

# Mild hyponatremia is associated with an increased risk of death in an ambulatory setting

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Hyponatremia is a common disorder associated with higher mortality in hospitalized patients, but its impact in an ambulatory setting remains unclear. Here we used data from the Dallas Heart Study, a prospective multiethnic cohort study that included ambulatory individuals, to determine the prevalence and determinants of hyponatremia (serum sodium < 135 mEq/l), and its impact on mortality. The analysis included 3551 individuals with a median age of 43 years followed up over a median of 8.4 years. The sample weight-adjusted prevalence of hyponatremia was 6.9%. Hyponatremia was mild (median serum sodium: 133 mEq/l), and was significantly associated with age, black ethnicity, presence of cirrhosis or congestive heart failure, and use of selective serotonin reuptake inhibitors. By the end of the follow-up period, there were 202 deaths including 29 in hyponatremic individuals. The unadjusted hazard ratio for hyponatremia and death was 1.94. Hyponatremia remained significantly associated with mortality after adjustment for age, gender, ethnicity, diabetes, hypertension, dyslipidemia, smoking, alcohol use, renal function, plasma C-reactive protein, use of antiepileptic drugs and selective serotonin reuptake inhibitors, and history of congestive heart failure, cirrhosis, and cancer (hazard ratio of 1.75). Thus, mild hyponatremia is associated with an increased risk of death in a young and ethnically diverse community population.

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Hyponatremia is the most common electrolyte disturbance in clinical practice.<sup>1,2</sup> It is more common in hospitalized patients than in ambulatory individuals, and the prevalence of hyponatremia in the ambulatory population has been estimated to be ~4–7%.<sup>3</sup> When occurring in the hospital setting, hyponatremia generally reflects the severity of an underlying illness such as congestive heart failure (CHF), liver cirrhosis, pneumonia, or chronic kidney disease (CKD). In these subgroups, as well as in the overall hospitalized population, several studies have shown that hyponatremia is independently associated with death.<sup>4–7</sup> On the other hand, mild hyponatremia, which is common in asymptomatic ambulatory individuals, is considered by many clinicians to be a generally benign finding. However, during the past decade, several community-based studies have shown that mild hyponatremia carries specific morbidity as it has been independently associated with gait and attention deficit, and with an increased risk of falls,<sup>8</sup> bone fractures,<sup>9</sup> and possibly osteoporosis.<sup>10,11</sup> Whether mild hyponatremia in a nonselected group of ambulatory individuals carries an increased risk of adverse outcome independent of other comorbidities remains unclear. So far, only two studies<sup>12,13</sup> have addressed this question, and although both suggested that hyponatremia in community individuals was associated with an increased risk of death, these studies focused on elderly white individuals, and one study<sup>12</sup> analyzed a composite end point of death or cardiovascular events in a relatively small number of patients. Therefore, it remains unknown whether mild hyponatremia associates with death in a young ambulatory population who is ethnically diverse. We examined this question in the Dallas Heart Study (DHS), a multiethnic, population-based cohort study of Dallas county residents.

## RESULTS

### Prevalence of hyponatremia in the DHS population and in Dallas County

In this multiethnic, population-based cohort of 3551 individuals, the median age was 43 years (interquartile range (IQR): 36–52 years) and the median serum sodium level was 138 mEq/l (IQR: 136–138 mEq/l). The distribution of serum

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sodium in the population is shown in Supplementary Figure S1 online. After correction for serum glucose, 285 (8.0%) individuals were found to have hyponatremia, defined as serum sodium level of <135 mEq/l (Table 1). The median serum sodium level in hyponatremic patients was 133 mEq/l (IQR: 132–134 mEq/l). Using sample weighting, we estimated the prevalence of hyponatremia in Dallas County at 6.3% (95% confidence interval (CI): 5.2–7.4), with a higher prevalence in Blacks than in Whites (9.0% (CI: 6.7–11.2) vs. 5.5 (CI: 3.9–7.1);  $P=0.011$ ; Supplementary Table S1 online). The prevalence of hypernatremia (serum sodium >145 mEq/l) was 0.2%.

### Determinants of and risk factors for hyponatremia

Table 1 shows a comparison of the demographic and clinical characteristics of participants with and without hyponatremia. Hyponatremic individuals were more likely to be Black, to be smokers, to have a history of diabetes, CHF, or cirrhosis, and to use selective serotonin reuptake inhibitors (SSRIs) or antiepileptic drugs (AEDs). Interestingly, no significant difference in the prevalence of diuretic use or thiazide diuretic use was noted between hyponatremic individuals and the rest of the study population (Table 1).

Logistic regression identified age, Black race, CHF, cirrhosis, and use of SSRI as being independently associated

**Table 1 | Baseline demographic and clinical characteristics of the subjects included in the study**

	Overall <i>n</i> = 3551	Na $\geq$ 135 mEq/l <i>n</i> = 3266	Na < 135 mEq/l <i>n</i> = 285	<i>P</i> -value
Age in years, median (IQR)	43 (36–52)	43 (36–52)	42 (35–49)	0.025
Men, no. (%)	1568 (44)	1453 (44)	115 (40)	0.18
Black race, no. (%)	1831 (52)	1657 (51)	174 (61)	0.001
Body mass index, median (IQR), kg/m <sup>2</sup>	27.7 (24.0–32.6)	28.8 (24.9–33.7)	28.5 (24.5–34.3)	0.63
Hypertension, no. (%)	1075 (30)	989 (30)	86 (30)	0.99
<i>Blood pressure, median (IQR) mm Hg</i>				
Systolic	122 (112–134)	122 (112–134)	123 (112–134)	0.69
Diastolic	77 (71–84)	77 (71–84)	79 (71–85)	0.63
Diabetes, no. (%)	410 (12)	364 (11)	46 (16)	0.012
Serum glucose, median (IQR), mg/dl	92 (85–102)	92 (85–102)	93 (84–105)	0.90
Hypercholesterolemia, no. (%)	458 (13)	432 (13)	26 (9)	0.047
<i>Lipids, median (IQR), mg/dl</i>				
Total cholesterol	177 (154–203)	177 (154–203)	175 (153–198)	0.28
Triglycerides	96 (67–147)	96 (68–147)	95 (62–148)	0.42
LDL cholesterol	104 (82–126)	104 (82–127)	99 (83–121)	0.14
HDL cholesterol	47 (40–57)	47 (40–57)	48 (39–57)	0.93
Metabolic syndrome, no. (%)	1189 (33)	1095 (34)	94 (33)	0.97
Current smoking, no. (%)	1033 (29)	931 (29)	102 (36)	0.010
Alcohol use (drink per week), median (IQR)	0.23 (0–3)	0.23 (0–3)	0.33 (0–4.5)	0.30
Use of diuretics, no. (%)	308 (9)	280 (9)	28 (10)	0.38
Use of thiazide diuretics, no. (%)	228 (7)	206 (6)	22 (8)	0.28
Use of potassium sparing diuretic, no. (%)	125 (4)	112 (4)	13 (5)	0.27
Use of loop diuretic, no. (%)	83 (2)	75 (2)	8 (3)	0.53
History of CHF, no. (%)	170 (6)	150 (6)	20 (9)	0.043
History of cirrhosis, no. (%)	20 (0.6)	14 (0)	6 (2)	0.004
History of cancer, no. (%)	143 (4)	129 (4)	14 (5)	0.42
Use of SSRI, no. (%)	149 (4.2)	130 (3.9)	19 (6.7)	0.042
Use of AED, no. (%)	51 (1.4%)	45 (1.4)	6 (2.1)	0.033
Serum sodium, median (IQR), mEq/l	138 (136–139)	138 (136–139)	133 (132–134)	<0.0001
Corrected sodium, median (IQR), mEq/l	138 (136–139)	138 (137–139.13)	134 (133–134)	<0.0001
Serum chloride, median (IQR), mEq/l	105 (104–107)	106 (104–107)	104 (102–106)	<0.0001
Serum creatinine, median (IQR), mg/dl	0.9 (0.7–1.0)	0.9 (0.7–1.0)	0.8 (0.7–1.0)	0.026
eGFR, median (IQR) ml/min per 1.73 m <sup>2</sup>	98 (84–113)	97 (84–112)	104 (86–119)	0.001
Serum cystatin-C, median (IQR)	0.82 (0.74–0.92)	0.82 (0.74–0.93)	0.80 (0.70–0.92)	0.007
Serum uric acid, median (IQR), mg/dl	5.3 (4.4–6.3)	5.3 (4.4–6.3)	5.1 (4.1–6.2)	0.008
Serum albumin, median (IQR), mg/dl	4.0 (3.7–4.2)	4.0 (3.8–4.2)	3.9 (3.6–4.1)	<0.0001
Urine microalbumin, median (IQR), mg/dl	0.4 (0.2–0.8)	0.4 (0.2–0.8)	0.3 (0.2–0.8)	0.78
Serum BNP, median (IQR), pg/ml	3.3 (0–13.6)	3.3 (0–13.9)	2.4 (0–10.7)	0.28
Serum CRP, median (IQR), mg/dl	2.8 (1.2–7.0)	2.8 (1.2–6.9)	3.3 (1.2–7.7)	0.35
All-cause death, no. (%)	202 (6)	173 (5)	29 (10)	0.001
Cardiovascular death, no. (%)	82 (2)	73 (2)	9 (3)	0.32

Abbreviations: AED, antiepileptic drugs; BNP, B-natriuretic peptide; CHF, congestive heart failure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; Na, sodium; no., number; SSRI, selective serotonin reuptake inhibitor. Data are presented as median (Q1–Q3) or number (% of total).

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