Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 19 December 2016, doi:10.4414/smw.2016.14385

Cite this as: Swiss Med Wkly. 2016;146:w14385

Profound hyponatraemia in the emergency department: seasonality and risk factors

Tibor Huwyler[a], Jérôme Stirnemann[b], Nicolas Vuilleumier[c], Christophe Marti[a,b], Sarah Dugas[a], Pierre-Alexandre Poletti[a], François P. Sarasin[a], Olivier T. Rutschmann[a,b]

[a] Emergency Department, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

[b] General Internal Medicine Department, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

[c] Genetic and Laboratory Medicine Department, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Summary

AIMS OF THE STUDY: Profound hyponatremia (<125 mmol/l) is frequent in the emergency department. Its incidence appears to increase during hot weather. Our objectives were to investigate seasonal variations in the incidence of profound hyponatraemia and identify its risk factors.

METHODS: The incidence of profound hyponatremia among patients admitted to the emergency department of a university hospital was compared between summer and winter periods over two successive years. Risk factors for profound hyponatraemia were analysed in a case-control retrospective study. Each adult patient admitted during the study periods with a blood sodium level <125 mmol/l was matched with two patients who had normal blood sodium concentrations.

RESULTS: Of 28 734 analysed patients, 264 cases of profound hyponatraemia (0.92%) were identified. The incidence of profound hyponatraemia was higher in summer than in winter (1.29% vs 0.54%; odds ratio [OR] 2.39, 95% confidence interval [CI] 1.83–3.12). In a multivariate analysis, age (OR 1.02, 95% CI 1.01–1.03), psychiatric disorders (OR 2.69, 95% CI 1.86–3.89), and use of thiazide diuretics (OR 7.79, 95% CI 4.73–12.85) or potassium-sparing diuretics (OR 4.69, 95% CI 2.31–9.52) were associated with increased risk. Mortality was higher in cases than in controls (11.7% vs 6.9%, OR 1.75, 95% CI 1.05–2.92).

CONCLUSIONS: The incidence of profound hyponatraemia was higher during the summer than the winter and was associated with excess risk of overall mortality. The use of thiazide and potassium-sparing diuretics was associated with the highest risk of hyponatraemia.

Key words: *hyponatraemia; hot temperature; seasonal variation; diuretics*

Introduction

Hyponatraemia is among the most commonly encountered electrolyte disorders in emergency departments. Even though profound hyponatraemia (<125 mmol/l) carries with it high morbidity and mortality, only a limited number of studies have investigated the incidence of this disorder and its risk factors in patients admitted to emergency departments [1].

Among the risk factors for profound hyponatraemia, intense physical exercise is frequently reported, as well as, to a lesser extent, exposure to high temperatures [2, 3]. Thus, an increase in hyponatraemia cases was observed during the 2003 European heatwave in patients admitted to emergency departments for heatstroke [4]. Following that particularly dramatic period of heatwave, which resulted in 14 000 deaths in France and more than 950 in Switzerland, a syndromic surveillance system was launched in France [5, 6]. It was able to identify hyponatraemia as a sensitive indicator of the effects of heat on the human body, but could not assess the severity, type and cause of the hyponatraemia cases observed [7].

Over the summers of 2013 and 2015, an uncommon number of cases of profound hyponatraemia (<125 mmol/l) was observed at the emergency department of Geneva University Hospitals (GUH), especially in elderly patients. This led us to hypothesise an association between weather conditions, patient characteristics and the risk of hyponatraemia.

The objectives of our study were to: (1) determine the incidence and seasonality of profound hyponatremia, and its correlation with weather conditions (daily temperature and Heat Index); (2) describe the types and aetiologies of the hyponatraemia cases; (3) identify the risk factors for hyponatraemia; (4) determine the impact of profound hyponatraemia on hospital mortality.

Methods

Study design

The incidence of profound hyponatraemia among patients admitted to the emergency department of a university hospital was compared between the summer and winter periods in a retrospective cohort study. Risk factors for profound hyponatraemia were analysed in a case-control retrospective study.

Participants and setting

All adult patients (16 years old) who had their blood sodium levels measured at the emergency department of GUH during the summer (June, July and August) and the winter periods (December, January and February) of two successive years (2011–2012 and 2012–2013) were included. The emergency department of GUH, which is the only public university hospital of the city and canton of Geneva, admits around 65 000 adult patients every year. Patients with blood sodium levels of less than 125 mmol/l were identified. When blood glucose was elevated, blood sodium concentrations were corrected for plasma glucose levels [1]. After correction, all patients with blood sodium levels of less than 125 mmol/l were considered as profound hyponatraemia cases [1].

All hyponatraemia cases (<125 mmol/l) were matched with two controls. Controls were identified on the basis of three criteria: (1) normal blood sodium levels of 135–144 mmol/l; (2) admission in the 48 hours before or after the admission of the case; (3) a care trajectory identical to that of the case (hospitalised in the same department or returned home).

Variables

The incidence of profound hyponatraemia was reported as a proportion of the total number of patients included and was compared between two seasons (summer vs winter) over two successive years (2011–2012 and 2012–2013).

In order to evaluate the impact of maximum daily temperature on the incidence of profound hyponatraemia, meteorological data were obtained from the Geneva station of the Swiss Federal Office of Meteorology and Climatology and the heat index (HI) was calculated. The HI represents the temperature felt by the body based on relative humidity and ambient air temperature. The incidence of profound hyponatraemia during the days when the HI reached or exceeded the value of 90 was recorded. This was only done in the summer months, as the HI never reaches 90 in winter.

Types of profound hyponatraemia cases were classed according to patient volaemic status (hypo-, normo- or hypervolaemic) and mechanism in accordance with the guidelines of the European Society of Endocrinology, the European Society of Intensive Care Medicine, the European Renal Association, and the European Dialysis and Transplant Association [1].

To identify the types, risk factors and impact of profound hyponatraemia, three types of data were extracted from electronic patient files: (1) demographic and trajectory data (gender, age, place of residence, date of admission to the emergency department, duration of stay in the emergency department and duration of hospitalisation, death during stay); (2) laboratory data (blood sodium level, blood osmolarity, urine sodium level, urine osmolarity, urea and plasma creatinine level, glomerular filtration rate calculated using the CKD-EPI formula, glycaemia); (3) clinical data (initial diagnoses, active comorbidities on admission, diuretics on admission). Volaemic status was evaluated through a standardised chart review performed by two primary investigators including emergency department medical records, admission and discharge notes, and specialised consultations, in addition to laboratory results (urine and blood analyses).

Ethics approval

The study received approval from the central ethics committee (CER 14-090R). The protocol was registered on Clinicaltrials.gov (NCT02012660).

Statistical analyses

Data analysis was performed with the SPSS program for Windows (Chicago, IL, Version 18.0.0) and the R program (the R Foundation for Statistical Computing, Version 3.1.1). Descriptive statistics (proportions, means and standard deviation [SD]) were generated for each of the case and control characteristics. These items were compared between cases and controls using the Mann-Whitney U test for means and Fisher's exact test for proportions. A p-value of less than 0.05 was considered statistically significant.

A logistic regression model including all clinically relevant variables was constructed to identify factors significantly associated with developing profound hyponatremia after adjustment (adjusted odds ratios [ORs]). For each OR, confidence intervals at 95% were calculated (95% CI). Similarly, a logistic regression model was built in order to evaluate the impact of hyponatraemia on mortality, with adjustment for potential confounders such as age, gender and comorbid conditions. In order to evaluate the impact of maximum daily temperature on the daily number of profound hyponatraemia cases, a lambda parameter was calculated with use of a Poisson model.

Results

Incidence of profound hyponatraemia and meteorological data

Over the summers of 2012 and 2013 and winters of 2011–2012 and 2012–2013, 28 734 patients had their blood sodium levels tested at the emergency department. Of these, 282 patients with blood sodium levels <125 mmol/l were identified. These values were corrected for plasma glucose levels when blood glucose was elevated. After this correction, 264 (0.92%) profound hyponatraemia cases were identified and were matched to 528 controls. The incidence of profound hyponatraemia was 0.54% (78/14 333) in winter and 1.29% (186/14 401) in summer (OR 2.39, 95% CI 1.83–3.12).

The criteria for a heatwave alert (HI ≥90) were met for 3 days in the summer of 2012 and 11 days in the summer of 2013. No case of profound hyponatraemia occurred during these days.

A significant association was observed between daily temperature and daily number of profound hyponatraemia cases (lambda parameter 0.036, p <0.001) (fig. 1). When analysis was restricted to summer periods, the lambda parameter was 0.018 (p = 0.28).

Types and mechanisms of profound hyponatremia cases

Mean blood sodium (± SD) in patients with profound hyponatraemia was 118 mmol/l (±4.3), the lowest individual value being 104 mmol/s. Mean calculated plasma osmolarity was 257 mosmol/l (±16). Mean urine sodium was 45 mmol/l (±36) and mean urine osmolarity was 314 (±146). Glomerular filtration rate was <30 ml/min/1.73 m^2 in 9.8% of the population and <10 ml/min/1.73 m^2 in 1.1% of the patients. Most patients were normovolaemic (51%), with 31% hypovolaemic and 18% hypervolaemic.

The most frequently identified mechanisms of profound hyponatraemia are summarised in table 1. There was no statistically significant difference on the distribution of hyponatraemia mechanisms between summer and winter periods. All cases of polydipsia were identified in patients suffering from psychiatric disorders. In this population, the use of diuretics was less frequently identified as the mechanism of hyponatraemia (21.0%) than in the population of patients without psychiatric disorders (diuretics as the mechanism of hyponatraemia in 32.9% of the cases).

Risk factors for profound hyponatraemia

Case and control characteristics and discharge diagnoses are described in table 2. On univariate analysis, cases were on average older than controls (73.0 vs 67.0 years), were more often women (59.5% vs 50.8%), and a greater proportion of them suffered from psychiatric disorders. Similarly, diuretics, particularly thiazide and potassium-sparing diuretics, were more commonly used in cases than in controls (50.8% of cases on diuretics vs 23.3% of controls).

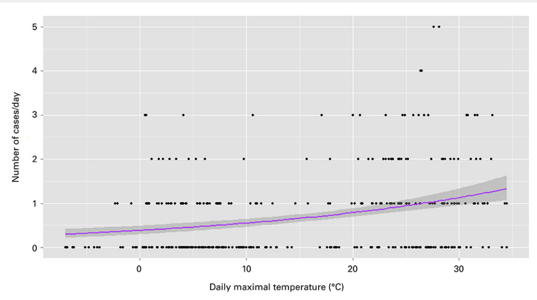

Figure 1

Poisson regression exploring the association between the daily number e of profound hyponatremia cases with maximum daily temperature (°C). Lambda parameter 0.036, p <0.001. Figure was created using R program (the R Foundation for Statistical Computing, Version 3.1.1)

In the multivariate analysis model (table 4) that included gender, age, diuretics and comorbidities (heart failure, cirrhosis, kidney failure, diabetes, cancer, cognitive disorders and psychiatric disorders), five variables were associated with an increased risk of profound hyponatraemia. Thus, age increased the risk of developing profound hyponatraemia (OR 1.02, 95% CI 1.01–1.03 for each additional year of age), as did psychiatric disorders (OR 2.69, 95% CI 1.86–3.89). Thiazide diuretics (OR 7.79, 95% CI 4.73–12.85) and potassium-sparing diuretics (OR 4.69, 95% CI 2.31–9.52) were also associated with an increased risk of profound hyponatraemia. Cognitive disorders were associated with a reduced risk of developing profound hyponatraemia (OR 0.56, 95% CI 0.34–0.91).

Prognostic impact of hyponatraemia

The presence of profound hyponatraemia was associated with excess all-cause in-hospital mortality (11.7% in cases vs 6.9% in controls). After adjustment for age, sex, comorbid conditions and the presence of profound hyponatraemia, the only factors associated with an increased risk of death were age, male gender, the presence of cancer and profound hyponatraemia (adjusted OR for profound hyponatraemia 1.75, 95%CI 1.05–2.92) (table 5).

Discussion

Hyponatremia is commonly observed in emergency departments and may be associated with an excess of mortality, especially when profound (<125 mmol/l) [1]. In the population of patients admitted to the emergency department and who had their blood sodium levels tested, 0.92% had profound hyponatremia. This incidence was higher in summer than in winter. Risk factors for developing profound hyponatraemia were the use of thiazide and potassium-sparing diuretics, age and psychiatric disorders.

The incidence rate of hyponatraemia observed in emergency departments varies between studies. The incidence of 1.4% reported by Lee et al. during a summer period is close to our observation during the summers of 2012 and 2013 [8]. Two studies have reported lower incidence rates (0.3–0.4% over the course of a whole year) [9, 10]. This may be due to a lower threshold for profound hyponatremia (121 mmol/l) than the one chosen in our study and to different observation periods.

Table 1: Mechanisms of profound hyponatremia during summer and winter periods.

Mechanisms of hyponatraemia	**Total (n = 264)** **n (%)**	**Summer (n = 186)** **n (%)**	**Winter (n = 78)** **n (%)**
Use of diuretics	75 (28.4%)	50 (26.9%)	25 (32.1%)
SIADH	47 (17.8%)	34 (18.3%)	13 (16.7%)
Extrarenal loss	24 (9.1%)	17 (9.1%)	7 (9.0%)
Heart failure	15 (5.7%)	9 (4.8%)	6 (7.7%)
Renal loss	17 (4.2%)	7 (3.8%)	4 (5.1%)
Polydipsia	8 (3.0%)	5 (2.7%)	3 (3.8%)
Reduced salt intake	7 (2.7%)	5 (2.7%)	2 (2.6%)
Cirrhosis	6 (2.3%)	3 (1.6%)	3 (3.8%)
Third spacing	4 (1.5%)	3 (1.6%)	1 (1.3%)
Adrenal insufficiency	1 (0.4%)	1 (0.5%)	0 (0%)
Undefined	66 (25.0%)	52 (28.0%)	14 (17.9%)

SIADH = syndrome of inappropriate antidiuretic hormone secretion

The link between ambient temperature and the incidence of hyponatraemia has been the subject of relatively few investigations. Following the 2003 heatwave, the French syndromic surveillance system OSCOUR showed that cases of hyponatraemia were more frequent during heatwaves and associated with a mortality excess [7]. Similarly, an American study in more than 25 million patients over 10 years demonstrated an increased risk of developing an electrolyte disorder during periods of very hot weather [11]. During those heatwaves, dehydration was the most common

Table 2: Discharge diagnosis categories.

Diagnostic categories	Total, n = 792 n (%)	Cases, n = 264 n (%)	Controls, n = 528 n (%)
Infectious diseases	172 (21.7%)	47 (17.8%)	126 (23.7%)
Cardiovascular diseases	122 (15.4%)	29 (11.0%)	93 (17.6%)
Trauma	60 (7.6%)	11 (4.2%)	49 (9.3%)
Neurological diseases	59 (7.4%)	10 (3.8%)	49 (9.3%)
Hyponatraemia	57 (7.2%)	56 (21.2%)	1 (0.2%)
Psychiatric disorders	54 (6.8%)	25 (9.5%)	29 (5.5%)
Lung diseases	51 (6.4%)	15 (5.7%)	36 (6.8%)
Cancer	44 (5.6%)	15 (5.7%)	29 (5.5%)
Gastrointestinal diseases	42 (5.63)	18 (6.8%)	24 (4.5%)
Haemorrhage	24 (3.0%)	8 (3.0%)	16 (3.0%)
Generalised weakness	20 (2.5%)	7 (2.7%)	13 (2.5%)
Renal diseases	18 (2.3%)	3 (1.1%)	15 (2.8%)
Rheumatological diseases	15 (1.9%)	6 (2.3%)	7 (1.3%)
Others	42 (5.3%)	11 (4.2%)	31 (5.9%)

Table 3: Characteristics of cases (patients with profound hyponatremia) and controls (patients with normal blood sodium levels).

Variables	Cases Profound hyponatraemia (n = 264)	Controls Blood sodium in normal range (n = 528)	p-value*
Age in years, mean ± SD (min-max)	73.0 ± 14.7 (27–97)	67.0 ± 20.9 (16–100)	<0.001
Male, n (%)	107 (40.5)	260 (49.2)	0.02
Comorbidities, n (%)			
Heart failure	47 (17.8)	94 (17.8)	1
Liver cirrhosis	16 (6.1)	17 (3.2)	0.09
Renal failure GFR <30 ml/min/1.73 m^2 GFR <10 ml/min/1.73 m^2	87 (33.0) 26 (9.8) 3 (1.1)	159 (30.1) 53 (10.0) 10 (1.9)	0.41
Diabetes	61 (23.1)	94 (17.8)	0.09
Cancer	39 (14.8)	65 (12.3)	0.37
Cognitive disorder	39 (14.8)	94 (17.8)	0.31
Psychiatric disorder	100 (37.9)	120 (22.7)	<0.001
Diuretics on admission, n (%)	134 (50.8)	123 (23.3)	<0.001
Loop diuretic	60 (22.7)	95 (18.0)	0.13
Thiazide diuretic	87 (31.1)	27 (5.1)	<0.001
Potassium-sparing diuretic	35 (13.3)	18 (3.4)	<0.001
In-hospital death, n (%)	33 (11.7)	39 (6.9)	0.03

GFR = glomerular filtration rate; SD = standard deviation
* Mann-Whitney U test and Fisher's exact test

Table 4: Risk factors for profound hyponatraemia in a multivariate analysis model.

Variables	Adjusted OR (95% CI)
Age (for each additional year)	1.02 (1.01–1.03)
Female	1.19 (0.84–1.68)
Heart failure	0.65 (0.40–1.67)
Liver cirrhosis	0.88 (0.37–2.12)
Kidney failure or nephrotic syndrome	1.00 (0.68–1.47)
Diabetes	1.36 (0.89–2.07)
Cancer	1.57 (0.97–2.54)
Cognitive disorder	0.56 (0.34–0.91)
Psychiatric disorder	2.69 (1.86–3.89)
Loop diuretic	1.02 (0.64–1.64)
Thiazide diuretic	7.79 (4.73–12.85)
Potassium-sparing diuretic	4.69 (2.31–9.52)

CI = confidence interval; OR = odds ratio complication, followed by hyponatraemia (<135 mmol/l). However, these two studies did not specifically identify cases of profound hyponatraemia, which are particularly at risk of severe complications. This made comparison with our data impossible. Only one study has directly investigated the relationship between heat and electrolyte disorders, and more particularly the risk of profound hyponatraemia [12]. Over two consecutive years, 0.85% of emergency admission patients had profound hyponatraemia. In that study, a significant inverse correlation was found between temperature variations and blood sodium values. Our findings revealing a link between periods of hot weather and profound hyponatraemia corroborate this correlation. As with our observations, very few heatwave periods were recorded in that study and no link could be made between those brief periods of heatwave and an increased risk of hyponatraemia [12].

Several hypotheses may explain the increased risk of profound hyponatraemia during summer periods. The Swiss Federal Office of Public Health recommends that the elderly increase their water intake (>1.5l/d) from the beginning of summer, and these recommendations are widely disseminated in the general population and passed on by home care bodies and in day care centres. These recommendations are usually disseminated at the beginning of summer even when no heatwave alert (HI ≥90) has been officially declared. Excessive free water intake may be a contributing factor to seasonal hyponatraemia [7, 12]. The fact that most of our cases were not hypovolaemic on admission and that the proportion of hypovolaemic patients did not significantly differ between winter and summer (37% in winter vs 29% in summer) may support this hypothesis.

Another aggravating factor may be the continuation of thiazide diuretic therapy despite very hot weather. The use of diuretics has been recognised to be associated with serious conditions in patients admitted to the emergency department [13]. National guidelines suggest that diuretics may negatively impact patient outcome in summer and international experts strongly recommend using diuretics with caution in the elderly because of the high risk of hyponatraemia [14]. Despite these recommendations, the proportion of patients receiving diuretics was identical in winter and summer (46% in winter vs 53% in summer) and thiazide or potassium-sparing diuretics were the most commonly identified factors contributing to profound hyponatraemia. Although we did not observe differences between the proportion of patients with diuretic-induced hyponatraemia in winter and summer, we can speculate that the combination of continuing thiazide or potassium-sparing diuretics and increasing water intake may heighten the risk of hyponatraemia.

Various risk factors for profound hyponatraemia were identified in our study. We found that the risk of hyponatraemia rose with age, as previously described [15, 16]. Diuretics, mainly thiazides, are recognised as major risk factors for developing hyponatraemia [14, 17, 18]. Our study confirmed the risk associated with using thiazides and also highlighted the risk associated with potassium-sparing diuretics, suggested by Liamis et al. [15]. Although this occurs less frequently than with thiazides, potassium-sparing diuretics interfere with renal concentration mechanisms, leading to hyponatraemia [15].

The increased risk of hyponatraemia in patients with psychiatric disorders has not been specifically reported in other studies. This heightened risk may be due to the use of psychotropics in that population, as these drugs are usually associated with the syndrome of inappropriate antidiuretic hormone secretion [1, 9, 19, 20]. Unfortunately, we did not specifically record the use of medications other than diuretics, and therefore could not confirm this hypothesis [15, 21, 22].

As previously described, high in-hospital mortality (11.7%) was observed in patients who had profound hyponatraemia on admission [10, 12, 15, 23]. This may be explained by various factors such as age, frequent comorbid conditions such as cancer, heart failure or cirrhosis, and severe admission conditions such as sepsis and stroke.

Our study has various limitations. First, it was a retrospective study, which investigated variables that were not systematically recorded in the emergency department, resulting in possible information bias. Second, the clinical evaluation of volaemic status has low specificity and sensitivity, which may lead to misclassification bias [1]. Consequently, the mechanism of hyponatraemia could not be established in a relatively high proportion of our cases. In addition, we used calculated osmolarity to classify our patients, which may underestimate osmolarity in patients with alcohol intoxication, lactic acidosis, ketoacidosis, advanced chronic kidney diseases, masked hyperlipidaemia or hyperproteinaemia. Third, our cases and controls were selected from patients who came to the emergency department and had their blood sodium levels tested. It is logical to suppose that such a population, being more ill than patients who did not have a blood test, may not accurately reflect the general population. Fourth, our matching based on a comparable hospital trajectory between cases and controls and time of arrival at the emergency department may be questioned in comparison with conventional matching based on age and gender. Matching based on destination on

Table 5: Risk factors for in-hospital mortality in a multivariate analysis model.

Variables	Adjusted OR (95%CI)
Age (for each additional year)	1.02 (1.001–1.04)
Male	1.84 (1.08–3.12)
Heart failure	1.06 (0.56–2.01)
Kidney failure or nephrotic syndrome	1.64 (0.96–2.81)
Diabetes	1.58 (0.90–2.78)
Cancer	3.45 (1.95–6.01)
Profound hyponatremia	1.75 (1.05–2.92)

CI = confidence interval; OR = odds ratio leaving the emergency department allowed us to analyse the impact of age and gender on the occurrence of profound hyponatraemia, and multivariate models were used to take account of potential confounders. Lastly, our medication assessment was limited to diuretics as these drugs are usually recognised as being a high risk for hyponatraemia or other serious conditions [13]. Therefore we were not able to analyse the impact of other medications such as psychotropic drugs or nonsteroidal anti-inflammatory drugs, on the risk of profound hyponatraemia.

In conclusion, profound hyponatraemia was more common during summer periods than winter periods. This difference was partly due to temperature variations. The most common mechanism of profound hyponatraemia was the use of thiazide or potassium-sparing diuretics. Our observations should encourage doctors to be cautious regarding the use of thiazide and potassium-sparing diuretics during the summer. Closer monitoring of electrolytes during the summer period could be a way to prevent the development of hyponatraemia in patients taking these diuretics.

Acknowledgments: The authors wish to thank Olivier Golaz, Emmanuel Durand, and Rodolphe Meyer of GUH for obtaining computerised data.

Disclosure statement: No financial support and no other potential conflict of interest relevant to this article was reported.

Correspondence: *Olivier T. Rutschmann, MD, MPH, Geneva University Hospitals, Emergency Department, 2 rue Gabrielle Perret-Gentil, CH-1205 Geneva, olivier.rutschmann[at]hcuge.ch*

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Figures (large format)

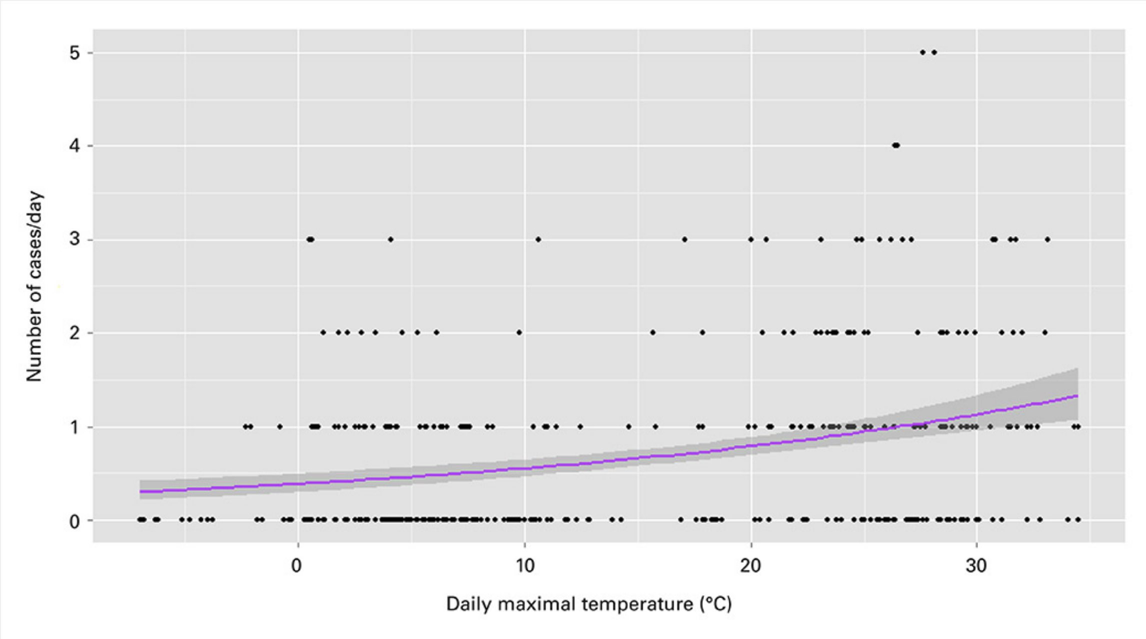

Figure 1

Poisson regression exploring the association between the daily number e of profound hyponatremia cases with maximum daily temperature (°C). Lambda parameter 0.036, p <0.001. Figure was created using R program (the R Foundation for Statistical Computing, Version 3.1.1)