SUPPLEMENTARY MATERIAL

Inclusion and Exclusion Criteria

Inclusion criteria:

- Subjects aged 18 years or older, regardless of gender, race or social status;
- Patients presenting an episode of behavioral change lasting 4 or more days characterized by elevated, expansive, or irritable mood, and abnormally increased energy. Additionally, at least three of the following were present: inflated self-esteem/grandiosity, decreased need for sleep, excessive talkativeness, flight of ideas, distractibility, increased goal-directed activity, and excessive involvement in activities with potentially harmful consequences.
- Reports not providing details on behavioral changes as defined in the previous point remained eligible if authors explicitly stated that contemporary criteria for manic, hypomanic or mixed affective state were met.
- At least one confirmed (either in vivo or post-mortem) brain lesion caused by a tumor or a vascular insult, i.e. infarctions, hemorrhage, arterio-venous malformations, regardless of location, size and age of occurrence.
- The lesion must have occurred before the first manifestations of manic or mixed affective symptoms.
- Patients with brain lesion diagnosed or documented after the first manifestations of mania, BPD or mixed affective state were still considered eligible given unequivocal evidence that the lesion was acquired before the psychiatric manifestations developed (e.g. indolent tumor with neurologic signs prior to psychiatric manifestations).

Exclusion criteria:

- Diagnosis of manic episode or mixed affective state before the age of 18 years.
- Evidence of manic episode or mixed affective state prior to the occurrence of the brain insult, or when the chronological relationship between the two events was unclear or equivocal.
- Presumed brain lesion that was not confirmed by in vivo imaging or post-mortem methods.
- Presence of factors other than the structural brain-insult that may have induced the manic episode, including, but not limited to, use of anti-depressant medication, corticosteroids or illicit substances, treatment with electroconvulsive therapy or deep-brain stimulation, or diagnosis of endocrine conditions or infection.
- Lesions depicted in group diagrams, when it was not possible to individualize each patient lesion.

Search Terms

PubMed: ((bipolar disorder) OR (manic) OR (mania)) AND ((cerebral) OR (cerebellum) OR (brain) OR (central nervous system)) AND ((injury) OR (tumor) OR (neoplasm) OR (mass) OR (infection) OR (abscess) OR (cyst) OR (stroke) OR (hemorrhage) OR (bleeding))

Web of Science: TS=(bipolar disorder OR manic OR mania) AND TS=(cerebral OR cerebellum OR brain OR central nervous system) AND TS=(lesion OR focus OR injury OR tumor OR neoplasm OR mass OR infection OR abscess OR cyst OR stroke OR hemorrhage OR bleeding) NOT TS=(animal OR monkey OR chimpanzee OR mouse OR mice OR rat OR cat OR dog OR rabbit OR bird OR fish OR child)

Supplementary Figures

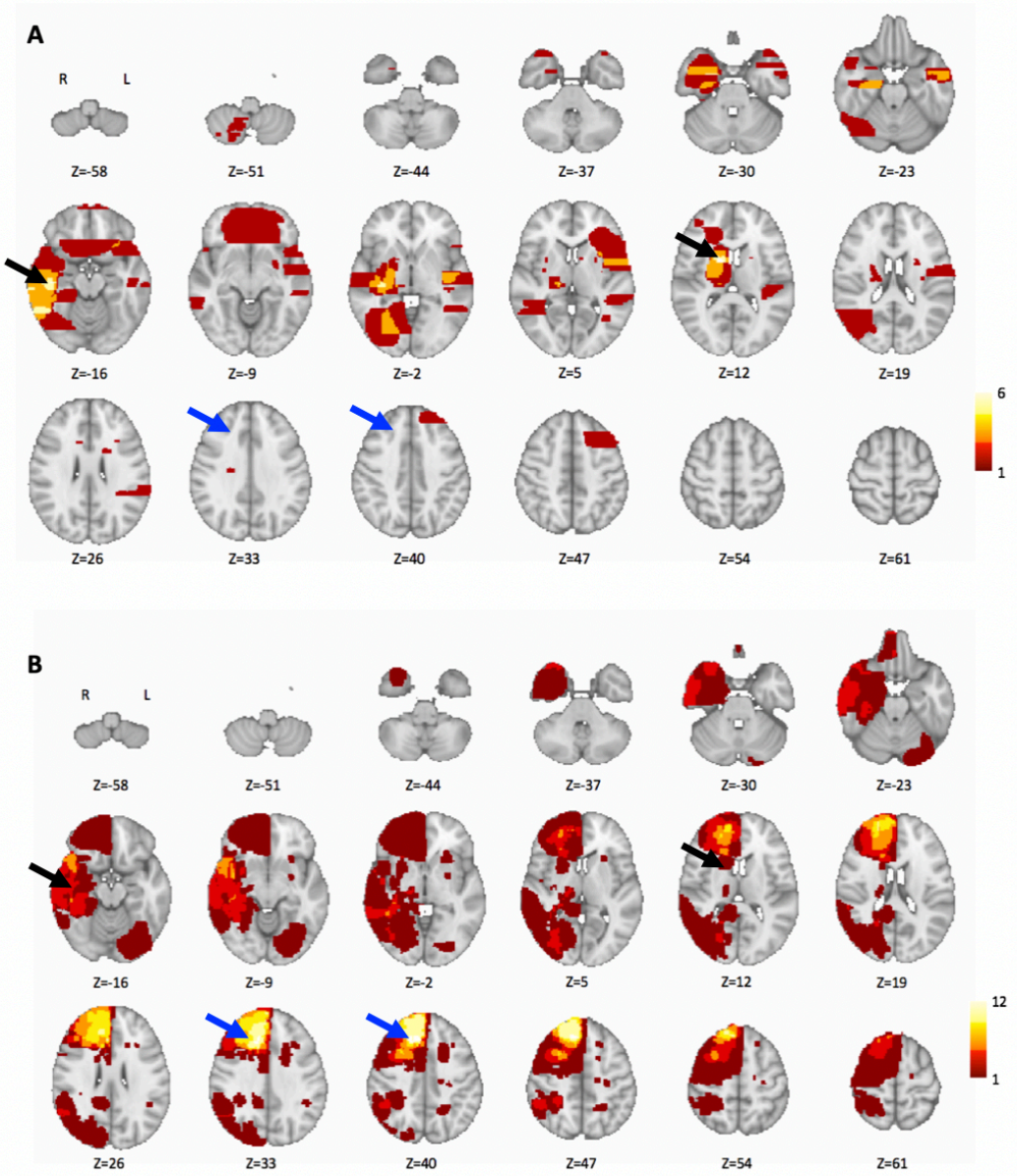


Figure S1. Overlap in lesion location for each mania lesion cohort. In the mania lesion cohort derived from a systematic literature search (N=41), where lesion locations are defined in two-dimensions (2D), maximum overlap (black arrows) included only 6/41 lesions and occurred in the right temporal lobe and right basal ganglia (**A**). In a mania lesion cohort derived from chart review at an academic medical center (N=15), where lesion locations are defined in three-dimensions, maximum overlap (blue arrow) included 12/15 lesions and occurred in the right superior frontal lobe (**B**). Note that lesion locations are heterogeneous between cohorts: regions of maximum overlap in the literature cohort were only impacted by one lesion in the clinical cohort (black arrows in panel B), while maximum overlap in the clinical cohort was not impacted by any lesion in the literature cohort (blue arrows in panel A).

Figure S2. Additional brain slices for mania lesion network maps.

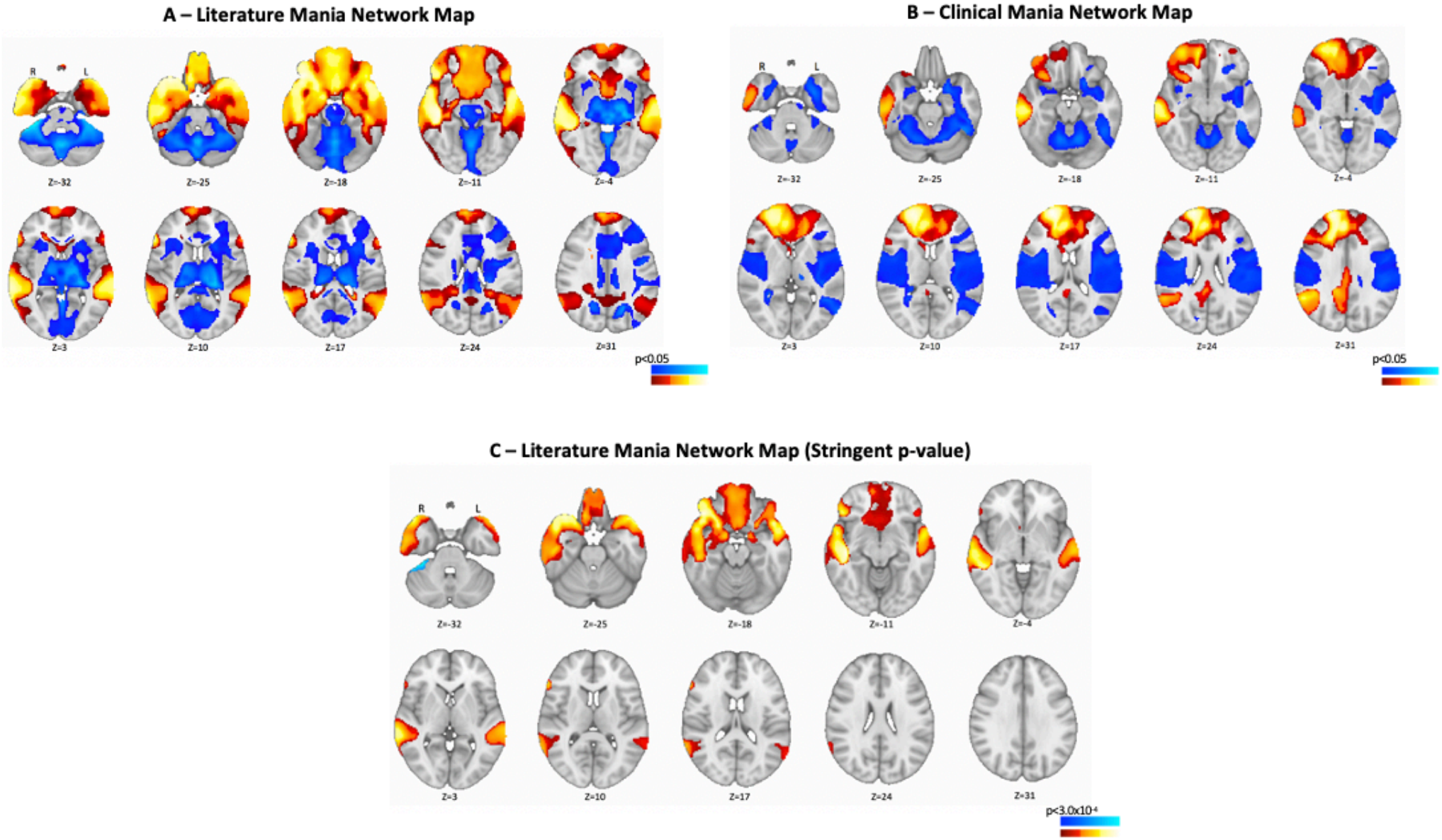


Figure S2. Additional brain slices for mania lesion network maps. Mania lesion network maps were obtained by statistically comparing lesion network maps from each mania cohort to lesion network maps from the respective control cohort. The literature mania lesion cohort (n = 41) was compared to a cohort of lesions causing several non-psychiatric symptoms (asterixis, aphasia, freezing of gait and post stroke pain), obtained from similar literature searches (n=79) (**A**). The clinical mania lesion cohort (n = 15) was compared to a cohort of control lesions from a database of stroke lesions not associated with any specific symptoms (n=490) (**B**). The mania lesion network maps in panels **A** and **B** were obtained using a voxel-wise permutation-based two-sample t-test performed within FSL PALM (two thousand permutations) and were corrected for multiple comparisons using threshold free cluster enhancement and displayed at an FWE-corrected level of $p<0.05$. A more stringent voxel-based FWE-corrected level of $p<3.0x10^{-4}$ was used also used for the literature mania lesion network map, to enhance demonstration of the peak regions of that map (**C**). Warm and cold colors represent areas that are more or less connected to mania lesions as compared to controls, respectively.

Figure S3. Reliability of lesion tracing and network mapping techniques.

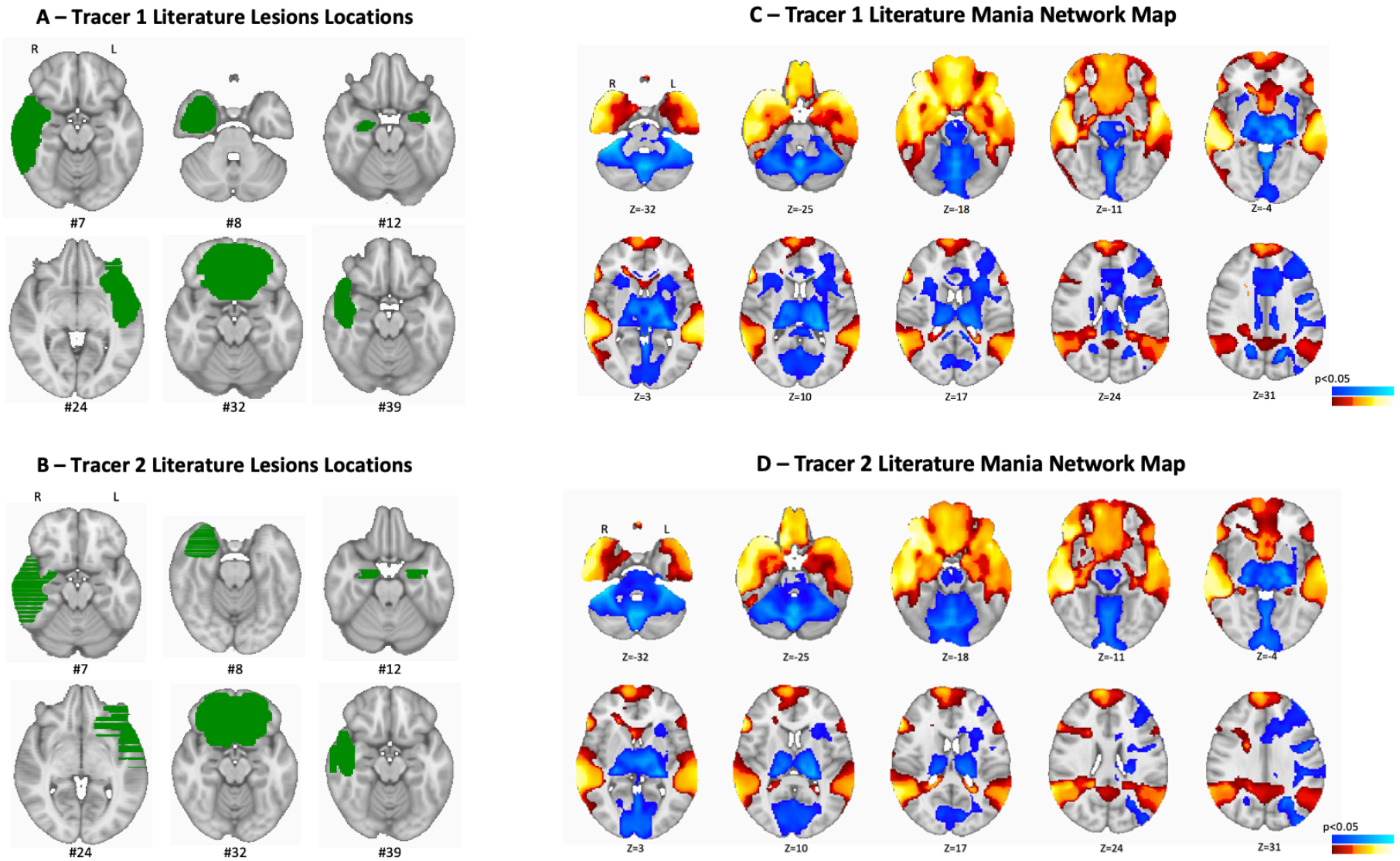


Figure S3. Reliability of lesion tracing and network mapping techniques. All 41 literature lesions were traced by two independent tracers onto a standard brain atlas, six representative example lesions are shown (**A** & **B**). To quantify the reliability of the tracing technique, the median distance between the center of gravity (CoG) for tracings of the same lesion was computed (8mm; 3 voxels) and was compared to the median distance between the CoG for different lesions (51mm; 26 voxels, $p<0.00001$). Literature mania lesion network maps contrasting each of the two sets of independent tracings of the mania lesions (n=41) with a set of control lesions (N=79) were also similar, with high spatial correlation (Pearson's r=0.96) reflecting very strong to excellent agreement between the two maps (**C** & **D**). Panels C and D were obtained using a voxel-wise permutation-based two-sample t-test performed within FSL PALM (two thousand permutations), corrected for multiple comparisons using threshold free cluster enhancement and displayed at an FWE-corrected level of $p<0.05$. Warm and cold colors represent areas that are more or less connected to mania lesions as compared to controls, respectively.

Figure S4. Additional brain slices for the conjunction and combined mania lesion network maps.

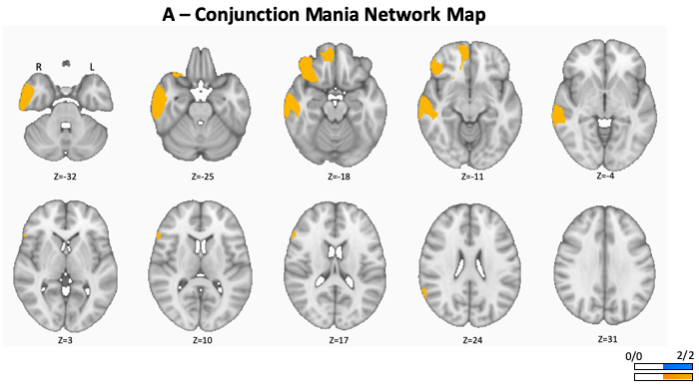


Figure S4. Additional brain slices for the conjunction and combined mania lesion network maps. A conjunction of the mania lesion network map derived from the literature cohorts and the mania lesion network map derived from the clinical cohorts shows connections significantly associated with mania in both cohorts tested independently (**A)**. This conjunction map was obtained by binarizing the maps depicted in figures S2B and S2C and computing their overlap. A combined mania lesion network map, obtained using a voxel-wise permutation-based two-sample t-test performed within FSL PALM (two thousand permutations). shows connections significantly associated with mania when including all mania lesion locations (n=56) and all control lesion locations (n=569) in a single combined analysis, including lesion dimensionality (2D in literature lesions vs. 3D in clinical lesions) as a covariate (**B**). Panel B was corrected for multiple comparisons using threshold free cluster enhancement and displayed at an FWE-corrected level of $p<0.05$. A more stringent voxel-based FWE-corrected level of $p<1.0x10^{-4}$ was used to enhance demonstration of peak regions of connectivity in the combined map (**C**). Warm and cold colors represent areas that are more or less connected to mania lesions as compared to controls, respectively.

Figure S5. Overlap of peak coordinates in the mania lesion network map with Brodmann Areas.

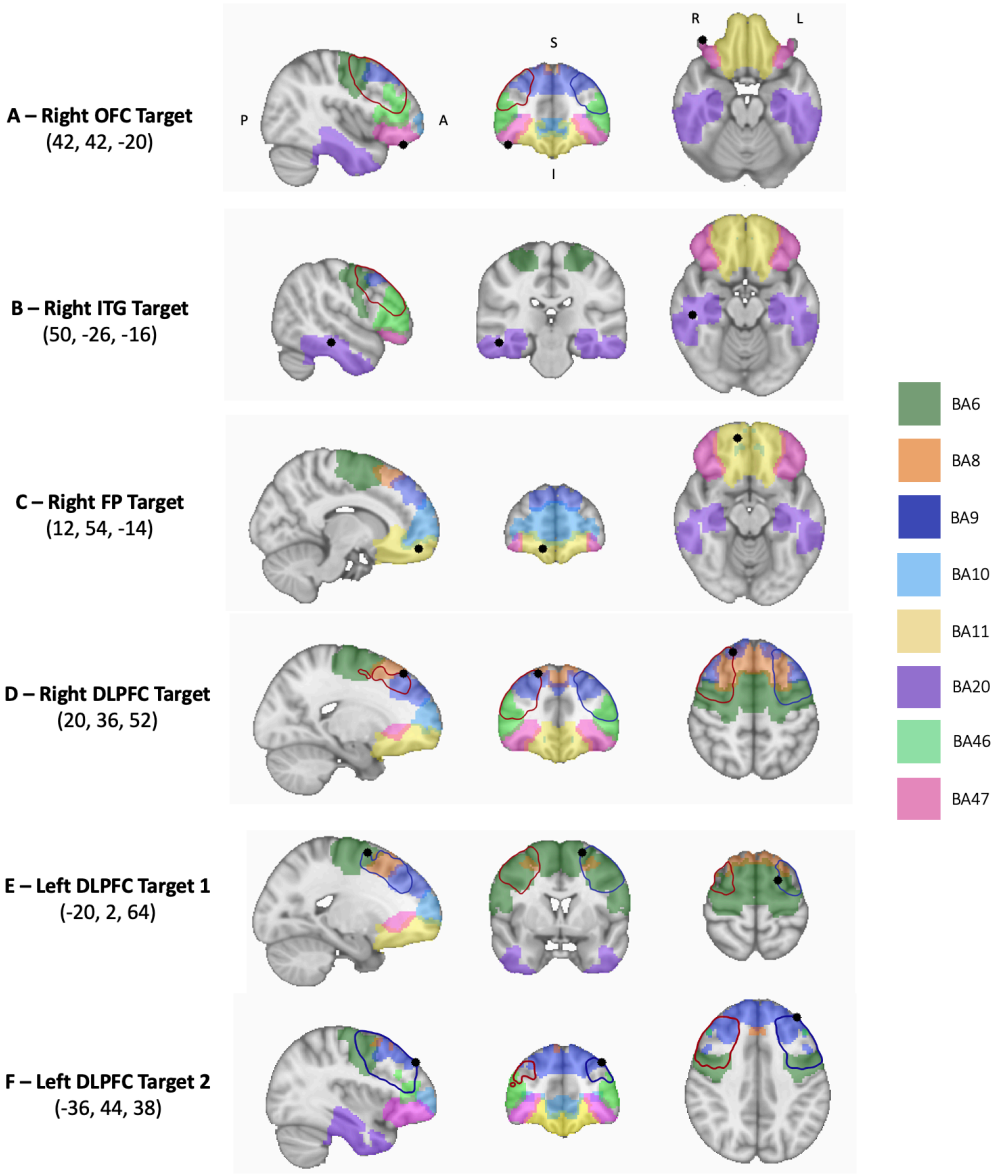
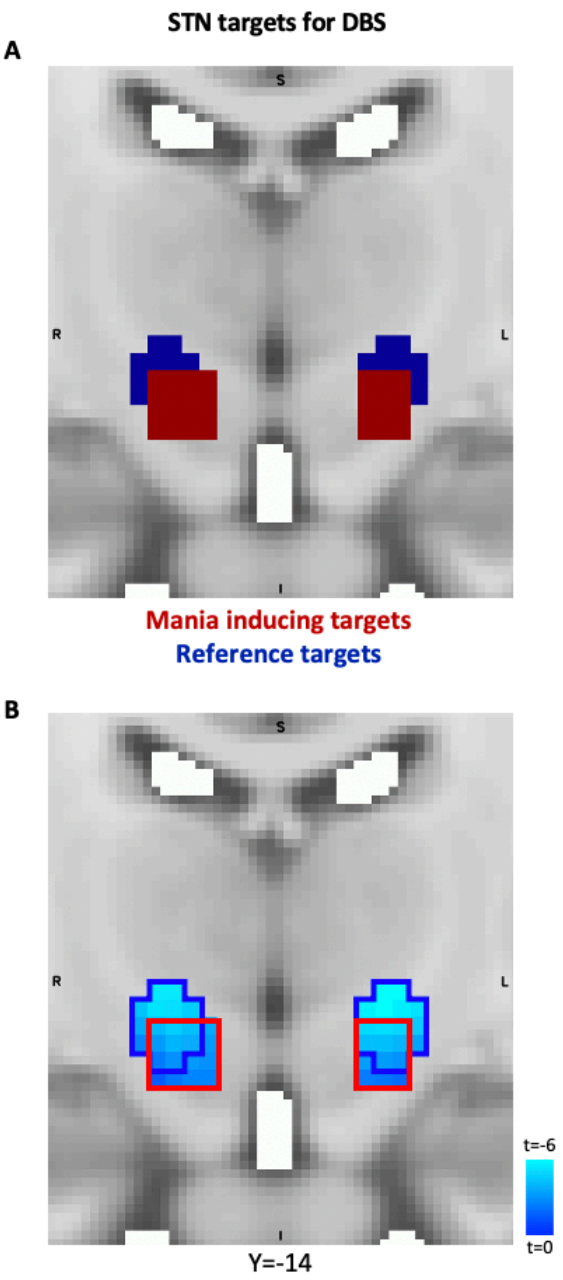


Figure S5. Overlap of peak coordinates in the mania lesion network map with Brodmann Areas. Peak coordinates from our combined mania lesion network map were identified across the entire brain (**A-C**, see Table S3), as well as in the right and left dorsolateral prefrontal cortex (**D-F**, see main text). In each image, the peak coordinate is represented as a black dot overlaid on a map of Brodmann areas. The outline for our a priori regions of interest in the left (blue outline) and right (red outline) dorsolateral prefrontal cortex are also shown for panels D-F. The positive peak in the right orbitofrontal cortex (OFC) overlaps with BA47 (pink) (**A**), while that in the right inferior temporal gyrus (ITG) overlaps with BA20 (purple) (**B**). The site in the right frontal pole (FP) overlaps with BA11 (yellow), very close to BA10 (light blue) (**C**). The positive peak in the right DLPFC overlaps with BA8 (orange) and BA9 (dark blue) (**D**), while the negative peaks in the left DLPFC overlap with BA6 (dark green), very close to BA8 (orange) (**E**) and with BA9 (dark blue) (**F**). Two negative peaks are reported for the left DLPFC since two distinct clusters of negative connectivity were found in the combined mania network map within this ROI (see Figure 7 in main text). Due to close proximity to some of the aforementioned areas, BA46 (light green) is also represented.

Figure S6. Intersection of subthalamic nucleus (STN) deep brain stimulation (DBS) sites with our mania lesion network map. DBS coordinates (**A**) previously associated with mania (red region) are slightly offset from the average STN DBS site (blue region). Intersection of these DBS sites with our combined mania lesion network map (**B**), is consistent with increased connectivity with the lesion network map at the mania inducing DBS site (red outline) compared to the standard DBS site (blue outline). Note that both STN DBS sites fall on negative regions in our mania lesion network, thus we would expect the overall incidence of mania following STN DBS to be low, but with greater *relative* risk at the mania inducing DBS site. Connectivity map in panel B was obtained using a voxel-wise permutation-based two-sample t-test performed within FSL PALM (two thousand permutations).



Supplementary Tables

Table S1. Demographics and clinical information for literature cases of lesion-induced mania.

Case #	Author	Year	Age (M)	Gender	Time E-M	Scan	Lesion Side	Etiology	D*	FH*	MM Recur.	Depr. Recur.	DSM 5 Criteria*										
													A	B1	B2	B3	B4	B5	B6	B7	C	Psy.	n.d.
1	Antelmi, E. (1)	2014	50	Female	1y	MRI	Bilateral	Infarction	0				1		1			1	1				
2	Asghar-Ali, A. A. (2)	2004	50	Female	n.d.	MRI	Bilateral	Multiple Sclerosis	0							1	1		1		1	1	
3	Belli, H. (3)	2012	62	Male	n.d.	MRI	Left	Infarction	0		0	0	1	1	1	1	1		1	1	1	1	
4	Benjamin, S. (4)	2000	41	Male	1w	MRI	Left	AVM	0		1	0	1	0	1	1			1			0	
5	Benke, T. (5)	2002	38	Male	48h	MRI	Bilateral	Infarction	0		0	0	1	1		1	1	1	1			0	
6	Bogousslavsky, J. (6)	1988	72	Female	i	CT	Right	Infarction	0		0	0	1			1	1		1				
7	Bornke, C. (7)	1998	67	Female	n.d.	CT	Right	Infarction	0		0	0	1	1	1	1	1		1		1	1	
8	Brooks, J. O. (8)	2005	60	Male	n.d.	MRI	Right	Tumor	1		0	0	1	1	1	1			1		1	1	
9	Claude, H. (9)	1928	52	Female	n.d.	Autposy	Right	Tumor	0				1	1	1	1	1		1		1	1	
10	Danel, T. (10)	1989	57	Male	11m	CT	Right	Infarction	0		1	1											1
11	Das, P. (11)	2015	86	Male	1m	MRI	Right	Infarction	0		1		1	1	1	1	1		1		1	1	
12	Filley, C. M. (12)	1995	56	Female	n.d.	MRI	Bilateral	Tumor	1							1	1		1				
13	Haq, M. Z. (13)	2009	26	Female	n.d.	CT	Bilateral	Tumor	0		0	0	1	1	1	1		1	1		1	1	
14	Hunt, N. (14)	1990	n.d.	Female	n.d.	CT	Right	AVM	1		1	1	1	1					1				
15	Koreki, A. (15)	2012	68	Male	6w	CT	Right	Hemorrhage	0		0	0	1		1	1	1		1				
16	Kulisevsky, J. (16)	1993	81	Female	<3d	MRI	Right	Infarction	0		0	0	1	1	1	1	1	1	1		1	1	
17	Liu, C. Y. (17)	1996	48	Male	4m	MRI	Left	Infarction	0		0	0	1	1	1	1	1		1			0	
18	Modrego, P. J. (18)	2000	19	Female	2m	MRI	Bilateral	Multiple Sclerosis	0	1	1		1		1	1	1		1		1	1	
19	Mumoli, N. (19)	2013	55	Male	n.d.	MRI	Right	Tumor	1		1		1					1	1	1			
20	Nagaratnam, N. (20)	2006	72	Female	3y	CT	Left	Infarction	0				1		1	1	1		1				
21			80	Male	n.d.	CT	Bilateral	Infarction	0				1		1	1			1		1	1	

Case #	Author	Year	Age (M)	Gender	Time E-M	Scan	Lesion Side	Etiology	D*	FH*	MM Recur.	Depr. Recur.	DSM 5 Criteria*										
													A	B1	B2	B3	B4	B5	B6	B7	C	Psy.	n.d.
22	Okun, M. S. (21)	2003	72	Female	i	MRI	Left	Surgery					1		1				1				
23			56	Female	i	MRI	Bilateral	Surgery						1	1	1			1				
24	Pathak, A. (22)	2014	65	Male	2d	CT	Left	Infarction	0				1	1	1	1			1		1	1	
25	Rocha, F. F. (23)	2008	57	Male	n.d.	MRI	Right	Infarction	0		0	0	1		1	1	1						
26	Salazar-Calderon, V. H. P. (24)	1993	27	Female	n.d.	CT	Right	Tumor	1				1	1	1	1			1		1	1	
27	Sidhom, Y. (25)	2014	23	Female	n.d.	MRI	Right	Surgery	0	1			1	1	1				1		1		
28	Starkstein, S. E. (26)	1988	66	Male	1y	CT	Bilateral	Infarction	0	1			1	1	1	1			1		1	1	
29			35	Female	n.d.	CT	Right	Hemorrhage	0	1			1	1	1	1	1		1		1	1	
30			63	Male	4w	CT	Bilateral	Surgery	0					1	1				1	1	1	1	
31			61	Female	i	CT	Right	Surgery	0		1		1		1	1			1				
32			48	Female	n.d.	CT	Right	Tumor	0		1		1			1			1				
33			28	Male	i	CT	Right	Surgery	0	0	1		1	1		1	1		1		1	1	
34	Starkstein, S. E. (27)	1990	55	Male	4wk	CT	Right	Infarction	0				1	1	1	1		1			1	1	
35			79	Female	i	CT	Right	Infarction	0		1		1	1	1	1	1		1		1	1	
36			49± 17	Male	n.d.	CT	Right	Infarction	0				1	1	1	1	1		1	1	1	1	
37				Male		MRI	Right	Infarction	0				1	1	1	1	1		1	1	1	1	
38				Male		MRI	Right	AVM	0	1			1	1	1	1	1		1	1	1	1	
39				Male		CT	Right	Hemorrhage	0				1	1	1	1	1		1	1	1	1	
40	Stern, K. (28)	1942	30	Female	n.d.	Scheme	Right	Tumor	0	1			1		1	1	1		1		1		
41	Trillet, M. (29)	1995	71	Male	2-3d	MRI	Left	Hemorrhage	0				1		1	1	0		1		0	0	

AVM – Arteriovenous malformation; CT – Computerized tomography; d – days; D – Depressive episode before the event; Depr. – Depressive episode; E – Event; FH – Family history of affective disorder or suicide; h – hours; Imm. – immediate after event; m – months; MM – Manic/mixed state episode; MRI – Magnetic resonance imaging; n.d. – non defined; Psy. – Psychotic symptoms; Recur. – Recurrence of affective episode; w – weeks; y – years

* 0 means absence; 1 means presence; blank means not defined/unknown

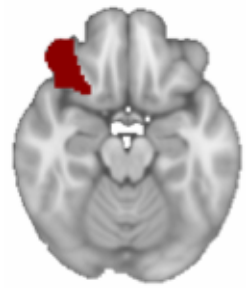
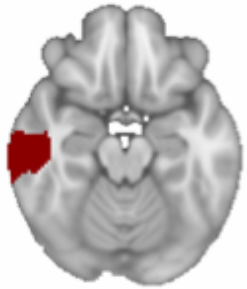
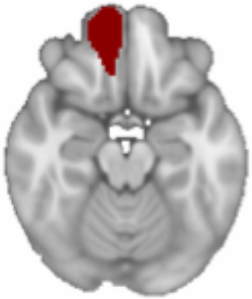
Table S2. Demographics and clinical information for clinical cases of lesion-induced mania.

Case #	Age (MM)	Gender	Time E-MM	Scan	Lesion Side	Etiology	D*	FH*	MM Recur.*	Depr. Recur.*	DSM 5 Criteria*										
											A	B1	B2	B3	B4	B5	B6	B7	C	Psy.	n.d.
1	64	Female	6m	MRI	Right	Infarction	0				1		1			1	1		1	1	
2	47	Female	i	MRI	Bilateral	Infarction	1	1	0	1	1		1	1			1				
3	72	Female	1y	MRI	Right	Infarction	1	1			1						1	1	1	1	
4	60	Male	n.d.	MRI	Right	Tumor	1		0	0	1		1		1	1	1				
5	70	Female	n.d.	MRI	Right	Hemorrhage					1				1	1	1		1		
6	50	Male	>3y	MRI	Right	Infarction	0	0	1	1	1		1				1	1			
7	51	Male	>10y	MRI	Bilateral	Tumor	1	0	0	1	1	1	1	1			1	1			
8	33	Male	8y	MRI	Right	Tumor	0	0	1	1	1		1				1	1			
9	64	Female	3y	MRI	Right	Infarction	0	0	0	0	1			1	1		1	1	1		
10	79	Female	1m	MRI	Right	Hemorrhage	0				1	1		1	1		1		1	1	
11	79	Male	n.d.	MRI	Bilateral	Tumor	1				1	1	1				1	1			
12	55	Male	i	MRI	Right	Hemorrhage	0	0	1	1	1		1	1			1	1			
13	74	Male	>4y	MRI	Right	Tumor					1		1	1	1	1	1	1			
14	77	Male	2y	MRI	Bilateral	Hemorrhage	0	0	1	0		1		1			1		1	1	
15	60	Male	<17y	MRI	Bilateral	Tumor	0	1	1	0	1			1			1	1	1		

D – Depressive episode before the event; Depr. – Depressive episode; E – Event; FH – Family history of affective disorder or suicide; i – immediate after event; m – months; MM – Manic/mixed state episode; MRI – Magnetic resonance imaging; n.d. – non defined; Psy. – Psychotic symptoms; Recur. – Recurrence of affective episode; w – weeks; y – years

* 0 means absence; 1 means presence; blank means not defined/unknown

Table S3. Selected regions of interest in the mania lesion network map and respective peak coordinates.

ROIs Anatomy (Harvard-Oxford Atlas)		ROIs Peak			
		X	Y	Z	T-value
	Right Frontal Orbital Cortex	42	42	-20	8.19
	Right Inferior Temporal Gyrus	50	-26	-16	8.01
	Right Frontal Pole	12	54	-14	7.95

Three regions of interest (ROI) were identified in the combined mania lesion network map (see Figure S4C, voxel-based FWE-corrected $p<1x10^{-4}$) using a Python 2 notebook, *nilearn*, and a clustered volume threshold of 200 mm^3 . The resulting ROIs were the right orbitofrontal cortex, right inferior temporal gyrus and right frontal pole, according to the Harvard-Oxford atlas (red regions). Peak coordinates within each ROI were identified from the combined mania lesion network map using *fslstats*.

Supplementary References:

1. Antelmi E, Fabbri M, Cretella L, Guarino M, and Stracciari A. Late onset bipolar disorder due to a lacunar state. *Behav Neurol.* 2014;2014:780742.
2. Asghar-Ali AA, Taber KH, Hurley RA, and Hayman LA. Pure neuropsychiatric presentation of multiple sclerosis. 2014.
3. Belli H, Akbudak M, Ural C, and Kulacaoglu F. Solitary lesion in ponto-mesencephalic area related secondary mania: a case report. *Psychiatr Danub.* 2012;24(2):223-5.
4. Benjamin S, Kirsch D, Visscher T, Ozbayrak KR, and Weaver JP. Hypomania from left frontal AVM resection. *Neurology.* 2000;54(6):1389-90.
5. Benke T, Kurzthaler I, Schmidauer C, Moncayo R, and Donnemiller E. Mania caused by a diencephalic lesion. *Neuropsychologia.* 2002;40(3):245-52.
6. Bogousslavsky J, Ferrazzini M, Regli F, Assal G, Tanabe H, and Delaloye-Bischof A. Manic delirium and frontal-like syndrome with paramedian infarction of the right thalamus. *J Neurol Neurosurg Psychiatry.* 1988;51(1):116-9.
7. Bornke C, Postert T, Przuntek H, and Buttner T. Acute mania due to a right hemisphere infarction. *European Journal of Neurology.* 1998;5(4):407-9.
8. Brooks JO, 3rd, and Hoblyn JC. Secondary mania in older adults. *Am J Psychiatry.* 2005;162(11):2033-8.
9. Claude H, Baruk H, Lamache A, and Cuel J. Manic Excitation and Cerebral Tumor. *Encephale-Revue De Psychiatrie Clinique Biologique Et Therapeutique.* 1928;23(1):9-19.
10. Danel T, et al. Mood disorders and right hemisphere infarction. *Encephale.* 1989;15(6):549-53.
11. Das P, Chopra A, Rai A, and Kuppuswamy PS. Late-onset recurrent mania as a manifestation of Wallenberg syndrome: a case report and review of the literature. *Bipolar Disorders.* 2015;17(6):677-82.
12. Filley CM, and Kleinschmidt-DeMasters BK. Neurobehavioral presentations of brain neoplasms. *West J Med.* 1995;163(1):19-25.
13. Haq MZ, Dubey I, Khess CR, Das U, and Kumar R. Bipolar disorder and tuberous sclerosis complex: is it a mere coincidence? *CNS Spectr.* 2009;14(11):643-7.
14. Hunt N, and Silverstone T. Seasonal affective disorder following brain injury. *The British journal of psychiatry : the journal of mental science.* 1990;156:884-6.
15. Koreki A, Takahata K, Tabuchi H, and Kato M. Increased left anterior insular and inferior prefrontal activity in post-stroke mania. *BMC Neurol.* 2012;12:68.
16. Kulisevsky J, Berthier ML, and Pujol J. Hemiballismus and Secondary Mania Following a Right Thalamic Infarction. *Neurology.* 1993;43(7):1422-4.
17. Liu CY, Wang SJ, Fuh JL, Yang YY, and Liu HC. Bipolar disorder following a stroke involving the left hemisphere. *Australian and New Zealand Journal of Psychiatry.* 1996;30(5):688-91.
18. Modrego PJ, and Ferrandez J. Familial multiple sclerosis with repetitive relapses of manic psychosis in two patients (mother and daughter). *Behavioural Neurology.* 2000;12(4):175-9.

19. Mumoli N, Pulera F, Vitale J, and Camaiti A. Frontal lobe syndrome caused by a giant meningioma presenting as depression and bipolar disorder. *Singapore Med J.* 2013;54(8):e158-9.
20. Nagaratnam N, Wong KK, and Patel I. Secondary mania of vascular origin in elderly patients: a report of two clinical cases. *Arch Gerontol Geriatr.* 2006;43(2):223-32.
21. Okun MS, Bakay RA, DeLong MR, and Vitek JL. Transient manic behavior after pallidotomy. *Brain and cognition.* 2003;52(2):281-3.
22. Pathak A, and Srivastava M. Post-stroke mania–a case report. *ASEAN Journal of Psychiatry.* 2014;15(2):209-12.
23. Rocha FF, Carneiro JG, Pereira Pde A, Correa H, and Teixeira AL. Poststroke manic symptoms: an unusual neuropsychiatric condition. *Rev Bras Psiquiatr.* 2008;30(2):173-4.
24. Salazar-Calderon Perriggo VH, Oommen KJ, and Sobonya RE. Silent solitary right parietal chondroma resulting in secondary mania. *Clin Neuropathol.* 1993;12(6):325-9.
25. Sidhom Y, et al. Bipolar Disorder and Multiple Sclerosis: A Case Series. *Behavioural Neurology.* 2014.
26. Starkstein SE, Boston JD, and Robinson RG. Mechanisms of mania after brain injury. 12 case reports and review of the literature. *J Nerv Ment Dis.* 1988;176(2):87-100.
27. Starkstein SE, et al. Mania after brain injury: neuroradiological and metabolic findings. *Ann Neurol.* 1990;27(6):652-9.
28. Stern K, and Dancey TE. Glioma of the diencephalon in a manic patient. *American Journal of Psychiatry.* 1942;98(5):716-9.
29. Trillet M, Vighetto A, Croisile B, Charles N, and Aimard G. Hemiballismus with logorrhea and thymo-affective disinhibition caused by hematoma of the left subthalamic nucleus. *Rev Neurol (Paris).* 1995;151(6-7):416-9.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	16-20
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	16-20 1-2 (Supp. Mat.)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	16-20 1-2 (Supp. Mat.)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	16-20 1-2 (Supp.)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	16-20
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	16-20
Bias	9	Describe any efforts to address potential sources of bias	18-20
Study size	10	Explain how the study size was arrived at	16-17

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	16-20
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	17-23
		(*b*) Describe any methods used to examine subgroups and interactions	18-20
		(*c*) Explain how missing data were addressed	18-20
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	16-20
		(*e*) Describe any sensitivity analyses	18-20
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8 14-16 (Supp.)
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8 14-16 (Supp.)
		(b) Indicate number of participants with missing data for each variable of interest	14-16 (Supp.)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	14-16 (Supp.)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-8 14-16 (Supp.)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(*b*) Report category boundaries when continuous variables were categorized	7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	16
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	16; 1-2 (Supp.)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3 (Supp.)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3 (Supp.)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	16; 1-2 (Supp.)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	16; 1-2 (Supp.)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	16; 14-16 (Supp.)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	18-20
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	17-20
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	17-20

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	17-20
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	20-23
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7; 1-2 (Supp.); 14-16 (Supp.)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7; 1-2 (Supp.); 14-16 (Supp.)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

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