Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Appendix: Lithium Use in Pregnancy and the Risk of Cardiac Malformations

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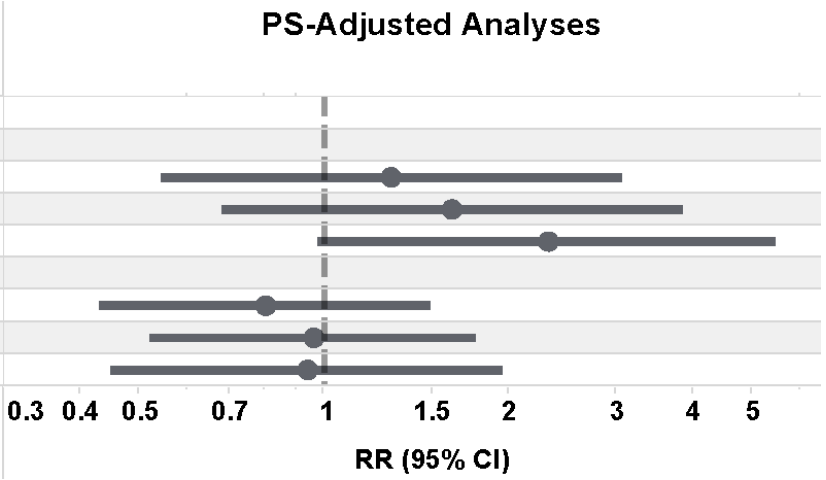
Figure S1. Absolute and relative risk of cardiac malformations among lithium-exposed and lamotrigine-exposed infants as compared with unexposed infants, stratified according to tertiles of the highest prescribed daily dose filled by the mother during the first trimester[1]

Exposure Group	Total	Events	Prevalence per 100 births	PS-adjusted RR (95% CI)
Unexposed	1,322,955	15,251	1.15	Ref.
Lithium (mg/day)				
≤600	280	<11	1.79	1.28 (0.54, 3.05)
600-900	242	<11	2.07	1.61 (0.68, 3.83)
>900	141	<11	4.26	2.31 (0.98, 5.46)
Lamotrigine (mg/day)				
≤100	795	<11	1.26	0.80 (0.43, 1.49)
101-200	673	<11	1.49	0.96 (0.52, 1.77)
>200	477	<11	1.47	0.94 (0.45, 1.95)



PS: propensity score; RR: risk ratios; CI: confidence intervals; Ref.: reference

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

Table S1. Studies evaluating the association between lithium exposure during pregnancy and the risk of cardiac malformations[1]

Study	Design	Exposed	Reference	Number exposed	Outcomes	Confounders adjusted	Results	Conclusion
Schou et al, 1973	Retrospective uncontrolled cohort	Lithium	None	118	Any congenital malformation	none	7.6% of exposed had a malformation, 6 cardiac, 2 Ebstein's anomaly	Inconclusive. Design overestimates risk
Nora, et al, 1974	case report + re-interpretation Registry	Lithium	None	2	Ebstein's anomaly	none	2 exposed cases described	**Five-fold increased risk of cardiac malformations and 400-fold increased risk of Ebstein's anomaly adding their 2 exposed cases to the report from the registry**
Weinstein and Goldfield, 1975	Retrospective uncontrolled cohort	Lithium	None	143	Any congenital malformation	none	10 (7%) of exposed had cardiac malformations. 4 had Ebstein's anomaly	Caution, consider reporting bias
Weinstein and Goldfield, 1979	Retrospective uncontrolled cohort	Lithium	None	212	Any congenital malformation	none	10.4% of exposed had a malformation. Estimated Ebstein's anomaly as 162-fold increased	Caution
Kallen et al, 1983	Prospective controlled cohort	Lithium	mood disorders	59	Cardiac malformations	none	4 cardiac defects (7%) compared with 2/228 unexposed	Support elevated risk of cardiac defects
Sipek et al, 1989	Case-control Study	Lithium	None	0 out of 89	Ebstein's anomaly	none	no exposed cases	Rise in recording of anomaly
Kallen et al, 1988	Case-control Study	Lithium	none	0 out of 25	Ebstein's anomaly	none	No anomaly exposed	Association with Ebstein's anomaly is weak
Czeizel et al, 1990	Case-control Study	Lithium	None	6 out of 10698 cases	Any congenital malformation	none	OR=1.3 (0.22-9.0)	No association
Edmonds et al, 1990	Case-control Study	Lithium	Non-exposed with mood disorders	0 out of 34	Ebstein's anomaly	none	No exposed case	Not a contributor to Ebstein's anomaly
Zalzstein et al, 1990	Case-control Study	Lithium	Non-exposed	0 out of 50 cases	Ebstein's anomaly	none	No exposed case, one case in the control group	Rule out a 28-fold increased risk
Kallen et al, 1991	Case-control Study	Lithium	none	0 out of 13	Cardiac malformations	none	No anomaly exposed	Rule out an 8-fold increased risk
Jacobson et al, 1992	Prospective controlled cohort	Lithium	Non-exposed	138	Any congenital malformation	Indication	RR 1.5 (0.4-6.7)	No association. 1 Ebstein's anomaly in exposed
Correa-Villasenor et al, 1994	Case-control Study	Lithium	None	0 out of 47 cases	Ebstein's anomaly	genetic and environmental	No exposed case	More studies needed
Briggs, 2002	Prospective uncontrolled	Lithium	None	62	Any congenital malformation	none	No cardiac malformation	No conclusion reported

	cohort							
Kramer et al, 2003	Prospective uncontrolled cohort	Lithium	None	20	Any congenital malformation	none	0 cases	Lithium relatively safe
Reis et al, 2008	Prospective uncontrolled cohort	Lithium	None	79	Any congenital malformation	none	8 cases, 4 mild cardiac	Concern for decades revise
Boden R et al, 2012	Prospective controlled cohort	Lithium	other mood stabilizers	107	Any congenital malformation	none	3 cases, 2 of them cardiac	No more cardiac defects than lamotrigine
Diav-Citrin et al, 2014	Prospective controlled cohort	Lithium	mood disorders	123	Any congenital malformation	indication	8 cases (6.5%) compared with 3.3% in nontreated women with bipolar disorder. 3 cardiacs (2.4%) compared with 0.3% in control. 1 Ebstein's anomaly	Association with cardiac anomalies

[1] The prevalence of Epstein's anomaly has been estimated to be in the order of 5 cases per 100,000 births[13], whereas the prevalence of RVOTO defects has been estimated to be over 5 cases per 10,000 births, with up to 10% of the RVOTO defects being Epstein's anomalies.[19]

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Table S2. Unadjusted and propensity-score-adjusted baseline characteristics of lithium-exposed and unexposed pregnant women[1]

	Unadjusted			Propensity-score adjusted		
Baseline characteristics	**Non-exposed (N=1,322,955)**	**Lithium (N=663)**	***St. Diff.***	**Non-exposed (N=928,767)**	**Lithium (N=663)**	***St. Diff.***
Age, mean (SD)	24.0 (5.8)	25.6 (6.1)	*0.28*	25.6 (6.2)	25.6 (6.1)	*0.01*
Race						
White	526,603 (39.8)	490 (73.9)	*0.73*	708,409 (76.3)	490 (73.9)	*-0.05*
Black	445,675 (33.7)	89 (13.4)	*-0.49*	113,987 (12.3)	89 (13.4)	*0.03*
Hispanic	195,174 (14.8)	36 (5.4)	*-0.31*	41,876 (4.5)	36 (5.4)	*0.04*
Other[2]	155,503 (11.8)	48 (7.2)	*-0.15*	64,495 (6.9)	48 (7.2)	*0.01*
Year						
2000	1,569 (0.1)	<11	*0.01*	2,145 (0.2)	<11	*-0.02*
2001	81,024 (6.1)	34 (5.1)	*-0.04*	50,686 (5.5)	34 (5.1)	*-0.01*
2002	92,771 (7.0)	41 (6.2)	*-0.03*	50,817 (5.5)	41 (6.2)	*0.03*
2003	126,822 (9.6)	67 (10.1)	*0.02*	94,992 (10.2)	67 (10.1)	*0.00*
2004	153,523 (11.6)	83 (12.5)	*0.03*	111,961 (12.1)	83 (12.5)	*0.01*
2005	154,733 (11.7)	69 (10.4)	*-0.04*	95,300 (10.3)	69 (10.4)	*0.00*
2006	154,415 (11.7)	72 (10.9)	*-0.03*	99,994 (10.8)	72 (10.9)	*0.00*
2007	146,133 (11.0)	73 (11.0)	*0.00*	102,872 (11.1)	73 (11.0)	*0.00*
2008	143,246 (10.8)	77 (11.6)	*0.02*	106,821 (11.5)	77 (11.6)	*0.00*
2009	149,472 (11.3)	86 (13.0)	*0.05*	123,657 (13.3)	86 (13.0)	*-0.01*
2010	119,247 (9.0)	60 (9.0)	*0.00*	89,520 (9.6)	60 (9.1)	*-0.02*
Multiple gestation	44,792 (3.4)	17 (2.6)	*-0.05*	25,131 (2.7)	17 (2.6)	*-0.01*
Psychiatric and neurological conditions, N (%)						
Bipolar disorder	9,485 (0.7)	436 (65.8)	*1.91*	608,904 (65.6)	436 (65.8)	*0.00*
Depression	63,110 (4.8)	167 (25.2)	*0.60*	257,475 (27.7)	167 (25.2)	*-0.06*
Anxiety	41,759 (3.2)	117 (17.6)	*0.49*	179,054 (19.3)	117 (17.6)	*-0.04*
Schizophrenia	1,639 (0.1)	33 (5.0)	*0.31*	39,603 (4.3)	33 (5.0)	*0.03*

Other psychosis	2,138 (0.2)	25 (3.8)	*0.26*	31,600 (3.4)	25 (3.8)	*0.02*
Personality disorder	2,160 (0.2)	36 (5.4)	*0.32*	42,984 (4.6)	36 (5.4)	*0.04*
Adjustment disorder	13,135 (1.0)	21 (3.2)	*0.15*	34,273 (3.7)	21 (3.2)	*-0.03*
Attention deficit hyperactivity disorder	10,118 (0.8)	48 (7.2)	*0.33*	71,611 (7.7)	48 (7.2)	*-0.02*
Delirium	698 (0.1)	<11	*0.10*	5,560 (0.6)	<11	*0.00*
Other psychiatric disorders	15,150 (1.1)	51 (7.7)	*0.32*	70,327 (7.6)	51 (7.7)	*0.00*
Alcohol abuse or dependence	6,754 (0.5)	32 (4.8)	*0.27*	40,514 (4.4)	32 (4.8)	*0.02*
Drug abuse or dependence	16,378 (1.2)	76 (11.5)	*0.43*	98,862 (10.6)	76 (11.5)	*0.03*
Chronic fatigue syndrome	36,215 (2.7)	38 (5.7)	*0.15*	56,635 (6.1)	38 (5.7)	*-0.02*
Sleep disorder	7,945 (0.6)	25 (3.8)	*0.22*	36,765 (4.0)	25 (3.8)	*-0.01*
Epilepsy or convulsions	3,894 (0.3)	13 (2.0)	*0.16*	16,304 (1.8)	13 (2.0)	*0.02*
Pain conditions[3]	183,219 (13.8)	184 (27.8)	*0.35*	272,867 (29.4)	184 (27.8)	*-0.04*
Migraine or headache	88,074 (6.7)	99 (14.9)	*0.27*	144,121 (15.5)	99 (14.9)	*-0.02*
Chronic maternal illness, N (%)						
Hypertension	24,529 (1.9)	22 (3.3)	*0.09*	30,197 (3.3)	22 (3.3)	*0.00*
Diabetes	23,287 (1.8)	18 (2.7)	*0.06*	26,222 (2.8)	18 (2.7)	*-0.01*
Renal disease	3,795 (0.3)	<11	*0.06*	6,526 (0.7)	<11	*0.01*
Obesity or overweight	22,123 (1.7)	19 (2.9)	*0.08*	28,494 (3.1)	19 (2.9)	*-0.01*
Smoking	38,975 (2.9)	51 (7.7)	*0.21*	77,809 (8.4)	51 (7.7)	*-0.03*
Psychotropic and other medications, N (%)						
Antidepressants	106,412 (8.0)	431 (65.0)	*1.47*	641,793 (69.1)	431 (65.0)	*-0.09*
Antipsychotics	12,366 (0.9)	308 (46.5)	*1.27*	394,767 (42.5)	308 (46.5)	*0.08*
Benzodiazepines	34,932 (2.6)	207 (31.2)	*0.82*	283,907 (30.6)	207 (31.2)	*0.01*
Other anxiolytics	4,288 (0.3)	31 (4.7)	*0.28*	41,285 (4.4)	31 (4.7)	*0.01*
Other hypnotics	43,150 (3.3)	114 (17.2)	*0.47*	154,213 (16.6)	114 (17.2)	*0.02*
Barbiturates	12,269 (0.9)	22 (3.3)	*0.17*	29,564 (3.2)	22 (3.3)	*0.01*
Stimulants	7,842 (0.6)	54 (8.1)	*0.38*	76,960 (8.3)	54 (8.1)	*-0.01*
Opioids	249,821 (18.9)	253 (38.2)	*0.44*	370,867 (39.9)	253 (38.2)	*-0.04*
Triptans	12,174 (0.9)	20 (3.0)	*0.15*	30,918 (3.3)	20 (3.0)	*-0.02*
Nonsteroidal anti-inflammatory drugs	211,001 (15.9)	166 (25.0)	*0.23*	243,096 (26.2)	166 (25.0)	*-0.03*
Antihypertensive medications	27,316 (2.1)	48 (7.2)	*0.25*	64,838 (7.0)	48 (7.2)	*0.01*

Non-insulin antidiabetic medications	8,681 (0.7)	<11	*0.08*	13,013 (1.4)	<11	*0.01*
Insulin	9,554 (0.7)	<11	*0.04*	10,621 (1.1)	<11	*-0.01*
Corticosteroids	75,693 (5.7)	73 (11.0)	*0.19*	104,859 (11.3)	73 (11.0)	*-0.01*
Fluconazole	22,091 (1.7)	26 (3.9)	*0.14*	37,053 (4.0)	26 (3.9)	*0.00*
Other teratogens[4]	16,321 (1.2)	11 (1.7)	*0.04*	16,018 (1.7)	11 (1.7)	*-0.01*
Methadone	595 (0.0)	<11	*0.06*	2,704 (0.3)	<11	*0.00*
Buprenorphine	1,068 (0.1)	<11	*0.12*	7,966 (0.9)	<11	*0.01*
Naltrexone	65 (0.0)	<11	*0.05*	1,295 (0.1)	<11	*0.00*
Naloxone	1,215 (0.1)	<11	*0.14*	10,569 (1.1)	<11	*0.01*
Markers of burden of disease						
Obstetric Comorbidity Index[5], mean (SD)	0.9 (1.4)	1.6 (1.8)	*0.44*	1.6 (1.8)	1.6 (1.8)	*0.02*
Number of distinct prescriptions, mean (SD)	1.6 (2.3)	4.5 (3.7)	*0.93*	4.6 (3.7)	4.5 (3.7)	*-0.04*
Number of diagnoses, mean (SD)	2.5 (3.1)	5.3 (4.5)	*0.73*	5.6 (4.5)	5.3 (4.5)	*-0.06*
Number of outpatient physician visits, mean (SD)	2.8 (4.0)	8.5 (9.8)	*0.76*	8.0 (8.5)	8.5 (9.8)	*0.05*
Patients hospitalized, N (%)	48,294 (3.7)	60 (9.0)	*0.22*	81,082 (8.7)	60 (9.0)	*0.01*
Number of hospitalizations, mean (SD)	0.0 (0.2)	0.1 (0.5)	*0.21*	0.1 (0.4)	0.1 (0.5)	*0.03*
Number of days hospitalized, mean (SD)	0.1 (0.9)	0.6 (3.1)	*0.22*	0.5 (2.0)	0.6 (3.0)	*0.07*
Number of emergency room visits, mean (SD)	0.3 (0.8)	0.8 (2.9)	*0.23*	0.7 (1.6)	0.8 (2.9)	*0.02*

St. Diff.: Standardized differences, i.e., the difference in means or proportions divided by the pooled standard deviation [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine 2009;28:3083-107]

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

[2] Other race includes Asian, Native American, Other, and Unknown

[3] Pain conditions include neuropathic and non-neuropathic conditions

[4] Other teratogens include methimazole, danazol, propylthiouracil, and progestins

[5] The obstetric comorbidity index predicts severe maternal morbidity. The range for the maternal comorbidity index is 0 to 45, with lower values associated with lower burden of maternal illness and higher values associated with higher burden of maternal illness [Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957-65]

Table S3. Unadjusted and propensity-score-adjusted baseline characteristics of lamotrigine-exposed and unexposed pregnant women[1]

	Unadjusted			Propensity-score adjusted		
Baseline characteristics	**Non-exposed (N=1,322,955)**	**Lamotrigine (N=1945)**	***St. Diff.***	**Non-exposed (N=1,233,824)**	**Lamotrigine (N=1945)**	***St. Diff.***
Age, mean (SD)	24.0 (5.8)	25.2 (5.8)	*0.20*	25.1 (5.9)	25.2 (5.8)	*0.01*
Race						
White	526,603 (39.8)	1446 (74.3)	*0.74*	941,365 (76.3)	1446 (74.3)	*-0.05*
Black	445,675 (33.7)	243 (12.5)	*-0.52*	147,490 (12.0)	243 (12.5)	*0.02*
Hispanic	195,174 (14.8)	107 (5.5)	*-0.31*	56,774 (4.6)	107 (5.5)	*0.04*
Other[2]	155,503 (11.8)	149 (7.7)	*-0.14*	88,195 (7.2)	149 (7.7)	*0.02*
Year						
2000	1,569 (0.1)	<11	*-0.05*	<11	<11	*0.00*
2001	81,024 (6.1)	17 (0.9)	*-0.29*	10,369 (0.8)	17 (0.9)	*0.00*
2002	92,771 (7.0)	19 (1.0)	*-0.31*	12,740 (1.0)	19 (1.0)	*-0.01*
2003	126,822 (9.6)	26 (1.3)	*-0.37*	18,123 (1.5)	26 (1.3)	*-0.01*
2004	153,523 (11.6)	97 (5.0)	*-0.24*	62,753 (5.1)	97 (5.0)	*0.00*
2005	154,733 (11.7)	154 (7.9)	*-0.13*	95,867 (7.8)	154 (7.9)	*0.01*
2006	154,415 (11.7)	224 (11.5)	*0.00*	145,180 (11.8)	224 (11.5)	*-0.01*
2007	146,133 (11.0)	286 (14.7)	*0.11*	180,420 (14.6)	286 (14.7)	*0.00*
2008	143,246 (10.8)	353 (18.1)	*0.21*	222,836 (18.1)	353 (18.2)	*0.00*
2009	149,472 (11.3)	436 (22.4)	*0.30*	276,583 (22.4)	436 (22.4)	*0.00*
2010	119,247 (9.0)	333 (17.1)	*0.24*	208,953 (16.9)	333 (17.1)	*0.00*
Multiple gestation	44,792 (3.4)	83 (4.3)	*0.05*	52,917 (4.3)	83 (4.3)	*0.00*
Psychiatric and neurological conditions, N (%)						
Bipolar disorder	9,485 (0.7)	798 (41.0)	*1.14*	505,264 (41.0)	798 (41.0)	*0.00*
Depression	63,110 (4.8)	402 (20.7)	*0.49*	284,035 (23.0)	402 (20.7)	*-0.06*
Anxiety	41,759 (3.2)	343 (17.6)	*0.49*	233,688 (18.9)	343 (17.6)	*-0.03*
Schizophrenia	1,639 (0.1)	29 (1.5)	*0.15*	19,142 (1.6)	29 (1.5)	*0.00*

Other psychosis	2,138 (0.2)	18 (0.9)	*0.10*	12,094 (1.0)	18 (0.9)	*-0.01*
Personality disorder	2,160 (0.2)	67 (3.4)	*0.25*	37,026 (3.0)	67 (3.4)	*0.03*
Adjustment disorder	13,135 (1.0)	53 (2.7)	*0.13*	36,711 (3.0)	53 (2.7)	*-0.02*
Attention deficit hyperactivity disorder	10,118 (0.8)	133 (6.8)	*0.32*	88,720 (7.2)	133 (6.8)	*-0.01*
Delirium	698 (0.1)	11 (0.6)	*0.09*	7,203 (0.6)	11 (0.6)	*0.00*
Other psychiatric disorders	15,150 (1.1)	118 (6.1)	*0.27*	75,180 (6.1)	118 (6.1)	*0.00*
Alcohol abuse or dependence	6,754 (0.5)	35 (1.8)	*0.12*	21,811 (1.8)	35 (1.8)	*0.00*
Drug abuse or dependence	16,378 (1.2)	101 (5.2)	*0.23*	64,517 (5.2)	101 (5.2)	*0.00*
Chronic fatigue syndrome	36,215 (2.7)	124 (6.4)	*0.18*	84,343 (6.8)	124 (6.4)	*-0.02*
Sleep disorder	7,945 (0.6)	79 (4.1)	*0.23*	52,227 (4.2)	79 (4.1)	*-0.01*
Epilepsy or convulsions	3,894 (0.3)	384 (19.7)	*0.68*	228,421 (18.5)	384 (19.7)	*0.03*
Pain conditions[3]	183,219 (13.8)	646 (33.2)	*0.47*	412,470 (33.4)	646 (33.2)	*0.00*
Migraine or headache	88,074 (6.7)	308 (15.8)	*0.29*	192,645 (15.6)	308 (15.8)	*0.01*
Chronic maternal illness, N (%)						
Hypertension	24,529 (1.9)	79 (4.1)	*0.13*	52,295 (4.2)	79 (4.1)	*-0.01*
Diabetes	23,287 (1.8)	45 (2.3)	*0.04*	31,288 (2.5)	45 (2.3)	*-0.01*
Renal disease	3,795 (0.3)	16 (0.8)	*0.07*	9,612 (0.8)	16 (0.8)	*0.00*
Obesity or overweight	22,123 (1.7)	63 (3.2)	*0.10*	39,654 (3.2)	63 (3.2)	*0.00*
Smoking	38,975 (2.9)	181 (9.3)	*0.27*	118,318 (9.6)	181 (9.3)	*-0.01*
Psychotropic and other medications, N (%)						
Antidepressants	106,412 (8.0)	1039 (53.4)	*1.13*	711,079 (57.6)	1039 (53.4)	*-0.08*
Antipsychotics	12,366 (0.9)	571 (29.4)	*0.86*	345,611 (28.0)	571 (29.4)	*0.03*
Benzodiazepines	34,932 (2.6)	516 (26.5)	*0.72*	322,332 (26.1)	516 (26.5)	*0.01*
Other anxiolytics	4,288 (0.3)	82 (4.2)	*0.26*	49,140 (4.0)	82 (4.2)	*0.01*
Other hypnotics	43,150 (3.3)	343 (17.6)	*0.48*	212,876 (17.3)	343 (17.6)	*0.01*
Barbiturates	12,269 (0.9)	47 (2.4)	*0.12*	29,128 (2.4)	47 (2.4)	*0.00*
Stimulants	7,842 (0.6)	209 (10.7)	*0.45*	125,946 (10.2)	209 (10.8)	*0.02*
Opioids	249,821 (18.9)	752 (38.7)	*0.45*	487,158 (39.5)	752 (38.7)	*-0.02*
Triptans	12,174 (0.9)	73 (3.8)	*0.19*	48,655 (3.9)	73 (3.8)	*-0.01*
Nonsteroidal anti-inflammatory drugs	211,001 (15.9)	510 (26.2)	*0.25*	337,363 (27.3)	510 (26.2)	*-0.03*
Antihypertensive medications	27,316 (2.1)	141 (7.3)	*0.25*	88,175 (7.2)	141 (7.3)	*0.00*

Non-insulin antidiabetic medications	8,681 (0.7)	42 (2.2)	*0.13*	28,551 (2.3)	42 (2.2)	*-0.01*
Insulin	9,554 (0.7)	19 (1.0)	*0.03*	13,178 (1.1)	19 (1.0)	*-0.01*
Corticosteroids	75,693 (5.7)	226 (11.6)	*0.21*	146,487 (11.9)	226 (11.6)	*-0.01*
Fluconazole	22,091 (1.7)	81 (4.2)	*0.15*	52,578 (4.3)	81 (4.2)	*0.00*
Other teratogens[4]	16,321 (1.2)	56 (2.9)	*0.12*	37,864 (3.1)	56 (2.9)	*-0.01*
Methadone	595 (0.0)	<11	*0.07*	4,336 (0.4)	<11	*0.00*
Buprenorphine	1,068 (0.1)	15 (0.8)	*0.11*	10,222 (0.8)	15 (0.8)	*-0.01*
Naltrexone	65 (0.0)	<11	*0.07*	2,212 (0.2)	<11	*0.02*
Naloxone	1,215 (0.1)	16 (0.8)	*0.11*	10,599 (0.9)	16 (0.8)	*0.00*
Markers of burden of disease						
Obstetric Comorbidity Index[5], mean (SD)	0.9 (1.4)	1.4 (1.8)	*0.31*	1.4 (1.8)	1.4 (1.8)	*-0.01*
Number of distinct prescriptions, mean (SD)	1.6 (2.3)	4.3 (3.7)	*0.86*	4.4 (3.6)	4.3 (3.7)	*-0.02*
Number of diagnoses, mean (SD)	2.5 (3.1)	5.4 (4.5)	*0.75*	5.7 (4.5)	5.4 (4.5)	*-0.05*
Number of outpatient physician visits, mean (SD)	2.8 (4.0)	7.4 (8.8)	*0.68*	7.1 (7.5)	7.4 (8.8)	*0.04*
Patients hospitalized, N (%)	48,294 (3.7)	115 (5.9)	*0.11*	74,398 (6.0)	115 (5.9)	*0.00*
Number of hospitalizations, mean (SD)	0.0 (0.2)	0.1 (0.3)	*0.10*	0.1 (0.3)	0.1 (0.3)	*-0.01*
Number of days hospitalized, mean (SD)	0.1 (0.9)	0.3 (1.4)	*0.11*	0.3 (1.7)	0.3 (1.4)	*-0.01*
Number of emergency room visits, mean (SD)	0.3 (0.8)	0.7 (2.0)	*0.28*	0.7 (1.4)	0.7 (2.0)	*0.01*

St. Diff.: Standardized differences, i.e., the difference in means or proportions divided by the pooled standard deviation [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine 2009;28:3083-107]

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

[2] Other race includes Asian, Native American, Other, and Unknown

[3] Pain conditions include neuropathic and non-neuropathic conditions

[4] Other teratogens include methimazole, danazol, propylthiouracil, and progestins

[5] The obstetric comorbidity index predicts severe maternal morbidity. The range for the maternal comorbidity index is 0 to 45, with lower values associated with lower burden of maternal illness and higher values associated with higher burden of maternal illness [Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957-65]

Table S4. Unadjusted and propensity-score-adjusted baseline characteristics of lithium- and lamotrigine-exposed pregnant women, with lamotrigine serving as the active reference group[1]

	Unadjusted			Propensity-score adjusted		
Baseline characteristics	**Lamotrigine (N=1945)**	**Lithium (N=663)**	***St. Diff.***	**Lamotrigine (N=1689)**	**Lithium (N=622)**	***St. Diff.***
Age, mean (SD)	25.2 (5.8)	25.6 (6.1)	*0.08*	25.9 (6.1)	25.6 (6.1)	*-0.04*
Race						
White	1,446 (74.3)	490 (73.9)	*-0.01*	1,301 (77.1)	461 (74.1)	*-0.07*
Black	243 (12.5)	89 (13.4)	*0.03*	205 (12.2)	85 (13.7)	*0.04*
Hispanic	107 (5.5)	36 (5.4)	*0.00*	71 (4.2)	32 (5.1)	*0.05*
Other[2]	149 (7.7)	48 (7.2)	*-0.02*	112 (6.6)	44 (7.1)	*0.02*
Year						
2000	<11	<11	*0.05*	<11	<11	*0.00*
2001	17 (0.9)	34 (5.1)	*0.25*	77 (4.6)	27 (4.3)	*-0.01*
2002	19 (1.0)	41 (6.2)	*0.28*	58 (3.5)	30 (4.8)	*0.07*
2003	26 (1.3)	67 (10.1)	*0.38*	142 (8.4)	50 (8.0)	*-0.01*
2004	97 (5.0)	83 (12.5)	*0.27*	244 (14.4)	80 (12.9)	*-0.05*
2005	154 (7.9)	69 (10.4)	*0.09*	195 (11.6)	68 (10.9)	*-0.02*
2006	224 (11.5)	72 (10.9)	*-0.02*	191 (11.3)	71 (11.4)	*0.00*
2007	286 (14.7)	73 (11.0)	*-0.11*	198 (11.7)	73 (11.7)	*0.00*
2008	353 (18.2)	77 (11.6)	*-0.18*	207 (12.3)	77 (12.4)	*0.00*
2009	436 (22.4)	86 (13.0)	*-0.25*	226 (13.4)	86 (13.8)	*0.01*
2010	333 (17.1)	60 (9.1)	*-0.24*	151 (8.9)	60 (9.6)	*0.02*
Multiple gestation	83 (4.3)	17 (2.6)	*-0.09*	40 (2.4)	17 (2.7)	*0.02*
Psychiatric and neurological conditions, N (%)						
Bipolar disorder	798 (41.0)	436 (65.8)	*0.51*	1,110 (65.7)	405 (65.1)	*-0.01*
Depression	402 (20.7)	167 (25.2)	*0.11*	389 (23.0)	158 (25.4)	*0.05*
Anxiety	343 (17.6)	117 (17.6)	*0.00*	301 (17.8)	108 (17.4)	*-0.01*
Schizophrenia	29 (1.5)	33 (5.0)	*0.20*	80 (4.7)	27 (4.3)	*-0.02*

Other psychosis	18 (0.9)	25 (3.8)	*0.19*	41 (2.4)	20 (3.2)	*0.05*
Personality disorder	67 (3.4)	36 (5.4)	*0.10*	97 (5.8)	33 (5.3)	*-0.02*
Adjustment disorder	53 (2.7)	21 (3.2)	*0.03*	52 (3.1)	17 (2.7)	*-0.02*
Attention deficit hyperactivity disorder	133 (6.8)	48 (7.2)	*0.02*	108 (6.4)	45 (7.2)	*0.03*
Delirium	11 (0.6)	<11	*0.00*	<11	<11	*0.01*
Other psychiatric disorders	118 (6.1)	51 (7.7)	*0.06*	95 (5.6)	46 (7.4)	*0.07*
Alcohol abuse or dependence	35 (1.8)	32 (4.8)	*0.17*	57 (3.4)	28 (4.5)	*0.06*
Drug abuse or dependence	101 (5.2)	76 (11.5)	*0.23*	171 (10.1)	68 (10.9)	*0.03*
Chronic fatigue syndrome	124 (6.4)	38 (5.7)	*-0.03*	105 (6.2)	38 (6.1)	*-0.01*
Sleep disorder	79 (4.1)	25 (3.8)	*-0.01*	75 (4.4)	25 (4.0)	*-0.02*
Epilepsy or convulsions	384 (19.7)	13 (2.0)	*-0.60*	37 (2.2)	13 (2.1)	*-0.01*
Pain conditions[3]	646 (33.2)	184 (27.8)	*-0.12*	531 (31.4)	172 (27.7)	*-0.08*
Migraine or headache	308 (15.8)	99 (14.9)	*-0.03*	291 (17.2)	93 (15.0)	*-0.06*
Chronic maternal illness, N (%)						
Hypertension	79 (4.1)	22 (3.3)	*-0.04*	45 (2.7)	21 (3.4)	*0.04*
Diabetes	45 (2.3)	18 (2.7)	*0.03*	50 (3.0)	17 (2.7)	*-0.01*
Renal disease	16 (0.8)	<11	*-0.01*	18 (1.1)	<11	*-0.03*
Obesity or overweight	63 (3.2)	19 (2.9)	*-0.02*	41 (2.4)	18 (2.9)	*0.03*
Smoking	181 (9.3)	51 (7.7)	*-0.06*	164 (9.7)	50 (8.0)	*-0.06*
Psychotropic and other medications, N (%)						
Antidepressants	1,039 (53.4)	431 (65.0)	*0.24*	1,041 (61.6)	402 (64.6)	*0.06*
Antipsychotics	571 (29.4)	308 (46.5)	*0.36*	834 (49.4)	284 (45.7)	*-0.07*
Benzodiazepines	516 (26.5)	207 (31.2)	*0.10*	552 (32.7)	192 (30.9)	*-0.04*
Other anxiolytics	82 (4.2)	31 (4.7)	*0.02*	71 (4.2)	29 (4.7)	*0.02*
Other hypnotics	343 (17.6)	114 (17.2)	*-0.01*	235 (13.9)	106 (17.0)	*0.09*
Barbiturates	47 (2.4)	22 (3.3)	*0.05*	73 (4.3)	19 (3.1)	*-0.07*
Stimulants	209 (10.8)	54 (8.1)	*-0.09*	152 (9.0)	52 (8.4)	*-0.02*
Opioids	752 (38.7)	253 (38.2)	*-0.01*	665 (39.3)	233 (37.5)	*-0.04*
Triptans	73 (3.8)	20 (3.0)	*-0.04*	28 (1.7)	19 (3.1)	*0.09*
Nonsteroidal anti-inflammatory drugs	510 (26.2)	166 (25.0)	*-0.03*	401 (23.7)	155 (24.9)	*0.03*
Antihypertensive medications	141 (7.3)	48 (7.2)	*0.00*	128 (7.6)	42 (6.8)	*-0.03*

Non-insulin antidiabetic medications	42 (2.2)	<11	*-0.05*	31 (1.8)	<11	*-0.02*
Insulin	19 (1.0)	<11	*0.01*	26 (1.6)	<11	*-0.04*
Corticosteroids	226 (11.6)	73 (11.0)	*-0.02*	204 (12.1)	67 (10.8)	*-0.04*
Fluconazole	81 (4.2)	26 (3.9)	*-0.01*	67 (4.0)	24 (3.9)	*-0.01*
Other teratogens[4]	56 (2.9)	11 (1.7)	*-0.08*	24 (1.4)	11 (1.8)	*0.03*
Methadone	<11	<11	*-0.01*	<11	<11	*0.00*
Buprenorphine	15 (0.8)	<11	*0.01*	14 (0.9)	<11	*0.01*
Naltrexone	<11	<11	*-0.02*	<11	<11	*0.02*
Naloxone	16 (0.8)	<11	*0.04*	15 (0.9)	<11	*0.02*
Markers of burden of disease						
Obstetric Comorbidity Index[5], mean (SD)	1.4 (1.8)	1.6 (1.8)	*0.11*	1.5 (1.7)	1.6 (1.8)	*0.06*
Number of distinct prescriptions, mean (SD)	4.3 (3.7)	4.5 (3.7)	*0.05*	4.7 (4.1)	4.4 (3.7)	*-0.07*
Number of diagnoses, mean (SD)	5.4 (4.5)	5.3 (4.5)	*-0.02*	5.6 (4.8)	5.3 (4.5)	*-0.05*
Number of outpatient physician visits, mean (SD)	7.4 (8.8)	8.5 (9.8)	*0.11*	10.0 (13.6)	8.3 (9.6)	*-0.14*[6]
Patients hospitalized, N (%)	115 (5.9)	60 (9.1)	*0.12*	140 (8.3)	56 (9.0)	*0.03*
Number of hospitalizations, mean (SD)	0.1 (0.3)	0.1 (0.5)	*0.14*	0.1 (0.4)	0.1 (0.5)	*0.03*
Number of days hospitalized, mean (SD)	0.3 (1.4)	0.6 (3.1)	*0.15*	0.4 (1.7)	0.6 (3.0)	*0.08*
Number of emergency room visits, mean (SD)	0.7 (2.0)	0.8 (2.9)	*0.03*	0.9 (3.2)	0.8 (3.0)	*-0.03*

St. Diff.: Standardized differences, i.e., the difference in means or proportions divided by the pooled standard deviation [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine 2009;28:3083-107]

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

[2] Other race includes Asian, Native American, Other, and Unknown

[3] Pain conditions include neuropathic and non-neuropathic conditions

[4] Other teratogens include methimazole, danazol, propylthiouracil, and progestins

[5] The obstetric comorbidity index predicts severe maternal morbidity. The range for the maternal comorbidity index is 0 to 45, with lower values associated with lower burden of maternal illness and higher values associated with higher burden of maternal illness [Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957-65]

[6] The covariate "number of outpatient physician visits" was included in the propensity score model as a categorical covariate (quartiles). Quartiles of number of physician visits were balanced with standardized differences <0.1

Table S5. Absolute and risk difference of cardiac, non-cardiac, and overall malformations among infants exposed to lithium during the first trimester as compared with lamotrigine-exposed or unexposed infants

Exposure Group:	Unexposed	Lamotrigine	Lithium
Total	1,322,955	1,945	663
Cardiac malformations			
Events	15,251	27	16
Prevalence per 100 births	1.15	1.39	2.41
Unadjusted RD (95% CI)	Ref.	0.24 (-0.28,0.76)	1.26 (0.09,2.43)
PS-adjusted RD (95% CI)	Ref.	-0.16 (-0.68,0.36)	0.95 (-0.22,2.12)
Unadjusted RD (95% CI)	.	Ref.	1.03 (-0.25,2.30)
PS-adjusted RD (95% CI)	.	Ref.	1.43 (0.09,2.77)
Non-cardiac malformations			
Events	27,816	49	22
Prevalence per 100 births	2.10	2.52	3.32
Unadjusted RD (95% CI)	Ref.	0.42 (-0.28,1.11)	1.22 (-0.15,2.58)
PS-adjusted RD (95% CI)	Ref.	-0.29 (-0.99,0.41)	0.60 (-0.76,1.97)
Unadjusted RD (95% CI)	.	Ref.	0.80 (-0.73,2.33)
PS-adjusted RD (95% CI)	.	Ref.	1.30 (-0.27,2.88)
Overall malformations			
Events	43,067	76	38
Prevalence per 100 births	3.26	3.91	5.73
Unadjusted RD (95% CI)	Ref.	0.65 (-0.21,1.51)	2.48 (0.71,4.25)
PS-adjusted RD (95% CI)	Ref.	-0.46 (-1.32,0.41)	1.55 (-0.22,3.32)
Unadjusted RD (95% CI)	.	Ref.	1.82 (-0.14,3.79)
PS-adjusted RD (95% CI)	.	Ref.	2.73 (0.69,4.77)

PS: propensity score; RR: risk ratios; CI: confidence intervals; Ref.: reference

Table S6. Unadjusted baseline characteristics of exposed and unexposed pregnant women by dose tertiles of the first lithium prescription filled during the first trimester[1]

Baseline characteristics	Non-exposed (N=1,322,955)	Lithium <=600 mg/day (N=305)	*St. Diff.*	Non-exposed (N=1,322,955)	Lithium 601-900 mg/day (N=235)	*St. Diff.*	Non-exposed (N=1,322,955)	Lithium >900 mg/day (N=123)	*St. Diff.*
Age, mean (SD)	24.0 (5.8)	25.3 (6.0)	*0.22*	24.0 (5.8)	25.8 (6.2)	*0.30*	24.0 (5.8)	26.3 (6.5)	*0.38*
Race									
White	526,603 (39.8)	237 (77.7)	*0.83*	526,603 (39.8)	169 (71.9)	*0.68*	526,603 (39.8)	84 (68.3)	*0.60*
Black	445,675 (33.7)	35 (11.5)	*-0.55*	445,675 (33.7)	37 (15.7)	*-0.42*	445,675 (33.7)	17 (13.8)	*-0.48*
Hispanic	195,174 (14.8)	13 (4.3)	*-0.36*	195,174 (14.8)	13 (5.5)	*-0.31*	195,174 (14.8)	<11	*-0.21*
Other[2]	155,503 (11.8)	20 (6.6)	*-0.18*	155,503 (11.8)	16 (6.8)	*-0.17*	155,503 (11.8)	12 (9.8)	*-0.06*
Year									
2000	1,569 (0.1)	<11	*-0.05*	1,569 (0.1)	<11	*0.06*	1,569 (0.1)	<11	*-0.05*
2001	81,024 (6.1)	14 (4.6)	*-0.07*	81,024 (6.1)	13 (5.5)	*-0.03*	81,024 (6.1)	<11	*-0.02*
2002	92,771 (7.0)	22 (7.2)	*0.01*	92,771 (7.0)	11 (4.7)	*-0.10*	92,771 (7.0)	<11	*-0.02*
2003	126,822 (9.6)	30 (9.8)	*0.01*	126,822 (9.6)	21 (8.9)	*-0.02*	126,822 (9.6)	16 (13.0)	*0.11*
2004	153,523 (11.6)	38 (12.5)	*0.03*	153,523 (11.6)	28 (11.9)	*0.01*	153,523 (11.6)	17 (13.8)	*0.07*
2005	154,733 (11.7)	34 (11.2)	*-0.02*	154,733 (11.7)	29 (12.3)	*0.02*	154,733 (11.7)	<11	*-0.25*
2006	154,415 (11.7)	32 (10.5)	*-0.04*	154,415 (11.7)	24 (10.2)	*-0.05*	154,415 (11.7)	16 (13.0)	*0.04*
2007	146,133 (11.1)	34 (11.1)	*0.00*	146,133 (11.1)	24 (10.2)	*-0.03*	146,133 (11.1)	15 (12.2)	*0.04*
2008	143,246 (10.8)	31 (10.2)	*-0.02*	143,246 (10.8)	33 (14.0)	*0.10*	143,246 (10.8)	13 (10.6)	*-0.01*
2009	149,472 (11.3)	41 (13.4)	*0.07*	149,472 (11.3)	31 (13.2)	*0.06*	149,472 (11.3)	14 (11.4)	*0.00*
2010	119,247 (9.0)	29 (9.5)	*0.02*	119,247 (9.0)	20 (8.5)	*-0.02*	119,247 (9.0)	11 (8.9)	*0.00*
Multiple gestation	44,792 (3.4)	<11	*-0.09*	44,792 (3.4)	<11	*-0.08*	44,792 (3.4)	<11	*0.07*
Psychiatric and neurological conditions, N (%)									
Bipolar disorder	9,485 (0.7)	188 (61.6)	*1.74*	9,485 (0.7)	157 (66.8)	*1.95*	9,485 (0.7)	91 (74.0)	*2.31*
Depression	63,110 (4.8)	82 (26.9)	*0.63*	63,110 (4.8)	59 (25.1)	*0.59*	63,110 (4.8)	26 (21.1)	*0.50*
Anxiety	41,759 (3.2)	59 (19.3)	*0.53*	41,759 (3.2)	42 (17.9)	*0.49*	41,759 (3.2)	16 (13.0)	*0.37*
Schizophrenia	1,639 (0.1)	12 (3.9)	*0.27*	1,639 (0.1)	15 (6.4)	*0.36*	1,639 (0.1)	<11	*0.31*
Other psychosis	2,138 (0.2)	<11	*0.21*	2,138 (0.2)	<11	*0.28*	2,138 (0.2)	<11	*0.33*

Personality disorder	2,160 (0.2)	17 (5.6)	*0.33*	2,160 (0.2)	13 (5.5)	*0.33*	2,160 (0.2)	<11	*0.30*
Adjustment disorder	13,135 (1.0)	12 (3.9)	*0.19*	13,135 (1.0)	<11	*0.14*	13,135 (1.0)	<11	*0.06*
Attention deficit hyperactivity disorder	10,118 (0.8)	25 (8.2)	*0.36*	10,118 (0.8)	18 (7.7)	*0.35*	10,118 (0.8)	<11	*0.22*
Delirium	698 (0.1)	<11	*-0.03*	698 (0.1)	<11	*0.12*	698 (0.1)	<11	*0.17*
Other psychiatric disorders	15,150 (1.1)	23 (7.5)	*0.32*	15,150 (1.1)	22 (9.4)	*0.37*	15,150 (1.1)	<11	*0.22*
Alcohol abuse or dependence	6,754 (0.5)	14 (4.6)	*0.26*	6,754 (0.5)	13 (5.5)	*0.30*	6,754 (0.5)	<11	*0.24*
Drug abuse or dependence	16,378 (1.2)	27 (8.9)	*0.35*	16,378 (1.2)	34 (14.5)	*0.51*	16,378 (1.2)	15 (12.2)	*0.45*
Chronic fatigue syndrome	36,215 (2.7)	18 (5.9)	*0.16*	36,215 (2.7)	12 (5.1)	*0.12*	36,215 (2.7)	<11	*0.18*
Sleep disorder	7,945 (0.6)	14 (4.6)	*0.25*	7,945 (0.6)	<11	*0.18*	7,945 (0.6)	<11	*0.19*
Epilepsy or convulsions	3,894 (0.3)	<11	*0.14*	3,894 (0.3)	<11	*0.19*	3,894 (0.3)	<11	*0.14*
Pain conditions[3]	183,219 (13.8)	86 (28.2)	*0.36*	183,219 (13.8)	60 (25.5)	*0.30*	183,219 (13.8)	38 (30.9)	*0.42*
Migraine or headache	88,074 (6.7)	41 (13.4)	*0.23*	88,074 (6.7)	38 (16.2)	*0.30*	88,074 (6.7)	20 (16.3)	*0.30*
Chronic maternal illness, N (%)									
Hypertension	24,529 (1.9)	<11	*0.07*	24,529 (1.9)	<11	*0.02*	24,529 (1.9)	<11	*0.23*
Diabetes	23,287 (1.8)	<11	*0.10*	23,287 (1.8)	<11	*-0.19*	23,287 (1.8)	<11	*0.24*
Renal disease	3,795 (0.3)	<11	*0.09*	3,795 (0.3)	<11	*0.07*	3,795 (0.3)	<11	*-0.08*
Obesity or overweight	22,123 (1.7)	<11	*0.07*	22,123 (1.7)	<11	*0.06*	22,123 (1.7)	<11	*0.14*
Smoking	38,975 (2.9)	21 (6.9)	*0.18*	38,975 (2.9)	22 (9.4)	*0.27*	38,975 (2.9)	<11	*0.17*
Psychotropic and other medications, N (%)									
Antidepressants	106,412 (8.0)	188 (61.6)	*1.36*	106,412 (8.0)	163 (69.4)	*1.62*	106,412 (8.0)	80 (65.0)	*1.46*
Antipsychotics	12,366 (0.9)	126 (41.3)	*1.14*	12,366 (0.9)	110 (46.8)	*1.27*	12,366 (0.9)	72 (58.5)	*1.62*
Benzodiazepines	34,932 (2.6)	93 (30.5)	*0.81*	34,932 (2.6)	72 (30.6)	*0.81*	34,932 (2.6)	42 (34.2)	*0.89*
Other anxiolytics	4,288 (0.3)	14 (4.6)	*0.28*	4,288 (0.3)	12 (5.1)	*0.30*	4,288 (0.3)	<11	*0.26*
Other hypnotics	43,150 (3.3)	56 (18.4)	*0.50*	43,150 (3.3)	39 (16.6)	*0.46*	43,150 (3.3)	19 (15.5)	*0.43*
Barbiturates	12,269 (0.9)	12 (3.9)	*0.20*	12,269 (0.9)	<11	*0.10*	12,269 (0.9)	<11	*0.20*
Stimulants	7,842 (0.6)	26 (8.5)	*0.39*	7,842 (0.6)	16 (6.8)	*0.33*	7,842 (0.6)	12 (9.8)	*0.42*
Opioids	249,821 (18.9)	120 (39.3)	*0.46*	249,821 (18.9)	77 (32.8)	*0.32*	249,821 (18.9)	56 (45.5)	*0.59*
Triptans	12,174 (0.9)	13 (4.3)	*0.21*	12,174 (0.9)	<11	*0.13*	12,174 (0.9)	<11	*-0.01*
Nonsteroidal anti-inflammatory drugs	211,001 (15.9)	83 (27.2)	*0.28*	211,001 (15.9)	58 (24.7)	*0.22*	211,001 (15.9)	25 (20.3)	*0.11*
Antihypertensive medications	27,316 (2.1)	20 (6.6)	*0.22*	27,316 (2.1)	17 (7.2)	*0.25*	27,316 (2.1)	11 (8.9)	*0.30*

Non-insulin antidiabetic medications	8,681 (0.7)	<11	*0.09*	8,681 (0.7)	<11	*-0.11*	8,681 (0.7)	<11	*0.23*
Insulin	9,554 (0.7)	<11	*0.03*	9,554 (0.7)	<11	*-0.04*	9,554 (0.7)	<11	*0.14*
Corticosteroids	75,693 (5.7)	31 (10.2)	*0.16*	75,693 (5.7)	26 (11.1)	*0.19*	75,693 (5.7)	16 (13.0)	*0.25*
Fluconazole	22,091 (1.7)	16 (5.3)	*0.20*	22,091 (1.7)	<11	*0.11*	22,091 (1.7)	<11	*0.00*
Other teratogens[4]	16,321 (1.2)	<11	*0.03*	16,321 (1.2)	<11	*0.04*	16,321 (1.2)	<11	*0.03*
Methadone	595 (0.0)	<11	*0.10*	595 (0.0)	<11	*-0.03*	595 (0.0)	<11	*-0.03*
Buprenorphine	1,068 (0.1)	<11	*0.17*	1,068 (0.1)	<11	*0.07*	1,068 (0.1)	<11	*-0.04*
Naltrexone	65 (0.0)	<11	*-0.01*	65 (0.0)	<11	*0.09*	65 (0.0)	<11	*-0.01*
Naloxone	1,215 (0.1)	<11	*0.20*	1,215 (0.1)	<11	*0.07*	1,215 (0.1)	<11	*-0.04*
Markers of burden of disease									
Obstetric Comorbidity Index[5], mean (SD)	0.9 (1.4)	1.4 (1.6)	*0.33*	0.9 (1.4)	1.6 (1.9)	*0.46*	0.9 (1.4)	2.0 (1.9)	*0.65*
Number of distinct prescriptions, mean (SD)	1.6 (2.3)	4.6 (3.9)	*0.93*	1.6 (2.3)	4.2 (3.7)	*0.85*	1.6 (2.3)	4.7 (3.2)	*1.09*
Number of diagnoses, mean (SD)	2.5 (3.1)	5.6 (4.6)	*0.77*	2.5 (3.1)	5.1 (4.5)	*0.67*	2.5 (3.1)	5.3 (4.3)	*0.74*
Number of outpatient physician visits, mean (SD)	2.8 (4.0)	7.9 (8.2)	*0.79*	2.8 (4.0)	8.3 (11.1)	*0.66*	2.8 (4.0)	10.2 (10.8)	*0.92*
Patients hospitalized, N (%)	48,294 (3.7)	27 (8.9)	*0.22*	48,294 (3.7)	21 (8.9)	*0.22*	48,294 (3.7)	12 (9.8)	*0.25*
Number of hospitalizations, mean (SD)	0.0 (0.2)	0.1 (0.6)	*0.21*	0.0 (0.2)	0.1 (0.4)	*0.22*	0.0 (0.2)	0.1 (0.4)	*0.23*
Number of days hospitalized, mean (SD)	0.1 (0.9)	0.7 (3.6)	*0.20*	0.1 (0.9)	0.6 (2.3)	*0.26*	0.1 (0.9)	0.7 (2.9)	*0.26*
Number of emergency room visits, mean (SD)	0.3 (0.8)	0.9 (4.1)	*0.22*	0.3 (0.8)	0.7 (1.4)	*0.35*	0.3 (0.8)	0.6 (1.3)	*0.30*

St. Diff.: Standardized differences, i.e., the difference in means or proportions divided by the pooled standard deviation [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine 2009;28:3083-107]

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

[2] Other race includes Asian, Native American, Other, and Unknown

[3] Pain conditions include neuropathic and non-neuropathic conditions

[4] Other teratogens include methimazole, danazol, propylthiouracil, and progestins

[5] The obstetric comorbidity index predicts severe maternal morbidity. The range for the maternal comorbidity index is 0 to 45, with lower values associated with lower burden of maternal illness and higher values associated with higher burden of maternal illness [Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957-65]

Table S7. Propensity-score-adjusted baseline characteristics of exposed and unexposed pregnant women by dose tertiles of the first lithium prescription filled during the first trimester[1]

Baseline characteristics	Non-exposed (N=955,873)	Lithium <=600 mg/day (N=305)	*St. Diff.*	Non-exposed (N=997,007)	Lithium 601-900 mg/day (N=235)	*St. Diff.*	Non-exposed (N=641,249)	Lithium >900 mg/day (N=123)	*St. Diff.*
Age, mean (SD)	25.2 (6.1)	25.3 (5.9)	*0.01*	25.7 (6.2)	25.8 (6.2)	*0.01*	26.3 (6.6)	26.3 (6.4)	*-0.01*
Race									
White	764,695 (80.0)	237 (77.7)	*-0.06*	731,938 (73.4)	169 (71.9)	*-0.03*	445,970 (69.6)	84 (68.3)	*-0.03*
Black	97,076 (10.2)	35 (11.5)	*0.04*	147,876 (14.8)	37 (15.7)	*0.03*	85,705 (13.4)	17 (13.8)	*0.01*
Hispanic	32,699 (3.4)	13 (4.3)	*0.04*	50,877 (5.1)	13 (5.5)	*0.02*	48,988 (7.6)	<11	*0.02*
Other[2]	61,404 (6.4)	20 (6.6)	*0.01*	66,315 (6.7)	16 (6.8)	*0.01*	60,586 (9.5)	12 (9.8)	*0.01*
Year									
2000	<11	<11	*0.00*	7,794 (0.8)	<11	*-0.05*	0 (0.0)	<11	*0.00*
2001	45,637 (4.8)	14 (4.6)	*-0.01*	62,812 (6.3)	13 (5.5)	*-0.03*	43,639 (6.8)	<11	*-0.05*
2002	63,895 (6.7)	22 (7.2)	*0.02*	43,324 (4.3)	11 (4.7)	*0.02*	36,528 (5.7)	<11	*0.03*
2003	95,718 (10.0)	30 (9.8)	*-0.01*	88,639 (8.9)	21 (8.9)	*0.00*	80,363 (12.5)	16 (13.0)	*0.01*
2004	118,634 (12.4)	38 (12.5)	*0.00*	117,106 (11.7)	28 (11.9)	*0.01*	89,087 (13.9)	17 (13.8)	*0.00*
2005	103,944 (10.9)	34 (11.1)	*0.01*	119,701 (12.0)	29 (12.3)	*0.01*	33,679 (5.3)	<11	*-0.02*
2006	101,802 (10.7)	32 (10.5)	*-0.01*	98,699 (9.9)	24 (10.2)	*0.01*	82,054 (12.8)	16 (13.0)	*0.01*
2007	109,175 (11.4)	34 (11.1)	*-0.01*	101,584 (10.2)	24 (10.2)	*0.00*	72,020 (11.2)	15 (12.2)	*0.03*
2008	98,460 (10.3)	31 (10.2)	*0.00*	132,070 (13.2)	33 (14.0)	*0.02*	64,307 (10.0)	13 (10.6)	*0.02*
2009	127,477 (13.3)	41 (13.4)	*0.00*	136,216 (13.7)	31 (13.2)	*-0.01*	78,018 (12.2)	14 (11.4)	*-0.02*
2010	91,131 (9.5)	29 (9.5)	*0.00*	89,063 (8.9)	20 (8.5)	*-0.01*	61,554 (9.6)	11 (8.9)	*-0.02*
Multiple gestation	20,756 (2.2)	<11	*-0.01*	21,610 (2.2)	<11	*0.00*	31,950 (5.0)	<11	*0.00*
Psychiatric and neurological conditions, N (%)									
Bipolar disorder	584,852 (61.2)	188 (61.6)	*0.01*	668,721 (67.1)	157 (66.8)	*-0.01*	482,477 (75.2)	91 (74.0)	*-0.03*
Depression	275,529 (28.8)	82 (26.9)	*-0.04*	266,462 (26.7)	59 (25.1)	*-0.04*	141,148 (22.0)	26 (21.1)	*-0.02*
Anxiety	192,671 (20.2)	59 (19.3)	*-0.02*	187,444 (18.8)	42 (17.9)	*-0.02*	95,934 (15.0)	16 (13.0)	*-0.06*
Schizophrenia	31,366 (3.3)	12 (3.9)	*0.04*	50,156 (5.0)	15 (6.4)	*0.06*	26,074 (4.1)	<11	*0.04*
Other psychosis	21,751 (2.3)	<11	*0.02*	35,906 (3.6)	<11	*0.03*	35,823 (5.6)	<11	*0.00*

Personality disorder	43,453 (4.5)	17 (5.6)	*0.05*	48,327 (4.8)	13 (5.5)	*0.03*	28,540 (4.5)	<11	*0.02*
Adjustment disorder	42,203 (4.4)	12 (3.9)	*-0.02*	34,729 (3.5)	<11	*-0.03*	10,834 (1.7)	<11	*0.00*
Attention deficit hyperactivity disorder	80,545 (8.4)	25 (8.2)	*-0.01*	78,239 (7.8)	18 (7.7)	*-0.01*	29,358 (4.6)	<11	*-0.03*
Delirium	<11	<11	*0.00*	7,292 (0.7)	<11	*0.01*	10,377 (1.6)	<11	*0.00*
Other psychiatric disorders	68,895 (7.2)	23 (7.5)	*0.01*	90,013 (9.0)	22 (9.4)	*0.01*	33,203 (5.2)	<11	*-0.01*
Alcohol abuse or dependence	39,066 (4.1)	14 (4.6)	*0.02*	49,308 (4.9)	13 (5.5)	*0.03*	21,124 (3.3)	<11	*0.04*
Drug abuse or dependence	80,846 (8.5)	27 (8.9)	*0.01*	130,956 (13.1)	34 (14.5)	*0.04*	75,279 (11.7)	15 (12.2)	*0.01*
Chronic fatigue syndrome	59,801 (6.3)	18 (5.9)	*-0.01*	54,450 (5.5)	12 (5.1)	*-0.02*	43,849 (6.8)	<11	*-0.01*
Sleep disorder	45,322 (4.7)	14 (4.6)	*-0.01*	34,196 (3.4)	<11	*-0.03*	27,181 (4.2)	<11	*-0.05*
Epilepsy or convulsions	14,680 (1.5)	<11	*0.01*	21,429 (2.2)	<11	*0.03*	11,290 (1.8)	<11	*-0.01*
Pain conditions[3]	278,856 (29.2)	86 (28.2)	*-0.02*	277,175 (27.8)	60 (25.5)	*-0.05*	200,691 (31.3)	38 (30.9)	*-0.01*
Migraine or headache	129,220 (13.5)	41 (13.4)	*0.00*	169,009 (17.0)	38 (16.2)	*-0.02*	104,013 (16.2)	20 (16.3)	*0.00*
Chronic maternal illness, N (%)									
Hypertension	27,178 (2.8)	<11	*0.01*	23,643 (2.4)	<11	*-0.02*	38,978 (6.1)	<11	*0.02*
Diabetes	33,883 (3.5)	<11	*-0.01*	74 (0.0)	<11	*-0.01*	47,888 (7.5)	<11	*-0.04*
Renal disease	7,087 (0.7)	<11	*0.03*	8,333 (0.8)	<11	*0.00*	24 (0.0)	<11	*-0.01*
Obesity or overweight	26,146 (2.7)	<11	*-0.01*	28,307 (2.8)	<11	*-0.02*	24,950 (3.9)	<11	*0.01*
Smoking	70,125 (7.3)	21 (6.9)	*-0.02*	94,824 (9.5)	22 (9.4)	*-0.01*	43,368 (6.8)	<11	*-0.01*
Psychotropic and other medications, N (%)									
Antidepressants	624,836 (65.4)	188 (61.6)	*-0.08*	723,884 (72.6)	163 (69.4)	*-0.07*	424,413 (66.2)	80 (65.0)	*-0.02*
Antipsychotics	356,163 (37.3)	126 (41.3)	*0.08*	420,697 (42.2)	110 (46.8)	*0.09*	354,348 (55.3)	72 (58.5)	*0.07*
Benzodiazepines	277,948 (29.1)	93 (30.5)	*0.03*	300,200 (30.1)	72 (30.6)	*0.01*	209,106 (32.6)	42 (34.1)	*0.03*
Other anxiolytics	39,221 (4.1)	14 (4.6)	*0.02*	46,798 (4.7)	12 (5.1)	*0.02*	22,737 (3.5)	<11	*0.03*
Other hypnotics	169,279 (17.7)	56 (18.4)	*0.02*	157,485 (15.8)	39 (16.6)	*0.02*	99,439 (15.5)	19 (15.4)	*0.00*
Barbiturates	34,052 (3.6)	12 (3.9)	*0.02*	20,339 (2.0)	<11	*0.01*	23,955 (3.7)	<11	*0.02*
Stimulants	79,041 (8.3)	26 (8.5)	*0.01*	69,897 (7.0)	16 (6.8)	*-0.01*	56,874 (8.9)	12 (9.8)	*0.03*
Opioids	387,251 (40.5)	120 (39.3)	*-0.02*	345,545 (34.7)	77 (32.8)	*-0.04*	301,456 (47.0)	56 (45.5)	*-0.03*
Triptans	43,037 (4.5)	13 (4.3)	*-0.01*	28,347 (2.8)	<11	*-0.02*	6,025 (0.9)	<11	*-0.01*
Nonsteroidal anti-inflammatory drugs	266,122 (27.8)	83 (27.2)	*-0.01*	260,194 (26.1)	58 (24.7)	*-0.03*	141,628 (22.1)	25 (20.3)	*-0.04*
Antihypertensive medications	56,743 (5.9)	20 (6.6)	*0.03*	74,937 (7.5)	17 (7.2)	*-0.01*	59,739 (9.3)	11 (8.9)	*-0.01*

Non-insulin antidiabetic medications	16,100 (1.7)	<11	*0.00*	47 (0.0)	<11	*-0.01*	32,256 (5.0)	<11	*-0.05*
Insulin	10,686 (1.1)	<11	*-0.01*	4,589 (0.5)	<11	*-0.01*	15,335 (2.4)	<11	*0.00*
Corticosteroids	98,487 (10.3)	31 (10.2)	*0.00*	117,411 (11.8)	26 (11.1)	*-0.02*	82,105 (12.8)	16 (13.0)	*0.01*
Fluconazole	52,475 (5.5)	16 (5.3)	*-0.01*	32,644 (3.3)	<11	*0.01*	11,193 (1.7)	<11	*-0.01*
Other teratogens[4]	15,847 (1.7)	<11	*0.00*	16,155 (1.6)	<11	*0.01*	11,268 (1.8)	<11	*-0.01*
Methadone	5,034 (0.5)	<11	*0.02*	14 (0.0)	<11	*-0.01*	<11	<11	*-0.01*
Buprenorphine	11,763 (1.2)	<11	*0.03*	4,578 (0.5)	<11	*-0.01*	13 (0.0)	<11	*-0.01*
Naltrexone	<11	<11	*0.00*	3,744 (0.4)	<11	*0.01*	<11	<11	*0.00*
Naloxone	15,937 (1.7)	<11	*0.05*	4,762 (0.5)	<11	*-0.01*	42 (0.0)	<11	*-0.01*
Markers of burden of disease									
Obstetric Comorbidity Index[5], mean (SD)	1.4 (1.7)	1.4 (1.6)	*-0.01*	1.6 (1.7)	1.6 (1.9)	*0.04*	2.0 (1.9)	2.0 (1.9)	*0.00*
Number of distinct prescriptions, mean (SD)	4.6 (3.7)	4.6 (3.9)	*-0.01*	4.4 (3.6)	4.2 (3.7)	*-0.05*	4.9 (3.7)	4.7 (3.2)	*-0.08*
Number of diagnoses, mean (SD)	5.7 (4.5)	5.6 (4.6)	*-0.03*	5.4 (4.6)	5.1 (4.5)	*-0.07*	5.6 (4.4)	5.3 (4.2)	*-0.06*
Number of outpatient physician visits, mean (SD)	7.7 (7.7)	7.9 (8.2)	*0.02*	7.9 (8.9)	8.3 (11.1)	*0.04*	8.9 (9.7)	10.2 (10.7)	*0.13*[6]
Patients hospitalized, N (%)	79,770 (8.3)	27 (8.9)	*0.02*	84,509 (8.5)	21 (8.9)	*0.02*	57,551 (9.0)	12 (9.8)	*0.03*
Number of hospitalizations, mean (SD)	0.1 (0.4)	0.1 (0.6)	*0.05*	0.1 (0.4)	0.1 (0.4)	*0.03*	0.1 (0.4)	0.1 (0.4)	*0.04*
Number of days hospitalized, mean (SD)	0.4 (2.0)	0.7 (3.6)	*0.08*	0.5 (2.0)	0.6 (2.3)	*0.06*	0.4 (1.8)	0.7 (2.9)	*0.10*[7]
Number of emergency room visits, mean (SD)	0.8 (1.5)	0.9 (4.1)	*0.06*	0.7 (1.7)	0.7 (1.4)	*-0.03*	0.8 (2.4)	0.6 (1.3)	*-0.08*

St. Diff.: Standardized differences, i.e., the difference in means or proportions divided by the pooled standard deviation [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine 2009;28:3083-107]

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

[2] Other race includes Asian, Native American, Other, and Unknown

[3] Pain conditions include neuropathic and non-neuropathic conditions

[4] Other teratogens include methimazole, danazol, propylthiouracil, and progestins

[5] The obstetric comorbidity index predicts severe maternal morbidity. The range for the maternal comorbidity index is 0 to 45, with lower values associated with lower burden of maternal illness and higher values associated with higher burden of maternal illness [Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957-65]

[6] The covariate "number of outpatient physician visits" was included in the propensity score model as a categorical covariate (quartiles). Quartiles of number of physician visits were balanced with standardized differences <0.1

[7] The covariate "number of days hospitalized" was included in the propensity score model as a categorical covariate (quartiles). Quartiles of number of physician visits were balanced with standardized differences <0.1

Table S8. Unadjusted baseline characteristics of exposed and unexposed pregnant women by dose tertiles of the first lamotrigine prescription filled during the first trimester[1]

Baseline characteristics	Non-exposed (N=1,322,955)	Lamotrigine <=100 mg/day (N=904)	*St. Diff.*	Non-exposed (N=1,322,955)	Lamotrigine 101-200 mg/day (N=620)	*St. Diff.*	Non-exposed (N=1,322,955)	Lamotrigine >200 mg/day (N=421)	*St. Diff.*
Age, mean (SD)	24.0 (5.8)	25.0 (5.7)	*0.18*	24.0 (5.8)	25.4 (5.9)	*0.23*	24.0 (5.8)	25.3 (5.8)	*0.22*
Race									
White	526,603 (39.8)	674 (74.6)	*0.75*	526,603 (39.8)	487 (78.5)	*0.86*	526,603 (39.8)	285 (67.7)	*0.58*
Black	445,675 (33.7)	115 (12.7)	*-0.51*	445,675 (33.7)	70 (11.3)	*-0.56*	445,675 (33.7)	58 (13.8)	*-0.48*
Hispanic	195,174 (14.8)	45 (5.0)	*-0.33*	195,174 (14.8)	26 (4.2)	*-0.37*	195,174 (14.8)	36 (8.6)	*-0.19*
Other[2]	155,503 (11.8)	70 (7.7)	*-0.14*	155,503 (11.8)	37 (6.0)	*-0.20*	155,503 (11.8)	42 (10.0)	*-0.06*
Year									
2000	1,569 (0.1)	<11	*-0.05*	1,569 (0.1)	<11	*-0.05*	1,569 (0.1)	<11	*-0.05*
2001	81,024 (6.1)	<11	*-0.31*	81,024 (6.1)	<11	*-0.33*	81,024 (6.1)	<11	*-0.20*
2002	92,771 (7.0)	<11	*-0.31*	92,771 (7.0)	<11	*-0.36*	92,771 (7.0)	<11	*-0.25*
2003	126,822 (9.6)	11 (1.2)	*-0.38*	126,822 (9.6)	<11	*-0.39*	126,822 (9.6)	<11	*-0.32*
2004	153,523 (11.6)	43 (4.8)	*-0.25*	153,523 (11.6)	25 (4.0)	*-0.28*	153,523 (11.6)	29 (6.9)	*-0.16*
2005	154,733 (11.7)	64 (7.1)	*-0.16*	154,733 (11.7)	57 (9.2)	*-0.08*	154,733 (11.7)	33 (7.8)	*-0.13*
2006	154,415 (11.7)	103 (11.4)	*-0.01*	154,415 (11.7)	63 (10.2)	*-0.05*	154,415 (11.7)	58 (13.8)	*0.06*
2007	146,133 (11.0)	121 (13.4)	*0.07*	146,133 (11.0)	102 (16.5)	*0.16*	146,133 (11.0)	63 (15.0)	*0.12*
2008	143,246 (10.8)	180 (19.9)	*0.25*	143,246 (10.8)	115 (18.6)	*0.22*	143,246 (10.8)	58 (13.8)	*0.09*
2009	149,472 (11.3)	206 (22.8)	*0.31*	149,472 (11.3)	134 (21.6)	*0.28*	149,472 (11.3)	96 (22.8)	*0.31*
2010	119,247 (9.0)	161 (17.8)	*0.26*	119,247 (9.0)	114 (18.4)	*0.28*	119,247 (9.0)	58 (13.8)	*0.15*
Multiple gestation	44,792 (3.4)	41 (4.5)	*0.06*	44,792 (3.4)	21 (3.4)	*0.00*	44,792 (3.4)	21 (5.0)	*0.08*
Psychiatric and neurological conditions, N (%)									
Bipolar disorder	9,485 (0.7)	406 (44.9)	*1.24*	9,485 (0.7)	287 (46.3)	*1.27*	9,485 (0.7)	105 (24.9)	*0.78*
Depression	63,110 (4.8)	239 (26.4)	*0.63*	63,110 (4.8)	102 (16.5)	*0.39*	63,110 (4.8)	61 (14.5)	*0.33*
Anxiety	41,759 (3.2)	184 (20.4)	*0.55*	41,759 (3.2)	104 (16.8)	*0.47*	41,759 (3.2)	55 (13.1)	*0.37*

Schizophrenia	1,639 (0.1)	17 (1.9)	*0.18*	1,639 (0.1)	<11	*0.13*	1,639 (0.1)	<11	*0.13*
Other psychosis	2,138 (0.2)	13 (1.4)	*0.14*	2,138 (0.2)	<11	*0.08*	2,138 (0.2)	<11	*0.02*
Personality disorder	2,160 (0.2)	35 (3.9)	*0.27*	2,160 (0.2)	27 (4.4)	*0.28*	2,160 (0.2)	<11	*0.13*
Adjustment disorder	13,135 (1.0)	33 (3.7)	*0.18*	13,135 (1.0)	13 (2.1)	*0.09*	13,135 (1.0)	<11	*0.06*
Attention deficit hyperactivity disorder	10,118 (0.8)	77 (8.5)	*0.37*	10,118 (0.8)	46 (7.4)	*0.34*	10,118 (0.8)	<11	*0.13*
Delirium	698 (0.1)	<11	*0.09*	698 (0.1)	<11	*0.08*	698 (0.1)	<11	*0.11*
Other psychiatric disorders	15,150 (1.1)	66 (7.3)	*0.31*	15,150 (1.1)	35 (5.7)	*0.25*	15,150 (1.1)	17 (4.0)	*0.18*
Alcohol abuse or dependence	6,754 (0.5)	21 (2.3)	*0.15*	6,754 (0.5)	<11	*0.11*	6,754 (0.5)	<11	*0.05*
Drug abuse or dependence	16,378 (1.2)	59 (6.5)	*0.28*	16,378 (1.2)	26 (4.2)	*0.18*	16,378 (1.2)	16 (3.8)	*0.16*
Chronic fatigue syndrome	36,215 (2.7)	60 (6.6)	*0.19*	36,215 (2.7)	47 (7.6)	*0.22*	36,215 (2.7)	17 (4.0)	*0.07*
Sleep disorder	7,945 (0.6)	37 (4.1)	*0.23*	7,945 (0.6)	27 (4.4)	*0.24*	7,945 (0.6)	15 (3.6)	*0.21*
Epilepsy or convulsions	3,894 (0.3)	85 (9.4)	*0.43*	3,894 (0.3)	110 (17.7)	*0.64*	3,894 (0.3)	189 (44.9)	*1.26*
Pain conditions[3]	183,219 (13.8)	311 (34.4)	*0.49*	183,219 (13.8)	221 (35.6)	*0.52*	183,219 (13.8)	114 (27.1)	*0.33*
Migraine or headache	88,074 (6.7)	143 (15.8)	*0.29*	88,074 (6.7)	95 (15.3)	*0.28*	88,074 (6.7)	70 (16.6)	*0.31*
Chronic maternal illness, N (%)									
Hypertension	24,529 (1.9)	38 (4.2)	*0.14*	24,529 (1.9)	26 (4.2)	*0.14*	24,529 (1.9)	15 (3.6)	*0.11*
Diabetes	23,287 (1.8)	24 (2.7)	*0.06*	23,287 (1.8)	15 (2.4)	*0.05*	23,287 (1.8)	<11	*-0.03*
Renal disease	3,795 (0.3)	<11	*0.04*	3,795 (0.3)	<11	*0.10*	3,795 (0.3)	<11	*0.08*
Obesity or overweight	22,123 (1.7)	28 (3.1)	*0.09*	22,123 (1.7)	25 (4.0)	*0.14*	22,123 (1.7)	<11	*0.05*
Smoking	38,975 (2.9)	102 (11.3)	*0.33*	38,975 (2.9)	51 (8.2)	*0.23*	38,975 (2.9)	28 (6.7)	*0.17*
Psychotropic and other medications, N (%)									
Antidepressants	106,412 (8.0)	540 (59.7)	*1.30*	106,412 (8.0)	343 (55.3)	*1.18*	106,412 (8.0)	156 (37.1)	*0.74*
Antipsychotics	12,366 (0.9)	285 (31.5)	*0.91*	12,366 (0.9)	215 (34.7)	*0.98*	12,366 (0.9)	71 (16.9)	*0.58*
Benzodiazepines	34,932 (2.6)	240 (26.5)	*0.72*	34,932 (2.6)	176 (28.4)	*0.76*	34,932 (2.6)	100 (23.8)	*0.66*
Other anxiolytics	4,288 (0.3)	42 (4.6)	*0.28*	4,288 (0.3)	30 (4.8)	*0.29*	4,288 (0.3)	<11	*0.18*
Other hypnotics	43,150 (3.3)	180 (19.9)	*0.54*	43,150 (3.3)	119 (19.2)	*0.52*	43,150 (3.3)	44 (10.5)	*0.29*
Barbiturates	12,269 (0.9)	24 (2.7)	*0.13*	12,269 (0.9)	14 (2.3)	*0.11*	12,269 (0.9)	<11	*0.10*
Stimulants	7,842 (0.6)	111 (12.3)	*0.49*	7,842 (0.6)	70 (11.3)	*0.46*	7,842 (0.6)	28 (6.7)	*0.33*
Opioids	249,821 (18.9)	365 (40.4)	*0.48*	249,821 (18.9)	244 (39.4)	*0.46*	249,821 (18.9)	143 (34.0)	*0.35*

Triptans	12,174 (0.9)	33 (3.7)	*0.18*	12,174 (0.9)	21 (3.4)	*0.17*	12,174 (0.9)	19 (4.5)	*0.22*
Nonsteroidal anti-inflammatory drugs	211,001 (15.9)	261 (28.9)	*0.31*	211,001 (15.9)	157 (25.3)	*0.23*	211,001 (15.9)	92 (21.9)	*0.15*
Antihypertensive medications	27,316 (2.1)	82 (9.1)	*0.31*	27,316 (2.1)	42 (6.8)	*0.23*	27,316 (2.1)	17 (4.0)	*0.11*
Non-insulin antidiabetic medications	8,681 (0.7)	19 (2.1)	*0.12*	8,681 (0.7)	17 (2.7)	*0.16*	8,681 (0.7)	<11	*0.08*
Insulin	9,554 (0.7)	<11	*0.03*	9,554 (0.7)	<11	*0.06*	9,554 (0.7)	<11	*-0.03*
Corticosteroids	75,693 (5.7)	117 (12.9)	*0.25*	75,693 (5.7)	72 (11.6)	*0.21*	75,693 (5.7)	37 (8.8)	*0.12*
Fluconazole	22,091 (1.7)	43 (4.8)	*0.18*	22,091 (1.7)	25 (4.0)	*0.14*	22,091 (1.7)	13 (3.1)	*0.09*
Other teratogens[4]	16,321 (1.2)	27 (3.0)	*0.12*	16,321 (1.2)	21 (3.4)	*0.14*	16,321 (1.2)	<11	*0.05*
Methadone	595 (0.0)	<11	*0.08*	595 (0.0)	<11	*0.06*	595 (0.0)	<11	*0.05*
Buprenorphine	1,068 (0.1)	<11	*0.13*	1,068 (0.1)	<11	*0.08*	1,068 (0.1)	<11	*0.07*
Naltrexone	65 (0.0)	<11	*0.06*	65 (0.0)	<11	*0.05*	65 (0.0)	<11	*0.10*
Naloxone	1,215 (0.1)	<11	*0.13*	1,215 (0.1)	<11	*0.09*	1,215 (0.1)	<11	*0.07*
Markers of burden of disease									
Obstetric Comorbidity Index[5], mean (SD)	0.9 (1.4)	1.5 (1.8)	*0.36*	0.9 (1.4)	1.4 (1.8)	*0.32*	0.9 (1.4)	1.2 (1.7)	*0.18*
Number of distinct prescriptions, mean (SD)	1.6 (2.3)	4.5 (3.7)	*0.94*	1.6 (2.3)	4.5 (3.8)	*0.94*	1.6 (2.3)	3.4 (3.6)	*0.59*
Number of diagnoses, mean (SD)	2.5 (3.1)	5.6 (4.4)	*0.81*	2.5 (3.1)	5.5 (4.7)	*0.76*	2.5 (3.1)	4.9 (4.4)	*0.63*
Number of outpatient physician visits, mean (SD)	2.8 (4.0)	7.8 (8.7)	*0.73*	2.8 (4.0)	7.8 (9.3)	*0.70*	2.8 (4.0)	6.1 (7.9)	*0.53*
Patients hospitalized, N (%)	48,294 (3.7)	57 (6.3)	*0.12*	48,294 (3.7)	31 (5.0)	*0.07*	48,294 (3.7)	27 (6.4)	*0.13*
Number of hospitalizations, mean (SD)	0.0 (0.2)	0.1 (0.3)	*0.12*	0.0 (0.2)	0.1 (0.2)	*0.05*	0.0 (0.2)	0.1 (0.3)	*0.11*
Number of days hospitalized, mean (SD)	0.1 (0.9)	0.3 (1.7)	*0.14*	0.1 (0.9)	0.2 (0.9)	*0.05*	0.1 (0.9)	0.3 (1.4)	*0.13*
Number of emergency room visits, mean (SD)	0.3 (0.8)	0.9 (2.6)	*0.30*	0.3 (0.8)	0.7 (1.4)	*0.30*	0.3 (0.8)	0.5 (1.0)	*0.23*

St. Diff.: Standardized differences, i.e., the difference in means or proportions divided by the pooled standard deviation [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine 2009;28:3083-107]

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

[2] Other race includes Asian, Native American, Other, and Unknown

[3] Pain conditions include neuropathic and non-neuropathic conditions

[4] Other teratogens include methimazole, danazol, propylthiouracil, and progestins

[5] The obstetric comorbidity index predicts severe maternal morbidity. The range for the maternal comorbidity index is 0 to 45, with lower values associated with lower burden of maternal illness and higher values associated with higher burden of maternal illness [Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957-65]

Table S9. Propensity-score-adjusted baseline characteristics of exposed and unexposed pregnant women by dose tertiles of the first lamotrigine prescription filled during the first trimester[1]

Baseline characteristics	Non-exposed (N=1,123,503)	Lamotrigine <=100 mg/day (N=904)	*St. Diff.*	Non-exposed (N=1,247,465)	Lamotrigine 101-200 mg/day (N=620)	*St. Diff.*	Non-exposed (N=1,238,899)	Lamotrigine >200 mg/day (N=421)	*St. Diff.*
Age, mean (SD)	25.1 (5.7)	25.0 (5.7)	*-0.02*	25.4 (6.0)	25.4 (5.9)	*0.00*	25.2 (5.8)	25.3 (5.8)	*0.02*
Race									
White	873,365 (77.7)	674 (74.6)	*-0.07*	1,002,596 (80.4)	487 (78.5)	*-0.05*	855,189 (69.0)	285 (67.7)	*-0.03*
Black	124,690 (11.1)	115 (12.7)	*0.05*	132,210 (10.6)	70 (11.3)	*0.02*	171,617 (13.9)	58 (13.8)	*0.00*
Hispanic	43,714 (3.9)	45 (5.0)	*0.05*	43,813 (3.5)	26 (4.2)	*0.04*	97,539 (7.9)	36 (8.6)	*0.02*
Other[2]	81,734 (7.3)	70 (7.7)	*0.02*	68,845 (5.5)	37 (6.0)	*0.02*	114,554 (9.2)	42 (10.0)	*0.02*
Year									
2000	<11	<11	*0.00*	<11	<11	*0.00*	<11	<11	*0.00*
2001	5,177 (0.5)	<11	*0.03*	4,004 (0.3)	<11	*0.00*	25,309 (2.0)	<11	*0.01*
2002	9,062 (0.8)	<11	*0.02*	4,516 (0.4)	<11	*-0.01*	28,134 (2.3)	<11	*-0.03*
2003	12,202 (1.1)	11 (1.2)	*0.01*	13,917 (1.1)	<11	*-0.01*	31,135 (2.5)	<11	*-0.02*
2004	51,748 (4.6)	43 (4.8)	*0.01*	50,689 (4.1)	25 (4.0)	*0.00*	87,689 (7.1)	29 (6.9)	*-0.01*
2005	76,509 (6.8)	64 (7.1)	*0.01*	110,337 (8.8)	57 (9.2)	*0.01*	95,123 (7.7)	33 (7.8)	*0.01*
2006	130,867 (11.6)	103 (11.4)	*-0.01*	128,679 (10.3)	63 (10.2)	*-0.01*	159,865 (12.9)	58 (13.8)	*0.03*
2007	150,363 (13.4)	121 (13.4)	*0.00*	203,883 (16.3)	102 (16.5)	*0.00*	181,150 (14.6)	63 (15.0)	*0.01*
2008	222,844 (19.8)	180 (19.9)	*0.00*	235,984 (18.9)	115 (18.6)	*-0.01*	174,960 (14.1)	58 (13.8)	*-0.01*
2009	261,726 (23.3)	206 (22.8)	*-0.01*	271,713 (21.8)	134 (21.6)	*0.00*	285,224 (23.0)	96 (22.8)	*-0.01*
2010	203,005 (18.1)	161 (17.8)	*-0.01*	223,743 (17.9)	114 (18.4)	*0.01*	170,310 (13.7)	58 (13.8)	*0.00*
Multiple gestation	52,093 (4.6)	41 (4.5)	*0.00*	43,064 (3.5)	21 (3.4)	*0.00*	62,870 (5.1)	21 (5.0)	*0.00*
Psychiatric and neurological conditions, N (%)									
Bipolar disorder	463,395 (41.3)	406 (44.9)	*0.07*	576,686 (46.2)	287 (46.3)	*0.00*	338,769 (27.3)	105 (24.9)	*-0.05*
Depression	329,301 (29.3)	239 (26.4)	*-0.06*	230,338 (18.5)	102 (16.5)	*-0.05*	185,500 (15.0)	61 (14.5)	*-0.01*
Anxiety	241,283 (21.5)	184 (20.4)	*-0.03*	214,594 (17.2)	104 (16.8)	*-0.01*	164,578 (13.3)	55 (13.1)	*-0.01*

Schizophrenia	19,815 (1.8)	17 (1.9)	*0.01*	15,207 (1.2)	<11	*-0.01*	14,264 (1.2)	<11	*0.00*
Other psychosis	15,392 (1.4)	13 (1.4)	*0.01*	7,550 (0.6)	<11	*0.01*	3,042 (0.3)	<11	*0.00*
Personality disorder	35,030 (3.1)	35 (3.9)	*0.04*	46,354 (3.7)	27 (4.4)	*0.03*	14,924 (1.2)	<11	*0.00*
Adjustment disorder	44,521 (4.0)	33 (3.7)	*-0.02*	28,839 (2.3)	13 (2.1)	*-0.01*	21,851 (1.8)	<11	*-0.01*
Attention deficit hyperactivity disorder	94,595 (8.4)	77 (8.5)	*0.00*	93,660 (7.5)	46 (7.4)	*0.00*	27,382 (2.2)	<11	*0.01*
Delirium	6,161 (0.5)	<11	*0.00*	6,899 (0.6)	<11	*-0.01*	9,886 (0.8)	<11	*-0.01*
Other psychiatric disorders	77,924 (6.9)	66 (7.3)	*0.01*	66,297 (5.3)	35 (5.6)	*0.01*	49,277 (4.0)	17 (4.0)	*0.00*
Alcohol abuse or dependence	23,462 (2.1)	21 (2.3)	*0.02*	18,586 (1.5)	<11	*0.01*	8,766 (0.7)	<11	*0.03*
Drug abuse or dependence	68,600 (6.1)	59 (6.5)	*0.02*	51,736 (4.1)	26 (4.2)	*0.00*	45,452 (3.7)	16 (3.8)	*0.01*
Chronic fatigue syndrome	78,701 (7.0)	60 (6.6)	*-0.01*	98,605 (7.9)	47 (7.6)	*-0.01*	53,258 (4.3)	17 (4.0)	*-0.01*
Sleep disorder	50,521 (4.5)	37 (4.1)	*-0.02*	60,405 (4.8)	27 (4.4)	*-0.02*	43,515 (3.5)	15 (3.6)	*0.00*
Epilepsy or convulsions	92,193 (8.2)	85 (9.4)	*0.04*	199,203 (16.0)	110 (17.7)	*0.05*	533,347 (43.1)	189 (44.9)	*0.04*
Pain conditions[3]	400,735 (35.7)	311 (34.4)	*-0.03*	445,150 (35.7)	221 (35.6)	*0.00*	337,997 (27.3)	114 (27.1)	*0.00*
Migraine or headache	177,508 (15.8)	143 (15.8)	*0.00*	185,997 (14.9)	95 (15.3)	*0.01*	200,969 (16.2)	70 (16.6)	*0.01*
Chronic maternal illness, N (%)									
Hypertension	50,112 (4.5)	38 (4.2)	*-0.01*	55,804 (4.5)	26 (4.2)	*-0.01*	44,075 (3.6)	15 (3.6)	*0.00*
Diabetes	31,592 (2.8)	24 (2.7)	*-0.01*	33,085 (2.7)	15 (2.4)	*-0.01*	20,837 (1.7)	<11	*-0.02*
Renal disease	5,888 (0.5)	<11	*0.00*	15,225 (1.2)	<11	*-0.01*	11,023 (0.9)	<11	*0.01*
Obesity or overweight	33,962 (3.0)	28 (3.1)	*0.00*	52,223 (4.2)	25 (4.0)	*-0.01*	32,097 (2.6)	<11	*-0.01*
Smoking	125,771 (11.2)	102 (11.3)	*0.00*	106,238 (8.5)	51 (8.2)	*-0.01*	79,771 (6.4)	28 (6.7)	*0.01*
Psychotropic and other medications, N (%)									
Antidepressants	735,750 (65.5)	540 (59.7)	*-0.12*	745,456 (59.8)	343 (55.3)	*-0.09*	490,228 (39.6)	156 (37.1)	*-0.05*
Antipsychotics	318,167 (28.3)	285 (31.5)	*0.07*	414,694 (33.2)	215 (34.7)	*0.03*	232,679 (18.8)	71 (16.9)	*-0.05*
Benzodiazepines	301,965 (26.9)	240 (26.6)	*-0.01*	355,822 (28.5)	176 (28.4)	*0.00*	300,485 (24.3)	100 (23.8)	*-0.01*
Other anxiolytics	48,886 (4.4)	42 (4.6)	*0.01*	58,432 (4.7)	30 (4.8)	*0.01*	31,670 (2.6)	<11	*-0.01*
Other hypnotics	217,574 (19.4)	180 (19.9)	*0.01*	233,405 (18.7)	119 (19.2)	*0.01*	141,822 (11.4)	44 (10.5)	*-0.03*
Barbiturates	31,885 (2.8)	24 (2.7)	*-0.01*	28,822 (2.3)	14 (2.3)	*0.00*	24,399 (2.0)	<11	*0.01*
Stimulants	126,366 (11.2)	111 (12.3)	*0.03*	131,622 (10.6)	70 (11.3)	*0.02*	73,415 (5.9)	28 (6.7)	*0.03*
Opioids	469,852 (41.8)	365 (40.4)	*-0.03*	498,400 (40.0)	244 (39.4)	*-0.01*	435,389 (35.1)	143 (34.0)	*-0.02*

Triptans	46,590 (4.1)	33 (3.7)	*-0.03*	44,828 (3.6)	21 (3.4)	*-0.01*	53,953 (4.4)	19 (4.5)	*0.01*
Nonsteroidal anti-inflammatory drugs	341,296 (30.4)	261 (28.9)	*-0.03*	328,928 (26.4)	157 (25.3)	*-0.02*	287,035 (23.2)	92 (21.9)	*-0.03*
Antihypertensive medications	100,764 (9.0)	82 (9.1)	*0.00*	84,823 (6.8)	42 (6.8)	*0.00*	52,002 (4.2)	17 (4.0)	*-0.01*
Non-insulin antidiabetic medications	25,597 (2.3)	19 (2.1)	*-0.01*	39,697 (3.2)	17 (2.7)	*-0.03*	15,416 (1.2)	<11	*0.02*
Insulin	12,060 (1.1)	<11	*-0.01*	16,925 (1.4)	<11	*-0.01*	8,432 (0.7)	<11	*-0.03*
Corticosteroids	151,350 (13.5)	117 (12.9)	*-0.02*	148,389 (11.9)	72 (11.6)	*-0.01*	108,641 (8.8)	37 (8.8)	*0.00*
Fluconazole	55,989 (5.0)	43 (4.8)	*-0.01*	53,359 (4.3)	25 (4.0)	*-0.01*	40,360 (3.3)	13 (3.1)	*-0.01*
Other teratogens[4]	35,500 (3.2)	27 (3.0)	*-0.01*	43,140 (3.5)	21 (3.4)	*0.00*	22,317 (1.8)	<11	*0.01*
Methadone	4,554 (0.4)	<11	*0.01*	5,020 (0.4)	<11	*-0.01*	4,516 (0.4)	<11	*-0.02*
Buprenorphine	12,305 (1.1)	<11	*0.00*	5,597 (0.5)	<11	*0.01*	3,972 (0.3)	<11	*0.02*
Naltrexone	1,768 (0.2)	<11	*0.01*	1,632 (0.1)	<11	*0.01*	3,846 (0.3)	<11	*0.03*
Naloxone	12,148 (1.1)	<11	*0.00*	6,874 (0.6)	<11	*0.01*	4,048 (0.3)	<11	*0.02*
Markers of burden of disease									
Obstetric Comorbidity Index[5], mean (SD)	1.5 (1.8)	1.5 (1.8)	*0.00*	1.4 (1.8)	1.4 (1.8)	*0.00*	1.1 (1.6)	1.2 (1.7)	*0.01*
Number of distinct prescriptions, mean (SD)	4.7 (3.6)	4.5 (3.7)	*-0.05*	4.7 (3.6)	4.5 (3.7)	*-0.04*	3.4 (3.4)	3.4 (3.6)	*-0.01*
Number of diagnoses, mean (SD)	5.9 (4.5)	5.6 (4.4)	*-0.06*	5.7 (4.4)	5.5 (4.6)	*-0.03*	5.0 (4.3)	4.9 (4.4)	*-0.02*
Number of outpatient physician visits, mean (SD)	7.4 (7.5)	7.8 (8.7)	*0.04*	7.2 (7.4)	7.8 (9.3)	*0.06*	6.0 (6.6)	6.1 (7.9)	*0.02*
Patients hospitalized, N (%)	67,655 (6.0)	57 (6.3)	*0.01*	62,895 (5.0)	31 (5.0)	*0.00*	79,394 (6.4)	27 (6.4)	*0.00*
Number of hospitalizations, mean (SD)	0.1 (0.3)	0.1 (0.3)	*0.01*	0.1 (0.3)	0.1 (0.2)	*0.00*	0.1 (0.3)	0.1 (0.3)	*0.00*
Number of days hospitalized, mean (SD)	0.3 (1.7)	0.3 (1.7)	*0.02*	0.2 (1.1)	0.2 (0.9)	*-0.01*	0.3 (1.6)	0.3 (1.4)	*0.00*
Number of emergency room visits, mean (SD)	0.8 (1.5)	0.9 (2.6)	*0.05*	0.6 (1.4)	0.7 (1.4)	*0.01*	0.5 (1.2)	0.5 (1.0)	*-0.03*

St. Diff.: Standardized differences, i.e., the difference in means or proportions divided by the pooled standard deviation [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine 2009;28:3083-107]

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

[2] Other race includes Asian, Native American, Other, and Unknown

[3] Pain conditions include neuropathic and non-neuropathic conditions

[4] Other teratogens include methimazole, danazol, propylthiouracil, and progestins

[5] The obstetric comorbidity index predicts severe maternal morbidity. The range for the maternal comorbidity index is 0 to 45, with lower values associated with lower burden of maternal illness and higher values associated with higher burden of maternal illness [Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957-65]

Table S10. Unadjusted baseline characteristics of exposed and unexposed pregnant women by dose tertiles of the highest lithium prescription filled during the first trimester[1]

Baseline characteristics	Non-exposed (N=1,322,955)	Lithium <=600 mg/day (N=280)	*St. Diff.*	Non-exposed (N=1,322,955)	Lithium 601-900 mg/day (N=242)	*St. Diff.*	Non-exposed (N=1,322,955)	Lithium >900 mg/day (N=141)	*St. Diff.*
Age, mean (SD)	24.0 (5.8)	25.0 (5.8)	*0.18*	24.0 (5.8)	25.9 (6.3)	*0.31*	24.0 (5.8)	26.4 (6.4)	*0.40*
Race									
White	526,603 (39.8)	220 (78.6)	*0.86*	526,603 (39.8)	171 (70.7)	*0.65*	526,603 (39.8)	99 (70.2)	*0.64*
Black	445,675 (33.7)	34 (12.1)	*-0.53*	445,675 (33.7)	38 (15.7)	*-0.43*	445,675 (33.7)	17 (12.1)	*-0.53*
Hispanic	195,174 (14.8)	<11	*-0.41*	195,174 (14.8)	15 (6.2)	*-0.28*	195,174 (14.8)	12 (8.5)	*-0.20*
Other[2]	155,503 (11.8)	17 (6.1)	*-0.20*	155,503 (11.8)	18 (7.4)	*-0.15*	155,503 (11.8)	13 (9.2)	*-0.08*
Year									
2000	1,569 (0.1)	<11	*-0.05*	1,569 (0.1)	<11	*0.06*	1,569 (0.1)	<11	*-0.05*
2001	81,024 (6.1)	14 (5.0)	*-0.05*	81,024 (6.1)	12 (5.0)	*-0.05*	81,024 (6.1)	<11	*-0.02*
2002	92,771 (7.0)	19 (6.8)	*-0.01*	92,771 (7.0)	11 (4.6)	*-0.11*	92,771 (7.0)	11 (7.8)	*0.03*
2003	126,822 (9.6)	26 (9.3)	*-0.01*	126,822 (9.6)	23 (9.5)	*0.00*	126,822 (9.6)	18 (12.8)	*0.10*
2004	153,523 (11.6)	36 (12.9)	*0.04*	153,523 (11.6)	30 (12.4)	*0.02*	153,523 (11.6)	17 (12.1)	*0.01*
2005	154,733 (11.7)	32 (11.4)	*-0.01*	154,733 (11.7)	29 (12.0)	*0.01*	154,733 (11.7)	<11	*-0.21*
2006	154,415 (11.7)	30 (10.7)	*-0.03*	154,415 (11.7)	23 (9.5)	*-0.07*	154,415 (11.7)	19 (13.5)	*0.05*
2007	146,133 (11.0)	30 (10.7)	*-0.01*	146,133 (11.0)	26 (10.7)	*-0.01*	146,133 (11.0)	17 (12.1)	*0.03*
2008	143,246 (10.8)	28 (10.0)	*-0.03*	143,246 (10.8)	35 (14.5)	*0.11*	143,246 (10.8)	14 (9.9)	*-0.03*
2009	149,472 (11.3)	41 (14.6)	*0.10*	149,472 (11.3)	29 (12.0)	*0.02*	149,472 (11.3)	16 (11.4)	*0.00*
2010	119,247 (9.0)	24 (8.6)	*-0.02*	119,247 (9.0)	23 (9.5)	*0.02*	119,247 (9.0)	13 (9.2)	*0.01*
Multiple gestation	44,792 (3.4)	<11	*-0.08*	44,792 (3.4)	<11	*-0.11*	44,792 (3.4)	<11	*0.08*
Psychiatric and neurological conditions, N (%)									
Bipolar disorder	9,485 (0.7)	169 (60.4)	*1.70*	9,485 (0.7)	164 (67.8)	*1.99*	9,485 (0.7)	103 (73.1)	*2.26*
Depression	63,110 (4.8)	78 (27.9)	*0.66*	63,110 (4.8)	58 (24.0)	*0.57*	63,110 (4.8)	31 (22.0)	*0.52*
Anxiety	41,759 (3.2)	51 (18.2)	*0.50*	41,759 (3.2)	47 (19.4)	*0.53*	41,759 (3.2)	19 (13.5)	*0.38*

Schizophrenia	1,639 (0.1)	<11	*0.24*	1,639 (0.1)	15 (6.2)	*0.35*	1,639 (0.1)	<11	*0.36*
Other psychosis	2,138 (0.2)	<11	*0.22*	2,138 (0.2)	<11	*0.24*	2,138 (0.2)	<11	*0.35*
Personality disorder	2,160 (0.2)	16 (5.7)	*0.33*	2,160 (0.2)	<11	*0.24*	2,160 (0.2)	12 (8.5)	*0.42*
Adjustment disorder	13,135 (1.0)	12 (4.3)	*0.21*	13,135 (1.0)	<11	*0.14*	13,135 (1.0)	<11	*0.04*
Attention deficit hyperactivity disorder	10,118 (0.8)	24 (8.6)	*0.38*	10,118 (0.8)	19 (7.9)	*0.35*	10,118 (0.8)	<11	*0.19*
Delirium	698 (0.1)	<11	*-0.03*	698 (0.1)	<11	*0.07*	698 (0.1)	<11	*0.20*
Other psychiatric disorders	15,150 (1.1)	21 (7.5)	*0.32*	15,150 (1.1)	21 (8.7)	*0.35*	15,150 (1.1)	<11	*0.28*
Alcohol abuse or dependence	6,754 (0.5)	<11	*0.22*	6,754 (0.5)	15 (6.2)	*0.32*	6,754 (0.5)	<11	*0.27*
Drug abuse or dependence	16,378 (1.2)	23 (8.2)	*0.33*	16,378 (1.2)	33 (13.6)	*0.49*	16,378 (1.2)	20 (14.2)	*0.50*
Chronic fatigue syndrome	36,215 (2.7)	18 (6.4)	*0.18*	36,215 (2.7)	12 (5.0)	*0.12*	36,215 (2.7)	<11	*0.15*
Sleep disorder	7,945 (0.6)	11 (3.9)	*0.22*	7,945 (0.6)	<11	*0.23*	7,945 (0.6)	<11	*0.17*
Epilepsy or convulsions	3,894 (0.3)	<11	*0.15*	3,894 (0.3)	<11	*0.16*	3,894 (0.3)	<11	*0.17*
Pain conditions[3]	183,219 (13.8)	80 (28.6)	*0.37*	183,219 (13.8)	62 (25.6)	*0.30*	183,219 (13.8)	42 (29.8)	*0.39*
Migraine or headache	88,074 (6.7)	37 (13.2)	*0.22*	88,074 (6.7)	37 (15.3)	*0.28*	88,074 (6.7)	25 (17.7)	*0.34*
Chronic maternal illness, N (%)									
Hypertension	24,529 (1.9)	<11	*0.04*	24,529 (1.9)	<11	*0.04*	24,529 (1.9)	<11	*0.23*
Diabetes	23,287 (1.8)	<11	*0.11*	23,287 (1.8)	<11	*-0.19*	23,287 (1.8)	<11	*0.21*
Renal disease	3,795 (0.3)	<11	*0.01*	3,795 (0.3)	<11	*0.14*	3,795 (0.3)	<11	*-0.08*
Obesity or overweight	22,123 (1.7)	<11	*0.08*	22,123 (1.7)	<11	*0.06*	22,123 (1.7)	<11	*0.12*
Smoking	38,975 (2.9)	20 (7.1)	*0.19*	38,975 (2.9)	22 (9.1)	*0.26*	38,975 (2.9)	<11	*0.16*
Psychotropic and other medications, N (%)									
Antidepressants	106,412 (8.0)	172 (61.4)	*1.35*	106,412 (8.0)	170 (70.3)	*1.65*	106,412 (8.0)	89 (63.1)	*1.40*
Antipsychotics	12,366 (0.9)	113 (40.4)	*1.11*	12,366 (0.9)	112 (46.3)	*1.26*	12,366 (0.9)	83 (58.9)	*1.63*
Benzodiazepines	34,932 (2.6)	82 (29.3)	*0.78*	34,932 (2.6)	77 (31.8)	*0.84*	34,932 (2.6)	48 (34.0)	*0.88*
Other anxiolytics	4,288 (0.3)	13 (4.6)	*0.28*	4,288 (0.3)	13 (5.4)	*0.31*	4,288 (0.3)	<11	*0.23*
Other hypnotics	43,150 (3.3)	49 (17.5)	*0.48*	43,150 (3.3)	43 (17.8)	*0.49*	43,150 (3.3)	22 (15.6)	*0.43*
Barbiturates	12,269 (0.9)	11 (3.9)	*0.20*	12,269 (0.9)	<11	*0.09*	12,269 (0.9)	<11	*0.21*
Stimulants	7,842 (0.6)	24 (8.6)	*0.39*	7,842 (0.6)	16 (6.6)	*0.33*	7,842 (0.6)	14 (9.9)	*0.43*
Opioids	249,821 (18.9)	107 (38.2)	*0.44*	249,821 (18.9)	82 (33.9)	*0.34*	249,821 (18.9)	64 (45.4)	*0.59*
Triptans	12,174 (0.9)	12 (4.3)	*0.21*	12,174 (0.9)	<11	*0.09*	12,174 (0.9)	<11	*0.10*

Nonsteroidal anti-inflammatory drugs	211,001 (15.9)	76 (27.1)	*0.27*	211,001 (15.9)	62 (25.6)	*0.24*	211,001 (15.9)	28 (19.9)	*0.10*
Antihypertensive medications	27,316 (2.1)	18 (6.4)	*0.22*	27,316 (2.1)	17 (7.0)	*0.24*	27,316 (2.1)	13 (9.2)	*0.31*
Non-insulin antidiabetic medications	8,681 (0.7)	<11	*0.08*	8,681 (0.7)	<11	*-0.03*	8,681 (0.7)	<11	*0.20*
Insulin	9,554 (0.7)	<11	*0.04*	9,554 (0.7)	<11	*-0.12*	9,554 (0.7)	<11	*0.16*
Corticosteroids	75,693 (5.7)	29 (10.4)	*0.17*	75,693 (5.7)	25 (10.3)	*0.17*	75,693 (5.7)	19 (13.5)	*0.26*
Fluconazole	22,091 (1.7)	15 (5.4)	*0.20*	22,091 (1.7)	<11	*0.11*	22,091 (1.7)	<11	*0.03*
Other teratogens[4]	16,321 (1.2)	<11	*0.05*	16,321 (1.2)	<11	*0.04*	16,321 (1.2)	<11	*0.02*
Methadone	595 (0.0)	<11	*0.07*	595 (0.0)	<11	*0.08*	595 (0.0)	<11	*-0.03*
Buprenorphine	1,068 (0.1)	<11	*0.18*	1,068 (0.1)	<11	*0.07*	1,068 (0.1)	<11	*-0.04*
Naltrexone	65 (0.0)	<11	*-0.01*	65 (0.0)	<11	*0.09*	65 (0.0)	<11	*-0.01*
Naloxone	1,215 (0.1)	<11	*0.21*	1,215 (0.1)	<11	*0.06*	1,215 (0.1)	<11	*-0.04*
Markers of burden of disease									
Obstetric Comorbidity Index[5], mean (SD)	0.9 (1.4)	1.3 (1.6)	*0.30*	0.9 (1.4)	1.7 (1.9)	*0.46*	0.9 (1.4)	2.0 (1.9)	*0.66*
Number of distinct prescriptions, mean (SD)	1.6 (2.3)	4.5 (4.0)	*0.89*	1.6 (2.3)	4.4 (3.7)	*0.90*	1.6 (2.3)	4.6 (3.2)	*1.06*
Number of diagnoses, mean (SD)	2.5 (3.1)	5.6 (4.7)	*0.76*	2.5 (3.1)	5.2 (4.6)	*0.69*	2.5 (3.1)	5.2 (4.1)	*0.73*
Number of outpatient physician visits, mean (SD)	2.8 (4.0)	7.6 (7.5)	*0.81*	2.8 (4.0)	8.3 (10.7)	*0.68*	2.8 (4.0)	10.4 (11.9)	*0.86*
Patients hospitalized, N (%)	48,294 (3.7)	25 (8.9)	*0.22*	48,294 (3.7)	21 (8.7)	*0.21*	48,294 (3.7)	14 (9.9)	*0.25*
Number of hospitalizations, mean (SD)	0.0 (0.2)	0.1 (0.6)	*0.21*	0.0 (0.2)	0.1 (0.4)	*0.20*	0.0 (0.2)	0.1 (0.4)	*0.24*
Number of days hospitalized, mean (SD)	0.1 (0.9)	0.7 (3.7)	*0.20*	0.1 (0.9)	0.5 (2.0)	*0.24*	0.1 (0.9)	0.8 (3.0)	*0.28*
Number of emergency room visits, mean (SD)	0.3 (0.8)	1.0 (4.2)	*0.22*	0.3 (0.8)	0.7 (1.4)	*0.32*	0.3 (0.8)	0.7 (1.3)	*0.34*

St. Diff.: Standardized differences, i.e., the difference in means or proportions divided by the pooled standard deviation [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine 2009;28:3083-107]

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

[2] Other race includes Asian, Native American, Other, and Unknown

[3] Pain conditions include neuropathic and non-neuropathic conditions

[4] Other teratogens include methimazole, danazol, propylthiouracil, and progestins

[5] The obstetric comorbidity index predicts severe maternal morbidity. The range for the maternal comorbidity index is 0 to 45, with lower values associated with lower burden of maternal illness and higher values associated with higher burden of maternal illness [Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957-65]

Table S11. Propensity-score-adjusted baseline characteristics of exposed and unexposed pregnant women by dose tertiles of the highest lithium prescription filled during the first trimester[1]

Baseline characteristics	Non-exposed (N=860,385)	Lithium <=600 mg/day (N=280)	*St. Diff.*	Non-exposed (N=907,181)	Lithium 601-900 mg/day (N=242)	*St. Diff.*	Non-exposed (N=616,329)	Lithium >900 mg/day (N=140)	*St. Diff.*
Age, mean (SD)	25.0 (6.0)	25.0 (5.8)	*0.01*	25.9 (6.3)	25.9 (6.3)	*0.00*	26.3 (6.5)	26.3 (6.4)	*0.01*
Race									
White	700,745 (81.4)	220 (78.6)	*-0.07*	659,837 (72.7)	171 (70.7)	*-0.05*	440,150 (71.4)	98 (70.0)	*-0.03*
Black	87,838 (10.2)	34 (12.1)	*0.06*	132,388 (14.6)	38 (15.7)	*0.03*	72,583 (11.8)	17 (12.1)	*0.01*
Hispanic	20,940 (2.4)	<11	*0.05*	49,466 (5.5)	15 (6.2)	*0.03*	46,724 (7.6)	12 (8.6)	*0.04*
Other[2]	50,862 (5.9)	17 (6.1)	*0.01*	65,490 (7.2)	18 (7.4)	*0.01*	56,873 (9.2)	13 (9.3)	*0.00*
Year									
2000	<11	<11	*0.00*	6,639 (0.7)	<11	*-0.04*	<11	<11	*0.00*
2001	46,700 (5.4)	14 (5.0)	*-0.02*	49,123 (5.4)	12 (5.0)	*-0.02*	37,608 (6.1)	<11	*-0.02*
2002	53,372 (6.2)	19 (6.8)	*0.02*	37,679 (4.2)	11 (4.5)	*0.02*	39,120 (6.3)	11 (7.9)	*0.06*
2003	82,155 (9.6)	26 (9.3)	*-0.01*	87,347 (9.6)	23 (9.5)	*0.00*	76,231 (12.4)	18 (12.9)	*0.01*
2004	109,209 (12.7)	36 (12.9)	*0.00*	108,841 (12.0)	30 (12.4)	*0.01*	68,935 (11.2)	17 (12.1)	*0.03*
2005	97,545 (11.3)	32 (11.4)	*0.00*	105,992 (11.7)	29 (12.0)	*0.01*	37,028 (6.0)	<11	*-0.01*
2006	93,682 (10.9)	30 (10.7)	*-0.01*	84,442 (9.3)	23 (9.5)	*0.01*	84,145 (13.7)	19 (13.6)	*0.00*
2007	90,263 (10.5)	30 (10.7)	*0.01*	97,119 (10.7)	26 (10.7)	*0.00*	79,528 (12.9)	16 (11.4)	*-0.05*
2008	87,581 (10.2)	28 (10.0)	*-0.01*	127,053 (14.0)	35 (14.5)	*0.01*	61,750 (10.0)	14 (10.0)	*0.00*
2009	125,152 (14.5)	41 (14.6)	*0.00*	113,938 (12.6)	29 (12.0)	*-0.02*	71,046 (11.5)	16 (11.4)	*0.00*
2010	74,727 (8.7)	24 (8.6)	*0.00*	89,009 (9.8)	23 (9.5)	*-0.01*	60,937 (9.9)	13 (9.3)	*-0.02*
Multiple gestation	19,999 (2.3)	<11	*-0.01*	16,341 (1.8)	<11	*-0.01*	29,173 (4.7)	<11	*0.01*
Psychiatric and neurological conditions, N (%)									
Bipolar disorder	512,967 (59.6)	169 (60.4)	*0.02*	612,227 (67.5)	164 (67.8)	*0.01*	467,050 (75.8)	102 (72.9)	*-0.07*
Depression	255,626 (29.7)	78 (27.9)	*-0.04*	235,624 (26.0)	58 (24.0)	*-0.05*	148,815 (24.1)	31 (22.1)	*-0.05*
Anxiety	165,970 (19.3)	51 (18.2)	*-0.03*	182,582 (20.1)	47 (19.4)	*-0.02*	101,627 (16.5)	19 (13.6)	*-0.08*
Schizophrenia	23,591 (2.7)	<11	*0.03*	45,181 (5.0)	15 (6.2)	*0.05*	36,134 (5.9)	<11	*0.02*

Other psychosis	20,984 (2.4)	<11	*0.03*	29,143 (3.2)	<11	*0.01*	35,671 (5.8)	<11	*0.03*
Personality disorder	39,973 (4.7)	16 (5.7)	*0.05*	29,687 (3.3)	<11	*0.00*	44,059 (7.1)	11 (7.9)	*0.03*
Adjustment disorder	40,803 (4.7)	12 (4.3)	*-0.02*	30,966 (3.4)	<11	*-0.03*	10,266 (1.7)	<11	*-0.02*
Attention deficit hyperactivity disorder	72,294 (8.4)	24 (8.6)	*0.01*	73,076 (8.1)	19 (7.9)	*-0.01*	26,400 (4.3)	<11	*-0.04*
Delirium	<11	<11	*0.00*	4,212 (0.5)	<11	*-0.01*	9,527 (1.5)	<11	*0.04*
Other psychiatric disorders	60,955 (7.1)	21 (7.5)	*0.02*	78,781 (8.7)	21 (8.7)	*0.00*	34,767 (5.6)	<11	*0.03*
Alcohol abuse or dependence	31,171 (3.6)	<11	*0.00*	47,886 (5.3)	15 (6.2)	*0.04*	29,110 (4.7)	<11	*0.01*
Drug abuse or dependence	67,652 (7.9)	23 (8.2)	*0.01*	115,760 (12.8)	33 (13.6)	*0.03*	83,152 (13.5)	19 (13.6)	*0.00*
Chronic fatigue syndrome	58,278 (6.8)	18 (6.4)	*-0.01*	46,364 (5.1)	12 (5.0)	*-0.01*	37,363 (6.1)	<11	*-0.01*
Sleep disorder	35,790 (4.2)	11 (3.9)	*-0.01*	39,633 (4.4)	<11	*-0.01*	19,585 (3.2)	<11	*-0.02*
Epilepsy or convulsions	13,739 (1.6)	<11	*0.01*	17,275 (1.9)	<11	*0.01*	12,276 (2.0)	<11	*0.01*
Pain conditions[3]	254,102 (29.5)	80 (28.6)	*-0.02*	250,687 (27.6)	62 (25.6)	*-0.05*	190,363 (30.9)	42 (30.0)	*-0.02*
Migraine or headache	114,372 (13.3)	37 (13.2)	*0.00*	146,144 (16.1)	37 (15.3)	*-0.02*	110,165 (17.9)	25 (17.9)	*0.00*
Chronic maternal illness, N (%)									
Hypertension	20,873 (2.4)	<11	*0.00*	23,240 (2.6)	<11	*-0.01*	42,323 (6.9)	<11	*-0.02*
Diabetes	34,127 (4.0)	<11	*-0.02*	58 (0.0)	<11	*-0.01*	36,764 (6.0)	<11	*-0.01*
Renal disease	2,677 (0.3)	<11	*0.01*	13,741 (1.5)	<11	*0.01*	30 (0.0)	<11	*-0.01*
Obesity or overweight	26,410 (3.1)	<11	*-0.01*	24,625 (2.7)	<11	*-0.01*	20,395 (3.3)	<11	*0.01*
Smoking	65,643 (7.6)	20 (7.1)	*-0.02*	85,593 (9.4)	22 (9.1)	*-0.01*	44,231 (7.2)	<11	*-0.03*
Psychotropic and other medications, N (%)									
Antidepressants	564,152 (65.6)	172 (61.4)	*-0.09*	661,054 (72.9)	170 (70.2)	*-0.06*	392,382 (63.7)	88 (62.9)	*-0.02*
Antipsychotics	308,623 (35.9)	113 (40.4)	*0.09*	383,427 (42.3)	112 (46.3)	*0.08*	343,806 (55.8)	82 (58.6)	*0.06*
Benzodiazepines	240,622 (28.0)	82 (29.3)	*0.03*	287,415 (31.7)	77 (31.8)	*0.00*	200,264 (32.5)	47 (33.6)	*0.02*
Other anxiolytics	36,444 (4.2)	13 (4.6)	*0.02*	45,958 (5.1)	13 (5.4)	*0.01*	21,966 (3.6)	5 (3.6)	*0.00*
Other hypnotics	143,527 (16.7)	49 (17.5)	*0.02*	157,416 (17.4)	43 (17.8)	*0.01*	96,264 (15.6)	21 (15.0)	*-0.02*
Barbiturates	30,628 (3.6)	11 (3.9)	*0.02*	19,715 (2.2)	<11	*-0.01*	23,359 (3.8)	<11	*0.03*
Stimulants	70,300 (8.2)	24 (8.6)	*0.01*	62,525 (6.9)	16 (6.6)	*-0.01*	57,552 (9.3)	14 (10.0)	*0.02*
Opioids	339,580 (39.5)	107 (38.2)	*-0.03*	318,335 (35.1)	82 (33.9)	*-0.03*	283,665 (46.0)	64 (45.7)	*-0.01*
Triptans	38,367 (4.5)	12 (4.3)	*-0.01*	22,895 (2.5)	<11	*-0.03*	15,683 (2.5)	<11	*-0.03*
Nonsteroidal anti-inflammatory drugs	240,623 (28.0)	76 (27.1)	*-0.02*	242,242 (26.7)	62 (25.6)	*-0.02*	131,951 (21.4)	28 (20.0)	*-0.03*

Antihypertensive medications	51,003 (5.9)	18 (6.4)	*0.02*	65,742 (7.2)	17 (7.0)	*-0.01*	56,378 (9.2)	13 (9.3)	*0.00*
Non-insulin antidiabetic medications	12,573 (1.5)	<11	*0.00*	3,963 (0.4)	<11	*0.00*	20,090 (3.3)	<11	*0.02*
Insulin	10,755 (1.3)	<11	*-0.02*	38 (0.0)	<11	*-0.01*	18,023 (2.9)	<11	*0.00*
Corticosteroids	92,603 (10.8)	29 (10.4)	*-0.01*	98,663 (10.9)	25 (10.3)	*-0.02*	79,673 (12.9)	19 (13.6)	*0.02*
Fluconazole	48,609 (5.6)	15 (5.4)	*-0.01*	30,198 (3.3)	<11	*0.00*	13,635 (2.2)	<11	*0.00*
Other teratogens[4]	15,264 (1.8)	<11	*0.00*	15,031 (1.7)	<11	*0.00*	10,721 (1.7)	<11	*-0.02*
Methadone	3,272 (0.4)	<11	*0.00*	2,992 (0.3)	<11	*0.01*	<11	<11	*0.00*
Buprenorphine	10,818 (1.3)	<11	*0.04*	3,964 (0.4)	<11	*0.00*	26 (0.0)	<11	*-0.01*
Naltrexone	<11	<11	*0.00*	3,181 (0.4)	<11	*0.01*	<11	<11	*0.00*
Naloxone	14,476 (1.7)	<11	*0.06*	3,851 (0.4)	<11	*0.00*	29 (0.0)	<11	*-0.01*
Markers of burden of disease									
Obstetric Comorbidity Index[5], mean (SD)	1.3 (1.6)	1.3 (1.6)	*0.00*	1.6 (1.7)	1.7 (1.9)	*0.04*	2.0 (1.9)	2.0 (1.9)	*0.00*
Number of distinct prescriptions, mean (SD)	4.5 (3.6)	4.5 (4.0)	*0.00*	4.5 (3.6)	4.4 (3.7)	*-0.04*	4.8 (3.6)	4.6 (3.2)	*-0.08*
Number of diagnoses, mean (SD)	5.7 (4.5)	5.6 (4.7)	*-0.03*	5.4 (4.6)	5.2 (4.5)	*-0.05*	5.6 (4.5)	5.2 (4.1)	*-0.09*
Number of outpatient physician visits, mean (SD)	7.6 (7.6)	7.6 (7.5)	*0.01*	7.8 (8.8)	8.3 (10.7)	*0.05*	8.8 (8.8)	10.1 (11.4)	*0.13*[6]
Patients hospitalized, N (%)	73,059 (8.5)	25 (8.9)	*0.02*	76,374 (8.4)	21 (8.7)	*0.01*	59,934 (9.7)	14 (10.0)	*0.01*
Number of hospitalizations, mean (SD)	0.1 (0.4)	0.1 (0.6)	*0.05*	0.1 (0.4)	0.1 (0.4)	*0.01*	0.1 (0.4)	0.1 (0.4)	*0.03*
Number of days hospitalized, mean (SD)	0.4 (2.0)	0.7 (3.7)	*0.08*	0.5 (2.2)	0.5 (2.0)	*0.02*	0.5 (2.0)	0.8 (3.0)	*0.11*[7]
Number of emergency room visits, mean (SD)	0.8 (1.5)	1.0 (4.2)	*0.07*	0.7 (1.6)	0.7 (1.4)	*-0.02*	0.7 (1.8)	0.7 (1.3)	*-0.04*

St. Diff.: Standardized differences, i.e., the difference in means or proportions divided by the pooled standard deviation [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine 2009;28:3083-107]

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

[2] Other race includes Asian, Native American, Other, and Unknown

[3] Pain conditions include neuropathic and non-neuropathic conditions

[4] Other teratogens include methimazole, danazol, propylthiouracil, and progestins

[5] The obstetric comorbidity index predicts severe maternal morbidity. The range for the maternal comorbidity index is 0 to 45, with lower values associated with lower burden of maternal illness and higher values associated with higher burden of maternal illness [Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957-65]

[6] The covariate "number of outpatient physician visits" was included in the propensity score model as a categorical covariate (quartiles). Quartiles of number of physician visits were balanced with standardized differences <0.1

[7] The covariate "number of days hospitalized" was included in the propensity score model as a categorical covariate (quartiles). Quartiles of number of physician visits were balanced with standardized differences <0.1

Table S12. Unadjusted baseline characteristics of exposed and unexposed pregnant women by dose tertiles of the highest lamotrigine prescription filled during the first trimester[1]

Baseline characteristics	Non-exposed (N=1,322,955)	Lamotrigine <=100 mg/day (N=795)	*St. Diff.*	Non-exposed (N=1,322,955)	Lamotrigine 101-200 mg/day (N=673)	*St. Diff.*	Non-exposed (N=1,322,955)	Lamotrigine >200 mg/day (N=477)	*St. Diff.*
Age, mean (SD)	24.0 (5.8)	24.8 (5.7)	*0.15*	24.0 (5.8)	25.4 (5.9)	*0.25*	24.0 (5.8)	25.4 (5.7)	*0.24*
Race									
White	526,603 (39.8)	580 (73.0)	*0.71*	526,603 (39.8)	534 (79.4)	*0.88*	526,603 (39.8)	332 (69.6)	*0.63*
Black	445,675 (33.7)	107 (13.5)	*-0.49*	445,675 (33.7)	73 (10.8)	*-0.57*	445,675 (33.7)	63 (13.2)	*-0.50*
Hispanic	195,174 (14.8)	41 (5.2)	*-0.32*	195,174 (14.8)	29 (4.3)	*-0.36*	195,174 (14.8)	37 (7.8)	*-0.22*
Other[2]	155,503 (11.8)	67 (8.4)	*-0.11*	155,503 (11.8)	37 (5.5)	*-0.22*	155,503 (11.8)	45 (9.4)	*-0.08*
Year									
2000	1,569 (0.1)	<11	*-0.05*	1,569 (0.1)	<11	*-0.05*	1,569 (0.1)	<11	*-0.05*
2001	81,024 (6.1)	<11	*-0.30*	81,024 (6.1)	<11	*-0.34*	81,024 (6.1)	<11	*-0.22*
2002	92,771 (7.0)	<11	*-0.30*	92,771 (7.0)	<11	*-0.36*	92,771 (7.0)	<11	*-0.26*
2003	126,822 (9.6)	11 (1.4)	*-0.37*	126,822 (9.6)	<11	*-0.41*	126,822 (9.6)	<11	*-0.32*
2004	153,523 (11.6)	38 (4.8)	*-0.25*	153,523 (11.6)	24 (3.6)	*-0.31*	153,523 (11.6)	35 (7.3)	*-0.15*
2005	154,733 (11.7)	57 (7.2)	*-0.16*	154,733 (11.7)	62 (9.2)	*-0.08*	154,733 (11.7)	35 (7.3)	*-0.15*
2006	154,415 (11.7)	94 (11.8)	*0.00*	154,415 (11.7)	67 (10.0)	*-0.06*	154,415 (11.7)	63 (13.2)	*0.05*
2007	146,133 (11.0)	98 (12.3)	*0.04*	146,133 (11.0)	115 (17.1)	*0.17*	146,133 (11.0)	73 (15.3)	*0.13*
2008	143,246 (10.8)	155 (19.5)	*0.24*	143,246 (10.8)	128 (19.0)	*0.23*	143,246 (10.8)	70 (14.7)	*0.12*
2009	149,472 (11.3)	180 (22.6)	*0.31*	149,472 (11.3)	151 (22.4)	*0.30*	149,472 (11.3)	105 (22.0)	*0.29*
2010	119,247 (9.0)	147 (18.5)	*0.28*	119,247 (9.0)	117 (17.4)	*0.25*	119,247 (9.0)	69 (14.5)	*0.17*
Multiple gestation	44,792 (3.4)	31 (3.9)	*0.03*	44,792 (3.4)	29 (4.3)	*0.05*	44,792 (3.4)	23 (4.8)	*0.07*
Psychiatric and neurological conditions, N (%)									
Bipolar disorder	9,485 (0.7)	352 (44.3)	*1.22*	9,485 (0.7)	316 (47.0)	*1.29*	9,485 (0.7)	130 (27.3)	*0.83*
Depression	63,110 (4.8)	208 (26.2)	*0.62*	63,110 (4.8)	122 (18.1)	*0.43*	63,110 (4.8)	72 (15.1)	*0.35*
Anxiety	41,759 (3.2)	160 (20.1)	*0.55*	41,759 (3.2)	118 (17.5)	*0.49*	41,759 (3.2)	65 (13.6)	*0.38*

Schizophrenia	1,639 (0.1)	14 (1.8)	*0.17*	1,639 (0.1)	<11	*0.15*	1,639 (0.1)	<11	*0.12*
Other psychosis	2,138 (0.2)	11 (1.4)	*0.14*	2,138 (0.2)	<11	*0.10*	2,138 (0.2)	<11	*0.01*
Personality disorder	2,160 (0.2)	32 (4.0)	*0.27*	2,160 (0.2)	28 (4.2)	*0.28*	2,160 (0.2)	<11	*0.15*
Adjustment disorder	13,135 (1.0)	30 (3.8)	*0.18*	13,135 (1.0)	15 (2.2)	*0.10*	13,135 (1.0)	<11	*0.06*
Attention deficit hyperactivity disorder	10,118 (0.8)	71 (8.9)	*0.39*	10,118 (0.8)	48 (7.1)	*0.33*	10,118 (0.8)	14 (2.9)	*0.16*
Delirium	698 (0.1)	<11	*0.09*	698 (0.1)	<11	*0.10*	698 (0.1)	<11	*0.10*
Other psychiatric disorders	15,150 (1.1)	58 (7.3)	*0.31*	15,150 (1.1)	37 (5.5)	*0.24*	15,150 (1.1)	23 (4.8)	*0.22*
Alcohol abuse or dependence	6,754 (0.5)	19 (2.4)	*0.16*	6,754 (0.5)	11 (1.6)	*0.11*	6,754 (0.5)	<11	*0.06*
Drug abuse or dependence	16,378 (1.2)	55 (6.9)	*0.29*	16,378 (1.2)	26 (3.9)	*0.17*	16,378 (1.2)	20 (4.2)	*0.18*
Chronic fatigue syndrome	36,215 (2.7)	52 (6.5)	*0.18*	36,215 (2.7)	52 (7.7)	*0.23*	36,215 (2.7)	20 (4.2)	*0.08*
Sleep disorder	7,945 (0.6)	33 (4.2)	*0.23*	7,945 (0.6)	28 (4.2)	*0.23*	7,945 (0.6)	18 (3.8)	*0.22*
Epilepsy or convulsions	3,894 (0.3)	73 (9.2)	*0.43*	3,894 (0.3)	106 (15.8)	*0.59*	3,894 (0.3)	205 (43.0)	*1.21*
Pain conditions[3]	183,219 (13.8)	281 (35.3)	*0.52*	183,219 (13.8)	232 (34.5)	*0.50*	183,219 (13.8)	133 (27.9)	*0.35*
Migraine or headache	88,074 (6.7)	123 (15.5)	*0.28*	88,074 (6.7)	106 (15.8)	*0.29*	88,074 (6.7)	79 (16.6)	*0.31*
Chronic maternal illness, N (%)									
Hypertension	24,529 (1.9)	36 (4.5)	*0.15*	24,529 (1.9)	25 (3.7)	*0.11*	24,529 (1.9)	18 (3.8)	*0.12*
Diabetes	23,287 (1.8)	24 (3.0)	*0.08*	23,287 (1.8)	13 (1.9)	*0.01*	23,287 (1.8)	<11	*-0.01*
Renal disease	3,795 (0.3)	<11	*0.03*	3,795 (0.3)	<11	*0.08*	3,795 (0.3)	<11	*0.11*
Obesity or overweight	22,123 (1.7)	27 (3.4)	*0.11*	22,123 (1.7)	22 (3.3)	*0.10*	22,123 (1.7)	14 (2.9)	*0.08*
Smoking	38,975 (2.9)	94 (11.8)	*0.34*	38,975 (2.9)	56 (8.3)	*0.23*	38,975 (2.9)	31 (6.5)	*0.17*
Psychotropic and other medications, N (%)									
Antidepressants	106,412 (8.0)	472 (59.4)	*1.29*	106,412 (8.0)	378 (56.2)	*1.20*	106,412 (8.0)	189 (39.6)	*0.80*
Antipsychotics	12,366 (0.9)	246 (30.9)	*0.90*	12,366 (0.9)	233 (34.6)	*0.98*	12,366 (0.9)	92 (19.3)	*0.64*
Benzodiazepines	34,932 (2.6)	208 (26.2)	*0.71*	34,932 (2.6)	185 (27.5)	*0.74*	34,932 (2.6)	123 (25.8)	*0.70*
Other anxiolytics	4,288 (0.3)	35 (4.4)	*0.27*	4,288 (0.3)	35 (5.2)	*0.30*	4,288 (0.3)	12 (2.5)	*0.19*
Other hypnotics	43,150 (3.3)	155 (19.5)	*0.53*	43,150 (3.3)	129 (19.2)	*0.52*	43,150 (3.3)	59 (12.4)	*0.34*
Barbiturates	12,269 (0.9)	18 (2.3)	*0.11*	12,269 (0.9)	17 (2.5)	*0.12*	12,269 (0.9)	12 (2.5)	*0.12*
Stimulants	7,842 (0.6)	99 (12.5)	*0.49*	7,842 (0.6)	74 (11.0)	*0.46*	7,842 (0.6)	36 (7.5)	*0.36*
Opioids	249,821 (18.9)	319 (40.1)	*0.48*	249,821 (18.9)	261 (38.8)	*0.45*	249,821 (18.9)	172 (36.1)	*0.39*

Triptans	12,174 (0.9)	28 (3.5)	*0.18*	12,174 (0.9)	22 (3.3)	*0.16*	12,174 (0.9)	23 (4.8)	*0.24*
Nonsteroidal anti-inflammatory drugs	211,001 (15.9)	220 (27.7)	*0.29*	211,001 (15.9)	187 (27.8)	*0.29*	211,001 (15.9)	103 (21.6)	*0.14*
Antihypertensive medications	27,316 (2.1)	73 (9.2)	*0.31*	27,316 (2.1)	44 (6.5)	*0.22*	27,316 (2.1)	24 (5.0)	*0.16*
Non-insulin antidiabetic medications	8,681 (0.7)	16 (2.0)	*0.12*	8,681 (0.7)	15 (2.2)	*0.13*	8,681 (0.7)	11 (2.3)	*0.14*
Insulin	9,554 (0.7)	<11	*0.04*	9,554 (0.7)	<11	*0.03*	9,554 (0.7)	<11	*-0.01*
Corticosteroids	75,693 (5.7)	107 (13.5)	*0.26*	75,693 (5.7)	72 (10.7)	*0.18*	75,693 (5.7)	47 (9.9)	*0.15*
Fluconazole	22,091 (1.7)	37 (4.7)	*0.17*	22,091 (1.7)	27 (4.0)	*0.14*	22,091 (1.7)	17 (3.6)	*0.12*
Other teratogens[4]	16,321 (1.2)	19 (2.4)	*0.09*	16,321 (1.2)	27 (4.0)	*0.17*	16,321 (1.2)	<11	*0.07*
Methadone	595 (0.0)	<11	*0.09*	595 (0.0)	<11	*0.06*	595 (0.0)	<11	*0.05*
Buprenorphine	1,068 (0.1)	<11	*0.13*	1,068 (0.1)	<11	*0.10*	1,068 (0.1)	<11	*0.07*
Naltrexone	65 (0.0)	<11	*0.07*	65 (0.0)	<11	*0.05*	65 (0.0)	<11	*0.09*
Naloxone	1,215 (0.1)	<11	*0.12*	1,215 (0.1)	<11	*0.11*	1,215 (0.1)	<11	*0.06*
Markers of burden of disease									
Obstetric Comorbidity Index[45], mean (SD)	0.9 (1.4)	1.5 (1.8)	*0.36*	0.9 (1.4)	1.4 (1.7)	*0.31*	0.9 (1.4)	1.2 (1.8)	*0.22*
Number of distinct prescriptions, mean (SD)	1.6 (2.3)	4.4 (3.6)	*0.94*	1.6 (2.3)	4.6 (3.8)	*0.95*	1.6 (2.3)	3.5 (3.7)	*0.62*
Number of diagnoses, mean (SD)	2.5 (3.1)	5.6 (4.4)	*0.82*	2.5 (3.1)	5.5 (4.6)	*0.77*	2.5 (3.1)	5.0 (4.5)	*0.64*
Number of outpatient physician visits, mean (SD)	2.8 (4.0)	7.9 (9.0)	*0.73*	2.8 (4.0)	7.6 (9.0)	*0.69*	2.8 (4.0)	6.4 (8.1)	*0.57*
Patients hospitalized, N (%)	48,294 (3.7)	53 (6.7)	*0.14*	48,294 (3.7)	33 (4.9)	*0.06*	48,294 (3.7)	29 (6.1)	*0.11*
Number of hospitalizations, mean (SD)	0.0 (0.2)	0.1 (0.3)	*0.13*	0.0 (0.2)	0.1 (0.3)	*0.05*	0.0 (0.2)	0.1 (0.3)	*0.10*
Number of days hospitalized, mean (SD)	0.1 (0.9)	0.3 (1.6)	*0.14*	0.1 (0.9)	0.2 (1.3)	*0.07*	0.1 (0.9)	0.3 (1.4)	*0.12*
Number of emergency room visits, mean (SD)	0.3 (0.8)	0.9 (2.6)	*0.29*	0.3 (0.8)	0.7 (1.4)	*0.32*	0.3 (0.8)	0.6 (1.5)	*0.23*

St. Diff.: Standardized differences, i.e., the difference in means or proportions divided by the pooled standard deviation [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine 2009;28:3083-107]

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

[2] Other race includes Asian, Native American, Other, and Unknown

[3] Pain conditions include neuropathic and non-neuropathic conditions

[4] Other teratogens include methimazole, danazol, propylthiouracil, and progestins

[5] The obstetric comorbidity index predicts severe maternal morbidity. The range for the maternal comorbidity index is 0 to 45, with lower values associated with lower burden of maternal illness and higher values associated with higher burden of maternal illness [Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957-65]

Table S13. Propensity-score-adjusted baseline characteristics of exposed and unexposed pregnant women by dose tertiles of the highest lamotrigine prescription filled during the first trimester[1]

Baseline characteristics	Non-exposed (N=1,099,188)	Lamotrigine <=100 mg/day (N=795)	*St. Diff.*	Non-exposed (N=1,254,157)	Lamotrigine 101-200 mg/day (N=673)	*St. Diff.*	Non-exposed (N=1,202,345)	Lamotrigine >200 mg/day (N=477)	*St. Diff.*
Age, mean (SD)	25.0 (5.7)	24.8 (5.7)	*-0.03*	25.4 (6.0)	25.4 (5.9)	*0.00*	25.2 (5.8)	25.4 (5.7)	*0.02*
Race									
White	837,896 (76.2)	580 (73.0)	*-0.08*	1,014,765 (80.9)	534 (79.4)	*-0.04*	850,727 (70.8)	332 (69.6)	*-0.03*
Black	128,090 (11.7)	107 (13.5)	*0.05*	128,900 (10.3)	73 (10.8)	*0.02*	162,754 (13.5)	63 (13.2)	*-0.01*
Hispanic	45,081 (4.1)	41 (5.2)	*0.05*	45,135 (3.6)	29 (4.3)	*0.04*	85,637 (7.1)	37 (7.8)	*0.02*
Other[2]	88,120 (8.0)	67 (8.4)	*0.01*	65,357 (5.2)	37 (5.5)	*0.01*	103,227 (8.6)	45 (9.4)	*0.03*
Year									
2000	<11	<11	*0.00*	<11	<11	*0.00*	<11	<11	*0.00*
2001	5,460 (0.5)	<11	*0.03*	3,912 (0.3)	<11	*0.00*	21,743 (1.8)	<11	*0.01*
2002	10,099 (0.9)	<11	*0.02*	4,515 (0.4)	<11	*-0.01*	22,009 (1.8)	<11	*-0.01*
2003	13,106 (1.2)	11 (1.4)	*0.02*	10,900 (0.9)	<11	*-0.01*	29,394 (2.4)	<11	*-0.02*
2004	50,260 (4.6)	38 (4.8)	*0.01*	46,236 (3.7)	24 (3.6)	*-0.01*	86,401 (7.2)	35 (7.3)	*0.01*
2005	75,052 (6.8)	57 (7.2)	*0.01*	110,615 (8.8)	62 (9.2)	*0.01*	85,931 (7.1)	35 (7.3)	*0.01*
2006	133,628 (12.2)	94 (11.8)	*-0.01*	126,797 (10.1)	67 (10.0)	*-0.01*	150,574 (12.5)	63 (13.2)	*0.02*
2007	135,243 (12.3)	98 (12.3)	*0.00*	212,386 (16.9)	115 (17.1)	*0.00*	180,268 (15.0)	73 (15.3)	*0.01*
2008	211,422 (19.2)	155 (19.5)	*0.01*	242,067 (19.3)	128 (19.0)	*-0.01*	182,133 (15.1)	70 (14.7)	*-0.01*
2009	257,971 (23.5)	180 (22.6)	*-0.02*	281,522 (22.4)	151 (22.4)	*0.00*	267,694 (22.3)	105 (22.0)	*-0.01*
2010	206,947 (18.8)	147 (18.5)	*-0.01*	215,206 (17.2)	117 (17.4)	*0.01*	176,199 (14.7)	69 (14.5)	*-0.01*
Multiple gestation	43,110 (3.9)	31 (3.9)	*0.00*	53,911 (4.3)	29 (4.3)	*0.00*	57,854 (4.8)	23 (4.8)	*0.00*
Psychiatric and neurological conditions, N (%)									
Bipolar disorder	443,314 (40.3)	352 (44.3)	*0.08*	581,632 (46.4)	316 (47.0)	*0.01*	376,646 (31.3)	130 (27.3)	*-0.09*
Depression	318,714 (29.0)	208 (26.2)	*-0.06*	253,072 (20.2)	122 (18.1)	*-0.05*	188,883 (15.7)	72 (15.1)	*-0.02*
Anxiety	233,239 (21.2)	160 (20.1)	*-0.03*	226,076 (18.0)	118 (17.5)	*-0.01*	167,178 (13.9)	65 (13.6)	*-0.01*

Schizophrenia	18,632 (1.7)	14 (1.8)	*0.01*	19,812 (1.6)	<11	*-0.01*	13,806 (1.1)	<11	*-0.01*
Other psychosis	14,436 (1.3)	11 (1.4)	*0.01*	11,617 (0.9)	<11	*0.00*	2,937 (0.2)	<11	*-0.01*
Personality disorder	35,067 (3.2)	32 (4.0)	*0.04*	45,027 (3.6)	28 (4.2)	*0.03*	19,415 (1.6)	<11	*-0.01*
Adjustment disorder	45,025 (4.1)	30 (3.8)	*-0.02*	31,187 (2.5)	15 (2.2)	*-0.02*	22,025 (1.8)	<11	*-0.01*
Attention deficit hyperactivity disorder	96,645 (8.8)	71 (8.9)	*0.00*	88,658 (7.1)	48 (7.1)	*0.00*	35,597 (3.0)	14 (2.9)	*0.00*
Delirium	5,731 (0.5)	<11	*0.00*	8,144 (0.6)	<11	*-0.01*	8,988 (0.7)	<11	*-0.01*
Other psychiatric disorders	75,058 (6.8)	58 (7.3)	*0.02*	66,593 (5.3)	37 (5.5)	*0.01*	56,456 (4.7)	23 (4.8)	*0.01*
Alcohol abuse or dependence	22,794 (2.1)	19 (2.4)	*0.02*	19,356 (1.5)	11 (1.6)	*0.01*	9,716 (0.8)	<11	*0.03*
Drug abuse or dependence	70,995 (6.5)	55 (6.9)	*0.02*	47,942 (3.8)	26 (3.9)	*0.00*	51,567 (4.3)	20 (4.2)	*0.00*
Chronic fatigue syndrome	74,692 (6.8)	52 (6.5)	*-0.01*	101,159 (8.1)	52 (7.7)	*-0.01*	55,010 (4.6)	20 (4.2)	*-0.02*
Sleep disorder	49,275 (4.5)	33 (4.2)	*-0.02*	59,703 (4.8)	28 (4.2)	*-0.03*	44,010 (3.7)	18 (3.8)	*0.01*
Epilepsy or convulsions	86,643 (7.9)	73 (9.2)	*0.05*	186,256 (14.9)	106 (15.8)	*0.02*	478,124 (39.8)	205 (43.0)	*0.07*
Pain conditions[3]	399,504 (36.3)	281 (35.3)	*-0.02*	435,516 (34.7)	232 (34.5)	*-0.01*	338,847 (28.2)	133 (27.9)	*-0.01*
Migraine or headache	170,263 (15.5)	123 (15.5)	*0.00*	194,514 (15.5)	106 (15.8)	*0.01*	194,502 (16.2)	79 (16.6)	*0.01*
Chronic maternal illness, N (%)									
Hypertension	52,470 (4.8)	36 (4.5)	*-0.01*	49,176 (3.9)	25 (3.7)	*-0.01*	44,080 (3.7)	18 (3.8)	*0.01*
Diabetes	34,852 (3.2)	24 (3.0)	*-0.01*	28,119 (2.2)	13 (1.9)	*-0.02*	22,573 (1.9)	<11	*-0.02*
Renal disease	4,999 (0.5)	<11	*0.01*	12,757 (1.0)	<11	*-0.01*	12,256 (1.0)	<11	*0.02*
Obesity or overweight	37,326 (3.4)	27 (3.4)	*0.00*	42,352 (3.4)	22 (3.3)	*-0.01*	35,618 (3.0)	14 (2.9)	*0.00*
Smoking	128,803 (11.7)	94 (11.8)	*0.00*	108,179 (8.6)	56 (8.3)	*-0.01*	79,471 (6.6)	31 (6.5)	*0.00*
Psychotropic and other medications, N (%)									
Antidepressants	714,957 (65.0)	472 (59.4)	*-0.12*	753,773 (60.1)	378 (56.2)	*-0.08*	515,882 (42.9)	189 (39.6)	*-0.07*
Antipsychotics	302,563 (27.5)	246 (30.9)	*0.08*	407,636 (32.5)	233 (34.6)	*0.04*	261,452 (21.7)	92 (19.3)	*-0.06*
Benzodiazepines	291,775 (26.5)	208 (26.2)	*-0.01*	345,982 (27.6)	185 (27.5)	*0.00*	320,415 (26.6)	123 (25.8)	*-0.02*
Other anxiolytics	45,140 (4.1)	35 (4.4)	*0.01*	62,036 (4.9)	35 (5.2)	*0.01*	33,991 (2.8)	12 (2.5)	*-0.02*
Other hypnotics	208,615 (19.0)	155 (19.5)	*0.01*	235,073 (18.7)	129 (19.2)	*0.01*	161,153 (13.4)	59 (12.4)	*-0.03*
Barbiturates	26,893 (2.5)	18 (2.3)	*-0.01*	31,127 (2.5)	17 (2.5)	*0.00*	26,697 (2.2)	12 (2.5)	*0.02*
Stimulants	126,303 (11.5)	99 (12.5)	*0.03*	124,603 (9.9)	74 (11.0)	*0.03*	84,682 (7.0)	36 (7.5)	*0.02*
Opioids	456,965 (41.6)	319 (40.1)	*-0.03*	497,227 (39.6)	261 (38.8)	*-0.02*	444,668 (37.0)	172 (36.1)	*-0.02*

Triptans	44,923 (4.1)	28 (3.5)	*-0.03*	43,950 (3.5)	22 (3.3)	*-0.01*	55,082 (4.6)	23 (4.8)	*0.01*
Nonsteroidal anti-inflammatory drugs	319,663 (29.1)	220 (27.7)	*-0.03*	362,522 (28.9)	187 (27.8)	*-0.02*	278,903 (23.2)	103 (21.6)	*-0.04*
Antihypertensive medications	101,342 (9.2)	73 (9.2)	*0.00*	81,200 (6.5)	44 (6.5)	*0.00*	62,252 (5.2)	24 (5.0)	*-0.01*
Non-insulin antidiabetic medications	23,981 (2.2)	16 (2.0)	*-0.01*	33,568 (2.7)	15 (2.2)	*-0.03*	27,374 (2.3)	11 (2.3)	*0.00*
Insulin	13,218 (1.2)	<11	*-0.01*	14,238 (1.1)	<11	*-0.01*	9,560 (0.8)	<11	*-0.02*
Corticosteroids	156,065 (14.2)	107 (13.5)	*-0.02*	138,633 (11.1)	72 (10.7)	*-0.01*	116,778 (9.7)	47 (9.9)	*0.00*
Fluconazole	54,937 (5.0)	37 (4.7)	*-0.02*	53,326 (4.3)	27 (4.0)	*-0.01*	44,885 (3.7)	17 (3.6)	*-0.01*
Other teratogens[4]	27,688 (2.5)	19 (2.4)	*-0.01*	52,708 (4.2)	27 (4.0)	*-0.01*	24,244 (2.0)	<11	*0.01*
Methadone	5,117 (0.5)	<11	*0.01*	3,891 (0.3)	<11	*0.00*	3,922 (0.3)	<11	*-0.02*
Buprenorphine	10,790 (1.0)	<11	*0.00*	8,673 (0.7)	<11	*0.01*	3,807 (0.3)	<11	*0.02*
Naltrexone	1,819 (0.2)	<11	*0.02*	1,385 (0.1)	<11	*0.01*	3,751 (0.3)	<11	*0.02*
Naloxone	10,752 (1.0)	<11	*0.00*	9,588 (0.8)	<11	*0.01*	3,681 (0.3)	<11	*0.02*
Markers of burden of disease									
Obstetric Comorbidity Index[5], mean (SD)	1.5 (1.8)	1.5 (1.8)	*-0.01*	1.4 (1.7)	1.4 (1.7)	*-0.01*	1.2 (1.7)	1.2 (1.8)	*0.02*
Number of distinct prescriptions, mean (SD)	4.6 (3.6)	4.4 (3.6)	*-0.05*	4.7 (3.5)	4.6 (3.8)	*-0.02*	3.6 (3.5)	3.5 (3.7)	*-0.01*
Number of diagnoses, mean (SD)	5.9 (4.5)	5.6 (4.4)	*-0.06*	5.7 (4.4)	5.5 (4.6)	*-0.04*	5.1 (4.4)	5.0 (4.5)	*-0.02*
Number of outpatient physician visits, mean (SD)	7.4 (7.6)	7.9 (9.0)	*0.05*	7.2 (7.3)	7.6 (9.0)	*0.05*	6.3 (7.0)	6.4 (8.0)	*0.02*
Patients hospitalized, N (%)	68,351 (6.2)	53 (6.7)	*0.02*	63,884 (5.1)	33 (4.9)	*-0.01*	73,191 (6.1)	29 (6.1)	*0.00*
Number of hospitalizations, mean (SD)	0.1 (0.3)	0.1 (0.3)	*0.02*	0.1 (0.3)	0.1 (0.3)	*-0.01*	0.1 (0.3)	0.1 (0.3)	*0.00*
Number of days hospitalized, mean (SD)	0.3 (1.7)	0.3 (1.6)	*0.01*	0.2 (1.2)	0.2 (1.3)	*0.00*	0.3 (1.5)	0.3 (1.4)	*0.00*
Number of emergency room visits, mean (SD)	0.8 (1.5)	0.9 (2.6)	*0.04*	0.7 (1.3)	0.7 (1.4)	*0.01*	0.6 (1.3)	0.6 (1.5)	*0.01*

St. Diff.: Standardized differences, i.e., the difference in means or proportions divided by the pooled standard deviation [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine 2009;28:3083-107]

[1] In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11

[2] Other race includes Asian, Native American, Other, and Unknown

[3] Pain conditions include neuropathic and non-neuropathic conditions

[4] Other teratogens include methimazole, danazol, propylthiouracil, and progestins

[5] The obstetric comorbidity index predicts severe maternal morbidity. The range for the maternal comorbidity index is 0 to 45, with lower values associated with lower burden of maternal illness and higher values associated with higher burden of maternal illness [Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957-65]

Development of study cohort and sociodemographic characteristics across sequential restriction criteria

Our study cohort included all pregnancies in women aged 12 to 55 years that resulted in live births for which Medicaid covered the healthcare expenses. Specific eligibility criteria based on Medicaid program provisions and arrangements were implemented to increase the completeness of claim information among women included in the cohort. Montana and Connecticut were excluded because of difficulty in linking data for mothers and infants, Michigan was excluded because of incomplete data, and data from Arizona were not available. From 21,524,000 deliveries and 33,589,989 child observations, 9,157,201 pregnancies ending in live birth were available after linkage. We restricted the cohort to 1,625,491women who were continuously eligible for Medicaid from three months before the estimated last menstrual period through one month after delivery. We also required that the linked infants met the same Medicaid eligibility criteria as their mothers for at least three months after birth, unless they died, in which case we allowed a shorter eligibility period (N=1,360,101). We excluded pregnancies with a documented chromosomal abnormality (ICD-9 code 758.xx or 759.81-759.83) and pregnancies with exposure to known teratogenic medications during the first trimester (warfarin, angiotensin converting enzyme (ACE) inhibitors, antineoplastic agents, isotretinoin, misoprostol, thalidomide). We also excluded patients exposed to anticonvulsants other than lamotrigine because of their known or possible teratogenic effects (N=1,325,563).

The Table below provides information on how the sequential restriction criteria applied to the overall Medicaid population of pregnant women affected the composition of our final study population. Both age and race remained stable across the sequence of restriction criteria (1 through 5, see table below). In line with expectations, we also observed that the proportion of low-income adults eligible independently of pregnancy increased throughout the sequence of restriction criteria, particularly when requiring continuous eligibility from 3 months before the last menstrual period (restriction criteria 4 and 5), whereas the proportion of low-income adults eligible through the occurrence of pregnancy decreased. (See table below) This may have resulted in the selection of a more disadvantaged subpopulation within Medicaid, mostly composed of low-income adults, multiparae, and women with disabilities.

The characteristics of this Medicaid-eligible population of pregnant women, i.e., young, racially diverse, and vulnerable population with a high burden of disabilities, are not expected to affect the biological relations studied. Therefore, our results should be generalizable to other populations.

Table. Sociodemographic characteristics of study population across sequential restriction criteria

	Restriction criteria:				
	1. Deliveries prior to linkage	**2. Deliveries linked to an infant**	**3. Deliveries linked to a live-born infant**	**4. Pregnancies eligible from 3 months before LMP to 1 month post-delivery, and no pregnancies with private insurance, restricted benefits, or with inappropriate enrollment type**	**5. Pregnancies with infants eligible for ≥3 months after birth, unless they died sooner, and no babies with private insurance, restricted benefits, or ineligible managed care plan during months 1 to 3 after delivery[1]**
	21,524,000	9,606,196	9,157,201	1,625,491	1,360,101
Age, Mean (SD); Median (25th-75th IQR)	24.9 (7.0); 23 (20-28)	24.4 (5.6); 23 (20-28)	24.5 (5.6); 23 (20-28)	24.1 (5.8); 23 (20-28)	24.1 (5.8); 23 (20-27)
Race					
White	42.6	45.3	45.1	39.2	40.3
Black or African American	27.8	24.9	24.7	33.3	33.4
Hispanic or Latino	19.6	18.2	18.4	16.1	14.6
Other race	10.1	11.6	11.8	11.5	11.7
Medicaid eligibility criterion					
Adults receiving cash assistance or eligible under section 1931, i.e. low-income adults eligible independently of pregnancy	25.4	33.3	33.5	53.0	52.5
Poverty-related eligible adults, i.e. low-income adults eligible because of pregnancy	32.1	26.6	26.8	6.0	6.1
Other eligibility criterion	42.5	40.0	39.7	41.0	41.4

[1] We included data from the following states: AK, AL, AR, CA, CO, DE, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, MD, ME, MN, MO, MS, NC, ND, NE, NH, NJ, NM, NV, NY, OH, OK, OR, PA, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV, WY

Detailed outcome definition

Congenital malformations were defined on the basis of inpatient or outpatient ICD-9 diagnoses and procedure codes in the maternal (first month postpartum) or infant records (first three months after date of birth). (See Table below) The maternal record was considered since Medicaid claims are sometimes recorded under the mother before the infant's eligibility has been processed. [1] We defined 13 specific malformation groups (central nervous system, ear, eye, cardiac, other vascular, respiratory, oral cleft, gastro-intestinal, genital, urinary, musculoskeletal, limb, other) and considered a specific malformation to be present if there was (i) an ICD-9 diagnosis recorded for the specific malformation on >1 date, (ii) a diagnosis on one date as well as a relevant surgery or procedure code, or (iii) a diagnosis on one date and the infant died before 90 days. If the malformation was identified using codes from the maternal record only and these codes were also present during the first 105 days of pregnancy, the outcome was excluded under the assumption that it reflected a pre-existing malformation in the mother.

Table. Diagnostic codes for congenital malformations

Malformation Group	ICD-9 Code
1. Central Nervous System defects	740.xx-742.xx
2. Eye anomalies	743.xx (exclude if only 743.6x and 743.8x)
3. Ear anomalies	744.xx (exclude if only 744.1x, 744.21, 744.29, and 744.4x-744.9x)
4. Cardiac malformations	745.xx-746.xx, 747.0x-747.4x, 747.83 (exclude if only 745.5 AND preterm, 746.02 AND preterm, 746.4x, 746.6x, 746.99, 747.0x AND preterm, 747.3 AND preterm)
▪ Right ventricular outflow obstruction (RVOTO) defects	746.00, 746.01, 746.02 (exclude if only 746.02 AND preterm), 746.09, 746.1x, 746.2x, 746.83, 747.3x (exclude if only 747.3x AND preterm).
5. Vascular (non-cardiac) malformations	747.6x-747.9x (exclude if only 747.83)
6. Respiratory malformations	748.xx (do not count if only 748.1x)
7. Oral cleft	749.xx
8. Gastrointestinal malformations	750.xx-751.xx (do not count if only 750.0x, 750.1x, 750.50, 751.0x)
9. Genital (male and female) malformations	752.xx (do not count if only 752.42, 752.52) (in addition, do not count 752.5x if preterm)
10. Urinary malformations	753.xx (do not include if only 753.7x)
11. Musculoskeletal malformations	754.xx and 756.xx (do not count if only 754.3x, 754.81, 754.82, 756.2x)
12. Limb defects	755.xx (exclude if only 755.65)
13. Other malformations	757.xx; 759.xx (exclude if only 757.2-757.6, 759.81-759.83)

[1] Centers for Medicare & Medicaid Services. Medicaid Analytic eXtract (MAX) general information. MAX 1999-2005 state claims anomalies from the "2005 files" zipped file within the "MAX Data 2005 to 2008 general information, data dictionaries, data element lists, data anomalies, validation table measures and SAS loads zipped file. http://www.cms.gov/research-statistics-data-and-systems/computer-data-and-systems/medicaiddatasourcesgeninfo/maxgeneralinformation.html. Accessed February 7, 2017.

Potential impact of missing terminations

Our study population only included information on pregnancies that resulted in liveborn infants. Thus, severe cardiac malformations that result in spontaneous abortions, stillbirths or pregnancy terminations for cardiac anomalies will be missed. If a depletion of affected offspring occurred preferentially among women exposed to lithium compared with unexposed women (e.g., due to differences in prenatal care and screening, or differences in the propensity to terminate a pregnancy), studies restricted to live births would underestimate relative risks of cardiac malformations associated with the use of lithium.

As previously described in detail by Huybrechts et al. [1], we used the methods proposed by Greenland and Khoury [2,3] to perform a sensitivity analysis and quantify the potential impact of missing terminations.

Observed (with selection bias)

	Case*	Non-case
Exposed	A_1	B_1
Unexposed	A_0	B_0

"Truth" (without selection bias)

	Case*	Non-case
Exposed	A_1/S_{11}	B_1/S_{01}
Unexposed	A_0/S_{10}	B_0/S_{00}

*: pregnancies with a cardiac malformation

A_1 = Total number of cases exposed
A_0 = Total number of cases unexposed
B_1 = Total number of non-cases exposed
B_0 = Total number of non-cases unexposed

S_{11}=probability of case selection (survival) among exposed
S_{10}=probability of case selection among unexposed
S_{01}=probability of non-case selection among exposed
S_{00}=probability of non-case selection among unexposed

The observed or apparent odds ratio (AOR) – in the presence of selection bias – is estimated as:
(A_1B_0/A_0B_1)
The corrected odds ratio is estimated as:
$[(A_1/S_{11})(B_0/S_{00})] / [(A_0/S_{10})(B_1/S_{01})] = (A_1B_0/A_0B_1)*(S_{10}S_{01}/S_{11}S_{00}) = AOR * (S_{10}S_{01}/S_{11}S_{00})$

It should be noted that bias will only occur if *both* the cardiac defect and the exposure affect pregnancy terminations; the selection probabilities would cancel out otherwise.

<u>The assumptions used for the selection probabilities are similar to those used by Huybrechts et al. [1]:</u>

- S_{00}: Around 48% of pregnancies are unintended, and the proportion of unintended pregnancies ending in abortion is around 45%. [4] Only a small proportion of these terminated unintended pregnancies would carry a fetus with a major congenital malformation. Therefore, around 20% of pregnancies (slightly less than 0.48*0.45) are terminated for reasons other than congenital malformations (e.g. social reasons). Therefore, the probability of non-case selection among unexposed (S_{00}) was assumed to be 80% (100%-20% [terminations due to social reasons]).
- S_{10}: Fewer than 20% of cardiac malformations are detected before 24 weeks of pregnancy, and less than 50% of those detected are terminated. [5] It has been estimated that around 10% of all pregnancies with cardiac malformations are terminated in the US. [6] Therefore, the probability of case selection among unexposed (S_{10}) was assumed to be 70% (100% – 20% [terminations due to social reasons] – 10% [terminations due to cardiac malformations detected early]). In addition

to considering the 70% best estimate based on the literature, we also evaluated the impact of lower selection probabilities among affected pregnancies (range considered: 50-70%).

- S_{01}, S_{11}: To explore the interaction of malformation status and exposure with respect to the selection probabilities, we assumed that lithium exposure would decrease the selection probability by up to 10% [7,8]. That is, $S_{01}=S_{00}+N\%$ and $S_{11}=S_{10}+N\%$ with N ranging from 0% to -10%.

This combination of the four selection probabilities resulted in broad ranges for the magnitude of the potential selection bias that were represented graphically. We evaluated the impact of these selection probabilities on the relative risk estimated for lithium and overall cardiac malformations compared with unexposed pregnancies in the main analysis (RR=1.65, 95% CI 1.02-2.68), after adjusting for other potential confounders via propensity score fine stratification.

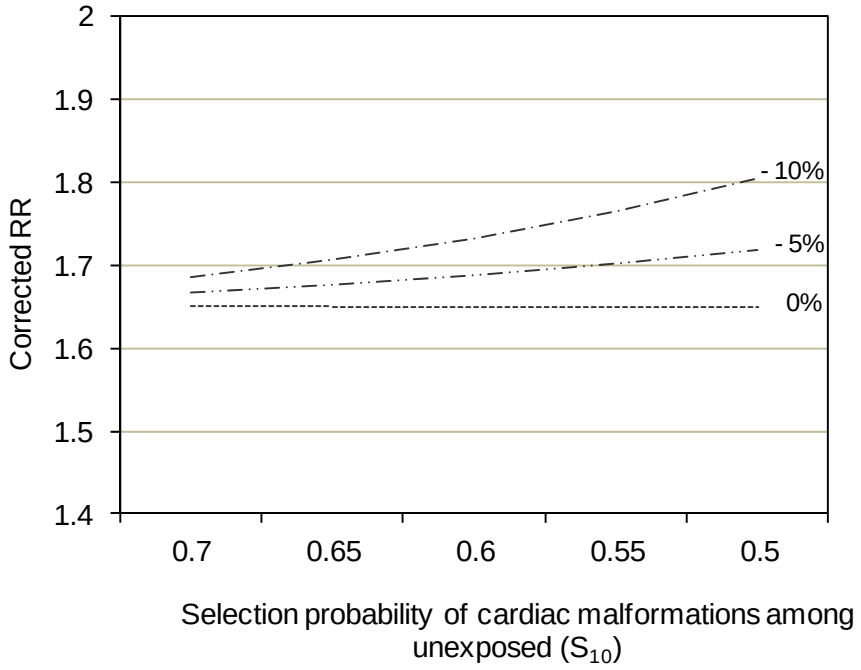
The range of values for the selection probabilities considered in the sensitivity analyses are summarized in the table below:

	Selection probabilities			
	Pregnancies with cardiac malformations		Pregnancies without cardiac malformation	
	Unexposed (S_{10})	Exposed (S_{11})	Unexposed (S_{00})	Exposed (S_{01})
Figure	50-70% (70% best estimate based on literature)	S_{10} S_{10}-5% S_{10}-10%	80%	S_{00} S_{00}-5% S_{00}-10%

The figure below shows the corrected estimate of relative risk across a range of selection probabilities (i.e., probability of being liveborn in malformed fetuses) in the unexposed. Three lines are shown, corresponding to livebirth probabilities for fetuses in the lithium-exposed group that are (1) the same as in the unexposed, (2) 5% lower than in the unexposed, and (2) 10% lower than in the unexposed. Even in the extreme scenario that the frequency of non-livebirth of a malformed fetus was 10% higher in the lithium-exposed group, the corrected RR estimate would be 1.80.

It should be noted that the selection probabilities used here are most likely conservative estimates since we adjusted for many covariates including a broad range of demographic, psychiatric and medical conditions, and healthcare utilization measures. Such adjustment would reduce not only confounding but also selection bias if the adjusted factors were common causes of lithium use and inclination to terminate (e.g. factors associated with psychiatric conditions). Thus, the relative risk estimate for lithium and cardiac malformations compared with unexposed pregnancies is unlikely to be significantly affected by the missing information on non-livebirths

Figure. Corrected relative risk for the association between lithium exposure during the first trimester and cardiac malformations. The graph represents a range of plausible values for selection probabilities (1-probability of termination) among unexposed. The different lines represent the corrected relative risk for a range of lower selection probabilities among lithium users.



In conclusion, findings from this sensitivity analysis show that the differences in the proportion of terminations among women exposed to lithium vs. those unexposed within levels of covariates used in the adjustment would have to be unrealistically strong to meaningfully affect the relative risk estimate for lithium and cardiac malformations.

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