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REVIEW ARTICLE

Insomnia symptoms as risk factor for somatic disorders: An umbrella review of systematic reviews and meta-analyses

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Summary

The objective of this umbrella review is to present a comprehensive summary of systematic reviews and meta-analyses on the longitudinal association between insomnia and the risk of developing somatic disorders. Pubmed, Medline, CINAHL, PsycInfo and PsycArticles were searched until 16 December 2022. Fourteen systematic reviews and meta-analyses met the inclusion criteria. Results suggest that insomnia symptoms (i.e. aspects of disturbed sleep continuity as a single symptom) convey a risk factor for cardiovascular diseases, hypertension and thyroid cancer. The presence of insomnia symptoms may also enhance the risk for obesity, cognitive decline and dementia—however, results are contradictory and not conclusive here. Results do not suggest an association between insomnia symptoms and mortality. No conclusions can be drawn regarding insomnia disorder because the reviews did not ensure a valid diagnosis. It remains unclear what proportion of participants with insomnia symptoms fulfil diagnostic criteria for insomnia disorder and/or suffer from an organic sleep disorder such as sleep-related breathing disorder. Moreover, most of the included reviews were assessed to have critically low confidence according to the AMSTAR-2 tool. Inconsistent definitions of insomnia and methodological unclarities further underline that results should be interpreted with caution. There is a need for future longitudinal studies that focus on a careful definition and differential diagnosis of both insomnia and the outcome.

KEYWORDS
insomnia, risk factor, somatic disorders, umbrella review

1 | INTRODUCTION

Sleep is a vital process, occupying up to a third of the human life span. Sleep is responsible for many cognitive and biological functions, and sleep disturbances are associated with several risks for health (Harvey et al., 2011; Medic et al., 2017). Specifically, sleep health is defined as a multifactorial construct, including five dimensions: sleep duration, efficiency, satisfaction, timing and daytime alertness (Buysse, 2014). Poor sleep health in one or more of these dimensions is associated with reduced quality of life and increased vulnerability to develop several mental and somatic symptoms (Buysse, 2014). Sleep health is a continuous dimension going from very healthy sleep to pathological sleep. The most frequent pathology associated with poor sleep health is insomnia, characterized especially by low sleep efficiency and reduced sleep satisfaction, though also the other dimensions may be impaired in the disorder. Nighttime insomnia symptoms include:

difficulties initiating sleep and/or difficulties maintaining sleep and/or early morning awakening. To fulfil the diagnostic criteria for insomnia disorder, these symptoms have to occur at least three times a week for a period of at least three months, and must be accompanied by daytime impairment (DSM 5, American Psychiatric Association, 2013). The presence of insomnia symptoms has been associated with reduced quality of life (Kyle et al., 2010), alterations in cognitive functions (Fortier-Brochu et al., 2012) and a general enhanced vulnerability for somatic disorders, as for example cardiovascular diseases (Spiegelhalder et al., 2015). Nevertheless, literature on the relationship between insomnia and somatic illnesses is at least in part inconclusive and often limited by non-standardized insomnia definitions and small sample sizes. In a recent large epidemiological study including 162,512 Norwegian university students aged between 18 and 35 years, insomnia as a clinical diagnosis was more frequent in women with multiple sclerosis and chronic fatigue syndrome and in men with cancer or diabetes or fibromyalgia, compared with individuals reporting no somatic disease (Sivertsen et al., 2021). In the same study, shorter sleep duration was found in persons with physical illness compared with healthy students. While it is indisputable that insomnia is associated with mental and medical disorders in cross-sectional studies, the question whether insomnia symptoms may be a risk factor for physical health in longitudinal investigations is of utmost relevance. As insomnia responds well to treatment, i.e. cognitive-behavioural therapy for insomnia (CBT-I, first-line treatment: see European guideline for the diagnosis and treatment of insomnia disorder by Riemann et al., 2017), findings indicating that insomnia is a risk condition for severe illness may guide clinical practice to invest in CBT-I as a preventive intervention. However, the existing literature on insomnia as a risk factor for somatic disorders is at least in part inconclusive with mixed findings. The aim of this systematic umbrella review is to provide a summary of the existing literature including systematic reviews and meta-analyses of longitudinal studies evaluating the longitudinal association of insomnia at baseline with a wide range of medical illnesses.

2 | METHODS

The present work was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Hutton et al., 2015) and the Cochrane recommendations for umbrella reviews (Pollock et al., 2022). The protocol for the systematic review was pre-registered in the PROSPERO database (ID: CRD42023425269).

2.1 | Search strategy

The literature search was performed using the databases PubMed, Medline, CINAHL, PsycInfo and PsycArticles. The primary search was conducted without limits for publication date on 16th December 2022. The following term was searched for in the abstract or title: (insomnia AND (risk OR predict* OR associate* OR longitudinal OR epidemiolog* OR prospect*) AND (meta-analy* OR systematic review)). The detailed search terms for the different databases are shown in the supplemental material (S1).

2.2 | Study selection

Eligible for the present work were systematic reviews and meta-analyses of longitudinal/prospective cohort studies written in English, German, Italian, Spanish or French that investigated the risk of insomnia symptoms or insomnia diagnosis on somatic disorders. Reviews that included different study designs were eligible if they separately reported the findings for the longitudinal studies. Reviews that included less than two longitudinal primary studies were excluded. More specifically, the following inclusion criteria were applied:

P = participants: participants who were at least 18 years old at baseline
E = exposure: insomnia symptoms or insomnia diagnosis
C = comparator: normal sleepers
O = outcome: somatic disorder/condition at follow-up

The first author (FB) performed the literature search, and screened all titles and abstracts. Two authors (FB and DM) independently screened full texts of potentially eligible studies against inclusion criteria. Doubts were discussed together with the other two authors (CB and EH), and resolved through decision by consensus.

2.3 | Data extraction

The following variables were manually extracted by the first author (FB) from all included studies: author, year, review type (systematic review/meta-analysis), information on the population, the number of included longitudinal studies, the definition/assessment of insomnia, outcome, follow-up, quality assessment and main findings.

2.4 | Quality assessment

The AMSTAR-2 tool was used for the assessment of the methodological quality of the included systematic reviews and meta-analyses (Shea et al., 2017). The tool comprises 16 items that assess the following domains: (1) inclusion of PICO components (P = Patient/Population, I = Intervention, C = Comparison, O = Outcome); (2) protocol before start of the review; (3) study design selection; (4) comprehensive literature search strategy; (5) duplicate study selection; (6) duplicate data extraction; (7) details of excluded studies; (8) description of included studies; (9) risk of bias assessment; (10) funding sources; (11) appropriate statistical methods; (12) assessment of impact of risk of bias; (13) discussion of impact of risk of bias; (14) heterogeneity; (15) investigation of publication bias; (16) report of conflict of interest. Each domain is judged with "yes", "partial yes" or "no". Seven of these

domains are considered as critical (2, 4, 7, 9, 11, 13, 15). According to the tool, the overall confidence in the results of the reviews can be classified as high (no or only one non-critical weakness), moderate (more than one non-critical weakness), low (one critical flaw with or without non-critical weaknesses) and critically low (more than one critical flaw with or without non-critical weaknesses; Shea et al., 2017). The quality of included reviews was assessed by the first author (FB), and doubts were discussed and resolved with the other authors (DM, CB and EH).

3 | RESULTS

3.1 | Study selection

A total of 1932 abstracts were identified through our literature search. The search flow is presented in Figure 1. Nine-hundred and forty-six abstracts were screened after removing duplicates. Twenty-seven potentially eligible full texts remained and were assessed for eligibility. Finally, 14 studies met our inclusion criteria and were included in this umbrella review. Details on the excluded studies with the reasons for exclusion can be found in the supplemental material (S2).

3.2 | Study characteristics

Thirteen of the included studies were systematic reviews, including a quantitative meta-analysis (Chan et al., 2018; de Almondes et al., 2016; Ge et al., 2019; He et al., 2017; Hu et al., 2021; Li et al., 2021, 2014; Lovato & Lack, 2019; Meng et al., 2013; Shi et al., 2018, 2020; Sofi et al., 2014; Xu et al., 2020) and one was a systematic review without meta-analysis (Jarrin et al., 2018). The number of included longitudinal primary studies investigating the risk of

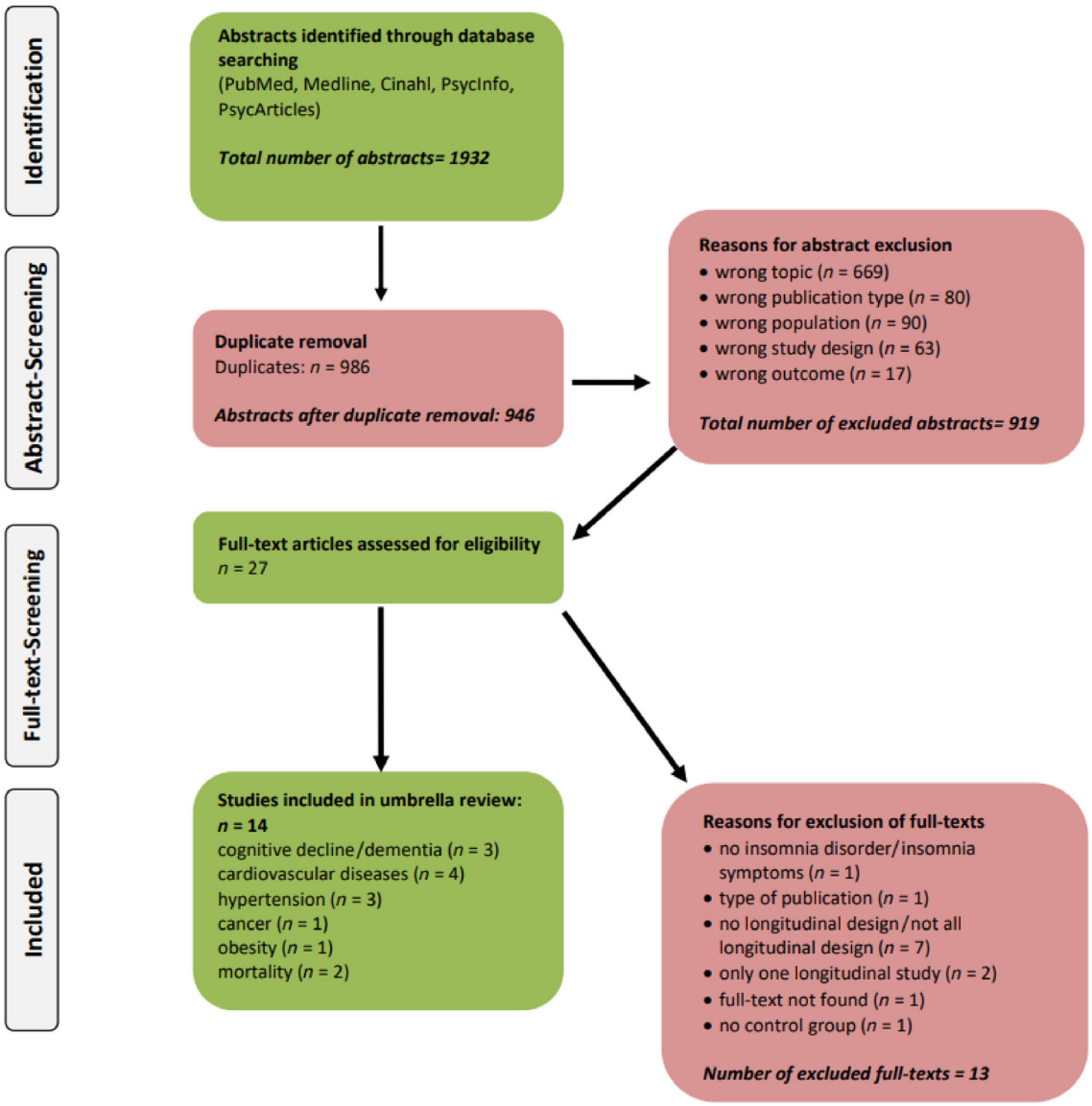

FIGURE 1 Flow of the study search

insomnia symptoms/insomnia disorder on somatic disorders ranged from 2 (Chan et al., 2018) to 31 (Ge et al., 2019) per systematic review. In one review, the number of included longitudinal studies with respect to insomnia was not indicated (Jarrin et al., 2018). Four reviews evaluated the longitudinal association between insomnia and cardiovascular diseases (He et al., 2017; Hu et al., 2021; Li et al., 2014; Sofi et al., 2014), three reviews investigated the association between insomnia and hypertension (Jarrin et al., 2018; Li et al., 2021; Meng et al., 2013). Li et al. (2021) updated the review of Meng et al. (2013) leading to some overlap of included studies. Another three reviews evaluated the association between insomnia and cognitive decline/dementia (de Almondes et al., 2016; Shi et al., 2018; Xu et al., 2020). The remaining reviews examined the longitudinal association between insomnia and cancer (Shi et al., 2020), obesity (Chan et al., 2018) and mortality (Ge et al., 2019; Lovato & Lack, 2019). The majority of studies assessed individual insomnia symptoms/combination of symptoms/insomnia disorder with self-reported questionnaires or single self-reported questions instead of a structured interview, and these methods did not capture frequency or severity of insomnia symptoms. Only one review defined frequency and chronicity as an inclusion criterion (Lovato & Lack, 2019). Details on the included studies are presented in Table 1.

3.3 | Main results

3.3.1 | Cardiovascular diseases

We identified four systematic reviews with meta-analysis investigating insomnia as a potential predictor of cardiovascular events or diseases (He et al., 2017; Hu et al., 2021; Li et al., 2014; Sofi et al., 2014). He et al. (2017) conducted a meta-analysis of 15 primary studies. The investigated predictor was the presence of at least one nighttime symptom of insomnia at baseline: trouble initiating or maintaining sleep, early morning awakening or non-restorative sleep. Daytime symptoms were not considered. The outcome was the occurrence of a cardio-cerebral vascular event at follow-up—acute myocardial infarction, coronary heart disease, heart failure, stroke, or a combined event. The authors found a risk increase of between 11% and 27% in participants with sleep-onset problems, sleep-maintenance problems and non-restorative sleep at baseline. They did not find an increased risk for participants with early morning awakening. In their meta-analysis published 4 years later, Hu et al. (2021) found very similar results: an increased risk of cardiovascular diseases for participants with sleep-onset and sleep-maintenance difficulties and with non-restorative sleep, but not for participants with early morning awakening. The magnitude of the risk increase was also similar in the two meta-analyses—in Hu et al. (2021), the risk increase was between 14% and 22% for the different sleep symptoms. Sofi et al. (2014) pooled studies that investigated participants with either troubles falling asleep, maintaining sleep or "restless" sleep at baseline. They report an overall risk increase of 45% for a combination of different cardiovascular events, including the occurrence of acute myocardial infarction, coronary heart disease, stroke or death from any of the aforementioned cardiovascular causes. The meta-analysis published in 2014 by Li et al. did not combine cardiovascular events into one variable but reported risks for different cardiovascular events separately. Regarding the predictor, the authors write "insomnia", but from their table it becomes evident that they also included participants who reported only one insomnia symptom such as trouble falling asleep. They report a risk increase of 55% for stroke, 33% for cardiovascular mortality and 28% for coronary heart disease across different insomnia symptoms.

Together, all four meta-analyses found significantly increased risks of cardiovascular events for participants with sleep complaints. No conclusions can be drawn regarding insomnia disorder because the meta-analyses did not ensure that the included participants had a valid diagnosis of insomnia disorder. The magnitude of the risk increase varies between meta-analyses, probably due to methodological differences (e.g. composite predictors/outcomes or reporting different symptoms/events separately).

3.3.2 | Hypertension

Two meta-analyses and one qualitative systematic review investigated the longitudinal relationship between insomnia and hypertension (Jarrin et al., 2018; Li et al., 2021; Meng et al., 2013). The two meta-analyses by Meng et al. (2013) and Li et al. (2021) used similar methodology and reported similar results (Li et al. updated the review of Meng et al.). As predictors, both used symptoms of disturbed sleep continuity, early morning awakening and difficulties falling asleep as individual predictors for separate calculations. As an outcome, both used hypertension defined either as a repeatedly elevated blood pressure (exceeding 140/90 mg Hg) determined in an interview or the use of antihypertensive medication or a diagnosis by a physician. For disturbed sleep continuity, the risk of developing hypertension was 20% (Meng et al., 2013) and 27% (Li et al., 2021), respectively. For early morning awakening, it was 14% in both meta-analyses. Both studies did not find an elevated risk for participants with sleep-onset difficulties. Jarrin et al. (2018) conducted a systematic review without a meta-analysis. Their results support the notion that symptoms of insomnia constitute a risk factor for the later onset of hypertension.

3.3.3 | Cognitive decline/dementia

The longitudinal relationship between insomnia and cognitive decline/dementia has been investigated in three meta-analyses (de Almondes et al., 2016; Shi et al., 2018; Xu et al., 2020). De Almondes et al. (2016) report that insomnia was associated with a 50% risk increase for all-cause dementia. However, their inclusion criterion regarding the definition of insomnia does not become entirely clear. It seems that at least some of their primary studies included patients that reported both insomnia and excessive daytime sleepiness, or insomnia and use of hypnotic medication, without ensuring a clear diagnosis of

TABLE 1 Study characteristics

Author (year)	Review type	Population	Number of included longitudinal studies	Definition/assessment of insomnia	Outcome	Follow-up	Quality assessment	Main findings
Chan et al. (2018)	Systematic Review & Meta-analysis	Adults with insomnia diagnosis or insomnia symptoms compared with participants without insomnia	2	Insomnia diagnosis: assessments of insomnia that meet the criteria specified in the DSM-IV, DSM-V or 10 ICSD-2 or subjective reports of having been diagnosed with insomnia by a health professional Insomnia symptoms: all other assessments of insomnia, even when reported as categorical variables (absence versus presence of insomnia symptoms)	Obesity	Not indicated	Multiple factors of quality (study design, types of insomnia assessments, assessments of body mass, screening out sleep apnea, assessment of sleep duration) were assessed instead of assigning each study a global quality score	Two longitudinal studies investigated the incidence of obesity in individuals who had insomnia symptoms at baseline. (1) Sivertsen et al.: no significant association between insomnia symptoms and future incidence of obesity (OR: 1.13 [0.96, 1.33]) after controlling for demographics, medical conditions and presence of obesity at baseline; (2) Vgontzas et al.: no significant association between insomnia diagnosis and future incidence of obesity (OR: 0.48 [0.15–1.53]); insomnia symptoms were associated with higher future incidence of obesity (OR: 1.78 [1.02–3.13], $p < 0.05$)
de Almondes et al. (2016)	Systematic Review & Meta-analysis	Population-based, prospective cohort studies investigating older adults with insomnia or insomnia complaints as compared with participants without insomnia	5	Insomnia/insomnia complaints according to clinical sleep scale, self-report, sleep-related questions interview or sleep-related questions in depression scale	Dementia	Ranging from 3 to 8 years	Newcastle–Ottawa Scale The methodological quality of the included studies was rated moderate to excellent	Insomnia was associated with a significant risk of all-cause dementia (RR = 1.53, 95% CI (1.07–2.18), $z = 2.36$, $p = 0.02$)
Ge et al. (2019)	Systematic Review & Meta-analysis	Adults with insomnia disorder/ individual insomnia symptoms Twenty-nine cohorts including 1,598,628 individuals (55.3% men; mean age 63.7 years)	31	Author's definitions of insomnia disorder and all individual insomnia symptoms (difficulty falling asleep = DFA, difficulty maintaining sleep = DMS, early morning awakening = EMA, and non-restorative sleep = NRS)	Mortality	Median follow-up duration of 10.5 years	Newcastle–Ottawa scale	DFA and NRS were associated with an increased risk of all-cause mortality (DFA: HR = 1.13, 95% CI 1.03–1.23, $p = 0.009$, moderate certainty; NRS: HR = 1.23, 95% CI 1.07–1.42, $p = 0.003$, high certainty) and cardiovascular disease mortality (DFA: 1.20, 95% CI: 1.01, 1.43; $p = 0.04$, moderate certainty; NRS: HR = 1.48, 95% CI 1.06–2.06, $p = 0.02$, moderate certainty). Insomnia disorder, DMS and EMA were not associated with all-cause and cardiovascular disease mortality. No associations with cancer-related mortality

(Continues)

TABLE 1 (Continued)

Author (year)	Review type	Population	Number of included longitudinal studies	Definition/assessment of insomnia	Outcome	Follow-up	Quality assessment	Main findings
He et al. (2017)	Systematic Review & Meta-analysis	Prospective cohort studies of adults with at least a 2-year follow-up duration/adults with at least one insomnia symptom	15	Insomnia symptoms including difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), early morning awakening (EMA), and non-restorative sleep (NRS) self-reported via interview or questionnaire	Cardio-cerebral vascular events	Ranging from 3 to 20 years	Newcastle–Ottawa Scale	DIS, DMS and NRS were associated with a higher risk of future cardio-cerebral vascular events (DIS: RR = 1.27, 95% CI (1.15–1.40); DMS: RR = 1.11, 95% CI (1.04–1.19); NRS: RR = 1.18, 95% CI (1.05–1.33)), especially in women. No association between EMA and cardio-cerebral vascular events was found
Hu et al. (2021)	Systematic Review & Meta-analysis	Adults with insomnia symptoms compared with participants without insomnia Prospective cohort studies with sample sizes ranging from 2960 to 487,200	7	Insomnia symptoms including difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), early morning awakening (EMA), and non-restorative sleep (NRS) assessed by self-reported questionnaires or interviews	Cardio-cerebral vascular diseases (CVDs)	Mean follow-up duration was 10.6 years	Newcastle–Ottawa Scale	Symptoms of DIS, DMS or NRS were associated with a higher risk of CVD incidence in insomnia patients free of CVDs at baseline (HR 1.19, 95% CI 1.05–1.34; HR 1.14, 95% CI 1.02–1.27; HR 1.16, 95% CI 1.07–1.24). No significant association between EMA and CVD (HR 1.06, 95% CI 0.99–1.13)
Jarrin et al. (2018)	Systematic Review	Adults with insomnia diagnosis or symptoms or syndrome	The number of longitudinal studies investigating the risk of insomnia on hypertension was not indicated	Insomnia symptoms or syndrome were assessed through non-diagnostic criteria such as self-reports (e.g. daily sleep diaries, questionnaires) or with recognized diagnostic criteria (e.g. clinical interviews)	Hypertension/ blood pressure (BP)	Not indicated	An adapted version of a widely used scale. Quality of studies was rated along a continuum that ranged from 0 to 17, with lower scores indicating poorer quality and higher scores indicating greater quality	Jarrin et al. (2018): "Based on longitudinal studies, a majority in the present review focused on the contributory role of insomnia on future hypertension. Notably, prospective data indicated that complaints of DMS increased the odds of subsequent hypertension (i.e. medication use, BP measures) by 1.2–4.10 [18, 22, 88] and by 21% if hypertension was based on self-report. Similar findings were observed for complaints of DIS (ORs range: 1.20–1.96); however, this was only found in studies with shorter versus longer follow-ups. While reports of EMA and NRS were also associated with 15% and 32% increased risk of hypertension, respectively, caution must be taken, as these were based on only one study"

TABLE 1 (Continued)

Author (year)	Review type	Population	Number of included longitudinal studies	Definition/assessment of insomnia	Outcome	Follow-up	Quality assessment	Main findings
Li et al. (2014)	Systematic Review & Meta-analysis	Adults with insomnia diagnosis or insomnia symptoms compared with participants without insomnia (total $N = 311,260$)	17	Insomnia symptoms or diagnosis	Risk of cardiovascular disease	Ranging from 3 to 22 years	No quality assessment	Insomnia was significantly associated with increased risk of cardiovascular outcomes and mortality after adjustment of established cardiovascular risk factors. Insomnia was associated with a significantly increased risk of myocardial infarction (RR, 1.41; 95% CI, 1.18–1.67; $p = 0.000$), a significantly increased risk of coronary heart disease (RR, 1.28; 95% CI, 1.10–1.50; $p = 0.002$) and stroke (RR, 1.55; 95% CI, 1.39–1.72; $p = 0.000$). Insomnia significantly increased the risk of CVD mortality (RR, 1.33; 95% CI, 1.13–1.57; $p = 0.001$).
Li et al. (2021)	Systematic Review & Meta-analysis	Fourteen prospective cohort studies involving 395,641 participants with and without insomnia	14	Diagnosis of insomnia was established based on any recognized classification (DFA and/or DMS or EMA or NRS) or clinical diagnostic criteria (e.g. DSM-IV/V, ICSD-2/3, ICD-9/10)	Incidence of hypertension	Ranged from 12 to 228 months, with an average of 130.4 months	Newcastle–Ottawa Scale	Insomnia was associated with a significantly increased risk of hypertension (pooled RR = 1.21; 95% CI: 1.10–1.33). High heterogeneity was found ($I^2 = 95.5\%$, $p < 0.001$). An increased risk of hypertension was found in participants with DMS (RR = 1.27; 95% CI: 1.04–1.55) and EMA (RR = 1.14; 95% CI: 1.08–1.20), but was not statistically significant in participants with DFA (RR = 1.14; 95% CI: 0.95–1.37). Furthermore, the results were statistically significant in the European population (RR = 1.08, 95% CI: 1.02–1.14), but not significant in Asian and American populations (RR = 1.54, 95% CI: 0.98–2.40; RR = 1.21, 95% CI: 0.89–1.65)

(Continues)

TABLE 1 (Continued)

Author (year)	Review type	Population	Number of included longitudinal studies	Definition/assessment of insomnia	Outcome	Follow-up	Quality assessment	Main findings
Lovato and Lack (2019)	Systematic Review & Meta-analysis	Adults with frequent (≥ 3 nights per week) and ongoing (≥ 1 month) insomnia compared with adults without insomnia (total $N = 36{,}938{,}981$; 366,024 (approximately 10%) were suffering from insomnia)	17	Symptoms of insomnia must be frequent (≥ 3 nights per week) and ongoing (≥ 1 month) 8 of the 17 studies included the presence of daytime impairments in their definition of insomnia "Most of the included papers assessed insomnia as self-reported according to the diagnostic criteria (DSM-IV or ICSD-IV). Of these studies, four required self-reported symptoms to be confirmed by a sleep physician or psychiatrist. Most of the studies used definitions including difficulty initiating and/or maintaining sleep, and/or waking too early, while others were broad in their definition, such as presence of a complaint of insomnia".	Mortality	Ranged from 2.2 to 28 years, with a mean follow up of 11.6 (SD = 2.3)	Five different domains were assessed: study participation (i.e. recruited sample is representative of the population of interest); study attrition; satisfactory measurement of the outcome variable; measurement of confounding variables; and adequate statistical analyses (Hayden et al., 2006)	Risk of mortality did not differ significantly for those with symptoms of insomnia when compared with those without symptoms (OR = 1.06, 95% CI = 0.61–1.84, $p = 0.84$)
Meng et al. (2013)	Systematic Review & Meta-analysis	Prospective cohort studies that reported the association between insomnia and hypertension incidence in normotensive adults (total $N = 42{,}636$)	7	Symptoms of insomnia were assessed using questionnaires or surveys, except in one study that used wrist actigraphy. Insomnia was categorized as difficulty falling asleep (DFA) or difficulty initiating sleep, sleep continuity disturbance (SCD) or difficulty maintaining sleep, early-morning awakening (EMA) and the combination of all symptoms, with the consideration of persistency of insomnia. Persistency of insomnia was defined as a duration of insomnia symptoms years, year or as frequency variations (from never to always).	Incidence of hypertension	Mean follow-up period of 8.2 years	Newcastle–Ottawa scale	SCD, EMA and combined symptoms of insomnia are significantly associated with an increased risk of hypertension incidence. The relative risks (95% CIs) were 1.20 (1.06–1.36) for SCD, 1.14 (1.07–1.20) for EMA, and 1.05 (1.01–1.08) for combined insomnia symptoms

TABLE 1 (Continued)

Author (year)	Review type	Population	Number of included longitudinal studies	Definition/assessment of insomnia	Outcome	Follow-up	Quality assessment	Main findings
Shi et al. (2018)	Systematic Review & Meta-analysis	Adults with and without insomnia	9	Insomnia refers to difficulty initiating sleep, trouble maintaining sleep, or waking up early and not being able to go back to sleep. Sleep disturbances were assessed via self-reported symptoms, questionnaires, clinical diagnosis, or objectively monitored sleep parameters.	All-cause dementia, Alzheimer's disease (AD) and vascular dementia	Average 9.49 years of follow-up	Newcastle–Ottawa scale (8 studies high quality, 1 medium quality)	Insomnia increased the risk of AD (RR = 1.51, 95% CI: 1.06–2.14, $I^2 = 57.4\%$, $p = 0.096$), but was not a risk factor for vascular dementia (RR = 1.13, 95% CI: 0.94–1.35, $I^2 = 0.0\%$, $p = 0.906$) or all-cause dementia (RR = 1.17, 95% CI: 0.95–1.43, $I^2 = 84.8\%$, $p = 0.000$)
Shi et al. (2020)	Systematic Review & Meta-analysis	Adults with and without insomnia diagnosis or insomnia symptoms	7	Self-reported data or self-administrated questionnaire (studies were excluded if they only examined broader sleep disorders, sleep duration or sleep quality but did not specifically consider insomnia)	Incidence of cancer	Ranging from 7.5 to 23 years	Newcastle–Ottawa scale	Subgroup analysis showed that the HR for cancer incidence was 1.20 (95% CI, 1.02–1.42) for prospective studies
Sofi et al. (2014)	Systematic Review & Meta-analysis	Adults with and without insomnia/ sleep complaints (total $N = 122{,}501$)	13	Insomnia was reported as trouble with falling asleep or difficulty in initiating sleep in most of the papers, with some of them reporting also other definitions such as presence of non-restorative sleep or a number of symptoms related to insomnia	Cardiovascular disease (occurrence of acute myocardial infarction, coronary heart disease, stroke or death from any of these cardiovascular causes)	Ranging from 3 to 20 years	No quality assessment	Subjects who reported suffering from insomnia had a 45% increased risk of morbidity and/or mortality from cardiovascular disease with respect to those who did not suffer from sleep complaints (RR 1.45, 95% CI 1.29–1.62; $p < 0.00001$)
Xu et al. (2020)	Systematic Review & Meta-analysis	23 cohort studies (total $N = 260{,}915$)	23	Not specified	All-cause cognitive disorders	Not indicated	Newcastle–Ottawa scale	Insomnia was significantly associated with 27% higher risk of cognitive disorders (RR = 1.27, 95% CI = 1.16–1.39, $I^2 = 82\%$)

insomnia disorder. The outcome was either a diagnosis of dementia or a drop of 9 or more points in the cognitive abilities screening instrument. Xu et al. (2020) report that insomnia was associated with a 27% increase in the risk for cognitive disorders. The authors of this meta-analysis do not specify how insomnia was diagnosed. It can be inferred from the primary studies that the results for insomnia include participants with insomnia symptoms rather than an actual insomnia diagnosis. Xu et al. (2020) do not specify how cognitive disorders/dementia were diagnosed. Shi et al. (2018), in contrast, found that insomnia alone was not a significant risk factor for all-cause dementia—whereas sleep-related breathing disorder was associated with an 18% increased risk, and other sleep problems, including excessive daytime sleepiness, sleep-related movement disorder and circadian rhythm sleep–wake disorder, were associated with a significant 20% risk increase. In this meta-analysis, the outcome was diagnosed dementia based on international diagnostic criteria and medical records. These findings underline the importance of a careful definition and differential diagnosis of both the predictor and the outcome variable, as different sleep disorders may highly differ regarding their predictive status.

Together, the three meta-analyses find strikingly different results regarding the status of insomnia as a predictor of cognitive decline/dementia, ranging from no increased risk to a 50% increased risk. A potential conclusion is that carefully diagnosed insomnia alone, independent of comorbidities and associated health risks such as obstructive sleep apnea and hypnotic use, may rather not be a predictor of dementia. Due to methodological unclarities, definitive conclusions are difficult to make. Because insomnia diagnosis was not always made by a clinician but in several cases assumed from self-reports and questionnaire data, it cannot be excluded that patients classified as insomnia patients had occult organic sleep disorders, most prominently sleep-related breathing disorders. Another limitation is that in some of the included primary studies, a clinical diagnosis of dementia was not mandatory but dementia was assumed from a decline in performance in a cognitive screening instrument. This may have led to biased results.

3.3.4 | Cancer

We included one meta-analysis investigating insomnia symptoms as a predictor of cancer (Shi et al., 2020). The authors report a 24% risk increase for patients with insomnia symptoms to develop cancer, compared with those without insomnia. This was only significant for thyroid cancer, not for other types of cancer, and the risk was higher in women than men with insomnia symptoms. Insomnia diagnosis in the primary studies was in part based on clinical interviews guided by the ICD-criteria, but in the majority of primary studies was made based on self-administered questionnaires and self-reported symptoms.

3.3.5 | Obesity

One qualitative systematic review investigated whether insomnia is a risk factor of obesity (Chan et al., 2018). The authors included both cross-sectional and longitudinal studies, and identified only two longitudinal studies on insomnia as a potential risk factor for obesity—one of them found that insomnia symptoms did not constitute a risk factor of obesity, the other found that insomnia symptoms were associated with an increased risk but insomnia diagnosis was not.

3.3.6 | Mortality

The longitudinal association between insomnia and mortality has been investigated in two meta-analyses (Ge et al., 2019; Lovato & Lack, 2019). Ge et al. found that difficulty falling asleep and non-restorative sleep as individual symptoms were associated with an increased risk of all-cause mortality (hazard-ratio: 1.13), but diagnosis of insomnia disorder was not a significant risk factor. Lovato and Lack did not find an increased risk of all-cause mortality in those with insomnia symptoms compared with those without insomnia symptoms. The two meta-analyses converge on the conclusion that insomnia does not increase the risk of mortality.

3.4 | Quality of included reviews

Based on the AMSTAR-2 tool guidelines (Shea et al., 2017), 13 of the included reviews were assessed to have critically low confidence, and one review to have low confidence. None of the included reviews was evaluated to have moderate or high confidence. Two domains that are considered to be critical were absent in almost all included reviews: only one review has been pre-registered, all other included authors did not register a protocol prior to the conduct of the review. Furthermore, none of the included reviews provided a list with the excluded studies and the justifications for the exclusion of these studies. With that, almost all studies indicated more than one critical flaw resulting in critically low confidence according to the AMSTAR-2 guidelines (Shea et al., 2017). Details on the AMSTAR-2 assessment of each included study are shown in Table 2.

4 | DISCUSSION

A graphical summary of the results is provided in Figure 2.

To our knowledge, this is the first umbrella review evaluating insomnia symptoms as risk factor of somatic disorders in general, adopting a systematic procedure and a pre-registered protocol. Results indicate that insomnia symptoms are a risk factor for cardiovascular diseases, hypertension and thyroid cancer. Insomnia symptoms may also contribute to enhanced vulnerability for obesity, cognitive decline and dementia, but results are contradictory and not conclusive. In contrast, insomnia symptoms do not seem to be associated with a higher risk of mortality.

This is a topic of utmost relevance as these results suggest that early and effective treatment of insomnia symptoms may play an important role in prevention—a hypothesis that so far has not yet

TABLE 2 AMSTAR-2 assessment

Review	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR16	Overall confidence
Chan et al. (2018)	No	No	No	p. yes	No	No	No	No	p. yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
de Almondes et al. (2016)	Yes	No	Yes	p. yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Ge et al. (2019)	No	Yes	Yes	p. yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
He et al. (2017)	No	No	Yes	p. yes	No	Yes	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Hu et al. (2021)	No	No	Yes	p. yes	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Jarrin et al. (2018)	No	No	Yes	p. yes	No	No	No	p. yes	Yes	No	n.a.	n.a.	Yes	No	n.a.	Yes	Critically low
Li et al. (2014)	No	No	Yes	p. yes	No	No	No	No	No	No	No	No	No	No	No	Yes	Critically low
Li et al. (2021)	No	No	Yes	p. yes	Yes	No	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Lovato and Lack (2019)	Yes	No	No	p. yes	Yes	No	No	No	p. yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Meng et al. (2013)	No	No	Yes	p. yes	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Yes	No	Critically low
Shi et al. (2018)	No	No	Yes	p. yes	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Shi et al. (2020)	No	No	Yes	p. yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Sofi et al. (2014)	No	No	Yes	p. yes	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Xu et al. (2020)	No	No	Yes	p. yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low

Note: AMSTAR 1: Did the research questions and inclusion criteria for the review include the components of PICO? AMSTAR 2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? AMSTAR 3: Did the review authors explain their selection of the study designs for inclusion in the review? AMSTAR 4: Did the review authors use a comprehensive literature search strategy? AMSTAR 5: Did the review authors perform study selection in duplicate? AMSTAR 6: Did the review authors perform data extraction in duplicate? AMSTAR 7: Did the review authors provide a list of excluded studies and justify the exclusions? AMSTAR 8: Did the review authors describe the included studies in adequate detail? AMSTAR 9: Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review? AMSTAR 10: Did the review authors report on the sources of funding for the studies included in the review? AMSTAR 11: If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? AMSTAR 12: If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis? AMSTAR 13: Did the review authors account for risk of bias in individual studies when interpreting/discussing the results of the review? AMSTAR 14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? AMSTAR 15: If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? AMSTAR 16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? p. yes = partial yes, n.a. = not applicable. Red indicates "no", yellow indicates "partial yes" and green indicates "yes". With respect to the overall confidence, red means "critically low" and the darker red indicates "low".

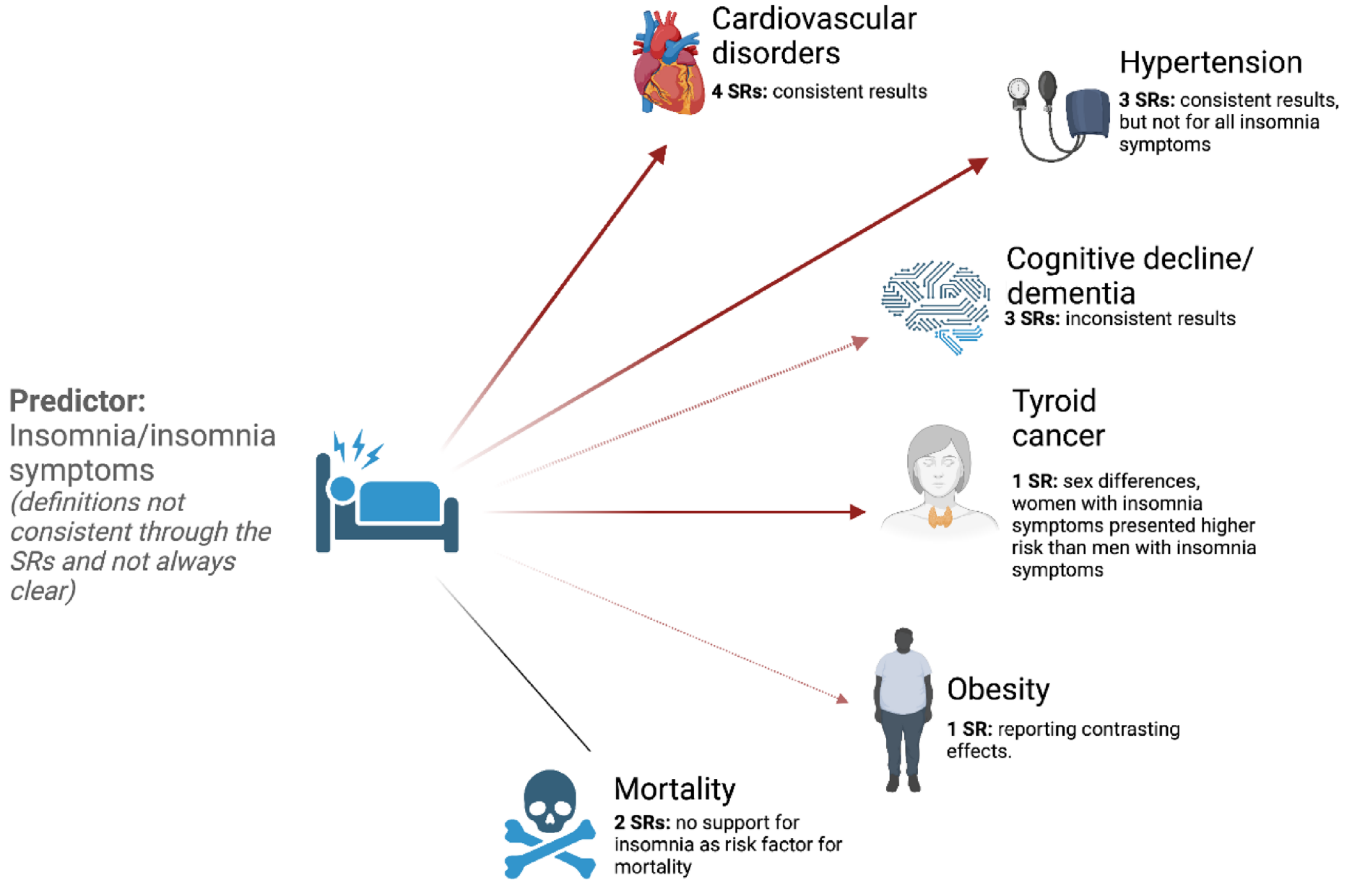

FIGURE 2 Summary of results on insomnia symptoms as a risk factor for somatic health. Outcomes of longitudinal studies observed in systematic reviews are displayed on the left side. Insomnia symptoms at baseline predict cardiovascular diseases, hypertension and thyroid cancer (thicker arrow). Less consistent evidence is available on the longitudinal association between insomnia symptoms and obesity, cognitive decline and dementia (dashed arrow). Results suggest that insomnia symptoms did not convey a risk factor for mortality (straight line). Created with BioRender.com

been adequately tested. Several international clinical guidelines recommend CBT-I as first-line intervention for insomnia disorder (Baglioni et al., 2020; Riemann et al., 2017). Nevertheless, this treatment is still poorly implemented in many countries, including some countries not recognizing psychological interventions in the primary care offer. A major effort in improving implementation and dissemination of the first-line intervention of insomnia disorder may not only have great potentials for reducing the high prevalence of insomnia itself, but may be also important to reduce the risk for negative health sequelae.

Nevertheless, our umbrella systematic review of meta-analyses and other systematic reviews has important limitations. One of the most important limitations in the reviewed literature is poor attention to the careful definition and diagnosis of insomnia symptoms and insomnia disorder, respectively. The definition of insomnia was inconsistent and most reviews did not account for the frequency or severity of insomnia. Furthermore, most reviews focused on (individual) nighttime symptoms of insomnia and daytime symptoms were not considered. In some studies, insomnia was measured with a single question, and in most studies, insomnia symptoms were self-reported and not based on structured clinical interviews based on diagnostic criteria. Thus, it often remains unclear which exact disorders or symptoms critically contribute to an increased vulnerability for somatic disorders. For example, in the absence of a careful diagnosis, instead of insomnia, participants with sleep-onset problems may suffer from a circadian rhythm sleep–wake disorder with a sleep phase delay, and participants with disturbed sleep continuity or low sleep quality may have an underlying sleep-related breathing disorder. Thus, a careful assessment and diagnosis of insomnia is important to evaluate the risk for somatic disorders. In addition, He et al. (2017) noticed that some of the included original studies did not carefully control for comorbid conditions, as for example depression, which may also be responsible for an increased risk for somatic diseases. Thirdly, while our search included all forms of somatic conditions, for several outcomes we could not identify reviews fulfilling our inclusion criteria. For instance, insomnia diagnosis has been found to be associated with an increased risk of type 2 diabetes in individual studies (LeBlanc et al., 2018), but systematic syntheses on this longitudinal association are lacking. Furthermore, gender and age differences have been poorly investigated. The risk of developing somatic conditions may differ between males

and females with insomnia disorder or insomnia symptoms (Shi et al., 2020), thus the role of gender differences should be explored more thoroughly. Lastly, there are a number of methodological limitations in the included reviews. For example, most included reviews did not mention a pre-registered protocol or reported their selection criteria following the PICO procedure. None of the included reviews reported detailed information about excluded studies and reasons for exclusion. In a similar vein, the majority of the reviews did not describe the included studies in detail.

5 | CONCLUSION

The present systematic umbrella review of systematic reviews and meta-analyses offers an update and comprehensive picture of the state-of-the-art with respect to empirical literature evaluating insomnia and insomnia symptoms as risk factors for somatic conditions. Results indicate a significant and crucial role of poor sleep for health, underlining the importance of early diagnosis and treatment of sleep problems in primary care. The present work points out the necessity for future longitudinal studies to carefully considering the definitions of the predictors and the outcomes.

AUTHOR CONTRIBUTIONS

Fee Benz: Conceptualization; methodology; visualization; project administration; writing – original draft; writing – review and editing. **Debora Meneo:** Methodology; visualization; writing – original draft; writing – review and editing. **Chiara Baglioni:** Conceptualization; methodology; writing – original draft; writing – review and editing. **Elisabeth Hertenstein:** Conceptualization; methodology; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

None of the authors report any conflict of interest.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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