

SUPPLEMENTAL DATA

Supplemental Table 1. Mean lithium measurements from 1998 to 2020 by California County.

Supplemental Table 2. Frequency and means of lithium concentration measurements by water source.

Supplemental Table 3. Demographic comparison between patient records with and without a unique patient identification number.

Supplemental Table 4. Association between lithium and hypertrophic cardiomyopathy (HCM) and/or selective IgA deficiency.

Supplemental Table 5. Association between air pollution measured in particulate matter with a diameter of $\leq 2.5\mu\text{m}$ (PM_{2.5}) in $\mu\text{g}/\text{m}^3$ and Wolff-Parkinson-White (WPW).

Supplemental Table 6. Association between lithium levels and diagnosis of WPW among pediatric patients seeking acute care in New York between 2010 and 2012.

Supplemental Table 7. Association between lithium levels and diagnosis of congenital heart disease among pediatric patients seeking acute care in California between 1998 and 2020.

Supplemental Table 8. Association between lithium and undergoing an ablation procedure.

Supplemental Table 9. Association between lithium and symptoms of accessory pathways, restricted by specified ages.

Supplemental Table 10. Association between lithium and diagnosis of WPW while assessing income with restricted cubic splines.

Supplemental Figure 1. Predicted adjusted probability of a congenital heart disease (CHD) diagnosis across levels of lithium exposure in California. Estimates derived from a multivariable logistic regression model adjusted for age, sex, race, ethnicity, income, and insurance type. Adjusted predicted probabilities and respective 95% confidence intervals were estimated with marginal standardization using the fitted model. The red dashed line corresponds to the health based screening limit (HBSL) of lithium at 10 parts per billion (ppb). The blue dashed line corresponds to the 75th percentile of dissolved lithium concentration levels observed in California at 32.56ppb. The blue shaded region represents the 95% confidence interval.

Supplemental File 1. International Classification of Diseases, Tenth Revision (ICD-10) codes used for analysis.

Supplemental Table 1. Mean lithium measurements from 1998 to 2020 by California County.

County	Number of Measurements	Mean ppb $\pm$ SD	County	Number of Measurements	Mean ppb $\pm$ SD
Alameda	66	24.03 $\pm$ 53	Orange	111	9.82 $\pm$ 14
Alpine	2	13.17 $\pm$ 15	Placer	60	11.85 $\pm$ 20
Amador	21	19.12 $\pm$ 51	Plumas	25	2.24 $\pm$ 3
Butte	55	3.64 $\pm$ 8	Riverside	766	10.48 $\pm$ 34
Calaveras	17	29.20 $\pm$ 23	Sacramento	364	2.70 $\pm$ 7
Colusa	30	23.58 $\pm$ 23	San Benito	124	45.01 $\pm$ 50
Contra Costa	14	21.36 $\pm$ 34	San Bernardino	1443	31.25 $\pm$ 121
Del Norte	9	1.49 $\pm$ 2	San Diego	424	77.39 $\pm$ 189
El Dorado	76	10.24 $\pm$ 54	San Francisco	5	10.77 $\pm$ 18
Fresno	260	10.98 $\pm$ 23	San Joaquin	423	4.69 $\pm$ 5
Glenn	48	8.91 $\pm$ 7	San Luis Obispo	47	66.14 $\pm$ 122
Humboldt	46	4.77 $\pm$ 4	San Mateo	15	32.56 $\pm$ 33
Imperial	37	56.30 $\pm$ 26	Santa Barbara	320	55.69 $\pm$ 81
Inyo	85	105.29 $\pm$ 313	Santa Clara	63	13.63 $\pm$ 28
Kern	236	212.65 $\pm$ 520	Santa Cruz	64	33.12 $\pm$ 30
Kings	50	5.02 $\pm$ 5	Shasta	102	3.21 $\pm$ 5
Lake	12	46.01 $\pm$ 59	Sierra	2	1.53 $\pm$ 0
Lassen	31	10.21 $\pm$ 17	Siskiyou	44	16.25 $\pm$ 27
Los Angeles	740	20.67 $\pm$ 45	Solano	20	24.62 $\pm$ 19
Madera	147	37.42 $\pm$ 146	Sonoma	301	31.29 $\pm$ 151
Marin	8	15.10 $\pm$ 9	Stanislaus	264	11.65 $\pm$ 17
Mariposa	19	9.65 $\pm$ 18	Sutter	38	1.60 $\pm$ 1
Mendocino	68	2.89 $\pm$ 2	Tehama	86	5.13 $\pm$ 6
Merced	121	8.77 $\pm$ 9	Trinity	13	3.41 $\pm$ 4
Modoc	14	7.73 $\pm$ 7	Tulare	183	8.25 $\pm$ 17
Mono	385	194.27 $\pm$ 440	Tuolumne	13	5.99 $\pm$ 3
Monterey	132	47.14 $\pm$ 69	Ventura	89	51.41 $\pm$ 36
Napa	87	190.35 $\pm$ 468	Yolo	28	22.63 $\pm$ 18
Nevada	72	6.17 $\pm$ 11	Yuba	30	1.84 $\pm$ 3

ppb = parts per billion. SD = standard deviation

Supplemental Table 2. Frequency and means of lithium concentration measurements by water source.

County	Groundwater		Surface Water	
	Number of Measurements	Mean pbb $\pm$ SD	Number of Measurements	Mean ppb $\pm$ SD
Alameda	64	24.5 $\pm$ 53.9	2	7.3 $\pm$ 5.8
Alpine	2	13.2 $\pm$ 15.2	0	N/A
Amador	21	19.1 $\pm$ 50.7	0	N/A
Butte	53	3.7 $\pm$ 7.7	2	1.4 $\pm$ 1.3
Calaveras	17	29.2 $\pm$ 23	0	N/A
Colusa	30	23.6 $\pm$ 23.3	0	N/A
Contra Costa	13	16.1 $\pm$ 28.6	1	90
Del Norte	9	1.5 $\pm$ 2.4	0	N/A
El Dorado	71	10.9 $\pm$ 55.9	5	1.4 $\pm$ 2.1
Fresno	260	11 $\pm$ 23	0	N/A
Glenn	48	8.9 $\pm$ 7.4	0	N/A
Humboldt	46	4.8 $\pm$ 3.6	0	N/A
Imperial	22	63.9 $\pm$ 31.9	15	45.2 $\pm$ 2.9
Inyo	78	106.3 $\pm$ 326.3	7	94.2 $\pm$ 88.7
Kern	235	213.5 $\pm$ 520.6	1	2.13
Kings	50	5 $\pm$ 4.8	0	N/A
Lake	12	46 $\pm$ 59.2	0	N/A
Lassen	31	10.2 $\pm$ 17.2	0	N/A
Los Angeles	686	20.7 $\pm$ 43.7	54	20.3 $\pm$ 54.3
Madera	147	37.4 $\pm$ 146.3	0	N/A
Marin	7	15.4 $\pm$ 9.6	1	13.3
Mariposa	5	19.8 $\pm$ 36	14	6 $\pm$ 3.1
Mendocino	46	3 $\pm$ 2.7	22	2.7 $\pm$ 0.7
Merced	121	8.8 $\pm$ 9.4	0	N/A
Modoc	14	7.7 $\pm$ 7.4	0	N/A
Mono	345	210.7 $\pm$ 460.6	40	52.7 $\pm$ 91
Monterey	132	47.1 $\pm$ 69.5	0	N/A
Napa	83	199 $\pm$ 477.7	4	11.1 $\pm$ 2.8
Nevada	64	6.9 $\pm$ 11.5	8	0.2 $\pm$ 0.2
Orange	111	9.8 $\pm$ 14	0	N/A
Placer	59	12 $\pm$ 19.9	1	0.32
Plumas	16	2.7 $\pm$ 3	9	1.4 $\pm$ 2
Riverside	580	11.6 $\pm$ 38.9	186	7 $\pm$ 4.4
Sacramento	171	3.5 $\pm$ 8	193	2 $\pm$ 6.6
San Benito	75	62.9 $\pm$ 56.7	49	17.7 $\pm$ 8.5

San Bernardino	1397	31.3 ± 122.6	46	29.8 ± 40.6
San Diego	367	85.5 ± 200.5	57	25 ± 64.9
San Francisco	5	10.8 ± 17.7	0	N/A
San Joaquin	223	4.4 ± 6.1	200	5 ± 3.1
San Luis Obispo	47	66.1 ± 122.1	0	N/A
San Mateo	15	32.6 ± 33.1	0	N/A
Santa Barbara	312	53.1 ± 75.3	8	158 ± 179
Santa Clara	63	13.6 ± 27.7	0	N/A
Santa Cruz	64	33.1 ± 29.9	0	N/A
Shasta	61	3.2 ± 5.1	41	3.2 ± 4.1
Sierra	2	1.5 ± 0.4	0	N/A
Siskiyou	44	16.2 ± 27.1	0	N/A
Solano	18	26.7 ± 18.8	2	6.3 ± 4
Sonoma	186	48.3 ± 190.4	115	3.8 ± 4.1
Stanislaus	234	11.3 ± 17.8	30	14.6 ± 8.1
Sutter	38	1.6 ± 1.4	0	N/A
Tehama	86	5.1 ± 5.8	0	N/A
Trinity	13	3.4 ± 4.1	0	N/A
Tulare	183	8.3 ± 17.2	0	N/A
Tuolumne	13	6 ± 3.1	0	N/A
Ventura	88	51.1 ± 36.4	1	74.7
Yolo	28	22.6 ± 18.2	0	N/A
Yuba	30	1.8 ± 3.1	0	N/A

ppb = parts per billion. SD = standard deviation

Supplemental Table 3. Demographic comparison between patient records with and without a unique patient identification number.

	Missing Patient ID Number	
	No (N = 2,345,305)	Yes (N = 11,349,181)
Sex		
Female	1,120,578 (47.8%)	5,358,585 (47.2%)
Mean First Age (Years $\pm$ SD)	8.37 $\pm$ 5.9	5.55 $\pm$ 5.6
Race/Ethnicity		
White	577,152 (24.6%)	2,748,891 (24.2%)
Black	236,604 (10.1%)	739,998 (6.5%)
Hispanic	1,171,283 (49.9%)	6,145,914 (54.2%)
Asian	172,276 (7.3%)	745,704 (6.6%)
American Indian	9,292 (0.4%)	31,124 (0.3%)
Hawaii/Pacific Islander	15,655 (0.7%)	51,336 (0.5%)
Multiracial	11,868 (0.5%)	40,046 (0.4%)
Other	110,538 (4.7%)	691,709 (6.1%)
Unknown	40,637 (1.7%)	154,459 (1.4%)
Median Income in Quartiles		
First (Lowest)	585,670 (25.1%)	2,836,802 (25.2%)
Second	579,936 (24.9%)	2,803,801 (24.9%)
Third	581,807 (25.0%)	2,820,772 (25.0%)
Fourth (Highest)	582,137 (25.0%)	2,813,523 (25.0%)
Insurance		
Private	1,014,931 (43.3%)	4,202,905 (37.0%)
Medicare	15,254 (0.7%)	110,508 (1.0%)
Indigent/MediCal	1,285,405 (54.8%)	6,800,217 (59.9%)
Federal	11,942 (0.5%)	120,258 (1.1%)
Other	17,307 (0.7%)	111,091 (1.0%)
Mean Lithium Exposure (ppb $\pm$ SD)	29.8 $\pm$ 39.6	29.5 $\pm$ 37.9

ID = Identification. SD = Standard
Deviation

Supplemental Table 4. Association between lithium and hypertrophic cardiomyopathy (HCM) and/or selective IgA deficiency.

	Lithium Levels $\geq$75th Percentile	
	aOR (95% CI)	p-value
HCM (n = 294)	1.19 (0.90 – 1.59)	0.23
Selective IgA Deficiency (n = 172)	0.88 (0.58 – 1.34)	0.55
Composite (n = 466)	1.08 (0.85 – 1.37)	0.52

Models adjusted for age, sex, race, ethnicity, income, and insurance.

Supplemental Table 5. Association between air pollution measured in particulate matter with a diameter of $\leq 2.5\mu\text{m}$ (PM2.5) in $\mu\text{g}/\text{m}^3$ and Wolff-Parkinson-White (WPW).

	Log PM2.5	
	aOR (95% CI)	p-value
WPW (n = 684)	0.99 (0.65 – 1.52)	0.96

Models adjusted for age, sex, race, ethnicity, income, and insurance.

Supplemental Table 6. Association between lithium levels and diagnosis of WPW among pediatric patients seeking acute care in New York between 2010 and 2012.

	OR (95% CI)	p-value	aOR (95% CI) ^A	p-value
75th Percentile (≥ 32.6 ppb)	1.16 (0.92 – 1.46)	0.22	1.16 (0.90 – 1.49)	0.24
HBSL (≥ 10 ppb)	1.25 (1.05 – 1.50)	0.014	1.22 (1.00 – 1.48)	0.047

HBSL = Health Based Screening Level. ppb = parts per billion. aOR = adjusted odds ratio.

^AModels adjusted for age, sex, race, ethnicity, income, and insurance type.

Supplemental Table 7. Association between lithium levels and diagnosis of congenital heart disease among pediatric patients seeking acute care in California between 1998 and 2020.

	OR (95% CI)	p-value	aOR (95% CI) ^A	p-value
75th Percentile (≥ 32.6 ppb)	1.14 (1.09 – 1.18)	<0.001	1.16 (1.11 – 1.21)	<0.001
HBSL (≥ 10 ppb)	1.04 (1.00 – 1.09)	0.045	0.99 (0.95 – 1.04)	0.76

HBSL = Health Based Screening Level. ppb = parts per billion. aOR = adjusted odds ratio.

^AModels adjusted for age, sex, race, ethnicity, income, and insurance type.

Supplemental Table 8. Association between lithium and undergoing an ablation procedure.

	Lithium Levels $\geq$75th Percentile	
	aOR (95% CI)	p-value
WPW (n = 684)	1.60 (1.34 – 1.90)	<0.001
Ablation (n = 416)	1.75 (1.41 – 2.17)	<0.001
WPW and Ablation (n = 152)	2.16 (1.52 – 3.05)	<0.001

Models adjusted for age, sex, race, ethnicity, income, and insurance.

Supplemental Table 9. Association between lithium and symptoms of accessory pathways, restricted by specified ages.

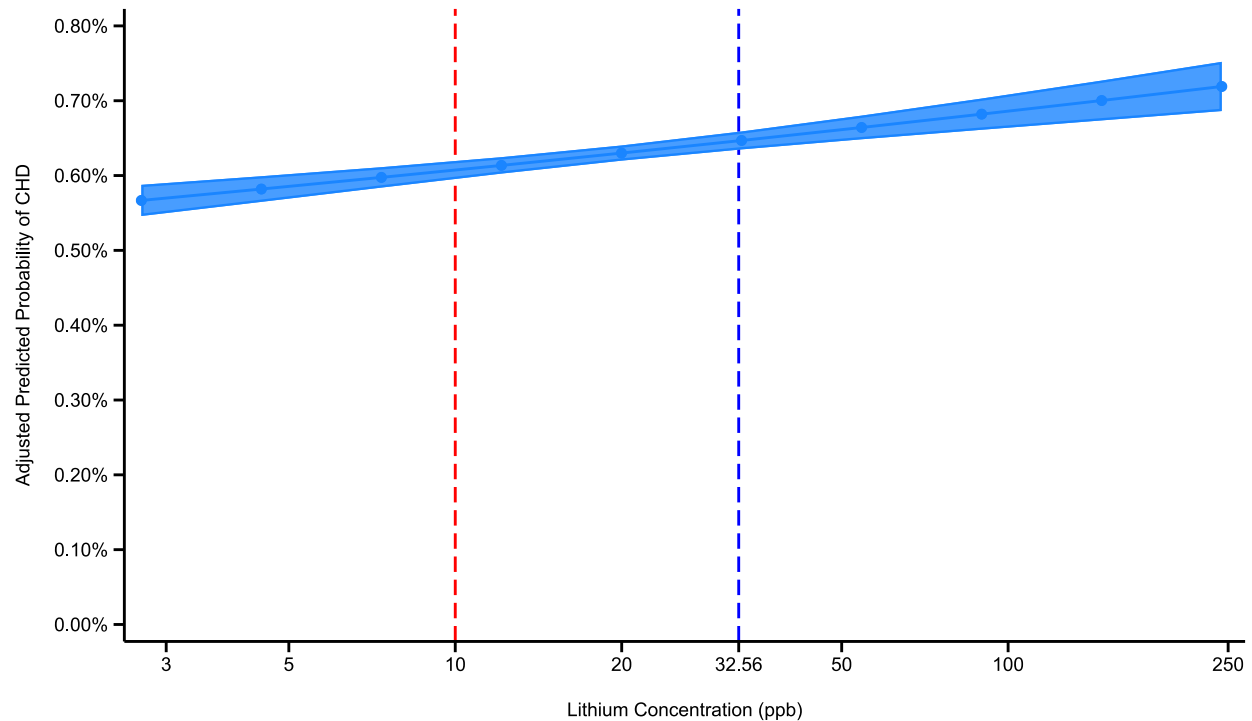
	Lithium Levels $\geq$75th Percentile	
	OR (95% CI)	p-value
Among patients < 1 year of age	1.35 (0.95 – 1.91)	0.094
Among patients < 2 years of age	1.38 (1.18 – 1.60)	<0.001

SVT = supraventricular tachycardia. ^aIncludes any occurrence of SVT, palpitations, or syncope.

Supplemental Table 10. Association between lithium and diagnosis of WPW while assessing income with restricted cubic splines.

	Income as Continuous		Income with Cubic Splines	
	aOR (95% CI) ^A	p-value	aOR (95% CI) ^A	p-value
75th Percentile (≥ 32.6 ppb)	1.60 (1.34 – 1.90)	<0.001	1.60 (1.34 – 1.90)	<0.001
HBSL (≥ 10 ppb)	1.33 (1.08 – 1.64)	0.0070	1.33 (1.08 – 1.64)	0.0070

HBSL = Health Based Screening Level. ppb = parts per billion. aOR = adjusted odds ratio. ^AModels adjusted for age, sex, race, ethnicity, income, and insurance type.



Supplemental Figure 1. Predicted adjusted probability of a congenital heart disease (CHD) diagnosis across levels of lithium exposure in California. Estimates derived from a multivariable logistic regression model adjusted for age, sex, race, ethnicity, income, and insurance type. Adjusted predicted probabilities and respective 95% confidence intervals were estimated with marginal standardization using the fitted model. The red dashed line corresponds to the health based screening limit (HBSL) of lithium at 10 parts per billion (ppb). The blue dashed line corresponds to the 75th percentile of dissolved lithium concentration levels observed in California at 32.56ppb. The blue shaded region represents the 95% confidence interval.