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Prevalence of hyponatremia and association with mortality: Results from NHANES

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Abstract

Background—Hyponatremia is the most common electrolyte abnormality in hospitalized patients and is associated with adverse outcomes, but its prevalence and significance in the general U.S. population is unknown. Our aims were to determine the prevalence of hyponatremia and its association with mortality in the population.

Methods—We performed a population-based cross-sectional study of 14,697 adults aged 18 years who participated in the nationally representative National Health and Nutrition Examination Survey for 1999 – 2004. Using measurements of serum sodium corrected for dilutional effect of hyperglycemia, we determined the association of hyponatremia with patient characteristics, comorbidities, and prescription medications, and performed unadjusted and adjusted Cox proportional hazards regression to find the association of hyponatremia with all-cause mortality.

Results—We provide the first estimate of the prevalence of hyponatremia in the U.S. population, which in our weighted analysis was 1.72%. Prevalence of hyponatremia was significantly higher in females (2.09%, $p=0.004$) and increased with age. Hyponatremia was more common in subjects with hypertension, diabetes, coronary artery disease, stroke, chronic obstructive pulmonary disease, cancer, and psychiatric disorders, and less common with those with no comorbidities (1.04%, $p<0.001$). There was a significant risk of death associated with hyponatremia in unadjusted (HR 3.61, $p<0.001$) and adjusted Cox models controlling for demographics, smoking, comorbidities and insurance status (HR 2.43, $p<0.001$). There was a U-shaped relationship between serum sodium and hazard ratio for mortality.

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Conclusions—Our findings suggest that hyponatremia is a predictor of mortality in the general population independent of age, gender, and comorbid conditions.

Keywords

hyponatremia; mortality; Epidemiology and outcomes; electrolytes; NHANES; medications; comorbidity; outpatient; general population

Introduction

Hyponatremia is the most common electrolyte abnormality encountered in the hospitalized patient, and the reported prevalence has varied with the nature of the patient population and health care setting studied.¹⁻⁵ Hyponatremia frequently develops during the course of hospitalization either as a complication of an underlying acute illness or as a consequence of therapeutic interventions.^{1, 3-8} Hyponatremia among hospitalized patients has been associated with increased morbidity and mortality, but whether the mortality is associated with hyponatremia itself or the underlying illness remains unclear.⁹⁻¹² However, not infrequently, hyponatremia is manifest at the time of presentation to the emergency room or ambulatory care setting and is either seemingly asymptomatic or associated with relatively subtle symptoms such as a nausea, headaches, and lethargy.^{13, 14} Other neurological symptoms associated with hyponatremia including attention deficit, impaired balance or memory are frequently mild and often overlooked, but may result in significant morbidity, including higher rates of falls/fractures.¹⁵⁻¹⁸ Despite its relative frequency among patients in the hospital setting, the prevalence of hyponatremia in the general population remains unknown, as does the clinical significance of the hyponatremia in the outpatient setting.^{1, 3, 19, 20} Analyses based on administrative data have been unable to adequately characterize hyponatremia in the outpatient population.²⁰ With the direct costs of hyponatremia in the range of \$1.6 – \$3.6 billion annually in the US, and the potential increase in mortality associated with this condition, a better understanding of this condition is essential.^{9, 13, 21-24}

Methods

The National Health and Nutrition Examination Survey (NHANES) is conducted by the National Center for Health Statistics (NCHS). Since 1999, data has been collected continuously from a representative sample of the civilian non-institutionalized population of the U.S. via in-home personal interviews and physical examinations in mobile examination centers, including laboratory measurements of serum electrolytes, creatinine, protein, and lipids.²⁵ NHANES uses a complex, multistage, probability sampling design with oversampling of some subgroups to increase the reliability and precision of health status indicator estimates for these groups.²⁵ Sample weights are provided to account for the complex survey design, including oversampling, survey non-response, and post-stratification, and are used in the analysis to create populations representative of the U.S. Census civilian non-institutionalized population. Detailed descriptions of the complex survey design, interviewing procedures, and physical examinations have been published previously.²⁵

Mortality outcome

Participants in NHANES 1999-2004 were prospectively followed up for mortality from the date of survey participation through December 31, 2006 using probabilistic matching between NHANES and National Death Index (NDI) death certificate records.²⁶ Additional sources of information used to determine the final mortality status of a NHANES survey

participant include indication of deceased status from the Social Security Administration, Centers for Medicare and Medicaid Services, or death certificate review.²⁶

Definitions

Participant characteristics including demographics and comorbidities were determined from self-reported information on household questionnaires and a combination of physical and laboratory findings. Detailed information on how comorbid conditions were defined is available in the supplement. Documentation on the different laboratories, methods, reference ranges and analyzers used over the survey period have been previously published and are publicly available.²⁷⁻²⁹

Definition of Hyponatremia

Hyponatremia was defined as serum sodium below the reference ranges provided by the NHANES laboratory testing centers, which were 133-145 mmol/L for the 1999-2002 survey cycles and 136-144 mmol/L for 2003-2004.²⁷⁻²⁹ Patients with hypernatremia (n=88), defined as sodium above the reference ranges, were excluded, given the differing etiologies of these derangements in serum sodium and to avoid confounding by the likely U shaped relationship between serum sodium and adverse outcomes.^{4, 14, 30} As serum sodium was measured using indirect ion selective electrodes and direct measurements of serum osmolality were not available, we used estimates of plasma water content to identify cases of pseudohyponatremia and excluded these subjects from our analysis.^{30,33} Sodium levels were corrected for the dilutional effect associated with hyperglycemia using the following previously validated methods: $\text{sodium}_{\text{corr}} = \text{sodium} + 1.6 * ((\text{glucose} - 100) / 100)$ for glucose between 200 and 400 mg/dL, and $\text{sodium}_{\text{corr}} = \text{sodium} + 3.2 + 2.4 * ((\text{glucose} - 400) / 100)$ for glucose > 400 mg/dL.³¹⁻³⁴

Participant characteristics

Age, gender, race/ethnicity, education, marital status, family poverty income ratio (PIR; ratio of family income to poverty guidelines determined by the Department of Health and Human Services)²⁵, insurance status, and number of hospital stays were determined from household questionnaires. BMI was calculated from the height and weight measurements taken in mobile examination centers. Subjects were considered underweight for BMI < 18.5, normal weight for BMI 18.5 to 24.9, overweight for BMI 25.0 to 29.9, and obese for BMI ≥ 30.0 kg/m². Health related behaviors such as smoking, drug use, and alcohol consumption was ascertained through interviews at the home at in mobile examination centers.²⁵

As hyponatremia is commonly associated with a number of medical conditions, we attempted to identify patients with these comorbidities in the NHANES cohort using a combination of laboratory results, responses to disease specific questions, and current medications as appropriate. Specifically, we identified participants with evidence of hypertension, diabetes, congestive heart failure³⁰, liver disease¹⁹, kidney disease⁵, stroke³⁵, Chronic Obstructive Pulmonary Disease³⁶, cancer²³, HIV³⁷, depression and other psychiatric disorders. We also identified subjects who were using medications with known or suspected associations with hyponatremia including diuretics, angiotensin-converting-enzyme (ACE) inhibitors^{38, 39}, angiotensin receptor blockers (ARBs), nonsteroidal anti-inflammatory agents (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs)⁴⁰, carbamazepine, and lamotrigine.⁶ Detailed description of methods used to identify comorbidities and medication usage is described in the Appendix.

Statistical Analysis

All analyses were conducted using Stata Version 12.1 (Stata Corp, College Station, TX). The Stata *svy* prefix command was used to incorporate the NHANES sampling weights and account for the complex sampling design, which included unequal probabilities of selection, oversampling, and nonresponse. Sampling weights were applied for all analyses to produce estimates that are representative of the U.S. population after combining data from the 1999 – 2000, 2001 – 2002 and 2003 – 2004 NHANES cohorts.⁴¹

Categorical variables were compared using the chi squared test. Continuous variables were compared using the Adjusted Wald test. Logistic regression was performed to obtain odds ratios of hyponatremia in subpopulations with comorbid conditions. Univariate Kaplan Meier survival curves were compared using the Cox regression based test for equality of survival curves. Cox proportional hazards models were used to estimate unadjusted and adjusted hazard ratios associated with hyponatremia for the entire cohort and for defined subgroups of subjects.

We assessed the nonlinear relationship between corrected sodium across the range of 119-145mEq/L with all-cause mortality using nonparametric restricted cubic splines. Five knots were used at the 10th, 25th, 50th, 75th, and 90th percentiles of the corrected sodium distribution. The median value of 139mEq/L was chosen as the reference for calculating the hazard ratios.

Missing Data

Data was missing for less than 5% of subjects on all variables of interest with the exception of information on alcohol use (9.5% missing), which was only available for subjects aged 18 and older, family income for the calculation of poverty income ratio (7.3% missing), and HIV status (37.8% missing) and as a result these were excluded from our multivariate models.

Results

Overall, 31,116 subjects were surveyed during the continuous NHANES cycles between 1999 and 2004. Our analysis included 14,804 subjects aged 18 years or greater who had a measured serum sodium concentration. Hyponatremia was defined as serum sodium below the reference ranges provided by the NHANES laboratory testing centers, which were 133-145 mmol/L for the 1999-2002 survey cycles and 136–144 mmol/L for 2003-2004.²⁷⁻²⁹ Subjects with hypernatremia were excluded (n=88), as were 19 subjects with evidence of pseudohyponatremia, resulting in a final cohort of 14,697 subjects.³¹ The mean (SD) age of our cohort was 45 (14.7) years. Subjects with evidence of dilutional hyponatremia (n=37) were identified among the 320 subjects with a serum glucose >200 mg/dL and reclassified as having normonatremia when the corrected sodium was found to be within the given reference range.

Prevalence of Hyponatremia

The sodium concentration in our population had a normal distribution with a mean (standard deviation) serum sodium concentration of 139 (1.94)mmol/L (Figure 1). The weighted prevalence of hyponatremia in our NHANES cohort was 1.72% (1.89% including cases of dilutional hyponatremia) and was significantly more common among females than males (2.1% vs. 1.3%, $p=0.0044$, see table 1 and figure 2). Subjects with hyponatremia were significantly older (52.8 vs. 45 years, $p<0.001$), and the prevalence of hyponatremia increased with age in both genders, but more so among female subjects (1.6% to 4.1%, table 1 and figure 3). The odds of having hyponatremia also increased significantly with

increasing age and among females compared to males (Figure 3). The prevalence of hyponatremia appeared to trend down with lower BMI but this was not statistically significant ($p=0.15$). Hispanic subjects were significantly less likely to have hyponatremia compared to white or black non-Hispanics (0.85% vs. 1.87% and 1.75%, $p=0.027$). Hyponatremia was significantly more common among subjects with health insurance and in those who had attained a high school level education, and less common among those with no history of smoking. Hyponatremia prevalence did not significantly vary with the family poverty income ratio or alcohol consumption.

Subjects with one or more comorbidities had a significantly higher prevalence of hyponatremia than the overall cohort at 2.26% ($p=0.0001$). Specifically, the prevalence of hyponatremia was significantly higher among subjects with hypertension, diabetes, coronary artery disease, cancer, stroke, Chronic Obstructive Pulmonary Disease, and psychiatric disorders. Of note, hyponatremia prevalence was not significantly higher among patients with congestive heart failure, thyroid, liver or kidney disease. In contrast, subjects without any identifiable comorbid conditions had a significantly lower prevalence of hyponatremia. Subjects with hyponatremia had significantly higher blood pressure, lower protein, and more hospital stays in the past year. Consistent with previous reports, subjects taking thiazide diuretics, carbamazepine, lamotrigine, ACE inhibitors or ARBs, and SSRIs had significantly higher prevalence of hyponatremia.⁶ However, we did not find a significant increase in the incidence of hyponatremia associated with the use of NSAIDs or TCAs.

Association of Hyponatremia with Mortality

Mortality data was available for 14,679 subjects (99.9%) of our cohort. The overall mortality rate over the period 1999-2006 for hyponatremic subjects was 11% versus 4% for subjects with normonatremia (unadjusted relative hazard ratio 3.61). The prevalence of hyponatremia was significantly higher among deceased subjects than among the overall cohort (4.47%, $p<0.001$). Cox regression models that included adjustment for age and gender attenuated the association of hyponatremia and all-cause mortality slightly (HR 2.24, $p=0.001$), but risk of mortality remained significantly elevated for subjects with hyponatremia after further adjustment for comorbidities, ethnicity, insurance status, and smoking (HR, 2.43; $P<0.001$, figure 4). Using cubic splines, we demonstrate a nonlinear but uniform increase in the hazard ratio with decreasing sodium concentrations with no discernible threshold effect (Figure 5).

In subgroup analysis, hyponatremia was associated with significantly increased hazard ratios among women and subjects with any known comorbid conditions, coronary artery disease, kidney disease, liver disease, and thyroid disorders as well as subjects with no known comorbid conditions, but not among subjects with hypertension, diabetes, COPD, cancer or psychiatric disorders (Figure 6 and Table 4). Significantly increased risk for mortality was seen in both subjects < 50 years of age (HR 5.76, $p=0.029$), and older subjects ≥ 50 years (HR 2.35, $p<0.001$). Among subjects with hyponatremia, mortality rates did not vary by gender or race/ethnicity. Mortality rates within hyponatremic subjects were significantly higher for subgroups with the greatest poverty, at 19% in those with family poverty income ratio (PIR) of 0-0.99, compared to 1.6% in those with PIR ≥ 5 ($p=0.035$), and in hyponatremic subjects with coronary artery disease, congestive heart failure, liver disease, kidney disease, HIV, and cancer. Mortality rates were significantly lower for those hyponatremic subjects with higher BMIs, at 7.1% for overweight and 0.19% for obese subjects ($p<0.001$). Mortality rates appeared higher for hyponatremic subjects with less than high school education (17%), current smoking (18%), and heavy alcohol use (19%) but these did not reach statistical significance.

Discussion

We report, for the first time, an estimate of the prevalence of hyponatremia in the general U.S. population and its relative prevalence in subjects with and without specific comorbidities. Our analysis demonstrates an increase in the prevalence of hyponatremia with age and a higher prevalence of hyponatremia among women in the general population, a finding that was suspected given similar trends previously reported among cohorts of patients in acute and long-term care facilities, and a previously unreported lower prevalence among Hispanics.^{8, 42} Subjects with comorbidities were significantly more likely to have hyponatremia compared to those with no comorbidities. In addition, subjects with hyponatremia were significantly older, had higher systolic blood pressure, lower diastolic blood pressure, and significantly higher rates of hospitalization in the year preceding participation. These findings demonstrate an association of hyponatremia with an increased burden of illness.

Subjects who were taking medications that have been previously associated with the development of hyponatremia were identified in our cohort. Our analysis confirms the association of thiazides, ACE inhibitors/ ARBs, SSRIs, carbamazepine and lamotrigine with hyponatremia. Notably, we did not see the association between NSAIDs and hyponatremia that has been previously reported.⁴³ However, this was not surprising given that the majority of studies that report this association include additional contributors such as extreme exercise, concomitant chemotherapy or other medications such as diuretics, while association of hyponatremia with NSAID therapy alone appears to be rare.⁴⁴⁻⁴⁶

Adverse consequences have previously been associated with hyponatremia among hospitalized patients;⁹ however, distinguishing whether hyponatremia is merely a marker of disease progression or whether the hyponatremia is itself detrimental has been a challenge.¹¹ Recent analyses of small inpatient cohorts with hyponatremia have suggested that hyponatremia is little more than a surrogate for an underlying pathophysiology rather than being an independently detrimental factor.^{11, 47} While our analysis confirms that hyponatremia occurs more commonly with various comorbidities, we did not find a significant increase in the incidence of hyponatremia among patients with congestive heart failure and liver disease, perhaps because the subjects in our cohort were not acutely ill with a decompensated physiological state. In addition, we also demonstrate a five-fold increase in mortality risk among subjects with hyponatremia and no identified comorbid conditions compared to similar subjects with normonatremia. After adjustment for age, gender, comorbidities and other factors that may affect mortality, hyponatremia remains associated with significantly increased risk of mortality in all subjects, suggesting an inherent negative impact associated with a chronic hypotonic state beyond that of the underlying illness. Recent small studies have shown similar associations of hyponatremia with all-cause mortality but have been limited to elderly patients in community settings.^{18, 48} Our study is the first to demonstrate the clinical significance of hyponatremia in a nationally representative outpatient population of all adults aged ≥ 18 years, and demonstrates the increased mortality risk with hyponatremia even among subjects aged 18-50. We demonstrate a U-shaped association of serum sodium with hazard ratio for mortality with no discernible threshold effect, suggesting even small derangements in serum sodium in the general population are clinically significant. Our results support the growing body of evidence that mild hyponatremia is not benign and highlights the need for a better understanding of the link between chronic hyponatremia and adverse outcomes, and whether for heightened vigilance for hyponatremia in the ambulatory care setting and treatment of these patients with mild hyponatremia could improve outcomes.

Using the NHANES dataset had several advantages, including the large cohort representative of the U.S. non-institutionalized population, allowing us to extrapolate our findings to the entire population. The extensive database allowed us to consider several key comorbidities and medications associated with hyponatremia as well as use follow-up mortality data to assess our primary outcome. Nevertheless, our study is a cross sectional cohort study with a single serum sodium measurement that does not reflect changes in clinical management such as the recent introduction of vasopressin receptor antagonists. Additionally, a number of comorbidities were based on self-report, which may be limited by participants' awareness of their health conditions and access to care although we attempted to verify self-reported information either with other laboratory data or with medication use when possible. During the NHANES 1999-2004 cycles, serum osmolality was not measured necessitating indirect methods to identify cases of pseudohyponatremia and dilutional hyponatremia. Excluding subjects with pseudohyponatremia and dilutional hyponatremia from the subgroup of subjects with hyponatremia lowered the overall prevalence of hyponatremia marginally but did not significantly impact our overall results.

In summary, after excluding cases of pseudohyponatremia and correcting for dilutional hyponatremia, our analysis of the NHANES 1999-2004 cohort estimates the overall prevalence of hyponatremia to 1.72% of the United States population. We demonstrate an increasing prevalence of hyponatremia with increasing age in the population, higher rates of hyponatremia among women as well as a significant association between hyponatremia and all-cause mortality that persists even after adjustments for age, gender and several comorbidities. Our results suggest that hyponatremia is an independent predictor of mortality in the general outpatient population and underscores the need for an improved understanding of hyponatremia and its adverse impact on health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Significance

1. This study provides the first estimate of hyponatremia in the general US population at 1.72% with a significantly greater prevalence among women and the elderly
2. Hyponatremia is more common among patients with hypertension, diabetes, coronary artery disease, stroke, chronic obstructive pulmonary disease, cancer, and psychiatric disorders.
3. Hyponatremia in the apparently asymptomatic outpatient appears to be independently associated with an marked increase in the risk of all-cause mortality.

Figure 1. Distribution of serum sodium concentrations (corrected for dilutional hyponatremia) (*Please note y axis extends from 0% to 20%*)

Figure 2.
Prevalence of hyponatremia by age and gender by weighted analysis in NHANES 1999-2004

Figure 3. Odds Ratio for hyponatremia in various subgroups on logarithmic scale (95% confidence interval). Values reported in Table 1.

Figure 4. Cumulative mortality in subjects with normonatremia and hyponatremia (*Please note y axis extends from 0% to 20%*) ($1\text{mmol/L} = 1\text{mEq/L}$ for Na)

Figure 5. Restricted cubic spline depicting relationship between corrected serum sodium and all-cause mortality. Dashed lines represent the 95% confidence interval.

Figure 6.

Hazard ratio associated with hyponatremia in patients with various comorbidities on logarithmic scale. (95% confidence interval). Confidence interval and p values reported in Table 4.

Table 1

Prevalence of hyponatremia across various population subgroups in NHANES 1999-2004

Characteristics	Overall		Normonatremia		Hyponatremia		Hyponatremia Prevalence ^a	p value	Odds Ratio ^b (95% CI)	p value
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)				
Overall	14697	100	14396	98.3 (97.9-98.6)	301	1.72 (1.42-2.07)	1.72%			
Age										
18 - 44	7418	52.5 (50.7-54.2)	7298	51.9 (50.1-53.7)	120	0.59 (0.42-0.83)	1.13%		Ref	
45 - 64	3798	31.4 (29.8-33.1)	3723	30.8 (29.3-32.5)	75	0.60 (0.46-0.80)	1.92%			1.72 (1.16-2.56) 0.008
65 - 84	3071	14.6 (13.8-15.5)	2984	14.2 (13.4-15.0)	87	0.46 (0.35-0.59)	3.11%	<0.001		2.82 (1.91-4.19) <0.001
> 85	410	1.5 (1.3-1.7)	391	1.4 (1.2-1.6)	19	0.07 (0.03-0.13)	4.52%			4.16 (2.01-8.63) <0.001
Gender										
Male	7029	48.2 (47.5-49.0)	6928	47.6 (46.9-48.3)	101	0.63 (0.47-0.85)	1.32%		Ref	
Female	7668	51.8 (51.1-52.5)	7468	50.7 (50.0-51.5)	200	1.08 (0.88-1.33)	2.09%	0.004	1.60 (1.16-2.20)	0.005
BMI								0.31		
Underweight	278	2.0 (1.8-2.3)	263	2.0 (1.7-2.2)	15	0.07 (0.03-0.14)	3.22%		1.54 (0.75-3.17)	0.23
Normal Weight	4684	33.4 (32.1-34.6)	4569	32.7 (31.5-34.0)	115	0.66 (0.49-0.89)	1.98%	0.15	Ref	
Overweight	4950	34.3 (33.0-35.6)	4863	33.8 (32.4-35.1)	87	0.53 (0.40-0.69)	1.54%		0.79 (0.54-1.16)	0.23
Obese	4387	30.3 (28.9-31.8)	4313	29.9 (28.5-31.3)	74	0.45 (0.31-0.64)	1.48%		0.81 (0.51-1.29)	0.37
Race/Ethnicity										
White Non-Hispanic	7073	71.5 (68.0-74.8)	6889	70.2 (66.7-73.4)	184	1.34 (1.09-1.64)	1.87%		Ref	
Black Non-Hispanic	2874	10.5 (8.6-12.6)	2824	10.3 (8.5-12.4)	50	0.18 (0.12-0.27)	1.75%	0.027	0.93 (0.66-1.32)	0.69
Hispanic	4218	13.3 (10.5-16.7)	4166	13.2 (10.4-16.6)	52	0.11 (0.08-0.17)	0.85%		0.45 (0.29-0.71)	0.001
Other	532	4.8 (3.9-5.9)	517	4.7 (3.8-5.8)	15	0.09 (0.04-0.18)	1.79%		0.96 (0.47-1.97)	0.91
Family PIR										
0 - 0.99	2727	14.2 (12.7-15.9)	2668	14.0 (12.5-15.6)	59	0.26 (0.18-0.39)	1.85%		1.20 (0.75-1.91)	0.44
1.00 - 1.99	3571	21.0 (19.4-22.7)	3498	20.7 (19.1-22.3)	73	0.33 (0.23-0.46)	1.55%	0.68	Ref	

Characteristics	Overall		Normonatremia		Hyponatremia		Hyponatremia Prevalence ^a	p value	Odds Ratio ^b (95% CI)	p value
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)				
2.00 - 2.99	2132	16.0 (14.9-17.1)	2086	15.7 (14.7-16.8)	46	0.29 (0.20-0.42)	1.82%		1.18 (0.69-2.01)	0.55
3.00 - 3.99	1545	13.6 (12.5-14.8)	1516	13.3 (12.3-14.5)	29	0.27 (0.17-0.41)	1.95%		1.26 (0.78-2.04)	0.33
4.00 - 4.99	1186	11.7 (10.8-12.7)	1172	11.6 (10.7-12.6)	14	0.14 (0.07-0.27)	1.17%		0.75 (0.34-1.65)	0.47
≥5.00	2290	23.5 (21.2-25.9)	2233	23.1 (20.8-25.5)	57	0.41 (0.29-0.58)	1.74%		1.13 (0.75-1.69)	0.56
Insurance Status										
Uninsured	3067	17.8 (16.5-19.2)	3034	17.7 (16.4-19.0)	33	0.18 (0.11-0.29)	1.00%		Ref	
Insured	11448	82.2 (80.8-83.5)	11181	80.6 (79.2-82.0)	267	1.55 (1.29-1.87)	1.89%	0.006	1.91 (1.20-3.03)	0.007
Education										
< High School	4971	21.0 (19.7-22.4)	4885	20.7 (19.5-22.1)	86	0.29 (0.21-0.41)	1.40%		Ref	
High School	3599	26.4 (24.9-27.9)	3509	25.7 (24.3-27.2)	90	0.63 (0.48-0.84)	2.39%	0.026	1.73 (1.19-2.51)	0.005
> High School	6100	52.6 (50.6-54.6)	5975	51.8 (49.8-53.9)	125	0.79 (0.59-1.07)	1.51%		1.08 (0.76-1.54)	0.65
Smoking Status										
Never Smoker	6747	50.0 (48.1-51.8)	6615	49.2 (47.4-51.1)	132	0.72 (0.57-0.92)	1.45%	0.039	Ref	
Former Smoker	3302	23.7 (22.4-25.1)	3216	23.2 (21.9-24.6)	86	0.52 (0.41-0.67)	2.20%		1.53 (1.12-2.10)	0.009
Current Smoker	3121	26.3 (24.8-27.9)	3051	25.8 (24.3-27.3)	70	0.52 (0.37-0.73)	1.96%		1.36 (1.01-1.83)	0.044
Alcohol Use										
Never	1841	12.6 (10.4-15.1)	1803	12.4 (10.3-14.9)	38	0.21 (0.14-0.33)	1.69%		Ref	
Former	2096	15.5 (14.4-16.6)	2047	15.2 (14.2-16.3)	49	0.28 (0.20-0.38)	1.79%	0.77	1.06 (0.58-1.93)	0.85
Moderate	6274	52.9 (50.5-55.3)	6141	52.0 (49.6-54.4)	133	0.91 (0.68-1.21)	1.71%		1.01 (0.67-1.53)	0.95
Heavy	2089	19.0 (17.8-20.3)	2045	18.6 (17.4-19.9)	44	0.39 (0.26-0.59)	2.07%		1.23 (0.72-2.10)	0.45
Hospital Stay in Past Year ^c	1785	10.7 (10.0-11.4)	1735	10.4 (9.7-11.1)	50	0.27 (0.18-0.43)	2.57%	0.06	1.61 (0.98-2.63)	0.06
Comorbidities	6457	44.6 (43.0-46.1)	6364	44.1 (42.6-45.6)	93	0.46 (0.31-0.68)	2.26%	<0.001	2.21 (1.51-3.24)	<0.001
Hypertension	4723	28.9 (27.4-30.4)	4585	28.0 (26.6-29.5)	138	0.84 (0.70-1.02)	2.92%	<0.001	2.57 (1.77-3.73)	<0.001
Diabetes	1601	8.3 (7.6-9.0)	1553	8.0 (7.3-8.7)	48	0.28 (0.19-0.40)	3.34%	0.001	2.16 (1.39-3.38)	0.001

Characteristics	Overall		Normonatremia		Hyponatremia		Hyponatremia Prevalence ^a	p value	Odds Ratio ^b (95% CI)	p value
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)				
CAD	1079	6.4 (5.7-7.1)	1047	6.2 (5.5-6.9)	32	0.17 (0.11-0.25)	2.64%	0.029	1.58 (1.05-2.38)	0.031
CHF	411	2.3 (2.0-2.7)	401	2.2 (1.9-2.6)	10	0.06 (0.04-0.14)	2.57%	0.28	1.49 (0.71-3.14)	0.29
Stroke	446	2.5 (2.1-2.9)	431	2.4 (2.1-2.8)	15	0.09 (0.05-0.17)	3.61%	0.016	2.15 (1.15-4.02)	0.018
Thyroid	1186	9.4 (8.8-10.1)	1151	9.2 (8.6-9.9)	35	0.23 (0.14-0.36)	2.41%	0.15	1.43 (0.87-2.36)	0.16
COPD	961	7.7 (7.0-8.5)	921	7.4 (6.8-8.2)	40	0.30 (0.21-0.44)	3.87%	<0.001	2.52 (1.67-3.78)	<0.001
Cancer	1114	8.0 (7.4-8.7)	1077	7.7 (7.1-8.4)	37	0.27 (0.20-0.38)	3.38%	<0.001	2.12 (1.49-3.03)	<0.001
Liver Disease	1697	11.3 (10.4-12.3)	1666	11.1 (10.3-12.1)	31	0.19 (0.12-0.30)	1.66%	0.78	0.93 (0.56-1.55)	0.78
Kidney Disease	1426	7.3 (6.8-7.9)	1397	7.2 (6.7-7.7)	29	0.14 (0.09-0.22)	1.94%	0.51	1.14 (0.76-1.71)	0.51
Psychiatric Disorder	1341	11.3 (10.5-12.1)	1302	10.9 (10.2-11.7)	39	0.32 (0.22-0.47)	2.86%	0.002	1.85 (1.28-2.68)	0.002
HIV	43	0.4 (0.3-0.6)	42	0.4 (0.3-0.6)	1	0.00 (0.00-0.03)	0.80%	0.67	0.65 (0.08-5.05)	<0.001
No Comorbidities	6457	44.6 (43.0-46.1)	6364	44.1 (42.6-45.6)	93	0.46 (0.31-0.68)	1.04%	<0.001	0.45 (0.31-0.66)	<0.001
Medications										
Thiazide Diuretics	1053	6.7 (5.9-7.6)	1001	6.3 (5.6-7.2)	52	0.33 (0.24-0.46)	4.94%	<0.001	3.49 (2.43-5.02)	<0.001
ACE-Inhibitors/ARBs	1835	11.0 (10.2-12.0)	1762	10.6 (9.8-11.6)	73	0.41 (0.30-0.56)	3.73%	<0.001	2.65 (1.84-3.81)	<0.001
NSAIDs	1501	12.4 (11.5-13.3)	1475	12.2 (11.3-13.1)	26	0.20 (0.13-0.30)	1.61%	0.78	0.93 (0.59-1.47)	0.74
SSRIs	664	6.00 (5.48-6.55)	642	5.82 (5.3-6.4)	22	0.17 (0.10-0.29)	2.91%	0.032	1.80 (1.03-3.11)	0.038
TCAs	180	1.48 (1.20-1.82)	176	1.45 (1.2-1.8)	4	0.03 (0.01-0.11)	2.23%	0.63	1.31 (0.41-4.24)	0.64
Carbamazepine	261	1.34 (1.13-1.60)	249	1.29 (1.1-1.6)	12	0.05 (0.03-0.11)	4.00%	0.028	2.43 (1.07-5.52)	0.035
Lamotrigine	7	0.06 (0.02-0.14)	6	0.05 (0.0-0.1)	1	0.01 (0.00-0.08)	16.9%	0.009	11.70 (1.14-120)	0.039
Mortality Status										
Alive	13781	95.8 (95.3-96.2)	13514	94.3 (93.7-94.8)	267	1.53 (1.25-1.87)	1.60%	<0.001	Ref	
Deceased	898	4.2 (3.8-4.7)	864	4.0 (3.6-4.5)	34	0.19 (0.12-0.30)	4.47%		2.88 (1.76-4.71)	<0.001

Abbreviations: n, unweighted number of subjects; %, weighted proportions; CI, confidence interval; BMI, body mass index (kg/m²); PIR, poverty income ratio; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ACE-Inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

^a Weighted proportion of subjects within each subgroup with hyponatremia.

^b Odds ratio: Odds of hyponatremia associated with each characteristic.

^c At least one overnight hospital stay in past year.

Table 2

Hazard ratio for mortality associated with hyponatremia in Cox regression models

Model	Hazard Ratio	95% Confidence Interval	p value
Unadjusted	3.61	2.31 – 5.63	<0.001
Model 1	2.24	1.41 – 3.56	0.001
Model 2	2.36	1.53 – 3.63	<0.001
Model 3	2.43	1.54 – 3.83	<0.001

Model 1: Adjusted for age and gender. Model 2: Adjusted for age, gender, coronary artery disease, congestive heart failure, liver disease, kidney disease, cancer and psychiatric disorders. 11.5% subjects with missing data. Model 3: Adjusted for age, gender, coronary artery disease, congestive heart failure, liver disease, kidney disease, cancer and psychiatric disorders, insurance, ethnicity, and smoking status. 12.5% subjects with missing data.

Table 3

Comparison of continuous variables between normonatremic and hyponatremic subjects

Characteristic	Overall (SD)	Normonatremia (SD)	Hyponatremia (SD)	p value
Age (years)	45.1 (14.7)	45.0 (14.5)	52.8 (16.7)	<0.001
BMI (kg/m ²)	28.0 (5.3)	28.0 (5.2)	27.4 (6.2)	0.31
Mean Systolic BP (mmHg)	123.0 (16.0)	122.8 (15.6)	128.7 (21.2)	0.002
Mean Diastolic BP (mmHg)	71.5 (10.9)	71.5 (10.6)	69.3 (12.5)	0.030
Hospitalizations in Past Year	0.15 (0.5)	0.14 (0.4)	0.30 (0.8)	0.009
Poverty Income Ratio	2.93 (1.4)	2.95 (1.3)	2.91 (1.5)	0.68
Laboratory Values				
Uncorrected Sodium (mEq/L)	139.1 (2.0)	139.2 (1.8)	132.3 (2.7)	<0.001
Corrected Sodium (mEq/L) ^a	139.1 (1.9)	139.2 (1.8)	132.3 (2.6)	<0.001
Creatinine (mg/dL)	0.90 (0.3)	0.90 (0.3)	0.89 (0.7)	0.81
eGFR by CKD-EPI (mL/min/1.73m ²)	94.9 (18.8)	94.97 (18.7)	93.7 (23.1)	0.42
Glucose (mg/dL)	94.5 (24.4)	94.4 (24.2)	97.4 (33.7)	0.25
Glycohemoglobin (%)	5.45 (0.7)	5.45 (0.7)	5.64 (1.2)	0.06
Total Protein (g/dL)	7.34 (0.4)	7.34 (0.4)	7.19 (0.5)	<0.001
Triglycerides (mg/dL)	141.8 (117.2)	141.1 (105.9)	156.7 (291.9)	0.53
Total Cholesterol (mg/dL)	199.5 (35.0)	199.4 (34.5)	204.5 (54.4)	0.25

Abbreviations: SD, standard deviation; BMI, body mass index; BP, blood pressure; eGFR by CKD-EPI, estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration Formula⁵⁴

^aSerum sodium corrected for dilutional effect of hyperglycemia

Table 4

Hazard ratios for mortality associated with hyponatremia in various subgroups

Subgroup	Hazard Ratio	95% CI	p value
Overall	3.61	(2.31-5.63)	<0.001
Age 18-50 yrs	5.76	(1.20-27.5)	0.029
Age 50 yrs	2.35	(1.50-3.69)	<0.001
Female	3.73	(1.96-7.12)	<0.001
Any Comorbidities ^a	2.67	(1.72-4.14)	<0.001
No Comorbidities	5.57	(1.24-25.0)	0.026
Hypertension	1.68	(1.00-2.80)	0.047
Diabetes	1.35	(0.48-3.79)	0.56
CAD	2.58	(1.12-5.97)	0.027
CHF	1.97	(0.70-5.52)	0.19
Stroke	1.59	(0.61-4.17)	0.34
Cancer	2.52	(1.00-6.36)	0.051
Liver Disease	10.7	(5.55-20.8)	<0.001
Kidney Disease	2.22	(1.05-4.67)	0.037
Thyroid Disorder	3.67	(1.53-8.81)	0.005

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval^a*One or more comorbidities*

Table 5

Comparison of all-cause mortality rates in hyponatremic subjects of different subgroups

Characteristics	Proportion of Hyponatremia ^a	Alive	Deceased	Relative % Deceased ^b	p-value
Overall		89.03%	10.97%		
Male	37%	32.2%	4.8%	13%	0.45
Female	63%	56.9%	6.2%	9.8%	
BMI					
Underweight	3.8%	3.4%	0.4%	11%	<0.001
Normal Weight	39%	32.1%	6.7%	17%	
Overweight	31%	28.9%	2.2%	7.1%	
Obese	26%	26.3%	0.1%	0.2%	
Race/Ethnicity					
Non-Hispanic Whites	78%	68.7%	9.1%	12%	0.77
Non-Hispanic Blacks	11%	9.7%	0.9%	8.6%	
Hispanic	6.6%	6.1%	0.4%	6.7%	
Other	5.0%	4.4%	0.6%	11%	
Family PIR					
0 - 0.99	15.6%	12.6%	3.0%	19%	0.035
1.00 - 1.99	19.3%	17.5%	1.8%	9.1%	
2.00 - 2.99	17.2%	15.1%	2.1%	12%	
3.00 - 3.99	15.7%	13.1%	2.6%	16%	
4.00 - 4.99	8.1%	7.6%	0.5%	6%	
5.00	24.2%	23.8%	0.4%	1.6%	
Insurance Status					
Uninsured	10.3%	10.0%	0.3%	3.2%	0.07
Insured	89.7%	79.0%	10.7%	12%	
Education					
Less than High School	17%	14.2%	2.8%	17%	0.33
High School	37%	32.4%	4.3%	12%	
More than High School	46%	42.4%	3.8%	8.2%	
Smoking Status					
Never Smoker	41%	38.2%	2.9%	7%	0.11
Former Smoker	30%	26.6%	3.1%	10%	
Current Smoker	29%	24.1%	5.2%	18%	
Alcohol Use					
Never	12%	11.3%	0.6%	5%	0.29
Former	15%	14.1%	1.3%	8.6%	
Moderate	51%	45.8%	4.9%	9.7%	
Heavy	22%	17.9%	4.1%	19%	

Characteristics	Proportion of Hyponatremia ^a	Alive	Deceased	Relative % Deceased ^b	p-value
Comorbidities	73%	63%	10%	14%	0.008
Hypertension	51%	43.5%	7.1%	14%	0.24
Diabetes	16%	13.9%	2.2%	13%	0.68
CAD	9.6%	6.7%	2.8%	30%	0.013
CHF	3.3%	2.1%	1.3%	38%	0.009
Stroke	5.1%	3.8%	1.3%	26%	0.081
Thyroid Disease	13%	10.1%	2.8%	22%	0.082
COPD	17%	15.0%	2.1%	12%	0.61
Cancer	15%	11.5%	3.8%	25%	0.029
Liver Disease	11%	6.7%	3.9%	37%	0.001
Kidney Disease	8.3%	5.6%	2.7%	32%	0.002
Psychiatric Disorder	19%	16.4%	2.4%	13%	0.63
No Comorbidities	27%	26%	0.7%	2.5%	0.008

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease

^aWeighted proportion among subjects with hyponatremia in each subgroup.

^bRatio of % deceased to % of all hyponatremics within each subgroup.