Original Article

Association between sleep traits and risk of colorectal cancer: a bidirectional Mendelian randomization study

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Background: Sleep traits have been linked to diseases; particularly, their impact on cancer has received increasing attention. This study aimed to investigate whether sleep traits have a causal relationship with colorectal cancer (CRC) using two-sample Mendelian randomization (TSMR).

Methods: Genetic instrumental variables (IVs) for seven sleep traits (sleep duration, ease of getting up in the morning, morning chronotype, daytime napping, insomnia symptoms, snoring, and daytime dozing) were selected from pooled data from published genome-wide association studies (GSWSs). Two-sample multivariate Mendelian randomization (MR) analyses were conducted to assess the causal association between sleep traits and CRC. Reverse MR analyses were performed to determine the causal relationship between CRC and sleep traits. Inverse variance weighted (IVW), MR-Egger, and weighted medians were calculated for all MR analyses.

Results: The multivariable MR (MVMR) analysis found that appropriate sleep duration [odds ratio (OR) =0.989; 95% confidence interval (CI): 0.980, 0.999; P=0.04] and ease of getting up in the morning (OR =0.990; 95% CI: 0.980, 1.000; P=0.04) were protective factors for CRC. Snoring (OR =1.021; 95% CI: 1.002, 1.041; P=0.03) was associated with the risk of CRC. Ease of getting up in the morning (OR =0.990; 95% CI: 0.983, 0.997; P=0.003) was associated with reduced risk of colon cancer. Morning chronotype (OR =1.004; 95% CI: 1.000, 1.007; P=0.04) was associated with the risk of colon cancer. Insomnia symptoms (OR =0.995; 95% CI: 0.990, 0.999; P=0.03) were a protective factor for rectal cancer. There was no evidence found for a causal association between other sleep traits and CRC, colon, or rectal cancer.

Conclusions: Proper sleep duration and ease of getting up in the morning may be protective factors against CRC, and snoring may increase the risk of CRC.

Keywords: Colorectal cancer (CRC); sleep traits; Mendelian randomization (MR); sleep duration; genome-wide association study (GSWS)

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Introduction

Cancer is a global public health problem and one of the leading causes of death worldwide (1). The global cancer burden is increasing as populations grow and malignancies develop at younger ages (2). Studies (3-7) have linked cancer to smoking, alcohol consumption, obesity, diabetes, reduced physical activity, irregular schedules, and other lifestyle factors. Reasonable sleep time arrangements are a part of a healthy lifestyle. However, inadequate (<7 hours) sleep, staying up late at night, insomnia, difficulty in getting up in the morning, and other poor sleep habits are becoming increasingly common in the general public (8,9).

Sleep disorders have been shown to increase the risk of diseases such as coronary heart disease, ischaemic stroke, and Parkinson's disease (10-12). In addition, some studies (13-15) have found that sleep disorders can increase the risk of breast, liver, and prostate cancers, as well as other malignant tumors. Although some evidence has found that an appropriate amount of sleep per day, less frequent insomnia, absence of snoring, and less frequent daytime sleepiness are associated with a reduced risk of colorectal cancer (CRC) (16-18), these findings are largely from observational studies, which are easily affected by selection and information biases.

Mendelian randomization (MR) analysis is a statistical method that utilizes a large genetic database to analyze the causal association between exposure factors and outcome indicators at the gene level (19). Alleles with genetic variations are used as instrumental variables (IVs) to mitigate measurement errors and biases. IVs used in MR studies must satisfy three conditions (20): (I) single nucleotide polymorphisms (SNPs) must be closely related to sleep traits; (II) SNPs must not be associated with confounders; and (III) SNPs must influence CRC through sleep traits and must not be directly associated. Therefore, the results are more credible when MR analysis is used to investigate causal associations between diseases. Two-sample MR (TSMR) utilizes data from two independent genome-wide association study (GWAS) samples to compute the effect size between exposure traits and outcomes (20). This study aimed to analyze the potential causal association between sleep traits and CRC through MR analysis, utilizing data on sleep traits and CRC data from large published genetic studies. We present this article in accordance with the STROBE-MR reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-11/rc).

Highlight box

Key findings

- Appropriate sleep duration and ease of getting up in the morning were identified as protective factors against colorectal cancer (CRC). Insomnia symptoms also showed a protective effect against CRC.
- Snoring was found to be an adverse factor for CRC.
- Morning chronotype was protective against CRC but showed adverse effects on colon cancer. Insomnia symptoms were protective against rectal cancer.

What is known and what is new?

- Prior studies have linked cancer risk to various lifestyle factors, including sleep disorders.
- This study adds to existing knowledge by employing Mendelian randomization analysis to examine causal relationships, offering more robust evidence than observational studies.

What is the implication, and what should change now?

- The findings suggest that maintaining appropriate sleep duration and ease of awakening may serve as protective factors against CRC, particularly colon cancer. Conversely, snoring appears to be an adverse factor for colon cancer. These results underscore the importance of healthy sleep habits in reducing cancer risk. Further research, particularly in diverse populations, and exploration of biological mechanisms are warranted to confirm and elucidate these findings. Promoting awareness of the role of sleep in cancer prevention could lead to interventions aimed at improving sleep quality and reducing cancer burden on a global scale.

Methods

Study design

We conducted a bidirectional MR analysis to explore the causal relationship between sleep traits and CRC. Multivariable MR (MVMR) analysis was employed to account for the causal effect of high body mass index (BMI), a known risk factor for CRC (21), and to increase confidence in the findings. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Since the study was conducted using publicly available data, no ethical approval or informed consent was required.

GWAS data on sleep traits

In this study, seven sleep traits were identified as exposure factors: sleep duration, ease of getting up in the morning, morning chronotype, daytime napping, insomnia symptoms, snoring, and daytime dozing. The data were obtained from

Table 1 Characters of sleep traits and CRC

Exposure/outcome	Consortium	Sample size	Population	Case, n
Exposure				
Sleep duration	Neale Lab	335,410	European	335,410
Getting up in morning	Neale Lab	336,501	European	336,501
Chronotype (morning)	Neale Lab	301,143	European	301,143
nap during in daytime	Neale Lab	337,074	European	337,074
Sleeplessness/insomnia	Neale Lab	336,965	European	336,965
Snoring	Neale Lab	314,449	European	314,449
Daytime dozing	Neale Lab	336,082	European	336,082
BMI	GIANT	322,154	European	322,154
Outcome				
Colorectal cancer	UK Biobank	377,673	European	5,657
Malignant neoplasm of colon	Neale Lab	361,194	European	2,226
Malignant neoplasm of rectum	Neale Lab	361,194	European	1,170

CRC, colorectal cancer; BMI, body mass index.

the Independent Education Union (IEU) open GWAS and primarily from the UK Biobank between 2006 and 2010, involving a study of 337,000 unrelated individuals aged 40–69 years (22). Sleep duration was determined by asking individuals about their daily hours of sleep, with 7–9 hours considered appropriate. Their genetic associations were derived from a GWAS of 335,410 samples from the UK Biobank. The ease of getting up in the morning was mainly determined through self-assessment. Aggregated GWAS data from 336,501 individuals in the UK Biobank database revealed a genetic association for an early rise. Chronotype refers to a person's tendency to sleep at particular times, with morning chronotype indicating someone who is identified as a "morning asleep" person. A GWAS association search of 301,143 samples published in the UK Biobank provided estimates of the genetic associations of chronotypes. People who sleep inadequately at night tend to nap during the day, mostly during the middle of the day. The genetic association of daytime napping was retrieved from a GWAS of 337,074 samples from the UK Biobank. Insomnia is characterized by difficulty in falling asleep or waking at night. A GWAS association search of 336,965 samples published in the UK Biobank provided estimates of genetic associations for insomnia. Snoring was assessed based on snoring complaints from partners or relatives. The genetic association of snoring was retrieved from a GWAS of 314,449 samples from the UK Biobank. Daytime dozing refers to a state in which a person falls asleep for a short time due to excessive fatigue or insufficient rest. Aggregated GWAS data from 336,082 individuals in the UK Biobank database revealed a genetic link with daytime dozing (*Table 1*).

We identified SNPs strongly associated with sleep traits to generate statistically significant thresholds ($P<5\times10^{-8}$), eliminated linkage disequilibrium (LD) (23) ($r^2<0.001$; LD distance >10,000 kb), and removed palindromic SNP to ensure the independence of IVs. To mitigate the bias caused by weak IVs, we assessed the R^2 for each IV's exposure interpretation. Additionally, the F-statistic was calculated to determine the strength of the relationship between the SNPs and sleep traits (24). It is generally believed that SNPs with F>10 may be closely associated with sleep traits (25).

GWAS data on CRC

Genetic outcome associations for CRC, colon cancer, and rectal malignancies, as defined by the International Statistical Classification of Diseases, were derived from publicly available GWAS summary statistics in the UK Biobank database (https://gwas.mrcieu.ac.uk/). We obtained three datasets, including 5,657 patients with CRC and 372,016 controls, 2,226 patients with malignant neoplasms

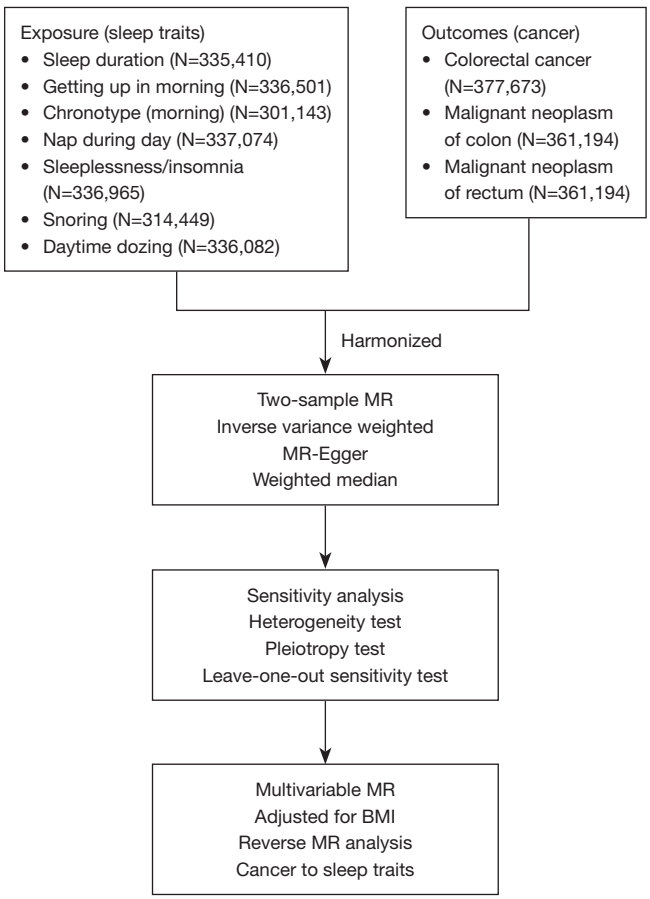

Figure 1 Flow chart of MR. MR, Mendelian randomization; BMI, body mass index.

of the colon and 358,968 controls, and 1,170 patients with malignant neoplasms of the rectum and 360,024 controls (*Table 1*).

Statistical analysis

TSMR analysis

The association between sleep traits and CRC was assessed using TSMR analysis (26). The inverse variance weighted (IVW) method was employed to obtain an unbiased estimate of the causal association between exposure and outcome measures, mitigating horizontal pleiotropic (27). The same procedure was applied to analyze its subtypes (colon and rectal cancer). Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). To assess the sensitivity of the results, MR-Egger regression (28) and weighted medians were utilized to evaluate causality.

MVMR analysis

Considering that BMI is a common risk factor for CRC, we performed an IVW MVMR assessment to adjust for the confounding effects of BMI. Genetic IVs for BMI were obtained using the IEU Open GWAS of 337,074 samples from the Anthropometric Traits Genetic Survey Consortium. MVMR analysis was employed to ascertain whether a true causal association exists between sleep traits and CRC (29). All the analyses were performed for colon and rectal cancers.

Sensitivity analysis

We performed the following sensitivity analysis to determine whether SNPs influence CRC risk through sleep traits.

Cochran's Q test

This test was used to test for differences between IVs in the presence of non-specific SNPs. Heterogeneity analysis was used to determine the effect of non-specific SNPs on the results (30). In cases of IV heterogeneity, the IVW aspect of the random effects model was employed to estimate causality.

Pleiotropy test

MR-Egger regression was utilized to assess whether there is a non-zero intercept in the regression of the causal estimate on its precision. Horizontal pleiotropy can distort MR tests, leading to inaccurate causal estimates and potentially false positive causal associations (31).

Leave-one-out sensitivity test

This test mainly calculates the residual MR results after removing each IV individually. Significant differences between the estimated MR results of other IVs and the total results after removal of the IV indicate sensitivity to that particular IV.

MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO)

To identify outliers in the MR analysis and re-analyze them after removal, we utilized the MR-PERSSO package in R for analysis using improved second-order weights.

All statistical analyses were conducted using R packages "TwoSampleMR (version 0.5.7)", "Forestposter (version 1.1.0)", and "MR-PRESSO (version 1.0)" in R software (version 4.2.1).

Results

We conducted bidirectional MR analyses using seven sleep traits and three CRC outcomes. *Figure 1* illustrates the study process. Each SNP was extracted from different sleep traits, and its F-statistics are shown in Table S1.

Casual association between sleep traits and CRC

Appropriate sleep duration (OR =0.989; 95% CI: 0.980, 0.998; P=0.01) and ease of getting up in the morning (OR =0.992; 95% CI: 0.984, 0.999; P=0.03) were protective factors in patients with CRC. The MVMR analysis produced the same result (P=0.04 for sleep duration and P=0.04 for ease of getting up in the morning). Insomnia symptoms were a protective factor against CRC (OR =0.988; 95% CI: 0.978, 0.997; P=0.01). However, the MVMR outcome for insomnia symptoms was not statistically significant (OR =0.993; 95% CI: 0.980, 1.006; P=0.31). In contrast, snoring did not significantly affect the incidence of CRC in the TSMR group (OR =1.010; 95% CI: 0.994, 1.027; P=0.22). Nevertheless, the MVMR results indicated that snoring had a negative effect on CRC (OR =1.021; 95% CI: 1.002, 1.041; P=0.03) (*Table 2*, *Figures 2*,*3A-3C*). The effects of morning chronotype, daytime napping, and daytime dozing were not statistically significant (P=0.97, P=0.63, and P=0.75, respectively). The entire MR results are presented in Table S2.

Casual association between sleep traits and colon cancer

We observed protective effects of appropriate sleep duration (OR =0.993; 95% CI: 0.986, 1.000; P=0.04) and ease of getting up in the morning (OR =0.995; 95% CI: 0.989, 1.000; P=0.04) on CRC. However, MVMR analyses yielded different results, with the effect of appropriate sleep duration on CRC risk not being statistically significant (OR =0.994; 95% CI: 0.987, 1.002; P=0.13). Morning chronotype did not significantly alter the incidence of CRC in the TSMR group (OR =1.002; 95% CI: 1.000, 1.005; P=0.07). However, MVMR showed that the morning chronotype had a negative effect on CRC (OR =1.004; 95% CI: 1.000, 1.007; P=0.04) (*Table 1*, *Figures 2*,*3D*,*3E*). Additionally, the effects of daytime napping, insomnia symptoms, snoring, and daytime dozing were not statistically significant (P=0.66, P=0.24, P=0.62, and P=0.53, respectively). All MR results are summarised in Table S2.

Casual association between sleep traits and rectal cancer

The results indicated that insomnia symptoms did not significantly affect the incidence of rectal cancer in the TSMR analysis (OR =0.996; 95% CI: 0.991, 1.000; P=0.06). However, MVMR showed that insomnia symptoms were a protective factor against rectal cancer (OR =0.995; 95% CI: 0.990, 0.999; P=0.03) (*Table 1*, *Figures 2*,*3F*). Little evidence of causal effects of other sleep traits was observed for rectal cancer (P=0.13 for appropriate sleep duration, P=0.053 for ease of getting up in the morning, P=0.88 for morning chronotype, P=0.98 for daytime napping, P=0.93 for snoring, and P=0.18 for daytime dozing). The entire MR results of the correlational analysis are presented in Table S2.

Reverse MR analysis

In our reverse MR analysis of sleep traits in CRC, the IVW found no evidence to support a causal relationship between CRC and sleep traits (P=0.84 for sleep duration, P=0.58 for ease of getting up in the morning, P=0.81 for chronotype, P=0.52 for daytime napping, P=0.89 for insomnia, P=0.38 for snoring, and P=0.24 for daytime dozing) (Table S3).

Sensitivity analysis

Heterogeneity was observed in appropriate sleep duration (P=0.01), daytime napping (P=0.01), and daytime dozing (P=0.03) in the CRC and colon cancer analyses. Additionally, snoring (P=0.04) showed heterogeneity only in the colon cancer analysis. No heterogeneity was observed in other MR results. A random benefit model was used for exposures with high heterogeneity for the MR Analysis. However, there were no significant changes in the results after the exclusion of any SNP in the leave-one-out test. The MR-Egger intercept test did not reveal any evidence of horizontal pleiotropy. Detailed heterogeneity tests and pleiotropy results are presented in Table S4. Additionally, several outlier SNPs (rs4767550, rs1983336, rs2390669, and rs1846644) were identified when MR-PRESSO was used for the outlier test. After excluding the above outlier values, an MR analysis was performed, and the results showed no significant changes.

Discussion

This study evaluated the causal association between sleep traits (appropriate sleep duration, ease of getting up in the morning, morning chronotype, daytime napping, insomnia symptoms, snoring, and daytime dozing) and CRC using MR analysis. Our study revealed that appropriate sleep duration and ease of getting up in the morning are protective factors for CRC, while snoring is identified as an adverse factor for CRC. Moreover, ease of getting up in the morning is a protective factor against colon cancer, while

Table 2 Two-sample and MVMR estimation showing the effects of different sleep traits on CRC

Cancer	Sleep trait	Method	OR	95% CI	P value
CRC	Sleep duration	IVW	0.989	0.980–0.998	0.01*
		MVMR adjusted for BMI	0.989	0.980–0.999	0.04*
	Getting up in morning	IVW	0.992	0.984–0.999	0.03*
		MVMR adjusted for BMI	0.990	0.980–1.000	0.04*
	Morning chronotype	IVW	1.000	0.996–1.004	0.97
		MVMR adjusted for BMI	1.000	0.995–1.005	>0.99
	Nap during in daytime	IVW	1.002	0.993–1.012	0.63
		MVMR adjusted for BMI	1.006	0.996–1.016	0.27
	Insomnia symptoms	IVW	0.988	0.978–0.997	0.01*
		MVMR adjusted for BMI	0.993	0.980–1.006	0.31
	Snoring	IVW	1.010	0.994–1.027	0.22
		MVMR adjusted for BMI	1.021	1.002–1.041	0.03*
	Daytime dozing	IVW	1.004	0.982–1.025	0.75
		MVMR adjusted for BMI	1.007	0.988–1.026	0.46
Colon cancer	Sleep duration	IVW	0.993	0.986–1.000	0.04*
		MVMR adjusted for BMI	0.994	0.987–1.002	0.13
	Getting up in morning	IVW	0.995	0.989–1.000	0.04*
		MVMR adjusted for BMI	0.990	0.983–0.997	0.003*
	Morning chronotype	IVW	1.002	1.000–1.005	0.07
		MVMR adjusted for BMI	1.004	1.000–1.007	0.04*
	Nap during in daytime	IVW	1.002	0.995–1.009	0.66
		MVMR adjusted for BMI	1.004	0.998–1.013	0.13
	Insomnia symptoms	IVW	0.996	0.989–1.003	0.24
		MVMR adjusted for BMI	0.996	0.987–1.005	0.35
	Snoring	IVW	0.996	0.982–1.011	0.62
		MVMR adjusted for BMI	1.007	0.992–1.023	0.34
	Daytime dozing	IVW	1.005	0.989–1.022	0.53
		MVMR adjusted for BMI	1.008	0.994–1.022	0.25
Rectal cancer	Sleep duration	IVW	0.997	0.993–1.001	0.13
		MVMR adjusted for BMI	0.998	0.994–1.002	0.24
	Getting up in morning	IVW	0.997	0.993–1.000	0.053
		MVMR adjusted for BMI	0.997	0.993–1.001	0.09
	Morning chronotype	IVW	1.000	0.998–1.002	0.88
		MVMR adjusted for BMI	1.000	0.998–1.002	0.85
	Nap during in daytime	IVW	1.000	0.996–1.004	0.98
		MVMR adjusted for BMI	1.000	0.996–1.004	0.92
	Insomnia symptoms	IVW	0.996	0.991–1.000	0.06
		MVMR adjusted for BMI	0.995	0.990–0.999	0.03*
	Snoring	IVW	1.000	0.992–1.007	0.93
		MVMR adjusted for BMI	1.003	0.996–1.011	0.38
	Daytime dozing	IVW	0.995	0.987–1.002	0.18
		MVMR adjusted for BMI	0.997	0.990–1.004	0.39

Sleep duration refer to persons who sleep 7–9 hours per day. Chronotype refer to persons who tend to sleep more in the morning. Insomnia refers to persons who suffering from insomnia. *, P<0.05. MVMR, multivariable MR; MR, Mendelian randomization; CRC, colorectal cancer; OR, odds ratio; CI, confidence interval; IVW, inverse variants weighted; BMI, body mass index.

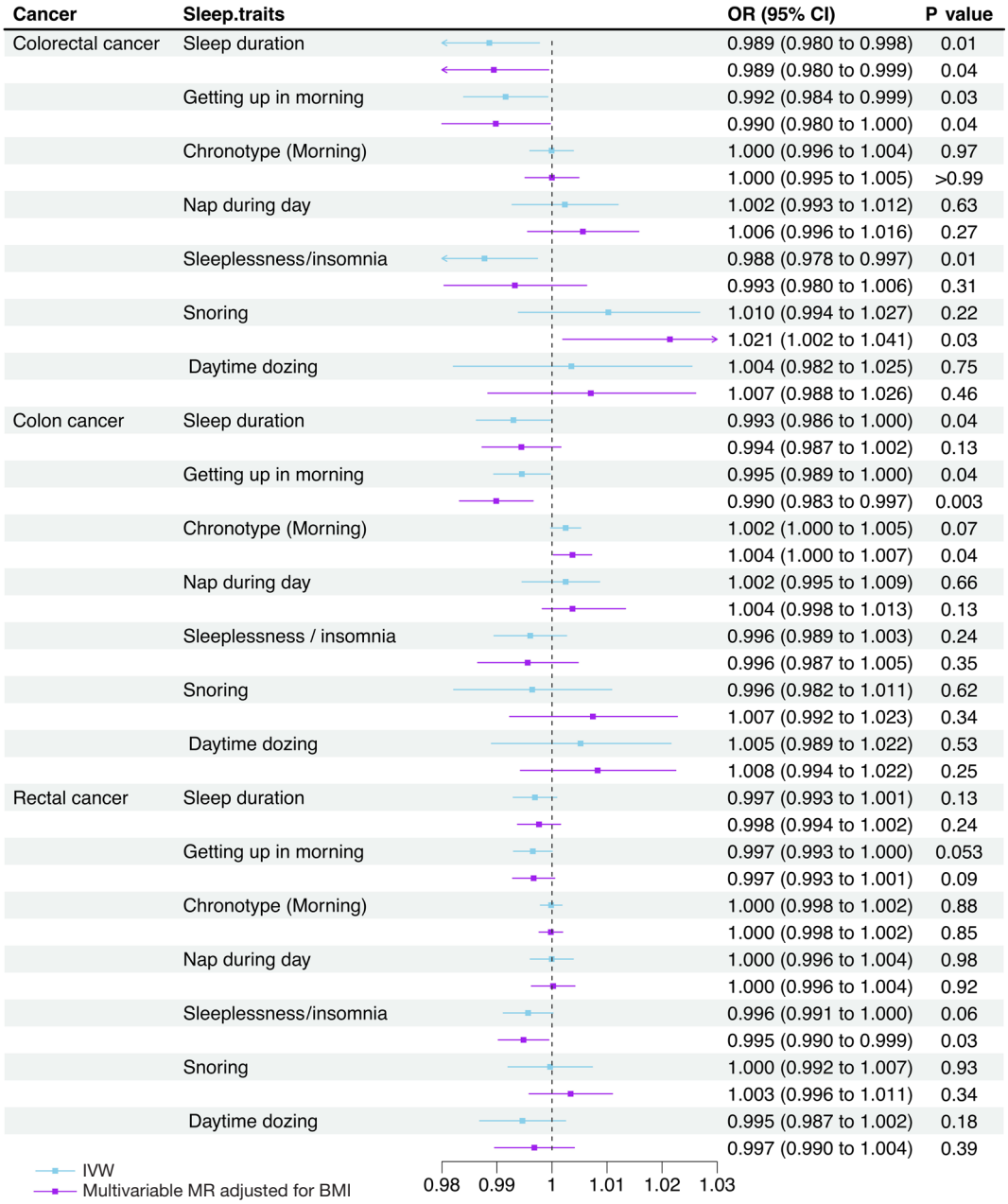

Figure 2 Forest plot of MR estimates for association between sleep traits and CRC. Sleep duration refer to persons who sleep 7–9 hours per day. Chronotype refer to persons who tend to sleep more in the morning. Insomnia refers to persons who suffering from insomnia. OR, odds ratio; CI, confidence interval; IVW, inverse variants weighted; MR, Mendelian randomization; BMI, body mass index; CRC, colorectal cancer.

morning chronotype is an adverse factor for colon cancer. Additionally, insomnia symptoms are protective factors for rectal cancer. However, no causal association was observed between daytime napping, daytime dozing, and CRC. These findings underscore the importance of considering sleep traits as modifiable risk factors for cancer. Promoting health awareness and adopting a healthy lifestyle may reduce the risk of CRC.

Epidemiological studies (31,32) have shown that sleep traits are risk factors for cancer, affecting tumor development.

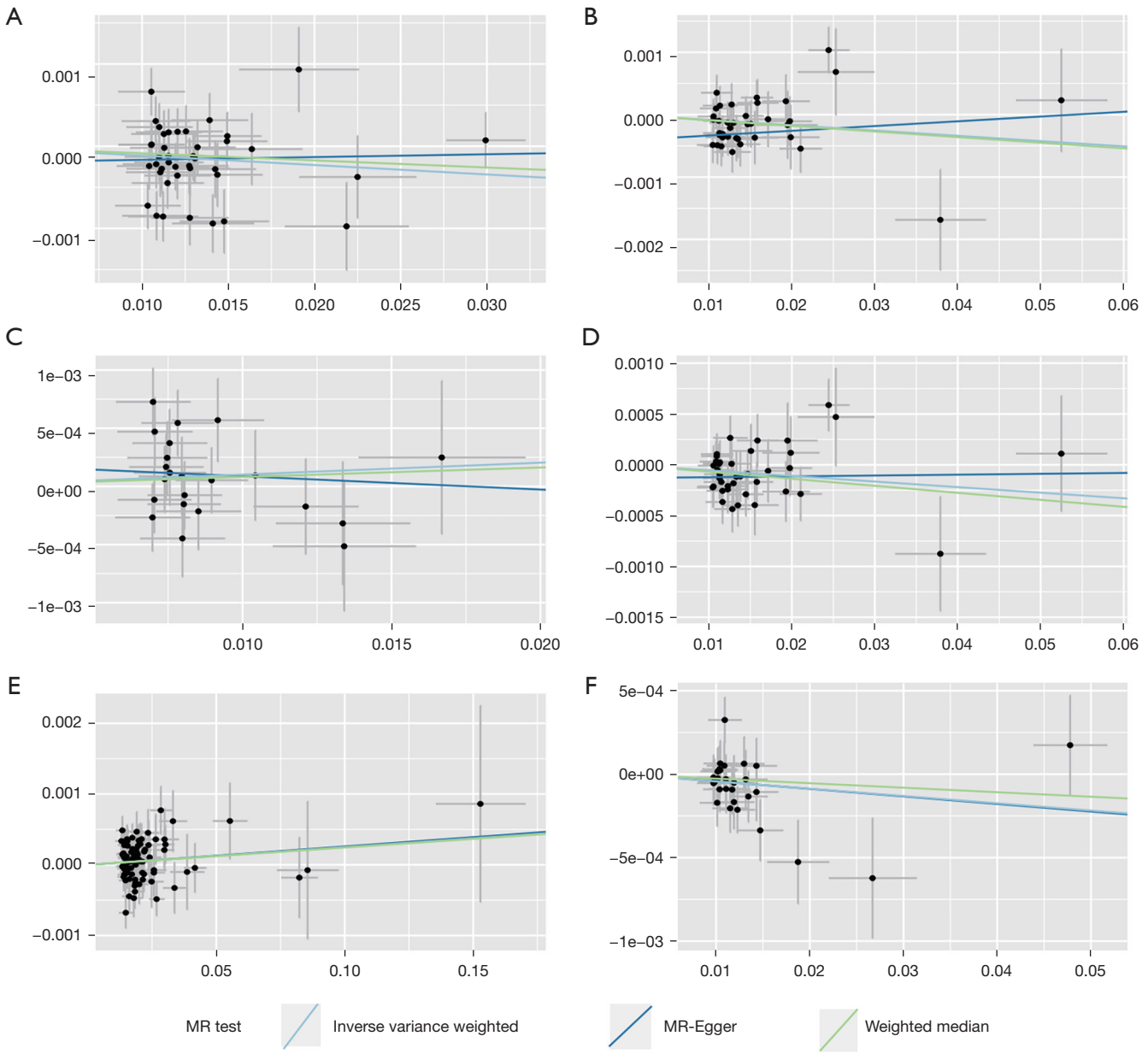

Figure 3 MR analysis of sleep traits on CRC. Scatter plot of CRC associations (Y-axis) against sleep traits (X-axis). (A) Scatter plot of sleep duration on CRC. (B) Scatter plot of getting up in the morning on CRC. (C) Scatter plot of snoring on CRC. (D) Scatter plot of getting up in the morning on colon cancer. (E) Scatter plot of morning chronotype on colon cancer. (F) Scatter plot of insomnia symptoms on rectal cancer. MR, Mendelian randomization; CRC, colorectal cancer.

Haus *et al.* (33) found that reduced sleep quality may lead to reduced melatonin production. Melatonin is a human hormone produced by the pineal gland and has many functions, such as regulating circadian rhythms and increasing immunity. Hohor *et al.* (34) found that the levels of melatonin and its metabolites decline gradually when shift workers are exposed to light at night. As an anticancer agent, melatonin plays a crucial role in inhibiting malignant tumors, including tumor proliferation, metastasis, and angiogenesis (35,36).

Sleep is a key mechanism for maintaining optimal immune (37), cellular (38), metabolic (39), and endocrine (40)

functions, with each neurophysiological dysfunction being associated with carcinogenic pathways. Moreover, sleep and rest disorders may affect innate and acquired immune capacity, increase reactive oxygen species, induce DNA damage, and disrupt metabolic function, consequently leading to the occurrence of tumors (34). In addition, people with some common carcinogenic factors, such as smoking, obesity, and a sedentary lifestyle, are more likely to develop sleep disorders, which also explains the higher incidence of tumors in this population (41).

Sleep traits also affect the occurrence of specific tumors through diverse mechanisms. For instance, repeated sleep disruption leads to an increase in the overall estrogen level in females (42), and heightened estrogen stimulation increases the risk of breast cancer. Males with sleep disorders tend to experience lower urinary tract symptoms (43), which can potentially promote the development of prostate cancer. Disorder in sleep rhythm leads to the downregulation of circadian genes, and disruption of the circadian rhythm of liver cells will impair the control of the central pacemaker, thereby facilitating the selective survival of cancer cells (44).

Our study indicates that ease of awakening in the morning is a protective factor against CRC, especially colon cancer. People who can easily get up early have better dietary habits. They tend to eat more fruits, whole grains, and other healthy foods for breakfast rather than indulging in sleeping late and immediately consuming greasy processed meat, beer, and coffee upon waking up (45). In addition, people who can easily get up early have a lower abundance of Alistipes and a higher abundance of Lachnospira in their intestinal flora (46). These enterobacteria hinder the development of CRC (47,48). Moreover, people who can easily get up early are more willing to exercise, and their incidence of obesity is lower (49). We also found that optimal sleep duration is a protective factor against CRC compared to sleep that is too short (<7 hours) or too long (>9 hours), which aligns with previous research (16,50). Adequate sleep can increase the adaptive immune response, while sleep disorders may induce immunosuppression, thereby favoring the dominance of cancer-stimulating cytokines in the body (51). Conversely, excessively long sleep duration is often indicative of frailty and may exacerbate inflammatory responses, increasing the risk of CRC (52). Furthermore, our MR analysis identified snoring as a risk factor for CRC, consistent with the findings of Zhang *et al.* (18). This association may be related to obstructive sleep apnoea syndrome, characterized by repeated sleep disruptions and intermittent hypoxemia. Intermittent hypoxemia can promote tumor cell growth cell proliferation by releasing pro-angiogenic mediators (53,54).

Our study found that insomnia symptoms are a protective factor against rectal cancer. Yoon *et al.*'s (55) large cohort study also reached the same conclusion, which may be attributed to the fact that patients with insomnia participate more in CRC screening (56). Early screening can be used to treat precancerous lesions in advance, thereby reducing the occurrence of rectal cancer. However, the genetic causes need to be explored further. Nevertheless, Chen *et al.* (17) came to a different conclusion, suggesting that insomnia increases the risk of CRC by 14%. This may be related to differences in the population composition, and the causal relationship may differ across age groups. Currently, there are a few studies on the causal relationship between insomnia and CRC (55,56), and further exploration of the causal relationship and influencing mechanisms is needed.

There are some limitations in this study. First, it relied on the European GWAS database of the UK Biobank, which may limit the generalizability of the findings to other ethnic groups, necessitating further validation. Second, this study utilized a pooled database of GWAS data, lacking original individual-level statistics, which may limit the analysis to genetic data only and not accounting for individual characteristics. Moreover, the causal relationship between sleep traits and CRC differs across age groups and sexes, and the study was unable to determine whether there is a dose-response relationship between sleep traits and CRC. Last, while several sleep traits showed significant associations with the risk of CRC, the OR values were small. Therefore, further large-scale MR analyses and basic biological experiments are warranted to verify the reliability of the results and elucidate their specific biological pathways.

Conclusions

Our study indicates that ease of awakening in the morning and appropriate sleep duration may serve as protective factors against CRC, especially in the context of colon cancer, while snoring may be an adverse factor for colon cancer. The findings from our MR analysis underscore the significance of healthy sleep in mitigating the risk of CRC. Future studies should further investigate the causal relationships between sleep traits and CRC across diverse populations and explore potential dose-response relationships. Additionally, examining specific biological pathways underlying these associations through large-scale

analyses and biological experiments is warranted.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-11/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-11/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-11/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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