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RESEARCH PAPER

Active management of hyponatraemia and mortality in older hospitalised patients compared with younger patients: results of a prospective cohort study

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Abstract

Introduction: Hyponatraemia is associated with increased morbidity and mortality; the aetiology and outcomes of hyponatraemia in older patients have not been defined in prospective studies.
Methods: A single-centre 9-month prospective observational study in which clinical outcomes in hospitalised patients ≥ 65 years (older patients with hyponatraemia (OP-HN)) and those <65 years (young patients with hyponatraemia (YP-HN)) with hyponatraemia were analysed, and compared with eunatraemic controls (older patients with normonatraemia (OP-NN) and young patients with normonatraemia (YP-NN)).
Results: In total, 1,321 episodes of hyponatraemia in 1,086 patients were included; 437 YP-HN, median age 54 years (IQR 44,60) and 884 OP-HN, median age 77 years (IQR 71,82). A total of 1,120 consecutive eunatraemic control patients were simultaneously recruited; 690 OP-NN, median age 77 years (IQR 71,83) and 430 YP-NN, median age 52 years (IQR 41,58). Euvolaemic hyponatraemia was the commonest cause of hyponatraemia in both age groups (48% in YP-HN and 46% in OP-HN). Sixty-two percent of OP-HN received hyponatraemia-directed treatment within the initial 48 h, compared with 55% of YP-HN, $P = 0.01$. Despite the greater treatment rates in OP-HN, younger patients were 24% more likely to be discharged with normal plasma sodium concentration (pNa) compared with older patients, relative risk (RR) 1.24 (95% confidence interval (CI) 1.12–1.37), $P < 0.001$. Using OP-NN as the reference group, the RR of in-hospital death in OP-HN was 2.15 (95% CI 1.3–3.56), $P = 0.002$. Using YP-NN as the reference group, the RR of in-hospital death in YP-HN was 4.34 (95% CI 1.98–9.56), $P < 0.001$.
Conclusion: Despite greater rates of HN-targeted treatment, the risk of in-hospital death is increased in older hyponatraemic patients compared with older eunatraemic controls. The impact of hyponatraemia on mortality is even greater in younger patients.

Keywords: hyponatraemia, syndrome of inappropriate antidiuresis, older people

Key Points

- The causes of hyponatraemia, and of SIAD, in hospitalised patients differ between older and younger patients.
- Hyponatraemia is corrected less often in older patients prior to discharge.
- In-hospital mortality is increased in older hyponatraemic patients compared with older eunatraemic controls.
- The impact of hyponatraemia on mortality is even greater in younger patients.

Introduction

The prevalence of hyponatraemia rises with age [1]; up to one third of hospitalised patients aged >65 years have a plasma sodium concentration (pNa) < 135 mmol/L [2]. Ageing is associated with physiological derangements in water homeostasis which predispose to hyponatraemia: physiological studies in healthy older subjects demonstrate age-related increases in basal and osmotically stimulated vasopressin (AVP) concentration [3,4], urine concentrating ability is attenuated and osmotically stimulated thirst is diminished [5]. In addition, there is a higher incidence of co-morbid illnesses associated with hyponatraemia, and a higher rate of prescription of medications which cause hyponatraemia, in older patients.

Chronic hyponatraemia is associated with subtle cognitive effects and unsteady gait [6,7], increased falls risk [8], osteoporosis [9] and an increased fracture rate [10]. All of these are complications to which older subjects are inherently more prone. Recent data have suggested that effective treatment of hyponatraemia can improve cognitive function and functional independence [11]. Despite this, hyponatraemia remains under-investigated and under-treated [12]. Prospective studies examining current approaches to hyponatraemia, and outcomes, specifically in older patients, are lacking.

Hyponatraemia is consistently associated with increased mortality, irrespective of the causative medical condition [13,14]. However, data for all-cause hyponatraemia mortality in older patients are conflicting; recent US data from 2 million hospitalised patients demonstrated a lower mortality in patients aged ≥65 years compared with younger patients with equivalent hyponatraemia (pNa < 130 mmol/L) [15]. Previous studies have reported mortality rates in all-cause hyponatraemia. However, recent prospective data have demonstrated higher mortality rates for hyper- and hypovolaemic hyponatraemia, compared with Syndrome of Inappropriate Antidiuretic Hormone (SIAD), in hospitalised patients [16].

In this study, analysis of data from a prospective observational study [16] has been used to determine the mortality rate in a large cohort of hospitalised patients aged ≥65 years with hyponatraemia (pNa < 130 mmol/L), and to compare it with younger hyponatraemic patients and eunatraemic controls aged ≥65 years. We have additionally evaluated whether older patients with hyponatraemia were being investigated, diagnosed and treated as recommended by international guidelines [17,18].

Methods

Setting and patients

A prospective single-centre observational study was conducted in a 600 bed university hospital which is the site for the national centre for neurosurgery. All patients admitted with hyponatraemia, or who developed hyponatraemia (defined as a pNa ≤ 130 mmol/l) between 1st January and 1st October 2015 were included. Patients who were eunatraemic on admission, and remained eunatraemic, were recruited as controls. Patients were classified into four groups, with an age cut-off ≥ 65 years used to define 'older' [19]:

Group 1: Older patients (≥65 years) with hyponatraemia (OP-HN),

Group 2: Older patients with normonatraemia (OP-NN),

Group 3: Young patients (<65 years) with hyponatraemia (YP-HN),

Group 4: Young patients with normonatraemia (YP-NN).

This was a non-interventional study; treatment decisions were made by the supervising medical teams. The only role of the study team was to ensure that minimum biochemical criteria for the diagnosis of SIAD were obtained within the initial 48 h (which in and of itself may have resulted in altered management). Clinical information was obtained from case notes and computerised laboratory records within 48 h of onset of hyponatraemia. Patients were classified as hypovolemic, euvolaemic or hypervolemic, using a combination of clinical and biochemical assessment, and pseudohyponatraemia excluded, based on standard guidelines [18]. Chronic hyponatraemia was defined as three or more documented episodes of pNa < 133 mmol/L prior to admission. Recurrent hyponatraemia in one admission was regarded as a single episode. The study was approved by the hospital's Research Ethics Committee.

Statistical analysis

Continuous data were expressed as median (interquartile range) and categorical data were expressed as number (percentage) unless otherwise stated. Mann–Whitney U test was used to compare continuous data (non-parametric) and Fisher Exact test to compare categorical data across groups. Mortality was reported as relative risk (RR) with 95% confidence intervals (95% CIs) compared to the reference group. The log rank test was used to compare overall survival across groups. A P-value < 0.05 was considered statistically significant unless otherwise specified. Statistical analysis was performed using Prism GraphPad 8.0.

Results

Patient characteristics

In total, 1,321 patient episodes of hyponatraemia in 1,086 patients were included over 9 months; 437 YP-HN, median age 54 years (IQR 44,60); and 884 OP-HN, median age 77 years (IQR 71,82) (Table 1). A total of 1,120 consecutive eunatraemic control patients were simultaneously recruited; 690 OP-NN, median age 77 years (IQR 71,83) and 430 YP-NN, median age 52 years (IQR 41,58) (Appendix 1, Supplementary Material A1).

Table 1. Baseline characteristics and treatments

	YP-HN ($n=437$)	OP-HN ($n=884$)	P
Age (years)	54 (44,60)	77 (71,82)	<0.001
Female, *n* (%)	194 (44%)	474 (54%)	0.002
pNa on admission (mmol/L)	129 (127,132)	129 (126,131)	0.14
Nadir pNa (mmol/L)	128 (125,129)	128 (125,129)	0.77
Nadir pNa < 120 mmol/L	16 (3.6%)	42 (4.8%)	0.4
Chronic hyponatraemia	178 (41%)	391 (44%)	0.28
CCI	3 (0,6)	2 (1,5)	0.37
Comorbidities*			
Malignancy	109 (25%)	215 (24%)	0.84
Heart failure	23 (5%)	149 (17%)	0.01
Liver failure	58 (13%)	33 (3.5%)	<0.001
Volume category			
Hypovolaemic	123 (28%)	302 (34%)	0.03
Euvolaemic	208 (48%)	407 (46%)	0.6
Hypervolaemic	106 (24%)	169 (19%)	0.07
Neurosurgical admission	55 (12.5%)	56 (6%)	<0.001
ICU admission	46 (10.5%)	34 (3.8%)	<0.001
Treatments administered			
IV 0.9% saline	181 (41.4%)	408 (46.2%)	0.11
Fluid restriction	44 (10%)	110 (12.4%)	0.24
Loop diuretics	31 (7%)	93 (10.5%)	0.03
IV 3% saline	15 (3.4%)	13 (1.5%)	0.05
Tolvaptan	4	3	0.23
≥1 treatment	25 (5.7%)	66 (7.5%)	0.55
No Treatment	196 (44.8%)	334 (37.8%)	0.01

*Multiple comorbidities in some cases.

Investigation of hyponatraemia

Urinary sodium concentration and osmolality were measured in 92.8% of older patient episodes with SIAD (OP-SIAD) (363/391) versus 81.9% of young patient episodes with SIAD (YP-SIAD) (154/188), $P=0.007$. Serum cortisol concentration was measured in 91% of OP-SIAD (264/290) versus 80.7% of YP-SIAD (109/135) (patients on glucocorticoid treatment excluded), $P=0.004$.

Aetiology of hyponatraemia

Euvolaemic hyponatraemia was the commonest cause of hyponatraemia in both age groups, (48% in YP-HN and 46% in OP-HN) (Table 1). The distribution of causes of SIAD in young and older patients is outlined in Table 2.

Treatment of hyponatraemia

62.2% (550/884) of OP-HN received hyponatraemia-directed treatment within the initial 48 hours, compared with 54.9% (239/437) of YP-HN, $P=0.01$. In patients with SIAD, 0.9% saline was the most commonly used treatment in both groups, 42.6% (80/188) YP-SIAD versus 46.5% (182/391) OP-SIAD, $P=0.37$. Fluid restriction (1–1.5 litre/24 h) was used in 19.1% (36/188) YP-SIAD and 19.7% (77/391) OP-SIAD, $P=0.91$. The rate of 3% saline use was three times higher in younger patients than older, 6% (11/188) YP-SIAD versus 2% (8/391) OP-SIAD, $P=0.02$.

Correction of hyponatraemia

Despite the greater treatment rates in OP-HN, pNa had corrected in 60.8% (266/437) of YP-HN by discharge, compared with only 49% (433/884) of OP-HN, RR 1.24 (95% CI 1.12–1.37), $P<0.001$. In patients with SIAD, 57% (107/188) of YP-SIAD had normal pNa at time of discharge, compared with 41% (162/391) of OP-SIAD, $P<0.001$. PNa on discharge in OP-HN categorised by treatment is summarised in Appendix 2, Supplementary Material A2. There were no cases of osmotic demyelination.

Mortality

In-hospital mortality was 7.1% (31/437) in YP-HN, 9.5% (84/884) in OP-HN, 1.6% (7/430) in YP-NN and 4.9% (34/690) in OP-NN (Table 3). There was no difference in mortality when OP-HN were compared to YP-HN, $P=0.33$. The Kaplan–Meier curves for overall survival are displayed in Figure 1.

Using OP-NN as the reference group, the RR of in-hospital death in OP-HN was 2.15 (95% CI 1.3–3.56), $P<0.001$. The relative risk of mortality in older patients with hypovolemic hyponatraemia was 2.5 (95% CI 1.6–3.87), $P<0.001$, while the RR of mortality in older patients with hypervolemic hyponatraemia was higher, 3.49 (95% CI 2.19–5.51), $P<0.001$ (Table 4). There was no significant increase in risk of mortality in older patients with SIAD compared with OP-NN, RR 1.15 (95% CI 0.68–1.92), $P=0.67$.

Table 2. Cause of SIAD in young and older patients

	YP-SIAD ($n = 188$)	OP-SIAD ($n = 391$)	P
CNS	62 (33%)	90 (23%)	0.01
Malignancy	40 (21.3%)	65 (16.6%)	0.2
Respiratory	20 (10.6%)	95 (24.3%)	<0.001
Medications	17 (9%)	24 (6.1%)	0.23
SSRIs	3	9	
AEDs	12	7	
Others/not recorded	2	6	
Post-operative	6 (3.2%)	6 (1.5%)	0.22
Physiological stimuli	4 (2.1%)	5 (1.3%)	0.48
Other	20 (10.6%)	50 (12.8%)	0.5
Idiopathic	5 (2.7%)	32 (8.2%)	0.01
Alcohol*	6 (3.2%)	1	0.006
IV Fluids*	14 (7.4%)	11 (2.8%)	0.02

Multiple contributing causes of SIAD in some cases. CNS, central nervous system; SSRIs, selective serotonin reuptake inhibitors; AEDs, antiepileptic drugs; IV, intravenous. *Precipitated hyponatraemia, but not the cause of SIAD.

Table 3. In-hospital mortality rates

Group	CCI	In-hospital mortality rates	RR (95% CI)	P
OP-NN (reference group)	3 (1,6)	34/690 (4.9%)		
OP-HN	2 (1,5)	84/884 (9.5%)	2.15 (1.3–3.56)	<0.001
YP-NN (reference group)	1 (0,4)	7/430 (1.6%)		
YP-HN	3 (0,6)	31/437 (7.1%)	4.34 (1.98-9.56)	<0.001

$P < 0.001$ for CCI in OP-HN versus OP-NN; $P < 0.001$ for YP-HN vs YP-NN; $P = 0.37$ for OP-HN versus YP-HN. RR, relative risk.

Using YP-NN as the reference group, the RR of in-hospital death in YP-HN was 4.34 (95% CI 1.98–9.56), $P < 0.001$. The RR of mortality in young patients with hypovolemic and hypervolemic hyponatraemia was 3.0 (95% CI 1.07–8.3), $P = 0.05$ and 7.6 (95% CI 3.3–17.8), $P < 0.001$, respectively, while the RR of mortality in young patients with SIAD was 3.3 (95% CI 1.3–8.2), $P = 0.01$.

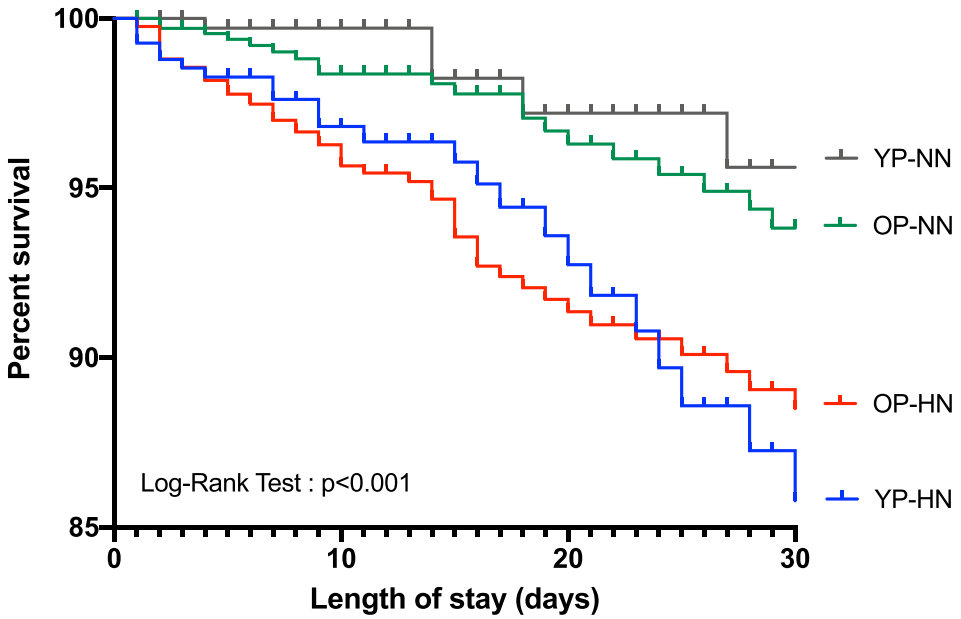
The increased mortality risk demonstrated both the younger and older hyponatraemic patient groups remained after removal of neurosurgical patients from the analysis, RR 5.0 (95% CI 2.27–11), $P < 0.001$ for YP-HN and RR 2.16 (95% CI 1.48–3.16), $P < 0.001$ for OP-HN.

Discussion

The relationship between hyponatraemia and mortality in older patients has been reported to be increased in some [15,20,21], but not all [22,23] studies. In this large, prospective study, hyponatraemia in older hospitalised patients was associated with a mortality rate twice that of eunatraemic older controls, despite a lower Charlson comorbidity index (CCI), an indicator of burden of co-morbidities in the hyponatraemic older group; this implies that the higher mortality in our older hyponatraemic patients is not entirely attributable to underlying comorbidities. Hyponatraemia in younger patients was also associated with increased mortality; the RR of in-hospital mortality compared to eunatraemic age-matched controls was double that reported in the older population. The CCI was significantly higher in YP-HN compared with YP-NN, 3 (IQR 0,6) versus 1(IQR 0,4), $P < 0.001$. This indicates that, in contrast to the older cohort, hyponatraemia in young patients was associated with greater burden of co-morbidities, in particular liver disease; these may have contributed to the greater mortality risk.

The differences in mortality risk associated with hyper-, hypo- and euvolaemic hyponatraemia in older and younger patients demonstrated in this prospective study have not been reported previously. Hypervolemic hyponatraemia was associated with the greatest RR of in-hospital mortality, in keeping with a previous report from our group [16]; the majority of deaths in this group were due to congestive heart failure and decompensated liver disease. While SIAD in younger patients was associated with increased mortality, this was not the case in older patients. The osmoregulatory changes associated with ageing increase vulnerability of older patients to the development of SIAD; therefore, less severe disease processes may lead to dysnatraemia in this patient group, and hyponatraemia may be less of a marker for life threatening disease than in younger patients.

We found significantly better ascertainment of key diagnostic biochemistry in older patients with SIAD, and higher treatment rates in older patients with all-cause hyponatraemia, the opposite of what we had anticipated. The higher treatment rates in older patients may partly reflect the higher rate of hypovolemic hyponatraemia, which is readily treatable with isotonic saline. In contrast, the rate of hypervolemic hyponatraemia, which is therapeutically challenging, was lower in OP-HN. Despite more frequent treatment of older patients, statistically fewer OP-HN patients were discharged with eunatraemia compared with



Number at risk				
OP-HN	846	467	252	159
YP-HN	415	226	109	59
OP-NN	688	415	251	162
YP-NN	428	186	85	50

Figure 1. Kaplan–Meier curve for overall in-hospital survival in four groups. Patients without data on length of stay excluded from analysis.

Table 4. In-hospital mortality rates according to volume category

	CCI	Nadir pNa (mmol/L)	In-hospital mortality rates	RR (95% CI)	*P*
OP-HN					
OP-NN (reference group)	3 (1,6)		34/690 (4.9%)		
OP-HON	2 (1,5)	128 (125,129)	37/302 (12.3%)	2.5 (1.6-3.87)	<0.001
OP-SIAD	2 (1,5)	127 (124,129)	22/391 (5.6%)	1.15 (0.68-1.92)	0.67
OP-HEN	2(1,6)	128 (125,129)	29/169 (17.2%)	3.49 (2.19-5.51)	<0.001
YP-HN					
YP-NN (reference group)	1 (0,4)		7/430 (1.6%)		
YP-HON	3 (0,6)	128 (126,130)	6/123 (4.9%)	3.0 (1.07-8.3)	0.05
YP-SIAD	2 (0,4)	127 (125,129)	10/188 (5.3%)	3.3 (1.3-8.2)	0.01
YP-HEN	3 (2,6)	127 (125,129)	15/106 (14.2%)	7.6 (3.3-17.8)	<0.001

$P < 0.001$ for CCI in OP-HN versus OP-NN; $P < 0.001$ for YP-HN versus YP-NN; $P = 0.37$ for OP-HN versus YP-HN. HON, hypovolaemic hyponatraemia; HEN, hypervolaemic hyponatraemia.

YP-HN. Clinicians may be more comfortable discharging older patients than younger patients with chronic mild hyponatraemia, accepting it as a benign entity.

Fluid restriction is the recommended first line treatment for SIAD in all published guidelines. Urea and tolvaptan are reserved as second-line therapies in European [17] and US consensus guidelines [18], respectively. In this study, only 20% of OP-SIAD and YP-SIAD cohorts were prescribed fluid restriction. The proportion of OP-SIAD patients who were treated with FR, and discharged with normal pNa, was the same as the untreated OP-SIAD group discharged with eunatraemia, which is a disappointing reflection of first line treatment for SIAD. Poor adherence to fluid restriction may have contributed to this, but data on fluid intake were not available. Surprisingly, pNa correction rates were higher in SIAD patients treated with isotonic saline, a treatment specifically not recommended for treatment of SIAD in hyponatraemia guidelines [18]. There was no significant difference in baseline UOsm in those patients with SIAD treated with

isotonic saline who corrected pNa prior to discharge, and those who did not; median UOsm was >400 mOsm/kg in both groups. The plasma sodium response to isotonic saline in half of OP-SIAD cases may partially reflect the transient nature of hyponatraemia in the older group; pulmonary infections and medications accounted for one third of cases of OP-SIAD and both are conditions in which hyponatraemia resolves with treatment (with antibiotics [24] and removal of the offending drug, respectively). Another possible explanation is that these patients had subclinical hypovolemia that responded to saline.

A contribution to the higher rate of normalisation of pNa in younger patients with SIAD could be the natural history of the aetiology of SIAD; central nervous system (CNS) pathology was a more common cause of SIAD in young patients, accounting for 33% of cases, compared with 23% of cases in OP-SIAD, $P = 0.01$, the rates reflective of the fact that our hospital is the national centre for neurosurgery. SIAD due to CNS causes, such as subarachnoid haemorrhage or pituitary surgery, is often transient, with normalisation of pNa by the time of discharge [25]. The greater use of intravenous (IV) 3% saline in the younger hyponatraemic group is likely to reflect the greater susceptibility to symptomatic hyponatraemia in younger patients, in which case emergency treatment with hypertonic saline is required [26].

We have shown that 51% of patients aged over 65 years with hyponatraemia are discharged from hospital with persistent hyponatraemia (pNa < 130 mmol/L). This is a significant finding, given that chronic mild hyponatraemia is known to be associated with a greater risk of attention deficits [7], falls [6,22] and fractures [10], complications to which this population are already at increased risk [27]. While it may be that older patients are simply more prone to chronic hyponatraemia, prospective randomised studies are required to determine if correction of hyponatraemia prior to discharge will improve clinically relevant outcomes such as readmissions with falls and fractures.

Strengths and Limitations

The strength of our study lies in the large patient numbers, prospective study design and the inclusion of two control groups. Although our hospital is the site of the national neurosurgical centre, the increased mortality risk associated with hyponatraemia was confirmed on *post hoc* analysis excluding neurosurgical patients, therefore our results are applicable to other centres. All patients were carefully categorised according to volume status and there was a high rate of ascertainment of key biochemical parameters in patients with SIAD; failure to achieve 100% ascertainment highlights the practical difficulties of collecting these data, even in the context of prospective studies. Assessment of volume status was based on clinical and biochemical data, which has inherent limitations [28]; the classification of patients with mild subclinical hypovolemia as SIAD may account for the response to saline in these patients.

We chose an age cut-off of 65 years to define 'older patients', consistent with other similar hyponatraemia studies [2,15,29]; however, the use of an arbitrary chronological age cut-off fails to take into account the biological heterogeneity of older subjects. Prospective assessment of frailty in future studies might provide a more relevant marker of physiological reserve and mortality risk [30]. We did not collect data on treatment beyond 48 h, so we may have underestimated treatment rates or duration which may have impacted on improvement in pNa and normalisation rates at discharge. We collected standard data on comorbidities according to the validated CCI proforma [31], it is worth commenting that the CCI does not account for the acute precipitating illness, or the severity of that illness, which may challenge its application to hyponatraemia. Indeed, in the seminal paper by Charlson *et al*. [32], it was the prospective rating of acute illness by the treating physician that was the most significant predictor of mortality. Despite no significant difference in CCI between OP-HN and YP-HN, the rate of admission to the intensive care unit was significantly higher in younger than older patients with hyponatraemia. Of course, this may reflect more aggressive medical management of younger patients and translate to better response to treatment; however intensive care unit (ICU) admission also probably provides a better indication of the severity of underlying acute illness than the CCI.

Conclusion

We have demonstrated increased in-hospital mortality in hyponatraemic patients aged ≥65 years compared with controls, confirming that hyponatraemia is a poor prognostic indicator in this patient population. Adherence to treatment guidelines was disappointing in both groups; despite higher treatment rates, fewer older patients are discharged from hospital with eunatraemia. Given the prevalence of hyponatraemia in an ageing population, and the associated morbidity and mortality, a targeted approach to the management of hyponatraemia is warranted. However, prospective interventional trials should be encouraged, in order to ascertain whether a more active approach translates to an increase in hyponatraemia correction rates prior to discharge, and improvement in long-term morbidities such as poor cognition, falls, osteoporosis, fractures, and mortality.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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