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Sex Differences in the Temperature-Dependence of Kidney Stone Presentations: a Population-Based Aggregated Case-Crossover Study

Ana M. Vicedo-Cabrera, PhD[a], **David S. Goldfarb, MD**[b], **Robert E. Kopp, PhD**[c], **Lihai Song, MS**[d], **Gregory E. Tasian, MD, MSc, MSCE**[d,e,f,h]

[a]Department of Public Health, Environments and Society, London School of Hygiene and Tropical Medicine; London, England WC1E 7HT

[b]Division of Nephrology, New York University School of Medicine, New York, New York 10016, USA

[c]Department of Earth and Planetary Sciences and Institute of Earth, Ocean & Atmospheric Sciences, Rutgers University; New Brunswick, New Jersey, 08901, USA

[d]Center for Pediatric Clinical Effectiveness, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

[e]Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104 , USA

[f]Department of Surgery, Division of Urology; Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA

[h]Department of Surgery, Division of Urology, The Children’s Hospital of Philadelphia, Philadelphia, PA 19104, USA

Abstract

Background—Previous studies assumed a uniform relationship between heat and kidney stone presentations. Determining whether sex and other characteristics modify the temperature-dependence of kidney stone presentations has implications for explaining differences in nephrolithiasis prevalence and improving projections of the effect of climate change on nephrolithiasis.

Methods—We performed an aggregated case-crossover study among 132,597 children and adults who presented with nephrolithiasis to 68 emergency departments throughout South Carolina from 1997-2015. We used quasi-Poisson regression with distributed lag non-linear models to estimate sex differences in the cumulative exposure- and lagged-response between maximum daily wet-

Corresponding Author: Dr. Gregory Tasian, Children’s Hospital of Philadelphia, Division of Urology, Wood Center, 3rd Floor, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, Phone: 215.590.0317 Fax 215.590.3985 tasiang@chop.edu.

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bulb temperatures and emergent kidney stone presentations, aggregated at the ZIP-code level. We also explored interactions by age, race, payer, and climate.

Results—Compared to 10°C, daily wet-bulb temperatures at the 99th percentile were associated with a greater increased relative risk (RR) of kidney stone presentations over 10 days for males (RR 1.73; 95% CI: 1.56, 1.91) than for females (RR 1.15; 95% CI: 1.01, 1.32; interaction P<0.001). The shape of the lagged response was similar for males and females, with the greatest risk estimated for the 2 days following high temperatures. There were weak differences by age, race, and climatic zone, and no differences by payer status.

Conclusions—The estimated risk of presenting emergently with kidney stones within 10 days of high daily wet-bulb temperatures was substantially greater among men than women, and similar between patients with public and private insurance. These findings suggest that the higher risk among males may be due to sexually dimorphic physiologic responses rather than greater exposure to ambient temperatures.

Keywords

Temperature; Calculi; renal; Nephrolithiasis; Urolithiasis; age; sex

Introduction

Kidney stone disease (nephrolithiasis) is a disorder of urinary crystallization that affects 9% of the United States population and accounts for over $10 billion in annual healthcare expenditures [1-3]. The risk of nephrolithiasis increases with lower urine volume, which results in increased urinary concentration and subsequent crystallization of calcium, oxalate, uric acid, and phosphate. This relationship is the likely mechanism underlying the association between high ambient temperatures and an increased risk of kidney stone presentations [4-6].

Prior studies of the temperature-dependence of kidney stone presentations have have assumed a uniform relationship for the entire population. However, men have lower urine volume than women during high ambient temperatures,[7] suggesting that sex may modify the association between heat and kidney stone presentations. Quantifying such sex differences would yield data regarding the greater prevalence of stones among men, a well known epidemiologic phenomenon that has been the topic of much speculation, but one that remains unclear. It would also inform public health efforts to mitigate the adverse effects of heat on human health and would have important implications for refining projections of the effects of climate change on future nephrolithiasis prevalence and healthcare costs.

In this study, we tested the hypothesis that males have a greater increased risk of kidney stone presentations after hot days than females. We explored alternative potential explanations of sex differences by testing whether patients' payer status modifies this association since public insurance is associated with the probability of outdoor temperature exposure, but not physiologic responses to heat. We also examined whether other individual characteristics (age, race, and climate) modified the association between daily wet-bulb temperatures and kidney stone presentations.

Methods

Study design and patient population

We used an aggregated-exposure case-crossover study design, which is a specific type of case-crossover study that can be applied when subjects have a common area-level exposure [8]. Contrary to the usual individual case-crossover analysis, the data consist of series of daily counts and environmental exposures aggregated by the defined area level keeping the usual time-series structure. But, unlike the usual time-series analysis, this approach applies the idea of the bi-directional time-stratified case-crossover design to control for long-term and seasonal trends by matching case and control days within year, month, and day of the week. At the same time, it is possible to run a single model across different exposure series defined at small areas within the study location, as done by Ragettli *et al.*, by matching case and control days within the small-area level [9]. By doing so, one can estimate associations even with low number of counts at the small-area level and, at the same time, assign exposure at a fine scale level, thereby reducing exposure misclassification. This design has been shown to be less computationally intense than the individual case-crossover analysis, and it allowed us to control for overdispersion and auto-correlation.

We included children and adults who presented with kidney stones to 68 unique emergency departments in South Carolina between January 1, 1997 and September 15, 2015. Individuals were identified in South Carolina Medical Encounter Data and Financial Reports, an all-payer hospital claims database that captures all emergency department visits, surgeries, and hospital admissions in South Carolina. This dataset included patients who are uninsured or have public insurance. The database contains individual-level data using encounter-level data elements, including the ZIP code of patient's mailing address, date and type of encounter, ICD-9/10 codes, sex, race, and payer classification. Regular audits of the dataset are conducted to ensure that the data are at least 99.9 percent accurate (valid codes) and 99.5 percent complete [10].

We excluded patients with residential ZIP codes outside South Carolina, those with missing geographic or demographic data, and individuals self-identified as Hispanic (<2% of population) due to conflation of race and ethnicity in the dataset. This study was determined to be exempt from review by the Insititutional Review Board at The Children's Hospital of Philadelphia.

Outcome

The outcome was an Emergency Department presentation with a primary diagnosis of kidney stones [5]. These diagnostic codes have been demonstrated to have 92% accuracy in identifying kidney stone events [11,12]. We chose presentations to the Emergency Department because this type of encounter is usually the first interaction with the healthcare system for patients with symptomatic kidney stones and would most accurately reflect a short-term relationship between heat and nephrolithiasis. The first qualifying claim in the database defined the date of presentation. Only the first Emergency Department presentation was considered to avoid misclassification of recurrent stone episodes or repeat Emergency Department visits for the same stone episode.

Exposure

The exposure was the maximum daily wet-bulb temperature for each ZIP code in South Carolina during the study period. Wet-bulb temperatures measure the combination of temperature and humidity [13]. People lose more water by sweating at higher wet-bulb temperatures both because of the higher temperatures and because sweating becomes less effective at lowering body temperatures. Consistent with these physiologic effects, wet-bulb temperatures have been reported to predict kidney stone presentations better than temperature alone [14]. The maximum daily wet-bulb temperatures was estimated at the ZIP-code level using hourly values for dry-bulb temperature, relative humidity, and surface pressure as previously described [15,16]. All data were obtained from the NASA Land Data Assimilation Systems, which interpolates values from real-time weather data and hydrology models [17,18].

Interaction terms

Sex was examined as a modifier of the temperature-dependence of kidney stone presentations. We also explored whether payer classification, age, race, and climate zone modified this association. Payer status was classified as privately insured, publicly insured (Medicare, Medicaid), or other (self-payment or uninsured). Age was dichotomized as ≤ 65 and > 65 years due to the greater magnitude of the associations between moist heat and health outcomes such as mortality and acute kidney injury among older adults [19,20]. Race was categorized as white and African-American. Individuals reporting Native Hawaiian/ American, Asian, and “mixed-race” were classified as “other”. For payer classification and race, “other” was excluded from the respective interaction analyses due to the heterogeneous characteristics of these subgroups and the imprecise estimates resulting from small sample sizes. These groups were included in the analysis of the total population and other interaction analyses (*e.g.* sex). The study population was also divided into two climatic areas according to their ZIP code of residence. ZIP-code-specific median daily maximum wet-bulb temperatures ranged from 14°C to 20.6°C. Because the median daily maximum wet-bulb temperature in the state across the study period was 18.6 °C, ZIP codes in which the median daily wet-bulb temperature was below and above 18.6°C were classified as “cold” and “hot” climatic zones, respectively (Supplemental Figure 1).

Statistical analysis

A conditional Poisson regression model accounting for overdispersion was fit to estimate the overall association between maximum daily wet-bulb temperature and emergent kidney stone presentations, where the outcome was daily counts of kidney stone presentations aggregated at the ZIP code level. We conditioned by stratum variables per day, month, year and ZIP code to control for long-term and seasonal trends at small-level areas. Distributed lag nonlinear models were fit to simultaneously assess the non-linear exposure-response association and distribution of the associations across lags [21]. Based on prior studies, we measured a lag period for 10 days after temperature exposure [5]. The non-linear exposure-lag-response relationship was modeled through the ususal cross-basis term of the temperature variable using natural cubic splines in both dimensions. The selection of the number and location of the knots was based on minimization of the quasi-Akaike

information criterion among different combinations: knots at the 10th, 25th, 50th, 75th, 90th percentiles in the temperature dimension and 1 to 4 equally-spaced knots on log scale in the lag dimension. The final cross-basis term included a natural cubic spline with 2 internal knots placed at the 50th and 90th percentile of the temperature indicator for the exposure-response function, and a natural cubic spline with intercept and 2 internal knots equally-spaced in the log scale in the lag dimension.

Relative risks (RR) of kidney stone presentations were expressed as the cumulative-exposure-response and the lagged-response over 10-days of lag when daily maximum wet-bulb temperatures reached the 99th percentile, relative to 10 °C. This referent value of 10°C, corresponding to the 20th percentile of daily maximum wet-bulb temperature distribution across the state, was identified in a preliminary analysis as the temperature at which the association was minimal. We also described the temperature-dependence of kidney stone presentations at moderate temperatures (90th percentile of daily maximum wet-bulb temperatures compared to 10 °C) and extreme temperatures (99th percentile of daily maximum wet-bulb temperatures compared to 90th percentile).

We assessed whether sex, payer classification, age, race, and climatic conditions modified the association between daily wet-bulb temperatures and kidney stone presentation through interaction models. Specifically, total daily counts of cases were stratified by categories of each category of the interaction term. A factor variable indicating the level of the characteristic was included in the model described above as well as an interaction term between this factor variable and the cross-basis term. Stratum variables per day, ZIP code and factor indicator were also included in the model.

Sensitivity analyses

We performed multiple sensitivity analyses to assess the potential influence of exposure metric choice and model assumptions (Supplemental Table 2). First, we considered mean daily wet-bulb temperature and daily maximum dry-bulb temperature. Next, we used three different splines within the cross-basis to evaluate the impact of smoothing functions on the estimated relationship. These functions were a quadratic spline with knots at the 50th and 90th percentile, natural cubic spline with knots at the 50th, 75th and 90th percentile, and a simpler cross-basis than the primary analysis using only one internal knot in the lag dimension. Finally, we excluded patients <20 years as children with nephrolithiasis are more likely to have metabolic abnormalities and thus may not reflect the risk of the broader population.

Results

Between 1997 and 2015, 132,597 individuals presented emergently for kidney stones in South Carolina (Table 1). ZIP-code-specific median daily maximum wet-bulb temperatures ranged from 14°C to 20.6°C; the median daily maximum wet-bulb temperature in the state across the study period was 18.6 °C (Supplemental Table 1). The greatest number of emergency department visits was observed in more recent years and during hot periods (Supplemental Figure 2).

Table 2 displays the estimated cumulative exposure-response relationship between daily maximum wet-bulb temperature and emergent kidney stone presentations in the overall population and stratified by patient characteristics. Among the entire study population, a steep increase in the risk of presenting with kidney stones was estimated as wet-bulb temperatures increased above 13 °C compared to 10 °C (Figure 1A). The association was most pronounced during the first 2 days following the higher temperatures (Figure 1B).

Sex differences in the temperature-dependence of kidney stone presentations

There was strong evidence that sex modified the cumulative exposure-response relationship between daily maximum wet-bulb temperatures and kidney stone presentations (Figure 2A). The association between daily maximum wet-bulb temperature and increased kidney stone presentations became statistically significant at lower daily wet-bulb temperatures for males compared to females. This risk difference increased across the temperature range. Compared to 10 °C, daily wet-bulb temperatures at the 99th percentile were associated with a significantly greater increased risk of kidney stone presentations for males (RR, 1.73; 95% confidence interval [CI]: 1.56, 1.91) than for females (RR 1.15; 95% CI: 1.01, 1.32; interaction P<0.001). Larger differences were estimated between males and females at moderate wet-bulb temperatures (90th percentile of temperatures versus 10 °C) than extreme wet-bulb temperatures (99th percentile of temperatures versus 90th percentile as reference). The magnitude of the estimated relative risk was higher for males compared to females for each day after high temperatures, but the shape of lag-response relationship was similar (Figure 2B).

Interaction of other characteristics and the cross-basis of temperature and emergent kidney stone presentations

The point estimates and confidence intervals of the exposure-reponse and lagged-response by private and public insurance were nearly identical across the wet-bulb temperature range (Table 2; Figure 3). There was weak evidence of a greater risk of kidney stone presentations among patients younger than 65 years (interaction P=0.067) at extreme wet-bulb temperatures (Table 2; Supplemental Figure 3). Overall, the magnitude of the risk for daily wet-bulb temperatures >10 °C was higher among white than African-American individuals, but a steeper increase in the risk of emergent kidney stone presentations was estimated for African-Americans at wet-bulb temperatures above the 90th percentile (Table 2; Supplemental Figure 4). However, these differences were not statistically significant. Relative to 10 °C, moderate daily wet-bulb temperatures were associated with a greater risk of kidney stone presentations for patients who lived in “cold” climates, compared to those who lived in “warm” climates. A higher risk was estimated for any daily temperature above the 90th percentile versus 10 °C for patients in “warm” climate zones, although the interaction was not statistically significant (Table 2; Supplemental Figure 5). Results did not change substantially in the sensitivity analyses although the age interaction term became statistically significant when patients <20 years were excluded, indicating a difference in relative across age categories (Supplemental Tables 2 and 3).

Discussion

We found that males had a substantially greater risk of emergent kidney stone presentations following daily maximum wet-bulb temperatures that exceeded 10 °C. Compared to 10°C , the risk difference for stone presentations was 58% greater for men than women within ten days of temperatures at the 99th percentile. These results suggest that there are sex differences in behaviors (*e.g.* exposure to outdoor temperatures), or physiologic responses to high heat, or both. These results may explain, in part, the well known higher prevalence of stone disease in men compared with women. These findings add to the burgeoning understanding that sex should be considered a biologically relevant variable and an important determinant of health outcomes [22]. Specifically, these results suggest that strategies to mitigate the effect of high temperatures may produce the greatest public health and economic benefit for men at risk for kidney stone presentation and indicate that climate change may affect kidney health outcomes among men and women differentially.

The prevalence of nephrolithiasis has increased 70% over the last 30 years and now affects 9% of the United States population [23,1]. Nephrolithiasis accounts for healthcare costs of over $10 billion annually,[24] exceeding the treatment costs for prostate cancer and urinary tract infection in women by more than 3 and 5 billion dollars, respectively,[25] and approaching 25% of healthcare expenditures for end stage renal disease [26]. An additional 1.6-2.2 million new cases of nephrolithiasis are expected to result from climate change by 2050, which is expected to increase annual healthcare expenditures by $1.3 billion by 2050 [27]. However, these prior projections of the effect of climate change on the human health and economic burden of nephrolithiasis did not account for sex differences in the temperature-dependence of nephrolithiasis. Our results indicate that these estimates may not be accurate. The sex-specific relationships from this study could be used to revise these projections.

Our findings are consistent with prior reports of sex differences in heat-related kidney outcomes. Ordon and colleagues reported that men have a greater risk of renal colic than women over 21 days following high daily temperatures in a northern climate [28]. Fakheri and Goldfarb also found that the prevalence of nephrolithiasis increased 10 times more for men than women for each degree increase in mean annual dry-bulb temperature [29]. This study has several strengths that further clarify the relationship between temperature and kidney stones. To our knowledge, this is the first study to test for interactions between sex and the cross-basis of temperature and emergent kidney stone presentations. This design allowed us to estimate the time between temperature exposure and kidney stone presentation. Accordingly, we found that the lag-response did not vary by sex or other characteristics. This finding indicates that the greater cumulative risk among males is due to a higher magnitude of risk on each day after high temperatures rather than a more extended period over which risk remains elevated following hot days. Second, we used an aggregated case-crossover study design, which eliminates confounding by patient-level characteristics or environmental factors that are constant in the short time frame of the 10-day exposure-response period (*e.g.* medical comorbidities) [30]. This design also allowed assignment of small area-level temperature exposures where patients lived, rather than averaging temperatures over a large geographic area as had been performed in prior studies. Given the

variation in daily temperatures across South Carolina, small area-level temperature assignment increased the precision and accuracy of exposure classification, and thereby decreased exposure misclassification. Finally, we used wet-bulb temperatures, which have been shown to predict kidney stone presentations better than dry-bulb temperatures [14].

Prior to this study, differential exposure to ambient temperature was thought to be the largest contributor to sex differences in nephrolithiasis because men work outside more than women. Individuals who have public insurance are also more likely to work in jobs that require exposure to ambient temperatures than individuals with private insurance [31]. However, we found that the temperature-dependence of kidney stone presentations was nearly identical for those with public and private insurance. This result suggests that any sex differences in temperature exposure is likely insufficient to account for the substantially greater risk of kidney stone presentation among males.

The most likely explanation for the sex differences we found is sexually dimorphic renal physiology. Among mammals, males produce more sweat per unit heat than females, which leads to greater evaporative water loss during high temperatures [32]. Additionally, *in vitro* studies have demonstrated that male rats have greater expression of aquaporin channels in the proximal tubule and thin descending loop of Henle [33,34]. Aquaporin mediates 80% of water reabsorption in the mammalian kidney; greater water reabsorption would lead to lower urine volume and increased concentration of urinary solutes that contribute to stone formation. The greater fluid intake but lower urine volumes reported among men with kidney stones during summer is consistent with this greater evaporative water loss and renal tubular water reabsorption [35,7]. However, increased urinary supersaturation would not necessarily explain the short lag between high temperatures and stone presentations since stone formation is generally thought to occur over weeks to months, rather than hours to days. One hypothesis is that decreased urine volume and turbulent urinary flow may contribute to detachment of previously formed stones from the renal papillae. Biophysical research is needed to explore these putative mechanism(s).

We did not find strong evidence that the risk of kidney stone presentations differed by other individual characteristics. There was weak evidence that individuals who are white, less than 65 years old, and who live in cooler areas had a higher risk of kidney stone presentations compared to other subgroups, but these differences did not reach statistical significance. These trends are generally consistent with the lower sweat rates among Africans in warm conditions [36] and blunted adaptive responses of individuals exposed to temperatures that deviate from the typical local climate [37]. However, the increased risk of emergent kidney stone presentations estimated for individuals less than 65 years at high temperatures was inconsistent with the greater effect of heat on other kidney health outcomes, such as acute kidney injury, among older adults [20].

We acknowledge several limitations of this study. First, although exposure was assigned at the ZIP code level, misclassification of temperature exposure is possible because we do not know which individuals had access to resources that counteract heat, such as air conditioning or fluid intake. Although we could not measure fluid intake, prior studies have found that men drink approximately 750 mL more water each day than women [35].

Accordingly, these adaptive responses, which would likely be greater at higher temperatures, would bias results toward the null. Second, these results may not be generalizable to other geographic areas with different climates. However, the shape of the exposure-lag-response relationships we observed in this study were similar to prior studies of the temperature-dependence of kidney stone presentations conducted elsewhere in the United States and the world [4,5]. Third, we did not consider kidney stones evaluated in the outpatient clinic or those that never presented for evaluation.

Conclusions

The estimated risk of presenting emergently with kidney stones within 10 days of high daily wet-bulb temperatures was substantially greater among men than women, and similar between patients with public and private insurance. These findings suggest that the higher risk among males may be due to sexually dimorphic physiologic responses rather than greater exposure to ambient temperatures. These results help clarify the potential impact of climate change on human health and suggest that strategies to mitigate the effect of high temperatures may produce the greatest public health benefit for men at risk for kidney stones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Scales CD Jr., Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America P (2012) Prevalence of kidney stones in the United States. Eur Urol 62 (1):160–165. doi:10.1016/j.eururo.2012.03.052 [PubMed: 22498635]
2. Scales CD Jr., Tasian GE, Schwaderer AL, Goldfarb DS, Star RA, Kirkali Z (2016) Urinary Stone Disease: Advancing Knowledge, Patient Care, and Population Health. Clinical journal of the American Society of Nephrology : CJASN 11 (7):1305–1312. doi:10.2215/CJN.13251215 [PubMed: 26964844]
3. Litwin M, Saigal C (2012) Economic impact of urologic disease Urologic Diseases in America. NIH Publication 12–7865
4. Yang C, Chen X, Chen R, Cai J, Meng X, Wan Y, Kan H (2016) Daily ambient temperature and renal colic incidence in Guangzhou, China: a time-series analysis. International journal of biometeorology 60 (8):1135–1142. doi:10.1007/s00484-015-1106-7 [PubMed: 26581758]
5. Tasian GE, Pulido JE, Gasparrini A, Saigal CS, Horton BP, Landis JR, Madison R, Keren R, Urologic Diseases in America P (2014) Daily mean temperature and clinical kidney stone

presentation in five U.S. metropolitan areas: a time-series analysis. Environ Health Perspect 122 (10):1081–1087. doi:10.1289/ehp.1307703 [PubMed: 25009122]

6. Lee S, Kim MS, Kim JH, Kwon JK, Chi BH, Kim JW, Chang IH (2016) Daily Mean Temperature Affects Urolithiasis Presentation in Seoul: a Time-series Analysis. J Korean Med Sci 31 (5):750–756. doi:10.3346/jkms.2016.31.5.750 [PubMed: 27134497]
7. Parks JH, Barsky R, Coe FL (2003) Gender differences in seasonal variation of urine stone risk factors. J Urol 170 (2 Pt 1):384–388. doi:10.1097/01.ju.0000071721.91229.27 [PubMed: 12853781]
8. Armstrong BG, Gasparrini A, Tobias A (2014) Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. BMC Med Res Methodol 14:122. doi:10.1186/1471-2288-14-122 [PubMed: 25417555]
9. Ragettli MS, Vicedo-Cabrera AM, Schindler C, Roosli M (2017) Exploring the association between heat and mortality in Switzerland between 1995 and 2013. Environ Res 158:703–709. doi:10.1016/j.envres.2017.07.021 [PubMed: 28735231]
10. Council SCDO (2014) Principles and Protocol For the Release of Health Care Data. http://rfa.sc.gov/files/DOC%20Principles%20and%20Protocols%20072014.pdf
11. Rule AD, Bergstralh EJ, Melton LJ 3rd, Li X, Weaver AL, Lieske JC (2009) Kidney stones and the risk for chronic kidney disease. Clinical journal of the American Society of Nephrology : CJASN 4 (4):804–811. doi:10.2215/CJN.05811108 [PubMed: 19339425]
12. Rule AD, Roger VL, Melton LJ 3rd, Bergstralh EJ, Li X, Peyser PA, Krambeck AE, Lieske JC (2010) Kidney stones associate with increased risk for myocardial infarction. J Am Soc Nephrol 21 (10):1641–1644. doi:10.1681/ASN.2010030253 [PubMed: 20616170]
13. Withers PC, Cooper CE (2014) Physiological regulation of evaporative water loss in endotherms: is the little red kaluta (Dasykaluta rosamondae) an exception or the rule? Proceedings of the Royal Society B: Biological Sciences 281 (1784):20140149. doi:10.1098/rspb.2014.0149
14. Ross ME, Vicedo-Cabrera AM, Kopp RE, Song L, Goldfarb DS, Pulido J, Warner S, Furth SL, Tasian GE (2018) Assessment of the combination of temperature and relative humidity on kidney stone presentations. Environ Res 162:97–105. doi:10.1016/j.envres.2017.12.020 [PubMed: 29289860]
15. Davies-Jones R (2008) An Efficient and Accurate Method for Computing the Wet-Bulb Temperature along Pseudoadiabats. Monthly Weather Review 136 (7):2764–2785. doi:doi:10.1175/2007MWR2224.1
16. Buzan JR, Oleson K, Huber M (2015) Implementation and comparison of a suite of heat stress metrics within the Community Land Model version 4.5. Geosci Model Dev 8 (2):151–170. doi:10.5194/gmd-8-151-2015
17. Mitchell KE, Lohmann D, Houser PR, Wood EF, Schaake JC, Robock A, Cosgrove BA, Sheffield J, Duan Q, Luo L, Higgins RW, Pinker RT, Tarpley JD, Lettenmaier DP, Marshall CH, Entin JK, Pan M, Shi W, Koren V, Meng J, Ramsay BH, Bailey AA (2004) The multi-institution North American Land Data Assimilation System (NLDAS): Utilizing multiple GCIP products and partners in a continental distributed hydrological modeling system. Journal of Geophysical Research: Atmospheres 109 (D7):n/a–n/a. doi:10.1029/2003JD003823
18. Cosgrove BA, Lohmann D, Mitchell KE, Houser PR, Wood EF, Schaake JC, Robock A, Marshall C, Sheffield J, Duan Q, Luo L, Higgins RW, Pinker RT, Tarpley JD, Meng J (2003) Real-time and retrospective forcing in the North American Land Data Assimilation System (NLDAS) project. Journal of Geophysical Research: Atmospheres 108 (D22):n/a–n/a. doi:10.1029/2002JD003118
19. Han J, Liu S, Zhang J, Zhou L, Fang Q, Zhang J, Zhang Y (2017) The impact of temperature extremes on mortality: a time-series study in Jinan, China. BMJ Open 7 (4):e014741. doi:10.1136/bmjopen-2016-014741
20. McTavish RK, Richard L, McArthur E, Shariff SZ, Acedillo R, Parikh CR, Wald R, Wilk P, Garg AX (2018) Association Between High Environmental Heat and Risk of Acute Kidney Injury Among Older Adults in a Northern Climate: A Matched Case-Control Study. Am J Kidney Dis 71 (2):200–208. doi:10.1053/j.ajkd.2017.07.011 [PubMed: 29074166]
21. Gasparrini A, Armstrong B, Kenward MG (2010) Distributed lag non-linear models. Stat Med 29 (21):2224–2234. doi:10.1002/sim.3940 [PubMed: 20812303]

22. Legato MJ, Johnson PA, Manson JE (2016) Consideration of Sex Differences in Medicine to Improve Health Care and Patient Outcomes. JAMA 316 (18):1865–1866. doi:10.1001/jama.2016.13995 [PubMed: 27802499]
23. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC (2003) Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int 63 (5):1817–1823. doi:kid917 [pii] 10.1046/j.1523-1755.2003.00917.x [PubMed: 12675858]
24. Pearle M, Calhoun E, Curhan G (2005) Urologic Diseases in America Project: Urolithiasis. The Journal of urology 173 (3):848–857. doi:10.1097/01.ju.0000152082.14384.d7 [PubMed: 15711292]
25. Khan SR, Pearle MS, Robertson WG, Gambaro G, Canales BK, Doizi S, Traxer O, Tiselius HG (2016) Kidney stones. Nat Rev Dis Primers 2:16008. doi:10.1038/nrdp.2016.8 [PubMed: 27188687]
26. System USRD (2014) 2014 USRDS annual data report: Epidemiology of kidney disease in the United States. Bethesda, MD
27. Brikowski TH, Lotan Y, Pearle MS (2008) Climate-related increase in the prevalence of urolithiasis in the United States. Proc Natl Acad Sci U S A 105 (28):9841–9846. doi:0709652105 [pii] 10.1073/pnas.0709652105 [PubMed: 18626008]
28. Ordon M, Welk B, Li Q, Wang J, Lavigne E, Yagouti A, Copes R, Cakmak S, Chen H (2016) Ambient Temperature and the Risk of Renal Colic: A Population-Based Study of the Impact of Demographics and Comorbidity. J Endourol 30 (10):1138–1143. doi:10.1089/end.2016.0374 [PubMed: 27538756]
29. Fakheri RJ, Goldfarb DS (2009) Association of nephrolithiasis prevalence rates with ambient temperature in the United States: a re-analysis. Kidney Int 76 (7):798. doi:10.1038/ki.2009.274 [PubMed: 19752864]
30. Gasparrini A, Armstrong B (2010) Time series analysis on the health effects of temperature: advancements and limitations. Environ Res 110 (6):633–638. doi:10.1016/j.envres.2010.06.005 [PubMed: 20576259]
31. Park CH (2000) Prevalence of employer self-insured health benefits: national and state variation. Medical care research and review : MCRR 57 (3):340–360 [PubMed: 10981189]
32. Gagnon D, Kenny GP (2012) Does sex have an independent effect on thermoeffector responses during exercise in the heat? J Physiol 590 (23):5963–5973. doi:10.1113/jphysiol.2012.240739 [PubMed: 23045336]
33. Veiras LC, Girardi ACC, Curry J, Pei L, Ralph DL, Tran A, Castelo-Branco RC, Pastor-Soler N, Arranz CT, Yu ASL, McDonough AA (2017) Sexual Dimorphic Pattern of Renal Transporters and Electrolyte Homeostasis. J Am Soc Nephrol. doi:10.1681/ASN.2017030295
34. Herak-Kramberger CM, Breljak D, Ljubojevic M, Matokanovic M, Lovric M, Rogic D, Brzica H, Vrhovac I, Karaica D, Micek V, Dupor JI, Brown D, Sabolic I (2015) Sex-dependent expression of water channel AQP1 along the rat nephron. Am J Physiol Renal Physiol 308 (8):F809–821. doi:10.1152/ajprenal.00368.2014 [PubMed: 25656365]
35. Rosinger A, Herrick K (2016) Daily Water Intake Among U.S. Men and Women, 2009-2012. NCHS Data Brief (242):1–8
36. Marino FE, Lambert MI, Noakes TD (2004) Superior performance of African runners in warm humid but not in cool environmental conditions. J Appl Physiol (1985) 96 (1):124–130. doi:10.1152/japplphysiol.00582.2003 [PubMed: 12949014]
37. MacKenzie MA (1997) Cold exposure and winter mortality in Europe. Lancet 350 (9077):590–591; author reply 591-592. doi:10.1016/S0140-6736(05)63178-9 [PubMed: 9284797]

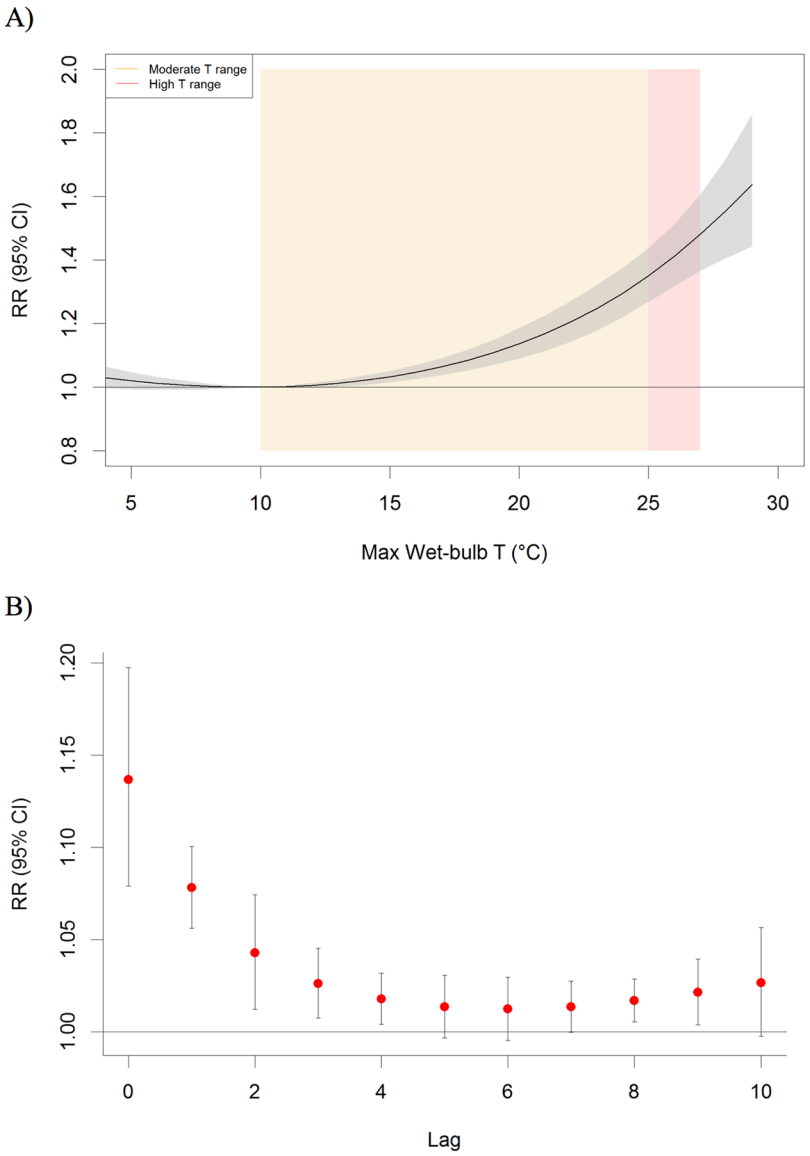

Figure 1. Temperature-Dependence of Kidney Stone Presentations for the Overall Population of South Carolina

A) Relative risk of kidney stone presentations associated with maximum daily wet-bulb temperatures for the overall population cumulated over a 10-day lag period, relative to 10 °C. The beige and pink areas represent the moderate range of daily temperatures, respectively. The black line is the RR and the surrounding gray area the 95% CI. B) Lagged RR associated with maximum daily wet-bulb temperature at the 99th percentile and kidney stone presentations over a 10-day period, relative to 10 °C. The red dots are the RRs and the whiskers the 95% CI for each day following exposure. Natural cubic spline knots were placed at the 50th and 90th percentile of the temperature range and 2 knots were placed at equal intervals in the log scale in the lag dimension.

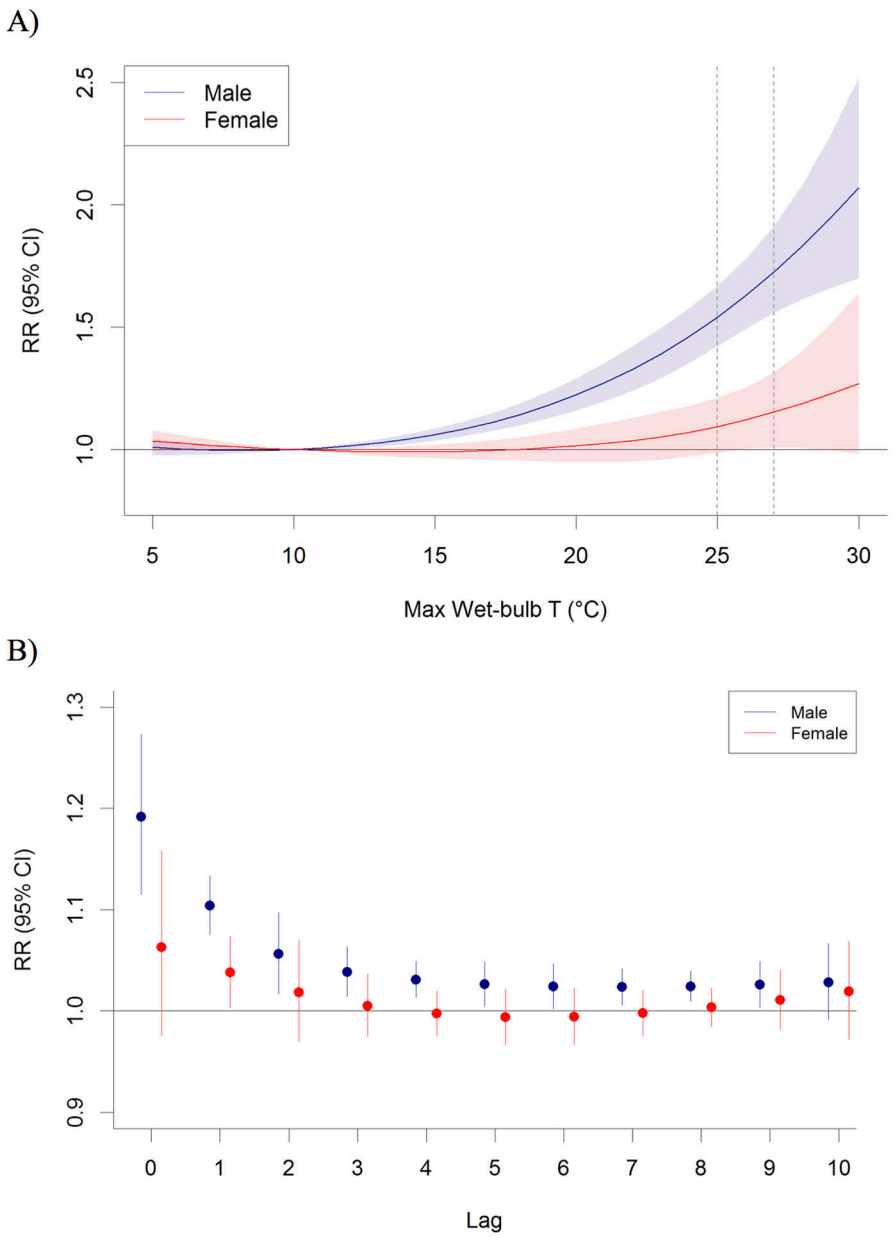

Figure 2. Temperature-Dependence of Kidney Stone Presentations in South Carolina by Sex

A) Relative risk of kidney stone presentations associated with maximum daily wet-bulb temperatures for males and females, cumulated over a 10-day lag period, relative to 10 °C. The vertical dashed lines at 25.1 °C and 27 °C represent the 90th and 99th percentile of maximum daily wet-bulb temperatures, respectively. The blue and red lines and shaded areas are the sex-specific RR and 95% CI, respectively. B) Lagged RR associated with maximum daily wet-bulb temperatures at the 99th percentile and kidney stone presentations for males and females over a 10-day period, relative to 10 °C. The blue and red dots are the RRs and the whiskers the 95% CI for each day following exposure for males and females, respectively. Natural cubic spline knots were placed at the 50th and 90th percentile of the

temperature range and 2 knots were placed at equal intervals in the log scale in the lag dimension.

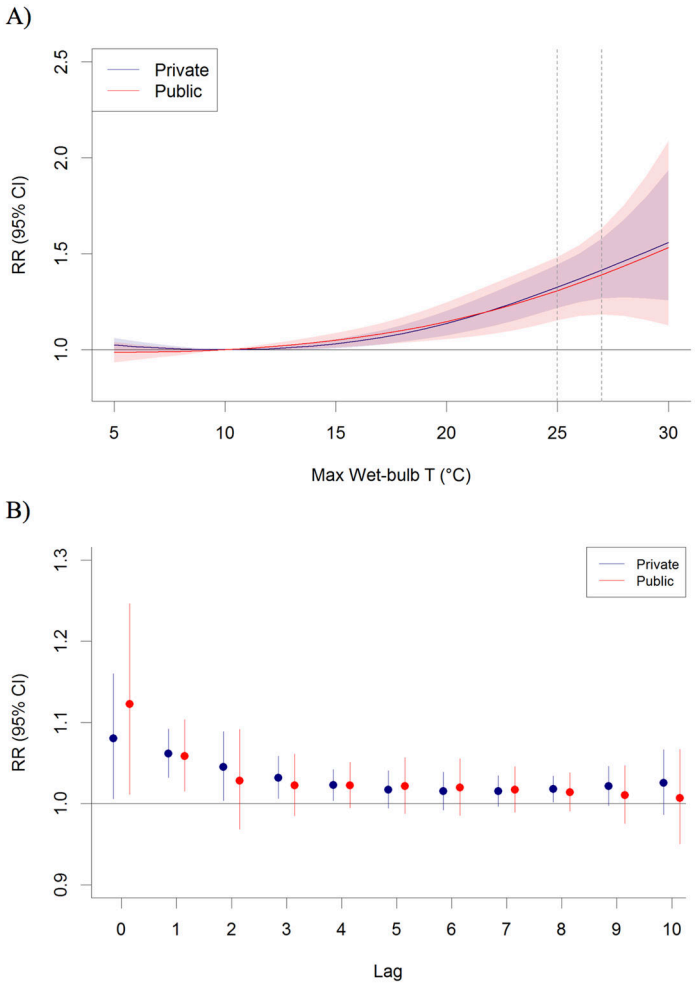

Figure 3. Temperature-Dependence of Kidney Stone Presentations in South Carolina by Payer Status

A) Relative risk of kidney stone presentations associated with maximum daily wet-bulb temperatures by private and public health insurance, cumulated over a 10-day lag period, relative to 10 °C. The vertical dashed lines at 25.1 °C and 27 °C represent the 90th and 99th percentile of maximum daily wet-bulb temperatures, respectively. The blue and red lines and shaded areas are the sex-specific RR and 95% CI, respectively. B) Lagged RR associated with maximum daily wet-bulb temperatures at the 99th percentile and kidney stone presentations for individuals with private and public health insurance over a 10-day period, relative to 10 °C. The blue and red dots are the RRs and the whiskers the 95% CI for each day following exposure for private and public health insurance, respectively. Natural cubic spline knots were placed at the 50th and 90th percentile of the temperature range and 2 knots were placed at equal intervals in the log scale in the lag dimension.

Table 1.

Characteristics of Patients who Presented to Emergency Rooms with Kidney Stones, South Carolina, 1997-2015 (N=132,597)

Characteristics		N (%)
Sex	Male	81,241 (61.3)
	Female	51,356 (38.7)
Age category	<20 years	6,453 (4.9)
	20-45	64,999 (49)
	45-65	44,960 (33.9)
	>65 years	16,185 (12.2)
Payer category	Public	32,983 (24.9)
	Private	72,590 (54.7)
	Other	27,024 (20.4)
Race	White	112,196 (84.6)
	African-American	17,423 (13.1)
	Other	2,978 (2.2)
Climatic area	Warm	48,743 (36.8)
	Cold	83,851 (63.2)

Table 2.

Relative Risk and 95% Confidence Intervals of Emergent Kidney Stone Presentations Cumulated over 10 days Following Daily Maximum Wet-Bulb Temperatures at the 99th Percentile Compared to 10 °C (Overall), Moderate Temperatures, and Extreme Temperatures.

Characteristics		Overall		Interaction p-value*	Moderate temperatures		Extreme temperatures	
		RR	95% CI		RR	95% CI	RR	95% CI
Total		1.48	1.37, 1.60		1.35	1.27, 1.44	1.09	1.04,1.14
Sex	Male	1.73	1.56, 1.91	<0.001	1.54	1.42, 1.67	1.12	1.06, 1.19
	Female	1.15	1.01, 1.32		1.09	0.99, 1.21	1.05	0.98, 1.14
Age	≤ 65 years	1.5	1.38, 1.63	0.067	1.35	1.26, 1.44	1.11	1.06, 1.17
	> 65 years	1.35	1.07, 1.71		1.37	1.15, 1.64	0.99	0.87, 1.12
Race	White	1.48	1.35, 1.61	0.199	1.37	1.28, 1.46	1.08	1.03, 1.14
	African-American	1.36	1.09, 1.69		1.21	1.02, 1.44	1.12	0.99, 1.26
Payer category	Public	1.42	1.27, 1.58	0.714	1.33	1.22, 1.44	1.07	1, 1.14
	Private	1.39	1.18, 1.63		1.31	1.15, 1.48	1.06	0.97, 1.16
Climatic area	Warm	1.45	1.29, 1.63	0.695	1.39	1.28, 1.51	1.05	0.97, 1.12
	Cold	1.46	1.3, 1.64		1.29	1.17, 1.42	1.13	1.07, 1.2

Moderate temperatures were defined as the 90th percentile of daily maximum wet-bulb temperature with 10 °C as reference. Extreme temperatures were defined as the 99th percentile of daily maximum wet-bulb temperature with the 90th percentile as reference. The exposure-response relationship was modeled through a cross-basis term, with a natural cubic spline with 2 internal knots placed at the 50^{th} and 90^{th} percentile of the temperature indicator for the exposure-response function, and a natural cubic spline with intercept and 2 internal knots equally-spaced in the log scale in the lag dimension.

*P-value of the test for interaction between levels of characteristics in the overall estimates.