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Title Page

Outdoor Temperature and Survival Benefit of Empiric Potassium in Users of High-Dose Furosemide: a Retrospective Cohort Study

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Systems/Research/ResearchGenInfo/ResearchDataAssistanceCenter.html) and the Research Data Assistance Center (ResDAC) website (https://www.resdac.org/cms-data/request/cms-data-request-center).

Abstract

Objective: Empiric potassium use is associated with a marked survival benefit in high-dose (≥40 mg/day) furosemide users. This study sought to examine whether the empiric potassium's survival benefit in users of high-dose furosemide increases with higher temperature (≥24 degrees Celsius).

Design: Retrospective cohort study.

Setting: Outpatient setting, captured by Medicaid claims supplemented with Medicare claims for dual-enrollees from 5 US states from 1999-2010, linked to meteorological data during the same period.

Population/Participants: High-dose furosemide initiators among adults continuously enrolled in Medicaid at least one year prior to cohort entry (defined as the day following the dispensing day of the initial furosemide prescription).

Exposure: Empiric potassium use, dispensed the day of or the day following the dispensing the initial furosemide prescription.

Outcome measure: All-cause mortality, ascertained by linkage to the Social Security Administration Death Master File.

Results: The unmatched study cohorts included 337,973 initiators of high-dose furosemide, of whom 106,937 individuals (32%) were empiric potassium users. In the 1:1 propensity-score matched cohorts (total N=213,754) that included 90,239 person-years and 9,112 deaths, the all-cause mortality rates per 1,000 person-years were 96.4 (95% confidence interval [CI]: 93.6 to 99.3) and 105.7 (95% CI: 102.7 to 108.7) for the potassium users and non-users, respectively. In multivariable logistic regression models, the odds ratio of all-cause mortality for potassium use appeared to decline (i.e., its protective effect increased), although the decline was not statistically

significant, with higher daily average temperature and daily maximum temperature; *p*-values for interactions of potassium with daily average temperature, daily average temperature squared, daily maximum temperature, and daily maximum temperature squared were 0.17, 0.17, 0.05, and 0.06, respectively.

Conclusions: If the relationships suggested by these results are real, use of empiric potassium in high-dose furosemide users might be particularly important on hot days.

Keywords: outdoor temperature; empiric potassium; furosemide; mortality; weather-drug interactions; drug interactions; pharmacoepidemiology

Strengths and limitations of this study

Strengths

- This study used large-scale real-world data, representing about 40% of individuals in the US Medicaid program that covers nearly one in five Americans.
- It also used ZIP code-level daily temperature data, which may reflect the outdoor temperature at each individual's place of residence more accurately than those based on larger geographic units.
- The study cohorts had good balance in the distribution of measured baseline covariates even before matching, and this balance improved further with propensity score matching, which suggests a limited role for potential confounding factors.

Limitations

- Data on the degree to which subjects were actually exposed to outdoor temperatures were not available, therefore, this study employed methodologies to mimic a randomized controlled study.
- Residual confounding may remain, as is the case with observational studies in general.

Text

Outdoor Temperature and Survival Benefit of Empiric Potassium in Users of High-Dose Furosemide: a Retrospective Cohort Study

Introduction

High outdoor temperature is associated with a number of adverse health outcomes including heat stroke, dehydration, renal failure, cardiovascular diseases, diabetes, electrolyte disorders, and respiratory diseases.[1-7] Older people and those with underlying health conditions or socioeconomic disadvantages are at increased risk from heat exposure.[2,5,7-15] People who take furosemide, a potent and commonly-used diuretic, may also be at increased risk, since furosemide leads to loss of potassium through the kidneys[16-17] while heat leads to potassium loss through sweat.[18] Although no randomized trials have investigated a survival benefit of empiric (i.e., prophylactic or preventive) potassium use in furosemide users, a recent cohort study found that empiric potassium was associated with a relative survival benefit of 7% in initiators of low-dose furosemide (< 40 mg/day) and of 16% in initiators of high-dose furosemide (≥ 40 mg/day).[19] We hypothesized that the apparent survival benefit of empiric potassium in users of high-dose furosemide is more marked with higher outdoor temperature. Such a relationship would suggest that potassium administration in furosemide users is particularly important when the outdoor temperature is high, which could have growing clinical and public health importance as global climate change continues, raising both the overall temperatures in general, and also the number and intensity of extreme hot days.[20-22]

Methods

Study design, population, and data

We conducted a retrospective propensity-score matched cohort study among adult US Medicaid enrollees using 1) Medicaid claims from California, Florida, New York, Ohio, and Pennsylvania from 1999-2010 supplemented with Medicare claims for the Medicaid-Medicare dual-enrollees for the same period, including Part D Event Files from 2006-2010 (Part D began in 2006); and 2) meteorological data obtained from the US National Oceanic and Atmospheric Administration (NOAA) from 1999-2010.[23] These five states include about 40% of the US Medicaid population.[24] Adults ($18 \leq$ age < 100 years) who had continuous enrollment in Medicaid for at least one year before the cohort entry date (described below) were eligible for our analysis.

Study cohort, exposure and outcome of interest, and follow-up time

The study cohort comprised apparent initiators of furosemide and whose starting dose (calculated from the index prescription) was 40 mg/day or higher. Apparent initiators of furosemide were defined as those in whom no furosemide dispensed in the 365 days before cohort entry – the baseline period – based on a given furosemide prescription; such prescriptions are referred to as index furosemide prescriptions, and the date of their dispensing referred to as the index date. Individuals entered a study cohort only once.

The exposure of interest was empiric potassium use, defined as a potassium prescription for an orally administered solid dosage form of a bicarbonate, chloride, citrate, or gluconate salt that was dispensed on the index date or the next day,[19] but not prior to the furosemide dispensing date. Exposure was defined in this way to better capture empiric potassium rather than potassium given as treatment for clinically recognized hypokalemia. Although potassium products are

available over-the-counter (OTC), such use is unlikely to have a large effect on study results because the strengths of OTC potassium (limited to less than about 2.5 mEq of potassium, which is about 2% of the daily recommendation of potassium for adults) are considerably lower than typical doses of potassium used to prevent hypokalemia (about 20 mEq/day). Prescription drug use was identified by using National Drug Codes and days' supply on prescription claims. We allowed a 15-day gap between contiguous prescriptions and at the end of the last prescription to account for potential incomplete adherence.

The cohort entry date was the day following the index date for both potassium users and non-users, since we defined exposure as being dispensed a potassium prescription on the index date or the following day. We excluded patients who: 1) used non-solid dosage forms of furosemide or potassium, which might be indicative of inability to swallow a solid dosage form and/or functional impairments that may not be reliably ascertained in the administrative data; 2) had a diagnosis before the cohort entry date of hypokalemia (International Classification of Diseases 9th Revision Clinical Modification [ICD-9-CM]: 276.8), hyperkalemia (ICD-9-CM: 276.7), or acidosis (ICD-9-CM: 276.2), since hypokalemia would suggest that in such persons potassium was used for treatment rather than empirically, and hyperkalemia and acidosis are contraindications for potassium; or 3) who, before the cohort entry date, were diagnosed with renal impairment or chronic kidney diseases (ICD-9-CM: 582*, 585*, 586-587, 588*), received hemo- or peritoneal dialysis (ICD-9-CM: V56*; Current Procedural Terminology [CPT]: 90918-90999), used potassium-sparing diuretics, or who were dispensed potassium before the index date. Supplementary material **Figure S1** presents the sample size and how the inclusion and exclusion criteria were applied.

The outcome of interest was all-cause mortality, ascertained by linkage to the US Social Security Administration Death Master File.

Follow-up time (**Figure S2**) began on the cohort entry date and ended with the first of the following events: 1) death; 2) end of days' supply of furosemide (following a 15-day grace period); 3) Medicaid enrollment discontinuation; or 4) end of the data set, i.e., December 31, 2010. We did not censor follow-up time based on initiation or discontinuation of potassium in either group (potassium user or non-user group) because our study was intended to examine the survival benefit of the strategy of providing or not providing *empiric* potassium, regardless of whether potassium was later discontinued or added.

Meteorological data

NOAA's meteorological data provide weather parameters, including daily minimum and maximum temperatures measured at weather stations, and the locations of these stations. For each furosemide user in our study cohort, we linked Zoning Improvement Plan code (ZIP code) of residence (ascertained from claims data) to the population-weighted centroid of that ZIP code area, which was estimated by using ZIP code boundaries, census block group boundaries, and 2010 census block group-level population data. Individuals who had missing or invalid ZIP code of residence were excluded. Each population-weighted centroid of ZIP code was linked to the ZIP code-level, daily maximum temperature and daily average temperature (*calculated* as the arithmetic mean of the daily minimum and daily maximum temperatures). These ZIP code-level, daily outdoor temperatures were estimated by using day-level meteorological data, locations of weather stations, and a spline interpolation method that is a commonly used geospatial analysis

method to estimate properties, such as temperature, at un-sampled sites based on the data of sampled sites, which may enable more precise estimation than a simple averaging method.[25-27]

Statistical analysis

Propensity score matching for the adjustment of potential confounders

We used propensity score matching to balance the potassium and no-potassium groups on measured baseline factors.[28-29] First, we estimated each subject's propensity score by fitting a logistic regression model where the dependent variable was the indicator of the receipt of empiric potassium and the independent variables (selected based on potential association with both potassium use and death; presented in **Table 1**) included: 1) demographic characteristics (e.g., age, sex, race, Medicaid-Medicare dual-eligibility, state of residence, etc.); 2) diseases (e.g., hypertension, lipid metabolism disorders, diabetes mellitus, ischemic heart diseases, heart failure/cardiomyopathy, asthma/chronic obstructive pulmonary disease/emphysema, etc.); 3) prescription drugs (e.g., renin-angiotensin-aldosterone system blockers, antihyperlipidemic agents, beta blockers, calcium channel blockers, corticosteroids, antidiabetics, etc.); and 4) healthcare services utilization intensity (including nursing home residence, number of inpatient hospitalizations, number of outpatient visits, and number of prescription drug fillings).[30] All independent variables were binary and assessed during the one-year baseline period, except for the age at cohort entry, a continuous variable. We then used 1:1 nearest neighbor propensity score matching to match users of empiric potassium to non-users.[31]

Baseline characteristics, incidence rates, and logistic regression analysis

We first calculated descriptive statistics on baseline characteristics (**Table 1**) and compared the mortality rates between users and non-users of empiric potassium before and after propensity-score matching. The balance in the baseline characteristics was assessed by standardized difference (i.e., the mean difference of a variable between the two groups in units of the estimated common standard deviation of that variable in the two groups), with a value exceeding 0.1 suggestive of potentially meaningful imbalance between groups.[29] Next, we examined the temperature-potassium-mortality association in the high temperature range (defined as ≥ 24°C or 75°F) by modeling the interaction between temperature (daily average temperature and daily maximum temperature, separately) and potassium exposure status on the log odds of mortality using a multivariable logistic regression model where the unit of observation was person-day, allowing temperature to vary by day for each individual. We examined potential autocorrelation from the multiple observations of the same individuals over time using the Durbin-Watson test,[32] and found that the autocorrelation was not statistically significant for daily average temperature ($p = 0.14$), daily average temperature squared ($p = 0.17$), daily maximum temperature ($p = 0.55$), and daily maximum temperature squared ($p = 0.73$), for the first-order to fourth-order Durbin-Watson tests. The 24°C minimum temperature was chosen in advance based on literature indicating a U-shape relationship between temperature and death, with a nadir between 22°C-26°C, although we recognize that this relationship varies by location.[33-36] We excluded rare, extremely high temperatures (daily average temperature > 43°C or 110°F; daily maximum temperature > 49°C or 120°F). Given that the true functional form of the relationship between potassium use, temperature, and mortality is unknown, we examined a model that included a linear term and a quadratic term of temperature and two temperature-potassium exposure

interaction terms (hereinafter referred to as a quadratic model). This model is expressed as Equation 1.

$$\text{logit}\left(Y_{ij}\right) = \alpha + \beta_0\left(T_{ij}\right) + \beta_1\left(T_{ij}^2\right) + \beta_2\left(K^+{}_i\right) + \beta_3\left(T_{ij} \times K^+{}_i\right) + \beta_4\left(T_{ij}^2 \times K^+{}_i\right) + \boldsymbol{\gamma_i}\mathbf{X'_i} + \epsilon_{ij} \quad \text{(Equation 1)}$$

In these equations, Y_{ij} is an indicator variable for the death outcome of person *i* on day *j*; T_{ij} is the outdoor temperature for person *i* at their ZIP code area on day *j*; $K^+{}_i$ is a binary variable indicating the potassium use or non-use of person *i*; and $\mathbf{X'_i}$ is a vector of time-invariant covariates of person *i* for which we used age group at cohort entry, sex, and race group. We examined daily average temperature and daily maximum temperature in separate models. We also considered a linear model but decided to use a quadratic model to avoid reliance on the assumption that the relationship is linear. As a sensitivity analysis, we examined a model that included daily relative humidity at the person-level.

Analyses were performed using ArcGIS version 10.3 (Esri, Redlands, CA), SAS version 9.4 (SAS Institute Inc., Cary, NC), and Stata version 14 (StataCorp, College Station, TX).

Ethical Approval

This study was approved by the institutional review board of the University of Pennsylvania, which waived the requirement for obtaining informed consent. We attest that we have obtained appropriate permissions and paid any required fees for use of copyright protected materials.

Patient and Public Involvement

Patients and public were not directly involved in this study.

Results

Supplemental **Figure S1** shows the number of potentially eligible and included subjects, with reasons for exclusion. Prior to matching, there were 337,973 eligible initiators of high-dose furosemide, 106,937 (32%) of whom were empiric potassium users. Nearly all of the empiric potassium users were pair-matched to a non-user, resulting in 106,877 subjects in each group. In the potassium cohort, 76% of the follow-up time was covered by an active prescription for potassium (follow-up continued as long as the furosemide prescription was active; Supplemental **Figure S2**), while only 19% of the follow-up time for the no-potassium group was covered by an active prescription for potassium; 85% of individuals in the no-potassium group received no potassium prescriptions during follow-up. As shown in **Table 1**, baseline variables were reasonably well balanced even before matching; this balance was improved by propensity score matching. In the matched cohorts, mean follow-up time was 156 days in potassium users and 152 days in potassium non-users, and the mortality rate (in deaths per 1,000 person-years) was 96.4 (95% confidence interval [CI]: 93.6, 99.3) in users and 105.7 (95% CI: 102.7, 108.7) in non-users.

Table 2 and **Figure 1** examine the associations between empiric potassium use and mortality as a) a function of daily average temperature and daily average temperature squared and b) a function of daily maximum temperature and daily maximum temperature squared, as well as the interaction between those temperatures and potassium use (daily average temperature and daily maximum temperature examined separately). Because the daily maximum temperature exceeds 24°C more often than does the daily average temperature, there were more observations for this metric. As seen in Figure 1, the odds ratio of all-cause mortality for potassium use (calculated by using the regression results shown in Table 2) appeared to be lower (i.e., its

protective effect appeared to increase) when both temperature metrics were higher, although *p*-values for the interaction with daily average temperature ($p = 0.17$), daily average temperature squared ($p = 0.17$), daily maximum temperature ($p = 0.05$) and daily maximum temperature squared ($p = 0.06$) were not statistically significant using a 2-tailed α of 0.05. The estimated association corresponds to approximately 6% point reduction in odds for each 1°C increase in daily average temperature between 27°C and 43°C, and a 3% point reduction in odds for each 1°C increase in daily maximum temperature between 31°C and 49°C. Results were similar when daily relative humidity was included (**Table S1**).

Discussion

This study examined whether the apparent survival benefit of empiric potassium in users of high-dose furosemide is larger with higher daily average and daily maximum temperature. Consistent with earlier findings in the same population using 1999-2007 data,[19] empiric potassium use was associated with a survival benefit in high-dose furosemide initiators. While the results suggest that this survival benefit may increase with daily average and daily maximum temperature, neither association was statistically significant at α=0.05, although the interactions between potassium and daily maximum temperature ($p = 0.05$) and daily maximum temperature squared ($p = 0.06$) were nearly so.

If there is a true relationship between temperature and the survival benefit of potassium, it would have potentially important clinical and public health implications. It is already well-known that high outdoor temperature is associated with an excess of cardiovascular deaths.[37-42] Some of these excess deaths might be avoidable through interventions to increase potassium

intake in furosemide users on hot days. The number of lives saved by such interventions would be expected to increase as global climate change continues.[20-22]

One might hypothesize seasonality in the association between temperature and mortality, or that individuals residing at warmer regions might tolerate increases in temperature better than those in cooler areas, or that other climate parameters might also influence the mortality. While we were unable to explore such relationships given the limited number of high-temperature deaths, such relationships would not bias the estimation on the temperature dependency of potassium's survival effect. For example, when we controlled for daily relative humidity in the sensitivity analysis (**Table S1**), the results of the temperature-potassium interaction changed little (both coefficients and 95% CIs), even though daily relative humidity was statistically significant when examining daily maximum temperature. A temperature-potassium interaction on mortality, if it exists, might differ across different subgroups, such as different geographic regions, sociodemographic characteristics, comorbidities, or degree of frailty. Future studies are warranted to investigate these potential relationships.

This study has several strengths. First, it used large-scale real world data, representing about 40% of individuals in the US Medicaid program that covers nearly one in five Americans. It also used ZIP code-level daily temperature data, which may better reflect the outdoor temperature at each individual's place of residence. Further, the study cohorts had good balance in the distribution of measured baseline covariates even before matching, and this balance improved further with propensity score matching, which suggests a limited role for potential confounding factors.

This study also has limitations. First, we did not have data on individuals' use of air conditioning or on the amount of time spent outdoors. Therefore, we do not know the degree to

which subjects were actually exposed to outdoor temperatures. However, prior studies that also lacked such data have associations between temperature and of a variety of health endpoints.[39-40,42] Further, given the observed similarity of potassium users and non-users, it seems unlikely that access to air conditioning would differ substantially by exposure group. Therefore, it seems most likely that lack of data on air conditioning would have introduced bias toward the null. Second, results observed in US Medicaid enrollees, who have lower incomes and poorer health than other groups, might not be generalizable to other populations. Nevertheless, about 20% of the US population is enrolled in Medicaid, so this is an important population in its own right, and biological relationships found in Medicaid enrollees are often confirmed in other populations. Third, although our study cohorts showed good balance in measured covariates, we cannot rule out the possibility of imbalances in unobserved factors. Finally, our study did not examine location-specific differences in the estimated associations, which may differ due to variation in the relationship between temperature and health.

Conclusions

The results of this study, while not meeting the conventional threshold for statistical significance, suggest that empiric potassium's apparent survival benefit may increase as daily average or daily maximum temperature increases in users of high-dose furosemide. This potential relationship should be confirmed in independent data sets. Also, future studies should investigate other functional forms of temperature such as lagged effects, cumulative days at high temperature, variation from the mean temperature at a given location, etc., using larger data with sufficient statistical power. Given the widespread use of furosemide, interventions based on this potential relationship have potential to benefit many people worldwide.

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Author contribution: Hennessy, Leonard, and Bilker conceived and designed the study. Hennessy and Leonard were involved in acquisition of data. Nam and Bilker performed statistical analysis. Nam, Bilker, Leonard, Bell, and Hennessy interpreted the results. Nam drafted the manuscript. Nam, Bilker, Leonard, Bell, and Hennessy critically revised the manuscript for important intellectual content. All authors approved the final manuscript to be submitted for publication and the authorship list.

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Figure Legends

Figure 1. Odds Ratios and 95% Confidence Intervals of All-Cause Mortality for Potassium Use vs. Non-use by Temperature

Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). Bold solid lines indicate odds ratios, and thin dash lines indicate 95% confidence intervals.

Table 1. Baseline Characteristics of the Unmatched and Matched Study Cohorts

	Before PS-Matching			After PS-Matching		
	Potassium group	No-potassium group	Standardized Difference	Potassium group	No-potassium group	Standardized Difference
	N=106,937	N=231,036		N=106,877	N=106,877	
Sociodemographic Characteristics						
Age at cohort entry, in years (%)						
18≤Age<35 (Ref)	3.92	4.27	0.02	3.93	3.89	0.00
35≤Age<50	15.03	14.94	0.00	15.03	15.24	0.01
50≤Age<65	23.82	24.77	0.02	23.81	23.66	0.00
65≤Age<80	34.79	33.76	0.02	34.79	34.91	0.00
80≤Age<100	22.44	22.27	0.00	22.44	22.29	0.00
Sex, female (%)	66.36	66.40	0.00	66.35	66.41	0.00
Race/Ethnicity (%)						
White	53.68	50.05	0.07	53.66	53.78	0.00
Black	15.35	18.15	0.08	15.36	15.36	0.00
Hispanic	15.58	14.03	0.04	15.58	15.54	0.00
Other/Unknown	15.39	17.78	0.06	15.40	15.33	0.00
Medicaid-Medicare dual-eligible (%)	70.37	67.43	0.06	70.35	70.13	0.00
State of residence (%)						
CA	45.90	40.74	0.10	45.92	46.17	0.01
FL	17.42	8.89	0.25	17.37	16.94	0.01
NY	17.13	29.26	0.29	17.14	17.11	0.00
OH	10.35	8.93	0.05	10.36	10.63	0.01
PA	9.20	12.18	0.10	9.21	9.15	0.00
Urban residents* (%)	85.86	87.05	0.03	85.87	85.81	0.00
Year of cohort entry						

	Before PS-Matching			After PS-Matching		
	Potassium group	No-potassium group	Standardized Difference	Potassium group	No-potassium group	Standardized Difference
	N=106,937	N=231,036		N=106,877	N=106,877	
2000	8.95	10.34	0.05	8.95	9.10	0.01
2001	9.84	9.93	0.00	9.84	9.83	0.00
2002	9.72	9.64	0.00	9.72	9.76	0.00
2003	9.55	9.42	0.00	9.55	9.53	0.00
2004	7.25	7.88	0.02	7.26	7.30	0.00
2005	8.36	8.37	0.00	8.36	8.38	0.00
2006	14.12	14.02	0.00	14.11	14.23	0.00
2007	9.12	7.99	0.04	9.11	8.93	0.01
2008	7.03	6.65	0.02	7.03	6.97	0.00
2009	7.89	7.49	0.02	7.89	7.79	0.00
2010	8.18	8.25	0.00	8.18	8.17	0.00
Diseases						
Alkalosis, metabolic (%)	0.20	0.20	0.00	0.20	0.21	0.00
Amyloidosis (%)	0.03	0.04	0.01	0.03	0.03	0.00
Anemia (%)	29.31	27.46	0.04	29.29	29.40	0.00
Ascites (%)	1.26	1.40	0.01	1.26	1.26	0.00
Asthma/COPD/emphysema (%)	31.41	27.43	0.09	31.39	31.27	0.00
Cardiac dysrhythmias/conduction disorder (%)	26.31	23.76	0.06	26.28	26.25	0.00
Cerebrovascular disease (%)	18.45	17.54	0.02	18.44	18.46	0.00
Diabetes insipidus (%)	0.06	0.06	0.00	0.06	0.06	0.00
Diabetes mellitus (%)	38.90	39.70	0.02	38.90	38.84	0.00
Edema (%)	23.65	19.86	0.09	23.63	23.59	0.00
Glaucoma (%)	9.54	9.84	0.01	9.55	9.53	0.00

	Before PS-Matching			After PS-Matching		
	Potassium group N=106,937	No-potassium group N=231,036	Standardized Difference	Potassium group N=106,877	No-potassium group N=106,877	Standardized Difference
Heart failure/cardiomyopathy (%)	36.48	32.97	0.07	36.45	36.40	0.00
HIV/AIDS (%)	0.45	0.69	0.03	0.45	0.44	0.00
Hyperosmolality (%)	0.46	0.59	0.02	0.46	0.47	0.00
Hypertensive disease (%)	66.66	64.48	0.05	66.65	66.44	0.00
Hyperthyroidism (%)	2.25	1.96	0.02	2.25	2.22	0.00
Hypothyroidism (%)	16.21	14.53	0.05	16.20	16.06	0.00
Ischemic heart disease (%)	36.52	32.90	0.08	36.49	36.59	0.00
Kidney disease[†] (%)	9.27	10.60	0.04	9.27	9.25	0.00
Lipoid metabolism disorder (%)	43.21	37.96	0.11	43.18	42.94	0.00
Liver disease (%)	20.13	19.54	0.01	20.13	20.19	0.00
Magnesium metabolism disorder (%)	0.63	0.62	0.00	0.63	0.64	0.00
Nocturia (%)	1.37	1.20	0.02	1.37	1.32	0.00
Pulmonary circulation disease (%)	5.00	4.40	0.03	4.99	5.03	0.00
Pulmonary congestion and hypostasis/pulmonary edema (%)	6.46	5.89	0.02	6.46	6.49	0.00
Pyloric stenosis (%)	0.07	0.08	0.00	0.07	0.07	0.00
Rheumatoid arthritis and other inflammatory polyarthropathies (%)	5.16	4.64	0.02	5.16	5.19	0.00
Systemic lupus erythematosus (%)	0.70	0.67	0.00	0.69	0.67	0.00
Urinary obstruction (%)	0.41	0.40	0.00	0.41	0.41	0.00
Prescription Drugs						
RAAS blockers (%)	52.01	54.36	0.05	52.02	51.66	0.01
Adrenergic agents (%)	11.99	12.29	0.01	11.99	11.87	0.00
Antiarrhythmics (%)	3.59	2.62	0.06	3.56	3.64	0.00

	Before PS-Matching			After PS-Matching		
	Potassium group N=106,937	No-potassium group N=231,036	Standardized Difference	Potassium group N=106,877	No-potassium group N=106,877	Standardized Difference
Antidiabetics (%)	31.61	34.30	0.06	31.62	31.54	0.00
Antiglaucoma agents (%)	19.45	18.52	0.02	19.44	19.39	0.00
Antihyperlipidemic agents (%)	39.66	38.39	0.03	39.65	39.38	0.01
Antiobesity agents (%)	0.18	0.11	0.02	0.18	0.18	0.00
Antiretrovirals (%)	0.74	1.14	0.04	0.74	0.73	0.00
Beta blockers, systemic (%)	34.20	33.88	0.01	34.19	34.13	0.00
Bisphosphonates (%)	2.95	2.43	0.03	2.94	2.93	0.00
Calcium channel blockers (%)	31.14	31.71	0.01	31.14	30.88	0.01
Corticosteroids, systemic (%)	30.54	28.13	0.05	30.52	30.31	0.00
Digoxin (%)	9.95	8.89	0.04	9.94	10.00	0.00
Diuretics, thiazides (%)	13.82	15.37	0.04	13.83	13.71	0.00
Immunosuppressives (%)	0.64	0.76	0.01	0.64	0.62	0.00
Thyroid hormones (%)	12.24	11.66	0.02	12.23	12.14	0.00
Vasodilators (%)	10.41	10.47	0.00	10.41	10.46	0.00
Warfarin (%)	10.00	9.11	0.03	9.98	10.01	0.00
Xanthine derivatives (%)	4.93	4.23	0.03	4.93	4.90	0.00
Healthcare Services Utilization Intensity						
Nursing home residence (%)	16.37	18.04	0.04	16.37	16.34	0.00
Inpatient hospitalization, mean number	0.71	0.68	0.02	0.71	0.72	0.01
Outpatient visits, mean number	47.15	49.40	0.03	47.15	47.54	0.01
Prescription drug fillings, mean number	25.71	24.73	0.05	25.71	25.77	0.00

PS: propensity score. RAAS: renin-angiotensin-aldosterone system. Ref: reference. *Urban residents: ascertained by the ZIP codes in the claims data used and ZIP Code to Carrier Locality File from the Centers for Medicare and Medicaid Services (Centers for Medicare and Medicaid Services, 2017). †Kidney disease: kidney diseases, except for chronic kidney diseases or renal impairment.

Table 2. Logistic Regression Results to Estimate Temperature-Modified Empiric Potassium's Effect on All-Cause Mortality

	Daily average temperature ≥ 24° C (N=6,475,333 person-days; 1,882 deaths)				Daily maximum temperature ≥ 24° C (N=15,352,988 person-days; 4,341 deaths)			
	Coefficient	95% CI		*p*-value	Coefficient	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
Temperature	0.0559	-0.4425	0.5543	0.83	-0.0632	-0.1949	0.0685	0.35
Temperature squared*	-0.0006	-0.0097	0.0085	0.90	0.0013	-0.0008	0.0034	0.24
Potassium†	-7.4720	-18.0158	3.0718	0.16	-3.0070	-5.9323	-0.0817	0.04
Temperature × Potassium	0.5467	-0.2269	1.3203	0.17	0.1911	-0.0012	0.3834	0.05
Temperature squared × Potassium	-0.0100	-0.0242	0.0042	0.17	-0.0031	-0.0062	0.0000	0.06

95% CI: 95% confidence interval. Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). *Temperature squared: 2nd degree polynomial term of temperature. †Potassium: empiric potassium exposure status (0=empiric potassium users; 1=empiric potassium non-users).

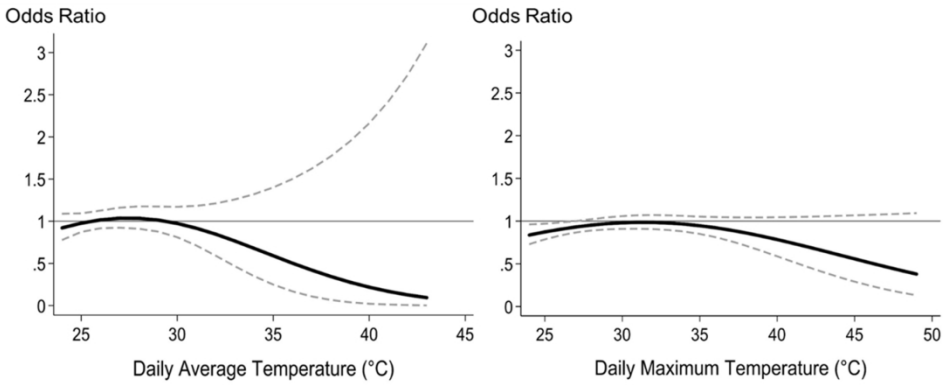


Figure 1. Odds Ratios and 95% Confidence Intervals of All-Cause Mortality for Potassium Use vs. Non-use by Temperature

Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). Bold solid lines indicate odds ratios, and thin dash lines indicate 95% confidence intervals.

Figure 1

178x110mm (300 x 300 DPI)

Table S1. Regression Results to Estimate Temperature-Modified Empiric Potassium's Effect on All-Cause Mortality in High-Dose Furosemide Users: Sensitivity Analysis with Daily Relative Humidity Included

	Daily average temperature ≥ 24° C (N=6,475,333 person-days; 1,882 deaths)				Daily maximum temperature ≥ 24° C (N=15,352,988 person-days; 4,341 deaths)			
	Coefficient	95% CI		*p*-value	Coefficient	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
Temperature	0.0847	-0.4225	0.5919	0.74	-0.0244	-0.1589	0.1101	0.72
Temperature squared*	-0.0011	-0.0103	0.0081	0.81	0.0006	-0.0016	0.0027	0.62
Potassium†	-7.6218	-18.2630	3.0194	0.16	-3.0794	-6.0388	-0.1200	0.04
Temperature × Potassium	0.5581	-0.2230	1.3392	0.16	0.1964	0.0016	0.3912	0.05
Temperature squared × Potassium	-0.0102	-0.0245	0.0041	0.16	-0.0031	-0.0063	0.0000	0.05
Relative Humidity‡	-0.0020	-0.0051	0.0011	0.21	-0.0053	-0.0075	-0.0031	<0.0001

95% CI: 95% confidence interval. Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). *Temperature squared: 2nd degree polynomial term of temperature. †Potassium: empiric potassium exposure status (0=empiric potassium users; 1=empiric potassium non-users. ‡Relative Humidity: daily relative humidity.

Figure S1. Sample Size and the Application of Inclusion and Exclusion Criteria

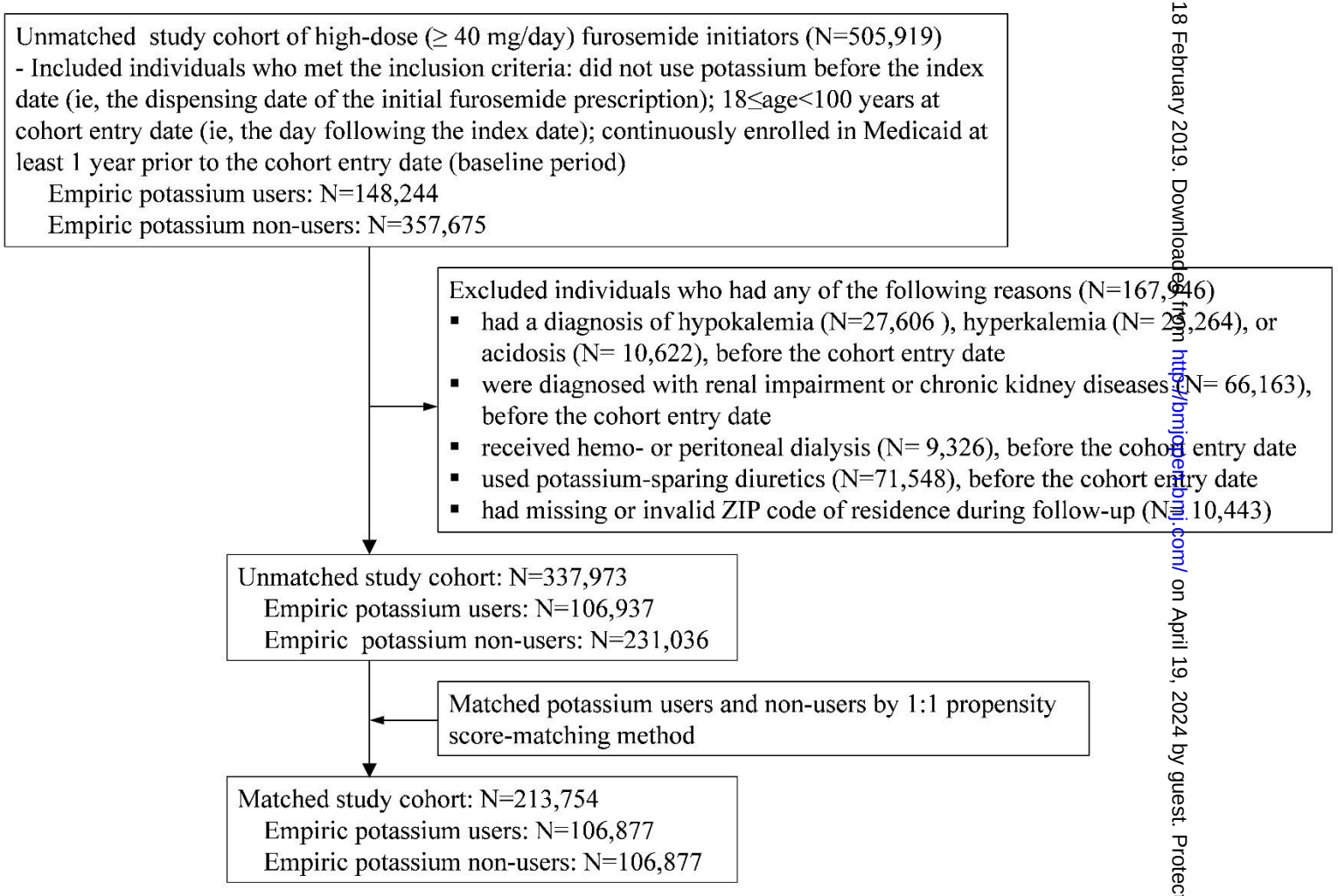
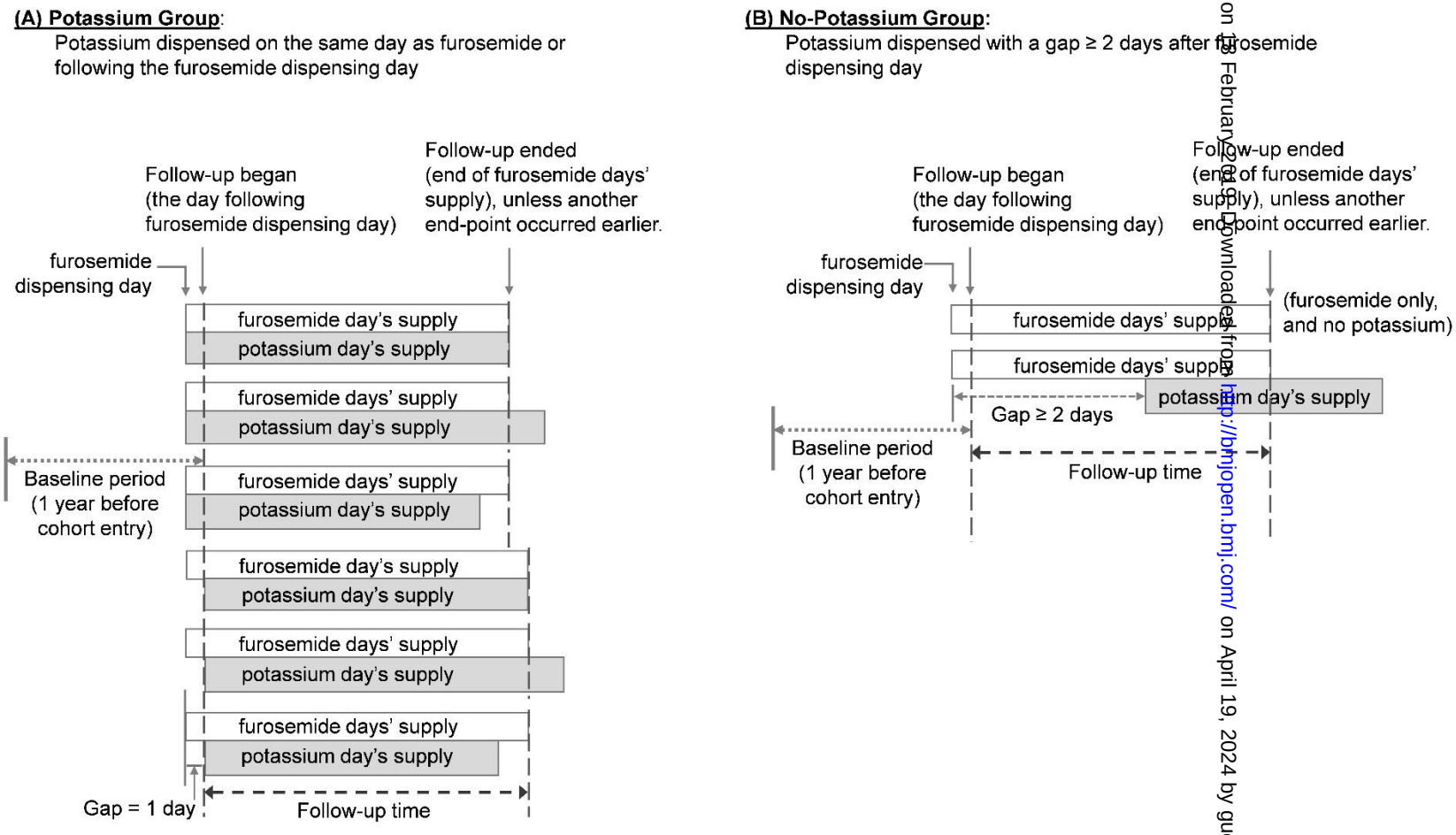


Figure S2. Study Cohorts and Follow-up Time



Note: This figure is a simplified illustration showing study cohorts and how follow-up time was determined, using hypothetical days' supply. Actual days' supply of furosemide, potassium use, and the length of follow-up time for each individual varied.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-10; Supplement 2-3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	11, 14
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-13, 26-29
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-13, 26-29
Bias	9	Describe any efforts to address potential sources of bias	11-13, 26-29
Study size	10	Explain how the study size was arrived at	8-14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-13
		(*b*) Describe any methods used to examine subgroups and interactions	11-13
		(*c*) Explain how missing data were addressed	11-13; Supplement 2
		(*d*) If applicable, explain how loss to follow-up was addressed	8-10
		(*e*) Describe any sensitivity analyses	13, 15; Supplement 1

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14, 26-29
		(b) Give reasons for non-participation at each stage	14; Supplement 2
		(c) Consider use of a flow diagram	Supplement 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	114, 26-29
		(b) Indicate number of participants with missing data for each variable of interest	Supplement 2
		(c) Summarise follow-up time (eg, average and total amount)	14
Outcome data	15*	Report numbers of outcome events or summary measures over time	14, 30
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14, 26-29
		(*b*) Report category boundaries when continuous variables were categorized	26-29
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	14-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15; Supplement 1
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Outdoor Temperature and Survival Benefit of Empiric Potassium in Users of Higher-Dose Furosemide in US Medicaid Enrollees: a Cohort Study

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Title Page

Outdoor Temperature and Survival Benefit of Empiric Potassium in Users of Higher-Dose Furosemide in US Medicaid Enrollees: a Cohort Study

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STROBE checklist Attached

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Competing interests: Drs. Nam, Bilker, Leonard, Bell, and Hennessy declare no conflicts of interests: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work within the last two years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing: No additional data available. The original US Medicaid and Medicare claims are third party data and available to obtain under a data use agreement from the Centers for Medicare & Medicaid Services (CMS) (https://www.cms.gov/). The authors did not have any special access privileges that others would not have, and others would be able to access these data in the same manner as the authors. The procedures to obtain access to these data are described in the CMS website (https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/ResearchGenInfo/ResearchDataAssistanceCenter.html) and the Research Data Assistance Center (ResDAC) website (https://www.resdac.org/cms-data/request/cms-data-request-center).

Abstract

Objective: Heat is associated with elevated all-cause mortality, and furosemide-induced potassium depletion might be worsened by heat-induced sweating. Because empiric potassium is associated with a marked survival benefit in higher-dose (≥40 mg/day) furosemide users, we hypothesized that empiric potassium's survival benefit in users of higher-dose furosemide increases with higher temperature (≥24°C).

Design: Cohort study.

Setting: Outpatient setting, captured by Medicaid claims, supplemented with Medicare claims for dual-enrollees, from 5 US states from 1999-2010, linked to meteorological data.

Population/Participants: Higher-dose furosemide initiators among adults continuously enrolled in Medicaid at least one year prior to cohort entry (defined as the day following the dispensing day of each individual's first observed furosemide prescription).

Exposure: Interaction between: 1) empiric potassium, dispensed the day of or the day following the dispensing of the initial furosemide prescription, and 2) daily average temperature and daily maximum temperature, examined separately.

Outcome: All-cause mortality.

Results: In 1:1 propensity-score matched cohorts (total N=211,878) that included 89,335 person-years and 9,007 deaths, all-cause mortality rates per 1,000 person-years were 96.0 (95% confidence interval [CI]: 93.2 to 98.9) and 105.8 (95% CI: 102.8 to 108.9) for potassium users and non-users, respectively. The adjusted odds ratio of all-cause mortality for potassium use declined (i.e., its protective effect increased) as temperature increased, from a daily average temperature of about 28°C and a daily maximum temperature of 31°C. This relationship was not statistically significant with daily average temperature, but statistically significant with daily

maximum temperature (*p*-values for the interaction of potassium with daily maximum temperature and daily maximum temperature squared were 0.031 and 0.028, respectively).

Conclusions: The results suggest that empiric potassium's survival benefit may increase as daily maximum temperature increases. If this relationship is real, use of empiric potassium in Medicaid enrollees initiating higher-dose furosemide might be particularly important on hot days.

Keywords: outdoor temperature; empiric potassium; furosemide; mortality; weather-drug interactions; drug interactions; pharmacoepidemiology

Strengths and limitations of this study

Strengths

- This study used large-scale real-world data, representing about 40% of individuals in the US Medicaid program, which covers nearly one in five Americans.
- It also used ZIP code-level daily temperature data, which may reflect the outdoor temperature at each individual's place of residence more accurately than those based on larger geographic units.
- The study cohorts were well-balanced on measured baseline covariates even before matching, and this balance improved further with propensity score matching, which suggests that any residual confounding may have played a limited role.

Limitations

- Data on the degree to which subjects were actually exposed to outdoor temperatures were not available, although it seems unlikely that it differed substantially between potassium users and non-users among the matched furosemide users in the Medicaid population.
- Potassium users and non-users may have differed on unmeasured factors.

Text

Outdoor Temperature and Survival Benefit of Empiric Potassium in Users of Higher-Dose Furosemide in US Medicaid Enrollees: a Cohort Study

Introduction

High outdoor temperature is associated with increased all-cause mortality and other adverse outcomes including heat stroke, dehydration, renal failure, cardiovascular diseases, diabetes, electrolyte disorders, and respiratory diseases.[1-7] Older people and those with underlying health conditions or socioeconomic disadvantages are at particularly increased risk from heat exposure.[2,5,7-15] People who take furosemide, a potent and commonly-used diuretic, might also be at increased risk, since furosemide leads to loss of potassium through the kidneys[16-18] which can increase mortality by mechanisms including cardiac arrhythmias. Heat could potentiate this risk because it leads to potassium loss through sweat.[19] Although no randomized trials have investigated a survival benefit of empiric (i.e., prophylactic or preventive) potassium use in furosemide users, a recent cohort study found that empiric potassium was associated with a relative survival benefit of 7% in initiators of low-dose furosemide (< 40 mg/day) and of 16% in initiators of higher-dose furosemide (≥ 40 mg/day).[20] We hypothesized that the survival benefit of empiric potassium in users of higher-dose furosemide would be more marked with higher outdoor temperature. Such a relationship would suggest that potassium administration in furosemide users may be particularly important when the outdoor temperature is high, which could have growing clinical and public health importance as global climate change continues,

raising both the overall temperatures in general, and also the number and intensity of extremely hot days.[21-23]

Methods

Study design, population, and data

We conducted a propensity-score matched cohort study among adult US Medicaid enrollees using 1) Medicaid claims from California, Florida, New York, Ohio, and Pennsylvania from 1999-2010 supplemented with Medicare claims for the Medicaid-Medicare dual-enrollees for the same period, including Part D Event Files from 2006-2010 (Part D began in 2006); and 2) meteorological data obtained from the US National Oceanic and Atmospheric Administration (NOAA) from 1999-2010.[24] These five states include about 40% of the US Medicaid population.[25] Adults ($18 \leq$ age < 100 years) who had continuous enrollment in Medicaid for at least one year before the cohort entry date (described below) were eligible for our analysis.

Study cohort, exposure and outcome of interest, and follow-up time

The study cohort comprised apparent initiators of furosemide whose starting dose (calculated from the index prescription) was 40 mg/day or higher. Apparent initiators of furosemide were defined as those in whom no furosemide dispensed in the 365 days before cohort entry—the baseline period—based on a given furosemide prescription; such prescriptions are referred to as index furosemide prescriptions, and the date of their dispensing referred to as the index date. Individuals could enter the study only once. We excluded persons whose initial furosemide dose was greater than two times daily recommended maximum dose of 600 mg/day.

The exposure of interest was empiric potassium use, defined as a potassium prescription for an orally administered solid dosage form of a bicarbonate, chloride, citrate, or gluconate salt that was dispensed on the index date or the next day,[20] but not prior to the initial furosemide dispensing date. Exposure was defined in this way to better capture empiric potassium rather than potassium given as treatment for clinically recognized hypokalemia. Although potassium products are available over-the-counter (OTC), such use is unlikely to have a large effect on study results because the strengths of OTC potassium (limited to less than about 2.5 mEq of potassium, which is about 2% of the daily recommendation of potassium for adults) are considerably lower than typical doses of potassium used to prevent hypokalemia (about 20 mEq/day). Prescription drug use was identified by using National Drug Codes and days' supply on prescription claims. We allowed a 15-day gap between contiguous prescriptions and at the end of the last prescription to account for potential incomplete adherence.

The cohort entry date was the day following the index date for both potassium users and non-users, since we defined exposure as being dispensed a potassium prescription on the index date or the following day. We excluded patients who: 1) used non-solid dosage forms of furosemide or potassium, which might be indicative of inability to swallow a solid dosage form and/or functional impairments that may not be reliably ascertained in the administrative data; 2) had a diagnosis before the cohort entry date of hypokalemia (International Classification of Diseases 9th Revision Clinical Modification [ICD-9-CM]: 276.8), hyperkalemia (ICD-9-CM: 276.7), or acidosis (ICD-9-CM: 276.2), since hypokalemia would suggest that in such persons potassium was used for treatment rather than empirically, and hyperkalemia and acidosis are contraindications for potassium; or 3) who, before the cohort entry date, were diagnosed with renal impairment or chronic kidney diseases (ICD-9-CM: 582*, 585*, 586-587, 588*), received

hemo- or peritoneal dialysis (ICD-9-CM: V56*; Current Procedural Terminology [CPT]: 90918-90999), used potassium-sparing diuretics, or who were dispensed potassium before the index date. Supplementary **Figure S1** presents the sample size and how the inclusion and exclusion criteria were applied.

The outcome of interest was all-cause mortality, ascertained by linkage to the US Social Security Administration Death Master File.

Follow-up time (**Figure S2**) began on the cohort entry date and ended with the first of the following events: 1) death; 2) end of days' supply of furosemide (following a 15-day grace period); 3) Medicaid enrollment discontinuation; or 4) end of the data set, i.e., December 31, 2010. We did not censor follow-up time based on initiation or discontinuation of potassium in either the potassium user or non-user group because we wished to examine the temperature dependency of the survival benefit of the strategy of providing vs. not providing *empiric* potassium, regardless of whether potassium was later discontinued or added.

Meteorological data

NOAA's meteorological data provide weather parameters, including daily minimum and maximum temperatures measured at weather stations, and the locations of these stations. For each furosemide user in our study cohort, we linked Zoning Improvement Plan code (ZIP code) of residence (ascertained from claims data) to the population-weighted centroid of that ZIP code area, which was estimated by using ZIP code boundaries, census block group boundaries, and 2010 census block group-level population data. Individuals who had missing or invalid ZIP code of residence were excluded. Each population-weighted centroid of ZIP code was linked to the ZIP code-level, daily maximum temperature and daily average temperature (calculated as the

arithmetic mean of the daily minimum and daily maximum temperatures). These ZIP code-level, daily outdoor temperatures were estimated by using day-level meteorological data, locations of weather stations, and a spline interpolation method that is a commonly used geospatial analysis method to estimate properties, such as temperature, at un-sampled sites based on the data of sampled sites, which may enable more precise estimation than a simple averaging method.[26-28]

Statistical analysis

Propensity score matching for balancing on potential confounders

We used propensity score matching to balance the potassium and no-potassium groups on measured baseline factors.[29,30] First, we estimated each subject's propensity score by fitting a logistic regression model where the binary dependent variable was the receipt of empiric potassium and the independent variables (selected based on potential association with both potassium use and death; presented in **Table 1**) included: 1) demographic characteristics (e.g., age, sex, race, Medicaid-Medicare dual-eligibility, state of residence, etc.); 2) diseases (e.g., hypertension, lipid metabolism disorders, diabetes mellitus, ischemic heart diseases, heart failure/cardiomyopathy, asthma/chronic obstructive pulmonary disease/emphysema, etc.); 3) prescription drugs (e.g., renin-angiotensin-aldosterone system blockers, antihyperlipidemic agents, beta blockers, calcium channel blockers, corticosteroids, antidiabetics, average daily dose of furosemide at cohort entry, etc.); and 4) healthcare services utilization intensity (including nursing home residence, number of inpatient hospitalizations, number of outpatient visits, and number of prescription drug fillings).[31] All independent variables were binary and assessed during the one-year baseline period, except for the age and average daily dose of furosemide at

cohort entry, continuous variables. We then used 1:1 nearest neighbor propensity score matching to match users of empiric potassium to non-users.[32]

Baseline characteristics, incidence rates, and logistic regression analysis

We first calculated descriptive statistics on baseline characteristics (**Table 1**) and compared the mortality rates between users and non-users of empiric potassium before and after propensity-score matching. The balance in the baseline characteristics was assessed by standardized difference (i.e., the mean difference of a variable between the two groups in units of the estimated common standard deviation of that variable in the two groups), with a value exceeding 0.1 suggestive of potentially meaningful imbalance between groups.[30] Next, we examined the temperature-potassium-mortality association in the high temperature range (defined as ≥ 24°C or 75°F) by modeling the interaction between temperature (daily average temperature and daily maximum temperature, separately) and potassium exposure status on the log odds of mortality using a multivariable logistic regression model where the unit of observation was person-day, allowing temperature to vary by day for each individual. The 24°C minimum temperature was chosen in advance based on literature indicating a U-shaped or similar relationship between temperature and death, with a nadir between 22°C-26°C, although we recognize that this relationship varies by location.[33-36] We excluded rare, extremely high temperatures (daily average temperature > 43°C or 110°F; daily maximum temperature > 49°C or 120°F). Given that the true functional form of the relationship between potassium use, temperature, and mortality is unknown, we examined a model that included a linear term and a quadratic term of temperature and two temperature-potassium exposure interaction terms (hereinafter referred to as a quadratic model). This model is expressed as Equation 1.

$$\text{logit}\left(Y_{ij}\right) = \alpha + \beta_0\left(T_{ij}\right) + \beta_1\left(T_{ij}^2\right) + \beta_2\left(K^+{}_i\right) + \beta_3\left(T_{ij} \times K^+{}_i\right) + \beta_4\left(T_{ij}^2 \times K^+{}_i\right) + \boldsymbol{\gamma_i}\mathbf{X'_i} + \epsilon_{ij} \quad \text{(Equation 1)}$$

In this equation, Y_{ij} is an indicator variable for the death outcome of person *i* on day *j*; T_{ij} is the outdoor temperature for person *i* at their ZIP code area on day *j*; $K^+{}_i$ is a binary variable indicating the potassium use or non-use of person *i*; and $\mathbf{X'_i}$ is a vector of time-invariant covariates of person *i* for which we used age group at cohort entry, sex, race group. We examined daily average temperature and daily maximum temperature in separate models. We also considered a strictly linear model but decided to use a quadratic model to avoid reliance on the assumption that the relationship between temperature and mortality is linear. Because older adults are known to be more vulnerable to the heat-related mortality, we performed a subgroup analysis for older adults (age ≥ 65 years). In addition, to examine whether our results from the propensity score-matched cohort would have been influenced by other meteorological parameters, we performed a sensitivity analysis that additionally controlled for daily relative humidity at the person-level. High humidity suppresses evaporation of sweat and sweat rate,[37,38] thus might affect potassium loss as well as humans' ability to thermoregulate, possibly influencing mortality and potassium-mortality relationship.

Analyses were performed using ArcGIS version 10.3 (Esri, Redlands, California), SAS version 9.4 (SAS Institute Inc., Cary, North Carolina), and Stata version 14 (StataCorp, College Station, Texas).

Ethical Approval

This study was approved by the institutional review board of the University of Pennsylvania, which waived the requirement for obtaining informed consent. We attest that we have obtained appropriate permissions and paid any required fees for use of copyright protected materials.

Patient and Public Involvement

Patients and public were not involved in planning or conducting this study.

Results

Supplementary **Figure S1** shows the number of potentially eligible and included/excluded subjects, with reasons for exclusion. Prior to matching, there were 337,885 eligible initiators of higher-dose furosemide, 106,907 (32%) of whom were empiric potassium users. Nearly all of the empiric potassium users were pair-matched to a non-user, resulting in 211,878 subjects (105,939 subjects in each group) that included 89,335 person-years and 9,007 deaths. In the matched potassium cohort, 76% of the follow-up time was covered by an active prescription for potassium (follow-up continued as long as the furosemide prescription was active; Supplementary **Figure S2**), while only 12% of the follow-up time for the no-potassium group was covered by an active prescription for potassium; 85% of individuals in the no-potassium group received no potassium prescriptions during follow-up. As shown in **Table 1**, baseline variables were reasonably well balanced even before matching; this balance was improved by propensity score matching. In the matched cohorts, median follow-up time was 69 days in potassium users and 65 days in potassium non-users, and the mortality rate (in deaths per 1,000 person-years) was 96.0 (95% confidence interval [CI]: 93.2 to 98.9) in users and 105.8 (95% CI: 102.8 to 108.9) in non-users.

Table 2 examines the associations between empiric potassium use and mortality as a) a function of daily average temperature and daily average temperature squared and b) a function of daily maximum temperature and daily maximum temperature squared, as well as the interaction between those temperature metrics and potassium use (daily average temperature and daily maximum temperature examined separately). Because the daily maximum temperature exceeds 24°C more often than does the daily average temperature, there were more observations for this metric. As seen in Figure 1 and Figure 2, the odds ratio of all-cause mortality for potassium use (calculated from regression results) appeared to be lower (i.e., its protective effect appeared to increase) when temperature was higher for both temperature metrics. The *p*-values for the interaction terms of potassium were not statistically significant with daily average temperature (interaction with daily average temperature, $p = 0.332$; and with daily average temperature squared, $p = 0.329$), but were statistically significant with daily maximum temperature (interaction with daily maximum temperature, $p = 0.031$; and with daily maximum temperature squared, $p = 0.028$) (**Table 2**). The estimated association corresponds to approximately a 6% point reduction in odds for each 1°C increase in daily average temperature between 28°C and 43°C, and a 4% point reduction in odds for each 1°C increase in daily maximum temperature between 31°C and 49°C. The results for older adults were similar, but the confidence intervals were larger. In the sensitivity analysis that additionally controlled for daily relative humidity, the results were similar, and the *p*-values for the interaction terms of potassium with daily maximum temperature were statistically significant (interaction with daily maximum temperature, $p = 0.028$; and with daily maximum temperature squared, $p = 0.025$) (**Table 3**).

Discussion

This study examined whether the survival benefit of empiric potassium in users of higher-dose furosemide increases with higher daily average and daily maximum temperature. Consistent with earlier findings in the same population using 1999-2007 data,[20] empiric potassium use was associated with a survival benefit in higher-dose furosemide initiators. The results suggest that this survival benefit may increase as daily maximum temperature increases. This relationship was statistically significant in the primary and the sensitivity analysis.

If this potential relationship between temperature and the survival benefit of potassium is true, it would have important clinical and public health implications. It is well-established that high outdoor temperature is associated with increase in mortality and morbidity.[39-43] Some excess deaths in furosemide users, especially among socioeconomically disadvantaged populations such as Medicaid enrollees in the US, might be avoidable through interventions to increase potassium intake on hot days. The number of lives saved by such interventions would be expected to increase as global climate change continues.[21-23]

One might hypothesize seasonality in the association between temperature and mortality, or that individuals residing at warmer regions might tolerate increases in temperature better than those in cooler areas. Also, a temperature-potassium interaction on mortality, if it exists, might differ across subgroups, such as geographic regions, sociodemographic characteristics, comorbidities, or degree of frailty. Because we were unable to explore such relationships given the limited number of high-temperature deaths, further research is warranted to investigate these potential relationships in diverse subgroups and health outcomes. In addition, future studies will need to investigate other functional forms of temperature, including lagged effects of heat,

cumulative days of high temperature, and variation from the mean temperature at a given location.

This study has several strengths. First, it used large-scale real world data, representing about 40% of individuals in the US Medicaid program, which covers nearly one in five Americans. It also used ZIP code-level daily temperature data, which may better reflect the outdoor temperature at each individual's place of residence than temperature over larger geographic areas. Further, the study cohorts had good balance in the measured baseline covariates even before matching, and this balance improved further with propensity score matching, which suggests a limited role for potential confounding factors.

This study also has limitations. First, we did not have data on individuals' use of air conditioning or the amount of time spent outdoors. Therefore, we do not know the degree to which subjects were actually exposed to outdoor temperatures. However, because all individuals in our study were enrolled in Medicaid, a public health insurance program for socioeconomically disadvantaged individuals who meet certain low-socioeconomic status criteria, it seems unlikely that the access to air conditioning is substantially different between users and non-users of empiric potassium. Prior studies that also lacked such data found associations between temperature and of a variety of health endpoints.[39,40,42] Therefore, it seems most likely that any potential bias introduced by lack of data on air conditioning would have been toward the null. Second, results observed in US Medicaid enrollees, who have lower incomes and poorer health than other groups, might not be generalizable to other populations. Nevertheless, about 20% of the US population is enrolled in Medicaid, thus this is an important population in its own right as well as from the public health and health policy perspectives. Third, although our study cohorts showed good balance in measured covariates, we cannot rule out the possibility of imbalances in

unobserved factors. Finally, our study did not examine location-specific differences in the estimated associations, which may differ due to variation in the relationship between temperature and health.

Conclusions

The results suggest that empiric potassium's survival benefit may increase as daily maximum temperature increases in Medicaid enrollees who initiate higher-dose furosemide. This potential relationship should be confirmed in independent data sets. Given the widespread use of furosemide, interventions based on this relationship might be able to benefit many people worldwide, especially those socioeconomically more vulnerable and living in high-temperature areas.

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Author contribution: Hennessy, Leonard, and Bilker conceived and designed the study. Hennessy and Leonard were involved in acquisition of data. Nam and Bilker performed statistical analysis. Nam, Bilker, Leonard, Bell, and Hennessy interpreted the results. Nam drafted the manuscript. Nam, Bilker, Leonard, Bell, and Hennessy critically revised the manuscript for important intellectual content. All authors approved the final manuscript to be submitted for publication and the authorship list.

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Figure Legends

Figure 1. Odds ratios and 95% confidence intervals of all-cause mortality for empiric potassium use vs. non-use by temperature

Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). Bold solid lines indicate odds ratios, and thin dash lines indicate 95% confidence intervals.

Figure 2. Odds ratios and 95% confidence intervals of all-cause mortality for empiric potassium use vs. non-use by temperature, additionally controlling for daily relative humidity

Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). Bold solid lines indicate odds ratios, and thin dash lines indicate 95% confidence intervals.

Supplementary Material

Figure S1. Sample size and the application of inclusion/exclusion criteria

Figure S2. Study cohort and follow-up time

Table 1. Baseline characteristics of the unmatched and matched study cohorts

	Before PS-Matching			After PS-Matching		
	Potassium group	No-potassium group	Standardized Difference	Potassium group	No-potassium group	Standardized Difference
	N=106,907	N=230,948		N=105,939	N=105,939	
Sociodemographic Characteristics						
Age at cohort entry, in years (%)						
18≤Age<35	3.92	4.27	0.02	3.94	3.84	0.01
35≤Age<50	15.03	14.94	0.00	15.04	15.15	0.00
50≤Age<65	23.82	24.77	0.02	23.83	23.86	0.00
65≤Age<80	34.78	33.75	0.02	34.77	34.97	0.00
80≤Age<100	22.44	22.26	0.00	22.42	22.18	0.01
Sex, female (%)	66.36	66.40	0.00	66.34	66.37	0.00
Race/Ethnicity (%)						
White	53.69	50.05	0.07	53.46	53.73	0.01
Black	15.36	18.15	0.07	15.44	15.30	0.00
Hispanic	15.58	14.03	0.04	15.63	15.65	0.00
Other/Unknown	15.38	17.77	0.06	15.46	15.32	0.00
Medicaid-Medicare dual-eligible (%)	70.36	67.43	0.06	70.20	70.21	0.00
State of residence (%)						
California	45.89	40.73	0.10	46.28	46.52	0.00
Florida	17.42	8.89	0.25	16.71	16.56	0.00
New York	17.13	29.27	0.29	17.29	17.22	0.00
Ohio	10.35	8.93	0.05	10.44	10.54	0.00
Pennsylvania	9.21	12.19	0.10	9.28	9.16	0.00
Urban residence[a] (%)	85.86	87.04	0.03	85.91	85.95	0.00
Year of cohort entry						

	Before PS-Matching			After PS-Matching		
	Potassium group	No-potassium group	Standardized Difference	Potassium group	No-potassium group	Standardized Difference
	N=106,907	N=230,948		N=105,939	N=105,939	
2000	8.95	10.34	0.05	9.01	9.22	0.01
2001	9.82	9.91	0.00	9.84	10.03	0.01
2002	9.72	9.64	0.00	9.72	9.76	0.00
2003	9.55	9.43	0.00	9.55	9.40	0.01
2004	7.25	7.88	0.02	7.31	7.48	0.01
2005	8.36	8.38	0.00	8.37	8.37	0.00
2006	14.12	14.03	0.00	14.07	14.05	0.00
2007	9.12	7.99	0.04	9.01	8.92	0.00
2008	7.03	6.66	0.01	7.07	6.92	0.01
2009	7.89	7.49	0.02	7.87	7.78	0.00
2010	8.18	8.26	0.00	8.18	8.09	0.00
Diseases						
Alkalosis, metabolic (%)	0.20	0.20	0.00	0.21	0.21	0.00
Amyloidosis (%)	0.03	0.04	0.01	0.03	0.02	0.01
Anemia (%)	29.31	27.46	0.04	29.19	29.22	0.00
Ascites (%)	1.26	1.40	0.01	1.26	1.29	0.00
Asthma/COPD/emphysema (%)	31.41	27.43	0.09	31.12	31.13	0.00
Cardiac dysrhythmias/conduction disorder (%)	26.31	23.76	0.06	26.10	26.18	0.00
Cerebrovascular disease (%)	18.45	17.54	0.02	18.39	18.52	0.00
Diabetes insipidus (%)	0.06	0.06	0.00	0.06	0.05	0.00
Diabetes mellitus (%)	38.90	39.70	0.02	38.95	38.93	0.00
Edema (%)	23.65	19.87	0.09	23.42	23.56	0.00
Glaucoma (%)	9.55	9.84	0.01	9.54	9.49	0.00

	Before PS-Matching			After PS-Matching		
	Potassium group N=106,907	No-potassium group N=230,948	Standardized Difference	Potassium group N=105,939	No-potassium group N=105,939	Standardized Difference
Heart failure/cardiomyopathy (%)	36.48	32.96	0.07	36.21	36.25	0.00
HIV/AIDS (%)	0.45	0.69	0.03	0.45	0.46	0.00
Hyperosmolality (%)	0.46	0.59	0.02	0.47	0.47	0.00
Hypertensive disease (%)	66.66	64.48	0.05	66.50	66.58	0.00
Hyperthyroidism (%)	2.25	1.96	0.02	2.24	2.18	0.00
Hypothyroidism (%)	16.21	14.53	0.05	16.09	16.19	0.00
Ischemic heart disease (%)	36.52	32.89	0.08	36.22	36.39	0.00
Kidney disease[b] (%)	9.27	10.60	0.04	9.32	9.24	0.00
Lipoid metabolism disorder (%)	43.21	37.95	0.11	42.88	43.07	0.00
Liver disease (%)	20.13	19.54	0.01	20.08	20.10	0.00
Magnesium metabolism disorder (%)	0.63	0.62	0.00	0.63	0.67	0.00
Nocturia (%)	1.37	1.20	0.02	1.36	1.31	0.00
Pulmonary circulation disease (%)	5.00	4.40	0.03	4.93	4.93	0.00
Pulmonary congestion and hypostasis/pulmonary edema (%)	6.47	5.89	0.02	6.44	6.45	0.00
Pyloric stenosis (%)	0.07	0.08	0.00	0.07	0.07	0.00
Rheumatoid arthritis and other inflammatory polyarthropathies (%)	5.16	4.64	0.02	5.15	5.13	0.00
Systemic lupus erythematosus (%)	0.70	0.67	0.00	0.68	0.68	0.00
Urinary obstruction (%)	0.41	0.40	0.00	0.41	0.41	0.00
Prescription Drugs						
RAAS blockers (%)	52.01	54.35	0.05	52.14	52.01	0.00
Adrenergic agents (%)	11.99	12.29	0.01	12.03	12.03	0.00
Antiarrhythmics (%)	3.59	2.62	0.06	3.51	3.63	0.01

	Before PS-Matching			After PS-Matching		
	Potassium group	No-potassium group	Standardized Difference	Potassium group	No-potassium group	Standardized Difference
	N=106,907	N=230,948		N=105,939	N=105,939	
Antidiabetics (%)	31.61	34.30	0.06	31.75	31.67	0.00
Antiglaucoma agents (%)	19.45	18.51	0.02	19.38	19.31	0.00
Antihyperlipidemic agents (%)	39.67	38.39	0.03	39.59	39.54	0.00
Antiobesity agents (%)	0.18	0.11	0.02	0.17	0.17	0.00
Antiretrovirals (%)	0.74	1.14	0.04	0.75	0.76	0.00
Beta blockers, systemic (%)	34.20	33.88	0.01	34.11	34.02	0.00
Bisphosphonates (%)	2.95	2.43	0.03	2.91	2.91	0.00
Calcium channel blockers (%)	31.14	31.70	0.01	31.15	30.94	0.00
Corticosteroids, systemic (%)	30.55	28.13	0.05	30.37	30.44	0.00
Digoxin (%)	9.95	8.89	0.04	9.86	10.01	0.01
Diuretics, thiazides (%)	13.82	15.37	0.04	13.88	13.66	0.01
Immunosuppressives (%)	0.64	0.76	0.01	0.64	0.62	0.00
Thyroid hormones (%)	12.24	11.66	0.02	12.19	12.31	0.00
Vasodilators (%)	10.41	10.47	0.00	10.40	10.48	0.00
Warfarin (%)	10.00	9.11	0.03	9.90	9.96	0.00
Xanthine derivatives (%)	4.93	4.23	0.03	4.89	4.93	0.00
Average daily dose of furosemide at cohort entry[c] ≥ 80 mg/day (%)	17.80	18.16	0.01	17.79	17.79	0.00
Healthcare Services Utilization Intensity						
Nursing home residence (%)	16.37	18.04	0.04	16.40	16.38	0.00
Inpatient hospitalization, mean number	0.71	0.68	0.02	0.71	0.72	0.01
Outpatient visits, mean number	47.16	49.40	0.03	47.13	47.67	0.01
Prescription drug fillings, mean number	25.71	24.73	0.05	25.66	25.74	0.00

PS: propensity score. RAAS: renin-angiotensin-aldosterone system. Ref: reference. [a]Urban residence: ascertained by the ZIP codes in

	Before PS-Matching			After PS-Matching		
	Potassium group	No-potassium group	Standardized Difference	Potassium group	No-potassium group	Standardized Difference
	N=106,907	N=230,948		N=105,939	N=105,939	
the claims data used and ZIP Code to Carrier Locality File from the Centers for Medicare and Medicaid Services (Centers for Medicare and Medicaid Services, 2017). [b]Kidney disease: kidney diseases, except for chronic kidney diseases or renal impairment. [c]Average daily dose of furosemide at cohort entry: excluded persons whose initial furosemide dose was greater than two times daily recommended maximum dose of 600 mg/day.						

Table 2. Logistic regression results to estimate temperature-modified empiric potassium's effect on all-cause mortality in higher-dose furosemide initiators

	Daily average temperature ≥ 24° C				Daily maximum temperature ≥ 24° C			
	(N=6,345,029 person-days; 1,862 deaths)				(N=15,147,407 person-days; 4,262 deaths)			
	Coefficient	95% CI		*p*-value	Coefficient	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
Temperature	0.1673	-0.3974	0.7320	0.561	-0.0908	-0.2176	0.0360	0.161
Temperature squared[a]	-0.0025	-0.0128	0.0078	0.642	0.0019	-0.0002	0.0040	0.077
Potassium[b]	-5.6046	-16.9577	5.7485	0.333	-3.1654	-6.0507	-0.2801	0.032
Temperature × Potassium	0.4130	-0.4218	1.2478	0.332	0.2083	0.0192	0.3974	0.031
Temperature squared × Potassium	-0.0076	-0.0229	0.0077	0.329	-0.0035	-0.0066	-0.0004	0.028
Age ≥ 65 years	(N=3,944,433 person-days; 1,491 deaths)				(N=9,371,901 person-days; 3,395 deaths)			
Temperature	0.1359	-0.5072	0.7790	0.679	-0.0970	-0.2397	0.0457	0.182
Temperature squared	-0.0021	-0.0139	0.0097	0.731	0.0019	-0.0004	0.0042	0.109
Potassium	-7.2166	-20.1761	5.7429	0.275	-2.6074	-5.8255	0.6107	0.112
Temperature × Potassium	0.5201	-0.4340	1.4742	0.285	0.1678	-0.0433	0.3789	0.119
Temperature squared × Potassium	-0.0094	-0.0269	0.0081	0.293	-0.0028	-0.0062	0.0006	0.115

95% CI: 95% confidence interval. Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F).
[a]Temperature squared: 2nd degree polynomial term of temperature. [b]Potassium: empiric potassium exposure status (0=empiric potassium users; 1=empiric potassium non-users).

Table 3. Logistic regression results to estimate temperature-modified empiric potassium's effect on all-cause mortality in higher-dose furosemide initiators, additionally controlling for daily relative humidity

	Daily average temperature ≥ 24° C				Daily maximum temperature ≥ 24° C			
	(N=6,345,029 person-days; 1,862 deaths)				(N=15,147,407 person-days; 4,262 deaths)			
	Coefficient	95% CI		*p*-value	Coefficient	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
Temperature	0.2069	-0.3639	0.7777	0.477	-0.0529	-0.1825	0.0767	0.423
Temperature squared[a]	-0.0032	-0.0136	0.0072	0.549	0.0011	-0.0010	0.0032	0.297
Potassium[b]	-5.6409	-17.0326	5.7508	0.332	-3.2621	-6.1831	-0.3411	0.029
Temperature × Potassium	0.4159	-0.4216	1.2534	0.330	0.2152	0.0235	0.4069	0.028
Temperature squared × Potassium	-0.0077	-0.0230	0.0076	0.327	-0.0036	-0.0067	-0.0005	0.025
Relative Humidity[c]	-0.0019	-0.0050	0.0012	0.233	-0.0055	-0.0077	-0.0033	<0.0001

95% CI: 95% confidence interval. Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F).
[a]Temperature squared: 2nd degree polynomial term of temperature. [b]Potassium: empiric potassium exposure status (0=empiric potassium users; 1=empiric potassium non-users). [c]Relative Humidity: daily relative humidity.

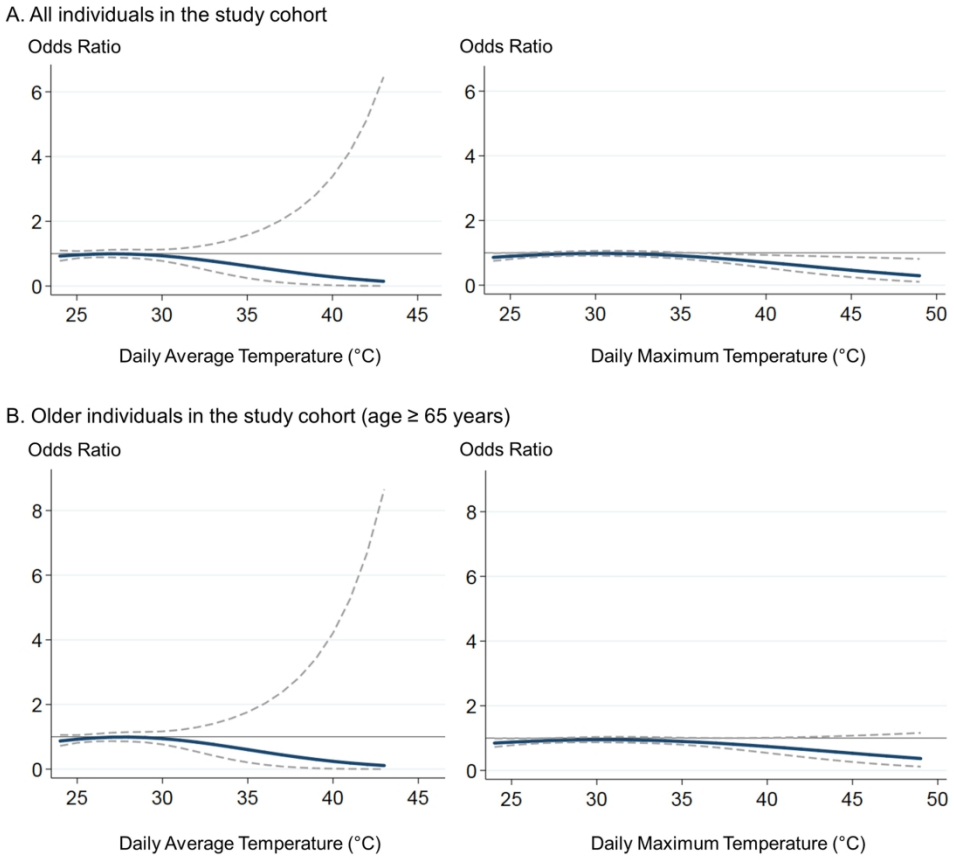

Figure 1. Odds ratios and 95% confidence intervals of all-cause mortality for empiric potassium use vs. non-use by temperature
Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). Bold solid lines indicate odds ratios, and thin dash lines indicate 95% confidence intervals.

190x169mm (300 x 300 DPI)

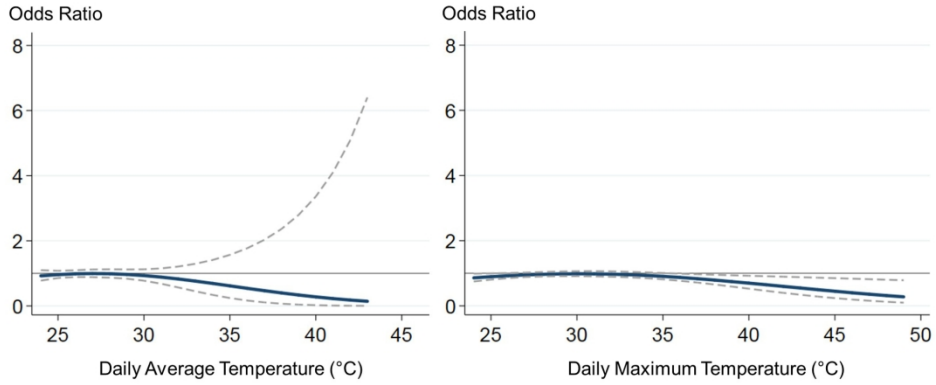

Figure 2. Odds ratios and 95% confidence intervals of all-cause mortality for empiric potassium use vs. non-use by temperature, additionally controlling for daily relative humidity
Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). Bold solid lines indicate odds ratios, and thin dash lines indicate 95% confidence intervals.

188x114mm (300 x 300 DPI)

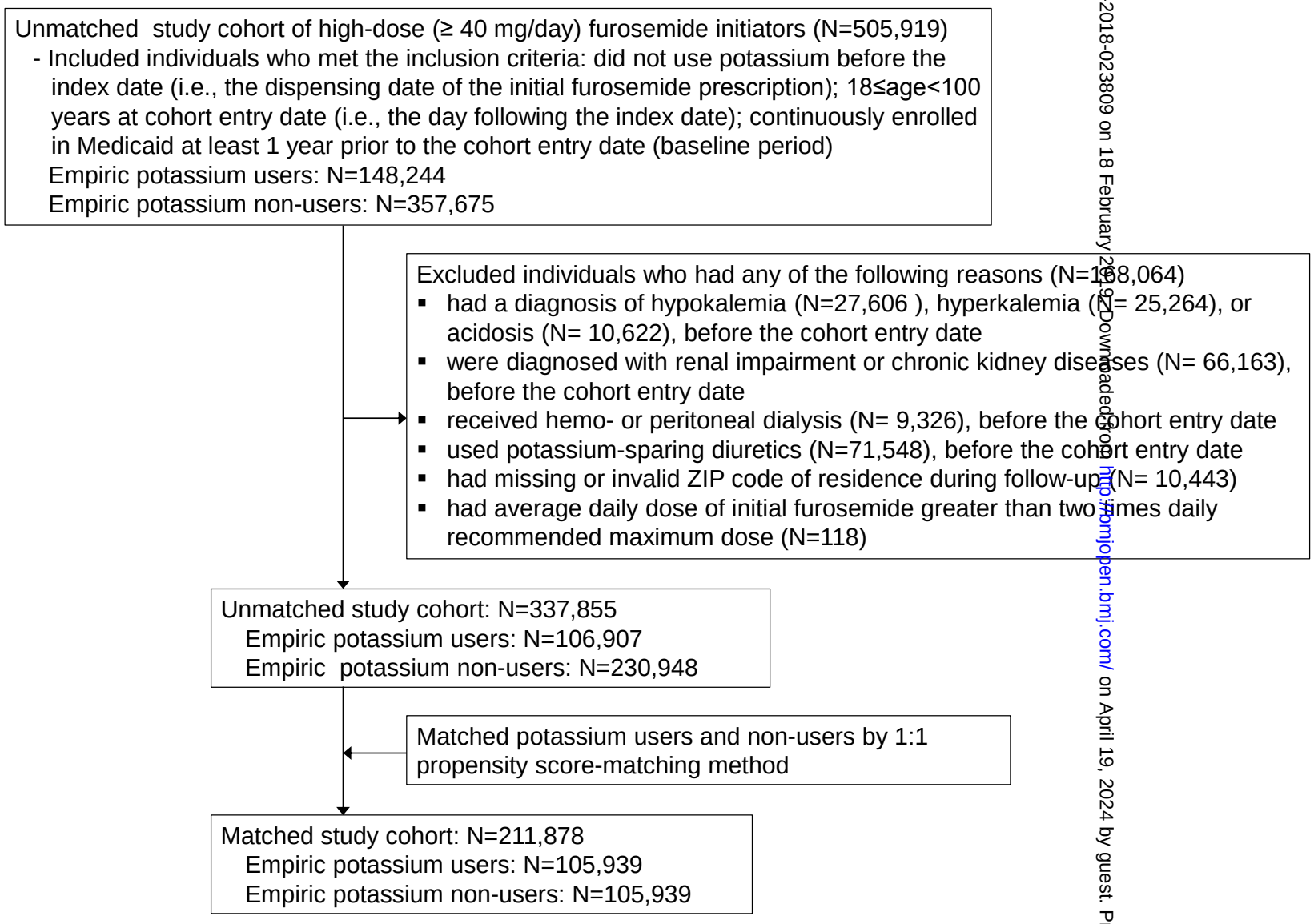

Figure S1. Sample size and the application of inclusion/exclusion criteria

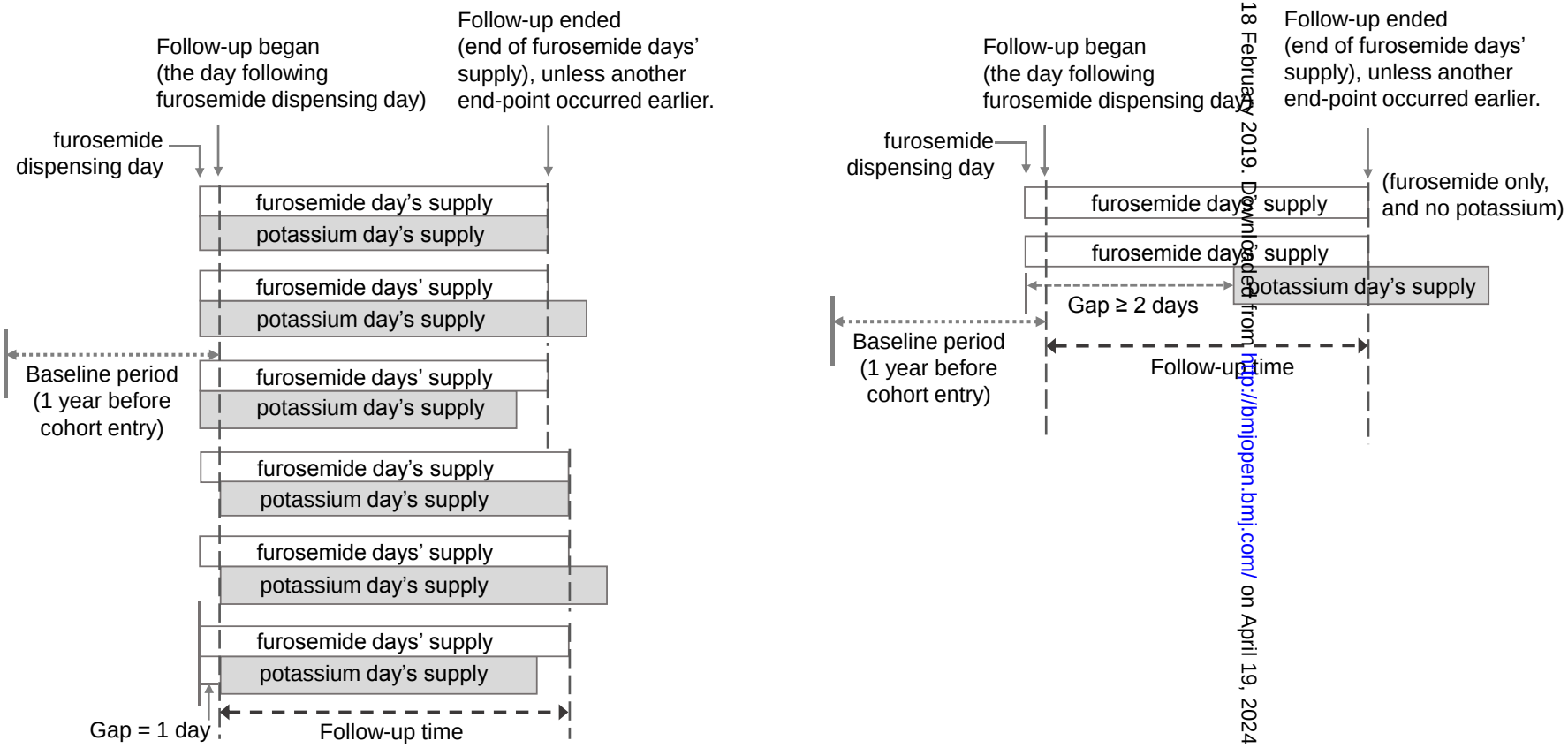

Figure S2. Study cohort and follow-up time

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9; Figures S1 and S2
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	10-11, 13
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-12, 25-29
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-12, 25-29
Bias	9	Describe any efforts to address potential sources of bias	10-12, 25-29
Study size	10	Explain how the study size was arrived at	7-13, Figure S1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-12
		(*b*) Describe any methods used to examine subgroups and interactions	10-12
		(*c*) Explain how missing data were addressed	7-12; Figure S1
		(*d*) If applicable, explain how loss to follow-up was addressed	7-9
		(*e*) Describe any sensitivity analyses	12, 14, 31

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13, 25-29
		(b) Give reasons for non-participation at each stage	13, Figure S1
		(c) Consider use of a flow diagram	Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13, 25-29
		(b) Indicate number of participants with missing data for each variable of interest	Figure S1
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	13, 30-31
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13, 25-29
		(*b*) Report category boundaries when continuous variables were categorized	25-29
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14, 30-31
Discussion			
Key results	18	Summarise key results with reference to study objectives	15, 17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Outdoor Temperature and Survival Benefit of Empiric Potassium in Users of Furosemide in US Medicaid Enrollees: a Cohort Study

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Title Page

Outdoor Temperature and Survival Benefit of Empiric Potassium in Users of Furosemide in US Medicaid Enrollees: a Cohort Study

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STROBE checklist Attached

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Competing interests: Drs. Nam, Bilker, Leonard, Bell, and Hennessy declare no conflicts of interests: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work within the last two years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing: No additional data available. The original US Medicaid and Medicare claims are third party data and available to obtain under a data use agreement from the Centers for Medicare & Medicaid Services (CMS) (https://www.cms.gov/). The authors did not have any special access privileges that others would not have. The procedures to obtain access to these data are described in the CMS website (https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/ResearchGenInfo/ResearchDataAssistanceCenter.html) and the Research Data Assistance Center (ResDAC) website (https://www.resdac.org/cms-data/request/cms-data-request-center).

Abstract

Objective:Heat is associated with elevated all-cause mortality, and furosemide-induced potassium depletion might be worsened by heat-induced sweating. Because empiric potassium is associated with a marked survival benefit in users of furosemide at a dose of ≥40 mg/day, we hypothesized that this empiric potassium's survival benefit would increase with higher temperature (≥24°C).

Design:Cohort study.

Setting:Outpatient setting, captured by Medicaid claims, supplemented with Medicare claims for dual-enrollees, from 5 US states from 1999-2010, linked to meteorological data.

Population/Participants:Furosemide (≥40 mg/day) initiators among adults continuously enrolled in Medicaid at least one year prior to cohort entry (defined as the day following the dispensing day of each individual's first observed furosemide prescription).

Exposure:Interaction between: 1) empiric potassium, dispensed the day of or the day following the dispensing of the initial furosemide prescription, and 2) daily average temperature and daily maximum temperature, examined separately.

Outcome:All-cause mortality.

Results:In 1:1 propensity-score matched cohorts (total N=211,878) that included 89,335 person-years and 9,007 deaths, all-cause mortality rates per 1,000 person-years were 96.0 (95% confidence interval [CI]:93.2 to 98.9) and 105.8 (95% CI:102.8 to 108.9) for potassium users and non-users, respectively. The adjusted odds ratio of all-cause mortality for potassium use declined (i.e., its apparent protective effect increased) as temperature increased, from a daily average temperature of about 28°C and a daily maximum temperature of 31°C. This relationship was not statistically significant with daily average temperature, but was statistically significant with daily

maximum temperature (*p*-values for the interaction of potassium with daily maximum temperature and daily maximum temperature squared were 0.031 and 0.028, respectively).

Conclusions:The results suggest that empiric potassium's survival benefit among furosemide (≥40 mg/day) initiators may increase as daily maximum temperature increases. If this relationship is real, use of empiric potassium in Medicaid enrollees initiating furosemide might be particularly important on hot days.

Keywords: outdoor temperature; empiric potassium; furosemide; mortality; weather-drug interactions; drug interactions; pharmacoepidemiology

Strengths and limitations of this study

Strengths

- This study used large-scale real-world data, representing about 40% of individuals in the US Medicaid program, which covers nearly one in five Americans.
- It also used ZIP code-level daily temperature data, which may reflect the outdoor temperature at each individual's place of residence more accurately than those based on larger geographic units.
- The study cohorts were well-balanced on measured baseline covariates even before matching, and this balance improved further with propensity score matching, which suggests that residual confounding may have played a limited role.

Limitations

- Data on the degree to which subjects were actually exposed to outdoor temperatures were not available, although it seems unlikely that it differed substantially between potassium users and non-users among the matched furosemide users in the Medicaid population.
- Potassium users and non-users may have differed on unmeasured factors.

Text

Outdoor Temperature and Survival Benefit of Empiric Potassium in Users of Furosemide in US Medicaid Enrollees: a Cohort Study

Introduction

High outdoor temperature is associated with increased all-cause mortality and other adverse outcomes including heat stroke, dehydration, renal failure, cardiovascular diseases, diabetes, electrolyte disorders, and respiratory diseases.[1-7] Older people and those with underlying health conditions or socioeconomic disadvantages are at particularly increased risk from heat exposure.[2,5,7-15] People who take furosemide, a potent and commonly-used diuretic, might also be at increased risk, since furosemide leads to loss of potassium through the kidneys[16-18] which can increase mortality by mechanisms including cardiac arrhythmias. Heat could potentiate this risk because it leads to potassium loss through sweat.[19] Although no randomized trials have investigated a survival benefit of empiric (i.e., prophylactic or preventive) potassium use in furosemide users, a recent cohort study found that empiric potassium was associated with a relative survival benefit in initiators of furosemide, 7% at < 40 mg/day and 16% at ≥ 40 mg/day, respectively.[20] We hypothesized that the survival benefit of empiric potassium in users of furosemide at a dose of ≥ 40 mg/day would be more marked with higher outdoor temperature. Such a relationship would suggest that potassium administration in furosemide users may be particularly important when the outdoor temperature is high, which could have growing clinical and public health importance as global climate change continues, raising both the overall temperatures in general, and also the number and intensity of extremely hot days.[21-23]

Methods

Study design, population, and data

We conducted a propensity-score matched cohort study among adult US Medicaid enrollees using 1) Medicaid claims from California, Florida, New York, Ohio, and Pennsylvania from 1999-2010 supplemented with Medicare claims for the Medicaid-Medicare dual-enrollees for the same period, including Part D Event Files from 2006-2010 (Part D began in 2006); and 2) meteorological data obtained from the US National Oceanic and Atmospheric Administration (NOAA) from 1999-2010.[24] These five states include about 40% of the US Medicaid population.[25] Adults ($18 \leq$ age < 100 years) who had continuous enrollment in Medicaid for at least one year before the cohort entry date (described below) were eligible for our analysis.

Study cohort, exposure and outcome of interest, and follow-up time

The study cohort comprised apparent initiators of furosemide whose starting dose (calculated from the index prescription) was 40 mg/day or higher. Apparent initiators of furosemide were defined as those in whom no furosemide dispensed in the 365 days before cohort entry—the baseline period—based on a given furosemide prescription; such prescriptions are referred to as index furosemide prescriptions, and the date of their dispensing referred to as the index date. Individuals could enter the study only once. We excluded persons whose initial furosemide dose was greater than two times daily recommended maximum dose of 600 mg/day.

The exposure of interest was empiric potassium use, defined as a potassium prescription for an orally administered solid dosage form of a bicarbonate, chloride, citrate, or gluconate salt that was dispensed on the index date or the next day,[20] but not prior to the initial furosemide dispensing date. Exposure was defined in this way to better capture empiric potassium rather

than potassium given as treatment for clinically recognized hypokalemia. Although potassium products are available over-the-counter (OTC), such use is unlikely to have a large effect on study results because the strengths of OTC potassium (limited to less than about 2.5 mEq of potassium, which is about 2% of the daily recommendation of potassium for adults) are considerably lower than typical doses of potassium used to prevent hypokalemia (about 20 mEq/day). Prescription drug use was identified by using National Drug Codes and days' supply on prescription claims. We allowed a 15-day gap between contiguous prescriptions and at the end of the last prescription to account for potential incomplete adherence.

The cohort entry date was the day following the index date for both potassium users and non-users, since we defined exposure as being dispensed a potassium prescription on the index date or the following day. We excluded patients who: 1) used non-solid dosage forms of furosemide or potassium, which might be indicative of inability to swallow a solid dosage form and/or functional impairments that may not be reliably ascertained in the administrative data; 2) had a diagnosis before the cohort entry date of hypokalemia (International Classification of Diseases 9th Revision Clinical Modification [ICD-9-CM]: 276.8), hyperkalemia (ICD-9-CM: 276.7), or acidosis (ICD-9-CM: 276.2), since hypokalemia would suggest that in such persons potassium was used for treatment rather than empirically, and hyperkalemia and acidosis are contraindications for potassium; or 3) who, before the cohort entry date, were diagnosed with renal impairment or chronic kidney diseases (ICD-9-CM: 582*, 585*, 586-587, 588*), received hemo- or peritoneal dialysis (ICD-9-CM: V56*; Current Procedural Terminology [CPT]: 90918-90999), used potassium-sparing diuretics, or who were dispensed potassium before the index date. Supplementary **Figure S1** presents the sample size and how the inclusion and exclusion criteria were applied.

The outcome of interest was all-cause mortality, ascertained by linkage to the US Social Security Administration Death Master File.

Follow-up time (**Figure S2**) began on the cohort entry date and ended with the first of the following events: 1) death; 2) end of days' supply of furosemide (following a 15-day grace period); 3) Medicaid enrollment discontinuation; or 4) end of the data set, i.e., December 31, 2010. We did not censor follow-up time based on initiation or discontinuation of potassium in either the potassium user or non-user group because we wished to examine the temperature dependency of the survival benefit of the strategy of providing vs. not providing *empiric* potassium, regardless of whether potassium was later discontinued or added.

Meteorological data

NOAA's meteorological data provide weather parameters, including daily minimum and maximum temperatures measured at weather stations, and the locations of these stations. For each furosemide user in our study cohort, we linked Zoning Improvement Plan code (ZIP code) of residence (ascertained from claims data) to the population-weighted centroid of that ZIP code area, which was estimated by using ZIP code boundaries, census block group boundaries, and 2010 census block group-level population data. Individuals who had missing or invalid ZIP code of residence were excluded. Each population-weighted centroid of ZIP code was linked to the ZIP code-level, daily maximum temperature and daily average temperature (calculated as the arithmetic mean of the daily minimum and daily maximum temperatures). These ZIP code-level, daily outdoor temperatures were estimated by using day-level meteorological data, locations of weather stations, and a spline interpolation method that is a commonly used geospatial analysis

method to estimate properties, such as temperature, at un-sampled sites based on the data of sampled sites, which may enable more precise estimation than a simple averaging method.[26-28]

Statistical analysis

Propensity score matching for balancing on potential confounders

We used propensity score matching to balance the potassium and no-potassium groups on measured baseline factors.[29,30] First, we estimated each subject's propensity score by fitting a logistic regression model where the binary dependent variable was the receipt of empiric potassium and the independent variables (selected based on potential association with both potassium use and death; presented in **Table 1**) included: 1) demographic characteristics (e.g., age, sex, race, Medicaid-Medicare dual-eligibility, state of residence, etc.); 2) diseases (e.g., hypertension, lipid metabolism disorders, diabetes mellitus, ischemic heart diseases, heart failure/cardiomyopathy, asthma/chronic obstructive pulmonary disease/emphysema, etc.); 3) prescription drugs (e.g., renin-angiotensin-aldosterone system blockers, antihyperlipidemic agents, beta blockers, calcium channel blockers, corticosteroids, antidiabetics, average daily dose of furosemide at cohort entry, etc.); and 4) healthcare services utilization intensity (including nursing home residence, number of inpatient hospitalizations, number of outpatient visits, and number of prescription drug fillings).[31] All independent variables were binary and assessed during the one-year baseline period, except for the age and average daily dose of furosemide at cohort entry, continuous variables. We then used 1:1 nearest neighbor propensity score matching to match users of empiric potassium to non-users.[32]

Baseline characteristics, incidence rates, and logistic regression analysis

We first calculated descriptive statistics on baseline characteristics (**Table 1**) and compared the mortality rates between users and non-users of empiric potassium before and after propensity-score matching. The balance in the baseline characteristics was assessed by standardized difference (i.e., the mean difference of a variable between the two groups in units of the estimated common standard deviation of that variable in the two groups), with a value exceeding 0.1 suggestive of potentially meaningful imbalance between groups.[30] Next, we examined the temperature-potassium-mortality association in the high temperature range (defined as ≥ 24°C or 75°F) by modeling the interaction between temperature (daily average temperature and daily maximum temperature, separately) and potassium exposure status on the log odds of mortality using a multivariable logistic regression model where the unit of observation was person-day, allowing temperature to vary by day for each individual. The 24°C minimum temperature was chosen in advance based on literature indicating a U-shaped or similar relationship between temperature and death, with a nadir between 22°C-26°C, although we recognize that this relationship varies by location.[33-36] We excluded rare, extremely high temperatures (daily average temperature > 43°C or 110°F; daily maximum temperature > 49°C or 120°F). Given that the true functional form of the relationship between potassium use, temperature, and mortality is unknown, we examined a model that included a linear term and a quadratic term of temperature and two temperature-potassium exposure interaction terms (hereinafter referred to as a quadratic model). This model is expressed as Equation 1.

$$\text{logit}\,(Y_{ij}) = \alpha + \beta_0(T_{ij}) + \beta_1(T_{ij}^2) + \beta_2(K^+{}_i) + \beta_3(T_{ij} \times K^+{}_i) + \beta_4(T_{ij}^2 \times K^+{}_i) + \boldsymbol{\gamma_i X'_i} + \epsilon_{ij} \qquad \text{(Equation 1)}$$

In this equation, Y_{ij} is an indicator variable for the death outcome of person i on day j; T_{ij} is the outdoor temperature for person i at their ZIP code area on day j; $K^+{}_i$ is a binary variable

indicating the potassium use or non-use of person *i*; and $\mathbf{X'}_i$ is a vector of time-invariant covariates of person *i* for which we used age group at cohort entry, sex, race group. We examined daily average temperature and daily maximum temperature in separate models. We also considered a strictly linear model but decided to use a quadratic model to avoid reliance on the assumption that the relationship between temperature and mortality is linear. Because older adults are known to be more vulnerable to the heat-related mortality, we performed a subgroup analysis for older adults (age ≥ 65 years). In addition, to examine whether our results from the propensity score-matched cohort would have been influenced by other meteorological parameters, we performed a sensitivity analysis that additionally controlled for daily relative humidity at the person-level. High humidity suppresses evaporation of sweat and sweat rate,[37,38] thus might affect potassium loss as well as humans' ability to thermoregulate, possibly influencing mortality and potassium-mortality relationship.

Analyses were performed using ArcGIS version 10.3 (Esri, Redlands, California), SAS version 9.4 (SAS Institute Inc., Cary, North Carolina), and Stata version 14 (StataCorp, College Station, Texas).

Ethical Approval

This study was approved by the institutional review board of the University of Pennsylvania, which waived the requirement for obtaining informed consent. We attest that we have obtained appropriate permissions and paid any required fees for use of copyright protected materials.

Patient and Public Involvement

Patients and public were not involved in planning or conducting this study.

Results

Supplementary **Figure S1** shows the number of potentially eligible and included/excluded subjects, with reasons for exclusion. Prior to matching, there were 337,885 eligible initiators of furosemide ≥ 40 mg/day, 106,907 (32%) of whom were empiric potassium users. Nearly all of the empiric potassium users were pair-matched to a non-user, resulting in 211,878 subjects (105,939 subjects in each group) that included 89,335 person-years and 9,007 deaths. In the matched potassium cohort, 76% of the follow-up time was covered by an active prescription for potassium (follow-up continued as long as the furosemide prescription was active; Supplementary **Figure S2**), while only 12% of the follow-up time for the no-potassium group was covered by an active prescription for potassium; 85% of individuals in the no-potassium group received no potassium prescriptions during follow-up. As shown in **Table 1**, baseline variables were reasonably well balanced even before matching, and this balance was improved by propensity score matching. In the matched cohorts, median follow-up time was 69 days in potassium users and 65 days in potassium non-users, and the mortality rate (in deaths per 1,000 person-years) was 96.0 (95% confidence interval [CI]: 93.2 to 98.9) in users and 105.8 (95% CI: 102.8 to 108.9) in non-users, which corresponds to number needed to treat of 102 (95% CI: 64 to 256) over a one-year period, i.e., 102 (95% CI: 64 to 256) furosemide (≥40 mg/day) initiators would need to be treated with empiric potassium for the prevention of one additional death over a one-year period.

Table 2 examines the associations between empiric potassium use and mortality as a) a function of daily average temperature and daily average temperature squared and b) a function of daily maximum temperature and daily maximum temperature squared, as well as the interaction

between those temperature metrics and potassium use (daily average temperature and daily maximum temperature examined separately). Because the daily maximum temperature exceeds 24°C more often than does the daily average temperature, there were more observations for this metric. As seen in Figures 1 and 2, the odds ratio of all-cause mortality for potassium use (calculated from regression results) appeared to be lower (i.e., its protective effect appeared to increase) when temperature was higher for both temperature metrics. The *p*-values for the interaction terms of potassium were not statistically significant with daily average temperature (interaction with daily average temperature, $p = 0.332$; and with daily average temperature squared, $p = 0.329$), but were statistically significant with daily maximum temperature (interaction with daily maximum temperature, $p = 0.031$; and with daily maximum temperature squared, $p = 0.028$) (**Table 2**). The estimated association corresponds to approximately a 6% point reduction in odds for each 1°C increase in daily average temperature between 28°C and 43°C, and a 4% point reduction in odds for each 1°C increase in daily maximum temperature between 31°C and 49°C. The results for older adults showed similar patterns, but the confidence intervals were larger. In the sensitivity analysis that additionally controlled for daily relative humidity, the results were similar, and the *p*-values for the interaction terms of potassium with daily maximum temperature were statistically significant (interaction with daily maximum temperature, $p = 0.028$; and with daily maximum temperature squared, $p = 0.025$) (**Table 3**).

Discussion

This study examined whether the survival benefit of empiric potassium in users of furosemide (≥ 40 mg/day) increases with higher daily average and daily maximum temperature. Consistent with

earlier findings in the same population using 1999-2007 data,[20] empiric potassium use was associated with a survival benefit in furosemide (≥ 40 mg/day) initiators. The results suggest that this survival benefit may increase as daily maximum temperature increases. This relationship was statistically significant in the primary analysis and the sensitivity analysis that adjusted for daily relative humidity.

If this potential relationship between temperature and the survival benefit of potassium is true, it would have important clinical and public health implications. It is well-established that high outdoor temperature is associated with increase in mortality and morbidity.[39-43] Some excess deaths in furosemide users, especially among socioeconomically disadvantaged populations such as Medicaid enrollees in the US, might be avoidable through interventions to increase potassium intake on hot days. The number of lives saved by such interventions would be expected to increase as global climate change continues.[21-23]

One might hypothesize seasonality in the association between temperature and mortality, or that individuals residing at warmer regions might tolerate increases in temperature better than those in cooler areas. Also, a temperature-potassium interaction on mortality, if it exists, might differ across subgroups, such as geographic regions, sociodemographic characteristics including age, comorbidities, or degree of frailty. Because we were unable to explore such relationships given the limited number of high-temperature deaths, further research is warranted to investigate these potential relationships in diverse subgroups and health outcomes. In addition, future studies will need to investigate other functional forms of temperature, including lagged effects of heat, cumulative days of high temperature, and variation from the mean temperature at a given location.

This study has several strengths. First, it used large-scale real world data, representing about 40% of individuals in the US Medicaid program, which covers nearly one in five Americans. It also used ZIP code-level daily temperature data, which may better reflect the outdoor temperature at each individual's place of residence than temperature over larger geographic areas. Further, the study cohorts had good balance in the measured baseline covariates even before matching, and this balance improved further with propensity score matching, which suggests a limited role for potential confounding factors.

This study also has limitations. First, we did not have data on individuals' use of air conditioning or the amount of time spent outdoors. Therefore, we do not know the degree to which subjects were actually exposed to outdoor temperatures. However, because all individuals in our study were enrolled in Medicaid, a public health insurance program for socioeconomically disadvantaged individuals who meet certain low-socioeconomic status criteria, it seems unlikely that the access to air conditioning is substantially different between users and non-users of empiric potassium who were matched on clinical variables. Prior studies that also lacked such data found associations between temperature and of a variety of health endpoints.[39,40,42] Therefore, it seems likely that any potential bias introduced by lack of data on air conditioning would have been toward the null. Second, results observed in US Medicaid enrollees, who have lower incomes and poorer health than other groups, might not be generalizable to other populations. Nevertheless, about 20% of the US population is enrolled in Medicaid, thus this is an important population in its own right as well as from the public health and health policy perspectives. Third, although our study cohorts showed good balance in measured covariates, we cannot rule out the possibility of imbalances in unobserved factors. Finally, our study did not

examine location-specific differences in the estimated associations, which may differ due to variation in the relationship between temperature and health.

Conclusions

The results suggest that empiric potassium's survival benefit may increase as daily maximum temperature increases in Medicaid enrollees who initiate furosemide (≥ 40 mg/day). This potential relationship should be confirmed in independent data sets. Given the widespread use of furosemide, interventions based on this relationship might be able to benefit many people worldwide, especially those socioeconomically more vulnerable and living in high-temperature areas.

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Author contribution: Hennessy, Leonard, and Bilker conceived and designed the study. Hennessy and Leonard were involved in acquisition of data. Nam and Bilker performed statistical analysis. Nam, Bilker, Leonard, Bell, and Hennessy interpreted the results. Nam drafted the manuscript. Nam, Bilker, Leonard, Bell, and Hennessy critically revised the manuscript for important intellectual content. All authors approved the final manuscript to be submitted for publication and the authorship list.

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Figure Legends

Figure 1. Odds ratios and 95% confidence intervals of all-cause mortality for empiric potassium use vs. non-use by temperature

Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). Bold solid lines indicate odds ratios, and thin dash lines indicate 95% confidence intervals.

Figure 2. Odds ratios and 95% confidence intervals of all-cause mortality for empiric potassium use vs. non-use by temperature, additionally controlling for daily relative humidity

Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). Bold solid lines indicate odds ratios, and thin dash lines indicate 95% confidence intervals.

Supplementary Material

Figure S1. Sample size and the application of inclusion/exclusion criteria

Figure S2. Study cohort and follow-up time

Table 1. Baseline characteristics of the unmatched and matched study cohorts

	Before PS-Matching			After PS-Matching		
	Potassium group N=106,907	No-potassium group N=230,948	Standardized Difference	Potassium group N=105,939	No-potassium group N=105,939	Standardized Difference
Sociodemographic Characteristics						
Age at cohort entry, in years (%)						
18≤Age<35	3.92	4.27	0.02	3.94	3.84	0.01
35≤Age<50	15.03	14.94	0.00	15.04	15.15	0.00
50≤Age<65	23.82	24.77	0.02	23.83	23.86	0.00
65≤Age<80	34.78	33.75	0.02	34.77	34.97	0.00
80≤Age<100	22.44	22.26	0.00	22.42	22.18	0.01
Sex, female (%)	66.36	66.40	0.00	66.34	66.37	0.00
Race/Ethnicity (%)						
White	53.69	50.05	0.07	53.46	53.73	0.01
Black	15.36	18.15	0.07	15.44	15.30	0.00
Hispanic	15.58	14.03	0.04	15.63	15.65	0.00
Other/Unknown	15.38	17.77	0.06	15.46	15.32	0.00
Medicaid-Medicare dual-eligible (%)	70.36	67.43	0.06	70.20	70.21	0.00
State of residence (%)						
California	45.89	40.73	0.10	46.28	46.52	0.00
Florida	17.42	8.89	0.25	16.71	16.56	0.00
New York	17.13	29.27	0.29	17.29	17.22	0.00
Ohio	10.35	8.93	0.05	10.44	10.54	0.00
Pennsylvania	9.21	12.19	0.10	9.28	9.16	0.00
Urban residence[a] (%)	85.86	87.04	0.03	85.91	85.95	0.00
Year of cohort entry						

	Before PS-Matching			After PS-Matching		
	Potassium group	No-potassium group	Standardized Difference	Potassium group	No-potassium group	Standardized Difference
	N=106,907	N=230,948		N=105,939	N=105,939	
2000	8.95	10.34	0.05	9.01	9.22	0.01
2001	9.82	9.91	0.00	9.84	10.03	0.01
2002	9.72	9.64	0.00	9.72	9.76	0.00
2003	9.55	9.43	0.00	9.55	9.40	0.01
2004	7.25	7.88	0.02	7.31	7.48	0.01
2005	8.36	8.38	0.00	8.37	8.37	0.00
2006	14.12	14.03	0.00	14.07	14.05	0.00
2007	9.12	7.99	0.04	9.01	8.92	0.00
2008	7.03	6.66	0.01	7.07	6.92	0.01
2009	7.89	7.49	0.02	7.87	7.78	0.00
2010	8.18	8.26	0.00	8.18	8.09	0.00
Diseases						
Alkalosis, metabolic (%)	0.20	0.20	0.00	0.21	0.21	0.00
Amyloidosis (%)	0.03	0.04	0.01	0.03	0.02	0.01
Anemia (%)	29.31	27.46	0.04	29.19	29.22	0.00
Ascites (%)	1.26	1.40	0.01	1.26	1.29	0.00
Asthma/COPD/emphysema (%)	31.41	27.43	0.09	31.12	31.13	0.00
Cardiac dysrhythmias/conduction disorder (%)	26.31	23.76	0.06	26.10	26.18	0.00
Cerebrovascular disease (%)	18.45	17.54	0.02	18.39	18.52	0.00
Diabetes insipidus (%)	0.06	0.06	0.00	0.06	0.05	0.00
Diabetes mellitus (%)	38.90	39.70	0.02	38.95	38.93	0.00
Edema (%)	23.65	19.87	0.09	23.42	23.56	0.00
Glaucoma (%)	9.55	9.84	0.01	9.54	9.49	0.00

	Before PS-Matching			After PS-Matching		
	Potassium group N=106,907	No-potassium group N=230,948	Standardized Difference	Potassium group N=105,939	No-potassium group N=105,939	Standardized Difference
Heart failure/cardiomyopathy (%)	36.48	32.96	0.07	36.21	36.25	0.00
HIV/AIDS (%)	0.45	0.69	0.03	0.45	0.46	0.00
Hyperosmolality (%)	0.46	0.59	0.02	0.47	0.47	0.00
Hypertensive disease (%)	66.66	64.48	0.05	66.50	66.58	0.00
Hyperthyroidism (%)	2.25	1.96	0.02	2.24	2.18	0.00
Hypothyroidism (%)	16.21	14.53	0.05	16.09	16.19	0.00
Ischemic heart disease (%)	36.52	32.89	0.08	36.22	36.39	0.00
Kidney disease[b] (%)	9.27	10.60	0.04	9.32	9.24	0.00
Lipoid metabolism disorder (%)	43.21	37.95	0.11	42.88	43.07	0.00
Liver disease (%)	20.13	19.54	0.01	20.08	20.10	0.00
Magnesium metabolism disorder (%)	0.63	0.62	0.00	0.63	0.67	0.00
Nocturia (%)	1.37	1.20	0.02	1.36	1.31	0.00
Pulmonary circulation disease (%)	5.00	4.40	0.03	4.93	4.93	0.00
Pulmonary congestion and hypostasis/pulmonary edema (%)	6.47	5.89	0.02	6.44	6.45	0.00
Pyloric stenosis (%)	0.07	0.08	0.00	0.07	0.07	0.00
Rheumatoid arthritis and other inflammatory polyarthropathies (%)	5.16	4.64	0.02	5.15	5.13	0.00
Systemic lupus erythematosus (%)	0.70	0.67	0.00	0.68	0.68	0.00
Urinary obstruction (%)	0.41	0.40	0.00	0.41	0.41	0.00
Prescription Drugs						
RAAS blockers (%)	52.01	54.35	0.05	52.14	52.01	0.00
Adrenergic agents (%)	11.99	12.29	0.01	12.03	12.03	0.00
Antiarrhythmics (%)	3.59	2.62	0.06	3.51	3.63	0.01

	Before PS-Matching			After PS-Matching		
	Potassium group N=106,907	No-potassium group N=230,948	Standardized Difference	Potassium group N=105,939	No-potassium group N=105,939	Standardized Difference
Antidiabetics (%)	31.61	34.30	0.06	31.75	31.67	0.00
Antiglaucoma agents (%)	19.45	18.51	0.02	19.38	19.31	0.00
Antihyperlipidemic agents (%)	39.67	38.39	0.03	39.59	39.54	0.00
Antiobesity agents (%)	0.18	0.11	0.02	0.17	0.17	0.00
Antiretrovirals (%)	0.74	1.14	0.04	0.75	0.76	0.00
Beta blockers, systemic (%)	34.20	33.88	0.01	34.11	34.02	0.00
Bisphosphonates (%)	2.95	2.43	0.03	2.91	2.91	0.00
Calcium channel blockers (%)	31.14	31.70	0.01	31.15	30.94	0.00
Corticosteroids, systemic (%)	30.55	28.13	0.05	30.37	30.44	0.00
Digoxin (%)	9.95	8.89	0.04	9.86	10.01	0.01
Diuretics, thiazides (%)	13.82	15.37	0.04	13.88	13.66	0.01
Immunosuppressives (%)	0.64	0.76	0.01	0.64	0.62	0.00
Thyroid hormones (%)	12.24	11.66	0.02	12.19	12.31	0.00
Vasodilators (%)	10.41	10.47	0.00	10.40	10.48	0.00
Warfarin (%)	10.00	9.11	0.03	9.90	9.96	0.00
Xanthine derivatives (%)	4.93	4.23	0.03	4.89	4.93	0.00
Average daily dose of furosemide at cohort entry[c] ≥ 80 mg/day (%)	17.80	18.16	0.01	17.79	17.79	0.00
Healthcare Services Utilization Intensity						
Nursing home residence (%)	16.37	18.04	0.04	16.40	16.38	0.00
Inpatient hospitalization, mean number	0.71	0.68	0.02	0.71	0.72	0.01
Outpatient visits, mean number	47.16	49.40	0.03	47.13	47.67	0.01
Prescription drug fillings, mean number	25.71	24.73	0.05	25.66	25.74	0.00

	Before PS-Matching			After PS-Matching		
	Potassium group N=106,907	No-potassium group N=230,948	Standardized Difference	Potassium group N=105,939	No-potassium group N=105,939	Standardized Difference

PS: propensity score. RAAS: renin-angiotensin-aldosterone system. Ref: reference. [a]Urban residence: ascertained by the ZIP codes in the claims data used and ZIP Code to Carrier Locality File from the Centers for Medicare and Medicaid Services (Centers for Medicare and Medicaid Services, 2017). [b]Kidney disease: kidney diseases, except for chronic kidney disease, or renal impairment. [c]Average daily dose of furosemide at cohort entry: excluded persons whose initial furosemide dose was greater than two times daily recommended maximum dose of 600 mg/day.

Table 2. Logistic regression results to estimate temperature-modified empiric potassium's effect on all-cause mortality in furosemide (≥ 40 mg/day) initiators

	Daily average temperature ≥ 24° C				Daily maximum temperature ≥ 24° C			
	(N=6,345,029 person-days; 1,862 deaths)				(N=15,147,407 person-days; 4,262 deaths)			
	Coefficient	95% CI		*p*-value	Coefficient	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
Temperature	0.1673	-0.3974	0.7320	0.561	-0.0908	-0.2176	0.0360	0.161
Temperature squared[a]	-0.0025	-0.0128	0.0078	0.642	0.0019	-0.0002	0.0040	0.077
Potassium[b]	-5.6046	-16.9577	5.7485	0.333	-3.1654	-6.0507	-0.2801	0.032
Temperature × Potassium	0.4130	-0.4218	1.2478	0.332	0.2083	0.0192	0.3974	0.031
Temperature squared × Potassium	-0.0076	-0.0229	0.0077	0.329	-0.0035	-0.0066	-0.0004	0.028
Age ≥ 65 years	(N=3,944,433 person-days; 1,491 deaths)				(N=9,371,901 person-days; 3,395 deaths)			
Temperature	0.1359	-0.5072	0.7790	0.679	-0.0970	-0.2397	0.0457	0.182
Temperature squared	-0.0021	-0.0139	0.0097	0.731	0.0019	-0.0004	0.0042	0.109
Potassium	-7.2166	-20.1761	5.7429	0.275	-2.6074	-5.8255	0.6107	0.112
Temperature × Potassium	0.5201	-0.4340	1.4742	0.285	0.1678	-0.0433	0.3789	0.119
Temperature squared × Potassium	-0.0094	-0.0269	0.0081	0.293	-0.0028	-0.0062	0.0006	0.115

95% CI: 95% confidence interval. Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F).
[a]Temperature squared: 2nd degree polynomial term of temperature. [b]Potassium: empiric potassium exposure status (0=empiric potassium users; 1=empiric potassium non-users).

Table 3. Logistic regression results to estimate temperature-modified empiric potassium's effect on all-cause mortality in furosemide (≥ 40 mg/day) initiators, additionally controlling for daily relative humidity

	Daily average temperature ≥ 24° C (N=6,345,029 person-days; 1,862 deaths)				Daily maximum temperature ≥ 24° C (N=15,147,407 person-days; 4,262 deaths)			
	Coefficient	95% CI		*p*-value	Coefficient	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
Temperature	0.2069	-0.3639	0.7777	0.477	-0.0529	-0.1825	0.0767	0.423
Temperature squared[a]	-0.0032	-0.0136	0.0072	0.549	0.0011	-0.0010	0.0032	0.297
Potassium[b]	-5.6409	-17.0326	5.7508	0.332	-3.2621	-6.1831	-0.3411	0.029
Temperature × Potassium	0.4159	-0.4216	1.2534	0.330	0.2152	0.0235	0.4069	0.028
Temperature squared × Potassium	-0.0077	-0.0230	0.0076	0.327	-0.0036	-0.0067	-0.0005	0.025
Relative Humidity[c]	-0.0019	-0.0050	0.0012	0.233	-0.0055	-0.0077	-0.0033	<0.0001

95% CI: 95% confidence interval. Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F).
[a]Temperature squared: 2nd degree polynomial term of temperature. [b]Potassium: empiric potassium exposure status (0=empiric potassium users; 1=empiric potassium non-users). [c]Relative Humidity: daily relative humidity.

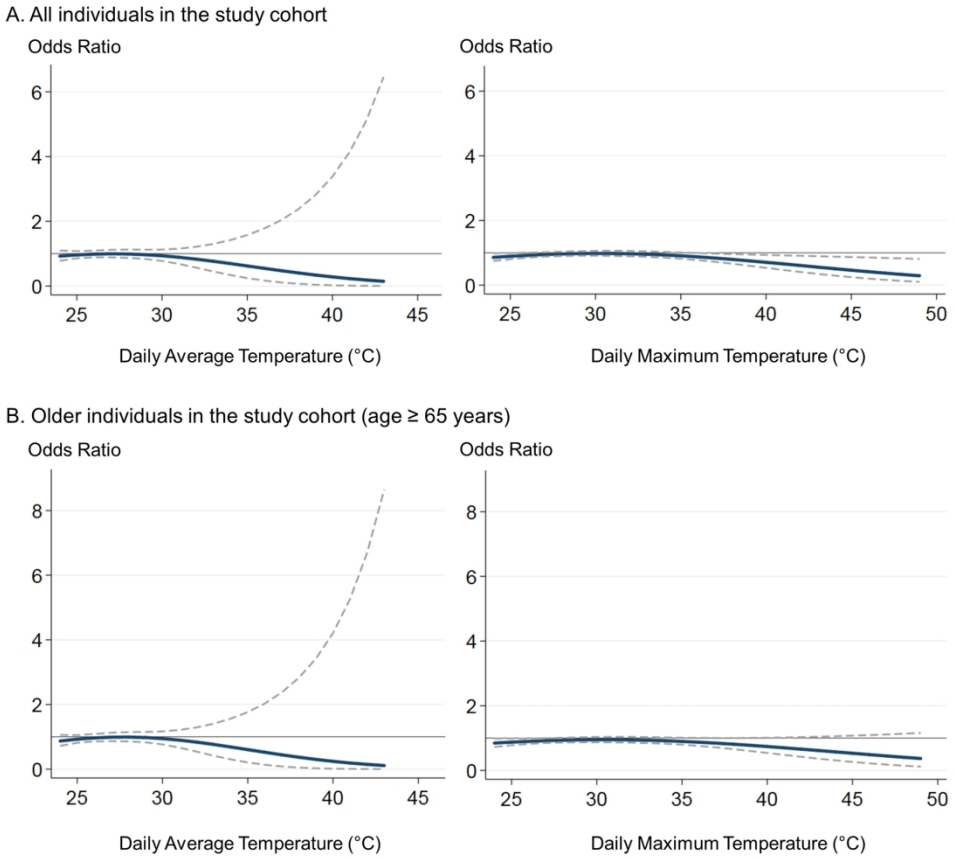

Figure 1. Odds ratios and 95% confidence intervals of all-cause mortality for empiric potassium use vs. non-use by temperature
Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). Bold solid lines indicate odds ratios, and thin dash lines indicate 95% confidence intervals.

190x169mm (300 x 300 DPI)

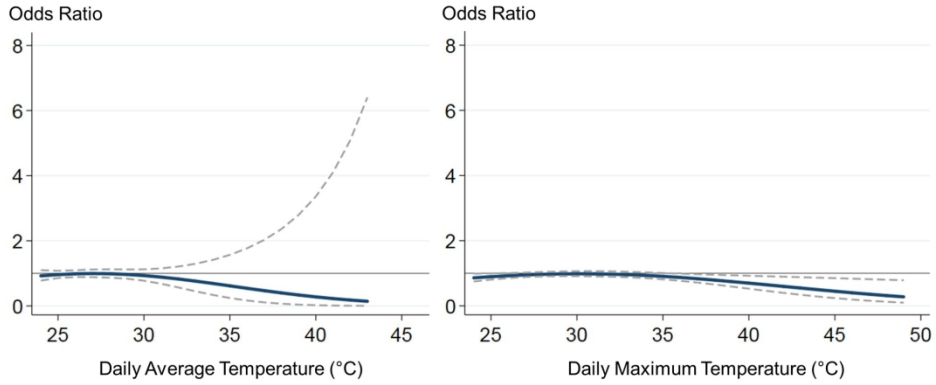

Figure 2. Odds ratios and 95% confidence intervals of all-cause mortality for empiric potassium use vs. non-use by temperature, additionally controlling for daily relative humidity
Daily average temperature: 24-43°C (75-110°F). Daily maximum temperature: 24-49°C (75-120°F). Bold solid lines indicate odds ratios, and thin dash lines indicate 95% confidence intervals.

188x114mm (300 x 300 DPI)

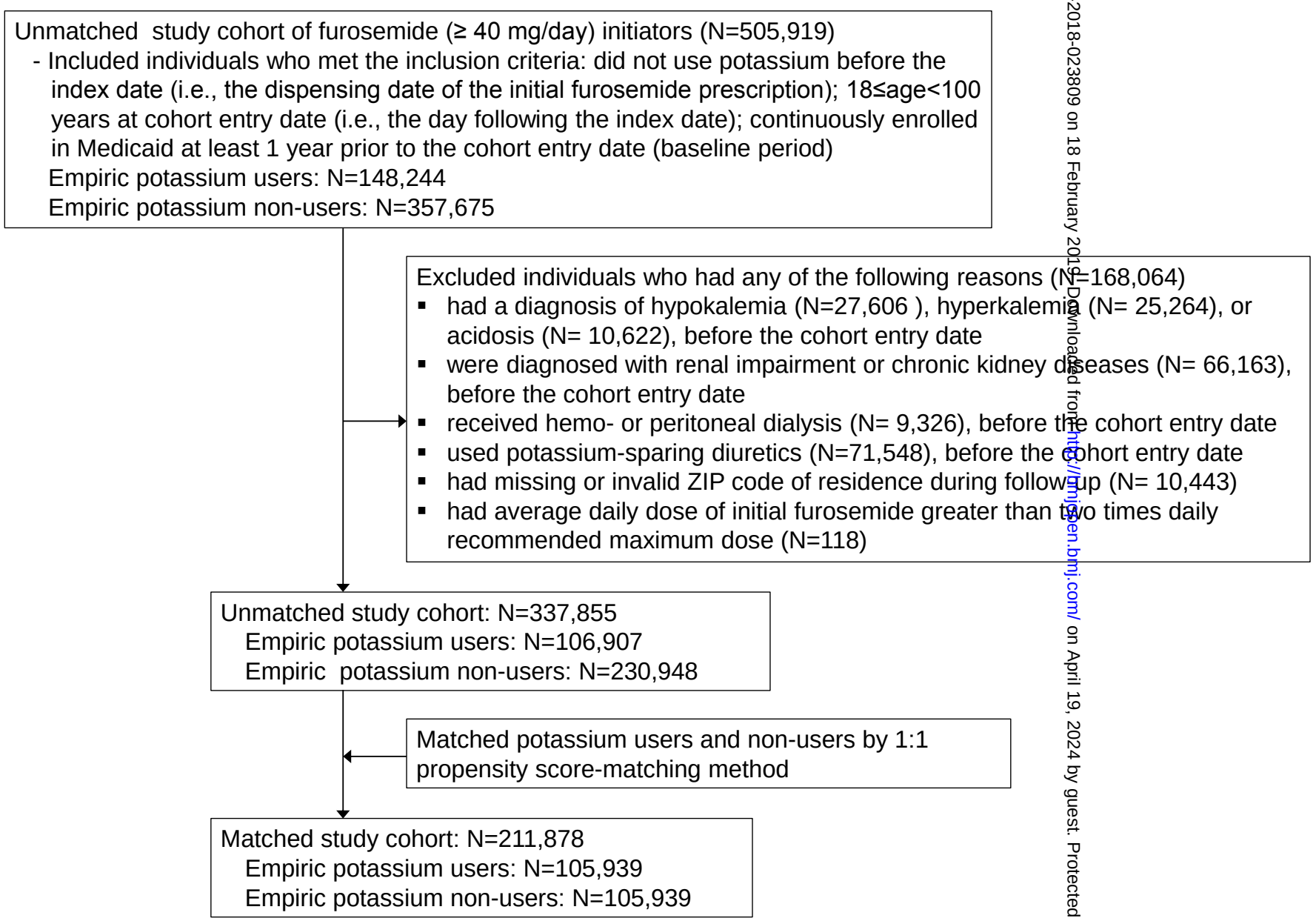

Figure S1. Sample size and the application of inclusion/exclusion criteria

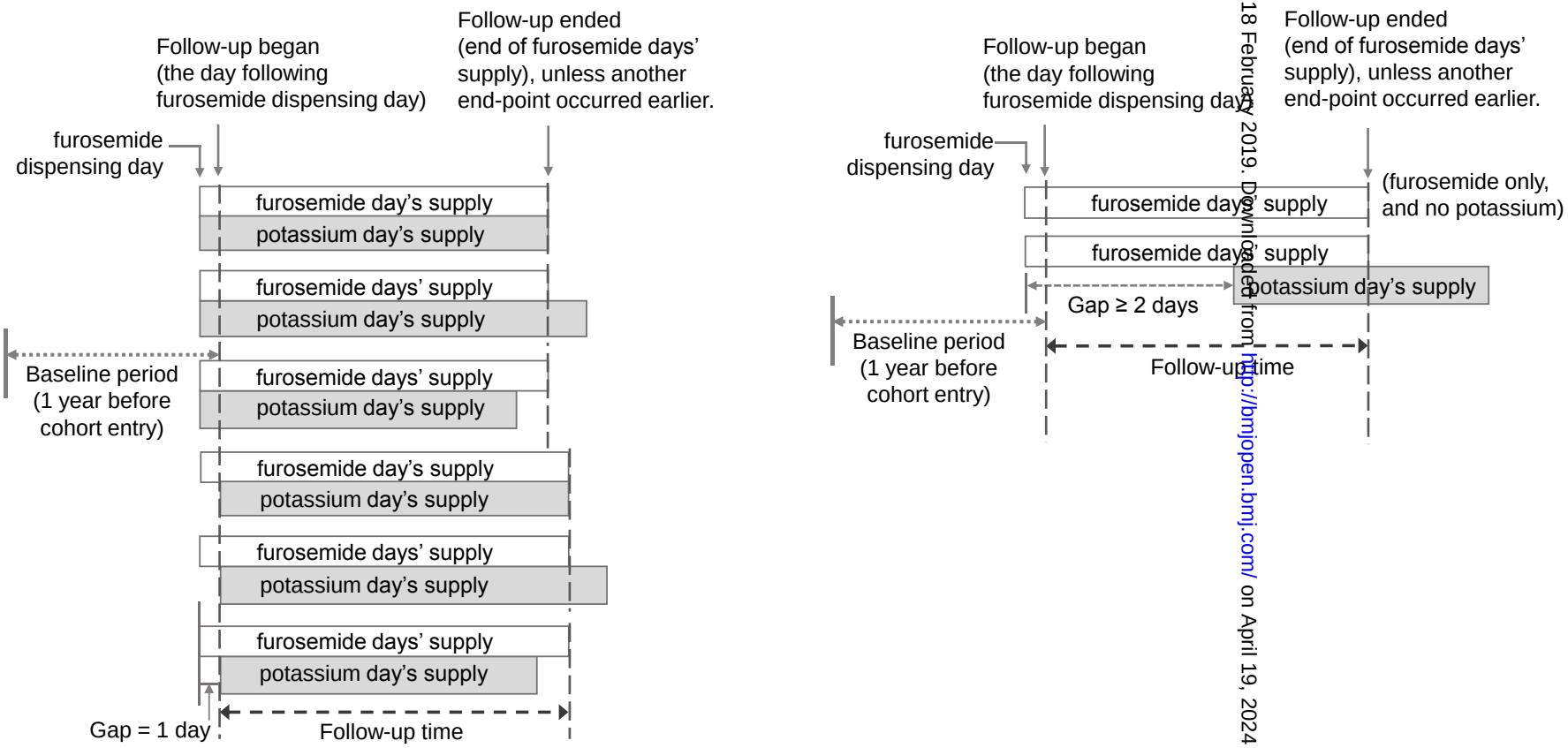

Figure S2. Study cohort and follow-up time

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9; Figures S1 and S2
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	10-11, 13
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-12, 25-29
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-12, 25-29
Bias	9	Describe any efforts to address potential sources of bias	10-12, 25-29
Study size	10	Explain how the study size was arrived at	7-13, Figure S1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-12
		(*b*) Describe any methods used to examine subgroups and interactions	10-12
		(*c*) Explain how missing data were addressed	7-12; Figure S1
		(*d*) If applicable, explain how loss to follow-up was addressed	7-9
		(*e*) Describe any sensitivity analyses	12, 14, 31

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13, 25-29
		(b) Give reasons for non-participation at each stage	13, Figure S1
		(c) Consider use of a flow diagram	Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13, 25-29
		(b) Indicate number of participants with missing data for each variable of interest	Figure S1
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	13, 30-31
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13, 25-29
		(*b*) Report category boundaries when continuous variables were categorized	25-29
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14, 30-31
Discussion			
Key results	18	Summarise key results with reference to study objectives	15, 17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.