitation observations for any given year between 1973 and 2002 were then dropped entirely.

Associations between environmental factors and mortality are likely nonlinear, but the precise functional forms are unknown a priori. Commonly postulated relationships for temperature and mortality are U- or J-shaped (29). One recent study presents evidence that the relationship between absolute humidity and all-cause mortality is reverse J-shaped (30). Consequently, for each station-day, the present study constructs all weather exposure assessments from piecewise splines. Splines allow the relationships between weather conditions and mortality to vary flexibly at different points along the factor's distribution, but do not require the researchers to choose a specific functional form ahead of time. For this reason, the use of splines is increasingly common in the epidemiologic literature (31).

In our application, piecewise cubic splines were constructed with the STATA11 command 'mkspline', so that the final relationship between mortality and the given weather condition is a piecewise function composed of polynomial segments (32). Note that the cubic spline allows for smoothness at the knots, unlike a linear spline. For the technically inclined reader, absolute humidity functions have knots at 3, 6, 9, 12, 15, and 18g/kg. Temperature functions have knots at 15, 30, 45, 60, 75, and 90°F (-9.4, -1.1, 7.2, 15.6, 23.9, and 32.2°C) and precipitation functions have knots at 0.25, 0.50, 0.75, 1.00 inches (6.4, 12.7, 19.1, and 25.4 mm).

Analysis Sample

The final unit of analysis is county by month. No spatial or temporal aggregation was necessary for mortality outcomes, which are reported at the county-month level in the Multiple Cause of Death Public Use dataset. However, both spatial and temporal aggregation was necessary for the weather exposure variables, as weather conditions are reported at the station-day level.

Aggregating weather exposure to county-month level independent variables involves three steps. First, the spline exposure variables described above were aggregated to the county-day level by calculating the inverse distance-weighted average over all stations within 50 miles of each county's geographic centroid (33). Second, the county-day exposure variables were averaged across days within a county-month. Note that averaging spline variables preserves weather information from all days, including extreme weather days. Third, the weather exposure variables were averaged over the current and preceding month. This two-month moving average lag structure allows time for disease transmission, permits lags between infection and death, and permits lags between surveillance culture results and ICD coding. Evidence suggests such lags may be important (6,34). An additional advantage of the two-month moving average is that it minimizes potential biases from short-term "harvesting" (29,35). If the weather accelerates some deaths by a few days or weeks, these deaths will not impact our estimates. We denote our final exposure functions as f(*HUMID*), g(*TEMP*), h(*PRCP*).

The final longitudinal dataset contains 129,240 observations on 359 urban counties observed over 360 months spanning January 1973 to December 2002. The 359 densely populated counties in the sample contained 65% of total the US population over the sample period. More rural counties were not evaluated for data availability reasons. Counties with fewer than 100,000 inhabitants between 1973 and 2002 lacked complete mortality data and were not evaluated. 11% of counties with complete mortality data lacked complete weather station data and were thus also not evaluated.

Statistical Analysis

This study's primary statistical strategy is to regress a given county's influenza mortality in a given time period on flexible non-linear functions of that county's absolute humidity, temperature, and precipitation in the recent past (a two month moving average). The basic statistical model is:

$$MORT = f(HUMID) + g(TEMP) + h(PRCP) + \mu_{cm} + \Phi_t + \varepsilon.$$

MORT is the influenza mortality rate for a given county and month. f(*HUMID*), g(*TEMP*), and h(*PRCP*) are the exposure functions for absolute humidity, temperature, and precipitation. The model estimates several parameters for each exposure function. μ_{cm} are estimated county by calendar-month fixed effect parameters and Φ_t are estimated time period fixed effect parameters. ε is a normally distributed error term.

The county by calendar-month fixed effects μ_{cm} are included so that our model estimates relationships between anomalous mortality rates and anomalous weather conditions for a given county and calendar month. This approach is equivalent to estimating seasonal mortality baselines for each county and then analyzing excess deaths only. These fixed effects also minimize omitted variable concerns that might arise from potential confounders that vary across counties and/or seasons but remain roughly constant across years. Examples of potential crosscounty or seasonal confounding factors in this context include miscoding of influenza deaths, income, socioeconomic status, race, age, industrial composition, population density, air pollution, air conditioning usage, school characteristics, and school attendance (29).

Time period fixed effects Φ_t are included to minimize omitted variable concerns that might arise from potential confounders that are common to all sample counties but vary over time. Examples of time varying confounding factors in this context include macroeconomic shocks that influence health behaviors, technological advances in health treatments, and trends in vaccination rates. Time period fixed effects are equivalent to fully flexible national time trends.

As an interpretation exercise, we also predict how much of the difference in influenza mortality between January and July can be explained by seasonal differences in humidity. To do so, we predict each month's average influenza mortality as a function of average absolute humidity in that month by multiplying: the average frequency of days at a given point on the humidity distribution –and– our core estimates of the humidity-influenza relationship. Second, we calculate the difference between the predicted influenza mortality in January and the predicted influenza mortality in July. Third, we calculate the difference between actual influenza mortality in January and actual influenza mortality in July. Fourth, we divide the predicted difference (step 2) by the observed difference (step 3) to obtain a ratio.

Analysis is carried out with STATA11 (32). Standard errors used to calculate confidence intervals are clustered to allow for arbitrary serial correlation at the state level.

RESULTS

Table 1 summarizes the sample data, over all months and by calendar month. For our 359 urban US counties, monthly influenza mortality rates averaged 0.071. Mortality rates were substantially higher when deaths containing pneumonia as a primary or secondary cause were also included. Influenza mortality was as much as 40 times higher during December to March than during June to September.

Perhaps the most striking feature of Table 1 is the seasonal correlation between absolute humidity and temperature. Monthly absolute humidity data in column 1 and monthly temperature data in column 2 have a correlation of 0.96. This large correlation implies that: (a) causal relationships are unlikely to be correctly identified in models that do not analyze humidity and temperature simultaneously, and (b) datasets with a large degree of spatial and temporal variation, like the one used here, are necessary to statistically distinguish the effects of humidity from temperature. Figure 1 illustrates the average cross-state differences in influenza mortality rates for the years 1973-2002. Like Table 1, the raw averages in Figure 1 are suggestive of a relationship between weather and influenza mortality.

Figure 2 shows the main results. The general relationship between absolute humidity and influenza mortality follows a downward sloping exponential shape. Low humidity levels are associated with statistically significant increases in influenza mortality. For example, on average, a shift in the annual distribution of humidity levels that produces one additional day at 3g/kg, and one less day at 9g/kg, is associated with a 0.6% (95% confidence interval [CI]: 0.3%, 0.9%) increase in mortality relative to the average annual influenza mortality rate. For mean daily specific humidity levels below 6g/kg, the lower the humidity level the greater the increase in average influenza mortality. Similarly, on average, a shift in the annual distribution of daily humidity levels that produces one additional day at 1g/kg, but one less day at 9g/kg, is associated with a 1.2% (95% CI: 0.6%, 1.8%) increase relative to the average annual influenza mortality rate. While there is a statistically significant negative relationship between humidity and influenza mortality at mean daily humidity levels below 6g/kg, this study detects no relationship between humidity and influenza mortality at mean daily humidity levels above 6g/kg.

The detected association between absolute humidity and influenza mortality is practically large, and our results indicate that changes in absolute humidity alone can explain much of influenza's seasonality in the US. The core model predicts that approximately one-half (51%) of the difference between the average US January influenza mortality rate and the average US July influenza mortality rate can be explained by average seasonal differences in absolute humidity alone.

The general relationship between temperature and influenza mortality follows a bell shaped curve. This study detects no statistically significant relationship between temperature and influenza mortality at mean daily temperatures below approximately 15°F (-9.4°C) or above approximately 60°F (15.6°C). Mean daily temperatures between 15°F (-9.4°C) and 30°F (-1.1°C) are also not associated with statistically significant changes in influenza mortality, but point estimates are large in magnitude. Mean daily temperatures between 30°F (-1.1°C) and 60°F (15.6°C) are associated with statistically significant increases in influenza mortality, with the peak influenza mortality impact around a mean daily temperature of 30°F (-1.1°C). On average, a shift in the annual temperature distribution that produces one additional day at 30°F (-1.1°C), but one less day at 65°F (18.3°C), is associated with a 0.8% (95% CI: 0.1%, 1.8%) increase in mortality relative to relative to the average annual influenza mortality rate. A shift in the annual temperature distribution that produces one additional day at 50°F (10°C), but one less day at 65°F (18.3°C), is associated with a smaller, but still significant, 0.3% (95% CI: 0.1%, 0.5%) increase relative to the average annual influenza mortality rate.

Sensitivity analysis

A natural concern is that influenza deaths are not always corroborated virologically. So, following Dushoff et al. (6), we conducted a sensitivity investigation that replicated the analysis using outcome measures that include both influenza and pneumonia as primary or secondary causes of death. Results in Figure 3 indicate that the qualitative humidity-mortality and temperature-mortality relationships are similar to main results in Figure 2. With much higher death rates from pneumonia and some pneumonia deaths being unrelated to influenza, relative magnitudes are considerably smaller in magnitude as expected.

Another concern is that ICD coding practices change over time. To address possible concerns about long-run changes in classification systems, we conducted a sensitivity investigation that replicated the analysis using only the ICD-9 years (1979-1998). Results in Figure 4 indicate that the humidity-mortality relationships are similar to main results in Figure 2. The relationship between temperature and influenza mortality, however, is less robust. To address possible concerns about seasonal differences in coding, we conducted a sensitivity investigation that replicated the analysis omitting summer months (where the probability of influenza misclassification may be higher). Results in Figure 5 are similar to our main results in Figure 2.

Next, we address concerns that our results are driven by our choice of lag structure (i.e. two months). Results in Web Figure 1 indicate that different exposure lag structures generate qualitative humidity-mortality and temperature-mortality relationships that are similar to main results in Figure 2. The only major difference is that the magnitude of weather-mortality relationships is diminished when exposure variables are based on contemporaneous months alone. This suggests that short-term exposure variables may underestimate relationships between weather and influenza mortality.

We verify that our estimates are robust to changes in how we control for potential confounders. Results in Web Figure 2 indicate that different fixed effect approaches generate humidity-mortality relationships that are similar to main results in Figure 2. The relationship between temperature and influenza mortality, however, is less robust. Note that all specifications with county fixed effects (as opposed to county by calendar-month fixed effects) generate smaller weather-mortality relationships. This suggests that failure to account for local seasonality may underestimate relationships between weather and influenza mortality.

Finally, we investigate whether estimated relationships vary geographically within the US Unfortunately, a full regional investigation is beyond the scope of the present study, as the high correlation between temperature and humidity in nature complicates estimation of models that select on counties with similar climates. Web Figures 3 and 4 indicate that relationships between weather and influenza mortality are roughly similar between "high" and "low" humidity counties and between "high" and "low" temperature counties. In Web Figure 3, we find a somewhat more pronounced effect of low absolute humidity on influenza mortality in those counties with typically high average humidity. In Web Figures 3 and 4, we find a somewhat more pronounced effect of temperature on influenza mortality in those counties with typically less humid conditions and in those counties with typically colder conditions.

DISCUSSION

This study provides novel ecologic evidence that absolute humidity and temperature impact influenza mortality in human populations. Most significantly, this research supports the emerging hypothesis that absolute humidity is a critical determinant of observed influenza outcomes, even after controlling for temperature. These results bolster recent laboratory findings from guinea pigs and state-level epidemiologic evidence (21,23). An additional key result is that the humidity-influenza relationship is nonlinear. Lower humidity levels only result in greater influenza mortality at mean daily specific humidity levels below 6g/kg. Incremental changes in humidity do not significantly affect influenza mortality when mean daily specific humidity exceeds a 6g/kg threshold. Temperature appears to be an important determinant of human influenza outcomes, even after controlling for absolute humidity. However, temperature-mortality estimates are sensitive to model specification.

Our results have important implications for public health and policy. Estimates can be used to help predict the location and timing of future influenza mortality. In addition, highlighted nonlinearities between influenza mortality and absolute humidity may be especially useful for understanding regional variation in influenza outcomes triggered by climate change.

The present study's data and methods permit an unusually large-scale and robust quantitative assessment of the relationship between weather conditions and influenza mortality. However, we note two limitations related to outcome measures. First, the outcome measure (mortality) does not directly incorporate impacts on influenza morbidity, which may be more directly linked to humidity and temperature than influenza mortality. Second, all outcome measures are measured with error. The present study's goal is to explore the relationship between weather conditions and *observed* influenza mortality, not to explore the total number of deaths that are attributable to influenza. Under the assumption of uncorrelated errors of measurement, quantitative assessments of weather-influenza relationships from regression models are correct on average (36). However, regression standard errors may be inflated. As a consequence, it may be more difficult to reject the null hypothesis of no relationship between weather conditions (i.e. temperature) and influenza mortality.

We note other limitations. First, we cannot completely rule out confounding factors. Our modeling strategy controls for confounding factors that are approximately fixed at the county-level, vary by season at the county-level, or vary across time at the national level. However, omitted variables can bias estimated relationships if the omitted factors are correlated with anomalous, rather than typical, weather outcomes. Specifically, pollution concentrations, air conditioning usage, school attendance, and ICD coding errors that vary with unusual weather conditions could bias results. Second, the present study remains agnostic on specific mechanisms. We cannot definitely differentiate between host susceptibility, disease transmission, and virus survival channels, nor can we definitively identify if indoor or outdoor exposure drives our results. It is interesting to note, however, that the present study's results show that absolute humidity significantly impacts influenza outcomes even after controlling for temperature and precipitation events that may cause crowding indoors. It is unlikely that behavior responds directly to absolute humidity in isolation, so results may be suggestive of virus survival or host susceptibility mechanisms. Third, SIR dynamics are not a feature of our model. Fourth, our study is set in the temperate climate of the US. Our results do not shed light on the long-standing puzzle of rainy season influenza epidemics in tropical countries or semi-tropical regions within the US (like the Gulf states) (7).

The collective limitations of this study and related research indicate that much work remains. More laboratory and modeling evidence is necessary to better understand influenza mechanisms. Also, more observational and ecologic evidence is necessary to understand influenza outcomes in a world complicated by human behavior. Nevertheless, this research demonstrates that future explorations that target absolute humidity may produce high returns.

REFERENCES

1. Centers for Disease Control and Prevention. Key facts about influenza (flu) and flu vaccine. 2010. Atlanta, GA: Centers for Disease Control and Prevention. (http://www.cdc.gov/flu/keyfacts.htm). (Accessed July 1, 2011).

2. Simonsen L, Clarke MJ, Williamson GD, et al. The impact of influenza epidemics on mortality: introducing a severity index. *Am J Public Health* 1997;87(12):1944-1950.

3. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;289(2):179-186.

4.Simonsen L, Reichert TA, Viboud C, et al. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med* 2005;165(3):265-272.

5. Greene SK, Ionides EL, Wilson ML. Patterns of influenza-associated mortality among US elderly by geographic region and virus subtype, 1968-1998. *Am J Epidemiol* 2006;163(4);316-326.

6. Dushoff J, Plotkin JB, Viboud C, et al. Mortality due to influenza in the United States – An Annualized Regression Approach Using Multiple-Cause Mortality Data. *Am J Epidemiol* 2006;163(2):181-187.

7. Tamerius J, Nelson MI, Zhou SZ, et al. Global influenza seasonality: Reconciling patterns across temperate and tropical regions. *Environ Health Perspect* 2011:119(4):439-445.

8. Shaman J, Goldstein E, Lipsitch M. Absolute humidity and pandemic versus epidemic influenza. *Am J Epidemiol* 2011;173(2):127-135.

9. Tamm I, Fluke DJ. The effect of monochromatic ultraviolet radiation on the infectivity and hemagglutinating ability of the influenza virus type A strain PR-8. *J of Bacteriol* 1950;59(4):449-461.

10. Powell WF, Setlow RB. The effect of monochromatic ultraviolet radiation on the interfering property of influenza virus. *Virology* 1956;2(3):337-343.

11. Jensen MM. Inactivation of airborne viruses by ultraviolet irradiation. *Appl Microbiol* 1964;12(5):418-420.

12. Cannell, JJ, Vieth R, Umhau, JC, et al. Epidemic influenza and vitamin D. *Epidemiol Infect* 2006;134(6):1129-1140.

13. Aloia, JF, Li-Ng M. Re: epidemic influenza and vitamin D [letter]. *Epidemiol Infect* 2007;135(7):1095-1096.

14. Urashima M, Segawa T, Okazaki M, et al. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* 2010;91(5):1255-1260.

15. Lowen AC, Mubareka S, Steel J, et al. Influenza virus transmission is dependent on relative humidity and temperature. *PLoS Pathog* 2007;3(10):1470-1476. (doi:10.1371/journal.ppat.0030151).

16. Lowen AC, Steel J, Mubareka S, et al. High temperature (30 degrees C) blocks aerosol but not contact transmission of influenza virus. *J Virol* 2008;82(11):5650-5652.

17. Polozov IV, Bezrukov L, Gawrisch, et al. Progressive ordering with decreasing temperature of the phospholipids of influenza virus. *Nat Chem Biol* 2008;4(4):248-255.

18. McDevitt J, Rudnick S, First M, et al. Role of absolute humidity in the inactivation of influenza viruses on stainless steel surfaces at elevated temperatures. *Appl Environ Microbiol* 2010;76(12):3943-3947.

19. Urashima M, Shindo N, Okabe N. A seasonal model to simulate influenza oscillation in Tokyo. *Jpn J Infect Dis* 2003;56(2):43-47.

20. Mikolajczyk RT, Akmatov MK, Rastin S, et al. Social contacts of school children and the transmission of respiratory-spread pathogens. *Epidemiol Infect* 2008;136(6):813-822.

21. Shaman J, Kohn M. Absolute humidity modulates influenza survival, transmission, and seasonality. *Proc Natl Acad Sci* 2009;106(9):3243-3248.

22. Lipsitch M, Viboud C. Influenza seasonality: Lifting the fog. *Proc Natl Acad Sci* 2009;106(10):3645-3646.

23. Shaman J, Pitzer V, Viboud C, et al. Absolute humidity and the seasonal onset of influenza in the continental United States. *PloS Bio* 2010;8(2):e1000316. (doi:10.1371/journal.pbio.1000316).

24. National Center for Health Statistics. Estimates of selected comparability ratios based on dual coding of 1976 death certificates by the eighth and ninth revisions of the international classification of diseases. Hyattsville, MD: National Center for the Health Statistics; 1980.

25. Anderson, RN, Minino AM, Hoyert DL, et al. Comparability of cause of death between ICD-9 and ICD-10: preliminary estimates. Hyattsville, MD: National Center for Health Statistics; 2001.

26. Cox NJ, Subbarao K. Influenza. *Lancet* 1999;354(9186):1277-1282.

27. University of Northern British Columbia. Thermodynamic variables: Interpretation of Thermodynamic Indices. Prince George, BC, Canada: University of Northern British Columbia; 2011. (http://weather.unbc.ca/408/data/lab5/thermo_def.html). (Accessed July 6, 2011).

28. World Meteorological Organization. Guide to Meteorological Instruments and Methods of Observation. 7th ed. Geneva, Switzerland: World Meteorological Organization; 2008.

29. Basu R, Samet JM. Relation between elevated temperature and mortality: a review of the epidemiologic evidence. *Epidemiologic Reviews* 2002;24(2):190-202.

30. Barreca, AI. Climate Change, Humidity, and Mortality in the United States. *Journal of Environmental Economics and Management* 2012; 63(1):19-34.

31. Nuvolone D, Balzi D, Chini M, et al. Short-term association between ambient air pollution and risk of hospitalization for acute myocardial infarction: Results of the Cardiovascular Risk and Air Pollution in Tuscany (RISCAT) study. *Am J Epidemiol* 2011;174(1):63-71.

32. Stata Corporation. Stata statistical software, release 11. College Station, TX: Stata Corporation; 2011.

33. Hanigan I, Hall G, Dear KBG. A comparison of methods for calculating population exposure estimates of daily weather for health research. *Intl J Health Geog*. 2006;5:38. (doi:10.1186/1476-072X-5-38).

34. Glezen WP, Payne AA, Snyder DN, et al. Mortality and influenza. *J Infect Dis* 1982;146(3):313-321.

35. Braga, AL, Zanobetti A, Schwartz J. The effect of weather on respiratory and cardiovascular deaths in 12 U.S. cities. *Environ Health Perspect* 2002;110(9):859-863.

36. Greene, WH. Econometric Analysis. 4th ed. Upper Saddle River, NJ: Prentice Hall; 2000.

Table 1. Average Monthly Weather Outcomes and Influenza Mortality Rates, 359 Urban United States Counties, 1973-2002.[a]

Month	Daily specific humidity (g/kg)	Daily temperature °F (°C)	Daily precipitation in inches (mm)	Monthly influenza deaths per 100,000[b,c]	Monthly influenza/ pneumonia deaths per 100,000[b,c,d]
All	7.75	57.7 (14.3)	0.102 (2.59)	0.071	6.254
Jan	4.01	38.4 (3.6)	0.102 (2.59)	0.251	8.744
Feb	4.30	41.6 (5.3)	0.097 (2.47)	0.242	7.526
Mar	5.13	48.3 (9)	0.113 (2.87)	0.162	7.419
Apr	6.30	56.4 (13.5)	0.104 (2.63)	0.043	6.199
May	8.58	64.6 (18.1)	0.109 (2.78)	0.014	5.694
Jun	11.00	71.9 (22.2)	0.108 (2.75)	0.008	5.221
Jul	12.64	75.9 (24.4)	0.104 (2.63)	0.007	5.236
Aug	12.61	74.9 (23.8)	0.106 (2.69)	0.006	5.117
Sep	10.66	69.2 (20.6)	0.107 (2.71)	0.008	5.103
Oct	7.68	59.6 (15.3)	0.087 (2.22)	0.016	5.804
Nov	5.72	50.1 (10.1)	0.097 (2.47)	0.022	5.881
Dec	4.37	41.5 (5.3)	0.091 (2.31)	0.072	7.108

Abbreviation: ICD, International Classification of Diseases.

[a] All summary statistics are calculated using population weights from 2000. [b] The ICD-8 codes were used for the years 1973-1978, ICD-9 codes for the years 1979-1998, and ICD-10 for the years 1999-2002. [c] Influenza deaths include all deaths where influenza is listed as a primary or secondary cause of death. The codes for influenza are 470 through 474 (ICD-8), 487 (ICD-9), and J-10 through J-11 (ICD-10). [d] Influenza/pneumonia deaths include all deaths where influenza and/or pneumonia are listed as a primary or secondary cause of death. The codes for pneumonia are 480 through 486 (ICD-8), 480 through 486 (ICD-9), and J-12 through J-18 (ICD-10).

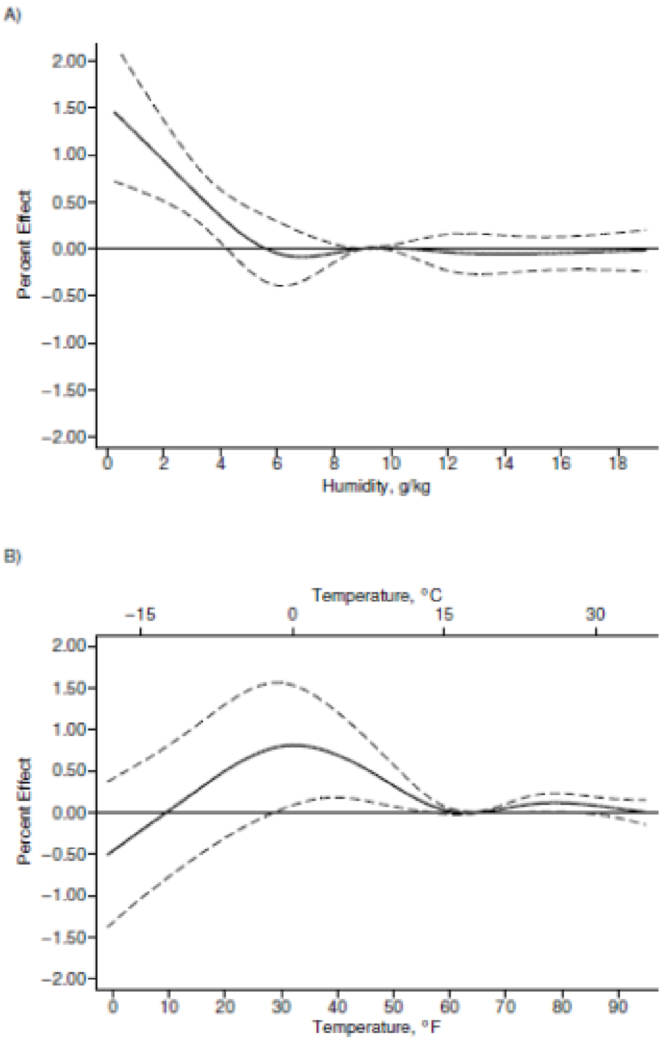


Figure 2: Regression estimates of the relationship between influenza mortality and weather conditions, 359 urban US counties, 1973-2002. In A, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given humidity level, relative to one additional day with a humidity of 9g/kg. In B, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given temperature, relative to one additional day with a temperature of 65°F (18.3°C). All dotted lines represent 95% confidence intervals. In A, low mean daily humidity is associated with statistically increased mortality after controlling for other weather conditions and potential confounders. In B, moderately low mean daily temperature is associated with statistically increased mortality after controlling for other weather conditions and potential confounders.

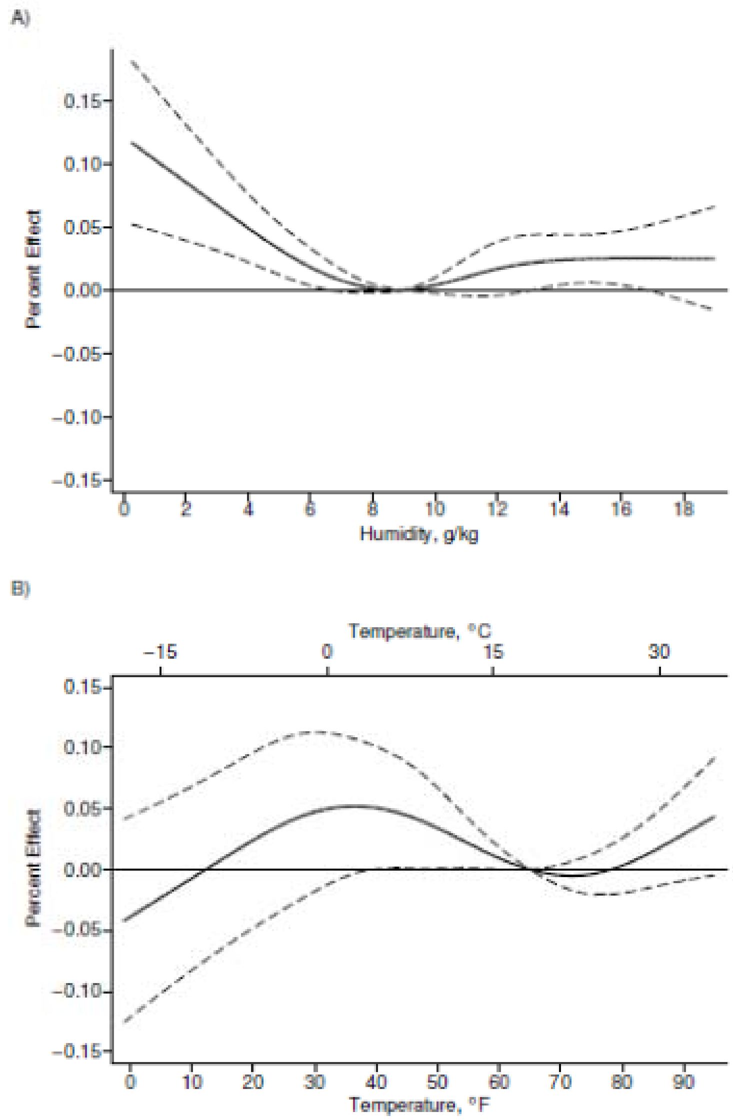


Figure 3: Regression estimates of the relationship between influenza/pneumonia mortality and weather conditions, 359 urban US counties, 1973-2002. In A, the solid line depicts the average percentage change in the annual influenza/pneumonia mortality rate from one additional day at a given humidity level, relative to one additional day with a humidity of 9 g/kg. In B, the solid line depicts the average percentage change in the annual influenza/pneumonia mortality rate from one additional day at a given temperature, relative to one additional day with a temperature of 65°F (18.3°C). All dotted lines represent 95% confidence intervals. Point estimates are qualitatively similar to Figure 2.

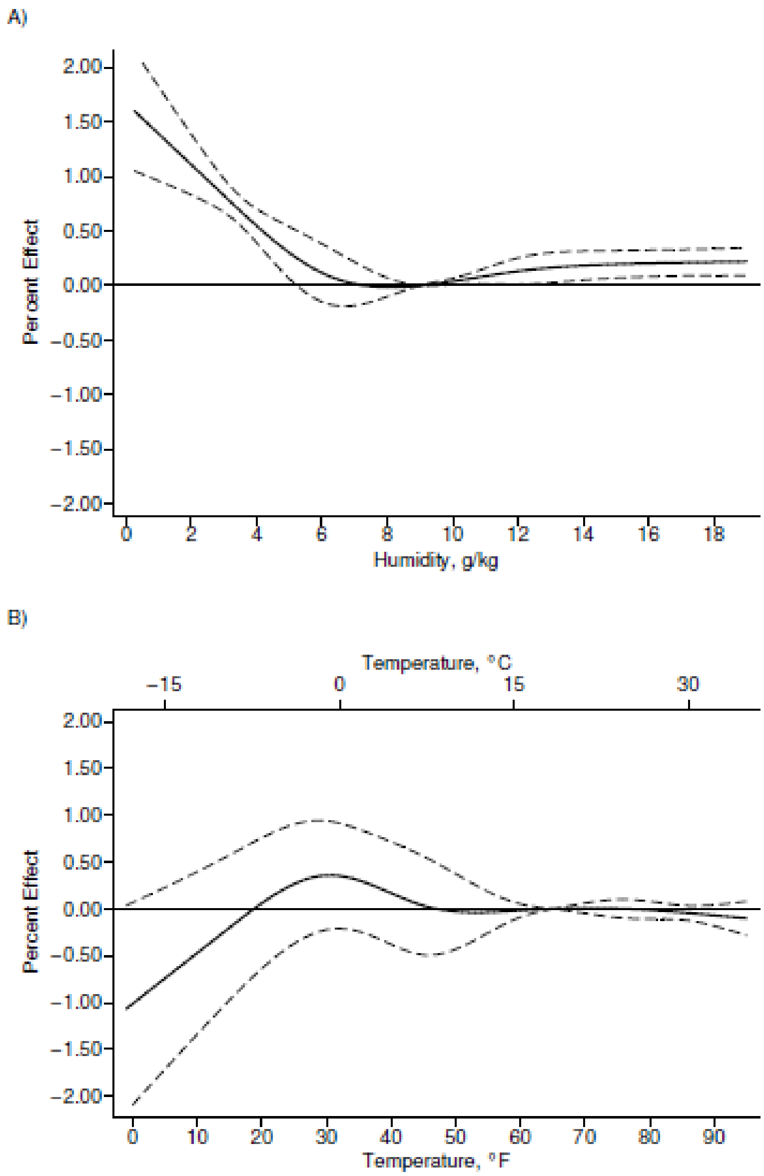


Figure 4: Regression estimates of the relationship between influenza mortality and weather conditions, 359 urban US counties, ICD-9 years (1979-1998) only. In A, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given humidity level, relative to one additional day with a humidity of 9 g/kg. In B, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given temperature, relative to one additional day with a temperature of 65°F (18.3°C). All dotted lines represent 95% confidence intervals. In A, the estimated relationship is qualitatively similar to Figure 2. In B, there is no significant relationship between temperature and mortality, unlike Figure 2.

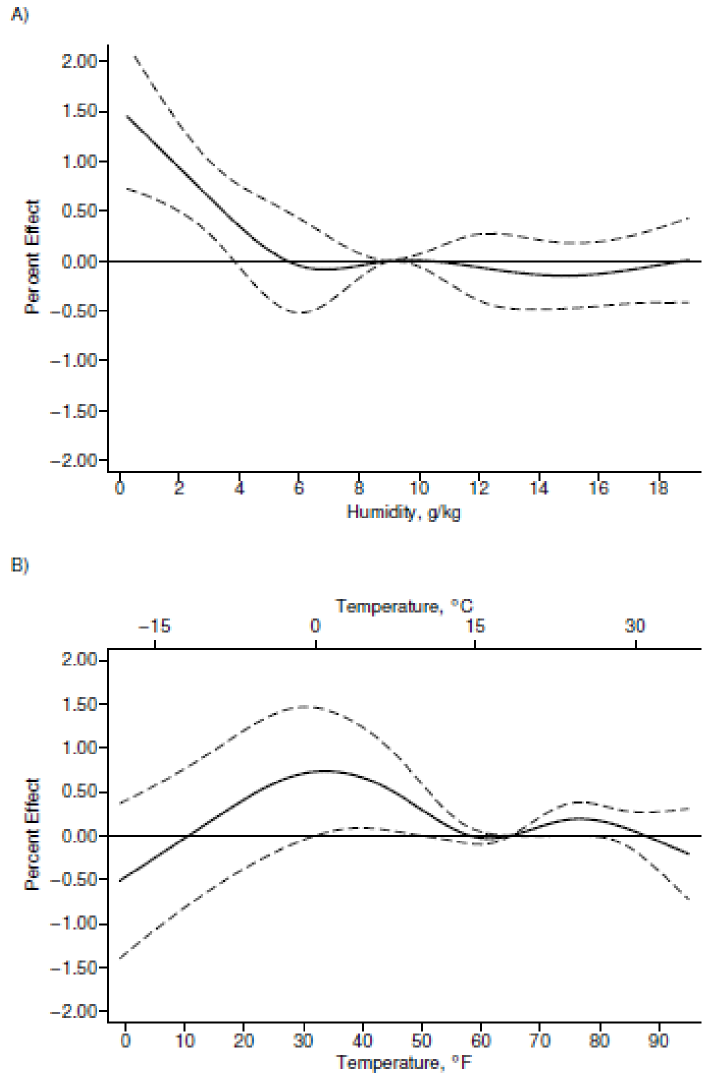
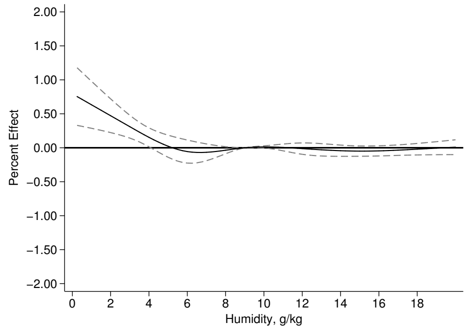


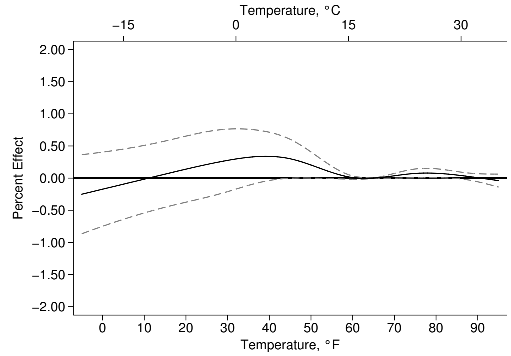
Figure 5: Regression estimates of the relationship between influenza mortality and weather conditions, 359 urban US counties, 1973-2002, excluding months June through September. In A, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given humidity level, relative to one additional day with a humidity of 9 g/kg. In B, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given temperature, relative to one additional day with a temperature of 65°F (18.3°C). All dotted lines represent 95% confidence intervals. Point estimates are qualitatively similar to Figure 2.

Panel 1: Contemporaneous month only

A

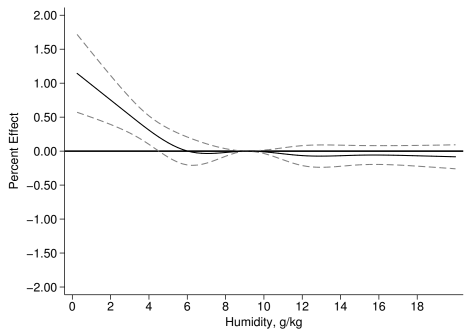


B

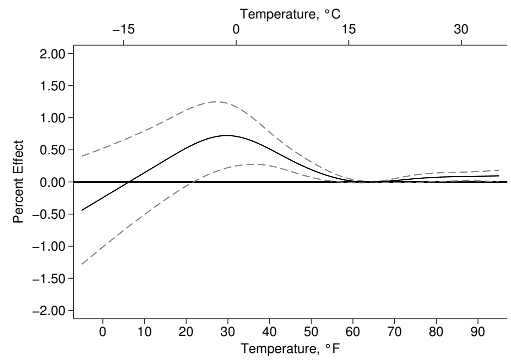


Panel 2: Last month only

A

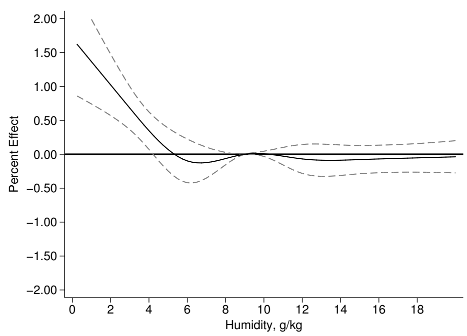


B

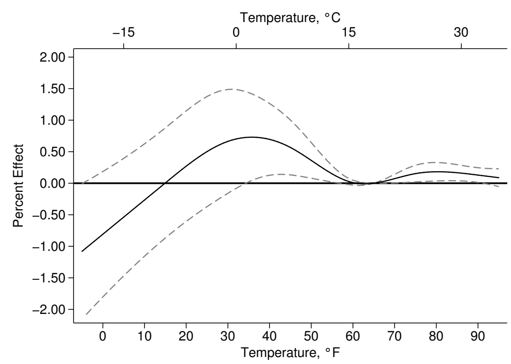


Panel 3: Three-month moving average

A



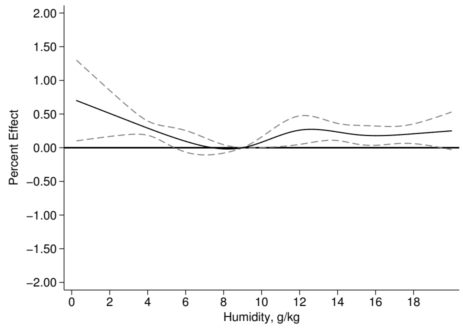
B



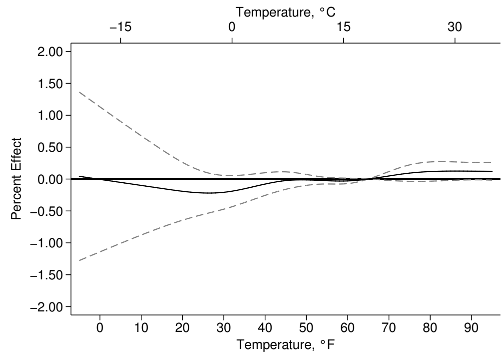
Web Figure 1: Sensitivity regression estimates of the relationship between influenza mortality and weather conditions, 359 urban US counties, 1973-2002. Panels replicate the analysis generating the results in Figure 2 with variations to the exposure lag structure. In A, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given humidity level, relative to one additional day with a humidity of 9 g/kg. In B, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given temperature, relative to one additional day with a temperature of 65°F (18.3°C). All dotted lines represent 95% confidence intervals. These estimates indicate that relationships between influenza mortality and weather conditions are generally robust to lag structure.

Panel 1: Dropping county by calendar month fixed effects
and adding county fixed effects

A

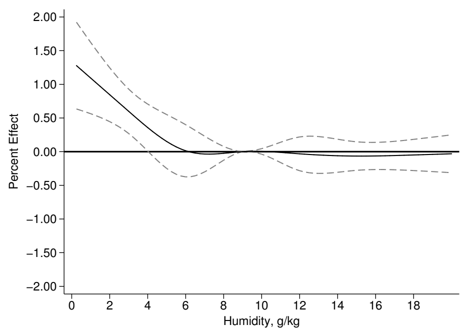


B

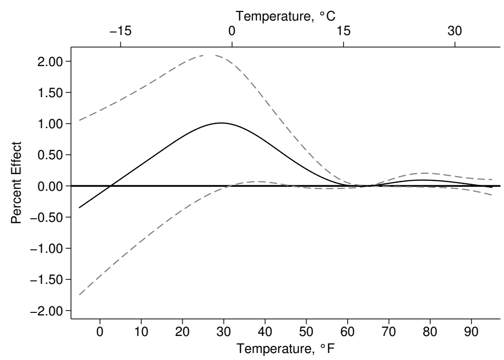


Panel 2: Adding linear time trends specific to each county by calendar month

A

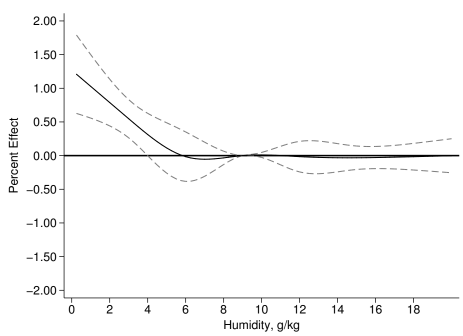


B

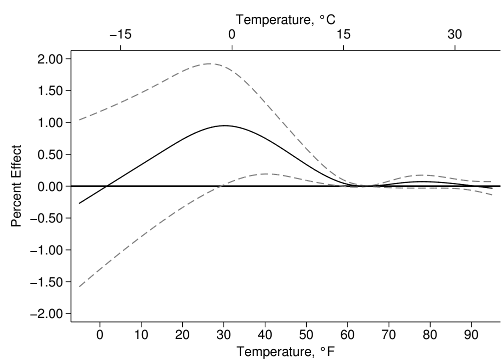


Panel 3: Adding quadratic trends specific to each county by calendar month

A



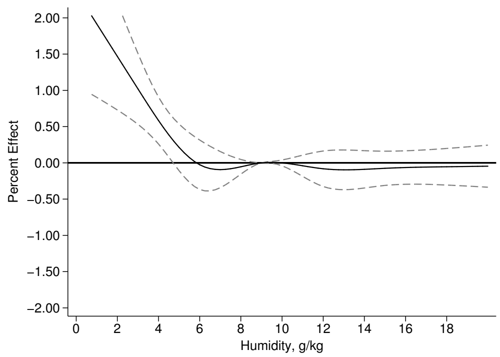
B



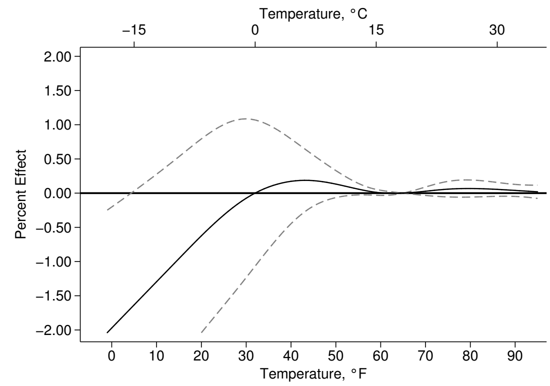
Web Figure 2: Sensitivity regression estimates of the relationship between influenza mortality and weather conditions, 359 urban US counties, 1973-2002. Panels replicate the analysis generating the results in Figure 2 with variations to the modeling structure. In A, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given humidity level, relative to one additional day with a humidity of 9 g/kg. In B, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given temperature, relative to one additional day with a temperature of 65°F (18.3°C). All dotted lines represent 95% confidence intervals. The A estimates indicate that the relationship between influenza mortality and absolute humidity is reasonably robust to modeling choices. The B estimates indicate that the relationship between influenza mortality and temperature is sensitive to modeling choices.

Panel 1: Counties above the median humidity level

A

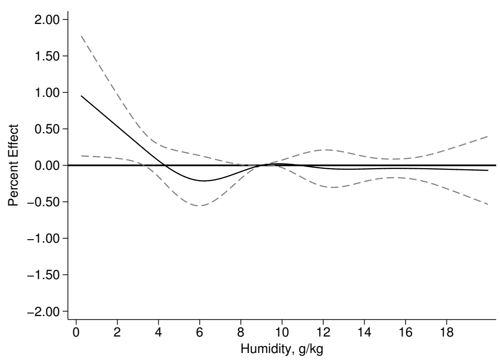


B

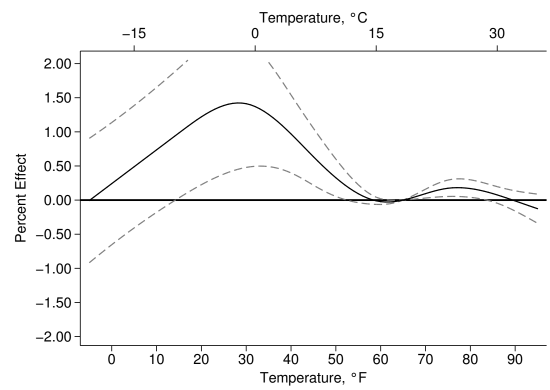


Panel 2: Counties below the median humidity level

A

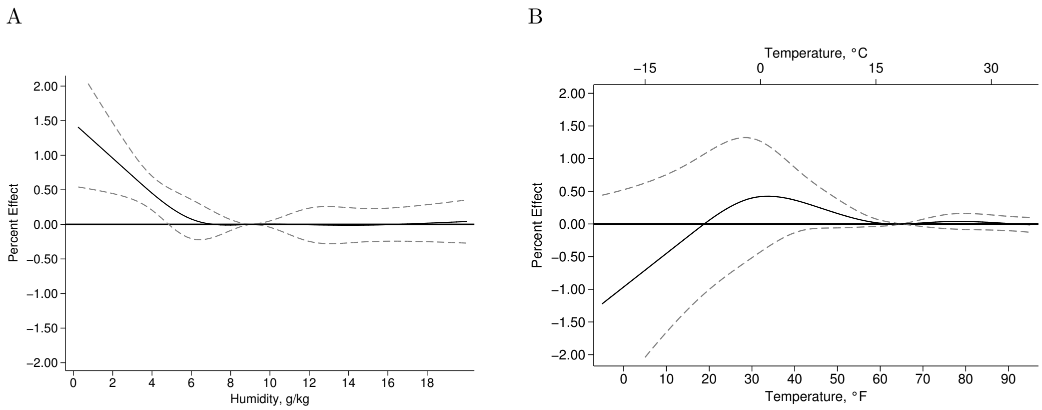


B

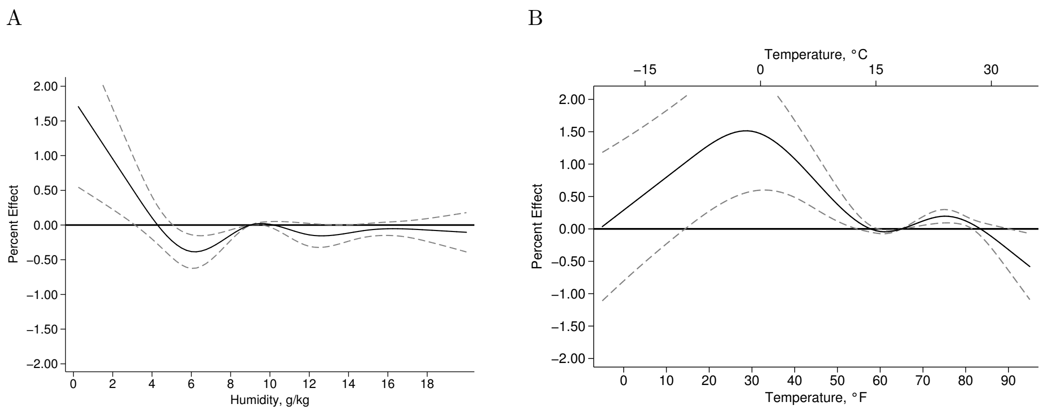


Web Figure 3: Sensitivity regression estimates of the relationship between influenza mortality and weather conditions, dividing counties based on their average absolute humidity, 1973-2002. Panel 1 is the sample of counties with average absolute humidity above the median for our sample. Panel 2 is the sample of counties with average absolute humidity below the median for our sample. In A, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given humidity level, relative to one additional day with a humidity of 9 g/kg. In B, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given temperature, relative to one additional day with a temperature of 65°F (18.3°C). All dotted lines represent 95% confidence intervals. The A estimates indicate that the relationship between influenza mortality and absolute humidity is reasonably robust to changes in the sample. The B estimates indicate that the relationship between influenza mortality and temperature is sensitive to changes in the sample.

Panel 1: Counties above the median temperature



Panel 2: Counties below the median temperature



Web Figure 4: Sensitivity regression estimates of the relationship between influenza mortality and weather conditions, dividing counties based on their average temperature, 1973-2002. Panel 1 is the sample of counties with average temperatures above the median for our sample. Panel 2 is the sample of counties with average temperatures below the median for our sample. In A, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given humidity level, relative to one additional day with a humidity of 9 g/kg. In B, the solid line depicts the average percentage change in the annual influenza mortality rate from one additional day at a given temperature, relative to one additional day with a temperature of 65°F (18.3°C). All dotted lines represent 95% confidence intervals. The A estimates indicate that the relationship between influenza mortality and absolute humidity is reasonably robust to changes in the sample. The B estimates indicate that the relationship between influenza mortality and temperature is sensitive to changes in the sample.