**Appendix 2**

**STROBE Statement - checklist for our study**

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| **STROBE requirement** | **#** | **Our review** |
| *Title and abstract* | 1 |  |
| *(a)* Indicate the study’s design with a commonly used term in the title and abstract |  | *(a)* Given. Lithium-associated hypothyroidism and potential for reversibility after lithium discontinuation – findings from the LiSIE 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, “We set up this study to determine whether lithium associated hypothyroidism was reversible in patients who subsequently discontinued lithium.  |
| *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, selection: inclusion and exclusion criteria, variable definitions, validation process, chart review, outcome parameters, control for bias, and statistical analysis. |
| Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5 | Setting and all relevant dates described in manuscript: “LiSIE invited all individuals in the Swedish regions of Västerbotten and Norrbotten of at least 18 years of age, who had either received a diagnosis of BPAD (ICD F31), schizoaffective disorder (ICD F25), or had used lithium as mood stabilizer between 1997 and 2011. …For this particular study, we included patients from Norrbotten who (1) had at least one prescription of lithium, (2) then discontinued lithium on at least one occasion at any time between 1997 and 2013,and (3) had received at least one prescription of thyroxine or liothyronine. …We retrospectively reviewed the medical records of all eligible patients from 1997 up to 31 December 2015**.** We additionally validated start date on lithium and TRT in medical records dated back to 1965.“ |
| Participants: *(a)* 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(*b*)For matched studies, give matching criteria and the number of controls per case | 6 | *(a*) As above“We retrospectively reviewed the medical records of all eligible patients from 1997 up to 31 December 2015**.** We additionally validated start date on lithium and TRT in medical records dated back to 1965.”(b) N/A. |
| Variables: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7 | Definition for exposures and variables given in text. Outcomes stratified by gender, age and, if discontinued, thyroid replacement therapy. |
| 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 | Data source for all variables: medical records.Definition for each variable given in text. |
| Bias: Describe any efforts to address potential sources of bias | 9 | Potential sources of bias discussed, including selection and observer bias.“We controlled for selection bias in the whole retrospective cohort study (LiSIE). Age, sex, maximum recorded lithium and creatinine concentrations were key parameters, available in anonymized form. In accordance with the ethics approval granted, we compared these parameters for consenting and non-consenting patients. No significant difference was found between the two groups.” |
| Study Size: Explain how the study size was arrived at | 10 | Cf. figure 2“For this study, 1340 patients were potentially eligible, meeting the sampling requirements. According to our consent procedures, we could include 1098 patients, 58% of whom were women. We identified 181 patients who had received an electronic prescription for TRT *after* starting lithium, 75% of whom were women (p < 0.01). Of the 181 patients, 91 patients were excluded according to our procedures. Thus, the final sample consisted of 90 patients (figure 2).” |
| Quantitative variables: Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 11 | Main outcome: Outcome summarized in two categories: (1) continuous TRT, or (2) discontinued TRT. Presented as proportion of patients who had continued or discontinued thyroid replacement therapy after having stopped lithium. Continuous variables (1) time from lithium start to TRT start, (2) TSH and fT4 levels at which TRT was initiated, (3) time from stopping lithium to stopping TRT (4) age at TRT start were presented as mean/SD, median and min/max/range.For age at TRT start, we stratified into two groups, < 60 years and ≥60 years. For the event “instating TRT after starting lithium”, we created separate Kaplan-Meier curves for men and women and patients < 60 years and ≥60 years. |
| 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 | *(a)* We first analysed the data descriptively, establishing means and medians for continuous variables and frequencies for nominal variables. TSH at the time of TRT start was analysed as a continuous variable. The distribution of this variable was presented in a histogram using a logarithmic scale to normalize data. We used the t- test for determining any potential differences in mean TSH level at TRT start for men and women and patients < 60 years and ≥ 60 years. The Chi2-test was applied to assess whether there were any age or sex differences. We used Kaplan-Meier plots to map the time (1) from starting lithium to first elevated TSH value, and (2) from starting lithium to instating TRT. (b) For the event “instating TRT after starting lithium”, we created separate Kaplan-Meier curves for men and women and patients < 60 years and ≥ 60 years. We tested potential differences between the two respective groups using the log rank test, setting the significance to p ≤ 0.05.*(c)* Sub-analysis of 85 patients available for follow-up. Cf. figure 2. *(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*(b)* Give reasons for non-participation at each stage*(c)* Consider use of a flow diagram | 13 | *(a+b)* For this study, 1340 patients were potentially eligible, meeting the sampling requirements. According to our consent procedures, we could include 1098 patients, 58% of whom were women. We identified 181 patients who had received an electronic prescription for TRT *after* starting lithium, 75% of whom were women (p < 0.01). Of the 181 patients, 91 patients were excluded according to our procedures. Thus, the final sample consisted of 90 patients (figure 2).*(c)* Flow diagram included in the manuscript as figure 2. |
| 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 2 of the manuscript.*(b)* Included in the flow diagram and in the text. |
| Outcome data:Report numbers in each exposure category, or summary measures of exposure | 15 | Outcome data presented in tables 2 and 3 and figures 3-5 in the text. |
| 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)* Results describe time from starting lithium to first elevated TSH and starting TRT, the laboratory values at which TRT was initiated, and how many that discontinued TRT once lithium treatment was stopped. Significance level set to 5% for group comparisons. *(b)* Categorization by sex and age. Age was categorized into two groups: under 60 years and 60 years and older.*(c)* N/A |
| Other analysis: Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses | 17 | Sub-analysis of 85 in whom the use of TRT was clearly documented after lithium discontinuation. |
| *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 potential for observer bias/recording error. |
| 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 (weaknesses) of our study design. Advantages and disadvantages of studies based on medical records compared to register studies discussed. |
| 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 | This work was supported by a grant of the Research & Development Fund of Norrbotten Region, Sweden. Conflict to interest statement for all authors included in manuscript. |

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