To Whom It May Concern,

In reference to the paper titled "Increased Ambient Air Temperature and Hyponatremia Presentations: A 10-Year Retrospective Study at an Australian Hospital," Dr Nicholls made the following contributions:

1. Collaborated with co-authors to plan and design the project
2. Updated and amended the ethics application
3. Supervised and directed the business intelligence team with data extraction
4. Interpreted, alongside co-authors, the results from the statistician led data analysis
5. Constructed relevant tables and graphs
6. Wrote the first draft of the manuscript
7. Collaborated with co-authors in editing the manuscript
8. Acted as corresponding author during the publication process

Thank you very much for your consideration.

Kind regards,

Professor Mathis Grossmann

Dr Annabelle M Warren | Professor Rudolf Hoermann | Dr Elizabeth Wootton

Negar Mansouri | Meg Stevens | Hung Vo

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Clinical Research Article

Increased Ambient Temperature and Hyponatremia Presentations: A 10-Year Retrospective Study at an Australian Hospital

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Abstract

Objective: To determine the relationship between ambient air temperature and the incidence of hyponatremia in a heat-prone region.

Methods: We conducted a retrospective study that correlated serum sodium concentrations documented at the Austin Hospital in Melbourne over 10 years from January 2014 to December 2023 with publicly available temperature data from the Australian Bureau of Meteorology. The main outcome measures were serum sodium concentrations and incidence of hyponatremia admissions when correlated to temperature, and, following heatwave events, defined as temperature above 30 °C over 5 consecutive days.

Results: Over this period, 45 718 low serum sodium results were identified from 26 557 unique patients. Serum sodium concentrations in January (Australian summer) were 0.55 mmol/L lower (95% CI 0.36 to 0.77, $P < .001$) than in September (Australian early spring). Women had lower sodium concentrations than men (−0.21 mmol/L, 95% CI −0.29 to −0.12, $P < .001$), as did patients older than 80 years when compared with those younger than 65 years (−0.39 mmol, 95% CI −0.50 to −0.29, $P < .001$). Hospital admissions with hyponatremia were more frequent during summer months. Profound hyponatremia admissions (sodium ≤125 mmol/L) were more frequent following a heatwave than without (7.6% vs 6.5%, $P = .04$).

Conclusion: Our study demonstrates that serum sodium concentrations are lower and profound hyponatremia-related hospital admissions higher when ambient temperatures are warmer. This suggests that hyponatremia is a climate-associated health issue. Local public health advice for water consumption during heatwaves should consider this risk, and prompt action to limit climate change is required to mitigate this risk.

Key Words: hyponatremia, temperature, climate change

Abbreviations: SIAD, syndrome of inappropriate antidiuresis; SIADH, syndrome of inappropriate antidiuretic hormone.

Hyponatremia is the most frequently observed electrolyte derangement and can have adverse health outcomes. Even mild hyponatremia has been associated with increased length of hospital stay, readmission, healthcare, costs, and mortality (1). There is existing evidence that the incidence of hyponatremia increases with higher ambient air temperatures. A recent systematic review identified 11 studies that directly assessed the relationship between climate metrics and emergency department attendances or hospitalizations with abnormal serum sodium concentrations (2). The majority were conducted in temperate climate regions: 8 originated from Western Europe (3-10), 2 from Japan (11, 12), and 1 case series from Australia (13). Lower serum sodium concentrations were observed during periods of warmer temperatures in all studies; however, some only demonstrated this correlation in older people. All studies were of short duration, most at high risk of bias, and there were no large studies in Australia. As a result of climate change, both global temperatures and the incidence of heatwave events are expected to rise (14). High-quality studies in climates that already experience greater heat conditions, such as Australia, may be informative globally. We seek to understand the local risks of heat-related hyponatremia and to subsequently guide public health advice (15).

Our aim was to retrospectively correlate publicly available meteorological data with serum sodium concentration results recorded from presentations to the Austin Hospital, a large tertiary hospital in Melbourne, Victoria, Australia, over a 10-year period. We hypothesized that the incidence of hyponatremia presentations would be higher on days with higher ambient temperature, and following heatwaves, here defined as 5 consecutive days of severe heat (>30 °C).

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Materials and Methods

Study Design

We extracted all serum sodium results <135 mmol/L from the Austin Hospital online *Cerner* database from 1 January 2014 to 31 December 2023, from patients presenting to the Emergency Department. For an individual patient, the first sodium recorded within 48 hours of their arrival was extracted. Over this 10-year period, 45 718 sodium results were extracted from 26 557 unique patients, which were used for the cross-sectional study. When available, ICD codes for syndrome of inappropriate antidiuretic hormone (SIADH; also known as syndrome of inappropriate antidiuresis [SIAD]), volume depletion, and hypervolemia were also extracted to determine the cause of hyponatremia.

Weather data were accessed from the Australian Bureau of Meteorology online database. We extracted daily maximum and minimum temperatures from January 1, 2014, to December 31, 2023, recorded at the Viewbank weather station in Victoria, Australia—the closest station to the Austin Hospital. These data were analyzed with the sodium results across the same period.

Statistical Analysis

Patient characteristics are reported for both the total sample and 2 strata of patients with and without profound hyponatremia (defined as a serum sodium ≤125 mmol/L) (16). They are reported as the mean (SD) or median (interquartile range [IQR]). Comparison of numeric data was based on Welch's t-test or the Wilcoxon rank-sum test for independent data. Categorical variables were presented as frequencies and proportions and compared using the chi-squared test.

For the analysis of time-related and seasonal effects in the cross-sectional part of the study, a regular time series was constructed. We note that sodium measurements were regularly spaced in time, based on single measurements per individual, and no autocorrelation was present. As for temperature records, a small number of missing maximum temperature entries (n = 117) and minimum temperatures (n = 157) in the data sets obtained from the Australian Bureau of Meteorology was imputed, based on the previous observation. As per official explanation from the bureau, "gaps in the temperature data may occur where a valid observation was not available. This is frequently associated with the observer being unavailable (where observations are undertaken manually), a failure in the observing equipment, or when an event has produced suspect data." The time series was described by descriptive statistics and graphical methods (box plots) and subjected to aggregate analysis (monthly average). The influence of covariables, such as sex and age categories, was further assessed by multivariable linear models or, in case of nonlinear relationships, multivariable general additive models.

In the second part of the study, 19 161 serial measurements from 8405 individuals were assessed with linear mixed effects models or in case of nonlinear association using third-order polynomial terms or additive mixed effects models.

A subgroup analysis was performed for patients who had an ICD code for "SIADH" recorded.

Statistical significance was denoted by a 2-sided P value less than .05. Statistical analyses were performed in the R statistical environment (version 4.4.0 for Mac) with the use of the additional packages xts 0.13.2, forecast 8.22.0, lme4 1.1-35.3, nlme 3.1-164, gam 1.22.3, gamm4 0.2.6, and effects 4.2-2 (17-24).

The study was approved by the Austin Health Human Research Ethics Committee (approval number: 86628).

Results

Temperatures in Melbourne showed a seasonal pattern with Fig. 1A showing the daily and (Fig. 1B) monthly maximum temperature over a 10-year period (from January 1, 2014 to December 31, 2023). The aggregated monthly temperature readings showed the typical drop in temperature in the winter months (June to August in the Southern Hemisphere) (Fig. 1C).

Table 1 shows available characteristics from the 26 557 patients included in the cross-sectional studies, stratified by serum sodium concentration of ≤125 or >125 mmol/L. There were 1736 patients identified with a serum sodium ≤125 mmol/L.

The data for serum sodium concentrations among patients presenting to the emergency department over the same period suggested a time-related seasonal pattern (Fig. 2A). Sodium concentrations were lower in the Australian summer months January and February, when temperature was higher (Fig. 2B). In aggregate over the 10-year observation period, serum sodium in the month of January was on average 0.55 mmol/L (95% CI 0.36 to 0.77, $P < .001$) lower than September (Australian early spring). The association between sodium and maximum temperature could be approximated by a multivariable linear model, with sex and age groups as covariables (Fig. 2C). Age groups and their baseline characteristics are listed in Table 1. The estimated mean change in sodium was −0.02 (95% CI −0.03 to −0.01, $P < .001$) mmol/L per +1 °C change in temperature. Sex and age groups were independently significant covariables, with lower sodium concentrations in women (−0.21, 95% CI −0.29 to −0.12, $P < .001$) mmol/L than in men, and in patients above 80 years (−0.39, 95% CI −0.50 to −0.29, $P < .001$) mmol/L than in patients aged younger than 65 years (Fig. 2C).

A period of temperatures above 30 °C on 5 consecutive days was defined as a heatwave. The influence of a heatwave on the sodium concentrations by using the 5-day trailing moving average is shown in Fig. 3. The decrease in the median sodium level after such a period was approximately 1 mmol/L ($P < .001$).

The frequency of total admissions and the proportion of presentations with profound hyponatremia (sodium ≤ 125 mmol/L) varied significantly ($P < .001$) by month, being higher during summer months (Fig. 4). Visits with profound hyponatremia were also more frequent after heatwaves (7.6% vs 6.5%, $P = .04$).

Serial Study

A total of 8405 patients had repeat sodium measurements taken at multiple visits (n = 19 161) across the 10-year study period, January 1, 2014, to December 31, 2023. This allowed for a serial study, complementing the above cross-sectional study. To examine the relationship between maximum temperature and sodium, a year, sex, and age group–adjusted linear mixed model proved sufficient to approximate the inverse relationship (Fig. 5). Sodium decreased on average by 0.03 mol/L (95% CI −0.04 to −0.02, $P < .001$) with any 1 °C of temperature increase.

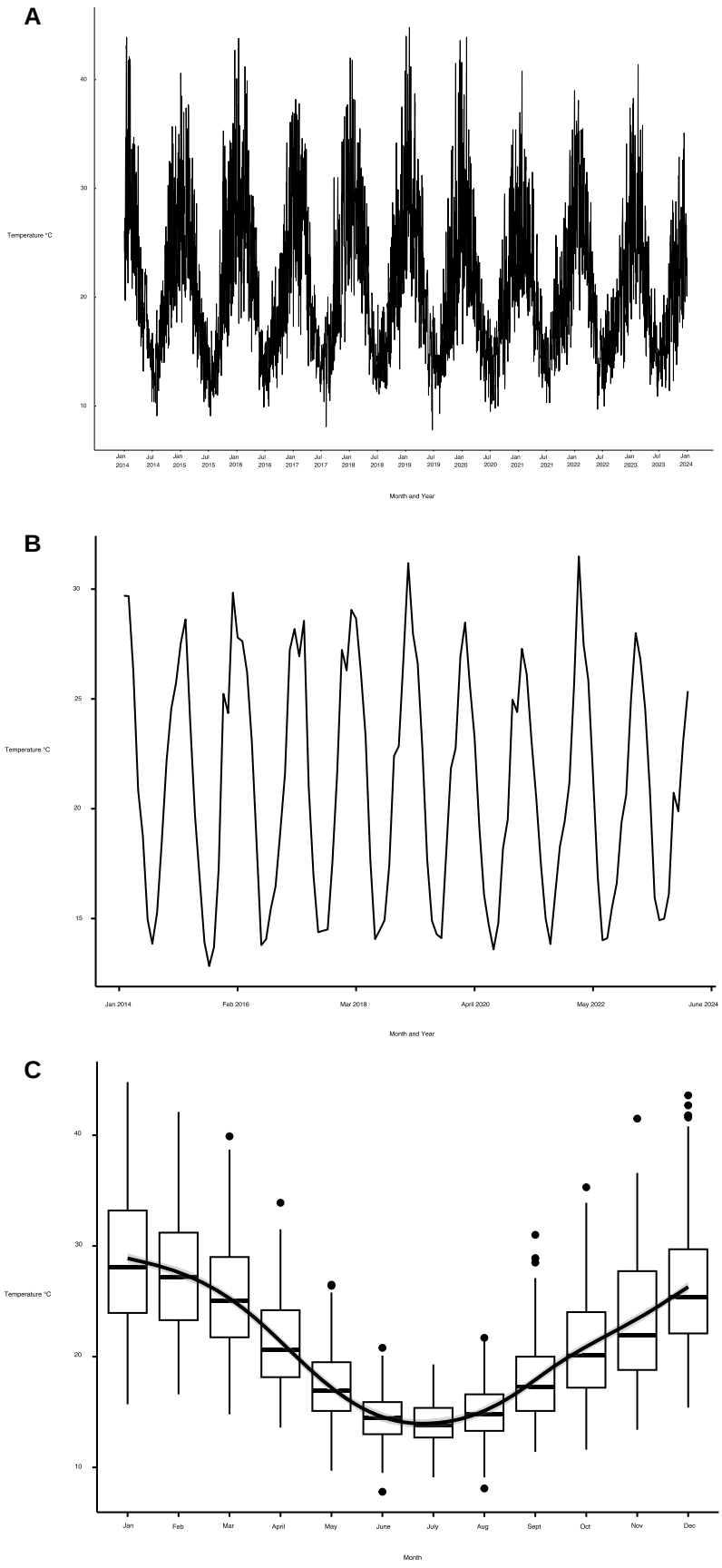

Figure 1. (A) Maximum daily temperature over a 10-year period in the Southern Hemisphere (summer Dec-Feb). (B) Maximum monthly temperatures over a 10-year period in the Southern Hemisphere (summer Dec-Feb). (C) Aggregated maximum monthly temperatures over a 10-year period in the Southern Hemisphere (summer Dec-Feb).

Table 1. Baseline characteristics

	All (n = 26 557)	Sodium > 125 (n = 24 821)	Sodium ≤ 125 (n = 1736)	*P* value
Sodium	133 (130;134)	133 (131;134)	122 (120;124)	.000
Sex[a]				<.001
Female	13 641 (51.4%)	12 658 (51.0%)	983 (56.6%)	
Male	12 913 (48.6%)	12 160 (49.0%)	753 (43.4%)	
Age	70.0 [53.0;81.0]	69.0 [53.0;81.0]	72.0 [58.0;82.0]	<.001
Age groups				<.001
<65 years	10 846 (40.8%)	10 223 (41.2%)	623 (35.9%)	
65-79 years	8001 (30.1%)	7431 (29.9%)	570 (32.8%)	
>79	7710 (29.0%)	7167 (28.9%)	543 (31.3%)	
Age and sex				<.001
Female <65 years	4985 (18.8%)	4710 (19.0%)	275 (15.8%)	
Female 65-79 years	3876 (14.6%)	3557 (14.3%)	319 (18.4%)	
Female >79	4780 (18.0%)	4391 (17.7%)	389 (22.4%)	
Male <65 years	5858 (22.1%)	5510 (22.2%)	348 (20.0%)	
Male 65-79 years	4125 (15.5%)	3874 (15.6%)	251 (14.5%)	
Male >79	2930 (11.0%)	2776 (11.2%)	154 (8.87%)	
Hypervolemia				<.001
Yes	953 (3.59%)	824 (3.32%)	129 (7.43%)	
No	25 604 (96.4%)	23 997 (96.7%)	1607 (92.6%)	
Volume depletion				<.001
Yes	2310 (8.70%)	1963 (7.91%)	347 (20.0%)	
No	24 247 (91.3%)	22 858 (92.1%)	1389 (80.0%)	
SIADH				<.001
Yes	303 (1.14%)	136 (0.55%)	167 (9.62%)	
No	26 254 (98.9%)	24 685 (99.5%)	1569 (90.4%)	

P values refer to the difference in groups and were derived by the Wilcoxon rank-sum test for independent data for numerical values, and chi-squared test for frequencies.
Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone.
[a]Three indeterminate gender assignments were not included.

Analysis of SIAD Subgroup

Interestingly, in the subgroup of 383 patients with documented SIAD and repeated visits (median 4, IQR 3-7, per patient) the sex- and age-adjusted association of sodium with maximum temperature was positive, increasing the sodium concentration nonsignificantly by 0.06 mol/L (95% CI −0.01 to 0.12, $P = .12$) with a temperature increase of 1 °C. Similarly, following heatwaves, the sodium concentration in patients with SIAD showed considerable variation, but on average was not significantly different (0.42 mmol/L, 95% CI −1.3 to 2.2, $P = .64$) compared with other times.

Discussion

Comparing the local climate data and serum sodium concentrations recorded at the Austin Hospital over 10 years, we found that mean serum sodium concentrations were lower and hyponatremia admissions—including those with profound hyponatremia (≤125 mmol/L)—were more prevalent during warmer months, and following 5 consecutive days of severe heat (>30 °C). Sodium concentrations were also noted to be lower in women and in patients older than 80 years during warmer months. Of note, those patients with known SIAD did not show a significant seasonal pattern; if anything in those with SIAD, serum sodium concentrations tended to be less low and hyponatremia admissions less frequent in warmer temperatures.

This study is the only large Australian study investigating the impact of ambient temperature on sodium concentration and is therefore particularly relevant amidst current concerns about global heating. The warm temperature climate of Melbourne, Australia, is more prone to heatwave events than the locations of previous association studies, for instance a Swedish study where heat was defined as mean daily temperature above 15 °C (3-13). Even mild hyponatremia is associated with unfavorable outcomes in hospitalized patients including increased mortality and length of hospital stay (1). Although our study was not designed to quantify hyponatremia-associated adverse health outcomes, our data are of potential public health relevance.

The underlying mechanisms driving the relationship between heat and hyponatremia are not fully understood (2). It is possible that the increased incidence of hyponatremia admissions during warm weather is related to the combined effect of relative hypovolemia (increased electrolyte and water loss from sweating) and consumption of excess hypotonic fluids, leading to dilutional hypovolemic hyponatremia. Certain populations have been shown to be more vulnerable to heat-related hyponatremia, including the extremes of age, those on diuretic medications, and those on dialysis (2).

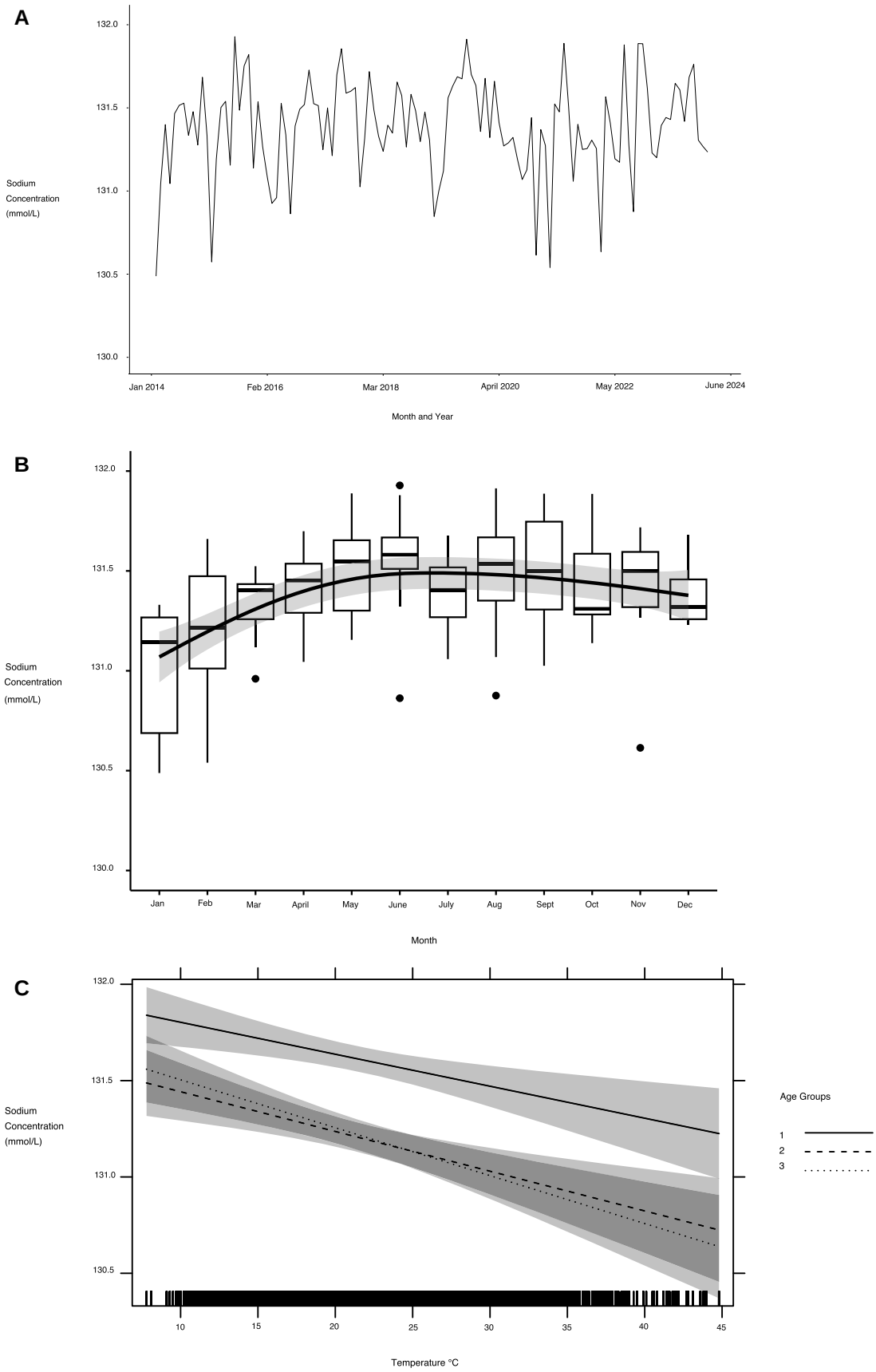

Figure 2. (A) Monthly average sodium concentration over a 10-year period in the Southern Hemisphere (summer Dec-Feb). (B) Monthly mean sodium concentrations over a 10-year period in the Southern Hemisphere (summer Dec-Feb). (C) Multivariable linear model, with sex as covariable, approximating the association between sodium and maximum temperature stratified by age groups.

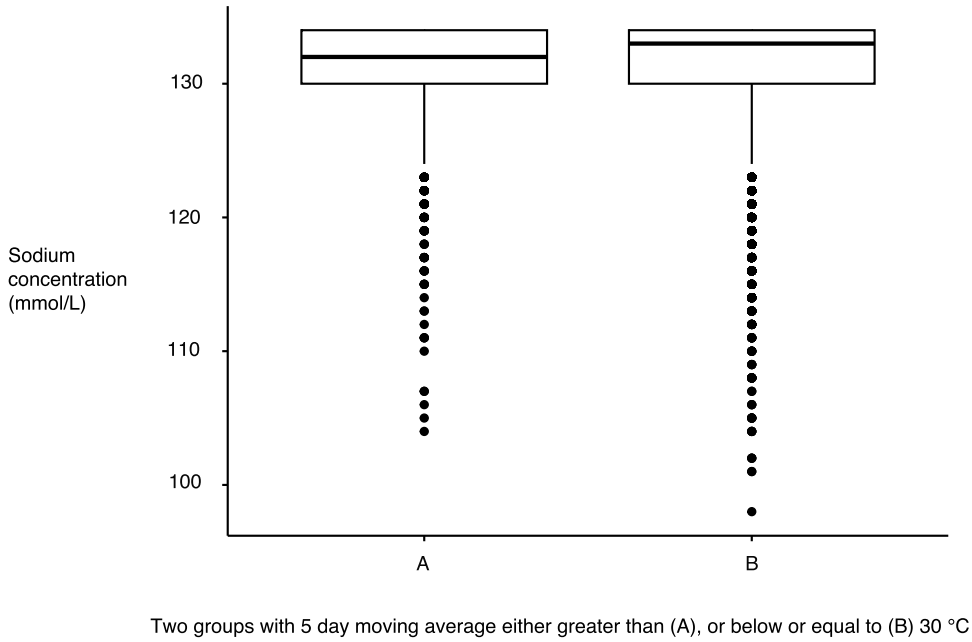

Figure 3. A 5-day trailing moving average demonstrating the influence of a heatwave on the sodium concentration.

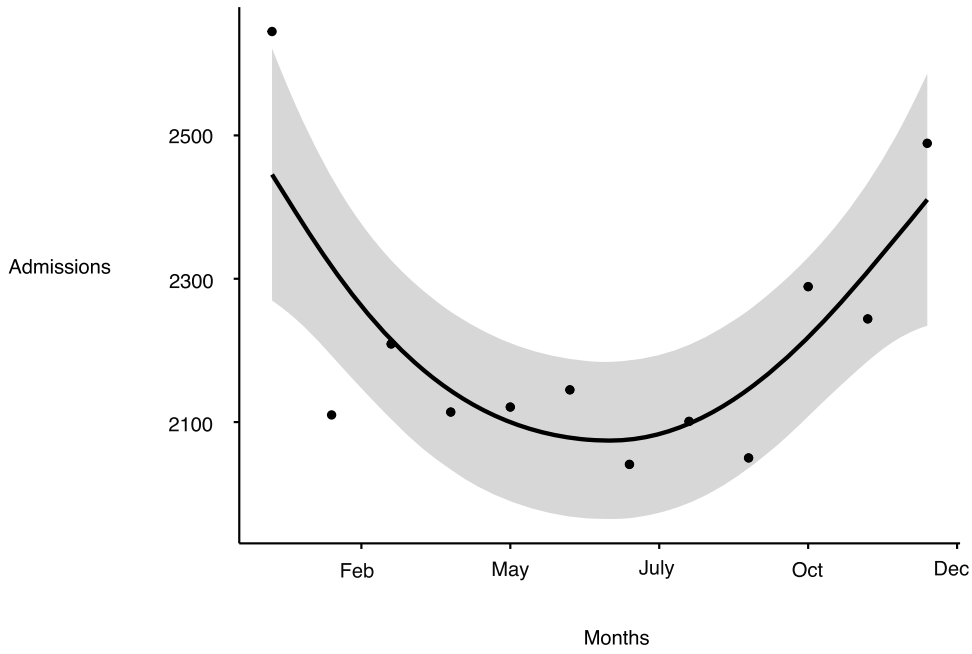

Figure 4. Hyponatremia admissions by month over a 10-year period in the southern Hemisphere (summer Dec-Feb).

Excess fluid consumption during hot weather may be exacerbated by current public health advice from the local Victorian Department of Health that during a heatwave, "keep drinking fluids before you feel thirsty" (15). Instead, drinking to thirst would be the more appropriate recommendation, noting that in certain populations such as children or older people with comorbidities, thirst perception might be impaired, and individualized recommendations are necessary. Our finding that older patients were more vulnerable to heat-related hyponatremia than younger patients is consistent with previous evidence that aging increases vulnerability to hyponatremia due to age-related impairments in aquaresis, increased arginine vasopressin responsiveness and low solute intake (1). Some studies have reported women to be more prone to hyponatremia than men for reasons that are not fully understood, though this observation is not consistent (1).

The finding that patients with known SIAD had less hyponatremia in warmer weather was unexpected. This may be because fluid restriction is the main treatment strategy for patients with SIAD, and such patients with an established diagnosis may have been educated to avoid excess fluid intake in hot weather. It may still be appropriate for patients to loosen their fluid restriction slightly during hot weather to compensate for increased sweating, but individualized advice is paramount for these patients to avoid dysnatremia. As a note of caution, the diagnosis of SIAD as derived from ICD

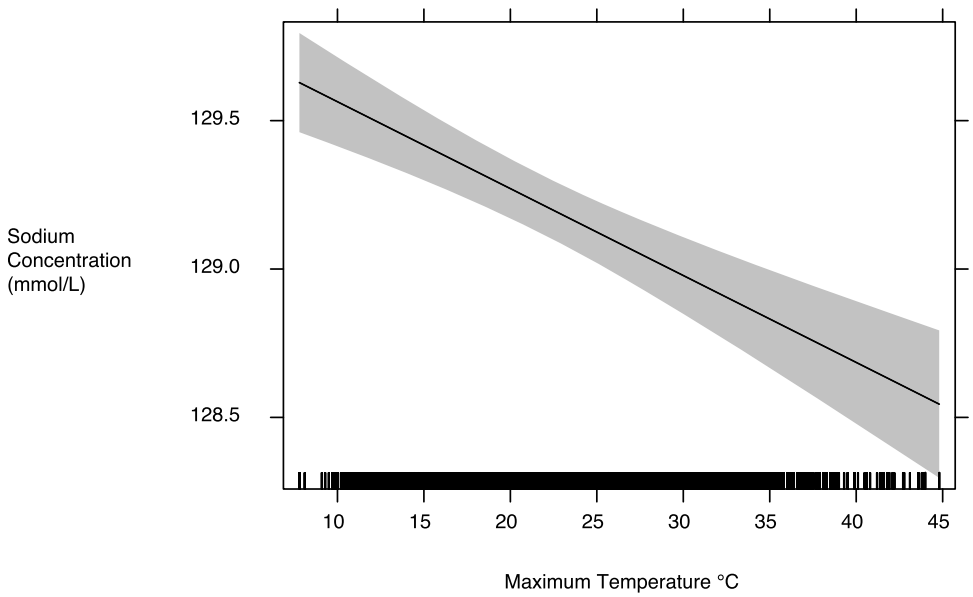

Figure 5. A year-, sex- and age-adjusted linear mixed model to demonstrate the relationship between maximum temperature and sodium.

coding has been known to be inaccurate, so this subgroup is likely an underestimation of the true prevalence in our cohort (25).

The findings of our study extend previous work from mostly temperate regions. A recent systematic review (2) identified 11 studies (3-13) examining the relationship between ambient air temperature and emergency or inpatient admissions with altered sodium concentrations. Seven of these studies were retrospective cohort studies, 3 cross-sectional, and 1 a prospective cohort study. The method of documenting temperatures was heterogeneous, including seasonal, monthly, and daily temperatures or assessing discrete heatwave events. All studies demonstrated lower sodium concentrations during periods of higher temperatures. This finding, however, in 3 studies, was only seen in elderly patients (5, 11, 12), and in 3 other studies this finding was more pronounced in the elderly cohort (3, 7, 8). Two studies also demonstrated a stronger association in women than in men (3, 8). There were several limitations to these studies. Most importantly, study duration in all studies was relatively short, of 6 years or less. All but 3 studies also had study populations of less than 30 000 participants. There were no large-scale studies in Australia.

The strengths of our study include its relatively large sample size due to the long duration (10 years of data collection), careful statistical analyses, and the identification of risk groups, such as older people and women, and the ability to perform a subgroup analysis on patients with SIAD. Other subgroups of potential interest such as patients with diuretic-induced hyponatremia and primary polydipsia were not available for analysis given the impractical number of drug charts to manually review and the lack of specific ICD coding, respectively. Our study did have some limitations inherent to the retrospective design. There were few temperature data missing from the Bureau of Meteorology resource, which is explained in the methods section. However, those were imputed to keep the time series regular and evenly spaced. One of the limitations of our work is that we focused on patients presenting to the emergency department as opposed to ambulatory patients. We did this to have a relatively unbiased sample as virtually all patients presenting to the emergency department have serum sodium measured, whereas for ambulatory patients there may be a specific indication for sodium measurement, which might bias the sample. We also sought to enhance the probability of capturing more clinically significant hyponatremia as patients presenting to the emergency department might be expected to have more profound homeostatic alterations in their serum sodium. However, further work is needed to evaluate the effect of climate events of serum sodium concentrations in ambulatory patients, an important question beyond the scope of our study. Another limitation is that the analyzed serum sodium levels were not corrected for raised glucose, or the potential impact of raised serum lipids or protein (pseudohyponatremia), and did not exclude potential spurious hyponatremia from hemolysis or other sample-related factors. Our study was not designed to examine sequelae of increased hyponatremia rates, such as impact on morbidity and mortality or length of hospital stay; this should be assessed in future prospective studies. This is especially relevant as increasing frequency of heatwaves and therefore hyponatremia admissions are likely to increase in the future with climate change. Future research to more clearly determine the causative factors behind increased hyponatremia presentations with ambient heat will assist formulating prevention and treatment strategies.

In summary, our study demonstrated lower serum sodium concentrations and a higher incidence of profound hyponatremia admissions during warmer weather in Melbourne, Australia, especially in women and older people. We speculate that this might be due to relative excess of consumption of hypotonic fluid when exposed to heat. This may potentially be influenced by outdated public heath advice, though this association between heat and hyponatremia has been observed in other locations globally that may have differing public health messages. Further studies are needed to examine whether tailored public health advice to avoid overhydration during heatwaves might mitigate this excess risk of hyponatremia during warmer temperatures and associated adverse health outcomes. Overall, our findings highlight a climate

associated health issue and, among other health warnings, emphasizes the importance of supporting prompt action on climate change to mitigate its effects on health.

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Disclosures

The remaining authors have no conflicts of interest to declare.

Data Availability

Datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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