



Clinical Review

Insomnia as risk factor for brain, mental and general health consequences: an umbrella systematic review

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ARTICLE INFO

Keywords:

Insomnia
Brain-health
Dementia
Stroke
Depression
Suicide
Injuries
Hospitalization
Epidemiology
Cohort studies
Systematic review

ABSTRACT

Sleep quality is a determinant of health, and insomnia could be a risk factor for brain health. We searched MEDLINE and EMBASE (last search August 2025) to identify systematic reviews with meta-analysis (SMRAs) that evaluated insomnia as a predictive factor of dementia, stroke, depression, suicide, death, occupational injuries, and hospitalization. Sixteen SMRA were included, and three additional original systematic reviews were conducted for stroke, occupational injuries and hospitalization, as no published SMRAs were found on these topics. SMRAs consistently identified insomnia as a predictor of dementia, depression, suicide, while death was not associated with this disorder. Our two original SMRAs revealed that insomnia is a predictor of stroke (9 studies, 1,343,164 participants, HR = 1.26, 95%CI 1.05-1.53) and hospitalization for any reason (5 studies, 517,620 participants, OR = 1.28, 95%CI 1.14-1.43). With regard to occupational injuries, it was not possible to perform a meta-analysis of the results of the two studies retrieved (143,942 participants). Although an association was found with unintentional fatal injuries and with commuting injuries, data should be considered insufficient to draw a conclusion on this outcome. This work contributes to better defining the association between insomnia and the key descriptors of brain health and possible links to general health.

1. Introduction

Insomnia is defined by disturbed sleep initiation and maintenance, and impairment of daytime functioning despite adequate opportunity and circumstances for sleep. The single category "chronic insomnia disorder", according to the International Classification of Sleep Disorders 3rd edition (ICSD-3 and ICSD-3 TR) [1], groups together the previously defined "primary" and "secondary" insomnia distinctions. Chronic insomnia conditions as a whole, regardless of the existence of comorbidities, share an imbalance in sleep-wake regulation with the development and perpetuation of a hyperarousal state in sleep, possibly due to a genetic component that predisposes to a maladaptive reaction to stressful life events [2].

Insomnia is the most common sleep disorder among adults [3]. Up to half of this population experiences transient insomnia [3], while the prevalence of chronic insomnia (according to international diagnostic criteria) is estimated at approximately 22% for the general population [4]. Remarkably, the risk is about 50% higher in females than in males [4] and the prevalence reaches nearly 30% in older adults [5]. From a socio-economic perspective, this last observation is particularly relevant considering the aging population in Europe and many other countries worldwide [6]. In addition, vulnerable people due to social restrictions [7,8], environmental emergencies [9] and wartime events [8] are particularly prone to developing sleep problems, with insomnia afflicting up to about 70% of at-risk populations. In comparison to good sleepers, people with insomnia have a double risk of two or more co-existing medical conditions [10]. Insomnia is more frequently

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<https://doi.org/10.1016/j.smr.2026.102372>

Received 10 April 2026; Received in revised form 7 August 2026; Accepted 3 September 2026

Available online 7 September 2026

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Abbreviations

HR =	Hazard Ratio
OR =	Odds Ratio
RR =	Risk Ratio
SMRA =	Systematic reviews with meta-analysis

Table 1

Scope of the umbrella systematic review according to the PECOS (Population, Exposure, Comparator, Outcomes, Study design) framework, definitions and operative inclusion criteria.

PECOS element	Definition	Operative inclusion criteria
Population	General population of all ages	Participants in primary studies conducted on general or clinical populations, included in systematic reviews in which the proportion of studies on general populations is greater than that of studies on clinical populations
Exposure	Insomnia disorder considering elements of the ICSD-3 definition: (1) a report of sleep initiation or maintenance problems, (2) adequate opportunity and circumstances to sleep, and (3) daytime consequences. The ICSD-3 duration criterion for chronic insomnia disorder is 3 months	Insomnia as a whole or as a combination of at least two components of the ICSD-3 definition (sleep initiation, maintenance problems, daytime consequences). The duration criterion for chronic insomnia was not required as inclusion criterion, but considered when specified. Tool for measurements: - Clinical diagnosis recorded in clinical charts - Clinical diagnosis recorded in administrative databases - Self-administered questionnaires for insomnia - Interview
Comparator	Absence of insomnia disorder	
Outcomes	Brain health - chronic: dementia - acute: stroke Mental health - depression - psychosis - suicide General health - death - occupational injuries - hospitalization	Tool for measurements: - Clinical diagnosis recorded in clinical charts - Clinical diagnosis recorded in administrative databases - Self-administered questionnaires
Study designs	Systematic reviews with meta-analysis of cohort studies	Systematic reviews with meta-analysis, including studies of at least 100 of subjects and with the design of historical or prospective cohorts or historical cohorts from health administrative databases comparing exposed and non-exposed subjects

reported in people with cancer, pulmonary, and cardiovascular disease [11–13]. Also, insomnia is more frequent among those experiencing psychiatric disorders [14,15] and many neurological disorders [16–19].

Moreover, an increasing amount of research [20–23] supports recognition of insomnia as a bidirectional contributor to disease pathophysiology rather than merely a secondary symptom. Disruption of sleep–wake regulatory networks, neuroinflammation, altered neurotransmitter signalling, and neurodegenerative processes promote chronic hyperarousal and impaired sleep continuity [20]. Conversely,

chronic insomnia may exacerbate neurodegenerative processes through impaired glymphatic clearance [21], increased accumulation of neurotoxic proteins [22], and sustained inflammatory activation [23], contributing to cognitive decline and poorer clinical outcomes. These reciprocal mechanisms highlight insomnia as a potential therapeutic target in neurological disease.

Consequently, insomnia is considered a close determinant of mental and physical health, as defined by WHO [24,25], and sleep quality is one of the key factors for preserving brain health [24,26,27]. Recently, WHO expanded the concept of mental health to that of “brain health” [24], which encompasses the state of cognitive, sensory, socio-emotional, behavioural and motor functions, as well as their interactions and adaptation to a person's individual context.

The treatment of insomnia is becoming increasingly multifaceted (both in terms of behavioural and pharmacological approaches) [28]. Cognitive behavioural therapy for insomnia (CBT-I), the first-line treatment for chronic insomnia [28,29], improves cognitive and emotional functioning and is associated with normalization of functional brain network activity. Dual orexin receptor antagonists [30] may offer an alternative for patients who do not respond to CBT-I or who are unwilling to complete it, as well as in cases where other pharmacological treatments are inappropriate (for example, in the presence of cognitive impairment or pulmonary disease) [31], or in elderly adults [32]. By restoring sleep continuity and reducing hyperarousal, insomnia treatment may also mitigate neuroinflammation, enhance glymphatic clearance, and facilitate the removal of neurotoxic metabolites, although evidence for long-term neuroprotective or disease-modifying effects remains preliminary [22]. Hence, it is important to raise awareness of the importance of treating it in both healthy individuals and those with underlying medical conditions.

Given the wide range of recent studies that points toward insomnia's multi-dimensional burden, an in-depth critical, systematic analysis to assess the entire impact on health is warranted [6]. Such insights could also provide duly needed evidence-based recommendations for policy-makers, patients' organizations, and opinion leaders.

The aim of this umbrella systematic review is to provide a comprehensive description of the burden of insomnia (see Table 1) on a wide basket of representative descriptors of brain, mental and physical health in the general population.

2. Methods

This systematic umbrella review follows the methodological steps proposed by Belbasis et al. [33], applying the “phenome wide approach” (associations of a risk factor with any disease), and the reporting rules of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist [34]. The protocol is registered with PROSPERO database (CRD42021285454).

2.1. Research question and inclusion and exclusion criteria

Under the auspices of the European Academy of Neurology (EAN), a group of experts in sleep medicine, neurology and psychiatry was appointed. By means of an informal iterative process, the group devised the research question according to the PECOS (Population, Exposure, Comparator, Outcomes, Study design) framework.

Inclusion criteria of studies are reported in Table 1. The exposure factor is insomnia, and studies were eligible if they considered insomnia (both as symptom or as disorder) when defining it as a whole (for example, based on the clinical diagnosis reported in medical records or recorded in administrative databases) or when they defined it as a final diagnosis when they assessed at least two of the three components of the ICSD-3 definition (sleep initiation, maintenance problems, daytime consequences). The criterion of chronic insomnia duration was not required as an inclusion criterion, but it was taken into account if specified.

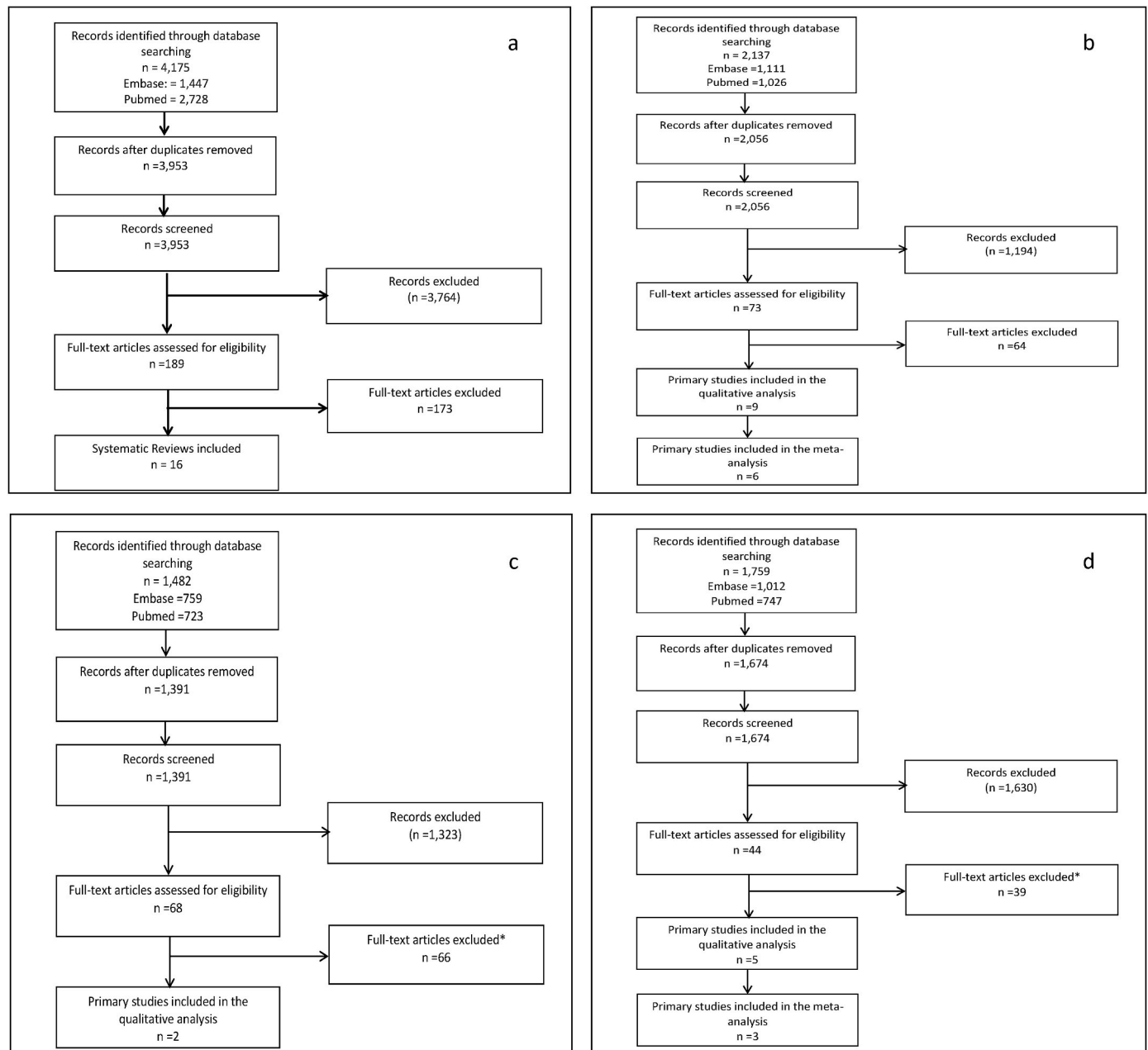


Fig. 1. PRISMA flow diagram of the results of the search a) for systematic reviews on outcomes (dementia, depression and psychosis, suicide, death) associated to insomnia; b) for primary study on stroke as outcome of insomnia; c) for primary study on occupational injury as outcome of insomnia; d) for primary study on hospitalization as outcome of insomnia. *For the reasons for exclusion see the online supplement material.

The comparison group consisted of subjects without insomnia from the same cohort or from a parallel cohort from the general population (see the eligible primary study designs below).

With regard to the selection of outcomes, the authors intended to include those falling within the conceptual framework of brain and mental health, as defined by WHO [24,25], as well as others related to overall health (see <https://www.who.int/data/gho/data/indicators>). Following discussions held during several online meetings, the final list included the most representative acute and chronic conditions (stroke and dementia, respectively) related to brain health, as well as depression and suicidal behaviour with regard to mental health. In addition, from among those proposed by the Global Health Observatory, mortality, hospitalization and occupational injuries were selected as general health indicators potentially related to insomnia. Other possible outcomes (anxiety, chronic headache, school achievements, job performance,

quality of life, economic consequences) were discussed but eventually excluded.

We included systematic reviews with meta-analysis (SRMA) where the unit of analysis are cohort studies. Possible designs could be retrospective or prospective clinical cohorts, and also historical cohorts from health administrative databases comparing (matched or unmatched) exposed and non-exposed subjects. We excluded systematic reviews not performing a meta-analyses and systematic reviews including cross-sectional and case-control design studies. In case of topics not covered by a SRMA we performed an original SRMA with the same inclusion criteria for primary studies.

2.2. Systematic literature search and study selection

We applied a step-wise hierarchical approach: at first, possible SRMA

Table 2

Systematic Reviews with meta-analysis including cohort studies on insomnia as risk for brain health, mental health, general health consequences.

Author, Year (last search update) AMSTAR quality	No of studies and participants	Length of follow-up (range)	Outcome	Risk in case of insomnia (95% CI)	Quality of included studies (NOS)	Methodological notes
de Almondes 2016 [37] (2015) Low	5 studies 36,005 participants	2-8 years	Dementia	5 studies adj OR 1.53 (1.07-2.18)	4 studies: 7 point score 1 study: 5 point score	Not specified the definition of insomnia Risk of primary studies adjusted Significant heterogeneity; modest evidence for publication bias
Shi 2018 [38] (2016) Low	9 studies 179,738 participants mean age range 50-79 years	2-40 years	Dementia	9 studies adj RR 1.17 (0.95-1.43)	7 studies: score ≥ 7 2 studies: score < 7	Insomnia definition included all dimensions
			Alzheimer disease	3 studies adj RR 1.51 (1.06-2.14)		Risk of primary studies adjusted
			Vascular dementia	3 studies adj RR 1.13 (0.94-1.35)		Significant heterogeneity; no evidence of publication bias
Xu 2020 [39] (2019) Low	23 studies 260,915 participants	16 studies < 10 years; 7 studies > 10 years	Dementia	23 studies adj RR 1.27 (1.16-1.39)	12 studies: score ≥ 7 11 studies: score < 7	Insomnia definition included all dimensions Risk of primary studies adjusted: results tend to be non-significant in strata of small-sample studies, studies with longer follow-up, studies adjusted for hypnotics Significant heterogeneity; possible publication bias.
Wang 2024 [40] (2023) Low	7 studies 3,115,942 participants mean age range 50-76 years	7-40 years	Alzheimer disease	7 studies adj RR 1.43 (1.17-1.74)	6 studies: score ≥ 7 1 study: score < 7	Insomnia definition included all dimensions Risk of primary studies adjusted Metaregression: not altered by age, gender, follow-up time, sample size. Adjusted risk Significant heterogeneity but sensitivity analysis did not modify results; risk of publication bias but fill-and-trim did not alter results
Ungvari 2025 [41] (2024) Critically low	39 studies	nr	Dementia	12 studies HR 1.36 (1.19-1.55)	nr	Not specified the definition of insomnia
			Alzheimer disease	8 studies HR 1.49 (1.27-1.74)		Not reported if risk of primary studies were adjusted
			Vascular dementia	4 studies HR 1.59 (1.01-2.51)		Significant heterogeneity; no evidence of publication bias
Our SRMA (2025)	9 studies 1,343,164 participants mean age range 48-61 years	4-19 years	Stroke	6 studies adj HR 1.27 (1.05-1.53)	2 studies: score = 8 1 study: score = 6 3 studies: score = 5	Insomnia defined by two to four dimensions Risk of primary studies adjusted Significant heterogeneity; no evidence of publication bias
Hertenstein 2023 [42] (2022) Low	11 studies 133,033 participants mean age range 20-60 years	53 months (mean)	Depression	11 studies OR 3.09 (1.78-5.36)	Moderate risk of bias for most studies (QUIPS)	Update of the Hertenstein 2019 ¹⁵ search Insomnia fulfilled DSM or ICSD criteria Not reported if risk of primary studies were adjusted Significant heterogeneity; not probable publication bias
Marino 2021 [43] (2019) Low	3 studies 9503 participants age < 25 years	12-72 months	Depression	3 studies adj OR 1.58 (1.14-2.18)	All with low risk of bias	Insomnia defined by two to four dimensions. Risk of primary studies adjusted Mixed population (clinical cohorts; general population cohorts) Significant heterogeneity; detected publication bias
Scott 2021 [44] (2020) Critically low	5 studies 7300 participants mean age range 14-20 years	> 1 year	Diagnosis of major mental disorders	5 studies OR 1.74 (1.41, 2.15)	Good to fair quality rating (8-14 point range out of 14)	Insomnia fulfilled ICSD criteria Mixed population (clinical; general) Not reported if risk of primary studies were adjusted Heterogeneity not reported; detected publication bias
Harris 2020 [45] (2019) Critically low	42 studies all ages (29.5% below 18 years)	11 years (median)	Suicide death	8 studies OR 1.54 (1.04-2.29)	Not reported	Not specified the definition of insomnia. Not reported if risk of primary studies were adjusted
		1 year (median)	Suicide attempt	16 studies OR 1.78 (1.38-2.29)		Mixed population (clinical cohorts; general population cohorts)
		1 year (median)	Suicide ideation	31 studies OR 2.10 (1.83-2.41)		Significant heterogeneity; no evidence of publication bias
Liu 2020 [46] (2019) Critically low	41 studies 698,829 participants mean age range 14.6-74.9 years	8.7 years (median)	Suicide death	8 studies d = 0.30 (0.20-0.41)	Not reported	Not specified the definition of insomnia. Not reported if risk of primary studies were adjusted
		2 years (median)	Suicide attempt	13 studies d = 0.38 (0.15-0.61)		Meta-analysis estimates with weighted effect (Cohen's d) Significant heterogeneity; possible publication

(continued on next page)

Table 2 (continued)

Author, Year (last search update) AMSTAR quality	No of studies and participants	Length of follow-up (range)	Outcome	Risk in case of insomnia (95% CI)	Quality of included studies (NOS)	Methodological notes
		10.5 months (median)	Suicide ideation	22 studies d = 0.45 (0.32-0.58)		bias; after adjustment of small study effect not substantial modification of results
Ge 2019 [47] (2018) High	29 studies 1,598,628 participants mean age range 43-87 years	2.9 months-20 years	Death	12 studies adj HR 1.07 (0.98-1.17)	Moderate certainty (GRADE)	Insomnia as disorder Risk of primary studies adjusted (not assessed the role of sleeping drugs) Significant heterogeneity; no evidence of publication bias
Lovato 2019 [48] (2017) Moderate	17 studies 36,938,981 individuals mean age range 45-74 years	2.2-28 years	Death	13 studies adj HR 1.07 (95%CI 0.96-1.19)	Nr	At least one symptom of insomnia, frequent and ongoing Risk of primary studies adjusted; studies that adjust for the use of hypnotic medications reported a lower mortality than studies that did not Significant heterogeneity; possible publication bias
Our SRMA (2025)	5 studies 517,620 participants mean age range 55-70 years	1-16 years	Hospitalization	3 studies adj OR 1.28 (1.14-1.43)	4 studies 7 1 study 6	At least two symptoms of insomnia Risk of primary studies adjusted; 1 study adjusted for the use of sleeping medications No heterogeneity; publication bias not assessable

were searched. Then, in the case of absence of SRMA or topics not covered by a SRMA, primary studies were searched. Published studies were identified from the National Library of Medicine's MEDLINE database and Elsevier's EMBASE database. Specific search strategies were launched for each outcome using a combination of exploded terms and free text, including concepts regarding insomnia and the outcomes (see the online supplement material for the detailed search strategies). All abstracts or full papers were reviewed independently by two TF members, to identify potentially relevant studies and to assess studies for inclusion.

2.3. Data extraction, assessment of quality of studies, statistical analysis

Two independent researchers extracted the data; in the case of discrepancies, the final decision was that of a third researcher. From each eligible article, we recorded the first author, journal, year of publication, examined outcomes and number of studies included. We also extracted the study-specific effect sizes along with the corresponding 95% confidence intervals (CI) and the number of cases in each study for each association. Whenever the sample sizes were not available through the meta-analysis, we retrieved the original reports on primary studies to record them.

The quality of evidence of each study was classified according to topic domain and type of publication: SRMA were assessed using the AMSTAR checklist [35], primary studies the Newcastle-Ottawa Scale [http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp], a tool that considers three domains (Selection, Comparability, Outcomes) and provides a rating from 0 to 9, with higher scores indicating better study quality.

For each meta-analysis, we reported the summary effect size and its 95% CI and the specific effect model applied. Between-study heterogeneity was assessed by the I² metric. We assessed whether there was evidence for small-study effects (possible publication bias) with the regression asymmetry test proposed by Egger et al. [36]. A P value less than 0.10 with a more conservative effect in the largest study than in random-effects meta-analysis was judged to be evidence for small-study effects. In case of original meta-analysis a random-effects model was applied and statistical analyses were performed with STATA version 16.0.

3. Results

A first search was performed between 2022 and 2023. An updated search was performed in August 2025. The search of systematic reviews yielded a total of 3953 records. The search for primary studies on topics not covered by systematic reviews yielded a total of 2056 records for stroke, 1391 for occupational injuries and 1647 for hospitalization. The number of studies evaluated in full text for possible inclusion and those and meeting the inclusion criteria are reported in the PRISMA flow charts (Fig. 1).

4. Insomnia and risk of dementia

4.1. Results of literature search

Five SRMA (see Table 2), four rated of low quality and one of critically low quality, were retrieved [37–41]. Cohort or administrative database studies from 3 continents (North America, Asia, Europe) were included. The total number of studies ranged from 5 to 39, the total number of participants from 36,005 to 3,115,942, the duration of follow-up from 2 to 40 years. Insomnia criteria, including all dimensions, were defined in three SRMA. None of the five SRMA considered chronic insomnia (lasting 3 months) or other time periods as a criterion for the duration of insomnia.

4.2. Overview of the evidence

Three SMRA [37,39,41] found insomnia as predictor for any cause of dementia (OR 1.53, 95% CI 1.07-2.18; RR 1.27, 95% CI 1.16-1.39; HR 1.36 95% CI 1.19–1.55). A fourth SMRA [38] did not find an association (RR 1.17 95% CI 0.95-1.43). Three SMRA [38,40,41] found a risk for Alzheimer disease (RR 1.51, 95% CI 1.06-2.14; RR 1.43, 95% CI 1.17-1.74; HR 1.49 95% CI 1.27–1.74). Two SMRA [38,41] reports contrasting results about the risk of vascular dementia (RR 1.13, 95% CI 0.94-1.35; HR 1.59, 1.01–2.51). The majority of these results stem from primary studies with adjustment for confounding factors, however those controlled for the use of hypnotic medications tended to be non-significant [39].

Table 3
primary studies published on insomnia as risk for stroke.

Author, Year	Country	Study type (design)	Participants	Insomnia concept and assessment	Baseline risk of insomnia	Outcome	Length of follow-up	Risk in case of exposure (95% CI)	Quality of the study#	Methodological notes
Elwood 2006 [49], ^a	UK	prospective cohort	1986; 100% M; age range 55-69 years	2 dimensions of insomnia (DIMS) Wisconsin sleep questionnaire	12%	ischaemic stroke (ICD-9-CM)	10 years	adjOR 1.75 (1.02-3.01)	4	Adjustement for demographic and main clinical factors
Wu 2014 [50]	Taiwan	retrospective cohort	85,752; 38% M; mean age 52.1 years	ICD-9-CM codes for insomnia	n.a.	all strokes (ICD-9-CM)	4 years	adjHR 1.54 (1.38-1.72)	8	Adjustement for demographic and main clinical factors
Hsu 2015 [51]	Taiwan	prospective case-cohort study	44,080; 43% M; mean age 48 years	ICD-9-CM codes for insomnia	n.a.	all strokes (ICD-9-CM)	10 years	adjHR 1.85 (1.62-2.12)	8	Adjustement for demographic and main clinical factors No increases of stroke in insomnia patients not using hypnotics
Gianfagna 2016 [52], ^a	Italy	prospective cohort	2277; 100% M; mean age 51 years	All dimensions of insomnia Jenkins Sleep Questionnaire	38%	all strokes (ICD-9-CM)	17 years	adjRR ^b 2.0 (1.2-2.9)	6	Adjustement for demographic and main clinical factors
Zheng 2019 [53]	China	prospective cohort	487,200; 41% M; mean age 51 years	All dimensions of insomnia Survey	16.4%	all strokes (ICD-9/ICD-10)	10 years	adjHR 1.04 (1.02-1.07)	5	Adjustement for demographic and main clinical factors
Sawadogo 2023 [57], ^a	USA	prospective cohort	31,126; M 43%; mean 61 years	All dimensions of insomnia Adapted Brief Insomnia Questionnaire	n.a.	all strokes (self reported)	9 years	adjHR 1.51 (1.29-1.77) (high insomnia sympt. vs no insomnia) adjHR 1.16 (1.02-1.33) (low insomnia sympt. vs no insomnia)	5	Adjustement for demographic and main clinical factors
Zhong 2023 [54]	China	prospective cohort	45,919; M 38%; mean age 53.5 years	2 dimensions of insomnia (DIMS) Questionnaire	16.1%	all strokes (ICD-10)	11 years	adjHR 1.17 (1.07-1.28)	6	Adjustement for demographic and main clinical factors
Guo 2024 [55]	UK	prospective cohort	502,383; 45,6% M; mean age 56 years	2 dimensions of insomnia (DIMS) Questionnaire	28%	all strokes (ICD-9/ICD-10)	13 years	adjHR 1.05 (1.01-1.11)	5	Adjustement for demographic and main clinical factors
Jung 2024 [56]	Korea	prospective cohort	8933; 47,3% M; mean age 52 years	Insomnia (clinical diagnosis)	16%	ischaemic stroke (physician diagnosis)	19 years	adjHR 1.13 (0.86-1.51)	5	Adjustement for not specified factors

DIMS = difficulty initiating or maintaining sleep.

Newcastle-Ottawa Scale (NOS).

^a not included in meta-analysis.

^b Rate Ratio calculated from the data in Appendix (Table S1) of the paper (Gianfagna et al., 2016).

5. Insomnia and risk of stroke

5.1. Results of literature search

No systematic review retrieved performed a meta-analysis of all possible eligible primary studies. Our original search found 9 eligible primary studies from 3 continents (North America, Asia, Europe) [49–57]. See Table 3 for the characteristics and results of the individual studies. According to the Newcastle-Ottawa Quality Assessment Scale, the quality score ranged from 4 to 8 (out of a maximum score of 9); the number of participants included per study from 1986 to 502,383; the duration of follow-up from 4 to 19 years. Insomnia was defined according to the presence of two to four symptoms, or according to ICD (International Classification of Disease) codes. Three studies considered insomnia symptoms lasting at least one month; two studies based on

administrative databases specified that they included participants with “transient” or “persistent” insomnia; the last four studies did not specify any time period as a criterion for the duration of insomnia. Baseline prevalence of insomnia ranged from 12% to 38%.

5.2. Overview of the evidence

Six out of the 9 studies found were included in the meta-analysis [50, 51, 53–56]; the original estimates were adjusted for main demographic and clinical confounding factors. Only one study [51] adjusted for the use of hypnotic medications and in this case insomnia patients without using hypnotics had no significant increase of stroke. Insomnia resulted a risk factor for stroke (HR 1.26, 95% CI 1.05-1.53, see Fig. 2 and Table 2), with heterogeneity among studies and no evidence of publication bias (Egger's test for small study effects $P = 0.58$).

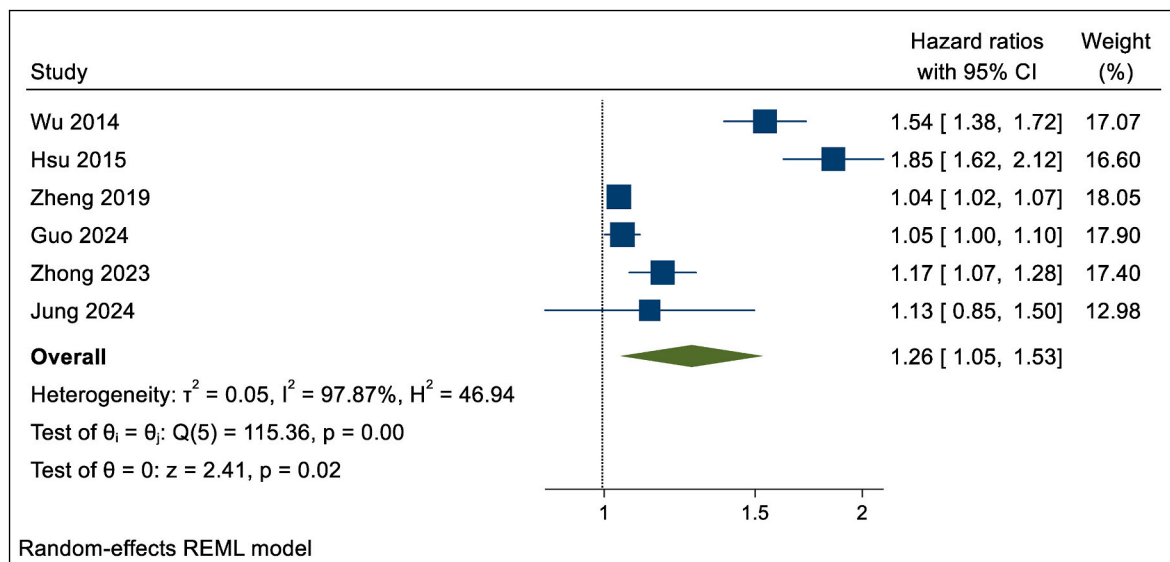


Fig. 2. forest plot of the meta-analysis of insomnia as a risk factor for stroke.

Other three primary studies [49,52,57], which were not included in the meta-analysis as they used different measures of association or multiple level of exposure, similarly found an association between insomnia and stroke (OR 1.75, 95% CI 1.02-3.01; RR 2.0, 95% CI 1.2-2.9; HR 1.51, 95% CI 1.29-1.77 high insomnia symptoms vs no insomnia; HR 1.16, 95% CI 1.02-1.33, low insomnia symptoms vs no insomnia) (see Table 3).

6. Insomnia and risk of depression and psychosis

6.1. Results of literature search

Six SRMA (Table 2), four rated of low quality and two of critically low quality, were eligible: four included all age participants [15,42,58,59], and two only participants with younger ages [43,44]. In chronological terms, Hertenstein et al. [42] provided the latest update on three previously published studies [15,58,59].

Cohort or administrative database studies from 3 continents (North America, Asia, Europe) were included in these SRMA. The total number of included studies ranged from 3 to 11; the total number of participants from 9503 to 133,033; the duration of follow-up from 12 to 72 months. Results for insomnia are reported as a whole. None of the SRMAs considered chronic insomnia (lasting 3 months) or other time periods as a criterion for the duration of insomnia. Depression was assessed by symptom scales or by physician/clinician diagnosis or structured clinical diagnostic interview. One SMRA included studies considering also bipolar disorder and psychosis [44].

6.2. Overview of the evidence

Regarding all ages, SRMA consistently found insomnia as risk factor for depressive symptoms/depression (OR 3.09 CI 95% 1.78-5.36) (Table 2). Results showed high heterogeneity and possible risk of publication bias. However, sensitivity analyses demonstrated the robustness of the results. One systematic review [58] reported results stratified by age (children/adolescents, working age, elderly) confirming a doubled risk of depressive symptoms/depression in people with insomnia for any age class. In participants of less than 25 years of age, one SRMA [43] confirmed higher risk of depression (OR 1.58; 95% CI 1.14-2.18), and a final SRMA [44] found a higher risk of mental disorders in broader terms (depression, bipolar disorder, psychosis) (OR 1.74, 95% CI 1.41-2.15).

7. Insomnia and risk of suicide

7.1. Results of literature search

Two SRMA (Table 2), rated of critically low quality, were retrieved [45,46]. Cohort or administrative database studies from 3 continents (North America, Asia, Europe) were included. The total number of studies was 42 in Harris 2020 [45] and 41 in Liu 2020 [46], covering all ages and both community and clinical populations (in majority community populations). The total number of participants, reported only by Liu 2020 [46], was 698,829. The duration of follow-up was similar according to the different outcomes: 11 years vs 8.7 years for suicide death; 1 year vs 2 years for suicide attempt; 1 year vs 10.5 months in case of suicide ideation. Results for insomnia are reported as a whole. None of the SRMA considered chronic insomnia (lasting 3 months) or other time periods as a criterion for the duration of insomnia. Suicide death was assessed by death population records, suicide attempts by medical records and suicide ideation by questionnaires.

7.2. Overview of the evidence

The two SRMA consistently found insomnia as risk factor for suicide death, suicide attempt and suicide ideation (Table 2): Harris et al. [45] reported ORs of 1.54 (95% CI 1.04-2.29), 1.78 (95% CI 1.38-2.29), and 2.10, 95% CI 1.83-2.41) for suicide death, attempt and ideation, respectively; Liu et al., 2020 [46] reported results in terms of mean weighted effect and found small-to-medium association for all the three outcomes. Results showed high heterogeneity but without substantial modification of risk after adjustment for publication bias.

8. Insomnia and risk of death

8.1. Results of literature search

Two SRMA were retrieved [47,48], rated as high and moderate quality. Cohort or administrative database studies from 5 continents (Africa, North America, Asia, Europe, Oceania) were included. The total number of studies ranged from 17 to 29; the total number of participants from 73,702 to 36,938,981; the duration of follow-up from 4.8 to 20 years. The two SRMA reported results for insomnia as a whole. None of the SRMA considered chronic insomnia (lasting 3 months) or other time periods as a criterion for the duration of insomnia.

Table 4
primary studies published on insomnia as risk for hospitalization.

Author, Year	Country	Study type (design)	Participants	Insomnia concept and assessment	Baseline risk of insomnia	Outcome	Length of follow-up	Risk in case of exposure (95% CI)	Quality of the study (NOS)	Methodological notes
Santos-Silva 2012 [63]	Brazil	Prospective cohort	1101; 44% M; adults	DSM-IV criteria (interview)	1/3	ED/hospitalization (interview)	2 yrs	Adj OR 1.6 (1.0–2.6)	7	Adjustment for demographic and main clinical risk factors No adjustment for sleeping drugs
Kaufmann 2013 ^c [62]	USA	Prospective cohort	14,355; 45% M; all > 55 yrs	Four dimensions of insomnia (questionnaire)	41%	Hospitalization (questionnaire)	2 yrs	Adj OR ^b 1.26 (1.10–1.44)	7	Adjustment for demographic and main clinical risk factors No adjustment for sleeping drugs
Wickwire 2019 [64] ^a	USA	Retrospective parallel cohort study	484,707; 37% M; mean age 70.6 yrs	ICD-9-CM and/or sleep medications Administrative databases	31%	Hospitalization (administrative databases)	1 year	Adj Rate Ratio 1.61 (1.59–1.64)	6	Adjustment for demographic and main clinical risk factors No use of sleeping drugs in the exposed insomnia cohort
Tzuang 2021 [66]	USA	Prospective cohort	4289; 44% M; all > 65 yrs	Two dimensions of insomnia (questionnaire)	11%	Hospitalization (administrative databases)	1 year	Adj OR 1.29 (0.99, 1.62)	7	Adjustment for demographic and main clinical risk factors Adjustment for sleeping drugs
Mahmood 2022 [65] ^{c a}	USA	Prospective cohort	13168; 42% M; all > 50 yrs	Four dimensions of insomnia (questionnaire)	16%	Hospitalization (administrative databases)	16 yrs	Hospitalization increased from 4.7% (95% CI: 3.7–5.6, $p < 0.001$) for one symptom, to 13.9% (95% CI: 10.3–17.5, $p < 0.001$) for four symptoms	7	Adjustment for demographic and main clinical risk factors No adjustment for sleeping drugs

Newcastle-Ottawa Scale = NOS.

^a not included in meta-analysis.

^b OR calculated from the data in Table 2 of the paper by Kaufmann et al. (2013).

^c Kaufmann 2013 and Mahmood 2022 same cohort in two different time points.

8.2. Overview of the evidence

The two SRMA [47,48] did not find insomnia to be a risk factor for mortality (Table 2). These findings were derived from studies adjusting for confounding factors, but fewer adjusted for sleeping drug use.

9. Insomnia and risk of occupational injuries

9.1. Results of literature search

No systematic review was retrieved. Two prospective cohort studies from Europe (Finland, Norway) were retrieved [60,61]. According to the Newcastle - Ottawa Quality Assessment Scale, the quality scored 7 (out of a maximum score of 9). These studies included a total of 143,942 participants with a mean age range of 46–54 years. Insomnia was defined by the presence of at least two dimensions. One study considered insomnia symptoms lasting at least one month; the other study did not specify any time period as a criterion for the duration of insomnia.

9.2. Overview of the evidence

Due to heterogeneity in the study design (follow-up duration; different outcomes and measures) it was not possible to perform a meta-

analysis. One cohort study [61] of 14-yrs of follow-up found insomnia as predictor of unintentional fatal injuries (HR 3.10, 95% CI 1.40–6.93). One cohort study of 1-yr of follow-up found insomnia as predictor of commuting injuries (OR 1.13, 95% CI 1.03–1.24) but not for workplace injuries (OR 1.06, 95% CI 0.99–1.13). Results were adjusted for several demographic and clinical confounding factors.

10. Insomnia and risk of hospitalization

10.1. Results of literature search

No systematic review was retrieved. Five primary studies (four from US and one Brazilian) were included [62–66]. According to the Newcastle - Ottawa Quality Assessment Scale, the quality score ranged from 6 to 7 (out of a maximum score of 9). The number of participants, mainly elderly people, ranged from 1101 to 484,707; the duration of follow-up from 1 to 2 years. Four studies based the diagnosis of insomnia on questionnaires or interviews (covering the ICSD or DSM criteria), one on ICD codes from administrative database. One study considered insomnia symptoms lasting at least one month; the last four studies did not specify any time period as a criterion for the duration of insomnia. The outcome was hospitalization in four studies [62,64–66], and admission to hospital or ED in one [63]. Only one study reported data on hospital

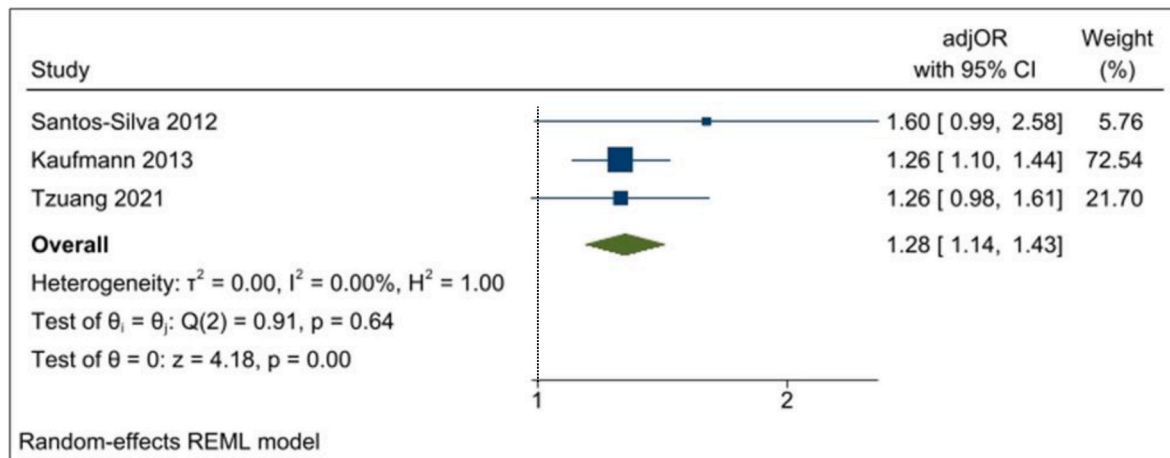


Fig. 3. forest plot of the meta-analysis of insomnia as a risk factor for hospitalization.

readmissions within 30 days [66]. No study reported data on the duration of hospitalization or the reason for hospitalization.

10.2. Overview of the evidence

For the characteristics and results of the individual studies, see Table 4.

Three studies (19,745 participants) [62,63,66] were eligible for inclusion in the meta-analysis (see Fig. 3). Insomnia was found to be a risk factor for hospitalization (OR 1.28, 95% CI 1.14–1.43, without heterogeneity among the studies; no small-study effects according to Egger's test). Results were adjusted for several demographic and clinical confounding factors.

Other two studies were not included in the meta-analysis. One of them [64] used a different measure (Rate Ratio) and found an association between insomnia and hospitalization (Rate Ratio 1.61, 95% CI 1.59–1.64). Another one [65] extended the observation of a previous study [62] on the same cohort and found, using another measure of risk, that likelihood of hospitalization for individuals reporting one symptom increased from 4.7% (95% CI 3.7–5.6) to 13.9% (95% CI 10.3–17.5) for those reporting four symptoms, relative to individuals experiencing no insomnia symptoms.

Only one study [66] showed that insomnia was also associated with a higher risk of hospital readmissions within 30 days (adjusted OR 1.88, 95% CI 1.08–3.29).

11. Discussion

Our umbrella systematic review clearly shapes the association between insomnia and the main descriptors of brain health (dementia, stroke, depression, suicide behaviour) and the possible links to general health (hospitalization for any reason). Other indicators of general health are not associated (death) or have insufficient data (occupational injuries).

11.1. Insomnia and risk of dementia

SRMAs consistently found insomnia as predictor of Alzheimer's disease and the result is confirmed by the more recent of them including about 3 million participants from 3 continents [41]. Dementia per se is also associated with insomnia even if with heterogeneous risk estimates [37–39,41], while results on vascular dementia are contrasting [38,41]. These differences are possibly due to the different criteria adopted for dementia and insomnia. Another possible confounding factor is the use of hypnotic medications; in fact, studies which controlled for the use of hypnotic medications tended to be non-significant.

Experimentally induced chronic sleep restriction demonstrates that cognitive deficits accumulate to severe levels [67]. Cognitive lapses associated to sleep restriction involve widespread changes, measured by functional neuroimaging, in brain regions including frontal and parietal control areas, secondary sensory processing areas, and thalamic areas [67].

Current hypotheses suggest that sleep restriction may contribute to neurodegeneration through multiple mechanisms, including altered expression of genes involved in neuronal inflammation [68], and impaired glymphatic clearance, which may increase amyloid-beta (A β) burden and cerebrospinal fluid tau protein levels [69].

11.2. Insomnia and risk of stroke

A novelty of our study is the finding of insomnia as possible predictor of stroke, supported by our original SRMA that included about one million participants.

Insomnia may contribute to the onset of stroke through several interconnected physiological processes. Persistent sleep disturbance triggers overactivation of the hypothalamic–pituitary–adrenal axis [70, 71] and the sympathetic nervous system [72]. These autonomic changes raise blood pressure, heart rate, and vascular tone while reducing heart rate variability [73]. Continuous cortisol release promotes hypertension, systemic inflammation and disrupts glucose and lipid metabolism, thereby facilitating atherosclerosis [74]. Sympathetic predominance further limits parasympathetic recovery, enhances arterial stiffness, and induces endothelial dysfunction, all of which compromise vascular integrity and increase cerebrovascular vulnerability and low-grade inflammation [75]. Elevated levels of inflammatory mediators accelerate atherosclerotic plaque development and increase the risk of rupture and thrombosis [76]. Inflammatory activation also generates reactive oxygen species that reduce nitric oxide bioavailability, disturbing the balance between vasodilation and vasoconstriction and further damaging the endothelium [74]. Metabolic disturbances provide an additional link between insomnia and stroke risk. Altered secretion of leptin and ghrelin promotes appetite dysregulation and weight gain, while chronic sleep loss impairs insulin sensitivity and disturbs lipid homeostasis [77]. These metabolic alterations foster obesity, dyslipidaemia, and small-vessel disease, which together weaken cerebrovascular resilience [78].

11.3. Insomnia and risk of depression and psychosis

Insomnia is a predictor of depressive symptoms/depression in any age group, as reported by three systematic reviews [42–44].

Chronic insomnia induces daytime fatigue, impaired attention, and

reduced executive function, which can exacerbate rumination, negative thinking, and maladaptive coping strategies which are recognized risk factors for depression and anxiety. Social and occupational dysfunction associated with insomnia further amplifies psychosocial stress, which may precipitate or exacerbate psychiatric disorders. Importantly, remission of depression is often incomplete until insomnia and associated daytime sleepiness are resolved [79]. At the neurobiological level, insomnia alters functional connectivity and neural activity in brain regions critical for emotional processing, including the prefrontal cortex, amygdala, and hippocampus [80]. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, circadian rhythms of cortisol, and the brain reward system also contribute to the co-occurrence and development of insomnia and depression [70]. Chronic insomnia can perturb synaptic plasticity, affecting neurotransmitter release, dendritic spine remodelling, and synaptic homeostasis, thereby creating a neural environment that favours the development of depressive symptoms [81]. Although studies evaluating a broad spectrum of serum and urine biomarkers, including inflammatory, neuroendocrine, and metabolic markers, have not demonstrated consistent associations between insomnia severity and biomarker levels [82], the interplay of physiological, neural, cognitive, and psychosocial mechanisms provides a biological and clinical framework for understanding how chronic insomnia elevates the risk of mental disorders [83]. Accordingly, chronic insomnia can be viewed as a contributing factor, with underlying mechanisms encompassing cognitive-behavioural dysregulation, neural network alterations, neuroendocrine hyperactivation, and psychosocial stress.

11.4. Insomnia and risk of suicide

Two SRMAs from three continents and including participants of all age groups consistently identified insomnia as a significant predictor of suicide death, suicide attempts, and suicide ideation [45,46]. Suicidal behaviour has several risk factors [84] and sleep disturbances are among them, also independently from depression [85]. Namely, non-pharmacological treatment specifically administered for insomnia seems to reduce “suicidogenic” thoughts [86]. The neurobiological mechanism connecting insomnia and suicidality is not clear, however could be mediated by increased impulsivity, negative cognitive bias and reward seeking [84] due to reduced functional activity in prefrontal cortex and impairment in executive functions [87].

11.5. Insomnia and risk of death

Across the two identified SRMAs [47,48], the overall evidence does not support insomnia as an independent risk factor for all-cause mortality. Confounding remains a major challenge. Insomnia may coexist with obstructive sleep apnoea, circadian rhythm disorders, chronic pain, cardiometabolic disease, and psychiatric conditions [58,88], all independently associated with mortality. Lifestyle factors such as smoking, alcohol use, physical inactivity, and socioeconomic adversity cluster with insomnia and may account for part of the observed associations. Medication use, particularly long-term hypnotics or sedative-hypnotics, introduces additional complexity. Another consideration is the discrepancy between subjective and objective sleep measures. Individuals with chronic insomnia and objectively short sleep duration (<6 h) consistently exhibit elevated cardiometabolic risk, higher inflammatory markers, and more pronounced neuroendocrine disturbances than those with insomnia complaints but normal objective sleep duration [89].

11.6. Insomnia and risk of occupational injury

Data are insufficient to draw a conclusion on the role of insomnia as predictor of occupational injury. Evidence from two cohort studies involving over 140,000 participants suggests a possible association

between insomnia and certain types of injuries (unintentional fatal injuries, commuting injuries), however meta-analysis could not be performed due to heterogeneity in study design, follow-up duration, and outcome measures.

Chronic insomnia impairs alertness, attention, and executive control, resulting in slower reaction times, diminished hazard perception, and poorer decision-making. Workers suffering from insomnia are more likely to experience concentration lapses, judgment errors, and reduced situational awareness [90]. Experimental and clinical studies show that insomnia and sleep restriction increase lapses on psychomotor vigilance tasks, prolong reaction times, and slow information processing, which together reduce the speed and reliability of hazard detection and response and execute timely corrective actions during work tasks or driving [91]. Sleep loss also impairs the perceptual and motor systems required for precise performance. Laboratory studies demonstrate that partial or total sleep restriction degrades visual search and braking responses, increases impulsive responding under time pressure, and worsens motor coordination [92]. Autonomic and postural control mechanisms are additionally affected by disturbed sleep. Insomnia-related sympathetic activation and disrupted autonomic balance reduce the efficiency of postural reflexes and can impair vestibular and proprioceptive function, increasing instability during transfers, stair negotiation, repetitive manual tasks [91,92]. The pharmacological management of insomnia can add a second layer of risk [93]. Taken together, these findings suggest that insomnia exerts a multifaceted impact on attention, coordination, and autonomic control, creating conditions conducive to injury.

11.7. Insomnia and risk of hospitalization

Another novelty of our study is the finding of insomnia as possible predictor of hospitalization for any reason, supported by an original SRMA that included three studies and a total of about half a million participants. This finding confirms that insomnia is a key marker of poor health status and exacerbates the severity of many underlying associated health conditions.

11.8. Comparison with previous umbrella reviews

Other recent umbrella reviews of SMRA assessed whether sleep characteristics are plausible risk factors for health outcomes: sleep restriction [94], sleep duration [94–96], generic sleep quality [95], insomnia [94,96–99], sleep-related breathing disorders [94]. Among those considering insomnia, the outcomes evaluated were hypertension [97], metabolic disorders [96–98], cardiovascular diseases [96–99], cancer [97,98], dementia [94,97,98], mental disorders [98], mortality [97,98]. Considering our scope (brain, mental and general health), our results are comparable to those reported for dementia, mental disorders and mortality. However, our umbrella review presents new findings that emerged from meta-analyses on stroke and hospitalization, as well as a systematic review, without meta-analysis, on occupational injuries. In particular the results relating to stroke underscore the importance of sleep for cerebrovascular health, while those relating to hospitalization can help estimate the economic burden of insomnia on healthcare systems.

11.9. General methodological issues and limitations

The primary epidemiological studies included in the SMRAs were in vast majority of satisfactory or high methodological quality. The evidence comes in almost all cases from three continents (Asia, Europe, North America). The most frequent design was the prospective cohort but, in some cases, also the historical cohort design from administrative databases. Regarding the definition of the exposure, insomnia was defined in various ways: either as a unique concept or according to the combination of elements of the ICSD definition; frequency was

Practice points

- For clinicians: insomnia is associated with a higher risk of dementia, stroke, depression and suicidal behaviour, and when reported chronically, it should be considered a warning sign to be addressed in the context of an intervention aimed at improving lifestyle and brain health at all ages.
- For scientific societies and patient advocacy groups: initiatives should be promoted to raise awareness of the consequences of insomnia and to promote its treatment.
- For health policy makers: health promotion campaigns targeting the general population, schools and workplaces should always consider sleep disorders and include sleep hygiene among their areas of focus.

Research agenda

In the future, prospective epidemiological studies should:

- be based on shared operational diagnostic criteria of insomnia;
- be focused on populations from continent neglected in current research, such as Africa, Australia, South America;
- be focused on the role of insomnia in the risk of various subtypes of dementia, stroke, hospitalization, injuries;
- disentangle the pharmacological role from that of insomnia.

considered in few studies; the duration of insomnia has almost never been considered a classification or inclusion criterion, and in no case was it required that the criteria for chronic insomnia (duration of at least three months) be met; diagnostic tools were several (clinical diagnosis, single questions, combinations of items of questionnaires). Depending on the outcomes, their definitions usually relied on independent administrative data (stroke, death, hospitalization) or on clinical diagnosis (dementia, depression, stroke), or self-reported (stroke), or on combination of items from diagnostic questionnaires (depression, suicide-related behaviour). Follow-up duration was usually informative related to the specific outcome. Regarding the risk estimates, majority of SMRA reported that data from primary studies was based on adjusted estimates, and usually the adjustment includes demographic and clinical covariates. Adjustment for the use of sleep medications was rarely reported or performed, and when considered, the association tended to decrease (dementia, death). The vast majority of SRMA found significant statistical heterogeneity in the estimates, that possibly could be explained by true difference in the population included, but also by difference in the definition criteria or diagnostic instrument of the insomnia and outcomes. Publication bias was detected in more than half of the SRMA, but the adjustment of small study effect (performed in several cases) did not affect significantly the final result.

Due to the lack of published SMRAs we performed systematic reviews on stroke, occupational injuries and hospitalization, which have important limitations. The association between insomnia and both stroke and hospitalization must be interpreted with caution due to heterogeneity (particularly for stroke) and the presence of unknown confounding factors. It is important to note that, while most primary studies adjusted for demographic and clinical confounders, only few considered the use of sleep medications. In one such study, insomnia patients not using hypnotics had no significantly increased risk of stroke [51]. Finally, the meta-analysis on occupational injuries was not performed because only two eligible studies were identified.

12. Conclusions

Human health, particularly in terms of brain health and mental health, can be partly predicted by insomnia. This does not mean that its

independent causal role has been proven. Epidemiological studies can only suggest such a role and, given that the causal chain is long, other types of evidence are needed [100]. However, we can say that insomnia is a clear warning sign that should always be considered when monitoring brain and mental health in the population and in individual patients.

Funding

This research was funded by the European Academy of Neurology. This project also received independent scientific grants from Idorsia, Jazz Pharmaceuticals and Takeda, which provided financial support without influencing the study design, data collection, analysis, or interpretation.

Conflicts of interest

Luca Vignatelli: No conflict of interest.
 Maurizio A. Leone: No conflict of interest.
 Elisabetta Pupillo: No conflict of interest.
 Stefan Seidel: No conflict of interest.
 Ulf Kallweit: Participation in advisory board activities for Bioprojet, Pharmanovia and Takeda.
 Natalia Colorado Prieto: No conflict of interest.
 Maria Lolic: No conflict of interest.
 Marina Tüzün: No conflict of interest.
 Claudio L.A. Bassetti: No conflict of interest.

Acknowledgements

We thank Oliviero Bruni (Department of Developmental and Social Psychology, Sapienza University, Italy, European Sleep Research Society), Andrea Fiorillo (Department of Psychiatry, University of Campania L. Vanvitelli, Naples, Italy, European Psychiatric Association), Iva Holmerová (Centre of Expertise in Longevity and Long-term Care, Charles University, Prague, Czech Republic, Alzheimer Europe), Joke Jaarsma (European Alliance for Restless Legs Syndrome, Brussels,

Belgium), Dirk Pevernagie (Department of Internal Medicine and Paediatrics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium, Department of Respiratory Diseases and Sleep Disorders Centre, AZ Delta, Roeselare, Belgium), Winfried Randerath (Institute of Pneumology, University of Cologne, Cologne, Germany, Clinic for Pneumology and Allergology center of sleep medicine and respiratory care, Hospital Bethanien Solingen, Solingen, Germany), for their comments to the manuscript preparation. We thank Maria Domenica Camerlingo (Regione Emilia-Romagna, Italy) and Serena Sassi (Istituto di Ricerche Farmacologiche “Mario Negri” IRCCS, Italy) for their help with search strategy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.smr.2026.102372>.

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