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CLINICAL REVIEW

Sleep and allostatic load: A systematic review and meta-analysis

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SUMMARY

The detrimental effects of sleep disturbances on health and wellbeing are well-established but not fully understood. The allostatic load model has been suggested as a framework for understanding the adverse effects of sleep disturbances. We conducted a systematic review and meta-analysis to examine the associations of sleep disturbance and sleep duration with allostatic load. PubMed, PsycINFO, Embase, and Web of Science were searched for records relating to sleep and allostatic load published from 1993 to January 14th, 2022. Two independent raters screened 395 titles and abstracts and 51 full texts. Data were extracted from 18 studies that were assessed for methodological quality. Of these, 17 studies of 26,924 participants were included in the meta-analysis. Sleep disturbance was significantly associated with higher allostatic load (effect size correlation [ESr] = 0.09, $p < 0.001$), and the association was weaker in samples with a larger proportion of women. When compared to normal sleep, long sleep was significantly associated with higher allostatic load (ESr = 0.12, $p = 0.003$). Results indicated heterogeneity. No association was found for short sleep (ESr = 0.05, $p = 0.069$) or sleep duration (ESr = −0.06, $p = 0.36$). Future research should identify mechanisms and directionality in longitudinal studies.

Introduction

It is well-established that sleep is of fundamental importance to health and well-being, including memory consolidation [1], immune system regulation [2], and restoring energy levels [3]. Adverse health outcomes such as diabetes and cancer have been linked with sleep disturbances and poor sleep quality [4–8]. The association of sleep duration with health is complex, as both short (often defined as ≤5 or <6 h) and long (often defined as ≥9 h) sleep duration has been shown to be associated with adverse health outcomes [6]. Whereas measures of sleep duration are relatively straightforward, the concept of sleep quality is more complex, and not consistently defined [9,10]. It can refer to the purely subjective perception of one's sleep, assessed for example using a single item Likert-scale rating of one's previous night's sleep, but also to multiple aspects of sleep including sleep latency, sleep efficiency, sleep fragmentation, sleep disturbances, use of sleeping medication, and daytime dysfunction. The Pittsburgh sleep quality index (PSQI) [11] encompasses both of these definitions, and allows for the computation of a global score as well as specific component scores. As this is one of the most widely used and well-validated instruments for sleep quality measurement, sleep quality is most commonly regarded as a multi-faceted construct in accordance with the PSQI. However, the sleep literature also contains a multitude of measures that may serve as sleep quality proxies, e.g., single-item sleep quality questions, sleep questionnaires other than the PSQI, or doctor-diagnosed sleep disorders such as insomnia or sleep apnea. Further, in addition to subjective assessment methods, objective methods such as actigraphy may also capture aspects of sleep quality, such as sleep onset latency and sleep efficiency. In the present review, sleep disturbance will be referred to as an overarching concept, encompassing both reduced sleep quality and specific sleep disorders. Since a substantial proportion of the population will experience sleep disturbances with potential consequences for health and quality of life [12], they represent an important public health issue. However, our understanding of sleep disturbances, particularly the physiological pathways linking sleep disturbances with health, remains unclear.

The allostatic load (AL) model has been suggested as a framework for understanding the adverse health effects of sleep

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Glossary of terms

AL	allostatic load
BF	Bayes factor
BMI	body mass index
BT	bedtime
ES	effect size
ESr	effect size correlation
K	the number of studies
fH0	fixed-effect null hypothesis
fH1	fixed-effect alternative hypothesis
PICO	population, intervention, comparison and outcome
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PROSPERO	the international prospective register of systematic reviews
rH0	random-effects null hypothesis
rH1	random-effects alternative hypothesis
RT	rise time
SE	sleep efficiency
SOL	sleep onset latency
TIB	time in bed
TST	total sleep time
WASO	wake after sleep onset
WHR	waist/hip ratio

disturbances [13]. The AL model was initially developed to describe the physiological mechanisms underlying the association between stress and disease. The process of adapting to stressful events and circumstances involves increased fluctuation and elevated activity across multiple regulatory biological systems. The AL model posits that while this process of allostasis (i.e., stability through change) is adaptive in the short term, it may over time lead to dysregulation (i.e., allostatic overload), predisposing the organism to disease [14]. An initial operational definition of AL was presented in 1997 by Seeman and colleagues [15] as a multi-system composite measure of biomarkers including systolic and diastolic blood pressure, waist-hip ratio, serum high-density lipoprotein, total cholesterol, glycosylated hemoglobin, dehydroepiandrosterone sulfate, cortisol, epinephrine, and norepinephrine. This index was found to predict increased risk of cardiovascular disease and decline in cognitive and physical functioning. Many studies have examined associations of AL indices with mental and physical health outcomes, including all-cause mortality, and AL is increasingly used as a model and measure to understand and quantify the toll of chronic stress [16]. Because measures of AL incorporate biomarkers from several regulatory systems (e.g., neuroendocrine, immune, cardiovascular, and metabolic systems), they may be influenced by not only psychological stressors but also behavioral factors such as dietary intake, physical activity, and sleep – the focus of the present review.

Sleep is likely to be associated with AL for several reasons. First, sleep is a biological process that depends on allostatic and homeostatic processes [17,18]. Second, stress is central to the AL model, and sleep problems are well-known behavioral consequences of stress [19,20]. Third, sleep difficulties may themselves represent a stressor, not only psychologically but also physiologically, as sleep is an important mechanism driving hormone release, cardiovascular activity, and metabolism [13,21]. This link is likely to be bidirectional in that physiological dysregulation of, for example, the hypothalamic–pituitary–adrenal axis may, in turn, reduce sleep quality [22,23]. Finally, because sleep deprivation has been shown to increase stress reactivity [23,24], it may create a vicious cycle whereby insufficient sleep increases an individual's vulnerability to the detrimental effects of stress.

Stress is just one risk factor shared by sleep and AL [17,25]. Thus, sleep may represent a pathway from several risk factors, e.g., lifestyle behaviors, socioeconomic disadvantage, poor social networks, to AL and vice versa. Similarly, because sleep disruptions perturb many of the physiological systems subsumed in AL indices, AL could act as a core mechanism linking sleep disruption to adverse health outcomes.

Numerous studies have examined associations between sleep and different health conditions [26], as well as with individual AL components such as neuroendocrine activity [23] and inflammation [27]. However, these systems are highly interconnected [28], and examining the association between sleep and whole-body multi-system physiological dysregulation could improve our understanding of the associations between sleep and health, with implications for treatment.

In this, to the best of our knowledge, first systematic review and meta-analysis on the topic, we summarize available findings on the association between sleep and AL. Our hypothesis was that sleep disturbance would be associated with higher AL scores. We also hypothesized a non-linear relationship between sleep duration and AL, with both short and long sleep being associated with higher AL. Finally, if an association was established, we planned to explore potential moderators thereof, such as participant characteristics (e.g., sex, age, whether it is a clinical sample) and study characteristics (e.g., whether the sleep AL-association was the primary focus of the study, number of biomarkers and physiological systems included in the AL index, covariate adjustment, study quality score).

Methods

This review was registered in the International prospective register of systematic reviews (PROSPERO) under ID #177881 and conducted in accordance with the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations [29].

Data sources and searches

Studies were identified by searching electronic databases PubMed, Embase, PsycInfo, and Web of Science. Search terms were selected using the PICO (population, intervention, comparison, and outcome) approach [30]. Sleep-related search terms were 'sleep' and names of specific sleep-related disorders or conditions that do not themselves contain the word 'sleep'. The full search string was (sleep* OR insomnia* OR somnipathy OR hypersomnia OR "excessive somnolence" OR hypersomnolence OR parasomnia* OR dyssomnia* OR "pavor nocturnus" OR "night terror" OR narcolepsy OR "restless leg syndrome") AND ("allostatic load" OR allosta*). Searches were conducted for the period from September 1993 (when the AL model was first introduced [14]) to January 14th 2022. Backward searches (snowballing) of reference lists and forward searches (citation tracking) were performed to identify additional records. The search was conducted by two independent researchers (DSC and LMW).

Selection and data extraction

Retrieved studies were evaluated based on predefined inclusion and exclusion criteria. Only English-language reports of studies of human participants published in peer-reviewed sources were eligible for inclusion. Studies had to include quantitative data on the association of relevant sleep measures, e.g., insomnia severity, sleep quality, and sleep duration, and the sleep diary variables of bedtime (BT), rise time (RT), wake after sleep onset (WASO), sleep onset latency (SOL), time in bed (TIB), total sleep time (TST), and sleep efficiency (SE), with AL. Sleep variables could be self-reported or objectively assessed (e.g., with actigraphy), whereas AL had to be objectively measured. Studies using clinimetric and questionnaire-based assessments of AL were excluded (e.g., Tomba & Offidani [31]). Measures of AL are sometimes referred to using other terms, e.g., multi-system biological risk or physiological dysregulation. For this reason, it was not a criterion that the index measure be termed AL, but studies which did not include a composite score of biomarkers from at least two regulatory systems were excluded, as were studies on other biomarker indices, such as metabolic syndrome. Studies based on healthy populations as well as clinical/patient populations were eligible for inclusion. As the link between sleep and AL is likely to be bidirectional, cross-sectional studies were also included. Likewise, sleep or AL could operate as the independent variable. Finally, publications which did not constitute primary original empirical research, e.g., reviews, meta-analyses, books/book chapters, and conference proceedings were excluded.

Study selection and data extraction were performed by two reviewers (DSC and LMW) using Covidence software (Veritas Health Innovation, Melbourne, Australia; http://www.covidence.org/). After duplicates were removed, screening by title, abstract, and then full text was conducted, and reasons for exclusion registered. If a full text was unavailable, this was requested from the corresponding author. In cases of disagreement, a third reviewer (AA) was consulted.

Data extraction was performed according to *a priori* determined characteristics, including 1) citation details, 2) study characteristics, 3) methods, 4) study findings, 5) study funding source, and 6) possible conflicts of interest (see Appendix 1 for more details). To increase comparability of AL indices across studies, we classified biomarkers into systems according to the method used by Juster et al. [32], irrespective of how the study authors had defined the systems. This entails a categorization of commonly used biomarkers into five types: neuroendocrine (e.g., cortisol, catecholamines), immune (e.g., interleukin-6, tumor necrosis factor-alpha, C-reactive protein, fibrinogen), metabolic (e.g., cholesterol, triglycerides, glucose, creatinine), cardiovascular and respiratory (e.g., systolic and diastolic blood pressure, heart rate/pulse), and anthropometric (waist/hip ratio, body mass index).

Study quality assessment

Quality assessment was based on the guidelines for Observational Cohort and Cross-Sectional Studies and Controlled Intervention Studies from the National Heart, Lung, and Blood Institute of the National Institutes of Health [33]. We considered sex, age, race and BMI (body mass index) or WHR (waist/hip ratio) to be primary potential confounders of the sleep-AL association. Three additional items were added: 1) "Did the AL index include at least one primary mediator and three secondary outcomes?" [34] Indices which include both of these are in greater concordance with the original AL construct. Primary mediators included stress-related hypothalamic–pituitary–adrenal axis hormones, catecholamines, and specific cytokines [35], whereas secondary outcomes referred to disturbances in physiological systems, e.g., inflammation, dyslipidemia, or hypertension; 2) "Were sleep disturbance and other sleep characteristics assessed with relevant measures, e.g., validated scales of sleep quality or insomnia and standard sleep diaries?"; 3) "If multiple comparisons were made, did the authors adjust results accordingly?" See Appendix 1 for a complete list of quality assessment items. Scores were 0 ("no"), 0.5 ("partly/unclear"), and 1 ("yes"), resulting in a total quality score range of 0–17. If an item was not met or not reported, it was scored 0. In addition, only relevant items were included, i.e., item 13 regarding loss to follow-up was not included in the final score for cross-sectional studies. Quality assessment was performed by two independent reviewers (DSC and LMW) and subjected to interrater reliability analyses [36]. Disagreements were resolved by discussion. A quality score percentage was calculated by summing ratings and dividing the sum by the number of applicable items. Lower percentages represent a higher risk of bias. In the meta-analysis, associations between effect sizes (ESs) and quality scores were explored with meta-regression.

Statistical analysis

All studies reporting an association between sleep and AL were eligible for inclusion in the meta-analysis. Studies needed to report results as either correlations, means and standard deviations, odds ratios, or provide other data that could be converted into an ES. In case of insufficient data, we attempted to contact the authors.

Frequentist meta-analytical strategy

The ES correlation (ESr) [37] was used as the standardized ES. Pooled ESs and 95% confidence intervals were calculated for each of the analyzed sleep variables using the inverse variance method, taking into account the precision of each study. A random-effects model was used in all analyses, with positive values indicating ESs in the hypothesized direction. If studies reported results for more than one measure per outcome, the ESs were averaged across outcomes so that only one result per study was used in each data synthesis, thereby ensuring the independence of results.

Heterogeneity was explored using Q and I^2 statistics [38]. Because of the generally low statistical power of heterogeneity tests, a more liberal p-value of $\leq$0.10 was used [39]. The I^2 statistic estimates the variance in a pooled ES accounted for by heterogeneity in the sample of studies and is unaffected by the number of studies (K) [40]. If the results indicated heterogeneous ESs ($I^2 > 0.0$), we calculated the 95% prediction interval that quantifies the distribution of the ESs, indicating that in 95% of cases, the true effect of a new and unique study (from the same family of studies) will fall within this range [41].

Publication bias was evaluated with funnel plots and Egger's test [42–44]. If the results indicated possible bias, adjusted ESs would be calculated with the Duval and Tweedie trim-and-fill method [45].

If the results indicated heterogeneity ($I^2 > 0.0$), possible sources of between-study differences were explored with meta-regression based on random-effects models and estimated with the Maximum Likelihood method when data were available for $\geq$8 studies. Possible moderators of the associations between sleep and AL were: 1) study mean sample age, 2) percent women, 3) the number of biomarkers and 4) the number of physiological systems included in the AL outcome, 5) whether the association between sleep and AL was the primary focus of the study 6) whether the results were adjusted for covariates, 7) whether the study was based on a clinical sample, and 8) the study quality score.

Analyses were conducted with Comprehensive Meta-Analysis, Version 3 [46], and supplementary formulas, such as formulas for calculating the prediction interval in Microsoft Excel.

Supplementary Bayesian analyses

To aid interpretation of the results, we also conducted a Bayesian Model-Averaged meta-analysis [47] of the associations between the sleep variables of sleep disturbance, short sleep, and long sleep and the outcome variable of AL. The procedure examines the results of four models: 1) Fixed-effect null hypothesis (fH0), 2) fixed-effect alternative hypothesis (fH1), 3) random-effects null hypothesis (rH0), and 4) random effects alternative hypothesis (rH1). The Bayesian meta-analysis thus avoids selecting a fixed- or random-effects model and addresses two questions in light of the observed data: What is the plausibility that the overall association is non-zero, and is there between-study variability in the ESs beyond what can be explained by sampling error? We chose an uninformed prior probability, i.e., 25%, of the four models and 2000 iterations. Concerning parameter distributions, we chose previously recommended defaults [47]. We thus used a zero-centered Cauchy prior with a scale of 0.707 for the ES. For the between-study variation, we used an empirically informed prior distribution of non-zero between-study deviation estimates based on standardized mean difference ESs from 705 meta-analyses published in Psychological Bulletin between 1990 and 2013 [48]. This distribution has been approximated by an Inverse-Gamma (1, 0.15) prior to the standard deviation (Tau) [47]. The Bayesian analyses were conducted with the computer software JASP (Version 0.12.2) [49].

Results

Search results and study selection

As seen in Fig. 1, the initial search identified a total of 707 records. After removal of 312 duplicates and screening of 395 titles and abstracts, 51 records were subjected to full-text screening, 31 of which were excluded based on prespecified criteria, and one additional duplicate was identified. Two additional records were excluded: although studies of children were not excluded beforehand, one study of children was excluded as all remaining studies investigated adults, thereby limiting comparability. Three studies were based on the Midlife in the United States (MIDUS) study [50–52]. Two of these reported on the same sleep disturbance outcome [50,52], so to avoid overlap, we only included the study that reported unadjusted results focused on the sleep-AL association [50]. Thirty-four studies were thus excluded at this stage. Initial agreement between the reviewers was 93% (Cohen's κ of 0.71) after the title and abstract screening and 86% (Cohen's κ of 0.69) after full-text screening. Seventeen publications were selected for inclusion in the systematic review [50,51,53–67]. Of these, one article reported findings from two independent studies [66], which were treated accordingly. Three studies were based on NHANES data [55,65,66 (study b)]. Two of these studies reported on sleep disturbance using different measurement approaches; one assessed sleep disturbance using extensive information about insomnia symptoms [55], and the other used just a single yes/no item (i.e., self-reported trouble sleeping) [65]. It was therefore decided to exclude the latter [65] from the meta-analysis. Thus, in the meta-analysis, 16 publications based on 17 independent samples were included [50,51,53–64,66,67].

Study characteristics

The included studies are shown in Table 1. The studies were published between 2011 and 2021 [50,51,53–67] and investigated 39,061 participants. Two studies used the MIDUS dataset with a potential 436 participant overlap [50,51], and three studies used the NHANES dataset ([55,65,66 (study b)]) with a potential overlap of 8412 participants. For the meta-analysis, overlapping samples were not included in the same analysis. Sample sizes ranged from 38 to 10,406, the sample mean age from 19.4 to 67.3 y, and the percentage of women from 31% to 100%. Studies were conducted in the USA (K = 14), Australia (K = 1), Denmark (K = 1), and Italy (K = 1).

The majority of studies were cross-sectional, except a randomized controlled trial where change in sleep quality from baseline to 4 or 16 mo was compared with the likelihood of remaining in an AL high-risk group [54]. In 14 studies [50,51,54,56–63,65–67], sleep was defined as the independent variable in the sleep-AL association. The sleep-AL association was the primary focus of eight studies [50,51,54–56,58,60,64]. In the remaining studies, sleep or AL was included as a covariate or a mediator, or was not a part of the study aims.

Table 2 describes the AL and sleep measures and study findings. Sleep measures included sleep duration, sleep quality, disturbed sleep, SE, BT, RT, TST, SOL, WASO, number of awakenings, insomnia and insomnia components, sleep apnea and sleep apnea symptoms, diagnosed sleep disorder, and various items on self-reported sleep problems. The most frequently used method of sleep assessment was the Pittsburgh sleep quality index (PSQI) (K = 9). Other assessment methods included actigraphy, clinical interviews, and other questionnaires, e.g., the Karolinska Sleep Questionnaire. The overlapping studies ([50,51] and [55,65,66 (study b)], respectively) all reported on different sleep measures.

The average number of biomarkers included in the AL indices was 12 (range 3–23), representing an average of four (range 2–5) physiological systems. The most frequently represented systems were metabolic, cardiovascular and respiratory, and anthropometric. A majority of studies based the AL index on biomarker dichotomization using risk cut-offs. Other methods included z-score summation and modeling based on factor analysis or principal component analysis.

Quality assessment

Results of the quality assessment (Table S1) indicated that the vast majority of studies were of high quality with respect to outlining clear objectives, definition of the study population, application of inclusion and exclusion criteria, and examining different levels of exposure. However, with respect to study design, all but one study were limited primarily due to the use of a cross-sectional design. Hence, the exposure was generally not assessed prior to the outcome, there was insufficient time to see an effect, and the exposure was not assessed more than once.

Qualitative synthesis

Fifteen studies examined the association between sleep quality or disturbance (e.g., insomnia) and AL [50,53–58,60–67], a majority of which found poor sleep quality or disturbance to be associated with higher AL scores [50,53,55–58,62,65,66 (study a)]. However, two of these studies [55,65] were based on potentially overlapping samples from the NHANES, though reporting on different sleep measures. Thus, both self-reported insomnia symptoms [55] and self-reported trouble sleeping [65] was associated with higher AL in the NHANES.

Four studies examined the association between sleep duration and AL using categorical sleep variables (e.g., long or short sleep compared to normal) [50,55,56,59], three of which examined both short and long sleep [50,56,59]. Of these, one study found both short and long sleep duration to be associated with higher AL scores [50], whereas another found higher AL in long sleepers only [56]. In the third study [59], participants with very short sleep

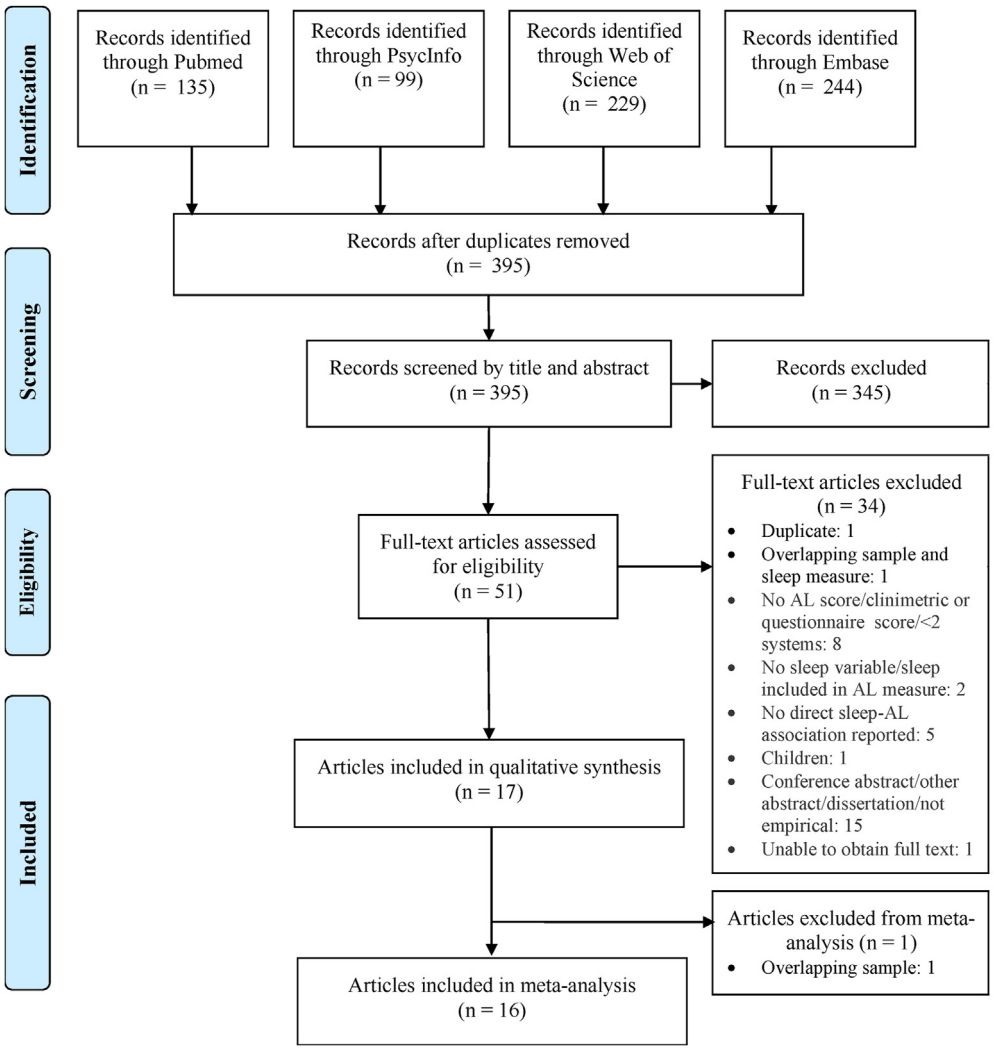

Fig. 1. PRISMA flow diagram.

(≤5 h) were found to have comparable AL scores to those with normal sleep (7–8 h), whereas those with short sleep (6 h) had lower mean AL, and those with long sleep (≥9 h) had higher mean AL. Finally, one study only examined short compared to normal sleep [55], finding an increased prevalence of high AL scores among short sleepers.

Two studies examined the association of continuous sleep duration with AL [51,66 (study b)]. One did not find self-reported hours of sleep per night to be significantly associated [66 (study b)], whereas the other, examining actigraphy-derived TST, found shorter sleep duration to be associated with higher AL [51]. This study also examined sleep intra-individual variability as a predictor of AL, and found later mean BT, and more variable SOL and WASO, to be associated with higher AL [51].

Two studies examined the joint effects of sleep quality and duration [50,56]. In one study, restricting analyses to long sleepers showed only those reporting poor sleep quality to have significantly elevated AL scores [50]. In the other, though short sleep in itself was not associated with higher AL, those who suffered from both short and disturbed sleep had higher AL scores than those with normal duration and undisturbed sleep [56].

Meta-analysis

Of the 17 studies included in the systematic review, 14 provided data on associations between sleep disturbance (including sleep quality) and AL [50,53–58,60–64,66,67], three examined long vs. normal sleep [50,56,59], four investigated short vs. normal sleep [50,55,56,59], and two examined sleep duration as a continuous variable [51,66 (study b)].

Sleep disturbance and AL

As seen in Table 3, 14 independent studies had investigated sleep disturbance and associations with AL in a total of 14,423 study participants. The pooled results yielded a small, statistically significant association (ESr = 0.09, $p < 0.001$) between sleep disturbance and higher AL [68]. Results are shown in Fig. 2. The Bayesian Model-Averaged meta-analysis revealed strong evidence for the alternative hypothesis, i.e., that the association is non-zero, corresponding to a Bayes Factor (BF), i.e., the likelihood ratio of the marginal likelihood of the two competing hypotheses [69], of 14.5. The statistically significant Q-value and the I^2 of 70.4 indicated that the associations were heterogeneous, an interpretation supported

Table 1
Overview of included studies.

Study	Year	N	Age (mean; SD)	% Female	Study design	Population/setting
Alebna P & Maleki M [63]	2021	2105	Migraineurs: 46.88 (2.81); Controls: 46.97 (2.71)	100%	Cross-sectional[a]	Clinical and community: Diagnosed with migraine headaches (per self-report) and controls
Bei B et al. [51]	2017	436	54.11 (11.7)	60.3%	Cross-sectional	Community (MIDUS)
Berger M et al. [53]	2019	329	YPC group: 19.39 (3.07); WPHC group: 40.3 (16.92)	YPC: 56.6%; WPHC: 55.6%	Cross-sectional	Community
Carroll JE et al. [50]	2015a	1023	54.5 (11.8)	56%	Cross-sectional	Community (MIDUS)
Carroll JE et al. [54]	2015b	109	CBT: 64.8 (6); Tai Chi: 67.3 (7.5); Sleep seminar: 66 (7.7)	CBT: 78.7%; Tai Chi 64.1%; Sleep seminar 69.6%	Randomized controlled trial	Clinical: Primary insomnia from community
Chen X et al. [55]	2014	3330	Not reported	47.4%	Cross-sectional	Community (NHANES)
Clark AJ et al. [56]	2014	5226	54 (4)	31%	Cross-sectional	Community (CAMB)
Cothran FA et al. [64]	2021	142	55 (9.7)	86%	Cross-sectional	Dementia caregivers in community (Great Village study)
Hawkley LC et al. [57]	2011	208	58.4 (−)	53%	Cross-sectional	Community (CHASRS)
Hux VJ et al. [58]	2017	103	29.8 (5)	100%	Cross-sectional	Clinical: Pregnant women from community (Sleep in Pregnancy Study)
Lunyera J et al. [59]	2019	5177	55.3 (12.8)	63%	Cross-sectional	Community (Jackson Heart Study)
Martucci M et al. [60]	2020	38	61 (5)	100%	Cross-sectional	Clinical: Bellaria Hospital, Bologna
Memiah P et al. [65]	2021	10,406	Not reported	51%	Cross-sectional	Community (NHANES)
Rogers JM et al. [66]	2021	Study a: 752; Study b: 8412	Study a: 37.7 (11.2) Study b: 42.8	Study a: 37.2% Study b: Not reported	Cross-sectional	Study a: Clinical (Individuals seeking treatment for opioid use disorder) and community; Study b: community (NHANES)
Shadlow J et al. [67]	2021	302	Native American: 30.60 (12.67); Non-hispanic white: 28.56 (13.53)	54%	Cross-sectional	Community (OK-SNAP)
Sotos-Prieto M et al. [61]	2015	787	56.7 (7.4)	72.7%	Cross-sectional	Community (The Boston Puerto Rican Health Study)
Tomfohr LM et al. [62]	2016	176	35.16 (9.70)	44.32%	Cross-sectional	Community

Abbreviations: CAMB = Copenhagen aging and midlife biobank; CBT = cognitive behavioral therapy; CHASRS = Chicago health, aging, and social relations study; MIDUS = midlife in the United States; NHANES = national health and nutrition examination survey; OK-SNAP = Oklahoma study of Native American pain risk; WPHC = well persons health check; YPC = Young persons check.
[a] baseline analysis of a longitudinal study.

by the supplementary Bayesian analysis yielding extremely strong evidence for heterogeneity as indicated by the BF of 2280. Sensitivity analyses examining non-clinical and clinical samples separately did not indicate substantial differences in associations (ESr = 0.11, $p < 0.001$ vs ESr = 0.16, $p = 0.011$, respectively), though restricting the analysis to non-clinical samples did reduce heterogeneity. A visual examination of the funnel plot and the statistically non-significant Egger's test ($p = 0.925$) suggested that publication bias was not an issue.

Long sleep and AL

The three studies of long versus short sleep included a total of 6950 participants. The aggregated results revealed that when compared to normal sleep (7–8 h), long sleep (≥9 h) was significantly associated with higher AL, with the association corresponding to a small ESr (0.12, $p = 0.003$). This result was not supported by the supplementary Bayesian analysis, which favored the null-hypothesis. The small BF of 1.8 only corresponds to anecdotal evidence. Both the frequentist and Bayesian analysis found support for heterogeneity with an I^2 of 89.7% and a BF of 867 in favor of heterogeneity. The small number of studies did not allow for the examination of possible publication bias. Results for long and short sleep, respectively, are shown in Supplementary Fig. S1.

Short sleep and AL

The association found in the four studies with data on short (≤5 h or ≤6 h) vs. normal sleep for a total of 12,367 participants did not reach statistical significance ($p = 0.069$), and Bayesian analysis offered moderate evidence in favor of the null hypothesis corresponding to a BF of 7.7. Results were heterogeneous with an I^2 of 89.1% and the likelihood of non-heterogeneity less than 1%. The possibility of publication bias was not examined.

Sleep duration

Combining the results of the two studies [51,66 (study b)] which had examined the association between sleep duration and AL, revealed a small, negative, non-significant association (ESr = −0.06 (N: 8845); $p = 0.364$).

Moderator analyses

Results of the moderator analyses are shown in Table 4. Only the percentage of women in the sample was found to moderate the effect, with a larger proportion of women being statistically significantly associated with weaker associations between sleep disturbance and AL ($p = 0.015$). None of the remaining moderator analyses reached statistical significance ($p > 0.05$).

Discussion

The results of the present systematic review and meta-analysis provide tentative support for the AL model's relevance to sleep medicine [17]. A frequentist approach found a significant association between sleep disturbance and higher AL and a small but significant association between long sleep and higher AL. However, analyses suggest that these findings are limited by heterogeneity. No association was found between short sleep or continuous sleep duration and AL.

Table 2
Overview of measures and findings of included studies.

Study	Year	Method of AL score construction	# of physiological systems (range 1–5)	# of biomarkers	List of included biomarkers	Sleep variables	Findings
Alebna P & Maleki M [63]	2021	Dichotomization of biomarkers, distribution-based, then summed across markers.	5	9	SBP, DBP, CRP, HDL, total cholesterol, WHR, blood glucose, triglycerides, dehydroepiandrosterone.	Number of nights in the past 14 d with trouble falling asleep, waking up several times during the night, and waking up earlier than usual.	Adjusted: neither sleep initiation (OR = 1.009 [0.971; 1.051]), sleep maintenance (OR = 1.016 [0.964; 1.070]) or early awakening (OR = 1.010 [0.959; 1.064]) were significantly associated with risk of high AL.
Bei B et al. [51]	2017	Bifactor model.	5	23	Resting pulse pressure, SBP, HOMA-IR, blood glucose, HbA1c, cortisol, DHEA-S, CRP, IL-6, fibrinogen, soluble E-Selectin, soluble ICAM-1, triglycerides, HDL, LDL, WHR, resting pulse rate, measures of HR variability (SD of beat-to-beat intervals, root mean square of successive differences, low- and high-frequency spectral power), epinephrine, norepinephrine.	Actigraphy (BT, RT, TST, SOL, WASO, SE)	Unadjusted: later mean BT and shorter mean TST associated with higher AL. More variable SOL and WASO associated with higher AL over and above intraindividual means. Adjusted: later mean BT associated with AL.
Berger M et al. [53]	2019	Dichotomization of biomarkers based on clinical guidelines where available, distribution for remaining. Proportion of high-risk biomarkers within each system summed.	5	14	HR, SBP, DBP, cortisol, IL-6, TNFa, hs-CRP, triglycerides, HDL, LDL, total cholesterol, blood glucose, HbA1c, BMI.	Insomnia item from Adapted Patient Health Questionnaire 9	Adjusted: insomnia associated with higher AL in YPC subgroup
Carroll JE et al. [50]	2015a	Dichotomization of biomarkers, distribution-based. Proportion of high-risk biomarkers within each system then summed.	5	22	SBP, pulse pressure, HR, triglycerides, HDL, LDL, BMI, WHR, blood glucose, HbA1c, HOMA-IR, CRP, IL-6, e-Selectin, ICAM-1, fibrinogen, norepinephrine, epinephrine, HR variability, cortisol, DHEA-S.	PSQI sleep duration and global sleep quality	Adjusted: compared to normal sleepers, short sleepers (<5 h per night) and long sleepers (≥8.5 h per night) had higher AL. Compared to those with normal sleep quality, those with poor sleep quality (≤5 on the PSQI) had higher AL.
Carroll JE et al. [54]	2015b	Dichotomization of biomarkers based on clinical guidelines where available, distribution for remaining. One measure constructed as a dichotomous variable (high AL ≥ 4 biomarkers in abnormal range), another as a summation of z-score distance from cut points, then averaged and multiplied by number of biomarkers.	2	8	HDL, LDL, triglycerides, fibrinogen, CRP, blood glucose, insulin, HbA1c.	PSQI global score	Improvement in sleep quality from baseline to 16 mo associated with significant shift into lower risk group. In baseline data the author provided, no significant difference in sleep quality between risk groups.
Chen X et al. [55]	2014	Dichotomization of biomarkers based on distributions and clinical guidelines, then summed. Converted into a dichotomous variable (high AL ≥ 3).	4	9	SBP, DBP, HR, total cholesterol, HDL, BMI, HbA1c, CRP and albumin.	Sleep apnea, sleep apnea symptoms, insomnia, short sleep duration, sleep disorder diagnosed by a physician or other	Unadjusted: higher prevalence of high AL among adults with diagnosed sleep apnea, snoring, snorting/stop breathing, insomnia, short sleep duration (<6 h), diagnosed sleep disorder than those without sleep disturbances. Adjusted: Associations remained for sleep apnea, insomnia, and short sleep duration.
	2014		4	8			

(*continued on next page*)

Table 2 (*continued*)

Study	Year	Method of AL score construction	# of physiological systems (range 1–5)	# of biomarkers	List of included biomarkers	Sleep variables	Findings
Clark AJ et al. [56]		Dichotomization of biomarkers based on clinical guidelines where available, distribution for remaining, then summed.			SBP, DBP, HbA1c, triglycerides, ratio of total cholesterol to HDL, hs-CRP, IL-6, WHR.	Sleep duration and disturbed sleep assessed by the Karolinska sleep questionnaire	Adjusted: long sleep (≥9 h) associated with higher AL compared to sleeping 7–8 h. Short sleep (≤6 h) not associated with AL. Disturbed sleep associated with higher AL.
Cothran FA et al. [64]	2021	Dichotomization of biomarkers based on clinical guidelines, then summed.	4	12	IL-6, CRP, SBP, DBP, BMI, WHR, triglycerides, cholesterol, HDL, LDL, blood glucose, insulin.	PSQI global score	Adjusted: allostatic load showed only a slight, non-significant association with increased sleep problems ($r = 0.13$, $p = 0.14$).
Hawkley LC et al. [57]	2011	Conversion of biomarkers to z-scores, summed across systems.	4	9	Norepinephrine, epinephrine, cortisol, SBP, DBP, cholesterol, HDL, HbA1c, waist circumference	PSQI global score	Adjusted: poor sleep quality associated with higher AL.
Hux VJ et al. [58]	2017	Within-system dichotomization of biomarkers, based on distributions of a nationally representative sample. Proportion of high-risk biomarkers within each system then summed.	4	9	SBP, DBP, pulse pressure, pre-pregnancy BMI, total cholesterol, HDL, triglycerides, TNFa, IL-6.	PSQI global score	Unadjusted: poor sleep quality associated with higher AL. Adjusted: nonsignificant.
Lunyera J et al. [59]	2019	Conversion of biomarkers to z-scores, averaged first within and then across systems.	4	11	Cortisol, HbA1c, total cholesterol, LDL, HDL, WHR, SBP, DBP, resting heart rate, CRP, white blood cell count.	Habitual sleep duration and quality assessed using modified Berlin Sleep Questionnaire	Unadjusted: no difference in AL between very short sleep (≤5 h) and normal sleep (7–8 h) but short sleep (6 h) significantly associated with lower AL, and long sleep (≥9 h) with higher AL.
Martucci M et al. [60]	2020	Dichotomization of biomarkers based on clinical guidelines, then summed.[a]	4	10	BMI, SBP, DBP, WHR, HbA1c, triglycerides, total cholesterol, HDL, LDL, hs-CRP.	Actigraphy (SE, WASO, awakenings' number), PSQI global score, obstructive sleep apnea assessed using the Berlin Questionnaire	AL scores did not significantly differ in insomnia patients compared to normal levels (unadjusted).
Memiah P et al. [65]	2021	Dichotomization of biomarkers, then summed.	4	11	SBP, DBP, HDL, triglycerides, total cholesterol, serum albumin, CRP, fibrinogen, creatinine clearance, HbA1c, BMI.	Self-reported sleep problems (yes/no)	Unadjusted: OR for high AL associated with sleep problems: 1.44, $p < 0.001$. Adjusted: OR for high AL associated with sleep problems 1.39, $p < 0.001$.
Rogers JM et al. [66]	2021	Study a: Weighted z-scores summed across markers. Clinically based dichotomized score in sensitivity analyses. Study b: Dichotomized, summed across markers. Distribution-based cut-offs used for albumin and creatinine.	Study a: 5; Study b: 3	Study a: 12; Study b: 10	Study a: SBP, DBP, WHR, BMI, creatinine clearance, albumin, HDL, HbA1c, CRP, DHEA-S, total cholesterol ratio, triglyceride Study b: SBP, DBP, resting heart rate, total cholesterol, HDL, HbA1c, urine albumin, urine creatinine, BMI, waist circumference.	Study a: PSQI global score Study b: Self-reported average hours of sleep per night	Study a: adjusting for age, poor sleep quality was not significantly associated with AL ($\beta = 0.06$ $p = 0.07$). Unadjusted for age because main predictor was years of regular drug use as a proportion of age, poor sleep quality was significantly associated with higher AL ($\beta = 0.10$, $p = 0.01$). Study b: AL not significantly associated with average sleep hours ($\beta = -0.01$, $p = 0.37$).
Shadlow J et al. [67]	2021	Standardized component scores for each participant generated based on principal component analyses.	2	3	BMI, blood pressure/ mean arterial pressure, HR variability	PSQI global score and Insomnia severity index	Neither PSQI global score ($r = 0.038$, $p = 0.512$) or Insomnia Severity Index score ($r = 0.097$, $p = 0.093$) was significantly associated with AL.[a]
Sotos-Prieto M et al. [61]	2015	Dichotomization of biomarkers based on clinical guidelines where available, distribution for remaining, then summed. Converted into a dichotomous variable (high AL ≥ 4).	4	10	Cortisol, norepinephrine, epinephrine, DHEA-S, HDL, total cholesterol, SBP, DBP, HbA1c, waist circumference.	Sleep quantity and quality assessed in self-report questionnaire	Unadjusted: no significant difference in sleep scores for high and low AL groups. Adjusted: Nonsignificant odds ratio for high AL resulting from a 5-unit change in sleep score.

Table 2 (*continued*)

Study	Year	Method of AL score construction	# of physiological systems (range 1–5)	# of biomarkers	List of included biomarkers	Sleep variables	Findings
Tomfohr, LM et al. [62]	2016	Conversion of biomarkers to z-scores, summed across systems.	5	11	SBP, DBP, WHR, blood glucose, HDL, ratio of HDL to total cholesterol, norepinephrine, epinephrine, cortisol, CRP, IL-6.	PSQI global score	Adjusted: poor sleep quality associated with higher AL.

Abbreviations: AL = allostatic load, BMI = body mass index, BT = bedtime, CRP = C-reactive protein, DBP = diastolic blood pressure, DHEA-S = dehydroepiandrosterone sulfate, HbA1c = glycated hemoglobin, HR = heart rate, HDL = high-density lipoprotein, HOMA-IR = the homeostasis model of assessment of insulin resistance, HR = heart rate, hs-CRP = high-sensitivity CRP, IL-6 = interleukin 6, ICAM-1 = intracellular adhesion molecule-1, LDL = low-density lipoprotein, PSQI = Pittsburgh Sleep Quality Index, RT = rise time, SBP = systolic blood pressure, SD = standard deviation, SE = sleep efficiency, SOL = sleep onset latency, TNFa = tumor necrosis factor alpha, TST = total sleep time, WASO = wake after sleep onset, WHR = waist-hip ratio, YPC = Young Persons Check.
[a] Via correspondence with author.

Despite indications of heterogeneity, our findings are in line with previous meta-analyses showing sleep disturbance to be associated with individual AL-related factors, such as hypertension [70], metabolic syndrome [71], type 2 diabetes [72], and obesity [73].

Regarding sleep duration, while the included studies are few, confidence intervals wide, and the evidence thus limited, our results are generally consistent with existing literature on the association between sleep duration and disease and mortality. While short sleep has been found to increase the odds of adverse health outcomes, the detrimental health effects of prolonged sleep are usually reported to be stronger. Thus, in a regression-based meta-analysis of 40 prospective studies on the association between sleep duration and risk of all-cause mortality showing a J-shaped association between sleep duration and all-cause mortality; the risk was substantially higher for very long sleep

Table 3
Pooled associations between sleep characteristics (sleep disturbance, short sleep, long sleep, sleep duration) and allostatic load.

Independent variable	Heterogeneity						Pooled effect size			
	K[a]	N[b]	Q	p	I^2	T^2	ESr[c]	95% CI	p[d]	95%PI[e]
Sleep disturbance[f]	14	14,423	44.0	<0.001	70.4	0.003	0.09	0.05–0.13	**<0.001**	−0.04 to 0.21
- Non-clinical samples	9	11,316	13.1	0.110	38.8	0.001	0.11	0.08–0.14	**<0.001**	0.03–0.19
- Clinical samples	3	250	1.8	0.397	0.0	0.0	0.16	0.04–0.28	**0.011**	NA
Short sleep vs. normal[g]	4	12,367	27.5	<0.001	89.1	0.003	0.05	−0.00 to 0.11	0.069	−0.88 to 0.90
Long sleep vs. normal[h]	3	6950	19.4	<0.001	89.7	0.004	0.12	0.04–0.20	**0.003**	−0.69 to 0.80
Sleep duration	2	8845	6.4	0.011	84.4	0.007	−0.06	−0.18 to 0.07	0.364	NA

[a] K = number of studies.
[b] N = total number of participants.
[c] ESr = effect size correlation.
[d] p-values (two-tailed): Statistically significant ($p < 0.05$) in **bold**.
[e] 95% prediction interval, i.e., the interval in which 95% of future observations from similar studies will fall.
[f] higher values indicate poorer sleep quality/increased sleep disturbance.
[g] Short sleep = ≤5 h or ≤6 h; normal sleep = 7–8 h.
[h] Long sleep = ≥9 h, normal sleep = 7–8 h.

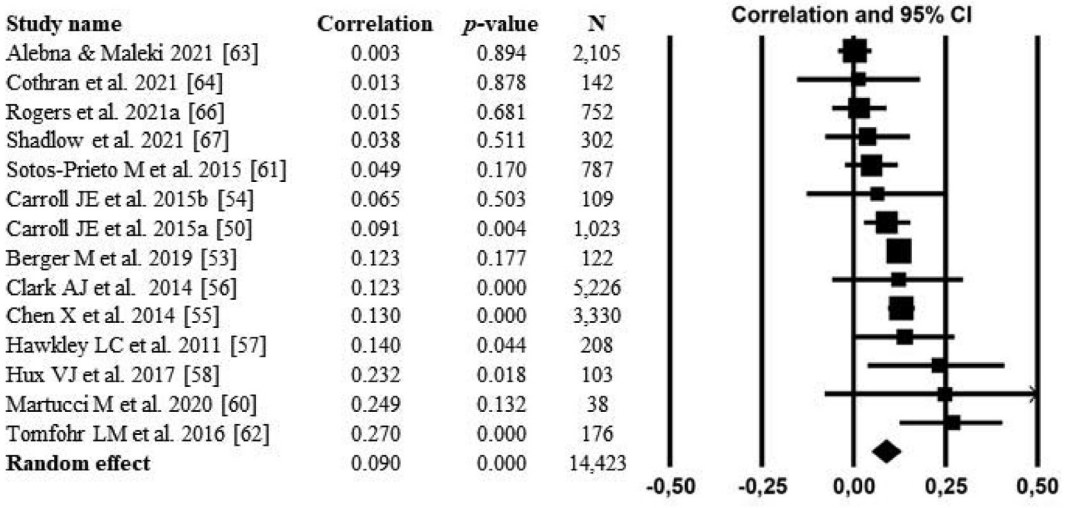

Fig. 2. Forest plot of the associations between sleep disturbance and AL.

Table 4
Moderators of the association between sleep disturbance and allostatic load. Results of exploratory meta-regression.

Moderator[a]	K[b]	Slope[c]	95% CI	p[d]	R^2
Mean sample age	13	−0.001	−0.004 to 0.003	0.807	0.00
Percent women	14	−0.001	−0.002 to −0.001	**0.015**	0.75
Number of biomarkers	14	0.000	−0.008 to 0.009	0.923	0.00
Number of systems	13	0.041	−0.015 to 0.098	0.153	0.09
Sleep-AL association primary focus of study (referent: no)	15	0.013	−0.050 to 0.075	0.695	0.06
Adjusted for covariates (referent: no)	14	−0.044	−0.113 to 0.002	0.058	0.65
Clinical samples (referent: non-clinical)	12	0.047	−0.081 to 0.175	0.471	0.00
Study quality score	14	0.014	−0.015 to 0.043	0.352	0.10

[a] Analyses only conducted for variables with K/parameter in the model ≥8.
[b] K = number of studies in the analysis.
[c] maximum likelihood method.
[d] P-values (two-tailed): statistically significant ($p < 0.05$) in **bold**.

compared with short sleep. Compared with 7 h of sleep, the relative risk of all-cause mortality was 1.25 for 10 h of sleep in contrast to only 1.05 for 4 h of sleep [74]. In the present study, the limited precision of the result for long sleep and the non-significant result for short sleep and continuous sleep duration may reflect the few available studies and insufficient statistical power.

Exactly why prolonged sleep is associated with health risk remains unclear, as is the direction of causality. It has been suggested that an increased need for sleep is an indicator of reduced physiological reserve increasing vulnerability to serious illness [75]. There is also the possibility that prolonged sleep is a consequence of disease or poor health, rather than a risk factor. Subclinical physiological states such as low-grade inflammation, may influence energy levels [76] leaving the question of directionality open.

The results of moderator analyses indicated that the association of sleep disturbance with AL was slightly weaker in samples with a greater proportion of women. While there is an emerging interest in sex differences in AL [77], research on this topic remains limited. Regarding sleep, it is well-established that women have more subjective sleep problems and a higher risk of insomnia, despite having better objective sleep quality [78,79]. Studies on sex differences in the association of sleep with outcomes related to AL, such as cardiometabolic risk, inflammation and mortality [80–82], do not support the interpretation that the effect of sleep disturbance on health is weaker in women compared to men. However, findings are inconsistent [83,84], indicating a need for further research in potential sex differences in the association of sleep with health.

None of the other moderators reached statistical significance, despite considerable variation in, for example, the number of biomarkers included. While this could suggest that the association between sleep and AL is not contingent upon the number of biomarkers, it might still be influenced by the systems encompassed in the AL indices, for which the included studies were more homogeneous.

While the majority of the studies were based on healthy, community-dwelling populations, three were based on clinical groups, i.e., sufferers of insomnia or pregnant women [54,58,60]. With insomnia patients, the tendency to subjectively underestimate the amount of sleep obtained compared to objective assessment is common [85], but since only one [54] of the two [54,60] insomnia patient studies relied on subjective sleep assessment, this is unlikely to represent a major source of bias. Regarding the study on pregnant women [58], it cannot be ruled out that the association between sleep and AL may differ in pregnant populations. However, findings were similar when analyzing non-clinical and clinical samples separately, and the moderator analyses did not indicate moderation by clinical vs. non-clinical sample.

Both sleep and AL may be influenced by psychosocial factors, e.g., stress [51,56]. However, because relatively few of the studies considered the role of such factors, potential confounding or moderation could not be examined. In one study [58], sleep was used as a measure of chronic stress, arguably conflating two related, yet distinct factors.

Strengths and limitations

This review has several strengths. All studies were of high quality with regard to central methodological parameters, including clarity of objectives, the definition of the study population, uniform application of inclusion and exclusion criteria, and the levels of exposure examined. The majority of studies also used well-validated measures of sleep, represented four or more physiological systems in their AL index, and reported the necessary data to calculate ESs. Further, this review was conducted in accordance with the PRISMA [29] guidelines, screening, data extraction and quality assessment performed by two independent reviewers. In the meta-analysis it was possible to analyze several outcomes and potential moderators as well as publication bias, and both a frequentist and Bayesian analysis were undertaken.

A number of limitations should be noted. First, all studies but one were based on cross-sectional data limiting our ability to make causal inferences. Second, the operational definitions and measurements of sleep and AL varied across studies, possibly limiting comparability of findings beyond what it was possible to test in moderator analyses. Thus, the studies included in the analysis on sleep disturbance varied with respect to how they measured sleep disturbance more broadly and sleep quality specifically (see Table 2). As noted in the introduction, we adopted a definition of sleep quality as a multi-faceted construct in line with the PSQI, but allowed the inclusion of studies using, e.g., insomnia diagnosis as well, in order to reflect sleep disturbance more generally. For AL, heterogeneity of measures across studies is frequently noted to be problematic, not least when reviewing and comparing study findings [86–88]. Third, while some of the studies were based on large sample sizes, only few reported data on associations with sleep duration, making those results less robust. Finally, two of the included studies were based on data from the MIDUS and three on the NHANES. However, they each reported on qualitatively different sleep parameters, and none were included in the same meta-analysis, ensuring independence.

Future directions

First, the field would benefit from prospective and experimental studies that assess sleep and AL over time, thus improving the possibility of identifying directionality, causality and temporality. Furthermore, while some AL subcomponents (e.g., neuroendocrine markers) may show acute variation in response to sleep disruption, others (e.g., anthropometric markers) may be affected only after prolonged exposure, necessitating studies of a longer duration.

Second, rigorous methods to assess sleep and sleep problems are important considerations. The strength of association between subjective and objective measures of sleep can vary substantially [89], leading some to suggest that they are in fact different constructs and that best practice is to include both [90]. Since sleep and stress are so closely linked, sole reliance on self-report measures may be problematic, as those who perceive themselves as highly stressed may be more likely to report sleep problems, irrespective of objective sleep quality. Further, it has been indicated that objective measures of sleep duration may help distinguish between different phenotypes of insomnia, with different consequences for health outcomes [91]. Thus, the field would benefit from increased use of more objective methods such as actigraphy.

Third, as suggested in some of the reviewed studies [50,58], our findings could indicate that AL is a possible mechanism linking disordered sleep with disease risk, but as Bei et al. [51] point out, there is a gap concerning knowledge of the association of sleep with overall physiology. The present review underscores the need to better understand physiological mechanisms linking sleep with health. In addition, a more in-depth examination of the associations of different physiological systems (e.g., Clark et al. [56]), with different sleep outcomes could help elucidate differences between sleep disturbance phenotypes. For example, in addition to the sleep variables examined here, circadian misalignment or high intra-individual variability in sleep factors such as total sleep time are also likely predictors of physiological dysregulation, and it has been suggested that circadian disruption may result in neurobehavioral changes, e.g., decreased neuron complexity in the prefrontal cortex which could lead to a reduction in cognitive flexibility and reduce stress resilience [92].

Finally, both sleep and AL are modifiable risk factors. The results of this review suggest that future studies could examine whether interventions that promote sleep quality could potentially be helpful for reducing AL. Conversely, our results also highlight the potential of AL and its subsystems as treatment targets themselves that could improve sleep. The development of such interventions is in its infancy with a recent scoping review finding only six such studies and only four of them reported on interventions that improved AL significantly [93]. The field is ripe for the development of interventions that could target the many facets of AL.

Conclusions

The present review and meta-analysis provides an overview of the existing scientific literature on the sleep-AL association. The meta-analytic results provide tentative evidence that sleep disturbance and prolonged sleep may be associated with higher AL. Short sleep and continuous sleep duration were not found to be associated with AL scores. However, given the limited number of available studies, heterogeneity amongst them, and the lack of longitudinal data, central issues regarding the association between sleep and AL remain unaddressed in current research.

Practice points

1) The allostatic load (AL) construct – a multi-system composite measure of biomarkers – may be useful for understanding the adverse health effects of sleep disturbances.
2) Although AL was originally developed to understand and quantify the toll of chronic stress, sleep is a biological process that depends on allostatic and homeostatic functions. Sleep may be both a behavioral consequence of stress, but may also be a cause of stress.
3) This meta-analysis indicates a small but significant association between sleep disturbance and higher AL.
4) Findings also indicate long sleep ($\geq$9 h) to be associated with higher AL, but no association was found with short sleep or continuous sleep duration.

Research agenda

1) Prospective observational and experimental studies could make a substantial contribution and improve the possibility of identifying mechanisms and causal direction, if any, between sleep and AL.
2) Rigorous methods to assess both objective and subjective sleep and sleep problems are indicated.
3) Further work is needed to better understand physiological mechanisms that link sleep and health.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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Appendix 1. Data extraction and quality assessment items

Data extraction

Data extraction was performed according to *a priori* determined characteristics, including 1) citation details (publication year, title, authors, journal title), 2) study characteristics (participant mean age and range, sex distribution, country, sample size, participation rate, loss to follow up and population [e.g., clinical, non-clinical or both]), 3) methods (study aims and design, whether sleep and/or AL was a primary variable of interest, which of these were considered the exposure, whether they were measured simultaneously, sampling strategy, study setting, statistical methodology, sleep measures included, and operational definition of AL, including number and type of biomarker, number and type of physiological systems represented, covariates, moderators), 4)

study findings (including association estimate), 5) study funding source, and 6) possible conflicts of interest.

Quality assessment items

Items 1–14 were adapted from the Observational Cohort and Cross-Sectional Studies and Controlled Intervention Studies from the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH, 2014). Items 15–17 were additions of relevance to this review.

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
15. Does the AL index includes at least one primary mediator and three secondary outcomes (Mauss et al., 2015)?
16. Are the main measures of sleep disturbance and sleep characteristics assessed with relevant measures, e.g., validated scales of sleep quality or insomnia, and standard sleep diaries?
17. If multiple comparisons were made, was this adjusted for?

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2022.101650.

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