Stroke

CLINICAL AND POPULATION SCIENCES

Dynamic Prevalence of Sleep Disorders Following Stroke or Transient Ischemic Attack

Systematic Review and Meta-Analysis

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BACKGROUND AND PURPOSE: The exact prevalence of sleep disorders following stroke or transient ischemic attack (TIA) remains unclear. We aimed to determine the prevalence of sleep-disordered breathing, insomnia, periodic leg movement during sleep, and restless leg syndrome following stroke or TIA in acute, subacute, and chronic phases and examine the moderating effects of patient characteristics (eg, age) and methodological features (eg, study quality) on the prevalence.

METHODS: We performed a systematic review and meta-analysis. Embase and PubMed were searched from inception to December 18, 2019. We included 64 047 adults in 169 studies (prospective, retrospective, case-control, and cross-sectional study designs) reporting the prevalence of sleep disorders following stroke or TIA.

RESULTS: In the acute phase, the overall prevalence of mild, moderate, and severe sleep-disordered breathing was 66.8%, 50.3%, and 31.6% (95% CIs, 63.8–69.7, 41.9–58.7, and 24.9–39.1). In the subacute phase, the prevalence of mild, moderate, and severe sleep-disordered breathing was 65.5%, 44.3%, and 36.1% (95% CIs, 58.9–71.5, 36.1–52.8, and 22.2–52.8). In the chronic phase, the summary prevalence of mild, moderate, and severe sleep-disordered breathing was 66.2%, 33.1%, and 25.1% (95% CIs, 58.6–73.1, 24.8–42.6, and 10.9–47.6). The prevalence rates of insomnia in the acute, subacute, and chronic phases were 40.7%, 42.6%, and 35.9% (95% CIs, 31.8–50.3, 31.7–54.1, and 28.6–44.0). The pooled prevalence of periodic leg movement during sleep in the acute, subacute, and chronic phases was 32.0%, 27.3%, and 48.2% (95% CIs, 7.4–73.5, 11.6–51.7, and 33.1–63.5). The summary prevalence of restless leg syndrome in the acute and chronic phases was 10.4% and 13.7% (95 CIs, 6.4–16.4 and 2.3–51.8). Age, sex, comorbidities, smoking history, and study region had significant moderating effects on the prevalence of sleep disorders.

CONCLUSIONS: Sleep disorders following stroke or TIA are highly prevalent over time. Our findings indicate the importance of early screening and treating sleep disorders following stroke or TIA.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: meta-analysis ■ prevalence ■ restless leg syndrome ■ sleep ■ smoking

Globally, stroke is one of the leading causes of morbidity and mortality in adults.[1] Stroke survivors often experience long-term physical and psychological problems that undermine their quality of life.[2,3]

Sleep-disordered breathing (SDB) has been recognized as an independent risk factor for stroke.[4] Notably, the American Heart Association and American Stroke Association stroke guidelines have recommended considering sleep studies for the prevention of recurrent stroke or transient ischemic attack (TIA) on the basis of high prevalence in this population.[5] Other sleep disorders, including insomnia, periodic leg movement during sleep (PLMS), and restless leg syndrome (RLS), have also been associated with an increased stroke risk.[6–8]

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Nonstandard Abbreviations and Acronyms

PLMS	periodic leg movement during sleep
RLS	restless leg syndrome
SDB	sleep-disordered breathing
TIA	transient ischemic attack

Sleep disorders after stroke or TIA may impair optimal stroke rehabilitation and functional recovery.[7,9] Untreated poststroke sleep disorders can contribute to recurrent stroke.[9] However, the nature of sleep disorders following stroke has not been fully recognized. A wide variation in the prevalence may be one of the contributors to a lack of recognition in clinical and community-based settings. Hence, the clinical importance and effect of sleep disorders following stroke or TIA have recently gained attention.

Understanding the prevalence of sleep disorders following stroke or TIA can increase awareness and acknowledge its clinical relevance among health care providers and health policymakers. Consequently, health professionals could perform sleep screening earlier before or after stroke or TIA onset and designing effective treatments for relieving sleep disorders.

In this study, we comprehensively updated data on the prevalence of sleep disorders, including SDB, insomnia, PLMS, and RLS, following stroke or TIA according to the different phases after stroke (acute, subacute, and chronic). Additionally, we examined the moderating effects of methodological features and patient characteristics on the prevalence of sleep disorders after stroke or TIA.

METHODS

Data Sources and Searches

The data of the current study are available from the corresponding author by reasonable request. This systematic review and meta-analysis were reported based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[10] It was prospectively registered with PROSPERO (no. CRD42019126422). PubMed and Embase were searched from their inception until December 18, 2019. The combinations of keywords used were as follows: ("stroke" OR "cerebrovascular accident" OR "transient ischemic attack" OR TIA) AND ("sleep" OR "sleep disorders" OR "circadian rhythm*" OR "insomnia" OR "hypersomnia" OR "sleep apnea" OR "sleep apnoea" OR "sleep–wake cycle disorder*" OR "narcolepsy" OR "sleep complaint*" OR "sleep change*" OR "sleep disturbance*" OR "sleep disruption*"). An example of the PubMed search strategy can be found in Table I in the Data Supplement. Additionally, the reference lists of all retrieved studies were manually searched for related studies.

Study Selection

We included full-text studies that met the following criteria: (1) participants' mean age ≥19 years; (2) diagnosis of stroke or TIA; (3) reporting the outcome of the prevalence of SDB, insomnia, PLMS, or RLS following stroke or TIA for ≥10 participants; (4) prospective, cross-sectional, retrospective, or case-control study design; and (5) published or accepted for publication by a peer-reviewed journal. No language restriction was applied. Two investigators (F. Hasan and O.F.D. Marta) independently reviewed and screened titles and abstracts according to the eligibility criteria. Any disagreement was resolved through discussion with the third investigator (H.-Y. Chiu.).

Data Extraction and Assessment of Methodological Quality

Two reviewers (F. Hasan and O.F.D. Marta) separately extracted data, and disagreements were resolved through discussion. We classified the prevalence of sleep disorders following stroke and TIA as acute (<1 month), subacute (1–3 months), and chronic (>3 months) phases.[11] Descriptions of outcome measures are listed in Table II in the Data Supplement.

The methodological quality of included studies was determined using the Critical Appraisal Checklist. Eight items were used to determine the quality of cross-sectional studies, 11 items were used for cohort studies, and 10 items for case-control studies.[12] Each item was rated as "yes," "no," "unclear," or "not applicable." Two researchers independently evaluated included studies (F. Hasan and O.F.D. Marta). Any disagreement was resolved by consensus.

Data Synthesis and Analysis

All analyses were conducted using Comprehensive Meta-Analysis version 2.0 software (Biostat, Englewood, NJ). A random-effects model was used to estimate the prevalence with a 95% CI of sleep disorders following stroke or TIA in acute, subacute, and chronic phases. Between-study heterogeneity was assessed using Cochran Q and I^2 tests. Substantial heterogeneity was determined if Cochran Q and I^2 values were <0.05 and at least 50%, respectively.[13] To identify possible reasons for heterogeneity, moderator, and metaregression analyses were performed. To ensure that sufficient data could be obtained for data analyses, moderator analyses were restricted to instances in which groups were represented by at least 2 studies. Egger intercept tests were used to test publication bias, and a P<0.05 represented a statistically significant publication bias.[14]

RESULTS

Selection, Inclusion, and Characteristics of Studies

We initially identified 7659 articles and screened abstracts and titles for inclusion (Figure 1). After removal of duplicates and irrelevant studies, 169 full-text articles were included in the review. Several studies reported more than one sleep outcome, resulting in that 132 examined SDB, 28 insomnia, 10 PLMS, and 15 RLS. The characteristics of the included studies are listed in Tables

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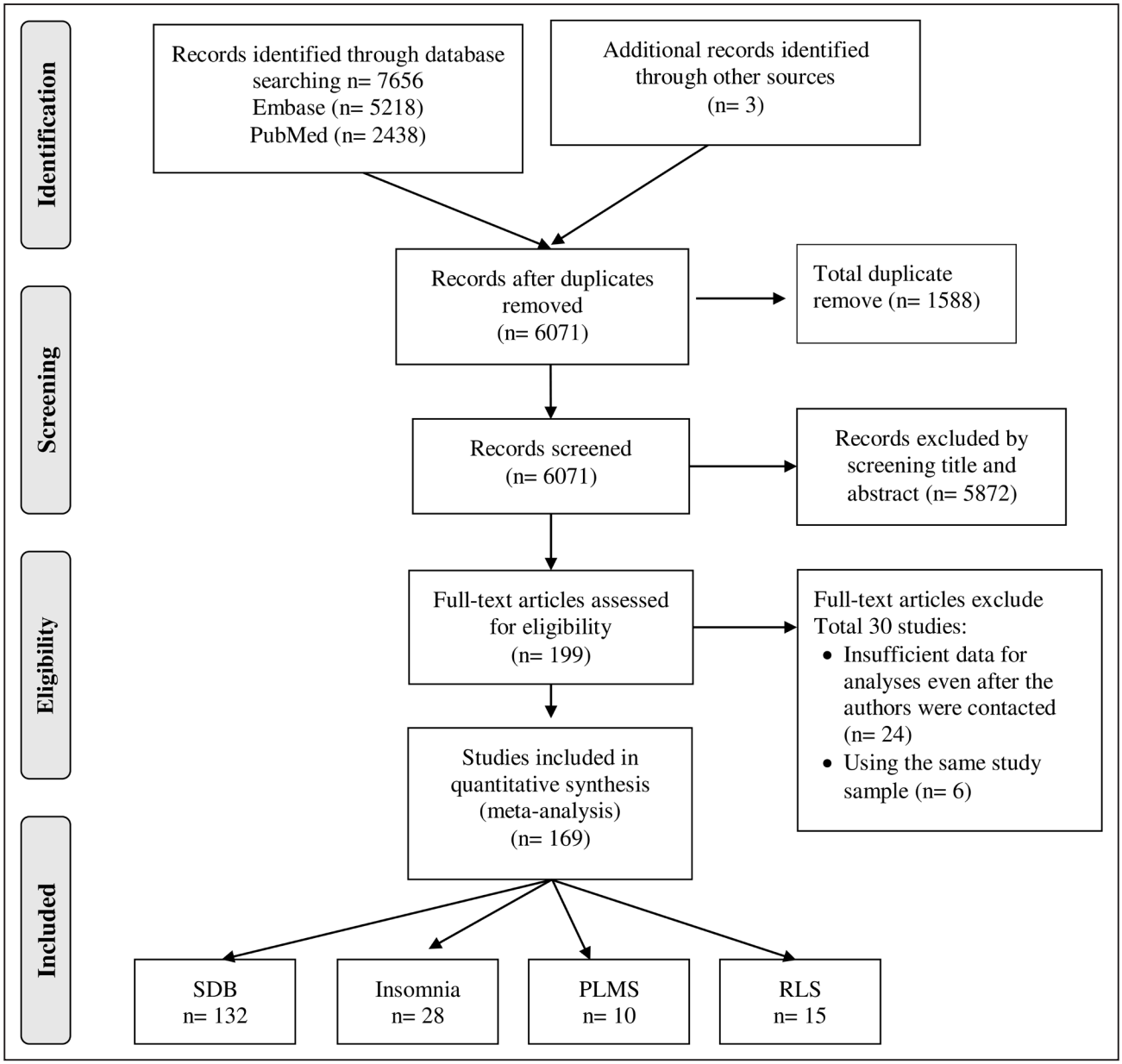

Figure 1. Study flow diagram.
n indicates number of studies; PLMS, periodic leg movement during sleep; RLS, restless leg syndrome; and SDB, sleep-disordered breathing.

III through VI in the Data Supplement. Details about the inclusion and exclusion criteria of the included studies are listed in Table VII in the Data Supplement (including the reference list of the included studies).

For studies reporting SDB prevalence, the total sample size was 14 032 (stroke survivors, 12 971 and TIA cases, 1061); mean age was 64.9 years; and 63% were men. All studies were diagnosed as having SDB through in-laboratory (n=77) or home-based (n=55) polysomnography. Most of the studies considered obstructive and central sleep apnea as SDB and reported combined prevalence. Therefore, it is difficult to report the prevalence separately.

The studies examining insomnia had a total of 46 169 participants (stroke survivors, 46 133 and TIA cases, 36); the mean age was 63.0 years; and 44.5% were women. Thirteen studies used the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and the International Classification of Sleep Disorders-2 as references for the diagnosis of insomnia. Fifteen studies assessed insomnia symptoms by using self-administered questionnaires (7-item Insomnia Severity Index, 16-item Sleep Diagnosis Questionnaire, 32-item Sleep Habit Questionnaire, 7-item Hong Kong version of Insomnia Questionnaire, and 14-item St Mary's Sleep Questionnaire).

For PLMS prevalence, 10 studies involving 1165 stroke survivors and 32 TIA cases with a mean age of 63.2 years were included. All participants were diagnosed as having PLMS on the basis of

results of the periodic limb movement index derived from the in-laboratory (n=8) or home-based (n=2) polysomnography.

In terms of RLS, 15 studies involving 2649 patients (stroke survivors, 10 305 and TIA cases, 17) with a mean age of 63.4 years were included. Fourteen studies used the International Restless Legs Syndrome Study Group questionnaire for the diagnosis of RLS, and one study used a single item to assess RLS.

Prevalence of Sleep Disorders Following Stroke or TIA

Sleep-Disordered Breathing

For the acute phase, the pooled prevalence of mild SDB was 66.8% (95% CI, 63.8–69.7), moderate SDB was 50.3% (95% CI, 41.9–58.7), and severe SDB was 31.6% (95% CI, 24.9–39.1; Figure 2A). For the subacute phase, 16, 13, and 9 included studies reported that the pooled prevalence of mild SDB was 65.5% (95% CI, 58.9–71.5), moderate SDB was 44.3% (95% CI, 36.1–52.8), and severe SDB was 36.1% (95% CI, 22.2–52.8; Figure 2A). For the chronic phase, the summary prevalence of mild SDB was 66.2% (95% CI, 58.6–73.1), moderate SDB was 33.1% (95% CI, 24.8–42.6), and severe SDB was 25.1% (95% CI, 10.9–47.6; Figure 2A).

Insomnia

Overall, the pooled prevalence was 40.7% (95% CI, 31.8–50.3) for the acute phase, 42.6% (95% CI, 31.7–54.1) for the subacute phase, and 35.9% (95% CI, 28.6–44) for the chronic phase. Among these, studies reporting insomnia against standard references had a pooled prevalence of 32.5% (95% CI, 17.4–52.5) in the acute phase, 34.8% (95% CI, 20.6–52.4) in the subacute phase, and 37.1% (95% CI, 32.5–41.9) in the chronic phase. For self-reported insomnia symptoms, the summary prevalence was 47.1% (95% CI, 33.5–61.1) in the acute phase, 50.4% (95% CI, 38.4–62.3) in the subacute phase, and 36.9% (95% CI, 27.2–47.9) in the chronic phase (Figure 2B).

Periodic Leg Movement Sleep Disorders

Ten studies reported the prevalence of PLMS. All studies included survivors of stroke with mild to moderate severity. The pooled prevalence in the acute phase was 32.0% (95% CI, 7.4–73.5), 27.3% (95% CI, 11.6–51.7) in the subacute phase, and 48.2% (95% CI, 33.1–63.5) in the chronic phase (Figure 2C).

Restless Leg Syndrome

RLS prevalence was estimated in the acute phase after stroke in 13 studies and in the chronic phase in 2 studies. The summary prevalence of RLS was 10.4% in the acute phase (95% CI, 6.4–16.4) and 13.7% (95% CI, 2.3–51.8) in the chronic phase (Figure 2D).

Heterogeneity Among Included Studies

As seen in Table VIII in the Data Supplement, considerable heterogeneity was identified among the included studies (all $P<0.001$).

Subgroup and Metaregression Analyses

Sleep-Disordered Breathing

In the acute phase, age was positively associated with the pooled prevalence of mild SDB (B=0.04; $P=0.009$). The studies that included patients with comorbidities had a higher pooled prevalence of mild SDB than did those without comorbidities ($P=0.009$, Table IX in the Data Supplement). Age, the percentage of men in the study, body mass index, the country in which the study was conducted, comorbidities, and smoking were not significant moderators of prevalence in terms of moderate and severe SDB.

In the subacute phase, the studies that included patients with comorbidities yielded a higher prevalence of mild and severe SDBs than did those without comorbidities ($P=0.01$ and 0.04, respectively).

In the chronic phase, the studies including patients with comorbidities yielded a higher prevalence of mild and moderate SDBs than did those without comorbidities ($P=0.02$ and 0.002, respectively). Studies conducted in Eastern countries yielded a higher prevalence of severe SDB than did those conducted in Western countries ($P=0.009$).

Insomnia

In the studies assessing insomnia, age, percentage of men in the study, the country in which the study was conducted, anxiety, depression, pain, comorbidities, and diagnosis were not significantly associated with insomnia prevalence (Table X in the Data Supplement).

Periodic Leg Movement During Sleep

In the subacute phase, advancing age was correlated with the pooled prevalence of PLMS (B=2.99; $P<0.001$; Table X in the Data Supplement). The studies, including patients with comorbidities, had a higher prevalence of PLMS than did those without comorbidities ($P=0.01$). Additionally, the studies including patients with the smoking habit exhibited a higher prevalence of PLMS than in patients without the smoking habit ($P=0.01$). In the chronic phase, only advancing age was positively associated with the pooled prevalence of PLMS (B=0.07; $P<0.001$).

Restless Leg Syndrome

As shown in Table X in the Data Supplement, the percentage of men and body mass index correlated with the summary prevalence of RLS in the acute phase (B=–0.06 and 0.30, respectively; $P=0.02$ and 0.01, respectively). Studies conducted in Western countries yielded a higher prevalence than did those conducted

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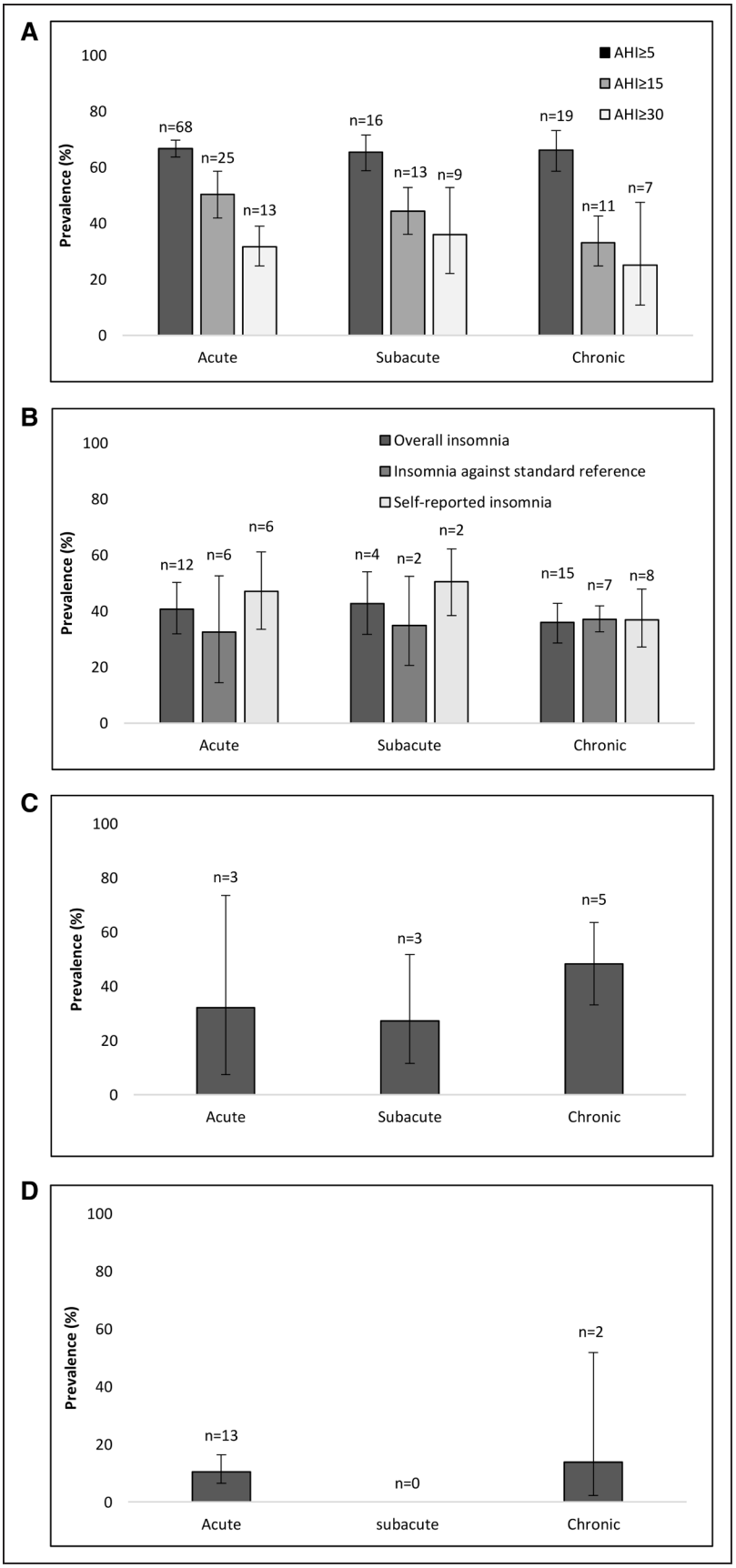

Figure 2. Prevalence of sleep disorders with 95% CI, including (A) sleep-disordered breathing, (B) insomnia, (C) periodic leg movement sleep disorder, and (D) restless leg syndrome following stroke or transient ischemic attack during acute, subacute, and chronic phases.

AHI indicates apnea-hypopnea index; and n, number of studies.

in Eastern countries ($P<0.001$). Because only 2 studies in the chronic phase were included, we did not perform moderator and metaregression analyses.

Publication Bias

The results with regard to publication bias are provided in Table XI in the Data Supplement. No publication bias was identified, except for mild SDB in the acute and chronic phases ($P=0.01$ and 0.004, respectively), insomnia in the chronic phase ($P=0.03$), and RLS in the acute phase ($P=0.01$).

Assessment of Methodological Quality of Included Studies

The results of the Critical Appraisal Checklist of included studies are listed in Table XII in the Data Supplement.

DISCUSSION

In the present meta-analysis, we examined the prevalence of SDB, insomnia, PLMS, and RLS in acute, subacute, and chronic phases following stroke or TIA. Previous meta-analyses have reported the prevalence of SDB and insomnia, but not PLMS and RLS, following stroke or TIA.[15,16] However, 2 meta-analyses of the prevalence of SDB did not further identify potential sources of high heterogeneity, thus limiting the internal validity of findings.[15,16] Furthermore, a meta-analysis[17] considered the prevalence of insomnia at different stroke phases as a whole because the number of studies included were few, which may have underestimated insomnia prevalence after stroke or TIA. Because we had a larger study sample, applied rigorous methodology, explored potential sources of heterogeneity, and analyzed prevalence rates according to different phases following stroke or TIA, our findings should be considered credible.

The overall prevalence of mild, moderate, and severe SDB was gradually decreased in acute, subacute, and chronic phases, respectively. For example, in the acute phase, mild, moderate, and severe SDB prevalence rates gradually decreased from 66.8% to 50.3% to 31.6%, respectively. The downward trend was also observed in subacute (65.5%, 44.3%, and 36.1%, respectively) and chronic phases (66.2%, 33.1%, and 25.1%, respectively). In other words, the prevalence of mild SDB did not substantially change over time, whereas the prevalence of moderate and severe SDB appeared to decrease from acute to chronic phases, which is in line with previous reports.[15,18,19] The present study could not elucidate the cause of moderate and severe SDB prevalence reduction over time. Improvement in brain damage and chest function, decreased supine position duration, and recovery from complications related to stroke may be attributed to the observed phenomenon.

Consistent with a previous publication,[15] our findings based on an additional 46 articles revealed that the prevalence of mild, moderate, and severe SDB was much higher in stroke survivors than in the general population (mild: 9%–38% and moderate to severe: 6%–17%).[20] However, the actual prevalence of SDB was likely to be misestimated because some of the included studies did not exclude participants with sleep disorders before stroke. The associations between SDB and stroke are complex.[21,22] Accumulating evidence indicates that stroke can cause (or worsen preexisting) SDB through different mechanisms, such as damage to brain stem respiratory drive centers (eg, medullary lesion),[23] hypoglossal nerve dysfunction,[24] disturbed coordination of the upper airway, reduction of voluntary chest movement on the paralyzed side,[22] and prolonged supine position.[25] These may also play critical roles in the development of SDB after stroke or TIA.

The findings of our study revealed that age and comorbidities, which were also considered stroke contributors, were associated with the prevalence of SDB.[26] Decreased size of the upper airway lumen, pharyngeal airway lengthening, and change in the structures surrounding the pharynx[27–29] in older patients might be attributable to this phenomenon. Comorbidities related to sleep apnea (eg, chronic heart failure)[30] may also contribute to an increased prevalence of SDB, particularly central sleep apnea. We observed that studies conducted in Eastern countries[31–33] had a higher prevalence of severe SDB in the chronic phase than those conducted in Western countries,[34–36] which presents a different perspective based on our existing knowledge. We did not find the role of body mass index and measure of obesity in the observation. Differences in the polysomnography setting may be a possible reason because we found that all included studies conducted in Eastern countries adopted in-laboratory polysomnography, whereas studies conducted in Western countries used home-based polysomnography. Moreover, unattended portable monitoring is not recommended in the diagnosis of obstructive sleep apnea in adult patients with major comorbidities, owing to inadequate accuracy of such monitoring.[37]

In contrast to the previous meta-analysis[17] that estimated the overall prevalence of insomnia after stroke or TIA, our findings examined the pooled prevalence according to different phases after stroke and various diagnostic methods. The prevalence of insomnia was found to be higher in patients with stroke or TIA than in the general population (6%–21%).[38] Although the cause of insomnia after stroke or TIA is not well understood, high stroke severity,[39–41] lesion location,[42,43] and negative emotions (ie, depression and anxiety) might play a major role in the higher prevalence of insomnia following stroke or TIA.[44] In accordance with a prior work,[45] a slightly downward trend of overall insomnia prevalence was observed from

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the subacute to chronic phases (42.6%–35.9%, respectively), supporting that insomnia is likely to subsequently recover over time following stroke or TIA. Neuronal regeneration and functional recovery after stroke may consolidate sleep continuity,[46] resulting in the improvement of insomnia.

Compared with the prevalence of PLMS in the general population (3.9%–28.6%),[47–50] stroke survivors were found to have a higher prevalence rate ranging from 27.3% to 48.2%. Possible mechanisms underlying the development of PLMS after stroke include white matter hyperintensities,[51] vascular brain damage,[52] and destructive brain lesions causing reticular formation on spinal pathways.[53] The pooled prevalence for PLMS after stroke or TIA exhibits an upward trend over time (32.0%–48.2%). Sleep consolidation may be attributed to the observation because we found that the prevalence of PLMS increased from the acute to the chronic phase, together with an expected improvement in insomnia. A consolidation in sleep continuity after the acute phase may result in more chances to produce a series of limb movements continuously.[52]

Age, presence of comorbidities, and smoking history were positively correlated with the prevalence of PLMS. PLMS can be found mostly in adults above 40 years of age.[54,55] Knowledge of potential mechanisms underlying this phenomenon is still limited; however, possible reciprocal influences between leg movements and the cyclic alternating pattern have been speculated.[56,57] In addition, evidence showed that Lewy body dementia was significantly correlated with PLMS in advancing age.[58] The association between comorbidities (eg, cardiovascular disease and renal disease) and elevated PLMS prevalence is not fully understood. Several reasons, such as sympathetic hyperactivity, peripheral vascular damage, and hypoxia, may partially explain the phenomenon in patients with cardiovascular diseases.[59] The increased risk of iron deficiency anemia was reported as a risk factor for elevated PLMS.[60] Patients with chronic kidney disease can be at particularly high risk of RLS; additionally, the positive effect of smoking on PLMS prevalence is potentially mediated by stimulatory dopamine effects triggered by nicotine intake, which is similar to that suggested for Parkinson disease.[61,62]

Analysis of patients after stroke yielded a slightly higher prevalence estimation of RLS (acute and chronic phases, 10.4% and 13.7%, respectively) compared with that of the general population (3.9% and 14.3%, respectively, based on the International Restless Legs Syndrome Study Group criterion),[50,63] reflecting that stroke may not be an aggravator of RLS. Coincidentally, a growing body of evidence has suggested RLS to be the first clinical manifestation related to cerebral infarction, such as brain stem and pontine infarction.[64–66] Additional studies are required to validate our findings.

Notably, women had a higher association with RLS prevalence after stroke. A growing body of evidence has suggested that RLS may appear for the first time during pregnancy, and parity increases the risk of RLS later in life.[67,68] Our findings are in line with those of previous studies[69,70] wherein increased body mass index was identified as a significant moderator of the prevalence of RLS. Possible explanations for the relationship between obesity and RLS include dysregulated dopamine metabolism, sympathetic hyperactivity, and chronic inflammation in the brain.[69,71] Racial difference is an independent risk factor related to the prevalence of RLS[72,73] because we found that studies conducted in Western countries yielded a higher prevalence than those conducted in Eastern countries. Our findings and currently available evidence suggest that RLS prevalence may vary depending on the specific population in question.

Limitations and Strengths

Several limitations of this meta-analysis must be acknowledged. First, some of the estimations of the prevalence of insomnia and RLS were obtained from a single question, which might result in biased reporting of intended sleep disorders. Second, because of the small number of included studies for the prevalence estimation of PLMS and RLS, our findings should be carefully interpreted. Additional investigations are warranted. Third, because only certain studies reported the exclusion of patients with sleep disorders before study enrollment, the effect of preexisting sleep disorders on our findings could not be avoided. Data on the prevalence of sleep disorders in African and Eastern populations, such as Russian and Indian populations, were limited. Fourth, we observed a statistical proof of publication bias in terms of mild SDB in acute and chronic phases, insomnia in chronic phase, and RLS in acute phase. However, in this meta-analysis, we applied a rigorous study methodology and included a large sample size for credibility.

Conclusions

We suggest that sleep disorders are highly prevalent in stroke survivors at different phases after stroke. Our findings indicate the clinical importance of early screening and treatment of sleep disorders following stroke or TIA. That is, sleep studies or sleep examinations should be performed earlier before or after stroke or TIA to provide primary or secondary preventive treatment. Additional prospective investigations that examine the prevalence and clinical effects of PLMS and RLS following stroke and TIA are required.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Tables I–XII
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