Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies

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Summary

Background Concerns about teratogenicity and maternal and offspring complications restrict the use of lithium during pregnancy for the treatment of mood disorders. We aimed to investigate the association between in-utero lithium exposure and risk of pregnancy complications, delivery outcomes, neonatal morbidity, and congenital malformations.

Methods In this meta-analysis, primary data from pregnant women and their children from six international cohorts based in the community (Denmark, Sweden, and Ontario, Canada) and in clinics (the Netherlands, UK, and USA) were analysed. Pregnancies were eligible for analysis if the pregnancy resulted in a liveborn singleton between 1997 and 2015, if health-related information was available for both mother and infant, and if the mother had a mood disorder (bipolar disorder or major depressive disorder) or if she had been given lithium during pregnancy (at least two dispensations of lithium during pregnancy that were dispensed any time from 1 month before conception until the delivery, or a single lithium dispensation during pregnancy when there was at least one other lithium dispensation within 6 months before or after this date). Pregnancies during which the mother had been prescribed known teratogenic drugs were excluded. Pregnancies were grouped into a lithium-exposed group and a mood disorder reference group. The main outcome measures were pregnancy complications, delivery outcomes, neonatal readmission to hospital within 28 days of birth, and congenital malformations (major malformations and major cardiac malformations). Analyses were done at each site by use of a shared protocol. Adjusted odds ratios (aORs) and 95% CIs were calculated by use of logistic regression models, and site-specific prevalence rates and ORs were pooled by use of random-effects meta-analytical models.

Findings 22 124 eligible pregnancies were identified across the six cohorts, of which 727 pregnancies were eligible for inclusion in the lithium-exposed group (557 [77%] from register-based cohorts and 170 [23%] from clinical cohorts). Lithium exposure was not associated with any of the predefined pregnancy complications or delivery outcomes. An increased risk for neonatal readmission within 28 days of birth was seen in the lithium-exposed group compared with the reference group (pooled prevalence 27·5% [95% CI 15·8–39·1] *vs* 14·3% [10·4–18·2]; pooled aOR 1·62, 95% CI 1·12–2·33). Lithium exposure during the first trimester was associated with an increased risk of major malformations (pooled prevalence 7·4% [95% CI 4·0–10·7] *vs* 4·3% [3·7–4·8]; pooled aOR 1·71, 95% CI 1·07–2·72) but for major cardiac malformations the difference was not significant (2·1% [0·5–3·7] *vs* 1·6% [1·0–2·1]; pooled aOR 1·54, 95% CI 0·64–3·70).

Interpretation Considering both the effect sizes and the precision of the estimates in this meta-analysis, treatment decisions for pregnant women with mood disorders must weigh the potential for increased risks of lithium during pregnancy—in particular those associated with use of lithium during the first trimester—against its effectiveness at reducing relapse.

Funding None.

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, and for reducing the risk of suicide.[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 about 2% of the population,[7] including women of reproductive age;[8] therefore, knowledge about the benefits and risks of treatment with lithium during pregnancy is essential. Treatment with lithium can reduce the risk of relapse during both pregnancy and post partum.[9,10] However, concerns about teratogenicity and maternal and offspring complications (eg, renal or thyroid problems, preterm birth) restrict its use. Congenital anomalies due to teratogenicity are

Research in context

Evidence before this study

Pregnant women who have bipolar disorder have a significant risk of relapse both during pregnancy and post partum. Lithium is an effective first-line pharmacological treatment for patients with bipolar disorder, but concerns about teratogenicity and maternal and offspring complications restrict its use during pregnancy. We searched PubMed for studies published in English, with no starting date restriction until July 3, 2017, that investigated lithium use in pregnancy among women with mood disorders. Search terms applied were "lithium", "pregnancy", "bipolar", "depression", and "mood disorder". After this initial search, we identified additional papers by checking the citations within the search results. Case studies were not included as references. A systematic review and meta-analysis of studies published before October, 2010, found six case-control studies on lithium use during pregnancy and risk of cardiovascular malformations. The risk of Ebstein's anomaly did not differ significantly between pregnancies exposed to lithium and controls; however, estimates were uncertain because of the low number of events. Subsequently, an observational study from Israel reported that lithium treatment during pregnancy is associated with a higher rate of cardiovascular anomalies. A recent study based on US data by Patorno and colleagues reported an increased risk of malformations after first-trimester exposure to lithium, but with low absolute numbers of malformations. Other potential adverse outcomes of lithium use were not investigated in this study.

Added value of this study

Our meta-analysis analysed new data from six countries and found an increased risk of major malformations specifically after first-trimester exposure to lithium, and an increased risk of hospital readmission of infants within 4 weeks of birth who had been exposed to lithium during pregnancy, a factor that, to our knowledge, has never been studied before. However, we did not find evidence of an increased risk of other investigated maternal or infant outcomes, such as pre-eclampsia, diabetes in pregnancy, fetal distress, preterm birth, low birthweight, and small for for gestational age.

Implications of all the available evidence

Lithium treatment decisions are key and need to be encouraged before conception. In particular, first-trimester lithium use should be cautioned and decided upon on the basis of the available evidence. To support balanced decision making, women should be informed of the malformation risks for infants exposed during the first trimester, and also about the high relapse risks during both pregnancy and post partum 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 post partum. Future research should focus on relapse risk if the dose of lithium is lowered during the first trimester, and also on alternative treatment options.

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mainly associated with use of lithium during the first trimester of pregnancy, since this is the period when the embryo is most vulnerable to teratogens while the organs are formed, such as 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 fetus.[11,12] In human studies, similar risks of malformations,[13–16] preterm birth, and other pregnancy and neonatal complications have been found;[13,17–19] however, these findings are not consistent across all studies.[1,20] Most previous studies[20,21] did not have the statistical power to detect significant effects, and others were subject to recall bias and poor consideration of key confounding variables.

Meta-analyses can improve the precision of estimates by increasing sample sizes. Such a study to investigate the safety of in-utero exposure to lithium was published in 2012.[20] This study found that the risk of Ebstein's anomaly (a rare congenital heart defect) was not significantly increased after lithium exposure during pregnancy. However, the authors cautioned that the strength of their interpretation was limited by the small number of cases of cardiac malformation included in their analysis, and that further studies with larger numbers of such cases would be needed to confirm their result.

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

Methods

Study design

This meta-analysis analysed primary data combined from six international cohorts: three population-level register-based cohorts in Denmark, Sweden, and Ontario, Canada; and three clinical cohorts (ie, women under psychiatric secondary care) in the Netherlands, UK, and USA. A joint study protocol was produced before dataset creation and analysis, including specific definitions for selection criteria, each included variable and statistical analyses; this protocol is provided in the appendix.

See Online for appendix

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

Patients

All cohorts comprised pregnant women, with no specific age restrictions, with pregnancies resulting in liveborn singleton deliveries from Jan 1, 1997, to Dec 31, 2015, for whom health-related information was available both for the mother and infant, and the mother either had a mood disorder (bipolar disorder or major depressive disorder) or had taken lithium during pregnancy (definitions of lithium exposure in grouping and definitions section). The only exclusion criterion was if the mother had been prescribed known teratogenic drugs during pregnancy (thalidomide, valproate, retinoids, antineoplastic drugs, misoprostol, and methotrexate). A detailed description of the identification of the study population and years of inclusion at each study site is in the appendix.

In agreement with local and national regulations and ethical board approval for each site, no written or oral consent was obtained for this particular study.

Grouping and definitions

Patients were assigned to one of two groups, the lithium-exposed group or the mood-disorder reference group. The lithium-exposed group comprised pregnant women with lithium exposure during the index pregnancy. For the register-based cohorts, lithium exposure during pregnancy was defined as at least two dispensations of lithium during pregnancy that were dispensed any time from 1 month before conception until delivery, or a single lithium dispensation during pregnancy when at least one other lithium dispensation had occurred within 6 months before or after this date. Dispensations of lithium were identified by use of 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, since non-psychiatric indications for lithium are rare.

For analyses with a 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, at least two dispensations of lithium in the first trimester (from 1 month before conception to 90 days of gestation), or one dispensation in the first trimester with at least one other dispensation within 6 months before or after this date; and for clinical cohorts, medical records were used to define lithium use in the first trimester.

The mood-disorder reference group comprised pregnant women with a known history of mood disorder (bipolar disorder or major depressive disorder), without exposure to lithium from 90 days before pregnancy until delivery (start of pregnancy was counted from the first day of the last menstrual period until delivery). For the register-based cohorts, maternal mood disorder was defined as at least one inpatient or two outpatient contacts for bipolar disorder (equivalent to the ICD-10 codes F30–31) or major depressive disorder (codes F32–33) from 2 years before the date of pregnancy until delivery. For the clinical cohorts, maternal mood disorder was defined as any medical history of bipolar disorder or major depressive disorder before delivery.

Outcomes

Outcomes of interest were selected on the basis of theoretical risks for general medication exposure in pregnancy and previous research on lithium use.[13,20] Outcomes were divided into four subcategories: (1) pregnancy complications, identified during pregnancy or within 42 days after delivery by use of hospital-based diagnoses for pre-eclampsia (ICD-10 code O14), diabetes during pregnancy (code O24), fetal distress (code O68), and post-partum haemorrhage (code O72); (2) labour and delivery outcomes, identified in hospital, including caesarean section (codes O82 and P03.4; surgical code KMCA), preterm birth (<37 weeks of gestation), low birthweight (<2500 g), and small for gestational age (ie, a birthweight below the 10th percentile of birthweight by gestational age and sex); (3) neonatal hospital readmission within 28 days of birth; and (4) congenital malformations in the infant. Excluding chromosomal abnormalities, major malformations considered were those 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 Q00–89, 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 Q20–26), but excluding atrial septal defect (code Q21.1) and patent ductus arteriosus (code Q25.0) in infants born before 37 weeks of gestation.[22]

Statistical analysis

All study sites did analyses independently according to an a-priori protocol. The site-specific prevalence and effect estimates were subsequently sent to Aarhus University, Aarhus, 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.

We identified the sites included because they had maternal and infant data available that could be linked. At each site, all outcomes were modelled as binary variables (ie, yes or no), and a binary logistic-regression model was used to estimate odds ratios (ORs) and 95% CIs comparing the lithium-exposed group to the reference group. We also estimated the ORs of major malformations and major cardiac malformations comparing the patients in the lithium-exposed group who had been exposed during the first trimester with the reference group. ORs 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 before pregnancy to the date of delivery (yes or no). We accounted for the number of participants for whom no data were available for specific outcomes, since not all sites contributed to the calculations of all outcomes. Data management and analyses were done using SAS 9.4 (Sweden and Canada), Stata 13.1 (Denmark and the UK), SPSS 20.0 (the Netherlands), and R package (the USA).

For the meta-analysis, we double entered data from each site into EpiData 3.1 software. We used Stata 13.1 for the meta-analysis. We pooled site-specific prevalence and effect estimates using random-effects meta-analytical models. In random-effects models, we used the inverse of within-study variation combined with the between-study variation as the weight. We computed the pooled prevalence of individual outcomes using Metaprop.[23] We calculated the 95% CIs of pooled prevalences using an exact binomial approach in a random-effects meta-analytical model. We presented overall estimates as forest plots with the pooled adjusted ORs (aORs) and 95% CIs. We quantified heterogeneity using the I^2 statistic (range 0–100%), which describes the proportion of variability in the effect sizes attributable to heterogeneity between study sites.

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

We did additional sensitivity analyses (post hoc) using Danish and Swedish data only to explore the potential for residual confounding. First, we repeated the primary analyses and further adjusted for marital and education status, use of antiepileptic drugs during pregnancy (other than valproate, since 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 for which the mothers used lithium before or after, but not during, pregnancy. Third, to estimate whether the use of a reference group with maternal mood disorder was an appropriate comparison group, we estimated the difference in pooled aORs of various adverse outcomes in lithium-exposed infants in comparison with two different reference groups: one with a maternal diagnosis of mood disorder and one with a maternal diagnosis of bipolar disorder.

Role of the funding source

All investigators did the research independently. The funders of each investigator had no role in the study design, data collection, data analysis, data interpretation or preparation, review, or approval of the manuscript. The corresponding author and XL had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	N	Age, years	Primiparity	Other psychotropic drugs
Denmark (register-based cohort, 1997–2012)				
Lithium-exposed group	118	32·9 (5·0)	67 (57%)	92 (78%)
Reference group	1335	29·3 (5·7)	651 (49%)	810 (61%)
Sweden (register-based cohort, 2005–13)				
Lithium-exposed group	238	32·3 (5·2)	123 (52%)	184 (77%)
Reference group	13 407	29·6 (5·9)	6395 (48%)	8648 (65%)
Canada (register-based cohort, 2002–13)				
Lithium-exposed group	201	27·6 (5·7)	84 (42%)	170 (85%)
Reference group	6333	26·4 (6·0)	2012 (32%)	3467 (55%)
Netherlands (clinical cohort, 2000–15)				
Lithium-exposed group	115	34·0 (4·3)	55 (48%)	61 (53%)
Reference group	88	32·7 (4·8)	18 (20%)	24 (27%)
UK (clinical cohort, 2007–13)				
Lithium-exposed group	27	35·0 (4·7)	16 (59%)	16 (59%)
Reference group	202	32·0 (5·7)	83 (41%)	131 (65%)
USA (clinical cohort, 2004–15)				
Lithium-exposed group	28	29·1 (5·8)	5 (18%)	21 (75%)
Reference group	32	29·4 (6·1)	5 (16%)	21 (66%)
Overall				
Lithium-exposed group	727	31·3 (5·2)	350 (48%)	544 (75%)
Reference group	21 397	28·7 (5·9)	9164 (43%)	13 101 (61%)

Data are n, mean (SD), or n (%).

Table 1: **Characteristics of participants at each study site and overall**

Results

From population-level data collected between Jan 1, 1997, and Dec 31, 2015, from three register-based cohorts (in Denmark, Sweden, and Ontario, Canada) and three clinical cohorts (in the Netherlands, UK, and USA), 22 124 eligible pregnancies were identified, of which 727 pregnancies were eligible for inclusion in the lithium-exposed group (557 [77%] from register-based cohorts and 170 [23%] from clinical cohorts). Baseline sample characteristics are in table 1. Compared with the reference group, women in the lithium-exposed group tended to be older, nulliparous, and more likely to have filled a prescription for a psychotropic drug other than lithium during pregnancy.

Lithium exposure during pregnancy was not associated with pre-eclampsia (pooled aOR 0·97, 95% CI 0·52–1·80), diabetes in pregnancy (1·20, 0·81–1·78), fetal distress (1·00, 0·76–1·32), or post-partum haemorrhage (1·28, 0·64–2·57; table 2). No differences between the lithium-exposed group and the reference group were observed for caesarean section (0·94, 0·66–1·33), preterm birth (1·24, 0·83–1·84), low birthweight (0·98, 0·72–1·35),

	Lithium-exposed group (n=727)			Reference group (n=21 397)			Pooled aOR (95% CI)	I^2 (%)
	N	Number with outcome	Pooled prevalence (%, 95% CI)	N	Number with outcome	Pooled prevalence (%, 95% CI)		
Pregnancy complications								
Pre-eclampsia*	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†	489	35	6·4% (4·1–8·8)	7990	512	5·4% (2·5–8·2)	1·20 (0·81–1·78)	0·0%
Fetal distress‡	727	90	14·1% (3·9–24·2)	21 397	1561	13·2% (4·0–22·4)	1·00 (0·76–1·32)	0·0%
Post-partum haemorrhage†	489	38	7·4% (3·3–11·6)	7990	391	7·1% (3·7–10·5)	1·28 (0·64–2·57)	53·5%
Labour and delivery outcomes								
Caesarean section‡	727	201	26·5% (20·3–32·6)	21 392	4844	25·8% (20·9–30·7)	0·94 (0·66–1·33)	62·0%
Preterm birth‡	717	96	13·1% (10·6–15·6)	21 397	1949	10·0% (7·3–12·7)	1·24 (0·83–1·84)	49·7%
Low birthweight‡	719	50	6·4% (4·5–8·2)	21 338	1339	7·2% (4·6–9·7)	0·98 (0·72–1·35)	0·0%
Small for gestational age§	692	58	7·5% (2·3–12·8)	21 302	1614	9·3% (1·5–17·1)	0·90 (0·67–1·21)	0·0%
Neonatal readmission to hospital within 28 days of birth‡	718	172	27·5% (15·8–39·1)	21 158	2625	14·3% (10·4–18·2)	1·62 (1·12–2·33)	56·6%
Congenital malformations								
Major malformations¶	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¶	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 (for lithium exposure in first trimester)								
Major malformations¶	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¶	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%

The number of participants is different for each outcome since not all sites contributed to the calculation of all outcomes and not all participants at each site had information on all outcomes. aOR=adjusted odds ratio. *Data from five cohorts (Denmark, Sweden, Canada, the UK, and the USA) were available for this pooled estimate. †Data from five cohorts (Denmark, Canada, the Netherlands, the UK, and the USA) were available for this pooled estimate. ‡Data from all six cohorts were available for this pooled estimate. §Data from four cohorts (Denmark, Sweden,Canada, and the Netherlands) were available for this pooled estimate. ¶Data from five cohorts (Denmark, Sweden, Canada, the Netherlands, and the USA) were available for this pooled estimate.

Table 2: **Pooled prevalence and aOR of health outcomes in the lithium-exposed group versus the reference group**

or small for gestational age (0·90, 0·67–1·21). In-utero lithium exposure was associated with an increased risk of neonatal readmission to hospital within 28 days of birth (1·62, 1·12–2·33). Forest plots with site-level ORs of these pregnancy complications, delivery outcomes, and neonatal admissions are in the appendix.

By age 1 year, diagnoses of major malformations were reported for 51 (pooled prevalence 7·2%, 95% CI 4·0–10·4) infants in the lithium-exposed group and 856 (4·3%, 3·7–4·8) in the reference group (table 2). Lithium exposure was not significantly associated with an increased risk of major malformation, nor with major cardiac malformations, but statistical heterogeneity was high (table 2). For example, in Denmark, lithium exposure was associated with increased risks of both major malformation and major cardiac malformation, but this association was not observed in the data from Sweden, Canada, the Netherlands, or the USA (data from the UK were not available; figure 1A and B). Of 727 infants who were exposed to lithium in utero, 654 (90%) were exposed during the first trimester (appendix). Of these infants, 47 were diagnosed with major malformations and 16 with major cardiac malformations. Lithium exposure was associated with an increased risk of major malformation (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 2A and 2B), compared with the reference group. Notably, no cases of Ebstein's anomaly were observed at any of the participating study sites.

The leave-one-out analyses showed an overall stability of the main findings, except for the association between lithium exposure in the first trimester and major malformations. This association became non-significant when each of Denmark, Sweden, and the USA were left out (appendix). Pooled ORs from the register-based cohorts substantially overlapped with those of the clinical cohorts, except for post-partum haemorrhage, for which a strong association was observed in the clinical cohorts (pooled aOR 2·58, 95% CI 1·21–5·52) but not in the register-based cohorts (0·79, 0·41–1·51; appendix).

Results from additional sensitivity analyses in a subgroup that included only Danish and Swedish data were generally consistent with those of the main analysis. Adjustments for educational and marital status, and use of antiepileptic and psychotropic medication during pregnancy did not affect the results compared with the main meta-analysis (appendix). When lithium-exposed pregnancies were compared with pregnancies for which women used lithium before and after but not during pregnancy, the results were also generally consistent with those of the main analysis. The risk of major malformation was increased among children exposed to lithium during pregnancy (pooled aOR 2·09, 95% CI 1·10–3·96); however, this increase in risk was not found specifically for major cardiac malformations

(1·28, 0·13–12·39; table 3). The aOR of adverse outcomes in children who had been exposed to lithium was similar when compared with the reference group with a maternal diagnosis of mood disorder or the reference group with a maternal diagnosis of bipolar disorder; although, the aOR of neonatal readmission within 28 days of birth was attenuated to zero when compared with the reference group with a maternal diagnosis of bipolar disorder (appendix).

Discussion

With combined data from six international cohorts, by use of a predefined protocol across all study sites, in-utero exposure to lithium was not associated with significantly increased risks for any of the pregnancy complications or delivery outcomes investigated. Lithium exposure during pregnancy was associated with a significantly increased risk of neonatal readmission to hospital within 4 weeks post partum. Furthermore, we found that lithium exposure in the first trimester specifically was associated with an increased risk of major malformations, but not major cardiac malformations; although, only 16 cases of major cardiac malformation were seen in this population across all sites. Across our analyses, results were robust to most sensitivity analyses, including stratification by study design, the leave-one-out approach, and adjustment for additional variables in a subcohort of Danish and Swedish data only.

This study has several strengths, including improving statistical power and generalisability over previous research. A shared protocol for analyses that was established a priori minimised heterogeneity associated with selection criteria, exposure, outcome and covariate definitions, and statistical methods. All data on lithium exposure were collected from data recorded before outcome occurrence, so the risk of recall bias was low. The potential for bias associated with the analysis was further reduced since each site did its own analyses independently, blind to the results of other sites. Our study also has limitations. First, we chose to include only pregnancies resulting in liveborn children because of the paucity of information on stillbirths at some study sites. If lithium use during pregnancy increases the risk of stillbirths or miscarriage,[24] this criterion could have led to underestimation of adverse effects.[25] Second, even with a large sample size, our investigation lacks power to study very rare events. For example, only 16 cases of major cardiac malformations among neonates exposed to lithium in the first trimester were observed, with subsequent restricted statistical power. Third, as with all observational studies, residual confounding cannot be ruled out, especially that due to the severity of an underlying maternal illness, or substance or alcohol misuse.[26] Fourth, we examined several outcomes, so the potential for type I error and chance findings cannot be excluded. Fifth, we did not use an active comparator approach—ie, we did not directly compare lithium with other drugs that are sometimes given for the treatment of bipolar disorder. Sixth, no data were available on lithium serum concentrations, which prevented our analyses of any potential dose-response associations. Furthermore, a wide defined lithium temporal exposure window could lead to misclassification of lithium exposure and could

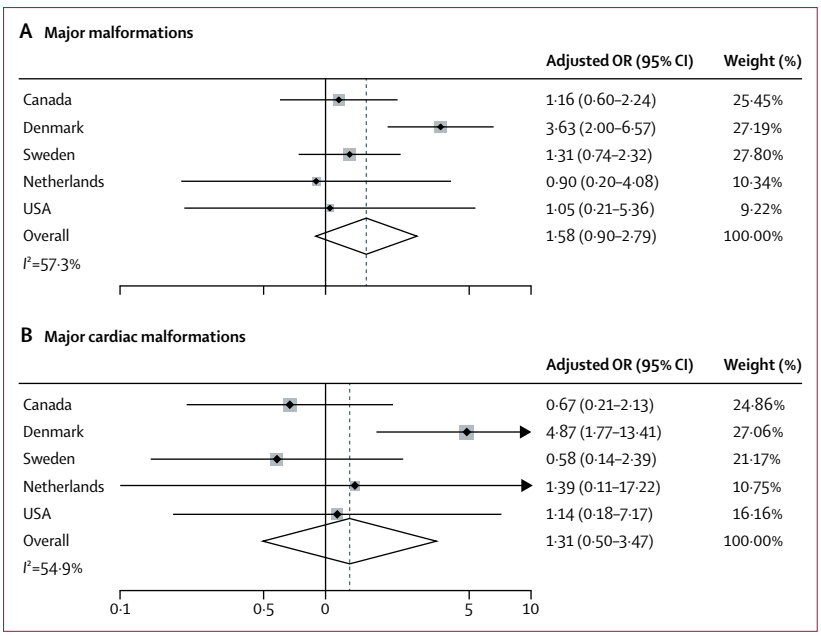

Figure 1: **Lithium exposure at any time during pregnancy and major malformations (A) and major cardiac malformations (B)**
Adjusted ORs of malformations in lithium-exposed pregnancies compared with reference group pregnancies. Data from the UK were not available for this outcome. Weights are from random-effects analysis. OR=odds ratio.

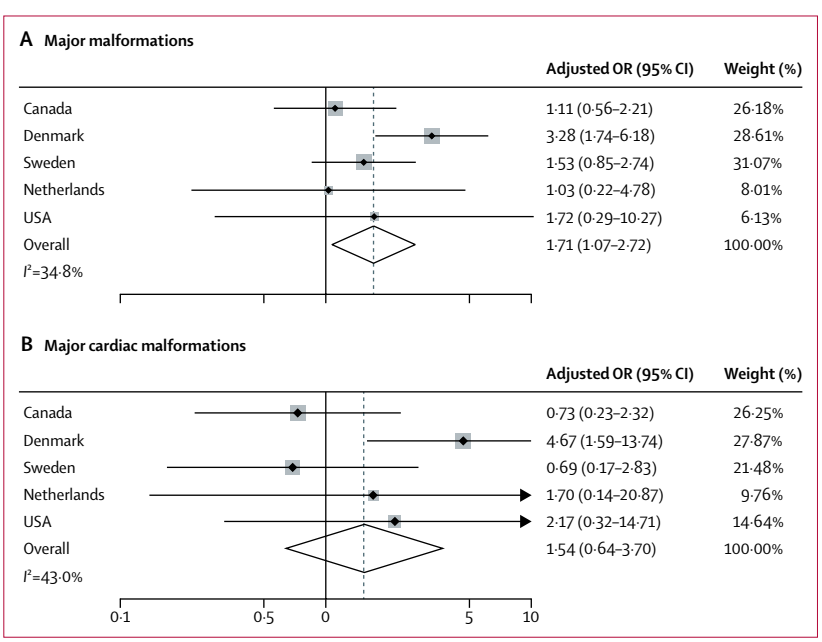

Figure 2: **Lithium exposure in the first trimester of pregnancy and major malformations (A) and major cardiac malformations (B)**
Adjusted ORs of malformations with lithium exposure in the first trimester compared with the reference group. Data from the UK were not available for this outcome. Weights are from random-effects analysis. OR=odds ratio.

	Lithium exposure during pregnancy (n=356)			Lithium exposure before or after pregnancy (n=597)			Pooled aOR (95% CI)	I^2 (%)
	N	Number with outcome	Pooled prevalence (%, 95% CI)	N	Number with outcome	Pooled prevalence (%, 95% CI)		
Pregnancy complications*								
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 birthweight	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 within 28 days of birth	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%

aOR=adjusted odds ratio. OR=odds ratio. *The number of pre-eclampsia, diabetes during pregnancy, and post-partum haemorrhage cases were too small to calculate the pooled OR.

***Table 3*: Pooled prevalence and aOR of health outcomes comparing lithium use during pregnancy with use before or after pregnancy in the Danish and Swedish cohorts**

have biased our results towards the null. Finally, we cannot rule out that less severe adverse outcomes are more likely to be reported and recorded in the lithium-exposed group than in the reference group because of a general concern about teratogenic effects. However, if this excess reporting had occurred, it would have probably biased the results towards finding an effect, which we did not observe for most outcomes.

Lithium use was not associated with any of the predefined pregnancy complications and adverse delivery outcomes in our study. However, mental illness itself has been associated with adverse pregnancy outcomes, including preterm birth and caesarean delivery, regardless of whether women were treated with any mood-stabilising medication (ie, lithium, antiepileptics, antipsychotic medications, or a combination of these).[27] This potential association could explain why previous studies,[13,17,18] with less rigorous control than our study for confounding associated with maternal mental illness, observed an increased risk for these outcomes associated with lithium while our study did not. Across our analyses, an increased risk for neonatal readmission to hospital within 4 weeks of birth was seen in infants exposed to lithium in utero. To our knowledge, this outcome has not been previously investigated for lithium exposure and the results could be explained through several different mechanisms. Lithium withdrawal after birth could lead directly to neonatal morbidity, requiring admission to a special-care baby unit or hospital, as could lithium exposure via lactation (breastfeeding while using lithium is generally not recommended). Furthermore, neonatal morbidity could be explained through the underlying maternal mood disorder (appendix) or be due to increased vigilance towards infants exposed to lithium with subsequent increased detection of neonatal morbidities. Detailed prospective studies are needed to investigate these mechanisms.

Most previous research on lithium use during pregnancy has focused on congenital malformations including Ebstein's anomaly;[13,15,16,28] however, most data come from small retrospective clinical studies, which are prone to over-reporting on malformed infants, and tend to lack confounder control and information on exposed children without adverse outcomes.[29–31] Adding to the complexities of any interpretation, major cardiac malformations might be associated with maternal mental illness and other associated factors, rather than with exposure to lithium.[29] In our study, comparisons were made with pregnancies among women with mental illness, rather than pregnancies among all women, because at least some adverse outcomes in offspring exposed to lithium during pregnancy could arise from factors other than lithium exposure alone. In our first-trimester-specific analysis, significantly more neonates in the lithium-exposed group had major malformations than in the mood disorder reference group (pooled aOR 1·71, 95% CI 1·07–2·72). This finding was supported by the sensitivity analysis that compared malformation risk in the children of women who were prescribed lithium during pregnancy versus those prescribed lithium before and after (but not during) pregnancy, with an increased risk of major malformations detected for use during pregnancy. Additionally, risk of major cardiac malformations in our main meta-analysis was 2·1% for the lithium-exposed group versus 1·6% for the reference group (pooled aOR 1·54, 95% CI 0·64–3·70). Concern about congenital malformations after in-utero exposure to lithium has been supported by the results of a US study by Patorno and colleagues[14] on 663 infants, in which the absolute risk for cardiac malformations (2·4%) was similar to ours (2·1%) during the first trimester. In their study,[14] Patorno and colleagues observed that for newborn babies who had been exposed to lithium in utero the risk of overall malformations was signficantly increased

(risk ratio 1·37, 95% CI 1·01–1·87), and the risk of major cardiac malformations was increased (1·65, 1·02–2·68) compared with newborn babies who had not been exposed to lithium in utero. In light of this evidence and our study results, we suggest that lithium exposure is associated with an increased risk of malformations and these findings should guide treatment decisions and future studies. An approach that could be adopted in future work is the further pooling of evidence across countries, study sites, and presented results that in the next few years could provide the data needed to quantify any magnitude of risk associated with lithium exposure during pregnancy.

In this study, an increased risk of congenital malformations attributable specifically to lithium use during the first trimester of pregnancy was found, but our results and those of Patorno and colleagues jointly suggest that the absolute risk of malformations is much smaller than those reported in earlier studies. We observed an increased risk for hospital readmission shortly after birth for lithium-exposed infants, which requires further study. Overall, considering both the specific effect sizes and precision of the estimates of this meta-analysis, treatment decisions must weigh the potential for increased risks associated with lithium use during pregnancy, and particularly during the first trimester, against its effectiveness at reducing the relapse of mood disorder.

Contributors

TM-O, XL, and VB conceived and designed the study after discussing design considerations with co-authors from all study sites. TM-O drafted the manuscript. XL, AV, ADF, HKh, and RW had full access to the data at individual study sites, analysed the data, and take responsibility for the integrity of the data and the accuracy of the data analysis. SNV supervised the analyst who had direct access to data and who analysed the data in Canada, and they take responsibility for the integrity of the data and accuracy of the data analysis. XL did the meta-analyses on results provided from all study sites. CLT designed and established the cohort at the UK site and also collected all data on women in the sample. All authors interpreted the data and revised the manuscript.

Declaration of interests

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