Network Mendelian randomization study: exploring the causal pathway from insomnia to type 2 diabetes

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ABSTRACT

Introduction Insomnia is a novel pathogen for type 2 diabetes mellitus (T2DM). However, mechanisms linking insomnia and T2DM are poorly understood. In this study, we apply a network Mendelian randomization (MR) framework to determine the causal association between insomnia and T2DM and identify the potential mediators, including overweight (body mass index (BMI), waist-to-hip ratio, and body fat percentage) and glycometabolism (HbA1c, fasting blood glucose, and fasting blood insulin).

Research design and methods We use the MR framework to detect effect estimates of the insomnia–T2DM, insomnia–mediator, and mediator–T2DM associations. A mediator between insomnia and T2DM is established if MR studies in all 3 steps prove causal associations.

Results In the Inverse variance weighted method, the results show that insomnia will increase the T2DM risk (OR 1.142; 95% CI 1.072 to 1.216; p=0.000), without heterogeneity nor horizontal pleiotropy, strongly suggesting that genetically predicted insomnia has a causal association with T2DM. Besides, our MR analysis provides strong evidence that insomnia is causally associated with BMI and body fat percentage. There is also suggestive evidence of an association between insomnia and the waist-to-hip ratio. At the same time, our results indicate that insomnia is not causally associated with glycometabolism. Higher BMI, waist-to-hip ratio, and body fat percentage levels are strongly associated with increased risk of T2DM.

Conclusions Genetically predicted insomnia has a causal association with T2DM. Being overweight (especially BMI and body fat percentage) mediates the causal pathway from insomnia to T2DM.

INTRODUCTION

Insomnia is a significant public health problem affecting 10%–30% of the general population.1 It can be a symptom of many medical, neurological, and mental disorders. As a disorder, it incurs substantial healthcare and occupational costs.2 3 Type 2 diabetes mellitus (T2DM) is a chronic condition that describes a group of metabolic disorders characterized by insulin resistance.4 Nowadays, half a billion people are living with diabetes worldwide, and the number is projected to increase by 25% in 2030 and 51% in 2045.5 Evidence from observational studies indicates that patients with insomnia have a higher risk of T2DM.6 7 More importantly, recently, two specific Mendelian randomization (MR) studies support findings for an adverse effect of genetically predicted insomnia on T2DM risk,8 9 indicating that insomnia is a novel pathogen for T2DM. However, mechanisms linking insomnia and T2DM are poorly understood. The causality between insomnia and T2DM are unclear, and the underlying mechanism values further investigation.

MR uses genetic variants as instrumental variables (IVs) to infer whether a risk factor causally affects a clinical outcome.10 11 The MR technique diminishes confounding by environmental factors because alleles are randomly allocated when passed from parents to offspring at conception. It avoids reverse causation bias because the disease can not
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The causality between insomnia and T2DM and the potential pathway have not been thoroughly investigated. In this study, the causality between insomnia and T2DM is identified by a network MR framework. Besides, we also explore the potential mediators, including overweight (body mass index (BMI), waist-to-hip ratio, and body fat percentage) and glycometabolism (HbA1c, fasting blood glucose, and fasting blood insulin).

RESEARCH DESIGN AND METHODS

Summary of GWAS data
We apply the UK Biobank + 23andMe consortium for insomnia analysis. In UK Biobank, insomnia is defined by self-reported information collected via a questionnaire on a touchscreen device and while in 23andMe, an online questionnaire survey defines insomnia. They include 1,331,010 individuals (all European ancestry, 386,533 (109,402 patients and 277,131 non-patients) from UK Biobank and 944,477 (288,557 patients and 655,920 non-patients) from 23andMe). Besides, data from Xue A are used for T2DM, MRC-IEU consortium data are used for BMI, GIANT consortium data are used for waist-to-hip ratio, Neale consortium data are used for body fat percentage, data from Pan-UKB team are used for glycated hemoglobin (HbA1c), and data from Wojcik GL are used for fasting blood glucose and fasting blood insulin. More details of studies and datasets used for analysis are presented in table 1.

Data extraction
As we describe, we extract the following data for each single-nucleotide polymorphisms (SNPs) from GWAS of the following outcomes: the effect allele (EA), effect allele frequency (EAF), Beta value, SE, SNP, and p value. We select SNPs which are shown to be associated with the insomnia trait at the genome-wide significance (p<5×10⁻⁸). We also request the following metrics of SNP genotype quality from disease and risk factor studies: strong evidence of between-study heterogeneity in the SNP–trait association (p<0.001), Hardy-Weinberg disequilibrium (p<0.001), or imputation quality metric (info or r²)≤0.90. Characteristics of the SNPs associated with insomnia and their associations with T2DM are shown in online supplemental table 1.

Two-sample MR and causality analysis
MR can be used to assess the causal effect of an exposure on an outcome using genetic variants as IVs. We explore the associations in the following scenarios.

1. Causality: The conventional MR approach (Inverse variance weighted, IVW) method, MR Egger method, Weighted median method, Simple mode method, and Weighted mode are used. 1.1 Causality between genetically determined insomnia and T2DM. 1.2 Causality between genetically determined insomnia and potential mediators including overweight (BMI, waist-to-hip ratio, and body fat percentage) and glycometabolism (HbA1c, fasting blood glucose, and fasting blood insulin). 1.3 Causality between genetically determined mediators and T2DM. (2) Heterogeneity: To solve the heterogeneity problem, we follow the previous protocol to determine the final tally of SNPs for inclusion in genetic instruments. (3) Horizontal pleiotropy: We assess it by MR-Egger intercept. (4) Leave-one-out analysis: It is applied to conduct the sensitivity. (5) Funnel plots: A tool

Table 1 Details of studies and datasets used for analysis

| Exposure/Outcomes | Participants | Sample size | PubMed ID/ MR base ID | First author | Consortium | Year | Units |
|-------------------|--------------|-------------|------------------------|--------------|------------|------|-------|
| Insomnia          | 651,923 European ancestry males, 679,087 European ancestry females | 1,331,010 | 30,804,565 | Jansen PR | UK Biobank+23andMe | 2019 | NA |
| T2DM European     | 62,892       | 30,054,458 | Xue A                  | NA           | 2018       | log OR |
| BMI European      | 454,884      | ukb-b-2303 | Ben Elsworth           | MRC-IEU     | 2018       | SD (kg/m²) |
| Waist-to-hip ratio| Mixed        | 124,591    | 25,673,412            | Shungin D    | GIANT      | 2015 | SD (%) |
| Body fat percentage| European, males and females | 331,117 | ukb-a-264 | Neale       | Neale Lab | 2017 | SD (%) |
| HbA1c             | African American or Afro-Caribbean, males and females | 5290 | ukb-e-30750_AFR | Pan-UKB team | NA | 2020 | % |
| Fasting blood glucose| Hispanic or Latin American | 13,556 | 31,217,584 | Wojcik GL | NA | 2019 | NA |
| Fasting blood insulin| Hispanic or Latin American | 12,687 | 31,217,584 | Wojcik GL | NA | 2019 | NA |

Details of studies and datasets used for analysis. BMI, body mass index; NA, not available; T2DM, type 2 diabetes mellitus.
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used in meta-analysis is the funnel plot in which the estimate for a particular SNP is plotted against its precision.21 Asymmetry in the funnel plot may be indicative of violations of the assumption through horizontal pleiotropy.

The ‘causal’ relationship is considered established if the observed association passes the IVW method without horizontal pleiotropy.

**Network MR analysis for ‘insomnia–mediator–T2DM’**

We apply the MR framework with two-sample MR and network MR design to detect the causality of insomnia–T2DM, insomnia–mediator, and mediator–T2DM.22 23 There are three two-sample MR tests in a network MR analysis: (1) the causality between genetically determined insomnia and T2DM; (2) the causality between genetically determined insomnia and the potential mediators; (3) the causality between the possible mediators on T2DM.

A mediator between insomnia and T2DM is established if MR studies in all three steps prove causal associations.

**Statistical analysis**

All analyses were performed using the Two Sample MR platform19 (http://app.mrbase.org). The F-statistic is estimated to examine the strength of the genetic instrument for each exposure, and an F-statistic above 10 is considered a sufficiently strong instrument. All the F-statistic in this MR study is above 10. We follow previous researchers’ statistical analysis way.24 The p value<0.007 (where α=0.05/7 outcomes) is considered strong causal association evidence. Also, p value between 0.05 and 0.007 is regarded as suggestive evidence of association.

**RESULTS**

**Causality between genetically determined insomnia and T2DM**

We use the UK Biobank+23 and Me consortia for insomnia to explore the causal associations between genetically determined insomnia and T2DM. In the IVW method, the causal estimate using 127 SNPs as IVs shows that insomnia will increase the risk of T2DM (OR 1.142; 95% CI 1.072 to 1.216; p=0.000) (table 2 and figure 1A). Results are consistent in weighted median method (OR 1.187; 95% CI 1.122 to 1.256; p=0.000), simple mode method (OR 1.244; 95% CI 1.044 to 1.482; p=0.016), and weighted mode method (OR 1.221; 95% CI 1.049 to 1.422; p=0.011) (table 2). The intercept of MR-Egger regression for these 127 SNPs is not statistically significant (p=0.859), suggesting no directional pleiotropy. The leave-one-out analysis (figure 1C) and funnel plot (figure 1D) indicate no SNPs exhibit horizontal pleiotropy.

| Trait               | Method                | nSNP | OR  | 95% CI          | P value | MR-Egger intercept P |
|---------------------|-----------------------|------|-----|-----------------|---------|-----------------------|
| Insomnia–T2DM       | MR Egger              | 127  | 1.155 | 0.852 to 1.459 | 0.429   | 0.859                 |
| Insomnia–T2DM       | Weighted median       | 127  | 1.187 | 1.122 to 1.256 | 0.000   |                       |
| Insomnia–T2DM       | **Inverse variance weighted** | 127  | 1.142 | 1.072 to 1.216 | **0.000** |                       |
| Insomnia–T2DM       | Simple mode           | 127  | 1.244 | 1.044 to 1.482 | 0.016   |                       |
| Insomnia–T2DM       | Weighted mode         | 127  | 1.221 | 1.049 to 1.422 | 0.011   |                       |

The genetically predicted insomnia has a causal association with T2DM (in bold).

MR, Mendelian randomization; SNP, single-nucleotide polymorphism; T2DM, type 2 diabetes mellitus.
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To sum up, our MR analysis provides strong evidence that genetically predicted insomnia has a causal association with T2DM.

Causality between genetically determined insomnia and potential mediators

Table 3 show the causal estimates between genetically determined insomnia and potential mediators, including overweight (BMI, waist-to-hip ratio, and body fat percentage) and glycometabolism (HbA1c, fasting blood glucose, and fasting blood insulin). The MR analysis provides strong evidence that insomnia is causally associated with BMI (Beta, 0.075; SE, 0.014; p=0.000) and body fat percentage (Beta, 0.064; SE, 0.011; p=0.000). There is also suggestive evidence of an association between insomnia and waist-to-hip ratio (Beta, 0.031; SE, 0.012; p=0.011). At the same time, our results indicate that insomnia is not causally associated with glycometabolism (HbA1c, fasting blood glucose, and fasting blood insulin, all p>0.05).

To sum up, being overweight (especially BMI and body fat percentage) but not glycometabolism may mediate the causal pathway from insomnia to T2DM.

Causality between genetically determined mediators and T2DM

We further evaluate whether overweight (BMI, waist-to-hip ratio, and body fat percentage) is associated with T2DM using MR analysis. We use the IVs of 332 SNPs, 20 SNPs, and 195 SNPs associated with BMI, waist-to-hip ratio, and body fat percentage. As we expected, higher BMI, waist-to-hip ratio, and body fat percentage levels are

| Trait                    | Method                | nSNP | Beta    | SE     | P value | MR-Egger intercept P |
|--------------------------|-----------------------|------|---------|--------|---------|----------------------|
| BMI                      | MR Egger              | 150  | 0.030   | 0.053  | 0.570   | 0.379                |
|                          | Weighted median       | 150  | 0.061   | 0.008  | 0.000   |                      |
|                          | **Inverse variance weighted** | 150  | **0.075** | **0.014** | **0.000** |                      |
|                          | Simple mode           | 150  | 0.067   | 0.022  | 0.002   |                      |
|                          | Weighted mode         | 150  | 0.057   | 0.016  | 0.001   |                      |
| Waist-to-hip ratio       | MR Egger              | 120  | −0.026  | 0.053  | 0.618   | 0.270                |
|                          | Weighted median       | 120  | 0.038   | 0.017  | 0.026   |                      |
|                          | **Inverse variance weighted** | 120  | **0.031** | **0.012** | **0.011** |                      |
|                          | Simple mode           | 120  | 0.080   | 0.047  | 0.090   |                      |
|                          | Weighted mode         | 120  | 0.056   | 0.045  | 0.215   |                      |
| Body fat percentage      | MR Egger              | 149  | 0.006   | 0.039  | 0.880   | 0.123                |
|                          | Weighted median       | 149  | 0.055   | 0.008  | 0.000   |                      |
|                          | **Inverse variance weighted** | 149  | **0.064** | **0.011** | **0.000** |                      |
|                          | Simple mode           | 149  | 0.070   | 0.021  | 0.001   |                      |
|                          | Weighted mode         | 149  | 0.061   | 0.019  | 0.002   |                      |
| HbA1c                    | MR Egger              | 117  | 0.036   | 0.263  | 0.893   | 0.949                |
|                          | Weighted median       | 117  | 0.048   | 0.088  | 0.585   |                      |
|                          | **Inverse variance weighted** | 117  | **0.019** | **0.061** | **0.751** |                      |
|                          | Simple mode           | 117  | −0.186  | 0.246  | 0.450   |                      |
|                          | Weighted mode         | 117  | −0.039  | 0.188  | 0.836   |                      |
| Fasting blood glucose    | MR Egger              | 139  | −0.070  | 0.082  | 0.394   | 0.476                |
|                          | Weighted median       | 139  | −0.014  | 0.030  | 0.638   |                      |
|                          | **Inverse variance weighted** | 139  | **0.014** | **0.021** | **0.513** |                      |
|                          | Simple mode           | 139  | −0.009  | 0.086  | 0.912   |                      |
|                          | Weighted mode         | 139  | 0.005   | 0.082  | 0.951   |                      |
| Fasting blood insulin    | MR Egger              | 139  | −0.109  | 0.098  | 0.268   | 0.239                |
|                          | Weighted median       | 139  | −0.013  | 0.035  | 0.702   |                      |
|                          | **Inverse variance weighted** | 139  | **0.003** | **0.025** | **0.908** |                      |
|                          | Simple mode           | 139  | −0.096  | 0.110  | 0.385   |                      |
|                          | Weighted mode         | 139  | −0.066  | 0.097  | 0.495   |                      |

Insomnia is causally associated with BMI and body fat percentage (in bold).
BMI, body mass index; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.
Cardiovascular and metabolic risk strongly associated with increased risk of T2DM (BMI: OR 2.932, 95% CI 2.706 to 3.176, p=0.000; waist-to-hip ratio: OR 2.271, 95% CI 1.651 to 3.123, p=0.000; body fat percentage: OR 2.515, 95% CI 2.026 to 3.121, p=0.000). The intercept of MR-Egger regression for these SNPs is not statistically significant (BMI: p=0.451; waist-to-hip ratio: p=0.066; body fat percentage: p=0.722), suggesting no directional pleiotropy (table 4).

To sum up, overweight serves as a mediator in the causal pathway from insomnia to T2DM. A network MR diagram of a summary from insomnia to T2DM is shown in figure 2.

**DISCUSSION**

In this study, we investigate the causality between genetically determined insomnia and T2DM. Mechanically, we further explore the potential pathways mediating effects from insomnia to T2DM, emphasizing overweight (BMI, waist-to-hip ratio, and body fat percentage) and glycometabolism (HbA1c, fasting blood glucose, and fasting blood insulin). Our MR analysis provides strong evidence that genetically predicted insomnia has a causal association with T2DM. Being overweight (especially BMI and body fat percentage) mediates the causal pathway from insomnia to T2DM. As we know, we are the first to address possible biological mechanisms in the causal pathway from insomnia to T2DM by a network MR study.

**Epidemiological evidence of the link between insomnia and T2DM**

Much previous epidemiological evidence has indicated the link between insomnia and T2DM. Both poor sleep habits and sleep disorders are highly prevalent among adults with T2DM. In observational studies, short sleep duration, obstructive sleep apnea, shift work, and insomnia are associated with a higher risk of incident T2DM and may predict worse outcomes in those with existing diabetes. A cohort study consists of 81,233 persons with pre-diabetes, 24,146 (29.7%) of whom have insomnia at some point during the 4.3-year average observation period. After adjusting for traditional risk factors, patients with insomnia were 28% more likely to develop T2DM than those without insomnia. As in northern China, insomnia is associated with T2DM independently. The aforementioned evidence suggests that insomnia may act as a novel risk factor for T2DM.

**Comparison with previous MR studies**

MR analysis provides a robust and cost-efficient approach to demonstrate temporal relationships and causal pathways between sleep and obesity through genetics. MR exploits the fact that genes are randomly assigned from parents to offspring, which are unlikely to be affected by confounding factors, and that genotypes are fixed at zygote formation and cannot be changed. Recently, a wide-angled MR study (34 exposures (19 risk factors and

| Trait | Method | nSNP | OR   | 95% CI    | P value | MR-Egger intercept P |
|-------|--------|------|------|-----------|---------|----------------------|
| BMI–T2DM | MR Egger | 332  | 3.171 | 2.546 to 3.948 | 0.000  | 0.451 |
|        | Weighted median | 332  | 2.932 | 2.652 to 3.241 | 0.000  |         |
|        | Inverse variance weighted | 332  | 2.932 | 2.706 to 3.176 | 0.000  |         |
|        | Simple mode | 332  | 2.996 | 2.213 to 4.055 | 0.000  |         |
|        | Weighted mode | 332  | 2.996 | 2.303 to 3.896 | 0.000  |         |
| Waist-to-hip ratio–T2DM | MR Egger | 20   | 5.062 | 0.948 to 27.029 | 0.074  | 0.066 |
|        | Weighted median | 20   | 2.106 | 1.693 to 2.619 | 0.000  |         |
|        | Inverse variance weighted | 20   | 2.271 | 1.651 to 3.123 | 0.000  |         |
|        | Simple mode | 20   | 2.343 | 1.466 to 3.746 | 0.002  |         |
|        | Weighted mode | 20   | 2.384 | 1.581 to 3.595 | 0.001  |         |
| Body fat percentage–T2DM | MR Egger | 195  | 2.899 | 1.287 to 6.531 | 0.011  | 0.722 |
|        | Weighted median | 195  | 3.200 | 2.758 to 3.713 | 0.000  |         |
|        | Inverse variance weighted | 195  | 2.515 | 2.026 to 3.121 | 0.000  |         |
|        | Simple mode | 195  | 3.398 | 2.132 to 5.415 | 0.000  |         |
|        | Weighted mode | 195  | 3.398 | 2.128 to 5.424 | 0.000  |         |

Higher BMI, waist-to-hip ratio and body fat percentage levels are causally associated with increased risk of T2DM (in bold).

BMI, body mass index; MR, Mendelian randomization; SNP, single-nucleotide polymorphism; T2DM, type 2 diabetes mellitus.
Potential mediators from insomnia to T2DM

There is no comprehensive description of the underlying mechanisms from insomnia to T2DM. As for the possible mediators from insomnia to T2DM, overweight (BMI, waist-to-hip ratio, and body fat percentage) and glycometabolism (HbA1c, fasting blood glucose, and fasting blood insulin) are chosen for our MR analysis. A previous study has demonstrated potential causal associations of genetic liability to insulin with increased risk of a broad range of cardiovascular diseases, including atrial fibrillation, heart failure, coronary artery disease, and so on.12 24 Most of the aforementioned cardiovascular diseases are also well-established risk factors for T2MD. In addition, there is burgeoning evidence of a causal association between obesity (including BMI, waist-to-hip ratio, body fat distribution, and abdominal adiposity) and increased risk of T2DM.29–32 Previous MR studies suggest robust causal effects of obesity (including BMI, waist-to-hip ratio, and body fat percentage) on higher BMI,33 and insomnia on a higher waist-to-hip ratio.5 Our analysis also provides strong evidence that insomnia is causally associated with BMI and body fat percentage. There is also suggestive evidence of an association between insomnia and the waist-to-hip ratio. So, our findings (weaker estimates) are directionally similar to the previous MR studies. We analyze the inconsistent increase in the T2DM risk ratio due to the different consortia we have chosen for analysis. Since insomnia is proved to be a modifiable risk factor for T2DM, management against insomnia among the population is recommended to prevent T2DM.

LIMITATION

First, in the insomnia dataset, only European descent participants are included. This population confinement may limit the generalizability of our findings to other populations in the whole world. Second, the ascertainment of insomnia is far from perfect. In UK Biobank, insomnia is defined by self-reported information collected via a questionnaire on a touchscreen device and while in 23andMe, an online questionnaire survey defines insomnia. As a result, the ascertainment of insomnia is entirely subjective. Last but not least, besides insomnia, the insomnia-related SNPs may affect T2DM through other causal pathways, such as daytime sleepiness, too long/too short sleep duration, and depression.

CONCLUSIONS

Genetically predicted insomnia has a causal association with T2DM. Being overweight mediates the causal pathway from insomnia to T2DM.

For patients with insomnia, to prevent overweight problems and the following T2DM, sleep intervention should be carried out in advance to improve sleep quality. Moreover, strong weight control management and routine screening for T2DM are also recommended for those who have insomnia. Strategies to reduce insomnia, especially for the overweight population, are cornerstones in preventing T2DM in public. The complex relationship between insomnia, obesity, and diabetes should be further explored in clinical studies in the future.
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