

Association between Insomnia and Risk of Stroke: A Systematic Review

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ABSTRACT

Background: Stroke is associated with high morbidity and mortality, straining the scarce healthcare resources. Therefore, stroke prevention becomes imperative. Insomnia and sleep disturbance may have a significant association with stroke due to its multifactorial causation. As studies regarding this are scarce. The present systematic review was conducted to assess the association between insomnia and the risk of stroke.

Method: Six case-control and prospective studies meeting the inclusion and exclusion criteria were included in the present systematic review. These studies were published in 2014 onwards. The studies included a total of 647368 patients. The studies were included after a thorough search of relevant databases like Embase, PubMed, ScienceDirect and Cochrane Library.

Results: A significant association was observed between insomnia and increased risk of stroke. A dose-response relationship was reported. The risk of stroke increased with an increase in the number of insomnia symptoms. The risk of stroke was also reported to increase with an increase in the duration of symptoms of insomnia. The risk was higher in younger individuals.

Conclusion: The present systematic review highlights the significant association between insomnia and stroke. It is of the essence as insomnia is a potentially modifiable risk factor. Thus, a screening programme for insomnia targeting young adults may be highly effective in the prevention of stroke.

Key-words: Insomnia, Ischemic stroke, Hemorrhagic stroke, Risk factors, Sleep disturbances, Stroke, Systematic review

INTRODUCTION

Stroke is a common neurological disorder with significant mortality and morbidity. It is the leading cause of disability and the second leading cause of death globally [1]. The associated disabilities include mobility disorders, problems with vision and speech, difficulty in swallowing and sexual dysfunction [2]. It is estimated that 1 in every 4 individuals will experience an episode of stroke in their lifetime [3]. Therefore, stroke prevention becomes imperative.

Sleep is a crucial part of daily activities and has been recognized as an important factor for long-term well-being [4]. Disturbances in sleep lead to insomnia and is a risk factor for stroke [5,6]. Insomnia may be characterized by difficulty falling asleep or maintaining sleep. Insomnia often leads to fatigue, irritability, mood changes, cognitive impairment and motor impairment. Insomnia has been recognized as the second most prevalent mental health disorder worldwide [7,8]. About 10% of the population worldwide is affected by insomnia, while 20% may experience occasional insomnia in their lifetime [9]. Thus, insomnia is a significant public health problem. Owing to the widespread distribution of insomnia, there has been a recent increase in interest in the association of insomnia with stroke. In addition to insomnia, other sleep disorders like sleep deprivation, lack of sleep and obstructive sleep apnea are also associated with

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increased risk of stroke [10]. Though the exact underlying mechanism is not fully understood, a multifactorial causation has been hypothesized. Insomnia directly influences the immune and autonomic nervous systems. It also dysregulates the hypothalamic-pituitary axis, resulting in hormonal imbalance and metabolic disturbances [7,11]. These are, in turn, found to negatively impact the cerebral circulation and increase the risk for stroke. It has been reported that shift work and sleep restriction reduce the non-rapid eye movement (NREM) sleep and may lead to increased risk of cardiovascular and cerebrovascular accidents [12,13]. Fragmented sleep has been linked to sympathetic hyperactivity leading to increased risk of stroke, especially ischemic stroke [14,15]. Oxidative stress and ensuing endothelial dysfunction may also lead to microvascular damage and increase the susceptibility to stroke [16]. Insomnia is a potentially modifiable risk factor with a multifactorial association with stroke. As the studies regarding this are scarce. The present systematic review

was conducted to evaluate the association between insomnia and stroke.

MATERIALS AND METHODS

Research Design- The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed during the study. As this systematic review did not involve human participants and no intervention was used, approval from the Institutional Ethics Committee and registration of the review in PROSPERO were not required.

Search Strategy- A thorough search was performed across all relevant electronic databases: PubMed, Embase, ScienceDirect, and the Cochrane Library. A Google search was also performed. The Medical Subject Headings (MeSH) keywords were used for insomnia, sleep quality, sleep initiation and maintenance disorder, stroke, cerebrovascular accident, and risk. The manual selection process is as per the flowchart in Fig. 1.

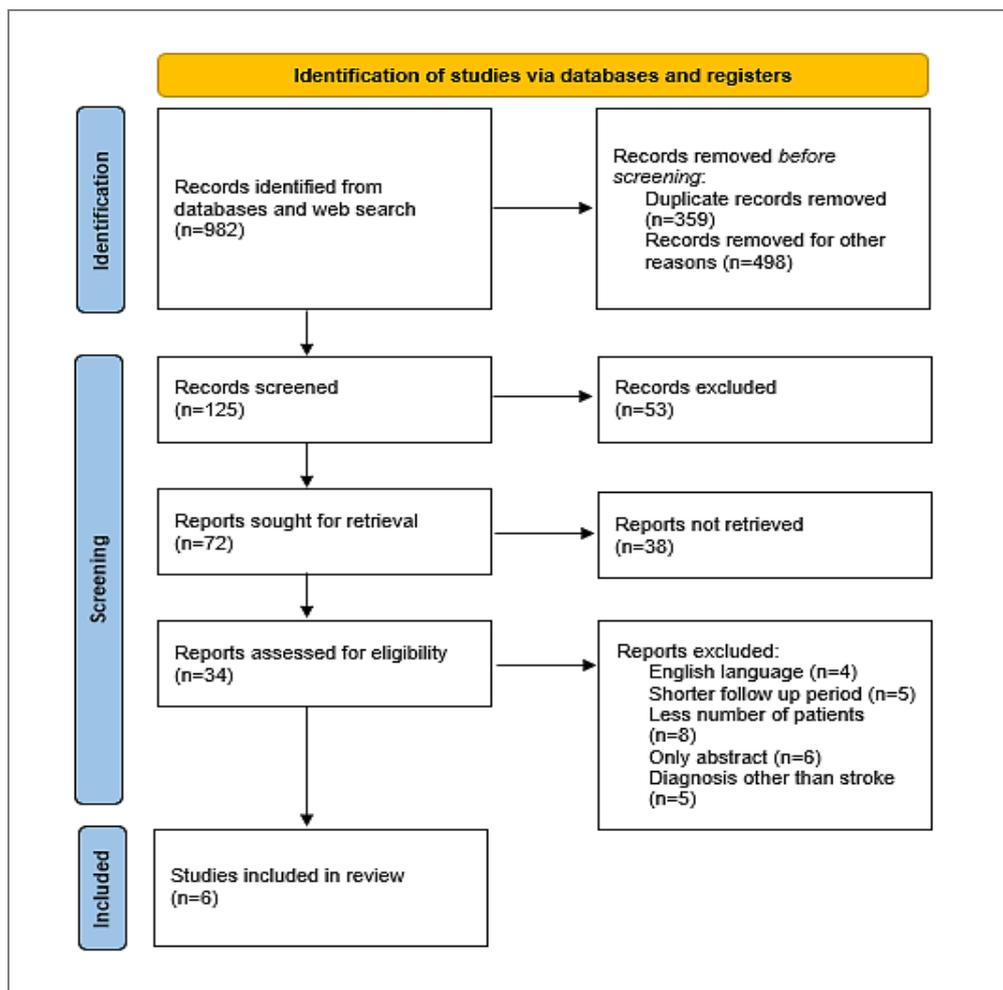


Fig. 1: PRISMA 2020 flow diagram

Inclusion criteria

- ✓ Studies involving patients more than 18 years of age.
- ✓ Studies involving patients of both genders.
- ✓ Studies involving patients with insomnia and assessing association with stroke.
- ✓ Prospective or retrospective cohort studies.
- ✓ Studies involving more than 100 patients.
- ✓ Studies published after 2010 (in the last 15 years).
- ✓ Studies with full-text publications.
- ✓ Studies having full-text article in English language.

Exclusion criteria

- ✓ Studies published more than 15 years ago.
- ✓ Studies with patients having transient ischemic attack.
- ✓ Studies that did not report hazard or odds ratio after adjusting for cofounders.

- ✓ Case reports, case series, randomized controlled trials and reviews.

RESULTS

A total of 982 records were retrieved following an extensive database search. 125 records were screened. Finally, 34 records were assessed for eligibility. Upon review of the inclusion and exclusion criteria, 28 records were excluded, and 6 studies were included in the systematic review. All the studies were published from 2014 onwards. There were three case-control studies with age- and gender-matched controls and three prospective cohort studies. A total of 647368 patients were included. The studies assessed the association between disturbances in various sleep characteristics and the risk of stroke. The findings are summarized in Table 1.

Table 1: Summary of the studies

Study	Year	Type of study	Study population	Findings
Wu <i>et al.</i> ^[17]	2014	Case control	85752 (Cases: 21438 and controls: 64314)	They reported that the risk of stroke was 54% higher in insomniacs as compared to controls [Adjusted hazard ratio: 1.54 (1.38-1.72)]. Subgroup analysis showed higher risk of 3-year cumulative incidence of stroke than in the remission group; p=0.02. Highest incidence rate ratio (8.06) was observed in young adults with insomnia (18 to 34 years).
Ao <i>et al.</i> ^[18]	2017	Case control	7044 (Cases: 1174 and controls: 5870)	They reported increased risk of stroke in patients with traumatic brain injury as compared to general population (5.54% vs 2.45%, respectively, p<0.01). The hazard ratio of stroke in patients with traumatic brain injury was 2.28 (1.70-3.06). When assessed for duration of insomnia, they reported increased risk of stroke with increased duration of insomnia symptoms [Hazard ratio for symptoms less than 3 months: 1.95 (1.05-3.62), hazard ratio for symptom duration of 3 to 12 months: 2.75 (1.73-4.37) and hazard ratio for symptom duration of 12 to 24 months: 2.66 (1.68-4.21)].
Zheng <i>et al.</i> ^[19]	2019	Prospective cohort	487200	They reported an overall increased risk of stroke in patients having insomnia [Hazard ratio: 1.04 (1.02-1.07)]. They also observed a dose-response relationship with increased risk of stroke with increase in number of symptoms of insomnia

				[Hazard ratio for 1 symptom: 1.01 (0.98-1.04); hazard ratio for 2 symptoms: 1.08 (1.04-1.12); hazard ratio for 3 symptoms: 1.10 (1.02-1.19)].
Zhou <i>et al.</i> ^[20]	2020	Prospective cohort	31750	They observed increased risk of stroke in patients with poor sleep quality. They estimated 29% higher risk of total stroke, 28% higher risk of ischemic stroke and 56% higher risk of hemorrhagic stroke in patients with poor sleep quality. Risk of stroke was significantly higher in patients with poor sleep quality [Hazard ratio: 1.82 (1.22-2.48)].
McCarthy <i>et al.</i> ^[21]	2023	Case control	4496 (Cases: 2238 and controls: 2258)	They reported increased risk of stroke with various symptoms of poor sleep in cases as compared to controls [Odds ratio for short sleep: 3.15 (2.09-4.76); odds ratio for long sleep: 2.67 (1.89-3.78); odds ratio for poor sleep quality: 1.52 (1.32-1.75), odds ratio for difficulty in getting sleep: 1.32 (1.13-1.55), odds ratio for difficulty in maintaining sleep: 1.33 (1.15-1.53), odds ratio for snoring: 1.91 (1.62-2.24), odds ratio for breathing cessation: 2.87 (2.28-3.60)]. They also reported higher risk of stroke with obstructive sleep apnea score of 2-3 [odds ratio: 2.67 (2.25-3.15)] and with 5 or more sleep symptoms [odds ratio: 5.38 (4.03-7.18)].
Sawadogo <i>et al.</i> ^[22]	2023	Prospective cohort	31126	In this questionnaire-based study, the risk of stroke was higher in patients with “constantly low symptoms” and “constantly high symptoms” [Hazard ratio: 1.15 (1.00-1.32) and hazard ratio: 1.42 (1.22-1.64), respectively] as compared to patients with “constantly no symptoms”. They reported that every 1 unit increase in the symptoms of insomnia led to 7% higher risk of stroke [Hazard ratio: 1.07 (1.04-1.09)]. They reported increased risk of stroke with an increase in the number of insomnia symptoms [Hazard ratio for 1 to 4 symptoms: 1.16 (1.02-1.33) and hazard ratio for 5 to 8 symptoms: 1.51 (1.29-1.77); p<0.01]. The increased risk was higher in patients aged less than 50 years than in older individuals [Hazard ratio: 3.84 (1.50-9.85) and hazard ratio: 1.38 (1.18-1.62), respectively].

An increased risk of stroke was noted with various characteristics of disturbed sleep and insomnia. There was a dose-response relationship with increasing risk of stroke with an increase in the number and duration of

insomnia symptoms. The risk was higher in younger individuals. The higher risk of stroke with insomnia was also noted in the subgroup of patients with traumatic brain injury.

DISCUSSION

In the present review, insomnia was found to be significantly associated with the risk of stroke. The risk was significantly higher in younger individuals than in older individuals. The underlying pathophysiologic mechanisms by which insomnia and sleep disturbances cause stroke is multifactorial. Also, insomnia and stroke have a bidirectional relationship.

Insomnia increases serum cortisol levels by increasing corticotropin-releasing hormone secretion [23]. Cortisol is proinflammatory, and elevated serum levels activate the inflammatory cascade and induce systemic inflammation, as indicated by increased levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) [24,25]. These pro-inflammatory cytokines promote atherosclerosis and cause endothelial dysfunction. Both of these mechanisms compromise the microvasculature in the brain and lead to a higher risk of stroke.

Insomnia also leads to activation of the sympathetic nervous system while inhibiting the parasympathetic nervous system. As a result, there is an increase in heart rate, blood pressure and peripheral resistance. Activation of the sympathetic nervous system also increases serum cortisol levels and norepinephrine levels, leading to elevated body temperature. All these abnormalities together lead to a state of physical hyperarousal [26,27]. This is a significant risk factor for cerebrovascular and cardiovascular accidents.

Insomniacs have been known to have metabolic abnormalities. It may be caused either directly by insomnia interfering with ghrelin and leptin, leading to increased appetite, weight gain, obesity, and insulin resistance [28-30], or indirectly through the inflammatory cascade [31]. Obesity, dyslipidemia and insulin resistance are risk factors for stroke.

Insomnia is also known to impair neurovascular coupling. The microvasculature in the brain ensures a continuous supply of glucose and oxygen despite fluctuations in blood pressure. In addition to this autoregulation system, local cerebral blood flow also responds to changes in neuronal activity, thereby matching the additional energy and oxygen demands during increased neuronal activity. This neurovascular coupling is impaired in insomniacs, leading to susceptibility to stroke, especially ischemic stroke [32]. This is further aggravated by endothelial dysfunction, which may result from the

complex interaction between ongoing inflammation and sympathetic nervous system activation [33]. There is an increase in oxidative stress leading to the formation of reactive oxygen species (ROS). This damages endothelial cells, promoting apoptosis, while also reducing nitric oxide (NO) availability through endothelial nitric oxide synthase uncoupling. The reduced bioavailability of NO compromises the endothelial-dependent vasodilation [33,34].

Stroke has also been known to cause insomnia [35,36,37] though the mechanisms are poorly understood. Stroke may directly damage the sleep centre in the brain, leading to disruption of the circadian rhythm and sleep disturbances. Thus, insomnia and stroke have a bidirectional relationship, which may lead to a vicious cycle and affect the functional recovery after stroke while negatively impacting cognition and mortality.

CONCLUSIONS

The present systematic review shows a significant association between insomnia and the risk of stroke. There is a dose-response relationship with respect to the number of symptoms of insomnia and also with the duration of insomnia, suggesting a cumulative effect and the importance of early intervention in the prevention of stroke. The younger adults with insomnia have a higher risk of stroke as compared to older individuals. This suggests the importance of targeting young adults in the screening programme. Accordingly, it is recommended that guidelines be devised for screening for insomnia and early intervention for prevention of stroke, though further large-scale, multicentric studies may be needed to understand the underlying pathophysiology of the vicious cycle of insomnia and stroke.

CONTRIBUTION OF AUTHORS

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