

Peer Review File

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Reviewer A

Comment 1: My major concern for this study is the inaccurate assessment and unstable exposure of sleep traits. For example, insomnia was not a clinical diagnosis of insomnia and the measurements of chronotype, and sleep duration are very crude.

Reply 1: We are indebted to the reviewers for their valuable suggestion that the term "insomnia" should be used to describe the condition in the manuscript. Simultaneously, we believe it is more appropriate to describe "sleep traits" as "sleep factors". We have accordingly revised the article to reflect this change. For chronotype and sleep duration, we utilized summary statistics from the UK Biobank, a large-scale prospective cohort comprising over 500,000 participants. The UK Biobank provides validated GWAS data, with individual chronotype and sleep duration assessed via self-report. While sleep-related factors were collected via questionnaires, the substantial sample size and Mendelian randomization analysis confirm the findings' clinical relevance. The demonstrated association with thyroid disorders merits further investigation through more meticulously designed studies to generate clinically significant conclusions.

Changes in the text: see Page 7, line 105-121; Page 8, line 122-124

Comment 2: In the abstract, the authors did not briefly analyze the underlying causes for the uncertain causal relationship and explain why MR is suitable to address this in the background, did not describe the assessment of exposure of sleep characteristics, diagnoses of thyroid illnesses, and the datasets used in the methods, describe the samples used and findings from the sensitivity analysis in the results, and have more detailed comments for the clinical implications of the findings in the conclusion.

Reply 2: In response to the reviewers' comments, we have revised the abstract accordingly. Given space constraints, comprehensive details regarding the exposure assessment methodologies for sleep-related factors and the diagnostic criteria for thyroid disorders have been systematically documented in the methods section. While the subjective assessment method utilizing questionnaires for sleep factors assessment may lack granularity, this dataset encompasses comprehensive anthropometric, health, lifestyle, and biological parameters, rendering the findings scientifically valuable. Further in-depth investigations could yield more significant conclusions, warranting continued research efforts in this domain.

Changes in the text: see Page 2-3, line 24-47; Page 8, line 118-136; Page 9, line 139-145

Comment 3: In the introduction of the main text, the authors need to extensively review findings from population-based studies on the sleep-thyroid conditions, list the inconsistent findings on their causal relationships, analyze the potential reasons, and explain why MR approach is suitable to address this problem. The authors need to analyze the measurements of sleep traits and thyroid conditions, which could explain the inconsistencies.

Reply 3: We thank the reviewers for their valuable comments. In the revised manuscript, the second paragraph of the background section now provides a comprehensive review of published studies examining the association between sleep factors and thyroid disorders. Additionally, the third paragraph elaborates on the rationale for selecting Mendelian randomization as the primary analytical approach. Previous studies on thyroid disorders and sleep factors have been mainly observational and may contain a large number of confounding factors, leading to inconsistencies in the conclusions of individual studies, so we used Mendelian randomisation to exclude the effects of these confounders and draw more reliable conclusions. Additional descriptions of both sleep characteristics and diagnostic criteria for thyroid disorders are provided in the Methods section.

Changes in the text: see Page 6-7, line 76-97; Page 8, line118-136; Page 9, line 139-145

Comment 4: In the methodology, I suggest the authors to describe the measurements of sleep traits and thyroid conditions in the two databases, and have comments on the accuracy of these measures.

Reply 4: Based on the reviewers' comments, we have modified the methods section of the manuscript. All study participants completed a comprehensive questionnaire assessing insomnia symptoms, sleep duration, and sleep chronotype (morningness or eveningness preference), with detailed methodological information provided in the Methods section. The diagnosis of thyroid disorders according to the International Classification of Diseases, 10th Revision (ICD-10). Thyroid nodule 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.

Changes in the text: see Page 8, line118-136; Page 9, line 139-145

Comment 5: Finally, please consider to cite several related papers: 1. Tang Y, Zhu B, Wen X, Chen Y. Development of a prediction model for the association between thyroid dysfunction and breast cancer. *Transl Cancer Res* 2024;13(6):2790-2798. doi: 10.21037/tcr-23-2164. 2. Cai C, Zhou S, Qu J, Zhou J. Immune-related thyroid dysfunction in patients with non-small cell lung cancer. *J Thorac Dis* 2024;16(1):253-263. doi: 10.21037/jtd-23-1092.

Reply 5: We have cited references in the manuscript in accordance with the reviewers' suggestions.

Changes in the text: see Page 5, line 64

Reviewer B

1. Please also define OR and CI in Abstract.

Reply: We have revised the abstract in accordance with the editor's comments.

2. Please define MR in the Highlight Box.

Reply: We have defined MR in the Highlight Box.

3. Ref.34 and Ref.36 are the same, please check and revise.

Reply: Thank the editor for their comments and we have accordingly revised Ref.36.

4. Please define ALL abbreviations in Table 1-3 footnotes separately.

Reply: We have defined all abbreviations in Table 1-3 footnotes separately.

5. And you should provide a **summarized legend** for Figure 2 and 3 separately.

Figure II XXX. ←

Scatter plot (A) estimating causal effects of chronotype on thyroid cancer ←

Figure II Funnel plot (B) estimating causal effects of chronotype on thyroid cancer ←

Reply: We have provided a summary title for Figure 2 and Figure 3 respectively.