Appendix 1

STROBE Statement - checklist for our study

STROBE requirement	#	Our study
Title and abstract	1	
(a) Indicate the study's design with a commonly used term in the title and abstract		(a) Given. Lithium treatment, nephrogenic diabetes insipidus and the risk of hypernatraemia – a retrospective cohort study
(b) Provide in the abstract an informative and balanced summary of what was done and what was found		(b) Structured abstract provided.
Introduction		
Background/rationale: Explain the scientific background and rationale for the investigations being reported	2	Background outlined in introduction.
Objectives: State specific objectives, including any pre-specified hypotheses	3	Aims clearly stated in text. The aims of this study were (1) to determine the frequency of episodes of hypernatraemia, (2) to assess the potential association with past and present lithium exposure; and (3) to evaluate the potential lethality of hypernatraemia episodes.
Methods		
Study design: Present key elements of the study design early in the paper	4	Study design: Retrospective cohort study. Key elements of the study included in the manuscript: study design, participants, variable definitions and outcomes, control for bias, data collection statistical analysis.
Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	Setting described in manuscript: For LISIE, we identified all patients in the Swedish region of Norrbotten, were at least 18 years of age and who had been either diagnosed with BPAD (F31) or SZD (F25), or who had been prescribed lithium as a mood stabiliser. We considered all patients who had consented, or who we were approved to include because they had deceased. The study covered a 17-year period from 1997 to 2013.
Participants: *(a)* Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the	6	(a) For this particular study, we included all patients who had experienced at least one episode with a sodium concentration ≥ 150 mmol/L as identified in our central laboratory database, where all sodium concentrations were stored. Stratification described in the method section. We compared episodes of hypernatraemia stratified by age and lithium treatment status.

choice of cases and controls (*b*) For matched studies, give matching criteria and the number of controls per case		
Variables: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7	Definition for each variable, lithium exposure, hypernatraemia, nephrogenic diabetes insipidus, causes of hypernatraemia given in text. Main outcome variable: Cause of clinically significant hypernatraemia as recorded in records. Secondary outcome variable: Lethality associated with the hypernatraemia episodes identified.
Data sources /measurement: 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	8	Source: medical records including laboratory results. The clinical information was abstracted and rated by two investigators, a specialist in general practice and senior trainee doctor in psychiatry (BF) and/or a consultant physician and specialist in nephrology (MO). Definition of hypernatraemia: We considered hypernatraemia to be clinically significant when it was at least moderate with a sodium concentration of at least 150 mmol/L. For each episode, we determined if the hypernatraemia was acute or chronic. A hypernatraemia value of ≥ 150 mmol/L was defined as acute, if abnormal sodium concentrations had emerged within three months prior to the current episode. Hypernatraemia was identified as chronic, if abnormal concentrations had existed for more than three months prior to the current hypernatraemia episode.
Bias: Describe any efforts to address potential sources of bias	9	Potential sources of bias discussed. "In accordance with the ethical approval granted, we controlled for selection bias in the whole retrospective cohort study, comparing age, sex, maximum recorded lithium and creatinine concentrations as key parameters, available in anonymized form." For the main outcome variable concerning the cause of hypernatraemia, data was missing for 8% of episodes. There was no significant difference regarding age and sex between episodes for which data was available and those for which data was missing. For the secondary outcome, lethality associated with the hypernatraemia episode, the data was complete.
Study Size: Explain how the study size was arrived at	10	Descriptive study. For this study, 3735 patients were potentially eligible, meeting the sampling requirements. Of these, we could include 2596 patients according to our consent procedures. Sodium concentrations were available for 2463 patients. Of these, 185

		(7.5%) patients had experienced sodium concentrations of ≥ 150 mmol/L on at least one occasion during the 17 years of review (Figure 1). For these patients, we identified 204 episodes of hypernatraemia.
Quantitative variables: Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11	Episodes of hypernatraemia, i.e. sample, stratified according to lithium exposure. Main outcome, cause of clinically significant hypernatraemia, and secondary outcome, lethality associated with the hypernatraemia episode, treated as nominal variables. Main outcome variable: descriptive analysis and stratification in two subgroups: age ≥ 65 years, age < 65 years. Secondary outcome variable analyses as a dichotomous variable, death: yes/no. Risk factors and potential confounders for this variable analysed with uni-and multivariate analysis.
Statistical methods: *a)* Describe all statistical methods, including those used to control for confounding *(b)* Describe any methods used to examine subgroups and interactions (*c)* Explain how missing data were addressed *(d)* If applicable, explain how matching of cases and controls was addressed *(e)* Describe any sensitivity analyses	12	All data was anonymized before analysis. We first analysed the data descriptively. We compared episodes of hypernatraemia stratified by age and lithium treatment status, using Chi^2 test. We assessed the correlation between hypernatraemia and age by linear regression. Risk factors for lethal outcome, we evaluated by univariate analysis. To account for potential confounders, we then conducted a logistic regression analysis, entering variables in a stepwise backward fashion. For all analyses, differences were considered statistically significant with a p-value of ≤ 0.05. (b) Univariate and multivariate analysis (logistic regression) to compare risk factors for lethal outcome (c) Mainly descriptive study. We tested whether the episodes with missing data systematically differed from episodes for which data was available. For the main outcome variable concerning the cause of hypernatraemia, data was missing for 8% of episodes. There was no significant difference regarding age and sex between episodes for which data was available and those for which data was missing. For the secondary outcome, lethality associated with the hypernatraemia episode, the data was complete. (d) N/A (e) N/A
Results		
Participants: *(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 analyzed	13	(a) Selection and consent procedures clearly described in the method section. Numbers given in the flow diagram, (figure 1) and results: 2 For this study, 3735 patients were potentially eligible, meeting the sampling requirements. Of these, we could include 2596 patients according to our consent procedures. Sodium concentrations were available for 2463 patients. Of these, 185 (7.5%) patients had experienced sodium concentrations of ≥ 150 mmol/L on at least one occasion during the 17 years of review (Figure 1). For these patients, we identified 204 episodes of hypernatraemia." (b) Cf. a and flow diagram (figure 1)

(b) Give reasons for non-participation at each stage *(c)* Consider use of a flow diagram		(c) Flow diagram included in the manuscript as figure 1.
Descriptive data: *(a)* Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders *(b)* Indicate number of participants with missing data for each variable of interest	14	(a) Baseline characteristics described in table 1 of the manuscript. (b) Included in the flow diagramme and in the text.
Outcome data: Report numbers in each exposure category, or summary measures of exposure	15	Outcome data presented in results section, tables 1 , 2 and figures 2 and 3.
Main results *(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 *(b)* Report category boundaries when continuous variables were categorized *(c)* If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16	(a) Cf. results section, table 1 and 2. (b) N/A, as outcome variables (hypernatraemia and lethality of hypernatremia) concern nominal variables. (c) N/A
Other analysis: Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	17	N/A
Discussion		

Key results: Summarize key results with reference to study objectives	18	Done
Limitations: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19	Limitation discussed in regard to selection bias, data quality, and variable definition.
Interpretation: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20	Results discussed in view of the limitations of our study design and in view of the available literature on this subject. Cautious conclusions: "Clinicians should remain vigilant and have a low threshold for checking sodium concentrations, particularly in elderly and intoxicated patients."
Generalisability: Discuss the generalizability (external validity) of the study results	21	Discussed in the context of bias. The sample under study is judged to be representative and the largest sample available for the topic under study.
Funding: 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	22	Source of funding included in manuscript Conflict to interest statement for all authors included in manuscript.

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