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Stroke risk following traumatic brain injury: systematic review and meta-analysis

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Abstract

Background

Traumatic brain injury (TBI) is a global health problem; worldwide, >60 million people experience a TBI each year and incidence is rising. TBI has been proposed as an independent risk factor for stroke.

Aims

To investigate the association between TBI and stroke risk.

Summary of review

We undertook a systematic review of MEDLINE, EMBASE, CINAHL, and The Cochrane Library from inception to 4th December 2020. We used random-effects meta-analysis to pool hazard ratios (HR) for studies which reported stroke risk post-TBI compared to controls.

Searches identified 10,501 records; 58 full texts were assessed for eligibility and 18 met the inclusion criteria. The review included a large sample size of 2,606,379 participants from four countries. Six studies included a non-TBI control group, all found TBI patients had significantly increased risk of stroke compared to controls (pooled HR 1.86; 95% CI 1.46-2.37). Findings suggest stroke risk may be highest in the first four months post-TBI, but remains significant up to five years post-TBI. TBI appears to be associated with increased stroke risk regardless of severity or subtype of TBI. There was some evidence to suggest an association between reduced stroke risk post-TBI and Vitamin K antagonists and statins, but increased stroke risk with certain classes of antidepressants.

Conclusion

TBI is an independent risk factor for stroke, regardless of TBI severity or type. Post-TBI review and management of risk factors for stroke may be warranted.

Introduction

Traumatic brain injury (TBI) is a global health problem; worldwide, more than 60 million people experience a TBI each year and incidence is rising.[1] Increased incidence of TBI has been attributed to increased falls in elderly populations, armed conflict, and sports related injury in high income countries, and increased road traffic accidents in low/middle income countries.[2, 3]

Advances in critical care, imaging, and the reorganisation of trauma health systems have led to a reduction in TBI-related mortality.[4] However, increased survival rates results in more people living with the long-term effects of TBI. These long-term effects are wide-ranging, including physical, psychological, and cognitive disabilities, and can cause huge burden at individual, family, and societal levels.[5] Long-term impacts are not exclusive to severe TBI and are often experienced by patients with mild and moderate TBI.[6]

TBI has also been associated with long-term risk of neurological diseases, including dementia, Parkinson's disease, Alzheimer's disease, and epilepsy.[7-10] TBI has been proposed as an independent risk factor for stroke;[11] however, to our knowledge, no systematic reviews have explored stroke risk post-TBI. Stroke is a leading cause of death and disability worldwide, but stroke prevention medication and lifestyle change can reduce stroke risk.[12] Therefore, understanding the association between TBI and stroke is important to help inform healthcare for TBI patients. Characterising stroke risk post-TBI is particularly important given the changing epidemiology of TBI in high income countries among the elderly and the fact that older age is an independent risk factor for stroke. The aim of this review was to investigate the association between TBI and risk of stroke.

Material and methods

The review protocol was registered on PROSPERO prior to conducting literature searches (CRD42019121149).[13] The review methodology and reporting is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.[14]

Eligibility criteria

Studies were eligible if they included adult participants (≥18 years) who had experienced a TBI (any severity) and reported frequency, incidence, or risk estimates of stroke and/or transient ischemic attack (TIA) at any time point post-TBI. Studies of mixed populations were eligible if it was possible to extract data of TBI participants.

Eligible study designs were controlled, cohort, cross-sectional, and case control studies. Only peer-reviewed, full text publications or theses were included. To avoid language bias, non-English papers were eligible.

Information sources and search strategy

Searches were performed with no publication date restrictions in the following bibliographic databases: MEDLINE, EMBASE, CINAHL, and The Cochrane Library. Grey literature was searched from the following sources: Grey Matters by CADTH, OpenGrey, and Epistemonikos. Reference lists of relevant studies were also reviewed. The initial search was performed from inception to 14th December 2018, followed by an updated search from 2018 to 4th December 2020.

A combination of text words and index terms related to the condition (TBI) and the outcome (stroke/TIA) were utilised (Supplementary Figure 1).

Study selection, data extraction and critical appraisal

Literature search results were exported to EndNote V.X8.0 (Thomson Reuters, New York) and duplicates removed. Titles and abstracts of search results were screened and full texts obtained for potentially eligible studies. A standardised, pre-determined eligibility criteria checklist was used to select eligible studies (Supplementary Table 1). Data were extracted on study design, population, outcomes, and findings using a standardised, piloted data extraction form (Supplementary Table 2). An adapted version of the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) checklist was used to assess quality of included studies.[15]

All study selection, data extraction, and quality assessment processes were conducted independently and in duplicate by three authors (GT, CM and OLA); discrepancies were resolved by an additional reviewer (AB).

Data synthesis and statistical analysis

A random effects meta-analysis pooled hazard ratios (HRs) for studies which reported stroke risk post-TBI compared to non-TBI controls. The meta-analysis was performed using Review Manager Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Studies without a non-TBI comparator were narratively summarised and tables were created to facilitate comparisons. A narrative subgroup analysis was conducted for studies which reported time to stroke onset post-TBI; severity or subtype of TBI; and stroke type (ischemic and haemorrhagic).

Data availability

Data are available on request.

Results

Searches identified 10,501 records, of which 58 full texts were assessed for eligibility, and 18 met the inclusion criteria (Figure 1).

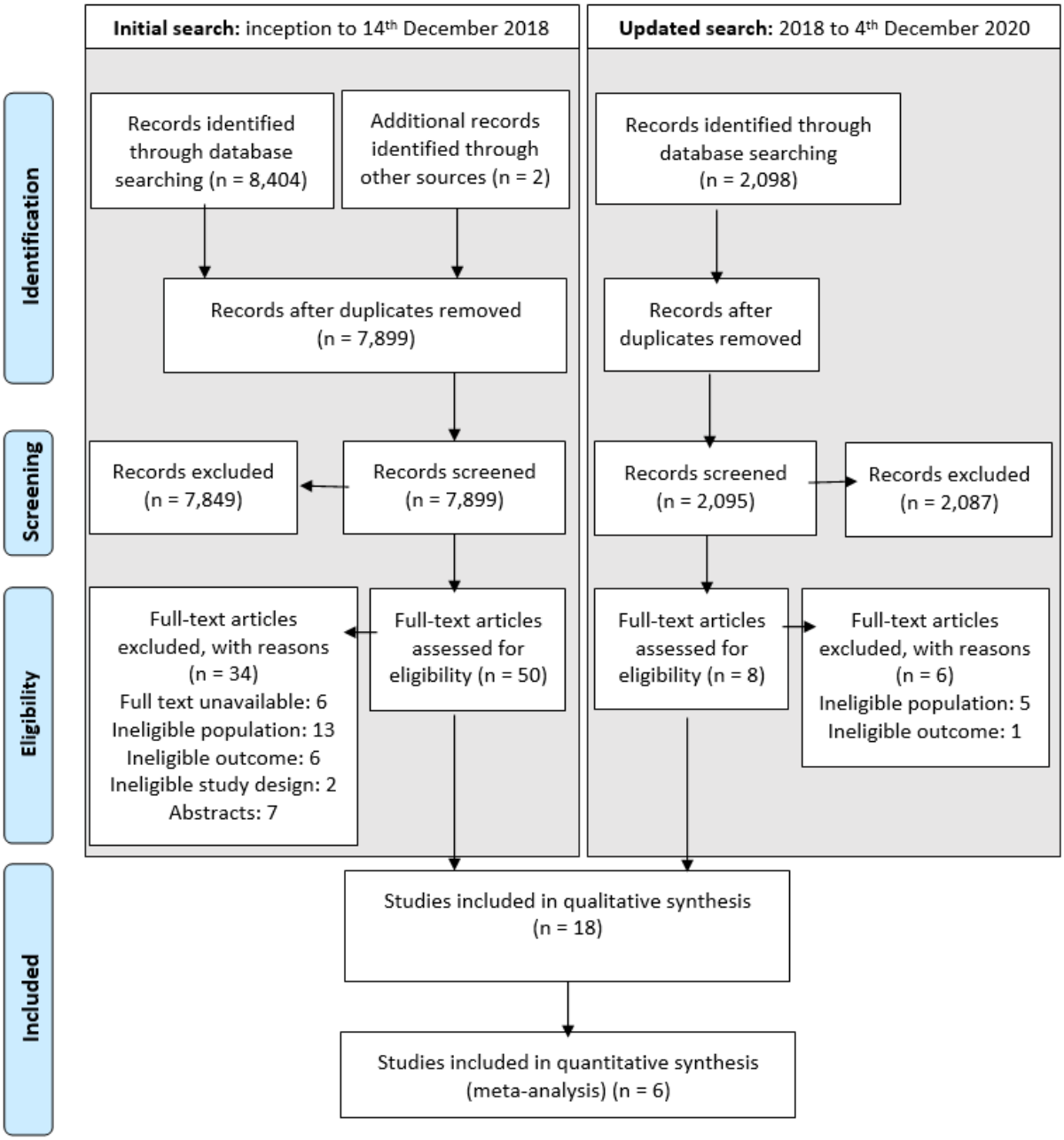

Figure 1: PRISMA flow chart

Study characteristics

The 18 studies included 2,606,379 participants and were from the United States,[16-24] Taiwan,[25-31] Croatia,[32] and Denmark.[33] All were retrospective cohort studies and eight different data sources were used (Table 1), most commonly the Taiwan National Health Insurance Research Database[16-18, 20, 21, 31] and United States Medicare administrative claims data.[24-30] The eligibility criteria and definitions of TBI and stroke for included studies are summarised in Supplementary Table 3.

Six studies explored stroke risk post-TBI compared to non-TBI controls (Table 1).[19, 26-29, 31] Eight studies investigated the association of stroke risk post-TBI with specific exposures: antidepressants;[18, 20] statins;[21] oral anticoagulants;[16, 33] traumatic subarachnoid haemorrhage (tSAH);[23] acupuncture;[30] and insomnia.[25] Two studies reported frequency of stroke post-TBI without a comparator[22, 32] and two studies compared stroke incidence pre- and post-TBI.[17, 24]

Table 1: Summary of the country, study period, data source, study arms, age, sex, and TBI severity for included studies (n=18 studies).

Author (year)	Country (study period)	Data source	Study arms (sample size)	Age (mean (SD), median [IQR])	Sex (Males: n, %)	TBI severity
Stroke risk post-TBI compared to non-TBI controls						
Burke (2013)	USA (2005-2009)	State Inpatient Databases; State Emergency Department Databases; Healthcare Cost and Utilization Project; and Agency for Healthcare Research and Quality	**Exposed:** TBI patients (n=436,630) **Unexposed:** non-TBI trauma patients (n=736,723)	TBI: 49.2 (22.4) Control: 50.3 (20.1)	TBI: 232,332 (53.2) Control: 373,513 (50.7)	Abbreviated Injury Scale: mean (SD): TBI: 4.6 (10.1) Control: 4.1 (3.6)
Chen (2011)	Taiwan (2001-2003)	Taiwan's National Health Insurance Research Database: Longitudinal Health Insurance Database 2000	**Exposed:** TBI patients (n=23,199) **Unexposed:** patients without TBI (n=69,597)	41.6 (18.4)	TBI: 12,431 (53.6) Control: 37,293 (53.6)	NR
Eric Nyam (2019)	Taiwan (2000-2012)	Taiwan's National Health Insurance Research Database:	**Exposed:** TBI patients (n=16,211)	NR	TBI: 9,829 (60.6)	NR

		Longitudinal Health Insurance Database 2000	**Unexposed:** patients without TBI (n=32,422)		Control: 19,676 (60.7)	
Lee (2014)	Taiwan (2007-2010)	Taiwan's National Health Insurance Research Database	**Exposed:** mild TBI patients (n=24,905) **Unexposed:** patients without TBI (n=719,811)	TBI: 46.1 (20.1) Control: 43.5 (16.3)	TBI: 11,814 (47.4) Control: 348,981 (48.5)	Mild
Liao (2014)	Taiwan (2000-2004)	Taiwan's National Health Insurance Research Database	**Exposed:** TBI patients (n=30,165) **Unexposed:** patients without TBI (n=120,660)	TBI: 44.5 (17.8) Control: 43.9 (17.3)	TBI: 15,202 (50.4) Control: 60,808 (50.4)	Mild: 10623 Skull fracture: 1281 Severe: 18261
Liu (2017)	Taiwan (1998-2005)	Taiwan's National Health Insurance Research Database	**Exposed:** patients with concussion (n=13,652) **Unexposed:** patients without concussion (n=13,652)	Concussion: 56.3 (12.1) Control: 56.2 (12.0)	Concussion: 6,267 (45.9) Control: 6,279 (46.0)	Mild: concussion
Association of stroke risk post-TBI with specific exposures						
Albrecht (2018)	USA (2006-2010)	Administrative claims data from USA Medicare beneficiaries	**Exposed:** antidepressant use after TBI (n=15,733)	79.7 (7.7)	9,852 (32)	NR

			Unexposed: no antidepressant use after TBI (n=15,153)			
Khokhar (2017)	USA (2006-2010)	Administrative claims data from USA Medicare beneficiaries	**Exposed:** antidepressant used at least once after TBI (n=20,859) **Unexposed:** No antidepressant use after TBI (n=43,355)	82.8 (8.0)	25,881 (40.2)	NR
Khokhar (2018)	USA (2006-2010)	Administrative claims data from USA Medicare beneficiaries	**Exposed:** statin use after TBI (n=50,173) **Unexposed:** no statins used after TBI (n=50,342)	81.0 (8.1)	34,965 (34.8)	NR
Albrecht (2014)	USA (2006-2009)	Administrative claims data from USA Medicare beneficiaries	**Exposed:** warfarin use after TBI (n=5,811) **Unexposed:** no warfarin use after TBI (n=4,971)	81.3 (7.3)	3,850 (36)	NR
Staerk (2018)	Denmark (2005-2016)	Danish national patient registry; Danish national prescription registry; Danish civil registration system	**Exposed:** VKAs/NOACs after TBI in AF patients (n=979) **Unexposed:** no VKAs/NOACs after TBI in AF patients (n=421)	79 [72, 85]	1,204 (60.4)	NR
Morris (2016)	USA (California: 2005-2010;	Inpatient discharges: data from California Office of Statewide Health Planning and	**Exposed:** TBI patients with tSAH (n=20,454)	48.9 (21.6)	TBI with tSAH: 14,826 (72.5)	NR

	NY: 2006-2013; Florida: 2005-2013)	Development, NY Statewide Planning and Research Cooperative System, and Florida Agency for Health Care Administration	**Unexposed:** TBI patients without tSAH (n=20,454)		TBI without tSAH: 14,950 (73.0)	
Shih (2014)	Taiwan (2000-2008)	Taiwan's National Health Insurance Research Database	**Exposed:** TBI patients receiving acupuncture (n=7,409) **Unexposed:** TBI patients without acupuncture (n=29,636)	Acupuncture: 42.5 (16.9) No acupuncture: 42.6 (17.1)	TBI with acupuncture: 3,895 (52.6) TBI without acupuncture: 15,580 (52.6)	Mild: 16,085 Moderate: 7,225 Severe: 13,735
Ao (2017)	Taiwan (1999-2013)	Taiwan's National Health Insurance Research Database: Longitudinal Health Insurance Database 2000	**Exposed:** TBI patients with insomnia (n=1,174) **Unexposed:** non-TBI patients with insomnia (n=5,870)	51.6 (17.3)	TBI 582 (49.6) Control: 2,910 (49.6)	NR
Frequency of stroke post-TBI without a comparator						
Kowalski (2017)	USA (2007-2015)	Traumatic Brain Injury Model Systems National Database	TBI patients (no comparator) (n=6,488)	42 (range 16–99)	4,725 (73)	Moderate to severe

Belavic (2015)	Croatia (2008-2013)	Database of brain injury patients hospitalised in the general ICU at Karlovac General Hospital	TBI patients (no comparator) (n=306)	56 (range 18–93)	NR	NR
Stroke incidence pre and post-TBI						
Albrecht (2015)	USA (2006-2009)	Administrative claims data from USA Medicare beneficiaries	Pre- and post-TBI (n=16,936)	81.0 (7.9)	6,379 (38)	NR
Glass (2019)	USA (2006-2009)	Administrative claims data from USA Medicare beneficiaries	TBI patients (no comparator) (n= 52,228)	82.9 (7.9)	18,439 (35.3)	NR

ICU: Intensive Care Units; NOACs: Novel Oral Anticoagulants; NR: Not Reported; NY: New York; TBI: Traumatic Brain Injury; tSAH: traumatic subarachnoid haemorrhage; USA: United States of America; VKAs: Vitamin K antagonists

Risk of stroke post-TBI

Stroke risk compared to non-TBI controls

Of the six studies that included a non-TBI control group, all found TBI patients had statistically significantly increased risk of stroke compared to controls. This association remained when confounding variables were adjusted for (Table 2). All studies matched on or adjusted for age and sex; the list of variables each study adjusted for are detailed in Supplementary Table 4. The pooled adjusted HR was 1.86 (95% Confidence Interval [CI] 1.46-2.37) (n=544,762 TBI patients and 1,692,865 controls) (Figure 2).

Table 2: Stroke risk compared to non-TBI controls and stroke risk pre/ post-TBI.

Author (year)	Sample size	Follow-up timeframe	Stroke type	Strokes in follow-up (n, %)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Stroke risk compare to non-TBI controls						
Burke (2013)	TBI: 436,630 Control: 736,723	Median years (IQR): 28 months (14-44)	Ischemic	TBI: NR (1.1) Controls: NR (0.9)	NR	1.31 (1.25-1.36)
Chen (2011)	TBI: 23,199 Control†: 69,597	3 months, 1 year, 5 years	Ischemic and haemorrhagic	**3 months:** TBI: 675 (2.91) Controls: 207 (0.30) **1 year:** TBI: 968 (4.17) Controls: 669 (0.96) **5 years:** TBI: 1,901 (8.20) Controls: 2,710 (3.89)	**3 months:** 10.20 (8.71-11.93) **1 year:** 4.61 (4.17-5.11) **5 years:** 2.34 (2.20-2.50)	**3 months:** 10.21 (8.71-11.96) **1 year:** 4.61 (4.16-5.11) **5 years:** 2.32 (2.17-2.47)
Eric Nyam (2019)	TBI: 16,211 Control: 32,422§	Median: 5 years, range 0.0027 to 5 years	Ischemic, haemorrhagic and unspecified	**TBI:** 637 (3.93) **Control:** 529 (1.63)	NR	**All strokes:** 2.89 (2.58-3.25) **Ischemic:** 2.10 (1.81-2.43) **Haemorrhagic:** 6.02 (4.80-7.55)

Lee (2014)	TBI: 24,905 Control: 719,811	Mean years (SD): TBI: 1.94 (1.18) Control: 3.88 (0.55) Person years: TBI 48,371 Control: 2,793,892	Ischemic	TBI: 412 (1.65) Controls: 9242 (1.34)	2.49 (2.25-2.74)	1.46 (1.33-1.62)
Liao (2014)	TBI: 30,165 Control‡: 120,660	Max 4 years	Ischemic and haemorrhagic	TBI: 1455 (4.8) Controls: 2903 (2.4)	NR	1.98 (1.86-2.11)
Liu (2017)	TBI: 13,652 Control¥: 13,652	Person years: 154,657	Ischemic and haemorrhagic	TBI: 779 Controls: 527	1.48 (1.32-1.66)	1.65 (1.47-1.85)
Stroke risk pre/ post-TBI						
Albrecht (2015)	TBI: 16,936	Min 6 months, max 48 months	Ischemic and haemorrhagic	**Incidence rate per 1,000** **Ischemic:** Pre-TBI: 70.5 Post-TBI: 84.4 **Haemorrhagic:** Pre-TBI: 3.7 Post-TBI: 23.9	NR	**Rate Ratio** **Ischemic:** 1.3 (1.2-1.4) **Haemorrhagic:** 6.5 (5.3-7.8)
Glass (2019)	TBI: 52,228	12 months	Ischemic and haemorrhagic	**Annual incidence rate/1000** **Ischemic:** Pre-TBI: 49.1 (46.5-51.9) Post-TBI: 37.7 (36.0-39.6) **Haemorrhagic:** Pre-TBI: 13.3 (12.0-14.8) Post-TBI: 16.2 (15.0-17.4)	**Rate Ratio** **Ischemic:** 0.8 **Haemorrhagic:** 1.2	NR

CI: Confidence Interval; HR: Hazard Ratio; IQR: Interquartile Range; Max: Maximum; Min: Minimum; n: number; NR: Not Reported SD: Standard Deviation; TBI: Traumatic Brain Injury; %: percentage

* Variables adjusted for are presented in Supplementary Table 4

† Matched 1:3 on age, sex and year of index use of health care services

§Matched 1:2 on age-, sex-, and age-adjusted Charlson Comorbidity Index score

‡ Matched 1:4 on age and sex

¥ Matched 1:1 on age, sex and propensity score

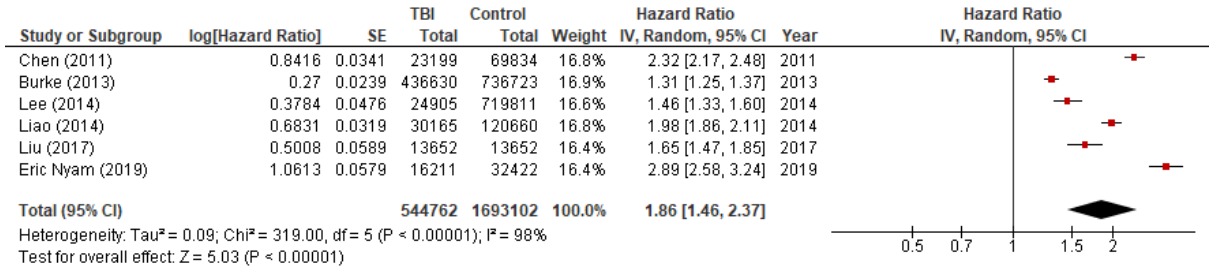

Figure 2: Random effects meta-analysis pooled estimates for stroke risk post-TBI compared to non-TBI controls (n=6 studies; 544,762 TBI patients and 1,692,865 controls).

Stroke risk pre- and post-TBI

Two studies investigated stroke rates pre- and post-TBI.[17, 24] Both studies reported higher incidence rates of ischemic and haemorrhagic stroke post-TBI, compared to pre-TBI (Table 2). .

Stroke risk associated with specified exposures

Three studies explored stroke risk associated with exposure to stroke prevention medication post-TBI (Table 3). For patients who had been prescribed Vitamin K antagonists (VKA) prior to TBI, continuation or resumption of these drugs after TBI was associated with reduced stroke risk post-TBI, compared to patients who had VKA prescriptions stopped post-TBI (Albrecht 2014: Relative Risk 0.83; 95% CI 0.72-0.96 and Staerk 2018: HR 0.58; 95% CI 0.37-0.90). However, no association was found for continuation or resumption of novel oral anticoagulants (NOACs) (HR 0.85; 95% CI 0.43-1.68). Prescription of statins post-TBI was associated with reduced risk compared to TBI patients not prescribed statins post-TBI (Relative Risk 0.86; 95% CI 0.81-0.91).

Two studies investigated antidepressant use in TBI patients aged ≥65 years, both used administrative claims data from United States Medicare beneficiaries between 2006 and 2010. Kokhar (2017) reported, compared to no use of antidepressants post-TBI, new use (i.e. not prescribed before TBI) of serotonin norepinephrine reuptake inhibitors (SNRIs) and phenylpiperazine antidepressants (PPAs) were associated with increased risk of ischemic stroke (Relative Risk 1.36; 95% CI 1.06-1.73 and 1.31; 95% CI 1.02-1.68, respectively). They found new use of selective serotonin reuptake inhibitors (SSRIs) was associated with increased risk of haemorrhagic stroke (Relative Risk 1.26; 95% CI 1.06-1.50). However, no

associations were found for other antidepressant drug classes (Table 3). Albrecht (2018) found, compared to tricyclic antidepressants (TCAs), SSRI use was associated with increased risk of haemorrhagic stroke (Risk Ratio 2.47; 95% CI 1.30-4.70). However, other antidepressant drug class comparisons were not associated with stroke risk (Table 3).

Exposures reported in the other three studies were insomnia,[25] acupuncture(30) and tSAH.[23] TBI patients with new onset insomnia (i.e. insomnia occurring post-TBI) had a 2-fold increased stroke risk (HR 2.28; 95% CI 1.70-3.06) compared to insomnia patients without TBI.[25] Acupuncture treatment post-TBI was associated with decreased stroke risk, compared to TBI patients not receiving acupuncture (HR 0.59; 95% CI 0.50-0.69).(30) TBI patients with tSAH had decreased stroke risk compared to TBI patients without tSAH (HR 0.77; 95% CI 0.63-0.94).

Table 3: Stroke risk post-TBI associated with specific exposures: anticoagulants, statins, antidepressants, insomnia, tSAH and acupuncture.

Author (year)	Exposure	Sample size	Follow-up timeframe	Strokes in follow-up (n, %)	Unadjusted risk estimate (95% CI)	Adjusted risk estimate (95% CI)
Albrecht (2014)	**Warfarin use post-TBI**	Exposed: 5,811 Unexposed: 4,971	12 months	**Events, n*** **Any stroke:** Exposed: 339 Unexposed: 494 **Ischemic:** Exposed: 293 Unexposed: 453 **Haemorrhagic:** Exposed: 75 Unexposed: 130	NR	**Relative Risk** **Any stroke:** 0.83 (0.72-0.96) **Ischemic:** 0.81 (0.69-0.95) **Haemorrhagic:** 0.70 (0.52-0.95)
Staerk (2018)	**VKAs/ NOAC use post-TBI**	Exposed: 979 Unexposed: 421	3 years	NR	NR	**Hazard Ratio** **VKA:** 0.58 (0.37-0.90) **NOAC:** 0.85 (0.43-1.68)
Khokhar (2018)	**Statin use post-TBI**	Exposed: 50,173 Unexposed: 50,342	Up to 54 months	**Ischemic:** 9,420 **Haemorrhagic:** 3,841	**Relative risk** **Any stroke:** 1.00 (0.96-1.04)	**Relative risk** **Any stroke:** 0.86 (0.81-0.91)

					Ischemic: 1.09 (1.04-1.14) **Haemorrhagic:** 0.81 (0.75-0.87)	**Ischemic:** 0.91 (0.85-0.96) **Haemorrhagic:** 0.75 (0.67-0.83)
Khokhar (2017)	**Antidepressant use post-TBI**	Exposed: 20,859 Unexposed: 43,355	Mean days (SD): Exposed: 719.5 (393.7) Unexposed: 621.5 (426.5)	**Ischemic:** Exposed: 2,413 (11.7) Unexposed: 3,121 (7.5) **Haemorrhagic:** Exposed: 949 (4.6) Unexposed: 1,448 (3.4)	**Relative risk** **Any stroke:** SSRI 1.27 (1.16-1.39) SNRI 1.62 (1.30-2.02) TCA 1.15 (0.82-1.61) TetCA 1.16 (0.96-1.41) PPA 1.48 (1.18-1.84) **Ischemic:** SSRI 1.29 (1.17-1.42) SNRI 1.70 (1.34-2.16) TCA 1.14 (0.78-1.67) TetCA 1.23 (0.99-1.52) PPA 1.48 (1.15-1.90) **Haemorrhagic:** SSRI 1.33 (1.13-1.57) SNRI 1.20 (0.73-1.96) TCA 1.09 (0.57-2.10) TetCA 0.91 (0.60-1.38) PPA 1.44 (0.96-2.18)	**Relative risk** **Any stroke:** SSRI 1.07 (0.98-1.18) SNRI 1.37 (1.10-1.72) TCA 1.13 (0.81-1.59) TetCA 0.96 (0.79-1.17) PPA 1.33 (1.07-1.66) **Ischemic:** SSRI 1.04 (0.94-1.15) SNRI 1.36 (1.06-1.73) TCA 1.11 (0.76-1.63) TetCA 0.95 (0.77-1.18) PPA 1.31 (1.02-1.68) **Haemorrhagic:** SSRI 1.26 (1.06-1.50) SNRI 1.19 (0.72-1.95) TCA 1.11 (0.58-2.14) TetCA 0.84 (0.55-1.27) PPA 1.30 (0.86-1.97)
Albrecht (2018)	**Antidepressant use post-TBI**	Exposed: 15,733 Unexposed: 15,153	2 years; person-months of antidepressant use: SSRI: 163,212	**Ischemic:** SSRI: 2,142 (1.31) SNRI: 466 (1.88) TCA: 243 (1.23) Unexposed: 5,243 (1.19)	**Risk ratios** **Ischemic:** SSRI vs SNRI (ref SNRI): 1 (0.88-1.12) SSRI vs TCA (ref TCA):	**Risk ratios** **Ischemic:** SSRI vs SNRI (ref SNRI): 0.92 (0.73-1.15) SSRI vs TCA (ref TCA):

			SNRI: 24,756 TCA: 19,734 Unexposed: 438,781	**Haemorrhagic:** SSRI: 431 (0.26) SNRI: 96 (0.39) TCA: 41 (0.21) Unexposed: 1,065 (0.24)	1.21 (1.02-1.44) SNRI vs TCA (ref TCA): 1.17 (0.99-1.38) **Haemorrhagic**: SSRI vs SNRI (ref SNRI): 0.95 (0.73-1.24) SSRI vs TCA (ref TCA): 1.69 (1.05-2.70) SNRI vs TCA (ref TCA): 1.60 (1.05-2.46)	0.99 (0.76-1.31) SNRI vs TCA (ref TCA): 0.98 (0.73-1.33) **Haemorrhagic**: SSRI vs SNRI (ref SNRI): 1.17 (0.71-1.92) SSRI vs TCA (ref TCA): 2.47 (1.30-4.70) SNRI vs TCA (ref TCA): 1.39 (0.59-3.25)
Ao (2017)	**New onset insomnia post-TBI vs insomnia without TBI**	Exposed: 1,174 Unexposed: 5,870	Mean years (SD): 2.71 (0.69)	TBI & insomnia: 65 (5.54) Insomnia: 144 (2.45)	2.33 (1.74-3.12)	2.28 (1.70-3.06)
Morris (2016)	**tSAH post-TBI**	Exposed: 20,454 Unexposed: 20,454	Mean years (SD) 4.3 (1.8)	Total sample: 531 (1.3) Cumulative stroke rate: Exposed: 1.79% (1.54-2.08) Unexposed: 2.12% (1.83-2.4)	**Hazard Ratio** 0.77 (0.63-0.94)	NR
Shih (2014)	**TBI patients receiving acupuncture post-TBI**	Exposed: 7,409 Unexposed: 29,636	Person-years: Exposed: 33,071 Unexposed: 17,3682	Exposed: 163 (2.2) Unexposed: 1250 (4.2)	NR	**Hazard Ratio** 0.59 (0.50-0.69)

CI: Confidence Interval; n: number; NOACs: Novel Oral Anticoagulants; NR: Not Reported; PPA: Phenylpiperazine Antidepressants SD: Standard Deviation; SNRI: Serotonin Norepinephrine Reuptake Inhibitors; SSRI: Selective Serotonin Reuptake Inhibitors;
TBI: Traumatic Brain Injury; TCA: Tricyclic Antidepressants; TetCA: Tetracyclic Antidepressants; tSAH: traumatic Subarachnoid Haemorrhage; VKA: Vitamin K Antagonists; %: percentage

*Note: numbers do not add up as a result of exclusion of events occurring during hospitalization for TBI and multiple simultaneous events.

Time to stroke onset post-TBI

Chen (2011) found stroke risk post-TBI was highest in the first three months of follow-up (HR 10.21; 95% CI 8.71-11.96), but remained significantly higher than non-TBI controls at five years follow-up (HR 2.32; 95% CI 2.17-2.47) (Table 2).

Albrecht (2015) reported stroke incidence rates for TBI patients were highest two and four month's post-discharge and there was a steep decrease between four to 12 months post-discharge: incidence rates (per 1,000) for ischemic stroke at two months 183.5; four months 112.3; six months 84.8; eight months 69.9; 10 months 70.3; 12 months 78.1, and haemorrhagic stroke at two months 98.5; four months 36.1; six months 17.3; eight months 11.7; 10 months 12.8; 12 months 8.2.

Similarly, Albrecht (2015) found stroke rates post-TBI were elevated in the first three months after discharge and levelled out between three to 24 months for ischemic stroke and 12 to 24 months for haemorrhagic stroke (Supplementary Figure 2).

In a subgroup analysis of people who survived longer than 12 months, Lee (2014) found TBI patients' stroke risk, compared to non-TBI controls, remained statistically significant (HR 1.38; 95% CI, 1.20-1.59).

Four studies reported average time between TBI and onset of stroke: Ao (2017) 0.93 years (mean follow-up 2.71 years; Standard Deviation [SD] 0.69); Belavic (2015) 8.56 days (mean follow-up 29.13 days; SD 27.16); Lee (2014) 1.12 years (mean follow-up 1.94 years; SD 1.18); Chen (2011) 1.49 years (maximum follow-up 5 years).

Two studies reported frequency of stroke diagnosed during acute hospitalisation for TBI. Kowalski (2017) found 2.5% (159/6,488) of moderate to severe TBI patients had an ischemic stroke (median hospital duration 25 days, range 4-125 days). Belavic (2015) found 7.5% (23/306) of TBI patients had a stroke (mean time to stroke after TBI 7 ± 8 days and mean hospital duration 29 ± 27 days).

Severity and subtype of TBI

Two studies had populations of mild TBI patients, both reported increased stroke risk post-TBI compared to non-TBI controls: Lee (2014) HR 1.46 (95% CI 1.33-1.62) and Liu (2017)

HR 1.65 (95% CI 1.47-1.85) (Table 2). In a secondary analysis stratified by trauma severity, Burke (2013) found ischemic stroke risk remained significantly higher than controls regardless of severity (tertile 1 [lowest severity]: HR 1.10; 95% CI 1.01-1.20, tertile 2: HR 1.29; 95% CI 1.16-1.43, tertile 3 [highest severity]: HR 1.25; 95% CI 1.16-1.35). Similarly, Liao (2014) found increased risk of stroke post-TBI compared to controls for all types of TBI: mild TBI: HR 1.74 (95% CI 1.57-1.93); severe TBI: HR 2.04 (95% CI 1.89-2.20); skull fracture: HR 3.00 (95% CI 2.42-3.71).

In a secondary analysis of trauma subtype, Burke (2013) found increased ischemic stroke risk compared to controls regardless of subtype: skull fracture HR 1.21 (95% CI 1.05-1.41); concussion HR 1.27 (95% CI 1.17-1.37); intracranial bleeding HR 1.21 (95% CI 1.12-1.31); other intracranial injury HR 1.38 (95% CI 1.07-1.76); and unspecified HR 1.33 (95% CI 1.27-1.40). Chen (2011) found stroke risk, compared to controls, was more pronounced for TBI patients with skull fracture at 3 months (skull fracture: HR 19.98; 95% CI 14.73-27.22 vs without skull fracture: HR 9.75; 95% CI 8.31-11.45), one year (skull fracture: HR 8.39; 95% CI 7.47-10.89 vs without skull fracture: HR 4.44; 95% CI 4.00-4.93), and five years (skull fracture: HR 3.54; 95% CI 2.86-4.37 vs without skull fracture: HR 2.26; 95% CI 2.12-2.42).

Stroke type

Five studies reported stroke risk post-TBI by stroke type. Eric Nyam (2019) found higher risk of haemorrhagic stroke post-TBI, compared to controls, than ischemic stroke (HR 6.02; 95% CI 4.80-7.55 and HR 2.10; 95% CI 1.81-2.43, respectively) Chen (2011) reported higher risk of stroke post-TBI, compared to controls, for subarachnoid and intra-cerebral haemorrhagic stroke types than ischemic and unspecific strokes (subarachnoid haemorrhage: HR 4.89; 95% CI 3.81-7.19, intra-cerebral haemorrhage: HR 6.33; 95% CI 5.60-7.83, ischemic: HR 1.43; 95% CI 1.31-1.56, unspecified: 2.21; 95% CI 1.99-2.44). Similarly, Albrecht (2015) and Glass (2019) found higher incidence rate ratios for haemorrhagic stroke post-TBI, compared to pre-TBI, than for ischemic stroke (Table 2). In contrast, Liu (2017) found higher cumulative incidence rates post-TBI for ischemic stroke compared to haemorrhagic stroke (8.9%; 95% CI 7.8-10.0 vs 2.7%; 95% CI 2.1-3.3, respectively) and similar adjusted HRs for stroke risk post-TBI, compared to controls, for both stroke subtypes (ischemic: HR 1.62; 95% CI 1.43-1.84 vs haemorrhagic: HR 1.73; 95% CI 1.36-2.20).

Study quality

Critical appraisal of included studies (Supplementary Table 5) identified that the study design – including setting, recruitment, and follow-up dates – and eligibility criteria, were well described by all included studies. All studies, except one, clearly reported the clinical codes used to identify exposures and outcomes; however, only three studies referenced validation studies for these clinical codes and nine studies did not provide a complete list of clinical codes for confounders and other variables. Statistical methods were described well by most studies; however, none of the studies explained how missing data were addressed. Furthermore, none of the studies clearly described data cleaning methods and most studies (n=10) did not report population selection based on data quality, data availability, and linkage.

Discussion

This systematic review is the first to explore the association between TBI and stroke risk. The meta-analysis found TBI patients have 86% increased risk of stroke compared to non-TBI controls (HR 1.86; 95% CI 1.46-2.37). Stroke risk may be highest in the first four months post-TBI, but remains significant five years post-TBI. TBI is associated with increased stroke risk regardless of TBI severity or subtype. Furthermore, TBI is associated with increased risk of both ischemic and haemorrhagic stroke. VKAs, statins, and acupuncture use is associated with reduced stroke risk post-TBI; however, no association was found for NOAC use. Some classes of antidepressants – SNRIs, PPAs, and SSRIs – are associated with increased stroke risk post-TBI.

Our findings suggest TBI is an independent risk factor for stroke regardless of TBI severity or subtype, even if it is mild and patients experience a good recovery. This is particularly noteworthy because 70-90% of TBIs are mild.[34] Stroke is the second leading cause of death and third leading cause of disability worldwide; however, urgent treatment can prevent stroke related death and long-term disability.[35, 36] Therefore, it may be beneficial to inform TBI patients of their potential increased stroke risk and educated them to recognise and respond urgently to stroke symptoms.

Primary stroke prevention is important to reduce stroke incidence and subsequent stroke-related death and disability; therefore, clinicians should review patients' stroke risk post-TBI and consider administering stroke prevention medication and lifestyle advice. Our review

found some evidence to suggest an association between reduced stroke risk post-TBI and the stroke prevention drugs VKAs and statins. Furthermore, Khokhar (2018) found statin use post-TBI was also associated with decreased mortality, depression, Alzheimer's disease, and related dementias. However, stroke prevention drugs are often stopped after an individual has experienced a TBI; Albrecht (2014) found 55% of patients who had been prescribed warfarin prior to TBI were not prescribed warfarin post-TBI(16) and Orlando (2013) found a statin discontinuation rate of 38% post-TBI for patients who took statins prior to TBI.(37) Other research has found older age and risk of falls are common barriers to clinicians' prescribing stroke prevention drugs.(38) This is particularly relevant given the shift in TBI epidemiology in high income countries to falls in the elderly.(3) Future research is required to investigate the effectiveness of stroke prevention medication post-TBI and related adverse events to help inform clinicians' prescribing and facilitate shared decision making. Future research should also explore clinical and demographic characteristics associated with increased stroke risk post-TBI to identify individuals most at risk of stroke post-TBI and help clinicians' tailor preventative healthcare.

Stroke risk may be highest in the first four months post-TBI; therefore, this time period is critical to educate patients about stroke risk and symptoms, and to administer stroke prevention medication and lifestyle advice. Importantly, stroke prevention medication, particularly VKAs and statins, should be re-started for patients who were prescribed these drugs prior to TBI. However, sequelae from TBI, such as physical and cognitive disability, may impair patients' ability to engage with lifestyle change, adhere to medication, or recognise and respond to stroke symptoms. Therefore, rehabilitation post-TBI, including the role of carers and family members, should provide ongoing support for stroke prevention. Future research is required to further understand the temporal nature of stroke risk post-TBI.

Our review found some evidence to suggest an association between some classes of anti-depressants and increased stroke risk post-TBI. This potential association is important given that many people experience anxiety and depression post-TBI,(5) which are often treated with antidepressants. Khokhar (2017) found that a third of TBI patients were prescribed new use of antidepressants. A recent systematic review found antidepressant use is associated with increase stroke risk (Risk Ratio 1.41; 95% CI 1.13-1.69).(39) However, a study published since that review suggested antidepressants strongly inhibiting serotonin reuptake may be associated with a small decrease in the rate of ischemic stroke.(40) Further research is required into the safety of antidepressants specifically for TBI patients.

The mechanism for increased stroke risk post-TBI is unknown and is an area for future research; however, a number of hypotheses have been suggested. Damage to the cerebrovascular system caused by TBI could cause stroke through clot formation, damaged arteries, dissection, or increased intracranial pressure and blood pressure.[26] This could be identified by routine screening for damage to the cerebral vasculature post-TBI and is an area for future research. Alternatively, increased stroke risk may be due to lifestyle changes post-TBI, such as a more sedentary lifestyle due to physical, cognitive, or psychological long-term effects.[28] Finally, TBI patients may be more likely to be prescribed antipsychotic and antidepressant drugs for TBI-related psychiatric and psychological disorders. These drugs have been associated with increased stroke risk.[18, 21, 41]

The review is methodologically robust; all screening, data extraction and quality assessment processes were completed in duplicate. Non-English language papers were eligible to reduce language bias, although none were eligible. However, only peer-reviewed journal articles or theses were eligible which may introduce publication bias. The review included a large sample size of 2,606,379 participants from four countries. However, only six out of the 18 studies compared stroke risk to non-TBI controls and studies were heterogeneous in terms of study population and duration of follow-up. Furthermore, all included studies were retrospective cohort studies which used data collected for routine clinical practice. Potential sources of bias from use of routine data for observational research include misclassification bias, missing data, unmeasured confounding, and changes in coding practices or database eligibility criteria.[15] In addition, information on stroke type, TBI classification and TBI severity were missing from the majority of studies. The association of stroke risk with treatment (in both directions) may be confounded by indication bias. Therefore, the review findings should be interpreted cautiously. The included studies were generally good quality in terms of study design and reporting; however, none of the studies clearly reported data cleaning processes and there was a lack of reporting of population selection based on data quality, availability, and linkage. This information is important because choice of data cleaning methods and population selection can affect study findings and reproducibility. Finally, most of the studies included administrative databases, which implies that the TBI definition might be inconsistent. However, in practice, these databases provide large sample sizes, thereby increasing reliability and validity.

Our findings suggest TBI is an independent risk factor for stroke, regardless of TBI severity or subtype. There is some evidence to suggest stroke risk may be highest in the first four

months post-TBI; however, remains increased up to five years post-TBI. VKAs and statins may reduce stroke risk post-TBI; however, are frequently stopped post-TBI. Post-TBI review and management of risk factors for stroke may be warranted to mitigate the excess risk of stroke associated with TBI. Future research should investigate which subgroups are most at risk of stroke post-TBI; the temporal nature of stroke risk post-TBI; the effectiveness of stroke prevention medication post-TBI; the safety of antidepressants post-TBI and the mechanism of stroke risk post-TBI.

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The funders had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Competing interests

Dr. Turner has nothing to disclose.

OLA declares personal fees from Gilead Sciences Ltd and GSK.

MC has received personal fees from PCORI, Astellas, Takeda, Glaukos, GSK and Merck outside the submitted work.

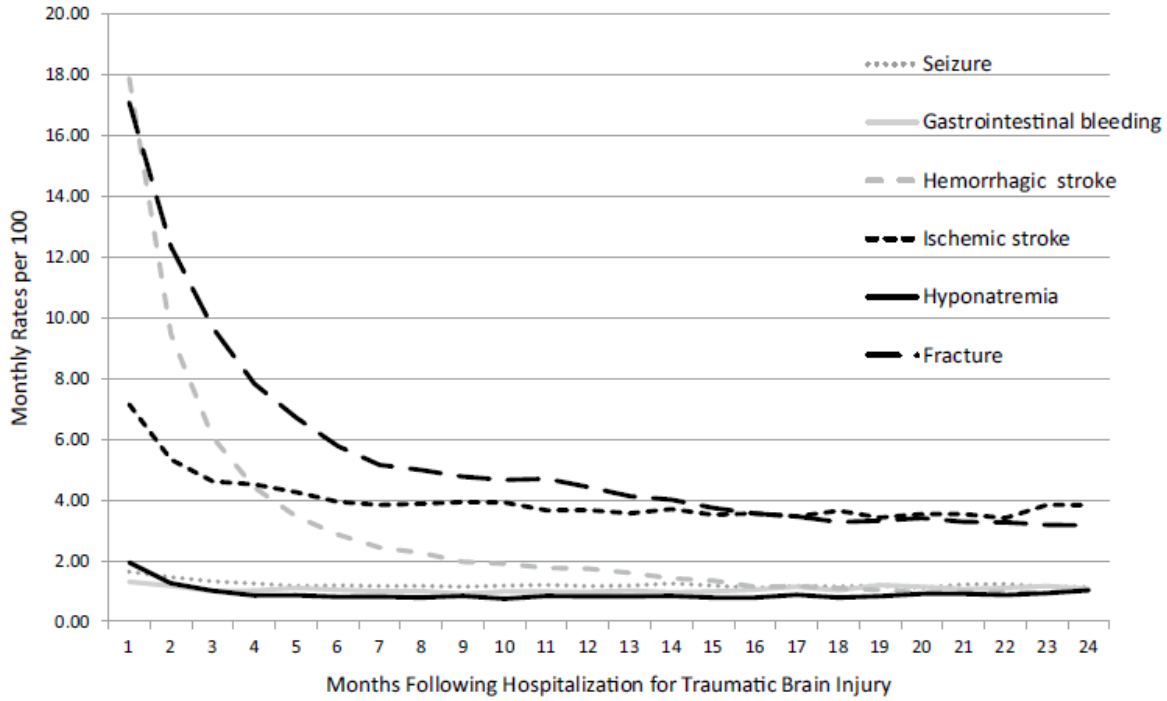
Supplementary material

Supplementary Figure 1: Search strategy for MEDLINE

1 traumatic brain injur$.mp.
2 brain injuries/ or brain hemorrhage, traumatic/ or exp brain injuries, diffuse/ or exp brain injuries, traumatic/
3 diffuse axonal injur$.ti,ab.
4 (brain adj1 (injur$ or damage$ or concussion$ or contusion$ or trauma$ or coup-contrecoup)).ti,ab.
5 head injuries, penetrating/ or head injuries, closed/ or Wounds, Penetrating/
6 ((head or skull) adj1 (injur$ or trauma$ or fracture$)).ti,ab.
7 Skull Fractures/
8 exp Intracranial Hemorrhage, Traumatic/ or exp Cerebral Hemorrhage, traumatic/
9 Craniocerebral Trauma/
10 ((craniocerebral or intracranial or intracerebral or intraventricular or subarachnoid) adj1 (trauma$ or injur$ or h?emorrhage$ or h?ematoma$)).ti.
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 exp Stroke/
13 "National Institute of Neurological Disorders and Stroke (U.S.)"/
14 exp "Intracranial Embolism and Thrombosis"/ or intracranial embolism.ti,ab. or intracranial thrombosis.ti,ab.
15 Cerebral Infarction/
16 Arteriovenous Malformations/ or arteriovenous malformation$.ti,ab.
17 Aneurysm/ or aneurysm.ti,ab.
18 Ischemic Attack, Transient/ or "transient isch?emic attack".ti,ab.
19 12 or 13 or 14 or 15 or 16 or 17 or 18
20 11 and 19
21 limit 20 to humans
22 21 not (editorial or letter or case report$ or comment$ or review or meta-analys?s or practice-guideline).pt.
23 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or (cohort or longitudinal or prospective or retrospective).ti,ab.

24 Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or (case$ adj3 (comparison$ or control$)).ti,ab.
25 (observational stud$ or comparative stud$ or controlled stud$).ti,ab.
26 Cross-Sectional Studies/ or Prevalence/ or (cross-sectional or prevalence or transversal).ti,ab.
27 clinical trials as topic/ or ((randomi?ed or non-randomi?ed) adj3 trial$).ti,ab.
28 23 or 24 or 25 or 26 or 27
29 22 and 28

Supplementary Figure 2: Monthly rates of adverse events/100 Medicare beneficiaries during the 2 years following hospitalization for traumatic brain injury, regardless of antidepressant use, n = 30,886. Figure copied from *Albrecht JS, Rao V, Perfetto EM, Daniel Mullins C. Safety of Antidepressant Classes Used Following Traumatic Brain Injury Among Medicare Beneficiaries: A Retrospective Cohort Study. Drugs & aging. 2018;35(8):763-72.*



1

Supplementary Table 1: Template eligibility criteria checklist

Endnote ID	
Author (year)	
Population (Y/N)	
Comparator (Y/N)	
Outcomes (Y/N)	
Study type (Y/N)	
Report characteristics (Y/N)	
Include? (Y/N)	
Reasons for exclusion	

Supplementary Table 2: Template data extraction form

Report characteristics	**Paper ID**		
	Author		
	Year of publication		
	Country of origin		
	Type of publication		
Study characteristics	**Aim**		
	Study design		
	Location		
	Setting		
	Eligibility criteria	Inclusion	
		Exclusion	
	Recruitment procedures		
	Recruitment timeframe		
	Follow-up timeframe		
	Sample size	TBI patients	
		Control/ comparator	
Population characteristics	**Study arms**		
	Diagnostic criteria for TBI		
	Mechanism of injury		
	Time since injury		
	Severity of TBI		
	TBI severity markers	Loss of consciousness	
		Post traumatic amnesia	
		GOS	
		Other	
	Age (mean + SD/ Median + IQR)		
	Sex (number + %)		

	Ethnicity		
	Deprivation		
	Comorbidities		
	Stroke risk factors	BMI	
		BP	
		Cholesterol	
		Smoking status	
	Other relevant characteristics		
Outcomes	**Summary of analyses**	Primary Secondary	
	Diagnostic criteria for stroke		
	Measurement of stroke/TIA e.g. self-report		
	Stroke or TIA in FU (n, %)	TBI patients	
		Control/ comparator	
	Risk estimates (RR/ OR/ HR)	Unadjusted	
		Adjusted	
		Variables adjusted for	
	Other relevant analyses		
	Predictor variables of stroke/ TIA risk		

Supplementary Table 3: Summary of participants, eligibility criteria, TBI severity, age, sex and length of follow-up for included studies.

Author (year)	Participants	Eligibility criteria	Length of follow up	Definition of TBI	Definition of stroke
Albrecht (2014)	TBI: 10,782	Age ≥65 years; survival to hospital discharge; receipt of warfarin sodium in the month preceding TBI; no TBI episode in the 6 months prior to the index TBI event.	12 months	ICD-9-CM codes: 800.xx, 801.xx, 803.xx, 804.xx, 850.xx-854.1x, 950.1-950.3, 959.01	Hemorrhagic stroke: ICD-9 CM 430.xx-432.xx ischemic stroke: ICD-9 CM 433.xx, 434.xx, 435.xx, 437.0x, 437.1x
Albrecht (2015)	TBI: 16,936	Aged ≥65 years; minimum of 6 months of observation time before the TBI hospitalization; excluded patients who died in the hospital or whose first hemorrhagic or ischemic stroke occurred within two weeks of admission for/discharge from TBI	Min 6 months, max 48 months	ICD-9 codes 800.xx, 801.xx, 803.xx, 804.xx, 850.xx- 854.1x, 950.1-950.3, 959.01 in any position on an inpatient claim between 1st Jun 2006 and 31st Dec 2009	Hemorrhagic stroke: ICD-9 codes 430.xx-432.xx. Ischemic stroke: ICD-9 codes 433.xx-435.xx, 437.0x, and 437.1x (in any position on a claim with an admission date at least 14 days after the discharge date for the first TBI hospitalization during the study period)

Albrecht (2018)	TBI: 30,886	Aged ≥65 years; first TBI; survival to hospital discharge; 24 months continuous coverage post-TBI hospitalization; exclusively using one class of antidepressants or another during the post-TBI period; excluded patients who switched from one antidepressant class to another during the follow-up period	2 years; person-months of antidepressant use: SSRI: 163,212 SNRI: 24,756 TCA: 19,734 Unexposed: 438,781	ICD-9-CM codes 800.xx, 801.xx, 803.xx, 804.xx, F16850.xx–854.1x, 950.1–950.3, or 959.01 in any position on an inpatient claim	Hemorrhagic stroke: ICD-9-CM codes 430.xx–432.xx Ischemic stroke: ICD-9-CM codes 433.xx, 434.xx, 435.xx, 437.0x, 437.1x
Ao (2017)	TBI patients with sleep disorder: 1,174 Non-TBI patients with sleep disorder: 5,870 (matched 1:5	TBI patients with new-onset insomnia; aged ≥18 years; 1:5 age- and gender-matched cohort with insomnia; excluded pre-existing insomnia and stroke history before the TBI diagnosis and patients with sleep apnoea	Mean years (SD): 2.71 (0.69)	Skull bone fracture TBI (ICD-9-CM: 801-804) and non-skull bone fracture TBI (ICD-9-CM: 850-854)	New-onset stroke of hospitalization after TBI, including hemorrhagic stroke (ICD-9-CM: 430e432), ischemic stroke (ICD-9-CM: 433e434, 437-438), transient ischemic attack (ICD-9-CM: 435), and acute but ill-defined

	on age and sex)				cerebrovascular disease (ICD-9-CM: 436)
Belavic (2015)	TBI: 306	Patients with brain injury who were hospitalised in the general ICU at Karlovac General Hospital (2008–2013).	Mean days (SD) 29.13 (27.16)	NR	NR
Burke (2013)	TBI: 436,630 Non-TBI trauma patients: 736,723	TBI: Aged ≥18 years who survived either an inpatient admission or an ED visit for TBI or trauma. Controls: patients who had a fracture, excluding fractures of the head and neck. Excluded individuals with stroke before TBI or trauma, and all patients with carotid or vertebral dissection at the index visit.	Median years (IQR): 28 months (14–44)	ICD-9-CM 800.0–801.9, 803.0–804.9, 850.0–854.1, or 959.01 in any discharge diagnosis field	Any hospitalization with a discharge diagnosis of ischemic stroke: ICD-9-CM 433.x1, 434.x1, and 436 from 2005 to 2009 ED visits that did not result in admission for ischemic stroke were not included in the primary outcome because of concerns about the accuracy of coding.

Chen (2011)	TBI: 23,199 Non-TBI: 69,597 (matched 1:3 on age, sex and year of index use of health care services)	Adults ≥18 years; excluded patients with diagnosis of acute stroke simultaneously during admission; diagnosed with stroke before their index use of health care services	3 months, 1 year, 5 years	ICD-9-CM codes 801–804 or 850–854	Any type of acute stroke (ICD-9-CM codes 430–437)
Eric Nyam (2019)	TBI: 16,211 Control: 32,422 (Matched 1:2 on age-, sex-, and age-adjusted Charlson Comorbidity Index score)	Adults ≥18 years; excluded people who had circulatory system disease before TBI occurrence and who had missing information about gender or age.	Median: 5 years, range 0.0027 to 5 years	ICD-9-CM codes: 800, 801, 803, 804, 850-853, 854.1, and 959.01	ICD-9-CM codes: 430-437

Glass (2019)	TBI: 52,228	Survival to hospital discharge with continuous enrollment in Medicare parts A, B, and D with no part C enrolment for 6 months before the date of hospital admission for TBI and 12 months after TBI	12 months	ICD-9-CM codes: 800.xx, 801.xx, 803.xx, 804.xx, 850.xx- 854.1x, 950.1-950.3, 959.01 on an inpatient claim	ICD-9-CM codes in any position on an inpatient claim. Hemorrhagic: 430.xx-432.xx Ischemic 433.xx, 434.xx, 435.xx, 437.0x, 437.1x
Khokhar (2017)	TBI: 64,214	Aged ≥65 years; excluded individuals with any antidepressant use six months prior to their TBI and those that did not survive the TBI hospital stay.	Mean days (SD): Exposed: 719.5 (393.7) Unexposed: 621.5 (426.5)	ICD-9-CM codes 800.xx, 801.xx, 803.xx, 804.xx, 850.xx–854.1x, 950.1–950.3, and 959.01 in any position. Any TBI occurring within 14 days of the previous TBI was collapsed as a single TBI event	Inpatient claims using ICD-9-CM codes 430.xx–432.xx (hemorrhagic stroke) and 433.xx, 434.xx, 435.xx, 437.0x, 437.1x (ischemic stroke) in any position.
Khokhar (2018)	TBI: 100,515	Aged ≥65 years; survived a TBI hospitalization; 6 months of observation time prior to TBI.	Up to 54 months	Identified by inpatient claims using ICD-9-CM codes 800.xx, 801.xx, 803.xx, 804.xx, 850.xx-	Inpatient claims using ICD-9 codes 430.xx-432.xx (hemorrhagic stroke) and 433.xx,

				854.1x, 950.1-950.3, and 959.01.	434.xx, 435.xx, 437.0x, 437.1x (ischemic stroke)
Kowalski (2017)	TBI: 6,488	Patients with acute, moderate to severe TBI; aged ≥16 years at injury, presentation to a Model System designated acute hospital within 72 hours of injury and at least one of the following: post-traumatic amnesia (PTA) >24 hours, loss of consciousness >30 minutes, a Glasgow Coma Scale score <13 on initial presentation to a health care facility, or trauma-related intracranial abnormalities identified on neuroimaging.	Median 25 days, range 4-125 days	ICD-9 433.01; 433.11; 433.21; 433.31; 433.81; 434.01; 434.11; 434.91 TBI is defined for the TBIMS NDB as brain tissue damage caused by an external mechanical force.	ICD-9 CM 433.01 to 433.91 and 434.01 to 434.91
Lee (2014)	TBI: 24,905 Non-TBI: 719,811	Aged ≥18 years; mild TBI; excluded patients with any type of stroke diagnosed before January 1, 2007, patients diagnosed with hemorrhagic stroke during the follow-up period	Mean years (SD): TBI: 1.94 (1.18) Control: 3.88 (0.55) Person years:	Mild TBI was defined by the ICD-9-CM code for head concussion (850.0, 850.1, 850.5, or 850.9), intracranial injury of other and unspecified nature	Ischemic: ICD-9-CM codes 433–437 (To maximize case ascertainment, only included patients hospitalized for stroke)

		and patients who had ever been hospitalized with TBI.	TBI 48,371 Control: 2,793,892	(854.0), or head injury, unspecified (959.01)	
Liao (2014)	TBI: 30,165 Non-TBI: 120,660 (matched 1:4 on age and sex)	Newly diagnosed TBI or patients without TBI; aged ≥20 years; excluded patients with TBI and stroke before the index date and patients who died within 30 days after TBI.	Max 4 years	ICD-9-CM codes 800, 801, 803, 804 and 850-854	ICD-9-CM codes 430-437
Liu (2017)	Concussion 13,652 Non-Concussion: 13,652 (matched 1:1 on age, sex and propensity score)	Concussion: first episode of concussion; aged >40 years; no intracranial injury identified at least one year before, no prior stroke events or an inadequate follow-up period (<6 months) Control: no concussion; no prior stroke events or an inadequate follow-up period (<6 months)	Person years: 154,657	Concussion: ICD-9 850.X at either an out-patient clinic or emergency department. (The first episode of concussion was defined by: (1) No other intracranial injury (ICD-9 801.x–805.x, 851.x–854.x, 907.0) diagnosed one week before and after the diagnosis of concussion;	Stroke-related hospitalization determined by the hospitalization records with a discharge diagnostic code of stroke (ICD-9 code, 430.x–435.x) or death by the date of 31 December 2009.

				(2) First concussion event happened between 1 January 1998 and 31 December 2005 without any intracranial injury identified at least one year before.)	
Morris (2016)	TBI with tSAH: 20,454 TBI without tSAH: 20,454 (matched* 1:1)	Aged ≥18 years; discharged alive after a first-recorded hospitalization with TBI; excluded patients with history of ischemic stroke	Mean years (SD) 4.3 (1.8)	ICD-9-CM codes 800.0-801.9, 803.0-804.9, 850.0-854.1, or 959.01 in any hospital discharge diagnosis field Patients with multiple visits for TBI were entered into the cohort at their index visit.	Ischemic stroke defined as ICD-9-CM codes 433.x1, 434.x1, or 436 in the absence of a primary discharge code for rehabilitation (V57) or any diagnosis code for intracerebral hemorrhage (431) or SAH (430).
Shih (2014)	TBI with acupuncture: 7,409 TBI without	Aged ≥20 years with newly diagnosed TBI; only new-onset TBI cases were included; excluded people with previous medical records of TBI within five years before the	Person-years: Exposed: 33,071 Unexposed: 17,3682	ICD-9-CM 800–805, 850–854	ICD-9-CM 430–438

	acupuncture: 29,636	index date; TBI patients with only one course of acupuncture treatment. The non-acupuncture group included patients with TBI who did not have acupuncture treatment before the end-point of follow-up.			
Staerk (2018)	TBI: 1,400 Hip fracture: 2,431 Traumatic torso or abdominal injury: 710	AF patients treated with VKA or NOAC the day before a traumatic injury hospital admission; aged 30-100 years; excluded patients with valvular disease, total hip or knee arthroplastic within five weeks, pulmonary embolism or deep vein thrombosis within six months or no OAC treatment before traumatic injury.	3 years	ICD10: S020, S021, S027, S028, S040, S06, S07, S097, S099.	Defined from diagnosis of ischemic stroke, transient ischemic attack, or systemic thromboembolism. ICD10: I63, I64, I74, G458, G459.

Supplementary Table 4: Variables adjusted for in regression analyses for the included studies (n=16 studies)

Author (year)	Variables
Albrecht (2014)	Age, sex, race, lagged warfarin use, 30-day period after TBI (continuous), other anticoagulant use in the 30-day period after TBI, length of hospital stay (categorical), and discharge to skilled nursing facility. hemorrhagic models were adjusted for atrial fibrillation, liver disease, chronic kidney disease, ethanol abuse, malignant neoplasm, hypertension, anemia, coagulation defect, neurological disease, pre-TBI hemorrhagic event, and thrombotic event during period. Thrombotic models were adjusted for stroke or transient ischemic attack, hypertension, diabetes mellitus, heart failure, pre-TBI thrombotic event, and hemorrhagic event during period.
Albrecht (2015)	Not reported
Albrecht (2018)	Ischemic: Age, sex, race, atrial fibrillation, heart failure, diabetes, liver disease, neurologic disease, hip fracture, hypertension, ischemic heart disease, stroke, pre-TBI use of each of the compared classes (2 indicator variables) Hemorrhagic: Age, sex, race, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, hip fracture, osteoarthritis, stroke, pre-TBI use of each of the compared classes (2 indicator variables)
Ao (2017)	Age, gender, socioeconomic status, and comorbidities (hypertension, diabetes, Hyperlipidemia, coronary artery disease, renal)
Belavic (2015)	Not applicable
Burke (2013)	Demographics, payer, vascular risk factors (hypertension, hyperlipidemia, diabetes, atrial fibrillation), all Charlson comorbidities, trauma severity, whether a patient had multiple visits for trauma/TBI, and trauma mechanism, while accounting for clustering at the hospital level.
Chen (2011)	Stratified on sex, age, and year of index healthcare use with cases censored if individuals died from non-stroke causes during the follow-up period. Adjustments were made for patient's monthly income, geographic region (Northern, Central, Eastern, and Southern Taiwan),

	and select comorbidities (hypertension, diabetes coronary heart disease, heart failure, atrial fibrillation and hyperlipidemia)
Eric Nyam (2019)	Age, sex, group of age-adjusted Charlson Comorbidity Index score, hypertensive, chronic obstructive pulmonary disease, diabetes mellitus, renal disease and liver disease.
Glass (2019)	Not applicable
Khokhar (2017)	All adjusted generalized estimating equation models included age, sex, race, discharge to skilled nursing facility, length of hospital stay, warfarin use in period, depression (history of and recently diagnosed), atrial fibrillation, Alzheimer's disease and related dementias, and hypertension. The ischemic stroke model also included hyperlipidemia, diabetes, ischemic heart disease, congestive heart failure, and prior ischemic stroke; while the hemorrhagic stroke model also included liver disease, chronic kidney disease, neurological disease, alcohol abuse, anemia, coagulation defect, valvular heart disease and prior hemorrhagic stroke. The composite stroke model included all variables from both ischemic and hemorrhagic stroke models.
Khokhar (2018)	Age, race, sex, county-level income, low-income subsidy status, region, congestive heart failure, acute myocardial infarction, ischemic heart disease, valvular heart disease, hyperlipidemia, hypertension, diabetes; Alzheimer's disease and related dementias; count of Chronic Condition Data Warehouse chronic conditions excluding cardiovascular disease and Alzheimer's disease and related dementias, and diabetes, length of hospital stay, discharge status, independent survival risk ratio, healthcare provider characteristics per 100 000 population (physicians, hospitals, hospitals with trauma services, hospitals with neurological services, beds); pre–TBI statin use, medication use in month (anticoagulant use, antiplatelet use, β-blocker) and history of any stroke, ischemic stroke, or hemorrhagic stroke 6 months prior to TBI.
Kowalski (2017)	Not applicable

Lee (2014)	Age, sex, urbanization level, socioeconomic status, diabetes, hypertension, coronary artery disease, hyperlipidemia, history of alcohol intoxication, malignancies, heart failure, atrial fibrillation, smoking, obesity, epilepsy, peripheral artery disease and Charlson Cormobidity Index score
Liao (2014)	Age, sex, urbanization, low income, hypertension, diabetes, mental disorders, chronic obstructive pulmonary disease, hyperlipidemia, parkinsonism, migraine, epilepsy, renal dialysis, smoking cessation and alcohol related illnesses
Liu (2017)	Age at index date, sex, hypertension, diabetes, arrhythmia, coronary artery disease, medication exposure
Morris (2016)	Not reported
Shih (2014)	Age, sex, low income, traditional Chinese medicine (TCM) physician density, type of TBI, diabetes mellitus, hypertension, hyperlipidemia, mental disorder, ischemic heart disease, migraine, epilepsy, anticoagulants, antiplatelet agents, and lipid lowering agents
Staerk (2018)	Calendar year, age (continuous), sex, and type of traumatic injury. All-cause mortality models were further adjusted for CHA2DS2-VASc and HAS-BLED factors, stroke models for CHA2DS2-VASc factors, major bleeding models for HAS-BLED factors, and recurrent traumatic injury models for CHA2DS2-VASc and HAS-BLED factors, osteoporosis, dementia, and benzodiazepine usage.

Supplementary Table 5: Critical appraisal of included studies using an amended version of the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) checklist.

	Albrecht (2014)	Albrecht (2015)	Albrecht (2018)	Ao (2017)	Belavic (2015)	Burke (2013)	Chen (2011)	Eric Nyam (2019)	Glass (2019)	Khokhar (2017)	Khokhar (2018)	Kowalski (2017)	Lee (2014)	Liao (2014)	Liu (2017)	Morris (2016)	Shih (2014)	Staerk (2018)
1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
3	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
4	N/A	N/A	N/A	●	N/A	N/A	●	●	N/A	N/A	N/A	N/A	N/A	●	●	●	●	N/A
5	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
6	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
7	N/A	N/A	N/A	N/A	N/A	●	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	●	N/A	●
8	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
9	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

10	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
11	N/A	N/A	N/A	●	N/A	●	●	●	N/A	●	N/A	N/A	●	●	●	●	●	●
12	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
13	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
14	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
15	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
16	●	●	●	N/A	N/A	●	●	●	●	N/A	N/A	N/A	●	●	N/A	●	N/A	●
17	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
18	●	N/A	●	N/A	N/A	●	N/A	N/A	N/A	●	●	●	N/A	N/A	●	●	N/A	●
19	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
20	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
21	N/A	N/A	N/A	N/A	N/A	●	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	●	N/A	●
22	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
23	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

24	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
25	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
26	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
27	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
28	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
29	●	●	●	●	●	●	●	●	●	●	●	●	●	●	N/A	●	●	●
30	●	●	●	●	N/A	●	●	●	●	●	●	●	●	●	●	●	N/A	●
31	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
32	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
33	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
34	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
35	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
36	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Key: ● Yes; ● No; ● Unclear; N/A Not applicable																		

METHODS		
1	Study design	Present key elements of study design early in the paper
2	Setting	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
3	Participants	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
4		For matched studies, give matching criteria and number of exposed and unexposed
5		The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.
6		Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.
7		If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.
8	Variables	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.
9		A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.

10	Data sources/ measurement	For each variable of interest, give sources of data and details of methods of assessment (measurement).
11		Describe comparability of assessment methods if there is more than one group
12	Bias	Describe any efforts to address potential sources of bias
13	Study size	Explain how the study size was arrived at
14	Quantitative variables	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why
15	Statistical methods	Describe all statistical methods, including those used to control for confounding
16		Describe any methods used to examine subgroups and interactions
17		Explain how missing data were addressed
18		Describe any sensitivity analyses
19	Data access and cleaning methods	Authors should describe the extent to which the investigators had access to the database population used to create the study population.
20		Authors should provide information on the data cleaning methods used in the study.
21	Linkage	State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.
RESULTS		
22	Participants	Report the numbers of individuals at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)

23		Describe in detail the selection of the persons included in the study (i.e., study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.
24	Descriptive data	Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders
25		Indicate the number of participants with missing data for each variable of interest
26		Summarise follow-up time (e.g., average and total amount)
27	Outcome data	Report numbers of outcome events or summary measures over time
28	Main results	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included
29		Report category boundaries when continuous variables were categorized
30	Other analyses	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses
DISCUSSION		
31	Key results	Summarise key results with reference to study objectives
32	Limitations	Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.
33	Interpretation	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
34	Generalisability	Discuss the generalisability (external validity) of the study results
OTHER INFORMATION		

35	Funding	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
36	Accessibility of protocol, raw data, and programming code	Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.

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