



Validity of the International Classification of Diseases, 10th revision (ICD-10) discharge diagnosis codes for hyponatremia in the Danish National Registry of Patients

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-004956
Article Type:	Research
Date Submitted by the Author:	29-Jan-2014
Complete List of Authors:	Holland-Bill, Louise; Aarhus University Hospital, Department of Clinical Epidemiology Christiansen, Christian F; Aarhus University Hospital, Dept. of Clinical Epidemiology; Aarhus University Hospital, Department of Clinical Epidemiology Ulrichsen, Sinna; Aarhus University Hospital, Department of Clinical Epidemiology Ring, Troels; Aalborg University Hospital, Department of Nephrology Jørgensen, Jens Otto; Aarhus University Hospital, Department of Endocrinology and Internal Medicine Toft Sørensen, Henrik; Aarhus University Hospital, Department of Clinical Epidemiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Research methods, Renal medicine, Diabetes and endocrinology
Keywords:	EPIDEMIOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, Nephrology < INTERNAL MEDICINE, GENERAL MEDICINE (see Internal Medicine)

SCHOLARONE™
Manuscripts

Validity of the International Classification of Diseases, 10th revision (ICD-10) discharge diagnosis codes for hyponatremia in the Danish National Registry of Patients

Authors and affiliations:

Louise Holland-Bill* MD

Christian Fynbo Christiansen* MD, PhD

Sinna Pilgaard Ulrichsen* MSc

Troels Ring# MD

Jens Otto Lunde Jørgensen§ MD, DMSc

Henrik Toft Sørensen* MD, PhD, DMSc.

*Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

#Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark

§Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

Corresponding author:

Louise Holland-Bill, MD

Department of Clinical Epidemiology, Aarhus University Hospital

Olof Palmes Allé 43-45

8200 Aarhus N, Denmark

E-mail: louise.bill@dce.au.dk

Tel: +45 871 68063

Fax: +45 871 67215

Keywords: validation study; ICD 10; hyponatremia; diagnosis; population register; clinical laboratory information system

Word count: 2,829

ABSTRACT

OBJECTIVE: To examine the validity of the *International Classification of Diseases*, 10th revision (ICD-10) codes for hyponatremia 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 hospital (n=819,701 individual patients) during the study period. Patient could be included in the study more than once, and we did not restrict to patients with serum sodium measurements (total of n=2,186,642 hospitalization).

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

RESULT: An ICD-10 code for hyponatremia was recorded in the DNRP in 5,850 of the 2,186,642 hospitalizations identified. According to laboratory measurements, however, hyponatremia was present in 306,418 (14%) hospitalizations. Sensitivity of hyponatremia diagnoses was 1.8% (95% confidence interval (CI): 1.7%-1.8%). For sodium values <115mmol/l, sensitivity was 34.3% (95% CI: 32.6%-35.9%). Overall PPV was 92.5% (95% CI: 91.8%-93.1%), and decreased with increasing hyponatremia severity. Specificity and NPV were high for all cut-off points ($\geq 99.8\%$ and $\geq 86.2\%$ respectively). Hyponatremic patients without a corresponding ICD-10 discharge diagnosis were younger and had higher Charlson Comorbidity Index scores than hyponatremic patients with a hyponatremia code in the DNRP.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

For peer review only

Article summary

Article focus

- Hospital discharge diagnoses for hyponatremia recorded in the Danish National Registry of Patients (DNRP) may constitute valuable data sources for epidemiologic studies, however the validity of data must be established.

Key Message

- ICD-10 coding of hyponatremia in the Danish National Registry of Patients (DNRP) is highly specific but greatly incomplete.
- Epidemiological studies relying on discharge diagnoses of hyponatremia may be susceptible to differential misclassification.

Strengths and limitation of this study

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

INTRODUCTION

Hyponatremia, defined as a serum sodium value $<135\text{mmol/l}$, 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 inappropriate antidiuretic hormone, vomiting, and diarrhea, 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 hyponatremia 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 etiology and prognosis of hyponatremia remain unknown.

The Danish population-based medical registries may offer a unique opportunity for studies of the epidemiology of hyponatremia, if data are valid. However, as symptoms of mild and moderate hyponatremia 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 hyponatremia in epidemiologic studies may cause bias that can affect the validity of study results.[11]

To date, only one study has investigated the validity of *International Classification of Diseases* (ICD), 10th revision (ICD-10) codes for hyponatremia. This Canadian study was restricted to patients 66 years of age or older presenting with a hyponatremic serum sodium value at time of emergency department contact or at admission.[12] The sensitivity of hyponatremia coding was found to be as low as 7%. For inpatients younger than 66 years, knowledge of the validity hyponatremia diagnoses is limited to a study performed in a single hospital in the Netherlands using ICD-9 codes for hyponatremia. In this study, sensitivity was found to be just below 2%, using hospital laboratory data as the reference standard.[3] Similar results were found in a study examining the validity of outpatient professional ICD-9 claims for hyponatremia in the US.[14]

1
2
3
4 We therefore conducted the first population-based study examining the validity of ICD-10 inpatient
5 discharge diagnoses of hyponatremia in the Danish National Registry of Patients (DNRP), in terms of
6 sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), including
7 patients of all ages.
8
9
10
11
12

13 14 15 **METHODS**

16 17 **Setting and data collection**

18
19 We used the DNRP to identify all admissions to hospitals in the North and Central Denmark Regions
20 (2.1 million inhabitants in the study period) from 1 January 2006 to 31 December 2011. The DNRP
21 contains information, including date of admission and discharge, department code and discharge
22 diagnoses, on all admissions to Danish non-psychiatric hospitals since 1977.[15,16]
23
24
25

26
27 By use of the unique 10-digit civil registration number, assigned to all Danish residents since 1968,[17]
28 we linked each patient's DNRP data to the clinical laboratory information system (LABKA) research
29 database. For patients living in the North and Central Denmark Regions, data on virtually all
30 specimens analyzed in clinical laboratories by hospitals and medical practitioners are entered into a
31 computer-based clinical laboratory information system, which functions as a routine diagnostic tool for
32 medical personnel.[18] Data are transferred electronically to the LABKA research database, managed
33 by Aarhus University. Analyses are coded according to the NPU (Nomenclature, Properties and Units)
34 system. The LABKA research database contains the civil registration number, time and date of blood
35 sampling, and identification code of the requesting physician or hospital department.[18] We used the
36 LABKA research database to retrieve information on all serum sodium measurements recorded during
37 each of the identified hospitalizations.
38
39
40
41
42
43
44
45
46
47
48
49
50

51 52 53 **Hyponatremia diagnosis (ICD-10 code algorithm)**

54
55
56
57
58
59
60

1
2
3
4 At hospital discharge, the attending physician assigns one primary diagnosis, reflecting the main
5 reason for hospitalization and treatment and up to 19 secondary diagnoses regarding additional
6 clinically relevant conditions, including underlying diseases, complications and symptoms.[19]

7
8
9 Diagnoses recorded in the DNRP have been coded according to the *International Classification of*
10
11
12
13 *Diseases* (ICD), 10th revision (ICD-10) since 1994.[16]

14
15 We developed an algorithm based on ICD-10 codes to identify discharge diagnoses of hyponatremia
16 recorded in the DNRP for each hospitalization. The following ICD-10 codes were included in the
17 algorithm: E87.1 (Hypo-osmolality and hyponatremia), E87.1A (Hyponatremia) and P74.2B
18 (Hyponatremia in newborns [Danish version of ICD-10]).
19
20
21
22
23
24
25

26 **Gold Standard (laboratory serum sodium measurements)**

27
28 We used serum sodium measurements recorded in the LABKA research database as the gold
29 standard to confirm or disconfirm a diagnosis of hyponatremia identified by the ICD-10 algorithm.
30 Hyponatremia was defined as serum sodium values <135 mmol/l for patients older than 30 days and
31 <133 mmol/l for infants 30 days of age or younger.[20] Patients were considered to have
32 hyponatremia if at least one hyponatremic serum sodium value was recorded during their
33 hospitalization. If no serum sodium measurement was available, the patient was assumed to have a
34 non-hyponatremic serum sodium value (135-145mmol/l). The following cut-off points for increasing
35 severity of hyponatremia were chosen: 135 mmol/l, 130mmol/l, 125mmol/l, 120mmol/l and
36 115mmol/l.[13] The corresponding levels for infants less than 31 days of age were 133mmol/l,
37 128mmol/l, 123mmol/l, 118mmol/l and 113mmol/l.
38
39
40
41
42
43
44
45
46
47
48
49
50
51

52 **Other Variables**

53
54 For each patient, we assessed comorbidity by information retrieved from the DNRP on the conditions
55 included in the Charlson Comorbidity Index (CCI). The CCI includes 19 medical conditions, each
56
57
58
59
60

1
2
3
4 assigned a weighted score between one and six. The sum of these individual scores is used as a
5
6 measure of a patient's comorbidity burden.[21, 22] We calculated CCI scores for each patient and
7
8 defined three comorbidity levels: low (CCI score 0), medium (CCI score 1-2) and high (CCI score of 3
9
10 or above). We included morbidities recorded within 10 years prior to the current hospitalization, as
11
12 conditions requiring hospital treatment within this timeframe would likely influence the attending
13
14 physician's diagnostic approach and evaluation during the current hospitalization.
15
16

17 Furthermore, we obtained information on department of admission and year of admission from the
18
19 DNRP. Departments were categorized in the following five groups: internal medicine, surgery,
20
21 gynecology/obstetrics, pediatrics, and other.
22
23

24 25 26 **Statistical analysis**

27
28 Patients with a hyponatremic serum sodium value recorded in the LABKA research database were
29
30 divided into two categories: Those with an ICD-10 code for hyponatremia in the DNRP and those
31
32 without. We described both groups of patients in terms of gender, age (median and associated
33
34 interquartile range (IQR)), department of admission, CCI score and specific comorbidities.
35
36

37 We estimated the sensitivity, specificity, PPV, and NPV (see Figure 1) for ICD-10 codes for
38
39 hyponatremia in the DNRP with corresponding 95% confidence intervals (CI), using the exact method
40
41 for binomial proportions. We defined sensitivity as the probability an ICD-10 code for hyponatremia
42
43 being registered in the DNRP, when the laboratory test result identified presence of hyponatremia.
44
45

46 Specificity was defined as the probability of an ICD-10 code for hyponatremia not being registered in
47
48 the DNRP, when hyponatremia was not identified in laboratory test results. We estimated the PPV as
49
50 the proportion of patients for whom an ICD-10 code for hyponatremia recorded in the DNRP could be
51
52 confirmed by a serum sodium measurement, and NPV as the proportion of patients with no ICD-10
53
54 code for hyponatremia in the DNRP, for whom non-hyponatremic, or no serum sodium values were
55
56
57
58
59
60

1
2
3
4 recorded in the LABKA research database. The analyses were repeated for all hyponatremia cut-off
5
6 points and after stratification by department of admission and admission year.
7

8
9 Finally, we conducted three sensitivity analyses. First, we performed a complete case analysis, a
10
11 method for dealing with missing data considering only subjects with recorded values for all
12
13 covariates,[23] meaning that only patients with at least one serum sodium measurement during their
14
15 hospitalization were included in the analysis. We did so, in order to evaluate the assumption that
16
17 patients without a serum sodium measurement were normonatremic. In the second sensitivity
18
19 analysis, we included only patients with more than one serum sodium measurement during their
20
21 hospitalization. In the third sensitivity analysis, we included only the ICD-10 codes E87.1A
22
23 (hyponatremia) and P74.2B (hyponatremia in newborns).
24
25
26
27

28 Data analyses were performed using the statistical software package STATA (version 12; Stata Corp,
29
30 College Station, TX, USA).
31

32 The study was approved by the Danish Data Protection Agency (record number 2006-53-1396).
33
34
35
36

37 RESULTS

38 Characteristics

39
40 We identified 2,186,642 hospitalizations (819,701 individual patients) within the study period. For
41
42 1,308,740 (60%) hospitalizations, at least one serum sodium measurement was recorded in the
43
44 LABKA research database, and for 1,037,647 (47%) subsequent measurements were recorded.
45
46

47 According to the recorded serum sodium value, hyponatremia was present in 306,418 hospitalizations
48
49 (14%). In the DNRP, we identified 5,850 hospitalizations with an ICD-10 code of hyponatremia (hypo-
50
51 osmolality and hyponatremia= 3,722, hyponatremia=2,124, hyponatremia in newborns=4) among all
52
53 2,186,642 hospitalizations. Of these, 440 did not have a hyponatremic serum sodium value recorded
54
55 in the LABKA research database.
56
57
58
59
60

Table 1 shows the distribution of hospitalizations by presence/absence of an ICD-10 diagnosis of hyponatremia recorded in the DNRP, by gender, age and comorbidity variables, for patients with hyponatremic serum sodium values. Patients who had an ICD-10 code of hyponatremia recorded in the DNRP and a corresponding hyponatremic serum sodium measurement, were on average older, more often female, more likely admitted to an internal medicine department, and characterized by lower comorbidity levels than patients with no hyponatremia diagnosis in the DNRP, but hyponatremic serum sodium values recorded in the LABKA research database. Cerebrovascular disease, dementia, and ulcer disease were the only comorbidities more frequently found in patients with an ICD-10 code for hyponatremia and corresponding hyponatremic serum sodium value, compared to hyponatremic patients without a hyponatremia diagnosis in the DNRP. (Table 1)

Table 1.

Characteristics of hospitalizations identified in the DNRP from 2006 to 2011

	Hospitalizations with at least on serum sodium value <135 mmol/l recorded in the LABKA research database		All hospitalizations (n=2,186,642) n (%)
	ICD-10 code of hyponatremia in the DNRP* (n=5,410) n (%)	No ICD-10 code of hyponatremia in the DNRP* (n=301,008) n (%)	
Sex			
Female	3,643 (67.3)	148,120 (49.3)	1,168,803 (53.5)
Male	1,767 (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	5,173 (95.6)	184,848 (61.6)	943,121 (43.1)
Surgical	184 (3.4)	88,378 (29.4)	630,525 (28.8)
Gynaecologic/obstetric	10 (0.2)	7,104 (2.4)	347,365 (15.9)
Pediatric	29 (0.5)	15,830 (5.3)	165,289 (7.6)
Other	14 (0.3)	4,848 (1.6)	100,342 (4.6)
CCI level_(score)			
Low (0)	2,075 (38.4)	100,398 (33.4)	1,232,762 (56.4)
Medium (1-2)	2,182 (40.3)	106,874 (35.5)	588,783 (26.9)
High (≥3)	1,153 (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	1,017 (18.8)	39,466 (13.1)	182,304 (8.3)
Dementia	107 (3.1)	4,247 (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)	6,279 (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)	2,462 (0.8)	16,060 (0.7)
Moderate to severe renal disease	143 (2.6)	20,123 (6.7)	75,441 (3.5)
Malignant tumor	781 (14.4)	64,882 (21.6)	312,845 (14.3)
Leukemia	22 (0.4)	4,636 (1.5)	17,190 (0.8)
Lymphoma	51 (0.9)	7,096 (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)	2,014 (0.1)

* DNRP = Danish National Registry of Patients

Sensitivity, specificity, PPV and NPV

For 440 (7.5%) of the 5,850 hospitalizations with an ICD-10 code for hyponatremia recorded in the DNRP, no hyponatremic serum sodium measurement was recorded in the LABKA research database during the hospitalization (for 178, no measurement was recorded at all). This corresponds to a PPV of an ICD-10 code for hyponatremia of 92.5% (95% CI: 91.8%–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 5,410 hospitalizations had both an ICD-10 code recorded in the DNRP and a corresponding hyponatremic laboratory measurement, resulting in a sensitivity of the ICD-10 codes of 1.8% (95% CI: 1.7%–1.8%). Sensitivity increased with lower cut-off points for serum sodium, reaching 34.3% (95% CI: 32.6%–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%–86.2%), respectively. Specificity and NPV remained high for all serum sodium cut-off points (Table 2).

Table 2.

Validity of ICD-10 codes for hyponatremia recorded in the DNRP*, using serum sodium measurements in the LABKA research database as gold standard.

Hyponatremic serum sodium value recorded in LABKA research database (mmol/l)	ICD-10 code for hyponatremia recorded in the DNRP*				Primary Analysis		Sensitivity Analyses		
	Yes	No	Total	Validity Measures		Requiring at least one serum sodium measurement during hospitalization % (95% CI)]	Requiring >1 serum sodium measurement during hospitalization % (95% CI)	ICD-10 algorithm restricted to code E87.1A and P74.2B % (95% CI)	
				% (95% CI)					
Overall									
Na<135 [□]	Yes	5,410	301,008	306,418	Sensitivity	1.8 (1.7-1.8)	1.8 (1.7-1.8)	1.9 (1.8-2.0)	0.7 (0.6-0.7)
	No	440	1,879,784	1,880,224	Specificity	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)
	Total	5,850	2,180,792	2,186,642	PPV	92.5 (91.8-93.1)	95.4 (94.8-95.9)	95.8 (95.2-96.3)	94.6 (93.6-95.6)
					NPV	86.2 (86.2-86.2)	76.9 (76.8-77.0)	74.7 (74.6-74.8)	86.1 (86.0-86.1)
Cut-off points for increasing severity of hyponatremia									
Na<130 [§]	Yes	4,528	80,605	85,133	Sensitivity	5.3 (5.2-5.5)	5.3 (5.2-5.5)	5.6 (5.4-5.7)	2.1 (2.0-2.2)
	No	1,322	2,100,187	2,101,509	Specificity	99.9 (99.9-99.9)	99.9 (99.9-99.9)	99.9 (99.9-99.9)	100 (100-100)
	Total	5,850	2,180,792	2,186,642	PPV	77.4 (76.3-78.5)	79.8 (78.7-80.9)	80.5 (79.4-81.6)	83.0 (81.4-84.6)
					NPV	96.3 (96.3-96.3)	93.8 (93.8-93.9)	93.0 (93.0-93.1)	96.2 (96.2-96.2)
Na<125 [#]	Yes	3,261	21,544	24,805	Sensitivity	13.1 (12.7-13.6)	13.1 (12.7-13.6)	13.6 (13.1-14.0)	5.4 (5.1-5.7)
	No	2,589	2,159,248	2,161,837	Specificity	99.9 (99.9-99.9)	99.8 (99.8-99.8)	99.8 (99.8-99.8)	100 (100-100)
	Total	5,850	2,180,792	2,186,642	PPV	55.7 (54.5-57.0)	57.5 (56.2-58.8)	57.9 (56.5-59.2)	62.5 (60.4-64.5)
					NPV	99.0 (99.0-99.0)	98.3 (98.3-98.4)	98.1 (98.1-98.1)	98.9 (98.9-98.9)
Na<120 [£]	Yes	2,061	6,219	8,280	Sensitivity	24.9 (24.0-25.9)	24.9 (24.0-25.8)	25.4 (24.5-26.4)	6.3 (5.8-6.9)
	No	3,789	2,174,573	2,178,362	Specificity	99.8 (99.8-99.8)	99.7 (99.7-99.7)	99.7 (99.7-99.7)	100 (100-100)
	Total	5,850	2,180,792	2,186,642	PPV	35.2 (34.0-36.5)	36.3 (35.1-37.6)	36.3 (35.0-37.6)	50.6 (47.5-53.7)
					NPV	99.7 (99.7-99.7)	99.5 (99.5-99.5)	99.5 (99.4-99.5)	99.6 (99.6-99.7)
Na<115 [§]	Yes	1,107	2,127	3,234	Sensitivity	34.3 (32.6-35.9)	34.2 (32.6-35.9)	34.9 (33.1-36.6)	9.3 (8.3-10.3)
	No	4,743	2,178,665	2,183,408	Specificity	99.8 (99.8-99.8)	99.7 (99.6-99.7)	99.6 (99.6-99.6)	100 (100-100)
	Total	5,850	2,180,792	2,186,642	PPV	18.9 (17.9-20.0)	19.5 (18.5-20.6)	19.5 (18.4-20.6)	28.8 (26.1-31.7)
					NPV	99.9 (99.9-99.9)	99.8 (99.8-99.8)	99.8 (99.8-99.8)	99.9 (99.9-99.9)

*DNRP = Danish National Registry of Patients

[□] Corresponding to <133 mmol/l for infants of 30 day or less of age

[§] Corresponding to <128 mmol/l for infants of 30 day or less of age

[#] Corresponding to <123 mmol/l for infants of 30 day or less of age

[£] Corresponding to <118 mmol/l for infants of 30 day or less of age

[§] Corresponding to <113 mmol/l for infants of 30 day or less of age

Sensitivity was higher among admissions to internal medicine departments than among admissions to surgical, gynecologic/obstetric, pediatric, and “other” departments (Table 3). The validity measures were virtually unchanged across strata of admission year.

Table 3.

Validity of ICD-10 codes for hyponatremia recorded in the DNRP, stratified by year and department of admission, for serum sodium values <135mmol/l[†] and <125mmol/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
Admission Year								
2006	1.5 (1.4-1.7)	12.5 (11.5-13.5)	100 (100-100)	99.9 (99.9-99.9)	92.8 (90.8-94.5)	66.6 (63.2-69.9)	86.8 (86.6-86.9)	99.0 (98.9-99.0)
2007	1.4 (1.3-1.5)	12.0 (11.0-13.1)	100 (100-100)	99.9 (99.9-99.9)	94.4 (92.4-96.0)	65.3 (61.6-68.8)	87.0 (86.9-87.1)	99.0 (99.0-99.1)
2008	1.7 (1.6-1.8)	12.3 (11.3-13.3)	100 (100-100)	99.9 (99.9-99.9)	91.1 (89.1-92.8)	53.6 (50.4-56.8)	85.9 (85.8-86.1)	99.0 (98.9-99.0)
2009	1.8 (1.7-1.9)	12.6 (11.6-13.6)	100 (100-100)	99.9 (99.8-99.9)	93.4 (91.7-94.8)	51.4 (48.4-54.5)	85.5 (85.3-85.6)	99.0 (98.9-99.0)
2010	1.9 (1.8-2.0)	14.2 (13.2-15.4)	100 (100-100)	99.9 (99.9-99.9)	91.6 (89.8-93.2)	54.4 (51.4-57.4)	86.3 (86.2-86.4)	99.1 (99.0-99.1)
2011	2.2 (2.0-2.3)	15.2 (14.1-16.4)	100 (100-100)	99.9 (99.9-99.9)	92.2 (90.6-93.6)	49.8 (47.0-52.7)	85.8 (85.7-85.9)	99.1 (99.0-99.1)
Department								
Internal medicine	2.7 (2.7-2.8)	16.5 (16.0-17.0)	99.9 (99.9-100)	99.7 (99.7-99.7)	92.8 (92.1-93.4)	56.0 (54.7-57.3)	80.3 (80.2-80.4)	98.3 (98.3-98.3)
Surgical	0.2 (0.2-0.2)	2.3 (1.9-2.8)	100 (100-100)	100 (100-100)	90.6 (85.8-94.3)	57.6 (50.5-64.5)	86.0 (85.9-86.1)	99.2 (99.2-99.2)
Gynecologic/ Obstetric	0.1 (0.1-0.3)	3.1 (1.2-6.7)	100 (100-100)	100 (100-100)	76.9 (46.2-95.0)	46.2 (19.2-74.9)	98.0 (97.9-98.0)	99.9 (99.9-100)
Pediatric	0.2 (0.1-0.3)	3.4 (1.7-5.8)	100 (100-100)	100 (100-100)	85.3 (68.9-95.0)	35.3 (19.7-53.5)	90.4 (90.3-90.6)	99.8 (99.8-99.8)
Other	0.3 (0.2-0.5)	1.5 (0.4-3.9)	100 (100-100)	100 (100-100)	58.3 (36.6-77.9)	16.7 (4.74-37.4)	95.2 (95.0-95.3)	99.7 (99.7-99.8)

* DNRP = Danish National Registry of Patients

[†]Corresponding to <133mmol/l for infants of 30 day or less of age

[#]Corresponding to <123mmol/l for infants of 30 day or less of age

Sensitivity analyses

Compared to the primary analyses, we observed no changes in neither sensitivity nor specificity estimates when including only patients with at least one serum sodium measurement during their

1
2
3
4 hospitalization in the analysis. PPV increased slightly for all serum sodium cut-off points, while NPV
5
6 decreased for the three highest cut-off points. Including only patients with more than one serum
7
8 sodium measurement also yielded almost identical results (Table 2).

9
10 After restriction to the most specific ICD-10 codes for hyponatremia, PPV increased slightly and
11
12 sensitivity decreased (94.6% (95% CI: 93.6%–95.6%) and 0.7% (95% CI: 0.6%–0.7%), respectively).
13
14 Estimates of specificity and NPV were virtually unchanged (Table 2).
15
16

17 18 19 **DISCUSSION**

20
21 This is the first study to report on the validity of ICD-10 coding of hyponatremia using comprehensive
22
23 population-based medical registries, and including patients of all ages. A record of a hyponatremia
24
25 diagnosis in the DNRP was found to be specific to and highly predictive of hyponatremia confirmed by
26
27 laboratory values. However, the disorder was greatly underreported, though to a lesser extent in
28
29 patients admitted to an internal medicine department compared to other departments. We found
30
31 sensitivity to be low even for severe degrees of hyponatremia. These results were robust when we
32
33 used a stricter definition of hyponatremia and complete case analysis.
34
35
36
37
38

39 Our findings correspond with those of Movig *et al.*'s single-center study conducted in The Netherlands,
40
41 in which ICD-9-CM coding of hyponatremia in inpatient discharge records was compared with hospital
42
43 laboratory data.[13] As in our study, sensitivity at the cut-off point of 135 mmol/l was 1.7%, and
44
45 increased with decreasing serum sodium levels. Sensitivity thus reached 30.6% for values below 115
46
47 mmol/l. In addition, their estimates for PPV, NPV, and specificity were similar to our results (91.7%,
48
49 79.5% and <99.9%, respectively). A Canadian study by Gandhi *et al.* examined ICD-10 coding for
50
51 hyponatremia and reported a sensitivity of 4.5% for the cut-off point of <135 mmol/l and 34.4% for the
52
53 cut-off point of 125 mmol/l.[12] The study was, however, restricted to patients ≥ 66 years of age
54
55 presenting with hyponatremic laboratory test result at admission or emergency department contact. In
56
57
58
59
60

1
2
3
4 line with their results, we found that the median age of patients with a ICD-10 code of hyponatremia
5 recorded in the DNRP, which could be confirmed by laboratory results, was higher than that of
6
7
8 hyponatremic patients with no ICD-10 code for hyponatremia recorded in the DNRP. Shea *et al.* also
9 reported higher sensitivity compared to our results (3.5% for a cut-off point of <136 mmol/l and 29.6%
10 for the cut-off point of 125 mmol/l) in their study examining the validity of ICD-9 codes of hyponatremia
11 in an outpatient managed-care population.[14] Outpatient serum sodium laboratory tests were
12 compared with outpatient professional ICD-9 claims registered within 15 days before or after the
13 laboratory claim. The PPV was 62.6% for serum sodium levels <136 mmol/l and 10.4% for levels <125
14 mmol/l. As noted in the paper, detected hyponatremia may be the cause for follow-up visits in an
15 outpatient setting, without the need for repeat measurements. This could lead to lower PPV compared
16 to our study and the study by Movig *et al.* In addition, managed-care claims databases encompass an
17 employer-based commercially insured population. Shea *et al.*'s study thus may not be representative
18 of elderly populations, in which prevalence of hyponatremia is high.[24, 25] This also may explain why
19 their results differed from ours.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36

37 The major strengths of our study are its population-based design and unambiguous individual-level
38 linkage between registries containing complete data on all hospitalizations and laboratory tests in a
39 well-defined population. This eliminates the risk of selection bias. Several potential study limitations
40 must be considered. We relied on only one (the lowest) serum sodium value recorded to define
41 presence of hyponatremia, and also did not consider duration of hyponatremia. Clinicians may be
42 more likely to regard hyponatremia as clinically relevant, and hence to include the condition in
43 discharge diagnoses, if it is detected in more than one measurement. In this context, it is important to
44 note that patient transfers between departments are registered as separate admissions in the DNRP
45 and we examined the validity of ICD-10 coding for each registered admission. The PPV may have
46 been even higher if we had considered contiguous admissions as a single admission. Finally, we
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 chose to include patients without serum sodium measurements and to consider them as
5
6 normonatremic in the main analysis. We did so to detect false positive diagnoses and thereby obtain
7
8 accurate estimates of predictive values. Serum sodium is often measured as a routine procedure, and
9
10 rarely due to specific suspicion. Though frequently measured, the proportion of patients with
11
12 unacknowledged hyponatremia is most often unknown. We therefore performed a complete case
13
14 analysis, including only patients with serum sodium measurements. As the results did not differ
15
16 markedly from those of the primary analysis, we believe that including patients without serum sodium
17
18 measurements in the normonatremic group was justified.
19
20
21
22
23

24 We can only speculate on reasons for the low sensitivity of the ICD-10 coding of hyponatremia found
25
26 in our study. Hyponatremia is mainly considered a part of the clinical picture of underlying diseases. If
27
28 hyponatremia is mild or transient, and does not require intervention or specific attention, it may not
29
30 warrant documentation. However, even for very severe hyponatremia (<115 mmol/l), which is
31
32 potentially fatal and requires immediate intervention, sensitivity was low. Our results suggest that
33
34 hyponatremia is not coded in the presence of coexisting illness deemed more important, and that the
35
36 fact that hyponatremia may be an important indicator of a poor prognosis is not yet acknowledged.
37
38
39
40

41 The results of this validation study emphasize the need for caution when relying on ICD-10 codes for
42
43 hyponatremia in research. Based on the estimated PPV and specificity, patients with an ICD-10 code
44
45 of hyponatremia can safely be assumed to actually have hyponatremia. However, the low sensitivity
46
47 renders the ICD-10 codes inappropriate for use in studies examining prevalence, incidence, and
48
49 absolute risk, due to a high degree of misclassification. Sensitivity increased with decreasing serum
50
51 sodium levels, suggesting that studies using ICD-codes to identify hyponatremia would be based
52
53 mainly on severe cases. Furthermore, our results indicate that quality of registration differs according
54
55
56
57
58
59
60

1
2
3
4 to age, gender, and morbidity status. Hence, studies may be susceptible to differential
5
6 misclassification, again resulting in biased results.
7
8
9

10 **CONCLUSION**

11
12 We found that the ICD-10 coding of hyponatremia in DNRP has high specificity but is highly
13
14 incomplete, resulting in very low sensitivity. When available, laboratory test results for serum sodium
15
16 will more correctly identify patients with hyponatremia.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Contributors

LHB participated in the design of the study, performed the data analysis, provided interpretation of study results and drafted the manuscript. SPU participated in 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 with interpretation of study results helped draft the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the Clinical Epidemiology Research Foundation and by the Danish Cancer Society (grant no. R73-A4284-13-S17).

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.

LHB, CFC, SPU and HTS are salaried employees of 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.

None of these grants or fees had any had any leverage on the design, implementation or reporting of the present study.

Reference list

1
2
3
4
5
6
7
8 1 Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med*
9 2006;**119**(Suppl 1):S30-5.

10
11
12
13 2 Rose BD. Clinical physiology of acid-base and electrolyte disorders. 3rd ed. New York: McGraw-Hill
14 information Services Company 1989.

15
16
17
18 3 Waikar SS, Curhan GC, Brunelli SM. Mortality associated with low serum sodium concentration in
19 maintenance hemodialysis. *Am J Med* 2011;**124**:77-84.

20
21
22
23 4 Doshi SM, Shah P, Lei X, *et al.* Hyponatremia in hospitalized cancer patients and its impact on
24 clinical outcomes. *Am J Kidney Dis* 2012;**59**:222-228.

25
26
27
28 5 Goldberg A, Hammerman H, Petcherski S, *et al.* Prognostic importance of hyponatremia in acute
29 ST-elevation myocardial infarction. *Am J Med* 2004;**117**:242-248.

30
31
32
33 6 Kovesdy CP, Lott EH, Lu JL, *et al.* Hyponatremia, Hypernatremia and Mortality in Patients with
34 Chronic Kidney Disease with and without Congestive Heart Failure. *Circulation* 2012;**125**:677-684

35
36
37
38 7 Scherz N, Labarere J, Mean M, *et al.* Prognostic importance of hyponatremia in patients with acute
39 pulmonary embolism. *Am J Respir Crit Care Med* 2010;**182**:1178-1183.

40
41
42
43 8 Wald R, Jaber BL, Price LL, *et al.* Impact of hospital-associated hyponatremia on selected
44 outcomes. *Arch Intern Med* 2010;**170**:294-302.

45
46
47
48 9 Chawla A, Sterns RH, Nigwekar SU, *et al.* Mortality and serum sodium: do patients die from or with
49 hyponatremia? *Clin J Am Soc Nephrol* 2011;**6**:960-965.

- 1
2
3
4 10 Marco J, Barba R, Matia P, *et al.* Low prevalence of hyponatremia codification in departments of
5 internal medicine and its prognostic implications. *Curr Med Res Opin* 2013;**29**:1757-1762
6
7
8
9
10 11 Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for
11 epidemiological research. *Int J Epidemiol* 1996;**25**:435-442.
12
13
14
15 12 Gandhi S, Shariff SZ, Fleet JL, *et al.* Validity of the International Classification of Diseases 10th
16 revision code for hospitalisation with hyponatraemia in elderly patients. *BMJ Open*
17 2012;**2**:10.1136/bmjopen-2012-001727. Print 2012.
18
19
20
21
22
23 13 Movig KL, Leufkens HG, Lenderink AW, *et al.* Validity of hospital discharge International
24 Classification of Diseases (ICD) codes for identifying patients with hyponatremia. *J Clin Epidemiol*
25 2003;**56**:530-535.
26
27
28
29
30
31 14 Shea AM, Curtis LH, Szczech LA, *et al.* Sensitivity of International Classification of Diseases codes
32 for hyponatremia among commercially insured outpatients in the United States. *BMC Nephrol*
33 2008;**9**:5.
34
35
36
37
38 15 Andersen TF, Madsen M, Jorgensen J, *et al.* The Danish National Hospital Register. A valuable
39 source of data for modern health sciences. *Dan Med Bull* 1999;**46**:263-268.
40
41
42
43
44 16 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*
45 2011;**39**(Suppl 7):30-33.
46
47
48
49 17 Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;**39**(Suppl 7):22-
50 25.
51
52
53
54
55
56
57
58
59
60

1
2
3
4 18 Grann AF, Erichsen R, Nielsen AG, *et al*. Existing data sources for clinical epidemiology: The
5 clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clin*
6
7
8
9 *Epidemiol* 2011;**3**:133-138.

10
11
12 19 SSI - Joint Content for Basic Registration of Hospital Patients.

13
14 <http://www.ssi.dk/Sundhedsdataogit/Indberetning%20og%20patientregistrering/Patientregistrering/Faellesindhold.aspx>
15
16 (accessed 18 Dec 2013; updated 9 Dec 2013).

17
18
19
20 20 Laboratory Manual for Hospitals in the North Jutland Region. 2011.

21
22 <http://www.laboratorievejledning.dk/prog/view.aspx?AfsnitID=103&KapitelID=26&UKapitelID=194>
23
24 (accessed 15 Dec 2013; updated 20 Dec 2011).

25
26
27
28 21 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in
29 longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373-383.

30
31
32
33 22 Thygesen SK, Christiansen CF, Christensen S, *et al*. The predictive value of ICD-10 diagnostic
34 coding used to assess Charlson comorbidity index conditions in the population-based Danish National
35 Registry of Patients. *BMC Med Res Methodol* 2011;**11**:83.

36
37
38
39
40 23 Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic
41 regression analyses. *Am J Epidemiol* 1995;**142**:1255-1264.

42
43
44
45
46 24 Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta*
47
48 2003;**337**:169-172.

49
50
51
52 25 Miller M, Morley JE, Rubenstein LZ. Hyponatremia in a nursing home population. *J Am Geriatr Soc*
53
54 1995;**43**:1410-1413.

		ICD-10 code of hyponatremia recorded in the DNRP*	
		Yes	No
Hyponatremic 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 2x2 table and validity measure estimation formulas
338x190mm (96 x 96 DPI)

review only

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8-9
		(b) Describe any methods used to examine subgroups and interactions	8-9
		(c) Explain how missing data were addressed	9
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(b) Report category boundaries when continuous variables were categorized	11-12
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15, 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Validity of the International Classification of Diseases, 10th revision (ICD-10) discharge diagnosis codes for hyponatremia in the Danish National Registry of Patients

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-004956.R1
Article Type:	Research
Date Submitted by the Author:	31-Mar-2014
Complete List of Authors:	Holland-Bill, Louise; Aarhus University Hospital, Department of Clinical Epidemiology Christiansen, Christian F; Aarhus University Hospital, Department of Clinical Epidemiology Ulrichsen, Sinna; Aarhus University Hospital, Department of Clinical Epidemiology Ring, Troels; Aalborg University Hospital, Department of Nephrology Jørgensen, Jens Otto; Aarhus University Hospital, Department of Endocrinology and Internal Medicine Toft Sørensen, Henrik; Aarhus University Hospital, Department of Clinical Epidemiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Health services research, Diagnostics, Renal medicine
Keywords:	EPIDEMIOLOGY, Nephrology < INTERNAL MEDICINE, STATISTICS & RESEARCH METHODS

SCHOLARONE™
Manuscripts

Validity of the International Classification of Diseases, 10th revision (ICD-10) discharge diagnosis codes for hyponatremia in the Danish National Registry of Patients

Authors and affiliations:

Louise Holland-Bill* MD

Christian Fynbo Christiansen* MD, PhD

Sinna Pilgaard Ulrichsen* MSc

Troels Ring# MD

Jens Otto Lunde Jørgensen§ MD, DMSc

Henrik Toft Sørensen* MD, PhD, DMSc.

*Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

#Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark

§Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

Corresponding author:

Louise Holland-Bill, MD

Department of Clinical Epidemiology, Aarhus University Hospital

Olof Palmes Allé 43-45

8200 Aarhus N, Denmark

E-mail: louise.bill@dce.au.dk

Tel: +45 871 68063

Fax: +45 871 67215

Keywords: validation study; ICD 10; hyponatremia; diagnosis; population register; clinical laboratory information system

Word count: 3,005

ABSTRACT

OBJECTIVE: To examine the validity of the *International Classification of Diseases*, 10th revision (ICD-10) codes for hyponatremia 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. Patient could be included in the study more than once, and we did not restrict to patients with serum sodium measurements (total of n=2,186,642 hospitalizations).

MAIN OUTCOME MEASURE: We validated ICD-10 discharge diagnoses of hyponatremia 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 hospitalization confirmed the diagnosis. We estimated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for ICD-10 codes for hyponatremia overall and for cut-off points for increasing hyponatremia severity.

RESULT: An ICD-10 code for hyponatremia was recorded in the DNRP in 5,850 of the 2,186,642 hospitalizations identified. According to laboratory measurements, however, hyponatremia was present in 306,418 (14%) hospitalizations. Sensitivity of hyponatremia diagnoses was 1.8% (95% confidence interval (CI): 1.7%-1.8%). For sodium values <115mmol/l, sensitivity was 34.3% (95% CI: 32.6%-35.9%). Overall PPV was 92.5% (95% CI: 91.8%-93.1%), and decreased with increasing hyponatremia severity. Specificity and NPV were high for all cut-off points ($\geq 99.8\%$ and $\geq 86.2\%$ respectively). Hyponatremic patients without a corresponding ICD-10 discharge diagnosis were younger and had higher Charlson Comorbidity Index scores than hyponatremic patients with a hyponatremia code in the DNRP.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

For peer review only

Article summary

Article focus

- Hospital discharge diagnoses for hyponatremia recorded in the Danish National Registry of Patients (DNRP) may constitute valuable data sources for epidemiologic studies, however the validity of data must be established.

Key Message

- ICD-10 coding of hyponatremia in the Danish National Registry of Patients (DNRP) is highly specific but greatly incomplete.
- Epidemiological studies relying on discharge diagnoses of hyponatremia may be susceptible to differential misclassification.

Strengths and limitation of this study

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

INTRODUCTION

Hyponatremia, defined as a serum sodium value $<135\text{mmol/l}$, 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 inappropriate antidiuretic hormone, vomiting, and diarrhea, 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 hyponatremia 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 etiology and prognosis of hyponatremia remain unknown.

The Danish population-based medical registries may offer a unique opportunity for studies of the epidemiology of hyponatremia, if data are valid. However, as symptoms of mild and moderate hyponatremia 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 hyponatremia in epidemiologic studies may cause bias that can affect the validity of study results.[11]

To date, only one study has investigated the validity of *International Classification of Diseases* (ICD), 10th revision (ICD-10) codes for hyponatremia. 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 hyponatremia coding was found to be as low as 7%. For inpatients younger than 66 years, knowledge of the validity hyponatremia diagnoses is limited to a study performed in a single hospital in the Netherlands using ICD-9 codes for hyponatremia. 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 hyponatremia in the US.[14]

1
2
3
4 We therefore conducted the first population-based study examining the validity of ICD-10 inpatient
5 discharge diagnoses of hyponatremia in the Danish National Registry of Patients (DNRP), including
6 patients of all ages.
7
8
9

10 11 12 13 **METHODS**

14 15 **Setting and data collection**

16
17 We used the DNRP to identify all admissions to hospitals in the North and Central Denmark Regions
18 (2.1 million inhabitants in the study period) from 1 January 2006 to 31 December 2011. The DNRP
19 contains information, including date of admission and discharge, department code and discharge
20 diagnoses, on all admissions to Danish non-psychiatric hospitals since 1977.[15,16]

21
22 By use of the unique 10-digit civil registration number, assigned to all Danish residents since 1968,[17]
23 we linked each patient's DNRP data to the clinical laboratory information system (LABKA) research
24 database. For patients living in the North and Central Denmark Regions, data on virtually all
25 specimens analyzed in clinical laboratories by hospitals and medical practitioners are entered into a
26 computer-based clinical laboratory information system, which functions as a routine diagnostic tool for
27 medical personnel.[18] Data are transferred electronically to the LABKA research database, managed
28 by Aarhus University. Analyses are coded according to the NPU (Nomenclature, Properties and Units)
29 system. The LABKA research database contains the civil registration number, time and date of blood
30 sampling, and identification code of the requesting physician or hospital department.[18] We used the
31 LABKA research database to retrieve information on all serum sodium measurements recorded during
32 each of the identified hospitalizations.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51

52 **Hyponatremia diagnosis (ICD-10 code algorithm)**

53
54 At hospital discharge, the attending physician assigns one primary diagnosis, reflecting the main
55 reason for hospitalization and treatment and up to 19 secondary diagnoses regarding additional
56
57
58
59
60

1
2
3
4 clinically relevant conditions, including underlying diseases, complications and symptoms.[19]

5
6 Diagnoses recorded in the DNRP have been coded according to the *International Classification of*
7
8
9 *Diseases* (ICD), 10th revision (ICD-10) since 1994.[16]

10
11 We developed an algorithm based on ICD-10 codes to identify primary and secondary discharge
12
13 diagnoses of hyponatremia recorded in the DNRP for each hospitalization. The following ICD-10
14
15 codes were included in the algorithm: E87.1 (Hypo-osmolality and hyponatremia), E87.1A
16
17 (Hyponatremia) and P74.2B (Hyponatremia in newborns [Danish version of ICD-10]).
18
19

20 21 22 **Gold Standard (laboratory serum sodium measurements)**

23
24 We used serum sodium measurements recorded in the LABKA research database as the gold
25
26 standard to confirm or disconfirm a diagnosis of hyponatremia identified by the ICD-10 algorithm.

27
28 Hyponatremia was defined as serum sodium values <135 mmol/l for patients older than 30 days and
29
30 <133 mmol/l for infants 30 days of age or younger.[20] Patients were considered to have
31
32 hyponatremia if at least one hyponatremic serum sodium value was recorded during their
33
34 hospitalization. If no serum sodium measurement was available, the patient was assumed to have a
35
36 non-hyponatremic serum sodium value (135-145mmol/l). The following cut-off points for increasing
37
38 severity of hyponatremia were chosen: 135 mmol/l, 130mmol/l, 125mmol/l, 120mmol/l and
39
40 115mmol/l.[13] The corresponding levels for infants less than 31 days of age were 133mmol/l,
41
42 128mmol/l, 123mmol/l, 118mmol/l and 113mmol/l.
43
44
45
46
47

48 **Other Variables**

49
50 For each patient, we assessed comorbidity by information retrieved from the DNRP on the conditions
51
52 included in the Charlson Comorbidity Index (CCI). The CCI includes 19 medical conditions, each
53
54 assigned a weighted score between one and six. The sum of these individual scores is used as a
55
56 measure of a patient's comorbidity burden.[21, 22] We calculated CCI scores for each patient and
57
58
59
60

1
2
3
4 defined three comorbidity levels: low (CCI score 0), medium (CCI score 1-2) and high (CCI score of 3
5
6 or above). We included morbidities recorded within 10 years prior to the current hospitalization, as
7
8 conditions requiring hospital treatment within this timeframe would likely influence the attending
9
10 physician's diagnostic approach and evaluation during the current hospitalization.

11
12
13 Furthermore, we obtained information on department of admission and year of admission from the
14
15 DNRP. Departments were categorized in the following five groups: internal medicine, surgery,
16
17 gynecology/obstetrics, pediatrics, and other.
18
19

20 21 22 **Statistical analysis**

23
24 Patients with a hyponatremic serum sodium value recorded in the LABKA research database were
25
26 divided into two categories: Those with an ICD-10 code for hyponatremia in the DNRP and those
27
28 without. We described both groups of patients in terms of gender, age (median and associated
29
30 interquartile range (IQR)), department of admission, CCI score and specific comorbidities.

31
32 We estimated the sensitivity, specificity, PPV, and NPV (see Figure 1) for ICD-10 codes for
33
34 hyponatremia in the DNRP with corresponding 95% confidence intervals (CI), using the exact method
35
36 for binomial proportions. We defined sensitivity as the probability an ICD-10 code for hyponatremia
37
38 being registered in the DNRP, when the laboratory test result identified presence of hyponatremia.

39
40 Specificity was defined as the probability of an ICD-10 code for hyponatremia not being registered in
41
42 the DNRP, when hyponatremia was not identified in laboratory test results. We estimated the PPV as
43
44 the proportion of patients for whom an ICD-10 code for hyponatremia recorded in the DNRP could be
45
46 confirmed by a serum sodium measurement, and NPV as the proportion of patients with no ICD-10
47
48 code for hyponatremia in the DNRP, for whom non-hyponatremic, or no serum sodium values were
49
50 recorded in the LABKA research database. The analyses were repeated for all hyponatremia cut-off
51
52 points and after stratification by age group categories, department of admission and admission year.
53
54
55
56
57
58
59
60

1
2
3
4 Finally, we conducted four sensitivity analyses. First, we performed a complete case analysis, a
5 method for dealing with missing data considering only subjects with recorded values for all
6 covariates,[23] meaning that only patients with at least one serum sodium measurement during their
7 hospitalization were included in the analysis. We did so, in order to evaluate the assumption that
8 patients without a serum sodium measurement were normonatremic. In the second sensitivity
9 analysis, we included only patients with more than one serum sodium measurement during their
10 hospitalization. In the third sensitivity analysis, we included only the ICD-10 codes E87.1A
11 (hyponatremia) and P74.2B (hyponatremia in newborns). Because epidemiologic studies often focus
12 on incident cases, we performed a post-hoc sensitivity analysis in which we restricted to the first
13 hospitalization for each patient in the study period

14
15
16
17
18
19
20
21
22
23
24
25
26 Data analyses were performed using the statistical software package STATA (version 12; Stata Corp,
27 College Station, TX, USA).

28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
The study was approved by the Danish Data Protection Agency (record number 2006-53-1396). 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 hospitalizations (819,701 individual patients) within the study period. For
1,308,740 (60%) hospitalizations, at least one serum sodium measurement was recorded in the
LABKA research database, and for 1,037,647 (47%) subsequent measurements were recorded.
According to the recorded serum sodium value, hyponatremia was present in 306,418 hospitalizations
(14%). In the DNRP, we identified 5,850 hospitalizations with an ICD-10 code of hyponatremia (hypo-
osmolality and hyponatremia= 3,722, hyponatremia=2,124, hyponatremia in newborns=4) among all

2,186,642 hospitalizations. Of these, 440 did not have a hyponatremic serum sodium value recorded in the LABKA research database.

Table 1 shows the distribution of hospitalizations by presence/absence of an ICD-10 diagnosis of hyponatremia recorded in the DNRP, by gender, age and comorbidity variables, for patients with hyponatremic serum sodium values. Patients who had an ICD-10 code of hyponatremia recorded in the DNRP and a corresponding hyponatremic serum sodium measurement, were on average older, more often female, more likely admitted to an internal medicine department, and characterized by lower comorbidity levels than patients with no hyponatremia diagnosis in the DNRP, but hyponatremic serum sodium values recorded in the LABKA research database. Cerebrovascular disease, dementia, and ulcer disease were the only comorbidities more frequently found in patients with an ICD-10 code for hyponatremia and corresponding hyponatremic serum sodium value, compared to hyponatremic patients without a hyponatremia diagnosis in the DNRP. (Table 1)

Table 1.

Characteristics of hospitalizations identified in the DNRP from 2006 to 2011

	Hospitalizations with at least on serum sodium value <135 mmol/l recorded in the LABKA research database		All hospitalizations (n=2,186,642) n (%)
	ICD-10 code of hyponatremia in the DNRP* (n=5,410) n (%)	No ICD-10 code of hyponatremia in the DNRP* (n=301,008) n (%)	
Sex			
Female	3,643 (67.3)	148,120 (49.3)	1,168,803 (53.5)
Male	1,767 (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	5,173 (95.6)	184,848 (61.6)	943,121 (43.1)
Surgical	184 (3.4)	88,378 (29.4)	630,525 (28.8)
Gynaecologic/obstetric	10 (0.2)	7,104 (2.4)	347,365 (15.9)
Pediatric	29 (0.5)	15,830 (5.3)	165,289 (7.6)
Other	14 (0.3)	4,848 (1.6)	100,342 (4.6)
CCI level_(score)			

Low (0)	2,075 (38.4)	100,398 (33.4)	1,232,762 (56.4)
Medium (1-2)	2,182 (40.3)	106,874 (35.5)	588,783 (26.9)
High (≥3)	1,153 (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	1,017 (18.8)	39,466 (13.1)	182,304 (8.3)
Dementia	107 (3.1)	4,247 (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)	6,279 (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)	2,462 (0.8)	16,060 (0.7)
Moderate to severe renal disease	143 (2.6)	20,123 (6.7)	75,441 (3.5)
Malignant tumor	781 (14.4)	64,882 (21.6)	312,845 (14.3)
Leukemia	22 (0.4)	4,636 (1.5)	17,190 (0.8)
Lymphoma	51 (0.9)	7,096 (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)	2,014 (0.1)

* DNRP = Danish National Registry of Patients

Sensitivity, specificity, PPV and NPV

For 440 (7.5%) of the 5,850 hospitalizations with an ICD-10 code for hyponatremia recorded in the DNRP, no hyponatremic serum sodium measurement was recorded in the LABKA research database during the hospitalization (for 178, no measurement was recorded at all). This corresponds to a PPV of an ICD-10 code for hyponatremia of 92.5% (95% CI: 91.8%–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 5,410 hospitalizations had both an ICD-10 code recorded in the DNRP and a corresponding hyponatremic laboratory measurement, resulting in a sensitivity of the ICD-10 codes of 1.8% (95% CI: 1.7%–1.8%). Sensitivity increased with lower cut-off points for serum

sodium, reaching 34.3% (95% CI: 32.6%–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%–86.2%), respectively. Specificity and NPV remained high for all serum sodium cut-off points (Table 2).

Table 2.

Validity of ICD-10 codes for hyponatremia recorded in the DNRP*, using serum sodium measurements in the LABKA research database as gold standard.

Hyponatremic serum sodium value recorded in LABKA research database (mmol/l)		ICD-10 code for hyponatremia recorded in the DNRP*			Validity Measures % (95% CI)	
		Yes	No	Total		
Overall						
Na<135 [□]	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)
Cut-off points for increasing severity of hyponatremia						
Na<130 [§]	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 [#]	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 [£]	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 [§]	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)

*DNRP = Danish National Registry of Patients

[□] Corresponding to <133 mmol/l for infants of 30 day or less of age

[§] Corresponding to <128 mmol/l for infants of 30 day or less of age

[#] Corresponding to <123 mmol/l for infants of 30 day or less of age

[£] Corresponding to <118 mmol/l for infants of 30 day or less of age

[§] Corresponding to <113 mmol/l for infants of 30 day or less of age

Sensitivity was higher among admissions to internal medicine departments than among admissions to surgical, gynecologic/obstetric, pediatric, and “other” departments (Table 3). The validity measures were virtually unchanged across strata of admission year.

Table 3.

Validity of ICD-10 codes for hyponatremia recorded in the DNRP, stratified by age group categories, year and department of admission, for serum sodium values <135mmol/l^a and <125mmol/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 (0.1-0.2)	3.0 (1.5-5.2)	100 (100-100)	100 (100-100)	84.4 (67.2-94.7)	34.4 (18.6-53.2)	94.6 (94.6-94.7)	99.9 (99.9-99.9)
15-34	0.2 (0.2-0.3)	4.7 (3.0-6.9)	100 (100-100)	100 (100-100)	80.0 (65.4-90.4)	51.1 (35.8-66.3)	95.5 (95.4-95.5)	99.9 (99.9-99.9)
35-49	0.9 (0.8-1.0)	7.8 (6.7-9.0)	100 (100-100)	100 (100-100)	91.3 (87.3-94.4)	67.2 (61.2-72.8)	90.8 (90.7-90.9)	99.3 (99.3-99.3)
50-64	1.3 (1.3-1.4)	9.6 (8.9-10.3)	100 (100-100)	99.9 (99.9-99.9)	93.9 (92.2-95.3)	69.6 (66.7-72.3)	83.6 (83.5-83.7)	98.5 (98.4-98.5)
65-79	1.8 (1.7-1.9)	13.6 (12.9-14.4)	100 (100-100)	99.8 (99.8-99.8)	92.9 (91.7-94.0)	57.2 (55.0-59.3)	79.1 (78.9-79.2)	98.5 (98.4-98.5)
≥80	3.4 (3.3-3.6)	21.0 (19.9-22.1)	99.9 (99.9-99.9)	99.5 (99.5-99.5)	92.0 (90.8-93.0)	47.7 (45.7-49.7)	75.7 (75.5-75.9)	98.3 (98.3-98.4)
Admission Year								
2006	1.5 (1.4-1.7)	12.5 (11.5-13.5)	100 (100-100)	99.9 (99.9-99.9)	92.8 (90.8-94.5)	66.6 (63.2-69.9)	86.8 (86.6-86.9)	99.0 (98.9-99.0)
2007	1.4 (1.3-1.5)	12.0 (11.0-13.1)	100 (100-100)	99.9 (99.9-99.9)	94.4 (92.4-96.0)	65.3 (61.6-68.8)	87.0 (86.9-87.1)	99.0 (99.0-99.1)
2008	1.7 (1.6-1.8)	12.3 (11.3-13.3)	100 (100-100)	99.9 (99.9-99.9)	91.1 (89.1-92.8)	53.6 (50.4-56.8)	85.9 (85.8-86.1)	99.0 (98.9-99.0)
2009	1.8 (1.7-1.9)	12.6 (11.6-13.6)	100 (100-100)	99.9 (99.8-99.9)	93.4 (91.7-94.8)	51.4 (48.4-54.5)	85.5 (85.3-85.6)	99.0 (98.9-99.0)
2010	1.9 (1.8-2.0)	14.2 (13.2-15.4)	100 (100-100)	99.9 (99.9-99.9)	91.6 (89.8-93.2)	54.4 (51.4-57.4)	86.3 (86.2-86.4)	99.1 (99.0-99.1)
2011	2.2 (2.0-2.3)	15.2 (14.1-16.4)	100 (100-100)	99.9 (99.9-99.9)	92.2 (90.6-93.6)	49.8 (47.0-52.7)	85.8 (85.7-85.9)	99.1 (99.0-99.1)
Department								
Internal medicine	2.7 (2.7-2.8)	16.5 (16.0-17.0)	99.9 (99.9-100)	99.7 (99.7-99.7)	92.8 (92.1-93.4)	56.0 (54.7-57.3)	80.3 (80.2-80.4)	98.3 (98.3-98.3)
Surgical	0.2 (0.2-0.2)	2.3 (1.9-2.8)	100 (100-100)	100 (100-100)	90.6 (85.8-94.3)	57.6 (50.5-64.5)	86.0 (85.9-86.1)	99.2 (99.2-99.2)
Gynecologic/ Obstetric	0.1 (0.1-0.3)	3.1 (1.2-6.7)	100 (100-100)	100 (100-100)	76.9 (46.2-95.0)	46.2 (19.2-74.9)	98.0 (97.9-98.0)	99.9 (99.9-100)
Pediatric	0.2 (0.1-0.3)	3.4 (1.7-5.8)	100 (100-100)	100 (100-100)	85.3 (68.9-95.0)	35.3 (19.7-53.5)	90.4 (90.3-90.6)	99.8 (99.8-99.8)
Other	0.3 (0.2-0.5)	1.5 (0.4-3.9)	100 (100-100)	100 (100-100)	58.3 (36.6-77.9)	16.7 (4.74-37.4)	95.2 (95.0-95.3)	99.7 (99.7-99.8)

* DNRP = Danish National Registry of Patients

^aCorresponding to <133mmol/l for infants of 30 day or less of age

[#]Corresponding to <123mmol/l for infants of 30 day or less of age

Sensitivity analyses

Compared to the primary analyses, we observed no changes in neither sensitivity nor specificity estimates, when including only patients with at least one serum sodium measurement during their hospitalization 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 hyponatremia, PPV increased slightly and sensitivity decreased (94.6% (95% CI: 93.6%–95.6%) and 0.7% (95% CI: 0.6%–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 hospitalization in the study period. PPV and NPV generally increased, although only very slightly for the overall estimate (Table 4).

Table 4.

Sensitivity Analyses.

Hyponatremic serum sodium value recorded in 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 hospitalization % (95% CI)	Requiring >1 serum sodium measurement during hospitalization % (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						
	Sensitivity	1.8 (1.7-1.8)	1.8 (1.7-1.8)	1.9 (1.8-2.0)	0.7 (0.6-0.7)	1.7(1.7-1.9)
	Specificity	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)
Na<135	PPV	92.5 (91.8-93.1)	95.4 (94.8-95.9)	95.8 (95.2-96.3)	94.6 (93.6-95.6)	93.5 (92.0-94.7)
	NPV	86.2 (86.2-86.2)	76.9 (76.8-77.0)	74.7 (74.6-74.8)	86.1 (86.0-86.1)	91.6 (91.6-91.7)
Cut-off points for increasing severity of hyponatremia						
	Sensitivity	5.3 (5.2-5.5)	5.3 (5.2-5.5)	5.6 (5.4-5.7)	2.1 (2.0-2.2)	6.3 (5.9-6.7)
Na<130	Specificity	99.9 (99.9-99.9)	99.9 (99.9-99.9)	99.9 (99.9-99.9)	100 (100-100)	100 (100-100)
	PPV	77.4 (76.3-78.5)	79.8 (78.7-80.9)	80.5 (79.4-81.6)	83.0 (81.4-84.6)	82.2 (80.7-84.8)
	NPV	96.3 (96.3-96.3)	93.8 (93.8-93.9)	93.0 (93.0-93.1)	96.2 (96.2-96.2)	97.9 (97.9-98.0)

	Sensitivity	13.1 (12.7-13.6)	13.1 (12.7-13.6)	13.6 (13.1-14.0)	5.4 (5.1-5.7)	15.6 (14.6-16.6)
	Specificity	99.9 (99.9-99.9)	99.8 (99.8-99.8)	99.8 (99.8-99.8)	100 (100-100)	99.9 (99.9-99.9)
Na<125	PPV	55.7 (54.5-57.0)	57.5 (56.2-58.8)	57.9 (56.5-59.2)	62.5 (60.4-64.5)	62.3 (59.6-64.8)
	NPV	99.0 (99.0-99.0)	98.3 (98.3-98.4)	98.1 (98.1-98.1)	98.9 (98.9-98.9)	99.4 (99.4-99.4)
	Sensitivity	24.9 (24.0-25.9)	24.9 (24.0-25.8)	25.4 (24.5-26.4)	6.3 (5.8-6.9)	29.3 (27.3-31.3)
	Specificity	99.8 (99.8-99.8)	99.7 (99.7-99.7)	99.7 (99.7-99.7)	100 (100-100)	99.9 (99.9-99.9)
Na<120	PPV	35.2 (34.0-36.5)	36.3 (35.1-37.6)	36.3 (35.0-37.6)	50.6 (47.5-53.7)	43.7 (41.0-46.4)
	NPV	99.7 (99.7-99.7)	99.5 (99.5-99.5)	99.5 (99.4-99.5)	99.6 (99.6-99.7)	99.8 (99.8-99.8)
	Sensitivity	34.3 (32.6-35.9)	34.2 (32.6-35.9)	34.9 (33.1-36.6)	9.3 (8.3-10.3)	38.8 (35.5-42.1)
	Specificity	99.8 (99.8-99.8)	99.7 (99.6-99.7)	99.6 (99.6-99.6)	100 (100-100)	99.9 (99.9-99.9)
Na<115	PPV	18.9 (17.9-20.0)	19.5 (18.5-20.6)	19.5 (18.4-20.6)	28.8 (26.1-31.7)	24.2 (22.0-26.6)
	NPV	99.9 (99.9-99.9)	99.8 (99.8-99.8)	99.8 (99.8-99.8)	99.9 (99.9-99.9)	99.9 (99.9-99.9)

DISCUSSION

This is the first study to report on the validity of ICD-10 coding of hyponatremia using comprehensive population-based medical registries, and including patients of all ages. A record of a hyponatremia diagnosis in the DNRP was found to be specific to and highly predictive of hyponatremia confirmed by laboratory values. However, the disorder was greatly underreported, though to a lesser extent in patients admitted to an internal medicine department compared to other departments. We found sensitivity to be low even for severe degrees of hyponatremia. These results were robust when we used a stricter definition of hyponatremia and complete case analysis.

Our findings correspond with those of Movig *et al.*'s single-center study conducted in The Netherlands, in which ICD-9-CM coding of hyponatremia in inpatient discharge records was compared with hospital laboratory data.[13] 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.* examined ICD-10 coding for hyponatremia 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.[12] The study was, however, restricted to patients ≥ 66 years of age presenting with serum sodium values at time of admission or emergency department contact. In line

1
2
3
4 with their results, we found that the median age of patients with an ICD-10 code of hyponatremia
5 recorded in the DNRP, which could be confirmed by laboratory results, was higher than that of
6
7
8 hyponatremic patients with no ICD-10 code for hyponatremia recorded in the DNRP. However, the
9
10 sensitivity estimates did not reach those found by Gandhi *et al.* even for patients 65-79 and ≥ 80 years
11
12 of age. Shea *et al.* also reported higher sensitivity compared to our results (3.5% for a cut-off point of
13
14 <136 mmol/l and 29.6% for the cut-off point of 125 mmol/l) in their study examining the validity of ICD-
15
16 9 codes of hyponatremia in an outpatient managed-care population.[14] Outpatient serum sodium
17
18 laboratory tests were compared with outpatient professional ICD-9 claims registered within 15 days
19
20 before or after the laboratory claim. The PPV was 62.6% for serum sodium levels <136 mmol/l and
21
22 10.4% for levels <125 mmol/l. As noted in the paper, detected hyponatremia may be the cause for
23
24 follow-up visits in an outpatient setting, without the need for repeat measurements. This could lead to
25
26 lower PPV compared to our study and the study by Movig *et al.* In addition, managed-care claims
27
28 databases encompass an employer-based commercially insured population. Shea *et al.*'s study thus
29
30 may not be representative of elderly populations, in which prevalence of hyponatremia is high.[24, 25]
31
32 This also may explain why their results differed from ours.
33
34
35
36
37
38

39 The major strengths of our study are its population-based design and unambiguous individual-level
40
41 linkage between registries containing complete data on all hospitalizations and laboratory tests in a
42
43 well-defined population. This eliminates the risk of selection bias. Several potential study limitations
44
45 must be considered. We relied on only one (the lowest) serum sodium value recorded to define
46
47 presence of hyponatremia, and also did not consider duration of hyponatremia. Clinicians may be
48
49 more likely to regard hyponatremia as clinically relevant, and hence to include the condition in
50
51 discharge diagnoses, if it is detected in more than one measurement. In this context, it is important to
52
53 note that patient transfers between departments are registered as separate admissions in the DNRP
54
55 and we examined the validity of ICD-10 coding for each registered admission. The PPV may have
56
57
58
59
60

1
2
3
4 been even higher if we had considered contiguous admissions as a single admission. Finally, we
5
6 chose to include patients without serum sodium measurements and to consider them as
7
8 normonatremic in the main analysis. We did so to detect false positive diagnoses and thereby obtain
9
10 accurate estimates of predictive values. Serum sodium is often measured as a routine procedure, and
11
12 rarely due to specific suspicion. Though frequently measured, the proportion of patients with
13
14 unacknowledged hyponatremia is most often unknown. We therefore performed a complete case
15
16 analysis, including only patients with serum sodium measurements. As the results did not differ
17
18 markedly from those of the primary analysis, we believe that including patients without serum sodium
19
20 measurements in the normonatremic group was justified.
21
22
23

24
25
26 We can only speculate on reasons for the low sensitivity of the ICD-10 coding of hyponatremia found
27
28 in our study. A diagnosis of hyponatremia was less likely recorded in patients with high levels of
29
30 comorbidity, which may indicate that hyponatremia is mainly considered a bystander of the underlying
31
32 diseases. If hyponatremia is mild or transient, and does not require intervention or specific attention, it
33
34 may not warrant documentation. However, even for very severe hyponatremia (<115 mmol/l), which is
35
36 potentially fatal and requires immediate intervention, sensitivity was low. We believe that this most
37
38 likely reflects negligence of proper coding practice rather than lack of attention to the clinical
39
40 importance of low serum sodium levels. With the increasing use of electronic medical records it would
41
42 be feasible and worthwhile to automatically assign discharge diagnoses to patients with gross
43
44 abnormal laboratory values. However, the ultimate responsibility for summarizing the most important
45
46 reasons for treatment and care still rests upon the discharging physician. Our results suggest that
47
48 hyponatremia is not coded in the presence of coexisting illness deemed more important, and that the
49
50 fact that hyponatremia may be an important indicator of a poor prognosis is not yet acknowledged.
51
52
53
54
55
56
57
58
59
60

1
2
3
4 The results of this validation study emphasize the need for caution when relying on ICD-10 codes for
5 hyponatremia in research. Based on the estimated PPV and specificity, patients with an ICD-10 code
6 of hyponatremia can safely be assumed to actually have hyponatremia. However, the low sensitivity
7 renders the ICD-10 codes inappropriate for use in studies examining prevalence, incidence, and
8 absolute risk, due to a high degree of misclassification. Sensitivity increased with decreasing serum
9 sodium levels, suggesting that studies using ICD-codes to identify hyponatremia would be based
10 mainly on severe cases. Furthermore, our results indicate that quality of registration differs according
11 to age, gender, and morbidity status. Hence, studies may be susceptible to differential
12 misclassification, again resulting in biased results.
13
14
15
16
17
18
19
20
21
22
23
24
25

26 **CONCLUSION**

27
28 We found that the ICD-10 coding of hyponatremia in DNRP has high specificity but is highly
29 incomplete, resulting in very low sensitivity. When available, laboratory test results for serum sodium
30 will more correctly identify patients with hyponatremia.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Contributors

LHB participated in the design of the study, performed the data analysis, provided interpretation of study results and drafted the manuscript. SPU participated in 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 with interpretation of study results helped draft the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the Clinical Epidemiology Research Foundation and by the Danish Cancer Society (grant no. R73-A4284-13-S17).

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.

LHB, CFC, SPU and HTS are salaried employees of 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.

None of these grants or fees had any had any leverage on the design, implementation or reporting of the present study.

Data Sharing Statement: No additional data

Reference list

- 1 Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med* 2006;**119**(Suppl 1):S30-5.
- 2 Rose BD. Clinical physiology of acid-base and electrolyte disorders. 3rd ed. New York: McGraw-Hill information Services Company 1989.
- 3 Waikar SS, Curhan GC, Brunelli SM. Mortality associated with low serum sodium concentration in maintenance hemodialysis. *Am J Med* 2011;**124**:77-84.
- 4 Doshi SM, Shah P, Lei X, *et al.* Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. *Am J Kidney Dis* 2012;**59**:222-228.
- 5 Goldberg A, Hammerman H, Petcherski S, *et al.* Prognostic importance of hyponatremia in acute ST-elevation myocardial infarction. *Am J Med* 2004;**117**:242-248.
- 6 Kovesdy CP, Lott EH, Lu JL, *et al.* Hyponatremia, Hypernatremia and Mortality in Patients with Chronic Kidney Disease with and without Congestive Heart Failure. *Circulation* 2012;**125**:677-684
- 7 Scherz N, Labarere J, Mean M, *et al.* Prognostic importance of hyponatremia in patients with acute pulmonary embolism. *Am J Respir Crit Care Med* 2010;**182**:1178-1183.
- 8 Wald R, Jaber BL, Price LL, *et al.* Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med* 2010;**170**:294-302.
- 9 Chawla A, Sterns RH, Nigwekar SU, *et al.* Mortality and serum sodium: do patients die from or with hyponatremia? *Clin J Am Soc Nephrol* 2011;**6**:960-965.

1
2
3
4 10 Marco J, Barba R, Matia P, *et al.* Low prevalence of hyponatremia codification in departments of
5 internal medicine and its prognostic implications. *Curr Med Res Opin* 2013;**29**:1757-1762
6
7

8
9
10 11 Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for
11 epidemiological research. *Int J Epidemiol* 1996;**25**:435-442.
12
13

14
15 12 Gandhi S, Shariff SZ, Fleet JL, *et al.* Validity of the International Classification of Diseases 10th
16 revision code for hospitalisation with hyponatraemia in elderly patients. *BMJ Open*
17 2012;**2**:10.1136/bmjopen-2012-001727. Print 2012.
18
19
20
21

22
23 13 Movig KL, Leufkens HG, Lenderink AW, *et al.* Validity of hospital discharge International
24 Classification of Diseases (ICD) codes for identifying patients with hyponatremia. *J Clin Epidemiol*
25 2003;**56**:530-535.
26
27
28

29
30 14 Shea AM, Curtis LH, Szczech LA, *et al.* Sensitivity of International Classification of Diseases codes
31 for hyponatremia among commercially insured outpatients in the United States. *BMC Nephrol*
32 2008;**9**:5.
33
34
35
36

37
38 15 Andersen TF, Madsen M, Jorgensen J, *et al.* The Danish National Hospital Register. A valuable
39 source of data for modern health sciences. *Dan Med Bull* 1999;**46**:263-268.
40
41
42

43
44 16 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*
45 2011;**39**(Suppl 7):30-33.
46
47

48
49 17 Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;**39**(Suppl 7):22-
50 25.
51
52
53
54
55
56
57
58
59
60

1
2
3
4 18 Grann AF, Erichsen R, Nielsen AG, *et al*. Existing data sources for clinical epidemiology: The
5 clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clin*
6
7
8
9 *Epidemiol* 2011;**3**:133-138.

10
11 19 SSI - Joint Content for Basic Registration of Hospital Patients.

12
13 <http://www.ssi.dk/Sundhedsdataogit/Indberetning%20og%20patientregistrering/Patientregistrering/Faellesindhold.aspx> (accessed 18 Dec 2013; updated 9 Dec 2013).

14
15
16
17
18
19 20 Laboratory Manual for Hospitals in the North Jutland Region. 2011.

20
21 <http://www.laboratorievejledning.dk/prog/view.aspx?AfsnitID=103&KapitelID=26&UKapitelID=194>
22
23 (accessed 15 Dec 2013; updated 20 Dec 2011).

24
25
26
27 21 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in
28 longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373-383.

29
30
31
32 22 Thygesen SK, Christiansen CF, Christensen S, *et al*. The predictive value of ICD-10 diagnostic
33 coding used to assess Charlson comorbidity index conditions in the population-based Danish National
34 Registry of Patients. *BMC Med Res Methodol* 2011;**11**:83.

35
36
37
38 23 Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic
39 regression analyses. *Am J Epidemiol* 1995;**142**:1255-1264.

40
41
42
43 24 Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta*
44
45
46
47
48 2003;**337**:169-172.

49
50
51
52 25 Miller M, Morley JE, Rubenstein LZ. Hyponatremia in a nursing home population. *J Am Geriatr Soc*
53
54
55
56
57
58
59
60 1995;**43**:1410-1413.

1
2
3
4
5
6
7
8
9
10 **Validity of the International Classification of Diseases, 10th revision (ICD-**
11 **10) discharge diagnosis codes for hyponatremia in the Danish National**
12 **Registry of Patients**
13

14
15
16
17 **Authors and affiliations:**

18 Louise Holland-Bill* MD

19
20 Christian Fynbo Christiansen* MD, PhD

21
22 Sinna Pilgaard Ulrichsen* MSc

23
24 Troels Ring# MD

25
26 Jens Otto Lunde Jørgensen§ MD, DMSc

27
28 Henrik Toft Sørensen* MD, PhD, DMSc.

29
30 *Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

31 #Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark

32 §Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark
33
34
35

36 **Corresponding author:**

37 Louise Holland-Bill, MD

38 Department of Clinical Epidemiology, Aarhus University Hospital

39 Olof Palmes Allé 43-45

40 8200 Aarhus N, Denmark

41 E-mail: louise.bill@dce.au.dk

42 Tel: +45 871 68063

43 Fax: +45 871 67215
44
45
46

47 **Keywords:** validation study; ICD 10; hyponatremia; diagnosis; population register; clinical laboratory

48
49 information system
50

51 **Word count:** 2,8293,005
52
53
54
55
56
57
58
59
60

ABSTRACT

OBJECTIVE: To examine the validity of the *International Classification of Diseases*, 10th revision (ICD-10) codes for hyponatremia 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. Patient could be included in the study more than once, and we did not restrict to patients with serum sodium measurements (total of n=2,186,642 hospitalizations).

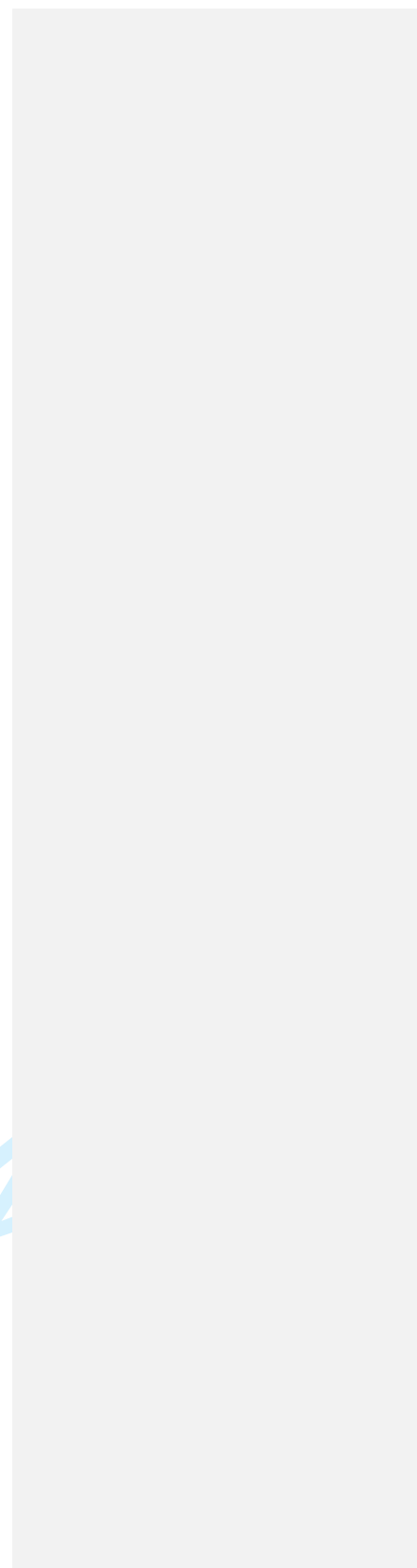
MAIN OUTCOME MEASURE: We validated ICD-10 discharge diagnoses of hyponatremia recorded in the DNRP, using serum sodium measurements obtained from the laboratory information systems (LABKA) research database as the gold standard. One sodium value <135 mmol/l measured at any time during hospitalization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

RESULT: An ICD-10 code for hyponatremia was recorded in the DNRP in 5,850 of the 2,186,642 hospitalizations identified. According to laboratory measurements, however, hyponatremia was present in 306,418 (14%) hospitalizations. Sensitivity of hyponatremia diagnoses was 1.8% (95% confidence interval (CI): 1.7%-1.8%). For sodium values <115mmol/l, sensitivity was 34.3% (95% CI: 32.6%-35.9%). Overall PPV was 92.5% (95% CI: 91.8%-93.1%), and decreased with increasing hyponatremia severity. Specificity and NPV were high for all cut-off points ($\geq 99.8\%$ and $\geq 86.2\%$ respectively). Hyponatremic patients without a corresponding ICD-10 discharge diagnosis were younger and had higher Charlson Comorbidity Index scores than hyponatremic patients with a hyponatremia code in the DNRP.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

For peer review only



Article summary

Article focus

- Hospital discharge diagnoses for hyponatremia recorded in the Danish National Registry of Patients (DNRP) may constitute valuable data sources for epidemiologic studies, however the validity of data must be established.

Key Message

- ICD-10 coding of hyponatremia in the Danish National Registry of Patients (DNRP) is highly specific but greatly incomplete.
- Epidemiological studies relying on discharge diagnoses of hyponatremia may be susceptible to differential misclassification.

Strengths and limitation of this study

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

INTRODUCTION

Hyponatremia, defined as a serum sodium value $<135\text{mmol/l}$, 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 inappropriate antidiuretic hormone, vomiting, and diarrhea, 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 hyponatremia 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 etiology and prognosis of hyponatremia remain unknown.

The Danish population-based medical registries may offer a unique opportunity for studies of the epidemiology of hyponatremia, if data are valid. However, as symptoms of mild and moderate hyponatremia 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 hyponatremia in epidemiologic studies may cause bias that can affect the validity of study results.[11]

To date, only one study has investigated the validity of *International Classification of Diseases* (ICD), 10th revision (ICD-10) codes for hyponatremia. This Canadian study was restricted to patients 66 years of age or older ~~presenting with a hyponatremic~~ serum sodium values at the time of emergency department contact or at hospital admission.[12] The sensitivity of hyponatremia coding was found to be as low as 7%. For inpatients younger than 66 years, knowledge of the validity hyponatremia diagnoses is limited to a study performed in a single hospital in the Netherlands using ICD-9 codes for hyponatremia. In this study, sensitivity was found to be just below 2%, using hospital laboratory data as the reference standard.[3] Similar results were found in a study examining the validity of outpatient professional ICD-9 claims for hyponatremia in the US.[14]

1
2
3
4
5
6
7
8
9
10 We therefore conducted the first population-based study examining the validity of ICD-10 inpatient
11 discharge diagnoses of hyponatremia in the Danish National Registry of Patients (DNRP), ~~in terms of~~
12 ~~sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)~~, including
13 patients of all ages.
14
15
16

17 18 **METHODS**

19 **Setting and data collection**

20 We used the DNRP to identify all admissions to hospitals in the North and Central Denmark Regions
21 (2.1 million inhabitants in the study period) from 1 January 2006 to 31 December 2011. The DNRP
22 contains information, including date of admission and discharge, department code and discharge
23 diagnoses, on all admissions to Danish non-psychiatric hospitals since 1977.[15,16]
24
25 By use of the unique 10-digit civil registration number, assigned to all Danish residents since 1968,[17]
26 we linked each patient's DNRP data to the clinical laboratory information system (LABKA) research
27 database. For patients living in the North and Central Denmark Regions, data on virtually all
28 specimens analyzed in clinical laboratories by hospitals and medical practitioners are entered into a
29 computer-based clinical laboratory information system, which functions as a routine diagnostic tool for
30 medical personnel.[18] Data are transferred electronically to the LABKA research database, managed
31 by Aarhus University. Analyses are coded according to the NPU (Nomenclature, Properties and Units)
32 system. The LABKA research database contains the civil registration number, time and date of blood
33 sampling, and identification code of the requesting physician or hospital department.[18] We used the
34 LABKA research database to retrieve information on all serum sodium measurements recorded during
35 each of the identified hospitalizations.
36
37
38
39
40
41
42
43
44
45
46
47
48

49 **Hyponatremia diagnosis (ICD-10 code algorithm)**

1
2
3
4
5
6
7
8
9
10 At hospital discharge, the attending physician assigns one primary diagnosis, reflecting the main
11 reason for hospitalization and treatment and up to 19 secondary diagnoses regarding additional
12 clinically relevant conditions, including underlying diseases, complications and symptoms.[19]
13 Diagnoses recorded in the DNRP have been coded according to the *International Classification of*
14 *Diseases* (ICD), 10th revision (ICD-10) since 1994.[16]
15
16
17
18 We developed an algorithm based on ICD-10 codes to identify **primary and secondary** discharge
19 diagnoses of hyponatremia recorded in the DNRP for each hospitalization. The following ICD-10
20 codes were included in the algorithm: E87.1 (Hypo-osmolality and hyponatremia), E87.1A
21 (Hyponatremia) and P74.2B (Hyponatremia in newborns [Danish version of ICD-10]).
22
23
24
25
26

27 **Gold Standard (laboratory serum sodium measurements)**

28 We used serum sodium measurements recorded in the LABKA research database as the gold
29 standard to confirm or disconfirm a diagnosis of hyponatremia identified by the ICD-10 algorithm.
30
31 Hyponatremia was defined as serum sodium values <135 mmol/l for patients older than 30 days and
32 <133 mmol/l for infants 30 days of age or younger.[20] Patients were considered to have
33 hyponatremia if at least one hyponatremic serum sodium value was recorded during their
34 hospitalization. If no serum sodium measurement was available, the patient was assumed to have a
35 non-hyponatremic serum sodium value (135-145mmol/l). The following cut-off points for increasing
36 severity of hyponatremia were chosen: 135 mmol/l, 130mmol/l, 125mmol/l, 120mmol/l and
37 115mmol/l.[13] The corresponding levels for infants less than 31 days of age were 133mmol/l,
38 128mmol/l, 123mmol/l, 118mmol/l and 113mmol/l.
39
40
41
42
43
44
45
46

47 **Other Variables**

48 For each patient, we assessed comorbidity by information retrieved from the DNRP on the conditions
49 included in the Charlson Comorbidity Index (CCI). The CCI includes 19 medical conditions, each
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10 assigned a weighted score between one and six. The sum of these individual scores is used as a
11 measure of a patient's comorbidity burden.[21, 22] We calculated CCI scores for each patient and
12 defined three comorbidity levels: low (CCI score 0), medium (CCI score 1-2) and high (CCI score of 3
13 or above). We included morbidities recorded within 10 years prior to the current hospitalization, as
14 conditions requiring hospital treatment within this timeframe would likely influence the attending
15 physician's diagnostic approach and evaluation during the current hospitalization.
16
17 Furthermore, we obtained information on department of admission and year of admission from the
18 DNRP. Departments were categorized in the following five groups: internal medicine, surgery,
19 gynecology/obstetrics, pediatrics, and other.
20
21
22
23
24
25
26

27 **Statistical analysis**

28 Patients with a hyponatremic serum sodium value recorded in the LABKA research database were
29 divided into two categories: Those with an ICD-10 code for hyponatremia in the DNRP and those
30 without. We described both groups of patients in terms of gender, age (median and associated
31 interquartile range (IQR)), department of admission, CCI score and specific comorbidities.
32
33 We estimated the sensitivity, specificity, PPV, and NPV (see Figure 1) for ICD-10 codes for
34 hyponatremia in the DNRP with corresponding 95% confidence intervals (CI), using the exact method
35 for binomial proportions. We defined sensitivity as the probability an ICD-10 code for hyponatremia
36 being registered in the DNRP, when the laboratory test result identified presence of hyponatremia.
37
38 Specificity was defined as the probability of an ICD-10 code for hyponatremia not being registered in
39 the DNRP, when hyponatremia was not identified in laboratory test results. We estimated the PPV as
40 the proportion of patients for whom an ICD-10 code for hyponatremia recorded in the DNRP could be
41 confirmed by a serum sodium measurement, and NPV as the proportion of patients with no ICD-10
42 code for hyponatremia in the DNRP, for whom non-hyponatremic, or no serum sodium values were
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10 recorded in the LABKA research database. The analyses were repeated for all hyponatremia cut-off
11 points and after stratification by [age group categories](#), department of admission and admission year.
12 Finally, we conducted [three-four](#) sensitivity analyses. First, we performed a complete case analysis, a
13 method for dealing with missing data considering only subjects with recorded values for all
14 covariates,[23] meaning that only patients with at least one serum sodium measurement during their
15 hospitalization were included in the analysis. We did so, in order to evaluate the assumption that
16 patients without a serum sodium measurement were normonatremic. In the second sensitivity
17 analysis, we included only patients with more than one serum sodium measurement during their
18 hospitalization. In the third sensitivity analysis, we included only the ICD-10 codes E87.1A
19 (hyponatremia) and P74.2B (hyponatremia in newborns). [Because epidemiologic studies often focus](#)
20 [on incident cases, we performed a post-hoc sensitivity analysis in which we restricted to the first](#)
21 [hospitalization for each patient in the study period](#)
22
23
24
25
26
27
28
29
30
31

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

34 The study was approved by the Danish Data Protection Agency (record number 2006-53-1396). [All](#)
35 [data were obtained from Danish public registries. According to Danish law their use does require](#)
36 [informed consent or ethics committee approval.](#)
37
38
39
40
41

42 RESULTS

43 Characteristics

44 We identified 2,186,642 hospitalizations (819,701 individual patients) within the study period. For
45 1,308,740 (60%) hospitalizations, at least one serum sodium measurement was recorded in the
46 LABKA research database, and for 1,037,647 (47%) subsequent measurements were recorded.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

(14%). In the DNRP, we identified 5,850 hospitalizations with an ICD-10 code of hyponatremia (hypo-osmolality and hyponatremia= 3,722, hyponatremia=2,124, hyponatremia in newborns=4) among all 2,186,642 hospitalizations. Of these, 440 did not have a hyponatremic serum sodium value recorded in the LABKA research database.

Table 1 shows the distribution of hospitalizations by presence/absence of an ICD-10 diagnosis of hyponatremia recorded in the DNRP, by gender, age and comorbidity variables, for patients with hyponatremic serum sodium values. Patients who had an ICD-10 code of hyponatremia recorded in the DNRP and a corresponding hyponatremic serum sodium measurement, were on average older, more often female, more likely admitted to an internal medicine department, and characterized by lower comorbidity levels than patients with no hyponatremia diagnosis in the DNRP, but hyponatremic serum sodium values recorded in the LABKA research database. Cerebrovascular disease, dementia, and ulcer disease were the only comorbidities more frequently found in patients with an ICD-10 code for hyponatremia and corresponding hyponatremic serum sodium value, compared to hyponatremic patients without a hyponatremia diagnosis in the DNRP. (Table 1)

Table 1.

Characteristics of hospitalizations identified in the DNRP from 2006 to 2011

	Hospitalizations with at least on serum sodium value <135 mmol/l recorded in the LABKA research database		All hospitalizations (n=2,186,642) n (%)
	ICD-10 code of hyponatremia in the DNRP* (n=5,410) n (%)	No ICD-10 code of hyponatremia in the DNRP* (n=301,008) n (%)	
Sex			
Female	3,643 (67.3)	148,120 (49.3)	1,168,803 (53.5)
Male	1,767 (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	5,173 (95.6)	184,848 (61.6)	943,121 (43.1)
Surgical	184 (3.4)	88,378 (29.4)	630,525 (28.8)

Gynaecologic/obstetric	10 (0.2)	7,104 (2.4)	347,365 (15.9)
Pediatric	29 (0.5)	15,830 (5.3)	165,289 (7.6)
Other	14 (0.3)	4,848 (1.6)	100,342 (4.6)
CCI level (score)			
Low (0)	2,075 (38.4)	100,398 (33.4)	1,232,762 (56.4)
Medium (1-2)	2,182 (40.3)	106,874 (35.5)	588,783 (26.9)
High (≥3)	1,153 (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	1,017 (18.8)	39,466 (13.1)	182,304 (8.3)
Dementia	107 (3.1)	4,247 (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)	6,279 (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)	2,462 (0.8)	16,060 (0.7)
Moderate to severe renal disease	143 (2.6)	20,123 (6.7)	75,441 (3.5)
Malignant tumor	781 (14.4)	64,882 (21.6)	312,845 (14.3)
Leukemia	22 (0.4)	4,636 (1.5)	17,190 (0.8)
Lymphoma	51 (0.9)	7,096 (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)	2,014 (0.1)

* DNRP = Danish National Registry of Patients

Sensitivity, specificity, PPV and NPV

For 440 (7.5%) of the 5,850 hospitalizations with an ICD-10 code for hyponatremia recorded in the DNRP, no hyponatremic serum sodium measurement was recorded in the LABKA research database during the hospitalization (for 178, no measurement was recorded at all). This corresponds to a PPV of an ICD-10 code for hyponatremia of 92.5% (95% CI: 91.8%–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 5,410 hospitalizations had both an ICD-10 code recorded in the

DNRP and a corresponding hyponatremic laboratory measurement, resulting in a sensitivity of the ICD-10 codes of 1.8% (95% CI: 1.7%–1.8%). Sensitivity increased with lower cut-off points for serum sodium, reaching 34.3% (95% CI: 32.6%–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%–86.2%), respectively. Specificity and NPV remained high for all serum sodium cut-off points (Table 2).

Table 2.

Validity of ICD-10 codes for hyponatremia recorded in the DNRP*, using serum sodium measurements in the LABKA research database as gold standard.

Hyponatremic serum sodium value recorded in LABKA research database (mmol/l)	ICD-10 code for hyponatremia recorded in the DNRP*			Validity Measures % (95% CI)		
	Yes	No	Total			
Overall						
Na<135 ^a	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)
Cut-off points for increasing severity of hyponatremia						
Na<130 ^b	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 ^c	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 ^d	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 ^e	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)

*DNRP = Danish National Registry of Patients

^a Corresponding to <133 mmol/l for infants of 30 day or less of age

^b Corresponding to <128 mmol/l for infants of 30 day or less of age

^c Corresponding to <123 mmol/l for infants of 30 day or less of age

^d Corresponding to <118 mmol/l for infants of 30 day or less of age

^s Corresponding to <113 mmol/l for infants of 30 day or less of age

Sensitivity was higher among admissions to internal medicine departments than among admissions to surgical, gynecologic/obstetric, pediatric, and "other" departments (Table 3). The validity measures were virtually unchanged across strata of admission year.

Table 3.

Validity of ICD-10 codes for hyponatremia recorded in the DNRP, stratified by age group categories, year and department of admission, for serum sodium values <135mmol/l^s and <125mmol/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 (0.1-0.2)	3.0 (1.5-5.2)	100 (100-100)	100 (100-100)	84.4 (67.2-94.7)	34.4 (18.6-53.2)	94.6 (94.6-94.7)	99.9 (99.9-99.9)
15-34	0.2 (0.2-0.3)	4.7 (3.0-6.9)	100 (100-100)	100 (100-100)	80.0 (65.4-90.4)	51.1 (35.8-66.3)	95.5 (95.4-95.5)	99.9 (99.9-99.9)
35-49	0.9 (0.8-1.0)	7.8 (6.7-9.0)	100 (100-100)	100 (100-100)	91.3 (87.3-94.4)	67.2 (61.2-72.8)	90.8 (90.7-90.9)	99.3 (99.3-99.3)
50-64	1.3 (1.3-1.4)	9.6 (8.9-10.3)	100 (100-100)	99.9 (99.9-99.9)	93.9 (92.2-95.3)	69.6 (66.7-72.3)	83.6 (83.5-83.7)	98.5 (98.4-98.5)
65-79	1.8 (1.7-1.9)	13.6 (12.9-14.4)	100 (100-100)	99.8 (99.8-99.8)	92.9 (91.7-94.0)	57.2 (55.0-59.3)	79.1 (78.9-79.2)	98.5 (98.4-98.5)
≥80	3.4 (3.3-3.6)	21.0 (19.9-22.1)	99.9 (99.9-99.9)	99.5 (99.5-99.5)	92.0 (90.8-93.0)	47.7 (45.7-49.7)	75.7 (75.5-75.9)	98.3 (98.3-98.4)
Admission Year								
2006	1.5 (1.4-1.7)	12.5 (11.5-13.5)	100 (100-100)	99.9 (99.9-99.9)	92.8 (90.8-94.5)	66.6 (63.2-69.9)	86.8 (86.6-86.9)	99.0 (98.9-99.0)
2007	1.4 (1.3-1.5)	12.0 (11.0-13.1)	100 (100-100)	99.9 (99.9-99.9)	94.4 (92.4-96.0)	65.3 (61.6-68.8)	87.0 (86.9-87.1)	99.0 (99.0-99.1)
2008	1.7 (1.6-1.8)	12.3 (11.3-13.3)	100 (100-100)	99.9 (99.9-99.9)	91.1 (89.1-92.8)	53.6 (50.4-56.8)	85.9 (85.8-86.1)	99.0 (98.9-99.0)
2009	1.8 (1.7-1.9)	12.6 (11.6-13.6)	100 (100-100)	99.9 (99.8-99.9)	93.4 (91.7-94.8)	51.4 (48.4-54.5)	85.5 (85.3-85.6)	99.0 (98.9-99.0)
2010	1.9 (1.8-2.0)	14.2 (13.2-15.4)	100 (100-100)	99.9 (99.9-99.9)	91.6 (89.8-93.2)	54.4 (51.4-57.4)	86.3 (86.2-86.4)	99.1 (99.0-99.1)
2011	2.2 (2.0-2.3)	15.2 (14.1-16.4)	100 (100-100)	99.9 (99.9-99.9)	92.2 (90.6-93.6)	49.8 (47.0-52.7)	85.8 (85.7-85.9)	99.1 (99.0-99.1)
Department								
Internal medicine	2.7 (2.7-2.8)	16.5 (16.0-17.0)	99.9 (99.9-100)	99.7 (99.7-99.7)	92.8 (92.1-93.4)	56.0 (54.7-57.3)	80.3 (80.2-80.4)	98.3 (98.3-98.3)
Surgical	0.2 (0.2-0.2)	2.3 (1.9-2.8)	100 (100-100)	100 (100-100)	90.6 (85.8-94.3)	57.6 (50.5-64.5)	86.0 (85.9-86.1)	99.2 (99.2-99.2)
Gynecologic/ Obstetric	0.1 (0.1-0.3)	3.1 (1.2-6.7)	100 (100-100)	100 (100-100)	76.9 (46.2-95.0)	46.2 (19.2-74.9)	98.0 (97.9-98.0)	99.9 (99.9-100)
Pediatric	0.2 (0.1-0.3)	3.4 (1.7-5.8)	100 (100-100)	100 (100-100)	85.3 (68.9-95.0)	35.3 (19.7-53.5)	90.4 (90.3-90.6)	99.8 (99.8-99.8)
Other	0.3	1.5	100	100	58.3	16.7	95.2	99.7

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	(0.2-0.5)	(0.4-3.9)	(100-100)	(100-100)	(36.6-77.9)	(4.74-37.4)	(95.0-95.3)	(99.7-99.8)
--	-----------	-----------	-----------	-----------	-------------	-------------	-------------	-------------

* DNRP = Danish National Registry of Patients
 † Corresponding to <133mmol/l for infants of 30 day or less of age
 ‡ Corresponding to <123mmol/l for infants of 30 day or less of age

Sensitivity analyses

Compared to the primary analyses, we observed no changes in neither sensitivity nor specificity estimates when including only patients with at least one serum sodium measurement during their hospitalization 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 24).

After restriction to the most specific ICD-10 codes for hyponatremia, PPV increased slightly and sensitivity decreased (94.6% (95% CI: 93.6%–95.6%) and 0.7% (95% CI: 0.6%–0.7%), respectively).

Estimates of specificity and NPV were virtually unchanged (Table 24).

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 hospitalization in the study period. PPV and NPV generally increased, although only very slightly for the overall estimate (Table 4).

Table 4.

Sensitivity Analyses.

Hyponatremic serum sodium value recorded in 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 hospitalization % (95% CI)	Requiring >1 serum sodium measurement during hospitalization % (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	Sensitivity 1.8 (1.7-1.8) Specificity 100 (100-100)	1.8 (1.7-1.8) 100 (100-100)	1.9 (1.8-2.0) 100 (100-100)	0.7 (0.6-0.7) 100 (100-100)	1.7(1.7-1.9) 100 (100-100)
Na<135	PPV 92.5 (91.8-93.1) NPV 86.2 (86.2-86.2)	95.4 (94.8-95.9) 76.9 (76.8-77.0)	95.8 (95.2-96.3) 74.7 (74.6-74.8)	94.6 (93.6-95.6) 86.1 (86.0-86.1)	93.5 (92.0-94.7) 91.6 (91.6-91.7)
Cut-off points for increasing severity of hyponatremia					

<u>Na<130</u>	<u>Sensitivity</u>	<u>5.3 (5.2-5.5)</u>	<u>5.3 (5.2-5.5)</u>	<u>5.6 (5.4-5.7)</u>	<u>2.1 (2.0-2.2)</u>	<u>6.3 (5.9-6.7)</u>
	<u>Specificity</u>	<u>99.9 (99.9-99.9)</u>	<u>99.9 (99.9-99.9)</u>	<u>99.9 (99.9-99.9)</u>	<u>100 (100-100)</u>	<u>100 (100-100)</u>
	<u>PPV</u>	<u>77.4 (76.3-78.5)</u>	<u>79.8 (78.7-80.9)</u>	<u>80.5 (79.4-81.6)</u>	<u>83.0 (81.4-84.6)</u>	<u>82.2 (80.7-84.8)</u>
	<u>NPV</u>	<u>96.3 (96.3-96.3)</u>	<u>93.8 (93.8-93.9)</u>	<u>93.0 (93.0-93.1)</u>	<u>96.2 (96.2-96.2)</u>	<u>97.9 (97.9-98.0)</u>
<u>Na<125</u>	<u>Sensitivity</u>	<u>13.1 (12.7-13.6)</u>	<u>13.1 (12.7-13.6)</u>	<u>13.6 (13.1-14.0)</u>	<u>5.4 (5.1-5.7)</u>	<u>15.6 (14.6-16.6)</u>
	<u>Specificity</u>	<u>99.9 (99.9-99.9)</u>	<u>99.8 (99.8-99.8)</u>	<u>99.8 (99.8-99.8)</u>	<u>100 (100-100)</u>	<u>99.9 (99.9-99.9)</u>
	<u>PPV</u>	<u>55.7 (54.5-57.0)</u>	<u>57.5 (56.2-58.8)</u>	<u>57.9 (56.5-59.2)</u>	<u>62.5 (60.4-64.5)</u>	<u>62.3 (59.6-64.8)</u>
	<u>NPV</u>	<u>99.0 (99.0-99.0)</u>	<u>98.3 (98.3-98.4)</u>	<u>98.1 (98.1-98.1)</u>	<u>98.9 (98.9-98.9)</u>	<u>99.4 (99.4-99.4)</u>
<u>Na<120</u>	<u>Sensitivity</u>	<u>24.9 (24.0-25.9)</u>	<u>24.9 (24.0-25.8)</u>	<u>25.4 (24.5-26.4)</u>	<u>6.3 (5.8-6.9)</u>	<u>29.3 (27.3-31.3)</u>
	<u>Specificity</u>	<u>99.8 (99.8-99.8)</u>	<u>99.7 (99.7-99.7)</u>	<u>99.7 (99.7-99.7)</u>	<u>100 (100-100)</u>	<u>99.9 (99.9-99.9)</u>
	<u>PPV</u>	<u>35.2 (34.0-36.5)</u>	<u>36.3 (35.1-37.6)</u>	<u>36.3 (35.0-37.6)</u>	<u>50.6 (47.5-53.7)</u>	<u>43.7 (41.0-46.4)</u>
	<u>NPV</u>	<u>99.7 (99.7-99.7)</u>	<u>99.5 (99.5-99.5)</u>	<u>99.5 (99.4-99.5)</u>	<u>99.6 (99.6-99.7)</u>	<u>99.8 (99.8-99.8)</u>
<u>Na<115</u>	<u>Sensitivity</u>	<u>34.3 (32.6-35.9)</u>	<u>34.2 (32.6-35.9)</u>	<u>34.9 (33.1-36.6)</u>	<u>9.3 (8.3-10.3)</u>	<u>38.8 (35.5-42.1)</u>
	<u>Specificity</u>	<u>99.8 (99.8-99.8)</u>	<u>99.7 (99.6-99.7)</u>	<u>99.6 (99.6-99.6)</u>	<u>100 (100-100)</u>	<u>99.9 (99.9-99.9)</u>
	<u>PPV</u>	<u>18.9 (17.9-20.0)</u>	<u>19.5 (18.5-20.6)</u>	<u>19.5 (18.4-20.6)</u>	<u>28.8 (26.1-31.7)</u>	<u>24.2 (22.0-26.6)</u>
	<u>NPV</u>	<u>99.9 (99.9-99.9)</u>	<u>99.8 (99.8-99.8)</u>	<u>99.8 (99.8-99.8)</u>	<u>99.9 (99.9-99.9)</u>	<u>99.9 (99.9-99.9)</u>

DISCUSSION

This is the first study to report on the validity of ICD-10 coding of hyponatremia using comprehensive population-based medical registries, and including patients of all ages. A record of a hyponatremia diagnosis in the DNRP was found to be specific to and highly predictive of hyponatremia confirmed by laboratory values. However, the disorder was greatly underreported, though to a lesser extent in patients admitted to an internal medicine department compared to other departments. We found sensitivity to be low even for severe degrees of hyponatremia. These results were robust when we used a stricter definition of hyponatremia and complete case analysis.

Our findings correspond with those of Movig *et al.*'s single-center study conducted in The Netherlands, in which ICD-9-CM coding of hyponatremia in inpatient discharge records was compared with hospital laboratory data.[13] 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.* examined ICD-10 coding for hyponatremia and reported a sensitivity of ~~4.56.4~~4.4% for the cut-off point of <135 mmol/l and ~~34.441.7~~34.4%.

1
2
3
4
5
6
7
8
9
10 for the cut-off point of 125 mmol/l.[12] The study was, however, restricted to patients ≥ 66 years of age
11 presenting with hyponatremic laboratory test result serum sodium values at time of admission or
12 emergency department contact. In line with their results, we found that the median age of patients with
13 an ICD-10 code of hyponatremia recorded in the DNRP, which could be confirmed by laboratory
14 results, was higher than that of hyponatremic patients with no ICD-10 code for hyponatremia recorded
15 in the DNRP. However, the sensitivity estimates did not reach those found by Gandhi et al. even for
16 patients 65-79 and ≥ 80 years of age. Shea *et al.* also reported higher sensitivity compared to our
17 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
18 study examining the validity of ICD-9 codes of hyponatremia in an outpatient managed-care
19 population.[14] Outpatient serum sodium laboratory tests were compared with outpatient professional
20 ICD-9 claims registered within 15 days before or after the laboratory claim. The PPV was 62.6% for
21 serum sodium levels <136 mmol/l and 10.4% for levels <125 mmol/l. As noted in the paper, detected
22 hyponatremia may be the cause for follow-up visits in an outpatient setting, without the need for repeat
23 measurements. This could lead to lower PPV compared to our study and the study by Movig *et al.* In
24 addition, managed-care claims databases encompass an employer-based commercially insured
25 population. Shea *et al.*'s study thus may not be representative of elderly populations, in which
26 prevalence of hyponatremia is high.[24, 25] This also may explain why their results differed from ours.

27
28
29
30
31
32
33
34
35
36
37
38
39
40 The major strengths of our study are its population-based design and unambiguous individual-level
41 linkage between registries containing complete data on all hospitalizations and laboratory tests in a
42 well-defined population. This eliminates the risk of selection bias. Several potential study limitations
43 must be considered. We relied on only one (the lowest) serum sodium value recorded to define
44 presence of hyponatremia, and also did not consider duration of hyponatremia. Clinicians may be
45 more likely to regard hyponatremia as clinically relevant, and hence to include the condition in
46 discharge diagnoses, if it is detected in more than one measurement. In this context, it is important to
47
48
49
50
51
52

1
2
3
4
5
6
7
8
9
10 note that patient transfers between departments are registered as separate admissions in the DNRP
11 and we examined the validity of ICD-10 coding for each registered admission. The PPV may have
12 been even higher if we had considered contiguous admissions as a single admission. Finally, we
13 chose to include patients without serum sodium measurements and to consider them as
14 normonatremic in the main analysis. We did so to detect false positive diagnoses and thereby obtain
15 accurate estimates of predictive values. Serum sodium is often measured as a routine procedure, and
16 rarely due to specific suspicion. Though frequently measured, the proportion of patients with
17 unacknowledged hyponatremia is most often unknown. We therefore performed a complete case
18 analysis, including only patients with serum sodium measurements. As the results did not differ
19 markedly from those of the primary analysis, we believe that including patients without serum sodium
20 measurements in the normonatremic group was justified.
21
22
23
24
25
26
27
28
29

30 We can only speculate on reasons for the low sensitivity of the ICD-10 coding of hyponatremia found
31 in our study. A diagnosis of hyponatremia was less likely recorded in patients with high levels of
32 comorbidity, which may indicate that Hhyponatremia is mainly considered a part of the clinical picture
33 of underlying bystander of the underlying diseases. If hyponatremia is mild or transient, and does not
34 require intervention or specific attention, it may not warrant documentation. However, even for very
35 severe hyponatremia (<115 mmol/l), which is potentially fatal and requires immediate intervention,
36 sensitivity was low. We believe that this most likely reflects negligence of proper coding practice rather
37 than lack of attention to the clinical importance of low serum sodium levels. With the increasing use of
38 electronic medical records it would be feasible and worthwhile to automatically assign discharge
39 diagnoses to patients with gross abnormal laboratory values. However, the ultimate responsibility for
40 summarizing the most important reasons for treatment and care still rests upon the discharging
41 physician. Our results suggest that hyponatremia is not coded in the presence of coexisting illness
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10 deemed more important, and that the fact that hyponatremia may be an important indicator of a poor
11 prognosis is not yet acknowledged.
12

13
14
15 The results of this validation study emphasize the need for caution when relying on ICD-10 codes for
16 hyponatremia in research. Based on the estimated PPV and specificity, patients with an ICD-10 code
17 of hyponatremia can safely be assumed to actually have hyponatremia. However, the low sensitivity
18 renders the ICD-10 codes inappropriate for use in studies examining prevalence, incidence, and
19 absolute risk, due to a high degree of misclassification. Sensitivity increased with decreasing serum
20 sodium levels, suggesting that studies using ICD-codes to identify hyponatremia would be based
21 mainly on severe cases. Furthermore, our results indicate that quality of registration differs according
22 to age, gender, and morbidity status. Hence, studies may be susceptible to differential
23 misclassification, again resulting in biased results.
24
25
26
27
28
29
30
31

32 **CONCLUSION**

33
34 We found that the ICD-10 coding of hyponatremia in DNRP has high specificity but is highly
35 incomplete, resulting in very low sensitivity. When available, laboratory test results for serum sodium
36 will more correctly identify patients with hyponatremia.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Contributors

LHB participated in the design of the study, performed the data analysis, provided interpretation of study results and drafted the manuscript. SPU participated in 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 with interpretation of study results helped draft the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the Clinical Epidemiology Research Foundation and by the Danish Cancer Society (grant no. R73-A4284-13-S17).

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.

1
2
3
4
5
6
7
8
9
10 LHB, CFC, SPU and HTS are salaried employees of Department of Clinical Epidemiology, Aarhus
11 University Hospital. The Department of Clinical Epidemiology receives funding from companies in the
12 form of research grants to (and administered by) Aarhus University.
13
14

15 None of these grants or fees had any had any leverage on the design, implementation or reporting of
16 the present study.
17
18
19
20
21
22
23
24
25
26
27

28 Reference list

29
30 1 Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med*
31 2006;**119**(Suppl 1):S30-5.
32
33

34 2 Rose BD. Clinical physiology of acid-base and electrolyte disorders. 3rd ed. New York: McGraw-Hill
35 information Services Company 1989.
36
37

38 3 Waikar SS, Curhan GC, Brunelli SM. Mortality associated with low serum sodium concentration in
39 maintenance hemodialysis. *Am J Med* 2011;**124**:77-84.
40
41

42 4 Doshi SM, Shah P, Lei X, *et al*. Hyponatremia in hospitalized cancer patients and its impact on
43 clinical outcomes. *Am J Kidney Dis* 2012;**59**:222-228.
44
45

46 5 Goldberg A, Hammerman H, Petcherski S, *et al*. Prognostic importance of hyponatremia in acute
47 ST-elevation myocardial infarction. *Am J Med* 2004;**117**:242-248.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10 6 Kovesdy CP, Lott EH, Lu JL, *et al.* Hyponatremia, Hypernatremia and Mortality in Patients with
11 Chronic Kidney Disease with and without Congestive Heart Failure. *Circulation* 2012;**125**:677-684
12
13
14 7 Scherz N, Labarere J, Mean M, *et al.* Prognostic importance of hyponatremia in patients with acute
15 pulmonary embolism. *Am J Respir Crit Care Med* 2010;**182**:1178-1183.
16
17
18 8 Wald R, Jaber BL, Price LL, *et al.* Impact of hospital-associated hyponatremia on selected
19 outcomes. *Arch Intern Med* 2010;**170**:294-302.
20
21
22
23 9 Chawla A, Sterns RH, Nigwekar SU, *et al.* Mortality and serum sodium: do patients die from or with
24 hyponatremia? *Clin J Am Soc Nephrol* 2011;**6**:960-965.
25
26
27 10 Marco J, Barba R, Matia P, *et al.* Low prevalence of hyponatremia codification in departments of
28 internal medicine and its prognostic implications. *Curr Med Res Opin* 2013;**29**:1757-1762
29
30
31
32 11 Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for
33 epidemiological research. *Int J Epidemiol* 1996;**25**:435-442.
34
35
36 12 Gandhi S, Shariff SZ, Fleet JL, *et al.* Validity of the International Classification of Diseases 10th
37 revision code for hospitalisation with hyponatraemia in elderly patients. *BMJ Open*
38 2012;**2**:10.1136/bmjopen-2012-001727. Print 2012.
39
40
41
42 13 Movig KL, Leufkens HG, Lenderink AW, *et al.* Validity of hospital discharge International
43 Classification of Diseases (ICD) codes for identifying patients with hyponatremia. *J Clin Epidemiol*
44 2003;**56**:530-535.
45
46
47
48
49
50
51
52
53
54

Formatted: English (U.S.)

1
2
3
4
5
6
7
8
9
10 14 Shea AM, Curtis LH, Szczech LA, *et al.* Sensitivity of International Classification of Diseases codes
11 for hyponatremia among commercially insured outpatients in the United States. *BMC Nephrol*
12 2008;**9**:5.
13

14
15 15 Andersen TF, Madsen M, Jorgensen J, *et al.* The Danish National Hospital Register. A valuable
16 source of data for modern health sciences. *Dan Med Bull* 1999;**46**:263-268.
17

18
19
20 16 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*
21 2011;**39**(Suppl 7):30-33.
22

23
24
25 17 Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;**39**(Suppl 7):22-
26 25.
27

28
29 18 Grann AF, Erichsen R, Nielsen AG, *et al.* Existing data sources for clinical epidemiology: The
30 clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clin*
31 *Epidemiol* 2011;**3**:133-138.
32

33
34
35 19 SSI - Joint Content for Basic Registration of Hospital Patients.
36 [http://www.ssi.dk/Sundhedsdataogit/Indberetning%20og%20patientregistrering/Patientregistrering/Fae](http://www.ssi.dk/Sundhedsdataogit/Indberetning%20og%20patientregistrering/Patientregistrering/Faellesindhold.aspx)
37 [llesindhold.aspx](http://www.ssi.dk/Sundhedsdataogit/Indberetning%20og%20patientregistrering/Patientregistrering/Faellesindhold.aspx) (accessed 18 Dec 2013; updated 9 Dec 2013).
38

39
40
41 20 Laboratory Manual for Hospitals in the North Jutland Region. 2011.
42 <http://www.laboratorievejledning.dk/prog/view.aspx?AfsnitID=103&KapitelID=26&UKapitelID=194>
43 (accessed 15 Dec 2013; updated 20 Dec 2011).
44

45
46
47 21 Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in
48 longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373-383.
49

1
2
3
4
5
6
7
8
9
10 22 Thygesen SK, Christiansen CF, Christensen S, *et al*. The predictive value of ICD-10 diagnostic
11 coding used to assess Charlson comorbidity index conditions in the population-based Danish National
12 Registry of Patients. *BMC Med Res Methodol* 2011;**11**:83.
13
14

15
16 23 Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic
17 regression analyses. *Am J Epidemiol* 1995;**142**:1255-1264.
18
19

20 24 Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta*
21 2003;**337**:169-172.
22
23

24 25 Miller M, Morley JE, Rubenstein LZ. Hyponatremia in a nursing home population. *J Am Geriatr Soc*
25 1995;**43**:1410-1413.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

		ICD-10 code of hyponatremia recorded in the DNRP*	
		Yes	No
Hyponatremic 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 2x2 table and validity measure estimation formulas
160x90mm (300 x 300 DPI)

review only

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8-9
		(b) Describe any methods used to examine subgroups and interactions	8-9
		(c) Explain how missing data were addressed	7 and 9
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-10
		(b) Give reasons for non-participation at each stage	9-10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	9-10
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	9-10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(b) Report category boundaries when continuous variables were categorized	11-13
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.