Current and future burdens of heat-related hyponatremia - a nationwide register-based study

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Abstract

Context

A seasonal variation in hyponatremia, with higher incidence rates during hot summer days has been demonstrated. Whether this applies to cool temperate regions is currently unknown.

Objective

The aim of this study was to investigate the influence of ambient temperature on hyponatremia in the Swedish population under current and future climate scenarios.

Design, setting and patients

Nationwide cohort study. All patients hospitalized with a first-ever principal diagnosis of hyponatremia between October 2005 and December 2014 were identified. Incidence rates for hyponatremia were calculated as number of hospitalizations divided by person-days at risk in the adult Swedish population at a given temperature, in increments of 1°C.

Results

The incidence of hyponatremia was stable at 0.3 per million person-days from -10°C to 10°C, but increased rapidly at 24h mean temperatures above 15°C, with 1.96 hospitalizations per million days at the highest recorded temperature of 26°C. Women and elderly carried the greatest risk, with an incidence of 30 hospitalizations per million days in individuals ≥80 years old on the hottest days, corresponding to a 15-fold increase in incidence compared to cool days. A future 1°C or 2°C increase in mean temperature is expected to increase the incidence of hyponatremia by 6.3% and 13.9%, respectively.

Conclusion

The risk of hospitalization due to hyponatremia increases rapidly at temperatures above 15°C, indicating a threshold effect. Over the next decades, rising global temperatures are expected to increase the inpatient burden of hyponatremia by approximately 10%. Strategies for protecting vulnerable groups are necessary to reduce this risk.

Key words: age differences; climate change; hot weather; outdoor temperature; sex differences

Introduction

Hyponatremia is the most common electrolyte disorder, affecting up to 30% of hospitalized patients, depending on the severity of underlying diseases(1). The clinical spectrum ranges from mild, non-specific symptoms such as lethargy, gait instability and confusion, to headache, nausea and seizures due to cerebral oedema. Endogenous causes of hyponatremia include a wide variety of diseases such as heart, renal and liver failure, while thiazides(2), antidepressants(3,4) and other pharmaceutical drugs(5-9) have been regarded the most important exogenic factors. However, although less studied, exogenic factors other than drugs are also important. Heat waves have been shown to increase mortality in the overall population, especially among the elderly(10), and seasonal variations in hyponatremia, with increased incidence in the summer months has also been documented(11-13). With few exceptions(14), data on the correlation between outside temperature and severe hyponatremia stems from small studies(15,16). Data on the incidence of hyponatremia associated with different temperatures, which is necessary to predict the health burden of hyponatremia in future climate scenarios, is also lacking. In addition, the identification of any threshold temperature above which the risk of hyponatremia is significantly increased, would be useful in a clinical setting.

Sweden is located in the continental climate zone according to the Köppen-Geiger classification, with the more densely populated areas in the south experiencing warm humid continental climate (Dfb), and with subarctic continental climate (Dfc) in the north(12). Hence, the building standard is mainly adapted for cold, but not hot weather. The prevalence of hyponatremia in Swedish healthcare has not been studied in detail, but estimates are at the lower end of what is reported elsewhere(1,17,18).

The aim of this study was to quantify the effect of increasing outdoor temperatures on the incidence of hospitalization due to hyponatremia, and to approximate the impact of future changes in climate on the incidence of severe hyponatremia.

Materials and Methods

The study was approved by the Regional Ethical Review Board in Stockholm. Informed consent was waived.

This was a retrospective, register-based study encompassing the entire Swedish population over 18 years-of-age. All cases of hospitalization with a first-ever main diagnosis of hyponatremia (ICD-10 E87.1) or SIADH (syndrome of inappropriate secretion of antidiuretic hormone, ICD-10 E22.2) between 1 October 2005 and 31 December 2014 were identified using the National Inpatient Register (NPR). The main diagnosis reflects the clinical condition that first and foremost motivated inpatient care, whereas secondary diagnoses represent significant comorbidities that may or may not have contributed to the need for inpatient care. The day of admission was considered a patient's index day, and for each such index day, the corresponding 24-hour mean (air) temperature of the municipality where the patient lived was retrieved from the Swedish Meteorological and Hydrological Institute (SMHI), a governmental expert agency with access to a comprehensive data on day-to-day observations retrieved from weather stations throughout Sweden(19). From this information, we calculated the number of admissions for each temperature level, at a resolution of 1 degree Celsius. Next, we calculated the total number of person-days exposure to each temperature level in the entire population over the study period. This was achieved by using day-by-day temperature data for each of the 290 municipalities in Sweden from the SMHI-database and census data for these municipalities. Census data was retrieved from Statistics Sweden´s open data(20).

Since census data was only available at a resolution of one year, the population of each municipality was assumed to be constant between 1 January and 31 December each year.

The number of person-days at risk for each temperature was calculated as follows: If the temperature on a given date was, e.g., 21°C in a particular municipality, each citizen living in that municipality at the time contributed with one person-day at risk for the temperature 21°C. Finally, the absolute risk (along with 95% confidence intervals) of being admitted to hospital for hyponatremia was calculated separately for each temperature level by dividing the number of cases associated with that particular temperature by the number of person-days at risk associated with the same temperature. Incidence rates were not calculated for temperatures with less than 10 million exposed person-days due to insufficient statistical power. The analysis was repeated in pre-specified subgroups based on gender and age (18-64, 65-79, and 80- years). In a secondary analysis, 24-hour mean temperature was replaced with 24-hour mean wet bulb temperature (WBT) calculated from 24-hour mean temperature and 24-hour mean relative humidity (both extracted from the SMHI-database). To visualize the seasonal variation in hospitalizations we also calculated the incidence of hospitalizations due to hyponatremia per calendar month.

The future burden of hyponatremia due to climate change was approximated by shifting the temperature curve 1 and 2°C upwards, and assuming that the incidence of hyponatremia for the highest predicted temperature strata in the model was equal to the incidence of hyponatremia in the highest stratum under current climate conditions. The 1 and 2°C increase in temperature was chosen based on the Sixth Assessment Report of the Intergovernmental Panel on Climate Change published in 2021(21), that predicts a rise in mean global temperatures of 0.6-1.4°C by 2050, depending on future carbon emissions, and a larger impact on continental and arctic regions than on tropical/subtropical regions.

All analyses were performed using R version 3.6.1 (ref: R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. (URL https://www.R-project.org/.).

Results

During the study period, 11,213 individuals over 18 years of age were hospitalized with a principal diagnosis of hyponatremia. The majority were of female gender (72%) and the median age (range) was 76 (18-103) years. The most common accompanying medical conditions were previous/current malignant disease, ischemic heart disease and diabetes (**Table 1**).

The incidence of hyponatremia was lowest in January and increased gradually towards the summer period peaking in July (**Figure 1**).

To investigate the effect of temperature we calculated the association between exposures for increasing 24-hour mean temperatures and incidence of hospitalizations due to hyponatremia. For the overall population, the number of hospitalizations was quite stable at approximately 0.3 per million person-days for temperatures up to 10°C. The incidence increased marginally up to 15 °C and then rapidly to the highest recorded temperature of 26°C with 1.96 hospitalizations per million days at risk (**Figure 2**).

The effect was then investigated in various subgroups. Although the risk differed widely between subgroups, a relatively stable baseline incidence at temperatures below 10°C, and a rapid increase in incidence at higher temperatures, was evident in all subgroups. The baseline risk among men and women was approximately 0.2 and 0.4 hospitalizations per million days, respectively. For men, the incidence peaked at 0.59 hospitalizations per million days at 26°C, with the corresponding risk for women being 3.3 hospitalizations per million days (**Figure 3**). Among individuals 18 to 64-years of age (regardless of sex) the baseline risk was low at around 0.15 hospitalizations per million days at temperatures below 10°C, with a modest increase to approximately 0.3 hospitalizations per million days during heatwaves. In the elderly age groups, both baseline risks and the effect of rising temperatures was more prominent. Thus, among 65 to 79-year-olds, the risk at low and high temperatures was around 0.8 and 3.6 hospitalizations per million days, respectively. Among individuals 80 years or older, the corresponding incidences were 2.0 and 30 hospitalizations per million days (**Figure 4**).

According to the climate change model, a 1°C increase in temperature resulted in an 6.3% overall increase in the incidence of hospitalization due to hyponatremia. Under the 2°C scenario, the incidence of hyponatremia increased by 13.9%. Incidence rate estimates based on wet bulb temperatures were only marginally different from estimates based on temperature alone (**Supplemental Figures 1-3**)(22).

Discussion

Using Swedish population-based data collected over a 9-year period, we were able to demonstrate an almost tenfold increased risk for hospitalization due to hyponatremia during the days with the highest temperatures. Women and elderly seemingly carried the greatest risk, with individuals 80 years or older 15 times more likely to be hospitalized for hyponatremia during heat waves. Over the next decades, the need for inpatient care of hyponatremia is expected to increase by 6-14% due to rising temperatures alone.

Our findings are consistent with previous studies, demonstrating an increased risk of hyponatremia during the summer months(11-13) and during periods with high ambient temperatures(14-16,23). However, the 10-15-fold increase in risk is larger than previously reported. This is partly explained by the population-based approach and the large study sample, enabling us to investigate relatively small temperature intervals in a spectrum including unusually high temperatures. In addition, the marked differences in risk as compared to older studies can also be explained by differences in outcome measures. The association between hyponatremia and high outdoor temperatures is most prominent for profound hyponatremia (<125mmol/L)(12,14). and a main ICD-diagnosis of hyponatremia typically reflect low sodium levels. In a validation study on a subset of patients included in our cohort, the mean serum sodium was 121 mmol/L(3), consistent with severe hyponatremia. Using a similar outcome measure, Kutz et al. examined seasonal variations in the prevalence of primary or secondary discharge diagnoses of hyponatremia among medical inpatients in Switzerland(11). Hyponatremia was significantly more common in the summer months, with an apex in July (4.5%) and a nadir in January (3.2%). The increase in prevalence during the summer months was paralleled by a gradual increase in mean outdoor temperature, but day-to-day temperatures were not taken into account. In another large, population-based Swiss study, Sailer et al. demonstrated increased odds ratios for profound hyponatremia with increasing temperatures, but their methodologic approach did not permit analysis of the risk associated with specific temperatures(14).

Interestingly, the incidence of hyponatremia in the present study was fairly stable across strata from -10°C to 10°C, albeit with varying baseline risks in subgroups. This contrasts with findings from the study by Sailer et al., that suggested an increase in risk of profound hyponatremia not only at high temperatures, but also during cold spells(14). Although a sharp increase in risk at mean daily temperatures above 15°C was observed across all subgroups, the relative impact appeared to be more pronounced among individuals carrying the highest baseline risk.

The risk of severe hyponatremia was approximately twice as high for women as for men (0.4 vs 0.2 hospitalizations per million days) on cool days, but at the highest temperatures, women experienced a 5 times higher risk than men (3.3 vs. 0.59 hospitalizations per million days at 26°C). The influence of age was even more pronounced. Compared to the youngest cohort (18-64 years), individuals 80 years or older were at a 10 times higher risk of hospitalization for hyponatremia at -10 to 10°C, and at a 15-fold higher risk at extreme temperatures (30 vs 2 hospitalizations per million days at 26°C) (Figure 4). These results are in line with previous studies, demonstrating higher risk among women and elderly(11,12,14). The influence of humidity appeared to be small, with marginal differences in risk estimates based on wet bulb temperature (**Supplemental Figures 1-3**)(22), which takes humidity into account, compared to estimates based on temperature alone. This observation is consistent with findings from other temperate climate settings(14), but in tropical/subtropical regions, humidity may be of greater importance for the risk of developing hyponatremia (24).

Following the 2003 heat wave in Europe, surveillance systems and public health plans designed to improve adaptation to extreme heat were implemented in several European countries. Over the next decade, excess mortality due to heat decreased in metropolitan areas of continental Europe, but not in the Nordic countries(25). Poor public awareness about the negative impact of extreme temperatures, and lack of strategies for protecting vulnerable subgroups have been cited as likely explanations for these differences(25,26).

The causal pathways by which high ambient temperatures lead to hyponatremia are not completely understood, and they cannot be explored in this study. Fluid and electrolyte losses through sweating and use of diuretics, in combination with intake of hypotonic fluids, has been proposed as an important mechanism (14). Still, most cases of diuretic-induced hyponatremia are caused by thiazides (9), and paradoxically, the pathophysiologic mechanism in thiazide induced hyponatremia involves fluid retention more than loss of electrolytes (27). The ability to increase sweating in response to rising ambient temperatures declines with age(28), much the same as the ability to excrete free water(29). Therefore, excessive fluid intake, with or without preexisting SIADH, may also be important causes of heat related hyponatremia.

Temperature thresholds, at which heat-related deaths accelerate, are known to vary by geographical location(30), which could be an effect of behavioral adaptations to local climates. The same is most likely true for hyponatremia, and the 15°C threshold observed in this study may therefore be representative for cool temperate regions only. The prevalence of profound hyponatremia (<125 mmol/L) in Emergency Departments or on admission to hospital varies greatly across regions. However, estimates originating from hot humid regions, exemplified by Australia, Singapore and Taiwan(31-33) are higher than estimates originating from temperate regions(14,18,34). This could reflect fundamental differences in healthcare systems, but it is consistent with higher ambient temperatures leading to hyponatremia. While rarely fatal in itself, hyponatremia is associated with increased length of hospital stay and higher readmission rates(35), and without adaptive measures the increased burden of hyponatremia and other heat-related morbidities will strain the healthcare system(36).

Strengths and limitations

A major strength of the present study is the population-based design and the inclusion of all individuals with hospitalizations due to hyponatremia in the adult Swedish population. This is also the first study to demonstrate a threshold effect for heat related hyponatremia, rather than a supposedly linear increase in risk, much the same as for heat-related mortality. The lack of clinical and laboratory data, most notably serum sodium values, is a limitation to this study. In a Danish population-based study, the sensitivity of a hyponatremia diagnosis (main or secondary) ranged from 1.8% for mild forms to 34% for serum sodium levels <115mmol/L(37). Thus, the burden of hyponatremia is considerably larger than suggested by the incidence rates presented in this study. Still, using only the main diagnosis, which reflects the clinical condition primarily motivating inpatient care, enabled us to isolate cases of clinically relevant hyponatremia. Consequently, the observed changes in risk with rising temperatures should reflect an increase in inpatient burden primarily caused by hyponatremia, rather than associated conditions. A further limitation to this study is that the climate prediction model is crude, and likely underestimates the effects of climate change, as extreme weather events are expected to increase more than mean temperatures. Also, it does not take changes in demographics into account. With the oldest-old (≥ 80 years) population in Sweden expected to double within 30 years(20), this will compound the effects of climate change on hyponatremia.

In conclusion, the present study shows that the risk of hospitalization due to hyponatremia increases drastically above threshold temperatures, and that women and elderly are particularly vulnerable. This finding suggests that over the next decades, rising global temperatures alone will increase the inpatient burden of hyponatremia by approximately 10%. It should be noted that the current study does not address the incidence of hyponatremia in outpatient settings, as only cases requiring hospital admission were included in the analysis.

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Authors contributions: JS, JL and BM conceived and designed the study. JL conducted statistical analyses. All authors interpreted the results. BM and JS wrote the manuscript, and all authors revised the manuscript.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable requests.

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Figure Legends

Figure 1: Shaded area indicates 95% confidence interval.

Figure 2: Shaded area indicates 95% confidence interval.

Figure 3: Shaded areas indicate 95% confidence intervals.

Figure 4: Shaded areas indicate 95% confidence intervals.

Table 1 Baseline characteristics

	Hospitalizations due to hyponatremia (n=11,213)
Age, years (median, interquartile range)	76 (65; 84)
Female gender	8,074 (72.0%)
Diagnosis	
Malignancy	3,096 (27.6%)
Ischemic heart disease	2,186 (19.5%)
Diabetes mellitus	1,939 (17.3%)
Alcoholism	1,764 (15.7%)
Congestive heart failure	1,453 (13.0%)
Cerebrovascular disease	1,448 (12.9%)
COPD	1125 (10.0%)
Renal disease	489 (4.4%)
Liver disease	421 (3.8%)
Antidepressants	2,817 (25.1%)
Antiepileptic drugs	1,061 (9.4%)
Thiazide diuretics	1,983 (17.7%)

Figure 1 Incidence of hospitalizations due to hyponatremia per calender month

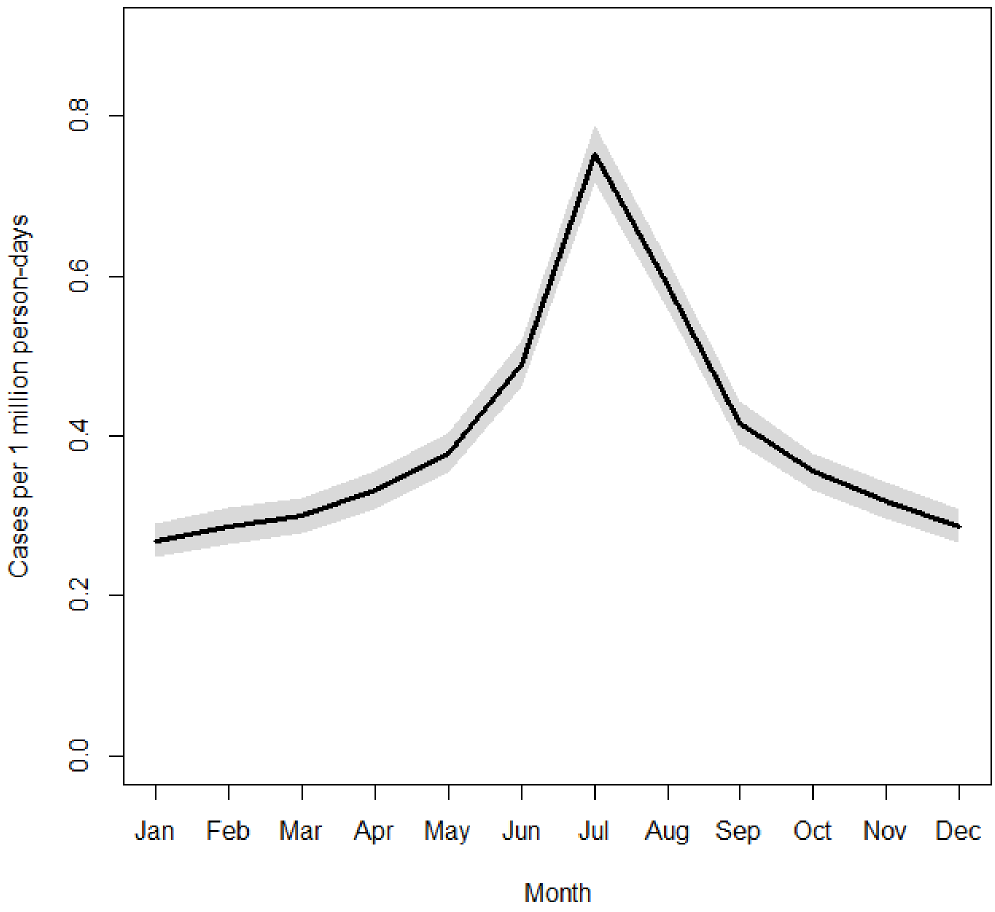

Figure 2 Incidence of hospitalizations due to hyponatremia according to temperature (°C).

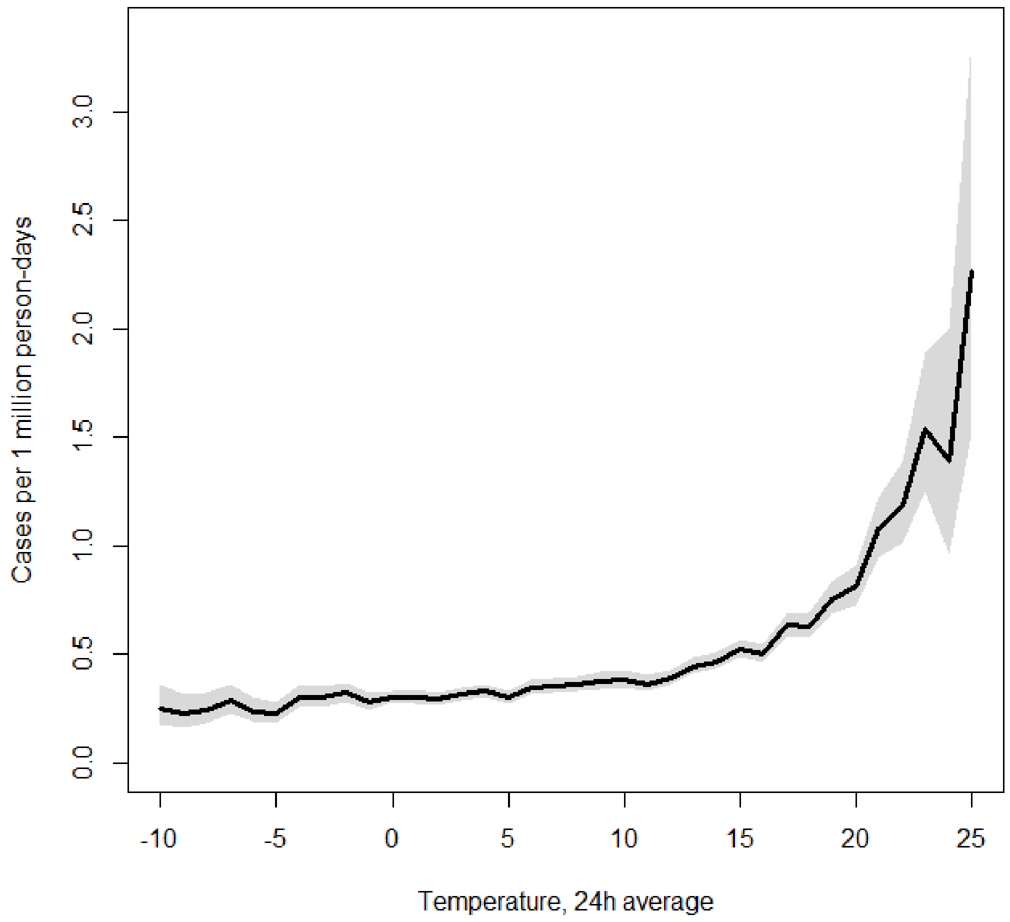

Figure 3 Incidence of hospitalizations due to hyponatremia according to temperature (°C) in men and women. The y axis is logarithmized to facilitate comparison of relative risks associated with increasing temperatures.

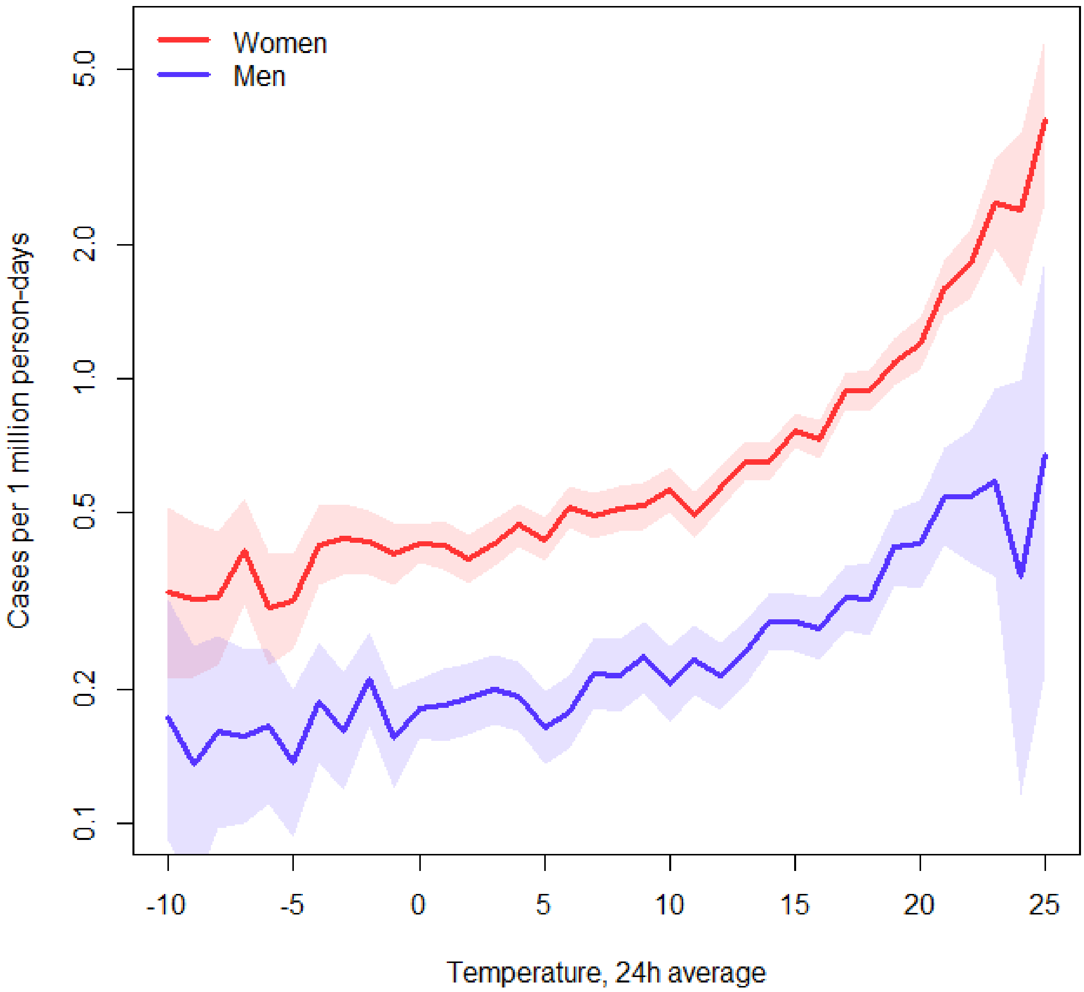

Figure 4 Incidence of hospitalizations due to hyponatremia according to temperature (°C) in different age groups. The y axis is logarithmized to facilitate comparison of relative risks associated with increasing temperatures.