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Sleep Behaviors, Genetic Predispositions, and Risk of Esophageal Cancer

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Abstract

Background

Risk factors contributing to more than tenfold increase in esophageal cancer in the last 50 years remain underexplored. We aim to examine the associations of sleep behaviors with esophageal adenocarcinoma (EAC) and squamous cell carcinoma (ESCC).

Methods

We prospectively assessed the associations between sleep behaviors (chronotype, duration, daytime napping, daytime sleepiness, snoring, and insomnia) and EAC and ESCC risk in 393,114 participants in the UK Biobank (2006-2016). Participants with 0, 1, and ≥2 unhealthy behaviors, including sleep <6 or >9 h/day, daytime napping, and usual daytime sleepiness were classified as having a good, intermediate, and poor sleep. For EAC, we also examined interactions with polygenic risk score (PRS). Cox models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results

We documented 294 incident EAC and 95 ESCC. Sleep >9 h/day (HR=2.05, 95%CI: 1.18, 3.57) and sometimes daytime napping (HR=1.36, 95%CI: 1.06, 1.75) were individually associated with increased EAC risk. Compared with individuals with good sleep, those with intermediate sleep had a 47% (HR=1.47, 95%CI: 1.13, 1.91) increased EAC risk, and those with poor sleep showed a 87% (HR=1.87, 95%CI: 1.24, 2.82) higher risk (P_{trend}<0.001). The elevated risks for EAC were similar within strata of PRS ($P_{interaction}$=0.884). Evening chronotype was associated with elevated risk of ESCC diagnosed after 2 years of enrollment (HR=2.79, 95%CI: 1.32, 5.88).

Conclusion

Unhealthy sleep behaviors were associated with an increased risk of EAC, independent of genetic risk.

Impact

Sleep behaviors may serve as modifiable factors for the prevention of EAC.

Introduction

Esophageal cancer is among the most lethal type of cancers worldwide, with 5-year overall survival of 15% to 25% (1). In western countries, the incidence of esophageal adenocarcinoma (EAC), the most common type of esophageal cancer, has been increasing substantially since the 1960s from 0.41 cases to 5.31 cases per 100,000 person-years in 2007, surpassing esophageal squamous cell carcinoma (ESCC) (2). However, besides obesity, the contributors to the dramatic increase in EAC have not been identified (3,4).

Sleep-related behaviors, such as excessively short/long sleep duration and insomnia, have become increasingly prevalent and emerged as a public health epidemic (5,6). From 1985 to 2012, US adults sleeping ≤ 6 hours increased from 38.6 to 70.1 million, and up to 38% of individuals aged 25-44 reported sleep duration less than 7 hours (6). A meta-analysis from the Netherlands, UK, and US revealed that poor sleep quality (13%) and insomnia symptoms (9.6-19%) were even more prevalent than short sleep duration (5). Accumulating evidence supports the link between sleep behaviors and EAC or ESCC. For instance, individuals who sleep 5-6 hours have increased risks for Barrett's esophagus (7) and ESCC (8) compared with those who sleep 7-8 hours. However, other sleep behaviors, such as chronotype, daytime sleepiness, and insomnia, have not yet been examined with risk of esophageal cancer, especially EAC. As these sleep behaviors are usually correlated, there is an imperative need to evaluate the collective impact of multiple sleep behaviors on esophageal cancer risk (9).

The development of esophageal cancer is partially attributed to genetic factors (10). Thus far, a total of 18 single nucleotide polymorphisms (SNPs) have been identified from genome-wide association studies (GWAS) for EAC (11-13). Yet, it remains unclear how lifestyle risk factors would mitigate the heightened genetic risk. Interestingly, recent research has also identified rs62423175 in MTRNR2L9, one of the GWAS-significant SNPs for EAC, as being associated with sleep traits such as chronotype, duration, daytime napping, daytime sleepiness, snoring, and insomnia (14). This adds a new dimension to the investigation of the role of sleep disturbance in EAC in the context of genetic predisposition.

To address these knowledge gaps, we prospectively examined the associations of major sleep behaviors (chronotype, duration, daytime napping, daytime sleepiness, snoring, and insomnia) with risk of EAC

overall and according to genetic predispositions and with ESCC, leveraging data from the UK Biobank, a large, prospective cohort with a comprehensive assessment of sleep behaviors and genetic profiling.

Materials and Methods

Study population

The UK Biobank is a population-based prospective study with over half a million participants aged 37-73 years recruited between 2006 and 2010. The detailed study design and methods have been described previously (15). In brief, at baseline visit, participants completed a self-administered touchscreen questionnaire and underwent physical examination for collecting sleep and other health-related information, and provided blood for genotyping. The UK Biobank study was approved by the National Information Governance Board for Health and Social Care in England and Wales, the North West Multicentre Research Ethics Committee, and the Community Health Index Advisory Group in Scotland.

Initially, data were obtained from 502,486 participants. After excluding individuals with cancer except for non-melanoma skin cancer prior to the baseline visit or missing values on any of the sleep behaviors, a total of 393,114 participants were included in the analyses (**Supplementary Figure 1**).

Ascertainment of outcome

Incident EAC and ESCC cases were identified through linkage to cancer registries and death records provided by the National Health Service (NHS) Information Centre and the NHS Central Register, National Records of Scotland, and defined using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code ‘C15’ and the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes 8140-8573 for EAC and 8050-8082 for ESCC. Complete follow-up was available up to March 31st, 2016 for England and Wales and October 31st, 2015 for Scotland.

Assessment of sleep behaviors

We extracted information on the following six sleep behaviors self-reported through a questionnaire at baseline: chronotype, duration, daytime napping, daytime sleepiness, snoring, and insomnia. Information on

chronotype was collected using the question: "Do you consider yourself to be: 1) definitely a "morning" person, 2) more a "morning" than "evening" person, 3) more an "evening" than "morning" person, or 4) definitely an "evening" person" and categorized as morning, more morning than evening, more evening than morning, and evening. Sleep duration was collected from the question: "About how many hours sleep do you get in every 24h? (please include naps)" and collapsed as <6, 6, 7, 8, 9, and >9 h/day. Frequencies of daytime napping were asked through the question: "Do you have a nap during the day?" with responses of never/rarely, sometimes, and usually. Daytime sleepiness was obtained from the question "How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g., when working, reading or driving)" and regrouped as never/rarely, sometimes, and usually (often and all of the time). Snoring was collected by asking "Does your partner or a close relative or friend complain about your snoring?" and grouped as yes and no. Insomnia coded the responses from the question "Do you have trouble falling asleep at night or do you wake up in the middle of the night?" as never/rarely, sometimes, and usually. Prior mendelian randomization studies suggest that the associations between the identified gene loci and self-reported measurement for chronotype (16), duration (17), daytime napping (14), daytime sleepiness (18), and insomnia (19) in the UK Biobank were consistent with those identified using accelerometers.

Derivation of polygenic risk score

Details of the genotyping process in UK Biobank were described elsewhere (20,21). We acquired imputed data of 487,409 participants initially. Using UK Biobank provided quality control sample file, participants were excluded if they were outliers with high missingness or for which heterozygosity rates were not explained by runs of homozygosity analysis nor mixed ethnicity, or were marked as sex chromosome aneuploidy (21,22). The UK Biobank dataset estimated a kinship coefficient for each pair of samples using KING's robust estimator (23). We further excluded third-degree (or higher) related individuals (kinship coefficient ≥ 0.0442) (24). After these exclusions, a total of 267,484 participants remained in the analyses.

We derived a polygenic risk score (PRS), based on 17 of the 18 previously identified GWAS-significant SNPs of EAC ($P < 5 \times 10^{-8}$) (11-13), to measure participants' genetic susceptibility to EAC (**Supplementary Table 1**). SNP rs66725070 was not available in the UK Biobank. Each SNP was coded based on the number of risk alleles as 0, 1 and 2. Weights were derived based on the reported effect size (log odds) from prior

GWASs (11-13). For each participant, PRS was calculated as the sum of the product of the SNP and its corresponding weight (25). We then grouped participants into three groups based on PRS quintiles: low- (Q1-Q2), intermediate- (Q3-Q4), and high-risk (Q5).

Assessment of covariates

At study enrollment, demographic characteristics and known or potential common predictors of EAC and ESCC were self-reported, including age, sex, race, education status, and smoking status and intensity. Height was measured (seca 202 stadiometer; seca) to the nearest 0.1 cm, and weight was measured to the nearest 0.1 kg (BC-418 MA body composition analyzer; Tanita Corp). Body mass index (BMI) was derived from weight in kilograms divided by height in meters squared. The Townsend Deprivation Index, a census-based index of material deprivation, was used as a proxy measure for socioeconomic status. Positive values of the index indicate areas with high material deprivation, whereas negative values indicate relative material affluence. Total physical activity in metabolic equivalent task (MET) was derived based on the frequency and duration of walking, and moderate and vigorous activities in the last 7 days, through the International Physical Activity Questionnaire (IPAQ) (26). Shift work status was derived based on two questions “Does your work involve shift work?” and “Does your work involve night shifts?”. History of gastro-esophageal reflux disease (GERD) was self-reported (27) and additionally included in EAC models. Alcohol consumption status and intensity were self-reported and additionally included in ESCC models. Information on sleep apnea was attained based on either the ICD-10-CM code G47.3 or participants’ self-reported diagnosis upon baseline (28).

Statistical analyses

Person-years were accrued from the date of initial assessment visit to the date of any cancer diagnoses (excluding non-melanoma skin cancer), the end of follow-up or death, whichever came first. We examined the associations between each of the six sleep behaviors (chronotype, duration, daytime napping, daytime sleepiness, snoring, and insomnia) and risk of EAC and ESCC using age- and multivariable-adjusted Cox proportional hazard models. In addition to age (in years), the common covariates included in the multivariable models for both EAC and ESCC were sex (female or male), race (White, Black, or other), education status (pre- or post-college), Townsend Deprivation Index (in quartiles), body mass index (BMI, underweight: <18.5

kg/m^2, normal: 18.5-24.9 kg/m^2, overweight: 25-29.9 kg/m^2, obese: ≥30 kg/m^2), smoking status and intensity (never smoker, past smoker 1-19 pack-years, past smoker >19 pack-years, past smoker unknown pack-year, current smoker 1-19 pack-years, current smoker >19 pack-years, current smoker unknown pack-year), total physical activity (metabolic equivalent task [MET] h/week, in quartiles, and missing), and shift work status (non-shift, day shift, sometimes night shift, usual/always night shift, missing). Self-reported history of GERD (yes or no) was additionally adjusted for EAC models. Alcohol consumption status and intensity (never, previous, current 0 g/day, current 0.1-14.9 g/day, current 15-29.9 g/day, current 30+ g/day, current unknown intensity) were additionally adjusted for ESCC models. No violation of the proportional hazard assumption was identified.

To create a composite sleep score, we adopted the similar approach used previously by only including sleep behaviors with significant impact on EAC or ESCC risk (29-31). We compared the multivariable models with and without a specific behavior using the likelihood ratio test (LRT). If the P_{LRT} was ≤0.25, we included this sleep behavior in the composite sleep score (32). Based on this pre-specified criterion, three sleep behaviors (duration, daytime napping, and daytime sleepiness) were selected for the association with risk of EAC; only daytime sleepiness was selected for the association with ESCC. Therefore, we only constructed the composite score for the association with EAC. An additional LRT test (P = 0.397) between the multivariable models with the selected three sleep behaviors and all six behaviors for the association with risk of EAC indicates that the two models had an equivalent performance. A parsimonious model with three sleep behaviors was therefore preferred. We further dichotomized these three behaviors and defined the following categories as unhealthy behaviors: sleep <6 or >9 h/day, sometimes or usual daytime napping, and usual daytime sleepiness. A score of 1 was assigned to each unhealthy behavior and a score of 0 otherwise. We summed the scores across the three behaviors and categorized participants into three levels of sleep: good sleep (score=0), intermediate sleep (score=1), and poor sleep (score≥2). Test for linear trend was performed by treating composite sleep score as a continuous variable. To evaluate competing risk by death, we further conducted Fine-Gray subdistribution hazard models. As the results are similar, we presented results from the Cox models.

As a sensitivity analysis, we also constructed a weighted sleep score based on the three unhealthy sleep behaviors (sleep <6 or >9 h/day, daytime napping and usual daytime sleepiness) by rescaling the weighted sleep score (β1×behaviors 1 + β2×behaviors 2 +β3×behaviors 3) to [0,3] to account for potential

nonlinear effects of sleep behaviors on EAC risk. In this way, the weighted score also ranges from 0 to 3 points but considers magnitudes of the adjusted relative risk for each unhealthy sleep behavior as a combination of all 3 behaviors. Weights were calculated as coefficients from the multivariate models with all three sleep behaviors adjusted for covariates (**Supplementary Table 2**). The weighted sleep score was further categorized into three groups: good (score <1), intermediate (score 1-<2), and poor (score ≥2).

For EAC, we also evaluated whether the association between the composite sleep score and cancer risk differs by genetic predispositions. In addition to the covariates adjusted in the multivariable-adjusted Cox proportional hazard models for EAC, the first ten principal components for ancestry and the genotype array type (UK BiLEVE vs. UK Biobank Axiom) were further adjusted. We tested the multiplicative interactions using the product terms of continuous composite sleep score and continuous PRS, and *P* for interaction was estimated using the Wald test. We further evaluated the joint associations between composite sleep score and PRS groups. Meanwhile, we assessed the additive interactions using the relative excess risk due to interaction (RERI), calculated from Cox proportional hazard models with the interaction terms between categorical sleep score (good, intermediate, and poor) and categorical PRS (low, intermediate, and high) with good sleep and low genetic risk as reference group using *interactionR* package (version 0.1.6).

The following sensitivity analyses were conducted: 1) excluded participants who were diagnosed with EAC and ESCC within the first two years of follow-up to reduce the likelihood of reverse causation, i.e., having poor sleep behaviors due to undiagnosed esophageal cancer at baseline, 2) excluded individuals with a history of GERD to examine the independent association not mediated by GERD, 3) excluded individuals with sleep apnea before or at baseline to confirm the robustness of our results, 4) expanded the categories of composite sleep score to four groups with sleep score as 0, 1, 2 and 3 to explore the dose-response relationship, 5) included deaths as competing events, 6) stratified by BMI categories (<25 and ≥25 kg/m2) to assess whether the associations were similarly observed within normal weight vs. overweight/obese participants, and 7) utilized a weighted sleep score to account for potential nonlinear effects of sleep behaviors on esophageal cancer risk. Missingness in covariates was either imputed using the most common category (0.1%-1.4% missing) or considered as a missing category (≥10% missing). No covariates had a missing proportion between 1.5% and 9.9%. All analyses were performed using R (version 4.0.5).

Data availability

The data that support the findings of this study were obtained from the UK Biobank and available publicly following the instruction provided at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access.

Results

Baseline characteristics of the study population are described in **Table 1**. Among 393,114 participants, those with higher composite sleep scores reflecting poorer sleep were more likely to be males, have higher BMI, be current smokers, and with a history of GERD. They were less likely to have a post-college education or be physically active.

During up to 9.3 years of follow-up with 2,682,759 person-years, a total of 294 EAC and 95 ESCC were diagnosed. In age-adjusted models, sleep <6 or >9 h/day, any daytime napping, usual daytime sleepiness, and snoring were associated with an increased risk of EAC (**Table 2**). After multivariable adjustment, two sleep behaviors, sleep >9 h/day and sometimes daytime napping, were individually associated with increased EAC risk; three sleep behaviors had P_{LRT}≤0.25, including sleep duration, daytime napping, and daytime sleepiness. Specifically, participants who slept <6 or >9 h/day had 1.53 (hazard ratio [HR]=1.53, 95%CI: 0.97, 2.42) and 2.05 (HR=2.05, 95%CI: 1.18, 3.57) times risk of EAC, compared with individuals who slept 7 hours. Participants who took daytime napping sometimes or usually had 36% (HR=1.36, 95%CI: 1.06, 1.75) and 40% (HR=1.40, 95%CI: 0.94, 2.09) increased EAC risk, compared with those who never took daytime napping. Compared with those who never had daytime sleepiness, participants with usual daytime sleepiness had elevated EAC risk (HR=1.30, 95%CI: 0.77, 2.20). Chronotype, snoring and insomnia were not associated with EAC risk. For ESCC, only evening chronotype was associated with an increased risk (HR=2.33, 95%CI: 1.22, 4.45) in age-adjusted model, compared with those with morning chronotype. The results were largely similar when EAC or ESCC diagnosed within the first two years of follow-up were excluded from the analyses, except for the re-emerging association between evening chronotype and ESCC risk after multivariable adjustment (HR=2.79, 95%CI: 1.32, 5.88, **Supplementary Table 3)**. Of note, the estimates for ESCC were subject to a small number of events and should be interpreted with caution.

Based on the composite sleep score, compared with participants with a good sleep, those with an intermediate sleep had a 47% (HR=1.47, 95%CI: 1.13, 1.91) increased risk of EAC, and individuals with a poor sleep had a 87% increased risk (HR=1.87, 95%CI: 1.24, 2.82) (P_{trend}<0.001, **Table 3**). These findings were similar in analyses that excluded EAC diagnosed within 2 years after baseline, or participants with a history of GERD, or participants with sleep apnea diagnosis (**Table 3**). The association was also similar with finer risk score groups (**Supplementary Table 4**), with the weighted sleep score (**Supplementary Table 5**), and with deaths as competing events (**Supplementary Table 6**). When stratified by BMI category, the association was more evident in those with BMI ≥25 kg/m^2, but not participants with BMI <25 kg/m^2 (**Supplementary Table 7**).

We further examined the interaction between the composite sleep score and PRS as well as their joint associations with risk of EAC. We observed similar associations between the composite sleep score and EAC risk across different PRS groups (**Figure 1**). No multiplicative interactions were observed ($P_{interaction}$=0.884) between genetic risk and sleep behaviors for EAC risk. In the joint analyses, compared to participants with a good sleep and low genetic risk, those with a poor sleep and high genetic risk had an HR of 5.37 (95%CI: 2.28, 12.66) (**Figure 1, Supplementary Table 8**). We also did not find evidence for additive interaction (**Supplementary Table 9).**

Discussion

In a large prospective cohort, we examined the associations between major sleep behaviors and their collective impact on the risk of EAC and ESCC. We also assessed the association with EAC according to genetic susceptibilities. Long duration (>9 h/day) and sometimes daytime napping were individually associated with increased EAC risk. The elevated EAC risks further increased with a greater number of potential high-risk behaviors, including short or long duration (<6 or >9 h/day), daytime napping, and usual daytime sleepiness, regardless of their genetic risk. Despite the small event size, there is emerging evidence that evening duration might be a risk factor of ESCC.

Growing evidence has linked unhealthy sleep behaviors with increased risk of multiple cancers (33-36), yet studies on esophageal cancer are sparse and largely limited to single sleep trait such as duration, snoring

(8), and daytime napping (37). A Mendelian randomization study among UK Biobank participants showed that genetic liability to short (<7 h/day) or long sleep (≥9 h/day) duration was not causally linked with esophageal cancer risk (38). One case-control study with 527 ESCC patients and 505 healthy controls from China reported that sleep <7 h/day was associated with an increased risk of ESCC, compared with those slept 7-8 h/day (8). Our prospective study, however, did not observe a similar association with ESCC even with a further breakdown of duration, which might be partially due to limited number of cases. In contrast, we found that extreme short or long sleep might be associated with increased risk of EAC, indicating the further need to evaluate extreme duration of sleep. Indeed, individuals who sleep 5-6 hours were found to have a higher risk of Barrett's esophagus, compared with those who sleep 7-8 hours each day (7). For daytime napping, the UK Million Women Study reported no association between sometimes/usually *vs*. rare/never daytime napping with risk of esophageal cancer after an average of 7.4 years of follow up in 795,238 women (37), while our analyses with a longer follow-up supported a positive association with EAC but not ESCC and even in sensitivity analyses that excluded the first two years of EAC or ESCC diagnoses to minimize the impact of undiagnosed cancers. In addition to reporting probable associations with individual sleep traits, our analyses for the first time constructed a composite sleep score to capture collective impact of sleep behaviors on EAC. Besides reporting a linear relationship between the number of unhealthy sleep behaviors and EAC risk, we also showed that these positive associations were independent of genetic risk. Of note, the development and validation of the composite sleep score were conducted in the same cohort, which might lead to better results due to overfitting. Taken together, our findings suggest that unhealthy sleep behaviors are likely important for EAC etiology and external validations are warranted.

The biological mechanisms linking unhealthy sleep behaviors and the risk of esophageal cancer remain to be elucidated. A number of possible pathways include regulation of immune function and circadian rhythms through regulation of melatonin secretion. For instance, evening chronotype and shortened sleep are linked with disrupted circadian rhythm, causing alternations in hormone and metabolic profiles, which are risk factors for esophageal cancer (39). Disruption of circadian physiology could also potentially result in gastrointestinal diseases such as GERD possibly via altering the expression of circadian clock genes in esophagus tissue or reducing the expression of melatonin, which could subsequently contribute to the esophageal sphincter

dysfunction and greater amounts of gastric acid production (40). Further evidence from animal trials supports the protective role of melatonin and reduced risk of EAC (41). Additionally, circadian rhythm misalignment could promote esophageal damage by impairing cell proliferation or cell repair (40). Both excess sleep and sleep deprivation might relate to immune dysfunction, which might lead to an increased susceptibility to infection and esophageal cancer (42,43). Having a history of GERD with excess sleep could also lead to a prolonged period of esophageal acid exposure to more proximal regions of the esophagus, which may further increase the risk for Barrett's esophagus and EAC (44). In addition, a recent Mendelian randomization study revealed that daytime napping is causally linked with greater waist circumference and high blood pressure (14), which are risk factors for EAC (45) and ESCC (46). Excessive daytime sleepiness occurs frequently among people with narcolepsy who tend to have autoimmune disorder (47), a risk factor for cancer (48). For example, narcolepsy patients are shown to have higher level of human leukocyte antigen (HLA) DRB1*1501 and HLA DQB1*0602 (49,50), resulting in a higher gastric and esophageal cancer risk (51). Intriguingly, GWAS studies have identified the association of MTRNR2L9 with EAC as well as chronotype, sleep duration, daytime napping, daytime sleepiness, insomnia, and snoring, suggesting a potential genetic pathway between sleep traits and EAC risk (11,14,16).

Primary strengths of our study include a large sample size and a prospective study design. More notably, our study is among the first to comprehensively examine the associations of sleep behaviors with EAC risk through integrating multiple sleep behaviors. We also evaluated the interaction and joint association between sleep behaviors and EAC genetic susceptibility. Our study has a few limitations. First, all sleep behaviors were self-reported and might not accurately reflect their sleep condition. However, Mendelian randomization studies have validated these traits against accelerometers and confirmed their causal links breast cancer (38) and lung cancer (52). Furthermore, non-differential misclassifications will likely bias the study association toward the null. In addition, all sleep behaviors were measured at a single timepoint, which did not take into account changes of sleep behaviors over time. However, a previous longitudinal study has found that participants' sleep quality did not change significantly over the study period (53). Residual confounding from unknown or unmeasured factors may still exist despite our efforts in adjusting for major confounders. The low prevalence of GERD also limits our ability to fully control for it in our study. Lastly,

findings were based on the UK Biobank participants composed of mostly European descendants and may not generalize to other populations.

In conclusion, individually, sleep >9 h/day and sometimes daytime mapping were associated with an elevated EAC risk; evening chronotype was associated with an increased risk of ESCC diagnosed after 2 years of enrollment. Collectively, unhealthy sleep behaviors including sleep <6 or >9 h/day, daytime napping, and usual daytime sleepiness were associated with an increased risk of EAC, independently of genetic risk. These findings suggest that sleep behaviors may serve as modifiable factors for the prevention of EAC.

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Table 1. Baseline characteristics of 393,114 participants according to composite sleep score, UK Biobank 2006-2010.

Characteristics	Composite sleep score [a]		
	Good (score=0)	Intermediate (score=1)	Poor (score≥2)
Total number of participants (N)	208,428	162,755	21,931
Age at baseline (in years, mean (SD))	55.7 (8.1)	58.1 (7.9)	58.3 (7.9)
Male (%)	40.7	50.7	50.0
Race (%)			
White	95.7	94.1	90.3
Black	1.0	1.7	3.7
Other	3.1	3.9	5.6
Missing	0.2	0.3	0.5
Education (%)			
Pre-college	57.2	61.8	68.1
Post-college	42.1	37.3	30.5
Missing	0.7	0.9	1.4
Townsend index (mean (SD))	-1.6 (2.9)	-1.3 (3.1)	-0.4 (3.5)
Missing (%)	0.1	0.1	0.1
GERD (%)	3.6	4.8	6.2
BMI (kg/m^2, mean (SD))	26.8 (4.5)	27.9 (4.9)	29.2 (5.7)
Missing (%)	0.3	0.5	1.1
Smoking status (%)			
Never	57.5	51.4	48.8
Past	33.1	36.8	35.7
Current	9.1	11.5	15.1
Missing	0.2	0.3	0.4
Pack-year in any smokers (mean (SD))	20.5 (16.2)	24.8 (19.5)	29.3 (22.8)
Missing (%)	35.1	31.2	26.8
Alcohol consumption status (%)			
Never	3.6	4.5	7.1
Previous	2.6	3.9	7.1
Current	93.7	91.5	85.7
Missing	0.1	0.1	0.1
Alcohol consumption among current drinkers (g/day, mean (SD))	22.7 (20.7)	23.2 (21.8)	22.9 (26.3)
Missing (%)	14.2	16.1	21.1
Physical activity (MET-h/week, mean (SD))	44.0 (43.9)	45.2 (46.2)	42.6 (49.2)
Missing (%)	15.9	18.0	21.1
Shift work status (%)			
Non-shift	56.4	41.9	29.0
Day shift	4.6	5.3	4.7
Sometimes night shift	2.5	3.2	3.2
Usual/always night shift	1.5	2.7	3.8
Missing	35.0	46.9	59.3
Sleep apnea (%)	0.4	0.8	2.2
Chronotype (%)			
Morning	25.2	28.8	31.8

Morning>evening	36.8	35.2	28.9
Evening>morning	29.5	27.3	26.7
Evening	8.5	8.7	12.6
Duration (h/day, mean (SD))	7.2 (0.8)	7.2 (1.1)	7.0 (2.4)
Daytime napping (%)			
Never/rarely	100	8.7	1.0
Sometimes	0	82.2	72.6
Usually	0	9	26.5
Daytime sleepiness (%)			
Never/rarely	89.3	65.8	31.0
Sometimes	10.7	33.6	25.0
Often/always	0	0.6	44.0
Snoring (%)	34.4	40.2	43.7
Insomnia (%)			
Never/rarely	27.5	22.0	16.5
Sometimes	49.0	48.4	32.0
Usually	23.5	29.5	51.5

Abbreviations: BMI: body mass index; GERD: gastro-esophageal reflux disease; MET: Metabolic Equivalent Task; SD: standard deviation.
[a] Composite sleep score was calculated by summing the individual scores of three unhealthy sleep behaviors: sleep <6 or >9 h/day, daytime napping and usual daytime sleepiness. Each unhealthy sleep behavior was assigned with score 1 otherwise with score 0. The composite sleep score was further categorized into three groups: good (score=0), intermediate (score=1), and poor (score≥2).

Table 2. Sleep behaviors and risk of EAC and ESCC

	EAC				ESCC			
	N events	HR (95%CI) [a]	HR (95%CI) [b]	P_{LRT} [c]	*N* events	HR (95%CI) [a]	HR (95%CI) [d]	P_{LRT} [e]
Chronotype								
Morning	81	1 (reference)	1 (reference)		24	1 (reference)	1 (reference)	
More morning than evening	101	0.99 (0.74, 1.33)	0.99 (0.74, 1.33)	0.817	29	0.96 (0.56, 1.66)	1.02 (0.59, 1.76)	0.299
More evening than morning	80	1.06 (0.78, 1.45)	0.96 (0.70, 1.31)		27	1.21 (0.70, 2.10)	1.15 (0.66, 2.01)	
Evening	32	1.47 (0.98, 2.22)	1.18 (0.78, 1.78)		15	2.33 (1.22, 4.45)	1.86 (0.96, 3.60)	
Duration (h/day)								
<6	23	1.64 (1.04, 2.58)	1.53 (0.97, 2.42)		8	1.80 (0.83, 3.91)	1.48 (0.67, 3.26)	
6	61	1.25 (0.91, 1.72)	1.17 (0.85, 1.62)		18	1.16 (0.65, 2.08)	1.09 (0.61, 1.95)	
7	98	1 (reference)	1 (reference)	0.057	31	1 (reference)	1 (reference)	0.968
8	77	0.94 (0.70, 1.27)	0.92 (0.68, 1.24)		29	1.12 (0.67, 1.86)	1.10 (0.66, 1.84)	
9	20	1.07 (0.66, 1.74)	0.93 (0.57, 1.51)		7	1.19 (0.52, 2.71)	1.11 (0.48, 2.53)	
>9	15	2.80 (1.62, 4.83)	2.05 (1.18, 3.57)		2	1.18 (0.28, 4.95)	0.97 (0.23, 4.08)	
Daytime napping								
Never/rarely	106	1 (reference)	1 (reference)		54	1 (reference)	1 (reference)	
Sometimes	154	1.81 (1.41, 2.32)	1.36 (1.06, 1.75)	0.039	32	0.73 (0.47, 1.13)	0.74 (0.47, 1.15)	0.271
Usually	34	2.55 (1.73, 3.77)	1.40 (0.94, 2.09)		9	1.29 (0.63, 2.63)	1.20 (0.58, 2.48)	
Daytime sleepiness								
Never/rarely	215	1 (reference)	1 (reference)		75	1 (reference)	1 (reference)	
Sometimes	64	0.90 (0.68, 1.19)	0.81 (0.61, 1.08)	0.182	15	0.60 (0.34, 1.04)	0.64 (0.37, 1.12)	0.131
Usually	15	1.69 (1.00, 2.86)	1.30 (0.77, 2.20)		5	1.61 (0.65, 3.97)	1.63 (0.65, 4.05)	
Snoring								
No	147	1 (reference)	1 (reference)	0.377	66	1 (reference)	1 (reference)	0.516
Yes	147	1.67 (1.33, 2.10)	1.11 (0.88, 1.40)		29	0.74 (0.48, 1.14)	0.86 (0.55, 1.35)	
Insomnia								
Never	67	1 (reference)	1 (reference)		16	1 (reference)	1 (reference)	
Sometimes	139	0.96 (0.71, 1.28)	1.17 (0.87, 1.57)	0.494	45	1.30 (0.73, 2.30)	1.24 (0.70, 2.21)	0.488
Often/always	88	1.00 (0.72, 1.37)	1.19 (0.86, 1.64)		34	1.61 (0.89, 2.93)	1.44 (0.78, 2.63)	

Abbreviations: BMI: body mass index; CI: confidence interval; EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; GERD: gastro-esophageal reflux disease; HR: hazard ratio; LRT: likelihood ratio test; MET: Metabolic Equivalent Task.

[a] Adjusted for age at baseline (in years).

[b] Additionally adjusted for sex (male, female), race (white, black, other), education(pre-/post-college), the Townsend Deprivation Index (in quartiles), history of GERD (yes, no), BMI (underweight, normal, overweight, obese), smoking status and intensity (never smoker, past smoker 1-19 pack-years, past smoker >19 pack-years, past smoker unknown pack-year, current smoker 1-19 pack-years, current smoker >19 pack-years, current smoker with unknown pack-year), physical activity (MET-h/week, in quartiles, and missing), and shift work status (non-shift, day shift, sometimes night shift, usual/always night shift, missing).
[c] P_{LRT} was calculated from comparing the multivariable models b with and without a specific behavior using the LRT.
[d] Additionally adjusted for sex (male, female), race (white, black, other), education(pre-/post-college), the Townsend Deprivation Index (in quartiles), BMI (underweight, normal, overweight, obese), smoking status and intensity (never smoker, past smoker 1-19 pack-years, past smoker >19 pack-years, past smoker unknown pack-year, current smoker 1-19 pack-years, current smoker >19 pack-years, current smoker with unknown pack-year), and alcohol consumption status and intensity (never, previous, current, current 0 g/day, current 0.1-14.9 g/day, current 15-29.9 g/day, current 30+ g/day, and current unknown intensity), physical activity (MET-h/week, in quartiles, and missing), and shift work status (non-shift, day shift, sometimes night shift, usual/always night shift, missing).
[e] P_{LRT} was calculated from comparing the multivariable models d with and without a specific behavior using the LRT.

Table 3. Composite sleep score and risk of EAC

Composite sleep score [a]	*N* events	HR (95%CI) [b]
All participants		
Good (score=0)	91	1 (reference)
Intermediate (score=1)	170	1.47 (1.13, 1.91)
Poor (score ≥2)	33	1.87 (1.24, 2.82)
P trend [c]		<0.001
Excluded cancers within 2 years of enrollment		
Good (score=0)	74	1 (reference)
Intermediate (score=1)	130	1.42 (1.06, 1.90)
Poor (score ≥2)	24	1.73 (1.08, 2.78)
P trend [c]		0.006
Participants without history of GERD		
Good (score=0)	82	1 (reference)
Intermediate (score=1)	163	1.57 (1.20, 2.07)
Poor (score ≥2)	32	2.06 (1.35, 3.13)
P trend [c]		<0.001
Participants without history of sleep apnea		
Good (score=0)	90	1 (reference)
Intermediate (score=1)	169	1.48 (1.14, 1.93)
Poor (score ≥2)	30	1.76 (1.15, 2.70)
P trend [c]		0.001

Abbreviations: CI: confidence interval; EAC: esophageal adenocarcinoma; HR: hazard ratio.

[a] Composite sleep score was calculated by summing the individual scores of three unhealthy sleep behaviors: sleep <6 or >9 h/day, daytime napping and usual daytime sleepiness. Each unhealthy sleep behavior was assigned with score 1 otherwise with score 0. The composite sleep score was further categorized into three groups: good (score=0), intermediate (score=1), and poor (score≥2).

[b] Adjusted for the same set of covariates as model b in Table 2.

[c] P value for trend was calculated using the composite sleep score as a continuous variable (i.e., 0-3).

Figure Legend

Figure 1. Joint associations of composite sleep score and genetic predisposition with risk of esophageal adenocarcinoma. Composite sleep score was calculated by summing the individual scores of three unhealthy sleep behaviors: sleep <6 or >9 h/day, daytime napping and usual daytime sleepiness. Each unhealthy sleep behavior was assigned with score 1 otherwise with score 0. The composite sleep score was further categorized into three groups: good (score=0), intermediate (score=1), and poor (score≥2). Genetic risk was defined by quintiles of polygenic risk score (PRS): low-(Q1-Q2), intermediate- (Q3-Q4), and high-risk (Q5). All hazard ratios were adjusted for the same set of covariates as model b in Table 2, the first ten principal components for ancestry, and the genotype array type.

Figure 1