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Original Article

Association between total sleep time and all cancer mortality: non-linear dose-response meta-analysis of cohort studies

Yingjun Li [a], Shaofang Cai [b], Yuxiao Ling [a], Shuai Mi [a], Chunhong Fan [a], Yaohong Zhong [a], Qing Shen [a, *]

[a] School of Public Health, Hangzhou Medical College, Hangzhou, China
[b] Department of Science and Education, Xiamen Second Hospital, Xiamen, China

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ABSTRACT

Objective: Appropriate total sleep time is reported to be associated with several important health outcomes. However, the relationship between total sleep time and all cancer mortality is not well defined because of inconsistent results from published studies, and no dose-response meta-analysis was performed to evaluate the exact dose-response relationship.

Methods: We conducted a literature search of PubMed and Web of Science to identify all relevant epidemiological studies published before August 9, 2018. We performed categorical and non-linear dose-response meta-analyses to quantify the association between total sleep time and all cancer mortality.

Results: Finally, we included 14 cohort studies in the present meta-analyses enrolling 866,877 participants with 43,021 cancer deaths. We found that total sleep time less than seven hours was not significantly associated with increased risk of all cancer mortality [relative risk (RR) = 1.02; 95% confidence interval (CI) = 0.99–1.05]. However, four to five hours total sleep time was related to an 8% increased risk of all cancer mortality (RR = 1.08; 95% CI = 1.02–1.13) in dose-response meta-analysis. Furthermore, long total sleep time (≥8 hours) was weakly associated with all cancer mortality (RR = 1.05; 95% CI = 1.02–1.08). However, the increment in total sleep time longer than nine hours was notably associated with an increased risk of cancer mortality.

Conclusion: The current meta-analysis provides evidence of a positive association between total sleep time of four to five hours and total sleep time longer than eight hours with the risk of all cancer mortality among the general population. Additional studies are needed to establish causality.

1. Introduction

Cancer has been the leading cause of death in both developed and developing countries, and the burden is growing faster than before because of the growth and aging of the population [1]. The International Agency for Research on Cancer (IARC) estimated that 9.6 million cancer-related deaths occurred in 2018, compared with 8.2 million in 2012 [2]. Appropriate total sleep time, usually reported to be seven to eight hours [3], has gained interest for its beneficial effect for several non-communicable diseases, including cancer [4], diabetes [5], stroke [6], and cardiovascular disease [7].

Recently, fair amounts of dose-response meta-analyses have been conducted to investigate the non-linear relationship between sleep duration with health outcomes [8–11]. It has been reported that long total sleep time was significantly associated with a 39% increased risk of all-cause mortality, 26% increased risk of incident diabetes mellitus, 25% increased risk of cardiovascular disease, 46% increased risk of stroke, 24% increased risk of coronary heart disease, and 8% increased risk of obesity [12]. Meanwhile, short total sleep time was shown to be significantly linked with an increased risk of obesity (38%), incident diabetes mellitus (37%), coronary heart diseases (26%), hypertension (17%), cardiovascular diseases (16%), and all-cause mortality (12%) [13]. Moreover, a 2016 meta-analysis showed that compared with reasonable total sleep time (seven to eight hours), more than nine hours total sleep time was associated with 11% increased risk of all cancer mortality, while no statistically significant association was found between less than six hours total sleep time with all cancer mortality [14]. However, they

* Corresponding author. School of Public Health, Hangzhou Medical College, 481 Binwen Road, Binjiang District, Hangzhou, 310053, Zhejiang, China.
E-mail address: shenqing1215@163.com (Q. Shen).

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only conducted categorical meta-analysis without a dose-response meta-analysis, thus precluding them from detecting the exact dose-response relationship between total sleep time and all cancer mortality. Several other large sample cohort studies also have been published since the 2016 meta-analysis [15–17].

To quantify precisely the association between total sleep time and all cancer mortality in the general population, we conducted an updated systematic review and dose-response meta-analysis of prospective cohort studies published up to August 9, 2018.

2. Material and methods

2.1. Literature search and study inclusion

A systematic search was performed in PubMed and Web of Science to identify relevant published studies up to August 9, 2018. The search strategy was as follows: (sleep OR sleep duration OR sleep disorders OR sleep deviation OR night sleep OR nap OR sleep pattern) AND (neoplasia OR cancer OR carcinoma OR adenomas OR adenocarcinoma) AND mortality AND (prospective OR cohort OR case-control OR case-cohort). Two of the authors (YJ and SF) reviewed all titles and abstracts. If either author included the study, the full-text paper was obtained for further reviewing. Three of the authors (YJ, SF, and FY) checked the reference lists of all full-text papers as well as previous relevant reviews and meta-analyses identified through the above search strategy to identify additional publications of interest manually.

We included studies that met the following criteria: (i) the exposure of interest was total sleep time in night-time or 24-hours which was assessed before cancer diagnosis; (ii) the endpoint of interest was all cancer mortalities among the general population who had no cancer diagnosis; (iii) the type of study was a cohort; (iv) and the relative risk (RR) and corresponding 95% confidence intervals (CIs), or sufficient data to calculate them, were reported. When several reports were from the same study, only the most updated one was included.

2.2. Data extraction and quality assessment

For each eligible study, detailed information was extracted by two of the authors (SF and FY), including publication year, country, study name, International Classification of Diseases code of cancers surveyed, number of deaths caused by cancers, number at risk, duration of follow-up, gender, age, variables adjusted or matched, total sleep time categories, and corresponding risk estimates with 95% CIs.

Two reviewers (SF and FY) independently evaluated the quality using the Newcastle-Ottawa Scale [18]. The scores ranged from zero (the lowest) to 16 (the highest), and a higher score indicated better quality. The discrepancies were resolved by consensus and discussion.

2.3. Statistical analyses

The multivariate-adjusted risk estimates were selected if they were reported in the original publication; otherwise, the unadjusted risk estimates were calculated using the original data. The forest plots for the association between short total sleep time and long total sleep time with all cancer mortalities were generated for less than seven hours versus seven to eight hours and more than eight hours versus seven to eight hours.

The heterogeneity among studies was assessed using Cochran Q test [19] and I-squared statistic [20], defining a statistically significant heterogeneity as $P<0.10$ or $I^2>50\%$. A fixed-effects model was applied when no statistically significant heterogeneity was presented; otherwise, the random-effects model was performed to provide more conservative estimates [21]. Meanwhile, subgroup analysis and meta-regression were used to analyze the sources of heterogeneity. Subgroup analyses were carried out stratified by gender, the source of cohort, ethnicity, sleep pattern, publication year, and quality score.

Publication bias was assessed by using Egger's linear regression [22] and Begg's rank correlation [23]. The Begg's funnel plots were drawn, and asymmetry of the funnel plot was equated with the existence of potential publication bias. To investigate the robustness of our primary analysis, we performed a sensitivity analysis to assess whether a particular study may have influenced the summary risk estimate.

For each study, the median or mean level of total sleep time was assigned to the corresponding RR estimate. We assigned the midpoint of the upper and lower boundaries in each category if median or mean were not reported. For open-ended categories, the range was assumed to be the same as the adjacent interval [24]. For the study reported risk estimates relative to a reference category other than seven to eight hours, but with available data for seven to eight hours, the risk estimates were recalculated using the seven to eight hours as a reference by using the Orsini's method [25]. We set the coefficient of the second, third, and fourth splines to be equal to zero to test the probability of a non-linearity relationship [26].

All statistical analyses were carried out using STATA version 15.0 (STATA Corp, College Station, Texas).

3. Results

3.1. Literature search and study characteristics

The flowchart of the literature search and study inclusion is presented in Fig. 1. 657 articles were identified in the initial search, and 626 studies were excluded after screening their titles and abstracts because of the duplication or the apparent irrelevance to the interest of our study. We next excluded 17 studies out of 31 after reviewing full-text papers, as five of them only focused on daytime napping without information for night-time sleep or 24-hour sleep,

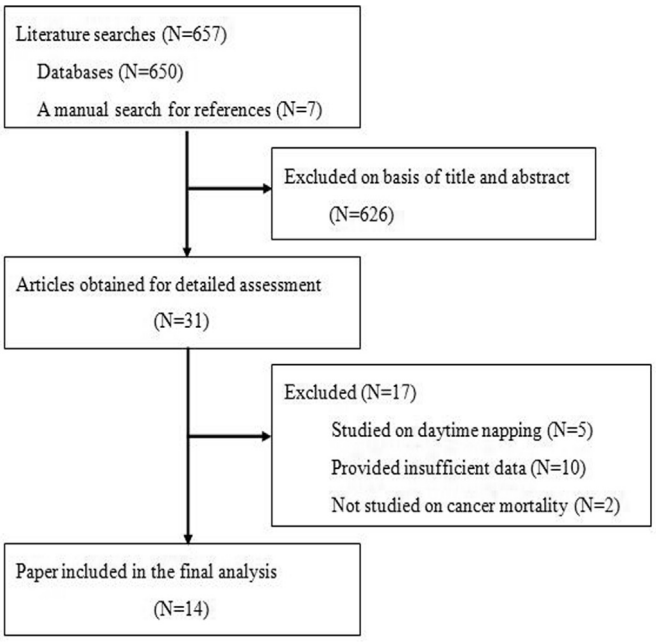

Fig. 1. Flowchart of study selection.

Table 1
Characteristics of cohort studies included in the meta-analysis of total sleep time and all cancer mortality.

Study ID	Country and name of the study	No. of death	No. at risk	Duration of follow-up (Years)	Gender	Age	Pattern	Definition of short sleep time (h/day)	Definition of normal sleep time (h/day)	Definition of long sleep time (h/day)	Variables adjusted or matched in the regression models
Soh et al. (2018)	Singapore,Singapore Chinese Health Study	1,989	39,523 (PR)	12.7	MF	45–74	24-hours	≤6	7	≥8	Age; year of recruitment; gender; dialect group; physical activity; level of education; smoking status; alcohol intake; BMI; and history of hypertension, ischaemic heart disease, stroke, diabetes, and cancer.
Åkerstedt et al. (2017)	Swedish,Swedish Cancer Society ("the Swedish National March")	627	337,328 (PY)	13	MF	<65	24-hours	≤6	7	≥8	Age; sex; BMI; smoking status; alcohol consumption; educational level; and physical activity and major diseases.
Bai et al. (2016)	China,Dongfeng-Tongji Cohort Study (DFTJ)	379	114,162 (PY)	4.5	M, F, MF	62.6 (mean)	Night-time	<7	7–8	>8	Age; BMI; family history of cancer; alcohol drinking and smoking status; and gender.
Cai et al. (2014)	China, Shanghai Women's and Men's Health Studies	4,277	113,138 (PR)	M:6.07; F:7.12	M, F, MF	M:40–75; F:44-79	24-hours	≤6	7	≥8	Age; education; income; smoking; alcohol Consumption; tea consumption; comorbidity score; history of night-shift work; participation in regular exercise; BMI; waist-to-hip ratio; cardiovascular disease; and upper gastrointestinal tract.
Qian et al. (2014)	America,NIH-AARP Diet and Health Study	16,644	3,363,604 (PY)	14	MF	50–72	24-hours	≤6	7–8	≥9	Age; sex; race/ethnicity; marital status; education; self-reported health; smoking status; smoking dose; years since quitting smoking; and alcohol drinking.
Rod et al. (2014)	UK,Whitehall II study	374	9,098 (PR)	22	M, F	35–55	Night-time	≤6	7	>9	Age; employment grade; ethnicity; and marital status.
Yeo et al. (2012)	Korea,Korean Multi-center Cancer Cohort (KMCC) Study	526	124,267 (PY)	18	M, F, MF	≥20	24-hours	≤6	7	≥8	Age; educational attainment; BMI; cigarette smoking; alcohol consumption; and past history of hypertension, type 2 diabetes, cardiovascular disease; metabolic syndrome.
Kim et al. (2013)	America,Multiethnic Cohort Study (MEC)	6,772	135,685 (PR)	12.9	M, F	45–75	24-hours	≤6	7	≥8	Age; cohort entry; ethnicity; education; marital status; history of hypertension or diabetes at enrollment, alcohol consumption, energy intake, body mass index, physical activity, hours spent daily watching television; and smoking history.
Kakizaki et al. (2012)	Japan,Ohsaki Cohort Study	2,764	49,256 (PR)	13	MF	40–79	24-hours	≤6	7	≥8	Age; sex; total caloric intake; marital status; level of education; job status; history of myocardial infarction, cancer, stroke, hypertension, diabetes mellitus; smoking status; alcohol drinking; time spent walking; perceived mental stress; and self-rated health, physical function.

(*continued on next page*)

Table 1 (*continued*)

Study ID	Country and name of the study	No. of death	No. at risk	Duration of follow-up (Years)	Gender	Age	Pattern	Definition of short sleep time (h/day)	Definition of normal sleep time (h/day)	Definition of long sleep time (h/day)	Variables adjusted or matched in the regression models
Ikehara et al. (2009)	Japan,Japan Collaborative Cohort study (JACC)	5,465	1,270,585(PY)	14.3	M, F	40–70	24-hours	≤6	7	≥8	Age; BMI; history of hypertension, diabetes; alcohol consumption; smoking; education level; hours of exercise; hours of walking; regular employment; perceived mental stress; depressive symptoms; and frequency of fresh fish intake.
Lan et al. (2007)	China,Survey of Health and Living Status of the Elderly	278	3,079 (PR)	10	M, F	≥64	Night-time	<7	7–7.9	≥8	Age; marital status; monthly income; cigarettes smoking; alcohol consumption; BMI; Exercise; disease history of heart disease, stroke, cancer; and depression.
Amagai et al. (2004)	JapanJichi Medical School Cohort Study	201	93,424 (PY)	8.2	M, F	19–93	24-hours	<7	7–7.9	≥8	Age; systolic blood pressure; total cholesterol; BMI; smoking habits; alcohol drinking habits; education; and marital status.
Patel et al. (2003)	America, Nurses' Health Study (NHS)	2,642	82,969 (PR)	14	F	30–55	24-hours	≤6	7	≥8	Age; smoking status; alcohol consumption; physical activity; depression; history of snoring; BMI; history of cancer, cardiovascular disease, hypertension, or diabetes; and shift-working history.
Mallon et al. (2002)	SwedenCounty of Dalarna Study	83	1,870 (PR)	12	M, F	45–65	Night-time	<6	7	>8	Age.

PR, the person at risk; PY, person-year; M, male; F, female; BMI, body-mass index.

10 provided insufficient data, and two were not focused on all cancer mortality. Finally, we included 14 cohort studies [15–17,27–37] in the present meta-analyses enrolling 866,877 participants with 43,021 cancer deaths.

Table 1 shows the detailed characteristics of the included studies. Three studies were conducted in Europe, eight in Asia, and three in North America. Nine studies presented the estimates for M (male), 10 for F (female), and seven for MF (male and female). The range of study periods was from 2004 to 2018. The quality scores ranged from 12 to 15 with a median of 14 for quality assessment. Ten studies reported the 24-hour sleep while four focused on night-time sleep.

3.2. Short total sleep time and long total sleep time with all cancer mortality

Fig. 2(A) presents the forest plots that provide study-specific and pooled RRs (95% CIs) of all cancer mortality for short total sleep time (<7 hours) versus normal total sleep time (seven to eight hours). Fig. 2(B) demonstrates the forest plots for long total sleep time (≥8 hours) versus normal total sleep time (seven to eight hours). The pooled RRs of all cancer mortality were 1.02 (95% CI = 0.99–1.05, *P* for heterogeneity = 0.966) for short versus normal total sleep time and 1.05 (95% CI = 1.02–1.08, *P* for heterogeneity = 0.673) for long versus normal total sleep time. No statistically significant asymmetry was found by the Egger's and Begg's tests ($P > 0.05$). In the sensitivity analysis, the omission of each study at a time did not materially alter the results.

Table 2 gives the relationship between short/long total sleep time and all cancer mortality among different subgroups stratified by potential modifying factors. For both short and long total sleep time, no statistically significant heterogeneity was found across strata of gender, the source of the cohort, ethnicity, sleep pattern, publication year, and quality score ($P_{\text{for meta-regression}} > 0.1$). When stratified by publication year, a marginally significant association between short total sleep time and all cancer mortality was depicted in studies published after 2010 (RR = 1.03, 95% CI = 1.00–1.06). Meanwhile, the positive association between long total sleep time and all cancer mortality was more pronounced in an occupation-specific cohort (RR = 1.12, 95% CI = 1.02–1.25), in Asian population (RR = 1.06, 95% CI = 1.02–1.10), in night-time sleep (RR = 1.19, 95% CI = 1.02–1.39), in studies published before 2010 (RR = 1.07, 95% CI = 1.02–1.12), and in quality scores less than 14 (RR = 1.13, 95% CI = 1.02–1.25).

3.3. Dose–response meta-analysis

Fig. 3 indicates that compared with seven to eight hours total sleep time, those with four to five hours, eight to nine hours, nine to 10 hours, and more than 10 hours had 8%, 3%, 4%, and 17% increased risk of all cancer mortality, respectively. On the other hand, Fig. 4 shows the results of the best-fitting dose-response relationship of total sleep time with all cancer mortality. The dose-response analysis indicated a J-shaped curve in the relationship between total sleep time and all cancer mortality. It showed that the increment in total sleep time longer than nine hours was significantly positively associated with risk of cancer mortality, while the dose-response relationship with total sleep time less than eight hours was not as obvious.

4. Discussion

To the best of our knowledge, this is the first dose-response meta-analysis to investigate the relationship between total sleep time and risk of all cancer mortality. We found a weak but statistically significant association between long total sleep time (≥8 hours) and all cancer mortality. Moreover, the increment in total sleep time longer than nine hours was notably associated with an increased risk of cancer mortality. Short total sleep time (<7 hours) was not significantly associated with increased risk of all cancer mortality. However, four to five hours total sleep time was related to an 8% increased risk of all cancer mortality in dose-response meta-analysis.

Short and long sleep duration has been associated with a range of adverse health outcomes including cancer mortality through complex biological processes. Previous studies have

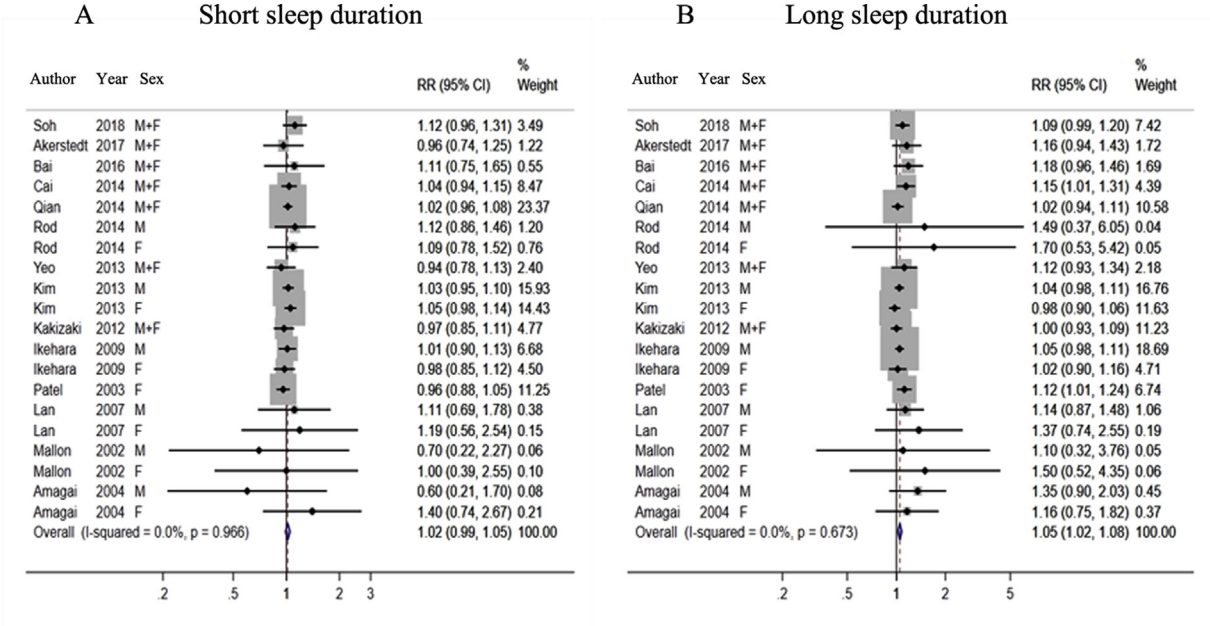

Fig. 2. Forest plots for pooled relative risks (RRs) and the corresponding 95% confidence intervals (CIs) of all cancer mortality for short total sleep time (<7 hours) (A) and long total sleep time (≥8 hours) (B).

Table 2
Pooled and subgroup analysis stratified by potential modifying factors.

	Stratified analyses of pooled RR for short total sleep time					Stratified analyses of pooled RR for long total sleep time				
	N[a]	Relative risk (95% CI)	I^2 (%)	*P* value of heterogeneity	Meta -regression[b]	N[a]	Relative risk (95% CI)	I^2 (%)	*P* value for heterogeneity	Meta -regression[b]
Overall	14	1.02 (0.99–1.05)	0.0	0.966	–	14	1.05 (1.02–1.08)	0.0	0.673	–
Gender [c]										
Male	9	1.02 (0.96–1.07)	0.0	0.787	0.927	9	1.06 (1.01–1.10)	0.0	0.910	0.765
Female	10	1.02 (0.97–1.07)	0.0	0.791		10	1.06 (1.00–1.11)	28.6	0.181	
Source of cohort										
Population-based	12	1.02 (0.99–1.06)	0.0	0.976	0.334	12	1.04 (1.02–1.07)	0.0	0.653	0.191
Occupation-specific	2	0.98 (0.90–1.06)	0.0	0.454		2	1.12 (1.02–1.25)	0.0	0.723	
Ethnicity										
Asian	8	1.01 (0.96–1.07)	0.0	0.852	0.801	8	1.06 (1.02–1.10)	0.0	0.627	0.218
Caucasian	3	1.04 (0.89–1.22)	0.0	0.887		3	1.19 (0.98–1.44)	0.0	0.949	
Mixed	3	1.02 (0.98–1.06)	0.0	0.452		3	1.03 (0.99–1.07)	31.5	0.224	
Pattern										
24-hour	10	1.02 (0.99–1.05)	0.0	0.796	0.364	10	1.05 (1.02–1.08)	0.0	0.447	0.111
Night-time	4	1.10 (0.93–1.29)	0.0	0.995		4	1.19 (1.02–1.39)	0.0	0.986	
Publication year										
≥2010	9	1.03 (1.00–1.06)	0.0	0.938	0.199	9	1.04 (1.01–1.08)	5.8	0.388	0.414
<2010	5	0.98 (0.92–1.04)	0.0	0.905		5	1.07 (1.02–1.12)	0.0	0.818	
Quality score										
≥ Median (14)	11	1.02 (0.99–1.06)	0.0	0.954	0.313	11	1.04 (1.02–1.07)	0.0	0.541	0.172
< Median (14)	3	0.98 (0.90–1.06)	0.0	0.755		3	1.13 (1.02–1.25)	0.0	0.921	

[a] The number of studies included.
[b] Represents the test for significance of the study modification across strata.
[c] Studies which reported or could calculate the gender-specific estimates were selected.

proved that sleep restriction might generate an insulin-resistant state in human adipocytes [38], increase ghrelin and decrease leptin [39,40], which could lead to subsequent outcomes related to obesity and diabetes mellitus [41], thus having a higher risk of cancer-related mortality [42]. On the other hand, long sleep duration was found to be positively associated with melatonin levels [43], which was related to tumor cells apoptosis, anti-angiogenesis, anti-proliferation, and anti-oxidative effect [44,45]. Prather et al. believed that excessive sleep might increase some inflammatory biomarkers, such as C-reactive protein and interleukin-6 [46], which had a strong relationship with cancer-related mortality [47].

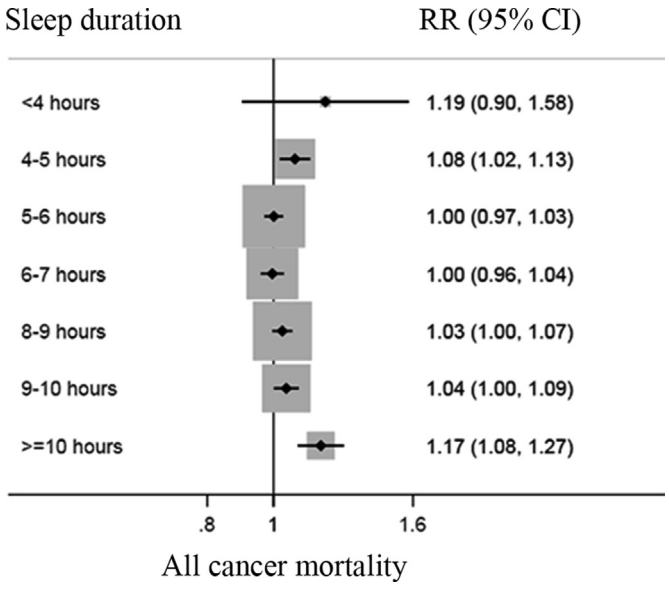

Fig. 3. Non-linearity relationship between total sleep time of fewer than four hours, four to five hours, five to six hours, six to seven hours, eight to nine hours, nine to 10 hours, and more than 10 hours with all cancer mortality.

Several cohort studies focused on mortality have revealed a similar U-shaped association between sleep duration with all-cause mortality [28,33] and cardiovascular disease mortality [33,48]. However, when it comes to cancer mortality, the U-shaped association was less clear [33,49]. In the present study, we found a J-shaped curve in the relationship between total sleep time and all cancer mortality, which was in accordance with the association between total sleep time and cancer risk [8]. Careful attention should be paid to the interpretation of the different relationship between short total sleep time and cause-specific mortality. Ma et al. [14], reported no association between total sleep time less than six hours with an increased risk of all cancer mortality in his meta-analysis. However, our results demonstrated that total sleep time of four to five hours was statistically significantly related to an 8% increased risk of all cancer mortality when compared with seven

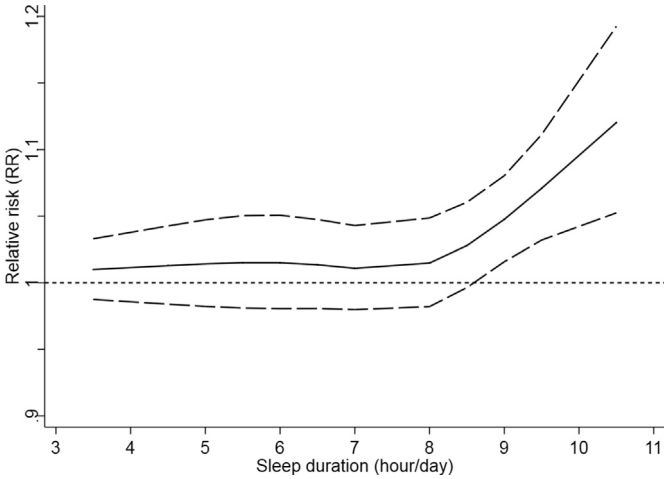

Fig. 4. Relative risks (RRs) (solid line) and the corresponding 95% confidence intervals (CIs) (dash lines) for the dose-response relationship between total sleep time (hours per day) with all cancer mortality among the general population. The *P* values for the nonlinearity test were all <0.001. Data fitting was based on fixed-effects restricted cubic spline models using the fixed percentiles 5%, 35%, 65%, and 95% as knot locations.

to eight hours. Meanwhile, total sleep time less than four hours was related to a 19% increased risk of all cancer mortality, while the association was not statistically significant. The discrepancy may be caused by insufficient data at this short duration of sleep.

Long total sleep time has been reported to be associated with risk of all-cause mortality [24] and several non-communicable diseases [12]. In the 2016 meta-analysis [14], they only revealed that total sleep time more than nine hours was at 11% greater risk of all cancer mortality without detecting eight to nine hours total sleep time. We found long total sleep time (≥8 hours) was associated with a 5% greater risk of all cancer mortality, though the association was weak. We further found that compared with seven to eight hours, eight to nine hours, nine to 10 hours, and more than 10 hours had 3%, 4%, and 17% increased risk of all cancer mortality, respectively. Otherwise, the National Sleep Foundation recommended seven to nine hours as the proper total sleep time for adults [50]. Our dose-response analysis showed that when total sleep time exceeded nine hours, the increment in duration was remarkably associated with increased risk of cancer mortality, which is in accordance with the recommendation.

The strengths of this meta-analysis should be mentioned. First, all included studies were prospective cohort studies that were less likely to have information bias. Besides, no statistically significant heterogeneity was found in both short and long total sleep time. Moreover, subgroup analysis and meta-regression analyses were applied to detect the potential sources of heterogeneity by using six predefined factors, and no statistically significant effect modification was found. Otherwise, the previous meta-analysis on this topic was only based on a two-category model, which lost much information in different exposure categories and had lower statistical power.

This study also has some limitations. First, the total sleep time assessment of included studies was all self-reported. The estimated total sleep time by participants might not reflect actual duration, as they might consider awake time in bed as a part of sleep time [51]. Second, although several theoretical pathways may explain the association between short/long total sleep time and increased risk of cancer mortality, the present meta-analysis based on observational studies could not establish causality nor avoid the possibility of residual confounding [52]. Third, the data available for our research limited our ability to determine whether attributes other than total sleep time, for instance, sleep quality, is also similarly related to all cancer mortality [53]. Finally, we were unable to analyze the association between total sleep time and the risk of cancer mortality in shift workers or the effect of obstructive sleep apnea on cancer mortality due to limited data in included studies.

5. Conclusion

In conclusion, the current meta-analysis provides evidence of a positive association between total sleep time of four to five hours and total sleep time longer than eight hours with the risk of all cancer mortality among the general population. Thus, public health recommendation for cancer prevention should consider encouraging the appropriate duration of sleep. However, additional studies, especially studies aimed at extremely short total sleep time (<4 hours) are warranted to clarify the aetiologic pathways underlying the association between total sleep time and cancer death.

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Conflict of interest

The authors declare no conflict of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.03.026.

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