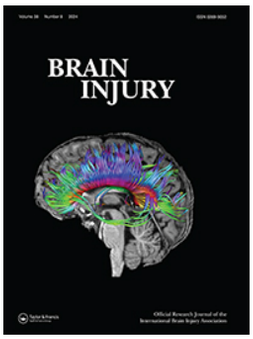

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Epidemiology and outcomes of brain trauma in rural and urban populations: a systematic review and meta-analysis

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ABSTRACT

Objective: To identify and describe differences in demographics, injury characteristics, and outcomes between rural and urban patients suffering brain injury.

Data Sources: CINAHL, Emcare, MEDLINE, and Scopus.

Review Methods: A systematic review and meta-analysis of studies comparing epidemiology and outcomes of rural and urban brain trauma was conducted in accordance with PRISMA and MOOSE guidelines.

Results: 36 studies with ~2.5-million patients were included. Incidence of brain injury was higher in males, regardless of location. Rates of transport-related brain injuries, particularly involving motorized vehicles other than cars, were significantly higher in rural populations (OR:3.63, 95% CI[1.58,8.35], $p = 0.002$), whereas urban residents had more fall-induced brain trauma (OR:0.73, 95% CI[0.66,0.81], $p < 0.00001$). Rural patients were 28% more likely to suffer severe injury, indicated by Glasgow Coma Scale (GCS)≤8 (OR:1.28, 95% CI[1.04,1.58], $p = 0.02$). There was no difference in mortality (OR:1.09, 95% CI [0.73,1.61], $p = 0.067$), however, urban patients were twice as likely to be discharged with a good outcome (OR:0.52, 95% CI[0.41,0.67], $p < 0.00001$).

Conclusions: Rurality is associated with greater severity and poorer outcomes of traumatic brain injury. Transport accidents disproportionally affect those traveling on rural roads. Future research recommendations include addition of prehospital data, adequate follow-up, standardized measures, and sub-group analyses of high-risk groups, e.g. Indigenous populations.

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Trauma; brain; injury; rural; urban

Introduction

Brain trauma is a leading cause of morbidity and mortality worldwide and is associated with significant healthcare costs (1–4). The etiology of brain trauma is varied, with vehicle accidents, falls and assaults the most common causes. Patients with traumatic brain injury are at increased risk of both short- and long-term mortality and morbidity including cognitive and psychiatric disturbances, reduced quality of life, and permanent disability (5–8). Several high-risk populations have been identified, including young males and Indigenous people (5,9–12).

Another important risk factor is rurality. Within Australia, one-third of the population live in rural areas, and brain injuries are the most common injury requiring medical transfer (13). Similarly, an increased incidence of brain trauma has been reported in rural populations in North America (14), Asia (15), Europe (16), and Africa (17). What is less clear, however, is differences in outcomes after brain trauma for rural and urban patients. While some studies have reported increased mortality in rural areas compared to urban areas (18,19), others have reported no difference (16,20), or reduced mortality (21,22).

Understanding the burden of brain trauma and key rural/urban differences is essential to improve patient outcomes, for example, through targeted prevention strategies. The aim of this systematic review and meta-analysis is to identify and describe the differences in demographic and injury characteristics, clinical features, and outcome trends between rural and urban patients with traumatic brain injury worldwide.

Materials and methods

Systematic review

This systematic review was conducted and is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix 1) (23). The protocol was registered and published with PROSPERO, an international register for systematic reviews (CRD42022336874).

Search strategy

All studies that reported epidemiology and outcomes of traumatic brain injuries with rural and urban comparisons were included. An independent literature search was conducted in CINAHL, Emcare, MEDLINE and Scopus for publications

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available up to February 7, 2022. The search strategy is outlined in Appendix 2. Reference lists of studies that were retrieved in full text were hand-searched to identify additional studies, and where necessary, authors of identified studies were contacted for access to full-text articles or additional data. There were no limitations placed on study size or date of publication. Studies published in a language other than English, review articles or commentaries, case studies, conference abstracts, Letters to the Editor, and animal studies were excluded. Studies were not eligible if only one mechanism of injury was analyzed, if no epidemiological data other than outcome was reported, if there was no rural and urban comparison, or if other traumatic injuries, such as cranio-facial or spinal injuries, were not reported separately from brain injuries.

Study selection

Following removal of duplicate studies, two investigators independently performed title and abstract screening to identify eligible articles. Full texts of eligible studies were retrieved and reviewed by the investigators, and a third investigator was consulted in the case of disagreement.

Data extraction

Data were extracted for general characteristics (authors, year, title, journal, publication type), study characteristics (design, follow-up, sample size, patient source, location, definition of rurality, eligible patient identification), patient characteristics (age, sex), injury characteristics (mechanism of injury, injury severity, confirmed pathology, clinical symptoms) and outcome data (mortality, length of hospital stay, discharge status).

Quality assessment

A modified Newcastle-Ottawa tool for quantitative research was used for quality assessment (Appendix 3). The tool included assessments for the following characteristics: representativeness of the study cohort, reporting of demographic data for both rural and urban populations, reporting of incidence/prevalence as well as outcome data, statistical methodology, inclusions of method used for determining injury severity and rural classification, and duration of follow-up. Each study was assessed as low, moderate, or high quality.

Meta-analysis

The meta-analysis was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Appendix 4) (24), using Review Manager software (V5.4.1) and a random-effects model. Medians and interquartile ranges (IQR) were converted to means and standard deviations (SD) using the methods and calculator of Wan *et al* (25). Statistical significance was defined as $p < 0.05$. Heterogeneity was determined by a significant Chi^2 and the I^2 statistic (I^2 <25% low, I^2 = 25–50% moderate, and I^2 >50% substantial heterogeneity).

Ethics approval

No ethical approval is required because data retrieved and analyzed was from previously published studies in which informed consent or a waiver of consent was obtained by the primary investigators.

Results

Study characteristics and quality assessment

A total of 1,310 studies were evaluated for rural/urban differences in patients with brain trauma (Figure 1). After title and abstract screening, 90 full-text articles were reviewed. No additional articles were obtained through reference list searching. Six articles were unable to be retrieved despite requests submitted to the authors. Based on our eligibility criteria, a total of 36 studies were included in the meta-analysis, representing 35 different study populations across 14 countries (Figure 1, Table 1). Most of the studies were population-based retrospective cohort studies of ≥1 year in duration. Of the 36 studies, 15 were conducted in North America (14,18,20,26–37) and nine in Australia and New Zealand (5,6,21,22,38–42). Additional information on study data sources, inclusion/exclusion criteria, and rural/urban classifications, can be found in Appendices 5–7. As per the quality assessment, 17 studies were identified as high quality (6,14,16,19,20,29,30,32,34,37–44), with the remainder determined to be of moderate quality.

Patient cohort

Seventeen studies included patients of all ages, while 12 reported on pediatric, adolescent, and/or young adult patients only (Table 2) (5,26,30,32,34,35,37,40,43–46). Nine studies, comprising a total of 5,241 patients, included comparisons of patient age between rural and urban populations (6,11,16,17,31,35,37,39,43). As demonstrated in Figure 2, there was no significant difference in age at time of brain injury between rural and urban patients (MD: 1.10, 95% CI [−3.17, 5.37, $p = 0.61$). Males were overrepresented in all cohorts, comprising 62–80% of patients with brain injury, with no difference between rural and urban areas (OR: 1.02, 95% CI [1.00, 1.04], $p = 0.11$) (Table 2, Figure 3). A subgroup analysis also showed no statistically significant difference between the number of male patients in pediatric/adolescent or adult age groups between rural and urban populations (OR: 1.01, 95% CI [1.00, 1.03], $p = 0.13$; and OR 1.16, 95% CI [0.82, 1.63], $p = 0.40$, respectively) (Figure 3). Injuries of all severities were reported in 22 studies (5,6,14,15,18–21,26,28,29,32–34,36,38,40,41,44–47), with the remaining studies reporting on either mild or severe traumatic brain injury only (Table 2).

Population-adjusted overall incidence rate of traumatic brain injury was reported in 12 studies (Table 3) (14,16,19,22,32,34,36–38,40,44,48). The incidence rate per 100,000 was reported to be higher in rural populations in seven out of the 12 studies (14,16,19,22,32,38,40), with a trend for higher rates in more remote areas (Table 3) (14,40).

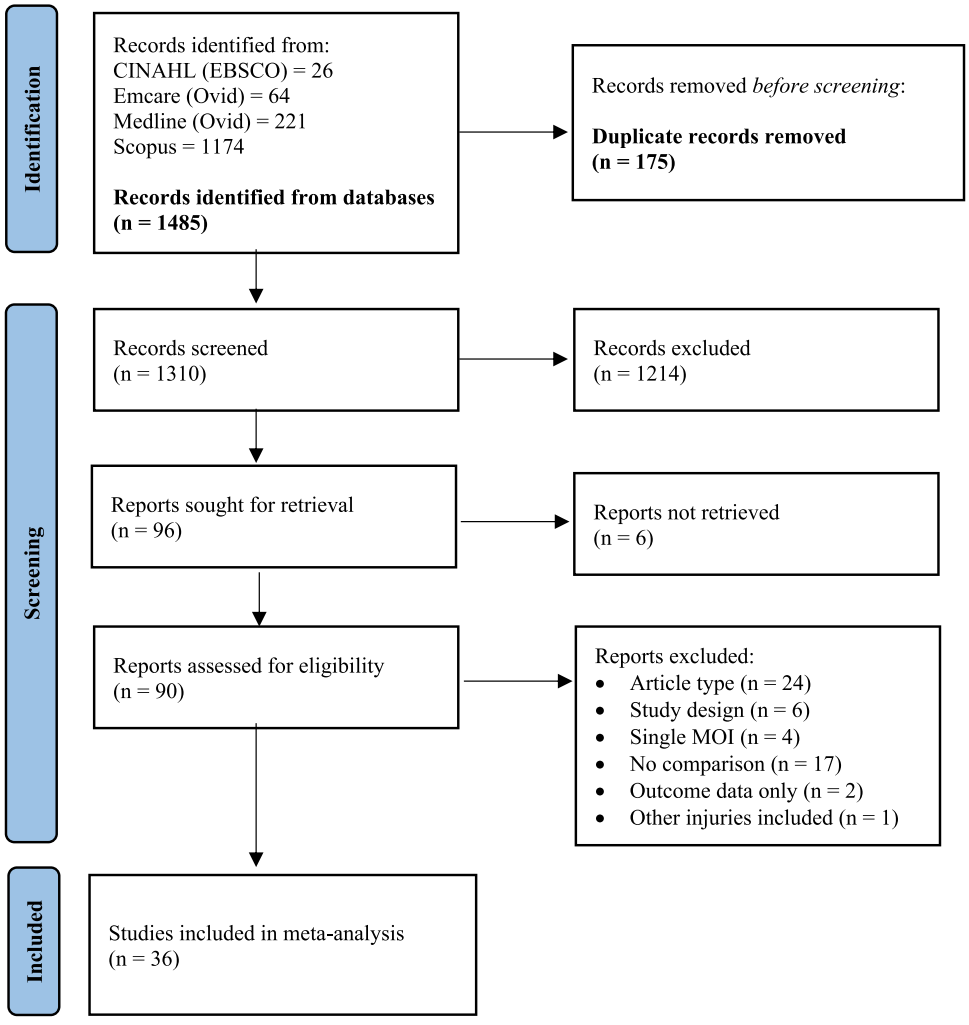

Figure 1. PRISMA Flow Diagram of the study selection process. A total of 1,310 studies were evaluated for rural/urban differences in patients with brain trauma. After title and abstract screening, 90 full-text articles were reviewed, 36 of which were included in the systematic review and meta-analysis after exclusions. CINAHL, Cumulative Index of Nursing and Allied Health; EBSCO, Elton B. Stephens Company; MOI, mechanism of injury.

Cause of injury

Transport-related brain trauma: Traumatic brain injuries caused by transport accidents were 1.3-fold more likely to occur in rural populations than in urban environments ($p = 0.001$) (Figure 4). A subgroup analysis by age groups of 15 studies and 79,558 patients revealed that transport-related brain injuries were significantly more common in rural pediatric and adolescent residents compared with their urban counterparts (OR: 1.27, 95% CI [1.10, 1.47], $p < 0.00001$). Four studies reported on different vehicle types, which enabled a further analysis of the types of transport accidents across 10,526 patients (6,19,37,43). The analysis revealed that there was no difference in car or bicycle accidents causing brain injury between rural and urban groups (OR: 1.32, 95% CI [0.82, 2.07], $p = 0.026$; and OR: 0.70, 95% CI [0.37, 1.30, $p = 0.26$, respectively) (Figure 5a,d). However, patients residing in urban locations were 64% more likely to suffer an injury as a pedestrian than those living rurally (OR: 0.36, 95% CI [0.17, 0.77], $p = 0.008$) (Figure 5b), while brain trauma resulting from accidents involving other motorized vehicles, such as all-terrain vehicles (ATVs) and motorcycles, was over 3.5 times more likely to have occurred in a rural setting (OR: 3.63, 95% CI [1.58, 8.35], $p = 0.002$) (Figure 5c).

Other causes of brain trauma: A total of 79,478 patients from 15 studies were analyzed for fall-related brain injury (5,6,16,19,22,32,37–43,46,49). Urban residents were 27% more likely to sustain brain injury following a fall when compared to those from rural areas (OR: 0.73, 95% CI [0.66, 0.81], $p < 0.00001$) (Figure 6). Subgroup analysis by age group shows a particularly high burden of fall-related brain trauma in children and adolescents in urban settings (OR: 0.65, 95% CI [0.52, 0.81], $p = 0.0002$).

Assault was investigated as a cause of brain trauma in rural and urban populations in 11 studies, representing a total 73,699 patients (5,6,16,17,19,22,38–40,42,43,49). As shown in Figure 7, no difference was found between urban and rural patients (OR: 0.84, 95% CI [0.59, 1.18], $p = 0.30$). However, when accounting for injury severity, assault-related mild brain injury was approximately half as likely to occur rurally (OR: 0.52, 95% CI [0.29, 0.94], $p = 0.03$) (Figure 7). There was no difference in sports injuries or other causes of injury such as work accidents, exposure to animate and inanimate mechanical forces, or use of firearms, between rural and urban

Table 1. Study characteristics and quality assessment.

Author	Year	Study Design	Year Range	Sample	Region[¶]	Patient Source	Follow-up	Rural/Urban Classification	Quality
Agrawal et al. (14)	2017	Prospective single-center cohort	6 months	337	Asia	ED	Hospital Discharge	Not defined	Moderate
Andelic et al. (16)	2012	Population-based prospective	2009–2010 (2 yr)	359	Europe	Hospital	Hospital Discharge	Region-specific[§]	High
Asemota et al. (26)	2013	Population-based retrospective	2005–2009 (4 yr)	139,798	North America	Hospital	Hospital Discharge	Not defined	Moderate
Berry et al. (5)	2010	Population-based retrospective	2000–2006 (6 yr)	95,485	Oceania	Hospital	None	Formal Classification[‡]	Moderate
Brown et al. (18)	2019	Population-based retrospective	2008–2014 (7 yr)	NR	North America	Death registry	Death	Formal Classification	Moderate
Chan et al. (43)	2005	Prospective multi-center cross-sectional	1998–2001 (4 yr)	165	Asia	ED	None	Region-specific	High
Chapital et al. (20)	2007	Retrospective single-center cohort	2000–2004 (5 yr)	3,447	North America	Hospital	Hospital Discharge	Region-specific	High
Cheng et al. (27)	2017	Population-based retrospective	2006–2013 (8 yr)	93,793	North America	Death registry	Death	Formal Classification	Moderate
Cheng et al. (45)	2020	Population-based retrospective	1999–2017 (19 yr)	99,796	Asia	Death registry	Death	Region-specific	Moderate
Chiang et al. (46)	2006	Population-based retrospective	2001–2004 (3 yr)	592	Asia	Hospital	Hospital Discharge	Region-specific	Moderate
Chiu et al. (19)	2007	Population-based retrospective	2001 (1 yr)	7,228	Asia	Hospital/death certificates	Hospital Discharge	Region-specific	High
Daugherty et al. (28)	2021	Population-based retrospective	2016–2018 (3 yr)	181,227	North America	Death registry	Death	Formal Classification	Moderate
Feigin et al. (38)	2013	Population-based prospective and retrospective	2010–2011 (1 yr)	1,369	Oceania	All Community	None	Region-specific	High
Gabella et al. (15)	1997	Population-based retrospective	1991–1992 (2 yr)	7,056	North America	Hospital/death certificates	Hospital Discharge/ Death	Formal Classification	High
Gontkovsky et al. (29)	2006	Prospective single-center cohort	1998–2002 (3.5 yr)	111	North America	Rehabilitation	1 yr	Goodall et al. method[63]	High
Graves et al. (30)	2019	Retrospective multi-center cohort	2007–2011 (5.5 yr)	387,846	North America	Hospital	180 days	Region-specific	High
Halldorsson et al. (44)	2007	Population-based prospective	1992–1993 (1 yr)	550	Europe	Hospital/death registry	Death	Region-specific	High
Harradine et al. (39)	2004	Prospective multi-center longitudinal	1999–2001 (2 yr)	198	Oceania	Rehabilitation	18 mths	Formal Classification	High
Harrison et al. (40)	2012	Population-based retrospective	2000–2006 (6 yr)	103,782	Oceania	Hospital	Hospital Discharge	Formal Classification	High
Johnstone et al. (31)	2003	Prospective single-center longitudinal	2 yr	78	North America	Rehabilitation	VR Completion	Formal Classification	Moderate
Karwat et al[†] (11,49)	2009	Population-based retrospective	1999–2002 (4 yr)	265	Europe	Hospital	Hospital Discharge/ Death	Not defined	Moderate
Leonhard et al. (32)	2015	Population-based retrospective	2009–2012 (4 yr)	2,794	North America	Hospital	Death	Formal Classification	High
Maier et al. (17)	2014	Retrospective multi-center cross-sectional	2005–2008 (R) 2003–2007 (U) (3.5 yr)	680	Africa	Hospital	None	Region-specific	Moderate
Ponsford et al. (6)	2012	Retrospective single-center cohort	1984–2006 (24 yr)	959	Oceania	Rehabilitation	2 yr	Region-specific	High
Pozzato et al. (21)	2019	Population-based retrospective	2007 (1 yr)	6,827	Oceania	Hospital	Hospital Discharge	Formal Classification	Moderate
Ratliff et al. (33)	2021	Population-based retrospective	2008–2014 (7 yr)	3,180	North America	Death registry	Death	Formal Classification	Moderate
Reid et al. (34)	2001	Population-based retrospective	1993 1 yr)	977	North America	Hospital/death certificates	Hospital Discharge/ Death	Goldsmith et al. method[64]	High
Ring et al. (41)	1986	Retrospective multi-center cohort	1997–1978 (2 yr)	991	Oceania	Hospital	Hospital Discharge/ Death	Region-specific	High

(*Continued*)

Table 1. (Continued).

Author	Year	Study Design	Year Range	Sample	Region[¶]	Patient Source	Follow-up	Rural/Urban Classification	Quality
Robertson & McConnel (35)	2011	Retrospective single-center cohort	5 yr	444	North America	Hospital	Hospital Discharge	Formal Classification	Moderate
Schootman & Fuortes (36)	2000	Population-based retrospective	1995–1997 (3 yr)	4,300,000	North America	Ambulatory care	End of Care Episode	Region-specific	Moderate
Simpson et al. (42)	2016	Prospective. multi-center cross-sectional	2007–2008 (1 yr)	503	Oceania	Rehabilitation	6 mths (minimum)	Formal Classification	High
Stewart et al. (37)	2014	Retrospective single-center cross-sectional	2006–2011 (6 yr)	2,112	North America	ED	None	Region-specific	High
Tesfaw et al. (47)	2021	Prospective single-center cross-sectional	2019 (2 mths)	370	Africa	Hospital	Hospital Discharge	Not defined	Moderate
Woodward et al. (22)	1984	Population-based retrospective	1980–1981 (2 yr)	12,201	Oceania	Hospital	Hospital Discharge	Formal Classification	Moderate
Yates et al. (48)	2006	Retrospective single-center cohort study	1997–2003 (6 yr)	11,700	Europe	ED	None	Not defined	Moderate

[†]Karwat et al. (2009A and 2009B) report different outcomes on the same patient population, and are therefore considered as one study. [¶] Locations of Asian studies included India (14), Malaysia (43), China (45), and Taiwan (19,46). European study locations were Norway (16), Iceland (44), Poland (11,49), and the United Kingdom (48). Seven of the North American studies were national studies (18,26–28,30,33,36), with others state-based (Hawaii (20), Colorado (15), Mississippi (29), Missouri (31), Oregon (32), Minnesota (34), and Texas (35)), and one Canadian study (37). Oceania studies were all conducted in Australia with the exception of Feigin et al. (38) which was a New Zealand study. The African studies were conducted in Tanzania (17) and Ethiopia (47). [§] Authors have designated a rural or urban label to a specific city, county or region based on its population, geographic or service provision characteristics. [‡] Authors have utilized a preexisting nationally recognized method of classification. ED, emergency department; VR, Vocational Rehabilitation; R, rural; U, urban.

populations (OR: 0.99, 95% CI [0.59, 1.65], $p = 0.97$; and OR: 1.18, 95% CI [0.77, 1.81], $p = 0.44$, respectively) (Figure 8a,b).

Injury severity

Rates of severe traumatic brain injury between rural and urban populations were reported by five studies, together representing 14,399 patients (19,21,32,34,46). Rural patients were 28% more likely to have obtained a severe traumatic brain injury than urban patients (OR: 1.28, 95% CI [1.04, 1.58], $p = 0.02$) (Figure 9a). However, the mean Glasgow Coma Scale (GCS), which was measured in 1,879 patients from four studies (6,16,35,39), did not show a statistically significant difference between rural and urban populations (MD: −0.25, 95% CI [−0.82, 0.34], $p = 0.39$) (Figure 9b). Rural patients were almost half as likely to have a normal CT following traumatic brain injury when compared to urban patients (OR: 0.52, 95% CI [0.41, 0.67], $p < 0.00001$) (Figure 9c). In contrast, the presence of skull fractures and intracranial hemorrhage was comparable across both populations (OR: 0.71, 95% CI [0.17, 2.96], $p = 0.64$; and OR: 1.05, 95% CI [0.68, 1.63], $p = 0.82$, respectively) (Figure 9d,e).

Clinical symptoms

Various signs and symptoms associated with traumatic brain injury were investigated by these studies. A total of 607 rural and urban patients were reported to have experienced loss of consciousness (LOC) and/or altered level of consciousness (ALOC) across three different studies (17,37,43). Meta-analysis revealed a significant disparity between rural and urban patients, with a 5-fold increased risk in the rural population (OR: 5.04, 95% CI [1.08, 23.62], $p = 0.04$) (Figure 10a). Other clinical symptoms, including headache, seizures, and nausea and vomiting, did not differ between rural and urban patients (Figure 10b–d).

Outcomes

Mortality: Mortality was the major outcome measure reported in 16 studies (14–16,18–22,27,32–35,41,46,49). Population-adjusted mortality rates and rate ratios were significantly higher in all rural cohorts, with further increases as level of rurality increased (Table 4) (14,32,33). However, meta-analysis of 11 studies including 32,984 patients which reported mortality events, failed to show a statistical difference between rural and urban populations (OR: 1.09, 95% CI [0.73, 1.61], $p = 0.67$) (Figure 11a). Sensitivity analysis involving removal of the Woodward *et al* (22) and Pozzato *et al* (21) cohorts significantly reduced heterogeneity (I^2 86% to 29%), and supported the mortality rate and rate ratio data (Table 4), with a 1.5-fold increased risk of mortality in rural patients (OR: 1.49, 95% CI [1.21, 1.84), $p = 0.00002$). There was no evidence of significant publication bias as indicated by the largely symmetrical funnel plot (Figure 11b).

Other outcomes: Discharge status of patients with brain trauma was reported in three studies, comprising 22,103 patients (Figure 12a) (19,22,46). The odds of rural patients suffering severe disability or being in a vegetative state on hospital discharge was not significantly greater when compared to urban patients (OR: 1.42, 95% CI [0.44, 4.62],

Table 2. Patient characteristics.

Author	Year	Age Group	Age Range (yr)	Male Sex (%)	Severity	Rural/Urban Ratio (%)
Agrawal et al. (14)	2017	All	1–90	271 (80.4%)	All	274 (72.6%)/54 (27.4%)
Andelic et al. (16)	2012	Adult	>16	214 (77%)	Severe	82 (29%)/196 (71%)
Asemota et al. (26)	2013	Adolescent/Young Adult	10–19	99,047 (71%)	All	7,631 (5%)/132,167 (95%)
Berry et al. (5)	2010	Pediatric	0–14	61,179 (64%)	All	11,160 (50.9%)/10,719 (50.0%)
Brown et al. (18)	2019	All	NR	NR	All	NR
Chan et al. (43)	2005	Pediatric/Adolescent	2–18	NR	Mild	112 (42%)/153 (58%)
Chapital et al. (20)	2007	All	0–106	2573 (75%)	All	358 (10.4%)/3,089 (89.6%)
Cheng et al. (27)	2017	All	0->75	NR	NR	NR
Cheng et al. (45)	2020	Adolescent/Young Adult	0–19	NR	All	NR
Chiang et al. (46)	2006	Adolescents	13–18	306 (65%)	All	131 (22%)/469 (78%)
Chiu et al. (19)	2007	All	NR	4698 (65%)	All	1,474 (20.4%)/5,754 (79.6%)
Daugherty et al. (28)	2021	All	NR	NR	All	NR
Feigin et al. (38)	2013	All	0->65	856 (63%)	All	361 (26.4%)/1,008 (73.6%)
Gabella et al. (15)	1997	All	0->65	4598 (67%)	All	1,338 (19%)/5,525 (81%)
Gontkovsky et al. (29)	2006	Adult	>16	79 (71%)	All	NR
Graves et al. (30)	2019	Pediatric/Adolescent	0–18	238,994 (62%)	Mild	49,643 (13%)/338,203 (87%)
Halldorsson et al. (44)	2007	Pediatric/Adolescent	0–19	NR	All	141 (26%)/409 (74%)
Harradine et al. (39)	2004	Adult	16–65	155 (78%)	Severe	51 (26%)/147 (74%)
Harrison et al. (40)	2012	Adolescent/Young Adult	15–24	NR	All	13,146 (47.2%)/14,728 (52.8%)
Johnstone et al. (31)	2003	Adult	NR	55 (71%)	NR	28 (35.9%)/50 (64.1%)
Karwat et al[†] (11,49)	2009	All	0->65	204 (77%)	NR	90 (34%)/175 (66%)
Leonhard et al. (32)	2015	Pediatric/Adolescent	0–19	1879 (67%)	All	799 (28.6%)/1,995 (71.4%)
Maier et al. (17)	2014	All	0.2–100	NR	NR	248 (36.5%)/432 (63.5%)
Ponsford et al. (6)	2012	All	11–89	671 (70%)	All	314 (32.7%)/645 (67.3%)
Pozzato et al. (21)	2019	All	0->70	2180 (74.5%)	All	2,240 (33.3%)/4,482 (66.7%)
Ratliff et al. (33)	2021	All	NR	NR	All	NR
Reid et al. (34)	2001	Pediatric/Adolescent	0–19	NR	All	343 (35.1%)/634 (64.9%)
Ring et al. (41)	1986	All	0->75	721 (73%)	All	309 (31.2%)/682 (68.8%)
Robertson & McConnel (35)	2011	Pediatric/Adolescent	0–18	298 (67%)	Severe	38 (8.6%)/406 (91.4%)
Schootman & Fuortes (36)	2000	All	0->75	NR	All	NR
Simpson et al. (42)	2016	Adult	18–65	389 (77%)	Severe	171 (34%)/332 (66%)
Stewart et al. (37)	2014	Pediatric/Adolescent	0–18	1415 (67%)	Mild	387 (19%)/1,687 (81%)
Tesfaw et al. (47)	2021	Adult	>18	265 (72%)	All	259 (70%)/111 (30%)
Woodward et al. (22)	1984	All	0->75	NR	NR	3,971 (32.5%)/8,230 (67.5%)
Yates et al. (48)	2006	All	0->85	NR	NR	NR

[†]Karwat et al. (2009A and 2009B) report different outcomes on the same patient population, and are therefore considered as one study. NR, not reported.

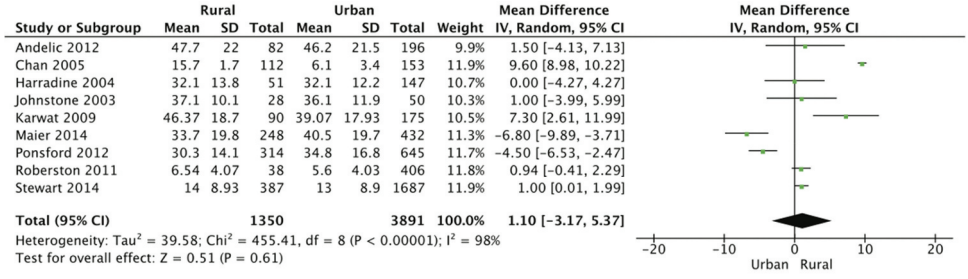

Figure 2. Forest plot demonstrating the mean difference in age (years) calculated using the random effects model. There was no statistical difference in age between rural and urban patients with brain trauma (MD: 1.10; 95% CI − 3.17, 5.37; p = 0.61). Mean [SD] for Stewart 2014 (37) was calculated using the methodology of Wan et al (25). SD, standard deviation; CI, confidence interval; I^2, test of heterogeneity; MD, mean difference.

p = 0.56). However, having a good recovery following traumatic brain injury was significantly more likely in urban compared with rural residents (OR: 0.53, 95% CI [0.35, 0.81], p = 0.003) (Figure 12b). The average length of hospital stay (LOS) for brain trauma care was several days shorter for urban patients, however this difference did not reach statistical significance (MD −3.23, 95% CI [−10.08, 3.63], p = 0.36) (Figure 12c). Finally, there were no differences in the likelihood of post-injury employment between rural and urban residents (OR: 1.06, 95% CI [0.59, 1.89],p = 0.85) (Figure 12d).

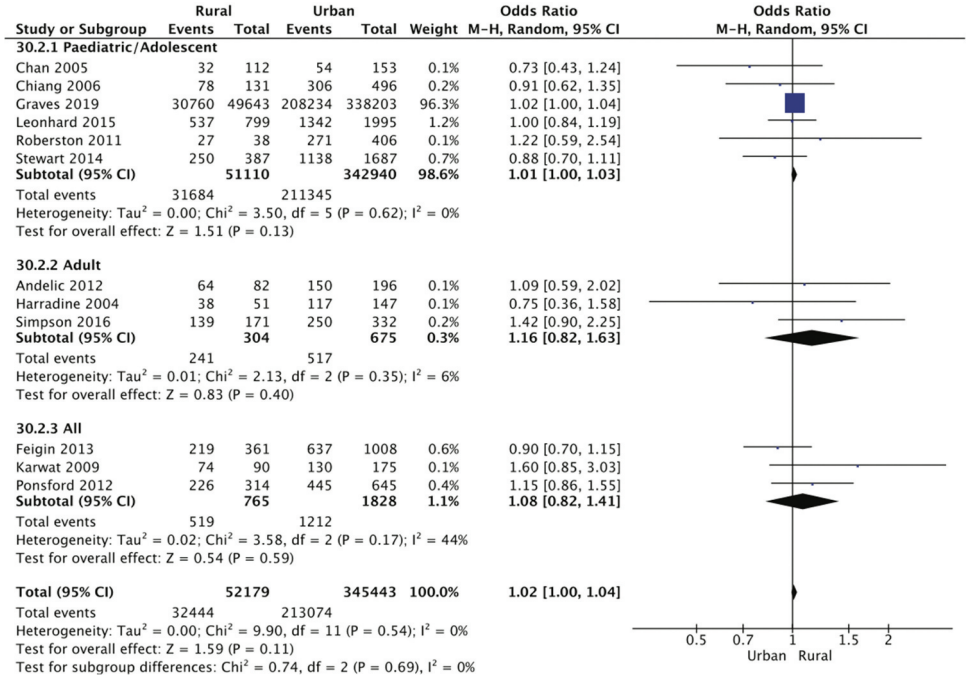

Figure 3. Forest plot demonstrating the odds ratio of male sex in rural and urban brain trauma populations with subgroup analysis of pediatric/adolescent cohorts, adult cohorts, and studies incorporating all ages. The proportion of males suffering brain trauma was comparable across rural and urban areas, regardless of age. SD, standard deviation; CI, confidence interval; I^2, test of heterogeneity.

Table 3. Incidence Rate of Brain Trauma (/100,000 persons) in Rural and Urban Populations.

Author	Year	Rural	Urban	p Value
Andelic et al[†] (16)	2012	5.9 (North) 4.3 (Central)	5.0 (West) 4.1 (Southeast)	NR
Chiu et al. (19)	2007	417	218	NR
Feigin et al[¶] (38)	2013	73	31	NR
Gabella et al[†] (15)	1997	123.9 (Rural non-remote) 172.1 (Rural remote)	97.8 (CMSA) 94.7 (Other metro)	NR
Halldorsson et al. (44)	2007	367	864	NR
Harrison et al. (40)	2012	664.2 (Inner regional) 949.9 (Outer regional) 366.9 (Remote) 1680.2 (Very remote)	522.1 (Major city)	NR
Leonhard et al. (32)	2015	107	71 (Large metropolitan) 59 (Small/medium metropolitan)	NR
Reid et al. (34)	2001	76.1	72.4	0.046
Schootman & Fuortes (36)	2000	410	570	NR
Stewart et al. (37)	2014	220	350	NR
Woodward et al. (22)	1984	570	430	<0.001
Yates et al. (48)	2006	223.8 (All BI) 29.6 (MSBI)	826.9 (All BI) 55.6 (MSBI)	NR

[†]Age-adjusted. [¶] Moderate-severe brain injury. NR, not reported; CMSA, Consolidated metropolitan statistical area; BI, brain injury; MSBI, moderate-severe brain injury.

Discussion

Brain trauma is a global healthcare problem affecting up to 69 million people annually (1). It is a leading cause of morbidity and mortality, and successful treatment requires a time-critical approach (2,50). Patients in rural areas may be disadvantaged by limited access to acute trauma care, complicated by longer transport times and distances to definitive care (51,52). We conducted a systematic review and meta-analysis of 36 studies with approximately 2.5 million patients with brain trauma to address this question and report the following: First, the incidence of traumatic brain injury was higher in males, regardless of location. Second, overall prevalence of brain trauma was significantly higher in rural populations and involved more transport accidents compared to urban environments. Third, patients with traumatic brain injury from urban areas were twice as likely to be discharged with a good outcome. These results will now be discussed.

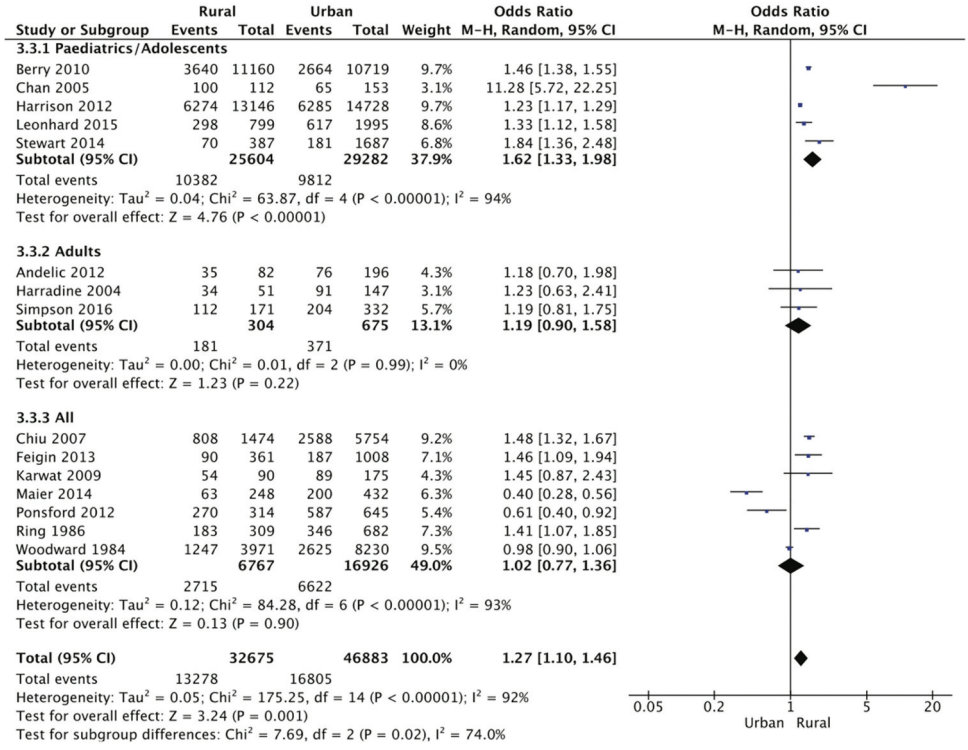

Figure 4. Forest plot demonstrating the odds ratio of transport being the cause of brain trauma in rural and urban populations with subgroup analysis of pediatric/adolescent cohorts, adult cohorts, and studies incorporating all ages. Overall, rural residents were significantly more likely to suffer brain trauma resulting from transport accidents, particularly those in pediatric and adolescent age groups (OR: 1.62; 95% CI 1.33, 1.98; p < 0.00001). CI, confidence interval; I^2, test of heterogeneity; OR, odds ratio.

Brain trauma is more prevalent in males regardless of geographical location

Our systematic review and meta-analysis showed a higher prevalence of brain trauma in males than in females in both rural and urban environments (Table 2). We found males represented 62–80% of patients with brain injury in all cohorts, and there was no significant difference among pediatric/adolescent or adult age groups (Table 2, Figure 3). Similar to other types of traumatic injury, a higher incidence of brain trauma in males is most likely related to an increased likelihood of involvement in high-risk activities, physical altercations, military service and contact sports (11,17,53).

The incidence and severity of traumatic brain injury is higher in rural areas

This meta-analysis confirmed a higher incidence of brain trauma in rural settings compared to urban environments, and further showed that injuries sustained in rural communities were more severe, indicated by the significantly higher proportion of rural patients with a GCS of 3–8 (Table 3, Figure 9a). Interestingly, a higher severity of injury in rural patients was not reflected in the mean GCS value, which did not significantly differ between rural and urban cohorts (Figure 9b). There are several possible reasons for this disparity. First is the fluctuating nature of GCS observed early after injury (54). Second are factors unrelated to the primary injury, such as the presence of alcohol, drugs, sedation and other medications (55,56), and third, the challenge of accurate measurement of GCS in children, linguistically diverse people, and people with disabilities or cognitive deficits (38,44,54,55). Furthermore, most of the published studies examined in the present analysis did not include prehospital data, and relied on the hospital admission GCS, which may not be an accurate representation of the true injury severity, particularly in patients with prolonged prehospital transport times.

An alternative to GCS and a more objective assessment of injury severity is noninvasive diagnostic imaging, such as CT. We found non-pathological (normal) CT was significantly more common amongst urban patients (Figure 9c), supporting our previous finding of fewer severe injuries in urban settings. However, this interpretation may be influenced by the greater availability and access to imaging modalities in urban hospitals. Rural hospitals may only perform imaging on more severely injured patients, reducing the number of CTs performed, and therefore the number of normal CT findings recorded (17).

A higher incidence of severe brain trauma in rural locations was also supported by the proportion of patients experiencing loss of, or altered, consciousness after injury, which was five times more prevalent in the rural patients (Figure 10a). Occurrence of other clinical symptoms, such as headache, nausea and vomiting, and seizures, was similar between rural and urban patients, however these are all nonspecific and highly subjective, and susceptible to variable reporting by both patients and healthcare providers. They may also be influenced by medications, comorbidities,

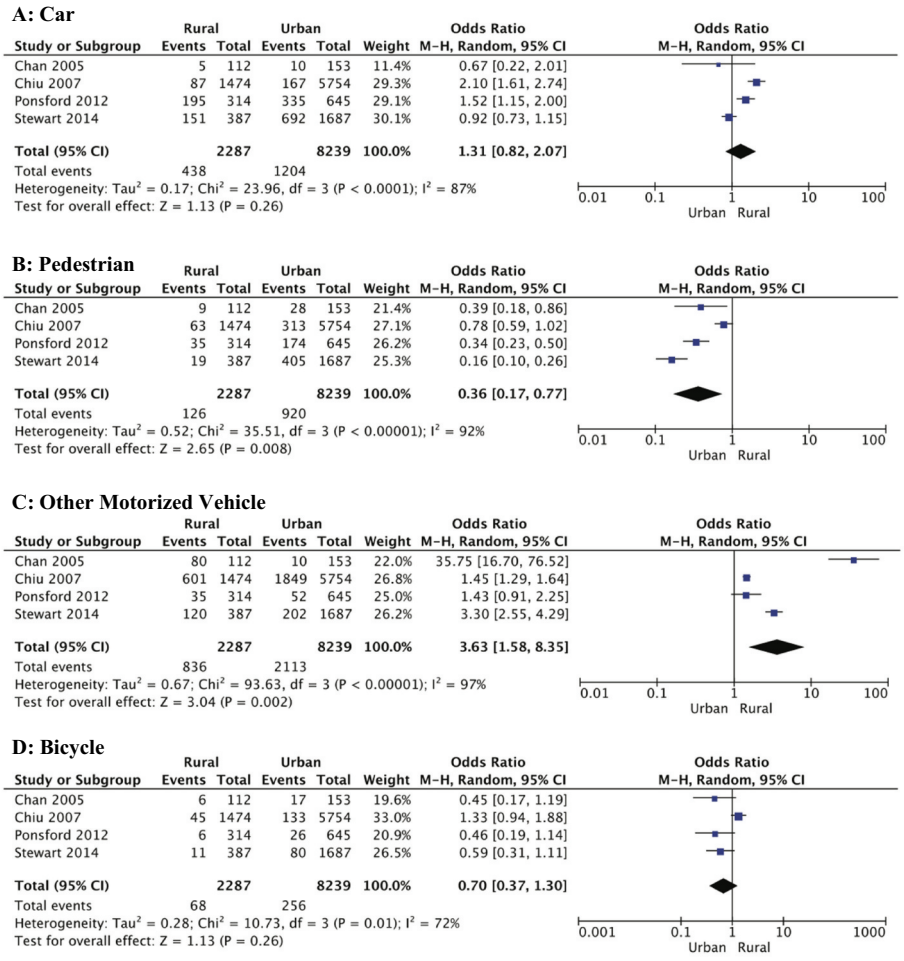

Figure 5. Forest plots showing types of transport accidents causing traumatic brain injury in rural and urban populations. (A), Car; (B), Pedestrian; (c), Other motorized vehicle; (D), Bicycle. Pedestrian-related brain injuries were 64% more likely in urban environments (p = 0.008), whereas motorized vehicles such as all-terrain vehicles, quad bikes, and motorcycles, were responsible for more injuries in rural areas (OR: 3.63; 95% CI 1.58, 8.35; p = 0.002). CI, confidence interval; I^2, test of heterogeneity; OR, odds ratio.

transport, and stress. Therefore, these symptoms may be significant when targeting supportive management on scene but provide minimal insight when determining severity.

Brain trauma due to transport accidents disproportionately affects young rural residents

Another major finding of our meta-analysis was that transport-related traumatic brain injuries were 27% more likely to occur in rural locations (Figure 4). This risk more than doubled for children and adolescents. Brain trauma resulting from motorized vehicle accidents (e.g., motorcycles and ATVs) was significantly more common in rural areas (Figure 5c). Several behavioral factors have been proposed as potential contributors to these findings. Cheng *et al* (2017) (27), Karwat *et al* (49) and Tesfaw *et al* (47) suggested lower rates of law-abiding behavior and higher rates of risk-taking behavior, including driving under the influence of alcohol, rurally. Greater occupational and recreational ATV use associated with rural farming regions may also account for the higher rate of brain injuries resulting from motorized vehicle accidents in rural areas. However, there has been minimal discussion on the environmental factors associated with rural roads. The Centre for Accident Research and Road Safety Queensland have stated that the risk of sustaining a road crash injury increases with the degree of remoteness, with lower rates of safe driving practices contributing to this (57). However, rural areas also have several unique characteristics that predispose drivers to accidents, including lower road quality, unpredictable weather conditions, livestock and wildlife (58). These environmental factors, in addition to human factors, are likely somewhat responsible for the increased risk of transport-related brain trauma in rural environments.

Fall-related brain trauma is more common in urban populations

Another interesting finding of our meta-analysis was the 2.7-fold greater odds of sustaining a traumatic brain injury after a fall in urban populations, with children and adolescents from these areas having almost double the risk of their rural counterparts (Figure 6). Similarly, urban cohorts

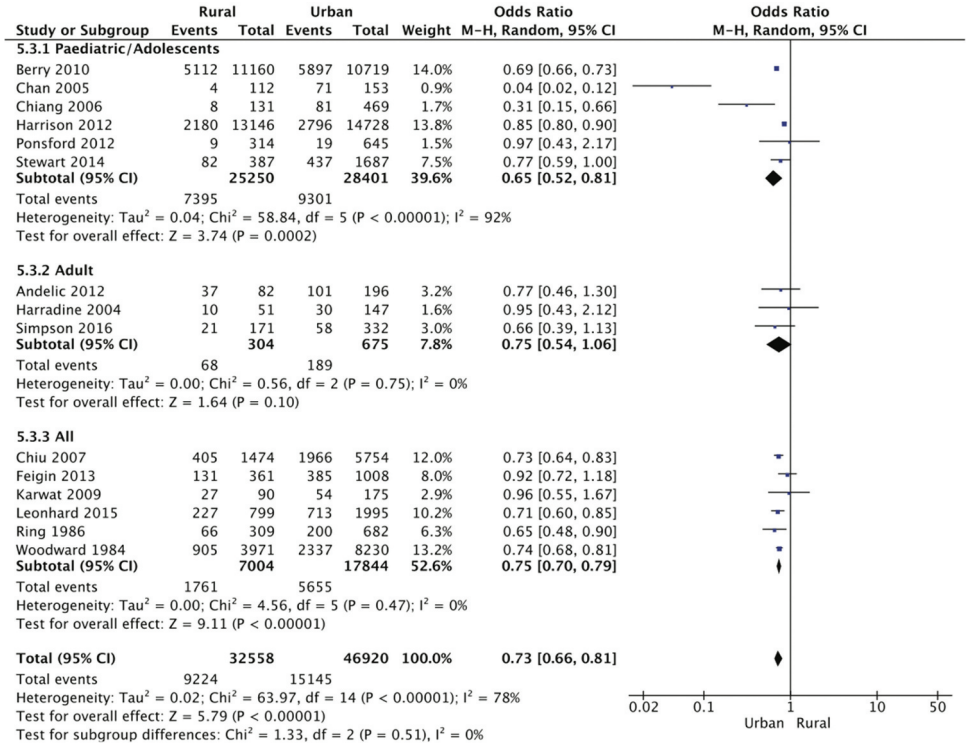

Figure 6. Forest plot demonstrating the odds ratio of falls being the cause of brain trauma in rural and urban populations with subgroup analysis of pediatric/adolescent cohorts, adult cohorts, and studies incorporating all ages. Overall, urban residents were 27% more likely to suffer brain trauma resulting from falls ($p < 0.00001$). The odds of fall-induced brain trauma was significantly less in rural children and adolescents (OR: 0.65; 95% CI 0.52, 0.81; $p < 0.0002$). CI, confidence interval; I^2, test of heterogeneity; OR, odds ratio.

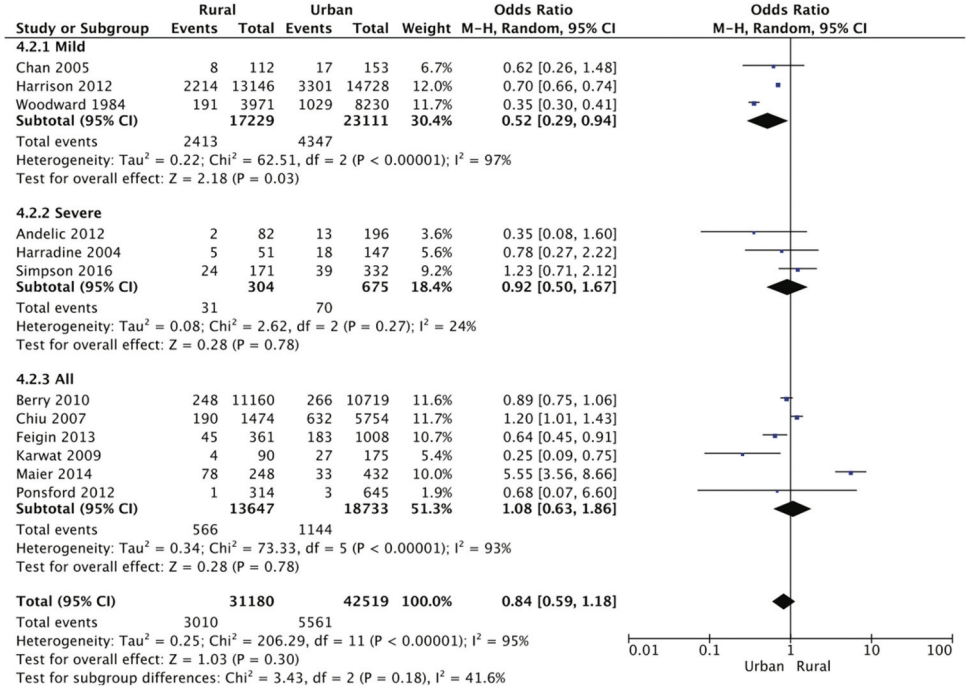

Figure 7. Forest plot demonstrating the odds ratio of assault being the cause of brain trauma in rural and urban populations with subgroup analysis of mild, severe, and injury severities. Overall, assault-related brain injury was comparable across rural and urban populations, except mild brain injuries caused by assault which were ~ 50% less likely in rural areas ($p = 0.03$). CI, confidence interval; I^2, test of heterogeneity.

were twice as likely to sustain a mild brain injury due to an assault, despite rural residents being more likely to experience intimate partner violence, which is a common cause of brain trauma (59). The increased incidence of both fall-related brain trauma, and assault-related mild brain injury, may reflect greater health-seeking behaviors and access to healthcare in urban areas, and thereby increased reporting of these injuries.

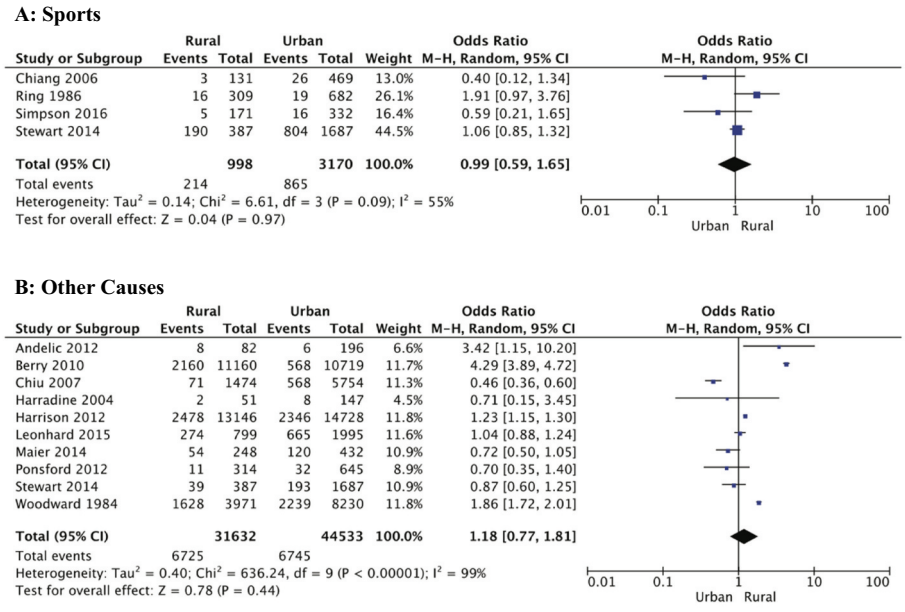

Figure 8. Forest plots showing no difference in (A) sports-related and (B) other causes of brain trauma in rural and urban populations. Other causes included exposure to animal and inanimate mechanical forces, work-related accidents, and use of firearms. CI, confidence interval; I^2, test of heterogeneity.

Mortality from brain trauma is similar, but good recoveries are more likely in urban patients

Despite showing population-adjusted mortality rates and rate ratios were significantly higher in all rural cohorts, with further increases as level of rurality increased (Table 4, Figure 9a), our meta-analysis involving 11 studies including 32,984 patients showed no statistically significant difference in mortality incidence between rural and urban populations (Figure 11a). Importantly of the studies examined, Gabella *et al* (14) and Reid *et al* (34) were the only studies that specifically reported prehospital mortality. Previous research has established that shorter prehospital times are associated with improved brain trauma survival (22,60), and since rural patients have longer travel times and distances, it is possible they experienced greater prehospital mortality. However, unfortunately these prehospital statistics were not documented in the majority of studies of our meta-analysis. In addition, mortality due to brain trauma can occur after hospital discharge and the follow-up time in some studies may not have been sufficient to capture all potential deaths and other complications (30).

Consistent with reduced severity and more normal CT findings, urban patients were 47% more likely to be discharged with a good outcome compared to their rural counterparts (Figure 12b). The initial analysis revealed no significant difference in severe disability or vegetative states between the two populations, however, a sensitivity analysis involving the exclusion of the Woodward *et al* study (22) revealed that rural residents were more than twice as likely to be discharged from hospital in a vegetative state or with severe disability (Figure 12a). This difference might be related to the standard of prehospital care when the study was conducted in 1984, reducing the chance of patients with traumatic brain injury even surviving to hospital discharge to be accounted for in this analysis. Moreover, the Woodward *et al* data (22) includes patients discharged to nursing homes, and admission to this type of facility may not accurately reflect the presence of severe brain trauma as much as it reflects the multifactorial need for round-the-clock care.

Strengths and limitations

To the best of our knowledge, this is the first time that a quantitative meta-analysis has been conducted to investigate epidemiological and outcome differences between rural and urban patients with traumatic brain injury. This comprehensive meta-analysis has included 36 studies from 14 countries with data spanning over 40 years. Most of these studies are population-based, which is considered the ideal approach to obtain objective measures and to understand disease patterns (21). Nevertheless, there are a number of limitations inherent in all brain trauma research that must be considered. Studies of brain injuries typically have considerable heterogeneity due to differences in defining and classifying brain trauma, its severity and outcomes (21,38). Of the 25 analyses performed in this study, 21 (84%) demonstrated substantial heterogeneity, indicated by high I^2 values. In addition, the studies also varied in their classification of rurality, with some using population measurements whilst others used distance to a specific healthcare facility (Table 1, Appendix 7). Inclusion and exclusion criteria also differed across studies (Appendix 6). We mitigated the impact of heterogeneity as best as possible by using a random effects model in our meta-analysis.

Another limitation of all brain trauma research is that mild injuries are frequently underreported. Traumatic brain injury is referred to as a silent epidemic because mild injuries can present with few symptoms or sequelae and consequently, patients may not present to a healthcare facility, or are exclusively treated in outpatient settings (26,30,38). Therefore, research sourcing patients exclusively from hospitals or death

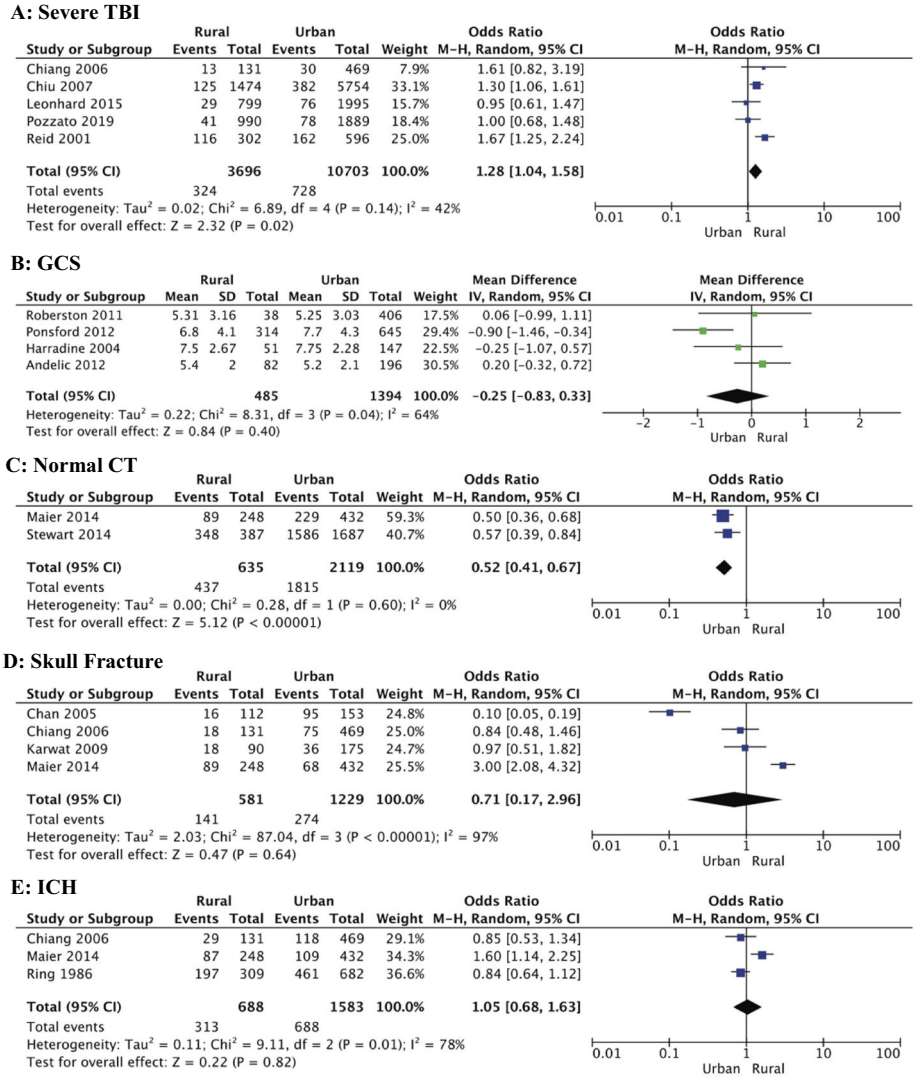

Figure 9. Forest plots showing measures of brain injury severity in rural and urban populations. (A), Proportion of severe brain injury (GCS 3–8); (B), GCS (mean [SD]); (C), Normal CT findings; (D), CT-diagnosed skull fracture; (E), CT-diagnosed ICH. Rural residents were significantly more likely to suffer severe brain trauma (OR: 1.28; 95% CI 1.04, 1.58; p = 0.02), and less likely to have a normal CT (OR: 0.52; 95% CI 0.41, 0.67; p < 0.00001). Mean [SD] GCS for Harradine 2004 (39) was calculated using the methodology of Wan et al (25). GCS, Glasgow Coma Scale; CT, computed tomography; ICH, intracranial hemorrhage; CI, confidence interval; I^2, test of heterogeneity; OR, odds ratio.

registries, which was the case for 95% of the studies included in this meta-analysis, will potentially underreport mild cases. This issue is amplified when considering the barriers to accessing healthcare in rural areas. Therefore, it is likely that the true incidence of traumatic brain injury, particularly in rural areas, is underestimated and skewed to higher severities.

Lastly, we have found that rural brain trauma research lacks Indigenous representation in its datasets, preventing important subgroup analysis. Only five studies reported on Indigenous status in their patient cohorts (21,26,32,38,42), however, none evaluated rural/urban differences in this specific population. This is a concern because not only do Indigenous Peoples often represent a greater proportion of rural communities than urban, but they also experience significant health disparities as a result. In Australia, First Nations people have, on average, a life expectancy 10 years shorter than non-Indigenous Australians, and 15 years less if they live in remote or very remote areas (51,61). Previous studies have shown Indigenous Australians and Americans are disproportionately affected by brain trauma (9,12,62), however, the specific contribution of rurality has not been assessed. Therefore, it is critical to define the impact that ethnicity may have as a risk factor for traumatic brain injury, particularly to develop acute care guidelines and preventative interventions.

Recommendations for future research

Despite these limitations, ongoing epidemiological brain trauma research is vital for identifying potential targets for all levels of prevention and management. We encourage the trauma research community to utilize standard definitions and classifications for brain injury diagnosis, severity, and outcomes. Mortality alone should not be the only outcome measure reported because it does not consider the significant disability burden among survivors. Additionally, we recommend the inclusion of community, primary care, and other

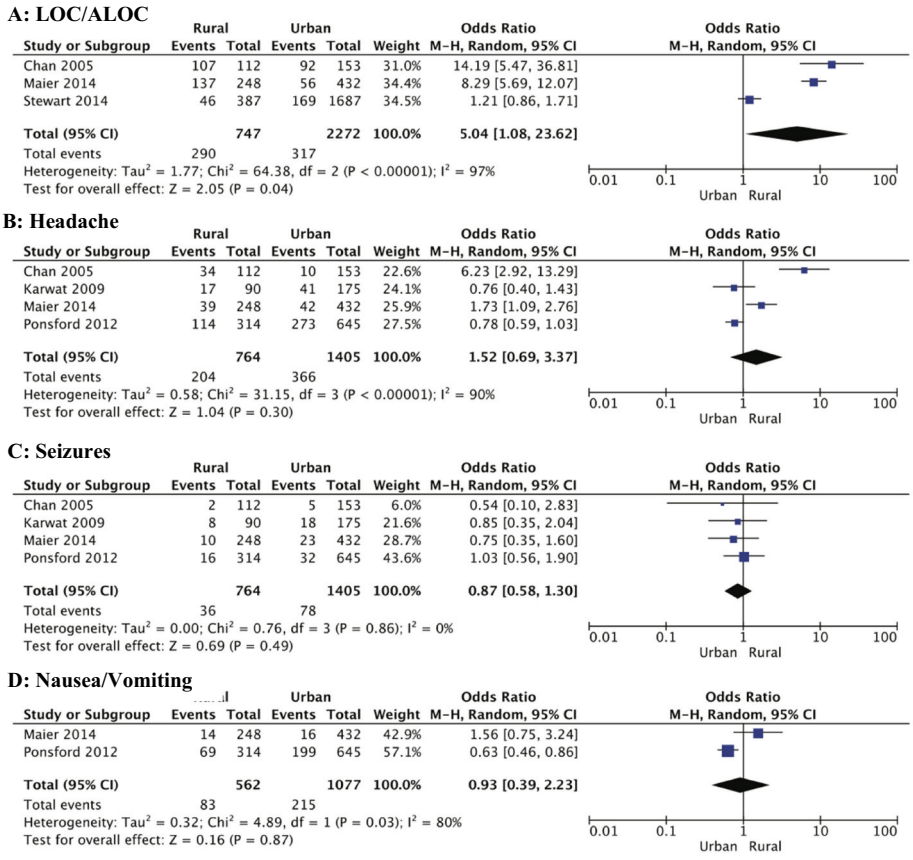

Figure 10. Forest plots showing clinical symptoms after brain injury in rural and urban populations. (A), LOC/ALOC; (B), Headache; (C), Seizures; (D), Nausea/Vomiting. Rural residents were five-fold more likely to suffer loss of, or altered, consciousness (p = 0.04). Incidence of headache, seizures, and nausea or vomiting was similar in patients from rural and urban areas. LOC, loss of consciousness; ALOC, altered level of consciousness; CI, confidence interval; I^2, test of heterogeneity.

Table 4. Brain Trauma Mortality Rate in Rural and Urban Populations.

Author	Year	Rural	Urban	p Value
Brown et al. (18)	2019	22.32	18.22	<0.001
Cheng et al.† (27)	2017	18.55	9.92	NR
Gabella et al.† (15)	1997	25.5 (Rural, non-remote) 33.8 (Rural, remote)	18.1 (CMSA) 18.6 (Other metro)	NR
Leonhard et al.¶ (32)	2015	2.5 [1.6–4.0]	1.00 (Large metro) 1.3 [0.6–2.8] (Small/medium metro)	0.001
Ratliff et al.¶ (33)	2021	1.75 (1.66–1.84)	1.00 (Metro) 1.33 [1.29–1.36] (Nonmetro counties)	<0.001
Reid et al. (34)	2001	15.4	6.5	0.001

Data presented as Mortality/100,000 persons or Mortality Rate Ratio [95% CI]¶. † Age-adjusted. NR, not reported; CMSA, consolidated metropolitan statistical area; CI, confidence interval.

prehospital data, with adequate follow-up data. Finally, we strongly recommend the identification and subgroup analysis of Indigenous patients in datasets, and the use of population-based classifications for rurality. This will more accurately define rural/urban disparities associated with traumatic brain injury and facilitate the development of evidence-based targeted interventions.

Implications and clinical translation

Addressing health inequities among people living in rural areas is part of the strategic framework for the World Health Organization, the Centers of Disease Control and Prevention in the US, Australia's National Health and Medical Research Council, and many others. This systematic review and meta-analysis demonstrates a clear disparity in both incidence and outcome for patients from rural areas with brain injury. Without immediate action, this inequity is likely to increase, based on the rising prevalence of brain trauma globally (1). Furthermore, the differences in mechanism of injury between urban and rural areas suggests that a 'one-size-fits-all' approach will not be effective, but rather different strategies and interventions are required. For example, public interventions targeting safer vehicle use in rural areas, through

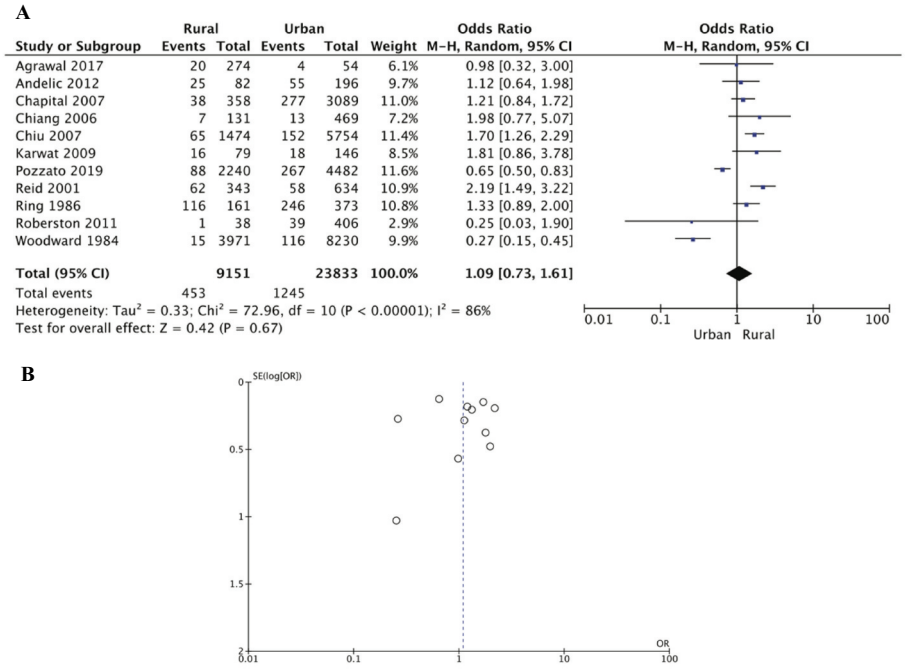

Figure 11. a, Forest plot showing mortality incidence in rural and urban brain trauma populations calculated using the random effects model. Mortality was comparable across rural and urban areas. b, Funnel plot of publication bias. CI, confidence interval; I^2, test of heterogeneity.

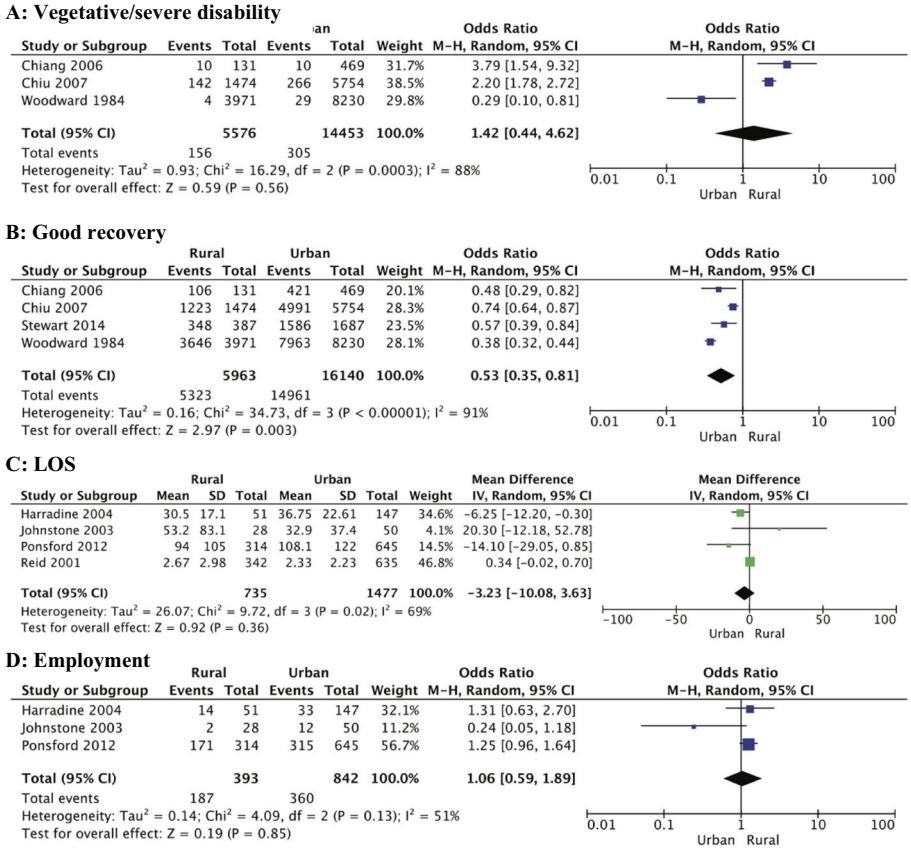

Figure 12. Forest plots showing outcomes after brain injury in rural and urban populations. a, Vegetative/severe disability; b, Good recovery; c, Length of hospital stay (days); d, Employed post-injury. Urban residents were more likely to have a good recovery (p = 0.003), and reduced hospital stay, however this difference was not statistically significant (MD: −3.23; 95% CI − 10.08, 3.63; p = 0.36). Mean [SD] LOS for Harradine 2004 (39) and Reid 2001 (34) was calculated using the methodology of Wan et al (25). LOS, length of stay; CI, confidence interval; I^2, test of heterogeneity; MD, mean difference.

improved road conditions, appropriate speed limits, and enforcement of seatbelt regulations, may reduce the impact and severity of brain injury in rural populations, whereas implementation of falls prevention programs and safer recreation areas in urban areas could decrease fall-related brain trauma in these communities.

Conclusions

Rurality is associated with greater incidence, severity, and poorer outcomes of traumatic brain injury. Transport accidents are a significant cause of brain trauma in rural environments. Future research should include primary care and prehospital data, as well as adequate follow-up for accurate incidence and mortality rates. The use of standardized severity and rural classifications, as well as the inclusion of Indigenous subgroup analyses are highly encouraged in future brain trauma studies.

Disclosure statement

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Data availability statement

This systematic review and meta-analysis is a synthesis of existing published data, openly available in cited references.

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Appendices

Appendix 1: PRISMA 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.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	5
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.	5-6
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Table 2
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).	5-6, Fig 1
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.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
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.	6, Supplementary Table 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
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.	6-7
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).	6, Supplementary Table 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
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.	8, Fig 1
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.	Table 1
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).	8, Table 1
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.	8-12, Fig 2-12, Table 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-12, Fig 2-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, 12, Table 1, Fig 11B
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-10, 12, Fig 3, 4, 6, 7
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).	13-17
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).	17-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
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.	1

Appendix 2: Search Strategy

Database Searched	Search Strategy
CINAHL <1982 to February 07, 2022>	
Ovid Emcare <1995 to 2022 Week 4>	1exp head injury/ 2exp rural health/or exp rural population/ 31 and 2 4limit 3 to (human and English language)
Ovid MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions < 1946 to February 04, 2022>	1exp Craniocerebral Trauma/ 2exp Rural Health/or exp Rural Population/ 31 and 2 4limit 3 to (English language and humans)
Scopus <1788 to February 07, 2022>	('head injur*' OR 'head trauma' OR 'traumatic brain injur*' OR tbi) AND (rural OR remote) AND (LIMIT-TO (DOCTYPE, 'ar')) AND (LIMIT-TO (SUBJAREA, 'MEDI') OR LIMIT-TO (SUBJAREA, 'NEUR')) AND (LIMIT-TO (LANGUAGE, 'English')) AND (LIMIT-TO (EXACTKEYWORD, 'Human') OR LIMIT-TO (EXACTKEYWORD, 'Humans'))

CINAHL, Cumulative Index of Nursing and Allied Health; EBSCO, Elton B. Stephens Company; TBI, traumatic brain injury.

Appendix 3: Modified Newcastle-Ottawa Quality Assessment Scale

Selection	
1	Is the study population likely to be representative of the whole population?
2	Was the non-exposed cohort (urban population) sourced from the same state/country or database?
3	Was the exposure ascertained through secure records, i.e., confirmed medical record?
4	Does the study specify the source of data?
5	Was the sample size appropriate for each cohort for statistical comparison of rural and urban populations?
6	Are inclusion and exclusion criteria clearly outlined?
7	Is the study population specifically sought for the purpose of the study i.e., not part of a larger shared database?
8	Is the date range of the data set clearly stated?
Comparability	
9	Is the research methodology clearly stated?
10	Is the data collection methodology clearly stated?
11	Is the statistical methodology appropriate?
12	Does the study report demographics for both rural and urban populations to enable comparison?
13	Does the study report incidence/prevalence as well as mortality/other outcome measure?
14	Does the study state the method of determining head injury severity?
15	Does the study state the method of determining urban and rural classifications?
Outcome	
16	Are the outcomes clearly stated and discussed in relation to the data collection?
17	Does the study report findings in relation to original aims?
18	Was follow-up long enough for outcomes to occur without missing data (e.g., mortality, length of stay)?
19	Were the differences between groups clinically meaningful? (i.e., was the clinical significance reported in addition to statistical significance)
20	Does the study account for confounding factors and is it considered in the analysis?

Score /20
Low quality < 10
Moderate quality 10-15
High quality > 15

Appendix 4: MOOSE Checklist for Meta-analyses of Observational Studies

Item	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	Not applicable
3	Description of study outcome(s)	4
4	Type of exposure or intervention used	Not applicable
5	Type of study designs used	Table 1
6	Study population	Table 1-Table 2
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	1 (Title page)
8	Search strategy, including time period included in the synthesis and key words	5, Appendix 2
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5, Appendix 2
11	Search software used, name and version, including special features used	5, Appendix 2
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	8, Fig 1
14	Method of addressing articles published in languages other than English	5
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	5, 8, Fig 1
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5–6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Table 3-Table 4
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6, Appendix 3
22	Assessment of heterogeneity	6–7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6–7
24	Provision of appropriate tables and graphics	Table 1-Table 4 Fig 1-12 Appendices 5–7
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig 2-12
26	Table giving descriptive information for each study included	Table 1-Table 2
27	Results of sensitivity testing (eg, subgroup analysis)	8–10, 12, Fig 3, 4, 6, 7
28	Indication of statistical uncertainty of findings	8–12
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	8, 12, Table 1, Fig 11B
30	Justification for exclusion (eg, exclusion of non-English language citations)	5, Fig 1
31	Assessment of quality of included studies	8, Table 1
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	13–19
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	17–19
34	Guidelines for future research	19
35	Disclosure of funding source	1

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

Appendix 5: Data Sources

Author	Year	Data Source(s)
Agrawal et al. (14)	2017	Prospective collection (single tertiary hospital)
Andelic et al. (16)	2012	Analysis of data from prospective population-based multicentre study
Asemota et al. (26)	2013	HCUP-NIS
Berry et al. (5)	2010	AIHW NHMD
Brown et al. (18)	2019	CDC WISQARS™
Chan et al. (43)	2005	Prospective collection (2 hospitals)
Chapital et al. (20)	2007	Queen's Medical Center trauma database
Cheng et al. (27)	2017	CDC WONDER
Cheng et al. (45)	2020	China DSP
Chiang et al. (46)	2006	Taiwan Head Injury Registry + hospital records (24 hospitals)
Chiu et al. (19)	2007	Prospective collection (26 hospitals)
Daugherty et al. (28)	2021	CDC NVSS
Feigin et al. (38)	2013	CT/MRI records, hospital discharge registers, private hospitals, GP practices, rehabilitation centers, outpatient clinics, coroner/autopsy records, rest homes, community health services, schools, sports centers, ambulance services, prison, ACC database, death certificates, hospital separation data
Gabella et al. (15)	1997	Colorado surveillance system (hospital discharge data + death certificate data)
Gontkovsky et al. (29)	2006	NIDRR TBI Model System + participant/family member interviews
Graves et al. (30)	2019	MarketScan CCAE
Halldorsson et al. (44)	2007	Icelandic hospitals + EDs + healthcare centers + death register
Harradine et al. (39)	2004	Prospective collection (11 rehabilitation units)
Harrison et al. (40)	2012	AIHW NHMD
Johnstone et al. (31)	2003	Missouri Division of Vocational Rehabilitation
Karwat et al.[†] (11,49)	2009	Lublin Regional Specialist Hospital records
Leonhard et al. (32)	2015	Oregon Trauma registry
Maier et al. (17)	2014	CT/MRI records (2 hospitals)
Ponsford et al. (6)	2012	Prospective collection (single rehabilitation center)
Pozzato et al. (21)	2019	NSW Department of Health hospital data
Ratliff et al. (33)	2021	CDC WISQARS™
Reid et al. (34)	2001	MDH TBI Registry + death certificates
Ring et al. (41)	1986	NSW Hospital Morbidity Statistics + hospital indices (133 hospitals) + death certificates
Robertson & McConnel (35)	2011	Children's Medical Center Dallas trauma census
Schootman & Fuortes (36)	2000	NAMCS & NHAMCS
Simpson et al. (42)	2016	Prospective collection (11 rehabilitation units) + NSW electronic database
Stewart et al. (37)	2014	NACRS
Tesfaw et al. (47)	2021	Prospective collection (single tertiary hospital)
Woodward et al. (22)	1984	South Australian Health Commission hospital separation discharges/transfers/deaths
Yates et al. (48)	2006	Royal Devon and Exeter Hospital ED database

[†]Karwat et al. (2009A and 2009B) report different outcomes on the same patient population, and are therefore considered as one study. HCUP-NIS, Healthcare Cost and Utilization Project Nationwide Inpatient Sample; AIHW NHMD, Australian Institute of Health and Welfare National Hospital Morbidity Database; CDC, Centers for Disease Control and Prevention; WISQARS™, Web-based Injury Statistics Query and Reporting; WONDER, Wide-ranging Online Data for Epidemiological Research; DSP, Disease Surveillance Points; NVSS, National Vital Statistics System; CT, computed tomography; MRI, magnetic resonance imaging; GP, General Practitioner; ACC, Accident Compensation Corporation; NIDRR, National Institute in Disability and Rehabilitation Research; TBI, traumatic brain injury; CCAE, Commercial Claims and Encounters database; ED, emergency department; NSW, New South Wales; MDH, Minnesota Department of Health; NAMCS, National Ambulatory Care Survey; NHAMCS, National Hospital Ambulatory Care Survey; NACRS, National Ambulatory Care Reporting System.

Appendix 6: Inclusion and Exclusion Criteria

Author	Year	Inclusion Criteria	Exclusion Criteria
Agrawal et al. (14)	2017	Consent provided	NR
Andelic et al. (16)	2012	≥16 yr; Norwegian resident; admitted within 72 h after injury; ICD-10 S06.0-S06.9; severe TBI	Injured abroad; progressive neurological diseases/injuries; severe psychiatric diseases; severe alcohol &/or narcotics abuse, homeless; no consent
Asemota et al. (26)	2013	10–19 yr; primary or secondary diagnosis of TBI; ICD-9-CM 800.00–804.09, 850.0–854.19	Interhospital transfers; discharged directly from ED; treated in outpatient settings
Berry et al. (5)	2010	0–14 yr; ICD-9-CM 800.0–801.9, 803.0–804.9, 850.0–854.1	Inward transfers from another acute care hospital
Brown et al. (18)	2019	CDC-recommended ICD-10 codes[¶]	NR
Chan et al. (43)	2005	2–18 yr; Isolated closed HI, mechanism witnessed & reported to police, HI symptoms, initial GCS ≥ 13 improving to 15, no abnormal or focal finding on neurological examination within 24 h of injury	History of bleeding diatheses or neurological disorders; multiple trauma; intentional head trauma; speech disturbances; altered mental status before incident
Chapital et al. (20)	2007	ICD-9-CM 800.0–801.9, 803.0–804.9, 850.0–854.1, 959.01	Second admission during study period
Cheng et al. (27)	2017	CDC-recommended ICD-10 codes[¶]	NR
Cheng et al. (45)	2020	0–19 yr; CDC-recommended ICD-10 codes[¶]	NR
Chiang et al. (46)	2006	13–18 yr, CT-diagnosed HI	NR
Chiu et al. (19)	2007	Concussion, skull fracture, neurological & cognitive deficit, PTA, neurological sequelae, ICH	NR
Daugherty et al. (28)	2021	CDC-recommended ICD-10 codes[¶]	NR
Feigin et al. (38)	2013	WHO criteria: acute brain injury resulting from mechanical energy to head from external physical forces. Presence of 1/more of: confusion/disorientation, LOC, PTA, other neurological abnormalities	NR
Gabella et al. (15)	1997	Colorado resident; injury occurred in Colorado; ICD-9-CM 800.0–801.9, 803.0–804.9, 850.0–854.1	Brain injuries resulting from a disease process or decreased O_2 supply to brain
Gontkovsky et al. (29)	2006	≥16 yr; in-patient rehabilitation patients with medically-documented TBI admitted to NIDRR TBI Model System center within 72 h discharge from acute care; treatment at Level 1 trauma center within 24 h injury	Not contactable to 1-yr follow-up; missing data; residing out of state or in jail at follow-up; history of major neurological deficit prior to sustaining TBI
Graves et al. (30)	2019	<18 yr; mTBI diagnosis; ICD-9-CM 800.0–801.9, 803.0–804.9, 850.0–854.1, 950.1–950.3, 995.55. Continuously enrolled for at least 180 days prior to and after index TBI diagnosis.	Cases missing region/MSA data; index TBI date coincident with a hospital admission (considered more severe injuries); cases with extremity AIS ≥ 3.
Halldorsson et al. (44)	2007	0–19 yr; ICD-9 850–854	NR
Harradine et al. (39)	2004	16–65 yr; >7 days PTA; de-novo TBI in previous 6 months; admitted to BIRP	No consent; previous TBI/acquired brain injury; past medical history likely to affect recovery
Harrison et al. (40)	2012	15–24 yr; received in-patient care at public & private hospitals; CDC-recommended ICD-10 codes[¶]	NR
Johnstone et al. (31)	2003	Qualified for VR services based on primary/secondary TBI diagnosis	Did not complete VR service
Karwat et al.[†] (11,49)	2009	Medically-diagnosed HI; hospitalized > 1 day	NR
Leonhard et al. (32)	2015	0–19 yr; ICD-9-CM[§] +959.01; meets prehospital triage criteria, or requires surgeon's evaluation or treatment or activation of trauma team, or requires transfer to a trauma center, or ISS > 8, death, major operative procedure to head/chest/abdomen within 6 h or admitted to ICU within 24 h	Out-of-state location of injury; non-trauma hospitals; no transfer to trauma center made; prehospital death
Maier et al. (17)	2014	Hospitalized with CT-confirmed TBI diagnosis	Cranial CT scanning performed for research purposes concerning epilepsy & neurocysticercosis.
Ponsford et al. (6)	2012	In-patient at Epworth Rehabilitation Centre; participated in 2-yr follow-up	Residing interstate or overseas
Pozzato et al. (21)	2019	NSW resident; 1st hospital admission of TBI; CDC-recommended ICD-10 codes (S01.0-S07.1 only)[¶]	Non-residents of NSW; non-acute episodes of care; subsequent admissions
Ratliff et al. (33)	2021	CDC-recommended ICD-10 codes[¶]	Counties with 20 or fewer TBI deaths
Reid et al. (34)	2001	0–19 yr; Minnesota resident; TBI resulting in hospitalization/death; ICD-9-CM codes 800.0–801.9, 803.0–804.9, 850.0–854.1, 873.0–873.9	NR
Ring et al. (41)	1986	Neurotrauma patients hospitalized in NSW with EDH, ASDH, CSDH, or other HI leading to death; ICD-8 851–3 or 800–804, 850 or 854 and operation code 1–19, 84 or 888 or 430–438	Hospitals outside the boundaries of NSW

(*Continued*)

(Continued).

Author	Year	Inclusion Criteria	Exclusion Criteria
Robertson & McConnel (35)	2011	0–18 yr; severe TBI; ICD-9 800, 801, 802, 804, 850–854, 959.01	Injury not accidental (abuse, assault, or injury through other purposeful means)
Schootman & Fuortes (36)	2000	ICD-9-CM 800–801, 803–804, 850–854	NR
Simpson et al. (42)	2016	18–65 yr; severe TBI; active client of BIRP (3 occasions of service during 6-month period)	Paediatric BIRP services
Stewart et al. (37)	2014	<18 yr; concussion; ICD-10-CA S06 & R40.29, R41.1–3, R41.8, S00-T98	Penetrating HI; return visits for reevaluation of same concussion
Tesfaw et al. (47)	2021	>18 yr; systematic random sampling of trauma patients admitted to DTTRH ED	NR
Woodward et al. (22)	1984	Hospitalised; ICD-9-CM 800.0–804.9, 850.0–854.9	Direct admissions from another hospital
Yates et al. (48)	2006	NHS Centre for Clinical Coding and Classification codes 18, 19	NR

[†]Karwat et al. (2009A and 2009B) report different outcomes on the same patient population, and are therefore considered as one study. [¶] S01.0-S01.9, S02.0, S02.1, S02.3, S02.7-S02.9, S04.0, S06.0-S06.9, S07.0, S07.1, S07.8, S07.9, S09.7-S09.9, T01.0, T02.0, T04.0, T06.0, T90.1, T90.2, T90.4, T90.5, T90.8, T90.9; [§] Barell et al. (65). NR, none reported; ICD, International Classification of Diseases; TBI, traumatic brain injury; CM, Clinical Modification; ED, emergency department; CDC, Centers for Disease Control and Prevention; HI, head injury; CT, computed tomography; PTA, post-traumatic amnesia; ICH, intracranial hemorrhage; WHO, World Health Organization; LOC, loss of consciousness; NIDRR, National Institute in Disability and Rehabilitation Research; mTBI, mild traumatic brain injury; MSA, Metropolitan Statistical Area; AIS, Abbreviated Injury Score; BIRP, Brain Injury Rehabilitation Program; VR, Vocational Rehabilitation; ISS, Injury Severity Score; ICU, intensive care unit; NSW, New South Wales; EDH, extradural hematoma; ASDH, acute and subacute subdural hematoma; CSDH, chronic subdural hematoma; CA, Canada; DTTRH, Debre Tabor Teaching and Referral Hospital; NHS, National Health Service.

Appendix 7: Rural/Urban Classifications

Author	Year	Data Source(s)
Agrawal et al. (14)	2017	Not defined
Andelic et al. (16)	2012	Rural = Northern & Central regions; Urban = Western and Southern regions
Asemota et al. (26)	2013	Not defined
Berry et al. (5)	2010	ABS ASGC: Rural = inner regional, outer regional, remote, very remote; Urban = major city
Brown et al. (18)	2019	US Department of Agriculture UIC: Rural = ≥3; Urban = ≤2
Chan et al. (43)	2005	Rural = Kota Bharu,;Urban = Ipoh
Chapital et al. (20)	2007	US Census criteria: Rural = jurisdictions outside Honolulu County; Urban = Honolulu County
Cheng et al. (27)	2017	Chinese CDC DSP: Rural = county; Urban = district
Cheng et al. (45)	2020	US CDC NCHS Urban-Rural Classification Scheme: Rural = rural area; Urban = large city and suburbs or medium or small city
Chiang et al. (46)	2006	Rural = Hualian County; Urban = Taipei
Chiu et al. (19)	2007	Rural = Hualian County; Urban = Taipei
Daugherty et al. (28)	2021	US Census Bureau: Rural = all non-urban population, housing, and territory; Urban = at least 2500 persons, at least 1500 live outside institutional group quarters
Feigin et al. (38)	2013	Rural = Hamilton, Urban = Waikato District
Gabella et al. (15)	1997	US Census Bureau: Rural = adjacent to MSA county or population of 2500, or not adjacent to MSA with population < 2500; Urban = MSA or CMSA
Gontkovsky et al. (29)	2006	Goodall et al. (63): Urbanicity scores calculated based on populations of 3 largest cities in each county. Higher urbanicity scores = more urban (less rural) county
Graves et al. (30)	2019	US Census Bureau: Rural = county with no MSA coding; Urban = MSA (metropolitan or micropolitan)
Halldorsson et al. (44)	2007	Rural = rest of Iceland; Urban = Reykjavik
Harradine et al. (39)	2004	ARIA RRMA: Rural = 3–7; Urban = 1–2
Harrison et al. (40)	2012	ABS ASGC: Rural = inner regional, outer regional, remote, very remote; Urban = major city
Johnstone et al. (31)	2003	US OMB: Rural = non-metropolitan; Urban = metropolitan
Karwat et al. (11,49)	2009	Not defined
Leonhard et al. (32)	2015	US CDC NCHS Urban-Rural Classification Scheme: Rural = rural area; Urban = large city and suburbs or medium or small city
Maier et al. (17)	2014	Rural = Haydom Lutheran Hospital; Urban = Aga Khan Hospital
Ponsford et al. (6)	2012	Rural = Regional Victoria (>25 km from central business district); Urban = Metropolitan Melbourne
Pozzato et al. (21)	2019	ABS ASGC: Rural = inner regional, outer regional, remote, very remote; Urban = major city
Ratliff et al. (33)	2021	US Department of Agriculture Rural-Urban Continuum Codes: Rural = 4–9; Urban = 1–3
Reid et al. (34)	2001	Goldsmith et al. (64): Rural = non-metropolitan and parts of large metropolitan counties without easy geographical access to central areas; Urban = metropolitan
Ring et al. (41)	1986	Rural = country base or small hospital; Urban = teaching and metropolitan surgical hospital or other private hospital
Robertson & McConnel (35)	2011	US Department of Agriculture RUCA2: Rural = small and isolated towns; Urban = urban and large towns
Schootman & Fuortes (36)	2000	US Census Bureau: Rural = county with no MSA coding; Urban = MSA (metropolitan or micropolitan)
Simpson et al. (42)	2016	ABS ASGC: Rural = inner regional, outer regional, remote, very remote; Urban = major city
Stewart et al. (37)	2014	Statistics Canada DA: Rural = non-urban DA; Urban = minimum population concentration of > 1000 people & population density > 400 people/km^2
Tesfaw et al. (47)	2021	Not defined
Woodward et al. (22)	1984	ABS: Rural = outside Adelaide Statistical Division; Urban = within Adelaide Statistical Division
Yates et al. (48)	2006	Not defined

† Karwat et al. (2009A and 2009B) report different outcomes on the same patient population, and are therefore considered as one study. ABS, Australian Bureau of Statistics; ASGC, Australian Standard Geographical Classification; US = United States; UIC, Urban Influence Code; CDC, Center for Disease Control and Prevention; DSP, Disease Surveillance Point; NCHS, National Center for Health Statistics; MSA, Metropolitan Statistical Area; CMSA, Consolidated Metropolitan Statistical Area; ARIA, Accessibility/Remoteness Index of Australia; RRMA, Rural, Remote and Metropolitan; OMB, Office of Management and Budget; RUCA2, Rural and Urban Commuting Area 2; DA, Dissemination Area.