Frequency of anxiety after stroke: an updated systematic review and meta-analysis of observational studies

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Abstract

Background

Anxiety is a common and distressing problem after stroke. A previous systematic review of observational studies [1] included 44 studies published to March 2011. The review needed updating: there were known to be more recent primary studies of anxiety after stroke and some sub-group analyses had previously been based on small samples, with resultant imprecision.

Aims

To undertake an updated systematic review and meta-analysis of observational studies of anxiety after stroke and integrate the findings with those reported previously.

Summary of review

Multiple databases were searched to May 2018 and 53 new studies were included following dual independent sifting and data extraction. These were combined with 44 previous studies to form a combined dataset of 97 studies, comprising 22,262 participants. Studies using interview methods were of higher quality. Rates of anxiety by interview were 18.7% (95% CI 12.5, 24.9%) and 24.2% (95% CI 21.5, 26.9%) by rating scale. Rates of anxiety did not lower meaningfully up to 24 months after stroke. Eight different anxiety sub-types were also reported.

Conclusions

The updated review has confirmed that anxiety occurs in around 1 in 4 patients (by rating scale) and 1 in 5 patients (by interview). More research on anxiety sub-types is needed for an informed understanding of its effects and the development of interventions.

Background

Mood problems are common after stroke with reported rates of depression, apathy and distress significantly higher than in the general population [2,3]. Anxiety is common in the general population [4] but its presence in stroke patients has been relatively under-recognised both in clinical and research settings. A systematic review of observational studies [1] included 44 studies and reported rates of anxiety as 18.3% when diagnosed by interview and 24.3% by rating scale. The review reported that rates lowered with time after stroke, although they remained higher than in the general population [4]. However the inclusion of relatively small numbers of studies at some time points meant that there was considerable imprecision in rates. Furthermore studies had also used a number of different scales and cut-off scores to define anxiety, producing considerable uncertainty around the true rate.

More recent research has argued for the importance of subtypes of anxiety (for example, panic disorder; specific or simple phobias) for understanding its impact and for developing and delivering suitable interventions [5] or adapting those shown to be effective in the general adult population [6]. Our review in 2013 had recorded sub-types when they were reported in primary studies but this information was available in only 3 of the 8 relevant studies.

Our review of 44 studies had searched databases until March 2011 and we are aware of the publication since then of further, potentially relevant studies. Another recent review in this area [7] was limited to publications over 2011-17, from a small range of languages, and only those using self-report measures of anxiety. Consequently, updating the Campbell-Burton (2013) review [1] could have several potential benefits, not only making the findings more current but also potentially increasing the sample size and precision, particularly on sub-group analyses. Therefore the aims of this study were to undertake an updated systematic review of observational studies of anxiety after stroke; to integrate the findings with those previously reported [1]; and to disaggregate rates of anxiety by sub-type, rating scale and time after stroke.

Method

This review and the original systematic review [1] were both undertaken according to the PRISMA guidelines [8]. The review update protocol was registered on PROSPERO: CRD42018093718.

Inclusion / exclusion criteria

Studies were included if undertaken in populations or groups of patients with a clinical diagnosis of haemorrhagic or ischaemic stroke or transient ischaemic attack (TIA) and were assessed for symptoms of anxiety on a rating scale such as the Hospital Anxiety and Depression Scale (HADS) [9] or were diagnosed by clinical interview. We translated papers published in languages other than English if the title and abstract indicated potential eligibility. We excluded studies if they:

- used proxy measures of anxiety;
- were intervention studies;
- were limited to patients with subarachnoid haemorrhage or other specific stroke sub-types or demographic characteristics;

- were not designed to screen expressly for anxiety, or used non-specific measures of psychological distress;
- used retrospective recruitment or mood reporting;
- employed convenience sampling;
- reported anxiety as a continuous outcome and we could not derive a categorical assessment.

Study identification and data extraction

We searched the following digital databases: Medline, Embase, CINAHL, PsycINFO, Allied and Complementary Medicine and Proquest dissertation, using a search strategy developed in Medline (see Appendix 1) and adapted to the other databases. We restricted the search to studies published from January 2009 (to ensure relevant studies were not missed) to May 2018 and applied no language restrictions. The search was undertaken by one investigator (ADR) and screening of title and abstract was undertaken by ADR with a second reviewer (NS) and decisions taken against the selection criteria. Independent data extraction was performed by two reviewers (two of: ADR, NS, PK) for all eligible studies.

Quality of evidence

We extracted information on study design, setting and patient characteristics. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies [10], see Appendix 2, which includes eight criteria. One criterion (comparability of cohorts) was recorded as not applicable because the included studies were all reporting prevalence rates derived from a single cohort. Study quality was not used to determine inclusion. Finally we assessed the quality of the 44 studies included in the original review using the NOS measure.

Data synthesis

We combined the studies reported in the 2013 review with those identified in the update.

Studies were grouped into two categories based on method of case ascertainment: those using clinical interview for diagnosis; and those using a rating scale. We also extracted data on rates: at five different time points after stroke (up to 1 month; 1-5 months; 6-12 months; 12-24 months; over 24 months) and did this separately for interview and rating scale studies; from different rating scales or different caseness thresholds on the same scale (using whatever had been used in the primary data study); and, for interview-based studies only, rates of anxiety sub-types.

We undertook several meta-analyses. We excluded from pooling one study [11] using the hierarchical diagnostic rule in the Diagnostic and Statistical Manual-III (DSM-III) [12], meaning that anxiety is not diagnosed in the presence of depression, which may falsely deflate the reported rate of anxiety. For studies using rating scales we used whatever caseness threshold had been used by the primary researchers. When studies reported rates of anxiety at more than one time period, we used the first-reported time period as the primary outcome prevalence rate.

The random effects model was used to summarize data. Chi-square was used to test for subgroup differences, and heterogeneity among the studies was assessed by the I-squared statistic. We used Review Manager 5.3 [13] for data analysis.

Results

The search from 2009 to 2018 produced 22,564 unique references (see Figure 1), of which 53 met the inclusion criteria and had not been included in the 2013 review, including three translated from non-English language publications. The following results are based on the integrated data set of 97 studies, comprising 44 studies from the original review [11, 14-58] and 53 studies from the update [59-114] (see Table 1).

Figure 1. PRISMA flow diagram

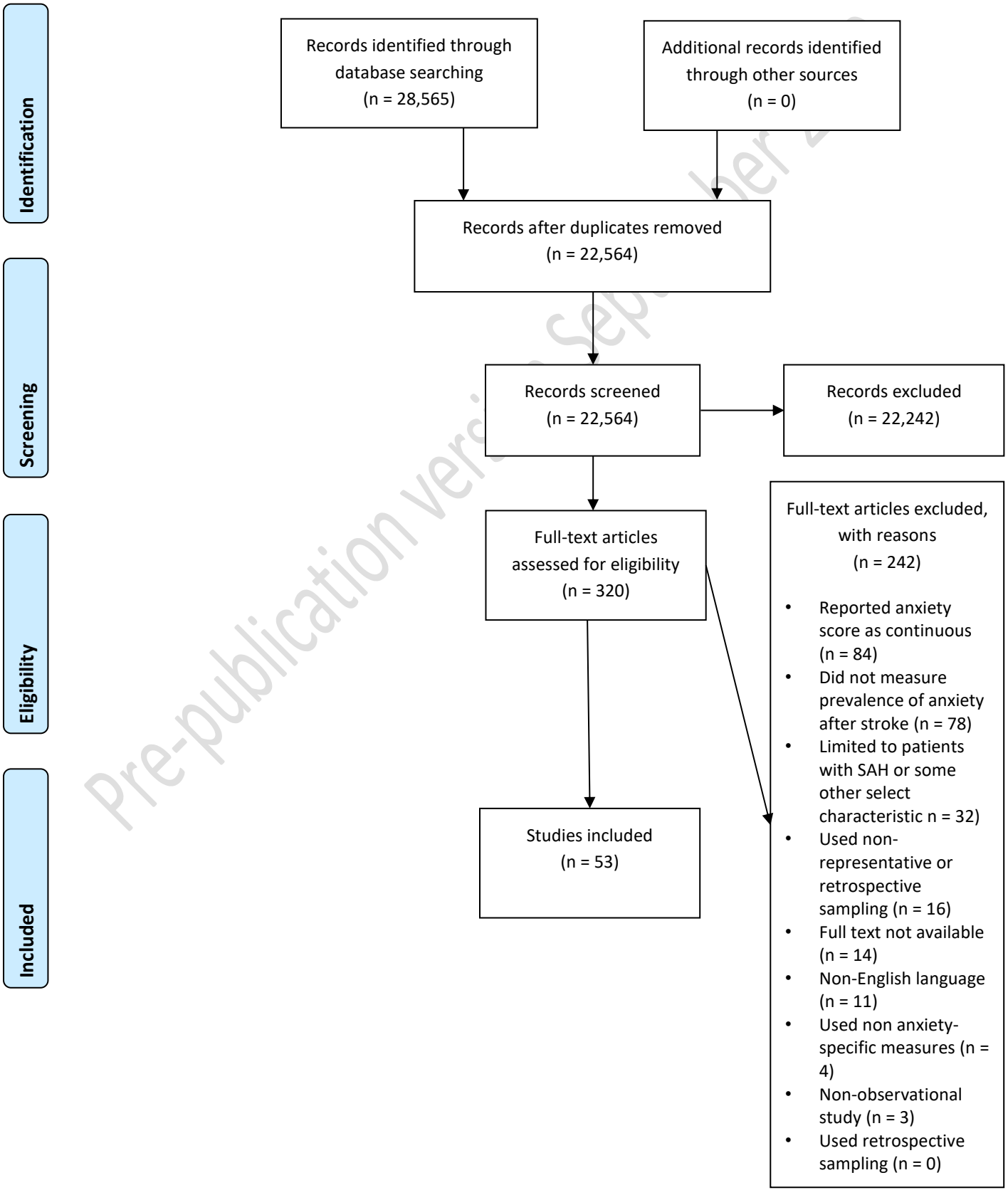
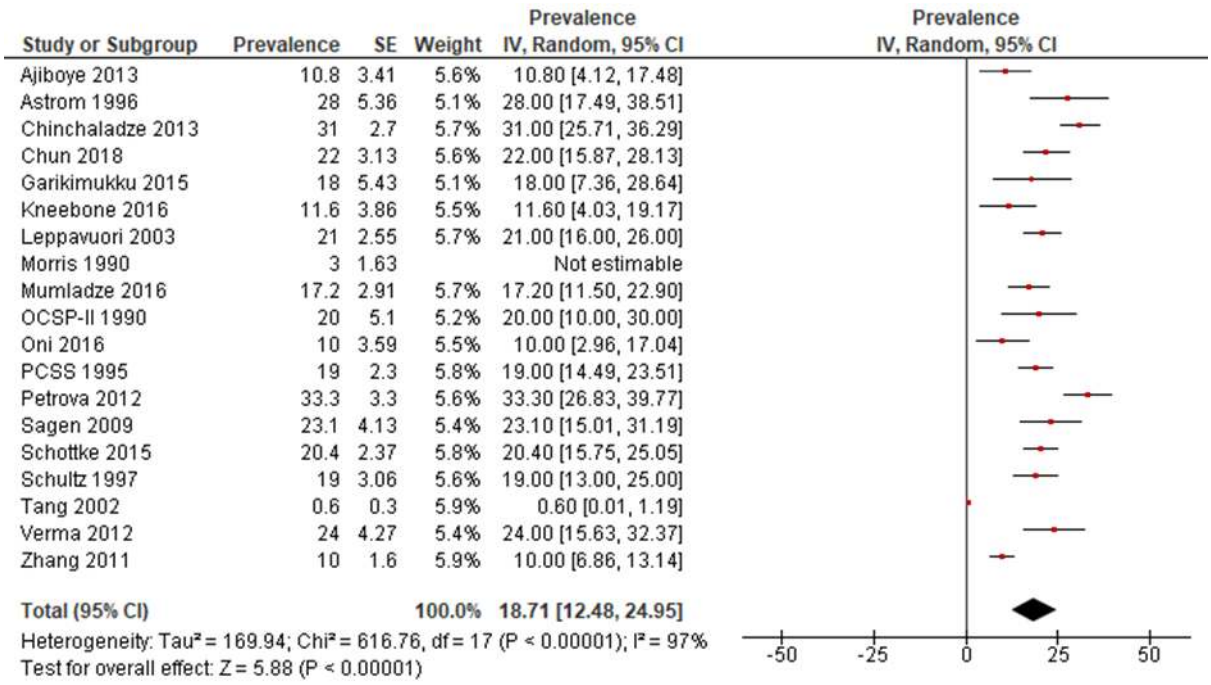


Figure 1: Meta-analysis of anxiety prevalence when diagnosed by interview



Study characteristics

The 97 studies included 26,262 participants and had been published between 1984 and 2018. Most had recruited patients from hospital (52), while other settings were rehabilitation (19), general population (15), a combination of settings (2) or not reported (8). Most studies were cross-sectional (78) or longitudinal cohort in design (15), although one used a case-control design and the design was not reported in two cases. Cohort studies included a range of data collection time points: 2 time points (n=4); 3 time points (n=4); 4 time points (n=4); 5 time points (n=2); 13 time points (n=1). Anxiety was recorded in patients in a very wide range of time periods after stroke (from 2 weeks to 10 years).

The studies had been undertaken in 34 different countries: UK (18); Netherlands (5); Norway, Italy, China and Australia (4 each); Sweden, Nigeria, Japan, India, Ireland, New Zealand, and Bosnia & Herzogovina (3 each); Thailand, Switzerland, South Korea, USA, Hong Kong and Croatia (2 each); and Benin, Brazil, Spain, Ukraine, Bahrain, Turkey, Tanzania, Finland, Slovakia, Georgia, Russia, France and Germany (1 each). Two studies were undertaken in more than 1 country; the country of origin was not reported in 6 studies.

Measurement and assessment of anxiety

Clinical diagnoses of anxiety disorder were made in 10 studies in accordance with different versions of the DSM (3 studies used the DSM-III [12]; 2 the DSM-III-R [115]; 5 used the DSM-IV [116]). The remaining studies used other interview methods: Structured Clinical Interview for DSM-V (SCID)

[117]; Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [118]; Mini-International Neuropsychiatric Interview-Plus (MINI-Plus) [119]; and the CCND-3 [114]. Anxiety prevalence was reported in the interview studies from samples ranging from 50 to 350 participants (total 3,109; median 149.5).

Nine different standardised scales were used to identify anxiety symptoms and generate caseness rates in 78 studies: the Generalised Anxiety Disorder (GAD) [120] (n=1); Hospital Anxiety and Depression Scale (HADS)-Anxiety subscale [9] (n=50); Hamilton Anxiety Rating Scale (HAM-A) [121] (n=7); Neuropsychiatric Inventory (NPI) [122] (n=1); Zung Self-rated Anxiety Scale [123] (n=3); Irritability Depression and Anxiety Scale, Anxiety subscale (IDA-A) [124] (n=1); Beck Anxiety Inventory (BAI) [125] (n=2); Adult Manifest Anxiety Scale (AMAS) [126] (n=1); and the General Health Questionnaire (GHQ-60 anxiety sub-scale) [127] (n=1). In addition, one study used a single question measure of anxiety, and another used a series of five researcher-developed questions. Three of these scales (HADS-A; BAI; HAM-A) were used with more than one caseness threshold. In total 20 different combinations of standardised scales and thresholds were used in the included studies. Anxiety prevalence was reported in the rating scale studies from samples ranging from 15 to 4,079 participants (total 23,153; median 81).

Anxiety prevalence

The overall prevalence of anxiety when assessed by interview ranged from 0.6% to 33.3% in the primary studies. The updated pooled prevalence derived from the 18 included studies was 18.7% (95% confidence interval 12.5 to 24.9%), see Figure 2. Heterogeneity among the included studies was very high (97%).

The assessment of anxiety by rating scale produced rates in the range 4.8% to 63.6% in the 78 included studies. The overall frequency of anxiety 'caseness' by rating scale was 24.2% (95% CI 21.5 to 26.9%), see Figure 3. Heterogeneity among the included studies was very high (95%).

Given the difference in prevalence rates obtained from the interview and rating scale studies, we did not calculate a rate combining data from the two study types.

Pooled anxiety prevalence at different times after stroke

Pooled rates of anxiety in the acute phase (within 1 month of stroke) were reported as 15.5% (95% CI 6.3 to 24.7%) in seven studies using interview, and as 25.5% (95% CI 18.6 to 32.3%) in 19 studies using rating scales.

Between 1 and 5 months after stroke rates of anxiety by interview were 21.4% (95% CI 19.2 to 23.5%) in eight studies using interview methods, and 23.6% (95% CI 18.9 to 28.2%) in 24 studies using rating scales.

In the 6-12 months period three studies used interviews methods and estimated the pooled prevalence as 31.8% (95% CI 17.8 to 27.3%), whereas 17 studies used rating scales and found the rate to be 21.5% (95% CI 15.3 to 27.8%).

Between 12 and 24 months after stroke only one study used interview methods to report a rate of 11.0% (95% CI 3.5 to 18.5%), whereas 11 studies used rating scale methods and found an overall rate of 26.6% (95% CI 16.8 to 36.3%).

In the period 24 months to 10 years the rate was reported in 3 studies using interview (20.4%; 95% CI 14.6 to 26.2%) and 10 studies using rating scales (26.0%; 95% CI 18.1 to 34.0%).

Anxiety prevalence using different caseness thresholds on rating scales

The rates obtained from meta-analysis were calculated for all combinations of standardised scales and thresholds; however in many cases only one or two studies were included per combination. Higher numbers per combination were available for the HADS-Anxiety scale, although seven different thresholds had been used and only two (>7 and >10) were reported in at least 10 studies. The reported pooled rates for each HADS-A caseness threshold are as follows: threshold >4, n=3 studies, 37.3% (17.8 to 56.8%); >5, n=2, 27.9% (0.4 to 55.3%); >6, n=1, 4.1% (1.4 to 6.8%); >7, n=27, 25.6% (20.9 to 30.3%); >8, n=2, 13.9% (-5.8 to 33.6%); >9, n=2, 29.1% (21.6 to 36.5%); >10, n=13, 18.9% (14.4 to 23.4%).

Anxiety sub-type caseness

Among the 19 studies that used interview methods to reach a definition of anxiety caseness, 10 also reported the rate of anxiety sub-types.

Agoraphobia was reported in four studies: 8.3% [43], 16.0% [45], 11.5% [47], 5.5% [103], and had a pooled prevalence of 8.4% (95% CI 6.5 to 10.4%; 1 squared =82%). Social phobia was reported just twice: 2.9% [47]; 2.1% [103], with a pooled prevalence of 2.3% (95% CI 0.9 to 3.7%; I squared 0%). Simple phobia was reported in three studies: 5.0% (OCSP-II), 8.7% [47], 2.1% [103], having a pooled prevalence of 2.1% (95% CI 1.5 to 4.3%; I squared 68%). Rates of Obsessive-Compulsive Disorder (OCD) were reported in two studies: 1.9% [47] and 2.1% [103], with a pooled prevalence of 2.0% (95% CI 0.8 to 3.2%; I squared 0%). Finally, panic disorder was reported in four studies: 2.0% [43], 17.3% [93], 10.6% [47] and 3.1% [103], with a pooled prevalence of 3.7% (95% CI 2.4 to 5.0%; I squared 90%).

Generalised Anxiety Disorder (GAD) was reported in eight studies [43, 45, 47, 59, 73, 81, 86, 103]. However, a pooled prevalence was not calculated because in some studies it is not clear if GAD had been reported as a sub-type of anxiety or as a generic anxiety diagnosis. Similarly rates were not pooled for Phobic Disorder, which was reported in three studies [59, 73, 101], because it is unclear whether the category 'phobic disorder' includes all types of phobias or is a distinct phobia sub-type.

Quality ratings of studies

Studies were rated on the seven relevant items of the NOS scale [10], with each item ranked as low or high risk of bias. Among the 97 studies low risk of bias was assigned to scale items ranging from 1 out of 7 to 6 out of 7 items (median 4/7). In studies using interview methods the range was 2/7 to 6/7 (median 4/7), and in studies using rating scale methods low risk of bias ranged from 1/7 to 5/7 items (median 4/7). Studies using interview methods had lower risk of bias than studies using rating

scales (Mann-Whitney U = 436.5; z = -2.763; p = .0058). Rates of low risk of bias varied considerably across the seven scored items. All 97 studies had low risk for length of follow-up, 83 for ascertainment of exposure, and 81 for representativeness of the exposed cohort. Low risk was present for 62 studies on adequacy of follow-up. Few studies had low risk of bias for the remaining three items: outcome assessment (n=20); anxiety shown not to be present at the study start (n=10); and selection of the non-exposed cohort (n=4).

Discussion

Brief summary of the findings

This updated systematic review included 53 studies, which were combined with the 44 studies included in the 2013 review [1]. The 97 primary data studies included 19 studies using interview methods and 78 studies using rating scales. The pooled prevalence of anxiety after stroke was 18.7% when diagnosed by interview and 24.2% by self-report rating scale, confirming the rates reported in the previous review and also confirming the previously reported pattern of lower rates when using interview. Increasing the number of studies in the data pooling produced increased rate precision, particularly for interview studies. Rates of anxiety were relatively stable in the years after stroke.

Strengths and weaknesses of the study

The updated and combined review used a number of systematic review methods that increase review rigour and tend to reduce bias: searching of multiple databases; dual, independent screening used to determine entry criteria and for extraction; no language or date limits were applied; included studies were assessed for quality; and data pooling was used and reported when appropriate. We searched ProQuest for dissertations, and included conference abstracts, but otherwise did not search for unpublished studies

The included primary data studies varied in quality, although study quality was not used as an entry criterion to the review. Studies using interview methods tended to be higher quality. Primary studies were included from many countries, although all studies except three were reported in English; this reflects a common finding in systematic reviews, although it is unclear if this would produce a reporting bias similar to that reported in reviews of intervention studies.

Combining the studies found with those reported in the 2013 review allowed further data pooling, although in some cases the pooled estimates were based on small numbers of primary data studies, and levels of heterogeneity were often very high. Rates were reported using a range of different interview methods and ratings scales (and cut-off scores); data pooling for the overall prevalence calculations used whatever cut-off and timing had been reported in the primary study, which inevitably led to the combination of a variety of methods and reported rates. However it was thought that this potential disadvantage was offset by the advantage gained by increased overall sample size; the rates have now been calculated using aggregate samples of 3,109 (in interview studies) and 23,153 (in rating scale studies).

We excluded studies reporting proxy ratings of anxiety as the focus of the review was on self-rating. However one consequence is the exclusion of studies of patients with strokes causing severe cognitive or language impairment, limiting the review's external validity.

What this review adds

Updating the review led to the addition of a large number of studies published up to 2018, allowing rates to be estimated from 19 studies (for interview) and 78 studies (for rating scale), resulting in increased precision in estimates. Caseness rates generated by interview are confirmed as meaningfully lower than those generated by rating scale (on average anxiety is shown to occur in 1 in 5 patients rather than 1 in 4), a direction of difference replicating that seen in depression after stroke [2,3]. The update confirmed that anxiety continues to be prevalent many years after stroke onset. The review update also allowed the calculation of rates for some anxiety sub-types such as panic disorder and phobias, which were shown to vary considerably, supporting the view [5] that this diagnostic detail is essential for an informed understanding of the phenomenon and development of effective interventions. However it is notable that only small numbers of studies reported sub-types; for example, rates of social phobia and OCD were based on just two studies with a combined sample size of 293. In some studies it was not clear whether sub-types were differentiated from a generic anxiety diagnosis.

Implications for research

This updated review has included almost 100 studies and 26,262 participants, reporting the rate of anxiety after stroke, although in the case of some primary studies, this was not their main objective. Almost 80 studies reported the rate of anxiety by rating scale and there seems little value in further new studies adding to this total. However there remains little evidence on rates of anxiety more than 12 and 24 months after stroke. A crucial advantage in future research would be gained by greater consensus on the rating scale (and its threshold for caseness) providing the most robust indication of anxiety after stroke: for example, receiver-operated characteristic (ROC) analysis of studies using interviews and rating scales could provide this. Further studies into anxiety sub-types (diagnosed by interview) would provide a useful addition to the published research. Similarly further studies assessing which factors tend to be associated with the onset and/or persistence of anxiety after stroke are warranted; quantitative and qualitative research could both make contributions to answering this important question.

Implications for practice

The updated review has confirmed the high rate of prevalence of anxiety after stroke and also confirmed that rates are sustained beyond the early months after stroke; that is, beyond what could be termed the initial reaction to stroke onset and discharge home after hospital admission. This suggests it is important to continue to assess or screen for anxiety 12 months or more after stroke onset, although the continued lack of evidence for interventions in this patient group does preclude evidence-based decisions about treatments if anxiety is identified [129]. Anxiety continues to be a problem for many patients, which also has implications for the mood and quality of life of unpaid carers [130], and its rate is similar to that of depression after stroke. Anxiety sub-types reported in this review tend to have a relatively low prevalence but their presence confirms the impact of

mental health problems, which may compound any physical and cognitive effects of the stroke as well as cause distress.

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Declaration of Conflicting Interests

Peter Knapp is an author on one study included in this review. Otherwise the authors have no conflicting interests to declare.

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Appendix 1: Search strategy for MEDLINE database

1. exp Cerebrovascular Disorders/
2. stroke*.mp
3. (poststroke* or post-stroke* or cva*).mp
4. (cerebrovasc* or brain vasc* or cerebral vasc*).mp
5. ((cerebr* or brain* or cerebellar* or cerebellum* or vertebrobasilar*) adj2 (infarct* or ischemi* or ischaemi* or thrombo* or emboli* or apoplex* or occlus*)).mp
6. ((cereb* or brain* or intracereb* or intracrani* or subarachnoid) adj2 (haemorrhag* or hemorrhag* or h?ematoma* or bleed*)).mp
7. Hemiplegia/ or exp Paresis/
8. (hemipleg* or hemipar* or paresis or paretic).mp
9. Or/1-8
10. exp Adjustment Disorders/
11. exp Anxiety Disorders/
12. exp Neurotic Disorders/
13. Mental Disorders/
14. anxiet*.mp
15. distress*.mp
16. mood.mp
17. (affect or affective) adj2 disorder.mp
18. (neuros?s or neurotic*).mp.
19. (depersonalization or depersonalisation or derealization or derealisation).mp.
20. fear.mp.
21. (worry* or worri* or apprehens*).mp
22. (tension* adj2 symptom*).mp
23. ((avoidanc* or avoidant*) adj2 (behaviour or behavior or symptom*)).mp.
24. (autonomic adj2 (arousal* or symptom*)).mp.
25. (hyperventil* adj2 (symptom* or syndrom*)).mp.
26. (HADS or GHQ or STAI)
27. Or/10-26
28. 9 and 27

Appendix 2: Newcastle-Ottawa Quality Assessment Scale: Cohort Studies (Wells et al, 2018)

1) Representativeness of the exposed cohort

2) Selection of the non-exposed cohort

3) Ascertainment of exposure

4) Demonstration that outcome of interest was not present at start of study

5) Comparability of cohorts on the basis of the design or analysis

6) Assessment of outcome

7) Was follow-up long enough for outcomes to occur

8) Adequacy of follow up of cohorts

Table 1: Risk of bias assessment for studies using interviews

Study name or author (year published)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that anxiety was not present at start of the study	Comparability of cohorts	Assessment of outcome	Was the follow up long enough for outcomes to occur?	Adequacy of follow up of cohorts	Scale score (low risk of bias / 7 items)
Ajiboye (2013)	★	☆	★	☆	N/A	★	★	☆	4/7
Astrom (1996)	★	☆	★	☆	N/A	★	★	★	5/7
Chinchaladze (2013)	☆	☆	☆	☆	N/A	★	★	☆	2/7
Chun (2018)	★	☆	★	☆	N/A	★	★	☆	4/7
Garikimukku (2015)	☆	☆	☆	★	N/A	★	★	☆	3/7
Kneebone (2016)	★	☆	★	☆	N/A	★	★	☆	4/7
Leppavuori (2003)	★	☆	★	★	N/A	★	★	★	6/7
Morris (1990)	★	☆	★	☆	N/A	★	★	★	5/7
Mumladze (2016)	☆	☆	☆	☆	N/A	★	★	★	3/7
OCSP (House 1991) and OCSP-II (Sharpe 1990)	★	☆	★	★	N/A	★	★	★	6/7
Oni (2016)	★	★	★	☆	N/A	★	★	★	6/7
PCSS (Burvill 1995)	★	★	★	★	N/A	★	★	☆	6/7

Study name or author (year published)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that anxiety was not present at start of the study	Comparability of cohorts	Assessment of outcome	Was the follow up long enough for outcomes to occur?	Adequacy of follow up of cohorts	Scale score (low risk of bias / 7 items)
Petrova (2012)	★	☆	★	☆	N/A	★	★	★	5/7
Sagen (2009)	★	☆	★	☆	N/A	★	★	☆	4/7
Schottke (2015)	★	☆	★	☆	N/A	★	★	☆	4/7
Schultz (1997)	★	☆	★	☆	N/A	★	★	☆	4/7
Tang (2002)	★	☆	★	☆	N/A	★	★	★	5/7
Verma (2012)	☆	☆	★	☆	N/A	★	★	★	4/7
Zhang (2011)	☆	☆	☆	☆	N/A	★	★	★	3/7
Key: ★, low risk of bias; ☆, high risk of bias; N/A, not applicable									

Table 2: Risk of bias assessment for studies using rating scales

Study name or author (year published)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that anxiety was not present at start of the study	Comparability of cohorts	Assessment of outcome	Was the follow up long enough for outcomes to occur?	Adequacy of follow up of cohorts	Scale score (low risk of bias / 7 items)
Ahlsio (1984)	★	☆	★	☆	N/A	☆	★	★	4/7
South London Stroke Register (Crichton, 2016; Ayerbe, 2014)	★	☆	★	☆	N/A	☆	★	☆	3/7
Azanmasso (2017)	☆	☆	☆	☆	N/A	☆	★	☆	1/7
Barker-Collo (2007)	★	☆	★	☆	N/A	☆	★	★	4/7
Barker-Collo (2017)	★	☆	★	☆	N/A	☆	★	☆	3/7
Beghi (2009)	★	☆	★	☆	N/A	☆	★	★	4/7
Bergerson (2010)	★	☆	★	☆	N/A	☆	★	★	4/7
Bovim (2016)	☆	☆	☆	☆	N/A	☆	★	☆	1/7
Bruggiman (2006)	★	☆	★	☆	N/A	☆	★	★	4/7
Broomfield (2014)	★	☆	★	☆	N/A	☆	★	★	4/7
Broomfield (2015)	★	☆	★	☆	N/A	☆	★	☆	3/7
Buijck (2012)	★	☆	☆	☆	N/A	☆	★	☆	2/7

Study name or author (year published)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that anxiety was not present at start of the study	Comparability of cohorts	Assessment of outcome	Was the follow up long enough for outcomes to occur?	Adequacy of follow up of cohorts	Scale score (low risk of bias / 7 items)
Carod-Artal (2009)	★	☆	★	☆	N/A	☆	★	★	4/7
Castellanos-Pinedo (2011)	★	☆	★	☆	N/A	☆	★	☆	3/7
Chanchaem (2013)	☆	☆	☆	☆	N/A	☆	★	☆	1/7
Crowley (2017)	★	☆	★	☆	N/A	☆	★	☆	3/7
D'Alisa (2005)	★	☆	★	☆	N/A	☆	★	★	4/7
D'Aniello (2014)	★	☆	★	☆	N/A	☆	★	★	4/7
De Weerd (2011)	★	☆	★	☆	N/A	☆	★	☆	3/7
De Weerd (2012)	★	☆	★	☆	N/A	☆	★	☆	3/7
Delva (2017)	★	☆	☆	★	N/A	☆	★	☆	3/7
DeWit (2008)	★	☆	★	☆	N/A	☆	★	★	4/7
Donnellan (2010)	★	☆	★	☆	N/A	☆	★	★	4/7
Donnellan (2016)	★	☆	★	☆	N/A	☆	★	☆	3/7
Elf (2016)	★	☆	★	☆	N/A	☆	★	☆	3/7
Field (2008)	★	☆	★	☆	N/A	☆	★	★	4/7

Study name or author (year published)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that anxiety was not present at start of the study	Comparability of cohorts	Assessment of outcome	Was the follow up long enough for outcomes to occur?	Adequacy of follow up of cohorts	Scale score (low risk of bias / 7 items)
Fure (2006)	★	☆	★	☆	N/A	☆	★	★	4/7
Galligan (2016)	★	☆	★	☆	N/A	☆	★	☆	3/7
Gangstad (2005)	★	☆	☆	☆	N/A	☆	★	★	3/7
Ghika-Scmid (1999)	★	☆	★	☆	N/A	☆	★	★	4/7
Giaquinto (1997)	★	☆	★	☆	N/A	☆	★	★	4/7
Gillespie (1997)	★	☆	★	☆	N/A	☆	★	★	4/7
HSRS (Ueki, 1999)	★	☆	★	☆	N/A	☆	★	★	4/7
Huzmeli (2017)	★	☆	★	☆	N/A	☆	★	★	4/7
Ibrahimagic (2005)	☆	★	★	☆	N/A	☆	★	☆	3/7
Ibrahimagic (2013)	☆	☆	★	☆	N/A	☆	★	☆	2/7
Jones (2012)	★	☆	★	☆	N/A	☆	★	☆	3/7
Kim (2012)	★	☆	★	☆	N/A	☆	★	☆	3/7
Kootker (2016)	★	☆	★	☆	N/A	☆	★	★	4/7
Knapp (1998)	☆	☆	☆	☆	N/A	☆	★	★	2/7

Study name or author (year published)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that anxiety was not present at start of the study	Comparability of cohorts	Assessment of outcome	Was the follow up long enough for outcomes to occur?	Adequacy of follow up of cohorts	Scale score (low risk of bias / 7 items)
Langhorne (2000)	★	☆	★	☆	N/A	☆	★	★	4/7
Li (2006)	★	☆	★	☆	N/A	☆	★	★	4/7
Lincoln (1997)	★	☆	★	☆	N/A	☆	★	★	4/7
Lincoln (2013)	★	☆	★	☆	N/A	☆	★	☆	3/7
Liu (2018)	★	☆	★	★	N/A	☆	★	☆	4/7
Macniven (2005)	☆	☆	★	☆	N/A	☆	★	★	3/7
Masskulpan (2008) & Kuptniratsalkul (2009)	★	☆	★	☆	N/A	☆	★	★	4/7
Mellon (2013)	★	☆	★	☆	N/A	☆	★	☆	3/7
Merriman (2007)	★	☆	★	☆	N/A	☆	★	★	4/7
Mihalov (2016)	★	☆	★	☆	N/A	☆	★	☆	3/7
Moon (2004)	★	☆	★	★	N/A	☆	★	★	5/7
Morrison (2000; 2005)	★	☆	☆	☆	N/A	☆	★	★	3/7
Mulroy (2012)	☆	☆	☆	☆	N/A	☆	★	☆	1/7

Study name or author (year published)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that anxiety was not present at start of the study	Comparability of cohorts	Assessment of outcome	Was the follow up long enough for outcomes to occur?	Adequacy of follow up of cohorts	Scale score (low risk of bias / 7 items)
Mutai (2017)	★	☆	★	☆	N/A	☆	★	★	4/7
Nakling (2017)	★	☆	★	☆	N/A	☆	★	☆	3/7
NEMSIS (Sturm, 2004; Paul, 2006)	★	☆	★	☆	N/A	☆	★	★	4/7
Nijsse (2017)	★	☆	★	☆	N/A	☆	★	★	4/7
Ojagbemi (2017)	★	☆	★	☆	N/A	☆	★	★	4/7
Ponchel (2016)	★	☆	★	☆	N/A	☆	★	☆	3/7
Raju (2010)	★	☆	★	☆	N/A	☆	★	★	4/7
Sampson (2003)	★	★	★	☆	N/A	☆	★	★	5/7
SELSS (Wilkinson, 1997)	★	☆	★	☆	N/A	☆	★	★	4/7
Sembi (1998)	★	☆	★	☆	N/A	☆	★	★	4/7
Solgajova (2017)	★	☆	★	☆	N/A	☆	★	★	4/7
Stojanovic (2015)	★	☆	★	☆	N/A	☆	★	★	4/7
Stone (2004)	☆	☆	★	☆	N/A	★	★	★	4/7

Study name or author (year published)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that anxiety was not present at start of the study	Comparability of cohorts	Assessment of outcome	Was the follow up long enough for outcomes to occur?	Adequacy of follow up of cohorts	Scale score (low risk of bias / 7 items)
Tang (2012)	★	☆	★	★	N/A	☆	★	★	5/7
Tang (2013)	★	☆	★	★	N/A	☆	★	★	5/7
Townend (2007)	★	☆	★	☆	N/A	☆	★	★	4/7
Vicentini (2016)	☆	☆	★	☆	N/A	☆	★	★	3/7
Vickery (2006)	★	☆	★	☆	N/A	☆	★	★	4/7
Visser-Kelzer (2002)	★	☆	★	☆	N/A	☆	★	★	4/7
Vuletic (2011)	★	☆	★	☆	N/A	☆	★	★	4/7
Vuletic (2012)	★	☆	★	☆	N/A	☆	★	★	4/7
Watanabe (1997)	☆	☆	★	☆	N/A	☆	★	★	3/7
Wu (2017)	★	☆	★	★	N/A	☆	★	★	5/7
Zalihic (2010)	★	☆	☆	☆	N/A	☆	★	★	3/7
Zhao (1999)	★	☆	★	☆	N/A	☆	★	★	4/7
Key: ★, low risk of bias; ☆, high risk of bias; N/A, not applicable									

Table 3: Characteristics of included studies: interview methods

Study name or author, **year published, Location**	**Setting/design/** **recruitment/** **year of study**	**Inclusion (I)/exclusion (E)**	**Mean age (% male)**	**Method of measuring anxiety**	**Time post-stroke**	**n**	**Rate of anxiety (95% CI)**
Ajiboye, 2013, Nigeria	Hospital/cross-sectional/ all consecutive patients/ Mar 2009 – Feb 2010	I: stroke diagnosed by consultant neurologist, age ≥18 E: past psychiatric history, too sick to be interviewed	60.6 years (44.6)	SCAN (interview)	<1 to >5 years	83	10.8 (4.2, 17.5) GAD: 9.6 (3.3, 16.0) Phobic disorder: 1.2 (0, 3.6)
Astrom, 1996, Sweden	Hospital / cohort / consecutive / 1979-1981	I: ischaemic, haemorrhagic & TIA (CT) E: congenital mental handicap	73 years (61)	DSM-III-R (GAD)	2 weeks 3 months 1 year 2 years 3 years	71 70 66 57 48	2 weeks 28 (18–39) 78 70 3 m 31 (21–42) 83 66 1 y 24 (14–35) 86 57 2 y 25 (13–36) 86 48 3 y 19 (7·7–30)
Chinchaladze, 2013, NR	NR/NR/NR/NR	NR	NR	DSM-IV (interview)	NR	294	31.0 (25.7, 36.2)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Chun, 2018, UK	Hospital/cohort/ consecutive/NR	I: ≥18 years, new stroke or TIA (clinical diagnosis), mental capacity to give informed consent, able to communicate in English over telephone E: SAH, subdural or extradural haematoma, ocular TIA, terminal stage of illness; difficult to follow up due to no fixed abode, current illicit drug or alcohol dependence	70 years (60)	SCID (interview)	3 months	175	21.7 (15.6, 27.8) GAD only: 4.0 (1.1, 6.9) Phobic disorder only: 10.3 (5.8, 14.8) GAD + phobic disorder: 7.4 (3.5, 11.3)
Garikimukku, 2015, India	Hospital/ cross-sectional/ NR/2014	I: ≥18 years, diagnosis of stroke E: other serious organic illness, previous history of psychiatric disorder, severe cognitive impairment	NR	MINI PLUS (interview)	Acute	50	18.0 (7.4, 28.6) GAD: 18.0 (7.4, 28.6)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Kneebone, 2016, UK	Hospital/ cross-sectional/ all patients/NR	I: ≥65 years, inpatients with stroke two weeks to six months previously, medically stable E: significant cognitive impairment (AMT ≤8, MMSE ≤24, or opinion of lead physician), aphasia, comorbid psychiatric disorder other than anxiety or depression	80 years (52)	SCID (interview)	3 days (range 1-7)	69	11.6 (4.0, 19.1)
Leppavuori, 2003, Finland	Hospital / cross-sectional / consecutive / NR	I: Ischaemic stroke E: SAH, ICH, no clinical neurological examination, severe aphasia, refusal of psychiatric examination	71 years (51)	DSM-IV_GAD	3-4 months	277	21 (16–26)
Morris, 1990, Australia	Hospital / cohort / consecutive / NR	I: ischaemia & haemorrhagic stroke (WHO) (CT) E: aphasia	71 years (51)	DSM-III	2 months 1 year	99 56	3·0 (0–6·4) 5·4 (0–11)
Mumladze, 2016, Georgia	NR/cohort/ NR/NR	NR	NR	DSM-IV (interview)	Acute	168	17.3 (11.5, 23)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
OCSP, 1991, UK OCSP-II, 1990, UK	Community / cohort / registry / 1981-1986	I: first-ever stroke (CT) E: recurrent stroke, TIA	71 years (45)	DSM-III (GAD)	1 month 6 months 1 year 2-5 years	89 119 112 60	1·1 (0, 3) 0·8 (0, 3) 0 (0, 0) 20 (10, 30) Agoraphobia 8·3 (1·3–15·3) GAD 5·0 (0–11) Simple phobia 5·0 (0–11) Panic disorder 2·0 (0–5)
Oni, 2016, Nigeria	Hospital/ cross-sectional/ consecutive/ 2013-2014	I: adult stroke survivors E: severe cognitive deficits	57 years (54)	SCAN (interview)	28 <1 year 9 1-2 years 33 >2 years	70	10.0 (3.0, 17.0)
PCSS, 1995, Australia	Community / cohort / ideal case finding / 1995-1996	I: first-ever or recurrent stroke or TIA (WHO)	73 (56)	DSM-III	4 months	294	19 (14–23) Agoraphobia 16 (12–20) GAD 3 (1–5)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Petrova, 2012, Russia	Hospital / cohort / consecutive / NR	I: stroke, admitted within 24 hours of onset. E: significant co-morbidity, cancer, amnesia	70 years (48)	DSM-IV	1, 7, 14 and 28 days, and 3, 6 and 12 months post-stroke	198	(overall period) GAD 33.3 (26.8, 39.8) Phobias 22.2%

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Sagen, 2009, Norway	Hospital/cohort/ consecutive/ 2003-2005	I: ischaemic stroke E: TIA, insufficient competence in Norwegian language, severe aphasia, psychosis, MMSE <20, terminal illness	65 years (59)	SCID (interview)	4 months	104	23.1 (15.0, 31.2) GAD: 5.8 (1.3, 10.3) PTSD: 2.9 (0, 6.1) Specific phobia: 8.7 (3.3, 14.1) Social phobia: 2.9 (0, 6.1) Panic with agoraphobia: 7.7 (2.6, 12.8) Panic without agoraphobia: 2.9 (0, 6.1) Agoraphobia without panic disorder: 3.8 (0.2, 7.5) OCD: 1.9 (0, 4.6) Anxiety NOS: 1 (0, 2.8)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Schottke, 2015, Germany	Rehabilitation/ cross-sectional/ NR/NR	I: acute cerebral infarction or intracerebral haemorrhage, neurological symptoms exceeding 24 hours, precise documentation of lesion, admission to rehabilitation clinic capability to attend facilities and undergo structured interview in German E: severe communication disorders	67 years (56)	SCID (interview)	6 weeks	289	20.4 (15.8, 25.0) GAD: 4.8 (2.4, 7.3) Specific phobia: 3.8 (1.6, 6) Social phobia: 2.1 (0.4, 3.7) Panic with agoraphobia: 1 (0, 2.2) Panic without agoraphobia: 2.1 (0.4, 3.7) Agoraphobia without panic disorder: 4.5 (2.1, 6.9) OCD: 2.1 (0.4, 3.7)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Schultz, 1997, USA	Hospital / cohort, consecutive / NR	I: stroke	58 years (57)	DSM-IV_GAD	Acute phase 3 months 6 months 12 months 2 years	142 77 79 70 66	19 (13–25) 77 3m 22 (13–31) 79 6m 25 (16–35) 70 12m 11 (4·0–19) 66 2y 18 (8·9–27)
Tang, 2002, Hong Kong	Rehabilitation/ cross-sectional/ consecutive / 1999–2000	I: First-ever stroke (CT) E: TIA, SAH, history of neurological impairment, comprehension and communication deficits, length of stay <2 weeks	71 years (45)	DSM-III-R	25 days	157	0·6 (0–1·9)
Verma, 2012, India	Hospital/cross-sectional/ NR/NR	NR	NR	NR	1-6 months	100	24.0 (15.6, 32.4)
Zhang, 2011, NR	Hospital/cross-sectional/NR/NR	NR	NR	CCND-3 (interview)	Acute	350	10.0 (6.9, 13.1)

Table 4: Characteristics of included studies: rating scale methods

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Ahlsio, 1984, Sweden	Community/ cross-sectional/ Consecutive / 1979	I: CI, TIA, SAH (CT) E: Severe disability, aphasia, dementia	71 years (60)	Self-report	2 years	53	26 (15–38)

South London Stroke Register (SLSR): Ayerbe, 2014, UK	Population/ cohort/all patients on register/Jan 1995 – Dec 2009	I: stroke (WHO) E: severe cognitive or communication impairment	53% male 55% 57% 58%	HADS-A >7	3 months 1 year 2 years 3 years 4 years 5 years 6 years	1104 1231 901 1096 889 659 604	At 3 months: 34.1 (31.3, 36.9) At 1 year: 32.9 (30.3, 35.5) At 2 years: 33.8 (30.7, 36.9) At 3 years: 31.9 (29.1, 34.7) At 4 years: 32.4 (30.8, 38.1) At 5 years: 34.4 (30.8, 38.1) At 6 years: 33.3 (29.5, 37.0)
Crichton, 2016, UK	1995 – 2003		57% Median: 62 years (59)	HADS-A >7	7 years 8 years 9 years 10 years 10 years 15 years	470 401 296 88 409 133	At 7 years: 34.0 (29.7, 38.3) At 8 years: 34.2 (28.0, 38.8) At 9 years: 33.4 (29.0, 38.8) At 10 years: 38.3 (31.9, 44.6) At 10 years: 31.4 (26.9, 36.3) At 15 years: 34.9 (26.8, 43.0)
Azanmasso, 2017, Benin	Hospital/cross-sectional/ NR/NR	NR	54.3 years	HADS (cut off NR)	>6 months	67	22.4 (12.4, 32.4)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Barker-Collo, 2007, New Zealand	Rehabilitation / cross-sectional / consecutive / NR	I: ischaemic or Haemorrhagic stroke (CT) E: aphasia, non-native language speaker	52 years (55)	BAI>25	3 months	81	21 (11–32)
Barker-Collo, 2017, New Zealand	Population/ cohort/all new hospitalised or non-hospitalised patients/2011-2012	I: stroke (WHO), resident of Auckland region, ≥16 years E: intracerebral haemorrhage, SAH, sensory or cognitive impairment, speech or language barrier, too unwell	69.2 years (53)	HADS-A >6	2 weeks 1 month 6 months 1 year	208 353 346 365	10.6 (8.4, 12.8) 7.1 (5.7, 8.5) 6.4 (5.0, 7.7) 4.1 (1.4, 6.8)
Beghi, 2009, Italy	Hospital / cross-sectional / consecutive / 2000-2001	I: stroke E: sufficient language for interview. MMSE > 18	70 years (68)	HAMA >17	> 2 years	82	12.2 (5.1, 19.3)
Bergerson, 2010, Norway	Rehabilitation / cross-sectional / mail-out all patients / 1998-2001	I: Ischaemic, ICH, SAH E: aphasia	54 years (64)	HADS-A>10	2-5 years	162	17 (11–22)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Bovim, 2016, NR	Hospital/cohort/NR /NR	I: >18 years E: receiving palliative care	76.8 years	HADS-A >7	≤14 days	390	63.6 (58.8, 68.4)
Broomfield, 2014, UK	Population/ cohort/all consecutive patients/ 2012-2013	I: on Glasgow LES database E: resident in care-home, housebound	70.3 years (57)	HADS-A >7	NR	4079	28.9 (27.5, 30.3)
Broomfield, 2015, UK	Community/ cross-sectional/ NR/2009-2010	I: patients on primary care stroke registers, who agreed to an annual health check E: resident in nursing home, housebound, serious comorbidity	70.4 years (55)	HADS-A >7	NR	3831	16.0 (14.8, 17.2)
Bruggiman, 2006, Switzerland	Community/ cross-sectional/ consecutive / NR	I: First-ever ischemic or hemorrhagic stroke E: NIHSS>3, history of psychiatric illness, neurologic comorbidity	51 years (67)	HADS-A >7	1 year	49	24 (12–37)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Buijck, 2012, Netherlands	Rehabilitation/ cohort/all patients/2008	I: all patients E: expected to be discharged within two weeks, critically ill	79 years (54)	NPI >0	NR	145	15.0 (9.2, 20.8)
Carod-Artal, 2009, Brazil	Rehabilitation / cross-sectional / consecutive / 2007-2008	I: Ischaemic or haemorrhagic stroke (clinical diagnosis & radiological findings) E: TIA, subdural haematoma, dementia, aphasia, severe disability due to previous neurological disorder	56 years (52)	HADS-A>10	20 months	300	24 (19–29)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Castellanos-Pinedo, 2011, Spain	Hospital/cohort/NR /2007-2008	I: stroke (neuroimaging), patient has responsible caregiver E: previous dementia or cognitive decline (clinical record or IQCODE), cerebral haemorrhage or other suspected cause aetiology of brain injury, TIA, persistent coma or severe alteration of consciousness four weeks after stroke, death or appearance of new lesion before four weeks	70 years (52)	HAMA >5	4 weeks	89	33.7 (23.9, 43.5)
Chanchaem, 2013, Thailand	NR/cross-sectional/ NR/2010-2012	NR	62.5 years	HADS (cut off NR)	NR	215	22.3 (16.7, 27.9)
Crowley, 2017, UK	Hospital-based acute unit and community-based stroke service /cohort/ consecutive/NR	I: first stroke three months previous, able to communicate E: MMSE <18, dementia, significant premorbid psychiatric illness, premorbid alcohol or drug addiction	62 years (66)	HADS-A >7	3 months	35	39.0 (22.8, 55.2)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
D'Alisa, 2005, Italy	Rehabilitation / cross-sectional / consecutive / 2002-2004	E: MMSE<24, aphasia	63 years (60)	HADS-A>10	5 years	73	21 (11–30)
D'Aniello, 2014, Italy	Rehabilitation/ cross-sectional/ NR/NR	I: first or second diagnosis of stroke E: global aphasia, behavioural disorders, dementia	62 years (59)	HADS-A >4	4 years (range 1-20)	81	55.6 (44.8, 66.4)
De Weerd, 2011, Netherlands	Hospital/cohort/ all patients/ 2006-2007	I: all patients admitted to department of neurology E: <65 years, referral to nursing home, rehabilitation centre, or another department	77 years (44)	HADS-A >7	12 months	57	9.1 (1.6, 16.6)
De Weerd, 2012, Netherlands	Hospital/cohort/ all patients/ 2007-2008	I: all ischaemic stroke patients E: <60 years, referral to nursing home, rehabilitation centre, or another department	75 years (65)	HADS-A >7	12 months	88	5.6 (0.8, 10.4)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Delva, 2017, Ukraine	NR/cohort/ NR/NR	I: acute stroke E: major illness that could cause secondary fatigue, alcohol abuse, consciousness impairment or MMSE <24, depressive or anxious disorders (HADS-A >10), severe aphasia or dysarthria, impaired language or written ability, mRS ≥4	64 years (47)	HADS-A >4	6 months	156	21.2 (14.8, 27.6)
DeWit, 2008, England, Belgium, Switzerland, Germany	Rehabilitation / cohort / consecutive / 2002-2004	I: first-ever stroke (WHO) (CT), RMA-GP<12 and/or leg trunk function <9 and/or arm function <13 E: neurological impairments, prestrike BI<50, subdural haematoma, admitted to rehab centre 6 or more weeks post-stroke	70 years (53)	HADS-A >7	2 months 4 months 6 months	491 478 467	25 (21–29) 4m 23 (19–27) 6m 21 (18–25)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Donnellan, 2010, Ireland	Hospital / cross-sectional / consecutive admissions / not stated	I: first or recurrent stroke (WHO, CT) & FAST ≥14 & Abbreviated Mental Test score ≥8 E: TIA, SAH, traumatic intracranial haemorrhage, dementia, extreme critical illness	Range 20-98 years [mean not reported] (51)	HADS-A >7	1 month 1 year	107 94	35 (26–44) 32 (24 - 42)
Donnellan, 2016, Bahrain	Hospital/ cohort/all consecutive/NR	I: ≥18 years, first or recurrent stroke, ability to participate in interview, FAST ≥14 E: TIA or related syndromes, aphasia, medically unstable, vascular dementia or pre-stroke cognitive impairment, TBI or traumatic intracranial or subarachnoid haemorrhage, visual or hearing impairment, neurodegenerative disease	61 years (67)	HADS (cut off NR)	1-2 weeks	64	27.0 (16.1, 37.9)
Elf, 2016, Sweden	Hospital/cohort/ all patients/ 2006-2007	I: living in community three months post-stroke E: NR	62 years (56)	HADS-A >4	6 years	102	36.3 (26.9, 45.6)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Field, 2008, UK	Hospital / cross-sectional / all patients meeting criteria	E: cognitive impairment, aphasia, acute medical problems	72 years (53)	HADS-A >10	<1 month	81	21 (12–30)
Fure, 2006, Norway	Hospital / cross-sectional / consecutive / 2000-2002	I: stroke (CT) E: TIA, moderate to severe aphasia, consciousness	69 years (63)	HADS-A >7	1 week	178	26 (20–33)
Galligan, 2016, Ireland	Mixed (clinic, hospital, and support group)/ cross-sectional/ NR/NR	I: ≥18 years, stroke (WHO) between one month and two years ago E: significant cognitive impairment, moderate to severe communication difficulties, major comorbid medical difficulties or acute health difficulties	65 years (71)	HADS (cut off NR)	NR	98	36.7 (27.2, 46.3)
Gangstad, 2009, UK	Rehabilitation/ cross- sectional/all patients attending clinic approached meeting inclusion/ NR	E: Cognitive impairment	NR (NR)	HADS-A>10	14 months	15	6·7 (0–19)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Ghika-Schmid, 1999, Switzerland	Rehabilitation/ cross- sectional/ consecutive / NR	I: First-ever stroke only (CT or MRI)	60 years (NR)	HAM-A>14	3 months	31	29 (13–45)
Giaquinto, 2007, Italy	Rehabilitation/ cross-sectional/ consecutive /2004–2005	I: First-ever stroke (CT or MRI) E: TIA, SAH, previous stroke but not TIA, admission to rehab >three-week poststroke, severe comorbidity, mental or comprehension impairment	70 years (46)	HADS-A >5	10 days	132	42 (33–50)
Gillespie, 1997, UK	Community/ cross-sectional/ mail-out to discharged patients/ NR	I: Stroke (WHO) E: Communication difficulties, cognitive impairment, significant comorbidity, recent major life event unrelated to stroke	69 years (66)	HADS-A >8	7 months	44	25 (12–38)
HSRS, 1999, Japan	Community / cohort / registry / 187	I: all strokes	66 years (64)	GHQ-60 > 4 out of 7 on anxiety subscale	2.5 years	66	43 (29–57)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Huzmeli, 2017, Turkey	Hospital/ cross-sectional/ all patients/NR	I: all patients with hemiplegic symptoms E: NR	61 years (73)	GAD-7 ≥15	6 months to 5 years	30	33.3 (16.4, 50.2)
Ibrahimagic, 2005, Bosnia and Herzegovina	Hospital / cohort / consecutive / NR	I: Ischaemic stroke (CT) and able to complete self-report questionnaire	65 years (50)	Zung ≥50	2 days 2 weeks	40 40	30 (16–44) 25 (12–38)
Ibrahimagic, 2013, Bosnia and Herzegovina	NR/cross-sectional/NR/ NR	I: stroke (CT) E: NR	65 years (50)	Zung SAS ≥50	Acute	40	30.0 (15.8, 44.2)
Jones, 2012, Tanzania	Community/ cohort/all patients/ 2003-2007	I: first of recurrent stroke (WHO) E: neurological deficit cause by infection or space-occupying lesion	67 years (48)	HADS-A >7	36 months (range 6-60)	51	21.6 (10.3, 32.9)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Kim, 2017, South Korea	Rehabilitation/ cohort/NR/NR	I: ≥18 years, first stroke (clinical presentation and MRI), ICD-10 codes 160-164, satisfactory cognitive function E: MMSE ≤10, MMSE 11-23 with physician confirmation of cognitive incompetence, TIA, severe auditory or visual impairment	60 years (58)	HADS-A >10	1 month	214	20.6 (15.2, 26.0)
Knapp, 1998, UK	Hospital / cross-sectional / consecutive / NR	I: stroke within past month, sufficient language and cognition for interview, named carer also willing to participate, living independently pre-stroke	69 years (53)	HADS-A >7	< 1 month 1 month post-discharge 6 months post-discharge	30 30 30	47 (29–65) 27 (11–43) 30 (14–47)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Kootker, 2016, Netherlands	Hospital / cohort/ consecutive / 2011-2013	I: Diagnosis of clinically confirmed cerebral stroke; aged >=18; sufficient knowledge of Dutch language to complete assessments; within first week post-stroke E: Serious comorbid condition that might influence study outcomes; pre-stroke Barthel Index <=17; pre-stroke Heteroanamnesis List Cognition >=1	67 years (65)	HADS-A >7	1 year	395	24.0 (19.0, 29.0)
Langhorne, 2000, UK	Rehabilitation/ cohort/ multi-centre consecutive / NR	I: Stroke (WHO) within seven-days of onset	76 years (52)	Single question	6 months post-discharge 18 months post-discharge 30 months post-discharge	220 181 155	34 (28–40) 44 (37–51) 49 (41–57)
Li, 2006, China	Hospital / cross-sectional / random selection / 2000-2002	I: Cerebral infarction	53 years (53)	HADS-A >9	NR	91	31 (21–40)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Lincoln, 1998, UK	Community/ cross-sectional/ 74 GP practices/ 1994–1996	I: Stroke (WHO)	76 years (67)	HADS-A >10	1 month	84	26 (17–36)
Lincoln, 2013, Belgium, UK, Switzerland & Germany	Rehabilitation/ cohort/ consecutive/NR	I: age 40-85, first stroke E: admitted >6 weeks after stroke, comorbid neurological impairments, poor prestrike functional ability (BI <50)	68 years (54)	HADS-A >7	6 years	220	29.0 (23.0, 35.0)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Liu, 2018, China	Hospital/ cross-sectional/ consecutive/ 2013-2014	I: 18-80 years, admitted with seven days of first or recurrent stroke, absence of thrombolysis or interventional therapy; CAT, SOD, and MDA measured on admission E: previous history or family history of psychiatric disorders, severe aphasia or dysarthria, significant physical illness (listed), history of antipsychotic medication or vitamins,	64 years (65)	HAMA >7	1 month	203	24.0 (18.1, 29.9)
Macniven, 2005, UK	Rehabilitation/ cross-sectional/ two-week audit of all patients on ward/ NR	E: Language problems	68 years (47)	HADS-A >7	58.5 days	57	65 (42–87)
Masskulpan, 2008 & Kuptniratsaikul, 2009, Thailand	Rehabilitation/ cohort/ national registry / 2006	I: Adult stroke patients E: Severe medical comorbidities, inability to communicate, dementia, schizophrenia or present psychotic episode	62 years (59)	HADS-A >10	24 days 2 months	327 251	5·8 (3·3–8·4) 26 (20–31)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Mellon, 2013, Ireland	NR/cohort/ consecutive/NR	NR	NR	HADS (cut off NR)	6 months	256	32.0 (26.3, 37.7)
Merriman, 2007, UK	Hospital / cross-sectional / in-hospital and postal mail-out to discharged patients / NR	I: adults & 1-12 months post-stroke, able to complete self-report questionnaire E: dysphasia, acute medical problems	74 years (56)	HAD-A > 10	1-12 months	102	20 (12–27)
Mihalov, 2016, Slovakia	Hospital/cohort/ consecutive/ 2013-2014	I: NR E: persistent severe aphasia or cognitive deficit, using antidepressants for >6 months	68 years (64)	HADS-A >7	6 months	47	17.0 (6.3, 27.7)
Moon, 2004, South Korea	Hospital / cross-sectional / consecutive / 2002	I: stroke (MRI)	NR (62)	BAI>21	2 months	69	49 (37–61)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Morrison, 2000 & 2005, UK	Hospital / cohort / patient admitted to hospital / NR	I: residual disability, pass screening test for cognitive & communicative problems	69 years (51)	HADS-A>10	<1 month 2 months 6 months 3 years	101 78 71 38	24 (15–32) 21 (12–29) 23 (13–32) 26 (12–40)
Mulroy, 2012, NR	NR/cross-sectional/ NR/NR	I: cognitively intact, mRS <3 E: NR	68 years (61)	HADS-A >7	NR	94	14.9 (7.7, 22.1)
Mutai, 2017, Japan	Hospital/ cross-sectional/ NR/2012-2013	I: ischaemic or haemorrhagic stroke (clinical or radiological findings) E: severe confusion, severe aphasia, severe moto complications with immobility	74 years (66)	HADS-A >10	2 weeks	101	24.7 (16.3, 33.1)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Nakling, 2017, Norway	Hospital/ cohort/all patients/ 2008-2011	I: stroke (MRI/CT), home-dwelling, NIHSS 2-26 or <2 with mRS ≥2 E: severe psychiatric illness, alcohol or substance abuse, serious conditions interfering with rehabilitation process, insufficient knowledge of Norwegian language	69 years (58)	HADS-A >7	1 year	105	13.6 (7.0, 20.2)
NEMSIS, 2004, Australia	Community / cohort / ideal case finding method	I: first and recurring stroke (WHO, CT or MRI)	Unclear	IDA-A (score 9-15)	3 months 1 year 2 years 5 years	475 498 201 424	13 (10–16) 10 (7–13) 11 (6–15) 8·5 (6–11)
Nijesse, 2017, Netherlands	Hospital/ cross-sectional/ NR/2011-2013	I: ≥18 years, stroke (clinically confirmed) in previous seven days E: other serious condition expected to interfere with study outcomes, BI <18, insufficient Dutch language ability, ≥1 on HLC pre-stroke	67 years (64)	HADS-A >7	2 months	350	20.4 (16.2, 24.6)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Ojagbemi, 2017, Nigeria	Hospital/ cross-sectional/ consecutive/NR	I: stroke (neuroimaging and clinical examination) E: severe communication difficulties or aphasia, dementia (CSID ≤20), mRS ≥3, significant comorbidity	57 years (64)	HADS-A >10	<1 month	391	19.7 (15.8, 23.6)
Ponchel, 2016, France	Hospital/cohort/ consecutive/NR	I: ≥18 years, admitted for stroke (MRI), MRI within 72 hours of symptom onset E: prestrike dementia (IQCODE >64); malformed, traumatic, pure-meningeal or intraventricular haemorrhage; patient under legal care of guardianship, contraindicated for MRI, inability to speak and understand French, neurological deficits including aphasia severe enough to impact understanding of questionnaires or tests	64 years (61)	HAMA >6	6 months	153	41.8 (34, 49.6)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Raju, 2010, India	Hospital / cross-sectional / patients completing at least 1 month clinical follow-up / 2008-2010	I: first-ever ischaemic & haemorrhagic stroke (WHO) (CT or MRI), at least 1 month post-stroke E: history of psychoactive substance abuse, dementia, psychiatric comorbidity, aphasia	54 years (70)	HADS-A>10	1.5 years	162	11 (6·3–16)
Sampson, 2003, UK	Hospital / case-control / recruit from 6 stroke units / NR	I: Ischaemic or haemorrhagic stroke E: Cognitive impairment, dysphasia, too unwell or with terminal illness, MRSA infection	NR	HADS-A>9	NR	69	26 (14–38)
SELSS, 1997, UK	Community / cohort/ registry / 1989-1990	I: first-ever stroke in persons <75 including those who did not survive initial event.	71 (54)	HADS >9	5 years	96	31 (22–41)
Sembi, 1998, UK	Rehabilitation/ cross-sectional/ recruited from three rehabilitation sites/ 1995–1996	I: adults, first-ever stroke or TIA, able to complete self-report Questionnaire E: Dysphasia	66 years (NR)	HADS-A >10	18 months	61	15 (5·9–24)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Solgajova, 2017, NR	Hospital/cross-sectional/ NR/2015-2016	I: first stroke, lucid consciousness, oriented, informed consent given E: aphasia	67 years (60)	HADS-A >7	NR	74	16.0 (7.6, 24.4)
Stojanovic, 2015, Bosnia and Herzegovina	Hospital/cross-sectional/ NR/NR	I: first stroke with macroscopic lesions in prosencephalon on CT E: comorbid state (heart decompensation, unstable angina, MI in previous year, infective, malignant, or immunological diseases), NIHSS, >10, moderate to severe dysphasia	Range 44–87 (50)	HAMA >13	NR	118	17.8 (10.9, 24.7)
Stone, 2004, UK	Hospital / nested cross-sectional / consecutive / 2004	E: severe stroke with high risk of death, dementia, aphasia, cognitive impairment, patients living alone, carer unable to talk with researcher	72 years (49)	HADS-A>7	1 month	89	20 (12–29)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Tang, 2012, Hong Kong	Hospital/cohort/ all admissions/ 2004-2009	I: first or recurrent acute ischaemic stroke with MRI E: history of CNS diseases or dementia, physical frailty, recurrent stroke within follow up period, aphasia, severe auditory or visual impairment, non-Chinese ethnicity or non-Cantonese speaking, MMSE <20, history of anxiety or other psychiatric disorder, history of alcohol or drug abuse	66 years (61)	HADS-A >7	1-5 months	693	6.1 (4.3, 7.9)
Tang, 2013, Hong Kong	Hospital / cross-sectional / consecutive / 2008-2011	I: Chinese ethnicity; Cantonese as primary language; adult; confirmed stroke (CT) within 7 days of admission. E: TIA, SAH CH or SDH; history of other CNS condition; MMSE <20; aphasia; physical frailty; severe auditory or visual impairment; recurrent stroke.	66 years (59)	HADS-A >7	3 months	374	23.0 (18.7, 27.3)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Townend, 2007, Australia	Hospital / cohort / consecutive / NR	I: Ischaemic or haemorrhagic stroke E: dysphagia, MMSE<20, reduced level of consciousness	76 years (49)	HADS-A>8	5 days 1 month 3 months	125 112 105	4·8 (1·1–8·6) 8·0 (3·0–13) 14 (7·6–21)
Vicentini, 2017, Brazil	Hospital/cross-sectional/ NR/2014-2015	I: 45-80 years, first ischaemic stroke (CT) E: severe aphasia or dysarthria, history of psychiatric or neurological disorders	NR	BAI >11	Acute	37	11.8 (1.4, 22.2)
Vickery 2006, USA	Rehabilitation/ cross-sectional/ sample of admitted patients/ NR	I: Stroke E: history of comorbid dementia, Non-stroke neurological process, acute delirium, severe psychiatric disturbance	69 years (45)	AMAS >64	20 days	141	7·8 (3·4–12)
Visser-Keizer, 2002, Netherlands	Community/ cross-sectional/ 350 GP clinics/ NR	I: First-ever ischemic stroke (CT) E: neurologic or psychiatric history, history of alcohol or drug abuse, insufficient language and cognitive ability for assessment, aphasia	67 years (59)	HADS-A >5	3 months	113	14 (7·7–21)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Vuletic, 2011, Croatia	Hospital/cross-sectional/all patients/2008	I: first stroke (CT) in previous three months E: recurrent stroke, major medical illness, alcohol abuse, decreased level of consciousness, dysphasia, severe cognitive impairment	62 years (57)	HADS (cut off NR)	1-5 months	35	37.0 (21, 53.0)
Vuletic, 2012, Croatia	Hospital/cross-sectional/all patients/2006	I: first stroke (CT) E: TIA, previous emotional problems, severe aphasia, clouding of consciousness	71 years (50)	HADS (cut off NR)	3-5 days	40	40.0 (24.8, 55.2)
Watanabe, 1984, Japan	Hospital / cross-sectional / random selection/ NR	E: aphasia, dementia	57 years (57)	TMAS	6 months	35	51 (35–68)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Wu, 2017, China	Hospital/cross-sectional/ NR/2013-2014	I: 18-80 years, acute stroke (CT/MRI) E: decreased consciousness, severe cognitive dysfunction, aphasia, dysarthria, history of anxiety or other psychiatric disorders, history of stroke or other CNS disease	63 years (63)	HAMA >7	≤7days	226	26.5 (20.7, 32.3)
Zahilic, 2010, NR	NR/cross-sectional/ NR/2008-2009	I: first cerebral stroke E: comorbidity which could influence development of depression, "both cerebral and heart stroke"	72 years (55)	HADS-A >7	NR	202	28.2 (22, 34.4)
Zhao, 1999, China	Hospital / cross-sectional / consecutive / NR	I: first-ever stroke (Chinese cerebral vascular disease symposium of 1995 definition) E: aphasia, mental disorder, epilepsy, mental retardation, cerebral trauma	63 years (61)	Zung SAS>49	1 month	206	18 (13–24)

Study name or author, year published, Location	Setting/design/ recruitment/ year of study	Inclusion (I)/exclusion (E)	Mean age (% male)	Method of measuring anxiety	Time post-stroke	n	Rate of anxiety (95% CI)
Abbreviations: AMT, Abbreviated Mental Test; BAI, Beck Anxiety Inventory; BI, Barthel Index; CAT, catalase; CCND-3, China psychiatric disorders classification and diagnosis standard version 3; CNS, central nervous system; CSID, Community Screening Interview for Dementia; CT, computed tomography used to diagnose stroke; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; FAST, Frenchay Aphasia Screening Test; GAD-7, General Anxiety Disorder 7-item scale; HADS, Hospital Anxiety and Depression Scale; HAMA, Hamilton Anxiety Rating Scale; HLC, Heteroanamniesis List Cognition; ICD-10, International Classification of Diseases, 10th Edition; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; LES, Local Enhanced Service; MDA, malondialdehyde; MINI PLUS, Mini-International Neuropsychiatric Interview-Plus; MMSE, Mini Mental State Examination; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NPI, Neuropsychiatric Inventory; NR, not reported; SCAN, Schedule for Clinical Assessment 2.1; SCID, Structured Clinical Interview for DSM-IV Disorders; SOD, superoxide dismutase; WHO, World Health Organisation definition of stroke; Zung SAS, Zung Self-rated Anxiety Scale							

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.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
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.	2
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.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	appendix
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).	3
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.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3

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.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
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.	3

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
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.	4
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.	tables
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).	tables
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.	Tables and figures 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5-6
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).	6-8
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).	6-8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	6-8
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.	9