Association Between Lithium Use and Risk of Alzheimer's Disease

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ABSTRACT

Objective: Current evidence for the association between use of lithium and risk of dementia is mixed. The objective of this study was to assess the risk of Alzheimer's disease associated with use of lithium.

Methods: A population-based, nested case-control study was conducted using data from the National Health Insurance Research Database in 2002 covering 24.5 million beneficiaries of the Taiwan National Health Insurance Program from January 1, 1997, to December 31, 2009. A total of 2,548,625 older people were included in the study cohort. We analyzed 63,347 cases of Alzheimer's disease (*ICD-9-CM* codes 290.0–290.3, and 331.0) and 2 controls per case matched by age, sex, and index date (the date of the first AD claim). Conditional logistic regression was performed, adjusting for health care utilization, use of other common mood stabilizers (valproic acid and carbamazepine), hypothyroidism, type 2 diabetes, hypertension, hyperlipidemia, chronic kidney disease, epilepsy, schizophrenia, and bipolar disorder.

Results: We identified 63,347 cases with Alzheimer's disease and 126,694 controls. The adjusted odds ratio (aOR) of Alzheimer's disease risk with lithium use was 1.79 (95% confidence interval [CI], 1.34–2.38) in the general population. However, when we restricted the analyses to patients with bipolar disorder to minimize potential confounding by indication, lithium was not associated with Alzheimer's disease risk (aOR = 1.36; 95% CI, 0.89–2.09), and there were no apparent trends of greater risk with increasing duration or dose.

Conclusions: These findings do not support an increased or decreased risk of lithium use with Alzheimer's disease when taking into account potential confounding by indication. Further investigations of the effect of lithium with dementia need to consider the influence of confounding by indication.

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The prevalence of dementia ranges from 5%–7% for those aged ≥ 60 years to over 30% for those over 90,[1] and Alzheimer's disease (AD) is the most common type of dementia. The rates of AD are increasing globally as the world's populations grow older. As a result, it is important to identify both risk and protective factors that may inform prevention strategies to reduce the growing public health burden of AD.

There have been recent reports in the literature that lithium may protect against the development of AD. Although the mechanism of action behind its therapeutic action largely remains unclear,[2] its neuroprotective abilities have been suggested by animal models and human studies. Lithium inhibits glycogen synthase kinase-3, a key enzyme in the metabolism of amyloid precursor protein and the phosphorylation of tau protein.[3,4] Lithium treatment also appears to preserve or increase the volume of prefrontal cortex, hippocampus, amygdala,[5] and gray matter[6,7] as well as increase *N*-acetyl aspartate levels[8] in human brains. Consistent with these findings, several epidemiologic studies have shown that lithium is associated with a lower risk of dementia or cognitive decline.[9–15] On the contrary, there are other reports of negative effects of lithium therapy on cognitive function and the development of dementia.[16–18] Potential explanations for the negative effects include lithium-induced hypothyroidism[19]; worse neuropsychological performance in lithium users, including attention, memory, word fluency, and psychomotor speed; or possibly the subjective experience of mental slowing caused by lithium.[16] The association between lithium and risk of dementia is complicated by the fact that bipolar disorder, the leading indication for lithium, has been itself associated with an increased risk of dementia,[20,21] raising the possibility of confounding by indication.

As a result of the conflicting evidence, the association between lithium use and risk of dementia remains controversial. In most previous clinical or epidemiologic studies, the sample sizes were small, the number of controllable confounders was limited (eg, confounding by indication or confounding medications), the follow-up periods were not long enough to

Clinical Points

- Literature on the association between lithium use and risk of dementia shows mixed results.
- Results of this study suggested that when clinicians treat patients with lithium, dementia is not a complication that should be considered.
- Data from this study do not support a protective effect of lithium against the development of Alzheimer's disease.

include the common age of risk for dementia, the focus was on the general population but the indications for lithium use were not known, or the outcome included dementia with heterogeneous etiologies, for example, combining Alzheimer's disease, vascular dementia, and dementia due to other conditions. To address these limitations, we carried out a nested case-control study to estimate the association between lithium use and risk of Alzheimer's disease among the older general population and older bipolar patients, using data from the Taiwanese National Health Insurance Research Database (NHIRD).

METHODS

Data

All citizens and foreign residents who have lived in Taiwan for at least 4 months are required to be insured by the National Health Insurance program. This program is a single-payer compulsory social insurance plan launched on March 1, 1995, and population coverage reached 99.9% by the end of 2014. Large computerized databases derived from this system by the National Health Insurance Administration (the former Bureau of National Health Insurance), Ministry of Health and Welfare (the former Department of Health), Taiwan, and maintained by the National Health Research Institutes, Taiwan, are provided to researchers in Taiwan for research purposes. The database includes patients' demographic characteristics, including sex, date of birth, place of birth, and diagnoses; medical or surgical procedures; laboratory tests; medical expenditures; and prescription claims data. Each prescription record contains type, dosage, and time of medication prescribed.[22]

The Cohort

We used information derived from the 2002 NHIRD, which covered approximately 24.5 million beneficiaries of the National Health Insurance Program during any period in 2002 and includes claims data for these individuals from January 1, 1997, to December 31, 2009. Data for people 65 years and older (birth year before 1938) were extracted as the geriatric cohort in this study (n = 2,548,625) (Figure 1). Our study was approved with certificate number CE14169A-1 by the IRB of Taichung Veterans General Hospital (Taichung, Taiwan).

Derivation of Case and Control Groups

Figure 1 depicts the flowchart for our sample selection. For cases, we first selected patients newly diagnosed with AD between January 1, 2007, and December 31, 2009. Among these patients, those with a history of vascular dementia or dementia of other kinds before their AD diagnosis were excluded. The definition of AD was based on at least 2 outpatient records or 1 inpatient record with a diagnosis of *ICD-9-CM* codes 290.0–290.3, 331.0. The date of the first AD claim was defined as the index date of AD. The definitions of vascular dementia and dementia of other kinds were based on records with a diagnosis of *ICD* 290.4 and *ICD* 294.X, respectively.[23,24] For the control group, those without any record of a diagnosis of any type of dementia between January 1, 1997, and December 31, 2009, were first identified. From these individuals, 2 controls were matched by age (in years), sex, and index date for each case. The index date for controls was defined as the same date that the matching cases were identified as AD to make sure the observation period was equal between cases and controls.

Lithium Exposure

We identified lithium use using the Anatomic Therapeutic Chemical classification system. Exposure to lithium was defined as the prescription of any lithium from January 1, 1997, to the index date. To examine potential dose and duration response effects, we also assessed cumulative defined daily dose (DDD) of lithium use, cumulative duration of lithium use (in days), and mean daily dose calculated as the cumulative defined daily dose of lithium use divided by the cumulative duration of lithium use (in days), each categorized into approximate quartile groups. The basic definition of the DDD, which is a commonly used method of drug standardization developed by the World Health Organization, is "the assumed average maintenance dose per day for a drug used for its main indication in adults."[25]

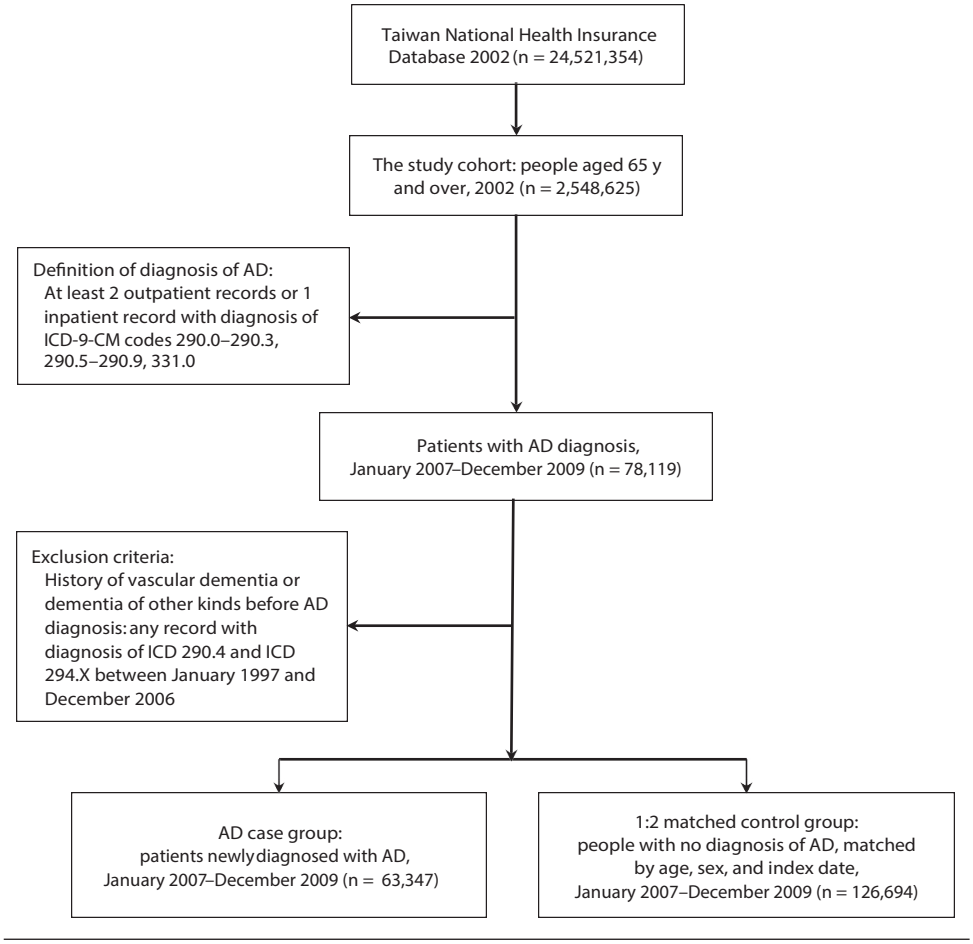
Measure of Other Covariates

We examined a variety of other covariates including health care utilization (frequency of outpatient consultation), any use of other common mood stabilizers (valproic acid and carbamazepine), and potential medical and neuropsychiatric diseases that might confound the association between lithium use and dementia, including hypothyroidism, type 2 diabetes, hypertension, hyperlipidemia, chronic kidney disease, epilepsy, schizophrenia, and bipolar disorder. All of these covariates were measured from January 1, 1997, to the index date.

Statistical Analysis

We used the χ^2 test for categorical variables and *t* test for continuous variables in order to compare demographic and clinical characteristics between cases and controls. As a nested, matched case-control study, multivariable conditional logistic regression models were used to estimate the adjusted odds ratios (aORs) of dementia for lithium use after controlling for potential confounding factors. Potential factors that might confound the association were identified and examined initially in univariate models.

Figure 1. Flowchart of the Selection of Alzheimer's Disease (AD) Cases and Controls



The preliminary multivariable model included lithium use status and other well-known risk factors for AD, such as diabetes and hypertension. Relevant covariates that might confound the lithium-AD association were selected based on their biological and clinical relation with lithium and whether inclusion or exclusion of these potential factors had an effect on the association. To address the potential for confounding by indication, we performed the analyses again among individuals diagnosed with bipolar disorder. We did not repeat the analyses among individuals without bipolar disorder, because the individuals taking lithium in this subgroup were primarily diagnosed with disorders such as schizophrenia and depression, and, therefore, the results in this subgroup are subject to the same potential for confounding by indication as in the entire population. All statistical analyses were performed using SAS 9.2 statistical package (SAS Institute, Inc; Cary, North Carolina).

RESULTS

Characteristics of the Study Subjects

A total of 2,548,625 older people were included in the study cohort. From these, 63,347 patients with AD were selected as cases, and 126,694 sex-, age-, and index date-matched individuals were selected as controls (Figure 1). The mean age of the cases and controls was 82.5 years (SD = 5.5), with slightly more women than men (53.8% female). The demographic characteristics, rates of comorbid medical and psychiatric disorders, and prescription status of selected medications are summarized in Table 1. Compared to matched controls, the cases with AD had a significantly higher Charlson Comorbidity Index score (2.6 vs 1.4, $P < .0001$), more frequent health care utilization (18.7 vs 17.1 visits/year), and a higher prevalence of selected medical and psychiatric comorbidities, including diabetes mellitus, hypertension, schizophrenia, and bipolar disorder. In total, 0.26% of AD cases and 0.07% of comparison controls were exposed to lithium. Among lithium users, 42.5% of them were patients with bipolar disorder. There were 3,537 subjects with bipolar disorder in the whole study sample, among whom 2,074 were cases of AD. A total of 4.5% of bipolar patients with dementia had a history of lithium exposure, compared to 2.2% of bipolar patients without dementia (Supplementary eTable 1).

Association Between Lithium Use and AD Risk in the General Population and Those With Bipolar Disorder

In the overall population, there was an increased risk of AD with lithium use (aOR = 1.79; 95% CI, 1.34–2.38) after adjusting for health care utilization, comorbid medical and

Table 1. Demographic Characteristics, Medical and Psychiatric Comorbidities, and Medication Prescription Status of the Whole Study Population[a]

Variable	Control Group (n = 126,694)	AD Cases (n = 63,347)	*P* Value for χ^2 Test
Age, mean ± SD, y	82.50 ± 5.5	82.50 ± 5.5	.832
Sex			1.00
Female	68,190 (53.82)	34,095 (53.82)	
Male	58,504 (46.18)	29,252 (46.18)	
Charlson Comorbidity Index score, mean ± SD	1.40 ± 1.5	2.60 ± 1.4	< .0001
Outpatient visits per year, mean ± SD	17.10 ± 22.5	18.70 ± 23.0	< .0001
Medical and psychiatric comorbidities			
Diabetes mellitus			< .0001
No	90,905 (71.75)	40,486 (63.91)	
Yes	35,789 (28.25)	22,861 (36.09)	
Hypertension			< .0001
No	36,425 (28.75)	13,204 (20.84)	
Yes	90,269 (71.25)	50,143 (79.16)	
Hyperlipidemia			< .0001
No	86,377 (68.18)	41,233 (65.09)	
Yes	40,317 (31.82)	22,114 (34.91)	
Hypothyroidism			< .0001
No	125,227 (98.84)	62,259 (98.28)	
Yes	1,467 (1.16)	1,088 (1.72)	
Chronic kidney disease			< .0001
No	118,137 (93.25)	57,951 (91.48)	
Yes	8,557 (6.75)	5,396 (8.52)	
Epilepsy			< .0001
No	124,884 (98.57)	61,305 (96.78)	
Yes	1,810 (1.43)	2,042 (3.22)	
Schizophrenia			< .0001
No	126,389 (99.76)	62,799 (99.13)	
Yes	305 (0.24)	548 (0.87)	
Bipolar			< .0001
No	125,230 (98.85)	61,274 (96.73)	
Yes	1,463 (1.15)	2,074 (3.27)	
Exposure to lithium			< .0001
Never	126,611 (99.93)	63,181 (99.74)	
Any	83 (0.07)	166 (0.26)	
Cumulative lithium DDDs			< .0001
No use	126,611 (99.93)	63,181 (99.74)	
< 60	35 (0.03)	52 (0.08)	
60–360	24 (0.02)	49 (0.08)	
> 360	24 (0.02)	65 (0.10)	
Cumulative lithium period			< .0001
No use	126,611 (99.93)	63,181 (99.74)	
< 60 d	53 (0.04)	91 (0.14)	
60–360 d	16 (0.01)	31 (0.05)	
> 360 d	14 (0.02)	44 (0.07)	
Mean daily dose			< .0001
No use	126,611 (99.93)	63,181 (99.74)	
> 0/ ≤ 1 DDD	8 (0.01)	15 (0.02)	
> 1/ ≤ 2 DDD	20 (0.02)	38 (0.06)	
> 2 DDD	55 (0.04)	113 (0.18)	
Exposure to other mood stabilizers			
Valproic acid			< .0001
Never	124,588 (98.30)	59,868 (94.50)	
Any	2,100 (1.65)	3,485 (5.50)	
Carbamazepine			< .0001
Never	111,979 (88.40)	53,945 (85.10)	
Any	14,709 (11.60)	9,408 (14.90)	

[a]All values are n (%) unless otherwise noted.
Abbreviations: AD = Alzheimer's disease, DDD = defined daily dose.

psychiatric disorders, and other mood stabilizers (Table 2). When we analyzed cumulative dose of exposure to lithium, cumulative duration of exposure to lithium, and mean daily dose, the risk of AD increased with increasing dose and duration, but after full adjustment these trends were no longer apparent. In these models, bipolar disorder, schizophrenia, and all medical comorbidities except hyperlipidemia were independently associated with a higher risk of AD after full adjustment. Use of other mood stabilizers, valproic acid and carbamazepine, was also associated with increased risk of AD.

Table 3 shows the association between lithium use and risk of AD among individuals with bipolar disorder. No excess risk was discernible among people with bipolar disorder (aOR = 1.36; 95% CI, 0.89–2.09). No association was seen between any use of lithium and AD risk, nor for associations between higher levels of use (cumulative dose, cumulative period of use, or mean daily dose) and AD risk in either the crude model or the adjusted models. There remained a positive and statistically significant association between use of valproic acid and AD in these stratified analyses. Use of the mood stabilizer valproic acid, but not carbamazepine, was associated with increased risk of AD.

DISCUSSION

In this nested case-control study, we initially observed that lithium was associated with an increased risk of AD in the general population, but this association was not found to increase with increasing dose or duration of use. Moreover, when we examined the association only in individuals with bipolar disorder to better account for the potential of confounding by indication, we no longer observed any significant association between lithium and risk of AD. These findings are important because of how commonly lithium is used and because of the morbidity and mortality associated with AD.

At least 8 epidemiologic studies have examined the association between lithium and risk of dementia, including 1 nested case-control study,[17] 4 cohort studies,[9,10,14,15] 1 longitudinal study,[11] 1 trial,[13] and 1 cross-sectional study.[12] The results from these investigations have been mixed. Dunn et al[17] used a nested case-control study design in the general population like ours and similarly found an increased risk of dementia among people aged over 60 years on lithium. Angst et al[11] used a cohort design among people with bipolar disorder or major depressive disorder and found no difference in the development of dementia between lithium users and nonusers, while they also found reduced severity of dementia among bipolar patients who later developed dementia. Another study in the general population by Kessing et al[10] found an increased rate of dementia among persons who used lithium at least once, but the increase was not significant if taking lithium continuously. Nonsignificant effects of lithium treatment were also found in a study that found no difference in change in Mini-Mental State Examination (MMSE) among people with mild to moderate AD.[13] On the

Table 2. Association of Lithium Use With Alzheimer's Disease in the Older General Population (N = 190,041)

Measure	Crude Model Crude OR (95% CI)[a]	Model 1 Adjusted OR (95% CI)	Model 2 Adjusted OR (95% CI)	Model 3 Adjusted OR (95% CI)	Model 4 Adjusted OR (95% CI)
Exposure to lithium					
Lithium use (any/never use)					
Any use (n = 249/189,792)	4.00 (3.07–5.20)	1.79 (1.34–2.38)			
Cumulative dose of lithium use					
No use (n = 189,792)	1.00		1.00		
< 60 DDD (n = 87)	2.97 (1.94–4.57)		1.80 (1.14–2.83)		
60–360 DDD (n = 73)	4.08 (2.51–6.65)		2.22 (1.32–3.73)		
> 360 DDD (n = 89)	5.42 (3.39–8.65)		1.39 (0.84–2.31)		
Cumulative period of lithium use					
No use (n = 189,792)	1.00			1.00	
< 60 d (n = 144)	3.40 (2.42–4.77)			1.99 (1.38–2.86)	
60–360 d (n = 47)	4.00 (2.19–7.29)			1.43 (0.75–2.72)	
> 360 d (n = 58)	6.29 (3.45–11.47)			1.59 (0.83–3.03)	
Mean daily dose [a]					
No use (n = 189,792)	1.00				1.00
> 0/ ≤ 1 DDD (n = 23)	3.75 (1.59–8.84)				2.11 (0.83–5.31)
> 1/ ≤ 2 DDD (n = 58)	3.80 (2.21–6.53)				2.17 (1.23–3.84)
> 2 DDD (n = 168)	4.14 (3.00–5.72)				1.62 (1.14–2.31)
Covariates					
Health care utilization	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Diabetes (yes/no, n = 58,650/131,391)	1.43 (1.41–1.46)	1.30 (1.27–1.33)	1.30 (1.27–1.33)	1.30 (1.27–1.33)	1.30 (1.27–1.33)
Hypertension (yes/no, n = 140,412/49,629)	1.53 (1.50–1.57)	1.40 (1.37–1.44)	1.40 (1.37–1.44)	1.40 (1.37–1.44)	1.40 (1.37–1.44)
Hyperlipidemia (yes/no, n = 62,431/127,610)	1.15 (1.13–1.17)	0.95 (0.93–0.97)	0.95 (0.93–0.97)	0.95 (0.93–0.97)	0.95 (0.93–0.97)
Hypothyroidism (yes/no, n = 2,555/187,486)	1.49 (1.38–1.61)	1.32 (1.22–1.44)	1.32 (1.22–1.44)	1.32 (1.22–1.44)	1.32 (1.22–1.44)
Chronic kidney disease (yes/no, n = 13,953/176,088)	1.29 (1.24–1.33)	1.13 (1.09–1.17)	1.13 (1.09–1.17)	1.13 (1.09–1.17)	1.13 (1.09–1.17)
Epilepsy (yes/no, n = 3,852/186,189)	2.30 (2.16–2.45)	1.63 (1.52–1.74)	1.63 (1.52–1.74)	1.63 (1.52–1.74)	1.63 (1.52–1.74)
Schizophrenia (yes/no, n = 853/189,188)	3.61 (3.14–4.15)	3.00 (2.60–3.47)	3.00 (2.59–3.47)	3.01 (2.60–3.47)	3.00 (2.60–3.47)
Bipolar disorder (yes/no, n = 3,537/186,504)	2.90 (2.71–3.10)	2.34 (2.18–2.51)	2.34 (2.18–2.51)	2.34 (2.18–2.51)	2.34 (2.18–2.51)
Valproic acid (yes/no, n = 5,585/184,456)	3.45 (3.27–3.65)	2.73 (2.57–2.89)	2.77 (2.61–2.93)	2.73 (2.57–2.89)	2.73 (2.57–2.89)
Carbamazepine (yes/no, n = 24,117/165,924)	1.33 (1.29–1.37)	1.16 (1.12–1.19)	1.16 (1.12–1.19)	1.16 (1.12–1.19)	1.16 (1.12–1.19)

[a]Unadjusted models showing the crude ORs and 95% confidence intervals for each covariate in a model by itself.
Abbreviations: DDD = defined daily dose, OR = odds ratio.

Table 3. Association of Lithium Use With Alzheimer's Disease Among Individuals With Bipolar Disorder (N = 3,537)

Measure	Crude Model Crude OR (95% CI)[a]	Model 1 Adjusted OR (95% CI)	Model 2 Adjusted OR (95% CI)	Model 3 Adjusted OR (95% CI)	Model 4 Adjusted OR (95% CI)
Exposure to lithium					
Lithium use (any/never use)					
Any use (n = 125/3,412)	2.10 (1.40–3.16)	1.36 (0.89–2.09)			
Cumulative dose of lithium use					
No use (n = 3,412)	1.00		1.00		
< 60 DDD (n = 28)	3.32 (1.26–8.76)		2.56 (0.95–6.89)		
60–360 DDD (n = 30)	1.69 (0.77–3.69)		1.28 (0.57–2.87)		
> 360 DDD (n = 67)	1.97 (1.14–3.39)		1.09 (0.62–1.94)		
Cumulative period of lithium use					
No use (n = 3,412)	1.00			1.00	
< 60 days (n = 51)	2.63 (1.34–5.14)			1.92 (0.97–3.84)	
60–360 days (n = 27)	0.90 (0.42–1.94)			0.52 (0.23–1.16)	
> 360 days (n = 47)	3.05 (1.47–6.33)			1.85 (0.87–3.93)	
Mean daily dose [a]					
No use (n = 3,412)	1.00				1.00
> 0/ ≤ 1 DDD (n = 7)	1.81 (0.35–9.32)				1.08 (0.20–5.78)
> 1/ ≤ 2 DDD (n = 21)	2.31 (0.85–6.32)				1.86 (0.67–5.20)
> 2 DDD (n = 97)	2.08 (1.31–3.30)				1.29 (0.80–2.09)
Covariates					
Health care utilization	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Diabetes (yes/no, n = 58,650/131,391)	1.23 (1.07–1.41)	1.28 (1.10–1.48)	1.28 (1.10–1.48)	1.28 (1.10–1.49)	1.28 (1.10–1.49)
Hypertension (yes no, n = 140,412/49,629)	0.96 (0.79–1.15)	0.98 (0.81–1.19)	0.99 (0.81–1.20)	0.99 (0.82–1.20)	0.98 (0.81–1.20)
Hyperlipidemia (yes/no, n = 62,431/127,610)	0.89 (0.78–1.03)	0.84 (0.72–0.97)	0.84 (0.72–0.97)	0.84 (0.72–0.97)	0.84 (0.72–0.97)
Hypothyroidism (yes/no, n = 2,555/187,486)	1.23 (0.81–1.85)	1.18 (0.77–1.80)	1.18 (0.78–1.80)	1.17 (0.77–1.79)	1.18 (0.78–1.81)
Chronic kidney disease (yes/no, n = 13,953/176,088)	0.91 (0.72–1.13)	0.93 (0.74–1.18)	0.92 (0.73–1.17)	0.92 (0.73–1.17)	0.93 (0.74–1.18)
Epilepsy (yes/no, n = 3,852/186,189)	1.74 (1.23–2.47)	1.44 (1.00–2.07)	1.43 (1.00–2.05)	1.41 (0.98–2.02)	1.44 (1.00–2.07)
Schizophrenia (yes/no, n = 853/189,188)	2.54 (1.63–3.94)	2.00 (1.27–3.14)	2.06 (1.31–3.23)	2.04 (1.29–3.19)	2.00 (1.27–3.14)
Valproic acid (yes/no, n = 5,585/184,456)	2.45 (1.98–3.04)	2.26 (1.81–2.82)	2.32 (1.86–2.89)	2.33 (1.87–2.91)	2.26 (1.81–2.83)
Carbamazepine (yes/no, n = 24,117/165,924)	1.12 (0.95–1.31)	1.06 (0.90–1.24)	1.08 (0.92–1.27)	1.08 (0.92–1.27)	1.06 (0.90–1.24)

[a]Unadjusted models showing the crude ORs and 95% confidence intervals for each covariate in a model by itself.
Abbreviations: DDD = defined daily dose, OR = odds ratio.

other hand, 3 cohort studies and a cross-sectional study focusing on people with bipolar or mood disorder showed a potentially protective effect of lithium treatment.[9,14,15] The observed protective effects included better MMSE scores,[14] lower cross-sectional prevalence of AD,[12] and reduced rates of dementia[9,15] among lithium users.

There are many possible explanations for the discrepancies between studies, including heterogeneous study designs and populations, diverse approaches for quantifying drug exposure, age differences, selection bias, and interactions with other medications. For example, in a cohort study, if the age of the study population is younger or the follow-up period is insufficiently long to observe the onset of late-onset dementia, then the results may reflect early-onset dementia only. Another example is that polypharmacy in older populations is common and varies largely with the characteristics of the study populations. The interaction of the drug of interest with other medications may vary between different study populations. Finally, age differences have been observed in certain previous studies regarding drug-associated risk,[26,27] and therefore it is reasonable to consider a difference between younger-elderly and the older-elderly on this topic.

In contrast to prior studies, we specifically compared the association of lithium and dementia in the general population as well as separately among those with bipolar disorder. This is important because lithium is mainly prescribed for bipolar disorder and bipolar disorder has itself been associated with increased risk of dementia.[20,21] The fact that there was no association between lithium and AD when we examined the relationship only among those with bipolar disorder suggests that the increased risk initially observed in the general population may have been driven by this confounding by indication. Although it is possible that among those with bipolar disorder an increased risk of lithium is nullified by its beneficial effects on bipolar disorder itself,[5–8] this explanation seems less likely given our other findings, especially with regard to the absence of any indication that there are effects for higher dose or duration levels.

In addition to examining the association between lithium and AD, we found that valproic acid, another mood stabilizer commonly used to treat bipolar disorder, was associated with an increased risk of AD that persisted even when we looked only among those with bipolar disorder and additionally controlled for the use of other mood stabilizers. Whether valproic acid is associated with the development of dementia is unclear. Several studies have found that valproic acid has neuroprotective effects in cellular and animal models[28] and is potentially neuroprotective in bipolar disorder and neurodegenerative diseases.[29,30] However, 2 previous studies focusing on the association between lithium and risk of dementia[9,10] reported results consistent with ours. It is possible that the findings from our study and these others are due to unaccounted for confounding, and more investigation is needed before any conclusions can be drawn about the relationship of valproic acid with Alzheimer's disease.

Our study has several noteworthy strengths. First, we used a nationwide population-level registry of individuals aged 65 years and older with and without AD in Taiwan and information on all lithium purchases by them from 1997 to 2009. Since medical care and treatment are easily accessible for everyone in Taiwan, our sample was representative of the general population and those with bipolar disorder. Second, we examined whether there were effects across different levels of cumulative dose of use, cumulative duration of use, and mean daily dose, rather than less granular assessments such as prescription counts or continuous duration of lithium therapy. Finally, we restricted the outcome solely to AD to make the association with drug exposure more specific and avoid possible contamination of the observed relationship due to heterogeneous pathophysiologies of other kinds of dementia, such as vascular diseases or brain trauma underlying dementia. The validity of the diagnosis of AD in NHIRD, although perhaps underregistered, was good once the diagnosis was made.[31] In addition, we excluded diagnoses of vascular dementia and dementia of other kinds prior to the diagnosis of AD to further enhance the validity.

Our study also has several limitations. First, lithium is known to be associated with worse cognitive performance,[16,18] whereas worse cognitive performance in the older population may be misidentified as dementia, but pathologically it is not the same. If they were misidentified, the real effect of lithium shown should have been toward the more beneficial direction. However, we do not think this is likely to happen in the present study, because the diagnosis of AD in Taiwan is strict, usually combined with brain imaging evidence, and primarily made by neurologists and psychiatrists. Second, people on lithium might have had more opportunity to be recognized with dementia. To address this, we controlled for a measure of health care utilization using the frequency of outpatient consultation prior to the date of diagnosis or index date. Controlling for consultation frequency did not have appreciable effects on the association of interest. Third, the rate of lithium use among people with bipolar disorder in our study is fairly low, 3.5% (Supplementary eTable 1), and most use was of relatively short duration. This was primarily because older people with bipolar disorder had a relatively lower prescription rate of lithium as compared to younger people, and once they were prescribed, the duration of use was usually short. The reasons for this may be because geriatric populations are thought to be more vulnerable to lithium toxicity and manic episodes are fewer during older ages. When we examined the proportion of lithium use among bipolar people of all ages using the same database, the prescription rate was 38%. This is compatible with the clinical experience in psychiatry. Finally, as polypharmacy is common in older populations, other confounding medications and drug-drug interactions may be an issue when studying drug effect in the elderly. We attempted to account for this by controlling for multiple medical and psychiatric diseases and examining their potential interaction with lithium, as medications commonly used in the elderly were highly correlated with the diseases they were

prescribed for, which we had covered most in the models.

In conclusion, in a nationwide study that included all patients with AD in Taiwan, lithium use was not associated with an increased or decreased risk of dementia when confounding by indication was considered. No apparent trends toward the risk of AD with increasing dose or duration were observed. In contrast, we found that valproic acid was associated with an increased risk of AD; this merits further investigation. These findings suggest that lithium would not be useful in the prevention of AD and motivate further studies to determine if the prescription of valproic acid for the treatment of bipolar disorder in the elderly is contraindicated due to concerns of increasing cognitive complications.

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Drug names: carbamazepine (Tegretol, Epitol, and others), valproic acid (Depakene and others.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Association Between Lithium Use and Risk of Alzheimer's Disease

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List of Supplementary Material for the article

1. eTable 1 Characteristics of the subjects with bipolar disorder in the study population

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Supplementary eTable 1. Characteristics of the subjects with bipolar disorder in the study population

	Total		Dementia cases		Comparison group		*P* value for
Medication exposure	n	(%)	n	(%)	n	(%)	χ^2 test
Bipolar disorder	**N = 3537**		**N = 1463**		**N = 2074**		
Lithium							0.0003
No	3412	96.5	1431	97.8	1981	95.5	
Yes	125	3.5	32	2.2	93	4.5	
Valproic acid							<.0001
No	3029	85.6	1339	91.5	1690	81.5	
Yes	508	14.4	124	8.5	11	18.5	
Carbamazepaine							0.144
No	2705	76.5	1137	77.7	1568	75.6	
Yes	832	23.5	326	22.3	506	24.4	