Lithium and stroke recovery: a systematic review and meta-analysis of stroke models in rodents and human data

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ABSTRACT

Background: Lithium has neuroprotective effects in animal models of stroke, but benefits in humans remain uncertain. Aim: To systematically review the available evidence of the neuroprotective and regenerative effects of lithium in animal models of stroke, as well as in observational and trial stroke studies in humans. Methods: This systematic review and meta-analysis was conducted according to PRISMA guidelines. We searched Medline, Embase, and PsycINFO for preclinical and clinical studies published between January 2000 and September 2021. A random-effects meta-analysis was conducted from observational studies. Results: From 1,625 retrieved studies, 42 were included in the systematic review. Of those, we identified 36 rodent models of stroke using pre- or post-insult treatment with lithium, and 6 studies conducted in human samples, of which 4 could be meta-analysed. The review of animal models was stratified according to the type of stroke and outcomes. Human data were subdivided into observational and intervention studies. Treatment of rodents with lithium was associated with smaller stroke volumes, decreased apoptosis, and improved post-stroke function. In humans, exposure to lithium was associated with a lower risk of stroke among adults with bipolar disorder in 2 of 4 studies. Two small trials showed equivocal clinical benefits of lithium post-stroke. Conclusions: Animal models of stroke show consistent biological and functional evidence of benefits associated with lithium treatment, whereas human evidence remains sparse and inconclusive. The potential role of lithium in post-stroke recovery is yet to be adequately tested in humans.

Keywords: stroke, lithium, ischaemic stroke, haemorrhagic stroke, neuroprotection.

NON-STANDARD ABBREVIATIONS AND ACRONYMS

BD, Bipolar disorder; BCCAo, bilateral common carotid artery occlusion; MCAO, middle cerebral artery occlusion; tMCAO, transient middle cerebral artery occlusion; pMCAO, permanent middle cerebral artery occlusions; ICH, intracerebral haemorrhage; CD, could not be determined; i.p., intraperitoneal; Li, lithium; LiCl, lithium chloride; NA, not applicable or not available; ns, not significant; P, postnatal day; s.c., subcutaneous; SD, Sprague-Dawley.

INTRODUCTION

John Cade, an Australian psychiatrist, observed that lithium salts had a tranquilizing effect on rodents[1]. This led him to test the clinical effects of lithium in people with 'psychotic excitement' and report in 1949 its antimanic properties[1]. Lithium salts have since become the 'gold standard' treatment for bipolar disorder (BD) worldwide[2]. More recent evidence suggests that the clinical effects of lithium may not be limited to its antimanic and mood-stabilizing properties in mood disorders. Lithium salts may have pleiotropic effects in preventing or delaying cognitive decline in the general population[3], in older adults with BD[4,5], and mild cognitive impairment[6], in addition to enhancing motor recovery[7] and verbal memory[8] after stroke.

There is evidence from preclinical studies that treatment with lithium may reduce post-ischaemic neuronal apoptosis and mitigate the extent of brain injury after stroke[9]. Such effects have been associated with better functional recovery in some animal models[10-15]. However, the translation of these findings into clinical practice is uncertain[7,8,16-20]. Lithium exerts its effect through modification of multiple intracellular signalling systems, with emphasis on the inhibition of glycogen synthase kinase-3β and subsequent downstream effects reducing inflammation, promoting maintenance of glial and neuronal structures, and downregulating apoptosis[21,22].

In this systematic review, we first sought to examine animal models of ischaemic and haemorrhagic stroke to determine if treatment with lithium decreased stroke volume and the apoptosis of neural cells, and increased post-stroke neurogenesis and function. Second, we reviewed observational data in humans and reported the association between exposure to lithium and the risk of stroke, and evaluated the results of clinical trials investigating the effects of treatment with lithium among adults after stroke.

METHODS

The conduct and reporting of the current systematic review and meta-analysis conform to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and recommendations[23]. This systematic review was not registered because of its concurrent inclusion of animal and human data. The results generated during the current study are available from the corresponding author upon reasonable request. This study was exempted from IRB approval.

Information sources and search strategy

We used Ovid to search the databases of Embase, MEDLINE, and PsycINFO. Database search details, report selection, synthesis of research findings, and statistical analysis are available in Expanded Materials & Methods S1.

Reporting bias assessment

The methodological quality of animal studies was assessed through the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE's RoB) tool[24]. The quality of studies in humans followed the NIH guidelines (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). The detail of the study quality assessment tools is presented in Expanded Materials & Methods S2.

RESULTS

The initial search yielded 1625 documents. After removing the duplicates, we reviewed the titles/abstracts of 1443 articles, of which 1365 were excluded. The full text of the remaining 78 articles was retrieved and reviewed. Of these, 40 articles met the inclusion criteria for the systematic review. Additionally, 2 records were identified through other sources and included in the study. Therefore 42 records were selected for this systematic review, of which 36 were preclinical[9-15,25-53] and 6 included humans[7,8,16-19]. Of these, 4 studies were included for quantitative analysis (meta-analysis)[16-19]. The study selection process is described in Figure 1.

Preclinical studies

A detailing of the 36 preclinical studies is presented in Table 1 and Table 2. Table 1 summarises the methodological characteristics of the studies, and Table 2 lists the key outcomes of each study. In addition, a description of the assessment methods, as well as the neurobiological and neurobehavioural effects of lithium treatment in animal models of stroke can be accessed in Table S1.

Briefly, as described in Table 1, most animal studies addressing the potential effects of lithium in experimental models of stroke were based on the induction of ischaemic insults (n=28, 77.7%), whereas haemorrhagic stroke was reported in eight studies (22.2%). Ischaemic stroke was induced by transient middle cerebral artery occlusion (tMCAO) (n=11, 39.2%) or bilateral common carotid artery occlusion (BCCAo) (n=8, 28.5%). Four studies used unilateral occlusion (14.2%), and three used permanent middle cerebral artery occlusions (pMCAO) (10.7%). Microsphere-induced cerebral embolism[26] or left middle cerebral artery electrocoagulation[41] were each used in one study (3.5% each). Of the eight studies that used models of intracerebral haemorrhage (ICH), five were based on the whole blood-induced ICH model (62.5%), and two used the collagenase-induced ICH model[46,47] (25%), and one used whole blood-induced intra-ventricular haemorrhagic model[48] (12.5%).

Concerning the treatment protocol, there was a large variation across studies in the frequency and duration of the intervention with lithium. Of all animal studies reviewed, six (16.6%) were based on pretreatment with lithium, twenty-four (66.6%) used post-insult interventions, and six studies (16.6%) performed both pre-and post-insult treatment. Most studies administered doses of lithium of 1.0mmol/kg (n=8, 22.2%), 1.5mmol/kg (n=6, 16.6%), or 2.0mmol/kg (n=9, 25%) at varying intervals. The lowest and the highest doses of lithium were respectively 0.03[10] and 12mmol/kg[35], each used in one study (2.7%). Seven studies used more than one therapeutic dose of lithium (19.4%), and one study (2.7%) used lithium-treated extracellular vesicles[45] in a concentration of

2.5mM. Finally, treatment duration ranged from 14 days before the vascular insult to 56 days post-insult. Serum lithium concentrations were determined in only five studies[10,11,25,27,46] (13.8%) (for more information, see Table 1).

Overall, in animal models of ischaemic stroke, sixteen studies (57.1%) investigated the effects of lithium on stroke volume and all showed reduced infarct volume. Of the 22 studies (78.5%) that addressed the effect of lithium on apoptotic markers, nineteen reported findings indicative of inhibition of apoptosis, and three showed possible effects related to this outcome[35,37,40]. The effect of lithium on neurogenesis was investigated in thirteen studies, twelve of which indicated positive (42.8%) and another possible positive result (3.5%). Finally, eighteen (64.2%) of the nineteen studies that addressed the effect of lithium in the neurobehavioural response reported treatment-related improvements in various measures of function. Of the 8 animal studies investigating the effect of lithium on haemorrhagic stroke, three (37.5%) reported a reduction of hemispheric atrophy or haematoma volume[46,49,53], seven (87.5%) described decreased apoptosis (5 positives and 2 possibly positive effects)[46-52], one study (12.5%) reported increased neurogenesis[53], one (12.5%) found no evidence of increased neurogenesis[47], and seven (87.5%) showed improved neurobehavioural function[46,47,49-53] (Table 2).

The SYRCLE tool revealed that 65.8% of preclinical studies were associated with low risk of bias, 25% with a high risk of bias, and in 9.1% the risk of bias was unclear. Only two items related to blinding procedures ('performance' and 'detection') were associated with a high risk of bias in more than 50% of studies, and one item related to outcome data ('incomplete outcome data') was considered unclear in approximately in 70% of studies (Table S2 and Figure S1).

Observational studies in humans

Table 3 describes the key findings of the 4 observational studies that reported data on the effect of lithium treatment on the risk of stroke in humans. These studies were largely based on samples of

patients with BD, representing the target population of lithium-treated adults, and accounted for the odds ratio of the occurrence of stroke among participants allocated in two groups (lithium/non-lithium). Two of these studies were retrospective, including a cohort[16] and a chart review study[17], and one was a prospective study with a cross-over design[18]. The remaining study was based on the assessment of a population-wide electronic database of health records with over 700,000 people with BD, addressing the incidence of neurodegenerative and cerebrovascular outcomes[19]. The forest plot (Figure 2) indicates that lithium decreased the risk of stroke (odds ratio [OR]=0.71, 95%CI=0.54-0.93)[16-19], although study heterogeneity was high (I^2=60.0%). Study quality was rated as good for one study[16], fair for two of them[18,19], and poor for another study[17] (Table S3).

Clinical trials in humans

We identified two interventional studies investigating the clinical, cognitive, and neuroimaging effects of treatment with lithium following a stroke (Table 4). The first reported the results of a single-site randomized, double-blind placebo-controlled treatment trial with oral lithium carbonate 300mg twice per day compared with placebo started within two days of the first-ever stroke and continued for 30 days (none of the participants underwent thrombolysis)[7]. Eighty adults aged 50-80 years were randomized (40 per group), but outcome data were reported for only 32 participants treated with lithium and 34 with placebo. After one month, modified National Institute of Health Stroke Scale scores of both treatment groups did not differ but hand motor function improved more among participants treated with lithium than with placebo.

The second intervention study was a small, uncontrolled open-label pre-post investigation of the effects of lithium carbonate (target serum concentration of 0.4-0.8mmol/L) for the treatment of 12 stroke survivors for 60 days, of whom 8 completed the trial[8]. The higher cumulative dose of lithium was correlated with improved scores on a task of delayed recall, and those who had received daily oral dosages of lithium ≥300mg showed greater global grey matter volume than their counterparts

treated with <300mg. The respective quality of these two studies was rated as fair[7] and poor[8] (Table S4).

DISCUSSION

Among multiple experimental approaches that have been proposed for the animal modelling of stroke[54], we found evidence that treatment with lithium reduces stroke volume and apoptosis, and improves function in rodent models of ischaemic and haemorrhagic stroke. Results from published observational studies of people with BD suggest that stroke is less frequent among those treated with lithium, but the quantity and quality of available data are limited. The effects of short-term treatment with lithium on stroke recovery in one trial and a pre-post observational study were consistent with benefits, but their results were not compelling.

The plausibility of the hypothesis that lithium may contribute to improving the clinical outcomes of stroke survivors is supported by various observations[22]. Neuroimaging studies have shown that the chronic use of lithium is associated with increased grey matter volume in the brain of people with BD[55], and there is cumulative evidence from experimental studies that lithium may also activate neuroprotective and trophic responses, with therapeutic implications for degenerative, traumatic, and vascular brain diseases[4,6]. The disruption of homeostasis caused by stroke activates signalling pathways that upregulate inflammatory, oxidative, and apoptotic responses, further increasing the magnitude of brain injury. At a molecular level, many signalling pathways modified by lithium may be relevant to the pathophysiology of stroke. These mechanisms include the inhibition of glycogen synthase kinase-3β, an important hub of signalling control in multiple cell types, with a central role in the regulation of apoptotic and neuro-regenerative processes[21,22,56].

Animal models of stroke have produced data consistent with a neuroprotective effect of lithium, as inferred by the reduced volume of infarcts[10,53], attenuation of post-ischaemic excitotoxicity[25,51], and the enabling of post-stroke recovery[10]. Other studies have shown that lithium treatment is associated

with anti-apoptotic effects [15,34,43,49,51,52], decreased expression of inflammatory markers[31,42,43,45,50], reduced oxidative stress[35,43,45], and activation of immuno-mediated responses involved in the restoration of blood-brain barrier integrity[44,50]. Finally, evidence of trophic responses is supported by the ability of lithium to up-regulate the brain-derived neurotrophic factor production[39,52,53], to promote neuronal differentiation, axonal plasticity, and endogenous neurogenesis[14,28,42,45], as well as to stimulate post-stroke angiogenesis[53]. According to the SYRCLE's tool, the overall assessment of the quality of animal studies included in the review was ranked as good, i.e., low risk of bias in most domains; except for 'performance-' and 'detection-blinding', where the risk of bias was observed in >50% of studies. Poor blinding may compromise the assessment of qualitative and quantitative outcomes, and lead to inaccuracies in the assessment of treatment effects[24].

The recognition of lithium as a therapeutic compound that may promote neurotrophic and restorative responses is the rationale for its repurposing as a candidate drug for the adjunctive treatment of stroke. In fact, the potential neuroprotective effects of lithium in humans may not be limited to stroke[5,22]. A nested case-control study of the Danish population found that the incidence rate ratio of dementia was lowest for older adults exposed to lithium concentration in drinking water >15µg/L compared with concentrations ≤5µg/L and that this benefit was extended to dementia caused by cerebrovascular disease[3]. Moreover, a randomized, placebo-controlled trial of 61 older adults with mild cognitive impairment (serum concentration of lithium between 0.25-0.5mmol/L) found that treatment with lithium was associated with a lower rate of cognitive decline, and a statistical trend for better function and improved cerebrospinal fluid concentration of amyloid beta-peptide compared with placebo after 2 years[6]. These results suggest that treatment with lithium may contribute to preserving the integrity of neurons, a conclusion that is reinforced by the compelling evidence from basic science about the neuroprotective properties of lithium[21]. However, treatment with lithium cannot be seen as a panacea for neurodegenerative disorders. For example, a randomized, double-blind, placebo-controlled trial of lithium carbonate (target serum concentration of 0.4-0.8mmol/L) for the treatment of 214 adults with amyotrophic lateral sclerosis found no

evidence of increased survival among those treated with lithium for 18 months, although the medication was well tolerated by participants[57].

CONCLUSION

The rationale for the testing of lithium in the management of stroke survivors is strongly supported by data derived from *in vitro* and animal models of stroke. However, the translation from basic to clinical science is yet to be adequately tested. Published information in humans remains limited in quantity and quality. High-quality data from well-designed randomized trials are now required to establish whether lithium can improve the health outcomes of people recovering from a haemorrhagic or ischaemic stroke.

SOURCES OF FUNDING

The study was supported by the National Institute for Biomarker Research in Neuropsychiatry (INBION) and INCT-CAPES (Institutos Nacionais de Ciência e Tecnologia; Grant no.465412/2014-9; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; Grant nos.88887.463672/2019-00 and 88887.514714/2020-00).

DISCLOSURES

None.

SUPPLEMENTAL MATERIAL

Expanded Materials & Methods S1-S2.

Tables S1-S4.

Figure S1.

Prisma Checklist

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FIGURE LEGENDS

Graphical Abstract. Neuroprotective effects of lithium treatment in ischaemic and haemorrhagic stroke. Servier Medical Art images were used in the making of the image.

Figure 1. PRISMA flow diagram of search.

Figure 2. Forest plot depicting the results of studies investigating the effect of treatment with lithium on the risk of stroke in humans. Odds ratio values<1 indicate decreased risk of stroke in association with lithium treatment.

Table 1. Methodological characteristics of the preclinical studies.

Study	Animal model			Intervention		
	Type of Stroke	*Animal strain (weight/age)*	*Stroke model/Duration of occlusion-reperfusion*	*Lithium doses/Administration route*	*Treatment protocol (frequency; duration)/Time to the evaluation of results*	*Serum lithium level*
Ma et al.(2003)[25]	Ischaemic	Male SD rats/250-300g	BCCAo/15min occlusion-6h reperfusion	2mg/kg(LiCl) (0.05mmol/kg)/i.p.	Pretreatment: 7 days, daily/6h post-insult	0.5-1.0 and 0.2-0.8mmol/L
Ren et al.(2003)[10]	Ischaemic	Male SD rats/250-300g	tMCAO/60min occlusion-reperfusion	0.5, 1, 2, 3mEq/kg(LiCl) (0.03, 0.06, 0.1 and 0.2mmol/kg)/s.c.	Post-treatment: immediate, 3h and 7 days, daily/up to 14 days	5-1.0mmol/L at 12h and 0.2-0.8mmol/L at 24h
Xu et al.(2003)[11]	Ischaemic	Male Wistar rats/200-230g	tMCAO/90min occlusion-reperfusion	1mmol/kg(LiCl)/s.c.	Pretreatment: 14 days, daily; post-treatment: 2 days, daily/up to 2 days post-insult	0.40±0.06mmol/L
Sasaki et al.(2006)[26]	Ischaemic	Male Wistar rats/220-270g	Microsphere-embolism/permanent occlusion	3mEq/kg(LiCl) (0.2mmol/kg)/i.p.	Post-treatment: 30min/up to 72h	NA
Xu et al.(2006)[12]	Ischaemic	Male SD rats/280-300g	Permanent MCAO/permanent	1mEq/kg(Li) (1mmol/kg)/s.c.	Pretreatment: 2 days, daily/24h post-insult	NA
Bian et al.(2007)[27]	Ischaemic	Male Mongolian Gerbils/55-70g	BCCAo/5min occlusion-reperfusion	3mEq/kg(LiCl) (0.2mmol/kg)/i.p.	Pretreatment: 7 days, daily; post-treatment: 24h/up to 7 days	0.49±0.09mM
Yan et al.(2007)[28]	Ischaemic	Male SD rats/200-220g	BCCAo/15min occlusion-2h reperfusion	1mmol/kg(LiCl)/i.p.	Pretreatment: 14 days, daily/up to 21 days post-insult	NA
Han et al.(2008)[29]	Ischaemic	Male SD rats/280-300g	Permanent MCAO/permanent	0.5mEq/kg(Li) (0.5mmol/kg)/s.c.	Pretreatment: 24h before and immediate/up to 24h post-insult	NA

Kim et al.(2008)[30]	Ischaemic	Male SD rats/250-350g	tMCAO/NA	1mmol/L(LiCl)/s.c.	Post-treatment: 12h and 14 days, daily/up to 14 days	NA
Li et al.(2010)[9]	Ischaemic	Male Wistar rats/9-day postnatal (P)	Unilateral occlusion/50min hypoxia	2mmol/kg(LiCl)/i.p.	Post-treatment: immediate and 24h/up to 72h	NA
Li et al.(2011)[31]	Ischaemic	Male Wistar rats/P9	Unilateral occlusion/50min hypoxia	2mmol/kg(LiCl)/i.p.	Post-treatment: immediate and 6 days, daily/up to 7 weeks	NA
Sheng et al.(2011) [13]	Ischaemic	Male SD rats/260-300g	Permanent MCAO/permanent	0.5mmol/kg(Li)/i.v.	Post-treatment: immediate/up to 24h	NA
Tsai et al.(2011)[32]	Ischaemic	Male SD rats/190-230g	tMCAO/60min occlusion-reperfusion	2.5mmol/kg(LiCl)/i.p.	Pretreatment: mesenchymal stem cells incubated for 24h; post-treatment: 14 days, daily/up to 15 days	NA
Shin et al.(2012)[33]	Ischaemic	Male SD rats/12-16g/P7	Unilateral occlusion/150min hypoxia	1mmol/kg(LiCl)/s.c.	Post-treatment: immediate and 14 days, daily/up to 14 days	NA
Takahashi et al.(2012)[34]	Ischaemic	Male SD rats/270-350g	BCCAo/30min occlusion-reperfusion	3mg/kg(LiCl) (0.1mmol/kg)/i.p.	Post-treatment: immediate/up to 48h	NA
Ozkul et al.(2014)[35]	Ischaemic	Female Wistar rats/188-260g/6-month-old	BCCAo/permanent occlusion	40-80mg/kg(Li) (6 or 12mmol/kg)/i.p.	Post-treatment: immediate/up to 28 days	NA
Xie et al.(2014)[36]	Ischaemic	Male Wistar rats/P8	Unilateral occlusion/45min hypoxia	2mmol/kg(LiCl)/i.p.	Post-treatment: 5 and 14 days, daily/up to 12 weeks	NA
Boyko et al.(2015)[37]	Ischaemic	Male Wistar rats/NA	tMCAO/NA	100mg/kg(LiCl) (2mmol/kg)/i.p.	Pretreatment: 2h before/ up to 24h post-insult	NA

Fan et al.(2015)[39]	Ischaemic	Male C57Bl/6 mice/22-25g/8-week-old	BCCAo/repeated ischemia-reperfusion	2-5mmol/kg(LiCl)/i.p.	Pretreatment: 7 days; post-treatment: 28 days, daily/up to 34 days	NA
Fan et al.(2015)[38]	Ischaemic	Male C57Bl/6 mice/22-25g	BCCAo/repeated ischemia-reperfusion	2mmol/kg(LiCl)/i.p.	Post-treatment: 2, 4, and 6 weeks, daily/up to 6 weeks	NA
Silachev et al.(2015)[40]	Ischaemic	Male Outbred White rats/320-350g	tMCAO/60min occlusion-reperfusion	3mmol/kg(LiCl or Li succinate)/i.p.	Post-treatment: immediate and 3h/up to 24h	NA
Silachev et al.(2016)[41]	Ischaemic	Male and Female rats/9-14g/P7	Middle cerebral artery electrocoagulation/120m in hypoxia	2mmol/kg(LiCl)/i.p.	Post-treatment: immediate, 24 and 48h/up to 4 days	NA
Taliyan et al.(2016)[42]	Ischaemic	Male Wistar Rats/250g	tMCAO/60min occlusion-reperfusion	40-60mg/kg(LiCl) (1 or 1.5mmol/kg)/i.p.	Post-treatment: 24h and 7 days, daily/up to 9 days	NA
Doeppner et al.(2017)[43]	Ischaemic	Male C57Bl/6 mice/NA	tMCAO/45min occlusion-reperfusion	1mmol/kg(LiCl)/i.p.	Post-treatment: immediate, 3, 6, or 9h after and daily by 56 days with doses of 2mmol/kg/up to 56 days	NA
Haupt et al.(2020)[44]	Ischaemic	Male C57Bl/6 mice/7-week-old	tMCAO/45min occlusion-reperfusion	1mmol/kg(LiCl)/i.p.	Post-treatment: immediate and 2mmol/kg doses for 6, 24 and/or 48h/up to 72h	NA
Xiao et al.(2020)[14]	Ischaemic	Male C57Bl/6 mice/22-26g/10-12-week-old	BCCAo/repeated ischemia-reperfusion	2mmol/kg(LiCl)/i.p.	Pretreatment: 7 days (84mg/kg); post-treatment: 2mmol/kg for 14 days, daily/up to 28 days	NA
Haupt et al.(2021)[45]	Ischaemic	Male C57Bl/6 mice/26-29g	tMCAO/60min occlusion-reperfusion	100µL of extracellular vesicles (2.5mM LiCl) (25mmol/L)/i.v.	Post-treatment: 1, 3 and 5 days/up to 3 months	NA
Ji et al.(2021)[15]	Ischaemic	Male C57Bl/6 mice/20-23g/8-10-week-old	tMCAO/60min occlusion-reperfusion	1.5, 3.0 or 6.0mmol/kg(LiCl)/i.p.	Post-treatment: immediate and 24h/up to 48h	NA

Kang et al.(2012)[46]	Haemorrhagic	Male SD rats/250-280g	Collagenase-induced ICH model/CD	2mEq/kg(LiCl) (0.1mmol/kg)/i.p	Pretreatment: daily 3 days and 24h before/up to 42 days post-insult	0.3-0.4mEq/l
Kang et al.(2014)[47]	Haemorrhagic	Male SD rats/250-280g	Collagenase-induced ICH model/CD	1, 2 and 4mEq/kg(LiCl) (0.05, 0.1 and 0.2mmol/kg)/i.p.	Pretreatment: 14 days before; post-treatment: 14 days after/up to 28 days	NA
Yuan et al.(2016)[48]	Haemorrhagic	Male SD rats/5-10g/P1-4	Whole blood-induced intraventricular hemorrhage/CD	3mmol/kg(LiCl)/i.p.	Post-treatment: 2 days after/up to 32 days	NA
Zheng et al.(2017)[49]	Haemorrhagic	Male SD rats/250-300g	Whole blood-induced ICH/CD	30, 60, or 90mg/Kg(LiCl) (0.5, 1.5, 2mmol/kg)/i.p.	Post-treatment: immediately, 2h, and twice a day for 21 days/up to 42 days	NA
Li et al.(2018)[50]	Haemorrhagic	Male SD rats/230-280g	Whole blood-induced ICH/CD	60mg/kg(LiCl) (1.5mmol/kg)/i.p.	Post-treatment: 2h after/up to 3 days	NA
Liu et al.(2018)[51]	Haemorrhagic	Male SD rats/250-300g	Whole blood-induced ICH/CD	60mg/kg(LiCl) (1.5mmol/kg)/i.p.	Post-treatment: 2h after and twice a day for 21 days/up to 21 days	NA
Li et al.(2019)[53]	Haemorrhagic	Male SD rats/250-300g	Whole blood-induced ICH/CD	60mg/kg(LiCl) (1.5mmol/kg)/i.p.	Post-treatment: 2h and daily for 14 days/up to 14 days	NA
Li et al.(2020)[52]	Haemorrhagic	Male C57Bl/6 mice/23-30g	Whole blood-induced ICH/CD	0.25-0.5mmol/L(LiCl)/i.p.	Post-treatment: every 24h after 1h of hemorrhage up to 21 days/up to 21 days	NA

SD, Sprague-Dawley; P, postnatal day; Li, lithium; LiCl, lithium chloride; i.p., intraperitoneal; i.v., intravenous; s.c., subcutaneous; NA, not applicable or not available; CD, could not be determined.

Table 2. Summary of the results from preclinical studies.

Study	Main results			
	Decreased stroke volume	*Decreased apoptosis*	*Increased neurogenesis*	*Improved function*
Ma et al.(2003)[25]	NR	Yes	NR	NR
Ren et al.(2003)[10]	Yes	Yes	Yes	Yes
Xu et al.(2003)[11]	Yes	Yes	NR	Yes
Sasaki et al.(2006)[26]	NR	Yes	Yes	NR
Xu et al.(2006)[12]	Yes	NR	Yes	Yes
Bian et al.(2007)[27]	NR	Yes	Yes	Yes
Yan et al.(2007)[28]	NR	NR	Yes	Yes
Han et al.(2008)[29]	Yes	NR	Yes	No
Kim et al.(2008)[30]	NR	NR	Yes	NR
Li et al.(2010)[9]	Yes	Yes	NR	NR
Li et al.(2011)[31]	Yes	Yes	Yes	NR
Sheng et al.(2011)[13]	Yes	Yes	NR	Yes
Tsai et al.(2011)[32]	Yes	Yes	Yes	Yes
Shin et al.(2012)[33]	Yes	Yes	NR	NR
Takahashi et al.(2012)[34]	Yes	Yes	NR	NR
Ozkul et al.(2014)[35]	NR	Possible	NR	Yes
Xie et al.(2014)[36]	Yes	NR	Yes	Yes
Boyko et al.(2015)[37]	NR	Possible	NR	Yes
Fan et al.(2015)[39]	NR	Yes	NR	Yes
Fan et al.(2015)[38]	NR	Yes	NR	Yes
Silachev et al.(2015)[40]	Yes	Possible	NR	Yes
Silachev et al.(2016)[41]	Yes	NR	NR	NR
Taliyan et al.(2016)[42]	NR	Yes	Possible	Yes
Doeppner et al.(2017)[43]	Yes	Yes	Yes	Yes
Haupt et al.(2020)[44]	NR	Yes	NR	NR
Xiao et al.(2020)[14]	NR	Yes	NR	Yes
Haupt et al.(2021)[45]	Yes	Yes	Yes	Yes
Ji et al.(2021)[15]	Yes	Yes	NR	Yes
Kang et al.(2012)[46]	Yes (Atrophy)	Yes	NR	Yes
Kang et al.(2014)[47]	NR	Possible	No	Yes
Yuan et al.(2016)[48]	NR	Yes	NR	NR
Zheng et al.(2017)[49]	Yes (Atrophy)	Yes	NR	Yes
Li et al.(2018)[50]	NR	Possible	NR	Yes
Liu et al.(2018)[51]	NR	Yes	NR	Yes
Li et al.(2019)[53]	Yes	NR	Yes	Yes
Li et al.(2020)[52]	NR	Yes	NR	Yes

NR, not reported.

Table 3. Characteristics of the observational studies in stroke humans.

Study	Setting and Population	Design	Measures	N	N Lithium	Findings
Lan et al.(2015)[16]	▪ NHIRD Taiwan; ▪ Random sample of adults diagnosed with BD between 2001-2006; ▪ Propensity score-matched sub-sample of controls for age, gender, and comorbidities.	Retrospective cohort study (participants followed until first stroke/death or December 2011)	▪ Recorded diagnosis of stroke according to ICD-9 (transient ischaemic attack excluded); ▪ Exposure to lithium.	3681	635	▪ 18/635 on lithium and 307/3046 controls had a recorded diagnosis of stroke (OR=0.26, 95%CI=0.15, 0.42); ▪ 18/635 on lithium and 68/1250 matched controls had a recorded diagnosis of stroke (OR=0.51, 95%CI=0.28, 0.87); ▪ Lithium use reduced the risk of stroke among participants with BD.
Prosser et al.(2016)[17]	▪ 4 lithium outpatient clinics; ▪ Men and women aged>18 years.	Chart review (1970-2015)	▪ Recorded clinical diagnosis of stroke; ▪ Regular use of lithium (0.1-30 years).	1028	577	▪ 6/577 on lithium and 7/451 clinic controls had a recorded diagnosis of stroke (OR=0.67; 95%CI=0.18, 2.34); ▪ A lower proportion of participants treated with lithium had a myocardial infarction.
Chen et al.(2019)[18]	▪ NHIRD Taiwan; ▪ Bipolar people aged 15-65 years free of stroke before diagnosis.	Case cross-over	▪ Outcome: stroke; ▪ Lithium exposure during four 14-day periods compared with 14-period preceding stroke; ▪ Analyses controlled for comorbidities and other medications.	609 BD participants who had a stroke	609	▪ 62/609 were on lithium during the case-period. The adjusted risk ratio of stroke compared with control periods was 0.96 (95%CI=0.72, 1.28).
Harrison and Luciano(2021)[19]	▪ TriNetX health network records, USA; ▪ BD compared with mixed disorders.	Longitudinal data (1-18 years)	▪ Outcome: stroke; ▪ Ever exposure to lithium.	1,209,856 (stroke=11,221)	156,507	▪ 996/156,407 adults on lithium had a stroke compared with 10,225/1,053,449 not on lithium (OR=0.65, 95%CI=0.61,0.70).

NHIRD, National Health Insurance Research Database.

Table 4. Characteristics of the trials with stroke survivors.

Study	Setting and Population	Design	Outcome	Duration	N lithium	N placebo	Findings
Mohammadianinejad et al.(2014)[7]	▪ Tertiary hospital in Iran; ▪ First-ever acute ischaemic stroke (<48h since onset) not eligible to receive antithrombotic treatment; ▪ Age 50-80 years.	Double-blind, placebo-controlled trial of lithium 300mg bd.	▪ Modified National Institute of Health Stroke Scale score (mNIHSS); ▪ 25% improvement of full-arm motor function on the hand score of the Fugl-Meyer Assessment (hFMA).	30 days	40	40	▪ 32-34 participants treated with lithium and placebo respectively completed the study; ▪ No difference between the groups on the mNIHSS (p=0.402); ▪ 14/32 and 5/34 participants treated with lithium and placebo showed ≥25% improvement in the hFMA (post-hoc OR=4.51; 5%CI=1.24, 18.41).
Sun et al.(2019)[8]	▪ Ischaemic stroke during the preceding year; ▪ Age>40years	Pre-post open-label use of lithium with a target concentration of 0.4-0.8mmol/L.	▪ Cognitive function; ▪ Grey matter volume.	60 days	12	NA	▪ No cognitive benefits; ▪ No change in grey matter volume; ▪ Post-hoc: percentage increase in grey matter volume was higher for patients treated with 300mg/d compared with those on lower daily dosages.

mNIHSS, Modified National Institute of Health Stroke Scale score.

Figure 1.

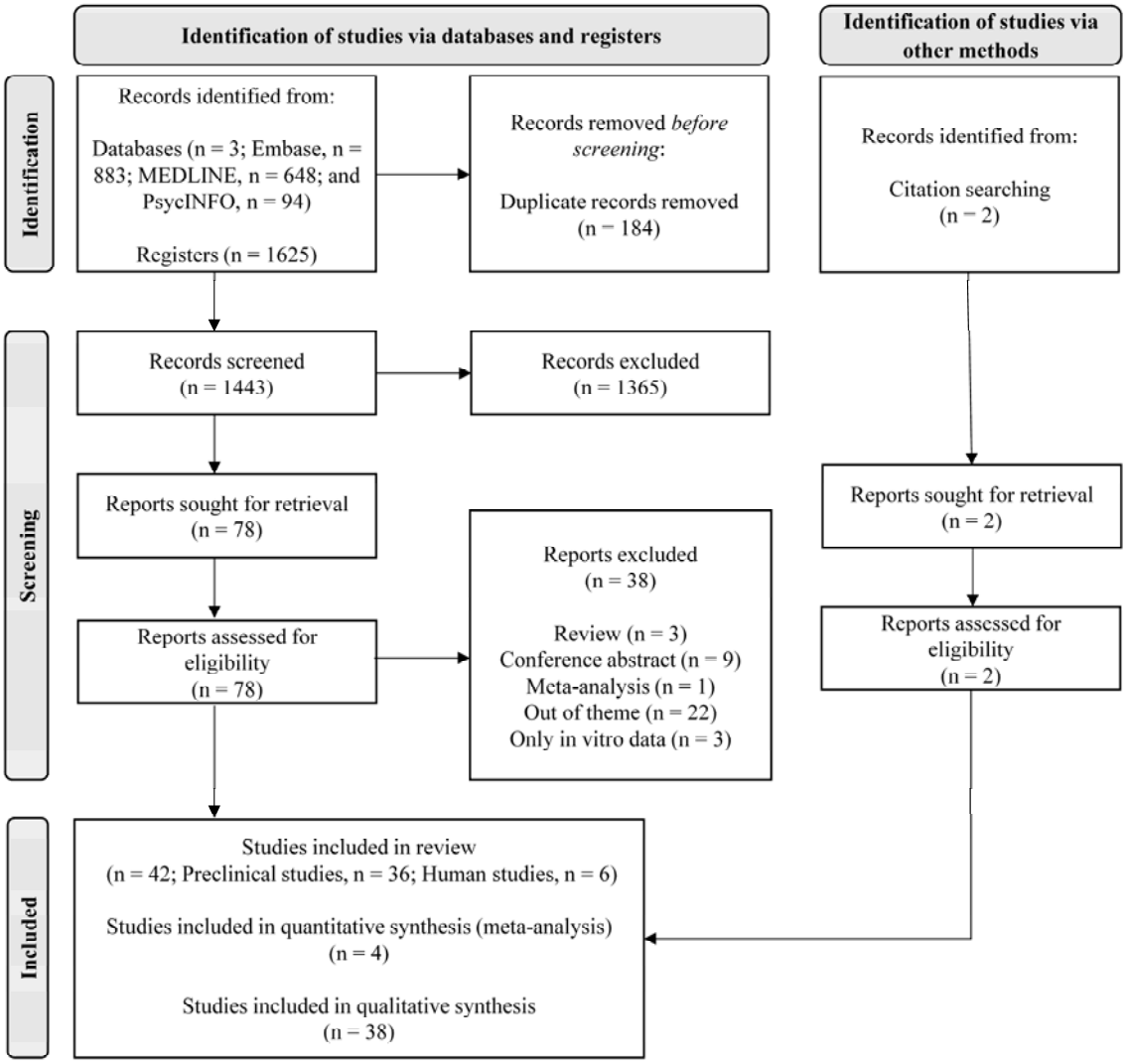
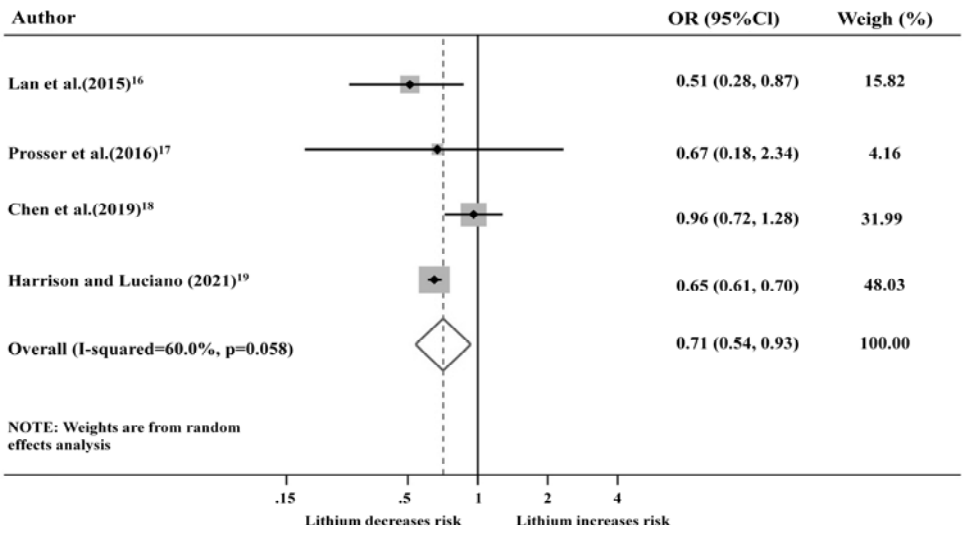
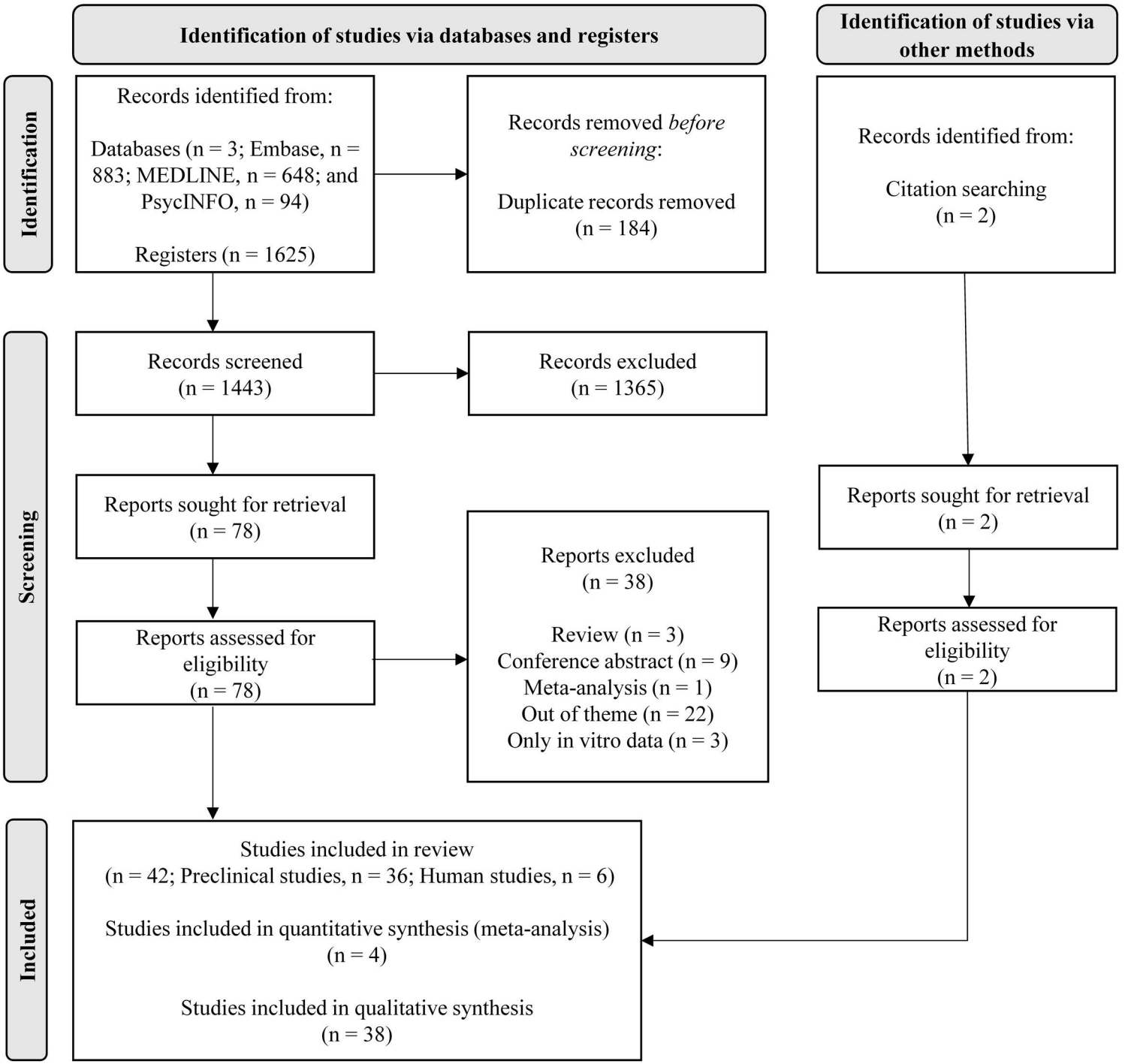
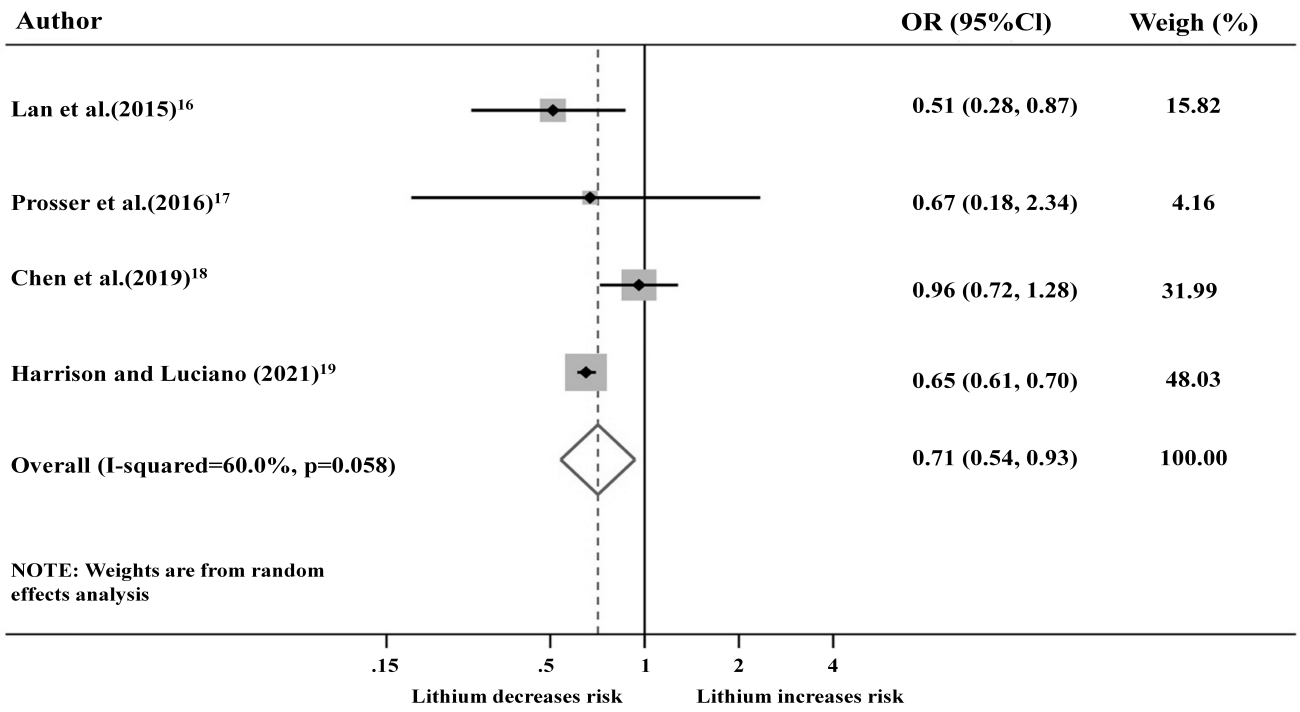


Figure 2.




Identification of studies via databases and registers
Identification of studies via other methods
Identification
Records identified from:
Databases (n = 3; Embase, n = 883; MEDLINE, n = 648; and PsycINFO, n = 94)
Registers (n = 1625)
Records removed *before screening*:
Duplicate records removed (n = 184)
Records identified from:
Citation searching (n = 2)
Screening
Records screened (n = 1443)
Records excluded (n = 1365)
Reports sought for retrieval (n = 78)
Reports sought for retrieval (n = 2)
Reports assessed for eligibility (n = 78)
Reports excluded (n = 38)
Review (n = 3)
Conference abstract (n = 9)
Meta-analysis (n = 1)
Out of theme (n = 22)
Only in vitro data (n = 3)
Reports assessed for eligibility (n = 2)
Included
Studies included in review (n = 42; Preclinical studies, n = 36; Human studies, n = 6)
Studies included in quantitative synthesis (meta-analysis) (n = 4)
Studies included in qualitative synthesis (n = 38)


Author
OR (95%CI)
Weigh (%)
Lan et al.(2015)[16]
0.51 (0.28, 0.87)
15.82
Prosser et al.(2016)[17]
0.67 (0.18, 2.34)
4.16
Chen et al.(2019)[18]
0.96 (0.72, 1.28)
31.99
Harrison and Luciano (2021)[19]
0.65 (0.61, 0.70)
48.03
Overall (I-squared=60.0%, p=0.058)
0.71 (0.54, 0.93)
100.00
NOTE: Weights are from random effects analysis
.15
.5
1
2
4
Lithium decreases risk
Lithium increases risk