Title:

Maternal and infant outcomes associated with lithium use in pregnancy

An international collaboration combining data from 6 cohort studies using meta-analysis covering 727 lithium exposed pregnancies and 21,397 bipolar or major depressive disorder reference pregnancies.

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Abstract

Background

Concerns about teratogenicity and offspring complications limit use of lithium in pregnancy. We aimed to investigate the association between in-utero lithium exposure and risk of pregnancy complications, delivery outcomes, neonatal morbidity and congenital malformations.

Methods

Meta-analysis of primary data analyzed using a shared protocol. Six study sites participated: Denmark, Canada, Netherlands, Sweden, UK, and US, totaling 727 lithium-exposed pregnancies compared to 21,397 reference pregnancies in mothers with a mood disorder, but unexposed to lithium.

Main outcome measures included: (1) pregnancy complications, (2) delivery outcomes, (3) neonatal readmission to hospital within 28 days of birth, and (4) congenital malformations (major malformations and cardiac malformations). Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were generated using logistic regression models. Site-specific prevalence rates and ORs were pooled using random-effects meta-analytic models.

Findings

Lithium exposure was not associated with any of the pre-defined pregnancy complications or delivery outcomes. There was an increased risk for neonatal readmission in lithium exposed (27·5%) versus reference group (14·3%) (Pooled aOR1·62; 95% CI: 1·12–2·33). Lithium exposure during first trimester was associated with increased risk of major malformations (7·4% versus 4·3%; pooled aOR 1·71, 95% CI: 1·07–2·72). Similarly, more lithium exposed children had major cardiac malformations, albeit not stasticially significant (2·1% versus 1·6%; pooled aOR 1·54, 95% CI: 0·64–3·70). Limitations in our study include: Serum lithium

levels were not available, hence no analyses related to dose-response effects could be performed, and residual confounding from e.g. substance abuse cannot be ruled out.

Interpretation

Treatment decisions must weigh the potential for increased risks, considering both effct sizes and the precision of the estimates, in particular associated with first-trimester lithium use against its effectiveness at reducing relapse.

Funding

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Introduction

Lithium is an effective first-line pharmacological treatment for patients with bipolar disorder,[1,2] with well-documented effects in the acute and maintenance phases for both depressive and manic symptoms, as well as in suicide risk reduction.[1,3,4] Lithium is also used as an adjunctive therapy for patients with unipolar depression,[5] and can reduce affective symptoms in schizophrenia and schizoaffective disorder.[6]

Bipolar disorder affects ~ 2% of the population,[7] including reproductive-age women,[8] so knowledge about benefits and risks of lithium treatment in pregnancy is essential. Lithium treatment can reduce the risk for relapse both in pregnancy and in the postpartum period.[9,10] However, concerns about teratogenicity, maternal- and offspring complications (e.g., renal or thyroid problems, preterm birth) limit its use. The specific concern related to congenital anomalies teratogenicity mainly relates to first-trimester lithium use. Here the embryo is most vulnerable to teratogens, as this is the period of organ formation including the heart. In animal studies lithium use in early pregnancy has been linked to abnormalities of the central nervous system, heart and blood vessels in the exposed fetuses.[11,12] In humans, studies have similarly found increased risks of malformations,[13-16] preterm birth and other pregnancy and neonatal complications,[13,17-19] while other studies have not.[1,20] Most previous studies had limited statistical power to detect significant effects, and others were subject to recall bias and poor consideration of important confounding variables.[20,21]

Meta-analyses can improve the precision of estimates regarding the safety of in-utero exposure to lithium by increasing sample size. This was done in 2012, where a meta-analysis found that risk of Ebstein's anomaly was not significantly elevated after lithium exposure in pregnancy.[20] Importantly however, the authors cautioned that the strength of their conclusion was limited by the small number of cardiac malformation cases, and that further studies with larger numbers of cases would be needed to establish this result more definitively.

Accordingly, the aim of this study was to conduct a meta-analysis of data from six international cohorts to investigate the association between in-utero lithium exposure and risk of a broad set of maternal and perinatal outcomes. Definitions of exposures, outcomes, potential confounders, and statistical analyses were harmonized across sites *a priori* using a shared study protocol to reduce heterogeneity and bias.

Methods

Participating cohorts

This study combined primary data from 6 cohorts using meta-analysis: three population-level register-based cohorts in Denmark, Sweden and Ontario, Canada, and three clinical cohorts (i.e., women under psychiatric secondary care) from the Netherlands, the United Kingdom, and the United States. A joint study protocol was created prior to dataset creation and analysis, including specific definitions for selection criteria, each included variable, and statistical analysis. Each study site obtained local ethical approval. All cohorts comprised pregnancies resulting in live-born singleton deliveries from 1997 to 2015, where health-related information was available both for the mother and for the infant (Table 1). Pregnancies in which mothers were prescribed known teratogenic medications in pregnancy (thalidomide, valproate, retinoids, antineoplastic drugs, misoprostol, and methotrexate) were excluded from the analysis. A detailed description of the identification of study population and years of inclusion in each study site is presented in eTable 1 in the supplement.

Lithium exposure

The lithium-exposed group comprised pregnancies with lithium exposure during the index pregnancy. For register-based cohorts, lithium exposure during pregnancy was defined as at least two dispensations of lithium during pregnancy that were dispensed any time from one month prior to conception until the delivery, or a single lithium dispensation during pregnancy when there was at least one other lithium dispensation within six months before or after this date. Dispensations of lithium were identified using the Anatomical Therapeutic

Chemical (ATC) Classification System code N05AN01 in Denmark and Sweden and the corresponding Drug Identification Numbers in Ontario, Canada. For clinical cohorts, medical records were used to define lithium use during pregnancy. For the lithium-exposed group, we did not require a documented psychiatric diagnosis, as non-psychiatric indications for lithium are rare.

For analyses with specific focus on congenital malformations, we were interested in lithium exposure during early pregnancy, and we further defined lithium exposure in the first trimester as follows: For register-based cohorts: 1) At least two dispensations of lithium in the first trimester (from one month before the date of conception to 90 days of gestation); or 2) One dispensation in the first trimester with at least one other dispensation within 6 months before or after this date. For clinical cohorts: Medical records were used to define lithium use in the first trimester.

Mood disorder reference group

The reference group comprised women with a known history of mood disorder (bipolar disorder or major depressive disorder) without exposure to lithium from 90 days before pregnancy until the delivery. For register-based cohorts, maternal mood disorder was defined as at least one inpatient and/or at least two outpatient contacts for bipolar disorder (equivalent to the International Classification of Diseases, 10th revision (ICD-10) codes F30–F31) or major depressive disorder (ICD-10 codes F32–F33) from 2 years prior to the date of pregnancy to the delivery date. For clinical cohorts, maternal mood disorder was defined as any medical history of bipolar disorder or major depressive disorder before delivery.

Outcomes of interest

Outcomes of interest were selected based on theoretical risks for general medication exposure in pregnancy and prior research on lithium use specifically.[13,20] Outcomes were divided into four subcategories: 1) Pregnancy complications, identified in pregnancy or within 42 days after delivery, using hospital-based diagnoses for

preeclampsia (ICD-10 code O14), diabetes during pregnancy (ICD-10 code O24), fetal distress (ICD-10 code O68), and postpartum hemorrhage (ICD-10 code O72); 2) Labour and delivery outcomes, identified in hospital, including caesarean section (ICD-10 codes O82 and P03·4; surgical code KMCA), preterm birth (<37 weeks gestation), low birth weight (<2500g), and small for gestational age (i.e. a birth weight below the 10th percentile of birth weight by gestational age and sex); 3) Neonatal hospital admission to a special care baby unit in the first 28 days of life; 4) Congenital malformations excluding chromosomal abnormalities in the child diagnosed by age 1 year, including all singular and combined structural defects, syndromes, sequences, and associations, such as cardiovascular defects, neural tube defects hypospadias, and epispadias (ICD-10 codes Q00–Q89, excluding minor malformations according to the EUROCAT Guide 1·4).[22] Major cardiac malformations were defined as atrial and atrioventricular septal defects and Ebstein's anomaly (ICD-10 codes Q20–Q26), but excluding atrial septal defect (ICD-10 code Q21·1) and patent ductus arteriosus (ICD-10 code Q25·0) in infants born prior to 37 weeks gestation.[22]

Statistical analysis

All study sites performed analyses independently according to a protocol established *a priori*. The site-specific prevalence rates and effect estimates were subsequently sent to Denmark, and combined by applying an aggregate level meta-analysis, because individual-level data could not be shared outside most jurisdictions as mandated by local ethical committees and regulations. At each site, all outcomes were modeled as binary variables (yes/no), and a binary logistic regression model was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) comparing the lithium-exposed group to the reference group. Due to a specific concern related to lithium exposure in the first trimester and congenital malformations, we estimated the ORs of major malformations and major cardiac malformations comparing lithium exposure in the first trimester group to the reference group. Odds ratios were adjusted for maternal age at delivery (in years), primiparity, calendar year of birth, and treatment with any other psychotropic medication during pregnancy according to ATC codes filed under N05 and N06 excluding N05AN01, from 1-month prior to pregnancy to the delivery (yes/no). Data

management and analyses were performed using SAS 9·4 (Canada and Sweden), Stata 13·1 (Denmark and UK), SPSS 20·0 (The Netherlands), and R package (US).

For the meta-analysis, data from each individual analysis were double entered in EpiData 3·1. The meta-analysis was performed using Stata 13·1. Site-specific prevalence rates and effect estimates were pooled using random-effects meta-analytic models. In random-effects models, the inverse of within-study variation combined with the between-study variation was used as the weight. The pooled prevalence rates of individual outcomes were computed using the program Metaprop.[23] The 95% CIs of pooled prevalence rates were calculated using an exact binomial approach. Overall estimates were presented as forest plots with the pooled adjusted ORs (aORs) and 95% CIs. Heterogeneity was quantified using the I^2 statistic (ranges from 0% to 100%), which describes the proportion of variability in the effect sizes attributable to heterogeneity between study sites.

Sensitivity analyses

To account for possible heterogeneity and estimate the influence of a single cohort on overall estimates, in a "leave-one-out approach", we recalculated the pooled aORs leaving one cohort out of the analyses each time. To determine whether results were influenced by the type of data source, we repeated each meta-analysis by stratifying based on whether the source of data was register-based or clinical cohort.

We conducted additional sensitivity analyses (post hoc) using Swedish and Danish data only to further explore the potential for residual confounding. First, we repeated the primary analyses and further adjusted for marital and education status, antiepileptic use during pregnancy (other than valproate as pregnancies exposed to this drug were excluded a priori), and treatment with other psychotropic drugs as individual covariates, including antidepressants, antipsychotics, benzodiazepines and hypnotics, and psychostimulants. Second, we compared outcomes between pregnancies exposed to lithium and those where mothers used lithium before or after, but not during, pregnancy. Third, to estimate whether the use of reference group with maternal mood disorder

represented an appropriate comparison group, we estimated the difference of relative risk of various adverse outcomes in lithium exposed children in comparison to two different reference groups: group with maternal diagnosis of mood disorder and group with maternal diagnosis of bipolar disorder.

Ethical approval

Each study site obtained local ethical approval. For meta-analysis, only site-specific aggregated data were sent to Denmark, and no personal identifiable information was shared among groups.

Role of the funding source

All investigators conducted the research independently. The funders had no role in study design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

A total of 727 lithium-exposed pregnancies were identified (n=557, or 76·6% from register-based cohorts). Baseline sample characteristics are presented in Table 1. Women in the lithium exposure group were more likely to be older, nulliparous, and to have filled a prescription for a psychotropic medication other than lithium during pregnancy, compared to the reference group (N=21,397).

Lithium use during pregnancy was not associated with preeclampsia (pooled prevalence of 1·8% in lithium-exposed vs. 2·1% in reference group, pooled aOR=0·97, 95% CI: 0·52–1·80), diabetes in pregnancy (6·4% vs. 5·4%, pooled aOR=1·20, 95% CI: 0·81–1·78), fetal distress (14·1% vs. 13·2%, pooled aOR=1·00, 95% CI: 0·76–1·32), or postpartum hemorrhage (7·4% vs. 7·1%, pooled aOR=1·28, 95% CI: 0·64–2·57). No differences between the lithium-exposed group and the reference group were observed for caesarean section (26·5% vs. 25·8%, pooled aOR=0·94, 95% CI: 0·66–1·33), preterm birth (13·1% vs. 10·0%, pooled aOR=1·24, 95% CI:

0·83–1·84), low birth weight (6·4% vs. 7·2%, pooled aOR=0·98, 95% CI: 0·72–1·35), or small for gestational age (7·5% vs. 9·3%, pooled aOR=0·90, 95% CI: 0·67–1·21). In-utero lithium exposure was associated with an increased risk of neonatal admission to a special care baby unit prior to 28 days of age (27·5% vs. 14·3%, pooled aOR=1·62, 95% CI: 1·12–2·33) (Table 2). Forest plots with site-level ORs of these pregnancy complications, delivery outcomes and neonatal admission are present in eFigures 1–3 in the Supplement.

There were 51 lithium-exposed children (7·2%) and 856 children from reference group (4·3%) with major malformations diagnosed by one year of age. Lithium exposure was not statistically significantly associated with increased odds of major malformation (pooled aOR=1·58; 95% CI: 0·90–2·79), nor major cardiac malformations (2·0% vs. 1·6%, pooled aOR=1·31, 95% CI: 0·50–3·47), but statistical heterogeneity was high (Table 2). For example, in Denmark, lithium exposure was associated with both major malformation and major cardiac malformation risk, but this association was not observed in data from the other 4 sites (Figure 1a–1b). Of 727 lithium exposed children, 654 (90·0%) were exposed to lithium in the first trimester (eTable 2). In total, 47 children from the lithium exposure in the first trimester group were diagnosed with major malformations and 16 with major cardiac malformations. Lithium exposure was associated with an increased risk of major malformations (7·4% vs. 4·3%, pooled aOR=1·71, 95% CI: 1·07–2·72), but not major cardiac malformations (2·1% vs. 1·6%, pooled aOR=1·54, 95% CI: 0·64–3·70) (Figure 1c–1d), in comparison to the reference group of mood disorders. Note, that no Ebstein's anomaly cases were observed in any of the participating study sites.

The "leave-one-out approach" analyses demonstrated an overall stability of the main findings, except for the association between lithium exposure in the first trimester and major malformations. This latter relation became non-significant when each of Denmark, Sweden, and the USA were left out (eTable 3 in the Supplement). Pooled ORs from the register-based cohorts substantially overlapped those of the clinical cohorts, except for postpartum hemorrhage, where a strong relation was observed in clinical cohorts (pooled aOR=2·58, 95% CI: 1·21–5·52) but not in register-based cohorts (pooled aOR=0·79, 95% CI: 0·41–1·51, eTable 4).

Results from additional analyses in a subgroup that included only the Danish and Swedish data were generally consistent with those of the main analysis. Adjustments for education status, marriage status, antiepileptic and psychotropic medication use during pregnancy did not differ from the main results (eTable 5). When lithium exposed pregnancies were compared to pregnancies where women were using lithium *before and after* pregnancy but not during pregnancy, results were also generally consistent with those of the main analysis. However, the odds of major malformations was elevated among children exposed to lithium in pregnancy (pooled aOR=2·09, 95% CI: 1·10–3·96), although this was not the case specifically for major cardiac malformations (pooled aOR=1·28, 95% CI: 0·13–12·39, Table 3). The relative risk of adverse outcomes in lithium exposed children were similar when comparing to the reference group with maternal diagnosis of mood disorder or to the reference group with maternal diagnosis of bipolar disorder, although the relative risk of neonatal readmission was attenuated to null when comparing to the reference group with maternal diagnosis of bipolar disorder (eFigure 4).

Discussion

With combined data from 6 countries using a harmonized protocol, in-utero exposure to lithium was not associated with statistically significantly increased risks for any of the pregnancy complications or delivery outcomes investigated. Lithium was associated with a significantly increased risk (~1·5 times, 27.5% vs. 14.3%) for neonatal readmission within four weeks postpartum. We furthermore found that lithium exposure in the first trimester specifically was associated with an increased risk of major malformations, but not major cardiac malformations, although the latter was studied only among 16 cases. Across our analyses, results were robust to the majority of sensitivity analyses, including stratification by study design, a leave-one-out approach, and adjustment for additional variables in a sub-cohort including Swedish and Danish data only.

This study has multiple strengths, including improving statistical power and generalizability over previous research. Analyses were performed following a shared protocol established a priori to minimize heterogeneity related to selection criteria, exposure, outcome and covariate definitions, and statistical methodology. All data on lithium exposure were collected from data recorded prior to outcome occurrence, so the risk of recall bias was low. The potential for bias related to the analysis was further minimized since each site performed its own analyses independently, blind to the results from other sites. Our study also has limitations. First, we chose to only include pregnancies ending with live-born children due to lack of information on stillbirths at some study sites. If lithium use during pregnancy increases the risk of stillbirths or miscarriage,[24] conditioning on live-born children could have led to underestimation of adverse effects, so this is a potential study limitation.[25] Second, even with a large sample size, our study lacks power to study very rare events. This e.g. relates to cardiac malformations, with only 16 observed cases, with subsequent limited statistical power. Third, as with all observational studies, residual confounding, especially that due to the severity of the underlying maternal illness, substance or alcohol abuse, cannot be ruled out.[26] Fourth, we examined multiple outcomes, so the potential for Type I error and chance findings cannot be excluded. Fifth, we did not use an active comparator approach, i.e., we did not directly compare lithium to other medications that are sometimes used for the treatment of bipolar disorder. Sixth, no available data on lithium serum levels prevented analyses related to any potential dose-response associations, and a relatively wide defined lithium exposure window can lead to misclassification of lithium exposure and have biased our results towards the null. Seventh, we cannot rule out that less severe adverse outcomes are more likely to be reported and recorded in the lithium-exposed pregnancies than in the pregnancies included in our defined reference group, due to a general concern about teratogenic effects. However, this would likely bias the results toward finding an effect, which we did not observe for most outcomes.

Lithium use was not associated with any of the pre-defined pregnancy complications and adverse delivery outcomes in our study. That being said, mental illness itself has been associated with adverse pregnancy

outcomes including preterm birth and cesarean delivery, regardless of whether women were treated with any mood stabilizing medication (i.e., lithium, antiepileptics, and antipsychotic medications, or some combination thereof).[27] This may explain why previous studies,[13,17,18] with less rigorous control for confounding related to maternal mental illness, might have observed an increased risk for these outcomes associated with lithium, while our study did not. Across our analyses there was an increased risk for neonatal admission within 4 weeks in lithium-exposed infants. To our knowledge, this is not an outcome previously investigated for lithium exposure and results could be explained through different mechanisms. Lithium withdrawal after birth could directly lead to neonatal morbidity requiring admission to a special care baby unit, as could lithium exposure in lactation (which is not generally recommended). Furhter, the neonatal morbidity could be explained through the underlying maternal disorder (supplement eFigure 4) or be due to increased vigilance towards infants exposed to lithium with subsequent detection of neonatal morbidities in these newborns. This will require detailed prospective studies to disentangle.

Most prior research on lithium in pregnancy has focused on congenital malformations including Ebstein's anomaly,[13,15,16,28] however there were major methodological limitations to previous research. Most data comes from small retrospective clinical studies, prone to over-reporting on malformed infants, lack of information on exposed children without adverse outcomes and lack of confounder control.[29-31] Adding further to the complexities of any interpretation, cardiac malformations may be associated with maternal mental illness and other related factors in general, rather than with exposure to lithium.[29] In our study, comparisons were made to pregnancies among women with mental illness, rather than to pregnancies among all women, because at least some adverse outcomes in offspring exposed to lithium during pregnancy may stem from factors other than the lithium exposure per se. In our first-trimester specific analysis, more neonates in the lithium-exposed group had major malformations (7·4%) compared to our mood disorder reference group (4·3%), indicating a statistically significant increased risk in the lithium group (pooled OR=1·71, 95% CI: 1·07–2·72). This finding was supported by the sensitivity analysis comparing malformation risk in children of women who were prescribed

lithium *during* versus *around (but not during)* pregnancy using Danish and Swedish data, where an increased risk of major malformations were detected. Additionally, risk of cardiac malformations in our meta-analysis was 2·1% vs. 1·6%, pooled aOR=1·54, 95% CI: 0·64–3·70. In comparison, concern about malformations after in-utero exposure to lithium was similarly supported by the results of a recent well-conducted U.S. study on 663 infants by Patorno et al., where the absolute risk for cardiac malformations (2·4%) was similar to ours (2·1%). [14] In this study there was a significantly increased risk of overall malformations in newborns exposed to lithium in-utero, risk ratio: 1·37 (95% CI: 1·01–1·87), as well as an increased risk of cardiac malformations, risk ratio: 1·65 (95% CI: 1·02–2·68).[14] At this point, an increased risk for malformations associated with lithium exposure is suggested and due to the serious complications of these findings this should guide treatment decisions as well as future studies. An approach aimed at further pooling evidence across countries/study sites and presented results, could in the next years provide the evidence needed to quantify any magnitude of risk associated with lithium exposure in pregnancy.

In our study an increased risk for congenital malformations attributable specifically to first-trimester lithium use was found, but our results and that of Paterno et al. jointly suggest that the absolute risk of malformations is much smaller than reported in earlier studies. Further, we observed an increased risk for hospital admission shortly after birth for lithium-exposed infants which requires further study. Overall, treatment decisions must weigh the potential for increased risks, considering both the specific effect sizes and the precision of the estimates, associated with lithium use in pregnancy and in particular first-trimester against its effectiveness at reducing relapse.

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Conflict of Interest Disclosures

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Contributors

TMO, XL and VB conceived and designed the study after discussing design considerations with co-authors from all study sites. TMO drafted the manuscript. XL, AV, ADF, HK, and RW had full access to the data at individual study sites, analyzed the data and can take responsibility for the integrity of the data and the accuracy of the data analysis. SV supervised the analyst who had direct access to data and who analyzed the data in Canada, and they take responsibility for the integrity of the data and the accuracy of the data analysis. XL further conducted the meta-analyses on results provided from all study sites. CT designed and established the cohort in the UK site and also collected all data on women in the sample. All authors interpreted the data and revised the manuscript critically.

Role of the funder/sponsor

The investigators conducted the research independently. The funders had no role in study design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Corresponding author TMO confirms that she has had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Table 1. Characteristics of the participating study sites, comparing lithium-exposed group to reference group with maternal diagnoses of mood disorder

Study site (population, year)	N	Age (years) mean ± SD	Primiparity, No. (%)	Other psychotropic drugs, No. (%)
Canada (register-based cohort, 2002–2013)				
Lithium-exposed group	201	27·6 ± 5·7	84 (41·8)	170 (84·6)
Reference group	6,333	26·4 ± 6·0	2,012 (31·8)	3,467 (54·7)
Denmark (register-based cohort, 1997–2012)				
Lithium-exposed group	118	32·9 ± 5·0	67 (56·8)	92 (78·0)
Reference group	1,335	29·3 ± 5·7	651 (48·8)	810 (60·7)
Sweden (register-based cohort, 2005–2013)				
Lithium-exposed group	238	32·3 ± 5·2	123 (51·7)	184 (77·3)
Reference group	13,407	29·6 ± 5·9	6,395 (47·7)	8,648 (64·5)
The Netherlands (Clinical cohort, 2000–2015)				
Lithium-exposed group	115	34·0 ± 4·3	55 (47·8)	61 (53·0)
Reference group	88	32·7 ± 4·8	18 (20·5)	24 (27·3)
United Kingdom (Clinical cohort, 2007–2013)				
Lithium-exposed group	27	35·0 ± 4·7	16 (59·3)	16 (59·3)
Reference group	202	32·0 ± 5·7	83 (41·1)	131 (64·9)
United States (Clinical cohort, 2004–2015)				
Lithium-exposed group	28	29·1 ± 5·8	5 (17·9)	21 (75·0)
Reference group	32	29·4 ± 6·1	5 (15·6)	21 (65·6)
Overall				
Lithium-exposed group	727	31·3 ± 5·2	350 (48·1)	544 (74·8)
Reference group	21,397	28·7 ± 5·9	9,164 (42·8)	13,101 (61·2)

Abbreviation: SD = Standard Deviation

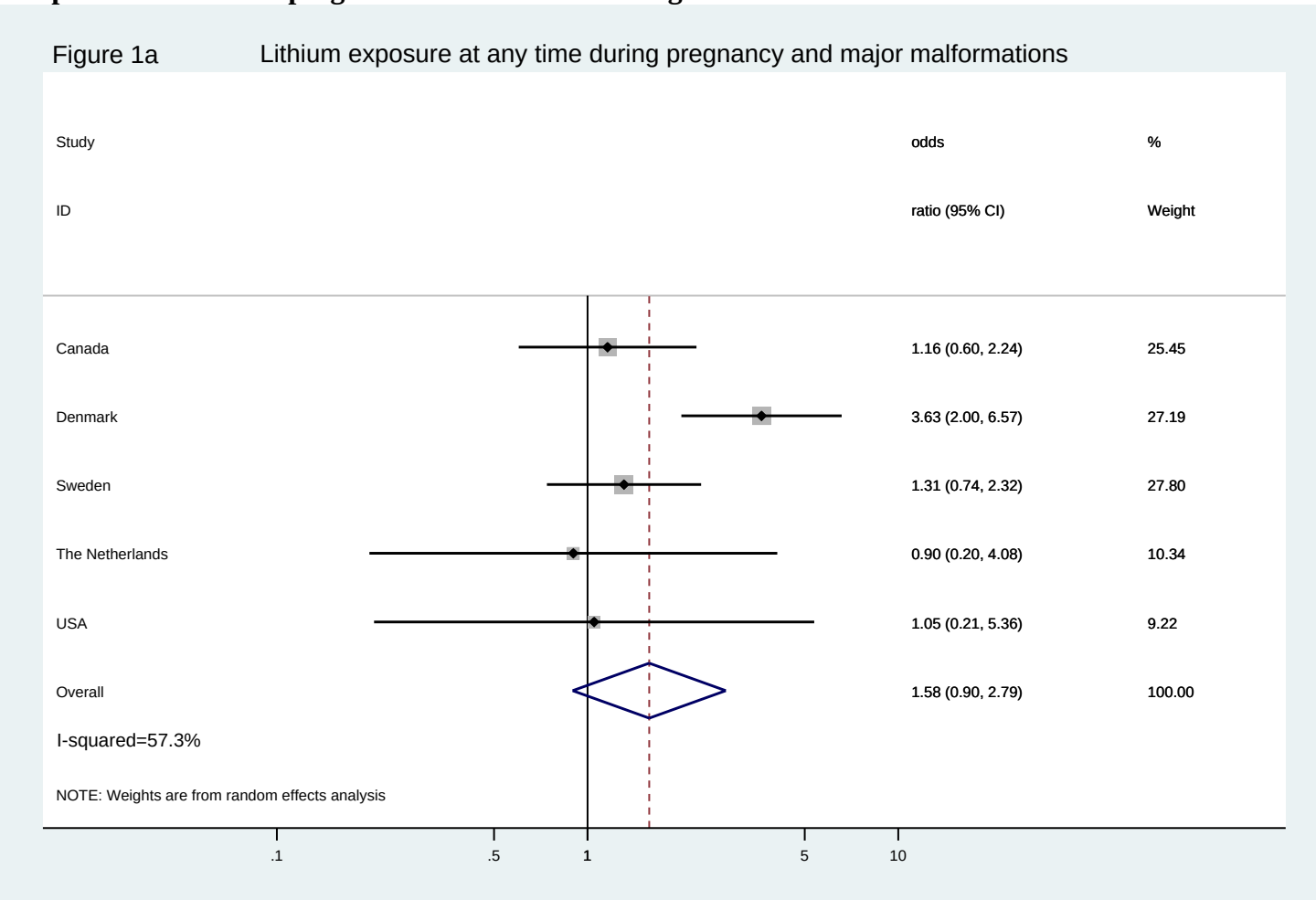
Table 2. Pooled prevalence rate and odds ratio of health outcomes in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder [a]

Health outcomes	Lithium-exposed group			Reference group			Pooled adjusted OR (95% CI) in lithium-exposed group versus reference group [b]	I-squared (%)
	Pooled N	N with outcome	Pooled prevalence with 95% CI (%)	Pooled N	N with outcome	Pooled prevalence with 95% CI (%)		
Pregnancy complications								
Preeclampsia [d]	612	13	1·8 (0·1, 3·5)	21,309	187	2·1 (0·9, 3·2)	0·97 (0·52, 1·80)	0·0
Diabetes [d]	489	35	6·4 (4·1, 8·8)	7,990	512	5·4 (2·5, 8·2)	1·20 (0·81, 1·78)	0·0
Fetal distress [c]	727	90	14·1 (3·9, 24·2)	21,397	1,561	13·2 (4·0, 22·4)	1·00 (0·76, 1·32)	0·0
Postpartum hemorrhage [d]	489	38	7·4 (3·3, 11·6)	7,990	391	7·1 (3·7, 10·5)	1·28 (0·64, 2·57)	53·5
Labour and delivery outcomes								
Caesarean section [c]	727	201	26·5 (20·3, 32·6)	21,392	4,844	25·8 (20·9, 30·7)	0·94 (0·66, 1·33)	62·0
Preterm birth [c]	717	96	13·1 (10·6, 15·6)	21,397	1,949	10·0 (7·3, 12·7)	1·24 (0·83, 1·84)	49.7
Low birth weight [c]	719	50	6·4 (4·5, 8·2)	21,338	1,339	7·2 (4·6, 9·7)	0·98 (0·72, 1·35)	0·0
Small for gestational age [e]	692	58	7·5 (2·3, 12·8)	21,302	1,614	9·3 (1·5, 17·1)	0·90 (0·67, 1·21)	0·0
Neonatal readmission < 28 days [c]	718	172	27·5 (15·8, 39·1)	21,158	2,625	14·3 (10·4, 18·2)	1·62 (1·12, 2·33)	56·6
Congenital malformations in lithium exposure group								
Major malformations [d]	693	51	7·2 (4·0, 10·4)	20,957	856	4·3 (3·7, 4·8)	1·58 (0·90, 2·79)	57·3
Major cardiac malformations [d]	693	17	2·0 (0·5, 3·6)	20,957	316	1·6 (1·0, 2·1)	1·31 (0·50, 3·47)	54·9
Congenital malformations in lithium first trimester exposure group								
Major malformations [d]	621	47	7·4 (4·0, 10·7)	20,957	856	4·3 (3·7, 4·8)	1·71 (1·07, 2·72)	34·8
Major cardiac malformations [d]	621	16	2·1 (0·5, 3·7)	20,957	316	1·6 (1·0, 2·1)	1·54 (0·64, 3·70)	43·0

[a] 95% confidence interval was calculated using an exact binomial approach in random-effects meta-analytic models; [b] adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medication use during pregnancy, and calendar year of birth; [c] Data from 6 countries were available for this pooled estimate; [d] Data from 5 countries were available for this pooled estimate; [e] Data from 4 countries were available for this pooled estimate.

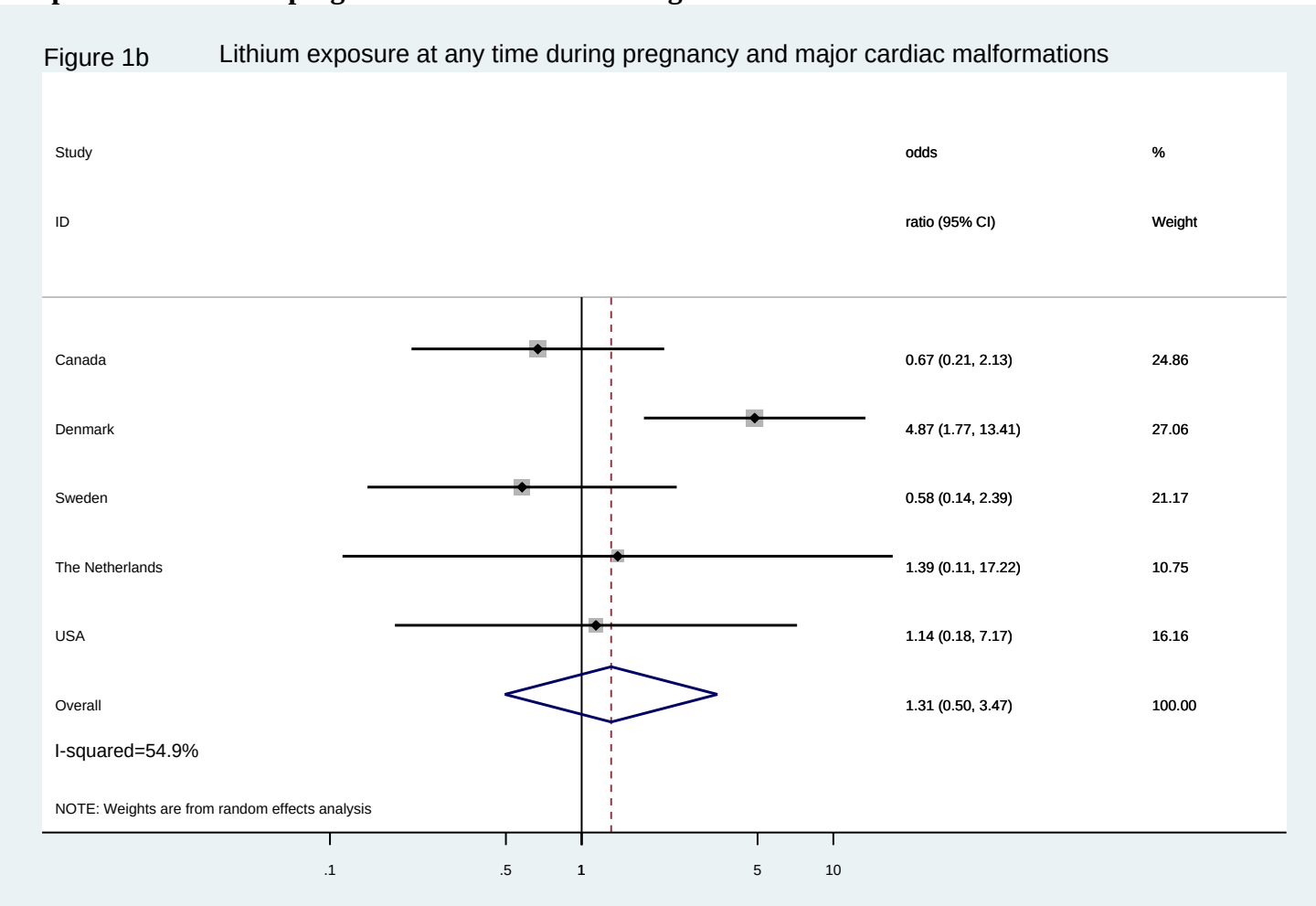
Note that N changed for different outcomes as not all sites contributed to the calculation of all outcomes and not all subjects in individual site had information on all outcomes.

Figure 1a. Pooled adjusted odds ratio of major congenital malformations in lithium exposed pregnancies compared to reference pregnancies with maternal diagnosis of mood disorder



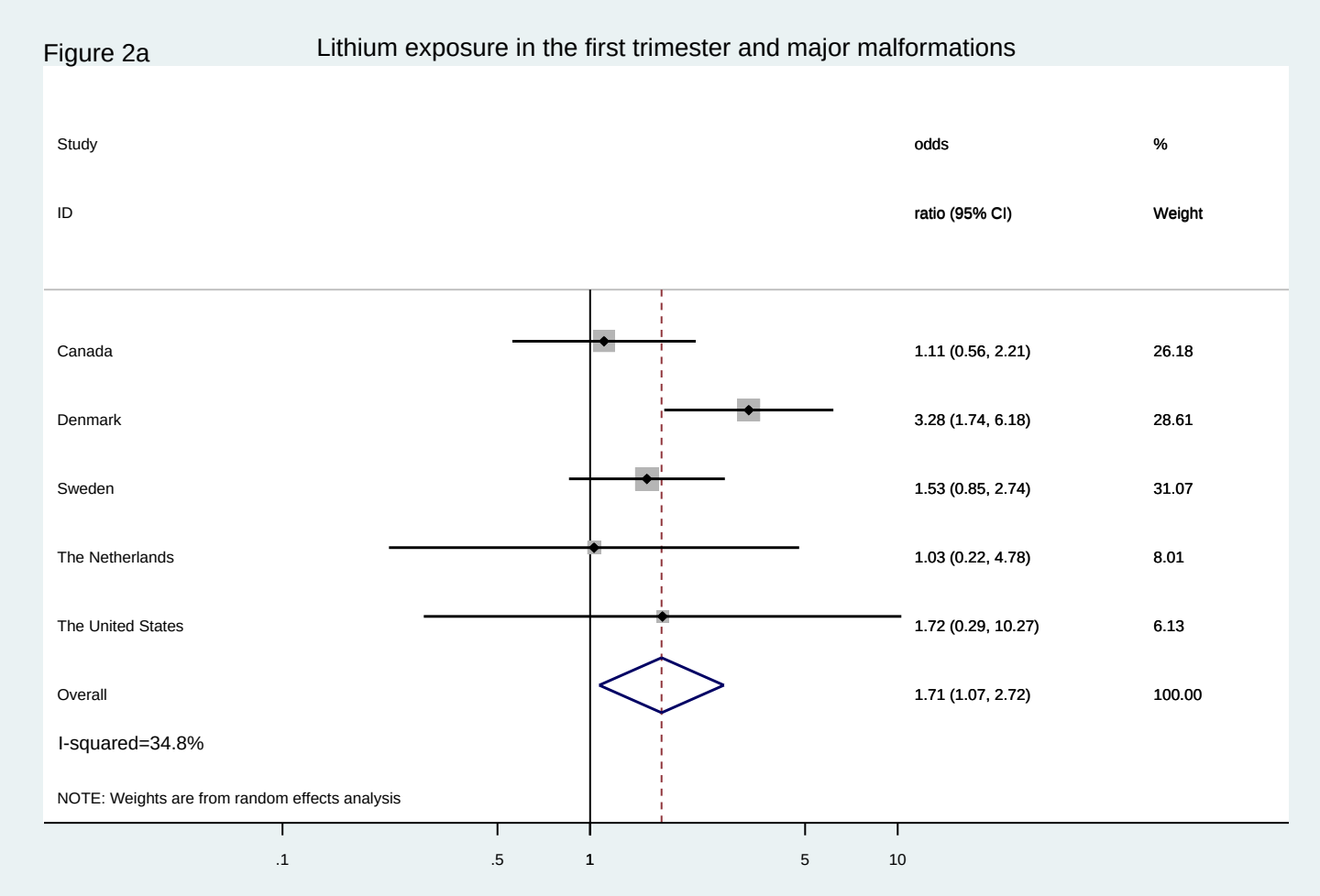
Adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medications during pregnancy and calendar year of birth.

Figure 1b. Pooled adjusted odds ratio of major cardiac malformations in lithium exposed pregnancies compared to reference pregnancies with maternal diagnosis of mood disorder



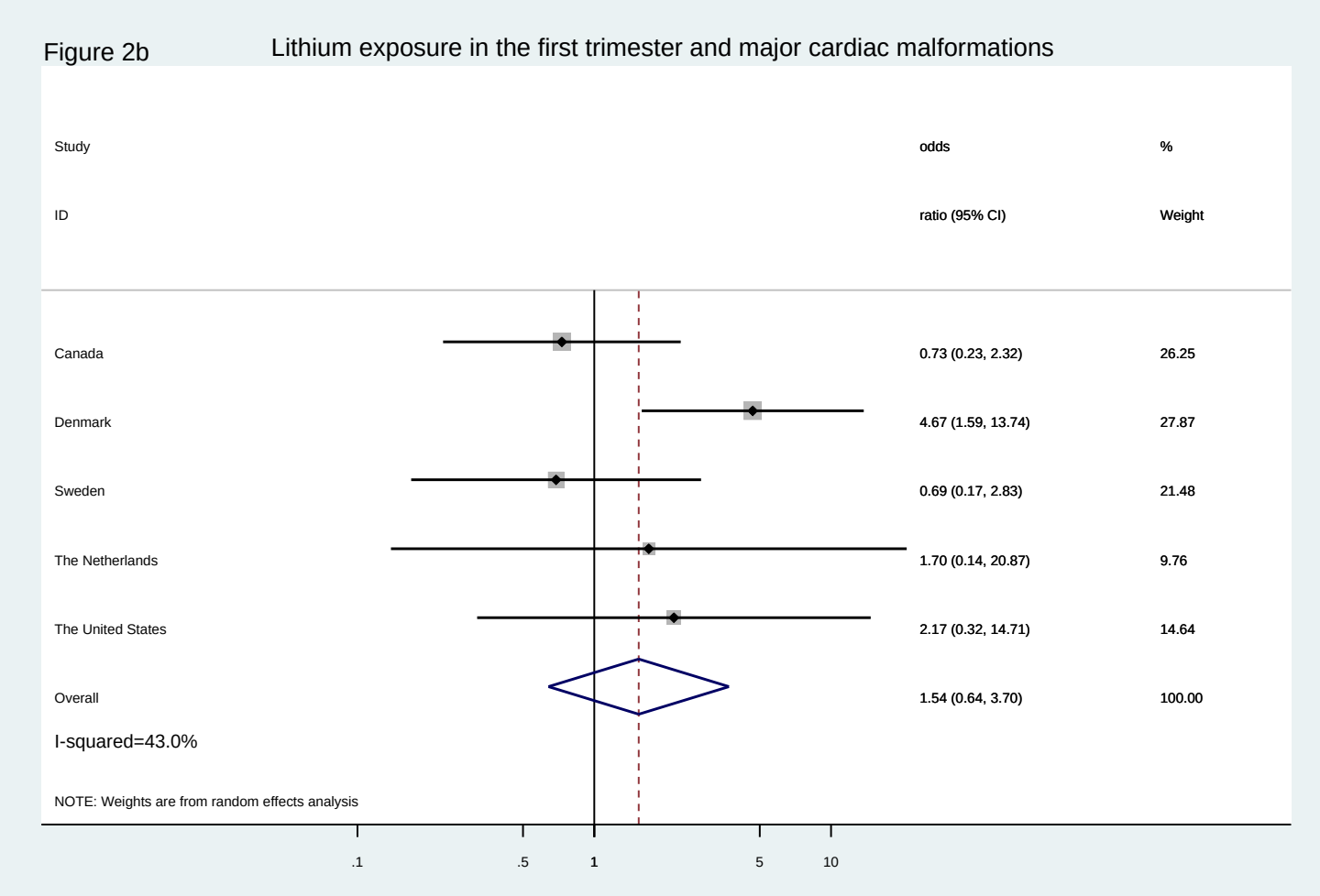
Adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medications during pregnancy and calendar year of birth.

Figure 2a. Pooled adjusted odds ratio of major congenital malformations in lithium first trimester exposure pregnancies compared to reference pregnancies with maternal diagnosis of mood disorder



Adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medications during pregnancy and calendar year of birth.

Figure 2b. Pooled adjusted odds ratio of major cardiac malformations in lithium first trimester exposure pregnancies compared to reference pregnancies with maternal diagnosis of mood disorder



Adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medications during pregnancy and calendar year of birth.

Table 3. Pooled prevalence rate and odds ratio of health outcomes in lithium use *during* pregnancy group compared to lithium use *around* pregnancy group in sub-analyses based on data from Sweden and Denmark

Health outcomes	Lithium exposure during pregnancy			Lithium exposure around pregnancy			Pooled adjusted OR (95% CI) in lithium exposure during pregnancy versus around pregnancy [a]	I-squared (%)
	Pooled N	N with outcome	Pooled prevalence with 95% CI (%)	Pooled N	N with outcome	Pooled prevalence with 95% CI (%)		
Pregnancy complications [b]								
Fetal distress	356	15	0·6 (0·0, 1·5)	597	16	1·7 (0·6, 2·7)	0·91 (0·35, 2·37)	3·5
Labour and delivery outcomes								
Caesarean section	356	97	26·4 (21·9, 31·0)	597	131	21·9 (18·6, 25·2)	1·02 (0·45, 2·34)	74·7
Preterm birth	356	46	12·9 (9·4, 16·4)	597	54	8·9 (6·6, 11·2)	1·44 (0·92, 2·26)	0·0
Low birth weight	356	26	7·2 (4·5, 9·9)	597	31	5·0 (3·2, 6·7)	1·22 (0·68, 2·17)	0·0
Small for gestational age	356	18	3·4 (1·6, 5·3)	597	27	4·3 (2·7, 6·0)	0·85 (0·32, 2·22)	43·8
Neonatal readmission <28 days	356	77	20·9 (16·7, 25·1)	597	83	13·8 (11·0, 16·6)	1·65 (1·14, 2·41)	0·0
Congenital malformations								
Major malformations	356	31	7·1 (4·4, 9·7)	597	20	3·1 (1·7, 4·5)	2·09 (1·10, 3·96)	0·0
Major cardiac malformations	356	8	1·2 (0·1, 2·3)	597	9	1·5 (0·5, 2·4)	1·28 (0·13, 12.39)	52·1

[a] adjusted for maternal age at delivery, primiparity, other psychotropic medication use during pregnancy, and calendar year of birth; [b] The number of preeclampsia, diabetes during pregnancy and postpartum hemorrhage cases were too small to calculate the pooled odds ratio.

Lithium use around pregnancy (N=597): Mothers with lithium treatment within 1) a period from 400 days prior to the beginning of pregnancy (conception) until 122 days prior to the beginning of pregnancy, or 2) a period from after childbirth until 280 days after childbirth. Lithium treatment in either period were defined as either A) having least two lithium dispensations during the period, or B) one dispensation during the defined period and at least another dispensation within 6 months before or after this date (not overlapping pregnancy);
Lithium exposure group (N=356): Mothers with at least two dispensations of lithium during pregnancy (from one month prior the date of conception to the delivery date), or one dispensation during pregnancy with at least one other dispensation within 6 months before or after this date.

Note: As results in Table 3 are based on data from only Denmark and Sweden, the presented pooled N in each category is smaller than the presented pooled N in Table 2, which includes data from entire study base from six countries.

List of supplementary material

1. Appendix Tables and Figures
2. Study protocol
3. Research in context panel
4. STROBE checklist

Appendix Tables and Figures

eTable 1. The identification of study population in each study site

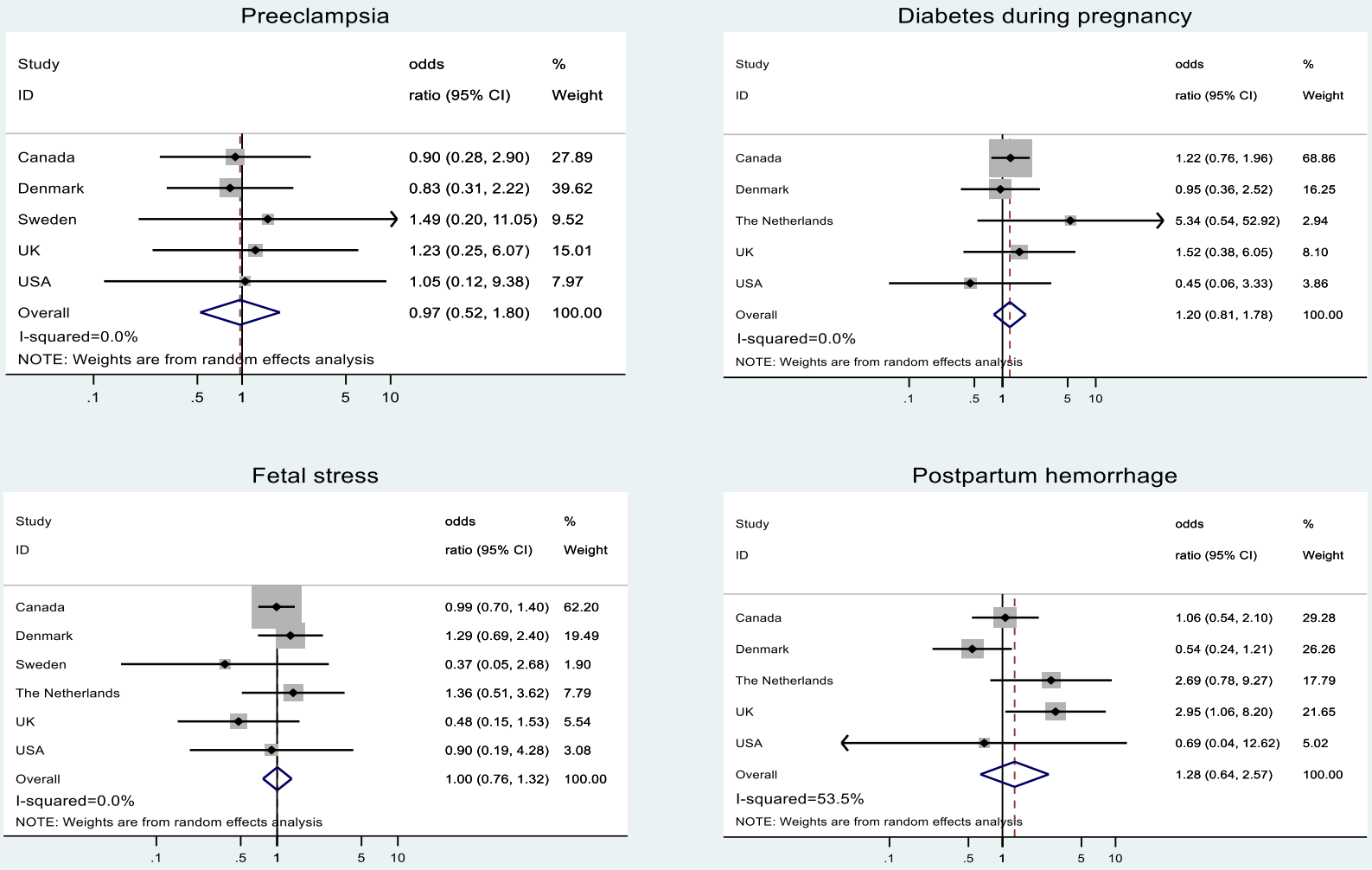
Study site	Study population
Canada (Register-based cohort, 2002–2013)	We drew our study cohort from the Institute for Clinical Evaluative Sciences (ICES), an independent, non-profit organization that holds health administrative data on all Ontario residents.[1] Databases for outpatient visits, hospitalizations, prescription drug use, and sociodemographic data were linked at the individual level using a unique encrypted identifier and analyzed at ICES. The cohort comprised all 16- to 50-year-old female Ontario residents who had a singleton liveborn delivery after 20 weeks gestational age, with a conception date between April 1, 2002 and March 31, 2013, and who were eligible for Ontario's publicly funded drug program. Eligibility for the publicly funded drug program was determined as having (1) filled at least 1 prescription under the Ontario Drug Benefit plan between 181-365 days prior to pregnancy and (2) filled at least 1 prescription under the plan from 180 days prior to pregnancy to 180 days subsequent to pregnancy. Women using known teratogenic medications (i.e., thalidomide, valproate, retinoid, antineoplastic agents, misoprostol, methotrexate) were excluded. Lithium exposure was identified as having at least two prescriptions from one month before conception until delivery or one prescription during pregnancy and another 6 months before after this date, using the following drug identification numbers: 00461733, 02216132, 02242837, 02013231, 09857532, 00236683, 02216140, 02242838, 00406775, 09857540, 00590665, and 02266695. Bipolar and major depressive disorder were identified as having at least 1 hospitalization for bipolar disorder or major depressive disorder and/or two outpatient contacts with a diagnosis of bipolar disorder/major depressive disorder from 2 years prior to the date of conception to the delivery date (in hospitalization data: ICD-9 296, 311; ICD-10 F30-F33; in psychiatric hospitalization data: bipolar disorder, major depressive disorder; in outpatient data: 296, 311). We identified 201 women with lithium exposure in pregnancy and who also had a bipolar or major depressive disorder, 6,333 women without lithium exposure who had a bipolar or major depressive disorder.
Denmark (Register-based cohort, 1997–2012)	All liveborn and new residents in Denmark are assigned a unique Civil Personal Register number, which enables individual level linkage across registers. We drew our study cohort from the Danish Medical Birth Register,[2] which holds data on all live births and their mothers since 1968. We identified 932,934 singletons born during Nov 1st, 1997 until Dec 31st, 2012 in Denmark. We excluded 6,639 children with missing or extreme gestational age and 581 children whose mothers used any known teratogenic medications during pregnancy. Of those 581 children, 556 children were exposed to valproate acid in utero. After exclusion, 925,714 singletons were left in the cohort. To obtain information on maternal bipolar or major depressive disorder before delivery (ICD-10 codes F30–F33) and lithium use during pregnancy (Anatomical Therapeutic Chemical Classification System (ATC) code N05AN01), we linked the Danish National Birth Cohort to the Danish National Prescription Registry[3] and the Danish Psychiatric Central Research Register.[4] The Danish National Prescription Register covers all prescriptions dispensed in Denmark since 1995. The Danish Psychiatric Central Research Register was established as an electronic database in 1969. The register holds information on all treatments at psychiatric hospitals and psychiatric wards in general hospitals since 1969. In 1995, data on emergency room visits and outpatient treatments was included. Altogether, 118 children born to mothers with lithium use during pregnancy and 1,335 to mothers with bipolar or major depressive disorders before delivery but with no lithium use during pregnancy were included.
Sweden (Register-based cohort, 2005–2013)	A birth cohort based on all liveborn singletons with gestational age information from October 1, 2005 to December 31, 2013 was established by linkage of Swedish National registers using the unique individual registration number.[5] Mothers and offspring were identified in the Swedish Medical Birth Register that covers 99% of all births nationwide since 1973 and provides information on gestational age at birth that were used to calculate the duration of pregnancy.[6] In Sweden, 95% of all pregnant women receive ultrasonography in the early second trimester, which provide the gestational age of the fetus with an error margin of ±7 days.[7] Maternal bipolar or major depressive disorder before delivery were identified in the Swedish Patient Register.[8] This register includes all psychiatric admissions since 1973 and outpatients since 2001, and provides admission dates along with the main and eight secondary diagnosis codes in accordance with the ICD codes, and bipolar or major depressive disorder were defines using ICD-10 codes F30–F33. Medication use during pregnancy was identified in the Swedish Prescribed Drug Register that hold information on all dispensed prescription medications in Sweden since July 2005 along with medication name, prescription- and dispensation dates, and the ATC code.[9] There were 702 children excluded whose mothers used any known teratogenic medications during pregnancy. The cohort included 632,089 children, with 238 children born to mothers with lithium use during pregnancy and 13,407 to mothers with bipolar or major depressive disorders before delivery but with no lithium use during pregnancy.
The Netherlands (Clinical cohort, 2000–2015)	The study was approved by the Institutional Review Board of the Erasmus University Medical Centre (MEC-2013-319 ABR). Women with bipolar spectrum disorders and/or lithium use during pregnancy referred to psychiatric/obstetric outpatient clinics in the Netherlands between 2000 and 2015 with live-born singleton deliveries were eligible for inclusion. Relevant obstetric and psychiatric data was extracted retrospectively from medical records and processed with data manager OpenClinica. We excluded 6 twin pregnancies, 4 pregnancies with an outcome of stillbirth (gestational age 22-39 weeks) and 6 pregnancies in which women used teratogenic medication; all six women used valproate in the first trimester. Together, 115 children born to mothers with lithium use during pregnancy were included. Of these, 77 children were born in the Erasmus University Medical Centre, 35 children in Leiden University Medical Centre and n=3 children in other hospitals in the Netherlands. Further, 88 children born to mother with a bipolar spectrum disorder were included (Erasmus University Medical Centre (n=63), Leiden University Medical Centre (n=11) and other hospitals (n=14). Of the included pregnancies, missing values were only present for birthweight (n=1) and Apgar scores (n=7).
The United Kingdom (Clinical cohort, 2007–2013)	We enrolled children of women who were treated by South London and Maudsley NHS Foundation Trust (SLAM) during their pregnancy.[10] SLAM provides almost exclusive secondary mental health care to a catchment population of 1·2 million people in South London. The psychiatric records of all SLAM patients are accessible to researchers via an anonymized mental health research case registry (CRIS). CRIS allows structured field and free-text searches, supported by validated Natural Language Processing applications (e.g. for diagnoses and medication use). This database was linked to the national Hospital Episode Statistics (HES) database, which holds data on all hospital-based livebirths, and to the local Neonatal Badger dataset, which holds data related to admissions to local neonatal intensive care units. We identified 255 singletons born during the period Jan 1st 2007 to March 31st 2013 to women who met the following inclusion criteria: under the care of SLAM during pregnancy and either (a) took lithium during pregnancy (exposed group) or (b) did not take lithium during pregnancy and had an ICD-10 diagnosis of manic episode (F30), bipolar affective disorder (F31) or psychotic depression (F32·3, F33·3) (reference group). After excluding 26 children whose mothers used any known teratogenic medications during pregnancy, 229 children were included in the cohort, comprising 27 children born to mothers with lithium use during pregnancy and 202 to mothers with bipolar disorder or psychotic depression before delivery but with no lithium use during pregnancy.
The United States (Clinical cohort, 2004–2015)	The Carolina Data Warehouse for Health (CDW-H) is a central data repository containing clinical, research, and administrative data sourced from the University of North Carolina (UNC) Health Care System. It functions to aid with a number of research processes, including retrospective analyses. A request was made for a dataset of all women with an ever lithium prescription and an ever live-birth diagnosis. The CDW-H contains 2 databases: a pre-electronic medical record (EMR) database of limited clinical data from 2004-2013 and a post-EMR database with data from 2013-2015 where data was mined directly from individual EMRs. This resulted in a dataset of 103

	women with 135 deliveries meeting criteria. Mother-child pairs are not linked in the UNC Health Care System so children had to be manually searched for using identifying clues in a mother's record. It was not always possible to find the child as the mother may have delivered at UNC but then her child did not receive care at UNC and therefore did not have a record. This limitation resulted in the exclusion of 60 deliveries due to no or inadequate follow-up information on the child. Additionally, 2 deliveries were excluded due to a twin delivery; 8 deliveries were excluded due to no prior psychiatric history in the mother (bipolar or major depressive comparison pregnancies only) and 5 deliveries were excluded due to lithium exposure in the 90 days prior to delivery (bipolar or major depressive comparison pregnancies only). This resulted in 75 excluded deliveries. The sample included in the final analysis included 60 deliveries: 28 lithium exposed pregnancies and 32 bipolar or major depressive comparison pregnancies.

eTable 2. Percentage of lithium exposure in the first trimester in each study site

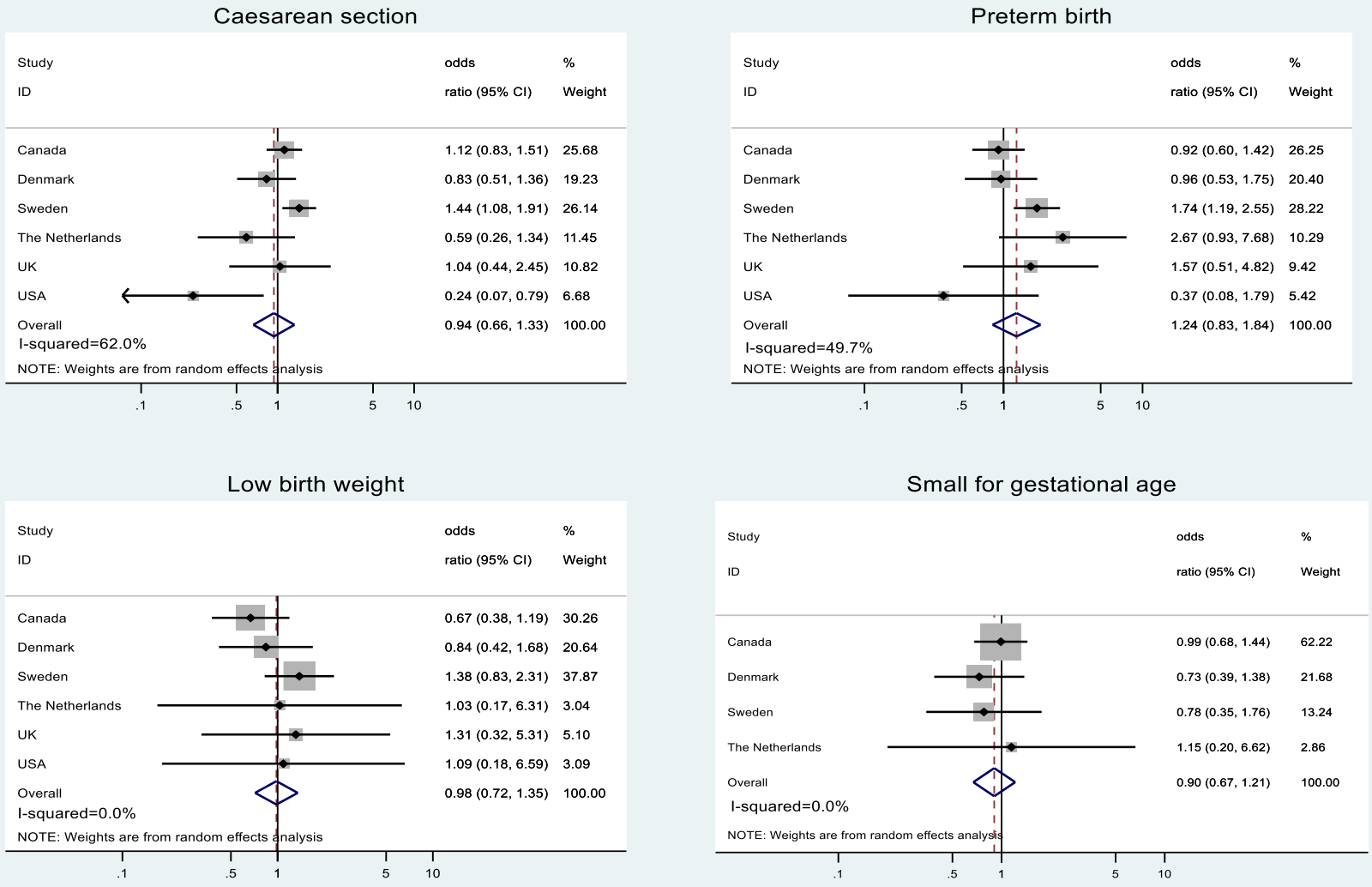
Study site	Lithium exposure during pregnancy	Lithium exposure in the first trimester	Percentage of first trimester exposure (%)
Cananda	201	187	93.0
Denmark	118	107	90.7
Sweden	238	214	89.9
The Netherlands	115	106	92.2
The United Kingdom	27	26	96.3
The United States	28	14	50.0
Overall	727	654	90.0

eFigure 1. Pooled adjusted odds ratio of pregnancy complications in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder



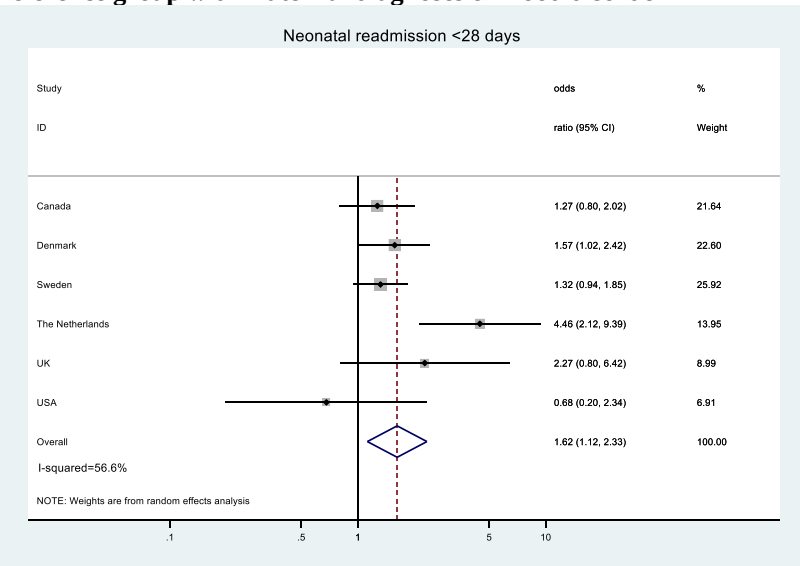
Adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medications during pregnancy and calendar year of birth.

eFigure 2. Pooled adjusted odds ratio of labour and delivery outcomes in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder



Adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medications during pregnancy and calendar year of birth.

eFigure 3. Pooled adjusted odds ratio of neonatal readmission in the first 28 days of life in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder



Adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medications during pregnancy and calendar year of birth.

eTable 3. Pooled adjusted odds ratio of health in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder using "leave-one-out approach"

Health outcomes	Leave Canada out	Leave Denmark out	Leave Sweden out	Leave the Netherlands out	Leave the UK out	Leave the USA out
Pregnancy complications						
Preeclampsia [b]	1·00 (0·48, 2·07)	1·08 (0·49, 2·38)	0·93 (0·48, 1·78)	0·97 (0·52, 1·80)	0·93 (0·48, 1·82)	0·96 (0·51, 1·84)
Diabetes [b]	1·15 (0·57, 2·33)	1·25 (0·82, 1·93)	1·20 (0·81, 1·78)	1·15 (0·77, 1·71)	1·17 (0·78, 1·77)	1·25 (0·84, 1·86)
Fetal distress [a]	1·03 (0·66, 1·61)	0·95 (0·70, 1·28)	1·02 (0·78, 1·35)	0·98 (0·74, 1·30)	1·05 (0·79, 1·39)	1·01 (0·76, 1·33)
Postpartum hemorrhage [b]	1·41 (0·50, 4·00)	1·67 (0·90, 3·09)	1·28 (0·64, 2·57)	1·09 (0·51, 2·33)	1·00 (0·51, 1·93)	1·34 (0·62, 2·87)
Labour and delivery outcomes						
Caesarean section [a]	0·83 (0·50, 1·38)	0·95 (0·63, 1·43)	0·81 (0·55, 1·21)	1·00 (0·70, 1·44)	0·91 (0·62, 1·35)	1·08 (0·83, 1·41)
Preterm birth [a]	1·38 (0·87, 2·19)	1·32 (0·81, 2·15)	1·07 (0·71, 1·63)	1·14 (0·76, 1·71)	1·21 (0·77, 1·89)	1·32 (0·91, 1·93)
Low birth weight [a]	1·16 (0·79, 1·69)	1·02 (0·72, 1·46)	0·80 (0·54, 1·19)	0·98 (0·71, 1·35)	0·97 (0·70, 1·34)	0·98 (0·71, 1·35)
Small for gestational age [c]	0·77 (0·48, 1·25)	0·96 (0·68, 1·34)	0·92 (0·67, 1·27)	0·90 (0·66, 1·21)	0·90 (0·67, 1·21)	0·90 (0·67, 1·21)
Neonatal readmission< 28 days [a]	1·75 (1·09, 2·79)	1·66 (1·01, 2·71)	1·75 (1·06, 2·88)	1·37 (1·10, 1·71)	1·57 (1·05, 2·34)	1·72 (1·19, 2·50)
Congenital malformations in lithium exposure group						
Major malformations [b]	1·72 (0·83, 3·54)	1·20 (0·81, 1·80)	1·63 (0·75, 3·57)	1·68 (0·90, 3·15)	1·58 (0·90, 2·79)	1·64 (0·87, 3·08)
Major cardiac malformations [b]	1·63 (0·52, 5·12)	0·75 (0·35, 1·62)	1·63 (0·53, 4·97)	1·28 (0·42, 3.97)	1·31 (0·50, 3·47)	1·33 (0·40, 4·37)
Congenital malformations in lithium first trimester exposure group						
Major malformations [b]	2·01 (1·21, 3·32)	1·33 (0·88, 2·01)	1·74 (0·87, 3·47)	1·78 (1·05, 3·01)	1·71 (1·07, 2·72)	1·69 (0·99, 2·90)
Major cardiac malformations [b]	2·03 (0·77, 5·38)	0·93 (0·43, 2·00)	1·92 (0·70, 5·25)	1·52 (0·54, 4·23)	1·54 (0·64, 3·70)	1·44 (0·49, 4·19)

Adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medications during pregnancy and calendar year of birth;
[a] Data from 6 countries were available for this pooled estimate;
[b] Data from 5 countries were available for this pooled estimate;
[c] Data from 4 countries are available for this pooled estimate.

eTable 4. Pooled adjusted odds ratio of health outcomes in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder stratified on the design of the cohort

Health outcomes	Register-based cohort	Clinical cohort	Total
Pregnancy complications			
Preeclampsia	0·92 (0·45, 1·86)	1·16 (0·32, 4·23) [a]	0·97 (0·53, 1·80)
Diabetes	1·16 (0·76, 1·78) [a]	1·43 (0·44, 4·69) [a]	1·20 (0·81, 1·78)
Fetal distress	1·03 (0·76, 1·39)	0·89 (0·45, 1·74)	1·01 (0·76, 1·32)
Postpartum hemorrhage	0·79 (0·41, 1·51) [a]	2·58 (1·21, 5·52)	1·28 (0·64, 2·57)
Labour and delivery outcomes			
Caesarean section	1·16 (0·88, 1·53)	0·58 (0·27, 1·23)	0·94 (0·66, 1·33)
Preterm birth	1·19 (0·76, 1·85)	1·33 (0·48, 3·71)	1·24 (0·84, 1·84)
Low birth weight	0·94 (0·60, 1·48)	1·17 (0·45, 3·00)	0·98 (0·72, 1·35)
Small for gestational age	0·90 (0·66, 1·21)	- [b]	0·90 (0·67, 1·21)
Neonatal readmission< 28 days	1·37 (1·09, 1·73)	2·09 (0·74, 5·91)	1·62 (1·12, 2·33)
Congenital malformations in lithium exposure group			
Major malformations	1·78 (0·87, 3·62)	0·97 (0·32, 2·93) [a]	1·58 (0·90, 2·79)
Major cardiac malformations	1·30 (0·31, 5·46)	1·22 (0·28, 5·39) [a]	1·31 (0·50, 3·47)
Congenital malformations in lithium first trimester exposure group			
Major malformations	1·78 (0·96, 3·30)	1·28 (0·70, 4·10) [a]	1·71 (1·07, 2·72)
Major cardiac malformations	1·39 (0·38, 5·07)	1·98 (0·43, 9·08) [a]	1·54 (0·64, 3·70)

Adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medications during pregnancy and calendar year of birth;

[a] Data from 2 countries were available for this pooled estimate;

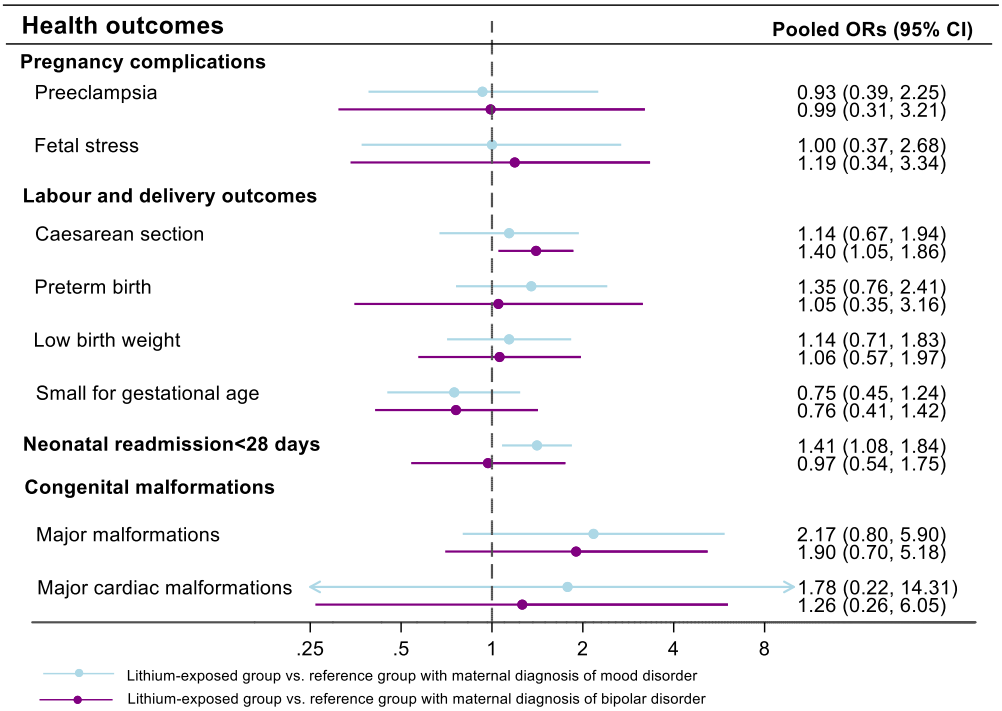
[b] Only data from the Netherlands was available.

eTable 5. Pooled adjusted odds ratio of outcomes in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder in four different models on Danish and Swedish data

Health outcomes	Model 1 [a]	Model 2 [b]	Model 3 [c]	Model 4 [d]
Pregnancy complications [e]				
Preeclampsia	0·93 (0·39, 2·25)	0·93 (0·39, 2·24)	0·85 (0·35, 2·08)	0·90 (0·37, 2·23)
Fetal distress	1·00 (0·37, 2·68)	1·00 (0·38, 2·68)	1·04 (0·38, 2·84)	0·92 (0·30, 2·83)
Labour and delivery outcomes				
Caesarean section	1·14 (0·67, 1·94)	1·11 (0·61, 2·02)	1·11 (0·63, 1·97)	1·12 (0·73, 1·71)
Preterm birth	1·35 (0·76, 2·41)	1·40 (0·76, 2·57)	1·41 (0·80, 2·49)	1·44 (0·97, 2·13)
Low birth weight	1·14 (0·71, 1·83)	1·19 (0·72, 1·97)	1·17 (0·69, 1·97)	1·13 (0·74, 1·74)
Small for gestational age	0·75 (0·45, 1·24)	0·82 (0·49, 1·36)	0·81 (0·49, 1·34)	0·79 (0·47, 1·32)
Neonatal readmission< 28 days	1·41 (1·08, 1·84)	1·44 (1·10, 1·88)	1·40 (1·07, 1·83)	1·37 (0·96, 1·97)
Congenital malformations				
Major malformations	2·17 (0·80, 5·90)	2·12 (0·82, 5·49)	2·06 (0·80, 5·29)	2·01 (0·71, 5·65)
Major cardiac malformations	1·78 (0·22, 14·31)	1·81 (0·24, 13·62)	1·87 (0·22, 16·03)	1·78 (0·18, 17·31)

[a] model 1 adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medications during pregnancy (yes/no), and calendar year of birth;
[b] model 2 adjusted for the same factors as model 1, and further adjusted for education status and marriage status;
[c] model 3 adjusted for the same factors as model 2, and further adjusted for treatment with antiepileptic medication during pregnancy (any dispensation of a medication with ATC code filing under N03A, yes/no);
[d] model 4 adjusted for maternal age at delivery, primiparity, calendar year of birth, education status, marriage status, and treatment during pregnancy with any medication according to: antidepressants (ATC codes filing under N06A, yes/no), antipsychotics (ATC codes filing under N05A or N05X, excluding N05AN01, yes/no), benzodiazepines and z-hypnotics (ATC codes filing under N05C, yes/no), psychostimulants (ATC codes filing under N05B, yes/no), and antiepileptics (ATC codes filing under N03A, yes/no);
[e] The number of diabetes during pregnancy and postpartum hemorrhage cases are too small to calculate the pooled odds ratio.

eFigure 4. Pooled adjusted odds ratio of outcomes in lithium-exposed group compared to reference group with maternal diagnosis of mood disorder and to reference group with maternal diagnosis of bipolar disorder on Danish and Swedish data



Adjusted for maternal age at delivery, primiparity, treatment with other psychotropic medications during pregnancy (yes/no), and calendar year of birth;

Research in context:

Evidence before this study

Pregnant bipolar disorder women have a significant risk of relapse both during pregnancy and postpartum. Lithium is an effective first-line pharmacological treatment for patients with bipolar disorder, but concerns about teratogenicity, maternal- and offspring complications limit its use in pregnancy. We searched PubMed for studies that investigated lithium use in pregnancy among women with mood disorders, (search performed July 3, 2017). Search terms applied were "lithium", "pregnancy", "bipolar", "depression", and "mood disorder". After this, we identified additional papers by checking citations. For our search we considered only English language journals. Case studies were not included as references, but no further search terms or search restrictions were used as the existing evidence in the field is relatively limited.

Mc Knight et al. conducted a systematic review and meta-analysis of studies published before October 2010 and found six case-control studies (n=264) on lithium use during pregnancy and risk of cardiovascular malformations. The odds of Ebstein's anomaly did not differ significantly between lithium exposure cases and controls; however, estimates were unstable because of the low number of events, OR 0·27, 95% CI 0·004–18·17. After 2010, an observational study from Israel reported no increase in severe cardiovascular malformations in lithium exposed pregnancy. A recent well conducted study based on US data reported an increased risk of malformations after first-trimester exposure to lithium (RR 1·65,95% CI: 1·02–2·68), but with low absolute numbers of malformations. Other potential negative outcomes of lithium use were not investigated in this study.

Added value of this study

This meta-analysis analyzed new data from 6 countries, comparing 727 lithium-exposed and 21,397 mood disorder control pregnancies. More neonates in the lithium-exposed group had major malformations compared to our mood disorder reference group, and analyses indicated a statistically significant increased risk of major malformations after first-trimester lithium use (aOR 1·71, 95% CI: 1·07–2·72).

Our study found an increased risk of major malformations specifically after first-trimester exposure to lithium, as well as an increased risk of hospital admission in infants exposed to lithium across pregnancy. However, we did not find evidence of increased risk on other important maternal or infant outcomes such as preeclampsia, diabetes in pregnancy and fetal distress, as well as preterm birth, small for gestational age and low birth weight.

Implications of all the available evidence

Lithium treatment decisions are key and need to be encouraged prior to conception. In particular, first trimester lithium use should be cautioned and weighted based on the available evidence. To support a balanced decision making, women should be informed on malformation risk in first-trimester exposed infants, but also about high relapse risks both during pregnancy and postpartum if lithium treatment is tapered during this sensitive period. Given the well documented effectiveness of lithium in reducing relapse in the perinatal period, one important clinical consideration in some patient groups is to restart lithium either after the first trimester or immediately postpartum.

Study protocol

Maternal and infant outcomes associated with lithium use in pregnancy: Data from an international lithium collaboration in six countries

Participants: Trine Munk-Olsen[1,2]; Xiaoqin Liu[1]; Alexander Viktorin[3]; Hilary K. Brown[4,5,6,7]; Arianna Di Florio[8,9]; Brian M. D'Onofrio[3,10]; Tara Gomes[7,11]; Louise M. Howard[12]; Hind Khalifeh[12]; Holly Krohn[9]; Henrik Larsson[3]; Paul Lichtenstein[3]; Clare L. Taylor[12]; Inge Van Kamp[13]; Richard Wesseloo[14]; Samantha Meltzer-Brody[9]; Simone N. Vigod[5,6,7]; Veerle Bergink[14]

Affiliations: [1] The National Center for Register-based Research, Aarhus University, Aarhus, Denmark; [2] Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark; [3] The Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [4] Interdisciplinary Centre for Health and Society, University of Toronto Scarborough, Toronto, Ontario, Canada; [5] Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada; [6] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; [7] Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; [8] Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK; [9] The Department of Psychiatry, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, N.C, USA; [10] Department of Psychological and Brain Sciences, Indiana University, Bloomington, USA; [11] Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada; [12] Section of Women's Mental Health/Women's Health Academic Centre, Department of Health Service and Population Research, King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, UK; [13] Department of Obstetrics, Section of Perinatal Psychiatry, Leiden University Medical Center, Leiden, The Netherlands; [14] The Department of Psychiatry, Erasmus Medical Centre, Rotterdam, The Netherlands

Contents

Study objective

Lithium is an effective first-line pharmacological treatment for patients with bipolar disorder; however, concerns about adverse maternal and offspring outcomes related to lithium exposure during pregnancy limit its use in women of childbearing age. We, therefore, plan to perform a meta-analysis of primary data and results from Canada, Denmark, Sweden, the Netherlands, the United Kingdom, and the United States to investigate the association between lithium exposure during pregnancy and risk of pregnancy complications, delivery outcomes, neonatal morbidity and congenital malformations.

Dataset creation

Register-based cohorts:

Definition of datasets in register-based cohorts in Canada, Denmark, and Sweden: Several important observation time windows must be determined: the entry and exit dates of the enrolment of the study population (Figure 1). To capture mothers with a psychiatric diagnosis, a minimum of 34 months lookback period before delivery (10 months during pregnancy and 2 years prior conception) in the hospital/psychiatric register is required. Similarly, to ensure a sufficient time window for defining lithium exposure and non-exposure, a minimum of 13 months is required (10 months during pregnancy and 3 months before conception) as the defined lookback period before the delivery. This information will be assessed through local prescription registers or similar data sources. To obtain the information on outcomes of interest, a minimum of one year follow-up time from delivery date is required.

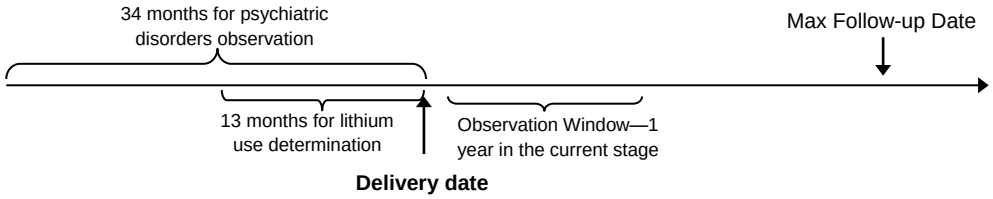


Figure 1 Timeframe for identifying study population

Clinical cohorts:

Definition of datasets in clinical cohort studies in the Netherlands, the United Kingdom, and the United States: The study population will be defined using the available recorded data parallel to the description above. Information on lithium use, maternal diagnosis of psychiatric disorders and outcomes of interest will be obtained from the medical records.

Study population

All liveborn singletons are eligible for inclusion in the study, but pregnancies with either of the following situations are excluded:

- Pregnancies by mothers who were prescribed any known teratogenic medications during the index pregnancy (*one filled prescription, or a clinical record of medication use from one month prior the date of conception to the delivery date*). These include: thalidomide (ATC code: L04AX02), valproate (ATC code: N03AG01), retinoids (ATC code: D05BB), antineoplastic drugs (ATC code: L01), misoprostol (ATC code: A02BB01, G02AD06, and M01AE56), or methotrexate (ATC code: L01BA01 and L04AX03).
- Children born with missing or likely errors in gestational age

Definition of the exposure

A different definition of lithium exposure will be used for register-based and clinical cohorts. See description below:

Register-based cohorts: Information on lithium medication will be identified by using the Anatomical Therapeutical Chemical (ATC) Classification System code N05AN01 in Denmark and Sweden, and the Drug Identification Numbers (DINS) 00461733, 02216132, 02242837, 02013231, 09857532, 00236683, 02216140, 02242838, 00406775, 09857540, 00590665, and 02266695 in Canada. Lithium exposure during pregnancy was defined as:

1) At least two dispensations of lithium during pregnancy (***from one month prior the date of conception to the delivery date***); or
2) One dispensation during pregnancy with at least one other dispensation within 6 months before or after this date.

Clinical cohorts: Lithium use during pregnancy was defined according to medical records. Information on lithium use can be collected both prospectively and retrospectively. To avoid recall bias, information on lithium exposure should be collected before the delivery date.

Definition of bipolar or mood disorder reference group

The reference group/category was defined as women with no dispensation of lithium from 90 days before conception to the delivery, but with at least one hospitalization for bipolar disorder (ICD-10 codes F30–F31) or major depressive disorder (ICD-10 code F32–F33) and/or two outpatient contacts (not including emergency room visit) with a diagnosis of bipolar disorder or major depressive disorder *from **2 years before the date of conception** to **the delivery date.***

Definition of outcomes of interest

Information on outcomes of interest can be extracted from different national registers, local or medical records.

Pregnancy/obstetric complications

Definitions: We will investigate specific complications including preeclampsia, fetal stress, postpartum hemorrhage, gestational diabetes, gestational hypertension, and nausea/vomit. Postpartum hemorrhage is defined as the loss of more than 500 ml of blood within the first 24 hours following childbirth.
ICD-10 codes: Preeclampsia (O14), fetal stress (O68), postpartum haemorrhage (O72), diabetes mellitus during pregnancy (O24).
Time of observation: During pregnancy or within 42 days after delivery

Labour and delivery outcomes

Definition: We will examine the following labor and delivery outcomes: cesarean section, preterm delivery, low birth weight, and small for gestational age. Gestational age is estimated on the basis of date of last menstrual period. Infants are classified as preterm delivery when they were born alive before 37 weeks' gestation. Low birth weight is defined as a birth weight less than 2500 g. SGA is used as a proxy measure for fetal growth restriction. Small for gestational age (SGA) is defined as a birth weight below the 10th percentile of birth weight by the gestational age and sex, and large for gestational age (LGA) as above the 90th percentile.
ICD-10 codes and surgery codes for cesarean section: ICD-10 codes O82 and P03.4; surgical codes KMCA
Time of observation: At birth

Neonatal readmissions

Definition: Neonatal readmissions is defined as any medical condition resulting in inpatient hospital readmission, observational stay, or mortality in the first 28 days of life.
Time of observation: 0–28 days after birth

Major congenital malformations and cardiac malformations

Definition: Malformation is classified as major when it causes functional impairment, including all singular and combined structural defects, syndromes, sequences, and associations. Major cardiac malformations are defined as atrial and atrioventricular septal defects and Ebstein's anomaly, excluding atrial septal defect and patent ductus arteriosus in infants born before 37 weeks gestation.[1]
ICD-10 codes: Major malformations (Q00–Q89 excluding codes for minor malformations listed in EUROCAT Guide 1.4);[1] major congenital heart defects (Q20–Q26, excluding Q21.1 and Q25.0 if gestational age<37 weeks).
Time of observation: 0–365 days after birth

Statistical analysis

Site-specific analysis

All analysis will be conducted using Stata (StataCorp, College Station, TX, USA), SAS (SAS Institute Inc., Cary, NC, USA), or equivalent statistical software. All outcomes will be binary variables (yes/no), and binary logistic regression model will be used to estimate odds ratios (ORs) and their respective 95% confidence intervals (CIs) of various adverse outcomes in pregnancies exposed to lithium, in comparison to pregnancies by mothers *with bipolar disorder or major depressive disorder and who did not take lithium during the index pregnancy (i.e. mood disorder reference group).*

Considering limited statistical power, we will only adjust for essential confounders such as maternal age at delivery (continuous variable), primiparity (yes/no), calendar year of birth (three categories according to the distribution of data in each study site), and other psychotropic medication use during pregnancy (yes/no). Other psychotropic medication use during pregnancy is defined as ATC codes N05 and N06 excluding N05AN01 from 1-month before conception to the delivery.

Site specific analyses will be performed locally by members of the local research team collaborting on the project. No group will share and disclose results with each other, but only provide results to the Danish group for meta-analytic purposes.

Meta-analysis

For the meta-analysis, data from each individual site will be double entered in EpiData 3.1. The meta-analysis will be performed using Stata 13.1. We will pool the site-specific prevalence rates and effect estimates using random-effects meta-analytic models. The pooled prevalence rates of individual outcomes will be computed using the program Metaprop,[2] and the 95% CIs will be calculated using an exact binomial approach. We will present overall estimates as forest plots with the pooled adjusted ORs (aORs) and 95% CIs. Heterogeneity will be quantified using the I^2 statistic (ranges from 0% to 100%).

The meta-analysis will be performed in Denmark by local members of the research team. After analyses have been performed results will be shared with the entire research group for discussion.

Sensitivity analyses

To test the robustness of our findings, we will perform the following two sensitivity analyses: First, to estimate the influence of a single cohort on overall estimates, in a "leave-one-out approach" we will recalculate the pooled adjusted ORs leaving one cohort out of the analyses each time. This will be done to ensure how results from individual groups potentially can drive the pooled estimates from the meta-analysis. Second, to determine whether results will be influenced by the data sources, we will repeat each meta-analysis by stratifying on the source of data (register-based versus clinical cohort). This will be done to ensure how results from specific datasets potentially can drive the pooled estimates from the meta-analysis.

Presentation of the results

Each study site will need to provide the following information on the study population.

For clinical cohort:

- How were the study subjects (i.e., the mother-child pairs) enrolled?
- What were the inclusion and exclusion criteria?
- How many pregnant women were invited to this study and what is the participation rate?
- What were the response rates at delivery and 1 year after delivery?
- Were the pregnant women chosen from a cohort designed for other study objectives? If yes, what were the objectives of this study? Please include relevant references available.

For register-based cohort:

- How was this study population identified?
- What were the inclusion and exclusion criteria?
- What was the coverage of the study population, i.e., the whole study population or provincial?
- Which registers were used and how were they linked? Please provide relevant references.
- How was information on lithium use and the diagnosis of bipolar or major depressive disorders obtained, for instance, the use of ICD codes, ATC codes, or drug Identification Numbers?

Table 1 (empty table to demonstrate how results will be presented). Baseline characteristics among women exposed to lithium during pregnancy and mood disorder reference group

Study site (population, year)	N	Age (years) mean ± SD	Primiparous, N (%)	Other psychotropic drugs, N(%)
Canada (register-based cohort, study period)				
Lithium-exposed group				
Mood disorder reference group				
Denmark (register-based cohort, study period)				
Lithium-exposed group				
Mood disorder reference group				
Sweden (register-based cohort, study period)				
Lithium-exposed group				
Mood disorder reference group				
The Netherlands (clinical cohort, study period)				
Lithium-exposed group				
Mood disorder reference group				
United Kingdom (clinical cohort, study period)				
Lithium-exposed group				
Mood disorder reference group				
United States (clinical cohort, study period)				
Lithium-exposed group				
Mood disorder reference group				
Overall				
Lithium-exposed group				
Mood disorder reference group				

Table 2 (empty table to demonstrate how results will be presented). Odds ratio of adverse pregnancy/obstetric complications in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder

Timing of lithium use	N	Cases (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Preeclampsia				
Mood disorder reference group			1(ref)	1(ref)
Lithium-exposed group				
Gestational diabetes				
Mood disorder reference group			1(ref)	1(ref)
Lithium-exposed group				
Fetal stress				
Mood disorder reference group			1(ref)	1(ref)
Lithium-exposed group				
Postpartum hemorrhage				
Mood disorder reference group			1(ref)	1(ref)
Lithium-exposed group				

Adjusted for maternal age at delivery, parity, calendar year of birth, and other psychotropic medication use during pregnancy

Table 3 (empty table to demonstrate how results will be presented). Odds ratio of adverse labor and delivery outcomes in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder

Timing of lithium use	N	Cases (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Caesarean section				
Mood disorder reference group			1(ref)	1(ref)
Lithium-exposed group				
Preterm birth				
Mood disorder reference group			1(ref)	1(ref)
Lithium-exposed group				
Low birth weight				
Mood disorder reference group			1(ref)	1(ref)
Lithium-exposed group				
Small for gestational age				
Mood disorder reference group			1(ref)	1(ref)
Lithium-exposed group				

Adjusted for maternal age at delivery, parity, calendar year of birth, and other psychotropic medication use during pregnancy

Table 4 (empty table to demonstrate how results will be presented). Odds ratio of neonatal readmissions in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder

Timing of lithium use	N	Cases (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Neonatal readmissions				
Mood disorder reference group			1(ref)	1(ref)
Lithium-exposed group				

Adjusted for maternal age at delivery, parity, calendar year of birth, and other psychotropic medication use during pregnancy

Table 5 (empty table to demonstrate how results will be presented). Odds ratio of major congenital malformations and cardiac malformations in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder

Timing of lithium use	N	Cases (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Major malformations				
Mood disorder reference group			1(ref)	1(ref)
Lithium-exposed group				
Major cardiac malformations				
Mood disorder reference group			1(ref)	1(ref)
Lithium-exposed group				

Adjusted for maternal age at delivery, parity, calendar year of birth, and other psychotropic medication use during pregnancy

References

1 EUROCAT. Guide 1.4 and Reference Documents: Instructions for the Registration and Surveillance of Congenital Anomalies. European Surveillance of Congenital Anomalies. 2013. Available from http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/guide1_4 Accessed 23 April 2016. 2013.

2 Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Archives of public health = Archives belges de sante publique* 2014; **72**: 39.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
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	7-9, eTable 1
Bias	9	Describe any efforts to address potential sources of bias	9-11
Study size	10	Explain how the study size was arrived at	7, 22, eTable 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(*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 loss to follow-up was addressed (*e*) Describe any sensitivity analyses	9-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11, 22, eTable 1
Descriptive data	14*	(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 (c) Summarise follow-up time (e.g., average and total amount)	11, 22
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12, 23, 26
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 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	11-13, 23-26
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	12-13, 26, eTable 2-5, eFigure 1–4
Discussion			
Key results	18	Summarise key results with reference to study objectives	13

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	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
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	17-18

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.