



Sleep factors and risk of thyroid cancer, nodules and dysfunction: Mendelian randomization study

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Background: The interplay between sleep physiology and endocrine regulation has been well-established, with the thyroid gland, as a key endocrine organ, demonstrating a physiologically plausible. Previous studies have indicated a potential correlation between sleep factors and thyroid diseases, yet causality remains uncertain. Given the complex interplay of confounders associated with sleep disorders and lifestyle factors, we employed a two-sample Mendelian randomization (MR) approach to minimize confounding bias and rigorously investigate the causal relationship.

Methods: The specific information on thyroid diseases—including thyroid cancer, thyroid nodules (TNs), and thyroid dysfunction—was obtained from the FinnGen Biobank using the International Classification of Diseases, 10th Revision (ICD-10). Information on sleep factors such as insomnia symptoms, chronotype, and sleep duration were sourced from genome-wide association studies (GWAS) conducted within the UK Biobank, which provides validated GWAS data through self-report assessment. We employed stringent single nucleotide polymorphisms (SNPs) selection criteria as instrumental variables (IVs) for analyzing sleep factors' causal impact on thyroid diseases. Statistical methods including inverse variance weighted (IVW), weighted median (WM), MR-Egger, and MR-PRESSO were utilized to determine causality, supplemented by F-statistics and sensitivity analyses to ensure robustness and detect biases.

Results: The analysis supported that a morning chronotype is protective against thyroid cancer, with results showing a significantly reduced risk [IVW: odds ratio (OR) =0.632, 95% confidence interval (CI): 0.426–0.937, P=0.02]. Conversely, insomnia symptoms were identified as a potential risk factor for developing TNs (IVW: OR =1.973, 95% CI: 1.152–3.377, P=0.01). Sensitivity analyses, including Cochran's Q test, MR-Egger intercept, and MR-PRESSO, showed no significant heterogeneity, horizontal pleiotropy, or outliers (all P values >0.05). However, no significant causal links were found between genetic predispositions to sleep factors and thyroid dysfunction.

Conclusions: These findings suggest that therapeutic management of sleep disorders could potentially reduce the risk of developing thyroid diseases, underscoring the importance of routine thyroid monitoring in individuals experiencing sleep disturbances.

Keywords: Thyroid cancer; thyroid nodules (TNs); sleep factors; thyroid dysfunction; Mendelian randomization (MR)

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Introduction

Thyroid disorders encompass thyroid nodules (TNs), thyroid cancer, and thyroid dysfunction. TNs, which are discrete lesions arising from aberrant localized growth of thyroid cells, represent the most common thyroid pathology. While palpation detects TNs in approximately 4–5% of adults, ultrasound and postmortem studies suggest a prevalence of as high as 50–67% (1). Approximately 5% of these nodules are malignant. Thyroid cancer, primarily originating from differentiated follicular cells, accounts for over 90% of cases and includes types such as papillary and follicular carcinoma (1). These cancers are often asymptomatic and typically detected during physical examinations or incidentally on imaging studies (2). Thyroid cancer ranks as the ninth most common cancer globally, with an increasing incidence over recent decades (3). Risk factors for thyroid cancer include age, gender, obesity, previous benign thyroid conditions, radiation exposure,

hormonal influences, and systemic lupus erythematosus, as reported by Cancer Research UK (<https://www.cancerresearchuk.org/about-cancer/thyroid-cancer/causes-risks>). Thyroid dysfunction, which includes hyperthyroidism and hypothyroidism, represents one of the most prevalent endocrine disorders (4,5), with hyperthyroidism affecting 1.2–1.6% of the population (6), and hypothyroidism rates reaching up to 3.8%, varying by iodine intake (7). Considering the substantial prevalence of thyroid disorders, numerous studies have investigated factors influencing their pathogenesis (8–10), with sleep-related factors progressively becoming the focus of attention (11,12).

In contemporary research, the influence of lifestyle factors on the development of diverse diseases has garnered increasing attention. An expanding segment of the population is experiencing sleep disturbances, including insomnia, insufficient sleep duration, reduced sleep quality, and frequent daytime napping. These conditions are hypothesized to increase vulnerability to several health issues such as neurodegenerative diseases, cardiovascular disorders, and various cancers, yet direct causal relationships are still under investigation (13,14). Afrashteh *et al.* identified a potential protective effect of high-quality sleep against thyroid cancer (11), while Papantoniou *et al.* observed a modestly increased risk of thyroid cancer associated with sleep difficulties (15), particularly among night shift workers. Additionally, conditions like obstructive sleep apnea (OSA) (16,17) and insomnia (18,19) have been tentatively linked to a heightened incidence of thyroid cancer. In contrast to those hypotheses, Li *et al.* found that insomnia was not an independent risk factor for thyroid disorders in the context of genetic variation (20). Rather, their study showed that thyroid cancer was linked to an increased risk of insomnia. While earlier studies have posited that short sleep duration independently increases the risk of TNs (21) and hypothyroidism (22) even after controlling for various confounders through multifactorial logistic analysis, the findings of Song *et al.* (23) reveal that subclinical hypothyroidism may be the primary cause of reduced sleep duration. Recent investigations by Wang *et al.* sought to elucidate the relationship between sleep traits and thyroid disorders in light of genetic variation (12). However, this study has not fully uncovered this causal relationship, especially concerning the connection between sleep factors and thyroid cancer. The heterogeneity observed across prior observational investigations may stem from methodological limitations inherent to such designs, particularly residual confounding and potential reverse causation. To address

Highlight box

Key findings

- This study suggests that morning chronotype may have a protective effect against thyroid cancer, while insomnia symptoms may increase thyroid nodules risk. These insights highlight the importance of managing sleep characteristics proactively in individuals at risk for or diagnosed with thyroid conditions, particularly thyroid cancer and nodules.

What is known and what is new?

- Given the prevalence of thyroid disorders, many studies have investigated the factors that influence their development, with a focus on sleep-related factors such as poor sleep quality and short sleep duration, which have been associated with an increased incidence of thyroid disorders.
- The precise role of sleep characteristics in the pathogenesis of thyroid disease remains to be fully elucidated. Owing to the substantial number of confounders associated with sleep disorders and lifestyle factors, two-sample Mendelian randomization analyses were employed to rigorously explore the causal relationship between sleep characteristics and thyroid disease risk.

What is the implication, and what should change now?

- These findings suggest that therapeutic management of sleep disorders could potentially reduce the risk of developing thyroid diseases, underscoring the importance of routine thyroid monitoring in individuals experiencing sleep disturbances. Although our study offers novel insights into the relationship between sleep traits and thyroid disorders, it is imperative to corroborate these findings through large-scale genome-wide association studies to reinforce the validity of our conclusions.

these constraints, future research should prioritize analytic approaches that minimize confounding bias [e.g., Mendelian randomization (MR) or prospective cohort studies with rigorous covariate adjustment]. Such methodological refinements are essential for elucidating potential causal pathways linking sleep parameters with different thyroid disorders.

MR is a robust method that exploits single nucleotide polymorphisms (SNPs) as instrumental variables (IVs), tracing back to the dependent variable through the effect of the IV on the explanatory variable to infer complex relationships between the explanatory and dependent variables, while reducing the interference of confounding factors (24). Given the extensive array of confounders related to sleep disorders and lifestyle factors, MR offers a unique advantage for investigating the links between sleep factors and thyroid disorders. Notably, research on the causal connections between sleep factors and thyroid disorders is limited. Sleep disturbances are commonly perceived as manifestations of central nervous system dysfunction, potentially instigated by disruptions in thyroid hormone levels. Yet, the precise contribution of sleep factors to the onset of thyroid disorders is not fully elucidated. Therefore, we employed a two-sample MR analysis to rigorously explore the causal relationship between sleep factors and the risk of thyroid diseases. We present this article in accordance with the STROBE-MR reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gs-24-435/rc>).

Methods

Study design

Our study employed a two-sample MR approach to explore the causal relationship between sleep factors (insomnia symptoms, chronotype, and sleep duration) and the prevalence of thyroid diseases (malignant and benign TNs, hyperthyroidism, hypothyroidism) in the European population. Subsequent mentions of TN in this article exclusively pertain to benign nodules. Insomnia, chronotype, and sleep duration were individually treated as the exposure and thyroid diseases as the outcome respectively to investigate the impact of sleep factors on the occurrence of thyroid disorders. SNPs were selected as IVs according to the stringent criteria (25), including: (I) strong correlation with the exposure variable; (II) lack of association with any confounding factors; and (III) absence of direct impact on the outcome. A comprehensive overview

of the design is presented in *Figure 1*.

Data sources

Data for exposure

Data from genome-wide association studies (GWAS) of self-reported insomnia/sleeplessness cases were obtained from the MRC Integrative Epidemiology Unit (IEU) OpenGWAS database (<https://gwas.mrcieu.ac.uk/datasets/ukb-b-3957/>). The summary dataset for insomnia comprised 462,341 participants of European descent in the UK Biobank, encompassing a total of 9,851,867 SNPs. Insomnia symptoms were evaluated using the query: “Do you have trouble falling asleep at night or do you wake up in the middle of the night? If this varies a lot, answer this question in relation to the last 4 weeks”. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The UK Biobank is a large-scale, long-term prospective cohort comprising over 500,000 participants between 2006 and 2010, with comprehensive data on anthropometrics, health, lifestyle, and biospecimens. Both sleep chronotype and sleep duration were derived from this cohort.

Chronotype, often denoted as circadian preference, describes an individual’s tendency towards earlier or later sleep cycles and is a physical and behavioral manifestation of the coupling between internal circadian cycles and the need for sleep, driven by sleep homeostasis (26). Genetic data pertaining to chronotype were sourced from GWAS, leveraging a published sample size of 413,343 individuals and 9,851,867 SNPs within the UK Biobank (<https://gwas.mrcieu.ac.uk/datasets/ukb-b-4956/>). Chronotype was reviewed by the question: “Do you consider yourself to be?”, “Definitely a ‘morning’ person”, “More a ‘morning’ than ‘evening’ person”, “More an ‘evening’ than ‘morning’ person”, “Definitely an ‘evening’ person”, “Do not know, prefer not to answer”.

Genetic association data for sleep duration were acquired from 460,099 European subjects enrolled in the UK Biobank database (<https://gwas.mrcieu.ac.uk/datasets/ukb-b-4424/>), building on HG19/GRCh37. Sleep duration was ascertained using the query: “About how many hours sleep do you get in every 24 hours? (please include naps)”. Responses can only contain integer values.

Data for outcome

The aggregated data on thyroid disease characteristics were obtained from the IEU (<https://gwas.mrcieu.ac.uk/>) and

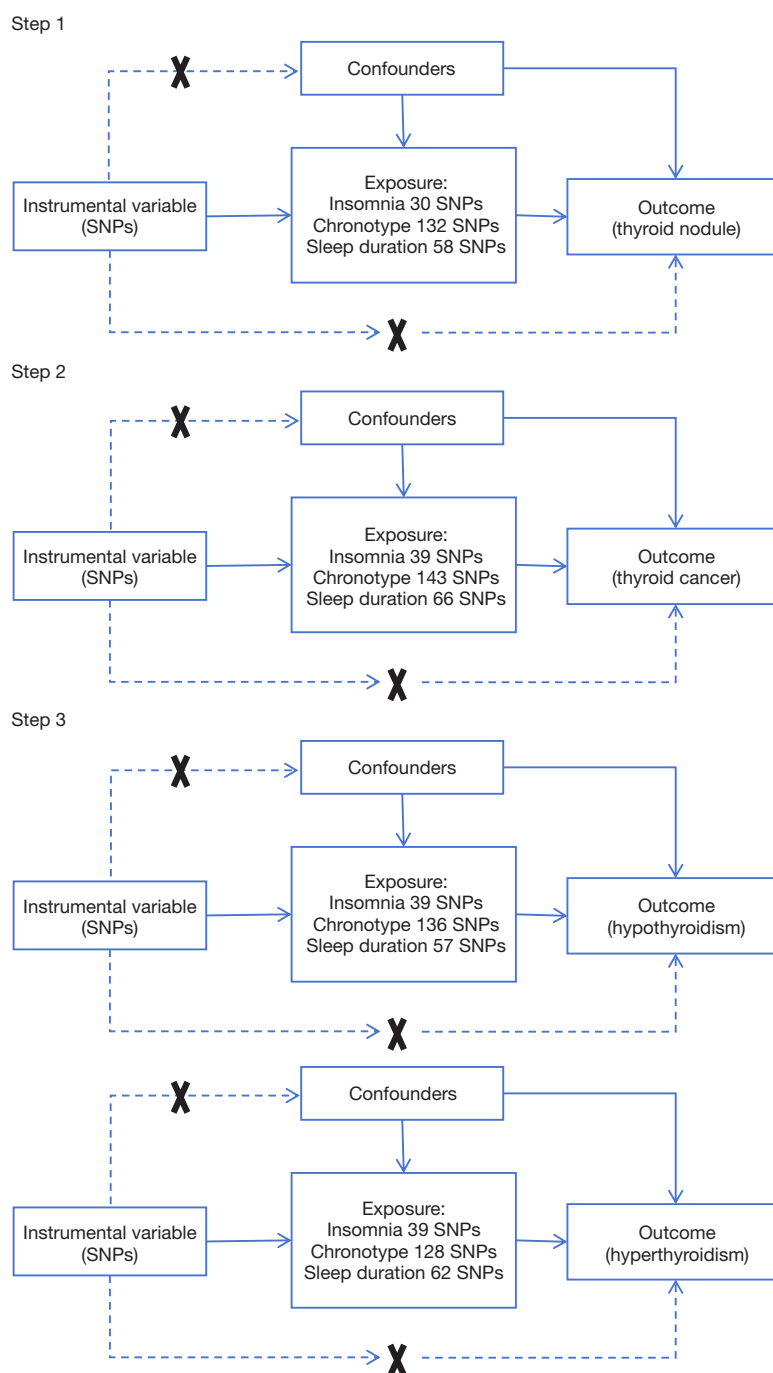


Figure 1 Flow chart of the MR analysis revealing causality from insomnia, chronotype and sleep duration on TN, thyroid cancer and thyroid dysfunction. MR, Mendelian randomization; SNP, single nucleotide polymorphism; TN, thyroid nodule.

FinnGen (<https://www.finnngen.fi/en>). The cohort was built by matching controls to the endpoint cases using year of birth and sex. The diagnosis of thyroid disorders according to the International Classification of Diseases, 10th Revision (ICD-

10). TN is defined as non-toxic single nodular goiter (ICD-10 E04.1), Thyroid cancer is classified under ICD-10 code E04.1. Hyperthyroidism (ICD-10 E05) is a hypermetabolic syndrome resulting from elevated serum thyroid hormone

levels due to various etiological factors. Hypothyroidism (ICD-10 E03) refers to abnormally low thyroid hormone levels, which may be congenital or acquired. For TNs, the analysis involved 351,920 individuals of European ancestry, with the case group consisting of 1,783 females and 420 males. The thyroid cancer cohort comprised 1,907 cases and 314,193 controls, with individuals diagnosed with any form of cancer excluded from the control group, and the mean age at the first event of thyroid cancer in the case group was 50.04 years. The GWAS on hypothyroidism included 26,342 cases and 59,827 controls from European populations, while the genetic association evaluations for hyperthyroidism were based on cohorts consisting of 4,142 cases and 213,693 controls.

All data used in this study were retrieved from publicly accessible databases, eliminating the need for patient consent or ethical approval.

Selection of IV

For the selection of suitable SNPs as IVs to ascertain the connection between exposure and outcome, distinct screening criteria were devised, customized to the nature of each exposure. Initially, to address the need for a high degree of correlation, distinct criteria were employed for SNP selection depending on the exposure variable. SNPs associated with insomnia symptoms, chronotype, and sleep duration were chosen based on a threshold of $P < 5e-08$ and a minor allele frequency > 0.01 . Subsequently, to ensure independence, the analysis utilized linkage disequilibrium thresholds set at $r^2 = 0.001$. Moreover, a consistent distance of 10000 kb was maintained for the exploration of linkage disequilibrium r^2 -values across all analytical stages. Applying the PhenoScanner database (<http://www.phenoscaner.medschl.cam.ac.uk/>), we examined the selected IVs to assess their associations with other phenotypes that could potentially impact the outcome. Potential confounders were meticulously addressed, and no confounding factors could be discerned in this analysis.

To address IV bias, we employed F-statistic values to screen out weak IVs. Those with an F-statistic less than 10 were excluded based on the formula: $F = R^2(n - k - 1)/k(1 - R^2)$, where R^2 denotes the exposure variance defined by the selected SNPs, n is the sample size, and k is the number of IVs (27).

Statistical analysis

The inverse variance weighted (IVW) method was

predominantly employed to evaluate the causal effect of exposure on outcome. We supplemented this with complementary analytical methods, including weighted median (WM) and MR-Egger. The IVW method estimates the causal effect of exposure on the outcome by aggregating ratio estimates for each SNP, effectively transforming MR estimates into a weighted regression of SNP-outcome effects against SNP-exposure effects (28). The WM method remains capable of delivering unbiased estimates, even if up to 50% of the information is based on invalid IVs (29). MR-Egger is a method utilized to estimate causal effects by analyzing the slope coefficient derived from Egger regression, while simultaneously detecting small study bias (30). Moreover, the MR-Egger intercept was employed to assess the existence of pleiotropy. Heterogeneity of the IVW was gauged by Cochran's Q test. When neither heterogeneity nor pleiotropy was detected, the results of IVW estimation were prioritized. In cases of heterogeneity without pleiotropy, preference was given to the results obtained from the WM method. Conversely, in the presence of pleiotropy, priority was given to the results derived from the MR-Egger method.

Furthermore, the MR-PRESSO test was employed to spot outliers contributing to heterogeneity (31). Any identified outliers were removed, and the MR analysis was rerun accordingly. To assess the robustness of the results, the leave-one-out method was utilized to systematically expunge individual SNPs that might have had an adverse impact on the study results, followed by a recalculation of the outcomes.

All analyses for the study were performed using R software (version 4.3.2). The MR analyses utilized the "Two-Sample-MR" (version 0.5.10) and "MR-PRESSO" packages.

Results

Sleep factors and thyroid cancer

After a comprehensive screening process, 39 SNPs associated with insomnia, 137 SNPs with chronotype, and 66 SNPs with sleep duration were identified as IVs to assess the causal impact of sleep factors on thyroid cancer risk. All selected IVs displayed F-statistic values exceeding 15, indicating robust instrument strength (table available at <https://cdn.amegroups.cn/static/public/10.21037gs-24-435-1.xlsx>).

The analysis exploring the impact of chronotype on

Table 1 MR estimates for the causal effect of sleep traits on thyroid cancer

Exposure	Outcome	NSNP	IVW		WM		MR-Egger		$P(I^2)$	$P_{(pleiotropy)}$	$P_{(global)}$
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P			
Insomnia	Thyroid cancer	39	0.341 (0.111, 1.043)	0.059	0.243 (0.050, 1.193)	0.08	0.097 (0.004, 2.660)	0.17	0.16	0.43	0.16
Chronotype	Thyroid cancer	137	0.632 (0.426, 0.937)	0.02	0.511 (0.278, 0.939)	0.03	0.636 (0.201, 2.004)	0.44	0.64	>0.99	0.63
Sleep duration	Thyroid cancer	66	1.750 (0.737, 4.152)	0.21	2.908 (0.911, 9.284)	0.07	10.698 (0.364, 314.428)	0.17	0.07	0.28	0.07

CI, confidence interval; IVW, inverse variance weighted; MR, Mendelian randomization; NSNP, number of single nucleotide polymorphism; OR, odds ratio; WM, weighted median.

thyroid cancer risk demonstrated a statistically significant reduction among individuals with a morning preference [IVW: odds ratio (OR) =0.632, 95% confidence interval (CI): 0.426–0.937, $P=0.02$; WM: OR =0.511, 95% CI: 0.278–0.939, $P=0.03$; MR-Egger: OR =0.636, 95% CI: 0.201–2.004, $P=0.44$]. Tests for heterogeneity and horizontal pleiotropy revealed no significant discrepancies, and the MR-PRESSO method did not identify any outliers. However, our analysis found no significant associations between genetic predispositions to insomnia or sleep duration and the risk of developing thyroid cancer. The results of these analyses are summarized in *Table 1* and illustrated in *Figure 2A-2C* and *Figures S1,S2*.

Sleep factors and TNs

For the assessment of the causal relationships between sleep factors and TNs, 30 SNPs for insomnia, 132 for chronotype, and 58 for sleep duration were utilized as IVs. The F-statistics for all IVs exceeded 15, suggesting a strong validity of the instruments (table available at <https://cdn.amegroups.cn/static/public/10.21037gs-24-435-1.xlsx>).

The results indicated that insomnia conditions may act as a risk factor in the development of TNs (IVW: OR =1.973, 95% CI: 1.152–3.377, $P=0.01$; WM: OR =3.374, 95% CI: 1.593–7.143, $P=0.001$; MR-Egger: OR =3.070, 95% CI: 0.192–49.224, $P=0.44$). There was no significant evidence suggesting that chronotype or sleep duration contributes as either protective or risk factors in the development of TNs. Sensitivity analyses, including Cochran's Q test, MR-Egger intercept, and MR-PRESSO, showed no significant heterogeneity, horizontal pleiotropy, or outliers (all P values >0.05). These findings are detailed in *Table 2* and visually represented through scatter plots, funnel plots, and leave-

one-out plots in *Figure 3A-3C* and *Figures S3,S4*.

Sleep factors and thyroid dysfunction

After controlling for confounding factors, we utilized 39 SNPs associated with insomnia, 136 SNPs linked to chronotype, and 57 SNPs related to sleep duration as IVs for hypothyroidism. Similarly, 39 SNPs related to insomnia, 128 SNPs associated with chronotype, and 62 SNPs associated with sleep duration served as IVs for hyperthyroidism (table available at <https://cdn.amegroups.cn/static/public/10.21037gs-24-435-1.xlsx>).

MR analyses found no causal associations between the examined sleep factors and either hyperthyroidism or hypothyroidism, as all P values exceeded 0.05 (*Table 3*). During the analysis, outliers were excluded to ensure the reliability of the results, which indicated no significant heterogeneity or genetic pleiotropy. These findings are further depicted in *Figures S5-S10*, including scatter plots, funnel plots, and leave-one-out plots.

Discussion

This study assessed the association between various sleep factors and thyroid disorders, highlighting a protective effect of a morning chronotype on the risk of thyroid cancer development and a potential positive causal relationship between insomnia symptoms and the development of TNs. Conversely, no causal association was identified between sleep factors and thyroid dysfunction.

Our study revealed a marked protective effect of morning preference against thyroid cancer. Prior researches have indicated that engaging in night shift work is linked to a heightened risk of developing cancers such as breast

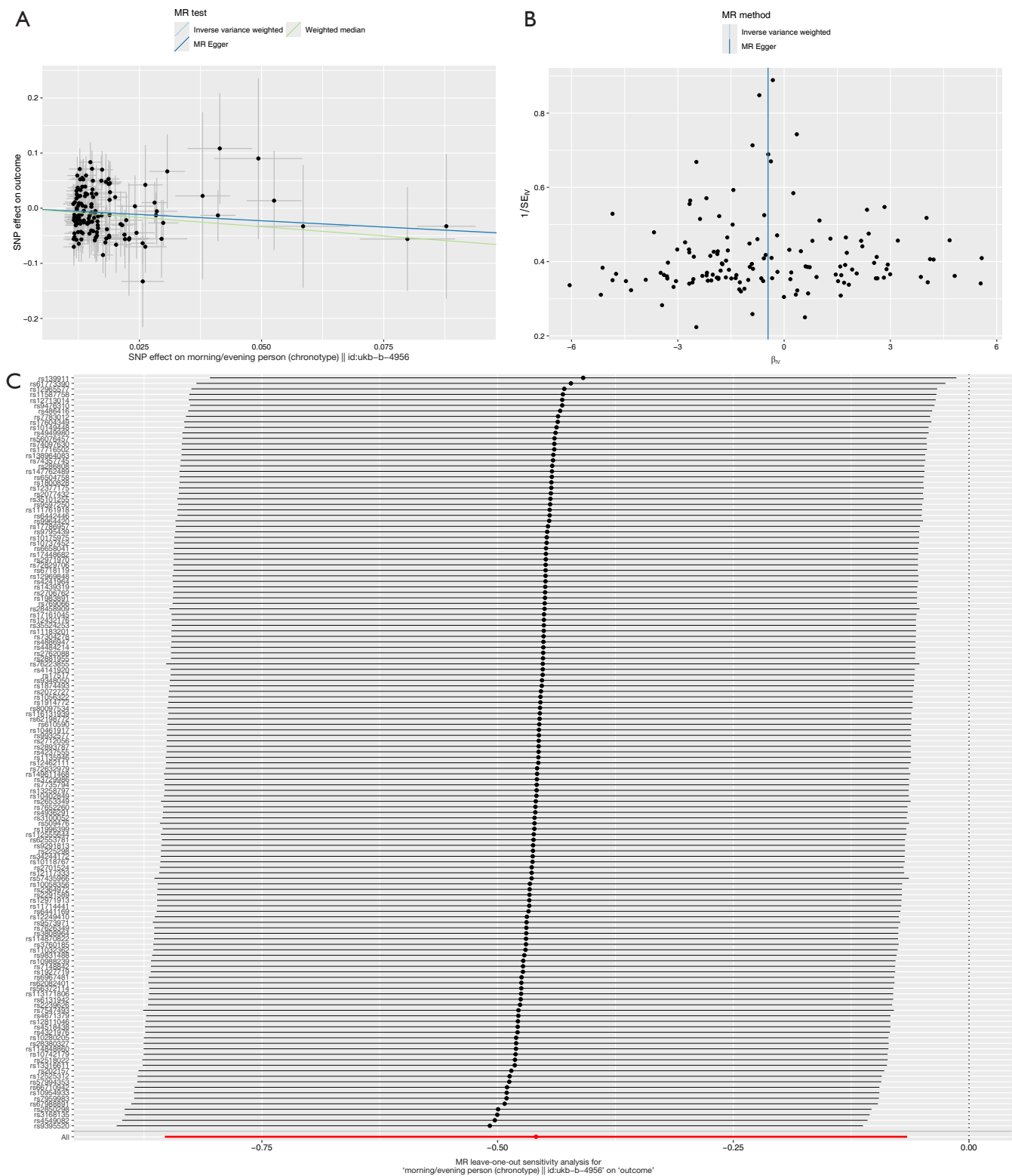


Figure 2 MR analysis of chronotype on thyroid cancer. (A) Scatter plot estimating causal effects of chronotype on thyroid cancer. (B) Funnel plot estimating causal effects of chronotype on thyroid cancer. (C) Leave-one-out analysis plot estimating causal effects of chronotype on thyroid cancer. IV, instrumental variable; MR, Mendelian randomization; SE, standard error; SNP, single nucleotide polymorphism.

Table 2 MR estimates for the causal effect of sleep strains on TNs

Exposure	Outcome	NSNP	IVW		WM		MR-Egger		$P(I^2)$	$P_{(pleiotropy)}$	$P_{(global)}$
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P			
Insomnia	TNs	30	1.973 (1.152, 3.377)	0.01	3.374 (1.593, 7.143)	0.001	3.070 (0.192, 49.224)	0.44	0.97	0.75	0.97
Chronotype	TNs	132	1.161 (0.957, 1.409)	0.13	1.139 (0.863, 1.502)	0.36	1.236 (0.686, 2.228)	0.48	0.07	0.83	0.07
Sleep duration	TNs	58	0.915 (0.610, 1.372)	0.67	1.397 (0.812, 2.403)	0.23	3.756 (0.820, 17.207)	0.09	0.06	0.07	0.06

CI, confidence interval; IVW, inverse variance weighted; MR, Mendelian randomization; NSNP, number of single nucleotide polymorphism; OR, odds ratio; TN, thyroid nodule; WM, weighted median.

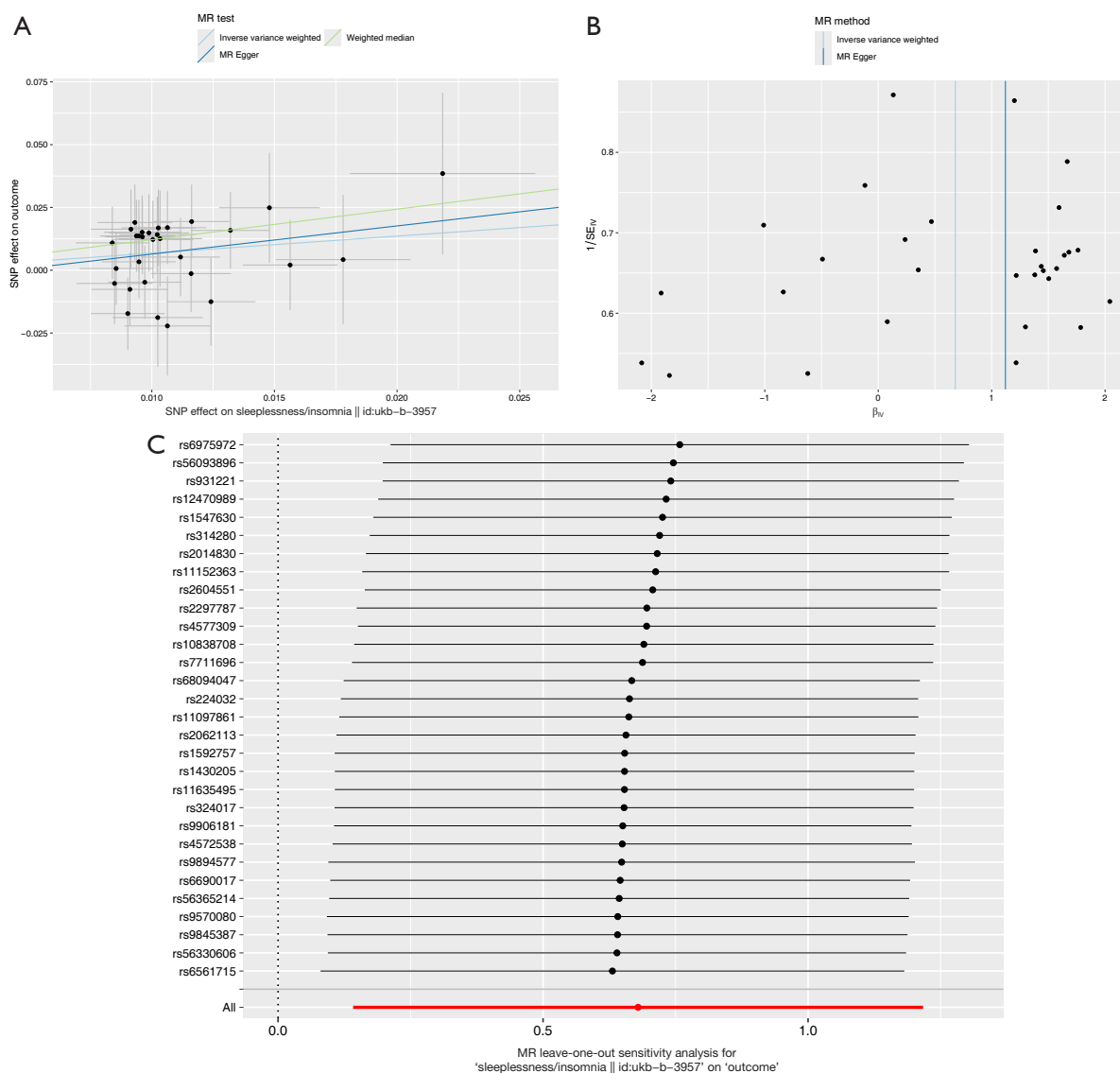


Figure 3 MR analysis of insomnia on TNs. (A) Scatter plot estimating causal effects of insomnia on TNs. (B) Funnel plot estimating causal effects of insomnia on TNs. (C) Leave-one-out analysis plot estimating causal effects of insomnia on TNs. IV, instrumental variable; MR, Mendelian randomization; SE, standard error; SNP, single nucleotide polymorphism; TN, thyroid nodule.

Table 3 MR estimates for the causal effect of sleep traits on thyroid dysfunction

Exposure	Outcome	NSNP	IVW		WM		MR-Egger		P(I ²)	P _(pleiotropy)	P _(global)
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P			
Insomnia	Hypothyroidism	39	1.072 (0.683, 1.681)	0.76	0.914 (0.490, 1.704)	0.78	0.547 (0.147, 2.046)	0.38	0.24	0.30	0.23
	Hyperthyroidism	39	0.954 (0.442, 2.057)	0.90	0.943 (0.324, 2.748)	0.92	0.143 (0.016, 1.283)	0.09	0.23	0.08	0.24
Chronotype	Hypothyroidism	136	1.047 (0.881, 1.245)	0.60	1.145 (0.886, 1.479)	0.30	1.249 (0.701, 2.228)	0.45	0.38	0.53	0.38
	Hyperthyroidism	128	1.189 (0.883, 1.600)	0.25	1.553 (0.998, 2.419)	0.051	1.056 (0.421, 2.646)	0.91	0.83	0.79	0.83
Sleep duration	Hypothyroidism	57	0.770 (0.549, 1.080)	0.13	0.805 (0.486, 1.334)	0.40	1.312 (0.358, 4.806)	0.68	0.67	0.41	0.67
	Hyperthyroidism	62	1.105 (0.635, 1.925)	0.72	1.223 (0.551, 2.716)	0.62	6.032 (0.685, 53.157)	0.11	0.54	0.12	0.53

CI, confidence interval; IVW, inverse variance weighted; MR, Mendelian randomization; NSNP, number of single nucleotide polymorphism; OR, odds ratio; WM, weighted median.

cancer (32), prostate cancer (33), and thyroid cancer (34). The discovery of a promotion effect of the evening chronotype on thyroid cancer risk supports the notion that individuals exposed to light during the night may encounter an augmented risk of cancer (35,36). Nighttime exposure to artificial light disrupts melatonin secretion, which possesses anti-growth and anti-tumor properties (37). Normally, thyroid-stimulating hormone (TSH) secretion diminishes during night rest, reducing TSH levels (38). Evening types, however, may have less suppressed TSH secretion, leading to higher TSH levels. Fluctuations in thyroid hormone levels can influence the expression of core clock genes and metabolic regulators in peripheral tissues (39,40), potentially altering circadian rhythms (41,42). Such disruptions may compromise central pacemaker functions, potentially promoting carcinogenesis. Yet, our findings did not link insomnia symptoms with thyroid cancer, contrasting with studies suggesting insomnia's role in increasing cancer risk (43), such as for cervical and lung cancers (44,45). This discrepancy might stem from our reliance on self-reported sleep issues, which could introduce bias. The role of insomnia in cancer risk might also be cumulative, requiring more precise methods for assessment.

Moreover, our results indicate that insomnia conditions may influence the development of TNs, corroborating previous clinical observations (46,47). Research has shown that insomnia can activate the hypothalamic-pituitary-adrenal/thyroid (HPA/HPT) axis, leading to TSH level

fluctuations (48), which might promote TN formation. Contrarily, Wang *et al.*'s MR study did not support this (12), likely due to insufficient differentiation between benign and malignant nodules and numerous confounders. In our analysis, we employed strict genotype quality controls and focused exclusively on participants with non-toxic single TNs. Furthermore, the apparent protective effect of morning preference seems to be specific to thyroid cancer, with no significant protective effect evident for the risk of benign TNs.

Our MR analyses did not detect any significant promoting or protective impact of sleep factors on thyroid dysfunction. Although biological circadian rhythms are thought to influence the HPT axis and thyroid function (38,49,50), our findings contradict previous observational studies linking sleep patterns with thyroid function (21,51). However, it does not conclusively establish the absence of a relationship between sleep and thyroid function. This could be due to an inadequate sample size or the inclusion of individuals with thyroid dysfunction caused by external factors such as medication or radiation therapy. Hence, additional mechanistic inquiries are essential to provide a more definitive understanding.

This study encompasses certain limitations. First, the mechanisms by which genetic markers influence risk factors are not fully elucidated. Second, while the MR-Egger analysis can detect and correct for cross-sectional confounding and pleiotropy, it yielded broad CIs and

non-significant P values. Nonetheless, adjustments made using this method suggest that our conclusions are robust, although undetected pleiotropic effects cannot be completely ruled out, indicating the need for further research. Third, the exclusive inclusion of individuals of European descent from the GWAS database calls for caution in generalizing these results to other ethnicities. Lastly, despite rigorous statistical methods employed in the MR analyses, the possibility remains that a genuine causal relationship between exposure and outcome may have been overlooked, such as sleep factors and thyroid dysfunction. Further refined research is necessary to explore these relationships more comprehensively.

Conclusions

In summary, our study demonstrates a potential protective effect of morning chronotype against thyroid cancer, as well as a positive causal relationship between genetic susceptibility to insomnia symptoms and the presence of TNs. These findings suggest that therapeutic management of sleep disorders could potentially reduce the risk of developing thyroid diseases, underscoring the importance of routine thyroid monitoring in individuals experiencing sleep disturbances. Although our study offers novel insights into the relationship between sleep factors and thyroid disorders, it is imperative to corroborate these findings through large-scale GWAS to reinforce the validity of our conclusions.

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None.

Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at <https://gs.amegroups.com/article/view/10.21037/gS-24-435/rc>

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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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