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CLINICAL REVIEW

Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: Systematic review and meta-analysis of prospective cohort studies

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SUMMARY

Growing evidence indicates that insomnia may be associated with mortality. However, these findings have been inconsistent. We systematically searched MEDLINE and EMBASE to identify prospective cohort studies that assessed the association between insomnia disorder/individual insomnia symptoms and the risk of mortality among adults aged ≥18 yrs. We addressed this association using summary hazard ratios (HRs) and 95% confidence intervals (CIs) calculated using random-effects meta-analysis, and the GRADE approach to rate the certainty of evidence. Twenty-nine cohorts including 1,598,628 individuals (55.3% men; mean age 63.7 yrs old) with a median follow-up duration of 10.5 yrs proved eligible. Difficulty falling asleep (DFA) and non-restorative sleep (NRS) were associated with an increased risk of all-cause mortality (DFA: HR = 1.13, 95%CI 1.03 to 1.23, $p = 0.009$, moderate certainty; NRS: HR = 1.23, 95%CI 1.07 to 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 to 2.06, $p = 0.02$, moderate certainty). Convincing associations between DFA and all-cause mortality were restricted to the mid to older-aged population (moderate credibility). Insomnia disorder, difficulty maintaining sleep, and early morning awakening proved to be unassociated with all-cause and cardiovascular disease mortality. No insomnia symptoms proved to be associated with cancer-related mortality.

Introduction

Insomnia, most commonly characterized by difficulty falling asleep, difficulty maintaining sleep, or early morning awakening, is an important public health problem with substantial medical, psychiatric, and financial ramifications [1]. Epidemiological surveys have reported a prevalence of insomnia symptoms in between 35% and 70% of the general adult population [2]. The total costs associated with insomnia exceed $100 billion annually in the United States of America [3]. Systematic reviews have established the association between insomnia and an increased risk of mental or medical disorders including depression [4], dementia [5], nonalcoholic fatty liver disease [6], hypertension [7], cardiovascular disease [8–10], and perinatal depressive symptoms [11].

Increasing evidence has also suggested that sleep disorders may be associated with mortality. Several meta-analyses have presented evidence that longer or shorter sleep duration is associated with a higher risk of mortality [12–15]. Published cohort studies have reported that some insomnia symptoms may be independently associated with mortality; these findings have, however, proved inconsistent [16–24]. For example, although several studies have reported associations between insomnia symptoms and mortality [16–19,21], others have not [20,22–24]. Varying assessment methods of insomnia symptoms, and approaches to adjusted analysis may, at least in part, explain these inconsistencies.

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To clarify this issue, we performed a systematic review and meta-analysis of prospective cohort studies from the general population. The aim of this was to comprehensively assess the association between mortality from all-cause, cardiovascular, and cancer and both insomnia disorder and individual insomnia symptoms (difficulty falling asleep, difficulty maintaining sleep, early morning awakening, and non-restorative sleep).

Methods

Our report follows the meta-analysis of observational studies in epidemiology (MOOSE) checklist [25] and the study protocol registered with PROSPERO: CRD42018086625.

Search strategy

We searched MEDLINE (via OVID) and EMBASE databases from their inception to January 5th, 2018, including terms for sleep AND mortality (see Supplementary Text S1 for detailed search strategy). There were no restrictions on the publication language and publication status. Additionally, we manually reviewed the reference lists from included studies and relevant systematic reviews (see Supplementary Text S2 for the list of references collected manually).

Eligibility criteria and study selection

We included prospective cohort studies that assessed the association between insomnia disorder and/or individual insomnia symptoms and mortality from all-cause, cardiovascular disease, or cancer among adults ($\geq$18 yrs of age) using a multivariable analysis (Cox proportional hazards models or logistic regression models). Insomnia symptoms focused on difficulty falling asleep (DFA), difficulty maintaining sleep (DMS), early morning awakening (EMA), and non-restorative sleep (NRS). We used the author's definitions of insomnia disorder and all individual insomnia symptoms. We included conference abstracts that reported details regarding the definition of insomnia disorder/symptoms and included multivariable-adjusted analyses. Studies that addressed a specific clinical condition, hospital population, or wrong exposures were not eligible. If duplicate publications were derived from the same cohort and reported the same associated events, we included only the latest published data, or results with the largest number of individuals in our analysis.

Initial search records were imported into the web-application systematic review software package "Rayyan" [26]. Six reviewers (BP, JL, YJC, HJL, JMZ, YHL), working independently in teams of three, screened all titles and abstracts and subsequently reviewed full-text records of all potentially eligible articles. We resolved disagreements through discussion or, if necessary, through adjudication by a third reviewer (LG).

Data extraction

Paired reviewers (LG and BP) independently extracted data of interest using a standardized data extraction sheet. This included the first author, year of publication, geographic location of the study, study design, setting, duration of follow-up, sample size, number of deaths, eligibility criteria, mean age, gender, comorbidities at baselines [e.g., diabetes mellitus, cardiovascular disease, depression, cancer], methods of assessment of insomnia disorder and individual insomnia symptoms, and variables adjusted in the multivariable model. We extracted risk estimates (hazard ratio, relative risks, or odds ratios) with their 95% confidence intervals from the multivariable-adjusted models with the most complete adjustment for potential baseline confounders.

Risk of bias of individual study

We independently assessed the risk of bias of individual studies by paired reviewers (LG and BP) using a modified version of the Newcastle-Ottawa scale [27,28], including seven questions: Was selection of exposed and non-exposed cohorts drawn from the same population?, Can we be confident in the assessment of exposure?, Can we be confident that the outcome of interest was not present at start of study?, Did the statistical analysis adjust for all confounders?, Can we be confident in the assessment of the presence or absence of potential confounders?, Can we be confident in the assessment of outcome?, Was the follow up of cohorts adequate?, in which we used response options of "definitely or probably yes" (assigned a low risk of bias) and "definitely or probably no" (assigned a high risk of bias). Regarding the adjustment of potential confounding factors, we considered the results adequately adjusted if they adjusted variables including sex, age, smoking, social-economic status, and baseline morbidity (cancers, cardiovascular disease, and diabetes).

We rated each study as being of high methodological quality (low risk of bias) and low methodological quality (high risk of bias) based on the following criteria: 1) studies were considered to be high methodological quality if all seven questions were assigned to be low risk of bias, or only 1 of the 7 questions was assessed as "definitely no", six questions were low risk of bias, or 2 of the 7 questions were assessed as "probably no", other five questions were low risk of bias; 2) studies were considered to be low methodological quality if they did not meet the criteria for high methodological quality as detailed above. Any conflict was resolved by discussion or, if necessary, through adjudication by a third reviewer (GG, JHT, or KHY).

Data synthesis and statistical analysis

We used hazard ratios (HRs) and 95% confidence intervals (CIs) as a measure of the association between insomnia disorder/symptoms and mortality. Due to the low risk of death, odds ratios (ORs) and relative risks (RRs) were included in the same meta-analysis. Subsequently, we conducted a subgroup analysis to identify possible differences between studies using HRs and those using ORs/RRs. If an interaction test indicated significant differences between subgroups, we used the results from studies with HRs for assessing the association between insomnia disorder/symptoms and mortality. The differences among subgroups were tested and the p values of interaction test ($p_{Interaction}$) were calculated by meta-regression analysis. We pooled HRs and 95%CIs through the inverse variance weighted method using random-effects meta-analysis.

We examined statistical heterogeneity among the studies with Cochrane's Q test and I^2 value [29]. We conducted a priori subgroup analysis based on the following factors if there were more than two studies in each subgroup category: sex (men vs. women vs. both), age (mixed age: studies enrolled all ages vs. older age: studies enrolled $\geq$65 yrs only), length of follow-up (<10 yrs vs. $\geq$10 yrs), methodological quality of individual study (high vs. low methodological quality), and definition of insomnia disorder (categorizing the definitions to stricter and less strict based on the reporting in primary studies). We conducted a post hoc subgroup analysis to observe the difference of effect between studies with health-status and without health-status adjusted, as well as the difference between European and non-European countries. We categorized studies to health-status adjusted if they adjusted for one or more variables related to sleep such as depression, anxiety, cognitive impairment, sleep duration, and hypnotics use. We performed a post hoc sensitivity analysis by excluding two studies (Dew et al., 2003 [38] and Smagula et al., 2017 [52]) as they were using the objective DFA measures.

Publication bias was assessed using the Begg's rank correlation test at the $p < 0.05$ level of significance for all meta-analyses with at least 10 studies [30]. All analyses were performed with Stata V.15.1 software (StataCorp, College Station, Texas, USA).

Credibility of subgroup analysis

A difference in effect between subgroups, if true, is likely to have important implications for clinical practice and policy making. Many subgroup claims are, however, subsequently shown to be false [31]. We considered that $p_{Interaction}$ <0.01 suggested significant subgroup effects. We further assessed the credibility of significant subgroup effects using the criteria suggested by Sun and colleagues, which was a structured checklist consisting of 11 items addressing design, analysis, and context of subgroup analysis [31].

Certainty of evidence assessment

Paired reviewers (LG, YPC) independently rated the certainty (quality) of evidence as high, moderate, low or very low using the grading of recommendations, assessment, development and evaluation (GRADE) approach considering risk of bias, imprecision, inconsistency, indirectness and publication bias [32]. Regarding the certainty of evidence in estimates: high certainty means that further research is very unlikely to change our certainty in the estimate of effect; moderate certainty means that further research is likely to have an important impact on our certainty in the estimate of effect and may change the estimate; low certainty means that further research is very likely to have an important impact on our certainty in the estimate of effect and is likely to change the estimate; and very low certainty means that any estimate of effect is very uncertain. Any conflict was resolved through the adjudication of a third reviewer (GG).

Results

Study selection and characteristics

Our search yielded 6389 records of which 74 proved potentially eligible on the basis of titles and abstracts (see Supplementary Text S3 for the reasons and lists of references excluded in full-text screening) and 31 articles including 29 cohort studies proved eligible (Supplementary Fig. S1) [16,17,19–24,33–55]. Lallukka et al. 's article [16] included three cohorts that we included as three separate studies [21,47,48]. One cohort [40] reported insomnia disorder and individual insomnia symptoms separately in two articles [40,42].

Table 1 presents the characteristics of 29 cohort studies that enrolled 1,598,628 participants. Studies typically enrolled both men and women with a mean age of 42.6–87.4 yrs old, were conducted in North America, Europe, or Asia and followed patients for over 10 yrs. Supplementary Table S1 presents the details on the assessment of insomnia symptoms, definitions of insomnia disorder, and variables for which studies adjusted.

Methodological quality of individual study

Ten (34.5%) cohorts [19,20,24,35,37,41,42,46,47,54] were at high risk of bias for assessment of exposure because they did not report any information or citations on the validity of the insomnia symptoms measure or measured only at baseline. Thirteen (44.83%) cohorts

Table 1
Study characteristics.

Author, Year	Location	Total sample	Number of deaths	Follow-up period, y	Age, mean (range), y	Sex, men (%)	Mortality outcomes
Almeida et al., 2011 [37]	Australia	5127	1146	m 6.0	nr (70.0–90.0)	100.0	All-cause
Althuis et al., 1998 [36]	US	778	175	6.0	73.9 (>65.0)	0.0	All-cause
Chen et al., 2013 [34]	Taiwan	4064	1004	m 7.0	73.8 (>65.0)	55.8	All-cause, CVD, Cancer
Chien et al., 2009 [53]	Taiwan	3430	901	m 15.9	56.0 (>35.0)	47.5	All-cause
Dew et al., 2003 [38]	US	184	66	m 12.8	74.5 (58.7–91.4)	46.2	All-cause
Eaker et al., 1992 [46]	US	774	79	20.0	nr (45.0–64.0)	0.0	CVD
Foley et al., 1995 [41]	US	9282	1392	3.0	74.1 (75.0–85.0)	39.0	All-cause
Gapstur et al., 2014 [54]	US	305,057	4974	28.0	52.5 (≥29.0)	100.0	Cancer
Gómez-Olivé et al., 2013 [55]	South Africa	4044	394	3.0	65.7 (≥50.0)	20.7	All-cause
Howrey et al., 2012 [23]	US	2526	1319	15.0	73.1 (65.0–98.0)	42.0	All-cause
Jaussent et al., 2013 [35]	France	6696	1307	m 8.9	72.8 (65.0–95.0)	41.3	All-cause
Kojima et al., 1999 [39]	Japan	5322	258	m 11.9	47.3 (20.0–67.0)	45.8	All-cause
Kripke et al., 2002 [20]	US	1 116 936	77,639	6.0	57.5 (30.0–102.0)	43.1	All-cause
Lallukka et al., 2016; Andruškienė et al., 2008 [16,48]	Lithuania	1602	158	m 6.0	nr (35.0–74.0)	37.5	All-cause
Lallukka et al., 2016; Lahelma et al., 2014 [16,47]	Finland	6605	213	m 12.7	nr (40.0–60.0)	20.4	All-cause
Lallukka et al., 2016; Sivertsen et al., 2014 [16,21]	Norway	6236	160	m 14.2	42.6 (40.0–45.0)	38.1	All-cause
Leigh et al., 2015 [50]	Australia	10,721	5261	15.0	72.5 (70–75)	0.0	All-cause
Li et al., 2014 [17]	US	23,447	2025	6.0	68.6 (40.0–75.0)	100.0	All-cause, CVD
Mallon et al., 2002; Mallon et al., 2000 [40,42]	Sweden	1870	266	12.0	56.0 (45.0–65.0)	48.5	All-cause, CVD, Cancer
Nilsson et al., 2001 [43]	Sweden	22,933	2299	17.0	46.7 (nr)	58.8	All-cause, CVD
Parthasarathy et al., 2015 [51]	US	1409	318	20.0	47.7 (21.0–79.0)	45.1	All-cause
Phillips et al., 2005 [22]	US	13,564	709	m 6.3	nr (44.0–66.0)	44.8	All-cause
Pollak et al., 1990 [45]	US	1855	309	m 3.5	75.4 (65.0–98.0)	nr	All-cause
Rockwood et al., 2001 [44]	Canada	1659	nr	5.0	73.3 (>65.0)	42.9	All-cause
Rod et al., 2011 [33]	France	16,989	1045	19.0	45.0 (36.0–52.0)	73.7	All-cause, CVD, Cancer
Rod et al., 2014 [19]	UK	9098	804	22.0	45.0 (35.0–55.0)	67.2	All-cause, CVD, Cancer
Smagula et al., 2017 [52]	US	2531	628	m 7.4	76.3 (≥65.0)	100.0	All-cause, CVD, Cancer
Suzuki et al., 2009 [24]	Japan	12,601	1074	m 5.3	71.4 (65.0–84.0)	51.0	All-cause, CVD
Tsapanou et al., 2016 [49]	US	1288	239	m 2.9	87.4 (>65.0)	30.4	All-cause

CVD, cardiovascular disease; m, mean; nr, not reported; y, year.

[19,23,36,38,39,41–46,51,54] were categorized as high risk of bias for adjustment of confounders, and 6 (20.69%) [23,24,34,36,42,49] reported that the loss to follow-up was more than 10%. All other items were at low risk of bias. We also graded the methodological quality of each study based on a priori criteria. More than half of the cohorts (65.52%) [17,20–22,33–35,37,39,43–45,47,48,50–53,55] were categorized as being of high methodological quality (Supplementary Fig. S2).

DFA and mortality

Nineteen studies [17,21,24,33,35–41,43,44,46–50,52] reported the association between DFA and mortality, seven [21,33,39,40,43,47,48] of which reported the results separately for men and women. DFA was associated with an increase in the hazard of all-cause mortality (HR = 1.13, 95%CI: 1.03, 1.23; $p = 0.009$; moderate certainty) (Fig. 1, Table 2). Begg's test suggested that the possibility of publication bias for all-cause mortality was small ($p = 0.09$) (Supplementary Fig. S3).

With moderate credibility, however, we found evidence of a subgroup effect (fulfilling seven of ten credibility criteria) (Table 3): the association of DFA and mortality existed in the younger mixed-age population but not in, the older population (HR: 0.98, 95%CI 0.91 to 1.06 in the older population; 1.33, 95%CI 1.16 to 1.53 in the mixed-age population; $p_{interaction} = 0.001$) (Supplementary Table S2).

For cardiovascular disease mortality, the pooled effect of studies with HRs was different from those with ORs/RRs ($p_{interaction} = 0.01$)

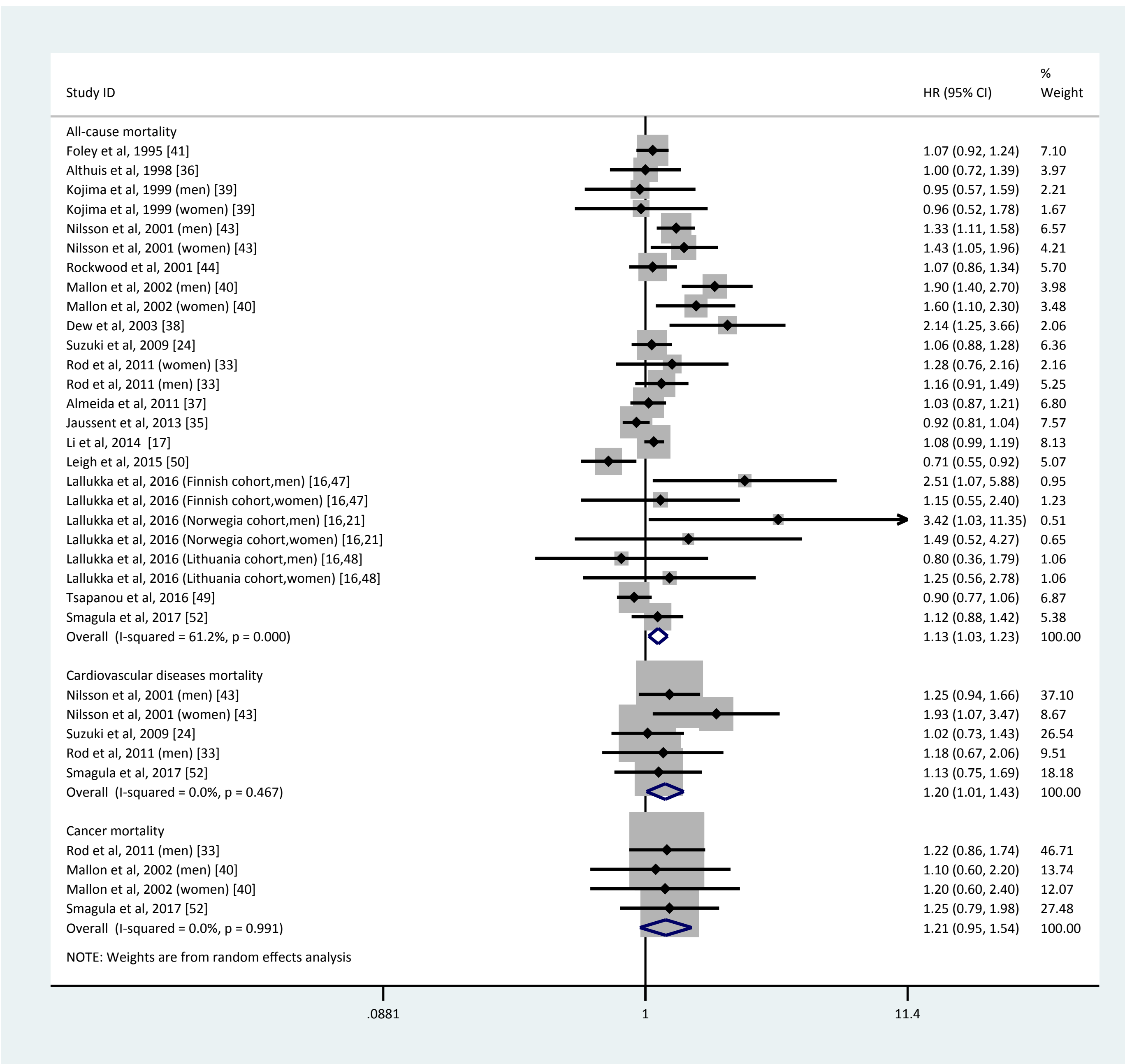

Fig. 1. Difficulty falling asleep and all-cause, cardiovascular disease, and cancer mortality. The results are shown as hazard ratio (HR) and 95% confidence interval (CI).

Table 2
Grading of recommendations, assessment, development, and evaluation—certainty in estimates of effect.

Exposures and outcomes	Number of studies	Study design	Certainty assessment					Effect estimates	Certainty
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	HR (95%CI)	
DFA									
All-cause mortality	26 estimates from 19 studies	Observational studies	Not serious	Serious[a]	Not serious[b]	Not serious	Not serious	1.13 (1.03, 1.23)	⊕⊕⊕○ Moderate
CVD mortality	7 estimates from 5 studies	Observational studies	Not serious	Not serious	Not serious	Serious[c]	Undetected	1.20 (1.01, 1.43)	⊕⊕⊕○ Moderate
Cancer mortality	4 estimates from 3 studies	Observational studies	Serious[d]	Not serious	Not serious	Serious[e]	Undetected	1.21 (0.95, 1.54)	⊕⊕○○ Low
DMS									
All-cause mortality	19 estimates from 13 studies	Observational studies	Not serious	Not serious	Not serious	Not serious	Not serious	1.05 (0.96, 1.14)	⊕⊕⊕⊕ High
CVD mortality	4 estimates from 3 studies	Observational studies	Serious[f]	Not serious	Not serious	Serious[g]	Undetected	1.03 (0.82, 1.31)	⊕⊕○○ Low
Cancer mortality	3 estimates from 2 studies	Observational studies	Serious[h]	Not serious	Not serious	Serious[i]	Undetected	1.04 (0.65, 1.69)	⊕⊕○○ Low
EMA									
All-cause mortality	20 estimates from 14 studies	Observational studies	Not serious	Not serious	Not serious	Not serious	Not serious	0.97 (0.91, 1.04)	⊕⊕⊕⊕ High
CVD mortality	4 estimates from 3 studies	Observational studies	Not serious	Not serious	Not serious	Serious[k]	Undetected	0.93 (0.76, 1.13)	⊕⊕⊕○ Moderate
Cancer mortality	1 estimates from 1 studies	Observational studies	Not serious	Not serious	Serious[j]	Serious[l]	Undetected	1.00 (0.81, 1.24)	⊕⊕○○ Low
NRS									
All-cause mortality	11 estimates from 7 studies	Observational studies	Not serious	Not serious	Not serious	Not serious	Not serious	1.23 (1.07, 1.42)	⊕⊕⊕⊕ High
CVD mortality	4 estimates from 3 studies	Observational studies	Not serious	Not serious	Not serious	Serious[m]	Undetected	1.48 (1.06, 2.06)	⊕⊕⊕○ Moderate
Cancer mortality	3 estimates from 2 studies	Observational studies	Serious[n]	Serious[o]	Not serious	Serious[p]	Undetected	0.95 (0.60, 1.49)	⊕○○○ Very low
Insomnia disorder									
All-cause mortality	18 estimates from 12 studies	Observational studies	Not serious	Serious[q]	Not serious	Not serious	Not serious	1.07 (0.98, 1.17)	⊕⊕⊕○ Moderate
CVD mortality	1 estimates from 1 studies	Observational studies	Not serious	Not serious	Not serious	Serious[r]	Undetected	1.66 (0.72, 3.83)	⊕⊕○○ Low
Cancer mortality	2 estimates from 2 studies	Observational studies	Not serious	Not serious	Not serious	Serious[s]	Undetected	0.94 (0.58, 1.54)	⊕⊕⊕○ Moderate

CVD, cardiovascular disease; DFA, difficulty falling asleep; DMS, difficulty maintaining sleep; EMA, early morning awakening; NRS, non-restorative sleep.
[a] $I^2 = 64.8\%$, and some of the confidence intervals did not overlap.
[b] The risk of all-cause mortality in older population was no longer statistically significant, which can explain partially the heterogeneity, we only rated down inconsistency one level, did not rate down indirectness.
[c] The confidence interval closed to no effect (1% increase) to a substantial increase (43% increase).
[d] All three studies did not adjust for baseline cancer.
[e] The confidence interval included a small reduction (5% reduction) and a substantial increase (54% increase).
[f] Two of three studies were at high risk of bias, and the weight of studies with high risk of bias was 81%.
[g] The confidence interval ranged from a considerable reduction (17% reduction) to a substantial increase (31% increase).
[h] All of two studies did not adjust for baseline cancer, one study was at high risk of bias for assessment of exposure.
[i] The confidence interval ranged from a substantial reduction (35% reduction) to a substantial increase (69% increase).
[j] Only including one study that focused on middle-aged men (36–52 yrs).
[k] Only included one study and the confidence interval ranged from a considerable reduction (23% reduction) to a considerable increase (13% increase).
[l] Only including one study and the confidence interval ranged from a considerable reduction (19% reduction) to a considerable increase (24% increase).
[m] The confidence interval ranged from a slight increase (6% increase) to a substantial increase (106% increase).
[n] The weight of studies with high risk of bias was 68%, and the point estimate of pooled effect was closer to studies with high risk of bias.
[o] $I^2 = 68.3\%$, and some of the confidence intervals did not overlap.
[p] The confidence interval included a substantial reduction (40% reduction) and a substantial increase (49% increase).
[q] $I^2 = 80.5\%$, and some of the confidence intervals totally did not overlap.
[r] Only including one study that focused on older population and the confidence interval was very wide.
[s] The confidence interval included a substantial reduction (42% reduction) and a substantial increase (54% increase).

Table 3
Credibility of subgroup effects for age for the association between difficulty falling asleep and all-cause mortality.

Criteria	Rating (Yes means higher credibility)
1 Is subgroup variable a characteristic measured at baseline or after randomization?	Not applicable because we are comparing studies enrolled mixed age and those enrolled ≥65 yrs only
2 Is effect suggested by comparisons within rather than between studies?	No, between studies
3 Was subgroup effect specified a priori?	Yes, specified in our protocol
4 Was direction of subgroup effect specified a priori?	Yes, we expected larger risk for studies enrolled mixed age
5 Is there indirect evidence that supports hypothesized interaction (biological rationale)?	Yes
6 Was subgroup effect one of a small number of hypothesized effects tested?	Yes, one of five
7 Does interaction test suggest low likelihood that chance explains the apparent subgroup effect?	Yes, significant in univariable subgroup analysis (P = 0.001)
8 Is significant subgroup effect independent?	Yes, significant in multivariable meta-regression (P = 0.03)
9 Is size of subgroup effect large?	Yes, 38% increasing in mixed age studies versus 2% decreasing in age ≥65 yrs studies
10 Is interaction consistent across closely related outcomes within study?	No, age could not explain the between-study variance for cardiovascular and cancer mortality outcomes
11 Is interaction consistent across studies?	No, mixed age studies showed larger risk in all-causes and cardiovascular mortality, but smaller risk in cancer mortality

(Supplementary Table S2). We used studies with HRs to assess the association between DFA and cardiovascular disease mortality. With moderate certainty of evidence, DFA significantly increased the risk of cardiovascular disease mortality (HR = 1.20, 95%CI: 1.01, 1.43; $p = 0.04$) (Fig. 1, Table 2). Although we did not find significant subgroup effect ($p_{interaction} = 0.56$, Supplementary Table S2), studies with health-status adjusted demonstrated a significant association between DFA and cardiovascular disease mortality, however, this significant association was not found in studies without health-status adjusted.

We found no significant association with cancer mortality (HR = 1.21, 95%CI: 0.95, 1.54; $p = 0.12$; low certainty) (Fig. 1, Table 2).

Sensitivity analysis by excluding studies that used objective insomnia measures showed similar results (Supplementary Fig. S4).

However, our subgroup analysis failed to identify the differences in sex, risk of bias, country, and length of follow-up for all-cause, cardiovascular, and cancer mortality (Supplementary Table S2).

DMS and mortality

Of 13 studies [17,21,24,33,35–37,39–41,47–49] that reported the association between DMS and mortality, six [21,33,39,40,47,48] reported results separately for men and women. We found no association between DMS and all-cause mortality (HR = 1.05, 95%CI: 0.96, 1.14; $p = 0.31$; high certainty) (Fig. 2, Table 2), cardiovascular disease mortality (HR = 1.03, 95%CI: 0.82, 1.31; $p = 0.78$; low certainty) (Fig. 2, Table 2), and cancer mortality (HR = 1.04, 95%CI: 0.65, 1.69; $p = 0.86$; low certainty) (Fig. 2, Table 2). We observed no suggestion of a subgroup effect (Supplementary Table S2). No statistically significant publication bias was found for all-cause mortality ($p = 0.60$) (Supplementary Fig. 5).

EMA and mortality

Six studies [21,33,39,40,47,48] reported the association between EMA and mortality for men and women separately. We found no association between EMA and all-cause mortality (HR = 0.97, 95% CI: 0.91, 1.04; $p = 0.37$; high certainty) (Fig. 3, Table 2), cardiovascular disease mortality (HR = 0.93, 95%CI: 0.76, 1.13; $p = 0.44$; moderate certainty) (Fig. 3, Table 2), and cancer mortality (HR = 1.00, 95%CI: 0.81, 1.24; $p = 1.00$; low certainty) (Fig. 3, Table 2). No suggestions of subgroup effects were found in all subgroup categories (Supplementary Table S2). Begg's test did not suggest a publication bias for all-cause mortality ($p = 0.40$) (Supplementary Fig. 6).

NRS and mortality

Only one study directly reported on NRS [17]. However, we identified six additional studies [19,33,39,41,44,55] that reported a sleep problem consistent with our definition of NRS: persistently feeling unrefreshed upon awakening in the presence of normal sleep duration [56]. Supplementary Table S1 presents the questions used for NRS. Seven studies provided 11 individual estimates of the association between NRS and mortality. We found that the presence of NRS increased all-cause mortality (HR = 1.23, 95%CI: 1.07, 1.42; $p = 0.003$; high certainty) and cardiovascular disease mortality (HR = 1.48, 95%CI: 1.06, 2.06; $p = 0.02$; moderate certainty), but did not increase the risk of cancer mortality (HR = 0.95, 95%CI: 0.60, 1.49; $p = 0.82$; very low certainty) (Fig. 4, Table 2). We observed no suggestion of a subgroup effect (Supplementary Table S2). Begg's test provided no evidence to suggest a publication bias for all-cause mortality ($p = 0.24$) (Supplementary Fig. 7).

Insomnia disorder and mortality

Eighteen individual estimates from 12 studies [17,20,22,23,34,36,41,42,45,51,53,54] addressing insomnia disorder and mortality yielded a pooled HRs of 1.07 (95%CI: 0.98, 1.17; $p = 0.12$; moderate certainty) for all-cause mortality; 1.66 (95%CI: 0.72, 3.83; $p = 0.24$; low certainty) for cardiovascular disease mortality; and 0.94 (95%CI: 0.58, 1.54; $p = 0.82$; moderate certainty) for cancer mortality (Fig. 5, Table 2). We did not specify the definition of insomnia disorder in advance. However, we subsequently categorized the definitions reported in the primary studies to stricter and less strict. Supplementary Table S1 presents the details of the definitions and categories. Although the association did not differ between strict and less strict definitions of insomnia disorder, studies with stricter definitions showed a stronger association with risk of all-cause mortality (HR = 1.14, 95%CI: 1.01, 1.29; $p = 0.03$) (Supplementary Table S2). Begg's test suggested that there was no statistically significant publication bias for all-cause mortality ($p = 0.12$) (Supplementary Fig. 8).

Discussion

Principal findings

Sleep is a critical determinant of health and well-being. Poor sleep is a common problem with 25% of adults in the United States of America, reporting insufficient sleep or rest, for at least 15 of

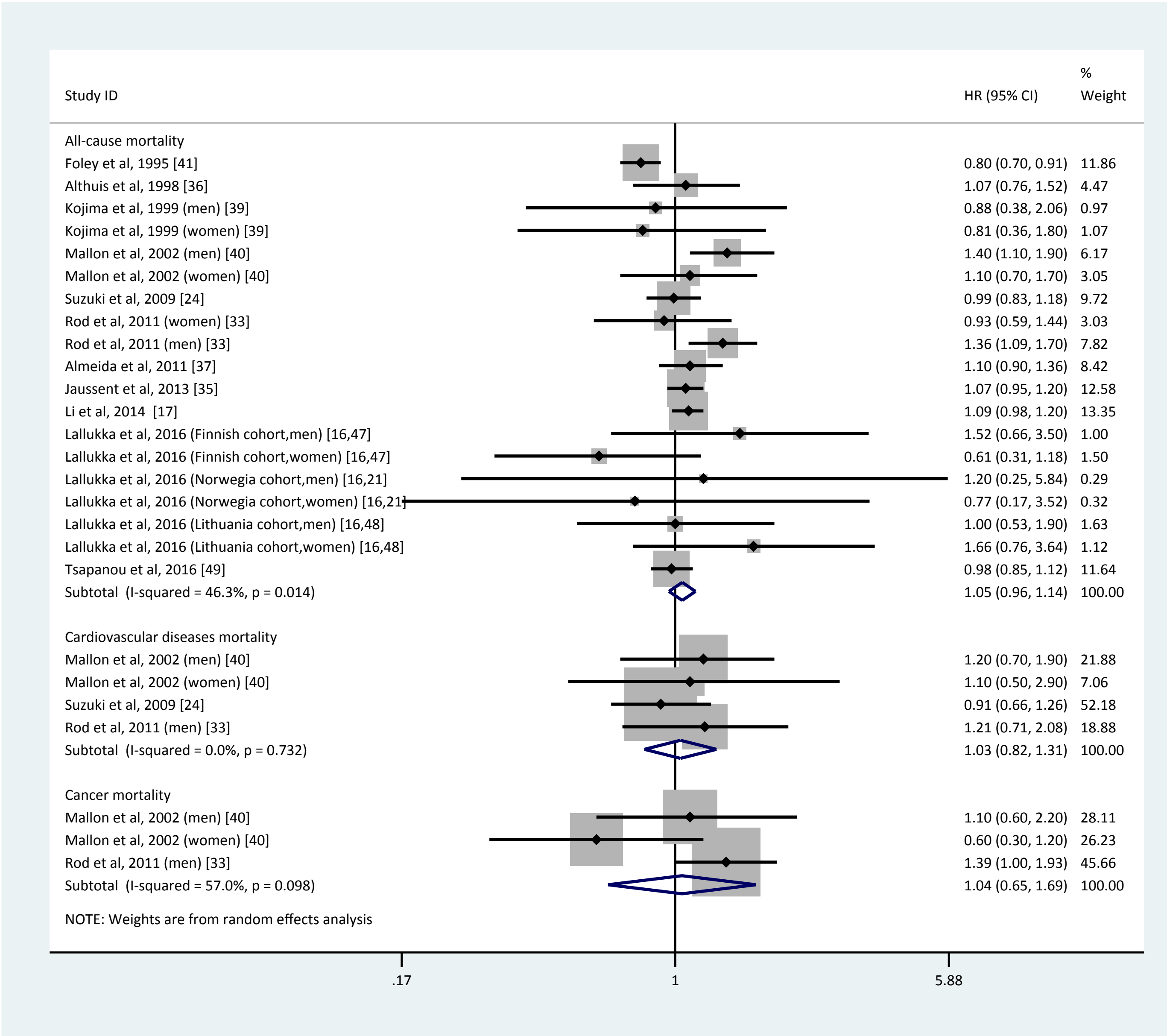

Fig. 2. Difficulty maintaining sleep and all-cause, cardiovascular disease, and cancer mortality. The results are shown as hazard ratio (HR) and 95% confidence interval (CI).

every 30 d [57]. This meta-analysis is the first to quantify the magnitude and certainty of the association between insomnia disorder/symptoms and mortality among adults aged ≥18 yrs old. We found that, with moderate to high certainty, difficulty falling asleep and non-restorative sleep were significantly associated with an increased risk of all-cause mortality and cardiovascular disease mortality. However, a subgroup analysis of moderate credibility suggested that this association was restricted to just the mid to older-aged population (Supplementary Table S2).

Contrastingly, with high certainty, difficulty maintaining sleep and early morning awakening was not associated with the risk of all-cause mortality. Insomnia disorder also proved unassociated with the risk of all-cause mortality and cardiovascular disease mortality with low to moderate certainty. We found no association with any of the insomnia variables and the risk of cancer-related mortality was uncertain, although in 4 out of 5 of the insomnia predictor variables the certainty of evidence was either low or very low.

Strengths and limitations

Strengths of our review include the relatively large number of studies (29) and the very large number of participants (1.5 million) from 12 countries. All of these studies were also conducted using multivariable analysis. We postulated a number of possible explanations of heterogeneity (sex, age, length of follow-up, and risk of bias) including a priori specification of direction. One of these proved moderately compelling, which suggested the association between DFA and mortality is restricted to younger individuals. We registered our study protocol on PROSPERO before our study started, as so to avoid selective reporting bias [58]. Moreover, under the guidance of GRADE methodologists we rated the certainty of evidence for each exposure using the GRADE approach that, for prognostic studies, has only recently become available [32,59].

Our work does have limitations, the most important of these relates to the measurement of insomnia disorder/symptoms. Firstly, the definition of insomnia disorder was inconsistent; we

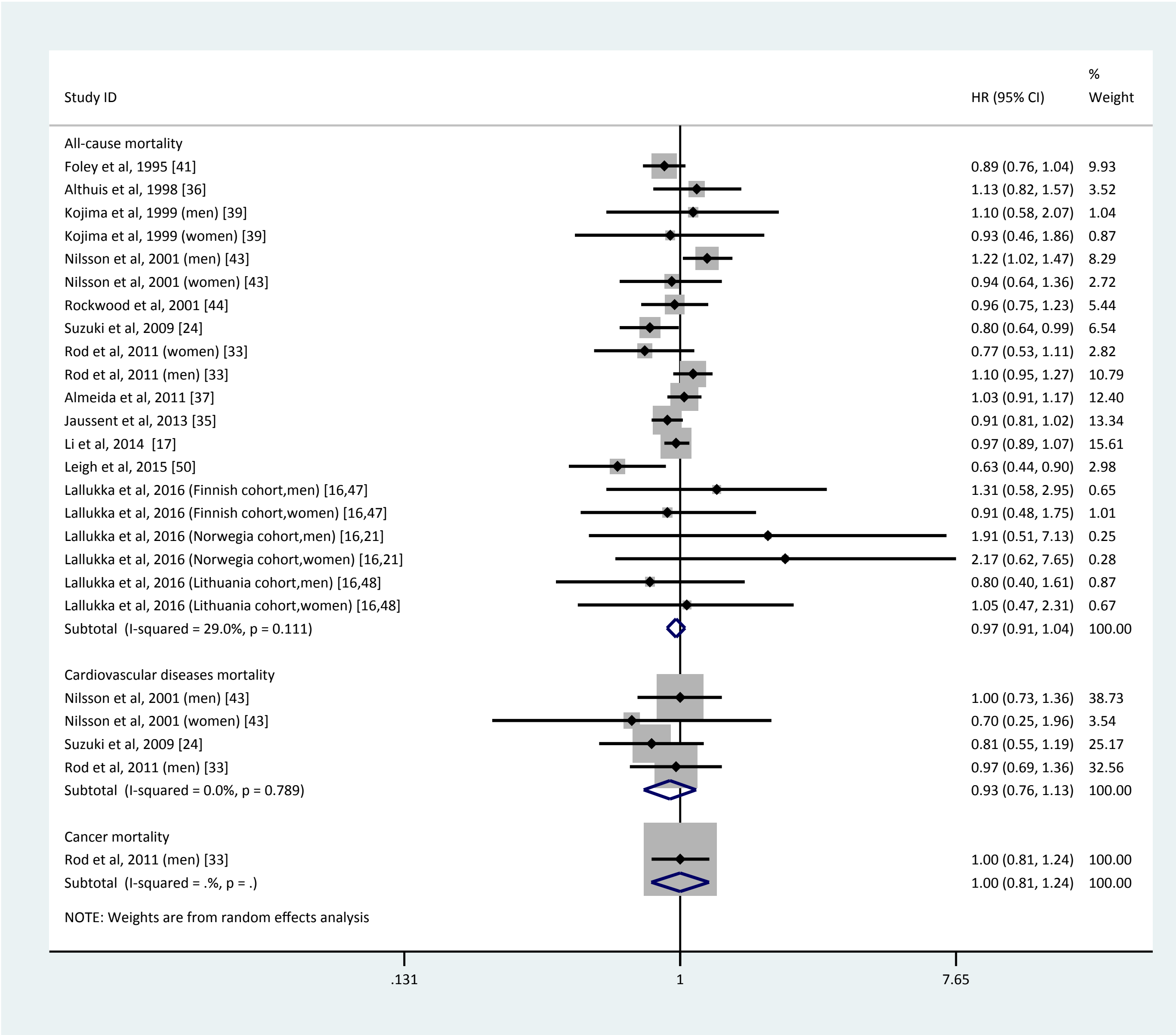

Fig. 3. Early morning awakening and all-cause, cardiovascular disease, and cancer mortality. The results are shown as hazard ratio (HR) and 95% confidence interval (CI).

categorized these definitions into stricter and less strict (Supplementary Table S1). We found that chance could easily explain differences in the estimates and that studies with stricter definitions of insomnia disorder showed a higher risk of mortality although the interaction test discrepancy (Supplementary Table S2). Some of studies reported different durations of insomnia. We only classified those with the largest duration as having insomnia because they had the largest possibility to be diagnosed as insomnia. For example, Kripke et al. reported the frequency of insomnia as 0, 1, 2, 3, 4 to 9, and 10 or more times per month. We determined that subjects had insomnia if 10 or more times per month was reported (Supplementary Table S1). Secondly, in most studies the assessment of individual insomnia symptoms was based on a single question that did not query severity and frequency. We could therefore not address the association of severity and the frequency of insomnia symptoms with mortality. Thirdly, measures of insomnia disorder and individual insomnia symptoms were based on self-reporting. Most of the studies (65.5%) did not report the validation or original references of the insomnia disorder measures, and half of them (51.7%) completed the measures using a mailed questionnaire. Two studies used relatively objective measures for insomnias disorder [38,52], our sensitivity analysis showed similar results. Limitations in accurately ascertaining insomnia should, however, introduce random rather than systematic error, and is thus an issue only when we failed to establish an association. Fourth, non-restorative sleep is a primary symptom of insomnia and our study finds that non-restorative sleep is significantly associated with an increased risk of all-cause mortality and cardiovascular disease mortality. However, non-restorative sleep is also common in patients with other organic sleep disorder such as sleep apnea which has been shown to be associated with cardiovascular disease [56]. Fifthly, although Begg's tests (p values) showed that there was no publication bias, funnel plots created showed that the larger studies were driving the

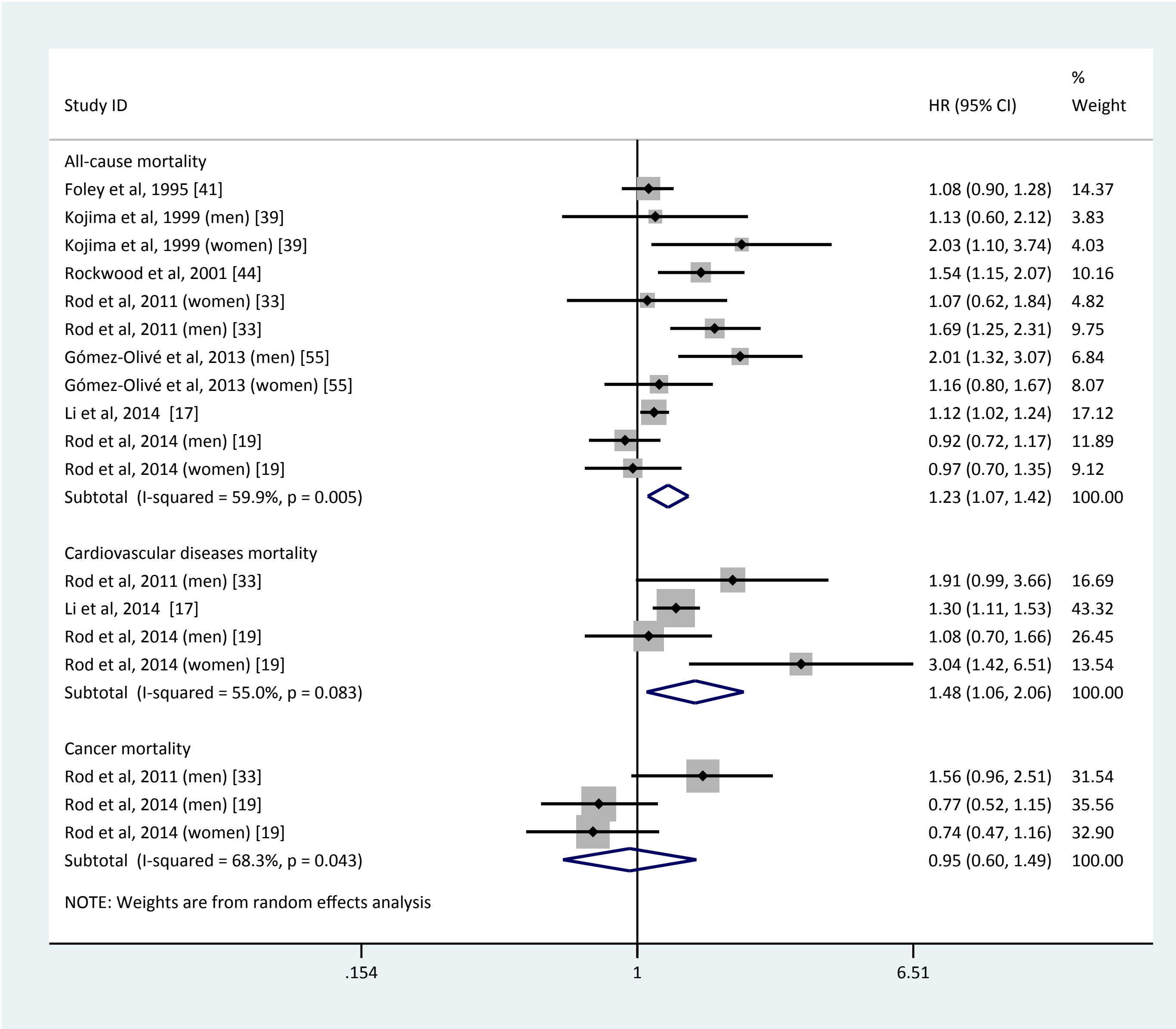

Fig. 4. Non-restorative sleep and all-cause, cardiovascular disease, and cancer mortality. The results are shown as hazard ratio (HR) and 95% confidence interval (CI).

results. For example, in the funnel plot that looks at insomnia disorder (Supplementary Fig. 8), all the studies seemed to find positive associations with the exception of just a few larger negative studies. Therefore, we could not conclude that there was no publication bias only using the Begg's test, however, the possibility of publication bias was small.

Moreover, our meta-analysis focused on a general adult population including all those ≥18 yrs old. Most studies, however, enrolled mid to older-aged populations. Although we did not rate down indirectness of population in our GRADE assessment, the application of our results to a younger population is questionable. Also, only a few studies addressed cardiovascular disease mortality and cancer mortality. Furthermore, our present study is looking at the general association between insomnia disorder, insomnia symptoms, and mortality. The impact of insomnia on survival among people with cardiovascular disease and cancer should be addressed in a further study. Finally, our present study only systematically searched MEDLINE (via OVID) and EMBASE databases. Although we manually reviewed the reference lists from included studies and relevant systematic reviews, the possibility of insufficient search still exited. There were no restrictions on publication language and publication status in our search strategies, however, we did not identify any studies published in languages other than English, and also did not identify any unpublished studies.

Comparison with other studies

Li et al. ‘s included a systematic review along with their prospective cohort study [17]. We included nine studies included in Li's analysis and an additional 20 studies that enrolled 1,490,800 patients. Additional contributions of our review include an assessment of the impact of insomnia disorder and the use of the GRADE approach to address the quality of the evidence. Although some findings of the two reviews were similar, we established a more powerful evidence to support that both of difficulty maintaining sleep and early morning awakening are unassociated with

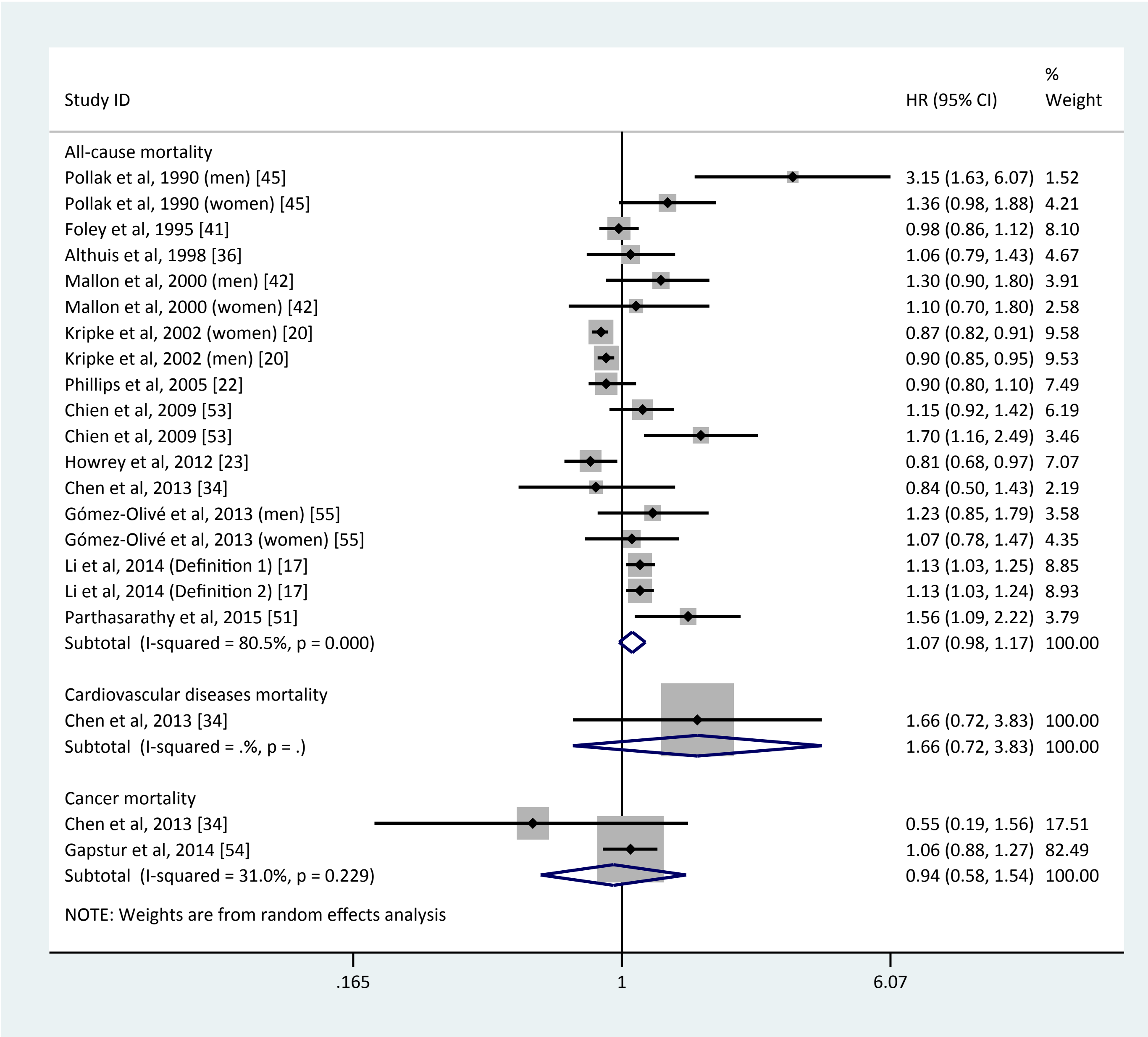

Fig. 5. Insomnia disorder and all-cause, cardiovascular disease, and cancer mortality. The results are shown as hazard ratio (HR) and 95% confidence interval (CI).

mortality. The association between non-restorative sleep and cardiovascular disease mortality and cancer mortality was uncertain in our study with three cohorts, but Li's study reported a more precise result with one cohort (HR = 1.48, 95%CI 1.06 to 2.06 versus HR = 1.30, 95%CI 1.11 to 1.53). Additionally, Li's study failed to conduct subgroup analyses to explore potential sources of the observed heterogeneity across studies.

Interpretation and application

Studies have suggested that chronic disorders cannot wholly explain the observed association between insomnia symptoms and mortality, and have considered that insomnia symptoms might independently predict mortality [17,42,60]. However, the underlying mechanisms of the association between insomnia disorder/symptoms and mortality remains unclear [51]. Several epidemiological and experimental studies considered that insomnia disorder probably was associated with known risk factors of mortality such as systemic inflammation. These findings, however, have been inconsistent [51,61–63]. For example, The Nord-Trondelag Health Study found no significant relationship between insomnia symptoms and C-reactive protein, a marker of systemic inflammation [64], whereas the Northern Finland 1966 Birth Cohort study reported that insomnia symptoms were associated with higher levels of C-reactive protein in men [65], while the National Health and Nutrition Examination Survey reported that non-restorative sleep, as opposed to nocturnal insomnia symptoms, was associated with an increase in C-reactive protein in both sexes [66]. Although C-reactive protein levels were themselves associated with increased mortality, the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD) cohort authors reported that the association between persistent insomnia and mortality did not notably change after adjusting for C-reactive protein [51]. Also, although we did not find a gender difference in the associations, explanations about the underlying mechanisms are lacking, and such mechanisms are also difficult to examine in epidemiological studies [16]. Moreover, measures of insomnia disorder and individual insomnia symptoms included in our study were mainly based on self-reporting. However, a population-based study reported that polysomnographic correlates of insomnia disorder/symptoms are significantly more prevalent among subjects with self-reported health disorders such as depression, low socioeconomic status, low level of physical activity and poor general health, thus possibly representing only confounding factors of other health conditions [67].

Conclusions

Our findings indicate that difficulty falling asleep and non-restorative sleep are probably associated with all-cause mortality and cardiovascular disease mortality. We did not find associations with other aspects of insomnia symptoms and mortality, nor with any aspect and cancer mortality (though quality of evidence for this outcome was generally low or very low).

Practice points

1. Difficulty falling asleep and non-restorative sleep are probably associated with a risk of all-cause and cardiovascular disease mortality.
2. The association between difficulty falling asleep and all-cause mortality may be restricted to mid to older aged population groups.
3. Early morning awakening proves unassociated with mortality.
4. There is no certain association between difficulty maintaining sleep and all-cause and cardiovascular disease mortality.

Research agenda

1. Further explore the underlying mechanisms of association between insomnia and mortality.
2. Study the association between insomnia and cancer mortality.
3. Address the association of severity of insomnia with mortality.
4. Study the impact of insomnia on survival in cancer survivors.

Conflicts of interest

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

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Abbreviations

CI	confidence interval
DMS	difficulty maintaining sleep
DFA	difficulty falling asleep
EMA	early morning awakening
GRADE	grading of recommendations, assessment, development and evaluation
HRs	hazard ratios
MOOSE	meta-analysis of observational studies in epidemiology
NRS	non-restorative sleep
OR	odds ratio
RRs	relative risks
TESAOD	Tucson Epidemiological Study of Airway Obstructive Disease

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.101215.

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