Hyponatremia in acute internal medicine patients: prevalence and prognosis

PhD dissertation

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Dissertation Papers

Paper I

Validity of the International Classification of Diseases, 10th revision Discharge Diagnosis Codes for Hyponatraemia in the Danish National Registry of Patients.

Louise Holland-Bill, Christian F. Christiansen, Sinna P. Ulrichsen, Troels Ring, Jens Otto L. Jørgensen, Henrik T. Sørensen. *BMJ Open.* 2014 Apr 23;4(4):e004956.

Paper II

Hyponatremia and Mortality Risk: A Danish Cohort Study of 279,508 Acutely Hospitalized Patients.

Louise Holland-Bill, Christian F. Christiansen, Sinna P. Ulrichsen, Uffe Heide-Jørgensen, Troels Ring, Jens Otto L. Jørgensen, Henrik T. Sørensen. *Eur J Endocrinol*. 2015;173(1):71-81

Paper III

Preadmission Diuretic Use is Associated with Increased Mortality in Patients with Hyponatremia – a Propensity Score-matched Cohort Study.

Louise Holland-Bill, Christian F. Christiansen, Sinna P. Ulrichsen, Troels Ring, Jens Otto L. Jørgensen, Henrik T. Sørensen. (*submitted*)

Abbreviations

aMRR	Adjusted mortality rate ratio
ATC	Anatomical therapeutic chemical
ADH	Antidiuretic hormone
CCI	Charlson Comorbidity Index
CI	Confidence interval
CPR	Central person registry
CRS	Civil registration system
DIP	Department of internal medicine
DM	Diabetes mellitus
DNHSPD	Danish National Health Service Prescription Database
DNPR	Danish National Patient Registry
ED	Emergency department
eGFR	Estimated glomerular filtration rate
HA	Hospital admission
ICD	International Classification of Disease
ICU	Intensive care unit
ISE	Ion selective electrode
LVSD	Left ventricular systolic dysfunction
MeSH	Medical Subject Heading
NPV	Negative predictive value
OR	Odds ratio
PPV	Positive predictive value
RR	Relative risk
SIADH	Syndrome of inappropriate antidiuretic hormone
SSRI	Selective serotonin reuptake inhibitors

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1. Introduction

Sodium plays a vital role in maintaining cellular homoeostasis and total sodium body content is the key determinant of extracellular fluid volume and, in most circumstances, effective arterial blood volume.[1] Several diseases and conditions can disrupt the delicate balance between intake and output of water and sodium, and serum sodium measurements are therefore among the most commonly performed laboratory tests.[2] Abnormalities in serum sodium, generally defined as hyponatremia if sodium concentration is <135 mmol/l and as hypernatremia if sodium concentration is >145 mmol/l, virtually always result from disturbances in water balance, with excess or deficit body water relative to body sodium content.[1,3,4]

This dissertation focuses on hyponatremia, which is often described as the most frequently encountered electrolyte disorder in clinical practice, with a reported occurrence ranging from 5% to over 45% depending on the setting and patients studied.[5,6] Hyponatremia is predominantly accompanied by hypotonicity[7] but can also occur under isotonic or even hypertonic conditions; for example, in the event of elevated glucose, where water is translocated from the intracellular fluid to the extracellular fluid, resulting in hyponatremia without sodium being excreted.[3] Because total body sodium can be decreased, normal, or increased in the presence of hyponatremia, hyponatremia is often classified according to the hydration status of the patient into hypovolemic, euvolemic, or hypervolemic hyponatremia.[3]

The prevalence of hyponatremia is associated with a wide range of medical conditions and pharmacological treatments. A growing body of evidence from case reports, case–control, and cohort studies in patients with some of these specific preexisting diseases suggests a link between hyponatremia and increased in-hospital mortality. In addition, experimental animal studies have provided possible explanations for a causal link between hyponatremia and mortality. Yet, whether hyponatremia in itself impacts mortality or is merely a marker of the underlying disease has become a matter of great controversy.[8] Key aspects of hyponatremia epidemiology, including risk factors for hyponatremia, indications for measuring serum sodium, and the occurrence and short- and long-term prognosis of hyponatremia, are poorly understood and may contribute to advance our knowledge about this condition.

Overall, clinical research concerns either risk factors for or prognosis of medical conditions or diseases.[9] The focus of this dissertation was to examine the prognosis of hyponatremia in a broad population of internal medicine patients. Studies on prognosis are often divided into clinical prediction studies, which aim to predict the probability of an outcome based on a set of patient characteristics, or prognostic studies, which examine the impact of a specific exposure on the outcome, also called causal prognostic studies. Serum sodium concentration is included in several clinical prediction models, such as the Model

for End-Stage Liver Disease (MELD) score, which predicts 3-, 6-, and 12-month mortality in patients awaiting liver transplantation,[10,11] the new Simplified Acute Physiology Score (called SAPS II) and the Acute Physiology and Chronic Health Evaluation II (called APACHE II) score for predicting in-hospital mortality in ICU patients.[12,13] In contrast, this dissertation centers on prognostic studies. A prerequisite for conducting clinical research is access to valid data. The Danish National Patient Registry (DNPR) has proven to be valuable for research in many contexts[14,15]; however, whether data registered in the DNPR could be useful when examining hyponatremia epidemiology was unknown.

This dissertation is based on three studies, referred to as studies I, II, and III. Study I examines the quality of International Classification of Diseases (ICD), 10th revision (ICD-10), codes for hyponatremia in the DNPR. Study II examines the prevalence of hyponatremia and its prognostic impact on short- and long-term mortality in patients acutely admitted to departments of internal medicine. Study III seeks to clarify whether diuretic use, a potential risk factor for the development of hyponatremia, affects prognosis.

The dissertation opens with an introduction to hyponatremia, including a review of the existing literature pertaining to the dissertation hypotheses and aims. Subsequently, it provides a summary of the methods used in each study, the main results, and the conclusions. This summary is followed by a discussion of clinical implications and perspectives based on methodological considerations and in relation to existing literature.

The appendices contain the three dissertation papers, and each appendix is numbered accordingly (I, II, and III). The three papers contain thorough descriptions of the research studies, including detailed tables and supplementary material referred to in the dissertation.

2. Background

As mentioned, serum sodium measurements are among the most commonly performed laboratory tests in clinical practice; patients often have their serum sodium measured repeatedly,[2] and hyponatremia is a common outcome. Here, some basic clinical aspects of hyponatremia, starting with risk factors, are reweived.

2.1 Risk factors and mechanisms for hyponatremia

A given clinical condition or disease is frequently associated with several factors, each of which may be necessary, sufficient, neither, or both in causing disease.[9] Hyponatremia can be associated with risk factors (characteristics, behavior, medical conditions, or other factors that increase susceptibility or trigger development of hyponatremia) and causative mechanisms (e.g., hormonal, neurologic, and cellular processes leading to disturbance in water and sodium balance).[16] Overall, mechanisms leading to hyponatremia are a decrease in total body sodium, an increase in total body water, or a combination of these.[3,7,17] Several diseases and medications are associated with alterations in water and sodium balance.[18-21] Furthermore, increased age,[22-25] female gender,[24,26,27] and low body mass[23,27] have been proposed as risk factors for developing hyponatremia. An overview of risk factors and mechanisms according to their proximity to hyponatremia is provided in Figure 1.

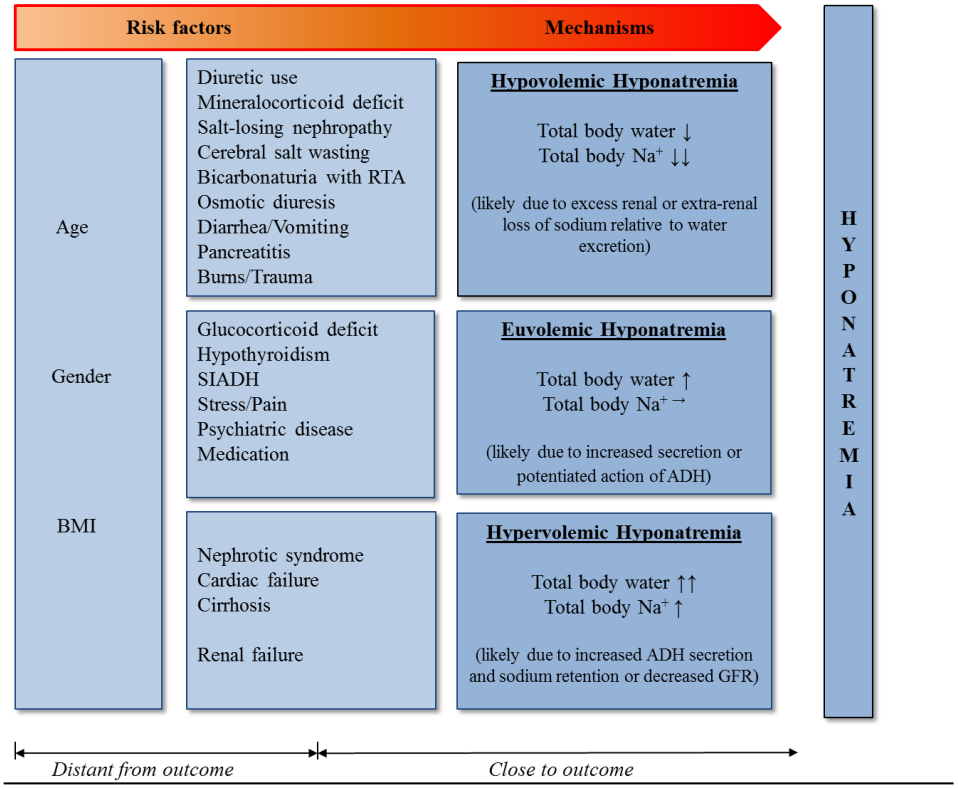


Figure 1. Risk factors for hyponatremia and mechanisms for development. Modified from figure 2. Schrier RW. Body water homeostasis: Clinical disorders of urinary dilution and concentration. *J Am Soc Nephrol*. 2006, 17(7):1820-1832,[18] and Fletcher R, Fletcher S, Wagner E, eds. Clinical Epidemiology - the Essentials. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1996:228-323.[16]

Abbreviations: ADH=antidiuretic hormone; BMI=body mass index; RTA=renal tubular acidosis; SIADH=syndrome of inappropriate antidiuretic hormone

Because of their widespread use, diuretics are an important cause of hyponatremia.[28-30] Even though all diuretics act in the kidneys by reducing sodium reabsorption from the urinary filtrate, different action sites of the individual types of diuretics along the nephron result in differences in the risk of developing hyponatremia (Figure 2).[3] Yet, the overall term 'diuretic-induced hyponatremia' is often used in the literature.[27,31] Thiazide diuretics primarily exert their effect in the early part of the distal tubule, where they inhibit reabsorption of sodium and chloride by blocking the apical membrane sodium–chloride symporter.[32] Because water cannot freely cross the cells in this part of the nephron, thiazides reduce renal urine diluting capacity. In addition, the medullary concentration gradient is not abolished and renal urine concentrating ability is sustained (Figure 2).[26,32-34] If accompanied by thirst and increased water intake, the risk of severe hyponatremia (<120 mmol/l) is imminent.[26,35-38]

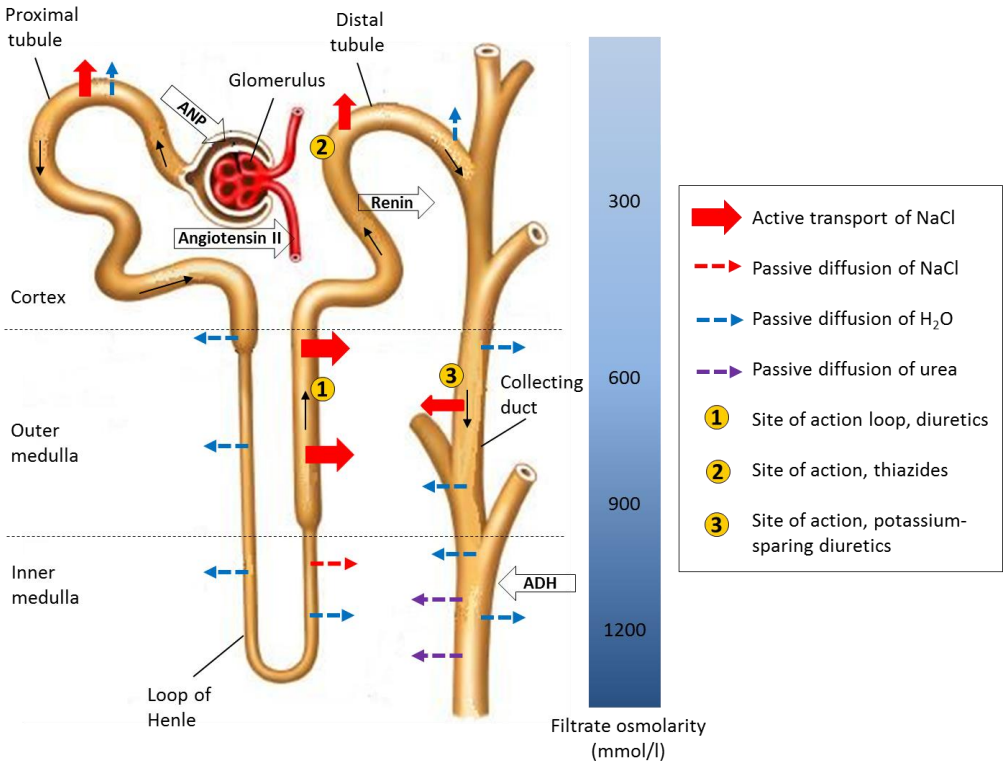


Figure 2. Site of action of diuretics (and hormones) in the renal nephron. Adapted from Figure 14-24 in Randal D, Burggren W, French K (eds); Eckert animal physiology: mechanisms and adaptions. 5th ed. New York, NY: W.H. Freeman and Co, 2001.[182]

Loop diuretics inhibit sodium and chloride reabsorption in the loop of Henle. Although loop diuretics can increase excretion of sodium to about 25% of the filtered amount,[32] they are less likely to cause hyponatremia.[34] The reason is that loop diuretics, by inhibiting sodium and chloride reabsorption in this segment, abolish the medullary osmotic gradient responsible for antidiuretic hormone (ADH)-mediated water reabsorption in the collecting duct.[32,34,39] Like thiazides, potassium-sparing diuretics also impair

nephron diluting ability. However potassium-sparing diuretics increase sodium excretion either by blocking or reducing the number of open aldosterone-sensitive sodium channels in the collecting ducts.[32]

Hyponatremia most likely occurs within the first two weeks of treatment, after which a steady state without further loss of solutes or water is established.[24,26,27,35,40] However, hyponatremia development within hours of diuretic administration has been reported.[26,33]

2.2 Prognosis of hyponatremia

Below the cellular effects of hyponatremia and the impact on prognosis in specific diseases are outlined.

2.2.1 Established and proposed cellular effects of hyponatremia

Symptoms of hyponatremia are mainly attributable to the effect of hypotonicity on the central nervous system.[4] The hypotonic state induces an osmotic shift of water into brain cells, resulting in brain swelling.[41] If a decrease in serum sodium occurs at a rate that exceeds the capacity of the adaptive forces to ensure loss of osmotic active solutes—and thereby water—from the brain, severe cerebral edema can develop (Figure 3).[42,43]

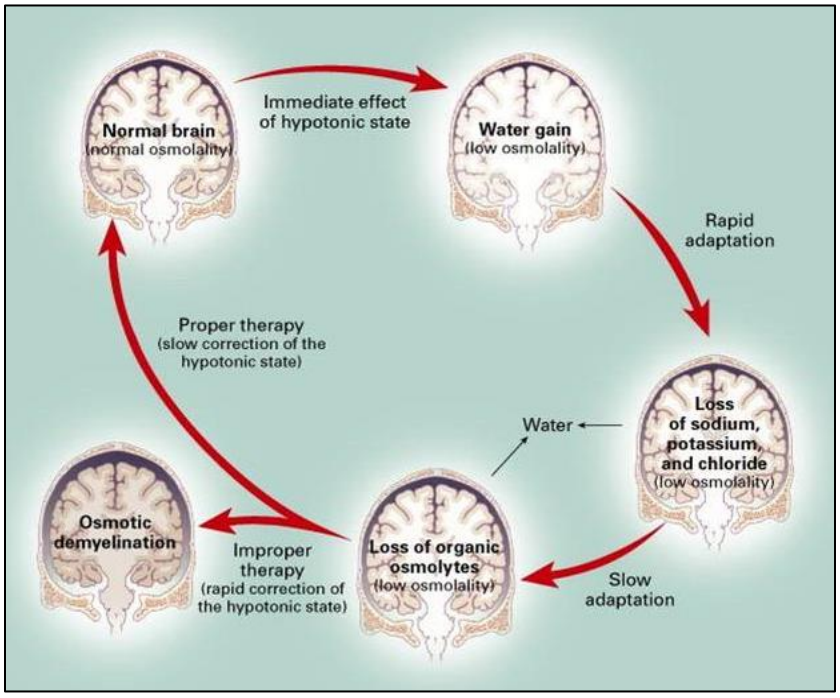


Figure 3. Brain adaptation to effects of hyponatremia. Reproduced with permission from Adrogue HJ & Madias NE. Hyponatremia. *N Engl J Med*. 2000;342(21):1581-1589. Copyright Massachusetts Medical Society.[4]

Depending on the severity of edema, possible outcomes include lethargy, confusion, gait disturbances, nausea, and vomiting, seizures, coma, respiratory arrest, and death.[41,44,45] Brain volume regulation is thought to be the explanation for the vague symptoms observed with even severe hyponatremia developed

over a longer period of time (chronic hyponatremia is often defined as >48 hours).[42] Experimental animal studies have shown that full adaptation to the hypotonic state is achieved within hours or a few days after induction of hyponatremia.[42,43] Although lost brain electrolytes are efficiently reaccumulated when hyponatremia is corrected, recovery of organic solutes appears to be much slower.[46] This phenomenon is thought to cause osmotic demyelination of the medullary neuron sheaths in the center base of the pons (central pontine myelinolysis), a rare but dreaded complication associated with overly rapid correction of chronic hyponatremia.[47] The finding of intramyelinic vacuoles in demyelinated neurons from patients with central pontine myelinolysis could indicate that intramyelinic edema plays a role in the pathogenesis.[48] Depending on the extent of the lesion, central pontine myelinolysis can cause severe and even fatal cerebral damage.[49]

Hyponatremia has recently been associated with an increased risk for osteoporotic and non-osteoporotic bone fractures.[50-53] Whether this association is a direct consequence of hyponatremia, secondary to an increased risk of falls and gait disturbances,[44] or even a matter of reverse causation remains to be determined. However, hyponatremia has been linked to low bone mineral density and increased osteoclast activity in experimental studies on rats.[54,55]

Furthermore, lowering extracellular sodium concentration inhibits the activity of ascorbic acid transporters located in the cell membrane of murine cells, resulting in intracellular accumulation of free oxygen radicals and subsequent changes in protein expression and oxidative DNA damage.[55] On the other hand, accumulating evidence suggests that elevated blood levels of interleukins 1 and 6 stimulate ADH secretion in both humans[56,57] and rats.[58,59]

Thus, several proposed explanations point toward a causal effect of hyponatremia on mortality,[41-48,51-55] evidence suggesting that hyponatremia is a marker of underlying disease severity also exists.[56-59]

2.2.2 Hyponatremia and mortality in specific diseases

The association between hyponatremia and mortality has been extensively studied in patients with specific preexisting diseases. Indeed, the clinical impact of hyponatremia in patients with liver cirrhosis was recognized already in the seventies.[60,61] However, initial data concerned the association with central pontine myelinolysis, and two decades passed before studies on the association with all-cause mortality emerged. In an Italian single-center study from 2000, hyponatremia was present in 30% of 191 patients with cirrhosis and associated with increased in-hospital mortality (26.3%, 95% confidence interval (CI): 14.5–38.1) compared to patients with normonatremia (8.9%, 95% CI: 4.1–13.8).[62] A later study of cirrhotic patients admitted to an intensive care unit (ICU) found that patients with hyponatremia (≤135 mmol/l) more likely had ascites, high illness severity scores, hepatic encephalopathy, sepsis, renal failure,

and increased odds of in-hospital mortality compared to cirrhotic patients without hyponatremia (odds ratio (OR)=2.145, 95% CI: 1.018–4.521).[63]

Even more extensively investigated is the prognostic impact of hyponatremia in patients with congestive heart failure. Hyponatremia has consistently been associated with increased mortality in this patient group.[64-69] In a US study of almost 116,000 patients admitted with heart failure, adjusted in-hospital mortality ORs of 1.78 (95% CI: 1.59–1.99) and 1.29 (95% CI: 1.19–1.40) were found for serum sodium values ≤130 mmol/l and 131–135 mmol/l, respectively, when compared to normonatremia.[66] Hyponatremia was associated with similarly high unadjusted in-hospital mortality OR in the OPTIMIZE-HF study[64]; even after multivariate adjustment, each 3 mmol/l decrease in serum sodium was associated with a 20% increased odds of dying during hospitalization in patients with left ventricular systolic dysfunction (LVSD) but 9% for non-LVSD heart failure patients. Also in patients admitted with acute myocardial infarction, hyponatremia present at admission was associated with increased in-hospital[70,71] and 30-day mortality.[72]

Few studies have investigated the prognostic impact of hyponatremia in patients with chronic renal disease.[73,74] Among 655,493 US veterans with non–dialysis-dependent renal disease (median follow-up=5.5 years), patient serum sodium levels of <130 mmol/l and 130–135.9 mmol/l had multivariable-adjusted mortality hazard ratios of 1.93 (95% CI: 1.83–2.03) and 1.28 (95% CI: 1.26–1.30), respectively. The risk seemed independent of severity of renal disease.[74] In a smaller study of 1549 oliguric or anuric hemodialysis-dependent patients, each 4 mmol/l increase in pre-dialysis serum sodium concentration was associated with a hazard ratio for all-cause mortality of 0.89 (95% CI: 0.82–0.96).[73]

Hyponatremia also has been associated with increased mortality in patients with pneumonia,[75] pulmonary embolism or hypertension,[76,77] acquired immunodeficiency syndrome,[78] and cancer.[79,80] Furthermore, hyponatremia is a predictor of in-hospital mortality in ICU patients.[81-83]

2.3 Literature review

We constructed a literature search using PubMed, including the MEDLINE journal citation database, and the Web of Science with the aim of identifying studies on the quality of ICD codes for hyponatremia, the impact of hyponatremia on mortality in hospitalized internal medicine patients, and the impact of diuretic use on mortality in hyponatremic patients. Primarily, a MEDLINE search was built using major and non-major Medical Subject Heading (MeSH) terms. If few results were obtained by this procedure, we performed a subsequent PubMed search using the same or similar non-MESH controlled terms.

The titles and abstracts for each paper listed in the search results were assessed for relevance based on the attributes of the population studied, the exposure (or diagnostic test), the choice of

comparator, and the outcome examined.[84] The reference list for each selected paper was browsed for additional relevant papers not obtained by the initial MEDLINE or PubMed search. Furthermore, papers indicated as related to the selected papers in PubMed or the Web of Science were assessed and selected for review if deemed relevant. Full text review was performed on all relevant English-language papers published before August 2015. Published dissertation papers are include for completeness.

Table 1 summarizes the result of the literature review. The specific PubMed search algorithms and MeSH terms are provided at the bottom of the table.

Table 1. Literature review summary.

Study I: Quality of ICD-10 codes for hyponatremia in the DNPR			
Author, year	**Design, setting, period, data sources**	**Population, diagnostic test, reference standard**	**Results, limitations**
Movig KL *et al.*[85] - 2003	- Cross-sectional study - Netherlands (single center) - 1999–2000 - Hospital information system	- Hospitalizations with at least one S-Na measurement (n=12,671) - ICD-9 codes for hyponatremia (primary and secondary diagnosis) - Laboratory confirmed hyponatremia (S-Na<135 mM)	- Sn=1.7%, Sp≥99.9%, PPV=91.7%, NPV=79.5% (95% CI: not provided) - S-Na laboratory tests performed only in 26% of all hospitalizations; patient characteristics not presented, limiting comparability with other studies
Shea AM *et al.*[86] - 2008	- Cross-sectional study - US (multicenter) - 2004–2005 - IHCIS	- Outpatients ≥18 y, with S-Na laboratory claims (n=1,901,254) - ICD-9 claim for hyponatremia (primary and secondary diagnosis) within ±15 days of S-Na measurement - Laboratory confirmed hyponatremia (S-Na<136 mM)	- Sn=3.5%, Sp≥99.90%, PPV=62.6%, NPV=97.9% (95% CI: not provided) - IHCIS contains data on an employer-based, commercially insured population, i.e., elderly and unemployed patients likely highly underrepresented; patients with no S-Na measurement not included
Gandhi S *et al.*[87] - 2012	- Cross-sectional study - Canada (multicenter) - 2003–2010 - Cerner, NACRS, CIHI-DAD, RPD, OHIPD, ODBD	- Patients ≥66 y, with a S-Na measurement within 24 h after presenting to an ED (n=64,581) or after HA (n=64,499) - ICD-10 codes for hyponatremia (primary and secondary diagnosis) - Laboratory confirmed hyponatremia (S-Na<132 mM) presenting to ED or at HA. Other categories: <135 mM, ≤130 mM, ≤125 mM	- ED: Sn=7.5% (95% CI: 7.0%–8.2%); Sp=>99.9% (95% CI: 99.9%–100.0%); PPV=96.4% (95% CI: 94.6%–97.6%); NPV=89.2% (95% CI: 89.0%–89.5%) - HA: Sn=10.6% (95% CI: 9.9%–11.2%); Sp=99.6.0% (95% CI: 99.6%–99.7%); PPV=82.3% (95% CI: 80.0%–84.4%); NPV=87.1% (95% CI: 86.8%–87.4%) - Restricted to elderly patients and to admission S-Na measurement; patients with no S-Na excluded, affecting ability to detect false-positive diagnoses
Holland-Bill L *et al.*[88] - 2014 (Study I)	- Cross-sectional study - Denmark (multicenter) - 2006–2011 - DNPR, LABKA	- All hospitalizations (n=2,186,642 in 819,701 individual patients) - ICD-10 codes for hyponatremia (primary and secondary diagnosis) - Hyponatremic laboratory test result (S-Na<135 mM) any time during hospitalization (lowest value measured during each hospitalization)	- Sn=1.8% (95% CI: 1.7%–1.8%); Sp=100% (95% CI: 100%–100%); PPV=92.5% (95% CI: 91.8%–93.1%); NPV=86.2% (95% CI: 86.2%–86.2%) - Duration of hyponatremia not accounted for

Study II: Prevalence of and mortality associated with hyponatremia in patients admitted to departments of internal medicine			
Author, year	**Design, setting, period, data sources**	**Population, exposure (or cases), controls (if applicable), outcome**	**Results, limitations**
Tierney *et al*.[89] **- 1986**	- Matched cohort study - US (single center) - Jan 1984–Oct 1984 - Computerized medical record system	- First-time admissions to DIP with S-Na measured within 1 day before or 1 day after day of admission (n=23,080) - Hyponatremia (s-Na<130 mM at admission) (n=954) - Normonatremic controls (S-Na=135–145 mM) matched 1:1 on age, gender, date of admission (±6 months) - Prevalence; in-hospital and post-discharge mortality	- Prevalence=4.1% - In-hospital mortality of 8.7% vs. 1.1% in normonatremic controls, OR=7.3 Post-discharge death of 13.1 vs. 67. OR=2.1 -20% of patients admitted had no admission S-Na measurement and were thus excluded; not adjusted for previous morbidities; 95% CI not provided.
Clayton JA *et al.*[90] **- 2006**	- Cohort study - UK (single center) - Aug 2002–Jan 2003 - Hospital laboratory system; medical chart review	- General internal medicine and geriatric inpatients with S-Na <125 mM during hospitalization (n=105) - Etiology of hyponatremia; Mortality rate; impact of etiology and admission serum sodium level.	- Mortality rate=41 deaths per 100 person-years. Mortality varied with etiology. Odds of death was lower in patient admitted with normonatremia compared to patient admitted with hyponatremia (ORs ranging from 0.08 (95% CI: 0.01-0.5) to 0.52 (95% CI: 0.14-1.98) - Small sample size. Unclear description of statistical methods applied and extent of confounder control.
Gill G et al.[91] **- 2006**	- Case-control study - UK (single center) - 6 months (year unstated) - Hospital laboratory system; medical chart review	- Hospitalized patients with S-Na measurement - Severe hyponatremia (S-Na <125 mM) during hospitalization (n=104) - Normonatremic controls (next consecutive patient on the daily laboratory print-out with s-Na>135mM) (n=100) - In-hospital mortality	- In-hospital mortality of 27% vs. 9% in normonatremic controls - Small sample size. No confounder control.
Zilberberg *et al.*[92] **- 2008**	- Cohort study - US (multicenter) - 2004–2005 - Solucient's ACTracker database	- All hospitalizations with at least one laboratory value for S-Na during hospitalization (n=198,281) - Hyponatremia (S-Na <135 mM within 2 d following admission with at least two subsequent S-Na measurements <135 mM within 24 h after the admission measurement (n=10,899) - Prevalence; in-hospital mortality	- Prevalence=5.5% - In-hospital mortality 5.9% vs. 3.0% in patients without hyponatremia; aOR=1.55 (95% CI: 1.42–1.69) - No information on severity of hyponatremia; immortal time bias cannot be excluded
Waikar SS *et al.*[94] **- 2009**	- Cohort study - US (multicenter) - 2000–2002 - RPDR	- Patients >18 y hospitalized for >48 h with a S-Na measurement (n=98,411) - Hyponatremia (<135 mM within 48 h) (n=12,562) with subcategories of 130–134 mM (n=10,469), 125–129 mM (n=1,591), 120–124 mM (n=353), and <120 mM (n=149) - Prevalence; in-hospital, 1-year, and 5-year mortality overall and according to hyponatremia severity	- Prevalence=14.5% - In-hospital: 5.4% vs 2.4% in normonatremic patients; aMRR=1.47 (95% CI: 1.33–1.62); subcategory aMRR 1.37 (95% CI: 1.23–1.52), 2.01 (95% CI: 1.64–2.45), 1.67 (95% CI: 1.09–2.56), and 1.46 (95% CI: 0.73–2.91) - 1-year: 21.4 vs. 11.7% in normonatremic patients; aMRR=1.38 (95% CI: 1.32–1.46); subcategory aMRR 1.35 (95% CI: 1.28–1.43), 1.53 (95% CI: 1.36–1.71), 1.78 (95% CI: 1.44–2.21), and 1.03 (95% CI: 0.68–1.56) - 5-year: 54.8 vs. 42.3% in normonatremic patients; aMRR=1.25 (95% CI: 1.21–1.30); subcategory aMRR 1.24 (95% CI: 1.19–1.29), 1.33 (95% CI: 1.23–1.44), 1.29 (95% CI: 1.09–1.53), and 1.09 (95% CI: 0.84–1.41). - Only patients with S-Na included; confounding by severity of underlying disease cannot be excluded

Whelan B *et al.*[93] **- 2009**	- Cohort study - Ireland (single center) - 2006–2006 - HIPE, PAS, laboratory database	- Patients acutely admitted to DIP with S-Na measured during hospitalization (n=14,239) - Hyponatremia (S-Na<135 mM at admission) (n=2,795) with subcategories of 130–134 mM (n=1,764), 125–129 mM (n=648), and <125 mM (n=347) - Prevalence; in-hospital mortality	- Prevalence=19.6% - In-hospital of 17.0% vs 7.9% in normonatremic patients; subcategory aOR 1.25 (95% CI: 1.05–1.49), 1.43 (95% CI: 1.12–1.83), and 2.00 (95% CI: 1.44–2.77) - Few patients with severe hyponatremia; only patients with S-Na included; unmeasured confounding cannot be excluded
Frenkel WN *et al.*[95] **- 2010**	- Cohort study - Netherlands (single center) - 2002–2007 - Hospital laboratory system; telephone interview	- Patients >65 y acutely admitted to DIP (n=895) - Hyponatremia (S-Na<130 mM within 24 h) - Prevalence. 3-month mortality	- Prevalence= 34,3% - 3-month mortality of 32.8% vs. 2.6% in normonatremic patients; aOR=1.2 (95% CI: 0.8–1.9) - Small sample size; no risk estimates according to hyponatremia severity; risk of recall bias; inaccurate information on preexisting morbidity; residual confounding by comorbidity and age cannot be excluded
Wald R *et al.*[96] **- 2010**	- Cohort study - US (single center) - Oct 2000–Sept 2007 - Hospital laboratory system; discharge abstracts review	- All hospitalizations (excl.obstetrical hospitalizations) with S-Na measurement on or 1 day before admission (n=53,236) - Hyponatremia (S-Na<138 mM at time of hospitalization) (n=20,181), with subcategories of 133–137 mM (n=16,023), 128–132 mM (n=3,075), 123–127 mM (n=759), 118–122 mM (n=211), and <118 mM (n=113) - Prevalence; in-hospital mortality	- Prevalence=38% - In-hospital mortality of 3.4% vs. 2.0% in non-hyponatremic patients; aOR=1.52 (95% CI: 1.36–1.69); subcategory aOR 1.34 (95% CI: 1.18–1.51), 1.99 (95% CI: 1.65–2.40), 2.54 (95% CI: 1.87–3.45), 2.46 (95% CI: 1.38–4.39), and 2.46 (95% CI: 1.19–5.10), respectively - Few observation with severe hyponatremia; patients without S-Na measurements not included; contains both surgical and non-surgical patients; confounding by previous morbidity cannot be excluded
Shapiro DS et al.[97] **-2010**	- Cohort study - Israel (single center) - Sep 2005 – Feb 2006 - Hospital laboratory system; medical chart review	- Hospitalized internal medicine patients≥65 y with severe hyponatremia (S-Na≤ 125 mM) (n=86) - In-hospital mortality	- Prevalence severe hyponatremia = 6.2% - Inhospital mortality= 19% - Small sample size; no comparison cohort
Chawla A *et al.*[98] **- 2011**	- Cohort study - US (single center) - 1996–2007 - Hospital laboratory system; medical chart review	- Hospitalized patients with a S-Na measurement (n=209,839) - Hyponatremia (S-Na<135 mM any time during hospitalization) (n=45,693) with subcategories of 130–134 mM (n=35,604), 125–129 mM (n=7601), 120–124 mM (n=1824), 115–119 mM (n=462), 110–114 mM (n=152), and <110 mM (n=50) - Prevalence; in-hospital mortality overall and according to hyponatremia severity	- Prevalence=22% - In-hospital mortality of 6.1% vs. 2.3% in non-hyponatremic patients (defined as S-Na>135 mM, n=164,146); absolute mortality increased until S-Na fell below 120 mM, after which mortality decreased - Medical chart review not blinded to outcome; no confounder adjustment; few patients with severe hyponatremia; admission S-Na not available in 17.5%
Elmi G *et al.*[99] **- 2014**	- Cohort study - Italy (single center) - 2013–2014 - Not described	- Patients admitted to DIP (n=2,034) - Hypotonic hyponatremia (S-Na<135 mM and low plasma osmolality at hospitalization at admission) (n=284) Subcategories of 130–134 mM (n=225), 125–129 mM (n=39), and <125 mM (n=20) - Prevalence; in-hospital mortality	- Prevalence of hypotonic hyponatremia=13.9% - In-hospital mortality of 8.5% vs. 4.7% among all patients hospitalized to DIP during the study period - Methods and data sources poorly described; small sample size; no adjustment for potential confounders

Sturdik I *et al.*[100] **- 2014**	- Case–control study - Slovakia (single center) - Jan 2012–Aug 2012 - Hospital laboratory system; medical chart review	- Admissions to DIP (if >1 hospitalization in the study period, the admission with the lowest S-Na was chosen) (n=2171) - Hyponatremia (S-Na<135 mM at admission) (n=278) Subcategories: 130–135 mM, 125–130 mM, and <125 mM - In-hospital mortality - Normonatremic controls admitted to DIP in the study period matched on sex, age and underlying disease (IHD, hypertension, DM, CKD, LC, COPD, endocrine or psychiatric disease)(n=278)	- Prevalence=13% - In-hospital mortality: 22% vs. 7% in normonatremic patients; for subcategories 21%, 24%, 15%; overall OR=3.75 (95% CI: 2.17–6.48) - Small sample size; no risk estimates according to hyponatremia severity; differential misclassification or measurement error due to non-blinded retrospective medical chart review cannot be excluded
Correia L et al.[101] **- 2014**	- Case–control study - Portugal (single center) - Dec 2007- Nov 2008 - Hospital laboratory system; medical chart review	- Hospitalized internal medicine patients ≥65 y (n=1060) - Severe hypoosmolar hyponatremia (S-Na<125 mM and plasma osmolality <275 mosmol/kg) at admission (n=63) - Normonatremic controls matched on age and gender. - In-hospital mortality	- Prevalence of hyponatremia (S-Na<135 mM)= 28% - In-hospital mortality of 27% vs. 16% in control group. OR 1.94 (95% CI: 0.93–4.04) - Small sample size. No adjustment impact of underlying disease.
Balling L *et al.*[102] **-2015**	- Cohort study - Denmark (single center) - April 1998- March 1999 - Laboratory file, medical chart review; DNPR;	- Patients >40 y admitted DIP or surgical (gastrointestinal and orthopedic) departments (n=3,644). Exclusion criteria: discharge or death before inclusion, lack of informed consent, lack of admission S-Na. - Hyponatremia (S-Na<137mM within 24 h admission) (n=1,105). Subcategories of <137mM–130mM (n=899) and <130mM (n=206) - Prevalence, 1-year and 'end of follow-up' mortality (median=5.16 y)	- Prevalence=37% - 1-year mortality: 25.7% vs. 17.7% in non-hyponatremic patients; aHR=1.4 (95% CI: 1.2-1.8). Crude HR for <130mM= 1.7 (95% CI: 1.3-2.2). Crude HR for <130mM vs. <137mM–130mM=1.2 (95% CI: 1.0-1.4) -'End of follow-up' mortality: 79.3% vs. 67.4% in non-hyponatremic patients; aHR=1.2 (95% CI: 1.1-1.3). Crude HR for <130mM= 1.5 (95% CI: 1.3-1.7) - 684 (19%) eligible patients excluded. Hypernatremic patients included in comparison cohort; Subgroup analysis unadjusted; Residual or unmeasured confounding due to underlying disease and severity hereof cannot be excluded.
Holland-Bill L *et al*. [103] **-2015** **(study II)**	- Cohort study - Denmark (multicenter) - 2006–2011 - DNPR, CRS, LABKA	- First-time admission to DIP during the study period (n=279,508) - Hyponatremia (S-Na<135 mmol/l within 24 h) (n=41,803) with subcategories of 130–134.9 mM (n=29,287), 125–129.9 mM (n=8,170), 120–124.9 mM (n=2,573), and <120 mM (n=1,773) - Prevalence: 30-day and 1-year mortality	- Prevalence=15.0% - 30-day mortality: 8.1% vs 3.6% in normonatremic patients; aRR=1.5 (95% CI: 1.4–1.5); subcategory aRR: 1.4 (95% CI: 1.3–1.4), 1.7 (95% CI: 1.6–1.8), 1.7 (95% CI: 1.4–1.9), and 1.3 (95% CI: 1.1–1.5) 1-year mortality: 21.5 vs 10.6 in normonatremic patients; aRR: 1.3 (95% CI: 1.3–1.4); subcategory aRR: 1.3 (95% CI: 1.3–1.3), 1.4 (95% CI: 1.4–1.5), 1.4 (95% CI: 1.3–1.5), and 1.3 (95% CI: 1.1–1.4) - Residual or unmeasured confounding due to lack of information of severity of underlying disease cannot be excluded.

Study III: Impact of diuretic use on hyponatremia-associated mortality			
Author, year	**Design, setting, period, data sources**	**Population, exposure, outcome**	**Results, limitations**
Clayton JA *et al.*[90] - 2006	- Cohort study - UK (single center) - Aug 2002–Jan 2003 - Hospital laboratory system; medical chart review	- General internal medicine and geriatric inpatients with S-Na <125 mM during hospitalization (n=105) - Causes of hyponatremia; hyponatremia severity; mortality	- Mortality rate=41 deaths per 100 person-years; patients with two or more etiologies at higher risk of dying than patients with a single identified etiology (often thiazide diuretics), OR=6.78 (95% CI: 1.39–33.04) and OR=15.91 (95% CI: 3.02–84.00); 62% readmitted - Small sample size; unclear description of statistical methods applied and extent of confounder control; no control for confounding by indication
Chawla A *et al.*[98] - 2011	- Cohort study - US (single center) - 1996–2007 - Hospital laboratory system; medical chart review	- Hospitalized patients with at least one S-Na (n=209,839) - Hyponatremia (S-Na <135 mM) (n=45,693); subcategories 130–134 mM (n=35,604), 125–129 mM (n=7601), 120–124 mM (n=1824), 115–119 mM (n=462), 110–114 mM (n=152), and <110 mM (n=50) - Characteristics and causes of hyponatremia in fatal cases with S-Na <120 mM (n=53) vs. survivors with S-Na <110 mM (n=32)	- Fatal cases: mean CCI score=5.5; sepsis=51%; acute renal failure=60%; thiazide or SSRI use not stated Survivors: mean CCI score=1.8; sepsis=none; acute renal failure=3%; thiazide or SSRI use=72% - Retrospective medical chart review not blinded to outcome; no adjustment for potential confounders, including confounding by indication; few patients with severe hyponatremia; no data on individual diuretic
Leung AA *et al.*[30] - 2011	- Cohort study (new user) - US (multicenter) - 2000–2005 - RPDR	- Adult outpatients with an incident diagnosis of hypertension (n=2,613) - Thiazide diuretics (n=220) vs. other antihypertensive drugs (n=2393) as initial treatment - Risk of hyponatremia (S-Na ≤130 mM). Secondary: total number of hyponatremia associated hospitalizations,all-cause mortality	- aIRR for developing hyponatremia=1.61 (95% CI: 1.15–2.25); aIRR for hyponatremia-associated hospitalization=1.04 (95% CI: 0.46–2.32); aMRR=0.41 (95% CI: 0.12–1.42) in thiazide users vs. non-users. - Only patients with continuous treatment throughout follow-up included; patients who died within 30 days of enrollment excluded; no attempts to account for confounding by indication

Abbreviations: aMRR=adjusted mortality rate ratio; aIRR=adjusted incidence rate ratio; aOR=adjusted odds ratio; aRR=adjusted relative risk; CCI=Charlson Comorbidity Index; CIHI-DAD=Canadian Institutes of Health Information Discharge Abstract Database; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; DIP=departments of internal medicine; DM=diabetes mellitus; DNPR=Danish National Patient Registry ; ED=emergency department; h=hours; HA=hospital admission; ICD-9=International Classification of Diseases, Ninth Revision; ICD-10=International Classification of Diseases, Tenth Revision; HIPE=hospital inpatient enquiry; IHCIS=Integrated Healthcare Information Services; IHD=ischemic heart disease; LC=liver cirrhosis; mM=mmol/l; NACRS=National Ambulatory Care Reporting System database; NIDDM=non-insulin-dependent diabetes mellitus; NPV=negative predictive value; ODBD=Ontario Drug Benefits database; OHIPD=Ontario Health Insurance Plan database; OR=odds ratio; PAS=patient administrative system; PPV=positive predictive value; RPDR=Research Patient Data Registry; Sn=sensitivity; Sp=specificity; S-Na=serum sodium; SSRI=selective serotonin reuptake inhibitors; UK=United Kingdom; US=United States; y=year

Literature search algorithms: Total number of papers reviewed=MEDLINE/PubMed search + other relevant
Study I: "Hyponatremia"[Majr] AND "International Classification of Diseases"[Majr] AND (("Sensitivity and Specificity"[Mesh]) OR ("Predictive Value of Tests"[Mesh])) + (Hyponatremia AND (International Classification of Diseases OR diagnosis) AND (Sensitivity OR specificity OR Predictive Value)) + related = 2 (of 2) + 2 (of 183) + 0 = 4
Study II (prevalence): "Hyponatremia"[Majr]) AND "Internal Medicine"[Mesh] AND ("Prevalence"[Mesh] OR "Epidemiology"[Mesh]) + Hyponatremia AND (Prevalence OR Epidemiology) AND Internal Medicine= 0 (of 1) + 2 (of 122) = 2
Study II (mortality): (("Hyponatremia"[Majr]) AND "Mortality"[Majr]) AND (("Internal Medicine"[Majr]) OR "Hospitalization"[Majr])) + Hyponatremia AND Mortality AND (Internal Medicine OR Hospitalization) =0 (of 1) + 9 (of 361) + 6 =15
Study III: "Hyponatremia"[Majr] AND "Diuretics"[Majr] AND ("Mortality"[Mesh] OR "Prognosis"[Mesh]) + (Hyponatremia AND Diuretics AND (Mortality OR Prognosis)) + related =0 (of 17) + 1 (of 232) + 2= 3

2.4 Quality of discharge diagnosis for hyponatremia (study I)

The nationwide population-based DNPR is extensively used for clinical research in Denmark, and equivalent registers cannot be found outside the Nordic countries.[14] A premise for research based on ICD-9 or ICD-10 codes is that they enable identification of exposure and effects in a valid manner.[15] The DNPR could be a useful tool for clinical hyponatremia research if the quality of ICD-10 codes for hyponatremia is sufficiently high.

As mentioned, the causes of hyponatremia are numerous, and the prevalence of hyponatremia is high.[5] Yet, reports have indicated that few patients receive a diagnosis of hyponatremia when discharged from the hospital.[104,105] Incomplete or invalid registration of discharge diagnosis codes could potentially affect the validity of study results, depending on the outcome measure under investigation.[104-107]

Three previous studies have examined the quality of ICD coding for hyponatremia, two of which were based on the ICD-9 system. All three studies found that less than 7% of patients with a serum sodium measurement <135 mmol/l received a hyponatremia diagnosis code.[85-87] The percentage of patients receiving a diagnosis consistently increased with increasing severity of hyponatremia. Still, even among patients with serum sodium<125 mmol/l, it did not exceed 35%.[85-87] In all three studies, very few patients received a diagnosis for hyponatremia if a hyponatremic sodium value had not been recorded, and the predictive value of having a diagnosis code for hyponatremia was high.

In both studies examining ICD-9 codes for hyponatremia, age and gender affected the probability of receiving a diagnosis code for hyponatremia, but in opposite directions.[85,86] The findings of the study by Gandhi *et al*., which was restricted to patients aged 66 years or older, supported that the probability of a proper diagnosis in the presence of documented hyponatremia increased with age.[87] Furthermore, the percentage of patients receiving an ICD-9 code for hyponatremia was slightly higher in the study of an outpatient claims database comprising an employer-insured population[86] compared to that found in a study based on data from a teaching hospital's administrative database.[85]

Although the existing literature gives some indication regarding the overall usefulness of hyponatremia diagnoses in epidemiologic studies, the coding practice used in ICD-9–based systems[85,86] and in selected employer-insured[86] or elderly populations[87] may not relate to the coding practice exercised in the uniform tax-supported Danish healthcare system.

2.5 Prevalence in patients acutely admitted to departments of internal medicine (study II)

The reported frequency of hyponatremia is subject to substantial variation and markedly influenced by the healthcare setting and patient population under study, the threshold and rate of testing, and the criteria used to define hyponatremia, including the serum sodium cutoff chosen, timing and number of measurements.[5] Prevalences as high as 38% to 42.6% among hospitalized patients (hyponatremia defined

as serum sodium <138 mmol/l at admission or <136 mmol/l any time during hospitalization, respectively)[25,96] and as low as 3% to 4% among emergency department patients (hyponatremia defined either as serum sodium <134 mmol/l or <135 mmol/l at presentation)[108-110] have been reported.

The prevalence of admission hyponatremia among patients admitted to departments of internal medicine, using a serum sodium of <135 mmol/l as the cutoff to define hyponatremia, ranges from 13.0% to 19.6%.[93,99,100] Although these overall results seem fairly consistent, studies among patients with specific internal medicine conditions point to great diversity in prevalence both between and within these subgroups.[5,72,80,111] The prevalence of hyponatremia has been reported to range from 28% to 34% among internal medicine patients aged ≥65 years (hyponatremia defined as <135 mmol/l and <130 mmol/l, respectively),[95,101] and specific discharge diagnosis of congestive heart failure, cancer, and pneumonia have been found to be more frequent in hyponatremic patients than normonatremiac patients.[89,94] Again, direct comparison of the prevalences is hampered by important differences in the definition of hyponatremia, and as of yet, information on the prevalence of hyponatremia in younger age groups and according to previous morbidity and primary reason for hospitalization among patients admitted to departments of internal medicine are lacking.

2.6 Hyponatremia and mortality in internal medicine patients (study II)

In 1984, Baran and Hutchinson showed that mortality was lower in patients with neurologic symptoms attributable to hyponatremia compared to patients with neurologic symptoms not attributable to hyponatremia.[112] This finding led them to dismiss a causal relation between hyponatremia and increased mortality.[112] Other study results have supported the finding that deaths among patients with even severe hyponatremia can rarely be explained by cerebral edema or central pontine myelinolysis.[47,98] Furthermore, cerebral edema or central pontine myelinolysis likely does not explain the increased mortality observed in patients with mild and moderate hyponatremia.[72-74,76,80,94,96,113]

Until recently, the impact of hyponatremia on mortality has predominantly been investigated in patient populations with certain preexisting diseases such as congestive heart failure,[64,69,114] myocardial infarction,[71,72] renal failure,[74] liver cirrhosis,[62,63] and cancer.[80,115] Tierney *et al*. were among the first to describe mortality in patients with hyponatremia (serum sodium <130 mmol/l) at the time of admission to an internal medicine department. Hyponatremia was associated with an almost 7.5 times increased odds of dying during hospitalization compared to normonatremic controls.[89] An association with increased mortality during hospitalization,[93,94,96,100] 30 days[94] and 1 year[94,102] after admission was supported by subsequent studies, but with substantial variation in the magnitude of impact (see Table 1). In 2010, Wald *et al*. conducted a study of adult patients admitted to an acute care hospital and presented a dramatic, almost linear association between decreasing serum sodium values and increased in-hospital mortality.[96]

Whelan *et al*. also reported increasing in-hospital mortality in three successive categories of hyponatremia severity.[93] However, although studies among patients with renal disease and congestive heart failure could support the existence of such a dose-response relationship,[64,74] others have challenged this finding.[94,98] Unfortunately, none of the studies among internal medicine patients was of sufficient sample size to provide reliable estimates of the effect of serum sodium values <120 mmol/l.[93,94,96,98]

2.7 Impact of diuretic use on hyponatremia-associated mortality (study III)

Waikar *et al.* found that severe hyponatremia was associated with lower in-hospital, 1-year and 5-year mortality than less severe hyponatremia.[94] Subsequently, Chawla *et al.* conducted a medical chart review of 32 inpatients with serum sodium <110 mmol/l surviving until discharge and 53 patients with serum sodium <120 mmol/l who died during hospitalization. They judged thiazides or selective serotonin reuptake inhibitors (SSRIs) to be the sole cause of hyponatremia in 72% of survivors while "significant acute progressive underlying illnesses" were identified in all fatal cases.[98] This finding led them to conclude that severe hyponatremia was likely attributable to medication use rather than to severe illness and that this could be the explanation for the paradoxical fall in mortality with increasing hyponatremia severity observed in their overall analysis.[94]

Because of their prevalent use in the treatment of illnesses[29,30,110] in which hyponatremia has been associated with increased mortality, diuretics are a likely candidate for studies on the effect of drug-induced hyponatremia. Nevertheless, the existing literature on this topic is sparse. Two studies have examined the association between use of selected diuretics and development of hyponatremia while also reporting the mortality associated with diuretic use.[30,90] Findings pointed to a protective effect of thiazides[30,90] and a harmful effect of loop diuretics.[90] However, only one of these studies examined the impact of diuretic use on hyponatremia-associated mortality as such[90], and both studies were of limited size[30,90] and made no attempt to control for the potential impact of prescribing practices.[30,90] Moreover, one study included a highly selective group of patients surviving at least 30 days after long-term antihypertensive treatment was initiated,[30] so that these results are merely suggestive of a link between diuretic use and hyponatremia-associated mortality.

2.8 Hypotheses and aims

<u>Study I</u>

Hypothesis: The DNPR could be a useful source for identifying patients hospitalized with hyponatremia.

Aim: To examine the usefulness of ICD-10 discharge diagnoses for registry-based studies on hyponatremia.

Study II

Hypothesis: Hyponatremia is frequent in internal medicine patients and associated with increased mortality if a certain severity threshold is crossed.

Aim: To examine the prevalence of and 30-day and 1-year mortality associated with mild to severe hyponatremia, using serum sodium both as a categorical and as a continuous variable

Study III

Hypothesis: Current diuretic use impacts mortality in internal medicine patients with hyponatremia.

Aim: To examine the association between 30-day mortality in current diuretics users compared to non-users and whether this risk was affected by duration of treatment, generic type of diuretic, and clinical subgroups

3. Methods

The following sections provide a thorough description of the methods used.

3.1 Setting

We conducted all three studies within the Northern and Central Regions of Denmark. These two regions have a long-standing tradition of collecting data for clinical epidemiologic research and cover a population of approximately 2 million residents, who are provided with universal tax-supported medical care and full or partial reimbursement of most prescription medications under the Danish National Health Service.[116,117]

3.2 Data sources

All three studies used prospectively collected data recorded in administrative registries and medical databases. The unique 10-digit identification number (central person registry (CPR) number) assigned by the Civil Registration System to all Danish residents upon birth or immigration enables unambiguous individual-level linkage between the databases. This linkage ensures virtually complete follow-up of patients receiving care from the Danish National Health Service.[116,118]

3.2.1 The Danish National Patient Registry (studies I, II and III)

Since 1977, information on all somatic hospitalizations in Denmark has been recorded in the DNPR.[119,120] The DNPR was primarily established to monitor hospital activities and was expanded in 1995 to include visits to emergency departments and outpatient specialist clinics. Reporting to the DNPR is mandatory. Besides administrative information including date of admission and discharge, hospital and department codes and codes describing the type of hospitalization and one primary and an unrestricted number of secondary diagnoses are recorded for each hospital contact. These diagnoses, which were coded according to the ICD, 8th revision (ICD-8), until the end of 1993, and according to the ICD-10 thereafter, are assigned by the discharging physician at the time of discharge. The primary diagnosis reflects the main reason for hospitalization and treatment while secondary diagnoses refer to additional conditions, including underlying diseases, complications, and symptoms, influencing the course of hospitalization.

3.2.2 The Civil Registration System (studies I, II and III)

Since 1968, vital statistics, including exact date of birth and death, date of emigration or immigration, and place of residence of all Danish citizens, have been recorded by The Danish Civil Registration System (CRS). The registry is updated daily.[116,118]

3.2.3 The LABKA database (studies I, II and III)

The results of all blood samples from in- and outpatients submitted for analysis at hospital laboratories in the Northern and Central Denmark Regions are stored in a laboratory information system functioning as a daily tool for healthcare personnel. From here, data including the Nomenclature, Properties, and Units code, time and date of the analysis, and test result and measurement unit are electronically transferred to a regional laboratory registry called the LABKA database.[2] For both the Central and Northern Denmark regions, data on serum sodium measurements are virtually complete from 2006 through 2011. For 2012, only data from the Central Denmark Region are available. Approximately one million serum sodium measurements are performed each year in the North and Central Denmark Regions, rendering it as common as potassium and creatinine measurements, which is indicative of its application in standard test panels performed to guide diagnosis and treatment.[2]

During the study period, direct or indirect ion selective electrode (ISE) assays have been the standard method for measuring serum sodium concentrations. In practices, indirect ISE equipment is calibrated to correspond with the direct ISE assay, and the results obtained by the two methods are in good agreement (personal communication with clinical biochemistry departments in the two regions). However, in the presence of extremely high plasma protein or lipid concentrations, the indirect method yields falsely low sodium concentrations (pseudohyponatremia).[121] If this phenomenon is suspected, a control measurement by direct ISE is performed (personal communication). The distribution of admission serum sodium measurements among acute internal medicine patients is presented in Figure 4.

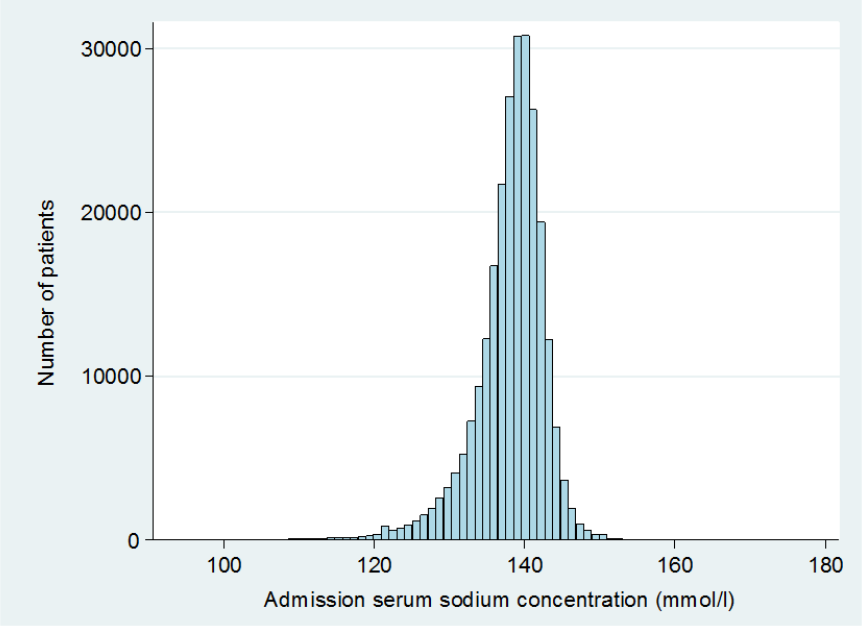


Figure 4. Distribution of admission serum sodium concentrations in patients acutely admitted to departments of internal medicine (own data)

In studies II and III, we used admission serum sodium measurements to determine exposure status and identify the study cohort, respectively. We defined admission serum sodium as the first measurement performed within 24 hours of admission, which was made possible by comparing the date and hour of admission recorded in the DNPR to the sampling time and date recorded in the LABKA database. An examination (unpublished material) of the sample-time distribution of laboratory tests in LABKA revealed that an inconceivably large proportion of tests appeared to have been performed between 12:00:00 and 12:24:59. Normally, seconds would be recorded as 00, which indicated that for some of these samples, 12 had erroneously been inserted and displaced the correct hour and minute information to the minute and second position, respectively. We therefore recoded all sample times starting with 12 and ending with anything other than 00, which resulted in a more plausible sample-time distribution (Figure 5).

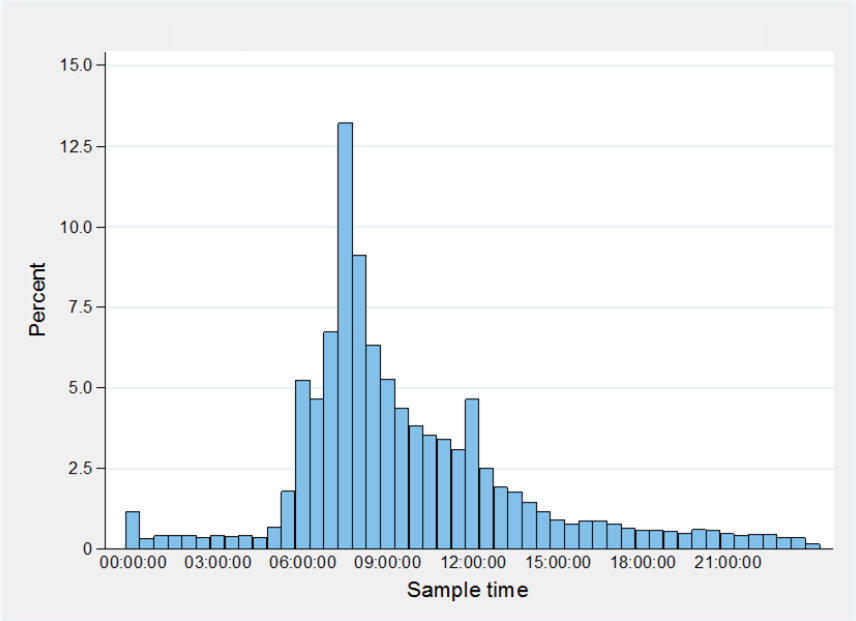


Figure 5. Sample-time distribution for serum sodium measurements recorded in LABKA from 2006–2012 (own data)

Another challenge arose because admission hour information was missing for some observations in the DNPR. We therefore developed the following algorithm to identify measurements performed within 24 hours of admission: 1) if admission date and sample date were the same, we assumed that the blood sample had been drawn upon hospital entry (under the assumption that the general practitioner would not likely draw a blood sample, if expecting to admit a patient, as it would not be tested before the next day); and 2) if admission date was the day before the sample date, samples were included if the sample hour was equal to or lower than the admission hour. Implicitly, samples with a missing admission hour for which admission date and sample date were separated by more than one day were not included as

an admission sample. Because admission time has no record of the exact minute count, some samples may theoretically have been performed 24 hours and 59 minutes after admission.

3.2.4 The Danish National Health Service Prescription Database (study III)

The Danish National Health Service Prescription Database (DNHSPD) contains data on all reimbursable prescriptions, dispensed by community pharmacies in Denmark since 2004.[122] The name and type according to the anatomical therapeutic chemical (ATC) classification code of the drug dispensed, date and place of dispensing, packet size, strength, and defined daily dose are recorded for each redeemed prescription. In Denmark, diuretic medications are available only by prescription.

3.3 Study designs

Using the population-based registries and databases described above, we conducted one analytic cross-sectional validation study and two cohort studies (Table 2). The choice of study period was based on the availability of complete data on serum sodium measurement.

3.4 Study populations

In all three studies, we identified the study population through the DNPR. As mentioned, the North and Central Denmark Regions cover approximately 2 million residents, and close to 400,000 somatic hospitalizations are managed by the hospitals in these two regions each year.[123] For study I, we identified all admissions to the hospital from 1 January 2006 to 31 December 2011, regardless of the patient's age, mode of admission, and specialty of the department. This approach contrasts with studies II and III, in which we restricted to first-time hospitalizations in the study period of patients aged >15 years acutely admitted to departments of internal medicine. A hospitalization was considered acute if coded as such in the DNPR[124] and if the patient had not been admitted to a surgical, oncologic, gynecologic, or obstetric department within 30 days before the current admission. In study III, we further restricted to patients with a hyponatremic serum sodium measurement within 24 hours following hospitalization and extended the study period to include data from the Central Denmark Region through 2012. For the remainder of this thesis, 'the current hospitalization' refers to the hospitalization causing a patient to be included in the study.

Table 2. Study design overview

	Study I	Study II	Study III
Aim	Examine quality of ICD-10 codes for hyponatremia in the DNPR	Examine the effect of hyponatremia on short and long-term mortality and identify potential thresholds for increased risk	Examine the effect of diuretic use on short and long-term mortality in patients with hyponatremia
Design	Population-based cross-sectional study	Population-based cohort study	Population-based cohort study
Data sources	CRS, DNPR, LABKA	CRS, DNPR, LABKA	CRS, DNPR, LABKA, DNHSPD
Study area and period	Central and Northern Denmark Regions, 2006–2011	Central and Northern Denmark Regions, 2006–2011	Central and Northern Denmark Regions, 2006–2012
Study population	All hospitalizations (n=2,186,642) (819,701 individual patients)	Patients with a first-time acute admission to departments of internal medicine (n=279,508; of which 91% had a serum sodium measurement within 24 hours of admission)	Hyponatremic patients with a first-time acute admission to departments of internal medicine (n=46,157)
Exposure (or diagnostic test)	ICD-10 discharge diagnosis codes for hyponatremia	Mild, moderate, severe, and very severe hyponatremia; serum sodium as a continuous variable	Current diuretic use (new and long-term) former use and no-use; generic type of diuretic
Outcome (or reference standard)	Hyponatremia serum sodium laboratory test result (gold standard)	30-day and 1-year all-cause mortality	30-day and 31–365-day all-cause mortality
Covariables	Age, gender, department of admission, year of admission, CCI level	Age, gender, specific previous morbidity, CCI level, primary discharge diagnosis for current hospitalization	Age, gender, specific previous morbidity, CCI level, eGFR, hyponatremia severity, concurrent medication, primary discharge diagnosis for current hospitalization, hyponatremia-related diagnoses
Statistical analyses	Sensitivity, specificity, positive predictive value, negative predictive value	Cumulative mortality using the Kaplan–Meier (1-survival function). Relative risk using pseudo-value linear regression model. Predicted probability of death using a restricted cubic spline model	Cumulative mortality using the Kaplan–Meier (1-survival function). Relative risk using pseudo-value linear regression model
Confounder control	Stratification	Restriction, multivariate adjustment, stratification	Restriction, propensity score matching, multivariate adjustment, stratification
Sensitivity analyses	Complete case analysis, restriction to first hospitalization in the study period, restriction to patients with >1 sodium measurement during hospitalization, narrowing the ICD-10 code algorithm	Complete case analysis, RR in additional subcategories of patients with S-Na<120 mmol/l	Complete case analysis, multiple imputation of missing values for serum sodium and creatinine

Abbreviations: CCI=Charlson Comorbidity Index; CRS=Civil Registration System; DNHSPD= Danish National Health Service Prescription Database; DNPR=Danish National Patient Registry; eGFR=estimated glomerular filtration rate; ICD-10=International Classification of Diseases, Tenth Revision; LABKA=laboratory database; S-Na=serum sodium concentration.

3.5 Exposures (or diagnostic test)

3.5.1 Discharge diagnosis for hyponatremia (study I)

Based on ICD-10 codes recorded in the DNRP, we developed an algorithm to identify patients who received a diagnosis of hyponatremia during hospitalization. The algorithm included primary and secondary discharge diagnoses with the following ICD-10 codes: E87.1 (Hypo-osmolality and hyponatremia), E87.1A (Hyponatremia), and P74.2B (Hyponatremia in newborns [Danish version of ICD-10]).

3.5.2 Admission hyponatremia (study II)

In study II, we used serum sodium measurements recorded in the LABKA database to identify patients with hyponatremia at admission. To diminish the potential impact of hospital treatment on serum sodium levels, we based our evaluation of serum sodium status on the first serum sodium measurement performed within 24 hours following hospitalization. Patients were defined as having hyponatremia if serum sodium was <135 mmol/l and normonatremia if serum sodium was between 135 mmol/l and 145 mmol/l. We considered patients with no serum sodium measurement within 24 hours of admission to be normonatremic and imputed a serum sodium value of 140 mmol/l for these patients. We divided patients with hyponatremia into four categories of increasing hyponatremia severity: <120 mmol/l, 120–124.9 mmol/l, 125–129.9 mmol/l, and 130–134.9 mmol/l.

3.5.3 Preadmission diuretic use (study III)

From the DNHSPD, we retrieved information on all redeemed prescriptions for diuretics (ATC code C03) among our study cohort of patients hospitalized with hyponatremia. Based on the most commonly dispensed packet size,[125,126] we categorized patients as current users, former users, or non-users depending on whether they had redeemed their last prescription for diuretics within 90 days, 91–365 days, or >1 year before the current hospitalization, respectively. If diuretic use truly affected mortality, we would expect current users to be at higher risk than former users. Patients who tolerate diuretics well are more likely to be adherent to treatment compared to patients who experience side effects. We accounted for potential biases associated with adherence by dividing current users into *new users* if the prescription in question was the patient's first for diuretics and *long-term users* if the patient had previously redeemed one or more prescriptions for diuretics.[127] To examine the effect across the different generic types, we further categorized diuretic use as monotherapy with thiazides, other low-ceiling diuretics, or loop diuretics or potassium-sparing diuretics, or as diuretic polytherapy.

3.6 Outcomes

3.6.1 Reference standard for hyponatremia diagnosis (study I)

To assess the quality of a diagnostic test, in this case ICD-10 codes for hyponatremia, the results of the test must be compared to the "true" status of the condition the test seeks to classify in every individual tested.[106] This measure is often termed 'the gold standard' of a test. To confirm or disconfirm a hyponatremia diagnosis, we used serum sodium measurements recorded in the LABKA database. Because serum sodium values recorded in the LABKA database reflect only the 'true status' of those who had their sodium measured, we refer to this as the 'reference standard'.[128] The reference standard for hyponatremia was defined as a serum sodium value <133 mmol/l for infants (30 days of age or younger) and 135 mmol/l for patients older than 30 days.[129] One hyponatremic sodium measurement during hospitalization was sufficient for the patient to be categorized as having hyponatremia. Patients were assumed to have non-hyponatremic sodium levels (≥133 mmol/l and ≥135 mmol/l respectively) if no serum sodium measurement was performed during the hospitalization. We defined cutoff points for increasing severity of hyponatremia: 133 mmol/l, 128 mmol/l, 123 mmol/l, 118 mmol/l, and 113 mmol/l for infants younger than 31 days of age and 135 mmol/l, 130 mmol/l, 125 mmol/l, 120 mmol/l, and 115 mmol/l for patients 31 days of age or older.[85]

3.6.2 All-cause mortality (studies II and III)

Mortality of any cause was the outcome in both studies II and III. From the CRS, we retrieved information on migration and vital status at the end of follow-up for each patient, including date of migration or date of death in deceased.[116,118]

3.7 Covariates

To describe the study population, examine different effects across subgroups of patients, and adjust for important confounders, we retrieved information on a wide range of covariables.

3.7.1 Demographic information

The patient's gender and age at time of admission were derived from the CPR number.[116,118]

3.7.2 Department and year of admission

To detect whether the quality of hyponatremia diagnoses varied across areas of specialization (i.e., internal medicine, surgery, gynecology/obstetrics, pediatrics, and others) or calendar year, we retrieved information on department and year of admission for each hospitalization included in study I.[120]

3.7.3 Preexisting morbidity and the Charlson Comorbidity Index

With the aim of evaluating the potential modifying effect of potential underlying diseases for hyponatremia and to ascertain the burden of preexisting disease for each patient, we retrieved inpatient and outpatient diagnoses recorded in the DNPR prior to hospitalization. We used this information to compute Charlson Comorbidity Index (CCI) scores,[130] with which we defined three morbidity levels: low (CCI score=0), medium (CCI score=1–2), and high (CCI score >2). In study I, we restricted to diagnoses recorded within 10 years before the hospitalization because conditions experienced before that would not likely influence the diagnostic approach during the current hospitalization. This approach was in contrast with studies II and III, in which the computed CCI score was based on any diagnosis ever recorded for each patient. In study III, this information was also used to categorize patients according to specific preexisting morbidities (i.e., congestive heart failure, myocardial infarction, hypertension, chronic liver disease, chronic respiratory disease, diabetes, and cancer).

3.7.4 Discharge diagnosis related to the current hospitalization

From the DNPR, we also retrieved the primary discharge diagnosis for the current hospitalization to ascertain the main indication for hospitalization in studies II and III. For study III, we further retrieved information on primary or secondary discharge diagnoses related to the development of hyponatremia.

3.7.5 Estimated glomerular filtration rate (eGFR)

In study III, we wished to account for potential differences in baseline renal function among included patients. For each person, we retrieved information on the latest serum creatinine measurement, if any, performed between one week and one year before hospitalization, and used the 4-variable "Modification of Diet in Renal Disease (MDRD)" formula, which includes gender, age, race and serum creatinine, to calculate the eGFR.[2,131] Because we had no information on race, all patients were assumed to be Caucasian. Renal function was assumed to be normal, defined as eGFR >90 ml/min/1.73 m^2, if a baseline serum creatinine concentration was not available.

3.7.6 Concurrent drug use

Also exclusively for study III, we retrieved information on prescriptions for angiotensin-converting enzyme inhibitors, angiotensin II antagonists, β-blockers, hydralazine, nitrates, calcium-channel blockers, anti-adrenergic drugs, antidepressants, anti-epileptic drugs, opioids, non-steroidal anti-inflammatory drugs, and acetaminophen redeemed within 90 days of the current admission.[122]

3.8 Statistical analyses

For each study, we presented contingency tables with summary statistics, providing the distribution of data according to all main variables.[132]

3.8.1 Data quality measures (study I)

Controversy exists about the terminology of data quality measures.[128] In this dissertation, the sensitivity, specificity, and positive predictive value (PPV) and negative predictive values (NPV) of the ICD-10 codes for hyponatremia are estimated. The sensitivity and specificity of a diagnostic test refer to the test's ability to correctly categorize patients as diseased or non-diseased,[106] respectively, and sensitivity is often used to describe the completeness of data. On the other hand, predictive values refer to the patient's probability of having the disease or not, given a positive or negative test result, respectively.[106] Predictive values are often used to describe the validity of data. We estimated sensitivity as the proportion of hospitalizations with a hyponatremic serum value recorded in the LABKA database for which an ICD-10 code for hyponatremia could be identified in the DNPR, and specificity as the proportion of hospitalizations with no record of a hyponatremic serum sodium measurement for which no ICD code for hyponatremia was recorded in the DNPR (Figure 6).

		ICD-10 code of hyponatremia recorded in the DNRP		
		Yes	No	
Hyponatremia recorded in the LABKA database (gold standard)	Yes	TP (true positive)	FN (false negative)	TP+FN
	No	FP (false positive)	TN (true negative)	FP+TN
		TP+FP	FN+TN	
Sensitivity=TP/(TP+FN) Specificity=TN/(FP+TN) PPV=TP/(TP+FP) NPV=TN/(FN+TN)				

Figure 6. Schematic 2×2 table and quality measure estimation formulas. Figure adapted from Holland-Bill *et al*., BMJ Open, 2014[88]

We estimated the PPV as the proportion of hospitalizations with an ICD-10 code for hyponatremia in the DNPR, for which the diagnosis was confirmed by laboratory test results, and the NPV as the proportion of hospitalizations not coded with an ICD-10 code for hyponatremia during which no hyponatremic serum sodium value was recorded in the LABKA database. Quality measures with 95% CIs were estimated for all predefined serum sodium cutoff points using the exact method for binomial data.[133] Finally, we examined the quality across age groups, department, and year of admission.

3.8.2 Prevalence (study II)

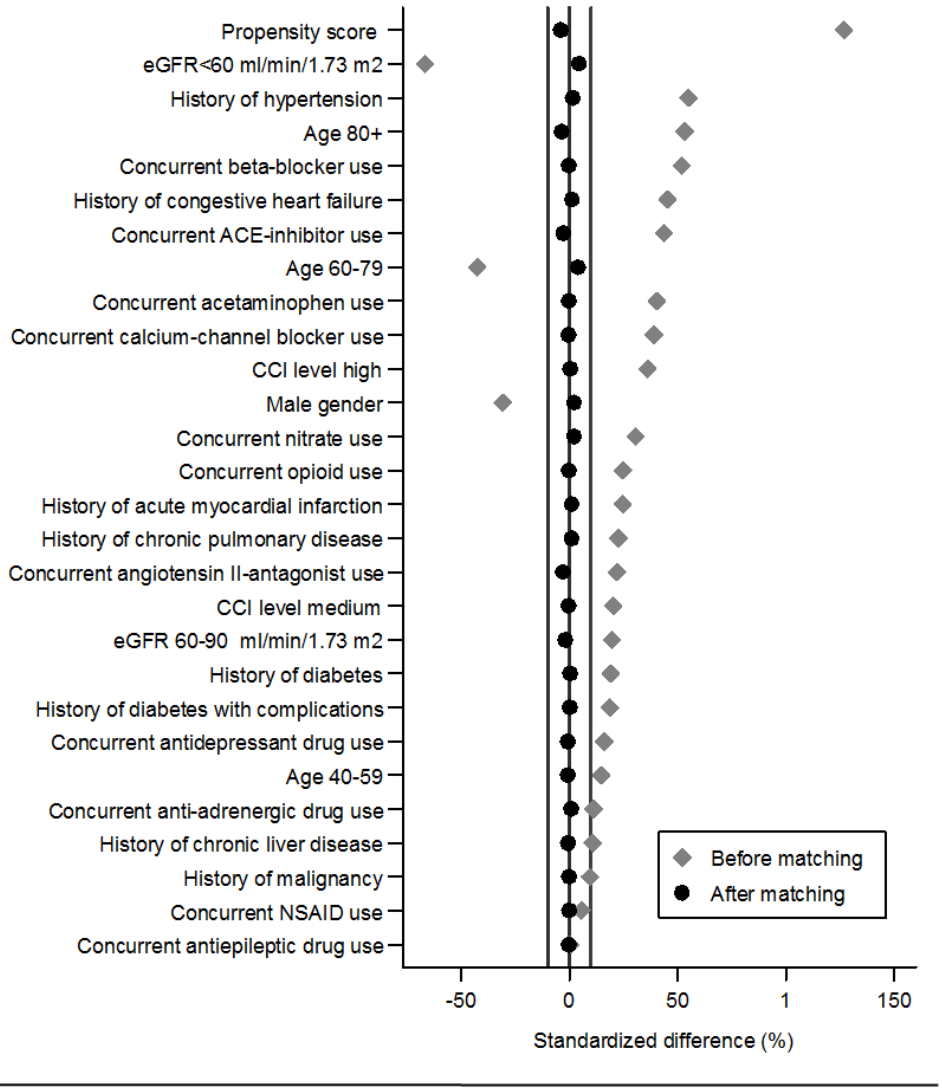
The prevalence of hyponatremia was computed as the number of patients acutely admitted to departments of internal medicine with a hyponatremic serum sodium measurement within 24 hours of hospitalization divided by the total number of first-time admissions to these departments during the study period. We further calculated the prevalence for each level of hyponatremia severity and according to subgroups based on preexisting morbidity and primary discharge diagnosis.

3.8.3 Mortality (studies II and III)

We used time-to-event data to measure the effect of hyponatremia (study II) or preadmission diuretic use (study III) on mortality. Patients were followed from day of hospitalization until death, migration, or end of follow-up, whichever came first. We used the Kaplan–Meier method (1- survivor function) to compute 30-day and 1-year mortality with corresponding 95% CIs in study II and 30-day mortality in study III. Relative risk (RR) of death with 95% CIs comparing mortality associated with hyponatremia (overall and for categories of increasing severity) versus normonatremia (study II) and current or former diuretic use versus non-use (study III) were computed using the pseudo-value approach, a general linear regression model method that allows for direct comparison of non-proportional failure (or survival) functions in right-censored data.[134] In study II, we further examined potential thresholds for the effect on mortality using restricted cubic spline regression models including serum sodium as a continuous variable (study II).[135,136]

In addition to using restriction when designing our studies (studies II and III), we controlled for confounding by propensity score matching (III), and by means of multivariate adjustment (studies II and III) and stratification (studies I–III). The propensity score expresses each patient's probability of receiving diuretic treatment, given his or her baseline covariables, thereby attempting to control for confounding by indication.[137,138] To calculate propensity scores, we included confounders and risk factors for death (i.e., gender, age, concurrent medication, eGFR, preexisting morbidities, and CCI level) in a logistic regression model.[139] We matched each diuretic user to the non-user with the nearest propensity score (maximum caliper range ±0.025) without replacement and assessed whether matching resulted in adequate balancing, defined as an absolute standardized difference of <0.1 for each covariate (Figure 7).[2]

For potential confounders, we selected factors known from the scientific literature or clinical experience to be associated with both mortality and risk of hyponatremia or diuretic use, but without being caused by the exposure.[140,141] We adjusted for these factors in our multivariate regression models and performed stratification when relevant to examine potential differences in effect in subgroups of patients (effect measure modification).[142]



Solid vertical lines represent the 10% limit for absolute standardized difference, indicating adequate balancing.
Abbreviation: ACE, angiotensin-converting enzyme; CCI, Charlson Comorbidity Index;
eGFR, estimated glomerular filtration rate; NSAID, Nonsteroidal anti-inflammatory drug

Figure 7. Standardized difference before and after matching on propensity score.

3.8.4 Sensitivity analyses (studies I–III)

The robustness of our results was examined through several sensitivity analyses. We performed complete case analysis, in which we included only patients without missing data on serum sodium (studies I–III) and serum creatinine (study III), evaluating the assumption of normal serum concentrations in patients for whom these laboratory tests were not performed.[143] In study III, we further used multiple imputation methods to deal with missing data. Based on the pattern of missing and observed data, this method creates a number of new datasets with imputed probable values for observations with missing serum sodium and/or serum creatinine with which we could estimate an average RR.[144]

In study I, we also examined whether the results were sensitive to a more narrow definition of hyponatremia in the ICD-10 algorithm, to restriction to patients with >1 sodium measurement during hospitalization, and to including only first-time admissions during the study period.

3.8.5 Additional information

All data analyses were performed using STATA statistical software package version 12 (Stata Corp, College Station, TX, USA). Informed consent from members of the study population is not required for register-based research in Denmark. The studies were approved by the Danish Data Protection Agency (record numbers 2006-53-1396 (study I), 2013-41-1924 (study II), and 2013-41-1924 (study III)).

4. Results

In the following sections, we will outline the main findings of each of the three studies. For further details, see appendices I–III.

4.1 Quality of ICD-10 codes for hyponatremia (study I)

At least one hyponatremic serum sodium value had been recorded in 14% (n=306,418) of all 2,186,642 hospitalizations identified. In comparison, an ICD-10 code for hyponatremia was recorded for 5,410 hospitalizations, corresponding to an overall sensitivity of 1.8% (95% CI: 1.7%–1.8%) (Table 3). Sensitivity increased with increasing severity of hyponatremia and reached 34.3% (95% CI: 32.6%–35.9%) for serum sodium values <115 mmol/l. Specificity was above 99%, regardless of hyponatremia severity. An ICD-10 code for hyponatremia was recorded for 5,850 hospitalizations in total, but 440 of these diagnoses could not be confirmed by a hyponatremic serum sodium measurement in the LABKA database, yielding a PPV of 92.5% (95% CI: 91.8%–93.1%) for serum sodium <135 mmol/l. NPV was slightly lower at 86.2% (95% CI: 86.2%–86.2%). As expected, PPV decreased and NPV increased when we used lower serum sodium cutoff points to define hyponatremia.

Table 3. Quality of ICD-10 codes for hyponatremia recorded in the DNPR, with serum sodium measurements in the LABKA database as the reference standard.

		ICD-10 code for hyponatremia recorded in the DNPR			Quality Measures	
		Yes	No	Total		
Overall						
Na<135 mmol/l*	Yes	5,410	301,008	306,418	Sensitivity	1.8 (1.7–1.8)
	No	440	1,879,784	1,880,224	Specificity	100 (100–100)
	Total	5,850	2,180,792	2,186,642	PPV	92.5 (91.8–93.1)
					NPV	86.2 (86.2–86.2)
Cutoff points for increasing severity of hyponatremia						
Na<130 mmol/l*	Yes	4,528	80,605	85,133	Sensitivity	5.3 (5.2–5.5)
	No	1,322	2,100,187	2,101,509	Specificity	99.9 (99.9–99.9)
	Total	5,850	2,180,792	2,186,642	PPV	77.4 (76.3–78.5)
					NPV	96.3 (96.3–96.3)
Na<125 mmol/l*	Yes	3,261	21,544	24,805	Sensitivity	13.1 (12.7–13.6)
	No	2,589	2,159,248	2,161,837	Specificity	99.9 (99.9–99.9)
	Total	5,850	2,180,792	2,186,642	PPV	55.7 (54.5–57.0)
					NPV	99.0 (99.0–99.0)
Na<120 mmol/l*	Yes	2,061	6,219	8,280	Sensitivity	24.9 (24.0–25.9)
	No	3,789	2,174,573	2,178,362	Specificity	99.8 (99.8–99.8)
	Total	5,850	2,180,792	2,186,642	PPV	35.2 (34.0–36.5)
					NPV	99.7 (99.7–99.7)
Na<115 mmol/l*	Yes	1,107	2,127	3,234	Sensitivity	34.3 (32.6–35.9)
	No	4,743	2,178,665	2,183,408	Specificity	99.8 (99.8–99.8)
	Total	5,850	2,180,792	2,186,642	PPV	18.9 (17.9–20.0)
					NPV	99.9 (99.9–99.9)

Abbreviations: CCI=Charlson Comorbidity Index; CI=confidence interval; DNPR=Danish National Patients Registry
***Corresponding to <133, <128, <123, <118, <113 mmol/l for infants aged 30 days or fewer, respectively**

Restricting to incident hospitalizations, hospitalizations during which serum sodium was measured at least once, or changing the ICD-10 algorithm to include only the most specific codes for hyponatremia yielded practically identical results, supporting the robustness of our findings. Sensitivity was highest for internal medicine hospitalization (2.7%; 95% CI: 2.7%–2.8%) compared to surgical, gynecologic/obstetric, pediatric, and "other" hospitalizations (sensitivity ranging from 0.1%, 95% CI: 0.1%–0.3% to 0.3%, 95% CI: 0.2%–0.5%). Patients with hyponatremia and a corresponding ICD-10 code were on average older and characterized by slightly lower comorbidity levels than patients with hyponatremia but no hyponatremia diagnosis (Table 1, Appendix I).

4.2 Prevalence of admission hyponatremia (study II)

Overall, 15.0% (41,803) of patients acutely admitted to departments of internal medicine (279,508 patients) had hyponatremia at the time of hospitalization. The prevalence of mild (130–134.9 mmol/l), moderate (125–129.9 mmol/l), severe (120–124.9 mmol/l), and very severe (<120 mmol/l) hyponatremia was 10.5%, 2.9%, 0.9%, and 0.6%, respectively. In total, 83.3% (232,911) of patients were classified as having normonatremia and 1.7% (4,794) of patients as having hypernatremia (these patients were excluded from the mortality analysis).

For all categories of hyponatremia, the prevalence increased with increasing age and morbidity level (see Appendix II). Approximately 30% of patients with preexisting liver disease and more than 20% of patients with preexisting malignancies had hyponatremic serum sodium measurements within 24 hours of admission. Hyponatremia was also extremely prevalent among patients for which liver disease (42.1%), malignancy (25.5%), diabetes (36.0%), sepsis (34.5%), and infection in general (26.1%) were coded as the primary diagnosis during the current hopsitalization.

4.3 Hyponatremia and mortality (study II)

Any degree of hyponatremia was associated with increased short- and long-term mortality compared to normonatremia (Table 4). At 30 days, mortality among patients with serum sodium levels of 130–134.9 mmol/l, 125–129.9 mmol/l, 120–124.9 mmol/l, and <120 mmol/l was 7.3%, 10.0%, 10.4%, and 9.6% compared to 3.6% in patients with normonatremia. The adjusted RR of death in patients with serum sodium of 130–134.9 mmol/l was 1.4 (95% CI: 1.3–1.4), increasing to 1.7 (95% CI: 1.6–1.8) and 1.7 (95% CI: 1.4–1.9) in patients with serum sodium of 125–129.9 mmol/l and 120–124.9 mmol/l, respectively, while decreasing to 1.3 (95% CI: 1.1–1.5) in patients with serum sodium <120 mmol/l. Subdividing patients with severe hyponatremia revealed a further decrease in relative risk, starting with an adjusted RR of 1.4 (95% CI: 1.1–1.8) in patients with serum sodium of 115–119.9 mmol/l, decreasing to 1.1 (95% CI:

0.8–1.6) and 1.1 (95% CI: 0.7–1.8) in patients with serum sodium levels of 110–114.9 mmol/l and <110 mmol/l, respectively (Supplementary Table 1, Appendix II). Hyponatremia remained associated with increased mortality relative to normonatremia one year following hospitalization, with RRs of 1.3 (95% CI: 1.3–1.3), 1.4 (95% CI: 1.4–1.5), 1.4 (95% CI: 1.3–1.5), and 1.3 (95% CI: 1.1–1.4) for serum sodium levels of 130–134.9 mmol/l, 125–129.9 mmol/l, 120–124.9 mmol/l, and <120 mmol/l, respectively. RR values for subcategories of severe hyponatremia were similar to those observed at 30 days.

Table 4. 30-day and 1-year mortality and relative risk in patients with and without hyponatremia, overall and according to hyponatremia severity.

Serum sodium level	Total (n)	30-day				1-year			
		Deaths (n)	Mortality, % (95% CI)	Crude RR (95% CI)	Adjusted RR* (95% CI)	Deaths (n)	Mortality, % (95% CI)	Crude RR (95% CI)	Adjusted RR* (95% CI)
Normonatremia	232,911	8,275	3.6 (3.5–3.6)	1 (ref.)	1 (ref.)	23,561	10.6 (10.4–10.7)	1 (ref.)	1 (ref.)
Hyponatremia overall	41,803	3,387	8.1 (7.9–8.4)	2.3 (2.2–2.4)	1.5 (1.4–1.5)	8,711	21.5 (21.2–22.0)	2.0 (2.0–2.1)	1.3 (1.3–1.4)
Hyponatremia category									
130–134.9 mmol/l	29,287	2,133	7.3 (7.0–7.6)	2.1 (2.0–2.1)	1.4 (1.3–1.4)	5,715	20.2 (19.8–20.7)	1.9 (1.9–2.0)	1.3 (1.3–1.3)
125–129.9 mmol/l	8,170	818	10.0 (9.4–10.7)	2.8 (2.6–3.0)	1.7 (1.6–1.8)	1,967	24.8 (23.8–25.7)	2.4 (2.3–2.4)	1.4 (1.4–1.5)
120–124.9 mmol/l	2,573	266	10.4 (9.2–11.6)	2.9 (2.6–3.3)	1.7 (1.4–1.9)	617	24.7 (23.0–26.4)	2.3 (2.2–2.5)	1.4 (1.3–1.5)
<120 mmol/l	1,773	170	9.6 (8.3–11.1)	2.7 (2.3–3.1)	1.3 (1.1–1.5)	412	23.9 (22.0–26.0)	2.3 (2.1–2.5)	1.3 (1.1–1.4)

*Adjusted for age group, gender, and history of specific morbidities included in the Charlson Comorbidity Index

Abbreviations: CI, confidence interval; RR, relative risk

The restricted cubic spline model further substantiated these findings. Predicted mortality started to increase markedly for serum sodium values of 139 mmol/l to 132 mmol/l, below which the risk plateaued (Figure 8). The plateauing was especially evident after controlling for potential confounders.

Our results did not change substantially when excluding patients without a serum sodium measurement (Supplementary Table 3, Appendix II) and were robust across most patient subgroups (Figure 9). One exception was patients for whom a diagnosis of hyponatremia and hypo-osmolality was indicated as the primary reason for treatment during the current hospitalization (RR of 0.2; 95% CI: 0.1–1.1). Also, in contrast to the decline in relative risk associated with serum sodium <120 mmol/l compared to less severe hyponatremia found in the overall analysis, an increase in relative risk was observed for patients with a primary discharge diagnosis of sepsis, respiratory disease, liver disease, and cancer (Supplementary Table 4, Appendix II).

Figure 8. Crude and adjusted* predicted probability of (A) 30-day and (B) 1-year mortality as a function of admission serum sodium concentration. *Adjusted for age group, gender, and specific morbidities included in the CCI. The gray area represents the 95% CI. Figure from Holland-Bill *et al*. Eur J Endocrinol. 2015.[45]

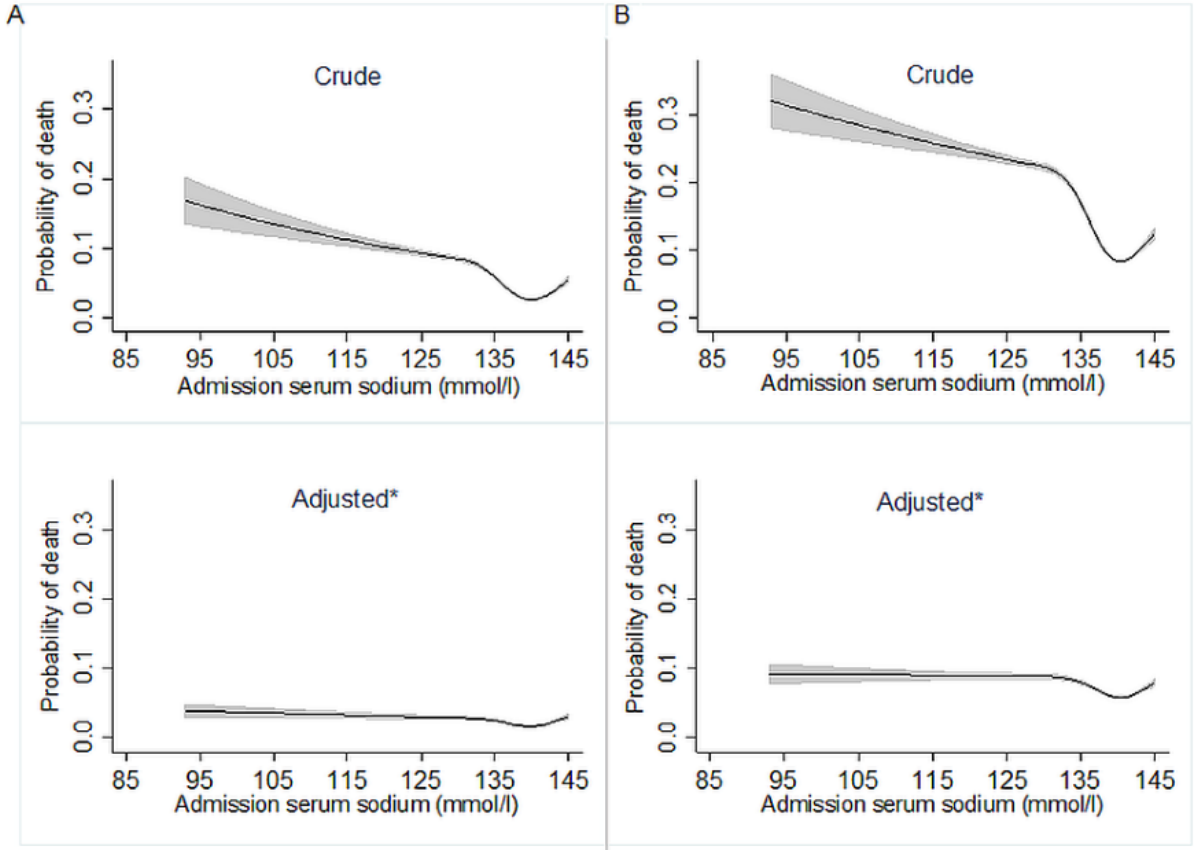
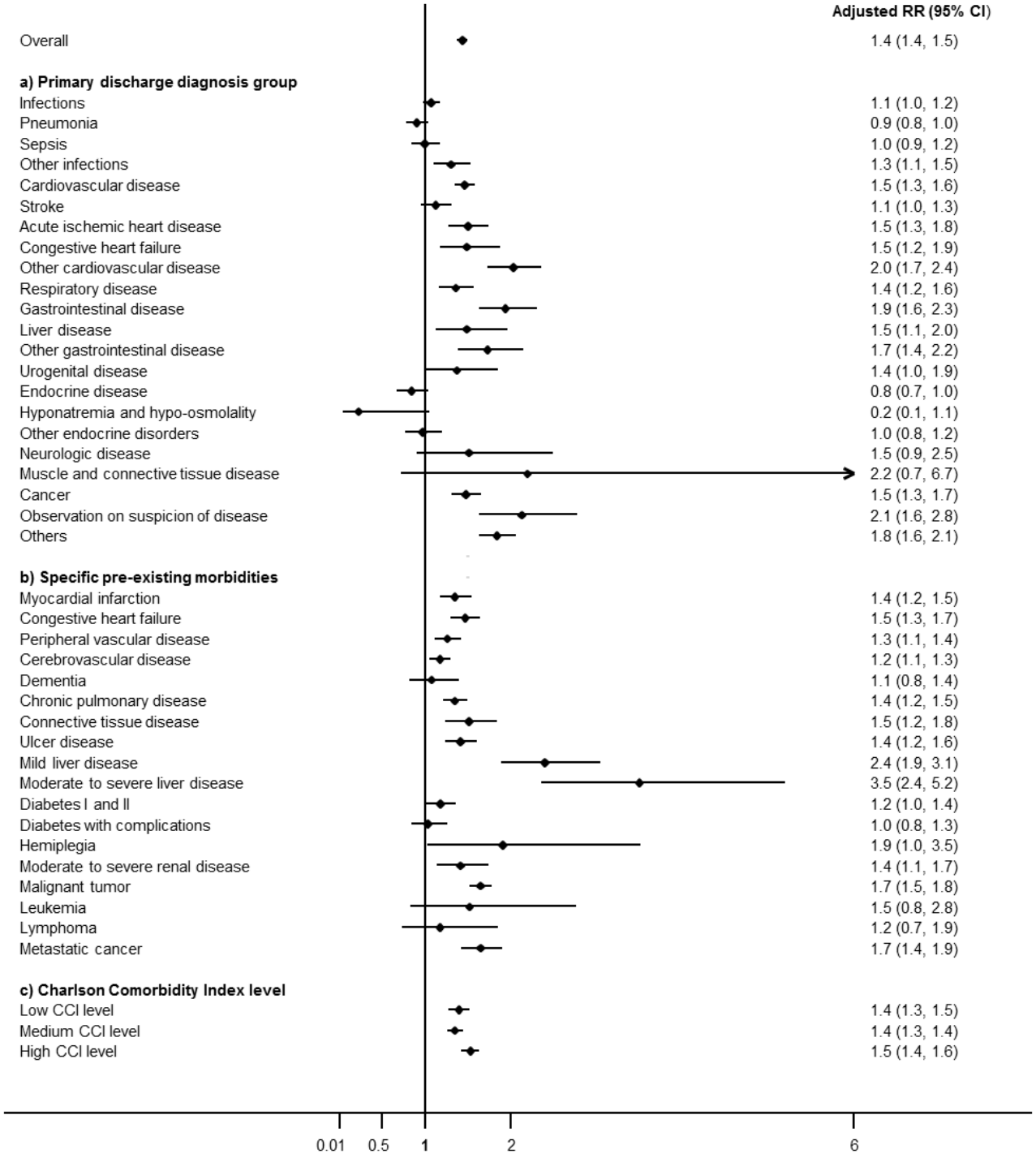


Figure 9. Adjusted 30-day relative risk (RR) of death among patients with hyponatremia compared to patients with normonatremia, stratified by patient subgroups. From Holland-Bill *et al*. Eur J Endocrinol. 2015.[45]



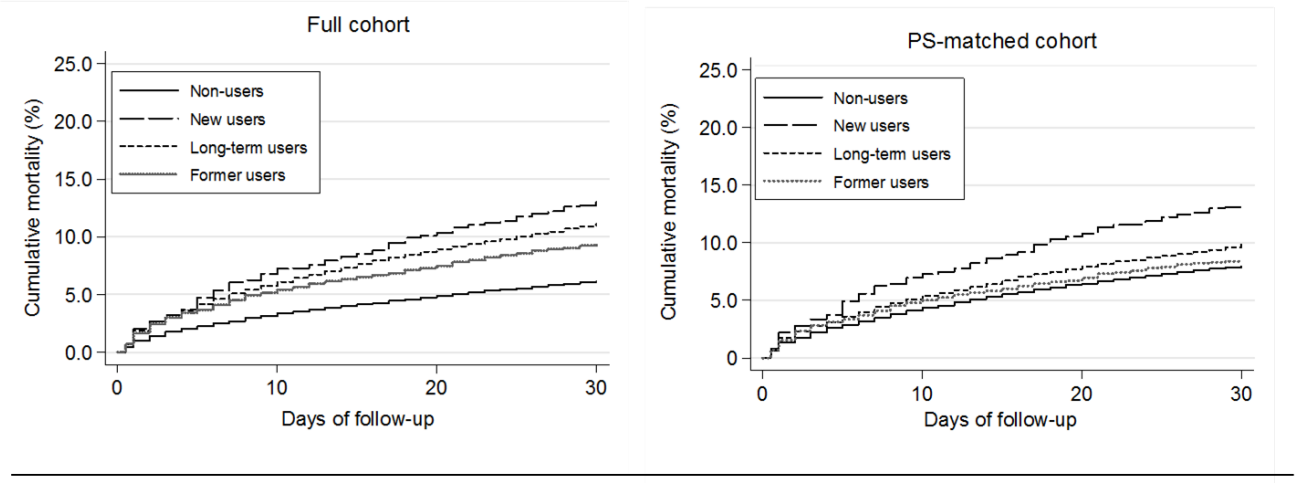
Adjusted for a) age group, gender, and CCI level, b) age group, gender, and CCI level (excl. the specific morbidity), and c) age group and gender.
Subgroups with too few events to yield meaningful estimates were left out.
Abbreviations: CCI, Charlson Comorbidity Index ; CI, confidence interval; RR, relative risk

4.4 Impact of diuretic use on hyponatremia-associated mortality (study III)

Approximately 32% (n=14,635) of patients admitted with hyponatremia (n=46,157) were current users and 9% (n=4091) were former users of diuretics. The majority of current users were long-term users (88.8%). As could be expected, diuretic polytherapy was less common among new users (13.7%) than among long-term users (33.3%) (Table 1, Appendix III). Thiazides were the most frequently prescribed diuretic monotherapy, and these patients were slightly more likely to present with very severe hyponatremia (7.0%) compared to patients receiving loop diuretic (3.7%) or potassium-sparing (5.3%) diuretic monotherapy (Supplementary eTable 2, Appendix III).

Current diuretic use was associated with increased mortality compared to former users and non-users at 30 days of follow-up both in the full cohort (11.1% versus 9.3 and 6.2%, respectively) and in the propensity score matched cohort (10.4% versus 8.5% and 8.0%, respectively) (Figure 10, Table 5). Yet, the adjusted 30-day RR associated with current use was only slightly higher than the adjusted 30-day RR associated with being a former user (1.3, 95% CI: 1.2–1.4 vs. 1.2, 95% CI: 1.0–1.3 in the full cohort, and 1.3, 95% CI: 1.2–1.4 vs. 1.1, 95% CI: 0.9–1.2 in the propensity score matched cohort), which could suggest that the underlying treatment indication contributed to the increased mortality. However, the small difference in RR between former and current use was mainly driven the association for long-term use (adjusted RR of 1.3, 95% CI: 1.2–1.4 and propensity score matched RR of 1.2, 95% CI: 1.1–1.4) and concealed a markedly increased risk among new users (adjusted RR of 1.7, 95% CI: 1.4–1.9) (Table 5).

Figure 10. 30-day mortality according to diuretic use



Abbreviation: PS, propensity score

Table 5. 30-day mortality and relative risk in diuretic users compared to non-users, overall and by diuretic type.

	Full cohort				Propensity score matched		
	Events/N	Mortality, % (95% CI)	Crude RR (95% CI)	Adjusted RR* (95% CI)	Events/N	Mortality, % (95% CI)	RR (95% CI)
Overall							
Non-users	1681/27431	6.2 (5.9–6.4)	1.0 (Ref.)	1.0 (Ref.)	957/12075	8.0 (7.5–8.5)	1.0 (Ref.)
Former users	380/4091	9.3 (8.5–10.2)	1.5 (1.4–1.7)	1.2 (1.0–1.3)	250/2945	8.5 (7.6–9.6)	1.1 (0.9–1.2)
Current users	1620/14635	11.1 (10.6–11.6)	1.8 (1.7–1.9)	1.3 (1.2–1.4)	948/9130	10.4 (9.8–11.1)	1.3 (1.2–1.4)
New users	226/1751	12.9 (11.5–14.6)	2.1 (1.8–2.4)	1.7 (1.4–1.9)	188/1401	13.5 (11.8–15.4)	1.7 (1.5–2.0)
Long-term users	1394/12884	10.8 (10.3–11.4)	1.8 (1.6–1.9)	1.3 (1.2–1.4)	760/7729	9.9 (9.2–10.5)	1.2 (1.1–1.4)
By diuretic type							
Diuretic monotherapy	1,008/10,099	10.0 (9.4-10.6)	1.6 (1.5-1.8)	1.2 (1.1-1.3)	636/6,721	9.5 (8.8-10.2)	1.2 (1.1-1.3)
Thiazide diuretics	456/6,070	7.5 (6.9-8.2)	1.2 (1.1-1.4)	1.0 (0.9-1.1)	302/4,342	7.0 (6.3-7.8)	0.9 (0.8-1.0)
Other low-ceiling	6/133	4.5 (2.1-9.8)	0.7 (0.3-1.6)	0.8 (0.3-1.7)	4/106	5.7 (2.6-12.2)	0.7 (0.3-1.6)
Loop diuretic	495/3,461	14.3 (13.2-15.5)	2.3 (2.1-2.6)	1.6 (1.4-1.8)	273/1,985	14.6 (13.1-16.2)	1.8 (1.6-2.1)
Potassium-sparing	51/435	11.7 (9.0-15.1)	1.9 (1.5-2.5)	1.6 (1.2-2.1)	34/288	13.6 (10.1-18.1)	1.7 (1.3-2.3)
Diuretic polytherapy	612/4,536	13.5 (12.6-14.6)	2.2 (2.0-2.4)	1.5 (1.3-1.7)	312/2,409	13.0 (11.7-14.4)	1.6 (1.5-1.8)

*Adjusted for age group, gender, previous morbidities, concurrent drug use, eGFR group, and hyponatremia severity
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; RR, relative risk

Users of loop diuretic monotherapy, potassium-sparing monotherapy, and diuretic polytherapy had equally high impact on 30-day mortality (adjusted RR of 1.6, 95% CI: 1.4–1.8; 1.6, 95% CI: 1.2–2.1; and 1.5, 95% CI: 1.3–1.7, respectively), while no increase in risk was found for thiazide monotherapy users overall compared to non-users (adjusted RR of 1.0, 95% CI: 0.9–1.1) (Table 3, Appendix III). However, patients with newly initiated thiazide use had a 50% increased mortality [adjusted RR= 1.5 (95% CI: 1.2-2.0)] compared to long-term thiazide users, and a 30% increased risk compared to non-users [adjusted RR= 1.3 (95% CI: 1.0-1.6)] (data not shown).

Furthermore, current use was associated with increased 30-day mortality across most subgroups based on age, specific previous morbidities, CCI level, primary discharge diagnosis for the current hospitalization, renal function, and hyponatremia severity (Figure 2, Appendix III). The results were robust to measures dealing with missing data on serum sodium or baseline serum creatinine (Supplementary eTables 3 and 4, Appendix III). Changing the definition for current use to include all prescriptions redeemed within 250 days did not change the overall estimate for current users. It did, however, attenuate the risk in new users (data not shown).

5. Discussion

5.1 Main conclusions

A serum sodium value <135 mmol/l was measured at some point during hospitalization in one in seven patients admitted to hospitals in the North and Central Denmark Regions. Yet, less than 2% received a diagnosis of hyponatremia at discharge. Even for sodium values <115 mmol/l, the diagnosis was greatly underreported, indicating that hyponatremia is often considered clinically unimportant compared to other coexisting or underlying illnesses. ICD-10 codes for hyponatremia were therefore deemed unsuitable for use in the subsequent studies. However, because of the high PPV and specificity, patients identified through these codes can safely be assumed to have hyponatremia. Challenging the perception that hyponatremia in itself does not affect mortality, we found that hyponatremia, regardless of the underlying disease, was markedly associated with increased mortality among internal medicine patients. Mortality was increased in hyponatremia of any severity. In fact, the risk increased steeply even in mild hyponatremia and tended to plateau when serum sodium decreased below 130 mmol/l. We also found that mortality was increased in current diuretic users with hyponatremia, especially those with newly initiated therapy, compared to hyponatremic non-users. Mortality was especially high for users of loop diuretics and diuretic polytherapy. Although current thiazide use was not associated with either increased or reduced mortality overall, the risk was increased in new users of thiazide diuretics compared to non-users and long-term users. Whether these results are attributable to an actual drug effect needs to be supported in further studies.

5.2 Comparison with existing literature

The succeeding paragraphs provide comparison of the study results to the existing literature and briefly touch on possible explanations of our findings.

5.2.1 Quality of ICD-10 codes for hyponatremia (study I)

No previous study has examined the quality of ICD-10 discharge diagnoses for hyponatremia among hospitalized patients of all ages. A Canadian multicenter study, among 129,080 patients aged ≥66 years, reported sensitivity estimates of 4.5% and 6.4%, using serum sodium measurements of <135 mmol/l at presentation to the emergency department or at hospital admission as reference standard.[87] These estimates exceed ours for the age groups of 65–79 and ≥80 years, which could suggest that coding increases if hyponatremia is the reason for referral. Despite using a higher cutoff point of <136 mmol/l, an earlier study validating ICD-9 codes for hyponatremia among employer-based commercially insured outpatients in the US also found a slightly higher sensitivity of 3.5%, potentially reflecting the financial

incentive for more exhaustive coding in professional claims databases.[86] Consistent with our result, a sensitivity of 1.7% was reported for ICD-9 hyponatremia diagnoses in a Dutch study among 48,423 patients admitted to a public hospital.[85] As in our study, in that work, sensitivity did not exceed 15% even for serum sodium values below <125 mmol/l while the probability of receiving a hyponatremia diagnosis at this cutoff ranged from 29.6% to 41.7% in the studies by Gandhi *et al*. and Shea *et al*.[86,87] Such low sensitivity makes ICD codes for hyponatremia ill-suited for studies on prevalence, incidence, and absolute risk. Except for a PPV of 62.6% reported by Shea *et al*. for the cutoff point of <136 mmol/l, reported specificities, NPVs, and PPVs were generally high. Therefore, ICD codes for hyponatremia can be assumed to represent the true presence of hyponatremia, making discharge diagnoses operable when the relative outcomes are of interest. However, the findings suggest that such studies would be based mainly on severe cases, and potentially on patients without other major illnesses, and hence may not be representative of all hyponatremic patients.[104]

In summary, the findings of four studies examining the quality of ICD codes, including ours, show that hyponatremia is not likely coded if mild or in the presence of other illnesses. The low sensitivity, which probably reflects that physicians view hyponatremia as a common consequence of a wide range of diseases and therefore not warranting coding, renders ICD-10 codes for hyponatremia unfit for use in studies of prevalence, incidence, and absolute risks. Actual serum sodium measurements, if available, are preferred for ascertainment of hyponatremia.

5.2.2 Prevalence of admission hyponatremia (study II)

In our study, among patients admitted to departments of internal medicine, 15% had hyponatremia upon hospital entry. This value is similar to the prevalence of admission hyponatremia among internal medicine patients reported in two single-center studies from Slovakia and Italy (13% and 14%, respectively).[99,100] In the latter, only hypotonic hyponatremia was detected. Whelan *et al*. also examined the prevalence among internal medicine patients exclusively and reported a prevalence of 19.6% when restricting to patients with serum sodium measured at hospital arrival.[93] Of interest, our results were almost identical to the prevalence found in a US study in a mixed population of internal medicine and surgical patients hospitalized for at least 48 hours at two Boston hospitals.[94] Other studies in hospitalized patients in general, restricting to patients with at least one[92,102] or two serum sodium meaurements[96,98] or using another cutoff for hyponatremia,[96,102] reported prevalences that vary substantially (see Table 1).

No study has reported the prevalence of hyponatremia simultaneously for multiple patient subgroups, thereby allowing for identification of subgroups that are more likely to experience hyponatremia relative to others. However, the prevalences found in our study resembled those previously reported for patients with ischemic stroke,[111] acute myocardial infarction,[72] chronic heart failure,[64] liver

disease,[62,145,146] and pneumonia.[147] We also found admission hyponatremia to be extremely prevalent in patients with diabetes, which has not previously been reported.

In summary, admission hyponatremia is highly prevalent in broad populations of hospitalized patients. This observation is not restricted to patients suffering from diseases generally known to cause hyponatremia.

5.2.3 Hyponatremia and mortality (study II)

We found that hyponatremia, regardless of severity and underlying disease, was associated with increased short- and long-term mortality. Serum sodium <132 mmol/l prompted essentially no further increase in mortality compared to milder degrees of hyponatremia, which could be suggestive of an 'all or nothing effect' of hyponatremia via oxidative stress–induced protein and cell damage.[55]

A 2009 single-center cohort study from Ireland of 14,239 patients admitted to departments of internal medicine found that increasing hyponatremia severity was associated with an increase in in-hospital mortality.[93] For serum sodium values of 130–134 mmol/l, 125–129 mmol/l, and <125 mmol/l, absolute mortality was 15.1%, 18.9%, and 22.5% compared to 7.9% in patients with normonatremia, resulting in adjusted ORs of 1.25 (95% CI: 1.05–1.49), 1.43 (95% CI: 1.12–1.83), and 2.00 (95% CI: 1.44–2.77), respectively.

This result was later supported by a US cohort study of hospitalized internal and surgical (not obstetric) patients (n=209,839),[96] in which the predicted probability of in-hospital death, depicted by a restricted cubic spline curve, continued to increase dramatically as admission serum sodium decreased. This finding is in contrast to the biphasic dose-response relationship we observed both before and after adjustment for covariables. However, in the latter study, adjusted analysis based on hyponatremia categories indicated a leveling of mortality relative to normonatremia for serum sodium values <127 mmol/l [for the subcategories 123–127 mmol/l, 118–122 mmol/l, and <118 mmol/l, adjusted OR was 2.54 (95% CI: 1.87–3.45), 2.46 (95% CI: 1.38–4.39), and 2.46 (95% CI: 1.19–5.10), respectively]. Of note, only 20 deaths occurred in the two lowest serum sodium categories.[96] Although the use of different cutoff points to define hyponatremia and levels of hyponatremia severity renders direct comparison difficult, it does seem that the proportion of patients dying during hospitalization in the study by Wald *et al*[96]. (2.0% in patients with normonatremia and 3.4% in patients with hyponatremia) was lower than the in-hospital mortality observed in our study (2.9% in patients with normonatremia and 6.8% in patients with hyponatremia) (Supplementary Table 1, Appendix II).

Two US cohort studies of mixed hospitalized surgical and internal medicine patients have previously reported a decline in absolute mortality when serum sodium decreased below 125 mmol/l.[94,98] Consistent with our result, adjusted mortality rate ratio (aMRR) among 98,411 patients hospitalized for

>48 hours tended to be lower in severe hyponatremia compared to mild and moderate hyponatremia [for sodium levels of 130–134 mmol/l, 125–129 mmol/l, 120–124 mmol/l, and <120 mmol/l, the aMRR was 1.37 (95% CI: 1.23–1.52), 2.01 (95% CI: 1.64–2.45), 1.67 (95% CI: 1.09–2.56), and 1.46 (95% CI: 0.73–2.91), respectively].[94] As evident by the wide confidence intervals, cautious interpretation is needed. Although only patients who survived the first two days of hospitalization were included this study, in-hospital mortality (2.4% in patients with normonatremia, and 4.8%, 8.9%, 8.5%, and 6.7% for sodium levels of 130–134 mmol/l, 125–129 mmol/l, 120–124 mmol/l, and <120 mmol/l, respectively) was only slightly lower than that observed in our study (Supplementary Table 1, Appendix II).

We found that mortality increased with increasing hyponatremia severity in patients with a primary diagnosis of sepsis, respiratory disease, liver disease, and cancer. This result is in contrast to our overall finding, and except for the diagnosis of cancer, at odds with the only other study examining the modifying effect of underlying disease.[94] Again, cautious interpretation is needed because of few observed events.[148]

In summary, although existing data are conflicting, a growing body of evidence points to an effect of hyponatremia on mortality with a near maximum impact obtained already at a threshold serum sodium level of 130 mmol/l.

5.2.4 Impact of diuretic use on hyponatremia-associated mortality (study III)

A single-center study from the UK including 105 hospitalized internal medicine patients with serum sodium ≤125 mmol/l examined the impact of pre-specified etiologies of hyponatremia on mortality. Overall in-hospital mortality was 20%, and use of loop diuretics was associated with increased mortality relative to mortality from all causes of hyponatremia (OR 1.91, 95% CI: 0.80–4.56) at the end of follow-up (maximum length of follow-up was 2 years).[90] However, the methods used to generate these results, and the extent of confounder adjustment are unclear. Furthermore, the study may be susceptible to confounding introduced by prescribing practices.[149] This factor could explain why, in contrast to our null result, they observed reduced mortality associated with thiazide use (OR 0.32, 95% CI: 0.12–0.82).[90]

A similar protective effect of thiazides was observed in a later multicenter study from the US of 2,613 adult outpatients with an incident diagnosis of hypertension (adjusted rate ratio of 0.41, 95% CI: 0.12–1.42).[30] In that study, current thiazide use increased the risk of developing hyponatremia by 60%, and thiazide users were more likely to develop severe hyponatremia than patients not currently using thiazides.[30]

Chawla *et al*. observed that a high proportion of patients with severe hyponatremia surviving until hospital discharge (n=32) were users of thiazide diuretics or SSRIs while a high proportion of fatal cases (n=53) had "significant acute progressive underlying disease." [98]Based on these findings, they concluded

that patients who survived did so because their hyponatremia was caused by medication and "not because they were severely ill." Because of an insufficient description of the methods used and selective reporting of patient characteristics, the validity of these findings is difficult to assess. Of note, it is not known whether medical chart review was blinded to outcome, and medication use in fatal cases was not reported. Because a large proportion of patients with severe hyponatremia were thiazide users and the majority of these were long-term users without increased mortality, our findings do, however, support that medication-induced hyponatremia could at least partially explain why mortality associated with severe hyponatremia did not exceed mortality associated with less severe hyponatremia, as hypothesized by Chawla *et al.*

In summary, to our knowledge, our study is the first to assess the impact of diuretic use on mortality in patients with hyponatremia, and no previous study to our knowledge has provided data to differentiate the risk associated with new and long-term diuretic use. The substantially increased mortality observed in patients with newly initiated diuretic therapy could indicate a drug effect, potentially through increased susceptibility to hypovolemic or hypotensive conditions at drug initiation,[36,150,151] when efficacy is highest.[152,153] However, no other studies are available to substantiate our findings, this is merely speculative. Furthermore, we did not have data explicitly on the severity of the underlying condition prompting diuretic prescription, and we cannot exclude that the condition prompting a prescription was more critical in patients admitted shortly after the first prescription than in patients admitted several months after initiating diuretic therapy.

5.3 Methodological considerations

Whether examining the performance of a diagnostic test or conducting etiologic prognostic studies examining the causal relation between an exposure and an outcome, assessing the degree to which random or systematic errors have affected the accuracy in estimation is of paramount importance for proper interpretation.[140] In the following, issues related to the precision and validity of our findings are discussed.

5.3.1 Precision

The large number of participants in all of our studies greatly reduces the risk of random errors that could be induced by sampling variation. However, although all main and most subgroup analyses yielded convincingly precise estimates, as judged by narrow 95% CIs,[148] we did experience problems with sparse data in some of our stratified analyses. This was especially evident when examining the effect of different degrees of hyponatremia or different diuretic types on mortality in subgroups based on primary discharge diagnosis.

In clinical and epidemiologic research, two general approaches to evaluating study results exist: a significance testing approach and an estimation-focused approach.[9,154] In statistical hypothesis testing, a specific hypothesis, often the null hypothesis, is refuted or not refuted based on whether the P value is lower than an arbitrarily chosen value (often 0.05). This approach often leads to a dichotomous declaration of a test result as either statistically significant or not, which again is often equated to whether or not there is an association between exposure and outcome.[148] In contrast, the estimation approach focuses on both the strength and precision of a result.[9,154] Both of these quantities can be extracted from the P value function (or confidence interval function), which plots the P values describing agreement between data and all possible values of the risk measure. A P value function contains all possible confidence levels between 0% and 100%.[148] We reported 95% CIs for the purpose of evaluating the strength and precision of our estimates, not to provide a surrogate significance test based on whether the value of a null effect was included in the interval.[148,154,155] That said, the reported confidence limits are dependent on the method used for calculation and the specific confidence level chosen.[9]

5.3.2 Selection bias

Generally, our use of prospectively collected data from population-based medical registries maintained under the Danish universal tax-supported healthcare system greatly reduces the risk of selection bias.[116,120,156] In addition, in contrast to most previous studies examining the quality of ICD discharge codes for hyponatremia or the association between hyponatremia and mortality, we did not condition entry on whether serum sodium was measured[85-87,89,92-94,96,98] or on a minimum length of hospital stay.[92,94] It is, however, important to recognize that even the process of being admitted to the hospital involves selection at some level, as does the decision of a physician to order a serum sodium measurement. In study III, our cohort comprised patients with hyponatremia at admission, thereby requiring study participants to survive until sodium measurement. With this requirement, we may have excluded the sickest patients from entering our study, which could have led us to underestimate absolute mortality. However, because 30-day mortality was virtually unchanged after multiple imputation of missing serum sodium values, we have no reason to suspect that this potential source of bias was important in our study. Furthermore, if physicians were more prone to request serum sodium measurements in current diuretic users than in non-users, then hyponatremia would more likely be detected among diuretic users, and non-users would be less likely to be included in the study. However, because serum sodium is generally included in standard laboratory test panels and measured within 24 hours of hospitalization in more than 90% of patients admitted to internal medicine departments,[103] we believe this source of bias to be of little importance in our study. We also do not think that missing information on admission hour led to systematic exclusion of patients in study III.

5.3.3 Information bias

In studies I and II, we may have misclassified patients with undetected hyponatremia as normonatremic. Because serum sodium is so frequently measured and patients without sodium measurements resembled patients with normonatremia in terms of age and burden of preexisting morbidity[88] and probably also in terms of mortality,[157] misclassification was likely non-differential in study II and thus would dilute our estimates of relative risk. This possibility was confirmed by sensitivity analysis restricted to patients with available sodium measurements. For study I, on the other hand, receiving a diagnosis of hyponatremia would likely have depended on whether or not serum sodium was measured. However, excluding patients without sodium measurements had virtually no effect on our quality estimates (Appendix I). Although data quality in the LABKA database has not been formally examined, we find it unlikely that errors in the serum sodium concentration recorded could have biased our results. We found few outliers, and the distribution resembled that observed by others.[64]

Although we had complete information on prescriptions redeemed for diuretics for all participants in study III, we could not ascertain the extent to which this medication was ingested.[122] However, the prospective recording of prescription data independent of vital status registration entails that misclassification of diuretic use due to non-adherence would be non-differential. We used a 90-day window to characterize diuretic use as current, former, or non-use based on the most frequently dispensed package size.[125] Consequently, patients prescribed larger packages would be incorrectly classified as former users. In the case of a non-dichotomous exposure variable, non-differential misclassification of high-exposure patients (current users) as low-exposure patients (former users) will lead to upward bias of the effect estimate for the low-exposure patients.[140,158] This effect could be an explanation for the non-null result observed for former users in our study.

We retrieved information on mortality from the CRS. The registry is updated daily and keeps track of all Danish residents, so that loss to follow-up was negligible and misclassification of mortality highly improbable.

In summary, it does not seem likely that information bias due to measurement errors or misclassification of exposure or outcome variables could explain the findings of low sensitivity of the ICD-10 codes for hyponatremia, the increased mortality associated with hyponatremia of any severity, or the increased mortality associated with current and particularly newly initiated diuretic use. However, misclassification of some current users as former users could have attenuated the difference in risk between former and current users.

5.3.4 Confounding

Confounding occurs when the effect of a factor other than the exposure of interest is mixed with or distorts the effect of the exposure on the outcome. Implicitly, confounding is an important issue in prognostic studies, which are tied to a specific hypothesis about the association between a specific exposure and outcome. This situation is opposed to prediction studies, in which variable selection is not restricted to those fulfilling the criteria for a confounder; i.e., it has to have an effect on the outcome, must be unevenly distributed across exposure groups, and cannot be an intermediate step on the causal pathway.[140] However, in our studies, confounders may not be so unequivocally defined. Many of the variables we adjusted for could be viewed also as intermediate steps on the causal pathway, or hyponatremia could be viewed as an intermediate step of another exposure. Nonetheless, we performed stratification (studies I–III), multivariate adjustment (studies II and III), and propensity score matching (study III) by all variables that could potentially give rise to a mixing of effects to provide the cleanest possible association between hyponatremia or diuretic use and mortality. We did so knowing that adjusting for factors on the causal pathway could attenuate the effect.[159] Concerns regarding inefficient or inadequate confounder control are discussed below.

In study II, we lacked information on severity of disease. Although some degree of disease severity can be inferred by the primary diagnosis, which we stratified upon, and although the CCI score, which we either stratified upon or adjusted for, adequately accounts for the impact of previous morbidities,[160-163] we may not have completely prevented confounding by severity of the underlying disease causing hyponatremia. Furthermore, Charlson conditions primarily treated in primary practice may be underreported in the DNPR, and the occurrence of discharge diagnosis coding errors[164-166] may have caused residual confounding. Also, we did not include information on laboratory measurements of inflammatory mediators in our analysis.

In study III, we used propensity score matching to ensure adequate balancing of measured variables between users and non-users of diuretics and thus to compare patients with the same probability of being a user and non-user to reduce confounding by indication. Propensity score matching can account for unmeasured confounders if these are related to the covariables included in the propensity score calculation. For example, because propensity score methods model the probability of treatment, not mortality, and allow for identification of patients who would not be treated, propensity score matching should be able to account for confounding by frailty.[167,168] This type of confounding occurs when primarily preventive medications are less likely to be prescribed to patients perceived to be near the end of life than medications mostly prescribed for tertiary prophylaxis.[169,170] If in our study, loop diuretics were generally prescribed to patients with, for example, pulmonary edema, and physicians refrained from treating hypertension with thiazides in the same patient category, these factors could have led to an

overestimation of the protective effect of thiazides and the harmful effect of loop diuretics.[30,169] Because of the underreporting in the DNPR of morbidities primarily treated in general practice and the lack of information on severity of congestive heart failure, we may not have been able to completely abolish residual confounding by indication or frailty. However, we included information on concurrent use of other cardiovascular medications, which could give some indication of severity of heart failure.

5.3.5 Statistical analysis

Generally, the methods used in this dissertation are well-established methods within the field of epidemiology. However, we also applied less conventional methods. For example, we used restricted cubic spline models to assess the dose-response relationship between serum sodium concentration and mortality in study II, and propensity score matching and multiple imputation to account for confounding by indication and address problems with missing data, thereby increasing the validity of our results in study III.[143,171] All of these methods are based on statistical modeling and, although they are appealing and useful, there are limitations and pitfalls associated with their use. We will briefly touch on some of these below.

Categorization of a continuous variable entails inefficient use of information stored within each category, and large jumps in the estimated risk between two successive categories are inherently irrational. As opposed to traditional categorical analysis, the near-nonparametric cubic spline regression allows for non-zero slopes (i.e., does not assume constant risks) within each interval and can take on practically any form, allowing for variation in risk both within and between categories and non-monotonic curves.[135,172] Furthermore, the cubic spline model ensures continuity from each fitted model to the next, eliminating jumps from one interval to the other.[135] As in traditional categorical analysis, intervals (usually defined by 3–7 'knots') still need to be specified. However, simulations have shown that the placing and number of knots do not alter the fit substantially.[173] We chose five knots based on Harrell's recommended percentiles.[173] Interpretation of the smooth cubic regression curve is not as straightforward as traditional parametric regressions, and cubic spline regressions are generally more valuable for determining the shape of the risk function and not the risk as such.[135] We used a restricted cubic spline model (requiring the function to be linear before and after the first and last knots, respectively) to overcome problems of instability at the extremes of the fit, where data are sparse.[173] Although this approach theoretically affects the shape for the entire curve, it is often preferred over instability.

The calculation and benefits of propensity score matching have been described earlier.[137] As in other multivariate statistical models, the validity of propensity score calculation is strongly dependent on accurate and correct measurement of all confounders.[168,174] Erroneous inclusion of variables that are not

true confounders (i.e., variables affecting exposure but not outcome) increases variance without reducing bias.[139] Furthermore, if treatment heterogeneity is pronounced, 1:1 nearest neighbor matching within a specified caliper range could result in the exclusion of numerous treated and untreated patients, potentially reducing the precision of the estimate, and could potentially affect any inferences.[174] Lastly, although propensity score matching has ensured adequate balancing of covariates between treated and untreated groups overall, this balancing may not apply within all covariate strata. Implicitly, repeating the propensity score calculations and matching within each stratum may be necessary in stratified analysis.[174]

Problems with missing data are frequent in epidemiologic research, and improper handling can greatly undermine the validity of study results. Based on the distribution of the observed data, multiple imputation by chained equations, known as MICE, involves regressions of each variable containing missing data, conditional on all other variables including the outcome variable, and creates a set of plausible values for the missing data.[144] These models are based on the assumption that data are 'missing at random', meaning that the probability of missing data depends on the observed data but not on the unobserved data. In our study, it is probable that younger persons would have been less likely to have their serum sodium (or creatinine) measured than older persons, and data therefore would be missing at random (given that age is included in the model). However, based on the observed data, it cannot be excluded that older persons with hyponatremia were more likely to have undergone serum sodium measurement than normonatremic patients of the same age, i.e., data were 'missing not at random'.[175] The risk of violating the 'missing at random' assumption is greatly reduced by increasing the number of variables included in the imputation model.[144] Furthermore, one should be aware that imputation of continuous data assumes normal distribution. We therefore included logarithmic-transformed serum creatinine concentrations (sodium distribution was near normal) in the imputation model and applied inverse transformation to reform imputed creatinine data on the original scale before performing the final combined analysis.[144]

5.4 Clinical implications

This dissertation adds to the growing body of evidence stemming from non-experimental observational studies about the prognostic impact of hyponatremia on mortality and contributes knowledge about the occurrence and clinical perception of hyponatremia in Danish hospitals, as well as about risk factors for hyponatremia-associated mortality.

A recent European clinical guideline on the diagnosis and treatment of hyponatremia recommends against active treatment of chronic hyponatremia without severe or moderate symptoms.[176] The rationale for the recommendation was based on 1) sparse and contradictory evidence about the dose-response relationship between serum sodium concentration and mortality, 2) inability to separate the role

of underlying disease from that of hyponatremia, and 3) lack of evidence that treating hyponatremia decreases mortality. These recommendations are of particular relevance in view of the recent availability of a pharmaceutical compound, a specific vasopressin antagonist (Tolvaptan), licensed to treat hyponatremia associated with the syndrome of inappropriate antidiuretic hormone (SIADH) (EU)[177] and heart failure (US).[178] Our studies can neither support nor refute this recommendation. We recognize that the lack of evidence from comparative studies on the effect of correcting hyponatremia precludes recommendation about active treatment. However, we do provide data supporting that even a small decrease below the reference standard is associated with increased mortality of death in patients acutely admitted to internal medicine departments—a risk independent of underlying diseases. In addition to the apparent problem that the recommendation relies on the ability to distinguish between acute and chronic hyponatremia, we argue that the absence of a monotonic dose-response relationship does not preclude a causal relation, and that establishing a causal relation is not reserved for randomized trials.[155,179] The guideline recommends that loop diuretics are to be used in the management of moderate to profound hyponatremia. Our data suggest an association between use of loop diuretics and increased mortality in hyponatremia patients, but more evidence is needed before arguing against this recommendation.

The low sensitivity of ICD-10 discharge diagnoses found in our study probably reflects that hyponatremia is not attributed major independent clinical importance compared to other coexisting conditions. It is our hope that our findings will raise awareness about hyponatremia. Serum sodium is easily accessible and could prove valuable in identifying high-risk patients upon hospital entry.

5.5 Perspective

During the course of our work, several questions emerged and remain unanswered.

Our studies revealed that serum sodium is measured upon hospital arrival in the majority of patients acutely admitted to departments of internal medicine.[103] However, measurement was less consistent in patients admitted to other departments,[88] and we lack knowledge about what triggers sodium measurement in these patients—or in outpatients, for that matter. Furthermore, we know very little about what prompts repeated sodium measurements and the consequences of these. These factors could be key issues in understanding hyponatremia and its clinical implications.

With regard to the quality of ICD-10 codes for hyponatremia, it could be interesting to examine how fluctuations in individual serum sodium concentrations would affect quality measures and/or the observed associations with morbidity and mortality, and whether sensitivity would increase if active steps were taken to correct hyponatremia. The latter would entail a rather comprehensive medical chart review because these data are not obtainable from the registries.

Future studies on the mortality associated with hyponatremia should target distinguishing between acute and chronic hyponatremia. As mentioned, the treatment recommendations for hyponatremia depend on whether hyponatremia is considered acute or chronic. Apart from the obvious problem of distinguishing between the two in clinical practice, it is of major concern that this recommendation is based primarily on the proposed cellular mechanisms underlying hyponatremia-induced brain edema and pontine myelinolysis. Although not always recognized,[180] the different impact of acute versus chronic hyponatremia has never been investigated in a clinical setting. Attempts have been made by examining the impact of hyponatremia in the outpatient setting or by investigating hospitalization-induced hyponatremia; however, whether these approaches reflect the impact of chronic versus acute hyponatremia is questionable. It also remains to be investigated whether medical treatment of hyponatremia with vasopressin antagonists has an effect on hard endpoints such as mortality.[181]

With the Danish data sources, we can assess and investigate the impact of outpatient serum sodium levels and fluctuations on mortality. Also, examining the effect on this association of increased or decreased serum levels of inflammatory mediators such as C-reactive protein and leukocyte count or other laboratory measures could reveal important information about potential causal pathways.

Finally, our findings of increased mortality in users of loop diuretics, diuretic polytherapy and in new users of thiazides warrant investigation in patient populations without hyponatremia and need to be confirmed by others.

6. Summary

Several medical conditions or medications can alter the fine balance between water and solute intake and output, leading to development of hyponatremia (serum sodium <135 mmol/l). Therefore hyponatremia is frequently encountered in clinical practice. Whether hyponatremia is a mediator or merely a marker of increased mortality is controversial.

To advance our knowledge, we aimed to examine the prevalence and prognostic impact of hyponatremia on short- and long-term mortality in patients acutely admitted to departments of internal medicine (study II), and whether preadmission use of diuretics, a common risk factor for developing hyponatremia, affected this risk (study III). The studies were based on data from national and regional Danish population-based databases. As prerequisite we examined the quality of the registration of ICD-10 codes for hyponatremia in the Danish National Patient Registry (study I).

In study I, we included all 2,186,642 admissions to somatic hospitals in Northern and Central Denmark Regions from 2006 through 2011. Among the 306,418 patients with at least one serum sodium value <135 mmol/l during hospitalization, 5,410 patients were coded with an ICD-10 code for hyponatremia at discharge, corresponding to a sensitivity of 1.8% (95% CI: 1.7%–1.8%). For severe hyponatremia (<115 mmol/l) sensitivity reached 34.3% (95% CI: 32.6%–35.9%). Overall PPV was 92.5% (95% CI: 91.8%–93.1%). Specificity was above 99.8% and NPV above ≥86.2% for all cutoffs.

Study II, included the 279,508 patients with a first-time acute admission to departments of internal medicine. Overall, 15% were admitted with hyponatremia and the prevalence increased with increasing age and CCI level. Thirty-day mortality was 7.3%, 10.0%, 10.4%, and 9.6% in patients with serum sodium of 130–134.9 mmol/l, 125–129.9 mmol/l, 120–124.9 mmol/l, and <120 mmol/l, compared to 3.6% in normonatremic patients, which resulted in adjusted RRs of 1.4 (95% CI: 1.3–1.4), 1.7 (95% CI: 1.6–1.8), 1.7 (95% CI: 1.4–1.9), and 1.3 (95% CI: 1.1–1.5), respectively. After one year, mortality was increased by 30% to 40%. Hyponatremia was associated with increased mortality regardless of age and underlying condition. A steep increase in probability of death was observed for sodium values between 139mmol/l and 132mmol/l, whereas the risk levelled off for lower concentrations.

In study III, we identified first-time acute admissions to departments of internal medicine from 2006 through 2012, and included 46,157 patients with hyponatremia at time of admission. Compared to 6.2% among non-users, 30-day mortality was 11.4% among current diuretic users. After multivariate adjustment the RR of death was 1.4 (95% CI: 1.2-1.5). New users had substantially higher RR than long-term users [adjusted RR of 1.7 (95% CI: 1.5-2.0) and 1.3 (95% CI: 1.2-1.4), respectively]. As compared to non-users, users of loop diuretics, potassium-sparing diuretics and diuretic polytherapy each had a 60% increased mortality, whereas mortality was not increased in current user of thiazides overall. However,

new users of thiazide diuretics had an adjusted RR of 1.5 (95% CI: 1.2–2.0) compared to long-term thiazide users.

In conclusion, although highly prevalent, hyponatremia is greatly underreported. Yet, we found that hyponatremia of any degree and regardless of underlying disease, was associated with markedly increased mortality. Current use of loop diuretics, potassium-sparing diuretics and diuretic polytherapy, as well as newly initiated thiazide therapy, were risk factors for increased mortality in hyponatremic patients.

7. Dansk resume

Mange sygdomme og medikamenter kan forstyrre regulering af kroppens væske- og elektrolytindhold. Natrium, der primært tilføres via salt i føden, er en af kroppens vigtigste elektrolytter. Hyponatriæmi, som forekommer når koncentrationen af natrium falder under <135mmol/l er blevet forbundet med øget dødelighed blandt patienter med f.eks. hjertesvigt, lever- og nyresygdomme. Om denne øgede dødelighed skyldes hyponatriæmi i sig selv eller hyponatriæmi blot er en markør for sværhedsgraden af den underliggende sygdom er uvist.

Denne afhandling bygger på data fra Landspatientregistret, laboratoriedatabasen for Region Nord og Region Midt, en landdækkende receptdatabase, samt CPR-registeret, og indeholder et tværsnitsstudie (studie I) og to kohortestudier (studie II og III).

Formålet med afhandling var, at undersøge forekomsten af hyponatriæmi blandt patienter indlagt akut på internt medicinske afdelinger (studie II), om patienter med hyponatriæmi havde øget risiko for at dø sammenlignet med patienter uden hyponatriæmi (studie II), og om brug af vanddrivende medicin forud for indlæggelsen påvirkede denne risiko (studie III). Derudover undersøgte vi om data fra Landspatient-registeret kunne anvendes til identifikation af patienter med hyponatriæmi (studie I).

Studie I, inkluderede alle 2.186.642 'ikke psykiatriske' indlæggelser på offentlige sygehuse i Region Nord og Midt i 2006 - 2011. Vi fandt at 1,8 % af patienter som ud fra laboratorie målinger havde hyponatriæmi, fik en diagnose svarende hertil ved udskrivelsen. Selv blandt patienter med meget svær hyponatriæmi (<115 mmol/l) fik kun en 1/3 en hyponatriæmi diagnose.

Studie II, inkluderede 279.508 patienter indlagt akut på internt medicinske afdelinger. I alt havde 15 % hyponatriæmi ved indlæggelse. Tredive-dages dødeligheden var 3,6% blandet patienter med normal natrium koncentration, og 7,3 %, 10,0 %, 10,4 % og 9,6 % hos patienter med henholdsvis mild, moderat, svær og meget svær hyponatriæmi. Selv efter justering for køn, alder og sygdomsbyrde havde patienter med mild, moderat, svær og meget svær hyponatriæmi en overdødelighed på henholdsvis 40 %, 70 %, 70 % og 30 %. Sandsynligheden for at dø steg betydeligt for natriumværdier mellem 139 mmol/l og 132 mmol/l, mens risikoen stort set stagnerede ved koncentrationer derunder.

Studie III, inkluderede 46.157 akutte internt medicinske patienter med hyponatriæmi. I alt havde 32 % indløst en recept på vanddrivende medicin indenfor 90 dage før indlæggelsen. Tredive-dages dødeligheden blandt disse var 11,4 % sammenlignet med 6,2 % blandt ikke-brugere. Efter justering for forskelle i køn, alder, tidligere sygdomme og brug af anden medicin, havde brugere fortsat 40 % højere dødelighed. Nye brugere (< 90 dage) og langtidsbrugere (>90 dage) af vanddrivende medicin havde en forøget risiko på henholdsvis 70 % og 30 %. Nye brugere havde en øget risiko for død uanset hvilken type af vanddrivende medicin de brugte, hvorimod langtidsbrugere af thiazider ikke havde øget risiko for død.

Vore studier viser, at hyponatremia er en meget hyppigt forekommende tilstand, som dog sjældent foranlediger kodning ved udskrivelse. Ikke desto mindre fandt vi, at hyponatriæmi af enhver grad og uanset underliggende sygdom, var forbundet med markant øget dødelighed. Vi fandt desuden, at hyponatræmiske brugere af vanddrivende medicin, og i særdeleshed dem med nyligt påbegyndt behandling, havde en øget risiko for at dø.

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9. Appendices

The appendices contain the full version of paper I, II and III, including supplementary material.

Paper I

- **Appendix I**

Paper II

- **Appendix II**

Paper III

- **Appendix III**

Paper I

BMJ Open

Validity of the International Classification of Diseases, 10th revision discharge diagnosis codes for hyponatraemia in the Danish National Registry of Patients

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ABSTRACT

Objective: To examine the validity of the *International Classification of Diseases*, 10th revision (ICD-10) codes for hyponatraemia in the nationwide population-based Danish National Registry of Patients (DNRP) among inpatients of all ages.

Design: Population-based validation study.

Setting: All somatic hospitals in the North and Central Denmark Regions from 2006 through 2011.

Participants:: Patients of all ages admitted to hospital (n=819 701 individual patients) during the study period. The patient could be included in the study more than once, and our study did not restrict to patients with serum sodium measurements (total of n=2 186 642 hospitalisations).

Main outcome measure: We validated ICD-10 discharge diagnoses of hyponatraemia recorded in the DNRP, using serum sodium measurements obtained from the laboratory information systems (LABKA) research database as the gold standard. One sodium value <135 mmol/L measured at any time during hospitalisation confirmed the diagnosis. We estimated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for ICD-10 codes for hyponatraemia overall and for cut-off points for increasing hyponatraemia severity.

Result: An ICD-10 code for hyponatraemia was recorded in the DNRP in 5850 of the 2 186 642 hospitalisations identified. According to laboratory measurements, however, hyponatraemia was present in 306 418 (14%) hospitalisations. Sensitivity of hyponatraemia diagnoses was 1.8% (95% CI 1.7% to 1.8%). For sodium values <115 mmol/L, sensitivity was 34.3% (95% CI 32.6% to 35.9%). The overall PPV was 92.5% (95% CI 91.8% to 93.1%) and decreased with increasing hyponatraemia severity. Specificity and NPV were high for all cut-off points (≥99.8% and ≥86.2%, respectively). Patients with hyponatraemia without a corresponding ICD-10 discharge diagnosis were younger and had higher Charlson Comorbidity Index scores than patients with hyponatraemia with a hyponatraemia code in the DNRP.

Conclusions: ICD-10 codes for hyponatraemia in the DNRP have high specificity but very low sensitivity. Laboratory test results, not discharge diagnoses, should be used to ascertain hyponatraemia.

Strengths and limitation of this study

- This is the first study to validate the International Classification of Diseases, 10th revision code for hyponatraemia in hospitalised patients of all ages.
- We used a population-based design, utilizing unambiguous individual-level linkage between registries containing complete data on all hospitalisations and laboratory measurements, thereby ensuring a large sample size and virtually eliminating the risk of selection bias.
- We did not consider the duration of hyponatraemia. Sensitivity may have been higher if the presence of hyponatraemia required that it was detected in more than one laboratory measurement during hospitalisation.

INTRODUCTION

Hyponatraemia, defined as a serum sodium value <135 mmol/L, is the most common electrolyte abnormality encountered in clinical practice.[1] It can be caused by a large variety of conditions, such as heart failure, kidney failure, cirrhosis, syndrome of an inappropriate antidiuretic hormone, vomiting and diarrhoea, and can also be a side effect of several medications.[2] Results of recent studies have indicated that even a mild-to-moderate level of hyponatraemia may be an important predictor of poor prognosis in patients with cardiovascular disease, kidney and liver disease and cancer.[3–8] However, key aspects of the aetiology and prognosis of hyponatraemia remain unknown.

The Danish population-based medical registries may offer a unique opportunity for studies of the epidemiology of hyponatraemia, if data are valid. However, as symptoms of mild and moderate hyponatraemia may be vague, and concealed by or construed as symptoms of an underlying disease, it is likely that the condition will not be reported.[9 10] Thus, use of only inpatient discharge diagnoses of hyponatraemia in epidemiological studies may cause bias that can affect the validity of study results.[11]

Until now, only one study has investigated the validity of the *International Classification of Diseases*, 10th revision (ICD-10) codes for hyponatraemia. This Canadian study was restricted to patients 66 years of age or older with serum sodium values at the time of emergency department contact or at hospital admission.[12] The sensitivity of hyponatraemia coding was found to be as low as 7%. For inpatients younger than 66 years, knowledge of the validity of hyponatraemia diagnoses is limited to a study performed in a single hospital in the Netherlands using ICD-9 codes for hyponatraemia. In this study, sensitivity was found to be just below 2%, using hospital laboratory data as the reference standard.[13] Similar results were found in a study examining the validity of outpatient professional ICD-9 claims for hyponatraemia in the USA.[14]

We therefore conducted the first population-based study examining the validity of ICD-10 inpatient discharge diagnoses of hyponatraemia in the Danish National Registry of Patients (DNRP), including patients of all ages.

METHODS

Setting and data collection

We used the DNRP to identify all admissions to hospitals in the North and Central Denmark Regions (2.1 million inhabitants in the study period) from 1 January 2006 to 31 December 2011. The DNRP contains information, including date of admission and discharge, department code and discharge diagnoses, on all admissions to Danish non-psychiatric hospitals since 1977.[15 16]

By use of the unique 10-digit civil registration number, assigned to all Danish residents since 1968,[17] we linked each patient's DNRP data to the clinical laboratory information system (LABKA) research database. For patients living in the North and Central Denmark Regions, data on virtually all specimens analysed in clinical laboratories by hospitals and medical practitioners are entered into a computer-based clinical laboratory information system, which functions as a routine diagnostic tool for medical personnel.[18] Data are transferred electronically to the LABKA research database, managed by Aarhus University. Analyses are coded according to the NPU (Nomenclature, Properties and Units) system. The LABKA research database contains the civil registration number, time and date of blood sampling, and identification code of the requesting physician or hospital department.[18] We used the LABKA research database to retrieve information on all serum sodium measurements recorded during each of the identified hospitalisations.

Hyponatraemia diagnosis (ICD-10 code algorithm)

At hospital discharge, the attending physician assigns one primary diagnosis, reflecting the main reason for hospitalisation and treatment and up to 19 secondary diagnoses regarding additional clinically relevant conditions, including underlying diseases, complications and symptoms.[19] Diagnoses recorded in the DNRP have been coded according to the ICD-10 since 1994.[16]

We developed an algorithm based on ICD-10 codes to identify primary and secondary discharge diagnoses of hyponatraemia recorded in the DNRP for each hospitalisation. The following ICD-10 codes were included in the algorithm: E87.1 (hypo-osmolality and hyponatraemia), E87.1A (hyponatraemia) and P74.2B (hyponatraemia in newborns (Danish version of ICD-10)).

Gold standard (laboratory serum sodium measurements)

We used serum sodium measurements recorded in the LABKA research database as the gold standard to confirm or disconfirm a diagnosis of hyponatraemia identified by the ICD-10 algorithm. Hyponatraemia was defined as serum sodium values <135 mmol/L for patients older than 30 days and <133 mmol/L for infants 30 days of age or younger.[20] Patients were considered to have hyponatraemia if at least one hyponatraemic serum sodium value was recorded during their hospitalisation. If no serum sodium measurement was available, the patient was assumed to have a non-hyponatraemic serum sodium value (135–145 mmol/L). The following cut-off points for increasing severity of hyponatraemia were chosen: 135, 130, 125, 120 and 115 mmol/L.[13] The corresponding levels for infants less than 31 days of age were 133, 128, 123, 118 and 113 mmol/L.

Other variables

For each patient, we assessed comorbidity by information retrieved from the DNRP on the conditions included in the Charlson Comorbidity Index (CCI). The CCI includes 19 medical conditions, each assigned a weighted score between 1 and 6. The sum of these individual scores is used as a measure of a patient's comorbidity burden.[21 22] We calculated CCI scores for each patient and defined three comorbidity levels: low (CCI score 0), medium (CCI score 1–2) and high (CCI score of 3 or above). We included morbidities recorded within 10 years prior to the current hospitalisation, as conditions requiring hospital treatment within this timeframe would most likely influence the attending physician's diagnostic approach and evaluation during the current hospitalisation.

Furthermore, we obtained information on the department of admission and year of admission from the DNRP. Departments were categorised in the following five groups: internal medicine, surgery, gynaecology/obstetrics, paediatrics and other.

Statistical analysis

Patients with a hyponatraemic serum sodium value recorded in the LABKA research database were divided into two categories: Those with an ICD-10 code for hyponatraemia in the DNRP and those without. We described both groups of patients in terms of gender, age (median and associated IQR), department of admission, CCI score and specific comorbidities.

We estimated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV; figure 1) for ICD-10 codes for hyponatraemia in the DNRP with corresponding 95% CI, using the exact method for binomial proportions. We defined sensitivity as the probability of an ICD-10 code for hyponatraemia being registered in the DNRP, when the laboratory test result identified the presence of hyponatraemia. Specificity was defined as the probability of an ICD-10 code for hyponatraemia not being registered in the DNRP, when hyponatraemia was not identified in laboratory test results. We estimated the PPV as the proportion of patients for whom an ICD-10 code for hyponatraemia recorded in the DNRP could be confirmed by a serum sodium measurement, and NPV as the proportion of patients with no ICD-10 code for hyponatraemia in the DNRP, for whom non-hyponatraemic or no serum sodium values were recorded in the LABKA research database. The analyses were repeated for all hyponatraemia cut-off points and after stratification by age group categories, department of admission and admission year.

Finally, we conducted four sensitivity analyses. First, we performed a complete case analysis, a method for dealing with missing data considering only participants with recorded values for all covariates,[23] meaning that only patients with at least one serum sodium measurement during their hospitalisation were included in the analysis. We did so, in order to evaluate the assumption that patients without a serum sodium measurement were normonatraemic. In the second sensitivity analysis, we included only patients with more than one serum sodium measurement during their hospitalisation. In the third sensitivity analysis, we included only the ICD-10 codes E87.1A (hyponatraemia) and P74.2B (hyponatraemia in newborns). Because epidemiological studies often focus on incident cases, we performed a post hoc sensitivity analysis in which we restricted to the first hospitalisation for each patient in the study period.

Data analyses were performed using the statistical software package STATA (V.12; Stata Corp, College Station, Texas, USA).

All data were obtained from Danish public registries. According to Danish law their use does require informed consent or ethics committee approval.

RESULTS

Characteristics

We identified 2 186 642 hospitalisations (819 701 individual patients) within the study period. For 1 308 740 (60%) hospitalisations, at least one serum sodium measurement was recorded in the LABKA research database, and for 1 037 647 (47%) hospitalisations subsequent measurements were recorded. According to the recorded serum sodium value, hyponatraemia was present in 306 418 hospitalisations (14%). In the DNRP, we identified 5850 hospitalisations with an ICD-10 code of hyponatraemia (hypo-osmolality and hyponatraemia=3722, hyponatraemia=2124, hyponatraemia in newborns=4) among all 2 186 642 hospitalisations. Of these, 440 did not have a hyponatraemic serum sodium value recorded in the LABKA research database.

Table 1 shows the distribution of hospitalisations by the presence/absence of an ICD-10 diagnosis of hyponatraemia recorded in the DNRP, by gender, age and comorbidity variables, for patients with hyponatraemic

		ICD-10 code of hyponatraemia recorded in the DNRP*	
		Yes	No
Hyponatraemic serum sodium value recorded in LABKA research database (gold standard)	Yes	A	C
	No	B	D

Validity measures:
Sensitivity= A/(A+C)
Specificity= D/(B+D)
Positive predictive value= A/(A+B)
Negative predictive value=D/(C+D)

*DNRP = Danish National Registry of Patients

Figure 1 Schematic 2×2 table and validity measure estimation formulas.

serum sodium values. Patients who had an ICD-10 code of hyponatraemia recorded in the DNRP and a corresponding hyponatraemic serum sodium measurement were on average older, more often female, more likely admitted to an internal medicine department and characterised by lower comorbidity levels than patients with no hyponatraemia diagnosis in the DNRP, but having hyponatraemic serum sodium values recorded in the LABKA research database. Cerebrovascular disease, dementia and ulcer disease were the only comorbidities that were more frequently found in patients with an ICD-10 code for hyponatraemia and corresponding hyponatraemic serum sodium value, compared to patients with hyponatraemia without a hyponatraemia diagnosis in the DNRP (table 1).

Sensitivity, specificity, PPV and NPV

For 440 (7.5%) of the 5850 hospitalisations with an ICD-10 code for hyponatraemia recorded in the DNRP, no hyponatraemic serum sodium measurement was recorded in the LABKA research database during the hospitalisation (for 178, no measurement was recorded at all). This corresponds to a PPV of an ICD-10 code for hyponatraemia of 92.5% (95% CI 91.8% to 93.1%) for serum sodium values <135 mmol/L (<133 mmol/L for infants 30 days of age or younger). As expected, PPV decreased with lower serum sodium cut-off points. A total of 5410 hospitalisations had both an ICD-10 code recorded in the DNRP and a corresponding hyponatraemic laboratory measurement, resulting in a sensitivity of the ICD-10 codes of 1.8% (95% CI 1.7% to 1.8%). Sensitivity increased with lower cut-off

Table 1 Characteristics of hospitalisations identified in the DNRP from 2006 to 2011

	Hospitalisations with at least on serum sodium value <135 mmol/L recorded in the LABKA research database		
	ICD-10 code of hyponatraemia in the DNRP (n=5410), n (%)	No ICD-10 code of hyponatraemia in the DNRP* (n=301 008), n (%)	All hospitalisations (n=2 186 642), n (%)
Sex			
Female	3643 (67.3)	148 120 (49.3)	1 168 803 (53.5)
Male	1767 (32.7)	152 588 (50.7)	1 017 839 (46.5)
Age, years			
Median (IQR)	77.3 (65.7–84.9)	67.4 (54.2–78.2)	54.7 (29.3–71.1)
Department of admission			
Internal medicine	5173 (95.6)	184 848 (61.6)	943 121 (43.1)
Surgical	184 (3.4)	88 378 (29.4)	630 525 (28.8)
Gynaecological/obstetric	10 (0.2)	7104 (2.4)	347 365 (15.9)
Paediatric	29 (0.5)	15 830 (5.3)	165 289 (7.6)
Other	14 (0.3)	4848 (1.6)	100 342 (4.6)
CCI level (score)			
Low (0)	2075 (38.4)	100 398 (33.4)	1 232 762 (56.4)
Medium (1–2)	2182 (40.3)	106 874 (35.5)	588 783 (26.9)
High (≥3)	1153 (21.3)	93 736 (31.1)	365 097 (16.7)
Specific comorbidities			
Myocardial infarction	312 (5.8)	23 269 (7.7)	108 373 (5.0)
Congestive heart failure	460 (8.5)	31 236 (10.4)	121 429 (5.6)
Peripheral vascular disease	464 (8.6)	29 356 (9.8)	115 620 (5.3)
Cerebrovascular disease	1017 (18.8)	39 466 (13.1)	182 304 (8.3)
Dementia	107 (3.1)	4247 (1.4)	20 711 (1.0)
Chronic pulmonary disease	870 (16.1)	48 726 (16.2)	231 121 (10.6)
Connective tissue disease	291 (5.4)	13 990 (4.7)	73 299 (3.4)
Ulcer disease	450 (8.3)	20 645 (6.9)	79 050 (3.6)
Mild liver disease	189 (3.5)	13 413 (4.5)	37 698 (1.7)
Moderate-to-severe liver disease	66 (1.2)	6279 (2.1)	14 999 (0.7)
Diabetes I and II	521 (9.6)	39 995 (13.3)	150 205 (6.9)
Diabetes with complications	269 (5.0)	25 083 (8.3)	85 035 (3.9)
Hemiplegia	35 (0.7)	2462 (0.8)	16 060 (0.7)
Moderate-to-severe renal disease	143 (2.6)	20 123 (6.7)	75 441 (3.5)
Malignant tumour	781 (14.4)	64 882 (21.6)	312 845 (14.3)
Leukaemia	22 (0.4)	4636 (1.5)	17 190 (0.8)
Lymphoma	51 (0.9)	7096 (2.4)	25 348 (1.2)
Metastatic cancer	183 (3.4)	23 948 (8.0)	105 512 (4.8)
AIDS	3 (0.1)	475 (0.2)	2014 (0.1)

CCI, Charlson Comorbidity Index; DNRP, Danish National Registry of Patients; ICD-10, International Classification of Diseases, 10th revision.

points for serum sodium, reaching 34.3% (95% CI 32.6% to 35.9%) for serum sodium <115 mmol/L. Specificity and NPV for serum sodium <135 mmol/L were 100% (97.5% CI 100%) and 86.2% (95% CI 86.2% to 86.2%), respectively. Specificity and NPV remained high for all serum sodium cut-off points (table 2).

Sensitivity was higher among admissions to internal medicine departments than among admissions to surgical, gynaecological/obstetric, paediatric and 'other' departments (table 3). The validity measures were virtually unchanged across the strata of the admission year.

Sensitivity analyses

Compared to the primary analyses, we observed no changes in either sensitivity or specificity estimates when including only patients with at least one serum sodium measurement during their hospitalisation in the analysis. PPV increased slightly for all serum sodium cut-off points, while NPV decreased for the three highest cut-off points. Including only patients with more than one serum sodium measurement also yielded almost identical results (table 4).

After restriction to the most specific ICD-10 codes for hyponatraemia, PPV increased slightly and sensitivity decreased (94.6% (95% CI 93.6% to 95.6%) and 0.7% (95% CI 0.6% to 0.7%), respectively). Estimates of specificity and NPV were virtually unchanged (table 4).

We observed a slight increase in sensitivity for serum sodium cut-off points <130 mmol/L but not for the overall estimate when restricting to the first hospitalisation in the study period. PPV and NPV generally increased, although only very slightly for the overall estimate (table 4).

DISCUSSION

This is the first study to report on the validity of ICD-10 coding of hyponatraemia using comprehensive population-based medical registries and including patients of all ages. A record of a hyponatraemia diagnosis in the DNRP was found to be specific to and highly predictive of hyponatraemia confirmed by laboratory values. However, the disorder was greatly under-reported, though to a lesser extent in patients admitted to an internal medicine

Table 2 Validity of ICD-10 codes for hyponatraemia recorded in the DNRP, using serum sodium measurements in the LABKA research database as the gold standard

Hyponatraemic serum sodium value recorded in the LABKA research database (mmol/L)		ICD-10 code for hyponatraemia recorded in the DNRP*			Validity measures, % (95% CI)	
		Yes	No	Total		
Overall						
Na<135*	Yes	5410	301 008	306 418	Sensitivity	1.8 (1.7 to 1.8)
	No	440	1 879 784	1 880 224	Specificity	100 (100 to 100)
	Total	5850	2 180 792	2 186 642	PPV	92.5 (91.8 to 93.1)
					NPV	86.2 (86.2 to 86.2)
Cut-off points for increasing severity of hyponatraemia						
Na<130†	Yes	4528	80 605	85 133	Sensitivity	5.3 (5.2 to 5.5)
	No	1322	2 100 187	2 101 509	Specificity	99.9 (99.9 to 99.9)
	Total	5850	2 180 792	2 186 642	PPV	77.4 (76.3 to 78.5)
					NPV	96.3 (96.3 to 96.3)
Na<125‡	Yes	3261	21 544	24 805	Sensitivity	13.1 (12.7 to 13.6)
	No	2589	2 159 248	2 161 837	Specificity	99.9 (99.9 to 99.9)
	Total	5850	2 180 792	2 186 642	PPV	55.7 (54.5 to 57.0)
					NPV	99.0 (99.0 to 99.0)
Na<120§	Yes	2061	6219	8280	Sensitivity	24.9 (24.0 to 25.9)
	No	3789	2 174 573	2 178 362	Specificity	99.8 (99.8 to 99.8)
	Total	5850	2 180 792	2 186 642	PPV	35.2 (34.0 to 36.5)
					NPV	99.7 (99.7 to 99.7)
Na<115¶	Yes	1107	2127	3234	Sensitivity	34.3 (32.6 to 35.9)
	No	4743	2 178 665	2 183 408	Specificity	99.8 (99.8 to 99.8)
	Total	5850	2 180 792	2 186 642	PPV	18.9 (17.9 to 20.0)
					NPV	99.9 (99.9 to 99.9)

*Corresponding to <133 mmol/L for infants ≤30 days of age.
†Corresponding to <128 mmol/L for infants ≤30 days of age.
‡Corresponding to <123 mmol/L for infants ≤30 days of age.
§Corresponding to <118 mmol/L for infants ≤30 days.
¶Corresponding to <113 mmol/L for infants ≤30 days of age.
DNRP, Danish National Registry of Patients; ICD-10, International Classification of Diseases, 10th revision; NPV, negative predictive value; PPV, positive predictive value.

Table 3 Validity of ICD-10 codes for hyponatraemia recorded in the DNRP, stratified by age group categories, year and department of admission, for serum sodium values <135* and <125 mmol/L†

	Sensitivity, % (95% CI)		Specificity, % (95% CI)		PPV, % (95% CI)		NPV % (95% CI)	
	<135 mmol/L	<125 mmol/L	<135 mmol/L	<125 mmol/L	<135 mmol/L	<125 mmol/L	<135 mmol/L	<125 mmol/L
Age, years								
<15	0.2 (0.1 to 0.2)	3.0 (1.5 to 5.2)	100 (100 to 100)	100 (100 to 100)	84.4 (67.2 to 94.7)	34.4 (18.6 to 53.2)	94.6 (94.6 to 94.7)	99.9 (99.9 to 99.9)
15–34	0.2 (0.2 to 0.3)	4.7 (3.0 to 6.9)	100 (100 to 100)	100 (100 to 100)	80.0 (65.4 to 90.4)	51.1 (35.8 to 66.3)	95.5 (95.4 to 95.5)	99.9 (99.9 to 99.9)
35–49	0.9 (0.8 to 1.0)	7.8 (6.7 to 9.0)	100 (100 to 100)	100 (100 to 100)	91.3 (87.3 to 94.4)	67.2 (61.2 to 72.8)	90.8 (90.7 to 90.9)	99.3 (99.3 to 99.3)
50–64	1.3 (1.3 to 1.4)	9.6 (8.9 to 10.3)	100 (100 to 100)	99.9 (99.9 to 99.9)	93.9 (92.2 to 95.3)	69.6 (66.7 to 72.3)	83.6 (83.5 to 83.7)	98.5 (98.4 to 98.5)
65–79	1.8 (1.7 to 1.9)	13.6 (12.9 to 14.4)	100 (100 to 100)	99.8 (99.8 to 99.8)	92.9 (91.7 to 94.0)	57.2 (55.0 to 59.3)	79.1 (78.9 to 79.2)	98.5 (98.4 to 98.5)
≥80	3.4 (3.3 to 3.6)	21.0 (19.9 to 22.1)	99.9 (99.9 to 99.9)	99.5 (99.5 to 99.5)	92.0 (90.8 to 93.0)	47.7 (45.7 to 49.7)	75.7 (75.5 to 75.9)	98.3 (98.3 to 98.4)
Admission year								
2006	1.5 (1.4 to 1.7)	12.5 (11.5 to 13.5)	100 (100 to 100)	99.9 (99.9 to 99.9)	92.8 (90.8 to 94.5)	66.6 (63.2 to 69.9)	86.8 (86.6 to 86.9)	99.0 (98.9 to 99.0)
2007	1.4 (1.3 to 1.5)	12.0 (11.0 to 13.1)	100 (100 to 100)	99.9 (99.9 to 99.9)	94.4 (92.4 to 96.0)	65.3 (61.6 to 68.8)	87.0 (86.9 to 87.1)	99.0 (99.0 to 99.1)
2008	1.7 (1.6 to 1.8)	12.3 (11.3 to 13.3)	100 (100 to 100)	99.9 (99.9 to 99.9)	91.1 (89.1 to 92.8)	53.6 (50.4 to 56.8)	85.9 (85.8 to 86.1)	99.0 (98.9 to 99.0)
2009	1.8 (1.7 to 1.9)	12.6 (11.6 to 13.6)	100 (100 to 100)	99.9 (99.8 to 99.9)	93.4 (91.7 to 94.8)	51.4 (48.4 to 54.5)	85.5 (85.3 to 85.6)	99.0 (98.9 to 99.0)
2010	1.9 (1.8 to 2.0)	14.2 (13.2 to 15.4)	100 (100 to 100)	99.9 (99.9 to 99.9)	91.6 (89.8 to 93.2)	54.4 (51.4 to 57.4)	86.3 (86.2 to 86.4)	99.1 (99.0 to 99.1)
2011	2.2 (2.0 to 2.3)	15.2 (14.1 to 16.4)	100 (100 to 100)	99.9 (99.9 to 99.9)	92.2 (90.6 to 93.6)	49.8 (47.0 to 52.7)	85.8 (85.7 to 85.9)	99.1 (99.0 to 99.1)
Department								
Internal medicine	2.7 (2.7 to 2.8)	16.5 (16.0 to 17.0)	99.9 (99.9 to 100)	99.7 (99.7 to 99.7)	92.8 (92.1 to 93.4)	56.0 (54.7 to 57.3)	80.3 (80.2 to 80.4)	98.3 (98.3 to 98.3)
Surgical	0.2 (0.2 to 0.2)	2.3 (1.9 to 2.8)	100 (100 to 100)	100 (100 to 100)	90.6 (85.8 to 94.3)	57.6 (50.5 to 64.5)	86.0 (85.9 to 86.1)	99.2 (99.2 to 99.2)
Gynaecological/ obstetric	0.1 (0.1 to 0.3)	3.1 (1.2 to 6.7)	100 (100 to 100)	100 (100 to 100)	76.9 (46.2 to 95.0)	46.2 (19.2 to 74.9)	98.0 (97.9 to 98.0)	99.9 (99.9 to 100)
Paediatric	0.2 (0.1 to 0.3)	3.4 (1.7 to 5.8)	100 (100 to 100)	100 (100 to 100)	85.3 (68.9 to 95.0)	35.3 (19.7 to 53.5)	90.4 (90.3 to 90.6)	99.8 (99.8 to 99.8)
Other	0.3 (0.2 to 0.5)	1.5 (0.4 to 3.9)	100 (100 to 100)	100 (100 to 100)	58.3 (36.6 to 77.9)	16.7 (4.74 to 37.4)	95.2 (95.0 to 95.3)	99.7 (99.7 to 99.8)

*Corresponding to <133 mmol/L for infants ≤30 days of age.
†Corresponding to <123 mmol/L for infants ≤30 days of age.
DNRP, Danish National Registry of Patients; ICD-10, International Classification of Diseases, 10th revision; NPV, negative predictive value; PPV, positive predictive value.

Table 4 Sensitivity analyses

Hyponatraemic serum sodium value recorded in the LABKA research database (mmol/L)		Primary analysis (including all admissions for all patients in the study period), % (95% CI)	Sensitivity analyses			
			Requiring at least one serum sodium measurement during hospitalisation, % (95% CI)	Requiring >1 serum sodium measurement during hospitalisation, % (95% CI)	ICD-10 algorithm restricted to code E87.1A and P74.2B, % (95% CI)	Restricting to first admission per patient in the study period, % (95% CI)
Overall						
Na<135	Sensitivity	1.8 (1.7 to 1.8)	1.8 (1.7 to 1.8)	1.9 (1.8 to 2.0)	0.7 (0.6 to 0.7)	1.7 (1.7 to 1.9)
	Specificity	100 (100 to 100)	100 (100 to 100)	100 (100 to 100)	100 (100 to 100)	100 (100 to 100)
	PPV	92.5 (91.8 to 93.1)	95.4 (94.8 to 95.9)	95.8 (95.2 to 96.3)	94.6 (93.6 to 95.6)	93.5 (92.0 to 94.7)
	NPV	86.2 (86.2 to 86.2)	76.9 (76.8 to 77.0)	74.7 (74.6 to 74.8)	86.1 (86.0 to 86.1)	91.6 (91.6 to 91.7)
Cut-off points for increasing severity of hyponatraemia						
Na<130	Sensitivity	5.3 (5.2 to 5.5)	5.3 (5.2 to 5.5)	5.6 (5.4 to 5.7)	2.1 (2.0 to 2.2)	6.3 (5.9 to 6.7)
	Specificity	99.9 (99.9 to 99.9)	99.9 (99.9 to 99.9)	99.9 (99.9 to 99.9)	100 (100 to 100)	100 (100 to 100)
	PPV	77.4 (76.3 to 78.5)	79.8 (78.7 to 80.9)	80.5 (79.4 to 81.6)	83.0 (81.4 to 84.6)	82.2 (80.7 to 84.8)
	NPV	96.3 (96.3 to 96.3)	93.8 (93.8 to 93.9)	93.0 (93.0 to 93.1)	96.2 (96.2 to 96.2)	97.9 (97.9 to 98.0)
Na<125	Sensitivity	13.1 (12.7 to 13.6)	13.1 (12.7 to 13.6)	13.6 (13.1 to 14.0)	5.4 (5.1 to 5.7)	15.6 (14.6 to 16.6)
	Specificity	99.9 (99.9 to 99.9)	99.8 (99.8 to 99.8)	99.8 (99.8 to 99.8)	100 (100 to 100)	99.9 (99.9 to 99.9)
	PPV	55.7 (54.5 to 57.0)	57.5 (56.2 to 58.8)	57.9 (56.5 to 59.2)	62.5 (60.4 to 64.5)	62.3 (59.6 to 64.8)
	NPV	99.0 (99.0 to 99.0)	98.3 (98.3 to 98.4)	98.1 (98.1 to 98.1)	98.9 (98.9 to 98.9)	99.4 (99.4 to 99.4)
Na<120	Sensitivity	24.9 (24.0 to 25.9)	24.9 (24.0 to 25.8)	25.4 (24.5 to 26.4)	6.3 (5.8 to 6.9)	29.3 (27.3 to 31.3)
	Specificity	99.8 (99.8 to 99.8)	99.7 (99.7 to 99.7)	99.7 (99.7 to 99.7)	100 (100 to 100)	99.9 (99.9 to 99.9)
	PPV	35.2 (34.0 to 36.5)	36.3 (35.1 to 37.6)	36.3 (35.0 to 37.6)	50.6 (47.5 to 53.7)	43.7 (41.0 to 46.4)
	NPV	99.7 (99.7 to 99.7)	99.5 (99.5 to 99.5)	99.5 (99.4 to 99.5)	99.6 (99.6 to 99.7)	99.8 (99.8 to 99.8)
Na<115	Sensitivity	34.3 (32.6 to 35.9)	34.2 (32.6 to 35.9)	34.9 (33.1 to 36.6)	9.3 (8.3 to 10.3)	38.8 (35.5 to 42.1)
	Specificity	99.8 (99.8 to 99.8)	99.7 (99.6 to 99.7)	99.6 (99.6 to 99.6)	100 (100 to 100)	99.9 (99.9 to 99.9)
	PPV	18.9 (17.9 to 20.0)	19.5 (18.5 to 20.6)	19.5 (18.4 to 20.6)	28.8 (26.1 to 31.7)	24.2 (22.0 to 26.6)
	NPV	99.9 (99.9 to 99.9)	99.8 (99.8 to 99.8)	99.8 (99.8 to 99.8)	99.9 (99.9 to 99.9)	99.9 (99.9 to 99.9)

ICD-10, International Classification of Diseases, 10th revision; NPV, negative predictive value; PPV, positive predictive value.

department compared to other departments. We found sensitivity to be low even for severe degrees of hyponatraemia. These results were robust when we used a stricter definition of hyponatraemia and complete case analysis.

Our findings correspond to those of Movig *et al*'s[13] single-centre study conducted in the Netherlands, in which ICD-9-CM coding of hyponatraemia in inpatient discharge records was compared with hospital laboratory data. As in our study, sensitivity at the cut-off point of 135 mmol/L was 1.7%, and increased with decreasing serum sodium levels. Sensitivity thus reached 30.6% for values below 115 mmol/L. In addition, their estimates for PPV, NPV and specificity were similar to our results (91.7%, 79.5% and <99.9%, respectively). A Canadian study by Gandhi *et al*[12] examined ICD-10 coding for hyponatraemia and reported a sensitivity of 6.4% for the cut-off point of <135 mmol/L and 41.7% for the cut-off point of 125 mmol/L. The study, however, was restricted to patients ≥66 years of age presenting with serum sodium values at the time of admission or emergency department contact. In line with their results, we found that the median age of patients with an ICD-10 code of hyponatraemia recorded in the DNRP, which could be confirmed by laboratory results, was higher than that of patients with hyponatraemia with no ICD-10 code for hyponatraemia recorded in the DNRP. However, the sensitivity estimates did not reach those found by Gandhi *et al* even for patients 65–79 and ≥80 years of age. Shea *et al*[14] also reported higher sensitivity compared to our results (3.5% for a cut-off point of <136 mmol/L and 29.6% for the cut-off point of 125 mmol/L) in their study examining the validity of ICD-9 codes of hyponatraemia in an outpatient managed-care population. Outpatient serum sodium laboratory tests were compared with outpatient professional ICD-9 claims registered within 15 days before or after the laboratory claim. The PPV was 62.6% for serum sodium levels <136 mmol/L and 10.4% for levels <125 mmol/L. As noted in the paper, detected hyponatraemia may be the cause for follow-up visits in an outpatient setting, without the need for repeat measurements. This could lead to a lower PPV compared to our study and the study by Movig *et al*. In addition, managed-care claims databases encompass an employer-based commercially insured population. Thus, Shea *et al*'s study may not be representative of elderly populations, in which prevalence of hyponatraemia is high.[24 25] This may also explain why their results differed from ours.

The major strengths of our study are its population-based design and unambiguous individual-level linkage between registries containing complete data on all hospitalisations and laboratory tests in a well-defined population. This eliminates the risk of selection bias. Several potential study limitations must be considered. We relied on only one (the lowest) serum sodium value recorded to define the presence of hyponatraemia, and did not consider the duration of hyponatraemia. Clinicians may be more likely to regard hyponatraemia as clinically relevant, and hence to include the condition in discharge diagnoses, if it is detected in more than one measurement. In this context, it is important to note that patient transfers between departments are registered as separate admissions in the DNRP and that we examined the validity of ICD-10 coding for each registered admission. The PPV may have been even higher if we had considered contiguous admissions as a single admission. Finally, we chose to include patients without serum sodium measurements and to consider them as normonatraemic in the main analysis. We did so to detect false-positive diagnoses and thereby obtain accurate estimates of predictive values. Serum sodium is often measured as a routine procedure, and rarely due to specific suspicion. Although frequently measured, the proportion of patients with unacknowledged hyponatraemia is most often unknown. We therefore performed a complete case analysis, including only patients with serum sodium measurements. As the results did not differ markedly from those of the primary analysis, we believe that including patients without serum sodium measurements in the normonatraemic group was justified.

We can only speculate on the reasons for the low sensitivity of the ICD-10 coding of hyponatraemia found in our study. A diagnosis of hyponatraemia was less likely to be recorded in patients with high levels of comorbidity, which may indicate that hyponatraemia is mainly considered a bystander of the underlying diseases. If hyponatraemia is mild or transient, and does not require intervention or specific attention, it may not warrant documentation. However, even for very severe hyponatraemia (<115 mmol/L), which is potentially fatal and requires immediate intervention, sensitivity was low. We believe that this most likely reflects negligence of proper coding practice rather than lack of attention to the clinical importance of low serum sodium levels. With the increasing use of electronic medical records, it would be feasible and worthwhile to automatically assign discharge diagnoses to patients with gross abnormal laboratory values. However, the ultimate responsibility for summarising the most important reasons for treatment and care still rests on the discharging physician. Our results suggest that hyponatraemia is not coded in the presence of coexisting illness deemed more important, and that the fact that hyponatraemia may be an important indicator of a poor prognosis is not yet acknowledged.

The results of this validation study emphasise the need for caution when relying on ICD-10 codes for hyponatraemia in research. Based on the estimated PPV and specificity, patients with an ICD-10 code of hyponatraemia can safely be assumed to actually have hyponatraemia. However, the low sensitivity renders the ICD-10 codes inappropriate for use in studies examining prevalence, incidence and absolute risk, due to a high degree of misclassification. Sensitivity increased with decreasing serum sodium levels, suggesting that studies using ICD-codes to identify hyponatraemia would be based mainly on severe cases. Furthermore, our results indicate that quality of

registration differs according to age, gender and morbidity status. Hence, studies may be susceptible to differential misclassification, again resulting in biased results.

Conclusion

We found that the ICD-10 coding of hyponatraemia in DNRP has high specificity but is highly incomplete, resulting in very low sensitivity. When available, laboratory test results for serum sodium will more correctly identify patients with hyponatraemia.

Contributors LH-B participated in the design of the study, performed the data analysis, provided interpretation of study results and drafted the manuscript. SPU participated in the acquisition and analysis of data. CFC and HTS participated in the design of the study, provided interpretation of study results and helped draft the manuscript. TR and JOLJ contributed to the interpretation of study results and helped draft the manuscript. All authors read and approved the final manuscript.

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Competing interests JOLJ has received an unrestricted research grant and lecture fees from Otsuka Pharma Scandinavia AB. TR has received lecture fees from Otsuka Pharma Scandinavia AB. LH-B, CFC, SPU and HTS are salaried employees of the Department of Clinical Epidemiology, Aarhus University Hospital. The Department of Clinical Epidemiology receives funding from companies in the form of research grants to (and administered by) Aarhus University.

Ethics approval The study was approved by the Danish Data Protection Agency (record number 2006-53-1396).

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Paper II

Hyponatremia and mortality risk: a Danish cohort study of 279 508 acutely hospitalized patients

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Abstract

Objective: We aimed to investigate the impact of hyponatremia severity on mortality risk and assess any evidence of a dose–response relation, utilizing prospectively collected data from population-based registries.
Design: Cohort study of 279 508 first-time acute admissions to Departments of Internal Medicine in the North and Central Denmark Regions from 2006 to 2011.
Methods: We used the Kaplan–Meier method (1 – survival function) to compute 30-day and 1-year mortality in patients with normonatremia and categories of increasing hyponatremia severity. Relative risks (RRs) with 95% CIs, adjusted for age, gender and previous morbidities, and stratified by clinical subgroups were estimated by the pseudo-value approach. The probability of death was estimated treating serum sodium as a continuous variable.
Results: The prevalence of admission hyponatremia was 15% (41 803 patients). Thirty-day mortality was 3.6% in normonatremic patients compared to 7.3, 10.0, 10.4 and 9.6% in patients with serum sodium levels of 130–134.9, 125–129.9, 120–124.9 and <120 mmol/l, resulting in adjusted RRs of 1.4 (95% CI: 1.3–1.4), 1.7 (95% CI: 1.6–1.8), 1.7 (95% CI: 1.4–1.9) and 1.3 (95% CI: 1.1–1.5) respectively. Mortality risk was increased across virtually all clinical subgroups, and remained increased by 30–40% 1 year after admission. The probability of death increased when serum sodium decreased from 139 to 132 mmol/l. No clear increase in mortality was observed for lower concentrations.
Conclusions: Hyponatremia is highly prevalent among patients admitted to Departments of Internal Medicine and is associated with increased 30-day and 1-year mortality risk, regardless of underlying disease. This risk seems independent of hyponatremia severity.

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Introduction

Serum sodium concentration is one of the most frequently performed laboratory measurements in clinical medicine (1). Changes in serum sodium concentrations are closely linked to extracellular volume regulation and cellular homeostasis, and are associated with several common conditions encountered in Departments of Internal Medicine (2). The reported prevalence of hyponatremia (serum sodium concentration <135 mmol/l) at hospital admission ranges from 5% to almost 35%, depending on the study population and the timing requirements specified for the serum measurement (3, 4, 5, 6). Hyponatremia has been associated with increased morbidity and mortality in patients with preexisting heart disease, kidney failure, cirrhosis and cancer (7, 8, 9, 10, 11). Still, few data exist on the prevalence and prognostic impact of hyponatremia in broader populations of

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patients admitted acutely to Departments of Internal Medicine.

In 2009, Whelan *et al*. (12) showed a positive association between degree of hyponatremia and in-hospital mortality risk compared to patients with normonatremia. While this finding was supported by two subsequent studies by Kovesdy *et al*. (9) and Wald *et al*. (13), others have not been able to confirm such a dose–response relation (4, 14). Varying effects of hyponatremia in different patient populations or in the setting of different underlying diseases offer one possible explanation for these diverse results. In a cohort study of 98 411 patients admitted to two teaching hospitals in Boston, Massachusetts and hospitalized for >2 days, Waikar *et al*. (4) found a twofold increased risk for in-hospital death associated with hyponatremia compared to normonatremia for patients with several, but not all, acute medical and surgical conditions.

To investigate these issues in further detail, we conducted a large population-based study on the prevalence and prognostic impact of mild to severe hyponatremia in patients acutely admitted to Departments of Internal Medicine across diagnostic groups defined by the primary diagnosis associated with the current hospitalization and by previous morbidities included in the Charlson comorbidity index (CCI).

Methods

Setting

We conducted this cohort study using Danish population-based medical registries. The Danish National Health Service guarantees free and unfettered access to tax-supported health care for all Danish citizens. The unique ten-digit identification number (CPR number) assigned by the Civil Registration System (CRS) to each person born in or immigrating to Denmark is used in all public records and allows for unambiguous individual-level linkage between Danish registries. This ensures virtually complete follow-up of patients receiving care from the Danish National Health Service (15).

Study cohort

We used the Danish National Patient Registry (DNPR) to identify all hospital admissions in the North and Central Denmark Regions from 1st January 2006 to 31st December 2011 (cumulative population ≈two million inhabitants). The study period was selected based on the availability of complete data in the clinical laboratory information system database (LABKA) for the entire study area (1). The DNPR is a population-based nationwide registry primarily established to monitor hospital activities. The registry contains records for all admissions to Danish non-psychiatric hospitals since 1977 and for all emergency department and outpatient specialist clinic visits since 1995. Reporting to the DNPR is mandatory (16).

For each patient identified, we included in the study only the first acute admission to a Department of Internal Medicine during the study period (in patients ≥15 years of age). Study criteria were: i) admission to a Department of Internal Medicine; ii) an 'acute' admission type, assigned by a secretary upon hospital entry and iii) no surgical, oncologic, gynecologic or obstetric hospitalizations recorded within 30 days prior to the current admission. Admissions on the same day as discharge or transfers between departments were considered as a single hospitalization.

Admission serum sodium value

The LABKA database contains results of all analyses of blood samples drawn from hospitalized patients or outpatients and submitted to hospital laboratories in the Northern and Central Denmark regions (1). Analyses are recorded according to the Nomenclature, Properties, and Units (NPU) coding system and/or local nomenclature. Each record contains information on time and date of the analysis and its results. From the LABKA database, we retrieved information on the first serum sodium measurement performed during hospitalization.

To reduce the probability that serum sodium levels were affected by hospital treatment, we focused on measurements performed within 24 h following admission. We defined normonatremia as serum sodium values between 135 and 145 mmol/l and hyponatremia as serum sodium values <135 mmol/l. Hyponatremia upon admission was divided into four further categories (<120, 120–124.9, 125–129.9 and 130–134.9 mmol/l), in accordance with previous studies (4). If no sodium measurement was performed within 24 h of admission, patients were categorized as having normonatremia and a serum sodium value of 140 mmol/l was imputed.

Mortality

Residence, migration and vital status of all Danish residents can be tracked through the CRS, which is updated daily (15). We obtained information from the

CRS on gender, age, migration and vital status, date of migration and date of death of deceased patients.

Diagnostic groups

For each hospitalization, one primary diagnosis and one or more secondary diagnoses are assigned by the discharging physician and recorded in the DNPR. Diagnoses were coded according to the International Classification of Diseases (ICD), 8th revision (ICD8) until the end of 1993 and according to the 10th revision (ICD10) thereafter (16).

We used the primary diagnosis recorded in the DNPR to determine the main indication for treatment during the current hospitalization. On this basis, we categorized patients into 11 major disease groups: infectious disease, cardiovascular disease, respiratory disease (excluding pneumonia diagnoses, which were included in the infectious disease group) gastrointestinal disease, urogenital disease, endocrine disease, neurologic disease, muscle and connective tissue disease, cancer, observation for suspected disease, and 'other'. Some major primary discharge diagnosis categories were subdivided for further examination.

We used inpatient and outpatient specialist clinic diagnoses recorded in the DNPR prior to the current hospitalization to identify previous morbidities included in the CCI. We used these diagnoses to compute CCI scores as a proxy for the preexisting morbidity burden of each patient. The CCI, a validated comorbidity scoring system, includes 19 specific conditions, each given a weighted score from 1 to 6 depending on its correlation with 1-year mortality (17, 18). We defined three CCI levels: low (CCI score = 0), medium (CCI score = 1–2) and high (CCI score > 2).

Statistical analysis

Baseline characteristics of patients with hyponatremia and normonatremia were described in contingency tables.

We computed the prevalence of hyponatremia overall and for each hyponatremia category. The denominator contained the total number of first-time admissions to a Department of Internal Medicine, including patients with hypernatremia or a missing admission sodium measurement. We further computed the prevalence of hyponatremia according to age and diagnostic groups (i.e. groups based on CCI level, specific preexisting morbidities, and primary discharge diagnosis).

Patients with hyponatremia and normonatremia were followed from the date of the first acute Internal Medicine admission until death, migration or up to 1 year. We used the Kaplan–Meier method (1 – the survival function) to compute 30-day and 1-year mortality with 95% CIs, and plotted cumulative mortality for categories of serum sodium values. Since the majority of previous studies only had access to in-hospital mortality data, we also computed in-hospital mortality rates for comparison. We computed relative risk (RR) of death with corresponding 95% CIs, comparing mortality risk at 30 days and 1 year in patients with hyponatremia with that in patients with normonatremia using the pseudo-value approach. This approach allows for direct regression modelling of right-censored data comparing survival (or failure) functions for non-proportional hazard rates at a fixed point in time (19). We repeated the analyses adjusting for gender, age group and the specific preexisting morbidities included in the CCI.

We fitted the regression using a restricted cubic spline function (five knots) and plotted the resulting curve against serum sodium concentration (20), in order to identify threshold values for the association between hyponatremia and increased mortality. Furthermore, we examined the impact of hyponatremia on mortality in different diagnostic groups, by computing 30-day adjusted RRs stratified by CCI level, specific preexisting morbidities and primary discharge diagnoses. In these analyses, we adjusted for CCI level rather than specific preexisting CCI morbidities to better comply with the rule of thumb for minimum outcome events per predictor variable in each cell. Finally, we performed a sensitivity analysis excluding all patients with no admission serum sodium measurement. This allowed us to evaluate the impact of classifying these patients as normonatremic (21).

The study was approved by the Danish Data Protection Agency (2013-41-1924). Data analyses were conducted using STATA Software V.12.1 (STATA, College Station, TX, USA).

Results

Prevalence

From the DNPR, we identified 279 508 patients with an acute admission to a Department of Internal Medicine during the study period. Among these, 254 284 (91.0%) patients had a serum sodium measurement within 24 h of admission. In total, 232 911 (83.3%) patients were categorized as normonatremic. The overall prevalence of hyponatremia at admission was 15.0% (41 803 patients). The proportion of patients in the four hyponatremia

categories (130–134.9, 125–129.9, 120–124.9 and <120 mmol/l) was 10.5, 2.9, 0.9 and 0.6% respectively. Characteristics of patients with hyponatremia and normonatremia are shown in Table 1.

Table 2 presents prevalence estimates according to age, CCI level and diagnostic groups. The prevalence of hyponatremia increased with age and CCI level. We found hyponatremia to be particularly prevalent in patients with previous liver disease or metastatic cancer, and in patients in whom diabetes, pneumonia, sepsis, kidney disease and liver disease were indicated as the primary reason for hospitalization based on the primary discharge diagnosis. A total of 4794 (1.7%) patients were hypernatremic (serum sodium >145 mmol/l) and therefore excluded from the mortality analyses.

Mortality

A total of 46 (0.02%) and 464 (0.17%) patients migrated before they could be followed for 30 days or 1 year respectively. In-hospital, 30-day and 1-year mortality were 6.8, 8.1 and 21.5% in patients with hyponatremia, compared to 2.9, 3.6 and 10.6% among patients with normonatremia (Table 3 and Fig. 1). Absolute mortality was increased in all categories of hyponatremia. The higher mortality risk in patients with hyponatremia of any severity compared to normonatremic patients persisted after controlling for age, gender and previous morbidities, yielding adjusted RRs at 30 days of 1.4 (95% CI: 1.3–1.4), 1.7 (95% CI: 1.6–1.8), 1.7 (95% CI: 1.4–1.9) and 1.3 (95% CI: 1.1–1.5) for sodium levels of 130–134.9, 125–129.9, 120–124.9 and <120 mmol/l respectively. At 1 year, the corresponding RRs were 1.3 (95% CI: 1.3–1.3), 1.4 (95% CI: 1.4–1.5), 1.4 (95% CI: 1.3–1.5) and 1.3 (95% CI: 1.1–1.4) respectively (Table 3). A secondary analysis of patients with serum sodium <120 mmol/l showed a further decrease in 30-day RR with decreasing serum sodium levels (RRs of 1.4 (95% CI: 1.1–1.8), 1.1 (95% CI: 0.8–1.6) and 1.1 (95% CI: 0.7–1.8) for sodium levels of 115–119.9, 110–114.9 and <110 mmol/l respectively).

Table 1 Characteristics of acute medical inpatients with and without hyponatremia[a]. Values are expressed as numbers (percentage) unless otherwise indicated.

	Serum sodium level (mmol/l)				
	Hyponatremia				Normonatremia
	<120 (*n*=1773)	120–124.9 (*n*=2573)	125–129.9 (*n*=8170)	130–134.9 (*n*=29 287)	135–145 (*n*=232 921)
Median age (IQR)	72 (61–82)	70 (60–80)	70 (59–81)	69 (55–80)	61 (43–75)
Gender (female)	1136 (64.1)	1420 (55.2)	4406 (53.9)	15 115 (51.6)	115 896 (49.8)
CCI level					
Low (CCI score 0)	876 (49.4)	1134 (44.1)	3593 (44.0)	13 735 (46.9)	139 106 (59.7)
Medium (CCI score 1–2)	670 (37.8)	992 (38.6)	3051 (37.4)	10 485 (35.8)	68 543 (29.4)
High (CCI score >2)	227 (12.8)	447 (17.4)	1526 (18.7)	5067 (17.3)	25 263 (10.9)
Specific pre-existing morbidity					
Myocardial infarction	76 (4.3)	160 (6.2)	468 (5.7)	1908 (6.5)	13 153 (5.7)
Congestive heart failure	75 (4.2)	143 (5.6)	569 (7.0)	1787 (6.1)	10 030 (4.3)
Peripheral vascular disease	120 (6.8)	207 (8.1)	657 (8.0)	2170 (7.4)	11 523 (5.0)
Cerebrovascular disease	169 (9.5)	306 (11.9)	927 (11.4)	3140 (10.7)	19 514 (8.4)
Dementia	21 (1.2)	234 (1.3)	84 (1.0)	305 (1.0)	2208 (1.0)
Chronic pulmonary disease	224 (12.6)	345 (13.4)	1101 (13.5)	3768 (12.9)	24 006 (10.3)
Connective tissue disease	57 (3.2)	116 (4.5)	353 (4.3)	1301 (4.4)	8270 (3.6)
Ulcer disease	150 (8.5)	262 (10.2)	685 (8.4)	2050 (7.0)	11 575 (5.0)
Mild liver disease	78 (4.4)	112 (4.4)	319 (3.9)	729 (2.5)	3083 (1.3)
Moderate/severe liver disease	16 (0.9)	47 (1.8)	104 (1.3)	221 (0.8)	793 (0.3)
Diabetes 1 and 2	129 (7.3)	241 (9.4)	822 (10.1)	2917 (10.0)	13 882 (6.0)
Diabetes with complications	59 (3.3)	136 (5.3)	448 (5.5)	1538 (5.3)	6954 (3.0)
Hemiplegia	16 (0.9)	20 (0.8)	52 (0.6)	165 (0.6)	992 (0.4)
Moderate/severe renal disease	29 (1.6)	57 (2.2)	251 (3.1)	873 (3.0)	5292 (2.3)
Malignant tumor	213 (12.0)	321 (12.5)	1173 (14.4)	3962 (13.5)	20 879 (9.0)
Leukaemia	4 (0.2)	10 (0.4)	33 (0.4)	122 (0.4)	817 (0.4)
Lymphoma	7 (0.4)	16 (0.6)	87 (1.1)	354 (1.2)	1693 (0.7)
Metastatic cancer	21 (1.2)	51 (2.0)	217 (2.7)	737 (2.5)	2850 (1.2)
AIDS	1 (0.1)	2 (0.1)	10 (0.1)	45 (0.2)	218 (0.1)

AIDS, acquired immunodeficiency syndrome; CCI, Charlson comorbidity index; IQR, interquartile range.
[a]Data for patients with serum sodium >145 mmol/l are not displayed.

Table 2 Prevalence of hyponatremia overall and by hyponatremia severity according to comorbidity level specific preexisting morbidity and primary discharge diagnosis of acute medical inpatients[a]. Values are expressed as numbers (percentage) unless otherwise indicated.

	Serum sodium concentration (mmol/l)					
	Hyponatremia *n*(%)					Normonatremia *n*(%)
	<120	120–124.9	125–129.9	130–134.9	Overall	135–145
Overall	1773 (0.6)	2573 (0.9)	8170 (2.9)	29 287 (10.5)	41 803 (15.0)	232 911 (83.3)
Age groups (years)						
15–19	1 (0.0)	13 (0.1)	70 (0.6)	631 (5.5)	715 (6.2)	10 468 (91.2)
20–29	5 (0.0)	19 (0.1)	114 (0.6)	1011 (5.5)	1149 (6.2)	16 855 (91.5)
30–39	21 (0.1)	53 (0.2)	240 (1.0)	1476 (6.4)	1790 (7.7)	21 040 (90.8)
40–49	117 (0.4)	179 (0.6)	572 (1.8)	2391 (7.3)	3259 (10.0)	28 981 (88.5)
50–59	285 (0.7)	406 (1.0)	1228 (2.9)	3979 (9.5)	5898 (14.1)	35 240 (84.4)
60–69	407 (0.8)	629 (1.2)	1859 (3.6)	5890 (11.4)	8785 (17.0)	42 443 (81.8)
70–79	420 (0.8)	621 (1.2)	1930 (3.8)	6743 (13.4)	9714 (19.3)	40 018 (79.3)
>80	517 (1.0)	653 (1.3)	2157 (4.4)	7166 (14.5)	10 493 (21.2)	37 866 (76.4)
CCI level						
Low (CCI score 0)	876 (0.5)	1134 (0.7)	3593 (2.2)	13 735 (8.5)	22 026 (12.5)	139 106 (86.3)
Medium (CCI score 1–2)	670 (0.8)	992 (1.2)	3051 (3.6)	10 485 (12.3)	13 025 (18.5)	68 543 (80.4)
High (CCI score >2)	227 (0.7)	447 (1.4)	1526 (4.6)	5067 (15.3)	5262 (23.0)	25 263 (76.3)
Specific pre-existing morbidity						
Myocardial infarction	76 (0.5)	160 (1.0)	468 (2.9)	1908 (12.0)	2612 (16.3)	13 153 (82.2)
Congestive heart failure	75 (0.6)	143 (1.1)	569 (4.4)	1787 (13.9)	2574 (20.0)	10 030 (77.9)
Peripheral vascular disease	120 (0.8)	207 (1.4)	657 (4.4)	2170 (14.6)	3154 (21.2)	11 523 (77.3)
Cerebrovascular disease	169 (0.7)	306 (1.2)	927 (3.8)	3140 (12.7)	4542 (18.4)	19 514 (79.2)
Dementia	21 (0.7)	34 (1.2)	84 (2.9)	305 (10.7)	444 (15.5)	2208 (77.3)
Chronic pulmonary disease	224 (0.8)	345 (1.2)	1101 (3.7)	3768 (12.6)	5438 (18.2)	24 006 (80.2)
Connective tissue disease	57 (0.6)	116 (1.1)	353 (3.5)	1301 (12.7)	1827 (17.8)	8270 (80.8)
Ulcer disease	150 (1.0)	262 (1.7)	685 (4.6)	2050 (13.6)	3147 (20.9)	11 575 (77.0)
Mild liver disease	78 (1.8)	112 (2.5)	319 (7.2)	729 (16.5)	1238 (28.0)	3083 (69.7)
Moderate/severe liver disease	16 (1.3)	47 (3.9)	104 (8.6)	221 (18.2)	388 (32.0)	793 (65.4)
Diabetes 1 and 2	129 (0.7)	241 (1.3)	822 (4.5)	2917 (16.0)	4109 (22.5)	13 882 (76.0)
Diabetes with complications	59 (0.6)	136 (1.5)	448 (4.8)	1538 (16.6)	2181 (23.6)	6954 (75.1)
Hemiplegia	16 (1.2)	20 (1.6)	52 (4.0)	165 (12.8)	253 (19.6)	992 (76.8)
Moderate/severe renal disease	29 (0.4)	57 (0.9)	251 (3.8)	873 (13.2)	1210 (18.2)	5292 (79.8)
Malignant tumor	213 (0.8)	321 (1.2)	1173 (4.6)	3962 (14.7)	5669 (21.0)	20 879 (77.5)
Leukaemia	4 (0.4)	10 (1.0)	33 (3.3)	122 (12.3)	169 (17.0)	1693 (77.8)
Lymphoma	7 (0.3)	16 (0.7)	87 (4.0)	354 (16.3)	464 (21.3)	1203 (75.6)
Metastatic cancer	21 (0.5)	51 (1.3)	217 (5.5)	737 (18.8)	1026 (26.2)	2850 (72.9)
AIDS	1 (0.4)	2 (0.7)	10 (3.6)	45 (16.3)	58 (20.9)	218 (78.7)
Primary discharge diagnosis						
Infections	295 (0.7)	530 (1.2)	2132 (4.8)	8604 (19.4)	11 561 (26.1)	32 082 (72.3)
Pneumonia	90 (0.7)	183 (1.3)	321 (5.4)	2809 (20.6)	3814 (27.9)	9515 (69.7)
Sepsis	38 (1.5)	43 (1.7)	179 (7.0)	631 (24.6)	891 (34.7)	1582 (61.6)
Other infections	167 (0.6)	304 (1.1)	1221 (4.3)	5164 (18.3)	6856 (24.3)	20 985 (74.5)
Cardiovascular disease	198 (0.4)	390 (0.7)	1292 (2.3)	4729 (8.4)	6609 (11.7)	49 173 (87.0)
Stroke	28 (0.3)	36 (0.4)	170 (2.0)	671 (7.9)	905 (10.7)	7457 (88.1)
Acute ischemic heart disease	48 (0.4)	114 (0.8)	383 (2.8)	1484 (10.8)	2029 (14.7)	11 636 (84.5)
Congestive heart failure	27 (0.8)	56 (1.6)	133 (3.8)	401 (11.5)	617 (17.6)	2632 (80.2)
Other cardiovascular disease	95 (0.3)	184 (0.6)	606 (2.0)	2173 (7.1)	3058 (9.9)	27 266 (88.6)
Respiratory disease (excl. pneumonia)	87 (0.8)	140 (1.3)	390 (3.6)	1267 (11.6)	1884 (17.3)	8849 (81.0)
Gastrointestinal disease	95 (1.0)	157 (1.7)	503 (5.4)	1321 (14.1)	2076 (22.1)	7216 (76.8)
Liver disease	41 (3.0)	61 (4.5)	160 (11.8)	311 (22.9)	573 (42.1)	773 (56.8)
Other gastrointestinal disease	54 (0.7)	96 (1.2)	343 (4.3)	1010 (12.6)	1503 (18.7)	6443 (80.2)
Urogenital disease	20 (0.7)	44 (1.6)	147 (5.3)	448 (16.2)	559 (26.4)	2057 (74.2)
Kidney disease	18 (0.9)	38 (1.8)	124 (5.9)	379 (17.9)	659 (23.8)	1512 (71.3)
Other urogenital disease	2 (0.3)	6 (0.9)	23 (3.5)	69 (10.6)	100 (15.4)	545 (83.7)
Endocrine disease	637 (5.4)	407 (3.5)	737 (6.2)	2105 (17.8)	3886 (32.9)	7593 (64.3)
Diabetes	46 (1.0)	85 (1.9)	318 (7.1)	1173 (26.0)	1622 (36.0)	2833 (62.9)
Hypothyroidism	3 (2.0)	2 (1.4)	3 (2.0)	11 (7.5)	19 (12.9)	128 (87.1)
Hyperthyroidism	4 (0.6)	1 (0.2)	4 (0.6)	24 (3.9)	36 (5.7)	592 (93.2)

Table 2 *Continued.*

	Serum sodium concentration (mmol/l)					
	Hyponatremia *n*(%)					Normonatremia *n*(%)
	<120	120–124.9	125–129.9	130–134.9	Overall	135–145
Hyponatremia and hypoosmolality	424 (55.1)	169 (22.0)	101 (13.1)	35 (4.6)	729 (94.8)	38 (4.9)
Other endocrine disease	160 (2.8)	160 (2.8)	311 (5.4)	859 (14.9)	1480 (25.8)	4002 (69.6)
Neurologic disease	22 (0.2)	78 (0.6)	246 (1.9)	737 (5.8)	1083 (8.5)	11 442 (90.2)
Muscle and connective tissue disease	32 (0.3)	68 (0.7)	202 (2.1)	789 (8.2)	1091 (11.4)	8400 (87.7)
Cancer	46 (0.9)	73 (1.4)	304 (5.7)	948 (17.6)	1371 (25.5)	3995 (73.5)
Observation for suspected disease	65 (0.2)	130 (0.4)	504 (1.4)	2164 (5.8)	2863 (7.7)	33 776 (91.2)
Other	276 (0.4)	556 (0.7)	1713 (2.2)	6175 (7.8)	8720 (11.0)	68 369 (86.5)

AIDS, acquired immunodeficiency syndrome; CCI, Charlson comorbidity index.
[a]Data for patients with serum sodium >145 mmol/l are not displayed.

Similar results were observed for in-hospital mortality and at 1 year (Supplementary Table 1, see section on supplementary data given at the end of this article).

Serum sodium concentrations of 139 to 141 mmol/l were associated with the lowest risk of death, based on the restricted cubic spline models (Fig. 2). A steep increase in predicted 30-day and 1-year mortality was observed with decreasing sodium levels, until the level dropped below 132 mmol/l. After this point, only minor increases were observed. Controlling for the confounding effects of age, gender and previous morbidities resulted in the curve further plateauing below this point.

Serum sodium was not measured within 24 h of admission in 25 224 patients. These patients were younger and had slightly lower CCI scores than patients with normonatremia (Supplementary Table 2, see section on supplementary data given at the end of this article). Excluding patients without admission serum sodium measurement had only a limited effect on absolute mortality and risk estimates (Supplementary Table 3).

Mortality risk according to diagnostic groups

Patients with hyponatremia had increased 30-day mortality across virtually all major categories of primary discharge diagnoses compared to patients with normonatremia (Fig. 3A and see Supplementary Table 4, see section on supplementary data given at the end of this article for RR estimates by hyponatremia category stratified by diagnostic group). One exception was the category of endocrine disease; patients given a primary discharge diagnosis of 'hyponatremia and hypoosmolality' had an RR of 0.2 (95% CI: 0.1–1.1). Notably, hyponatremic patients with an unspecific diagnosis of 'observation for suspected disease' had more than a twofold increased risk of death within 30 days of admission. In contrast to the overall findings, mortality risk increased with increasing hyponatremia severity in patients with a primary discharge diagnosis of sepsis (from 0.9 (95% CI: 0.7–1.1) for sodium levels of 130–134.9 mmol/l to 1.9 (95% CI: 1.2–3.0) for sodium levels <120 mmol/l), respiratory disease (from 1.2 (95% CI: 1.0–1.4) for sodium levels of 130–134.9 mmol/l to 2.9 (95% CI: 1.9–4.3) for sodium levels <120 mmol/l), liver disease (from 1.1 (95% CI: 0.8–1.6) for sodium levels of 130–134.9 mmol/l to 2.6 (95% CI: 1.5–4.6) for sodium levels <120 mmol/l) and cancer (from 1.4 (95% CI: 1.3–1.6) for sodium levels of 130–134.9 mmol/l to 1.9 (95% CI: 1.2–3.0) for sodium levels <120 mmol/l) (see Supplementary Table 4 for further details).

Hyponatremia was associated with increased risk of death among patients in most groups of previous morbidity (Fig. 3B and C). Overall, the RR increased with increasing CCI level. However, when we computed RRs for each hyponatremia category separately within each stratum of CCI level, we found that RRs decreased with increasing CCI level for patients with serum sodium <120 mmol/l (Supplementary Table 4).

Discussion

In this large population-based cohort study in a hospital setting with complete follow-up, hyponatremia was present at admission in nearly one of seven patients. Any degree of hyponatremia was associated with increased short- and long-term mortality compared to normonatremia. For hyponatremic serum sodium values, a biphasic dose–response relation was observed. The probability of death increased with decreasing serum sodium until a

Table 3 Thirty-day and 1-year cumulative mortality and crude and adjusted RRs stratified by serum sodium concentration at hospital admission.

Serum sodium level (mmol/l)	Total (*n*)	30-day mortality				1-year mortality			
		Deaths (*n*)	Cumulative mortality (95% CI)	Crude RR (95% CI)	Adjusted RR[a] (95% CI)	Deaths (*n*)	Cumulative mortality (95% CI)	Crude RR (95% CI)	Adjusted RR[a] (95% CI)
Normonatremia	232 911	8275	3.6 (3.5–3.6)	1 (ref.)	1 (ref.)	23 561	10.6 (10.4–10.7)	1 (ref.)	1 (ref.)
Hyponatremia overall	41 803	3387	8.1 (7.9–8.4)	2.3 (2.2–2.4)	1.5 (1.4–1.5)	8711	21.5 (21.2–22.0)	2.0 (2.0–2.1)	1.3 (1.3–1.4)
Hyponatremia category									
130–134.9	29 287	2133	7.3 (7.0–7.6)	2.1 (2.0–2.1)	1.4 (1.3–1.4)	5715	20.2 (19.8–20.7)	1.9 (1.9–2.0)	1.3 (1.3–1.3)
125–129.9	8170	818	10.0 (9.4–10.7)	2.8 (2.6–3.0)	1.7 (1.6–1.8)	1967	24.8 (23.8–25.7)	2.4 (2.3–2.4)	1.4 (1.4–1.5)
120–124.9	2573	266	10.4 (9.2–11.6)	2.9 (2.6–3.3)	1.7 (1.4–1.9)	617	24.7 (23.0–26.4)	2.3 (2.2–2.5)	1.4 (1.3–1.5)
<120	1773	170	9.6 (8.3–11.1)	2.7 (2.3–3.1)	1.3 (1.1–1.5)	412	23.9 (22.0–26.0)	2.3 (2.1–2.5)	1.3 (1.1–1.4)

RR, relative risk.
[a]Adjusted for age group, gender and history of specific morbidities included in the CCI.

threshold of 132 mmol/l, below which there was no further increase in mortality. Mortality risk was increased across virtually all major primary discharge diagnosis groups and categories of previous morbidity.

As indicated by the divergent results of previous studies, the prevalence of hyponatremia is highly influenced by study population composition (4, 12), criteria applied to define hyponatremia at hospital admission (3, 4), and composition of the denominator (i.e. whether only patients for whom serum sodium was measured were included) (3, 4, 6, 12). The 15% overall prevalence of hyponatremia observed in our study is comparable with that observed among 2171 internal medicine patients in a recent single-center study (5). Furthermore, the prevalence among patients hospitalized with chronic heart failure (7), acute myocardial infarction (22), ischemic stroke (23) and pneumonia (24) concurs with previous reports. The in-hospital mortality in our study was equivalent to previous reports applying the same definition for hyponatremia (4, 12, 13).

Our study challenges the hypothesis that mortality risk attributed to hyponatremia continues to increase when serum sodium decreases, as found by Wald *et al*. (13) among hospitalized patients in general and by Kovesdy *et al*. (9) among patients with chronic kidney disease. Notably, these studies were based on very few (~10 or less) deaths among patients with serum sodium <120 mmol/l. In contrast, we found that decrease in serum sodium below a threshold of 132 mmol/l, did not contribute to further increase in overall mortality risk. However, in the stratified analysis, we did find that mortality risk increased by hyponatremia severity in patients with a primary diagnosis of cancer, liver disease, respiratory disease and sepsis. Still, <25 deaths were observed in the two lower hyponatremia categories for each of the patient subgroups, and cautious interpretation about the pattern of the dose–response relation in these patients is needed.

We utilized prospective, independently collected data without restrictions on patients' sodium measurements at admission (4, 12, 13, 14) or on length of hospitalizations (4), thereby essentially eliminating the risk of selection bias. The study also benefitted from the long-term and virtually complete follow-up provided by registry data (15, 16, 25). Importantly, our large study population allowed us to examine the mortality risk associated with different levels of hyponatremia and across numerous diagnostic groups, while controlling for important confounders. Hyperglycemia causes osmotic shift of water out of cells, which can potentially result in hyponatremia. Some previous studies have applied a correction factor to the

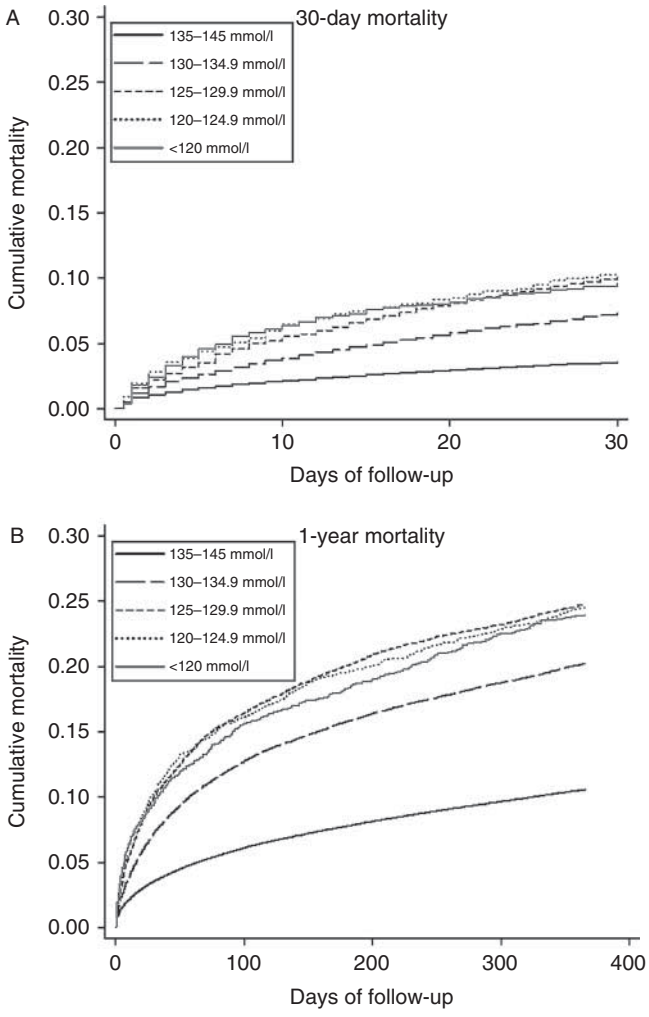

Figure 1

(A) Thirty-day and (B) 1-year cumulative mortality according to categories of serum sodium concentration at hospital admission.

measured serum sodium concentration in the presence of hyperglycemia. In the present study, we aimed to examine the prognostic impact of low serum sodium concentration regardless of cause, and therefore refrained from such correction. Adjusting for the ICD10 discharge diagnosis for hyperglycemia and ketoacidosis associated with the current admission ($n=559$) had no influence on RR estimates (data not shown), consistent with findings of studies in which a correction factor was used (4, 14).

Some limitations should be considered when interpreting our results. By assigning patients with no admission sodium measurement to the normonatremic group, we may have misclassified some patients with hyponatremia. However, we believe the effect of this potential bias is small. Generally, serum sodium is measured for a wide range of indications and the mortality rate in patients lacking admission laboratory measurements has been found to resemble that of patients with laboratory test results within reference values (26). Furthermore, the misclassification of some patients with undetected hyponatremia as normonatremic would likely be non-differential with regard to outcome and would bias our results towards the null, as supported by the results of our sensitivity analyses. Another limitation was our inability to measure the severity of illness during hospitalization. Finally, we cannot rule out residual confounding through our use of ICD10 discharge diagnoses recorded in the DNPR to categorize patients into diagnostic groups (27, 28, 29). Thirty-eight patients categorized as normonatremic had received a primary diagnosis of 'hyponatremia and hypoosmolality'. Among these, only nine patients developed hyponatremia during hospitalization. For the remaining patients, it is possible that a hyponatremic serum sodium value, measured at the request of the general practitioner, had triggered hospitalization. However, we cannot dismiss coding error as an alternative explanation.

A possible mechanism for the increased mortality associated with hyponatremia independent of underlying disease, and for the overall absence of further increase in mortality risk when serum sodium decreased below 132 mmol/l, may be hyponatremia-induced oxidative

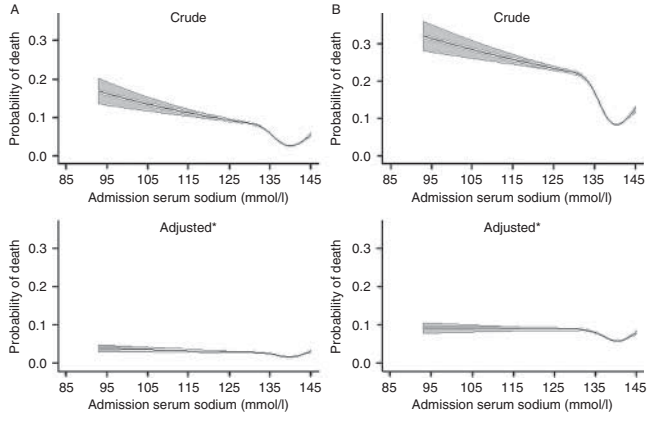

Figure 2

Crude and adjusted* predicted probability of (A) 30-day and (B) 1-year mortality as a function of admission serum sodium concentration. *Adjusted for age group, gender and history of specific morbidities included in the Charlson comorbidity index. The gray area represents the 95% CI.

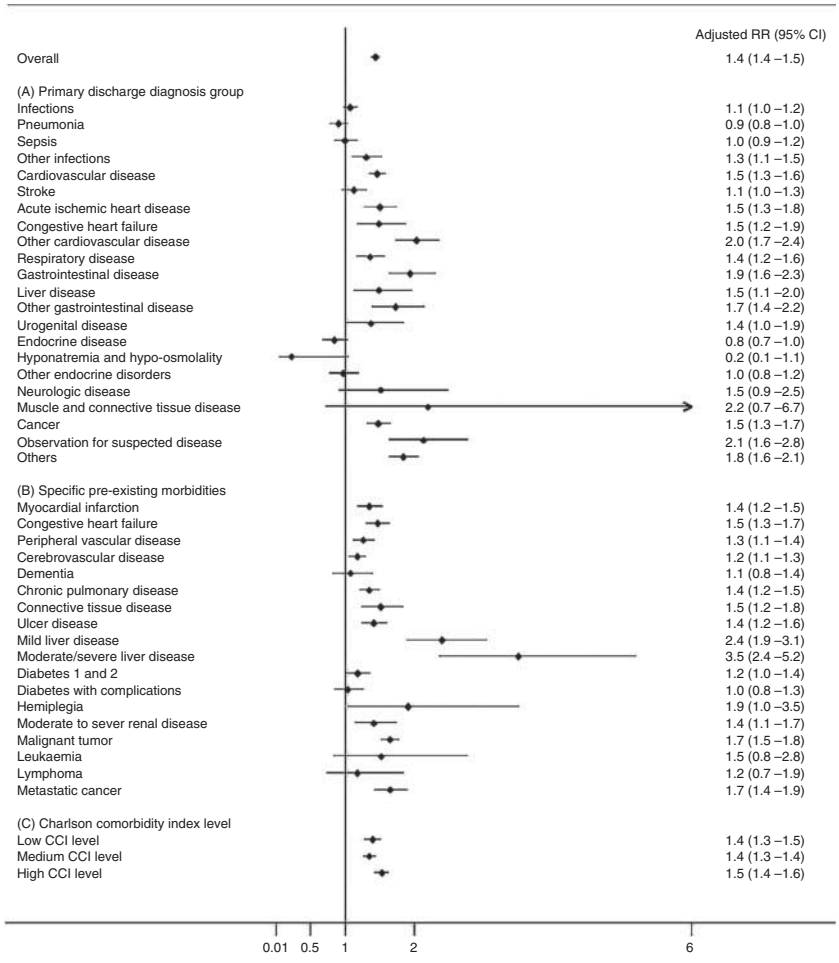

Figure 3

Adjusted 30-day relative risk (RR) of death among patients with hyponatremia compared to patients with normonatremia, stratified by diagnostic groups. Adjusted for (A) age group, gender and Charlson comorbidity index (CCI) level, (B) age group, gender and CCI level (excl. the specific morbidity) and (C) age group and gender. Subgroups with too few events to yield meaningful estimates were left out.

stress (30). It is possible that even small decreases in serum sodium below 139 mmol/l may be sufficient to induce accumulation of free oxygen radicals and thereby induce damage to proteins, lipids and DNA. A growing body of evidence indicates that inflammatory mediators, such as interleukins 1 and 6, can induce hyponatremia through excessive vasopressin release (31, 32). This could explain the potential lower mortality observed in patients with serum sodium <120 mmol/l, among who a large proportion is believed to have hyponatremia caused by medication rather than severe underlying disease, and consequently a lower level of inflammation (14). In support of this hypothesis, one-quarter ($n=424$) of patients with serum sodium <120 mmol/l had a primary discharge diagnosis of 'hyponatremia and hypoosmolality'. Given the very low sensitivity of this ICD10 discharge diagnosis even in severe hyponatremia (34% for serum sodium values ≤ 115 mmol/l), this could indicate absence of other critical morbidities (33). Alternatively, assignment of the 'hyponatremia and hypoosmolality' diagnosis could indicate that active steps to correct hyponatremia were taken. However, it was beyond the scope of this study to examine whether the lower mortality observed in patients with serum sodium <120 mmol/l could be attributed to treatment of hyponatremia.

Discussion of possible underlying mechanisms should not divert attention from the finding that hyponatremia

at admission, regardless of severity, is associated with a poor prognosis in patients acutely admitted with medical disorders. Our study clarifies the clinical course of hyponatremia and underscores the pronounced negative impact of even mild hyponatremia at hospital admission on mortality risk. Sodium measurement should be considered in future risk stratification models for acute medical patients.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-15-0111.

Declaration of interest

Prof. J O L Jørgensen received an unrestricted research grant from Otsuka Pharma Scandinavia AB for the submitted work. L Holland-Bill and J O L Jørgensen have received lecture fees from Otsuka Pharma Scandinavia AB. L Holland-Bill, C F Christiansen, U Heide-Jørgensen and S P Ulrichsen are employees at the Department of Clinical Epidemiology, Aarhus University Hospital. The Department of Clinical Epidemiology, Aarhus University Hospital receives funding from companies in the form of research grants to (and administered by) Aarhus University. There are no other relationships or activities that could appear to have influenced the submitted work.

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Author contribution statement

L Holland-Bill, C F Christiansen, T Ring, J O L Jørgensen and H T Sørensen contributed to conception and design of the study. U Heide-Jørgensen and S P Ulrichsen acquired the data. L Holland-Bill conducted the statistical analyses. All authors contributed to the interpretation of data and in drafting the manuscript. All authors critically revised and approved the final version for submission. All authors had full access to the data in the study, and can take responsibility for the integrity of the data and accuracy of data analysis. L Holland-Bill is the guarantor for the study.

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Supplementary Table 1. Inhospital, 30-day and 1-year cumulative mortality and crude and adjusted RRs with extended serum sodium categories.

Serum sodium level (mmol/l)	Total (n)	Inhospital mortality				30-day mortality				1-year mortality			
		Deaths (n)	Cumulative mortality (95% CI)	Crude RR (95% CI)	Adjusted RR* (95% CI)	Deaths (n)	Cumulative mortality (95% CI)	Crude RR (95% CI)	Adjusted RR* (95% CI)	Deaths (n)	Cumulative mortality (95% CI)	Crude RR (95% CI)	Adjusted RR* (95% CI)
Normonatremia	232,911	6,781	2.9 (2.9-3.0)	1 (ref.)	1 (ref.)	8,275	3.6 (3.5-3.6)	1 (ref.)	1 (ref.)	23,561	10.6 (10.4-10.7)	1 (ref.)	1 (ref.)
Hyponatremia overall	41,803	2,799	6.8 (6.5-7.0)	2.3 (2.2-2.4)	1.5 (1.4-1.6)	3,387	8.1 (7.9-8.4)	2.3 (2.2-2.4)	1.5 (1.4-1.5)	8,711	21.5 (21.2-22.0)	2.0 (2.0-2.1)	1.3 (1.3-1.4)
Hyponatremia category													
130-134.9	29,287	1,728	6.0 (5.7-6.2)	2.0 (1.9-2.1)	1.4 (1.3-1.5)	2,133	7.3 (7.0-7.6)	2.1 (2.0-2.1)	1.4 (1.3-1.4)	5,715	20.2 (19.8-20.7)	1.9 (1.9-2.0)	1.3 (1.3-1.3)
125-129.9	8,170	697	8.6 (8.0-9.3)	2.9 (2.7-3.2)	1.8 (1.6-1.9)	818	10.0 (9.4-10.7)	2.8 (2.6-3.0)	1.7 (1.6-1.8)	1,967	24.8 (23.8-25.7)	2.4 (2.3-2.4)	1.4 (1.4-1.5)
120-124.9	2,573	221	8.7 (7.6-9.8)	3.0 (2.6-3.4)	1.7 (1.4-1.9)	266	10.4 (9.2-11.6)	2.9 (2.6-3.3)	1.7 (1.4-1.9)	617	24.7 (23.0-26.4)	2.3 (2.2-2.5)	1.4 (1.3-1.5)
115-119.9	985	89	9.1 (7.5-11.1)	3.1 (2.5-3.8)	1.6 (1.3-2.1)	96	9.8 (8.1-11.8)	2.7 (2.3-3.3)	1.4 (1.1-1.8)	238	24.9 (22.3-27.8)	2.4 (2.1-2.6)	1.4 (1.2-1.5)
110-114.9	500	37	7.5 (5.5-10.2)	2.6 (1.8-3.5)	1.0 (0.7-1.5)	44	8.8 (6.6-11.7)	2.5 (1.9-3.3)	1.1 (0.8-1.6)	117	24.1 (20.5-28.1)	2.3 (1.9-2.7)	1.1 (1.0-1.4)
<110	288	27	9.4 (6.5-13.4)	3.2 (2.2-4.6)	1.3 (0.9-2.1)	30	10.4 (7.4-14-6)	2.9 (2.1-4.1)	1.1 (0.7-1.8)	57	20.4 (16.1-25.6)	1.9 (1.5-2.4)	1.1 (0.8-1.5)

*Adjusted for age group, gender, and history of specific morbidities included in the CCI.
Abbreviations: CI, confidence interval; RR, relative risk

Supplementary Table 2. Characteristics of acute medical patients with and without serum sodium measurement at hospital admission.

	Hyponatremia <135 mmol/l (n = 41,803)	**Normonatremia 135-145 mmol/l** (n = 207,688)	**No admission serum sodium measurement** (n=25,224)
Median age (IQR)	69 (57-80)	61 (44-75)	56 (38-71)
Female gender	22,077 (52.8)	103,232 (49.7)	12,664 (50.2)
Comorbidity level			
Low (CCI score 0)	19,338 (46.3)	123,339 (59.4)	15,767 (62.5)
Medium (CCI score 1-2)	15,198 (36.4)	61,658 (29.7)	6,885 (27.3)
High (CCI score >2)	7,267 (17.4)	22,691 (10.9)	2,572 (10.2)
Specific pre-existing morbidity			
Myocardial infarction	2,612 (6.3)	11,970 (5.8)	1,183 (4.7)
Congestive heart failure	2,574 (6.1)	9,182 (4.4)	848 (3.4)
Peripheral vascular disease	3,154 (7.5)	10,447 (5.0)	1,076 (4.3)
Cerebrovascular disease	4,542 (10.9)	17,730 (8.5)	1,784 (7.1)
Dementia	444 (1.1)	2,044 (1.0)	164 (0.7)
Chronic pulmonary disease	5,438 (13.0)	21,644 (10.4)	2,362 (9.4)
Connective tissue disease	1,827 (4.4)	7,362 (3.5)	908 (3.6)
Ulcer disease	3,147 (7.5)	10,435 (5.0)	1,140 (4.5)
Mild liver disease	1,238 (3.0)	2,652 (1.3)	431 (1.7)
Moderate/severe liver disease	388 (0.9)	685 (0.3)	108 (0.4)
Diabetes I and II	4,109 (9.8)	12,452 (6.0)	1,430 (5.7)
Diabetes with complications	2,181 (5.2)	6,240 (3.0)	714 (2.8)
Hemiplegia	253 (0.6)	880 (0.4)	112 (0.4)
Moderate/severe renal disease	1,210 (2.9)	4,682 (2.3)	610 (2.4)
Malignant tumor	5,669 (13.6)	18,728 (9.0)	2,151 (8.5)
Leukaemia	169 (0.4)	724 (0.4)	93 (0.4)
Lymphoma	464 (1.1)	1,458 (0.7)	235 (0.9)
Metastatic cancer	1,026 (2.5)	2,468 (1.2)	382 (1.5)
AIDS	58 (0.1)	190 (0.1)	28 (0.1)
Primary discharge diagnosis			
Pneumonia	3,814 (9.1)	8,915 (4.3)	600 (2.4)
Sepsis	891 (2.1)	1,482 (0.7)	100 (0.4)
Other infections	6,856 (16.4)	19,571 (9.4)	1,413 (5.6)
Stroke	905 (2.2)	7,008 (3.4)	449 (1.8)
Acute ischemic heart disease	2,029 (4.9)	10,548 (5.1)	1,088 (4.3)
Congestive heart failure	617 (1.5)	2,627 (1.3)	187 (0.7)
Other cardiovascular disease	3,058 (7.3)	25,096 (12.1)	2,170 (8.6)
Respiratory disease (excl. pneumonia)	1,884 (4.5)	8,136 (3.9)	713 (2.8)
Liver disease	573 (1.4)	651 (0.3)	122 (0.5)
Other gastrointestinal disease	1,503 (3.6)	5,734 (2.8)	709 (2.8)
Kidney disease	559 (1.3)	1,345 (0.7)	167 (0.7)
Other urogenital disease	100 (0.2)	494 (0.2)	51 (0.2)
Diabetes	1,622 (3.9)	2,594 (1.3)	239 (1.0)
Hypothyroidism	19 (0.1)	115 (0.1)	13 (0.1)
Hyperthyroidism	36 (0.1)	520 (0.3)	72 (0.3)
Hyponatremia and hypo-osmolality	729 (1.7)	18 (0.0)	20 (0.1)
Other endocrine disease	1,480 (3.5)	3,640 (1.8)	362 (1.4)
Neurologic disease	1,083 (2.6)	10,196 (4.9)	1,246 (4.9)
Muscle/connective tissue disease	1,091 (2.6)	7,457 (3.6)	943 (3.7)
Cancer	1,371 (3.3)	3,507 (1.7)	448 (1.8)
Observation for suspected disease	2,863 (6.9)	30,100 (14.5)	3,676 (14.6)
Other	8,720 (20.9)	57,934 (27.9)	10,435 (41.4)

Values are expressed as numbers (percentage) unless otherwise indicated.
Abbreviations: AIDS, acquired immunodeficiency syndrome; CCI, Charlson Comorbidity Index; IQR, Interquartile range;

Supplementary Table 3. Thirty-day and 1-year cumulative mortality and RRs after excluding patients without a serum sodium measurement at hospital admission.

Serum sodium concentration (mmol/l)	30-day mortality				1-year mortality			
	Death (n/N)	Cumulative mortality (95% CI)	Crude RR (95% CI)	Adjusted RR* (95% CI)	Death (n/N)	Cumulative mortality (95% CI)	Crude RR (95% CI)	Adjusted RR* (95% CI)
135-145	7024/204,071	3.5 (3.4-3.5)	1.0 (ref.)	1.0 (ref.)	20529/204,071	10.5 (10.4-10.7)	1.0 (ref.)	1.0 (ref.)
130-134.9	2,133/29,287	7.3 (7.0-7.6)	2.1 (2.0-2.2)	1.4 (1.3-1.5)	5,715/29,287	20.2 (19.8-20.7)	1.9 (1.9-2.0)	1.3 (1.3-1.4)
125-129.9	881/ 8,170	10.0 (9.4-10.7)	3.0 (2.7-3.1)	1.7 (1.6-1.9)	1,967/8,170	24.7 (23.8-25.7)	2.4 (2.3-2.5)	1.4 (1.4-1.5)
120-124.9	266/2,573	10.4 (9.2-11.6)	3.0 (2.7-3.4)	1.7 (1.5-2.0)	617/2,573	24.3 (23.0-26.4)	2.4 (2.2-2.5)	1.4 (1.3-1.5)
<120	170/1,773	9.6 (8.3-11.1)	2.8 (2.4-3.2)	1.3 (1.1-1.5)	412/1,773	23.9 (22.0-26.0)	2.3 (2.1-2.5)	1.3 (1.1-1.4)

*Adjusted for age group, gender, and specific comorbidities included in the Charlson Comorbidity Index.
Abbreviations: CI, confidence interval; RR, relative risk

Supplementary Table 4. Thirty-day adjusted RR stratified by primary discharge diagnoses, Charlson Comorbidity Index morbidities, and serum sodium concentration level.

	Total n (cumulative mortality %)	Adjusted RR* (95% CI) according to serum sodium concentration (mmol/l)				
		135-145	130-134.9	125-129.9	120-124.9	<120
Primary discharge diagnosis						
Infections	43,643 (5.5)	1.0 (ref.)	1.0 (0.9-1.1)	1.3 (1.1-1.5)	1.5 (1.2-2.0)	1.3 (0.9-2.0)
Pneumonia	13,329 (8.3)	1.0 (ref.)	0.9 (0.7-1.0)	0.9 (0.7-1.2)	1.4 (0.9-2.1)	1.7 (0.9-2.9)
Sepsis	2,473 (21.1)	1.0 (ref.)	0.9 (0.7-1.1)	1.2 (0.9-1.6)	1.3 (0.7-2.3)	1.9 (1.2-3.0)
Other infections	27,841 (2.7)	1.0 (ref.)	1.2 (1.0-1.4)	1.7 (1.3-2.2)	2.0 (1.3-3.2)	0.9 (0.4-2.1)
Cardiovascular disease	55,782 (6.5)	1.0 (ref.)	1.4 (1.2-1.5)	1.6 (1.4-1.9)	1.9 (1.5-2.4)	1.6 (1.1-2.4)
Stroke	8,362 (14.7)	1.0 (ref.)	1.1 (0.9-1.3)	1.2 (0.9-1.7)	1.6 (0.9-2.7)	0.8 (0.3-2.0)
Acute ischemic heart disease	13,665 (6.5)	1.0 (ref.)	1.4 (1.2-1.7)	1.8 (1.4-2.4)	1.6 (0.9-2.7)	2.1 (1.1-3.9)
Congestive heart failure	3,431 (10.5)	1.0 (ref.)	1.4 (1.0-1.8)	1.7 (1.1-2.5)	1.7 (0.9-3.1)	2.1 (0.9-5.0)
Other cardiovascular disease	30,324 (3.8)	1.0 (ref.)	1.9 (1.5-2.2)	2.4 (1.8-3.1)	2.8 (1.9-4.3)	1.9 (0.9-3.8)
Respiratory disease (excl. pneumonia)	10,733 (8.8)	1.0 (ref.)	1.2 (1.0-1.4)	1.4 (1.1-1.9)	2.1 (1.4-3.0)	2.9 (1.9-4.3)
Gastrointestinal disease	9,292 (6.2)	1.0 (ref.)	1.5 (1.2-1.9)	2.6 (2.1-3.4)	2.1 (1.4-3.3)	3.5 (2.2-5.6)
Liver disease	1,346 (14.9)	1.0 (ref.)	1.1 (0.8-1.6)	1.8 (1.3-2.6)	1.9 (1.2-3.1)	2.6 (1.5-4.6)
Other gastrointestinal disease	7,946 (4.7)	1.0 (ref.)	1.5 (1.2-2.0)	2.4 (1.7-3.3)	1.1 (0.5-2.4)	2.4 (1.2-5.1)
Urogenital disease	2,716 (7.0)	1.0 (ref.)	1.1 (0.8-1.7)	2.0 (1.3-3.0)	2.7 (1.3-5.4)	0.1 (0.0-1.2)
Kidney disease	2,071 (8.8)	1.0 (ref.)	0.9 (0.6-1.4)	2.1 (1.4-3.1)	2.8 (1.8-4.6)	0.2 (0.0-2.5)
Other Urogenital diseases	645 (1.3)	1.0 (ref.)	NA	NA	NA	NA
Endocrine disease	11,479 (3.7)	1.0 (ref.)	1.0 (0.8-1.3)	0.9 (0.6-1.4)	0.7 (0.4-1.2)	0.4 (0.2-0.8)
Hyponatremia and hypo-osmolality	767 (2.2)	1.0 (ref.)	NA	0.3 (0.0-2.6)	0.2 (0.0-1.9)	0.2 (0.0-1.2)
Other endocrine disease	10,712 (3.8)	1.0 (ref.)	1.0 (0.8-1.3)	1.0 (0.7-1.5)	1.0 (0.5-1.9)	0.4 (0.1-1.1)
Neurologic disease	12,525 (1.4)	1.0 (ref.)	1.3 (0.7-2.3)	2.1 (1.0-4.4)	1.4 (0.3-7.2)	NA
Muscle and connective tissue disease	9,491 (0.7)	1.0 (ref.)	1.7 (0.6-4.9)	3.4 (0.7-15.9)	NA	NA
Cancer	5,326 (19.3)	1.0 (ref.)	1.4 (1.3-1.6)	1.5 (1.2-1.8)	1.6 (1.1-2.4)	1.9 (1.2-3.0)
Observation for suspected disease	36,639 (1.2)	1.0 (ref.)	1.9 (1.4-2.5)	3.2 (2.2-4.8)	1.8 (0.7-4.9)	2.1 (0.6-7.8)
Other	77,089 (2.4)	1.0 (ref.)	1.7 (1.5-2.0)	2.2 (1.8-2.6)	1.9 (1.3-2.7)	1.6 (1.0-2.7)
Specific preexisting morbidity						
Myocardial infarction	15,765 (7.4)	1.0 (ref.)	1.2 (1.0-1.4)	1.7 (1.3-2.2)	2.2 (1.5-3.2)	1.0 (0.4-2.2)
Congestive heart failure	12,604 (10.7)	1.0 (ref.)	1.3 (1.2-1.5)	1.8 (1.5-2.2)	1.6 (1.0-2.4)	1.2 (0.6-2.3)
Peripheral vascular disease	14,677 (8.8)	1.0 (ref.)	1.1 (1.0-1.3)	1.7 (1.3-2.0)	1.4 (0.9-2.1)	0.9 (0.5-1.8)
Cerebrovascular disease	24,056 (8.2)	1.0 (ref.)	1.1 (1.0-1.2)	1.5 (1.3-1.8)	1.2 (0.8-1.7)	0.7 (0.3-1.3)
Dementia	2,652 (14.3)	1.0 (ref.)	1.0 (0.7-1.4)	1.2 (0.7-2.1)	1.5 (0.7-3.2)	1.2 (0.4-3.4)
Chronic pulmonary disease	29,444 (6.2)	1.0 (ref.)	1.2 (1.1-1.4)	1.6 (1.3-1.9)	1.7 (1.2-2.3)	1.4 (0.9-2.1)
Connective tissue disease	10,097 (5.2)	1.0 (ref.)	1.4 (1.1-1.8)	1.9 (1.4-2.7)	1.5 (0.8-2.9)	0.7 (0.2-2.4)
Ulcer disease	14,722 (7.3)	1.0 (ref.)	1.3 (1.1-1.5)	1.7 (1.3-2.1)	1.6 (1.1-2.3)	1.1 (0.6-2.1)
Mild liver disease	4,321 (7.3)	1.0 (ref.)	2.1 (1.6-2.8)	3.0 (2.2-4.2)	2.2 (1.3-3.8)	2.1 (1.0-4.1)
Moderate/severe liver disease	1,181 (11.2)	1.0 (ref.)	3.1 (1.9-5.1)	4.3 (2.7-6.8)	2.7 (1.2-5.9)	5.2 (2.4-11.4)
Diabetes I and II	17,991 (5.9)	1.0 (ref.)	1.1 (0.9-1.3)	1.5 (1.1-1.9)	1.6 (1.0-2.4)	0.7 (0.3-1.8)
Diabetes with complications	9,135 (6.3)	1.0 (ref.)	0.9 (0.7-1.1)	1.5 (1.1-2.1)	1.6 (0.9-2.7)	1.0 (0.3-3.0)
Hemiplegia	1,245 (5.2)	1.0 (ref.)	2.9 (1.5-5.8)	0.1 (0.0-1.2)	0.7 (0.1-7.1)	0.7 (0.1-7.4)
Moderate/severe renal disease	6,502 (8.1)	1.0 (ref.)	1.4 (1.1-1.8)	1.6 (1.1-2.3)	0.8 (0.3-2.5)	0.7 (0.1-4.5)
Malignant tumor	26,548 (10.0)	1.0 (ref.)	1.6 (1.4-1.7)	2.0 (1.7-2.2)	1.8 (1.4-2.3)	1.1 (0.7-1.6)
Leukaemia	986 (7.3)	1.0 (ref.)	1.6 (0.6-3.9)	1.3 (0.2-8.3)	NA	NA
Lymphoma	2,157 (6.2)	1.0 (ref.)	1.3 (0.8-2.0)	0.7 (0.2-1.8)	2.5 (0.8-7.2)	0.3 (0.0-5.6)
Metastatic cancer	3,876 (17.8)	1.0 (ref.)	1.6 (1.3-1.9)	1.9 (1.5-2.4)	2.0 (1.3-3.1)	0.9 (0.3-2.7)
AIDS	276 (1.5)	1.0 (ref.)	NA	NA	NA	NA
Charlson Comorbidity Index levels[§]						
Low CCI	158,444 (2.4)	1.0 (ref.)	1.3 (1.2-1.5)	1.5 (1.3-1.7)	1.6 (1.3-2.0)	1.6 (1.2-2.1)
Medium CCI	83,741 (5.6)	1.0 (ref.)	1.3 (1.2-1.4)	1.6 (1.4-1.8)	1.6 (1.3-1.9)	1.0 (0.7-1.3)
High CCI	32,530 (10.0)	1.0 (ref.)	1.4 (1.3-1.6)	1.9 (1.6-2.1)	1.7 (1.3-2.2)	1.1 (0.8-1.7)

[*] Adjusted for age group, gender, and Charlson Comorbidity Index level, if not otherwise specified

[§] Adjusted for age group and gender

NA: Not applicable due to few events

Paper III

Preadmission Diuretic Use and Mortality in Patients Hospitalized with Hyponatremia: A propensity-score matched cohort study

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ABSTRACT

Importance: While diuretics are a leading cause of hyponatremia, the prognostic impact of diuretic use in patients with hyponatremia remains unknown.

Objective: To examine the impact of diuretic use on 30-day mortality among patients hospitalized with hyponatremia.

Design: Cohort study utilizing population-based medical and administrative registries. Eligible patients were identified from 2006 – 2012 and followed for 30 days.

Setting: Patients admitted to departments of internal medicine, Western Denmark (cumulative population of 2.2 million)

Participants: 46,157 first-time acute admissions with serum sodium <135 mmol/l measured within 24 hours after hospitalization.

Exposure: Preadmission diuretic use. Patients were categorized as current users (new and long-term) or former users depending on whether the last prescription for diuretics was redeemed within 90 days or 91-365 days before hospitalization, and as non-users if they had not redeemed a prescription for diuretics within 1 year before hospitalization.

Main outcomes and measures: 30-day mortality; cumulative mortality and relative risk with 95% confidence interval (CI), controlled for demographic characteristics, previous morbidity, renal function and comedications; divided by diuretic type; analyses repeated after propensity-score matching.

Results: 30-day mortality was 11.4% among the 14,635 current diuretic users and 6.2% among the 27,431 non-users, yielding an adjusted relative risk of 1.4 (95% CI: 1.2-1.5). Among new and long-term users, the adjusted relative risk was 1.7 (95% CI: 1.5-2.0) and 1.3 (95% CI: 1.2-1.4), respectively. Users of loop diuretics, potassium-sparing diuretics and diuretic polytherapy had adjusted relative risks of 1.6 (95% CI: 1.4-1.8), 1.6 (95% CI: 1.2-2.2) and 1.6 (95% CI: 1.4-1.8), respectively. While the adjusted relative risk was

1.0 (95% CI: 0.9-1.2) for thiazide users overall, the adjusted relative risk was 1.5 (95% CI: 1.2-2.0) for new users of thiazides. Propensity-score analyses confirmed the results.

Conclusions and Relevance: Diuretic use, particularly if newly initiated, is a prognostic factor in patients admitted with hyponatremia.

INTRODUCTION

Diuretics are the most frequently reported cause of drug-induced hyponatremia.[1-5] They are a mainstay treatment for hypertension and fluid retention in congestive heart failure, chronic kidney disease and cirrhosis -- conditions in which hyponatremia is known to predict increased mortality.[6-9]

Three recent studies have reported that the mortality risk associated with severe hyponatremia (<120 mmol/l) is lower than the risk associated with milder degrees of hyponatremia.[10-12] One proposed explanation for this paradox is that severe hyponatremia is medication-induced rather than caused by severe illness.[11] In a single-center study among 105 patients with a serum sodium measurement <125mmol/l during hospitalization, Clayton *et al*. observed a lower mortality rate in patients with hyponatremia associated with thiazide use, compared to patients with hyponatremia due to either congestive heart failure or liver disease.[13] Similar results were reported by Leung *et. al.*. [3] However, most existing studies are limited by their focus on thiazide use.[3,11] As well, none were designed or sufficiently powered to examine mortality differences among different diuretics,[3,11,13] and none accounted for confounding by indication.[3,11,13] The prognostic impact of diuretic use on hyponatremia-associated mortality therefore remains uncertain. Prescriptions for diuretic drugs are among the most frequently redeemed at Danish community pharmacies.[14,15] Given the high prevalence of diuretic use and hyponatremia, identifying patient subgroups at increased mortality risk has important public health implications. It could improve our understanding of the effects of hyponatremia and motivate studies on alternative treatment strategies for diuretic users with hyponatremia.

We therefore investigated the association between preadmission diuretic use and mortality in acute medical patients with hyponatremia, while also examining the potential different effect across clinical subgroups of underlying morbidities, reason for hospitalization, renal function and hyponatremia severity.

METHODS

Setting

We conducted this population-based cohort study among 354,045 patients acutely admitted to departments of internal medicine in Western Denmark from 2006 through 2012, using prospectively collected data from administrative registries and medical databases maintained by the Danish National Health Service. The cumulative population of 2.2 million Danish residents in the study area during 2006-2012 received universal tax-supported medical care and full or partial reimbursement of most prescription medications. Upon birth or immigration, all Danish residents are issued a 10-digit Danish Civil Registration (CPR) Number.[16] This unique identifier allows for individual-level linkage between all Danish registries, enabling us to obtain comprehensive medical histories for study participants and virtually complete follow-up.[16] To ensure availability of complete prescription and laboratory data, participants were required to reside in the study area for at least 2 years to be eligible for the study.

The study was approved by the Danish Data Protection Agency (Record no. 2013-41-1924).

Study Population

We identified all patients ≥15 years of age with a first-time acute admission to eighty-four departments of internal medicine within twenty-two hospitals in Western Denmark, using the Danish National Patient Registry (DNPR). This nationwide registry contains information on all non-psychiatric hospitalizations since 1977 and visits to emergency departments and outpatient specialist clinics since 1995.[17] An admission was considered acute if registered as such,[18] and if the patient had no surgical, oncologic, gynecologic or obstetric hospitalizations within 30 days before the current admission. For each study patient, we also obtained information on serum sodium measurements performed within 24 hours of hospital admission through linkage to a regional laboratory database (LABKA). Test results for all blood samples drawn from inpatients and outpatients and submitted for analysis at hospital laboratories in Western Denmark are stored in a hospital laboratory information system. From this information system, data including the Nomenclature, Properties, and Units (NPU) code, time and date of analysis, test result and measurement

unit are electronically transferred to the LABKA database for research purposes.[19] Virtually complete data on serum sodium measurements are available in the LABKA database from 2006 through 2012 for Western Denmark's Central Region and from 2006 through 2011 for its Northern Region. Our study cohort was comprised of patients identified as having hyponatremia upon hospital admission (serum sodium <135mmol/l).[20]

Preadmission diuretic use

The Danish National Health Service Prescription Database (DNHSPD) contains data on all prescriptions for reimbursable drugs, including all diuretic agents, dispensed by community pharmacies in Denmark since 2004. The information includes the name and anatomical therapeutic chemical (ATC) classification code of the dispensed drug, date of dispensing and cumulative dose.[21] In Denmark, diuretics are only available by prescription.

Patients qualified as *current* diuretic users if they redeemed a prescription for diuretics within 90 days before the current hospitalization (see eAppendix in the Supplement for ATC codes), as *former* users if their last prescription was redeemed within 91-365 days before the current hospitalization, and as *non-users* if they had not redeemed a prescription for diuretics within 1 year before the current hospitalization. We based the 90-day exposure window on the most commonly dispensed packet size.[22] In order to account for prevalent user bias, current users were categorized as *new users* if their first prescription for a diuretic was redeemed within 90 days of the current admission, or *long-term users* if they had also previously redeemed such a prescription.[23] Finally, we categorized diuretic use according to generic type as follows: monotherapy with either thiazides, other low-ceiling diuretics (primarily indapamide and clopamide), loop diuretics or potassium-sparing diuretics, and diuretic polytherapy (see eAppendix).

Covariates

Besides gender and age derived from the CPR number, we obtained from the DNPR, the DNHSPD and the LABKA database baseline patient characteristics for use in multivariate regression and propensity score

models. For all hospital and outpatient clinic contacts, the DNPR contains one primary and one or more secondary diagnoses, coded according to the *International Classification of Diseases* (ICD), 8th revision (ICD-8) during 1977-1994, and 10th revision (ICD-10) starting in 1994.[17] We used DNPR data to ascertain each individual's history of specific preadmission morbidities (congestive heart failure, myocardial infarction, hypertension, chronic liver and respiratory disease, diabetes and malignant disease), and comorbidity level based on Charlson Comorbidity Index (CCI) scores. We defined three levels of comorbidity (low = CCI score 0, medium = CCI score 1-2, high = CCI score>2). We used the estimated glomerular filtration rate (eGFR) calculated by the "Modification of Diet in Renal Disease (MDRD)" formula to evaluate baseline renal function.[24] For this purpose, we obtained information from the LABKA database on the latest serum creatinine concentration, measured within one year and one week before admission. If no baseline creatinine value was available, eGFR was assumed to be normal (>90 ml/min/1.73m^2). From the DNHSPD, we retrieved information on concurrent use (prescriptions redeemed within 90 days of the current admission) of ACE-inhibitors, angiotensin II-antagonists, β-blockers, hydralazine, nitrates, calcium-channel blockers, anti-adrenergic drugs, antidepressants, anti-epileptic drugs, opioids, nonsteroidal anti-inflammatory drugs and acetaminophen. Finally, we retrieved information from the DNPR specifically related to the current hospitalization, *i.e.* the primary discharge diagnosis and hyponatremia-associated diagnosis codes (see eAppendix).

Statistical analysis

We presented baseline patient characteristics and characteristics of the current hospitalization for current diuretic users, former users and non-users in contingency tables. To account for bias introduced by nonrandom assignment of preadmission diuretic therapy we also assembled and presented propensity-score matched cohorts. The propensity score is each patient's predicted probability of being a diuretic user. We computed the propensity scores using multivariate logistic regression based on the patient's observed baseline characteristics (*i.e.,* gender, age, concurrent medication, preexisting morbidities, comorbidity level and eGFR). We used 1:1 matching, without replacement, of each diuretic user to a non-

user with an equal propensity score (maximum caliper range of ± 0.025), thereby creating two groups with an equal distribution of covariates. Matching was possible for 12,075 diuretic users (81.9%). Balancing of covariates was deemed adequate, based on absolute standardized differences below 10% (eFigure 1 in Supplement).

The Danish Civil Registration System tracks vital and migration status for all Danish residents and is updated daily.[25] We followed patients up to 30 days after hospital admission, and computed 30-day mortality for current diuretic users, former users and non-users using the Kaplan-Meier method (1-survival function) before and after propensity score matching. We compared mortality using a pseudo-value regression model, allowing for direct comparison of incidence functions in right-censored data,[26] estimating the crude and adjusted relative risk (RR) of death with 95% confidence intervals (CIs), accounting for matched pairs in the propensity-score matched cohort. [27] We also estimated RRs based on type of diuretic treatment and compared mortality risk in new users to that of long-term users for each diuretic type. To detect potential effect measure modification, we performed stratified analyses across clinical subgroups, based on age, gender, specific previous morbidities (including possible indications for diuretic treatment), baseline eGFR, primary diagnosis for the current hospitalization and severity of admission hyponatremia, after recalculating propensity scores within each of these subgroups to ensure adequate balancing of covariates.

We evaluated the impacts of excluding patients with no sodium measurement upon admission and of classifying patients with no baseline serum creatinine as having normal eGFR in two sensitivity analyses. First, we conducted a complete case analysis, including only patients with information on all covariates. Second, we performed multiple imputations, utilizing the pattern of missing and observed data in all first-time acute admissions to departments of internal medicine in the study period, to predict admission serum sodium and baseline serum creatinine for patients missing this information. Apart from the covariates listed in Table 1 (excluding CCI level), we included death and the Nelson-Aalen cumulative baseline hazard

in our multiple imputation model. We generated twenty imputed datasets and estimated the average RR, taking into account between- and within-imputation variation.[28]

Data analyses were performed using STATA statistical software version 12 (Stata Corp, College Station, TX, USA).

RESULTS

Baseline characteristics and diuretic prescriptions

Among the 46,157 hyponatremic patients included in the study, 14,635 (31.7%) redeemed a prescription for diuretics within 90 days before hospitalization. Of these, 89% were long-term users (n=12,994). Table 1 presents baseline patient characteristics. A considerably higher proportion of current users than non-users were aged ≥ 80 years (41.4% vs. 15.6%) and had CCI scores >2 (25.8% vs. 11.5%). Congestive heart failure and hypertension in particular were more common among current users than among non-users, corresponding well with common concurrent cardiovascular medication use among diuretic users. Thirty-five percent of long-term users had a baseline eGFR <60ml/min/1.73m^2, compared to 18.4% of new users and 8.1% of non-users. The distribution of covariates among former diuretic users resembled that of current diuretic users.

The majority of new users received only one diuretic agent (86.3%), with thiazides representing the most frequently prescribed drug (46.0%). Long-term users were more likely than new users to receive diuretic polytherapy (33.3% vs. 13.7%). Baseline patient characteristics and characteristics of current hospitalization by diuretic type are presented in eTable 1 and 2 (see Supplement). Thiazide users had lower morbidity burden and were less likely to have impaired renal function (CCI score ≤2= 85.3%; eGFR <60ml/min/1.73m^2= 20.4%), compared to users of loop diuretics (CCI score ≤2 = 64.5%; eGFR

<60ml/min/1.73m^2= 40.9%) and diuretic polytherapy (CCI score ≤2 = 66.0%; eGFR <60ml/min/1.73m^2= 44.2%).

Characteristics of the current hospitalization

Table 2 displays characteristics associated with the current hospitalization. Compared to non-users, current users more often had a primary diagnosis of cardiac failure and were less likely to receive a primary diagnosis of pneumonia or "other infection". New users also were more likely to have a cirrhosis diagnosis. Otherwise, there were only small differences in the diagnoses recorded for users and non-users. No difference in length of hospital stay was observed. Severe hyponatremia (serum sodium <120mmol/l) was more common among new users than among non-users (9.5% vs. 3.5%), and slightly more common among patients receiving thiazide monotherapy (7.0%) than among those receiving diuretic polytherapy (6.0%), potassium-sparing (5.3%) or loop diuretic monotherapy (3.7%) (see eTable 2 in the Supplement).

30-day mortality

Within 30 days after admission, 11.1% of current diuretic users and 6.2% of non-users died, corresponding to a crude RR of death of 1.8 (95% CI: 1.7-1.9) (Figure 1, Table 3). The mortality risk among current users remained increased after adjustment for age, gender, previous morbidities, concurrent drug use, eGFR and hyponatremia severity [adjusted RR (aRR)= 1.3 (95% CI: 1.2-1.4)]. For new and long-term users aRRs were 1.7 (95% CI: 1.4-1.9) and 1.3 (95% CI: 1.2-1.4), respectively. Former users had an aRR of 1.2 (95% CI: 1.0-1.3). The highest mortality risk was observed in users of loop diuretics [aRR= 1.6 (95% CI: 1.4-1.8)], potassium-sparing diuretics [aRR= 1.6 (95% CI: 1.2-2.1)] and diuretic polytherapy [aRR= 1.5 (95% CI: 1.3-1.7)]. Overall thiazide use was not associated with increased risk [aRR= 1.0 (95% CI: 0.9-1.1)]. Generally, new users had an increased mortality risk compared to long-term users. This applied also for new thiazide users [aRR of 1.5 (95% CI: 1.2-2.0) compared to long-term thiazide users] (data not shown).

Propensity-score matched analyses (Table 3), complete case analyses excluding patients without baseline creatinine, and multiple imputation analyses (see eTable 3 and 4 in the Supplement) yielded virtually the

same results. Very few patients emigrated or were otherwise lost to follow up within 30 days of hospital admission (n=35).

Mortality risk according to clinical subgroups

Current diuretic use was associated with increased risk of death at 30 days following hospital admission across most propensity-score matched subgroups (Figure 2). Diuretic use had the greatest impact on mortality in patients with a history of chronic liver disease [RR = 2.4 (95% CI: 1.7-3.4)], diabetes with complications [RR = 1.9 (95% CI: 1.2-2.9)] and myocardial infarction [RR = 1.8 (95% CI: 1.3-2.6)], and in patients diagnosed with sepsis or endocrine disease other than hyponatremia and hypoosmolality [RR = 1.7 (95% CI: 1.2-2.5) and RR = 1.7 (95% CI: 1.0-2.8), respectively]. The impact of current diuretic use on mortality tended to decrease with increasing age, but to increase with increasing CCI score. An almost identical pattern was seen among users of diuretic polytherapy (eFigure 2 in Supplement), while the risk decreased with increasing CCI level in loop diuretic users (eFigure 3 in Supplement). Again, mortality risk was increased across virtually all subgroups of current loop diuretics users and diuretic polytherapy users. An increased risk was observed even in loop diuretic and diuretic polytherapy users without previous history of congestive heart failure [RR of 1.8 (95% CI: 1.6-2.1) and 1.6 (95% CI: 1.5-1.9), respectively], no previous history of chronic liver disease [RR of 1.8 (95% CI: 1.6-2.0) and 1.5 (95% CI: 1.3-1.7), respectively], and in patients with normal baseline eGFR [RR of 1.1 (95% CI: 0.8-1.4) and 1.3 (95% CI: 1.0-1.7)]. Generally, use of thiazide diuretics was not associated with increased mortality risk across subgroups (eFigure 4 in Supplement).

CONCLUSIONS

We followed 46,157 patients hospitalized with hyponatremia and observed a overall negative prognostic impact of preadmission diuretic use on 30-day mortality. At particularly high risk were patients with newly initiated diuretic therapy regardsless of type. Both new and long-term use of loop diuretics, potassium-

sparing diuretics or diuretic polytherapy was associated with increased mortality risk. Our findings remained robust after accounting for important measured confounders, and after handling missing data by multiple imputation.

The observed high mortality risk among loop diuretic users is consistent with findings reported by Clayton *et al*. for 105 internal medicine and geriatric inpatients with severe hyponatremia <125mmol/l.[13] They observed increased odds of dying within 2 years after hospitalization among loop diuretic users (n=34), compared to the odds for the entire study population [age- and gender-adjusted odds ratio (OR) = 1.91 (95% CI: 0.80-4.56)]. While we found a null association for thiazide users overall, Clayton *et al.'s* study even suggested a "protective" effect of thiazide use (n=29), with an OR of 0.32 (95% CI: 0.12-0.82). A comparable incidence rate ratio of 0.41 (95% CI: 0.12-1.42) was reported by Leung *et al.* in a later study that used registry-based data to compare thiazide users to thiazide-non-users.[3] Through medical chart review, Chawla *et al.* compared 32 inpatients with serum sodium <110mmol/l surviving until discharge to 53 patients with serum sodium <120mol/l who died during hospitalization.[11] Thiazides or selective serotonin reuptake inhibitors were judged the sole cause of hyponatremia in 72% of survivors, while "significant acute progressive underlying illnesses", such as sepsis and acute kidney failure, were identified in all fatal cases. It is important to note that these studies had several limitations. Of particular importance is their inability to account for factors influencing prescribing patterns,[29] and the potential bias introduced by retrospective assessment of etiologic factors without blinding reviewers to the outcome.

Our use of prospectively collected data, obtained from population-based medical registries maintained under Denmark's universal healthcare system, allowed us to study the association between diuretic use and mortality in a large heterogeneous cohort likely to resemble the source population of patients with hyponatremia. In addition, the study benefitted from having access to comprehensive medical background assessment and virtually complete follow up. However, our study also had limitations. We lacked information on the actual timing of medication intake; non-adherence may have caused us to misclassify some non-users as users. As well, the 90-day window used to define current use,[22] may have caused us to

classify some current users as former users if they were prescribed larger packages. However, because of the prospective and independent registration of prescription data and vital status, such exposure misclassification would likely be non-differential with respect to outcome. Thus, it would bias our results towards unity and cannot explain the increased risks observed. To approximate the intention-to-treat approach of clinical trials, we did not include information on in-hospital or post-discharge medication. This may also have biased our estimates towards unity. Another concern is confounding by frailty, which occurs when patients, perceived by physicians to be near end of life, are less likely prescribed preventive medications, such as thiazides for hypertension, but more likely prescribed medications for immediate life-threatening conditions (for example furosemide for pulmonary edema) than other patients. [30,31] However, contrary to previous studies we did not find a protective effect of thiazides.[3,30] Finally, lack of detailed information on preadmission severity of congestive heart failure or liver disease may have reduced our ability to completely eliminate confounding by indication.

The indications for each type of diuretic are numerous, which could be an explanation for the difference in mortality risk by type of diuretic.[32,33] However, loop diuretics and polytherapy – but not thiazides – were associated with increased risk also in patients with no previous history of congestive heart failure, chronic liver disease or impaired renal function -- despite uniform baseline risk profile for measured variables obtained by propensity-score matching. This may suggest that the actions of the various diuretic agents, rather than the indication for treatment, underlie their effect on mortality. Considering the burst-like action and high potency of loop diuretics, it could be hypothesized that patients treated with these drugs may become more frail and susceptible to hypovolemic or hypotensive conditions.[33-35] Furthermore, new users had the highest mortality risk, which could indicate that such susceptibility is most prominent at drug initiation when efficacy is highest.[36-38] However, this also remains speculative. Studies examining the effect of diuretic treatment on mortality risk using a broader perspective are needed.

A large proportion of patients with severe hyponatremia were thiazides users. Given the null result associated with prevalent thiazide use, our findings may partly explain the lower mortality risk among

patients with severe hyponatremia compared to patients with milder degrees of hyponatremia observed in previous studies.[10-12] Our results should not be taken as an argument to discontinue diuretic treatment in patients hospitalized with hyponatremia. However, our study emphasizes that patients treated with these diuretics who have hyponatremia, are at substantially increased mortality risk.

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Data access statement

Louise Holland-Bill and Sinna Pilgaard Ulrichsen had full access to the data.

Conflict of interest statement

Jens Otto Lunde Jørgensen has received an unrestricted research grant from Otsuka Pharma Scandinavia AB; Louise Holland-Bill and Jens Otto Lunde Jørgensen have received lecture fees from Otsuka Pharma Scandinavia AB within the previous 3 years; Louise Holland-Bill, Christian Fynbo Christiansen, Sinna Pilgaard Ulrichsen and Henrik Toft Sørensen are employees at The Department of Clinical Epidemiology, Aarhus University Hospital. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding from companies in the form of research grants to (and administered by) Aarhus University; no other relationships or activities that could appear to have influenced the submitted work.

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Other contributors

None

Ethics committee approval

The study was approved by the Danish Data Protection Agency (Record no. 2013-41-1924). Informed consent from members of the study population is not required for register-based research in Denmark.

TABLES

Table 1. Characteristics of current diuretic users and non-users [overall and after propensity-score (PS) matching]

	Full cohort (n= 46,157)				PS-matched cohort (n=24,150)	
	Current users					
	New-users	Long-term users	Former users	Non users	Users	Non users
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Overall	1,751 (100)	12,884 (100)	4,091 (100)	27,431(100)	12,075 (100)	12,075 (100)
Age group (years)						
15-39	33 (1.9)	100 (0.8)	45 (1.1)	3,950 (14.4)	178 (1.5)	127 (1.1)
40-59	331 (18.9)	1,341 (10.4)	563 (13.8)	7,874 (28.7)	2,003 (16.6)	1,820 (15.1)
60-79	883 (50.4)	6,113 (47.4)	2,110 (51.6)	11,332 (41.3)	6,386 (52.9)	6,433 (53.3)
80+	504 (28.8)	5,330 (41.4)	1,373 (33.6)	4,275 (15.6)	3,508 (29.1)	3,695 (30.6)
Female gender	961 (54.9)	8,105 (62.9)	2,495 (61.0)	12,759 (46.5)	6,812 (56.4)	6,942 (57.5)
Concurrent drug use						
Ace-inhibitors	383 (21.9)	4,002 (31.1)	1,009 (24.7)	3,204 (11.7)	2,591 (21.5)	2,728 (22.6)
Angiotensin II antagonists	258 (14.7)	2,212 (17.2)	647 (15.8)	2,558 (9.3)	1,921 (15.9)	2,040 (16.9)
β-blockers	375 (21.4)	4,446 (34.5)	949 (23.2)	2,879 (10.5)	2,553 (21.1)	2,573 (21.3)
Nitrates	110 (6.3)	1,324 (10.3)	251 (6.1)	571 (2.1)	595 (4.9)	538 (4.5)
Calcium-channel blocker	352 (20.1)	3,412 (26.5)	880 (21.5)	2,798 (10.2)	2,425 (20.1)	2,450 (20.3)
Anti-adrenergic drugs	21 (1.2)	210 (1.6)	60 (1.5)	126 (0.5)	128 (1.1)	119 (1.0)
Antidepressants	342 (19.5)	3,039 (23.6)	756 (18.5)	4,344 (15.8)	2,498 (20.7)	2,535 (21.0)
Anti-epileptic drugs	92 (5.3)	756 (5.9)	223 (5.5)	1,554 (5.7)	734 (6.1)	744 (6.2)
Opioids	418 (23.9)	3,255 (25.3)	916 (22.4)	4,044 (14.7)	2,598 (21.5)	2,612 (21.6)
NSAIDs	313 (17.9)	1,956 (15.2)	559 (13.7)	3,604 (13.1)	1,877 (15.5)	1,888 (15.6)
Acetaminophen	433 (24.7)	3,977 (30.9)	983 (24.0)	3,479 (12.7)	2,758 (22.8)	2,774 (23.0)
Comorbidity level						
Low (CCI score=0)	700 (40.0)	3,933 (30.5)	1,527 (37.3)	15,465 (56.4)	4,774 (39.5)	4,761 (39.4)
Medium (CCI score 1-2)	700 (40.0)	5,493 (42.6)	1,643 (40.2)	8,813 (32.1)	4,969 (41.2)	4,995 (41.4)
High (CCI score>2)	351 (20.0)	3,458 (26.8)	921 (22.5)	3,153 (11.5)	2,332 (19.3)	2,319 (19.2)
Specific pre-existing diseases						
Congestive heart failure	90 (5.1)	2,191 (17.0)	381 (9.3)	576 (2.1)	592 (4.9)	553 (4.6)
Acute myocardial infarction	103 (5.9)	1,371 (10.6)	313 (7.7)	964 (3.5)	761 (6.3)	732 (6.1)
Hypertension	377 (21.5)	4,723 (36.7)	1,408 (34.4)	3,367 (12.3)	3,036 (25.1)	2,964 (24.5)
Chronic liver disease	93 (5.3)	540 (4.2)	168 (4.1)	646 (2.4)	483 (4.0)	496 (4.1)
Malignancy	310 (17.7)	1,747 (13.6)	623 (15.2)	3,057 (11.1)	1,830 (15.2)	1,838 (15.2)
Diabetes I and II	139 (7.9)	1,831 (14.2)	491 (12.0)	2,020 (7.4)	1,241 (10.3)	1,233 (10.2)
Diabetes with end-organ damage	65 (3.7)	1,090 (8.5)	264 (6.5)	922 (3.4)	607 (5.0)	603 (5.0)
Chronic pulmonary disease	226 (12.9)	2,372 (18.4)	638 (15.6)	2,643 (9.6)	1,712 (14.2)	1,667 (13.8)
Baseline eGFR						
>90 ml/min/1,73 m2	850 (48.5)	4,195 (32.6)	1,735 (42.4)	18,613 (67.9)	1,925 (15.9)	2,071 (17.2)
60-90 ml/min/1,73 m2	579 (33.1)	4,227 (32.8)	1,359 (33.2)	6,607 (24.1)	4,319 (35.8)	4,424 (36.6)
<60 ml/min/1,73 m2	322 (18.4)	4,462 (34.6)	997 (24.4)	2,211 (8.1)	5,831 (48.3)	5,580 (46.2)
Type of diuretic therapy*						
Diuretic monotherapy	1,511 (86.3)	8,588 (66.7)	NA	NA	2,409 (20.0)	NA
Thiazide diuretics	806 (46.0)	5,264 (40.9)	NA	NA	4,342 (36.0)	NA
Other low-ceiling diuretics	13 (0.7)	120 (0.9)	NA	NA	106 (0.9)	NA
Loop diuretic	615 (35.1)	2,846 (22.1)	NA	NA	1,985 (16.4)	NA
Potassium-sparing diuretics	77 (4.4)	358 (2.8)	NA	NA	288 (2.4)	NA
Diuretic polytherapy	240 (13.7)	4,296 (33.3)	NA	NA	2,409 (20.0)	NA

Data are presented as numbers (%)

Abbreviations: CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; NA, not applicable; NSAIDs, Nonsteroidal anti-inflammatory drugs

*Counted for current users only. In the propensity-score matched user category 2,695 were former users.

Table 2. Characteristics of the current hospitalization among current diuretic users and non-users [overall and after propensity-score (PS) matching]

	Full Cohort (n= 46,157)				PS- matched cohort (n=24,150)	
	Current users		Former users	Non users	Users	Non users
	New-users	Long-term users				
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Overall	1,751 (100)	12,884 (100)	4,091 (100)	27,431(100)	12,075 (100)	12,075 (100)
Admission sodium level						
130-134.9 mmol/l	1,038 (59.3)	8,502 (66.0)	2,711 (66.3)	20,128 (73.4)	7,846 (65.0)	8,482 (70.2)
125-129.9 mmol/l	382 (21.8)	2,802 (21.7)	900 (22.0)	4,934 (18.0)	2,608 (21.6)	2,345 (19.4)
120-124.9 mmol/l	167 (9.5)	890 (6.9)	288 (7.0)	1,460 (5.3)	923 (7.6)	739 (6.1)
<120 mmol/l	164 (9.4)	690 (5.4)	192 (4.7)	909 (3.3)	698 (5.8)	509 (4.2)
Median length of stay in days (IQR)	6 (2-11)	6 (2-11)	5 (2-10)	5 (2-9)	5 (2-10)	5 (2-11)
Primary discharge diagnosis for current hospitalization						
Pneumonia	118 (6.7)	1,117 (8.7)	376 (9.2)	2,653 (9.7)	1,035 (8.6)	1,113 (9.2)
Sepsis	33 (1.9)	319 (2.5)	71 (1.7)	588 (2.1)	264 (2.2)	275 (2.3)
Other infections	174 (9.9)	1,787 (13.9)	576 (14.1)	5,161 (18.8)	1,629 (13.5)	1,849 (15.3)
Stroke	30 (1.7)	271 (2.1)	103 (2.5)	570 (2.1)	281 (2.3)	301 (2.5)
Acute ischemic heart disease	55 (3.1)	538 (4.2)	182 (4.4)	1,357 (4.9)	488 (4.0)	583 (4.8)
Congestive heart failure	62 (3.5)	365 (2.8)	48 (1.2)	191 (0.7)	235 (1.9)	105 (0.9)
Other cardiovascular diseases	188 (10.7)	1,201 (9.3)	334 (8.2)	1,597 (5.8)	1,025 (8.5)	935 (7.7)
Respiratory disease (excl. pneumonia)	101 (5.8)	750 (5.8)	198 (4.8)	1,037 (3.8)	704 (5.8)	567 (4.7)
Gastrointestinal and liver disease	120 (6.9)	637 (4.9)	200 (4.9)	1,372 (5.0)	654 (5.4)	579 (4.8)
Urogenital disease	29 (1.7)	288 (2.2)	60 (1.5)	340 (1.2)	185 (1.5)	170 (1.4)
Hypoosmolality and hyponatremia	70 (4.0)	319 (2.5)	85 (2.1)	364 (1.3)	301 (2.5)	247 (2.0)
Other endocrine diseases	111 (6.3)	1,070 (8.3)	255 (6.2)	2,022 (7.4)	838 (6.9)	724 (6.0)
Cancer	72 (4.1)	362 (2.8)	135 (3.3)	920 (3.4)	407 (3.4)	466 (3.9)
Observation for suspected disease	108 (6.2)	820 (6.4)	312 (7.6)	1,896 (6.9)	817 (6.8)	922 (7.6)
Other	480 (27.4)	3,040 (23.6)	1,156 (28.3)	7,363 (26.8)	3,212 (26.6)	3,239 (26.8)
Hyponatremia-related diagnoses*						
Glucocorticoid deficiency	2 (0.1)	12 (0.1)	2 (0.0)	67 (0.2)	10 (0.1)	23 (0.2)
Mineralocorticoid deficiency	2 (0.1)	4 (0.0)	1 (0.0)	42 (0.2)	6,812 (56.4)	6,942 (57.5)
Hypothyroidism	14 (0.8)	162 (1.3)	38 (0.9)	180 (0.7)	113 (0.9)	123 (1.0)
SIADH	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Cerebral salt wasting	23 (1.3)	129 (1.0)	52 (1.3)	354 (1.3)	151 (1.3)	168 (1.4)
Cardiac failure	150 (8.6)	1,053 (8.2)	174 (4.3)	717 (2.6)	665 (5.5)	396 (3.3)
Gastroenteritis	49 (2.8)	436 (3.4)	139 (3.4)	1,195 (4.4)	373 (3.1)	455 (3.8)
Pancreatitis	6 (0.3)	46 (0.4)	25 (0.6)	188 (0.7)	55 (0.5)	61 (0.5)
Cirrhosis	78 (4.5)	192 (1.5)	72 (1.8)	301 (1.1)	274 (0.5)	111 (0.5)
Acute or chronic renal failure	47 (2.7)	660 (5.1)	146 (3.6)	551 (2.0)	392 (3.2)	317 (2.6)
Nephrotic syndrome	11 (0.6)	11 (0.1)	2 (0.0)	14 (0.1)	21 (0.2)	3 (0.0)
Nephropathy	4 (0.2)	18 (0.1)	6 (0.1)	21 (0.1)	16 (0.1)	13 (0.1)
Renal tubular acidosis	(0.0)	1 (0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Burn trauma	(0.0)	1 (0.0)	1 (0.0)	5 (0.0)	1 (0.0)	1 (0.0)
Other trauma	51 (2.9)	351 (2.7)	150 (3.7)	706 (2.6)	375 (3.1)	356 (2.9)

Data are presented as numbers (%), if not stated otherwise.

Abbreviations: IQR, interquartile range; PS, propensity score; SIADH, syndrome of inappropriate antidiuretic hormone secretion

*Recorded either as a primary or secondary discharge diagnosis.

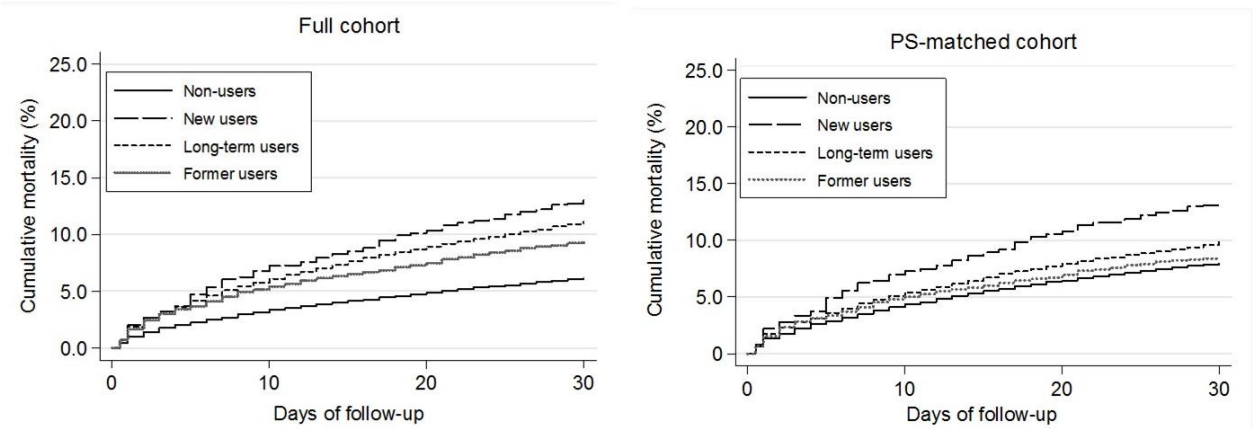
Table 3. 30-day mortality and relative risk (RR) of death in diuretic users compared to non-users.

	Full cohort				Propensity score matched		
	Events/N	Cumulative mortality % (95% CI)	Crude RR (95%CI)	Adjusted RR* (95%CI)	Events/N	Cumulative mortality % (95% CI)	RR (95%CI)
30 day mortality							
Overall							
Non-users	1,681/27,431	6.2 (5.9-6.4)	1.0 (Ref.)	1.0 (Ref.)	957/12,075	8.0 (7.5-8.5)	1.0 (Ref.)
Former users	380/4,091	9.3 (8.5-10.2)	1.5 (1.4-1.7)	1.2 (1.0-1.3)	250/2,945	8.5 (7.6-9.6)	1.1 (0.9-1.2)
Current users	1,620/14,635	11.1 (10.6-11.6)	1.8 (1.7-1.9)	1.3 (1.2-1.4)	948/9,130	10.4 (9.8-11.1)	1.3 (1.2-1.4)
New users	226/1,751	12.9 (11.5-14.6)	2.1 (1.8-2.4)	1.7 (1.4-1.9)	188/1,401	13.5 (11.8-15.4)	1.7 (1.5-2.0)
Long-term users	1,394/12,884	10.8 (10.3-11.4)	1.8 (1.6-1.9)	1.3 (1.2-1.4)	760/7,729	9.9 (9.2-10.5)	1.2 (1.1-1.4)
By diuretic type							
Diuretic monotherapy	1,008/10,099	10.0 (9.4-10.6)	1.6 (1.5-1.8)	1.2 (1.1-1.3)	636/6,721	9.5 (8.8-10.2)	1.2 (1.1-1.3)
Thiazide diuretics	456/6,070	7.5 (6.9-8.2)	1.2 (1.1-1.4)	1.0 (0.9-1.1)	302/4,342	7.0 (6.3-7.8)	0.9 (0.8-1.0)
Other low-ceiling diuretics	6/133	4.5 (2.1-9.8)	0.7 (0.3-1.6)	0.8 (0.3-1.7)	4/106	5.7 (2.6-12.2)	0.7 (0.3-1.6)
Loop diuretic	495/3,461	14.3 (13.2-15.5)	2.3 (2.1-2.6)	1.6 (1.4-1.8)	273/1,985	14.6 (13.1-16.2)	1.8 (1.6-2.1)
Potassium-sparing diuretics	51/435	11.7 (9.0-15.1)	1.9 (1.5-2.5)	1.6 (1.2-2.1)	34/288	13.6 (10.1-18.1)	1.7 (1.3-2.3)
Diuretic polytherapy	612/4,536	13.5 (12.6-14.6)	2.2 (2.0-2.4)	1.5 (1.3-1.7)	312/2,409	13.0 (11.7-14.4)	1.6 (1.5-1.8)

*Adjusted for age group, gender, previous morbidities, concurrent drug use, eGFR group and hyponatremia severity.
Abbreviations: CI, Confidence interval; eGFR, estimated glomerular filtration rate; RR, Relative risk

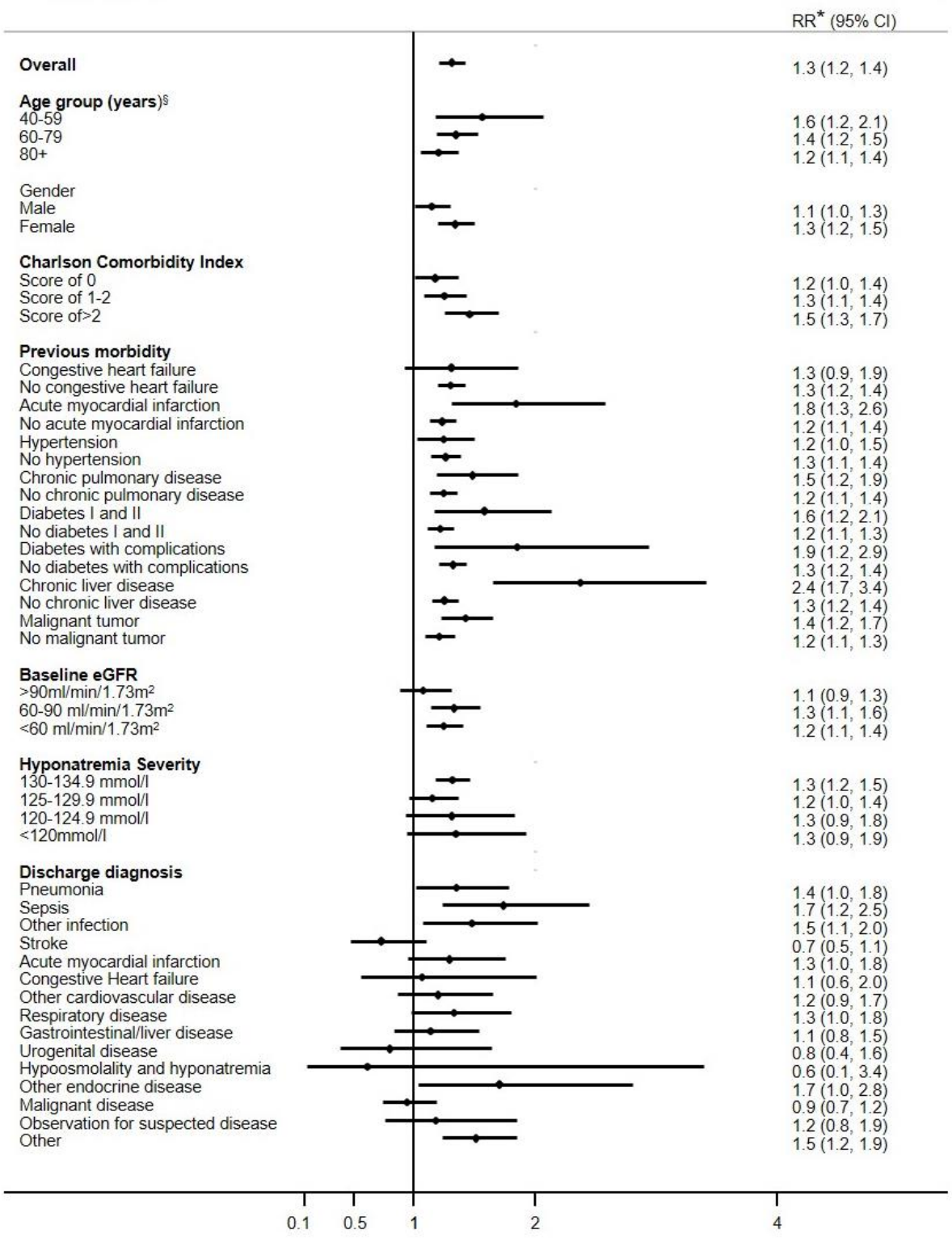
FIGURES

Figure 1. Cumulative 30-day mortality according to diuretic use in patients admitted to departments of internal medicine.



Abbreviation: PS, propensity score

Figure 2. Stratified 30-day RR comparing diuretic users to non-user (propensity score-matched cohort).



*Propensity score matching equates to multivariable adjustment
§ The subgroup of age 15-39 years had too few events to yield meaningful estimates.
Abbreviations: CCI, Charlson Comorbidity Score; CI, confidence interval; eGFR. Estimated glomerular filtration rate; RR, relative risk.

SUPPLEMENTARY ONLINE CONTENT

Holland-Bill L, Christiansen CF, Ulrichsen SP, Ring T, Jørgensen JOL, Sørensen HT. Preadmission Diuretic Use and Mortality in Patients Hospitalized with Hyponatremia: A propensity-score matched cohort study.

eAppendix. Codes used to identify diuretic users and covariates

eTable 1. Patient baseline characteristics by diuretic type

eTable 2. Characteristics of current hospitalization by diuretic type

eTable 3. 30-day mortality and relative risk (RR) of death in diuretic users compared to non-users based on complete case data.

eTable 4. 30-day mortality and relative risk in hyponatremic diuretic users and non-users based on multiple imputed data.

eFigure 1. Absolute standardized differences before and after matching for covariates used in the propensity score.

eFigure 2. Stratified 30-day RR comparing thiazide diuretic users to non-users (propensity score-matched cohorts)

eFigure 3. Stratified 30-day RR comparing loop diuretic users to non-users (propensity score-matched cohorts)

eFigure 4. Stratified 30-day RR comparing diuretic polytherapy users to non-users (propensity score-matched cohort

eAppendix. Codes used to identify diuretic users and covariates	
Covariate	**ICD-8, ICD-10 or ATC code**
Diuretic use (information on all prescriptions filled within 365 days of admission)	
Thiazide diuretics	C03A
Other low-ceiling diuretics	C03B
Loop diuretic	C03C
Potassium sparing diuretics	C03D
Diuretic polytherapy	C03E or any of the above in combination
Preadmission morbidity (any code recorded before the current hospital admission)	
Congestive heart failure	ICD-8: 412-414. ICD-10: I50, I11.0, I13.0, I13.2
Myocardial infarction	ICD-8: 410, 411. ICD-10: I21, I22, I23
Hypertension	ICD-8: 400-404. ICD-10: I10-I15 I270, I272 + ATC kode C02
Chronic liver disease	ICD-8: 571.09–571.11, 571.19, 571.90–571.94, 571.99 572.00-573.09. ICD-10: K70-K70.9, K71, K72.1, K72.9, K73, K74, K75.2-K75.9, K76, I85
Malignancy	ICD-8: 140–207, 275.59, 275.59. ICD-10: C00-C96
Charlson Comorbidity diseases (weighted score)	
Myocardial infarction (1)	ICD-8: 410, 411. ICD-10: I21, I22, I23
Congestive heart failure (1)	ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49. ICD-10: I50, I11.0, I13.0, I13.2
Peripheral vascular disease (1)	ICD-8: 440, 441, 442, 443, 444, 44. ICD-10: I70, I71, I72, I73, I74, I77
Cerebrovascular disease (1)	ICD-8: 430–438. ICD-10: I60-I69, G45, G46
Dementia (1)	ICD-8: 290.09–290.19, 293.09. ICD-10: F00-F03, F05.1, G30
Chronic pulmonary disease (1)	ICD-8: 490–493, 515–518. ICD-10: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease (1)	ICD-8: 712, 716, 734, 446, 135.99. ICD-10: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease (1)	ICD-8: 530.91, 530.98, 531–534. ICD-10: K22.1 K25-K28
Mild liver disease (1)	ICD-8: 571, 573.01, 573.04. ICD-10: B18, K70.0-K70.3, K70.9, K71, K73, K74, K76,
Diabetes types 1 and 2 (1)	ICD-8: 249.00, 249.06, 249.07, 249.09250.00, 250.06, 250.07, 250.09. ICD-10: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Hemiplegia (2)	ICD-8: 344. ICD-10: G81, G82
Moderate/severe renal disease (2)	ICD-8: 403, 404, 580–583, 584, 590.09, 593.19, 753.10–753.19, 792. ICD-10: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Diabetes with end-organ damage (2)	ICD-8: 249.01–249.05, 249.08, 250.01–250.05, 250.0. ICD-10: E10.2-E10.8, E11.2-E11.8
Any tumor (2)	ICD-8: 140–194. ICD-10: C00-C75
Leukemia (2)	ICD-8: 204–207. ICD-10: C91-C95
Lymphoma (2)	ICD-8: 200–203, 275.59. ICD-10: C81-C85, C88, C90, C96
Moderate to severe liver disease (3)	ICD-8: 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00–456.09. ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastatic solid tumor (6)	ICD-8: 195–198, 199. ICD-10: C76-C80
AIDS (6)	ICD-8: 079.83. ICD-10: B21-B24

Abbreviations: ATC; Anatomical Therapeutic Chemical, ICD-8; *International Classification of Diseases,* 8th revision, ICD-10; *International Classification of Diseases,* 10th revision

eAppendix (continued). Codes used to identify diuretic users and covariates	
Covariate	**ICD-8, ICD-10 or ATC code**
Concurrent medication use (prescription filled within 90 days of admission)	
ACE inhibitor	C09A, C09B
Angiotensin II-antagonists	C09C, C09D
β-blockers	C07A
Hydralazine	C02DB
Nitrates	C01DA
Calcium-channel blocker	C08
Anti-adrenergic drug	C02
Anti-depressive drug	N06A
Anti-epileptic drug	N03A
Opioids	N02A
NSAIDs	M01AA ; M01AB; M01AC ; M01AE; M01AG
Acetaminophen	N02BE01, N02BE51, N02BE71
Hyponatremia-related diagnoses (either primary or secondary diagnosis for current hospitalization)	
Glucocorticoid deficiency	E271, E272, E273, E274
Mineralocorticoid deficiency	E271, A187A
Cerebral salt wasting	C70, C71, C72, D32, D33, I60, I61, I62
Cardiac failure	I099A, I110, I130, I132, I50, I971A, O291A, O742A, O754C, O754D, O891A, P290, Z035E
Gastroenteritis	A0, J108A, J118B, K52
Pancreatitis	K85, B252, K860, K861
Cirrhosis	K703, K717, K732E, K743, K744, K745, K746, P788A
Hypothyroidism	E00, E0, E03
SIADH	E222A
Acute or chronic renal failure	I120, I131, I132, N17, N18, N19, O084, O904, P960
Nephrosis and nephrotic syndrome	B520, M103, M350E, N04, N07, N08, N138A, DN14, DN150, DN16, DN289A, DO268C,DP001A
Renal tubular acidosis	N258A
Burn trauma	T20-T32
Other trauma	S00-S99, T00-T14

Abbreviations: ACE; Angiotensin Converting Enzyme, ATC; Anatomical Therapeutic Chemical, ICD-8; *International Classification of Diseases,* 8th revision, ICD-10; *International Classification of Diseases,* 10th revision

eTable 1. Patient baseline characteristics by diuretic type

	Monotherapy				Polytherapy
	Thiazide	Other low-ceiling	Loop	Potassium-sparing	
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	6,070 (100.0)	133 (100.0)	3,461 (100.0)	435 (100.0)	4,536 (100.0)
Age group (years)					
15-39	32 (0.5)	1 (0.8)	48 (1.4)	9 (2.1)	43 (0.9)
40-59	681 (11.2)	15 (11.3)	407 (11.8)	85 (19.5)	484 (10.7)
60-79	2,970 (48.9)	75 (56.4)	1,571 (45.4)	223 (51.3)	2,157 (47.6)
80	2,387 (39.3)	42 (31.6)	1,435 (41.5)	118 (27.1)	1,852 (40.8)
Female gender	3,991 (65.7)	76 (57.1)	1,988 (57.4)	238 (54.7)	2,773 (61.1)
Concurrent drug use					
Ace-inhibitors	1,847 (30.4)	38 (28.6)	993 (28.7)	142 (32.6)	1,365 (30.1)
Angiotensin II antagonists	997 (16.4)	38 (28.6)	632 (18.3)	86 (19.8)	717 (15.8)
β-blockers	1,818 (30.0)	36 (27.1)	1,180 (34.1)	156 (35.9)	1,631 (36.0)
Nitrates	367 (6.0)	5 (3.8)	412 (11.9)	45 (10.3)	605 (13.3)
Calcium-channel blocker	1,739 (28.6)	40 (30.1)	838 (24.2)	99 (22.8)	1,048 (23.1)
Anti-adrenergic drugs	72 (1.2)	2 (1.5)	67 (1.9)	11 (2.5)	79 (1.7)
Antidepressants	1,296 (21.4)	32 (24.1)	861 (24.9)	95 (21.8)	1,097 (24.2)
Anti-epileptic drugs	326 (5.4)	9 (6.8)	245 (7.1)	16 (3.7)	252 (5.6)
Opioids	1,192 (19.6)	23 (17.3)	1044 (30.2)	98 (22.5)	1,316 (29.0)
NSAIDs	926 (15.3)	21 (15.8)	567 (16.4)	55 (12.6)	700 (15.4)
Acetaminophen	1,519 (25.0)	20 (15.0)	1,202 (34.7)	101 (23.2)	1,568 (34.6)
Comorbidity level					
Low (CCI score=0)	2,636 (43.4)	44 (33.1)	747 (21.6)	127 (29.2)	1,079 (23.8)
Medium (CCI score 1-2)	2,539 (41.8)	67 (50.4)	1,487 (43.0)	186 (42.8)	1,914 (42.2)
High (CCI score>2)	895 (14.7)	22 (16.5)	1,227 (35.5)	122 (28.0)	1,543 (34.0)
Specific pre-existing diseases					
Congestive heart failure	265 (4.4)	6 (4.5)	763 (22.0)	73 (16.8)	1,174 (25.9)
Acute myocardial infarction	342 (5.6)	5 (3.8)	471 (13.6)	49 (11.3)	607 (13.4)
Hypertension	2,014 (33.2)	65 (48.9)	1,199 (34.6)	140 (32.2)	1,682 (37.1)
Chronic liver disease	124 (2.0)	1 (0.8)	106 (3.1)	64 (14.7)	338 (7.5)
Malignancy	777 (12.8)	11 (8.3)	549 (15.9)	61 (14.0)	659 (14.5)
Diabetes I and II	513 (8.5)	22 (16.5)	638 (18.4)	51 (11.7)	746 (16.4)
Diabetes with complications	233 (3.8)	15 (11.3)	443 (12.8)	30 (6.9)	434 (9.6)
Chronic pulmonary disease	718 (11.8)	12 (9.0)	763 (22.0)	66 (15.2)	1,039 (22.9)
eGFR <60ml/min/1.73m^2	1,237 (20.4)	24 (18.0)	1,415 (40.9)	103 (23.7)	2,005 (44.2)

Abbreviation: CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate; NSAIDs, Nonsteroidal anti-inflammatory drugs

eTable 2. Characteristics of current hospitalization by diuretic type

	Monotherapy				Polytherapy
	Thiazide	Other low-ceiling	Loop	Potassium-sparing	
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	6,070 (100.0)	133 (100.0)	3,461 (100.0)	435 (100.0)	4,536 (100.0)
Admission sodium level					
130-134.9 mmol/l	3,829 (63.1)	82 (61.7)	2,484 (71.8)	271 (62.3)	2,874 (63.4)
125-129.9 mmol/l	1,346 (22.2)	30 (22.6)	661 (19.1)	105 (24.1)	1,042 (23.0)
120-124.9 mmol/l	473 (7.8)	11 (8.3)	189 (5.5)	36 (8.3)	348 (7.7)
<120 mmol/l	422 (7.0)	10 (7.5)	127 (3.7)	23 (5.3)	272 (6.0)
Specific diagnosis groups					
Pneumonia	1,693 (27.9)	25 (18.8)	710 (20.5)	118 (27.1)	974 (21.5)
Sepsis	507 (8.4)	13 (9.8)	357 (10.3)	29 (6.7)	329 (7.3)
Other infections	104 (1.7)	3 (2.3)	109 (3.1)	5 (1.1)	131 (2.9)
Stroke	813 (13.4)	19 (14.3)	526 (15.2)	42 (9.7)	561 (12.4)
Acute ischemic heart disease	169 (2.8)	8 (6.0)	47 (1.4)	10 (2.3)	67 (1.5)
Congestive heart failure	277 (4.6)	10 (7.5)	131 (3.8)	17 (3.9)	158 (3.5)
Other cardiovascular diseases	75 (1.2)	2 (1.5)	120 (3.5)	6 (1.4)	224 (4.9)
Respiratory disease (pneumonia)	579 (9.5)	12 (9.0)	334 (9.7)	45 (10.3)	419 (9.2)
Gastrointestinal/ liver disease	273 (4.5)	4 (3.0)	233 (6.7)	20 (4.6)	321 (7.1)
Urogenital disease	251 (4.1)	6 (4.5)	163 (4.7)	50 (11.5)	287 (6.3)
Hypoosmolality or hyponatremia	62 (1.0)	3 (2.3)	135 (3.9)	4 (0.9)	113 (2.5)
Other endocrine diseases	239 (3.9)	3 (2.3)	39 (1.1)	9 (2.1)	99 (2.2)
Cancer	367 (6.0)	14 (10.5)	284 (8.2)	41 (9.4)	475 (10.5)
Observation for suspected disease	200 (3.3)	1 (0.8)	100 (2.9)	11 (2.5)	122 (2.7)
Other	461 (7.6)	10 (7.5)	173 (5.0)	28 (6.4)	256 (5.6)

Abbreviation: CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate; NSAIDs, Nonsteroidal anti-inflammatory drugs

eTable 3. 30-day mortality and relative risk (RR) of death in diuretic users compared to non-users based on complete case data.

	Full cohort				Propensity score matched		
	Events/N	Cumulative mortality % (95% CI)	Crude RR (95%CI)	Adjusted RR* (95%CI)	Events/N	Cumulative mortality % (95% CI)	RR (95%CI)
30-day mortality							
Non-users	956/15,787	6.8 (6.4-7.2)	1.0 (Ref.)	1.0 (Ref.)	753/9,500	8.0 (7.4-8.5)	1.0 (Ref.)
Former users	297/3,321	9.0 (8.0-10.0)	1.3 (1.2-1.5)	1.1 (1.0-1.3)	198/2,294	8.7 (7.6-9.9)	1.1 (0.9-1.3)
Current users	1,377/12,262	11.3 (10.7-11.8)	1.7 (1.5-1.8)	1.4 (1.2-1.5)	738/7,206	10.3 (9.6-11.0)	1.3 (1.2-1.4)
New users	185/1,332	13.0 (11.3-14.8)	1.9 (1.7-2.2)	1.7 (1.5-2.0)	152/1,117	13.6 (11.8-15.9)	1.7 (1.5-2.0)
Long-term users	1,192/9,641	11.0 (10.4-11.6)	1.6 (1.5-1.8)	1.3 (1.2-1.4)	586/6,089	9.6 (8.9-10.4)	1.2 (1.1-1.3)

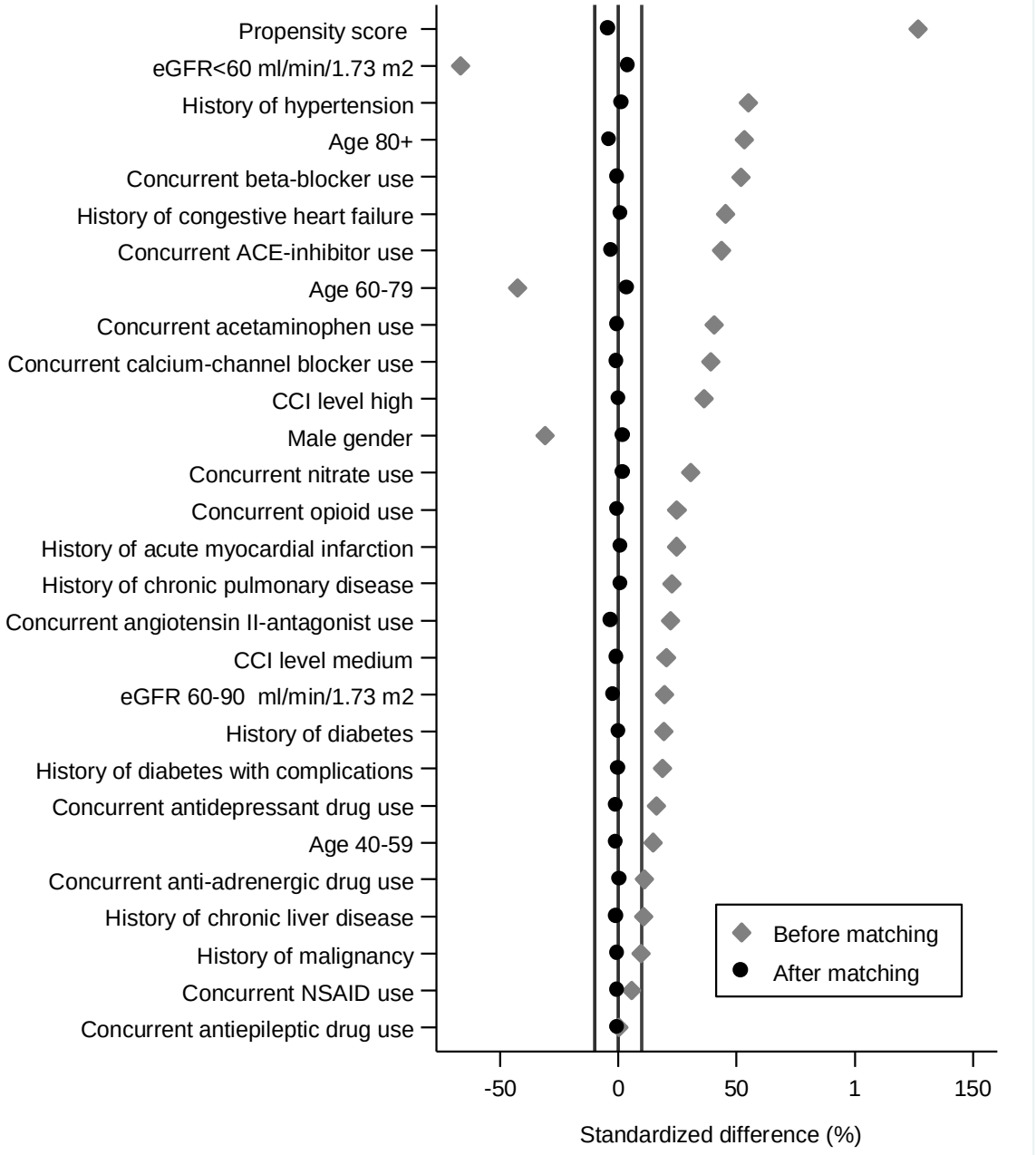
*Adjusted for age group, gender, previous morbidities, concurrent drug use, eGFR group and hyponatremia severity.
Abbreviations: CI, Confidence interval; eGFR, estimated glomerular filtration rate; RR, Relative risk

eTable 4. 30-day mortality and relative risk in hyponatremic diuretic users and non-users based on multiple imputed data.

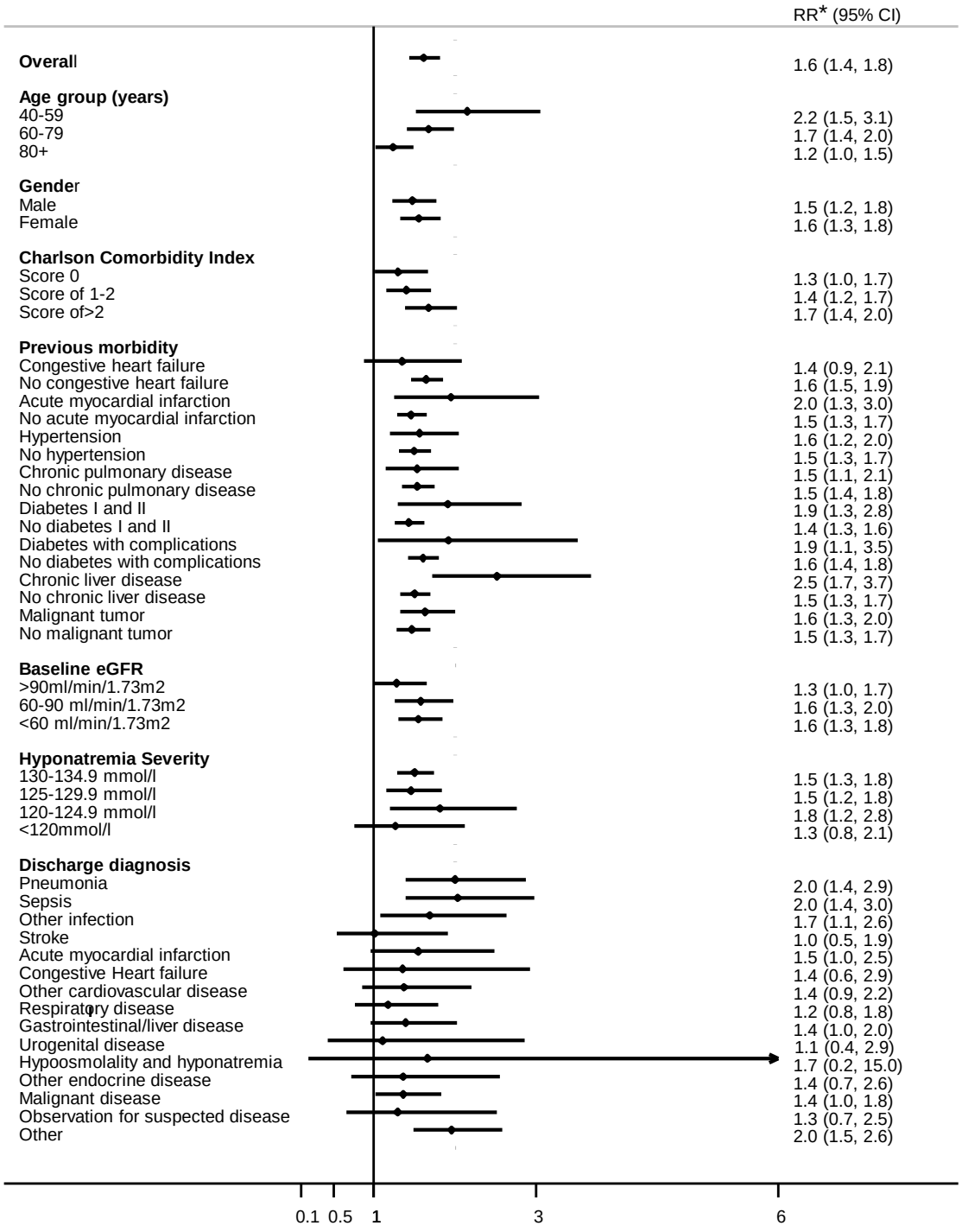
	Full cohort (n=1,022,798)				Propensity score matched (n=495,668)		
	Events/N	30-day mortality % (95% CI)	Crude RR (95%CI)	Adjusted RR* (95%CI)	Events/N	30-day mortality % (95% CI)	RR (95%CI)
30 day overall							
Non-user	41,717/808,781	5.5 (5.4-5.5)	1.0 (Ref.)	1.0 (Ref.)	20,242/260,618	7.8 (7.7-7.9)	1.0 (Ref.)
Former users	9,524/110,333	9.2 (9.0-9.4)	1.7 (1.5-1.9)	1.2 (1.1-1.4)	5,492/63,200	8.7 (8.5-8.9)	1.1 (1.0-1.3)
Current users	40,639/381,231	10.9 (10.8-11.0)	2.0 (1.9-2.1)	1.3 (1.2-1.4)	20,375/197,418	10.3 (10.2-10.5)	1.3 (1.2-1.5)
New users	5,556/44,410	12.7 (12.4-13.0)	2.3 (2.1-2.6)	1.7 (1.5-1.9)	3,933/30,262	13.0 (12.6-13.4)	1.7 (1.4-1.9)
Long-term users	35,083/336,821	10.6 (10.5-10.7)	2.0 (1.8-2.1)	1.3 (1.2-1.4)	16,442/167,156	9.8 (8.5-8.9)	1.3 (1.1-1.4)

*Adjusted for age group, gender, previous morbidities, concurrent drug use, eGFR group and hyponatremia severity.
[§]Compared to the subgroup of non-users with >365 days since last prescription.
Abbreviation: CI, Confidence interval; eGFR, estimated glomerular filtration rate; RR, Relative risk

eFigure 1. Absolute standardized differences before and after matching for covariates used in the propensity score



eFigure 2. Stratified 30-day RR comparing diuretic polytherapy users to non-users (propensity score-matched cohorts)

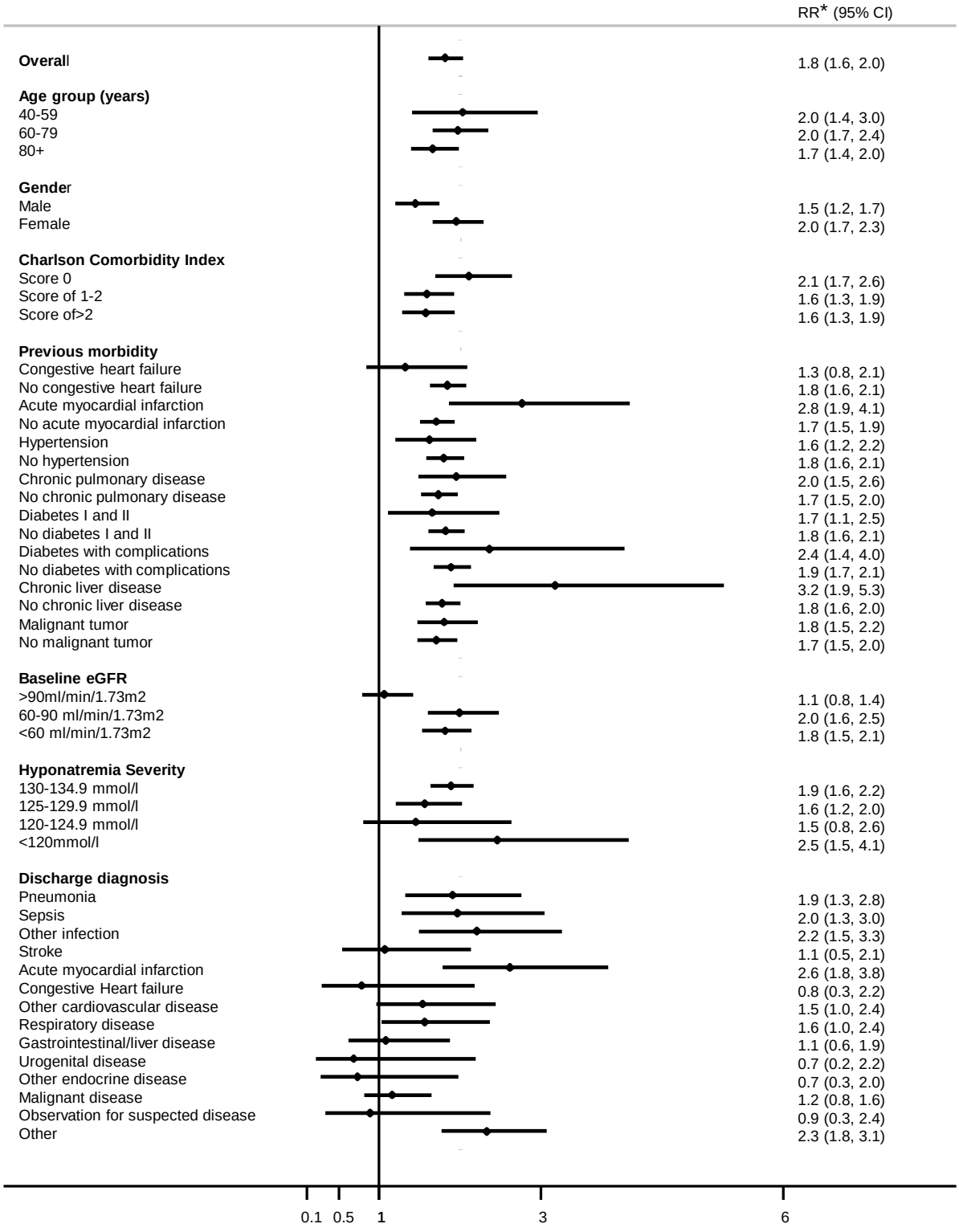


*Propensity score matching equates to multivariable adjustment

The subgroup of age 15-39 years had too few events to yield meaningful estimates.

Abbreviations: CCI, Charlson Comorbidity Score; CI, confidence interval; eGFR. Estimated glomerular filtration rate; RR, relative risk.

eFigure 3. Stratified 30-day RR comparing loop diuretic users to non-users (propensity score-matched cohorts)

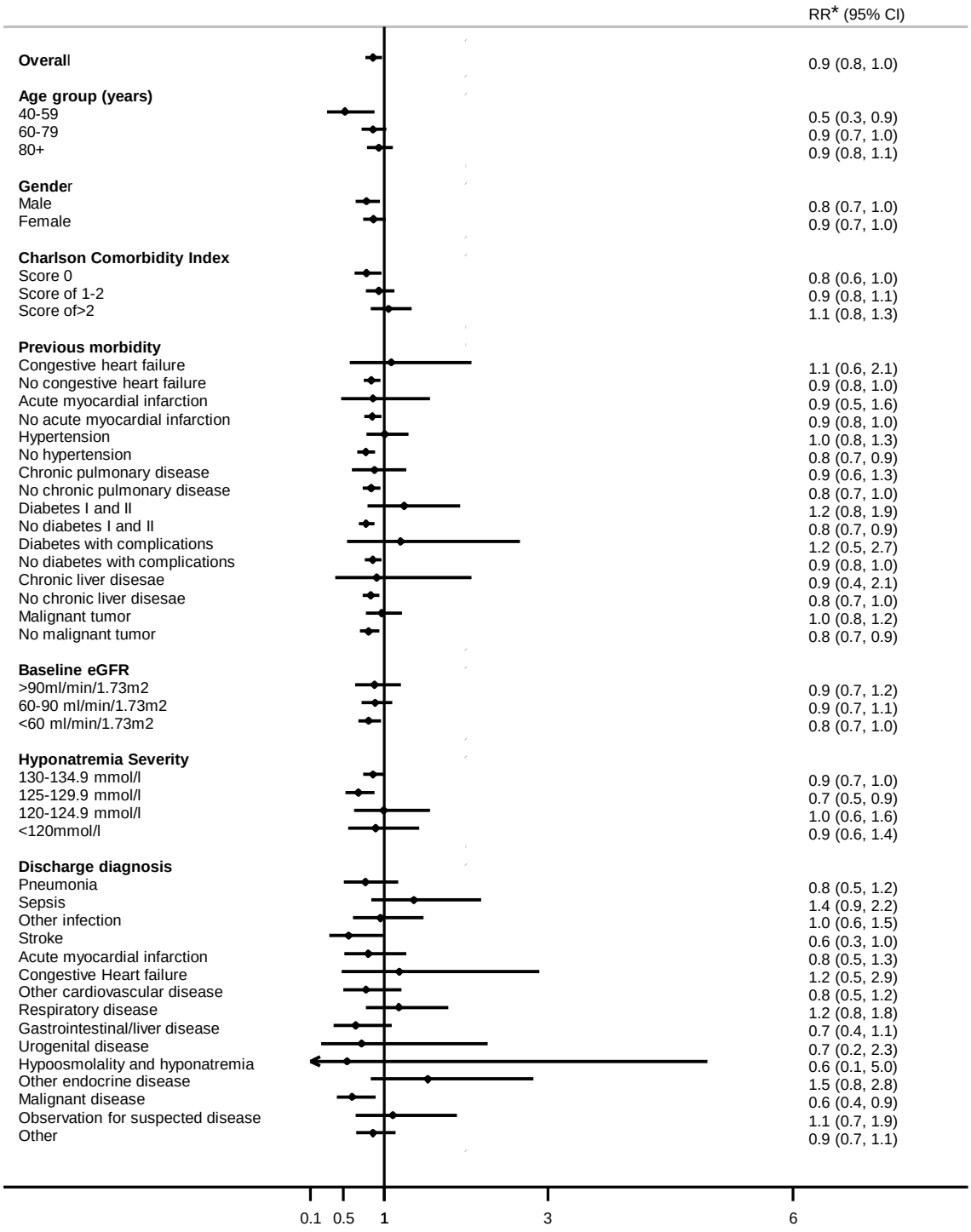


*Propensity score matching equates to multivariable adjustment

The subgroup of age 15-39 years and discharge diagnosis of hyponatremia and hypoosmolality had too few events to yield meaningful estimates.

Abbreviations: CCI, Charlson Comorbidity Score; CI, confidence interval; eGFR. Estimated glomerular filtration rate; RR, relative risk.

eFigure 4. Stratified 30-day RR comparing thiazide diuretic users to non-users (propensity score-matched cohorts)



*Propensity score matching equates to multivariable adjustment
The subgroup of age 15-39 years had too few events to yield meaningful estimates.
Abbreviations: CCI, Charlson Comorbidity Score; CI, confidence interval; eGFR. Estimated glomerular filtration rate; RR, relative risk.

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