Incidence and prevalence of post-stroke insomnia: a systematic review and meta-analysis

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Incidence and prevalence of post-stroke insomnia: a systematic review and meta-analysis

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Summary

Problems with sleep are reported to be common after stroke but the incidence and prevalence of insomnia and insomnia symptoms following stroke is not yet established.

The aim of this review was to conduct a systematic review and meta-analysis of the incidence and prevalence of insomnia and insomnia symptoms in individuals affected by stroke.

We searched seven main electronic databases to identify studies until September 25, 2018.

No studies examining incidence of post-stroke insomnia were identified. Twenty-two studies on prevalence of insomnia or insomnia symptoms including individuals with stroke were included with fourteen studies suitable for inclusion in the meta-analysis. Meta-analysis indicated pooled prevalence of 38.2% (CI 30.1-46.5) with significantly higher prevalence estimates for studies using non-diagnostic tools, 40.70% (CI 30.96-50.82) compared to studies using diagnostic assessment tools 32.21% (CI 18.5–47.64). Greater insomnia symptoms were indicated in those with comorbid depression and anxiety.

The prevalence of both insomnia and insomnia symptoms are considerably higher in stroke survivors compared to the general population. Studies investigating the incidence, insomnia symptom profile and changes in insomnia prevalence over time are needed to inform clinical practice and to encourage tailored interventions that consider this symptomatology.

PROSPERO registration number CRD42017065670.

Abbreviations

BBT-I	Brief Behavioural Treatment-Insomnia
CBT-I	cognitive behavioural therapy for insomnia
CI	confidence interval
CT	computerised tomography
DFS	Difficulty falling asleep
DMS	Difficulty maintaining sleep
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMA	Early morning awakening
ICD	International classification of disease
ICSD	International Classification of Sleep Disorders
MeSH	Medical subject heading
MRI	magnetic resonance imaging
NRS	Non-restorative sleep
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PROSPERO	International prospective register of systematic reviews
PSQI	The Pittsburgh Sleep Quality Index
TIA	Transient ischaemic attack

Stroke

Stroke is the second leading cause of death [1] and one of the leading causes of disability with an increasing prevalence worldwide [2]. Stroke survivors are often left with sequelae of long term effects including impairments in mobility, cognition, language and communication, as well as emotional problems, difficulties with activities of daily living and social isolation. [3-5]. Changes in sleep are commonly reported following stroke but have been less extensively researched and receive less attention during rehabilitation despite poor sleep being a risk factor for stroke [4, 6] and an independent predictor of life satisfaction six months after stroke, alongside depression and stroke severity [6].

Insomnia

Insomnia is diagnostically defined as difficulty initiating/maintaining sleep, or early-morning awakening for at least 3 nights per week over a period of at least 3 months that affects daytime functioning [7]. In the general population, insomnia prevalence is relatively low (6%) when insomnia is diagnosed using the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) [8]. However, the prevalence insomnia symptoms is considerably higher (30–48%) when insomnia is defined based on the core insomnia symptom profile [9]. Prevalence of insomnia and insomnia symptoms are estimated to be higher in stroke survivors [10]. Current diagnostic systems have moved away from the classification of insomnia into primary and secondary insomnia so that insomnia is considered an independent disorder and not related to, or an outcome of, another mental or physical disorder [11]. The terminology throughout this review will be based on the recent guidelines on the diagnosis and treatment of insomnia using the terms insomnia and insomnia disorder interchangeably and the concept of comorbidity [11].

High associations between post-stroke insomnia and depression [12], disability [13] and fatigue [10] have been reported in addition to significant impact on return to work one year after stroke [13]. Frequent night time awakenings in the absence of other insomnia symptoms also shows an association with suicidal ideation in this group [14].

A number of reviews have explored the impact of sleep disorders including insomnia as a risk factor for stroke [15, 16], or the role of sleep in recovery following stroke [17]. However, no published systematic reviews of the prevalence or incidence of insomnia post-stroke exist. In an unpublished doctoral thesis, Dixon presented a systematic review of studies examining

prevalence of insomnia after stroke [18]. Eleven studies were identified, but methodological inconsistencies of the studies included made ascertaining overall insomnia prevalence difficult. The aim of this systematic review is to offer a detailed synthesis of the existing evidence on the incidence and prevalence of insomnia following stroke. The main question this review aims to answer is what is the incidence and prevalence of insomnia and insomnia symptoms in individuals following stroke. In order for healthcare professionals and services to provide accurate and tailored assessment, advice and interventions on insomnia and insomnia symptoms following stroke, we need to develop a better understanding of the prevalence of this disorder.

Method

The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration CRD42017065670. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA), [19] was employed to guide study selection and reporting. MG, SB and NG performed the database and hand searches. MG and SB independently screened titles and abstracts, reviewed full-texts and performed quality ratings. Data was extracted by MG, SB, NG and SG.

Literature search

A concept based search strategy with medical subject headings (MeSH) and keywords relating to stroke and insomnia developed in collaboration with a librarian was used to search the following electronic databases: MEDLINE (OVID) including ahead of print, In-process and other non-indexed citations, EMBASE (OVID), EBSCOhost including CINAHL, PsycINFO, PsychARTICLES, Cochrane Library (CENTRAL) and Web of Science to identify studies from inception to 20th April 2017 with a further update to September 25,

2018. We restricted the searches to studies in humans and publications in English. Details of the search strategy are provided in the supplement. The searches were exported to EndNote X7.8 and duplicates removed. Titles and abstracts generated from the electronic database searches were screened for relevance independently by two reviewers using Rayyan QCRI [20]. Irrelevant titles and abstracts were excluded. Potentially eligible full text articles identified were obtained and inspected to determine eligibility by the same independent reviewers. Any disagreements were resolved by discussion. For full-texts that could not be accessed, an attempt to request a copy from the authors directly was made. Titles specific to sleep, insomnia and stroke were hand searched.

Inclusion criteria

We used the following criteria to determine eligibility (further details provided in the supplement). Where eligibility could not be determined from the publication directly, an attempt to contact the study authors to clarify methodology used was made.

Types of Studies

We included original full-text articles published in peer-reviewed journals in English. We included cohort and cross sectional studies (standalone, or part of a prospective study). We excluded case studies or case series (defined as <10 participants).

Population

We included studies of adult stroke survivors (≥18 years of age) in any location, and any time post-stroke. We included studies of people with a clinical diagnosis of stroke ('rapidly developing signs of focal or global disturbance of cerebral functions lasting more than 24 hours or leading to death' as defined by the [21] regardless of whether first ever or recurrent,

ischemic or haemorrhagic. We also included diagnosis of clinician advised stroke (self-report), stroke reported on medical reports as well as self-reported strokes. We excluded studies reporting transient ischemic attacks (TIA) defined as 'acute loss of focal cerebral or monocular function with symptoms lasting <24 hours and that is thought to be due to inadequate cerebral or ocular blood supply as a result of arterial thrombosis or embolism' [22] and sub arachnoid haemorrhage (SAH) defined as a 'haemorrhage from a cerebral blood vessel, aneurysm or vascular malformation into the subarachnoid space (the space surrounding the brain where blood vessels lie between the arachnoid and pia mater)[23] due to the presentation of SAH usually differing from the presentation of other types of stroke. Studies with a "mixed" population (e.g. stroke and TIA), where the results had not been reported separately for stroke, were included if the overall stroke sample was more than 80%.

Outcomes

The primary outcomes were prevalence (number of persons with the condition at a specific time point) and incidence (number of new cases of disease in the population, within a year) of post-stroke insomnia/insomnia symptoms. Incidence rate was calculated as the number of new events in the specific period divided by the number of persons exposed to risk during this period. Prevalence was calculated by dividing the total number of all individuals with the condition at a particular time with the population at risk of having the condition at this time point [24].

Diagnosis of insomnia was based on any recognised classification or clinical diagnostic criteria (e.g. DSM-IV/V, ICSD-2, ICD-10). All other instruments such as questionnaires [e.g. Pittsburgh Sleep Quality Index (PSQI), Hamilton Depression Scale (HDS), Epworth Sleepiness Scale (ESS)] or self-reported insomnia were classed as insomnia symptoms using

author defined cut offs and definitions of insomnia. (Table 3). These symptoms were likely to reflect some but not always all of the DSM diagnostic criteria and insomnia symptom profileincluding issues with sleep onset, maintenance or early morning awakenings in association with feeling rested upon awakening and daytime consequences of poor sleep. We included studies using both subjective (e.g. questionnaires) and/or objective measures (e.g. actigraphy or polysomnography) as well as studies with self-reported insomnia/insomnia symptoms.

Secondary outcomes

Where available, we collected data on demographic, stroke and sleep related factors and comorbidity.

Data extraction

A study specific proforma was created, piloted and refined before data extracted. Extracted data included: Citation details (authors, year, title, journal, volume, pages); demographic characteristics (age, gender, employment, education, country; study characteristics (numbers at baseline and follow up); methods (study design, sampling method, setting, comparison group characteristics); stroke characteristics (type, severity, laterality, method of diagnosis, recurrence, time since stroke); insomnia/insomnia symptoms (assessment method and instrument, definition, incidence, prevalence, pre-stroke sleep quality; comorbidity (current/premorbid psychological, psychiatric or physical health problems); funding source and conflicts of interest.

Study quality

The methodological quality of the included studies was assessed using the critical appraisal tool for prevalence studies [25] with further guidance from Munn et al., [26]. More specifically, for the evaluation of valid methods, we split this question into two to cover both methods used for the identification of 1. Stroke (Y= stroke confirmed clinically, e.g. WHO classification, and/or using imaging, N = self-report, U= assessment method not reported) and 2. Insomnia (Y= use of clinical diagnostic tool for insomnia/validated questionnaires ,e.g. PSQI, for insomnia symptoms, N= e.g. self-report U= unclear of method and/or its validity). No study was excluded based on quality rating but data were synthesised separately for studies using diagnostic and non-diagnostic tools. Any disagreements in quality ratings between reviewers were resolved by discussion.

Data analysis

Our primary approach was to present a narrative review of results, supported by tabulated detail of included studies; summary of findings and quality of included studies. We also pooled data using meta-analysis techniques. Where the results of the same study were reported in multiple publications, we only included the article reporting the largest sample size in the data synthesis. We split the included studies by subgroup for analysis in order to look at the effect of different diagnostic approaches on prevalence (given that non-diagnostic tools are likely to reflect some but not always all of the DSM diagnostic criteria)stroke type, severity, geography, quality, study setting. Where available, we described prevalence rates separately for different types of stroke, demographic characteristic and insomnia comorbidities.

Meta-analysis was carried out using ‘Metafor’ [27] and ‘Meta’ [28] packages implemented in R Statistical Software [29] with random effects (to account for heterogeneity following

assessment of the I^2 statistic) model and double arcsine transformation. Pooled prevalence estimates are reported using 95% confidence intervals (CIs) with the results and 95% CIs back-transformed for ease of interpretation.

Results

We identified 2183 records through database searches (2098 through initial search up to 20th April 2017, and an additional 85 through updated search up to 25th September 2018) and two additional references through other sources (one through initial search and one through updated search). After removal of duplicates, 1659 titles and abstracts were screened for inclusion and 1480 were excluded leaving 179 for full-text screening. Of these, 157 were excluded leaving 22 studies to be included in the data synthesis with 14 studies contributing data to the meta-analyses (Figure 1).

Study characteristics

Characteristics of included studies [6, 10, 12, 13, 30-47] are provided in Table 1.

The identified studies were published between 1996 and 2018. Seventeen studies were cross-sectional, three longitudinal and two prospective cohort studies of which one was longitudinal. These reported data for 75,273 participants of which 19,125 were individuals with stroke (sample size n=16–12,045).

Study setting

Sixteen studies were hospital based (including rehabilitation centres) and six were population based covering a wide geographical area: South America (Brazil), n=1; North America

(USA), n=2; Europe (UK, Finland, Bosnia/Herzegovina, Italy), n=5, Asia (China, Japan, Republic of Korea, Turkey), n=12, Australia, n=1 as well as a multi-country study n=1.

Insomnia assessment

Six of the twenty-two studies used a diagnostic tool to assess insomnia (Table 2). The DSM (IV or V, American Psychiatric Association was used in all alongside other diagnostic tools. For studies assessing insomnia symptoms the PSQI [48] was most commonly used, followed by sets of questions designed by researchers (Table 3). Eight studies reported insomnia subtypes.

Incidence of post-stroke insomnia/insomnia symptoms

No studies assessing incidence were identified.

Prevalence of post-stroke insomnia/insomnia symptoms using clinical diagnostic tools

All six studies (n=983 participants) assessing insomnia using a recognised classification or a clinical diagnostic criteria (Table 2) used DSM IV/V criteria. In addition, one reported also using ICSD-II, one KECA-R and one ICSD-R. The prevalence of insomnia ranged from 14.8% to 59.8%.

Prevalence of post-stroke insomnia symptoms non-clinical diagnostic tools

Sixteen studies (n=18,142 participants) assessed insomnia symptoms (Table 3). The prevalence of insomnia symptoms, assessed using a variety of questionnaire measures, ranged from 19.8% to 69% (to 78% using a lenient definition of sleep disorder). Nine studies provided further information on insomnia symptom profile: Difficulties in sleep initiation ranged from 28.6-47.8% with the exception of one study reporting prevalence of 6.5% [42].

Difficulties in sleep maintenance varied considerably (14.3%-65.2%) with Li et al, again reporting lower prevalence at 4.8% [42]. Early morning awakening ranged from 17-34.1% with the exception of Li et al, (4.2%). The rates of non-restorative sleep ranged from 15.4% to 52.2%. Two studies reported impacts on daytime consequences (12.6% and ~52%)[12, 33] and four reported daytime sleepiness (8.7%-50%) [30, 37, 43, 45]. Only one study assessed symptom profile at two different time-points [6] reporting a reduction in prevalence from baseline to 18 months across sleep initiation, maintenance and early morning awakenings.

Stroke characteristic

Stroke type was reported in 13 of the 22 studies. Eight studies included ischemic strokes only, four included ischemic and haemorrhagic strokes, and one used another classification scheme. Strokes were identified using MRI (n=6), CT (n=2), MRI or CT (n=3) or self-report (n=6). Four studies did not provide a detailed account of stroke diagnosis. Time since stroke ranged from 3.1 days to 18 months. Nine studies did not report time since stroke.

Impact of stroke characteristics on prevalence of insomnia/insomnia symptoms

Three studies reported the presence of insomnia/insomnia symptoms by stroke type with no significant differences. Stroke severity was reported in three studies, with only one showing greater severity in those with insomnia. With regards to lesion location, two studies reported no significant differences in sleep disorder and insomnia complaint frequency and one reported poor sleep quality being associated with cortical lesions.

Three studies assessed insomnia/insomnia symptoms at multiple time points. One reported 47% of those with insomnia symptoms at baseline (1 month post-stroke) still having insomnia at 6 months with 67% of those at 6 months still having insomnia at 12 months post-

stroke. By contrast, 21% of those without insomnia at baseline had developed insomnia by 6-months with 56% of those having insomnia at 6 months still having insomnia at 12 months post-stroke [13]. At 14 days post-stroke insomnia prevalence of 46% and 67.7% were reported with prevalence of 38.4% at 12-months and 48.9% at 18 months [6, 42].

Demographic characteristics

Five studies did not report mean age for individuals with stroke, and three only reported age range(s) or minimum age for those with stroke. The average age across the remaining 14 studies was 62.7. Seven studies did not report the gender breakdown. In the 15 remaining studies on average, 59.8% were male. Only one study had less than half of the stroke sample being male.

Insomnia/insomnia symptoms preceding stroke

Only one study assessed pre-stroke insomnia/insomnia complaints prevalence indicating that 38.6% had pre-stroke onset whereas 18.1% had developed insomnia/insomnia symptoms post-stroke.

Impact of comorbidity on prevalence of insomnia/insomnia symptoms

Depression and anxiety were the most commonly reported insomnia co-morbidities (Tables 2 and 3). Depression in the presence of insomnia/insomnia symptoms ranged from 24% to 72% compared to 9.25% to 25% in those without insomnia symptoms. Similarly, anxiety ranged from 30% to 41% in those with insomnia symptoms compared to 9.2% to 15.1% in those without. One study reported higher rates of dementia in those with insomnia symptoms (24.2%) compared to those without (13.3%). Lower but not significantly different rates of cognitive impairment in those with insomnia symptoms were reported compared to those without (13% and 19.8% respectively). Other comorbidities reported were hypertension

(66.7-75.8% with insomnia symptoms vs. 68.9-70.5% without), diabetes (21.9-40.9% with insomnia symptoms vs 21.2%-31.7% without) and previous strokes (20.4% with frequent insomnia symptoms vs. 20.5% without).

Study quality

Quality of the included studies was variable. A summary of quality ratings is provided in Table 4.

Four studies were rated as having the highest possible quality rating. The two areas that received the greatest number of low quality ratings were the methods used for the identification of stroke and insomnia.

Meta-analyses

Pooled estimates of prevalence were calculated for 14 studies that included data from 16,894 individuals with stroke. Studies assessing sleep quality and those reporting prevalence for symptom profile only were excluded from the meta-analysis. The overall pooled prevalence was 38.2% (CI 30.1-46.5, I^2=98%, p<0.01) indicating substantial heterogeneity using a random effects model (Figure 2). Publication bias was assessed using a funnel plot (Figure 3) followed by the Egger test indicating not significant bias (p = 0.9985).

Prevalence was further analysed by subgroup according to type of assessment tool used (clinical diagnostic tools vs. non-diagnostic tools). Two of the studies [10, 33] contributed data to both diagnostic and non-diagnostic tool analysis. Subgroup analysis (Figure 4) revealed significantly higher pooled prevalence estimates for non-diagnostic tools, 40.70%, (CI 30.96-50.82, I^2=99%) than for diagnostic tools, 32.21% (CI 18.5-47.64, I^2=79%) although assessment tool type was not found to have a moderating effect p=0.3645. Further

subgroup analyses were considered for stroke type, severity, geography, quality and study setting. However these were not feasible due to low number of studies reporting these outcomes and/or high between study heterogeneity.

Discussion

There has been a sharp increase in the number of studies investigating the prevalence of post-stroke insomnia with half of the included studies published since 2015, yet no systematic review examining post-stroke insomnia prevalence and incidence has been published to date. Six of the twenty-two included studies used diagnostic assessment tools with the remaining sixteen using non-diagnostic tools. The quality of the included studies was variable with the majority of lower ratings relating to the validity of the methods used to identify insomnia, insomnia symptoms and strokes. For example, some population based studies included lower than expected number of strokes in the general population which may indicate that only those most able participated.

Despite a comprehensive search strategy, no studies assessing the incidence of post-stroke insomnia/insomnia symptoms were identified. Leppävuori et al. (2002) reported the incidence of new onset insomnia of 18.1% at 3-months post-stroke, however is not a true measure of incidence, as it does not account for those who had potentially experienced insomnia that had resolved prior to re-assessment at 3-months post-stroke [10]. Glozier et al. (2017) reported that 29% (71/244) of those without insomnia at 1-month post-stroke had new onset insomnia at 12-months[13]. However, as it is not clear whether those with insomnia at baseline (n124) were new onset insomnia, new cases over the following 11-months could be only inferred from 66% (n244) of the sample and should be interpreted with caution.

The included studies using diagnostic criteria to assess the presence of insomnia following stroke highlighted prevalence rates exceeding those of the general population [9] including healthy older adults that show prevalence estimates of 15.9-27.6% with prevalence ranging from 14.8% [31] based on DSM-IV-TR criteria to 59.8%, using SCID-P (DSM-IV) [44] with a pooled prevalence of 38.15% (CI 30.04-46.60). These rates are comparable to those found in post other neuropsychological injuries, such as traumatic brain injury where prevalence for insomnia is reported as 29% and insomnia symptomsas 50%[49]. Sleep difficulties and insomnia symptoms are likely to increase with age [50], however the prevalence estimates of insomnia has not shown to be dissimilar in older adults compared to younger ones [51, 52].

The highest quality study [10] using DSM-IV criteria for insomnia in MRI ascertained stroke cases, reported a prevalence of 37.6% for insomnia increasing to 56.7% for insomnia complaints. Subgroup analysis of studies of diagnostic tools, revealed a pooled prevalence estimate of 32.21% (CI 18.5–47.64).

Drawing on the common characteristics of studies using non-diagnostic tools, such as sleep quality (PSQI) and sleep symptoms, the prevalence ranged from 19.8% to 69%. Subgroup meta-analysis of studies using non-diagnostic tools, excluding studies with measures of sleep quality (e.g. PSQI), excessive daytime sleepiness (e.g. ESS), data for subgroup prevalence and secondary time points, revealed a pooled prevalence estimate of 40.7% (CI 30.96–50.82) indicating significantly higher prevalence estimates with the use of non-diagnostic tools, a pattern also seen in the general population [53].

Included studies exploring insomnia symptom profile such initiation, maintenance and daytime consequences in greater detail indicated wide variation in prevalence estimates across symptoms. A recent meta-analysis of polysomnography studies [54] indicated poorer sleep efficiency, shorter total sleep time, and a tendency for more wake after sleep onset in stroke survivors compared to controls. More recently, differences in post-stroke sleep quality, latency and duration compared to healthy controls [55] have also been reported. Just one study included a control group of healthy adults reporting lower prevalence for sleep onset but not for maintenance or restorative sleep [41]. These rates, however, were within symptom profile ranges of included studies for stroke reported above. Lower prevalence of difficulties in sleep initiation in men and women without a history of stroke was also noted in another study with a population based comparator [32].

Three of the included studies reported similar insomnia symptom prevalence for different types of stroke [13, 37, 43]. Unlike Palomäki et al. [6] and Tang et al. [46], Li et al. [42] found that those with insomnia symptoms had significantly greater stroke severity (NIHSS score) than those without. Evidence regarding lesion location was mixed making it difficult to ascertain conclusions [6, 43, 45, 56]. Previously, greater sleep disturbance has been reported following anterior circulation strokes and frontal lesions [57, 58] compared to posterior circulation strokes and left-sided cerebral infarctions [57]. Two studies investigated laterality showing no differences [6, 43]. Reviews on stroke laterality and post-stroke depression report mixed findings Bhogal et al. 2004 [59] (but see Carson et al. [60] and Wei et al. 2015 [61] and warrant further investigation.

Most studies assessed sleep at 1-3 months post-stroke. Low number of studies reporting prevalence at multiple time points made it difficult to ascertain how the insomnia status of

individual patients had changed over time. Glozier et al. [13] offered a succinct depiction of the bidirectional change over time in the onset and maintenance of chronic insomnia. They reported cross-sectional prevalence rates of 33.7% at 1-month and 29.9% at 6-months post-stroke. By contrast, at 6-month assessment point, the prevalence of chronic insomnia (present at baseline) was 16% and the remaining 13.9% were instances of acute insomnia. Transition to chronic insomnia is a difficult phenomenon to capture [62] with one study employing polysomnography analysis indicating that transition may be facilitated by the development of depression [63].

Studies using diagnostic tools showed significantly higher prevalence in older participants [10, 38] whilst those using non-diagnostic tools [6, 12, 13, 37, 42] did not. This finding conflicts with a recent meta-analysis suggesting lower prevalence in older adults and no gender differences in prevalence in the Chinese general population [64]. Higher prevalence of insomnia and insomnia symptoms were reported in females with the exception of one study that reported no significant gender differences in prevalence. A previous meta-analysis has indicated that women have 41% greater risk of developing insomnia than men [65].

Less than half of the included studies reported comorbidities relating to post-stroke insomnia. Depression and anxiety were most commonly reported ranging from 24%-72% for depression and 30-41% for anxiety with all but one study [33] reporting significantly higher prevalence or ratings in those with insomnia and/or insomnia symptoms (7) making it difficult to disentangle the contribution of comorbidities on post-stroke insomnia. The high rates reported for depression are unsurprising given that there is a bidirectional relationship with depression, anxiety and insomnia [66, 67]. It has been suggested, that individuals with post-stroke depressive symptoms are more likely to experience disturbed sleep early post-stroke

[68]. This is line with evidence suggesting that over 40% of individuals with insomnia have a psychiatric disorder [69] and the argument that sleep disturbances and insomnia may facilitate the onset of affective disorders [70].

Diabetes is a known risk factor for post-stroke sleep disorders [71]. One study [12] found higher rates of diabetes in those reporting insomnia symptoms [12] whilst two other studies [42, 46] found no significant difference between groups. Diabetes was also found to be an independent predictor of night-time sleep quality [45]. All three studies reporting rates for comorbid hypertension with insomnia found no significant differences between those with and without insomnia [12, 42, 46].

Cognitive behavioural therapy for insomnia (CBT-I) is the recommended treatment for insomnia [11] with studies showing small to large effects on sleep efficiency, sleep quality and sleep onset latency together with reduction in insomnia severity, wake after sleep onset and number of awakenings [72]. Suitability or effectiveness of CBT-I post-stroke has only been investigated in two small studies (n15, Herron) (n5, Nguyen) reporting improved sleep quality, reduction in fatigue, depression and dysfunctional sleep-related beliefs. Improvement in sleep efficiency has also been reported post Brief Behavioural Treatment-Insomnia (BBT-I) using single case methodology in two individuals post-stroke [73]. Given the high frequency of cognitive and communication difficulties in this population, tailored stroke-specific interventions targeting the behavioural components should be further developed. Knowledge of post-stroke insomnia prevalence, comorbidities and symptom profiles will allow better tailoring of non-medication interventions and addressing comorbidity such as the maintenance of insomnia and depression. This is of importance as the side effects of hypnotic medications are unclear, especially in relation to neural plasticity and functional recovery post injury [74]. Individuals with stroke have a greater risk of hypnotic side effects, including cognitive daytime carry over effect, increased risk of falls and issues with polypharmacy due

to being older on average [75]. Therefore, whether the benefits of using hypnotic medication in this population outweigh the increased risk of adverse events is questionable. The greater than population prevalence of insomnia and insomnia symptoms post-stroke indicated by this review, highlights the need to assess insomnia in the context of other relevant factors.

Our review is the first to provide a systematic overview of post-stroke insomnia/insomnia symptoms prevalence estimates. However, it has some limitations, such as the inclusion of articles published in English only. Additionally, study quality was not an exclusion criterion and may have contributed to the wide variance in prevalence. Several methodological approaches, definitions of insomnia and diagnostic tools were employed to estimate prevalence, which also limits the conclusions of the review. It was not possible to conduct a meta-analysis of all studies due to not all reporting prevalence at the main group level and the heterogeneity of assessment tools used, as many employed bespoke questionnaires. Future studies should ensure that sample characteristics are reported for all main and subgroups of interest with greater detail provided on stroke and insomnia characteristics including comorbidity. Further research should address the instances of insomnia pre-stroke as only one study provided details of pre-stroke insomnia and insomnia complaints (38.6%) [10].

Conclusions

Post-stroke sleep disturbance is disabling and is associated with greater mortality [42] and reduced quality of life [56]. This systematic review provides a comprehensive overview of the prevalence of insomnia and insomnia symptoms post-stroke, indicating that approximately a third of stroke survivors experience insomnia or insomnia symptoms at a given time, which is considerably higher than observed in the general population. It also highlights the lack of studies examining the incidence of insomnia and insomnia symptoms

post-stroke. Research on insomnia after stroke is very much in its infancy and more work is needed, especially on tailored psychological interventions such as BT-I and CBT-I.

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Conflicts of interest

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Practice points

- Post-stroke insomnia is common with approximately a third estimated to meet the diagnostic criteria for insomnia, increasing to four in ten for insomnia symptoms only.
- Routine screening of sleep disorders specifically for insomnia using diagnostic tools post-stroke is warranted, particularly in the presence of comorbid depression, anxiety or diabetes.
- Greater attention should be paid to the assessment and monitoring of insomnia and insomnia symptoms over time and in treatment context post-stroke.

Research Agenda

- Studies assessing the incidence of insomnia are currently lacking

- Studies should include a measure of pre-stroke insomnia and current insomnia symptoms whenever possible.
- Larger high quality longitudinal studies are needed to assess the progression and maintenance of insomnia and insomnia symptoms.
- In addition to overall prevalence, studies should collect data on stroke characteristics (e.g. severity) in order to predict which individuals will be more likely to develop insomnia.
- There is a need to better understand the daytime consequences of insomnia and insomnia symptoms over and above the effects of stroke.
- Insomnia treatment interventions carefully adapted to meet the cognitive, communication and neurological needs of this population based on current theoretical frameworks (including assessment) and stroke patients' perspectives are needed, and should be evaluated using validated diagnostic-based tools.

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Figure Legends

Figure 1 PRISMA flowchart

Figure 2. Forest plot of prevalence of insomnia and insomnia symptoms

Figure 3. Funnel plot of publication bias

Figure 4. Forest plot of the subgroup analysis by assessment tool

Table 1. Study characteristics

Study details					Sample characteristics (stroke sample)				
Study	**Country**	**Total N (%, n of stroke)**	**Design**	**Sampling**	**Mean Age, years (SD)**	**Gender %male**	**Setting**	**Stroke type**	**Time since stroke (Mean, SD)**
Araujo et al 2011[30#]	Brazil	400 (4% n=16)	Cross-sectional interview	Consecutive	NR	NR	Haemodialysis Centres	NR	NR
Benbir et al 2015[31ǂ]*	Turkey	4,758 (0.6%, n=27)	Cross-sectional population based Survey	Random stratified	NR	NR	Population based	NR	NR
Chen et al 2011[12#]*	China	508 (100%)	Cross-sectional interview	Consecutive	65.7(11.7)	64%	Acute Stroke Unit	Ischemic 100%	3mo
Glozier et al 2017[13#]*	Australia	368 (100%)	Prospective cohort interview	Consecutive	Range 18-65	60%	Hospital	Ischaemic 83% Haemorrhagic 13%	1, 6 and 12mo
Ito et al. 2000[32#]	Japan	518 (4%, n=21)	Cross-sectional Population based survey	Population-based health examination for those aged 65	65 only	66.7%	Population based	NR	NR
Joa et al 2017[33ǂ]*	Republic of Korea	208 (100%)	Cross sectional Cohort self-administered questionnaire	Multicenter	61.53(12.58)	54%	Hospital	Ischaemic 62% First ever strokes only Mild, K-NIHSS 0-5 (41.8%), Moderate, K-NIHSS 6-13 (58.2%), Severe, K-NIHSS ≥14, excluded	1mo
Kalmbach et al 2016[34ǂ]*	USA	3,911 (1.5%, n=57)	Cross-sectional Web-based survey	HMO database	NR	NR	Population based	NR	NR
Karaca et al 2016[35#]	Turkey	23 (100%)	Cross-sectional questionnaire	Retrospective	60.2(9.9) range 46-78	60.9%	Rehabilitation Hospital	Ischemic 82.6% Haemorrhagic 17.4%	NR
Kaufmann et al 2012[36#]*	USA	14,355 (8.7%, n=1,258)	Population based longitudinal Survey	multistage probability sampling with clustering	NR	NR	Population based	NR	NR

Kim et al 2017[a38ǂ*]	Republic of Korea	214 (100%)	Cross-sectional questionnaire	NR	60.48(NR)	55.1%	Rehabilitation centres	Ischemic 57% Haemorrhage 43% First ever strokes only	1mo
Kim et al 2017[b37#*]	Republic of Korea	241 (100%), includes 36 TIA (14.9%)	Cross-sectional self-administered questionnaire	Consecutive	64.17(11.89)	60.6 %	Hospital	Ischemic 100%	5.4(3.1)d
Kishimoto et al 2016[39#]	Japan	3,732 (5.8%, n=218)	Cross-sectional cohort Self-administered questionnaire and interview	NR	>65	NR	Population based	NR	NR
Koyanagi et al 2014[40#*]	Multiple[1]	42,116 (28.6%, n=12,045)	Cohort interview	multistage clustered	≥18 years, oversampling of age ≥50	NR	General population	NR	NR
Küçükdeveci et al 1996[41#]	UK	46 (100%) 47 (non-stroke control)	Cross-sectional interview	Consecutive	58.3(1.3) 58.2(1.3) non-stroke p>0.05	56.5% 53.2% (non-stroke) p>0.05	Rehabilitation based	Collected, NR	median 15.9mo (range 3.1-38.2) but at least 1.5mo post-discharge
Leppävuori et al 2002[10ǂ*]	Finland	277 (100%)	Cross-sectional interview	Consecutive	70.7(7.5)	50.9%	Hospital	Ischemic 100%	3-4mo
Li et al 2018[42#*]	China	1062 (100%)	Longitudinal Prospective cohort Questionnaire	NR	60.47(11.57)	65.7%	Hospital	Ischemic 81.3% First ever strokes only	14d, 3mo, 6mo (NR), 12mo
Palomäki et al 2003[6#*]	Finland	100 (100%)	Longitudinal RCT/Interview	Consecutive	55.2 (median 56.0, range 27–70)	68 %	Hospital	Ischemic 100%	14d (range 4-30); 18mo
Pasic et al 2011[43#]	Bosnia and Herzegovina	200 (100%)	Cross-sectional interview	Consecutive	NR	NR	Hospital	Haemorrhagic and ischemic (breakdown NR)	NR
Spalletta et al 2005[44ǂ*]	Italy	200 (100%)	Cross-Sectional/ interviews	Consecutive	65.7	42%	Hospital	Ischemic 82% First ever strokes only	40.5d (range 3wk-3m)
Suh et al	Republic of	282	Cross-sectional	Consecutive	62.34(12.76)	58.9%	Hospital	Large artery disease 37.2%	6.7(1.89)d

2014[45#]	Korea	(100%)	Interview					Small artery disease 27.7% Others 18.4% Cardiogenic 16.7%	
Tang et al 2015[46#]*	China	336 (100%)	Cross-sectional Self-administered questionnaire	Consecutive	66.1(10.2)	66.4%	Hospital	NR	At least 7d prior inclusion
Yang et al 2017[47#]	China	1418 (100%)	Cross-sectional interview	Consecutive	61.9(11.3)	66.6%	Hospital	Ischemic 100%	14±2d; 1y

[1]SAGE (China, Ghana, India, Mexico, Russia and South Africa), COURAGE (Finland, Poland and Spain)

HMO, Health Maintenance Organization; K-NIHSS, Korean version of the National Institute's Health stroke scale; NR, not reported; RCT, Randomised controlled trial; SD, standard deviation; TIA, Transient ischemic attack

* included in meta-analysis

‡ Study using diagnostic assessment tool(s)

Study using non-diagnostic assessment tool(s)

Table 2. Studies assessing insomnia using clinical diagnostic tools (stroke sample only)

First Author, year	Insomnia Assessment	Stoke Assessment	Overall prevalence %	Insomnia demographic characteristics %, mean (SD)	Insomnia stroke/clinical characteristics	Insomnia Comorbidity %
Benbir 2015[31]	ICSD-II DSM-IV-TR	Self-report	14.8% insomnia	NR	NR	NR
Joa 2017[33]	DSM-IV	ICD-10, Brain imaging (not specified) K-NIHSS	26.9% insomnia 56.7% any sleep disturbance 43.3% DIS 47.6% DMS 33.7% EMA 40.4% NR Approx. 52% DC (detailed data NR)	NR	NR	Depression Insomnia vs non-insomnia, NS (NR) Anxiety Insomnia vs non-insomnia, NS (NR) Both significantly correlated with all sleep measures
Kalmbach 2016[34]	DSM-V	Self-report	36.8% insomnia disorder	NR	NR	NR
Kim 2017a[34]	Questionnaire from KECA-R used to assess insomnia according to DSM-IV.	MRI and neurological presentation assessment	59.8% at least 1 of 4 sleep complaints over the previous month. Prevalence of specific complaint: 42.5%, DIS 46.7%, DMS 34.1%, EMA 41.5%, NR	Age Insomnia 62.66 (15.11) Non-insomnia 58.29 (14.06), p=0.034 Gender (%male) Insomnia 48.4 % Non-insomnia 65.1%, p=0.016	57.8% ischemic 42.2% haemorrhage	Depression Insomnia 59.4% Non-insomnia 24.4%, p<0.001 Anxiety Insomnia 38.3% Non-insomnia16.3%, p=0.001
Leppävuori 2002[10]	DSM-IV	MRI	37.6% of all patients/ 66.2% of all insomniacs fulfilled the DSM-IV criteria of insomnia, the remaining 53 (19.1%/33.8%) did not. 56.7% insomnia complaints 38.6% pre-stroke onset of insomnia/insomnia complaints 69.2% fulfilled diagnostic criteria for insomnia,	Age Insomnia 71.6 (7.8) Non-insomnia 69.5 (6.8), p<0.05 Gender (%male Insomnia 45.2% Non-insomnia 58.3%, p<0.05	Pre-stroke onset 70.1% Primary 17.8% Due to depression or anxiety 12.1% Due to physical illness Post-stroke onset 52.0% Primary 4.0 % due to depression or	Depression 51.6% all insomnia, p<0.0001, 52.0% new insomnia, p<0.001; 25.0% non-insomnia. Major depression 34.4% all insomnia, p<0.001, 34.0%, p<0.01 new insomnia, 15% non-insomnia. Anxiety disorder 31.2% all insomnia, p<0.0001, 30.0% new insomnia, p<0.001,

			30.8% criteria for insomnia complaints only Post-stroke insomnia (new insomnia) 18.1% 60.0% fulfilled diagnostic criteria for insomnia, 40.0% insomnia complaints only		anxiety 44% due to physical illness	9.2% of non-insomnia. Dementia (DSM-III-R) 24.2% all insomnia, p<0.05, 38.0% new insomnia, p<0.001 13.3% non-insomnia
Spalletta 2005[44]	SCID-P for DSM-IV	MRI	43.5% insomnia	NR	NR	72% Major Depressive Disorder 48.4% Minor Depressive Disorder 23.9% No depressive disorder

DC, Daytime consequences; DIS, Difficulty in initiating sleep; DMS, Difficulty in maintaining sleep; EMA, Early morning awakening; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International classification of disease; ICSD, International Classification of Sleep Disorders; KECA-R, Korean Epidemiologic Catchment Area Study Replication; K-NIHSS, Korean version of the National Institute's Health stroke scale; MRI, Magnetic resonance imaging; NR, Nonrestorative sleep; SD, Standard deviation; SCID, Structured clinical interview for DSM-IV patient edition

Table 3. Studies assessing Insomnia symptoms

First author, year	Insomnia Symptoms Assessment	Classification	Stoke Assessment	Prevalence %	Insomnia demographic characteristics %, mean (SD), Age/education (years), gender (%male)	Insomnia stroke/clinical characteristics (%), mean (SD)	Insomnia Comorbidity % significant interactions
Araujo 2011[30]	PSQI Berlin questionnaire, ESS	PSQI>5 poor sleep quality ESS>10	NR	69% PSQI>5 50% ESS>10	NR	NR	NR
Chen 2011[12]	An insomnia questionnaire (Chiu et al., 1999) Symptoms for the past 1 month: 1. On average, how many hours do you spend asleep per night?; 2. How many hours of sleep per night do you think you need?; 3. Do you have difficulty in falling asleep?; 4. Do you have frequent wakening in the night?; 5. Do you wake up very early in the morning and have difficulty in going back to sleep?; 6. Do you consider yourself as having insomnia?; 7. Do you need to take sleeping pills at times in the past 1 month? If yes, how often?; 8. Do you frequently feel tired in daytime?	Insomnia symptoms: answer ''frequent'' in any of questions 3, 4, and 5. DC:answer to question 8 'yes.'	MRI, NIHSS	36.6% insomnia symptoms 12.6% DC	Age FIS 65.5(11.1) No FIS 65.8(12.0), p>0.05. Gender FIS 61.3% No FIS 65.5%, p>0.05 Education FIS 5.7(4.7) No FIS 5.6(4.6), NS	Previous stroke FIS 20.4% No FIS 20.5%, p>0.05. Severity (NIHSS on admission) FIS 4.8(3.5) No FIS 4.2(3.3), p=0.068 Frontal infarct FIS 12.4% No FIS 6.8%, p<0.05 Other brain areas, NS Cognition (MMSE) FIS 26.1(3.2) No FIS 26.2(3.2), p>0.05.	Depression (GDS score) FIS 5.2(3.3) No FIS 3.9(2.8), p< 0.001. Diabetes FIS 40.9% No FIS 31.7%, p<0.05. Hypertension FIS 75.8% No FIS 70.5%, p>0.05. COPD FIS 6.5% No FIS 7.8%, p>0.05.
Glozier	Karolinska Sleep	Insomnia if	Self-	1 month 33.7%	Age (baseline)	Stroke subtype	Depression at baseline

2017[13]	Questionnaire (modified for stroke, assesses insomnia for the past 4 weeks): "Since your stroke, (1) have you had any problems getting to sleep?" (2) how often have you woken too early and not been able to get back to sleep?" (3) how often have you been tired or sleepy at work or during your spare time?"	reported problems with either of the 2 nocturnal symptoms (sleep onset and/or early morning awakening) more frequently than "often/several times per week," in addition to reporting daytime consequences of tiredness or sleepiness more frequently than "often/several times per week."	report	6 months 29.9% 12 months 37.0% Chronic insomnia during first 6 months 16% indicating 47% still had insomnia at 6 months, 53% had recovered Of 66% non-insomnia at baseline, 79% remained good sleepers at 6 months, of whom 78% remained good sleepers at 12 months, 21% had developed insomnia by 6 months, of whom 56% still had insomnia at 12 months	18-46 Insomnia 30% Non-insomnia 21% 46-65 insomnia 70% Non-insomnia 79% p>0.05. Gender Insomnia 57% Non-insomnia 74%, p<0.01. Education N.S Employment N.S Marital status N.S	Ischaemic 84% Haemorrhagic 11%, p=0.66 Unknown 5%, p=0.17 Cognitive impairment at baseline Insomnia symptoms 13%, Non-insomnia symptoms 19.8%, p=0.12.	24% insomnia symptoms 9.5% non-insomnia symptoms, p<0.001 Anxiety at baseline 41% insomnia symptoms 15.1% non-insomnia symptoms, p<0.001
Ito 2000[32]	Insomnia symptom questionnaire: 1.How many hours do you sleep at night on an average?; 2.How long does it take from going to bed to falling asleep?; 3.How many times do you usually wake up at night?; 4.How do you feel when you wake up in the morning?	Sleep disturbance DIS: difference between bedtime and falling asleep 30min DMS: awakenings more than twice NR: felt bad in the morning.	Self-Report	NR	Males vs. 241/497 non-stroke 30.8%; DIS (14.5 % Non-stroke) 30.8% DMS (32.2% non-stroke) 15.4% NR (15.4% non-stroke). Any of the 3 disturbances 66.7% (41.7% non-stroke) Females vs. 256/497 non-stroke 28.6% DIS (22.3% non-	NR	NR

					stroke) 14.3% DMS (28.5% non-stroke) 27.3% NR (18.7% non-stroke) 42.9% Any disturbance (49.6% non-stroke)		
Karaca 2016[35]	PSQI	>5=poor sleep quality	NR	≤5=60.9% >5=39.1%	NR	NR	NR
Kaufmann 2012[36]	How often had: trouble "falling asleep", "waking up during the night", "waking up too early and not able to fall asleep again", and when they felt "really rested".	Categorised as having 0,1 or ≥2 insomnia symptoms	Self-report	0=53.2% 1=21.6% ≥2 25.2%	NR	NR	NR
Kim 2017b[37]	ISI-K PSQI-K ESS-K	ISI-K≥15.5=clinical insomnia PSQI-K≥8.5=poor sleep quality ESS-K≥11=significant excessive daytime sleepiness	MRI, NIHSS mRS-3	12% Insomnia 32.8%, PSQI-K 8.7% ESS-K	NR	Stroke subtype NS between Large artery atherosclerosis, Cardioembolism, small vessel occlusion on ISI-K, PSQI-K, ESS-K. Stroke severity mRS-3 associated with ISI-K, p=0.001	NR
Kishimoto 2016[39]	PSQI-Japanese	>5.5=sleep disturbance	Self-report	46.3% sleep disturbance	NR	NR	NR
Koyanagi 2014[40]	Overall in the last 30 days, how much of a problem did you have with sleeping, such as falling asleep, waking up frequently during the	Sleep Problems none, mild, moderate, severe, extreme/cannot do	Self-report and/or with symptoms	19.8% Severe/extreme sleep problems	Prevalence by country China 7.2%, Mexico 12%, Spain 13.8%, South Africa 18.4%, Finland 19.2%, Ghana 20.8%, Poland 27.5,	NR	NR

	night or waking up too early in the morning?				India 31.3%, Russia 21.6%		
Küçükdeveci 1996[41]	A four-item sleep assessment questionnaire	Higher scores indicate higher frequency of sleep disturbance Categorised according to frequency per month: Not at all, 1-3 days, 4+ days	NR	Sleep initiation 47.8% stroke 34.0% control Staying asleep 65.2% stroke 59.6% control Frequent awakening 39.1% stroke 46.8% control Waking up tired 52.2% stroke 44.7% control	NR	NR	NR
Li 2018[42]	HDS	insomnia symptoms if reported experiencing: ▪1≥ sleep conditions for at least 3 nights/week; ▪1≥ sleep conditions at two consecutive visits.	CT/MRI within 14 days	14 days 46% Insomnia 6.5% DIS 4.8% DMS 4.2% EMA 4.9% DIS+DMS 6.9% DIS+EMA 2.3% DMS+ EMA 19.8% All three complaints 1 year 38.4% Insomnia 15.5% One symptom 33.9% Multiple symptoms	Age Insomnia 48.9(46.0) Non-insomnia 57.3(54.0) P<0.08, N.S Gender Insomnia 60.1% Non-insomnia 70.5% P<0.001 Employment Insomnia 44.1% Non-insomnia 50.4%, p=0.04	Severity (NIHSS) Insomnia 5.21(4.38), Non-insomnia 4.12(3.65), p<0.001	Depression (at 1 year) 54.8% Insomnia 20.8% Non-insomnia, p<0.001 Diabetes 21.9% Insomnia 21.2% Non-insomnia, p=0.82 Hypertension 66.7% Insomnia 68.9% Non-insomnia, p=0.47
Pasic 2011[43]	Berlin Questionnaire ESS	NR	CT scan	78% sleep disorder, 42% very serious, 20% moderately	NR	Stroke subtype Ischemic 76.8% Haemorrhagic 82.5%,	NR

				severe, 16% medium severe, 22% no symptoms of sleep disorder. 49.5% ESS		NS Lesion location 33% LHL, 39.5% RHL, 27% bilateral lesion. NS differences in Sleep disorder frequency	
Palomäki 2003[6]	HDS	Insomnia if one or more positive ratings in any of the three sleep items in HDS.	CT or MRI	14 days, 67.7% positive for at least 1/3 sleep items on HDS: 41.5% DIS, 44.1% DMS 32.3% EMA. 18 months, 48.9% at least one sleep item on HDS: 33.7% DIS, 23.6% DMS 17.0% EMA.	Age 14 days: young (<56 years, 66.7%), old (>56, 68.9%), NS 18 months: NS, p=0.2 Gender Men (65.1%), women (73.3%), NS	Severity mild (SSS>47, 69.4%) severe stroke (<47, 65.9%), NS Lesion location, left (63.9%), right (70.3%), brain stem infarction (70.0%), NS	NR
Suh 2014[45]	Verran–Snyder-Halpern (VSH) Sleep Scale	Higher scores indicate better sleep quality, 0(min)-80(max)	MRI within 7 days	Sleep latency 20min+ 29.8% Increased daytime sleepiness 39.0% Sleep duration: <6h 21.3%, 6-8h 54.6%, 8h 24.1%	NR	Cortical lesions, lower VSH Sleep Scale score than other lesions (p=.049). Subcortical lesions (p=.005) and fatigue (p<.001) had higher increased daytime sleepiness	Depression Lower VSH score (p=<.001 Longer sleep latency (p<.001) Greater frequency of waking after sleep onset (p=.023) Diabetes Lower VSH score (p=.022) Fatigue Lower VSH score (p=.006). Greater frequency of waking after sleep onset (p=.010) Hypertension, hyperlipidemia, metabolic

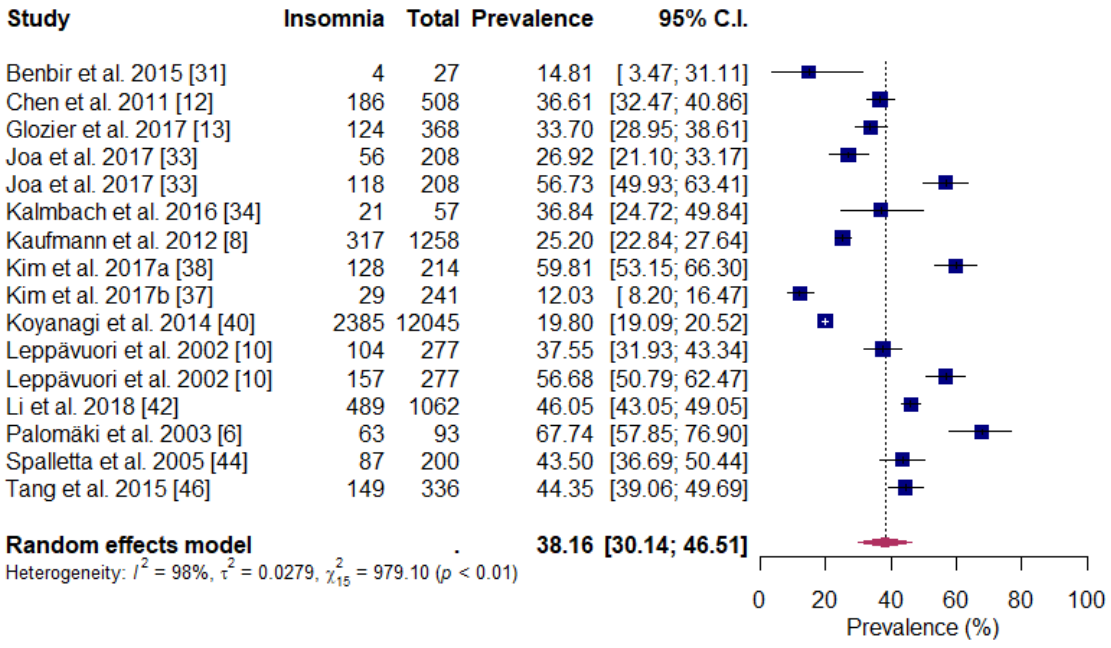
							syndrome, and stroke subtypes not associated with VHS Sleep Scale score
Tang 2015[46]	7-item Insomnia Questionnaire derived from Chen 2011, ESS	self-reported insomnia if experienced 1 or more days of insomnia per week in the current month	CT	44% experiencing insomnia in the past month.	Age Insomnia 66.1(9.7) Non-insomnia 66.0(10.6), p=0.893 Gender Insomnia 49.3% Non-insomnia 69.5%, p<0.01 Education Insomnia 6.1(5.0) Non-insomnia 6.9(5.0), p=0.210	Severity (NIHSS), Insomnia 3.7(3.3) Non-insomnia 3.1(3.3), p=0.137 Previous stroke Insomnia 12.2% Non-insomnia 9.1%, p=0.350 Cognition (MMSE) Insomnia 27.5(2.3) Non-insomnia 27.4(2.5), p=0.690	Depression (GDS score), Insomnia 6.2(4.2) Non-insomnia 3.1(3.6) p<0.01 diabetes 36.3%insomnia 30.5%, no insomnia p=0.267 Hypertension 73.5%,Insomnia 74.3%, no insomnia p<.859
Yang 2017[47]	HDS	Insomnia if rated 1 or 2 on at least 1/3 items.	MRI or CT within 14 days	29.0% DIS 22.4% DMS 25.4% EMA	NR	NR	NR

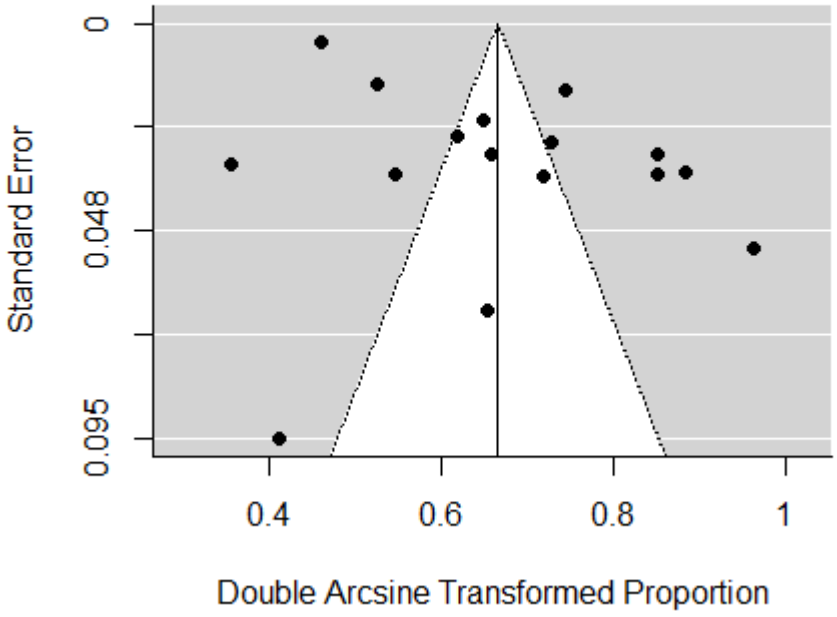
CT, computerised tomography; COPD, chronic obstructive pulmonary disease; DC, Daytime consequences; ESS, Epworth Sleepiness Scale (range 0-24); ESS-K, Epworth Sleepiness Scale Korean version; FIS, Frequent insomnia symptoms; GDS, Geriatric depression Scale; HDS, Hamilton Depression Scale, items #4(DIS), #5(DMS), #6(EMA); IKI-K, Korean version of Insomnia Severity Index; LHL, Left Hemisphere lesion, MMSE, Mini-Mental State Examination; MRI, Magnetic Resonance Imaging; mRS, Modified Rankin Scale; PSQI, Pittsburgh Sleep Quality Index; RHL, Right hemisphere lesion; SD, Standard deviation; SSS, Scandinavian Stroke Scale; TIA, transient ischemic attack.

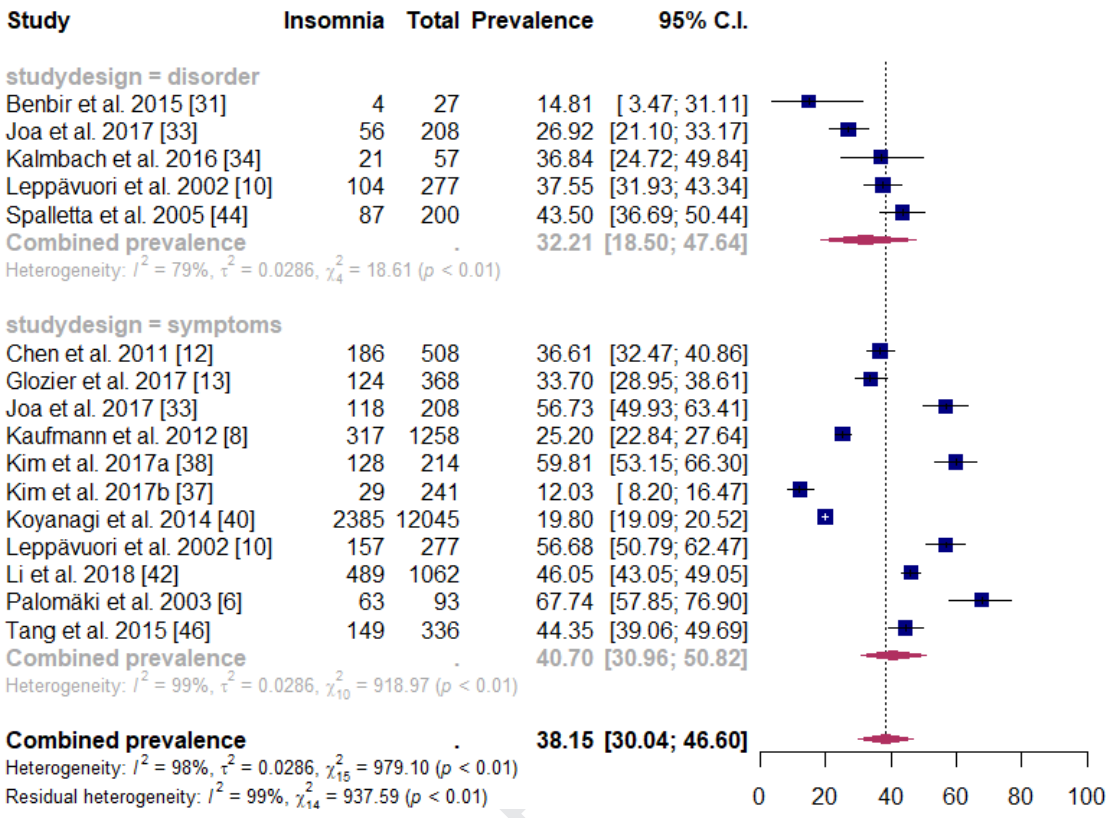
Table 4. Study quality

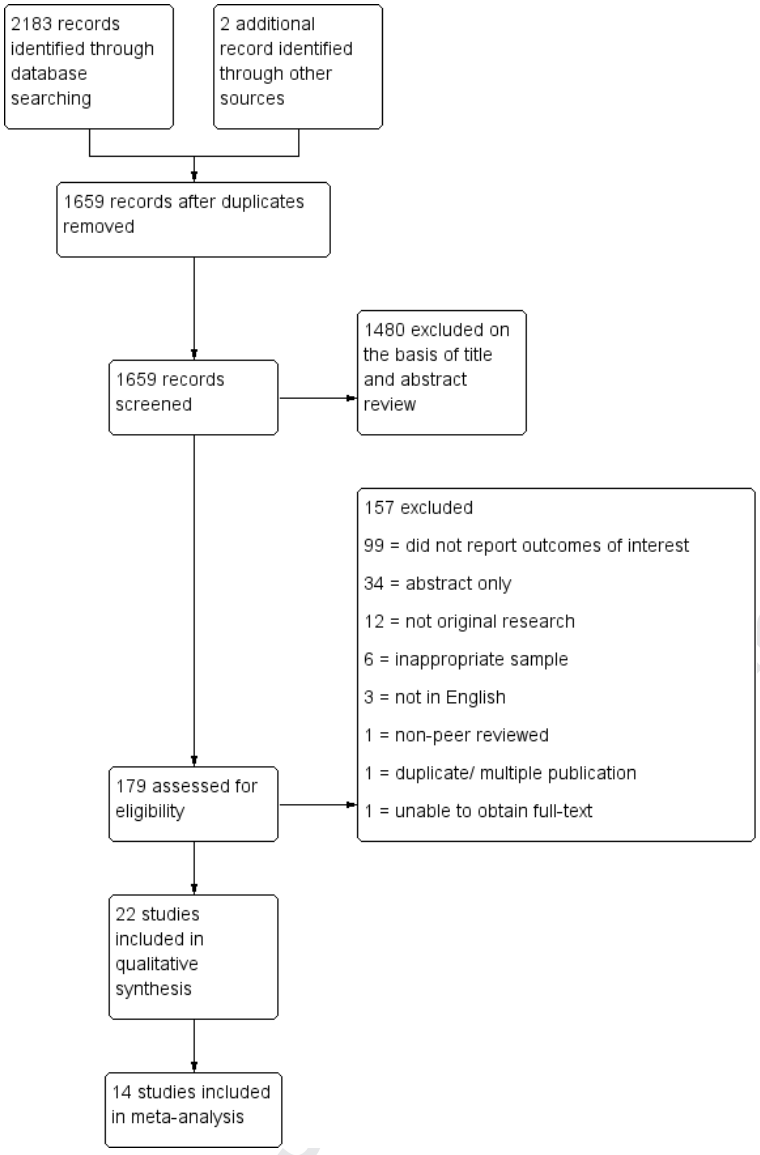
Study	Sample frame appropriate to address the target population	Appropriate sampling of study participants	Adequate sample size	Study subjects and setting described in detail	Data analysis conducted with sufficient coverage of the identified sample	Valid methods used for the identification of insomnia or insomnia symptoms	Valid methods used for the identification of stroke	Condition measured in a standard, reliable way for all participants	Appropriate statistical analysis	Adequate response rate, if not, was low response rate managed appropriately
Araujo 2011[30]	N	Y	N	Y	Y	Y	Y	Y	Y	Y
Benbir 2015[31]	Y	N	N	Y	N	Y	N	U	Y	Y
Chen 2011[12]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y
Glozier 2017[13]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ito 2000[32]	U	Y	Y	Y	Y	N	N	Y	Y	U
Joa 2017[33]	Y	U	Y	Y	Y	Y	Y	Y	Y	Y
Kalmbach 2016[34]	Y	Y	N	Y	Y	N	N	U	Y	U
Karaca 2016[35]	Y	Y	N	N	Y	Y	N	U	Y	U
Kaufmann 2012[36]	Y	Y	Y	Y	Y	U	N	U	Y	Y
Kim[a]2017[38]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kim[b] 2017[37]	Y	Y	Y	Y	Y	Y	Y	U	Y	Y
Kishimoto 2016[39]	N	U	U	Y	Y	N	Y	Y	Y	N
Koyanagi 2014[40]	Y	Y	Y	U	Y	N	N	Y	Y	Y
Küçükdeveci 1996[41]	Y	Y	U	U	U	U	U	U	Y	U
Leppävuori 2002[10]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Li 2018[42]	Y	U	Y	Y	Y	Y	Y	Y	Y	Y
Pasic 2011[43]	Y	U	Y	N	Y	Y	Y	U	N	U
Palomäki 2003[6]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Spalletta 2005[44]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Suh 2014[45]	Y	Y	Y	Y	Y	U	Y	U	Y	Y
Tang 2015[46]	Y	U	Y	Y	Y	Y	Y	Y	Y	Y
Yang 2017[47]	N	Y	Y	Y	Y	Y	Y	Y	Y	U

Colour code: green, yes; red, no; yellow, unclear








2183 records identified through database searching
2 additional record identified through other sources
1659 records after duplicates removed
1659 records screened
1480 excluded on the basis of title and abstract review
157 excluded
99 = did not report outcomes of interest
34 = abstract only
12 = not original research
6 = inappropriate sample
3 = not in English
1 = non-peer reviewed
1 = duplicate/ multiple publication
1 = unable to obtain full-text
179 assessed for eligibility
22 studies included in qualitative synthesis
14 studies included in meta-analysis