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EPIDEMIOLOGY • REVIEW

Sleep and frailty risk: a systematic review and meta-analysis

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Abstract

Purpose Studies on the association between sleep and frailty risk have yielded contradictory outcomes. Therefore, a systematic review and meta-analysis were designed to examine the relationship between sleep and frailty risk.

Methods Relevant studies were identified by searching PubMed, Embase, and Scopus databases until 30 November 2019. Data were available from ten studies. Selected articles were published between 2009 and 2019. The odds ratios of 41,233 individuals were used for the meta-analysis.

Results Pooled analysis demonstrated that when compared to the reference category of 6 to 8 hours nightly sleep duration, both the highest category (more than 8 hours, OR 1.21; 95% CI 1.10–1.32) and lowest category of sleep (under 6 hours, OR 1.13; 95% CI 1.08–1.18), were significantly correlated with increased risk of frailty. Furthermore, daytime drowsiness (OR 1.25; 95% CI 1.02–1.52), sleep disordered breathing (OR 1.28; 95% CI 1.03–1.58), and prolonged sleep latency (OR 1.18; 95% CI 1.06–1.31) enhanced the risk of frailty. Subgroup analyses by frailty status suggest that a shorter sleep duration was associated with risk of frailty but not pre-frailty. However, prolonged sleep time was significantly related with enhanced risk of pre-frailty and frailty. In addition, subgroup analyses via sex revealed that longer and shorter sleep durations increased risk of frailty in both men and women.

Conclusion The present study revealed that longer and shorter sleep durations are associated with increased risk of frailty.

Keywords Sleep · Frailty · Systematic review · Meta-analysis

Introduction

Frailty is a condition in which a person becomes less able to respond to a variety of stressors, whether physical or mental. Frailty may be a pre-disability that leads to future disabilities or hospitalization [1–5]. Fried et al. described the physical phenotype of frailty with five criteria, including weight loss (10 pounds in 1 year), exhaustion (self-report), weakness (grip strength: lowest 20%), walking speed (15 ft: slowest 20%), and low physical activity (kcal/week expenditure: lowest 20%) [3]. Fried's phenotype classified individuals into one of the three frailty states: lack of all criteria (robust), one or two criteria (pre-frail), and three or more criteria (frail). A recent systematic review and meta-analysis reported that the prevalence estimate ranged between 31.3 and 45.8% for pre-frailty, and 10.4 and 37.0% for frailty among community-dwelling older persons [6]. In fact, at least one in ten elderly people are classified as frail, whereas four in ten are classified as pre-frail [7]. It is projected that by 2030, the USA will have 70 million elderly people at risk of pre-frailty and frailty [8]. Major causes of frailty include fatigue, sarcopenia, polypharmacy, weight loss, and reversible conditions. Many medical conditions can also cause fatigue, including sleep apnea, depression, hypothyroidism, anemia, hypotension, and sleep–wake disturbances [9]. Approximately half of older adults report sleep problems [10]. Prevalent sleep-related disorders are symptoms of insomnia, excessive daytime sleepiness, impaired sleep quality, and disrupted sleep–wake

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patterns [11]. Wai et al. have suggested the feasible relationships between sleep problems and frailty in older adults [9]. Previous reports have demonstrated that frailty may disrupt the probable sleep cycle and have also proposed a bilateral relationship between frailty and sleep problems [12].

Both short and long sleep durations can be disadvantageous to the health of elderly individuals [13, 14]. Ensrud et al. reported that sleep-disordered breathing sleep, low sleep quality, latency more than 60 min, and sleep efficiency lower than 70% were related with frailty status, although shorter sleep duration was not related with frailty [15]. Nevertheless, the relationships between sleep disorders and frailty status in older people are unknown; to our knowledge, no systematic review study has previously summarized these findings. Hence, this study was designed as a systematic review and meta-analysis of literatures to examine the relationship between sleep parameters and frailty risk.

Methods

Literature search and selection

This study was conducted based on the PRISMA guidelines [16]. We carried out a systematic search of PubMed, Embase, and Scopus databases until 30 November 2019. Search strategies used subject medical headings and keywords but did not use language and date restrictions. The following terms were used in the electronic search: ("sleep" OR "insomnia" OR "insomnias" OR "sleep problems" OR "sleep quality" OR "sleep duration" OR "sleep deprivation" OR "sleep disturbance" OR "sleep disorders") AND ("frailty" OR "frailties" OR "frailness" OR "frailty syndrome" OR "pre-frailty"). We also manually searched the references cited in the retrieved review studies.

Eligibility criteria

Studies were selected in the ultimate analysis if they met the below characteristics: (a) assessed sleep parameters including sleep duration, daytime drowsiness, sleep-disordered breathing, prolonged sleep latency, and sleep quality or efficiency; (b) observational articles (using cross-sectional or cohort research setting); and (c) stated cause-specific multivariable odds ratios (OR) with corresponding 95% confidence intervals (CI) of sleep parameters with frailty risk among elderly individuals (≥ 65 years of age). Articles were omitted if (a) the reported data could not be used; (b) they were conference papers, letters to editor, all kinds of reviews, or case-report articles; (c) they did not stated sleep-related parameters as an exposure and frailty risk as an results; or (e) abstracts with insufficient data or they were dissertation articles.

Study selection

Titles and abstracts of all research obtained in the primary search were assessed individually by two researchers (SM and AB). Literatures not meeting the mentioned criteria were removed by using a screen form with a step by step process via research setting, participant individuals or exposure, and outcomes. The citation lists of related review articles recognized during this procedure were also evaluated to select more articles. Full-text articles were retrieved if the citation was identified probable for the analysis, and then the articles were subjected to a second assessing for relevance by the same investigators. Any differences were discussed and reconsidered via consensus.

Data collection

For selected articles, two authors (SM and HM) extracted data individually applying valid data extraction tools. They discussed any differences in data extraction and sought the evaluation of a third reviewer (AP) for resolution. The extracted characteristics are reported in Table 1.

Quality assessment for individual studies

Two authors (SM and AB) determined the quality of individual studies by the Newcastle-Ottawa tools [17]. The quality assessment process has been previously described in our studies [18, 19]. The quality evaluation outcomes for each study are reported in Table 1.

Statistical analysis

In the current study, "short" sleep duration was determined as ≤ 5–6 h per day and "long" sleep duration as ≥ 8–9 h per day [20]. Odds ratios were extracted as an outcome of the relationship between sleep parameters and incidence of frailty. In order to detect the feasible sources of heterogeneity in articles, subgroup analyses were carried out based on sex (women and men) and frailty status (pre-frail and frail). Pooled OR and 95% CI were computed via a weighted random-effects model (DerSimonian-Laird approach). Heterogeneity in the articles was examined by the Cochran Q and the I^2 statistics ($I^2 = (Q\text{-}df)/Q \times 100\%$; $I^2 < 25\%$, no heterogeneity; $I^2 = 25\text{–}50\%$, moderate heterogeneity; $I^2 = 50\text{–}75\%$, large heterogeneity, $I^2 > 75\%$, extreme heterogeneity). The heterogeneity was considered significant if either the Q statistic had $P < 0.1$ or $I^2 > 50\%$. Begg's exam and Egger's exam were carried out to evaluate publication bias. All statistical exams for present research were performed with STATA (version 14.0; Stata Corporation, College Station, TX).

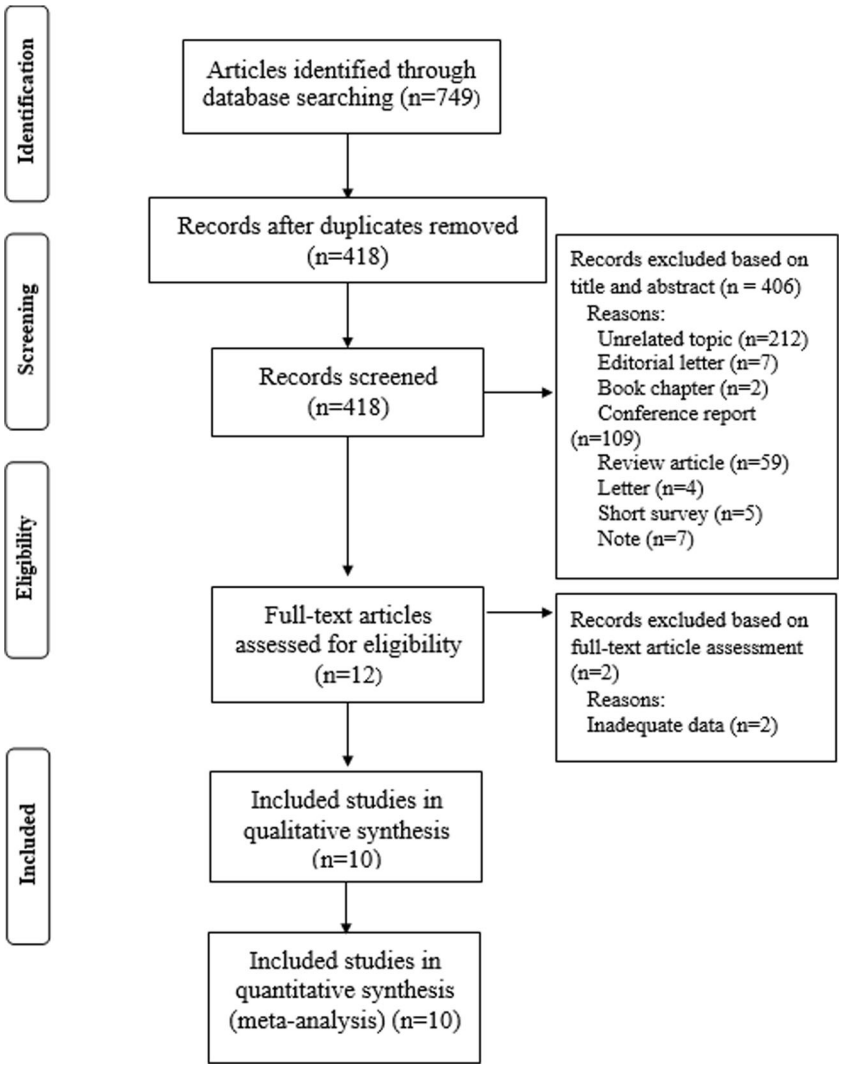

Fig. 1 Flowchart of the process of study selection

Results

Characteristics of the studies

A total of 418 articles without duplicates were found from the database systematic search. At first, 406 articles were removed based on eligibility criteria (Fig. 1). Ultimately, 10 studies were selected for the qualitative synthesis [1, 2, 12, 15, 21–26], and they all met the eligibility criteria for the quantitative synthesis [1, 2, 12, 15, 21–26]. Nine studies applied a cross-sectional approach [1, 12, 15, 21–26], and one applied a longitudinal setting [2]. The odds ratios of 41,233 participants in these literatures were extracted for the meta-analysis. Nine articles measured sleep duration [1, 2, 15, 21–26], three [12, 21, 24] reported daytime drowsiness, two [1, 15] evaluated sleep-disordered breathing, two [15, 23] measured prolonged sleep latency, and one examined the association between sleep quality and efficiency [15] with frailty risk. These articles were published between 2009 and 2019, and they were performed in the USA [1, 2, 12, 15, 21], China [22, 26], Korea [23], and Japan [24, 25]. The quality measurement of each selected article was examined by the Newcastle-Ottawa tools, which revealed that all articles were of high quality [1, 2, 12, 15, 21–26] (Table 2).

Quantitative synthesis

Sleep duration and frailty risk

Pooled effect size revealed that the short sleep duration (< 6 h) in compared with the normal sleep duration (6–8 h) significantly increased risk of frailty (OR 1.13; 95% CI 1.08–1.18, $P_{\text{heterogeneity}}$: 0.40, $I^2 = 48.9\%$; Fig. 2). The stratified analysis by frailty status indicated that the relationship between pre-frailty risk and short sleep duration was not significant (OR 1.07; 95% CI 0.99–1.15). However, short sleep duration was related with increased risk of frailty (OR 1.17; 95% CI 1.10–1.23) (Fig. 2). Subgroup analyses by sex revealed that a short

Table 1 Description of the included studies

Author (location, year)	Study design	Population Age BMI	Sleep assessment method	Frailty risk assessment	Outcomes	Adjusted variables	Quality score
Ensrud et al. (USA, 2009)	Cross-sectional	$N = 3133$ Age = > 65 years BMI = NR	PSQI and ESS	Fried et al., 2001	Sleep parameters were associated with either frailty status	Age, race, site, health status, educational level, social support, alcohol intake, smoking status, antidepressant use, benzodiazepine use, non-benzodiazepine non-barbiturate sedative hypnotic use, number of selected medical conditions, depressive symptoms, cognitive function, functional disabilities, and BMI	+ 10/10
Endeshaw et al. (USA, 2009)	Cross-sectional	$N = 1042$ Age = 76.4 ± 4.3 years BMI = 27 ± 4 kg/m^2	Questionnaire	Fried et al., 2001	Significant association between sleep-disordered breathing and frailty	Gender and BMI	+ 8/10
Fragoso et al. (USA, 2009)	Cross-sectional	$N = 374$ Age = >78 years BMI = NR	ESS and ISI	Fried et al., 2001	Significant association between drowsiness and frailty	Age, sex, number of chronic conditions, self-reported health status, number of medications, use of a medication with adverse central nervous system effects, cognitive impairment (Mini-Mental State Examination score), and significant depressive symptoms	+ 10/10
Ensrud et al. (USA, 2012)	Prospective cohort study	$N = 2505$ Age = > 67 years BMI = NR	PSQI and ESS	Fried et al., 2001	Sleep parameters were not associated with either frailty status	Age, race, site, health status, BMI, education, social support, alcohol intake, smoking, antidepressant, benzodiazepine use, non-benzodiazepine sedative hypnotic use, medical conditions, cognition, and baseline frailty status	+ 10/10
Baniak et al. (USA, 2018)	Cross-sectional	$N = 3632$ Age = > 60 years BMI = mostly overweight or obese (73.1%)	PSQI	Fried et al., 2001	Shorter sleep duration was not associated with either a frail or pre-frail state. Specifically, those individuals who slept > 10 h per night had	Sociodemographic status, BMI, change in health status, number of hospitalizations, hemoglobin level, medication use, comorbidity index, depressive symptoms, diet, and confusion	+ 10/10

Table 1 (continued)

Author (location, year)	Study design	Population Age BMI	Sleep assessment method	Frailty risk assessment	Outcomes	Adjusted variables	Quality score
					an increased risk of being in the frail group		
Zhang et al. (China, 2018)	Cross-sectional	$N = 1953$ Age = 73.66 ± 0.38 years BMI = NR	Questionnaire	FRAIL Scale, 2012	Sleep duration was associated with increased risk of frailty	Age, gender, race/ethnicity, marital status, family medical history, health and medical conditions, lifestyle or behavioral factors, and dietary factors	+ 10/10
Kang et al. (Korea, 2018)	Cross-sectional	$N = 1168$ Age = 70–84 years BMI = 24.9 ± 2.9 kg/m^2	PSQI	Fried et al., 2001	Longer sleep duration was associated with increased risk of frailty	Age, BMI, COPD, DM, HTN, physical activity, depression, CVD, CHF, and number of medications	+ 10/10
Nakakubo et al. (Japan, 2018)	Cross-sectional	$N = 9824$ Age = 73.6 ± 5.5 years BMI = 23.17 ± 3.02 kg/m^2	Questionnaire	Fried et al., 2001	Longer and shorter sleep duration were associated with increased risk of frailty	Age, educational level, total use of medication, BMI, Mini-Mental State Examination, smoking and drinking habits, self-perceived health, and medical history (HTN, DM, stroke, CVD, respiratory disease, and depression)	+ 10/10
Nakakubo et al. (Japan, 2019)	Cross-sectional	$N = 4427$ Age = 71.9 years BMI = 23.40 ± 3.21 kg/m^2	Questionnaire	Makizako et al., 2015	Longer sleep duration was associated with increased risk of frailty	Age, sex, body mass index, education, medication, medical history (HTN, CVD, respiratory disease, DM), current drinking habits, current smoking habits, physical activity, gait speed, depressive symptoms, and Mini-Mental State Examination score	+ 10/10
Guo et al. (China, 2019)	Cross-sectional	$N = 13,175$ Age = >50 years BMI = NR	Questionnaire	Fried et al., 2001	Shorter sleep duration was associated with increased risk of frailty	Gender, age, residence, education, family assets, vegetable consumption, smoking status, drinking habits, and physical activity	+ 9/10

BMI body mass index, *CVD* cardiovascular disease, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *ESS* Epworth Sleepiness Scale, *HTN* hypertension, *ISI* Insomnia Severity Index, *NR* not reported, *PSQI* Pittsburgh Sleep Quality Index

Table 2 Subgroup analysis to assess the association between sleep duration and frailty risk

Subgrouped by	No. of studies	OR[1]	95% CI	I^2 (%)	*P* for heterogeneity
Shorter sleep duration					
Women	5	1.18	1.13–1.23	1.3	0.39
Men	5	1.16	1.08–1.24	41.6	0.11
Longer sleep duration					
Women	5	1.17	1.02–1.35	74.6	0.003
Men	4	1.23	1.06–1.43	85.9	0.001

[1] Calculated by random-effects model

sleep duration increased the risk of frailty among women (OR 1.18; 95% CI 1.13–1.23) and men (OR 1.16; 95% CI 1.08–1.24) (Table 2).

Moreover, pooled OR suggested that the long sleep duration (> 8 h) was significantly correlated with increased risk of frailty compared with the normal sleep duration (6–8 h) (pooled OR 1.21; 95% CI 1.10–1.3; $P_{heterogeneity}$: $P < 0.001$; $I^2 = 76.5\%$; Fig. 3). Subgroup analyses suggested that the prolonged sleep time led to a higher risk of pre-frail (OR 1.14; 95% CI 1.08–1.20) or frail (OR 1.28; 95% CI 1.09–1.50) status compared with the normal sleep duration (Fig. 3). In the same analysis considering sex and frailty risk, longer sleep durations increased the risk of frailty among women (OR 1.17; 95% CI 1.02–1.35) and men (OR 1.23; 95% CI 1.06–1.43) (Table 2).

Other sleep parameters and frailty risk

As illustrated in Fig. 4, when all ORs were combined, daytime drowsiness increased the risk of frailty among older adults (OR 1.25; 95% CI 1.02–1.52; $I^2 = 85.5\%$; $P = 0.001$). In addition, sleep-disordered breathing (OR 1.28; 95% CI: 1.03–1.58; $I^2 = 54.4\%$; $P = 0.11$) and prolonged sleep latency (OR 1.18; 95% CI 1.06–1.31; $I^2 = 0.0\%$; $P = 0.45$) were significantly correlated with risk of frailty in older adults.

Sensitivity analysis and publication bias

The sensitivity analysis revealed that the outcomes were not affected by any one study. There was no observation of publication bias for articles examining the relationship between the risk of frailty and lower sleep duration ($P = 0.18$ for Begg's exam and $P = 0.59$ for Egger's exam), prolonged sleep duration ($P = 0.09$ for Begg's exam and $P = 0.33$ for Egger's exam), daytime drowsiness ($P = 0.60$ for Begg's exam and $P = 0.29$ for Egger's exam), or sleep-disordered breathing ($P = 0.11$ for Begg's exam and $P = 0.18$ for Egger's exam). But, the outcomes from Egger's exam suggested publication bias for articles

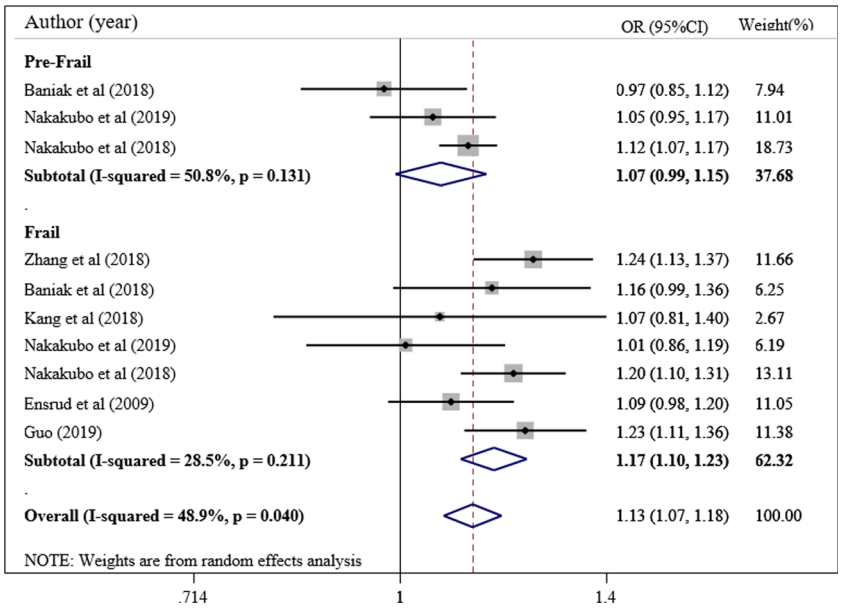

Fig. 2 Forest plots showing OR with 95% CI of pooled results from random-effects model for lowest category of sleep duration (< 6 h) versus reference category (6–8 h)

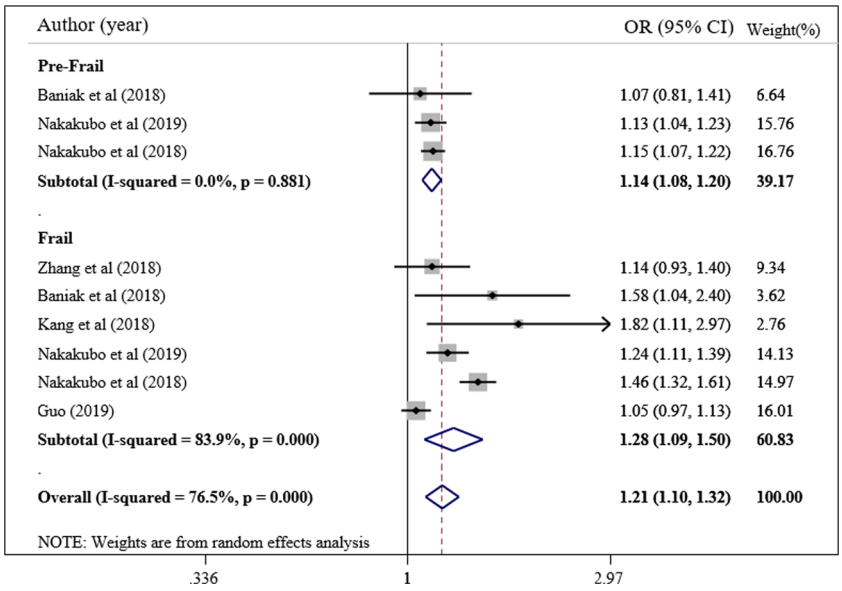

Fig. 3 Forest plots showing RR with 95% CI of pooled results from random-effects model in highest category of sleep duration (> 8 h) versus reference category (6–8 h)

evaluating the relationship between frailty risk and the prolonged sleep latency ($P = 0.001$), though this was not confirmed by Begg's exam ($P = 0.31$).

Discussion

This study was conducted with the goal of assessing the relationship between sleep and frailty risk. Our outcomes demonstrate that both the highest category (> 8 h) and lowest category (< 6 h) of sleep duration, when compared to the reference category (6–8 h), were significantly correlated with increased risk of frailty. Furthermore, other sleep parameters including daytime drowsiness, sleep-disordered breathing, and prolonged sleep latency increased the risk of frailty among older adults. Subgroup analyses by frailty status revealed that shorter sleep durations are related with increased risk of frailty but not pre-frailty in older adult. Although, long sleep durations are associated with increased risk of pre-frailty and frailty. Moreover, subgroup analyses by sex indicate longer and shorter sleep durations increase the risk of frailty among both men and women.

Our findings demonstrated that sleep parameters may be associated with increased risk of frailty among older adults. Various potential mechanisms that may underlie the relationship between sleep disorders and frailty risk are outlined in

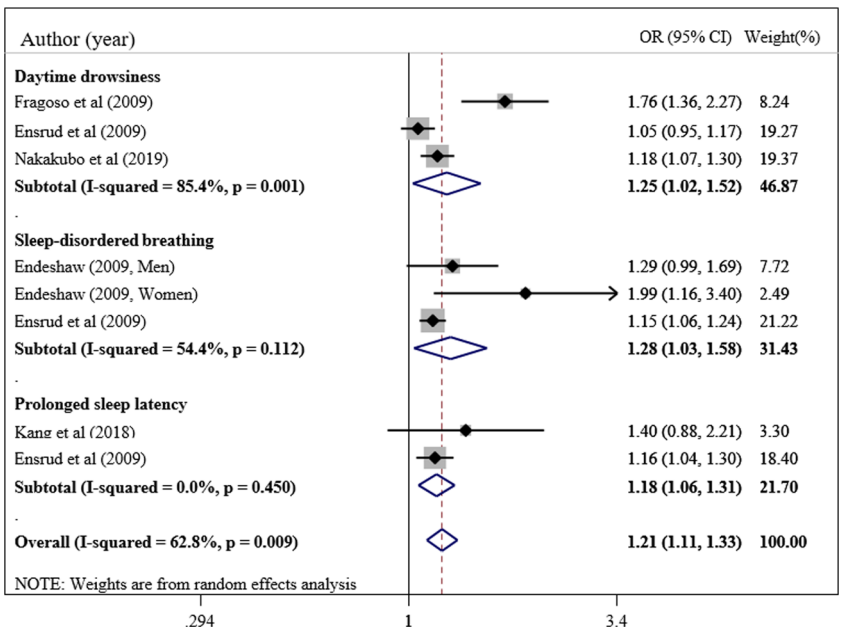

Fig. 4 Forest plots showing OR with 95% CI of pooled results from random-effects model in other sleep parameters

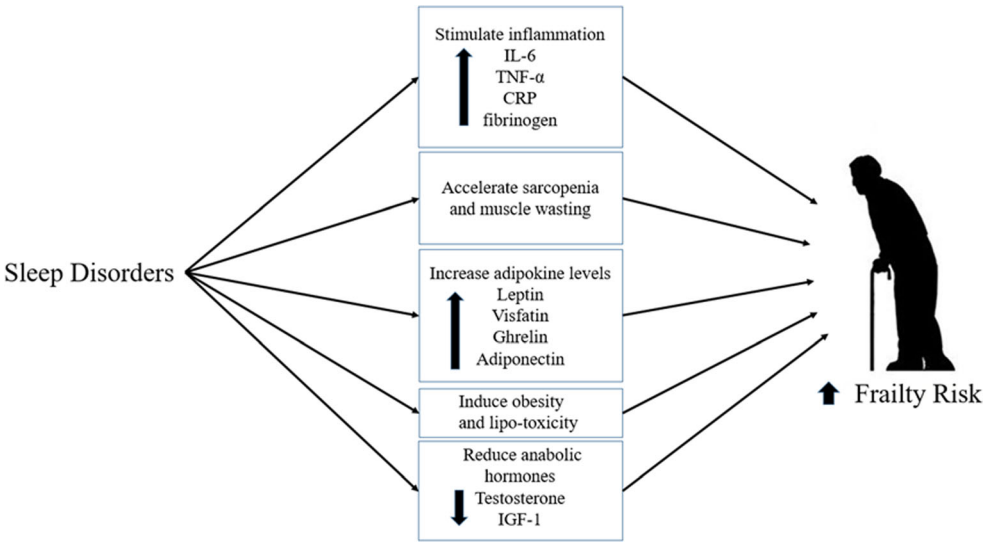

Fig. 5 An overview of various possible mechanisms involved in the relationship between sleep disorders and frailty risk

Fig. 5. Previous studies have suggested that sleep parameters have a direct correlation with adipokine concentrations [27]. For instance, Hayes et al. [27] suggested that shorter sleep duration was related with enhanced levels of leptin and visfatin. In addition, Ursavas et al. [28] discovered a significant positive association between serum ghrelin and sleep apnea syndrome, or Epworth Sleepiness Scale. Furthermore, sleep apnea syndrome is related with enhanced levels of adiponectin independently of body mass index and insulin resistance [29, 30]. However, Simpson et al. [31] revealed that reduced sleep duration may lead to decreased adiponectin levels and increased cardiovascular disease risk. Furthermore, several studies have suggested that elevated levels of adipokines may be related to greater risk of frailty in older adults [32–35]. Lana et al. [20] indicated that higher leptin levels were associated with greater risk of frailty in older adults. This relationship was explained by leptin-induced insulin resistance and inflammation [32]. Adiponectin, an important adipokine associated with frailty, has received more focused attention in recent medical research [33–36], and these studies have suggested that adiponectin concentrations are significantly higher in frail individuals when compared to non-frail individuals [33–36]. This evidence suggests that sleep disorders may first affect adipokines, and thereby increase risk of frailty through their primary effects on adipokines. Therefore, adipokines should be considered in future studies as a potential novel link between sleep parameters and increased frailty risk.

Additionally, inflammatory processes may also be a possible mechanism by which sleep and frailty risk are associated. Inflammation is one of the important pathophysiological changes that may be closely associated with frailty [37]. Pro-inflammatory cytokines may induce frailty directly by increasing proteolysis or indirectly by altering principal metabolic pathways [38]. A direct association, independent of other common chronic disease states, between frailty and increased inflammatory markers, noticeable by elevated interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen, and factor VIII, has been previously indicated [39]. Various risk factors, namely advanced age, adiposity, sex hormones disorder, unhealthy diet, stress, smoking, and sleep disorders, led to low-level inflammatory reactions [40]. An earlier study reported that sleepiness enhanced monocytes that are powerful manufacturer of TNF-α and IL-6 mRNA [41]. With normal sleep hours (6 to 8), blood pressure is at its lowest point, and indicators of endothelial dysfunction decrease [41]. During sleepless nights, shear stresses, or physical stress forces related with hypertension, may activate inflammatory mediators, such as IL-6, via enhanced endothelial activation [42]. Also, studies have indicated that sleep deprivation alters markers of stress response, such as cortisol and norepinephrine [43]. Enhanced amount of norepinephrine has been indicated to induce in vitro manufacture of TNF-α and IL-6 [44, 45]. Besides, inflammatory situation can also event among individual with long sleep duration [46]. In longer duration sleepers, the frequency of waking after falling asleep increases, and sleep efficiency decreases. These situations may also be associated with some disadvantageous health outcomes. For instance, cognitive action and physical activity decrease with longer sleep durations [25]. Hence, it is feasible that adiposity and insulin resistance, which are usual results related with low physical activity status, lead to enhanced concentrations of IL-6 and CRP [14]. Furthermore, obstructive sleep apnea is a prevalent reason for excessive daytime sleepiness (EDS) [47]. Intermittent hypoxemia (IH) may result from sleep fragmentation through the alteration of gut bacterium and may also be associated with decreased production of butyrate and short-chain fatty

acids (SCFAs), as well as increased production of lactate. These alterations can elevate the risk of cardiovascular disease, obesity, and insulin resistance by reducing gut barrier function and progressing inflammatory pathways, which are independent predictors of frailty [48]. Thus, inflammatory reactions are demonstrated as one of the main factors affecting the association between sleep parameters and frailty risk.

A recent epidemiological study suggested that both low sleep time and prolonged durations of sleep may be related with an enhanced risk of sarcopenia [49]. Sarcopenia leads to an attenuated quality of muscle shrinkage, power, and coordination of actions, predisposing the individual to functional restrictions, thereby potentially leading to mobility problems [50]. Sarcopenia plays a crucial role in the pathogenesis of frailty [51]. The principle pathogenic pathway for frailty and sarcopenia is similar and includes age-related changes in body composition, inflammation, and endocrine factors [51]. The diminish in anabolic hormones including testosterone, growth hormone, and insulin-like growth factor 1 (IGF-1) leads to reducing protein synthesis, which is more lessened by reduced insulin sensitivity. Obesity-derived intracellular lipo-toxicity resulted from changes in body composition in frail or sarcopenic individuals, thereby leading to elevated inflammation, oxidative stress, and insulin resistance in older adults [52]. It seems that sleep disorders, via several pathways, may also affect sarcopenia and frailty. Thus, more attention to high-quality sleep with sufficient duration among older adults can help in the prevention, handling, and therapy of frailty as well as reducing the risk of frailty-associated complications.

Strengths and limitations

Based on our research, this study is the first meta-analysis summarizing the relationship between frailty risk and sleep. Although, this study had some restrictions that should be noted. First, significant statistical heterogeneity was observed in some comparisons, as well as subgroup analyses, even though various subgroups and sensitivity analyses were used. Second, small number of studies assessed sleep parameters as outcomes and frailty risk as exposure. Third, the effects of confounding factors, including age, physical activity levels, drug use, health status, effects of inflammatory cytokine, diet, and genetic differences, remain unknown, and these outcomes should be interpreted with caution. Ultimately, the selected articles used various valid tools for evaluation sleep indices or frailty risk. Even though the diverse evaluations of sleep parameters and frailty risk in articles have performed validity and reliability, the commensurability of these assesses is a main gap that should be mentioned.

Conclusion

The present systematic review and meta-analysis was performed to assess the relationship between sleep and frailty risk. Our results revealed that both the highest category (> 8 h) and lowest category of sleep duration (< 6 h), when compared to the reference category (6–8 h), were significantly associated with increased risk of frailty. Furthermore, other sleep parameters including daytime drowsiness, sleep-disordered breathing, and prolonged sleep latency increase the risk of frailty among older adults. Additionally, subgroup analyses by frailty status indicated that shorter sleep durations were associated with risk of frailty but not pre-frailty. However, longer sleep durations were also significantly associated with increased risk of pre-frailty and frailty. In addition, subgroup analyses by sex indicated that longer and shorter sleep durations increase risk of frailty among both men and women. Further longitudinal and in-depth qualitative studies are needed to confirm the possible relationship between various aspects of sleep and frailty risk. We propose that the next researches should be a point of attention according to our outcomes:

- Further research on the effects of different indices of sleep and their feasible molecular pathogenesis associated with frailty
- Examining the relationship between sleep indices and each one of the frailty parameters
- Assessing the feasible interactions between sleep indices and well-known frailty management methods

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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