Relationship of sleep duration and annual changes in sleep duration with the incidence of gastrointestinal cancers: a prospective cohort study

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Abstract

Background: Prospective analyses have yet to identify a consistent relationship between sleep duration and the incidence of gastrointestinal (GI) cancers. The effect of changes in sleep duration on GI cancer incidence has scarcely been studied. Therefore, we aimed to examine the association between baseline sleep duration and annual changes in sleep duration and GI cancer risk in a large population-based cohort study.

Methods: A total of 123,495 participants with baseline information and 83,511 participants with annual changes in sleep duration information were prospectively observed from 2006 to 2015 for cancer incidence. Cox proportional-hazards models were used to calculate hazard ratios (HRs) and their confidence intervals (CIs) for GI cancers according to sleep duration and annual changes in sleep duration.

Results: In baseline sleep duration analyses, short sleep duration (≤5 h) was significantly associated with a lower risk of GI cancer in females (HR: 0.31, 95% CI: 0.10–0.90), and a linear relationship between baseline sleep duration and GI cancer was observed ($P = 0.010$), especially in males and in the >50-year-old group. In the annual changes in sleep duration analyses, with stable category (0 to −15 min/year) as the control group, decreased sleep duration (≤−15 min/year) was significantly associated with the development of GI cancer (HR: 1.29; 95% CI: 1.04–1.61), especially in the >50-year-old group (HR: 1.32; 95% CI: 1.01–1.71), and increased sleep duration (>0 min/year) was significantly associated with GI cancer in females (HR: 2.89; 95% CI: 1.14–7.30).

Conclusions: Both sleep duration and annual changes in sleep duration were associated with the incidence of GI cancer.

Keywords: Gastrointestinal cancer; Sleep duration; Annual changes; Prospective cohort; Cancer risk

Introduction

The incidence of gastrointestinal (GI) cancers, mainly colorectal cancer, gastric cancer, liver cancer, gallbladder cancer, pancreatic cancer, and esophageal cancer, is increasing worldwide and has caused a critical public health problem.[1-3] The burden of GI cancers is serious in China, with approximately 1.9 million diagnoses and 1.5 million deaths expected in 2020, accounting for nearly 38% and 41% of GI cancer cases and deaths globally.[4]

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The epidemiology of GI cancers is complex in China for considering the incidence and mortality of GI cancers vary by area (urban/rural), sex, age group, and cancer sites,[5] so the identification of modified risk factors associated with the development of GI cancers remains the key strategy to reduce the disease burden in the foreseeable future. Given the high incidence and mortality, the identification of modifiable risk factors associated with the development of

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GI cancers is important for public health. In addition to the traditional risk factors, including diabetes,[6,7] tobacco smoking,[8] obesity, and a high vitamin D status,[9,10] we found some new risk factors for GI cancers, such as sleep.[11-14]

Sleep is a basic human need and might be related to cancer occurrence.[15,16] An optimal sleeping condition appears to be imperative for health.[17] Recent evidence is mixed and inconsistent regarding the association between sleep duration and risk of GI cancers. One study provided evidence of a U-shaped association between sleep duration and colorectal cancer risk, with both short and long sleep duration associated with a greater risk.[11] One study suggested that only a long sleep duration is associated with an increased risk of colorectal cancer,[12] while another study indicated no association between sleep duration and colorectal cancer.[13] In contrast, one recent publication reported that a short sleep duration was associated with stomach cancer in males, and there was a null association between short or extremely long sleep duration and esophageal cancer, colorectal cancer, liver cancer, and pancreatic cancer risk.[14]

Prospective analyses have yet to identify a consistent relationship between sleep duration and the incidence of GI cancers. Moreover, prior studies have had significant limitations in exploring an independent association between sleep duration at one time point and cancer risk. The effect of changes in sleep duration on cancer incidence has scarcely been studied. Therefore, we aimed to examine the association between baseline sleep duration, changes in sleep duration (calculated over the entire study period), and GI cancer risk in a large population-based cohort study. The Chinese Kailuan cohort, with a follow-up of >9 years, offers a unique possibility to investigate the association between baseline sleep duration and changes in sleep duration and GI cancer risk-adjusted for potential confounders.

Methods

Ethical approval

This study was jointly approved by the Medical Ethics Committee of the Kailuan Medical Group, Kailuan Company (No. 2016-5). Kailuan General Hospital was not only responsible for the ethical approval of its own but also for that of the other ten hospitals which were also affiliated to Kailuan Group and in charge of the routine check-up and the cohort study. Written informed consent was obtained from all the subjects at their baseline interview visit.

Study design and population

The Kailuan study is a prospective dynamic cohort study among the community-based population in Kailuan Group in Tangshan City in Northern China.[18] Kailuan Group is a comprehensive company that managed coal production, bauxite, machine manufacturing, chemical production, healthcare, etc.[19] Since May 2006, 138,150 subjects over the age of 18 years were recruited to participate in a standardized questionnaire interview and physical examination at 11 affiliated hospitals in the Kailuan Company.

Among these subjects, we excluded participants with a cancer diagnosis before the baseline examination ($n = 371$) and those who did not provide the information on baseline sleep duration ($n = 14,284$). Thus, a total of 123,495 participants were included in the analyses of baseline sleep duration. Then, the following participants were excluded for the analyses of annual changes in sleep duration: 10,646 subjects who participated in the baseline survey in 2010 to 2011 (only with baseline sleep duration), 778 subjects who had a cancer diagnosis before the last questionnaire interview, and 1578 subjects who had missing values. In addition, 26,982 subjects were failed to follow up their next sleep duration (follow-up rate 75.6%). After exclusion, 83,511 individuals remained for further analysis [Supplementary Figure 1, http://links.lww.com/CM9/A770].

Assessment of sleep duration

Baseline sleep duration

Sleep duration data were collected through a self-reported answer to the question "How many hours of sleep have you had on an average night in the preceding 3 months?" We placed baseline sleep duration into four categories according to the response: (1) ≤5 h, (2) 6 h, (3) 7 h (as a reference), and (4) ≥8 h.

Annual changes in sleep duration

We calculated these changes over the entire study period as the relative difference between the sleep duration identified in the last survey and the sleep duration recorded at baseline divided by the time interval (year of the last survey –the baseline year). The annual changes could be calculated if subjects participated in at least two surveys. We were interested in comparing the macro trends in subjects who had a decrease in their sleep duration, those who maintained a stable sleep duration, and those who had an increase in their sleep duration. Therefore, we used three categories for annual changes in sleep duration: (1) decrease (<−15 min/year), (2) stable (0 to −15 min/year, as a reference), and (3) increase (>0 min/year).

Assessment of potential covariates

The present study adjusted for potential confounding factors by including the following covariates: the demographic variables included age at baseline (continuous) and sex. Socio-economic and lifestyle risk factors suspected to affect sleep and health outcomes; cigarette smoking (never, ever), alcohol consumption (never, ever), tea consumption (never, ever), and body mass index (BMI; overweight/obese, normal/underweight) were included. BMI was calculated as weight (kg) divided by height squared (m^2). Normal/underweight was defined as a BMI <24 kg/m^2, and overweight or obese was defined as a BMI ≥24 kg/m^2. Additionally, participants were asked to answer "yes" or "no" to the question "Do you generally snore when you sleep?"

Follow-up and cancer ascertainment

Person years of follow-up were calculated from the date of baseline questionnaire completion (baseline sleep duration) or the return of the last questionnaire (annual changes in sleep duration) until the date of cancer diagnosis, death, or termination of follow-up (December, 2015), whichever occurred first. For the duration of the follow-up, incident cancer cases were identified by tracking subjects once they participated in regular health examinations biennially. Sleep duration in 2006 to 2007, 2008 to 2009, and 2010 to 2011 was used to determine changes in sleep duration over the three exposure periods. Besides, incident GI cancer cases were assessed by record linkage with the Tangshan medical insurance system. Furthermore, death certificates were identified from the Kailuan social security system and discharge summaries were also tracked from the 11 affiliated hospitals where participants were diagnosed and treated each year to obtain further outcome information. The diagnosis of incident GI cancers was confirmed by a review of medical records by study physicians. Information on pathological diagnoses and imaging diagnoses were collected to assess incident GI cancer cases. Cancer was defined based on the 10th version of the International Classification of Diseases 10. The classification was as follows: main types of GI cancers (C15–C16, C18–C20, C22, and C25), esophageal cancer (C15), stomach cancer (C16), colorectal cancer (C18–C20), liver cancer (C22), and pancreatic cancer (C25).

Statistical analysis

First, descriptive analyses of the subject characteristics and incidence statistics were performed. We evaluated the differences in demographics and risk factors using either the chi-square test (for categorical variables) or analysis of variance (for continuous variables). Second, hazard ratios (HRs) associated with baseline sleep duration and annual changes in sleep duration for the incidence of GI cancer and five common types of GI cancers were estimated using Cox multiple regression analysis. These analyses were performed with three models. Model 1 was adjusted for age and sex. Model 2 was further adjusted for cigarette smoking, alcohol consumption, tea consumption, and BMI; and baseline sleep duration was added to the adjusted Cox models to examine its effect on the relationship between annual changes in sleep duration and GI cancer risk. To address possible reverse causality, sensitivity analyses excluding the first 2 years of follow-up were conducted (Model 3). All models were stratified by age at baseline and sex. Moreover, we examined the linear trend in the relationship of baseline sleep duration and annual changes in sleep duration with GI cancer incidence by modeling a numeric value for each category [baseline sleep duration: 1 for ≤5 h, 2 for 6 h, 3 for 7 h, and 4 for ≥8 h; annual changes in sleep duration: 1 for decrease (<−15 min/year), 2 for stable (−15 to 0 min/year), and 3 for increase (>0 min/year)].

All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA) and all those reported were two-sided; differences at P values of <0.05 were accepted as significant.

Results

Among all 138,150 individuals, 123,495 had data available on baseline sleep duration. For 83,511 subjects, a full dataset from at least two complete sleep duration records could be obtained [Supplementary Figure 1, http://links.lww.com/CM9/A770].

Characteristics

Baseline sleep duration

At baseline, the 123,495 participants were aged 18 to 104 (50.23 ± 13.11) years, and the majority reported sleeping 8 h (7.29 ± 1.11 h). When the individuals were divided into four groups, the percentages of participants who reported sleeping for ≤5, 6, 7, and ≥8 h per night were 6.48% (8004/123,495), 17.74% (21,908/123,495), 16.05% (19,819/123,495), and 59.73% (73,764/123,495), respectively. There were significant associations between baseline sleep duration and age, sex, cigarette smoking, alcohol consumption, tea consumption, snoring, and BMI categories [Table 1]. Compared with participants without GI cancer, patients with incident GI cancer were significantly older, were more often men, had a low level of tea consumption, were more likely to smoke, and snored more often [Table 2].

Annual changes in sleep duration

A total of 83,511 participants reported at least two complete sleep duration. These participants were aged 18 to 98 (49.28 ± 11.96) years, and the majority maintained a stable sleep duration (−15 to 0 min/year, 49.52%) in the observational intervals. A significant association was found between annual changes in sleep duration and age, sex, cigarette smoking, alcohol consumption, tea consumption, snoring, BMI, and baseline sleep duration [Table 1]. Compared with the participants without GI cancer, those with GI cancer were typically older, were more likely to be male, and snored [Table 2].

Associations between sleep duration and GI cancers

Baseline sleep duration

We observed the HRs for GI cancer according to baseline sleep duration in the total population and the population after stratification by age and sex [Figure 1]. During an average of 8.13 years of follow-up, 1193 incident GI cancer cases were identified. In the multivariable-adjusted model (Model 2), females who reported a short sleep duration were slightly less likely to develop GI cancer ($HR_{\leq 5\ vs.7h}$, 0.31; 95% confidence interval [CI]: 0.10–0.90), but no statistically significant association was observed in the other groups. Moreover, we observed that the increased trend in baseline sleep duration was linearly associated with an increased risk of GI cancer ($P = 0.010$), especially in males ($P = 0.010$) and in the >50-year-old group ($P = 0.050$). We found an association between sleep duration and pancreatic cancer ($HR_{6\ vs.\ 7h}$, 2.67; 95% CI: 1.08–6.61). A linear relationship between sleep duration and colorectal cancer was observed

Table 1: Basic characteristics of participants in the Chinese Kailuan Cohort according to sleep duration, 2006–2015.

Characteristics	Baseline sleep duration (h/day)					Annual relative changes in sleep duration (min/year)			
	≤5	6	7	≥8	*P* value	≤−15	0 to −15	>0	*P* value
N	8004 (6.48)	21,908 (17.74)	19,819 (16.05)	73,764 (59.73)		22,158 (26.53)	41,352 (49.52)	20,001 (23.95)	
Age, years	55.14 ± 12.41	51.73 ± 12.67	48.60 ± 13.20	49.84 ± 13.13	<0.001	47.97 ± 11.75	49.10 ± 12.01	51.10 ± 11.86	<0.001
Gender					<0.001				<0.001
Male	6689 (83.57)	18,570 (84.76)	16,416 (82.83)	57,148 (77.47)		17,906 (80.81)	31,523 (76.23)	16,641 (83.20)	
Female	1315 (16.43)	3338 (15.24)	3403 (17.17)	16,616 (22.53)		4252 (19.19)	9829 (23.77)	3360 (16.80)	
Cigarette smoking					<0.001				<0.001
Ever	3947 (49.31)	10,787 (49.24)	9392 (47.39)	18,598 (25.21)		7251 (32.72)	11,893 (28.76)	9520 (47.60)	
Never	3467 (43.32)	9516 (43.44)	9025 (45.54)	51,656 (70.03)		13,609 (61.42)	27,325 (66.08)	8933 (44.66)	
Missing	590 (7.37)	1605 (7.33)	1402 (7.07)	3510 (4.76)	<0.001	1298 (5.86)	2134 (5.16)	1548 (7.74)	
Alcohol consumption									<0.001
Ever	4520 (56.47)	12,725 (58.08)	11,199 (56.51)	22,223 (30.13)		8815 (39.78)	14,736 (35.64)	11,301 (56.50)	
Never	3482 (43.50)	9177 (41.89)	8614 (43.46)	51,534 (69.86)		13,343 (60.22)	26,616 (64.36)	8700 (43.50)	
Missing	2 (0.02)	6 (0.03)	6 (0.03)	7 (0.01)					
Tea drinking					<0.001				<0.001
Ever	3276 (40.93)	10,050 (45.87)	9697 (48.93)	26,256 (35.59)		10,815 (48.81)	17,312 (41.86)	9373 (46.86)	
Never	4726 (59.05)	11,854 (54.11)	10,117 (51.05)	47,491 (64.38)		11,343 (51.19)	24,040 (58.14)	10,628 (53.14)	
Missing	2 (0.02)	4 (0.02)	5 (0.03)	17 (0.02)					
Snoring					<0.001				<0.001
Yes	4323 (54.01)	12,073 (55.11)	10,573 (53.35)	18,868 (25.58)		7356 (33.20)	12,420 (30.03)	10,670 (53.35)	
No	3670 (45.85)	9812 (44.79)	9206 (46.45)	54,754 (74.23)		14,802 (66.80)	28,932 (69.97)	9331 (46.65)	
Missing	11 (0.14)	23 (0.10)	40 (0.20)	142 (0.19)					
Overweight/obesity					<0.001				<0.001
Underweight/normal weight	3901 (48.74)	10,706 (48.87)	9847 (49.68)	37,521 (50.87)		11,462 (51.73)	21,650 (52.36)	9979 (49.89)	
Overweight/obesity	4076 (50.92)	11,120 (50.76)	9885 (49.88)	35,831 (48.58)		10,687 (48.23)	19,694 (47.63)	10,013 (50.06)	
Unclear	27 (0.34)	82 (0.37)	87 (0.44)	412 (0.56)		9 (0.04)	8 (0.02)	9 (0.04)	
Baseline sleep duration, per day									<0.001
≤5 h	NA	NA	NA	NA	NA	187 (0.84)	756 (1.83)	4091 (20.45)	
6 h	NA	NA	NA	NA	NA	1083 (4.89)	4548 (11.00)	9121 (45.60)	
7 h	NA	NA	NA	NA	NA	2818 (12.72)	4342 (10.50)	5934 (29.67)	
≥8 h	NA	NA	NA	NA	NA	18,070 (81.55)	31,706 (76.67)	855 (4.27)	

Data are presented as *n* (%) or mean ± standard deviation. NA: Not available.

Table 2: Differences in baseline characteristics between patients with and without GI cancer in the Chinese Kailuan Cohort, 2006–2015.

Characteristics	Total	GI cancer		*P* value
		Yes	No	
Baseline sleep duration				
N	123,495	1193	122,302	
Age, years	50.32 ± 13.11	58.2 ± 9.94	50.24 ± 13.11	<0.001
Gender, *n* (%)				<0.001
Male	98,823 (80.02)	1071 (89.77)	97,752 (79.93)	
Female	24,672 (19.98)	122 (10.23)	24,550 (20.07)	
Cigarette smoking, *n* (%)				0.002
Ever	42,724 (34.60)	468 (39.23)	42,256 (34.55)	
Never	73,664 (59.65)	655 (54.90)	73,009 (59.70)	
Missing	7107 (5.75)	70 (5.87)	7037 (5.75)	
Alcohol consumption, *n* (%)				0.100
Ever	50,667 (41.03)	510 (42.75)	50,157 (41.01)	
Never	72,807 (58.96)	682 (57.17)	72,125 (58.97)	
Missing	21 (0.02)	1 (0.08)	20 (0.02)	
Tea drinking, *n* (%)				0.020
Ever	49,279 (39.90)	431 (36.13)	48,848 (39.94)	
Never	74,188 (60.07)	762 (63.87)	73,426 (60.04)	
Missing	28 (0.02)	0 (0.00)	28 (0.02)	
Snoring, *n* (%)				0.020
Yes	45,837 (37.12)	484 (40.57)	45,353 (37.08)	
No	77,442 (62.71)	709 (59.43)	76,733 (62.74)	
Missing	216 (0.17)	0 (0.00)	216 (0.18)	
Overweight/obesity, *n* (%)				0.520
Underweight/normal weight	61,975 (50.18)	616 (51.63)	61,359 (50.17)	
Overweight/obesity	60,912 (49.32)	570 (47.78)	60,342 (49.34)	
Unclear	608 (0.49)	7 (0.59)	601 (0.49)	
Baseline sleep duration, per day				0.400
≤5 h	8004 (6.48)	78 (6.54)	7926 (6.48)	
6 h	21,908 (17.74)	227 (19.03)	21,681 (17.73)	
7 h	19,819 (16.05)	173 (14.50)	19,646 (16.06)	
≥8 h	73,764 (59.73)	715 (59.93)	73,049 (59.73)	
Annual changes in sleep duration				
N	83,511	503	83,008	
Age, years	49.28 ± 11.96	56.30 ± 9.70	49.24 ± 11.96	<0.001
Gender, *n* (%)				<0.001
Male	66,070 (79.12)	452 (89.86)	65,618 (79.05)	
Female	17,441 (20.88)	51 (10.14)	17,390 (20.95)	
Cigarette smoking, *n* (%)				0.010
Ever	28,664 (34.32)	201 (39.96)	28,463 (34.29)	
Never	49,867 (59.71)	268 (53.28)	49,599 (59.75)	
Missing	4980 (5.96)	34 (6.76)	4946 (5.96)	
Alcohol consumption, *n* (%)				0.310
Ever	34,852 (41.73)	221 (43.94)	34,631 (41.72)	
Never	48,659 (58.27)	282 (56.06)	48,377 (58.28)	
Tea drinking, *n* (%)				0.180
Ever	37,500 (44.90)	211 (41.95)	37,289 (44.92)	
Never	46,011 (55.10)	292 (58.05)	45,719 (55.08)	
Snoring, *n* (%)				<0.001
Yes	30,446 (36.46)	220 (43.74)	30,226 (36.41)	
No	53,065 (63.54)	283 (56.26)	52,782 (63.59)	
Overweight/obesity, *n* (%)				0.070
Underweight/normal weight	43,091 (51.60)	268 (53.28)	42,823 (51.59)	
Overweight/obesity	40,394 (48.37)	234 (46.52)	40,160 (48.38)	
Unclear	26 (0.03)	1 (0.20)	25 (0.03)	
Baseline sleep duration				0.480
≤5 h	5034 (6.03)	33 (6.56)	5001 (6.02)	
6 h	14,752 (17.66)	101 (20.08)	14,651 (17.65)	
7 h	13,094 (15.68)	76 (15.11)	13,018 (15.68)	
≥8 h	50,631 (60.63)	293 (58.25)	50,338 (60.64)	
Annual relative changes in sleep duration, min/year				0.020
≤−15	22,158 (26.53)	142 (28.23)	22,016 (26.52)	
−15 to 0	41,352 (49.52)	220 (43.74)	41,132 (49.55)	
>0	20,001 (23.95)	141 (28.03)	19,860 (23.93)	

Data are presented as *n* (%) or mean ± standard deviation. GI: Gastrointestinal.

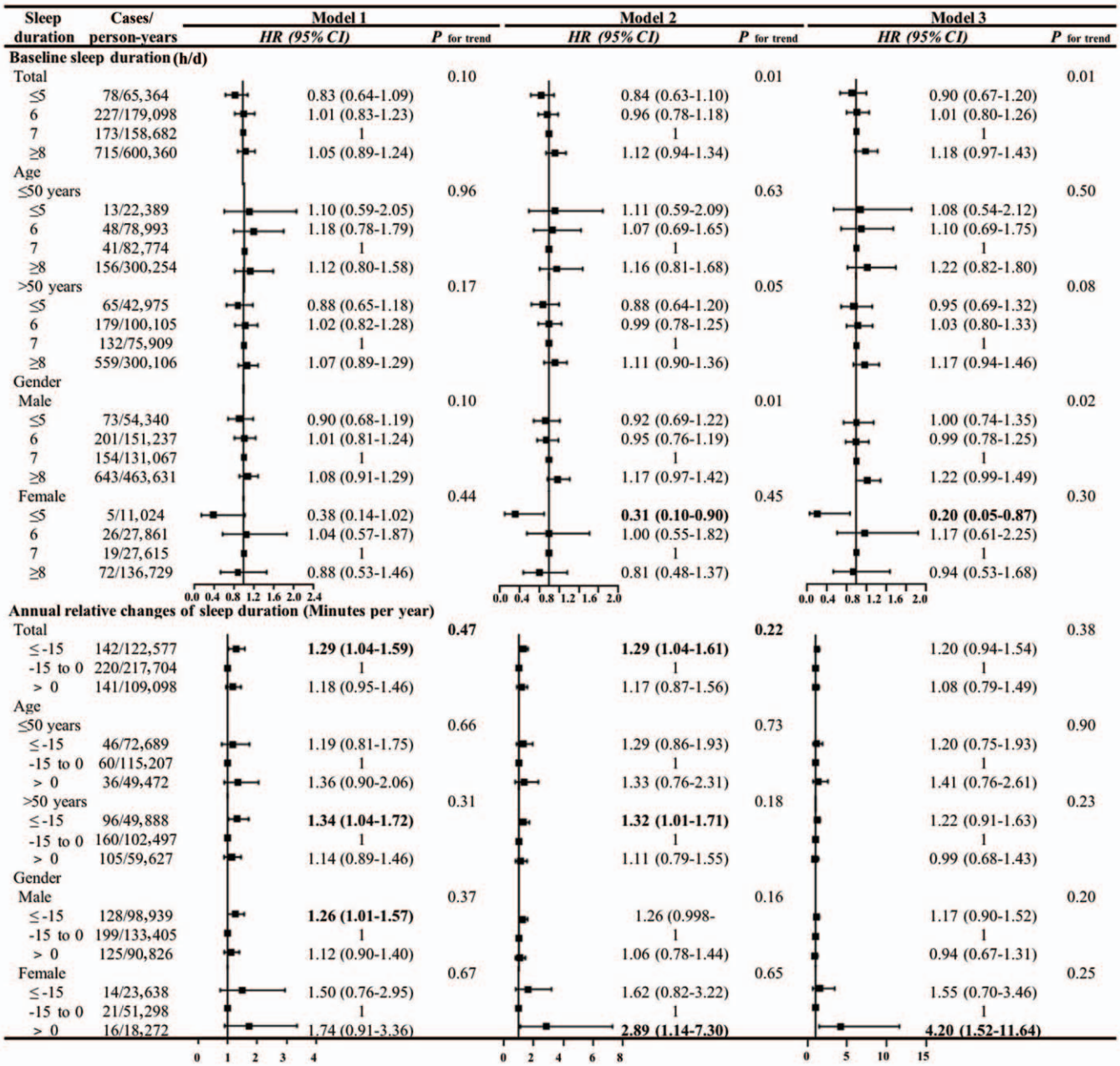

Figure 1: Forest plot of independent associations of sleep duration and annual changes in sleep duration with GI cancer in the Chinese Kailuan Cohort, 2006 to 2015. Model 1: Adjusted for age (continuous variable) and sex (male, female); Model 2: Adjusted for cigarette smoking (ever, never), alcohol drinking (ever, never), tea drinking (ever, never), snoring (no, yes), BMI (underweight/normal weight, overweight/obesity), and baseline sleep duration (≤5, 6, 7, and ≥8 h/day); Model 3: Adjusted for same variables as Model 2 and excluded cases who were diagnosed with GI cancer in the first 2 years from baseline. BMI: Body mass index; CI: Confidence interval; GI: Gastrointestinal.

($P = 0.040$) [Supplementary Table 1, http://links.lww.com/CM9/A770].

We found a U-shaped association between sleep duration and pancreatic cancer in the sensitivity analysis ($HR_{6vs.7h}$, 3.81; 95% CI: 1.30–11.16; $HR_{\geq 8vs.7h}$, 3.22; 95% CI: 1.14–9.05), but the linear relationship between baseline sleep duration and pancreatic cancer did not exist.

Annual changes in sleep duration

A total of 503 individuals (452 men and 51 women) had at least one incident of GI cancer during the follow-up period (mean 5.38 ± 1.17 years). The analysis using Model 2 indicated that those who reported decreases in sleep duration (≤−15 min/year) were significantly more likely to develop GI cancer (HR: 1.29; 95% CI: 1.04–1.61), especially in the >50-year-old group (HR: 1.32; 95% CI: 1.01–1.71) compared with the control group (−15to 0 min/year). In females, the increase in sleep duration (>0 min/year) was significantly associated with GI cancer (HR: 2.89; 95% CI: 1.14–7.30). We found an association between decreased sleep duration (≤−15 min/year) and liver cancer risk in Model 2 (HR: 1.85; 95% CI: 1.20–2.83) [Supplementary Table 2, http://links.lww.com/CM9/A770]. A linear relationship between annual changes in sleep duration and all GI cancers and five common types of GI cancers was not observed.

In the sensitivity analysis, females with a trend toward an increased annual sleep duration had an increased risk of GI cancer (HR: 4.20; 95% CI: 1.52–11.64). However, the association between the trend toward a decrease in annual sleep duration and GI cancer incidence was not significant (HR: 1.20; 95% CI: 0.94–1.54). According to the subgroup analyses, the results related to older adults (HR: 1.22; 95% CI: 0.91–1.63) and liver cancer (HR: 1.54; 95% CI: 0.91–2.58) were not significant.

Discussion

This is the first large cohort study in a general population to investigate the association of baseline sleep duration and annual changes in sleep duration with GI cancer and five common types of GI cancer risk. In the baseline sleep duration analyses, extremely short sleep duration (≤5 h) were significantly associated with a low risk of GI cancer in females, and a linear relationship between baseline sleep duration and GI cancer was observed, especially in males and in the >50-year-old group. In the annual changes in sleep duration analyses, decreased sleep duration was significantly associated with the development of GI cancer, especially in the >50-year-old group, and increased sleep duration was significantly associated with GI cancer in females.

To our knowledge, there was no prior study examining the association between annual changes in sleep duration and the risk of GI cancers, and most of the studies have focused on sleep duration at one time point and GI cancer risk. Four cohort studies demonstrated a correlation between baseline sleep duration and GI cancer risk, especially colorectal cancer, although some have shown absent or inverse associations.[11-14] Jiao *et al*[11] reported a U-shaped association between sleep duration and colorectal cancer risk in women, with both short and long sleep duration associated with a greater risk. However, one study showed that only long sleep duration were associated with an increased risk of colorectal cancer in both sexes[12] while another study indicated a null association between sleep duration and colorectal cancer in females.[13] In our study, we did not observe an association between baseline sleep duration and colorectal cancer. We then extended our analysis to annual changes in sleep duration, but the data suggested no associations of sleep duration and annual changes in sleep duration with colorectal cancer. One recent publication reported that a short sleep duration was associated with stomach cancer in males and that there was a null association between short or extremely long sleep duration and esophageal cancer, colorectal cancer, liver cancer, and pancreatic cancer risk.[14] Interestingly, we found that short sleep duration (6 h per day) and long sleep duration (8 h per day) were both associated with the incidence of pancreatic cancer. We also observed a suggestive correlation between an annual decrease in sleep duration and liver cancer. The differences in race, sleep habits, sample size, and integrity of controlling for potential confounders might explain the variation in the results to some extent.

The etiology of GI cancer is multifactorial, including genetic, environmental, behavioral, metabolic, and social and cultural factors. Some potential pathophysiological mechanisms support the biological plausibility of sleep duration loss being related to GI cancer risk. One possible mechanism is the reduced production of melatonin caused by exposure to light at night.[20] Melatonin has been demonstrated to suppress the initiation phase of tumorigenesis and inhibit the proliferation of human cancer cell lines in experimental studies.[21,22] Another hypothesis is that impaired immune function may underlie the link between sleep loss and carcinogenesis.[23] In previous studies among poor sleepers, we found that the changes in sleep duration may suppress immune function and change the balance of cytokine production.[24,25] The disruption of circadian rhythms is a possible mechanism. Disruption of circadian physiology, due to sleep loss or sleep disturbance, may lead to impaired glucose and appetite control[22] and various GI diseases. Furthermore, circadian disruption can promote the occurrence of cancer in the liver and GI tract.[26] Finally, metabolic pathways are related to obesity.[27] Sleep loss may be a response to chronic stress and unhealthy emotions. Both chronic stress and depression play a meaningful role in the occurrence and progression of cancer.[28] In our study, to take this concept into consideration, BMI was considered a confounder. After adjusting for BMI, the result was consistent.

Conversely, a positive association between an annual increase in sleep duration and GI cancer risk was observed. To our knowledge, the mechanism explaining the effect of an increase in sleep duration on cancer risk is still unknown. Sleep might influence cancer incidence via alterations in the levels of appetite-regulating hormones,[29,30] which leads to increased appetite and subsequently obesity,[31-33] which especially impacts the risk of GI cancers.[34] The association between an increase in sleep duration and cancer may be explained by comorbidities and residual confounding.[35] For instance, some other mental or physiological disorders, a low socioeconomic status, a low level of physical activity, and undiagnosed chronic comorbid conditions have been suggested to be correlated with long sleep duration and can confound the association with cancer incidence.[36,37] Our analyses revealed a significant association between an increase in sleep duration and GI cancers, which suggested that changes in hormones involved in appetite regulation might be a major pathway involved in the observed association.

Our study had several strengths. First, we proposed the hypothesis that there is an association between annual changes in sleep duration and cancer risk, and the final results support this hypothesis. Sleep duration was assessed at one time point in most of the previous studies, which might not accurately reflect the sustained effects of sleep duration over time while relating them to the long-term development of cancer. Therefore, this study supplied robust evidence to assess the relationship between sleep duration and cancer risk. Second, to our knowledge, this is the first study to comprehensively examine sleep duration in relation to all major GI cancer types. The large sample size permits sufficient power to assess associations with major GI cancer sites. In addition, its prospective design with a long follow-up time minimized the potential

selection or recall bias of sleep duration, and its questionnaire design that included relevant covariates allowed us to adjust for important potential confounders during the statistical analysis. Finally, the Kailuan cohort study allowed us to control for most potential confounders using prospectively collected data. Sensitivity analyses were performed by excluding cases diagnosed within the first 2 years of follow-up to exclude reverse causation. Our findings must be considered in light of the limitations of this study. First, our study included only one question to assess sleep duration, and our measures were based on self-reported assessments of sleep duration, which may have led to an overestimation of absolute sleep duration values.[38] Second, we had no information on factors such as sleep (daytime sleep duration; insomnia; sleep quality; the use of sleep medication; the presence of sleeping disorders) or hormone-related variables (menopausal status; hormonal rhythms) that can lead to unstable results.[39] However, we adjusted for snoring as a confounder in the statistical analysis. Third, most participants in the Kailuan cohort study were males, and the sex distribution of participants was unbalanced. Moreover, we also did not have information on disease history such as atrophic gastritis, and hepatitis B or C virus chronic infection nor on family history of GI cancers that may be important confounders. Furthermore, the number of incident GI cancers cases in our cohort is limited, particularly among those with $\leq$5 h of sleep, further limiting our statistical power to detect risks. And we had limited power to observe significant associations for the five common types of GI cancers due to low case counts. The loss to follow-up rate in our cohort study may result in biased association estimates in the analyses of annual changes in sleep duration.

This study explored the relationship between sleep duration and annual changes in sleep duration and GI cancer risk. The relationship between these variables likely depends on age and sex. In females, a short sleep duration ($\leq$5 h) was associated with a low risk of GI cancer, and an annual increase in sleep duration was associated with a higher risk of GI cancer. In older adults (>50 years old), an annual decrease in sleep duration (>15 min/year) was a risk factor for GI cancer occurrence. Moreover, in males and older adults, we observed that the trend toward increased sleep duration was linearly associated with an increased risk of GI cancer. Studies with larger sample sizes, longer follow-up times, more cancer types, shorter follow-up intervals, and more detailed measures of sleep duration were warranted to confirm these results.

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Conflicts of interest

None.

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