Original Contribution

Relation of Temperature and Humidity to the Risk of Recurrent Gout Attacks

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Gout attack risk may be affected by weather (e.g., because of volume depletion). We therefore examined the association of temperature and humidity with the risk of recurrent gout attacks by conducting an internet-based case-crossover study in the United States (in 2003–2010) among subjects with a diagnosis of gout who had 1 or more attacks during 1 year of follow-up. We examined the association of temperature and humidity over the prior 48 hours with the risk of gout attacks using a time-stratified approach and conditional logistic regression. Among 632 subjects with gout, there was a significant dose-response relationship between mean temperature in the prior 48 hours and the risk of subsequent gout attack ($P = 0.01$ for linear trend). Higher temperatures were associated with approximately 40% higher risk of gout attack compared with moderate temperatures. There was a reverse J-shaped relationship between mean relative humidity and the risk of gout attacks ($P = 0.03$ for quadratic trend). The combination of high temperature and low humidity had the greatest association (odds ratio = 2.04, 95% confidence interval: 1.26, 3.30) compared with moderate temperature and relative humidity. Thus, high ambient temperature and possibly extremes of humidity were associated with an increased risk of gout attack, despite the likelihood that individuals are often in climate-controlled indoor environments.

case-crossover study; gout; humidity; internet; risk factor; temperature; weather

Abbreviation: ACR, American College of Rheumatology.

Gout is presently the most common inflammatory arthritis in the United States, affecting an estimated 3.9% of adults (8.3 million individuals) (1). It is characterized by recurrent flares due to monosodium urate deposition in the joints. These flares have been linked to dietary factors (2, 3), alcohol intake (4), and the use of low-dose aspirin (5) or diuretics (6), presumably because of their effects on serum urate levels. Although the risk of gout flare may vary by weather factors, such as ambient temperature and humidity, the few studies that have investigated potential seasonal variation of gout flares have produced conflicting results (7–11). This may be the result of wide variations in temperature and humidity in different geographical locations in any given season.

Lower temperatures could decrease the solubility of urate crystals, leading them to precipitate, particularly in the distal joints (7, 8). On the other hand, higher temperatures can cause sweating, potentially leading to dehydration and metabolic acidosis, both of which can increase serum urate levels. Furthermore, these effects may be compounded by humidity levels, because high humidity leads to increased sweating (9, 10), and low humidity may contribute to dehydration through evaporative fluid loss. Temperature and humidity may also trigger behavioral changes, such as drinking more fluids, including alcoholic or sugar-sweetened beverages (which can affect the risk of gout) in hot, humid weather. For example, in an online survey of more than 2,000 adults, 27% reported drinking more alcohol in warmer weather (12).

To date, no study has examined specific weather factors in relation to the risk of recurrent gout attacks. In this study, we assessed the potential impact of temperature and relative humidity using an online case-crossover study design.

METHODS

Study subjects

We conducted an internet-based case-crossover study of triggers of recurrent gout attacks. The details of this study have been described previously (3, 13). Specifically, we constructed a study website on an independent secure server in the Boston University School of Medicine domain (14). The study was advertised on the Google (Mountain View, California) search engine (www.google.com) by linking an advertisement to the search term "gout." Individuals who clicked on the study advertisement were directed to the study website and were asked for the following items: sociodemographic information, gout-related data (e.g., diagnosis of initial gout attack, age of onset, medication used for the treatment of gout, and the number of gout attacks in the last 12 months), and history of other diseases and medication use.

To be eligible for the study, a subject had to 1) report gout diagnosed by a physician, 2) have had a gout attack within the past 12 months, 3) be at least 18 years of age, 4) reside in the United States, 5) provide informed consent, and 6) agree to release medical records pertaining to gout diagnosis and treatment. To confirm a diagnosis of gout, we obtained medical records pertaining to the participant's gout history and/or a checklist of the features listed in the American College of Rheumatology (ACR) preliminary classification criteria for gout (15) completed by the subject's physician. Two rheumatologists (T.N. and D.J.H.) reviewed all medical records and the checklists to determine whether participants had a diagnosis of gout according to the ACR criteria. Similar methods of gout diagnosis confirmation have been used in the Health Professionals Follow-Up Study (16). The study was approved by the institutional review board of Boston University Medical Campus, and subjects provided electronic informed consent.

Ascertainment of recurrent gout attacks

Data were collected regarding the date of onset of the recurrent gout attack, the anatomical location of the attack, clinical symptoms and signs (e.g., maximal pain within 24 hours or redness), and medications used to treat the attack (e.g., colchicine, nonsteroidal antiinflammatory drugs, systemic corticosteroids, intraarticular corticosteroid injections). This method of identifying gout attacks is consistent with approaches used in acute and chronic gout trials and the provisional definition of gout attacks that includes only patient-reported elements (17–19).

Ascertainment of weather-related factors

At the time of recurrent gout attacks, participants were asked to provide zip codes for their location in the 0- to 24-hour period and the 25- to 48-hour period prior to that attack using an online questionnaire. Using these zip codes, we retrieved information on temperature (in °F) and relative humidity (as %) during the 0–24 hours and 25–48 hours prior to the gout attack through the National Oceanic and Atmospheric Administration website (www.noaa.gov), a publicly accessible national weather data bank. We obtained the same

weather-related information for control periods by matching the weekday within a 35-day interval using a time-stratified case-crossover study design (20). Specifically, we divided the calendar into blocks consisting of 35-day intervals starting on January 1, 2003. Within a particular 35-day interval (i.e., block), the day the gout attack occurred was used as the index day to anchor the corresponding control periods (i.e., anchored to the same day in the other weeks contained within the same block), enabling matching of each case period to 4 control periods. For example, if the gout attack occurred on the second Monday of a block, then the first, third, fourth, and fifth Mondays in that 35-day interval were used to define the index day for each of 4 control periods. We chose 2 days preceding the index date as the effect period (i.e., the exposure window) because we hypothesized that the gout attack would not occur immediately after exposure to the specific weather factors.

The time-stratified case-crossover study design can control for cyclical variation of the underlying hazard of gout attacks according to day of the week. For example, even though weather variation does not depend on the day of the week, individuals may have different behaviors on weekdays versus weekends that could have bearing on the risk of gout attacks, such as drinking alcohol. In addition, temperature and humidity can vary greatly over a long period of time. Thus, by restricting the control periods to the same day of the week within a short period of time (e.g., 35 days), potential control selection bias and time trend of exposure are minimized (21, 22). This design has been successfully applied in several studies to assess the effect of weather-related factors on the risk of acute disease conditions (23–26).

Statistical analysis

We first examined the relation of mean temperature to the risk of recurrent gout attacks using conditional logistic regression. Specifically, we examined the associations of the mean temperatures over 0- to 24-hour, 25- to 48-hour, and 0- to 48-hour exposure windows. For each exposure window, we divided mean temperature into the following 7 categories: less than 30°F, 30–39°F, 40–49°F, 50–59°F, 60–69°F, 70–79°F, and 80°F or higher. (To convert degrees Fahrenheit to degrees Celsius, subtract 32, multiply by 5, and divide by 9.) We used the category that contained the median temperature (50–59°F) as the reference group because it is very rare that the temperature would change from the lowest category (<30°F) to the highest category (>80°F) within a consecutive 35-day period. Because the 0- to 48-hour exposure window appeared to generate more robust effect estimates for the risk of recurrent gout attacks in terms of providing maximal risk ratios (27), those results are presented here. To better depict the dose-response relationship between mean temperature and the risk of gout attacks, we used quadratic spline regression to smooth the dose-risk curve (28).

We then examined relative humidity, defined as the amount of atmospheric moisture (i.e., water vapor) present relative to the amount that would be present if the air were saturated at any given time and temperature (29). We divided mean relative humidity into the following 6 categories: less than 40% (very dry), 40%–49%, 50%–59%, 60%–74% (reference

category containing the median relative humidity), 75%–84%, and 85% or more (very humid), and we used the same approach as described above to evaluate its association with the risk of recurrent gout attacks. Because a J-shaped dose-response relationship between humidity and the risk of recurrent gout attacks was noted in the spline curve, we added a quadratic term for humidity in the regression model.

Finally, we evaluated the combined association of temperature and relative humidity with the risk of recurrent gout attacks. To obtain robust effect estimates, we collapsed average temperature and humidity into 3 categories each (≤49°F, 50–69°F, and ≥70°F for temperature; <60%, 60%–74%, and ≥75% for humidity). In sensitivity analyses, we examined the association of temperature and relative humidity with the first attack during study follow-up, as well as with attacks affecting the lower extremities.

RESULTS

Of 632 subjects who had experienced at least 1 recurrent gout attack during the follow-up period, we were able to obtain data on temperature for 626 (99%) subjects and on relative humidity for 624 (99%) subjects. A total of 619 subjects (98%) had temperature or humidity data in both case and control periods; of these subjects, 536 (87%) met the ACR preliminary classification criteria for gout.

The characteristics of the participants are presented in Table 1. The average age was 54 years. Participants were predominantly men (78%) of white race (88%), and more than half had received a college education. Subjects were recruited from 49 states and the District of Columbia. Most gout attacks occurred in the lower extremity (92%), particularly in the first metatarsophalangeal joint, and had features of either maximal pain within 24 hours or redness (89%). Approximately 89% of the gout attacks were treated with colchicine, nonsteroidal anti-inflammatory drugs, systemic corticosteroids, intraarticular corticosteroid injections, or a combination of these medications. The median time between the onset of a gout attack and completion of the hazard-period questionnaire was 3 days.

Higher temperatures over the prior 48 hours were associated with higher risks of recurrent gout attacks (Figure 1). The odds ratios were 0.60, 0.75, 0.89, 1.0 (reference group: 50–59°F), 1.18, 1.43, and 1.40, respectively, for each of 7 temperature categories starting from less than 30°F over the prior 48 hours (P for linear trend = 0.01) (Table 2). In contrast, there was a reverse "J-shaped" dose-response relationship between relative humidity and the risk of recurrent gout attacks (Figure 2). Risk of gout attacks appeared to be higher when relative humidity was low. Compared with the reference category (which contained the median humidity level of 60%–74%), both extreme humidity categories tended to be associated with a higher risk of recurrent gout attacks (P for quadratic trend = 0.03) (Table 2 and Figure 2).

The combined associations of temperature and relative humidity on the risk of gout attacks are presented in Table 3. The risk of recurrent gout attacks was elevated with higher temperature and lower humidity. For example, the odds

Table 1. Characteristics of 619 Participants in the Internet-Based Case-Crossover Study of Gout, United States, 2003–2010

| Participant Characteristic	No.	%	Median	Range
Male sex	484	78		
Age, years			54	21–88
Education				
Less than high school graduate	10	2		
High school graduate	54	9		
Some college/technical school	196	32		
College graduate	152	25		
Some professional/graduate school	68	11		
Completed professional/graduate school	132	22		
Household income, $				
<25,000	52	8		
25,000–49,999	122	20		
50,000–74,999	119	19		
75,000–99,999	87	14		
≥100,000	159	26		
Refused to answer	80	13		
Race				
Black	19	3		
White	547	88		
Other	46	7.4		
Refused to answer	7	1.1		
Body mass index[a]			30.6	14.7–69.9
Disease duration, years			5	0–51

[a] Weight (kg)/height (m)^2.
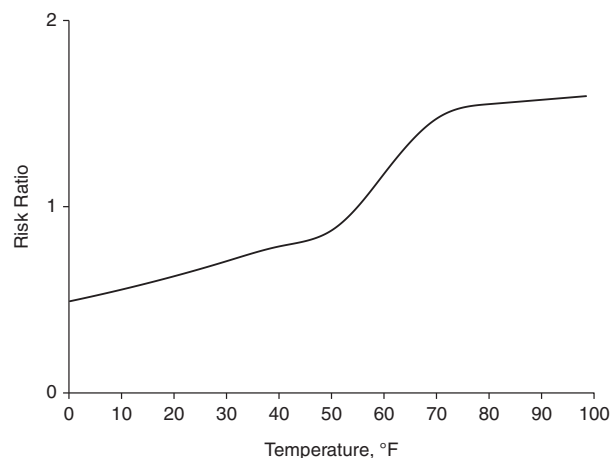
Figure 1. Depiction of the association between average ambient temperature over the prior 48-hour period and risk of recurrent gout attacks using quadratic spline regression in the whole study sample. Internet-based case-crossover study of gout, United States, 2003–2010. (To convert degrees Fahrenheit to degrees Celsius, subtract 32, multiply by 5, and divide by 9.)

Table 2. Temperature and Humidity Over the Prior 48 Hours and Risk of Recurrent Gout Attacks, Internet-Based Case-Crossover Study of Gout, United States, 2003–2010

Weather Factors Over Past 48 Hours	No. of Control Periods	No. of Hazard Periods	OR	95% CI
Temperature, °F[a]				
<30	181	37	0.60	0.33, 1.08
30–39	217	51	0.75	0.46, 1.23
40–49	340	83	0.89	0.62, 1.27
50–59	445	106	1.00	Referent
60–69	561	138	1.18	0.85, 1.63
70–79	535	144	1.43	0.94, 2.17
≥80	196	49	1.40	0.77, 2.57
P for linear trend		0.01		
Relative humidity, %				
<40	137	39	1.55	0.90, 2.66
40–49	178	50	1.37	0.92, 2.02
50–59	386	97	1.17	0.88, 1.54
60–74	989	221	1.00	Referent
75–84	547	141	1.14	0.89, 1.47
≥85	228	57	1.11	0.78, 1.57
P for quadratic trend		0.03		

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] To convert degrees Fahrenheit to degrees Celsius, subtract 32, multiply by 5, and divide by 9.

Table 3. Combined Associations of Temperature and Humidity Over the Prior 48 Hours With the Risk of Recurrent Gout Attacks, Internet-Based Case-Crossover Study of Gout, United States, 2003–2010

Humidity Over Prior 48 Hours, %	Temperature Over Prior 48 Hours, °F[a]	No. of Control Periods	No. of Hazard Periods	OR	95% CI
<60	<49	263	71	0.93	0.57, 1.50
<60	50–69	209	46	1.40	0.96, 2.04
<60	≥70	228	69	2.04	1.26, 3.30
60–74	<49	436	86	0.98	0.63, 1.53
60–74	50–69	269	62	1.00	Referent
60–74	≥70	284	73	1.40	0.90, 2.16
≥75	<49	300	86	1.00	0.63, 1.61
≥75	50–69	259	62	1.41	0.99, 2.00
≥75	≥70	215	50	1.18	0.73, 1.90

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] To convert degrees Fahrenheit to degrees Celsius, subtract 32, multiply by 5, and divide by 9.

50–69°F and the relative humidity was between 60%–74%. There was also a suggestion of increased risk of gout attack with the combination of higher temperature and higher humidity; however, the association was smaller than that of the combined effect of higher temperature and lower humidity.

When these sets of analyses were restricted to participants who met ACR gout criteria (*n* = 536), the results did not change materially. Additionally, the results remained similar when analyses were limited to the first attack occurring during the study period and to attacks affecting the lower extremity.

DISCUSSION

In this large study of prospectively recruited subjects with preexisting gout, we found a trend for higher average ambient temperatures being associated with a higher risk of recurrent gout attacks. We also found a reverse J-shaped relationship for relative humidity, with increasing trends for the risk of gout attacks in both humidity level extremes. Finally, the increased risk of gout attacks appeared to be greatest with the combination of hot and dry weather. These findings provide the first prospective evidence that these weather variables may be important risk factors that should be considered in the prevention of recurrent gout attacks.

Although it is commonly thought that gout attacks likely occur in distal joints because of the cooler temperature of those joints, we did not find that colder temperatures were associated with higher risk of gout attacks. One possibility is that most individuals in North America are unlikely to be exposed to cold temperatures for substantial periods of time. Ambient temperatures, therefore, do not necessarily reflect the actual temperatures experienced, particularly for extreme temperatures. On the other hand, increased temperature can lead to volume depletion and contribute to metabolic acidosis, both of which can decrease renal urate excretion and increase serum urate. Acidosis can also reduce urate solubility

ratio of recurrent attacks increased by 2-fold when the temperature was above 70°F and the relative humidity was below 60% compared with that when the temperature was between
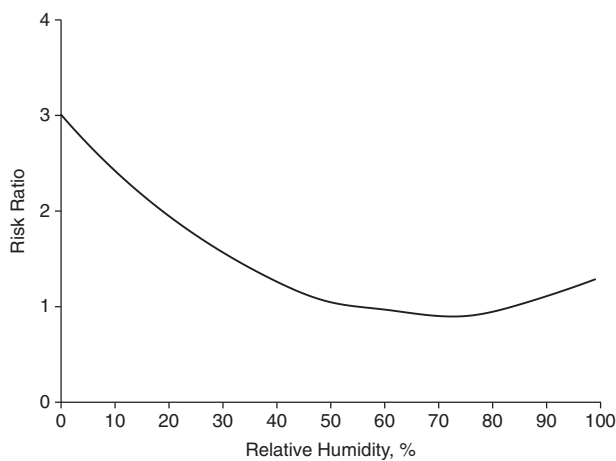

Figure 2. Depiction of the association between average relative humidity (defined as the amount of atmospheric moisture (i.e., water vapor) present relative to the amount that would be present if the air were saturated at any given time and temperature (29)) over the prior 48-hour period and risk of recurrent gout attacks using quadratic spline regression in the whole study sample. Internet-based case-crossover study of gout, United States, 2003–2010.

and lead to precipitation of crystals. Thus, distal joints, which tend to be exposed to lower blood pH than proximal ones, are likely to experience greater adverse effects on serum urate solubility.

In high humidity, the thermoregulatory evaporative cooling related to sweating is less effective, leading to a further increase in body temperature and, in turn, more perspiring in an attempt at further cooling. Thus, there is a greater risk of dehydration with the combination of high temperature and high humidity. On the other hand, low humidity can also lead to dehydration because of increased evaporation from the skin and mucous membranes. Such volume loss may go relatively unnoticed because perspiration does not necessarily accumulate on the skin as it does in more humid weather. Indeed, lower humidity can make the air "feel" cooler than it actually is because of this evaporative effect. It is well known that long-distance flights can increase the sensation of dryness and the risk of dehydration owing to the low relative humidity in the cabin despite comfortable temperatures (30, 31).

Temperature and humidity may also affect the risk of recurrent gout attacks through other mechanisms. It is possible that subjects exposed to high temperatures or to high relative humidity may change certain behaviors. For instance, in hot, humid weather, people may increase their liquid consumption (e.g., of water or sugar-sweetened soda), or stereotypically drink more beer (12), which can influence the risk of gout attacks. Because the main objective of our study was to assess the total effect of temperature or relative humidity on the risk of gout attacks, not to elucidate the mechanisms responsible for the risk of gout attacks after exposure to such weather factors, we did not attempt to assess the indirect effect of either temperature or humidity through potential mediators on the risk of recurrent gout attacks. Nevertheless, studies assessing such biological mechanisms could provide valuable guidance regarding feasible preventive measures when faced with weather elements that could influence the risk of gout attacks.

It is worth commenting on several characteristics of our study. First, the time-stratified case-crossover study is an ideal design to assess the relation of ambient temperature and relative humidity to the risk of recurrent gout attacks (22). Previous studies have successfully used this design to evaluate ambient temperature in relation to the risk of acute events, such as stroke (32), migraine (33), and preterm delivery (34). Because the control periods were chosen randomly on the same day of the week within close proximity to the hazard period, potential biases are minimized, such as those that arise from control selection and time trends in exposures (i.e., temperature and humidity). Second, weather data were obtained from publicly available resources; thus, recall bias would not account for the findings of the study. Third, lifestyle factors, such as alcohol consumption or purine-rich food intake, may affect the risk of recurrent gout attacks. These lifestyle factors are not the causes of ambient temperature or humidity and should not have confounded our results, but they could potentially mediate the effects of temperature or humidity on the risk of gout attack. When we limited our analyses to those who reported drinking no alcohol, the magnitude of associations was similar to the main results, although we acknowledge that conditioning on an intermediate in the causal pathway can result in selection

bias. Finally, when we limited our analyses to those gout cases confirmed by the ACR criteria to the first attack during the study period or to attacks affecting the lower extremity, our results did not change materially.

Our study has some limitations. We obtained average temperature and relative humidity data from a National Weather Service website. These exposures, however, may not represent the true conditions to which individuals were exposed, as noted above. For example, individuals in North America are often in climate-controlled settings, whereby indoor temperature and humidity can be modulated (e.g., by air conditioning (which decreases both temperature and humidity), heating, dehumidifiers, and humidifiers). Indeed, in our study sample, the median number of hours spent outdoors in the prior 24- and 48-hour periods was 2.5 hours (mode, 1 hour). Thus, misclassification of exposure likely occurred. However, this bias is likely to be nondifferential, biasing the effect estimates toward the null. The measures of temperature and relative humidity of the case period were similar to those of the control periods within the relatively short 35-day intervals. For example, the median difference in relative humidity between hazard and control periods in each 5-week block was −1% (interquartile range for difference in humidity between hazard and control periods within a block, −9.25–8.75%). This positive autocorrelation tends to decrease the efficiency (i.e., precision) of the study (21). Therefore, even though more than 600 subjects with gout were included in this analysis, the confidence intervals for each point estimate were relatively wide.

In summary, we found that high ambient temperature and possibly low relative humidity, more so than high relative humidity, were associated with an increased risk of gout attack. The biological mechanisms underlying these associations require further exploration and may include volume depletion or behavioral changes in response to the weather that may influence gout attack risk. Patients with gout may be advised that under conditions of hot and/or dry weather, appropriate measures, such as increased water intake, should be considered to minimize the risk of recurrent gout attacks.

REFERENCES

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum*. 2011;63(10):3136–3141.
2. Zhang Y, Neogi T, Chen C, et al. Cherry consumption and decreased risk of recurrent gout attacks. *Arthritis Rheum*. 2012; 64(12):4004–4011.
3. Zhang Y, Chen C, Choi H, et al. Purine-rich foods intake and recurrent gout attacks. *Ann Rheum Dis*. 2012;71(9):1448–1453.
4. Neogi T, Chen C, Niu J, et al. Alcohol quantity and type on risk of recurrent gout attacks: an internet-based case-crossover study. *Am J Med*. 2014;127(4):311–318.
5. Zhang Y, Neogi T, Chen C, et al. Low-dose aspirin use and recurrent gout attacks. *Ann Rheum Dis*. 2014;73(2):385–390.
6. Hunter DJ, York M, Chaisson CE, et al. Recent diuretic use and the risk of recurrent gout attacks: the online case-crossover gout study. *J Rheumatol*. 2006;33(7):1341–1345.
7. Arber N, Vaturi M, Schapiro JM, et al. Effect of weather conditions on acute gouty arthritis. *Scand J Rheumatol*. 1994; 23(1):22–24.
8. Elliot AJ, Cross KW, Fleming DM. Seasonality and trends in the incidence and prevalence of gout in England and Wales 1994–2007. *Ann Rheum Dis*. 2009;68(11):1728–1733.
9. McLeod J. Gout and fibrositis in cold weather. *Med J Aust*. 1972;1(18):943.
10. Gallerani M, Govoni M, Mucinelli M, et al. Seasonal variation in the onset of acute microcrystalline arthritis. *Rheumatology (Oxford)*. 1999;38(10):1003–1006.
11. Schlesinger N, Gowin KM, Baker DG, et al. Acute gouty arthritis is seasonal. *J Rheumatol*. 1998;25(2):342–344.
12. Brits drink more alcohol in warmer weather. Opinium. http://news.opinium.co.uk/survey-results/brits-drink-more-alcohol-warmer-weather. Published May 25, 2012. Accessed July 31, 2013.
13. Zhang Y, Chaisson CE, McAlindon T, et al. The online case-crossover study is a novel approach to study triggers for recurrent disease flares. *J Clin Epidemiol*. 2007;60(1):50–55.
14. Online gout study. Boston University Medical Campus. https://dcc2.bumc.bu.edu/goutstudy/. Accessed June 19, 2014.
15. Wallace SL, Robinson H, Masi AT, et al. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum*. 1977;20(3):895–900.
16. Choi HK, Atkinson K, Karlson EW, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med*. 2004;350(11):1093–1103.
17. Gaffo AL, Schumacher HR, Saag KG, et al. Developing a provisional definition of flare in patients with established gout. *Arthritis Rheum*. 2012;64(5):1508–1517.
18. So A, De Meulemeester M, Pikhlak A, et al. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: results of a multicenter, phase II, dose-ranging study. *Arthritis Rheum*. 2010;62(10):3064–3076.
19. Terkeltaub RA, Furst DE, Bennett K, et al. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum*. 2010; 62(4):1060–1068.
20. Levy D, Lumley T, Sheppard L, et al. Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemiology*. 2001;12(2):186–192.
21. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology*. 2005;16(6): 717–726.
22. Mittleman MA. Optimal referent selection strategies in case-crossover studies: a settled issue. *Epidemiology*. 2005; 16(6):715–716.
23. Karr C, Lumley T, Shepherd K, et al. A case-crossover study of wintertime ambient air pollution and infant bronchiolitis. *Environ Health Perspect*. 2006;114(2):277–281.
24. Wasilevich EA, Rabito F, Lefante J, et al. Short-term outdoor temperature change and emergency department visits for asthma among children: a case-crossover study. *Am J Epidemiol*. 2012;176(suppl 7):S123–S130.
25. Fletcher BA, Lin S, Fitzgerald EF, et al. Association of summer temperatures with hospital admissions for renal diseases in New York State: a case-crossover study. *Am J Epidemiol*. 2012; 175(9):907–916.
26. Barnett AG. Temperature and cardiovascular deaths in the US elderly: changes over time. *Epidemiology*. 2007;18(3): 369–372.
27. Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health*. 2000;21:193–221.
28. Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. *Epidemiology*. 1995;6(4):356–365.
29. Relative humidity. National Oceanic and Atmospheric Administration's National Weather Service. http://www.nws.noaa.gov/glossary/index.php?word=relative+humidity. Updated June 25, 2009. Accessed July 26, 2013.
30. Barnes RM. Study of fluid balance in civil aircrew. *Aerosp Med*. 1973;44(10):1130–1135.
31. Guéhenneux S, Gardinier S, Morizot F, et al. Skin surface hydration decreases rapidly during long distance flights. *Skin Res Technol*. 2012;18(2):238–240.
32. Kyobutungi C, Grau A, Stieglbauer G, et al. Absolute temperature, temperature changes and stroke risk: a case-crossover study. *Eur J Epidemiol*. 2005;20(8):693–698.
33. Villeneuve PJ, Szyszkowicz M, Stieb D, et al. Weather and emergency room visits for migraine headaches in Ottawa, Canada. *Headache*. 2006;46(1):64–72.
34. Basu R, Malig B, Ostro B. High ambient temperature and the risk of preterm delivery. *Am J Epidemiol*. 2010;172(10): 1108–1117.