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ORIGINAL ARTICLE

Sub-acute more than chronic hyponatraemia is associated with serious falls and hip fractures

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Abstract

Background: Falls and hip fractures among older people are associated with high morbidity and mortality. Hyponatraemia may be a risk for falls/hip fractures, but the effect of hyponatraemia duration is not well understood.
Aims: We sought to evaluate individuals with periods of sub-acute and chronic hyponatraemia on subsequent risk for serious falls and/or hip fractures.
Methods: Retrospective cohort study in the period 1 January 1998 to 14 June 2016 within an integrated health system of individuals aged ≥55 years with ≥2 outpatient serum sodium measurements. Hyponatraemia was defined as sodium <135 mEq/L with sub-acute (<30 days) and chronic (>/=30 days) analysed as a time-dependent exposure. Multivariable Cox proportional hazards modelling was used to estimate hazard ratios (HRs) for serious falls/hip fractures based on sodium category.
Results: Among 1 062 647 individuals totalling 9 762 305 sodium measurements, 96 096 serious falls/hip fracture events occurred. Incidence (per-1000-person-years) of serious falls/hip fractures were 11.5, 27.9 and 19.8 for normonatraemia, sub-acute, and chronic hyponatraemia. Any hyponatraemia duration compared to normonatraemia had a serious falls/hip fractures HR (95%CI) of 1.18(1.15, 1.22), with sub-acute and chronic hyponatraemia having HRs of 1.38(1.33, 1.42) and 0.91(0.87, 0.95), respectively. Examined separately, the serious falls HR was 1.37(1.32, 1.42) and 0.92(0.88, 0.96) in sub-acute and chronic hyponatraemia, respectively. Hip fracture HRs were 1.52(1.42, 1.62) and 1.00(0.92, 1.08) for sub-acute and chronic hyponatraemia, respectively, compared to normonatraemia.
Conclusions: Our findings suggest that early/sub-acute hyponatraemia appears more vulnerable and associated with serious falls/hip fractures. Whether hyponatraemia is a marker of frailty or a modifiable risk factor for falls remains to be determined.

Background

Hyponatraemia remains the most common electrolyte abnormality among the older people affecting 10% of the ambulatory, 20% of the nursing home, and over 40% of the hospitalised older people population.[1–4] Acute (<48 h) hyponatraemia has been associated with neurologic disturbances including cerebral oedema and encephalopathy, respiratory disturbances including respiratory failure and noncardiogenic pulmonary oedema, and increased mortality.[3,5–8] Observational studies suggest that even mild and chronic hyponatraemia may be associated with worsened outcomes including gait disturbances, falls and serious fractures.[1,3,9–17]

Falls and fractures represent serious health concerns in older people and are associated with significant morbidity and mortality.[4] The prevalence of gait disturbances is thought to affect 35% of older people, resulting in serious fractures or head trauma in 10–20% of this population.[18–21]

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Individuals who suffer hip fractures are estimated to experience a five- to eight-fold greater 3-month mortality and an overall 1-year mortality exceeding 20%.[22–24] Among those who survive hip fractures, nearly half are unable to recover their functional capabilities.[22,24] Nonfatal falls lead to direct medical costs of 19 billion dollars a year.[20] Fall prevention strategies are an important priority in the older population.

Hyponatraemia has been mechanistically associated with falls and bone fractures through its effects on lowering bone density, thereby contributing to osteoporosis, and neurologic impairments including gait abnormalities.[3,14,25–29] Even mild hyponatraemia has been associated with higher rates of falls and fractures.[1,9–16] However, many prior observations on sodium assessments have been derived from single, baseline serum sodium measurements.[9–12,17] The duration of hyponatraemia and its specific impact on fall and fracture risk may be an important consideration in timely management and prevention of these skeletal complications though this has not been well-studied.

To address this knowledge gap, we hypothesised that different durations of hyponatraemia present differential risk for serious falls and/or hip fractures. Using a large diverse population of men and women from a routine clinical practice environment with serial serum sodium measurements, we sought to evaluate the risk for serious falls and/or hip fractures among men and women during episodes of hyponatraemia (sodium <135 mEq/L) further classified as sub-acute (< 30 days) and chronic (≥ 30 days) compared to normonatraemia.

Methods

Study population

A retrospective cohort study of Kaiser Permanente Southern California (KPSC) members was performed between 1 January 1998 and 14 June 2016. KPSC is a prepaid integrated health system comprised of 15 medical centres and over 200 satellite clinics that provides comprehensive care to over 4.5 million members throughout Southern California. As of December 31, 2017, there were over 2.5 million adult members within KPSC. The patient population is racially, ethnically and socioeconomically diverse, reflecting the general population of Southern California.[30] This includes approximately 13% Medicare funded members and up to 8% Medical or state funded members. All KPSC members have similar benefits and access to healthcare services, clinic visits, procedures and copays for medications. Complete healthcare encounters are tracked using a common electronic health record (EHR) from which all study information was extracted. The study protocol was reviewed and approved by the KPSC Institutional Review Board (#10758) and was exempt from informed consent.

Individuals aged 55 years and older with at least two documented serum sodium measurements on different days performed in an outpatient setting were included in the study. All individuals were required to have one-year continuous membership (up to 45-day gaps allowed) in the health care plan prior to their first sodium measurement to accurately capture any comorbidities. Individuals were followed until they experienced any outcome (serious fall or hip fracture), disenrollment from the healthcare plan, death, or the end of the observation period (December 31, 2015). Laboratory values with high glucose levels ≥200 mg/dL measured concurrently with their sodium measurements (potential pseudohyponatraemia) were excluded. Patients with a history of hip fracture prior to the first sodium measurement were excluded due to the possibility of repeat coding for hip fracture that may have occurred in the past.

Data collection and laboratory measurements

Laboratory data, vital sign assessments (including BP measurements), and diagnostic and procedure codes were collected in the EHR as part of routine clinical care encounters. Comorbidities, including hypertension (HTN), diabetes mellitus (DM), coronary artery disease, peripheral vascular disease, and hypothyroidism were assessed based on inpatient and outpatient International Classification of Diseases (ICD) diagnoses coding and evaluated in the year prior to the first sodium measurement date. All laboratory measurements were performed by an American College of Pathology/Clinical Laboratory Improvement Act certified laboratory. When available, laboratory values on serum albumin, haemoglobin, calcium, potassium, bicarbonate, blood urea nitrogen, creatinine, thyroid stimulating hormone, alkaline phosphatase, phosphorus and haemoglobin A1C were extracted. Glomerular filtration rate was estimated from serum creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration Equation.[31] Clinical characteristics and laboratory data were ascertained in the year prior to the first sodium measurement. Prescription orders, pharmacy fills and refills are tracked for KPSC members with pharmacy benefits and were retrieved from the KPSC pharmacy dispensing records. Data on hospitalizations and diagnoses that occurred outside the health system were extracted through administrative billing and claims records.

Sodium measurements and definitions of hyponatraemia

Serum sodium levels were measured using a standard colorimetric method with normal reference values of 135–145 mEq/L (Roche Diagnostics, Alameda, California). Hyponatraemia was defined as a serum sodium of <135

mEq/L. Hyponatraemia was further defined as sub-acute when multiple serum sodium values <135 mEq/L occurred with less than 30 days elapsed between the first and last sodium measurement which was followed by a sodium ≥135 mEq/L. Chronic hyponatraemia was defined as multiple serum sodium measurements <135 mEq/L with 30 or more days between first and last serum hyponatraemia measurement. Normonatraemia was defined as all serum sodium measurements ≥135 mEq/L. These sodium episodes were considered separately. Thus, an individual may have contributed to one or all three sodium categories during the observation window. All sodium values collected are outpatient sodium measurements and also reflect only those values that ***preceded*** a fall or hip fracture outcome.

Outcomes

The outcome evaluated was a composite of serious fall injury and/or hip fracture. Serious fall injuries were identified by a combination of ICD-9 (and the analogous ICD-10 codes) and current procedure terminology codes.[32,33] Serious falls were defined as outpatient, emergency department and inpatient diagnoses with fall-related E code (8800–8889) and an injury code for nonpathological skull, facial, cervical, clavicle, humeral, forearm, pelvic, hip, fibula, tibia or ankle fractures (80000–80 619, 8070–8072, 8080–8089, 81 000–81 419, 8180–8251 or 8270–8291), brain injury (85200–85 239), or dislocation of the hip, knee, shoulder or jaw (8300–8321, 83 500–83 513 or 83 630–83 660). In the absence of a fall-related E code, an emergency department or inpatient diagnosis with any of these codes was considered a serious fall injury as long as there was no motor vehicle accident E code (8100–8199) within ±7 days.[32–35] Hip fractures were identified by: (i) at least one inpatient ICD-9 diagnosis code (820.0X, 820.2X, 820.8X), (ii) at least one outpatient ICD-9 diagnosis code and at least one procedure code (27230–27 248) within 7 days of the diagnosis code or (iii) via administrative billing records for hip fractures that were treated outside of the KPSC system. Any diagnosis code that occurred within 3 months of another was considered to identify the same hip fracture episode. Individuals were observed until the occurrence of an outcome, death, disenrollment from the health plan or the end of the study observation period. Thus, no individual in the study could have contributed to more than 1 event (combined serious fall/hip fracture, serious fall or hip fracture).

Statistical analyses

Demographic information, laboratory values, and comorbidities among individuals who experienced any episode of hyponatraemia, sub-acute hyponatraemia, chronic hyponatraemia, and normonatraemia were compared. The chi-square test was used to test relationships between categorical variables, and the Wilcoxon two sample test was used to test relationships between continuous variables.

Analyses were conducted using a time varying approach based on serial sodium measurements.[36] These values were then used to compare the risk of serious fall injuries and hip fractures during normonatraemia, sub-acute hyponatraemia, and chronic hyponatraemia episodes. An individual may move into and out of sodium categories, and for various durations where each episode would be considered separately.[36] Event rates were determined for all three sodium categories. Cox proportional hazards regression modelling was used to estimate hazard ratios (HRs) and 95% confidence interval (95% CI) for serious falls and/ or hip fractures in (i) sub-acute hyponatraemia versus normonatraemia and (ii) chronic hyponatraemia versus normonatraemia. Multivariable models included adjustment for: demographics (age, gender, race/ethnicity), comorbidities (DM, ischaemic heart disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, HTN and hypothyroidism), laboratory results (creatinine, calcium, haemoglobin, thyroid stimulating hormone and albumin), and medication use (bisphosphonates, antihypertensive medication, antiarrhythmic medication, anti-coagulation medication, anti-seizure medication, hormone therapies, corticosteroids, benzodiazepines, anti-depressants and proton pump inhibitors).

All statistical analyses were conducted using the SAS Enterprise Guide (version 5.1, SAS Institute Cary, GA, USA). Results with $P < 0.05$ were considered statistically significant.

Results

Cohort characteristics

A total of 1 062 647 individuals with a total of 9 762 305 sodium measurements were included in the study (Fig. 1). The median age was 61 years, with 64% of the study cohort between 55 and 64 years. Females accounted for 53% of the study population. The race/ethnicity composition of the population was 51% non-Hispanic white, 11% black, 22% Hispanics and 10% Asian (Table 1). HTN was identified in 47%, while DM was present in 21% of the study cohort. The median sodium was 139 mg/dL with 18% having had three or more sodium measurements during the observation window. Median haemoglobin was 14.0 g/dL, and median albumin was 4.0 g/dL. Among 156 113 individuals who had dual-energy X-ray absorptiometry results available, osteoporosis (T-score < −2.5) was present in 35%. The mean duration of follow-up was 7.4 years.

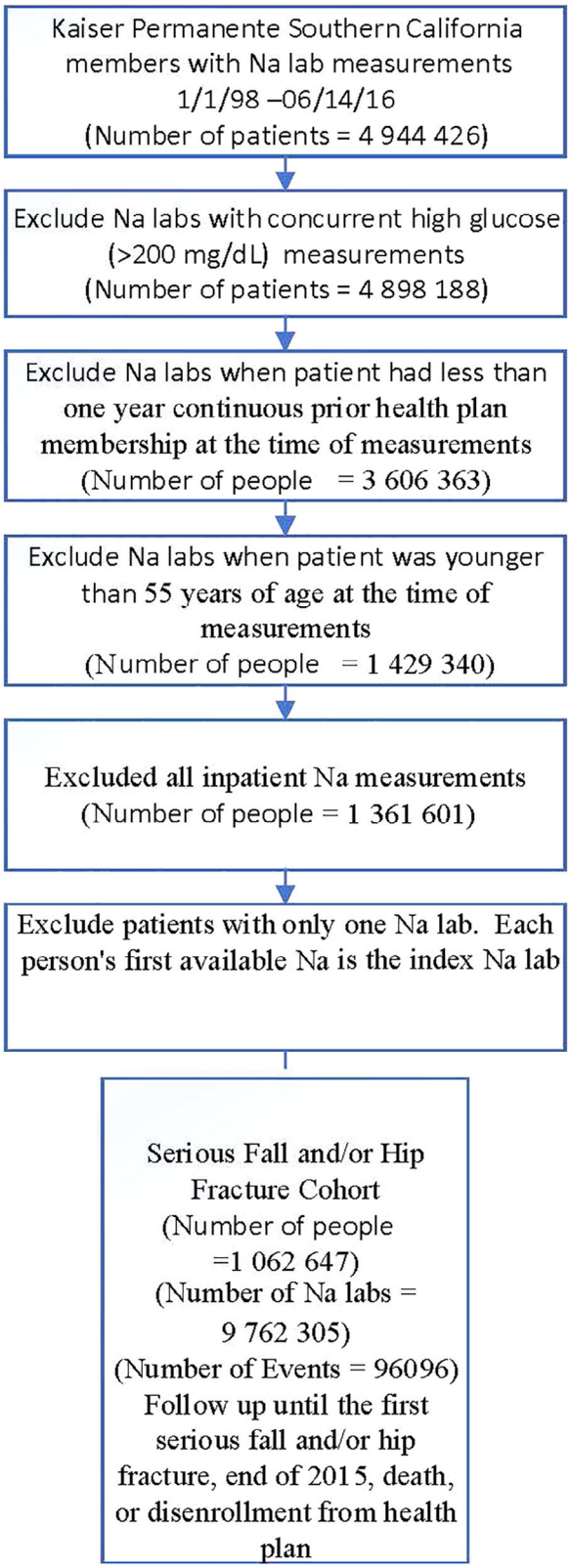

Figure 1 Study population. A total of 1 062 647 individuals with a total of 9 762 305 sodium measurements were included in the study.

Sub-acute, chronic and normonatraemia subgroup characteristics

A total of 275 804 (26%) individuals experienced a hyponatraemic episode of any duration with 205 055 individuals experiencing sub-acute hyponatraemia only. The remaining 70 749 individuals experienced chronic hyponatraemic episodes, but they may have also had episodes of sub-acute hyponatraemia during the observation window (Table 1). The mean Na for all the sodium measurements was 140 and 137 mEq/dL among individuals categorised into sub-acute and chronic hyponatraemia, respectively. The normonatraemic population had lower rates of pre-existing conditions including HTN, DM, cardiovascular disease, peripheral vascular disease and hypothyroidism. Individuals who experienced chronic hyponatraemia had higher rates of HTN (50%) and were more frequently on antihypertensive medications (38%) compared to the sub-acute (29%) and normonatraemia (28%) individuals (Table 1).

Outcomes

Overall, 96 096 (9%) of the study population experienced a serious fall and/or hip fracture, with 95 687 experiencing a serious fall and 2723 experiencing a hip fracture. Serious falls and/or hip fracture rates by each sodium category were 11.5 (incidence per 1000-person years), 27.9, and 19.8 among normonatraemia, sub-acute hyponatraemia and chronic hyponatraemia, respectively. Serious falls and hip fracture incidence rates, separately, were also highest during sub-acute hyponatraemia followed by chronic hyponatraemia and normonatraemia (Table 2).

Regressions

Hyponatraemia of any duration had a serious fall and/or hip fracture HR (95% CI) of 1.18 (1.15, 1.22) compared to normonatraemia. The serious fall HR was 1.19 (1.15, 1.22) and hip fracture HR was 1.30 (1.22, 1.39) among any hyponatraemia compared to normonatraemia (Table 3).

When comparing sub-acute hyponatraemia versus normonatraemia, the serious fall and/or hip fracture HR was 1.38 (1.33, 1.42). The serious fall HR was 1.37 (1.32, 1.42) and hip fracture HR was 1.52 (1.42, 1.62) for sub-acute hyponatraemia compared to normonatraemia.

Compared to normonatraemia, chronic hyponatraemia had HR's (95% CI) of 0.91 (0.87, 0.95), 0.92 (0.88, 0.96) and 1.00 (0.92, 1.08) for serious falls and/or hip fractures, serious falls and hip fractures, respectively (Table 3).

Sensitivity analyses

We performed several sensitivity analyses to evaluate different aspects of serum sodium and serious fall and/or

Table 1 Characteristics of normonatraemia versus hyponatraemia (sub-acute vs chronic)

Characteristics	All	No hyponatraemia of any duration	Chronic hyponatraemia†	Sub-acute hyponatraemia only	*P* value
n (%)	1 062 647 (100)	786 843	70 749	205 055	
Age, median	61	60.1	66.2	63.4	<0.001
55–64 years, %	64.3	68.4	45.6	55.4	
65–74 years, %	23.9	21.8	32.9	28.8	
75–84 years	9.7	8.1	17.9	13.3	
≥85 years	2	1.7	3.6	2.6	
Male, %	47	46.9	42.6	48.9	<0.001
Race, %					<0.001
White	51.4	50.3	58.9	53.1	
Black	10.6	10.6	7.9	11.4	
Hispanic	22.4	22.5	21.2	22.8	
Asian/Pacific	9.5	9.8	8.7	8.6	
Other	6.1	6.9	3.3	4.6	
SBP, median	129	129	132	130	<0.001
DBP, median	75	75	75	75	<0.001
BMI, median	28.4	28.4	27.1	28.5	<0.001
Hypertension, %	47.3	46.7	50.5	48.4	<0.001
Diabetes mellitus, %	20.7	18.4	27.4	27.4	<0.001
Cardiovascular disease, %	15.2	13.6	20.7	19.5	<0.001
Peripheral Vascular Disease, %	3.8	3.5	4.7	4.5	<0.001
Hypothyroid, %	7.5	7.6	7.8	6.7	<0.001
BMD, lowest t score, %					<0.001
Missing	85.3	83.9	89.3	89.3	
≥ −1.0	3.1	3.5	1.9	2.2	
−1.0 to −2.5	6.4	7.2	4.1	4.4	
≤ −2.5	5.1	5.4	4.6	4.2	
Medication exposure, %					
Bisphosphonates	2.5	2.5	3.1	2.3	<0.001
Other osteoporosis meds	0.2	0.1	0.3	0.2	<0.001
Anti-hypertensive meds	36.47	33.98	48.27	41.96	<0.001
ACE	20.37	19.07	25.76	23.48	
ARB	3.47	3.58	3.38	3.09	
Loop diuretics	1.67	1.36	2.89	2.46	
MRA	0.18	0.14	0.41	0.25	
Thiazides	10.76	9.82	15.79	12.66	
Benzodiazepines	5.5	5	8.5	6.5	<0.001
Anti-depressant meds	10.4	10	12.8	11.3	<0.001
Proton-pump inhibitors	5.5	5.4	6.4	5.8	<0.001
Sodium (mEq/L), median	139	140	137	138	<0.001
Potassium (mEq/L), median	4.2	4.1	4.2	4.2	<0.001
Bicarbonate (mEq/L), median	28	28	27	27	<0.001
Chloride (mEq/L), median	103	104	101	102	<0.001
BUN (mg/dL), median	15	15	14	15	<0.001
Creatinine (mg/dL), median	0.9	0.9	0.9	0.9	<0.001
eGFR (mL/min/1.73m^2), median	82.4	82.9	79.3	79.9	<0.001
Calcium (mg/dL), median	9.4	9.4	9.4	9.4	<0.001
Phosphorus, median	3.5	3.5	3.6	3.5	<0.001
Magnesium (mEq/L), median	1.8	1	1.8	1.8	<0.001
TSH (uIU/mL), median	1.5	1.4	1.5	1.5	<0.001
Uric acid (mg/dL), median	5.9	5.9	5.8	6	<0.001
Alkaline phosphatase (U/L),median	72	71	74	74	<0.001
Vitamin D (ng/mL), median	29	29	29	28	<0.001
HgbA1C, median	6.1	6.1	6.6	6.5	<0.001
Albumin (g/dL), median	4	4	3.9	3.9	<0.001
Haemoglobin (g/dL), median	14	14	13.6	13.9	<0.001

†These individuals may also have had sub-acute hyponatraemia episodes during the observation window.

Table 2 Event rates for primary outcome of serious falls and/or hip fracture, serious falls, and serious hip fractures

Outcome	Normal Sodium		Sub-Acute Hyponatraemia		Chronic Hyponatraemia	
	Person years	Incidence per 1000 person years (number of outcomes)	Person years	Incidence per 1000 person years (number of outcomes)	Person years	Incidence per 1000 person years (number of outcomes)
Serious falls and/ or hip fracture	7 471 801	11.50 (86265)	239 088	27.90 (6671)	159 991	19.80 (3160)
Serious falls	7 475 587	11.50 (85890)	239 364	27.73 (6637)	160 377	19.70 (3160)
Hip fractures	8 021 440	2.48 (19889)	261 232	6.83 (1785)	180 512	5.81 (1049)

hip fracture risk. We assessed whether there was a dose dependent effect of the sodium level on serious fall and/or hip fracture risk. Compared to mean serum sodium value of ≥135 mEq/L, the adjusted HR for serious falls and hip fractures were 1.22 (1.19, 1.25), 1.57 (1.48, 1.66), 3.07 (2.48, 3.81) and 2.57 (1.46, 4.53) for mean sodium 130–134, 125–129, 120–124 and < 120 mEq/L, respectively. We also performed a subgroup analysis on patients who had a prior history of hip fracture which were not included in our study cohort. Among this subpopulation, the adjusted HR for serious falls and/or hip fractures were 1.23 (1.1, 1.38) for hyponatraemia compared to normonatraemia. The serious fall and/or hip fracture HR were 0.91 (0.79, 1.06) and 1.46 (1.29, 1.64) for chronic hyponatraemia and sub-acute hyponatraemia respectively. Lastly, we observed that DM, peripheral vascular disease, and use of antidepressants and benzodiazepines were also associated with higher risk of serious falls and/or syncope among the study population (Supplemental Table 2).

Discussion

Using serial sodium measurements to determine duration of hyponatraemia, we performed a time varying analysis to establish preceding episodes of hyponatraemia and their relationship to serious falls and/or hip fractures. Our study of men and women age 55 years and older within a real-world clinical environment revealed that episodes of hyponatraemia had a 18% greater association with serious falls and hip fractures. The increased risk was driven primarily by sub-acute hyponatraemia or the period immediately after individuals were found to be hyponatraemic (within 30 days). In contrast, people who experienced chronic hyponatraemia (≥30 days) did not appear to have a higher association with serious falls/hip fractures compared to those with normonatraemia. In fact, the HR for combined serious falls and/or hip fracture was lower for chronic hyponatraemia compared to normonatraemia. Rather than chronic hyponatraemia being protective, we feel that this was a result of a survival bias where those who experienced serious falls and fractures during the acute period were already captured in the analyses. It is also plausible that those who made it to the chronic phase of hyponatraemia may represent a more resilient population less prone to falls and hip fracture. In addition, individuals who had hyponatraemia for a longer period were more likely to draw the attention of their providers whereby they may have intervened to prevent adverse outcomes associated with the hyponatraemia going forward. Whether hyponatraemia is a risk for serious falls and hip fractures or rather a marker of frailty is yet to be determined.

Our study used serial sodium measurements to establish a time frame for hyponatraemia. The current findings may not have been detected had we used single baseline sodium measurements for each individual or calculated mean or median sodium values. For example, the median sodium levels for people who experienced serious falls and/or hip fractures and those who did not experience serious falls and/or hip fractures were within normal sodium ranges (139 mEq/L and 139 mEq/L respectively) (Supplemental Table 1). Past observations evaluating hyponatraemia and serious falls and/or hip fractures have been mostly based on single sodium values and within acute care settings.[12–14,17,27] They could not determine risk based on serial sodium levels to evaluate the impact of chronicity of hyponatraemia on outcomes.

The mechanism by which hyponatraemia leads to increased risk of falls and fractures is not well understood.[5–8] Hyponatraemia has been associated with reduced bone mineral density.[25,27] Animal models have shown increased bone resorption and decreased bone formation leading to osteoporosis.[27,28] Similarly, we observed lower rates of falls and hip fractures among individuals who were taking thiazide diuretics which since thiazide use has also been associated with increased bone density.[37] This benefit may have offset the risk associated with hyponatraemia among thiazide users. We previously reported a modest increase in the

Table 3 Hazards ratios (95%) CI for serious falls and hip fractures, serious falls, and hip fractures

	Outcomes							
	Serious fall and/or hip fracture			Serious falls			Hip fractures		
	Hyponatraemia versus normal Na	Chronic hyponatraemia versus normal Na	Sub-acute hyponatraemia versus normal Na	Hyponatraemia versus normal Na	Chronic hyponatraemia versus normal Na	Sub-acute hyponatraemia versus normal Na	Hyponatraemia versus normal Na	Chronic hyponatraemia versus normal Na	Sub-acute hyponatraemia versus normal Na
Unadjusted HR (95% CI)	1.97 (1.93, 2.01)	1.71 (1.65, 1.78)	2.14 (2.08, 2.20)	1.97 (1.93, 2.01)	1.72 (1.66, 1.79)	2.13 (2.08, 2.19)	2.54 (2.45, 2.64)	2.31 (2.17, 2.46)	2.70 (2.57, 2.83)
Adjusted HR (95% CI)†	1.19 (1.15, 1.23)	0.91 (0.87, 0.95)	1.38 (1.33, 1.42)	1.19 (1.15, 1.23)	0.92 (0.88, 0.96)	1.37 (1.33, 1.42)	1.30 (1.22, 1.39)	1.00 (0.92, 1.08)	1.52 (1.42, 1.62)

†Adjusted for age at first Na measurement, gender, race, ethnicity, comorbidities (cardiovascular disease, peripheral vascular disease, hypertension, diabetes mellitus, hypothyroidism), lab results (creatinine, haemoglobin, and for every decrease of 3 in mg/dL of sodium measurement) and medications (bisophosphonates, other corticosteroids, antidepressants, benzodiazepines, thiazide diuretics, antihypertensive medications, proton-pump inhibitors, anti-coagulation medications, anti-arrhythmia medications, anti-seizure medications, and other endocrine/hormonal medications).

association of osteoporosis with chronic hyponatraemia (defined as two consecutive sodium measurements <135 mEq/L on different days) in a cross-sectional evaluation of men and women.[29] Hyponatraemia is also known to produce subtle cognitive deficits and gait disturbances.[14,18] Among emergency room patients presenting with asymptomatic chronic hyponatraemia, Renneboog *et al*. observed that the hyponatremic patients were more likely to have unstable gait and attention impairments which resolved after correction of the sodium.[14]

Falls and fractures remain a significant public health concern among older people given their association with increased morbidity and mortality. Effective fall and fracture prevention strategies among older people are important. Early identification and management of electrolyte disorders such as hyponatraemia may be one means to potentially lower and prevent these adverse events. Our findings seem to underscore the importance of detecting and managing outpatient hyponatraemia in a timely manner which may lead to prevention of serious falls and/or hip fractures. KPSC has had patient safety measures (KPSC SureNet) in place that have addressed abnormal outpatient labs to prevent care gaps with an emphasis on the ambulatory care environment compared to most existing patient safety models which target inpatient encounters.[38,39] In the past, these safety net programs have targeted chronic kidney disease, abnormal PSA values, cancer screening, and medication interactions. KPSC has over 20 million outpatient encounters per year.[40] There are over 60 million laboratory tests performed each year of which 77% are drawn from the ambulatory care setting. The integrated health system with the EHR repository of laboratory values (including sodium values) would appear to be one of the better suited environments to capture hyponatraemia results that may be missed or delayed. Our current study findings derived from the same KPSC clinical environment suggests that a safety program targeting hyponatraemia is possible. A population-based intervention to detect and act on outpatient hyponatremic patients may ultimately lead to prevention of adverse outcomes including serious falls and fractures.

Potential limitations

There are several potential limitations that may affect the interpretation of our study findings. The greater comorbidities such as diabetes and cardiovascular disease among the hyponatraemia patients suggest that there were a sicker population. Thus, hyponatraemia may just as equally be a marker of frailty rather than a causative agent for falls and hip fractures. We also recognise that there may have been an indication bias for sodium

measurements among individuals who were tested versus those who were not. Low sodium values may reflect a sicker population and serve as a surrogate for poor nutritional status.[41,42] Though our retrospective design cannot provide a causal relationship between serum sodium and fall/hip fractures, we were able to determine the chronological sequence of sodium values and captured subsequent outcomes using a time varying approach. Our study evaluated the duration but not the degree or dose dependent effect of hyponatraemia on fall/hip fracture risk *per se*. In sensitivity analyses, we did observe a 2% greater risk for serious falls and/or hip fracture for every 3 mEq/L decrease in sodium. Chronic hyponatraemia covers a longer time period than sub-acute hyponatraemia and so is more susceptible to misclassification between laboratory tests. If there are long periods between laboratory checks, and if a patient is in reality alternating back and forth from chronic hyponatraemia to normonatraemia during this time frame, we may not be able to capture those changes well since testing is not continuous. Additional limitations include the fact that we were unable to fully account for the specific causes of each hyponatremic episode (e.g. medication use, syndrome of inappropriate diuretic hormone, volume depletion, *etc*.). This information may give additional insight whereby hyponatraemia may have been an intermediary variable or a separate manifestation of what may have caused serious fall or hip fracture. Despite these limitations, our study was strengthened by the availability of longitudinal data and the ability to control for several confounders utilising a time varying model.

Conclusion

Among a large, ethnically diverse population of men and women with serial outpatient sodium values, we observed an increased risk for serious falls and/or hip fractures among people during episodes of hyponatraemia. This effect was driven by episodes of sub-acute hyponatraemia (< 30 days) whereas chronic hyponatraemia was not associated with higher risk. Our findings suggest that the initial period of hyponatraemia poses the greatest risk for serious falls and/or hip fractures. Patient safety measures that lead to early identification and early correction of outpatient hyponatraemia seem warranted given the potential to prevent future adverse outcomes including serious falls and hip fractures.

Reference

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Supporting information.