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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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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.

Conflict of Interest Disclosures

No support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; SMB reports grants from Sage Therapeutics and Janssen outside the submitted work and HL reports having served as a speaker for Eli-Lilly and Shire and a grant from Shire. BMD reports grants from Swedish Initiative for Research on Microdata in the Social and Medical Sciences. No other co-author report any relationships or activities that could appear to have influenced the submitted work.

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.

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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 aOR 1.62; 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 statistically 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 effect sizes and the precision of the estimates, in particular associated with first-trimester lithium use against its effectiveness at reducing relapse.

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.

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). Further, 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 Paterno 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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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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.

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 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 $\pm$ SD	Primiparity, No. (%)	Other psychotropic drugs, No. (%)
Canada (register-based cohort, 2002–2013)				
Lithium-exposed group	201	27.6 $\pm$ 5.7	84 (41.8)	170 (84.6)
Reference group	6,333	26.4 $\pm$ 6.0	2,012(31.8)	3,467 (54.7)
Denmark (register-based cohort, 1997–2012)				
Lithium-exposed group	118	32.9 $\pm$ 5.0	67 (56.8)	92 (78.0)
Reference group	1,335	29.3 $\pm$ 5.7	651 (48.8)	810 (60.7)
Sweden (register-based cohort, 2005–2013)				
Lithium-exposed group	238	32.3 $\pm$ 5.2	123 (51.7)	184 (77.3)
Reference group	13,407	29.6 $\pm$ 5.9	6,395 (47.7)	8,648 (64.5)
The Netherlands (Clinical cohort, 2000–2015)				
Lithium-exposed group	115	34.0 $\pm$ 4.3	55 (47.8)	61 (53.0)
Reference group	88	32.7 $\pm$ 4.8	18(20.5)	24 (27.3)
United Kingdom (Clinical cohort, 2007–2013)				
Lithium-exposed group	27	35.0 $\pm$ 4.7	16(59.3)	16 (59.3)
Reference group	202	32.0 $\pm$ 5.7	83 (41.1)	131 (64.9)
United States (Clinical cohort, 2004–2015)				
Lithium-exposed group	28	29.1 $\pm$ 5.8	5(17.9)	21 (75.0)
Reference group	32	29.4 $\pm$ 6.1	5 (15.6)	21 (65.6)
Overall				
Lithium-exposed group	727	31.3 $\pm$ 5.2	350 (48.1)	544 (74.8)
Reference group	21,397	28.7 $\pm$ 5.9	9,164 (42.8)	13,101 (61.2)

Abbreviation: SD = Standard Deviation

Pooled prevalence rate and odds ratio of health outcomes in lithium-exposed group compared to reference group with maternal diagnoses of mood disorder^a

Table 2.

Health outcomes	Lithium-exposed group			Reference group			Pooled adjusted OR (95% CI) in lithiumexposed 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;

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^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.

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-square d (%)
	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)	3.5	
Labour and delivery outcomes								
Caesarean section	356	97	26.4 (21.9, 31.0)	597	131	21.9 (18.6, 25.2)	74.7	
Preterm birth	356	46	12.9 (9.4, 16.4)	597	54	8.9 (6.6, 11.2)	0.0	
Low birth weight	356	26	7.2 (4.5, 9.9)	597	31	5.0 (3.2, 6.7)	0.0	
Small for gestational age	356	18	3.4 (1.6, 5.3)	597	27	4.3 (2.7, 6.0)	43.8	
Neonatal readmission <28 days	356	77	20.9 (16.7, 25.1)	597	83	13.8 (11.0, 16.6)	0.0	
Congenital malformations								
Major malformations	356	31	7.1 (4.4, 9.7)	597	20	3.1 (1.7, 4.5)	0.0	
Major cardiac malformations	356	8	1.2 (0.1, 2.3)	597	9	1.5 (0.5, 2.4)	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.