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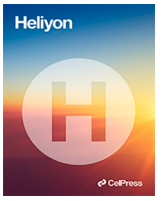

Research article

Establishing causal relationships between insomnia and gestational diabetes mellitus using Mendelian randomization

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a common condition observed globally, and previous studies have suggested a link between GDM and insomnia. The objective of this study was to elucidate the causative relationship between insomnia and GDM, and to investigate the influence of factors related to insomnia on GDM.

Methods: We performed bidirectional Mendelian randomization (MR) analyses using single nucleotide polymorphisms (SNPs) as genetic instruments for exposure and mediators, thereby minimizing bias due to confounding and reverse causation. The Cochran Q test was utilized for heterogeneity analysis, MR-Egger regression for pleiotropy assessment, and the leave-one-out method for evaluating the robustness of the results. Additionally, we determined the causal relationships between GDM and other factors such as coffee consumption, alcohol intake, and household income.

Results: Insomnia was positively associated with GDM, as indicated by 39 SNPs (OR = 1.27, 95 % CI 1.12–1.439, P-value = 0.008). Conversely, the MR analysis did not reveal any causal relationship between GDM and insomnia (OR = 1.032, 95 % CI 0.994–1.071, P-value = 0.99). Additionally, no causal relationship was observed between coffee consumption, alcohol intake, household income, and GDM (all P-values >0.05).

Conclusion: Our study indicates that insomnia elevates the risk of GDM, thereby establishing a causal link with GDM, independent of coffee consumption, alcohol intake, and household income.

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1. Introduction

Gestational diabetes mellitus (GDM) is characterized by hyperglycemia that develops during pregnancy and typically resolves after childbirth [1]. In recent years, the incidence of GDM has been escalating. According to the International Diabetes Federation (IDF) data in 2021, the global prevalence of abnormal glucose levels during pregnancy is 16.7 %, of which 80.7 % are diagnosed as GDM [2]. Consequently, GDM has morphed into a global public health concern, rendering the health status of pregnant women a matter of utmost importance.

Insomnia is a clinical sleep disorder characterized by persistent difficulty in initiating sleep, maintaining sleep, or experiencing early-morning awakenings from which one cannot return to sleep [3]. Individuals may present with one or more of these disturbances. To qualify for a diagnosis of insomnia disorder, these nighttime sleep challenges must be present for at least three nights per week and persist for a minimum duration of three months. Moreover, insomnia is not merely a nocturnal problem; it is defined by its significant daytime sequelae, which impair one's cognitive, emotional, and functional capacity [4,5]. Insomnia is prevalent, affecting up to 10 % of adults, and contributes significantly to the risk and severity of cardiovascular, metabolic, mood, and neurodegenerative disorders [4, 6]. Suzuki et al. [7] reported that 88.8 % of healthy pregnant women experienced alterations in sleep structure during pregnancy, primarily characterized by an increase in insomnia and a decrease in daytime alertness. In a systematic review [8], overall sleep disturbance was found to be significantly associated with GDM. A meta-analysis [9] found that 38.2 % of pregnant women experience poor sleep quality during pregnancy, and inadequate sleep during this period is associated with a range of complications, including GDM, preterm birth, cesarean section, hypertension, and prolonged labor, thereby increasing the likelihood of adverse pregnancy outcomes. However, the causal relationship between insomnia and GDM remains ambiguous, necessitating more supportive evidence.

MR uses genetic variations closely associated with exposure as instrumental variables (IV) to explore the causal relationship between exposure and outcome [10]. Because gametes follow Mendel's laws of inheritance during their formation, the random allocation of alleles at conception eliminates confounding bias and maintains the temporality of the causal relationship [11]. Utilizing SNPs published in the open-access genome-wide association study (GWAS) database as genetic instrumental variables, we applied a two-sample bidirectional MR method to identify the causal association between insomnia and GDM. This study aims to comprehend the risk factors of GDM and furnish new insights into its prevention.

2. Methods

2.1. Study design

In this study, a bidirectional MR approach was used to assess the causal relationship between insomnia and GDM, as detailed in the flowchart depicted in Fig. 1. Initially, insomnia was treated as the "exposure", and a pregnancy diagnosis of GDM was treated as the "outcome". Instrumental variables for MR analysis were selected, and Cochran's Q analysis was employed to assess heterogeneity.

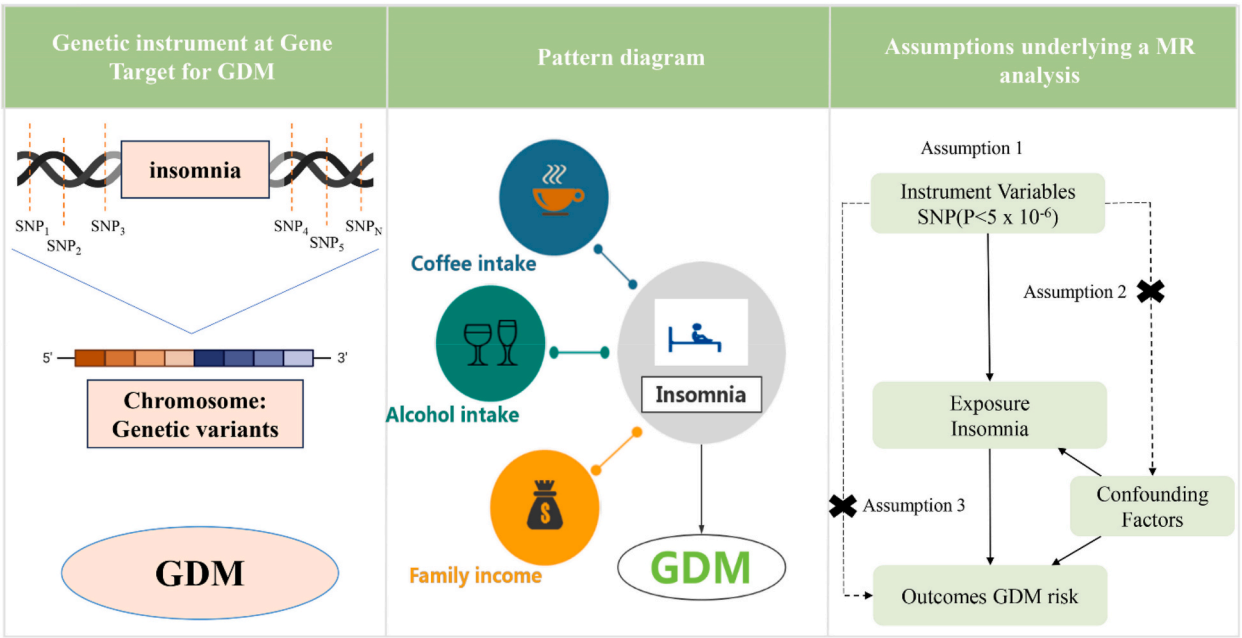

Fig. 1. Mendelian randomization model of insomnia and risk of gestational diabetes. The design is under the assumption that the genetic variants are associated with insomnia, but not with confounders, and the genetic variants influence gestational diabetes only through insomnia. SNP indicates single nucleotide polymorphism.

Subsequently, a sensitivity analysis was conducted to validate the reliability of the causal results. Finally, a reverse MR was performed, treating GDM as the "exposure" and insomnia as the "outcome".

2.2. Data sources

Genome-wide data related to insomnia were obtained from the website https://gwas.mrcieu.ac.uk. The insomnia data (finn-b-G6_SLEEPAPNO) were sourced from publicly published GWAS statistical result data in 2021, which included 16,761 cases, 201,194 controls, and 16,380,465 SNPs.

Data on genetic variants associated with GDM were obtained from the FinnGen consortium, an ongoing Finnish national study started in 2017. The dataset of GDM with the GWAS-ID of finn-b-O15_PREG_DM was downloaded from FinnGen, which included 6033 GDM cases in 123,000 women, and the dataset consisted entirely of Europeans [12].

Additionally, summarized data on coffee consumption, alcohol intake, and family income were obtained from the GWAS database, available at https://gwas.mrcieu.ac.uk. The dataset for coffee consumption was publicly available from the MRCIEU Open GWAS data and MR-Base with the GWAS-ID ukb-b-9508. This dataset was generated from the GWAS pipeline using Phesant-derived variables from the UK Biobank. For the alcohol intake GWAS, the dataset included 83,626 cases and 7,914,362 controls, obtained from the Within Family GWAS consortium. The family income GWAS dataset (ID: ukb-b-7408) comprised 397,745 cases and 9,851,867 controls from the MRC-IEU, and was also generated using Phesant-derived variables from the UK Biobank. All the datasets were derived from European populations (Table 1).

2.3. Selection of instrumental variables

Genes associated with insomnia were meticulously selected from the GWAS database through a rigorous quality control process. When using genetic variations SNPs as IVs for MR analysis, the IVs must satisfy three assumptions [13]: (1) The selected IV must exhibit a strong association with the exposure; (2) The selected IV must not be associated with potential confounders; (3) The selected IV can only affect the outcome through the exposure, and not through other pathways. The random-effects inverse-variance weighted (IVW) method was performed to assess the causal relationship between the two variables, supplemented by MR-Egger regression, weighted median, weighted mode, and simple mode to improve the accuracy and stability of the results [14].

To avoid analysis bias induced by linkage disequilibrium (LD) between SNPs, the selection criteria were as follows: (1) $P < 5 \times 10^{-6}$; (2) The physical distance M between two genes >10,000 kb; (3) The LD r^2 threshold between genes <0.001, F value > 10. Initially, SNPs associated with insomnia were extracted ($P < 5e^{-8}$). To garner more instrumental variables, the threshold was relaxed, setting the maximum threshold at 5e^-6, a method reported in the previous study [15]. Ultimately, mutually independent SNPs significantly associated with insomnia were obtained as the final instrumental variables [11].

To further comprehend whether the selected genetic variations were related to potential confounding factors and outcomes, several factors related to insomnia were examined, including coffee intake, alcohol intake, and family income. The causal relationship between these variables and GDM was examined by MR.

2.4. Statistical analysis

In this study, IVW was used as the primary outcome, while MR-Egger and weighted median methods were employed to enhance IVW, although they are less efficient (wider CI), they can provide more robust results in a broader range of scenarios. Heterogeneity testing is employed to examine the differences between individual IVs; if $P > 0.05$, it indicates no heterogeneity. For the IVW method, the P-value of the Cochran Q test was used to assess heterogeneity; if $P < 0.05$, it indicates the presence of heterogeneity; otherwise, $P > 0.05$ indicates no heterogeneity. The pleiotropy test [16] was utilized to validate the reliability of MR analysis results. The intercept term of the MR-Egger method is commonly employed; an intercept $P > 0.05$ indicates no horizontal pleiotropy, and if pleiotropy exists, it suggests that the MR analysis results are not reliable. The "leave-one-out" approach [17] was conducted to test sensitivity, which involves assessing the results after sequentially excluding individual SNPs to determine if there are any outliers and to observe the stability of the results after excluding each SNP. All analyses were performed using the TwoSampleMR package and RStudio version 2023.06.1524. Statistical significance was set at $P < 0.05$.

Table 1
Details of the GWASs included in the Mendelian randomization.

Phenotype	Participants	Web Source
insomnia	217,955	https://gwas.mrcieu.ac.uk/datasets/finn-b-G6_SLEEPAPNO/
gestational diabetes	123,000	https://risteys.finregistry.fi/endpoints/O15_PREG_DM
coffee intake	64,949	https://gwas.mrcieu.ac.uk/datasets/datasets/ukb-b-9508
alcohol intake	83,626	https://gwas.mrcieu.ac.uk/datasets/datasets/ieu-b-4834
family income	397,751	https://gwas.mrcieu.ac.uk/datasets/datasets/ukb-b-7408

3. Results

3.1. Effect of insomnia on gestational diabetes mellitus

In the MR analysis investigating the impact of insomnia on the risk of GDM (Fig. 2), the odds ratios (ORs) with 95 % confidence intervals (CIs) were obtained using different MR estimation methods. Specifically, the IVW method yielded an OR of 1.270 (95%CI 1.120–1.439, P = 0.0002), indicating a statistically significant association suggesting that insomnia may increase the risk of GDM. The Weighted Median Estimator (WME) method also supported this association with an OR of 1.268 (95 % CI 1.068–1.506, P = 0.007). However, the MR Egger method, which provides adjustment for potential pleiotropic effects, showed an OR of 1.008 (95 % CI 0.693–1.466, P = 0.966), indicating no statistically significant association.

Conversely, the bidirectional MR analysis exploring the potential effect of GDM on insomnia risk presented ORs that were not statistically significant across the estimation methods: IVW method (OR = 1.032, 95 % CI 0.994–1.071, P = 0.099), MR Egger method (OR = 1.056, 95 % CI 0.975–1.144, P = 0.193), and WME method (OR = 1.045, 95 % CI 0.991–1.101, P = 0.105). This suggests a lack of evidence for a reciprocal causal relationship between GDM and insomnia based on the genetic instruments used in this study.

3.2. Causal relationship between coffee consumption, alcohol intake, family income, and GDM

In assessing the causal relationships between coffee consumption, alcohol intake, family income, and GDM via MR, we utilized genetic instruments associated with these exposures based on the premise that they also influence insomnia, a known risk factor for GDM. The MR analyses, grounded in the same SNP selection criteria established for insomnia, were conducted to elucidate the impact of these variables on GDM risk.

The two-sample MR approach revealed no statistically significant causal associations between these lifestyle and socioeconomic factors and GDM. Specifically, the analysis yielded an OR of 1.012 (95 % CI: 0.944–1.084, P = 0.746) for alcohol intake, suggesting that genetic predisposition to higher alcohol consumption does not significantly alter the risk of GDM. Similarly, the OR for coffee consumption was 0.946 (95 % CI 0.503–1.342, P = 0.599), indicating that genetic variants associated with coffee intake do not confer

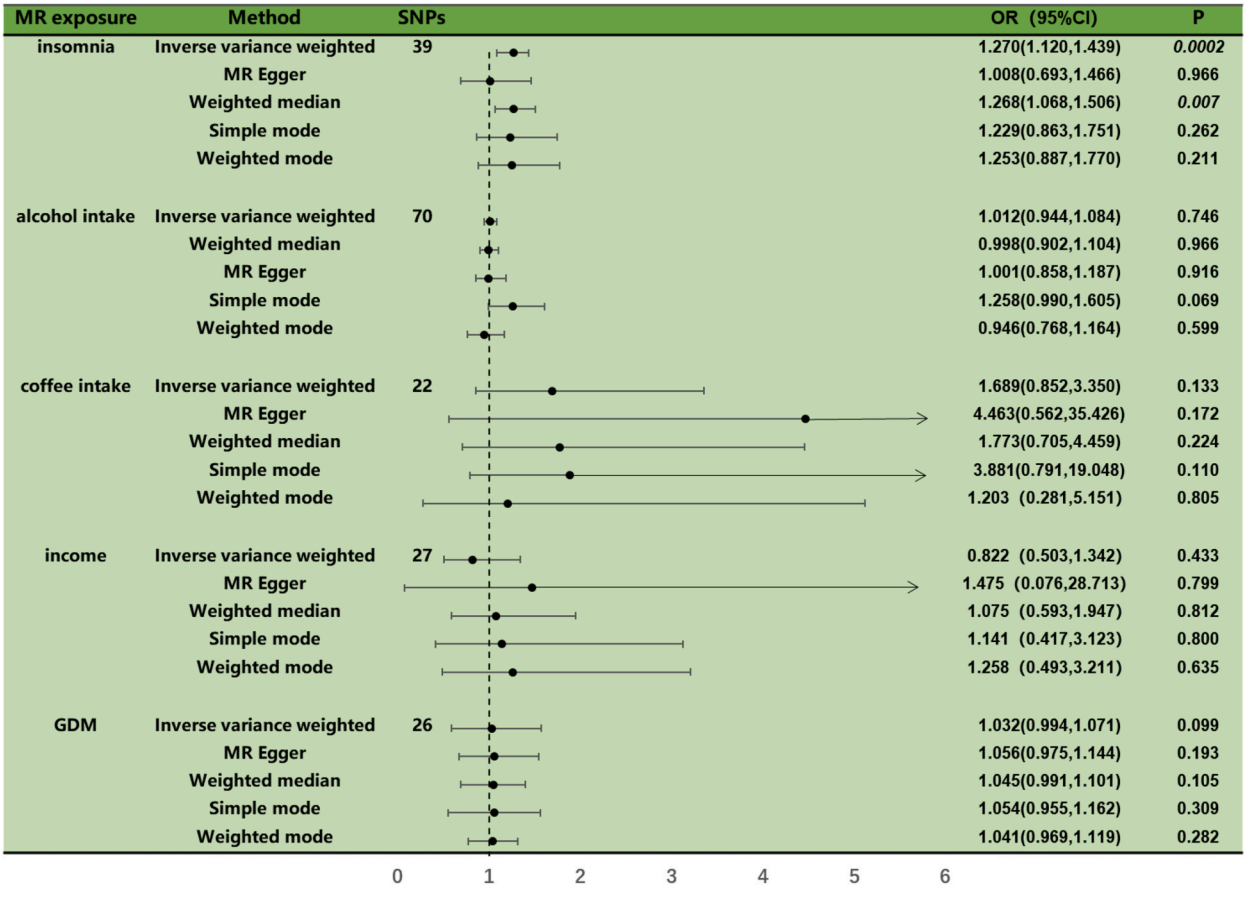

Fig. 2. Odds ratios for the associations between genetically predicted GDM and risk of insomnia, alcohol intake, coffee intake and family income. SNPs: the number of SNPs used as instrumental variables; P: P-value of the causal estimate; OR: odds ratio; CI: confidence interval.

a significant risk for GDM. Additionally, family income, represented through its genetic proxies, showed an OR of 0.822 (95 % CI: 0.503–1.342, P = 0.433), also demonstrating a lack of significant causal relationship with GDM. These findings, illustrated in Fig. 2 an by P-values greater than 0.05 for all exposures, indicate that, within the genetic framework of this MR analysis, there is no evidence to suggest that coffee consumption, alcohol intake, or family income have a direct causal effect on the development of GDM.

3.3. Heterogeneity and horizontal pleiotropy

The selection of instrumental variables was stringently conducted to ensure their validity, and subsequent analyses were performed to assess heterogeneity and the potential for horizontal pleiotropy among these IVs (Table 2). Heterogeneity tests, quantified by the Q statistic for the IVW method and the QP statistic for MR-Egger, yielded values of 37.336 (P = 0.168) and 35.342 (P = 0.194) respectively, both indicating no significant heterogeneity across the selected instrumental variables.

To evaluate the presence of horizontal pleiotropy, which occurs when genetic variants affect the outcome through pathways other than the exposure of interest, the MR-Egger intercept was employed. The intercept value was 0.021 with a standard error (SE) of 0.016 and a P-value of 0.211, suggesting no evidence of horizontal pleiotropy in the data (Supplementary Fig. S1). This was further corroborated by the symmetry observed in the funnel plot (Supplementary Fig. S4), indicating a pleiotropy-free analysis.

Sensitivity analyses, particularly the “Leave-one-out” approach, were conducted to ascertain the influence of individual SNPs on the overall MR estimates. This involved sequentially omitting one SNP at a time and recalculating the IVW estimates. The resultant effect sizes remained consistent, with no significant deviations observed from the pooled estimate (all P-values >0.05), as depicted in Supplementary Figs. S2 and S3. The stability of these results, evidenced by the lack of considerable influence from any single SNP, affirms the robustness and reliability of the initial IVW findings.

4. Discussions

To determine the causal relationship between insomnia and GDM, we employed bidirectional MR analysis. The results indicate that insomnia elevated the risk of GDM by 27 % (OR = 1.270, 95 % CI 1.120–1.439, P = 0.0002), suggesting a significant increase in the risk of GDM during pregnancy. The direction of the β values was consistent across all three analysis methods. Therefore, from the perspective of MR analysis, it can be concluded that insomnia increases the risk of GDM during pregnancy, thereby establishing a causal relationship. Moreover, no statistically significant results were observed in the MR-Egger, weighted model, and simple model tests, which could be attributed to the residual pleiotropy. Further multivariable Mendelian Randomization (MVMR) analysis, after accounting for risk factors such as coffee consumption, alcohol intake, and household income, revealed that these factors related to insomnia did not have a causal relationship with GDM, indicating that insomnia is independently associated with GDM.

Insomnia is characterized by difficulty in initiating or maintaining sleep, early waking, or restless sleep despite adequate opportunities for sleep, occurring three or more times a week. Symptoms of insomnia are prevalent throughout pregnancy and postpartum period [9]. The incidence of insomnia in early and mid-pregnancy is about 25 %, peaking at 60 % in late pregnancy, and the incidence of postpartum insomnia remains as high as 55 % [18]. Previous studies have shown a correlation between sleep duration and GDM, but the relationship between sleep duration and GDM reported in the literature is inconsistent and therefore controversial. For example, a systematic review and meta-analysis [19] using data from 16 studies involving 2,551,017 participants found that extreme sleep duration, poor sleep quality, and higher GDM risk were correlated. A U-shaped relationship was observed between sleep duration and subsequent GDM risk, with the lowest risk of GDM observed in pregnant women who slept 8 h. Myoga et al. [20] reported that after adjusting for confounding factors such as age, pre-pregnancy BMI, weight gain during pregnancy, and GDM history, pregnant women who slept <5 h or ≥10 h had a higher risk of GDM. Conversely, after adjusting for maternal age and race, pregnant women who slept ≤4 h had a higher risk of GDM, but there was no significant difference for those sleeping ≥10 h [21]. However, a meta-analysis showed that pregnant women with short sleep duration (<6–7 h/night) were more likely to develop GDM, with an elevated 70 % risk, and 1-h blood glucose levels were higher in pregnant women sleeping ≤6.25 h compared to those sleeping >6.25 h [22].

Currently, the mechanism of the impact of insomnia on GDM remains unclear. Some studies did not find a relationship between

Table 2
Susceptibility testing (insomnia, coffee intake, alcohol intake, income and GDM).

Exposure	Method	Q Cochran's Q	Q_Df	P-value	Egger_Intercept MR-Egger intercept	SE	P-value
	GDM as the outcome						
Insomnia	MR Egger	32.342	29	0.194	–		
	IVW	37.336	30	0.168	0.021	0.016	0.211
Coffee intake	MR Egger	16.869	20	0.661	–		
	IVW	17.817	21	0.661	−0.018	0.018	0.342
Alcohol intake	MR Egger	77.343	68	0.205	–		
	IVW	77.344	69	0.230	0.0005	0.014	0.971
Income	MR Egger	33.125	25	0.128	–		
	IVW	33.328	26	0.153	−0.012	0.031	0.699
	Insomnia as the outcome						
GDM	MR Egger	35.342	29	0.194	–		
	IVW	37.335	30	0.168	−0.0053	0.0081	0.522

sleep duration and GDM [23,24]. Insomnia may negatively affect glucose homeostasis through various pathways, including increased oxidative stress, systemic inflammation, energy imbalance, endothelial dysfunction, intermittent hypoxia (often occurring in sleep apnea), and activation of the hypothalamic-pituitary-adrenal (HPA) axis [25–27]. Due to hormonal and physiological changes, sleep quality declines during pregnancy [28,29]. Zhong et al. [30] involving 4066 Chinese pregnant women in early and mid-pregnancy found that compared to those with good sleep quality (rarely experiencing insomnia), women with poor sleep quality (frequently experiencing insomnia) in early pregnancy had a 1.77-fold increased GDM risk. A recent cross-sectional study found that pregnant women with poor sleep quality (PSQI>5) had a 1.75-fold higher GDM risk compared to those with good sleep quality (PSQI≤5) [31]. Most of these studies used questionnaires to determine sleep quality, which is subjective and may overestimate or underestimate the correlation between sleep quality and GDM, necessitating more objective sleep quality measurement studies to clarify the relationship.

The MTNR1B gene plays a very important role in insomnia and GDM. The protein encoded by the MTNR1B gene is melatonin receptor 1B, a G-protein-coupled receptor expressed in β-cells that stimulates insulin and glucagon secretion in human pancreatic islets, and is associated with fasting blood glucose and early insulin response to oral and intravenous glucose. Melatonin is a neuro-endocrine hormone synthesized in a series of enzymatic steps mainly in the pineal gland, which plays an important role in circadian rhythms and sleep but also has important metabolic roles [32]. Studies on human pancreatic islets [32]have shown that melatonin stimulates the secretion of glucagon and insulin from α- and β-cells, respectively. The metabolic and other actions of melatonin are mediated by binding to the transmembrane G protein-coupled receptors MT1 and MT2, the latter encoded by MTNR1B.Genetic variants of MTNR1B have been associated with several serum metabolisms, including fasting glucose, glycosylated haemoglobin, early insulin response to oral and intravenous glucose, and accelerated deterioration of insulin secretion over time [33–36]. Variants in the MTNR1B gene have also been associated with fasting and 1-h post-load blood glucose during pregnancy [37]. In addition to its role in regulating circadian rhythms, melatonin is a potent antioxidant that scavenges reactive oxygen species, which is important during pregnancy [38]. Given the genetic associations observed with MTNR1B and the multifaceted role of melatonin in both sleep and metabolic regulation, this may partly explain the cause-and-effect relationship.

The current diagnosis of GDM is based on the oral glucose tolerance test (OGTT) test conducted between 24 and 28 weeks of pregnancy, which is already in the late stage of pregnancy. Poor sleep quality is common among pregnant women in the late stage of pregnancy, and some studies suggest that this may be related to the activation of the sympathetic nervous system [39]. Sedov et al. [40] found that the quality of sleep gradually declined from mid to late pregnancy, with about 45.7 % of pregnant women experiencing poor sleep quality, and this was even more pronounced in women with GDM, possibly due to concerns that diabetes could affect the health of the newborn. Currently, no genetic-level correlation has been found between the effects of GDM on insomnia. A single-center retrospective study [41] reported that compared to non-GDM pregnant women, those with GDM had poorer sleep quality and a higher probability of developing obstructive sleep apnea-hypopnea syndrome. Another study [42] indicated that insomnia during pregnancy in women with GDM affects glycemic control, leading to adverse pregnancy outcomes. Sleep intervention at 35 weeks of pregnancy can help improve glycemic control during pregnancy [43]. The intervention discussed is known as the “Sleep-4-2″ educational program. This program was meticulously developed by a team of experts specializing in sleep medicine, psychiatry, and maternal-fetal medicine. “Sleep-4-2″ is a two-session intervention designed to educate pregnant women about optimal sleep hygiene practices during pregnancy. The key focus areas include timing, regularity, efficiency, and duration of sleep. During the sessions, participants engage with sleep specialists to identify and address their specific sleep issues, facilitating tailored behavioral interventions that promote healthier sleep patterns.Therefore, clinicians should pay close attention to the sleep quality of pregnant women with GDM, providing new ideas for further prevention and management of adverse pregnancy outcomes.In maternal health care, medical staff can regularly assess the sleep of pregnant women in the early, middle and late stages of pregnancy, and provide health guidance and intervention in advance for pregnant women with poor sleep quality, with the aim of providing a basis for improving maternal and foetal health, improving outcomes for mothers and babies, and promoting the reproductive health of society.

To our knowledge, this is the first MR analysis has been used to examine the causal relationship between insomnia and GDM. Previous epidemiological studies have shown controversy over the relationship between insomnia and GDM, which may be affected by confounding factors and reverse causality. Based on MR analysis, the Mendelian randomization law was used to select genetic variants as exposure factors, making the findings more reliable. Secondly, the genes appeared before the onset of the disease, which eliminates the influence of reverse causality. Additionally, combining the data from published GWAS summary studies for MR analysis, a large sample size can increase the validity of the test. The results provide new theories and ideas for the prevention of gestational diabetes and improvement of pregnancy outcomes in early pregnancy. However, our study has some limitations. Firstly, the GWAS dataset included in the MR analysis is from Europe, so further research is needed in other populations to increase the generalizability of the results. Secondly, some unpublished SNPs may be related to GDM, which would affect our research results. Our results are based on a significance level of $5 \times 10\hat{}-6$, and although there are not enough SNPs related to the genome-wide significance threshold of $5 \times 10\hat{}-8$, we still conducted a two-sample MR analysis. Finally, while this study provides insights into the relationship between insomnia and gestational diabetes mellitus (GDM), it acknowledges the complexity of the underlying factors influencing insomnia. Future research should employ complex multivariate models to explore additional variables such as physical activity levels and dietary habits. It is also critical to investigate the interactions and contributions of these potential confounding variables to fully understand the dynamics influencing the association between insomnia and GDM.

5. Conclusions

In conclusion, our study indicates a causal relationship between insomnia and GDM, and that insomnia increases the risk of developing GDM. However, factors associated with insomnia, such as coffee intake, alcohol consumption, and household income, do

not have a causal relationship with GDM. In the future, we can potentially reduce the incidence of GDM by screening for sleep disorders in early pregnancy. This will provide further guidance for improving sleep during pregnancy and exploring its impact on glucose metabolism.

Consent for publication

The authors take full responsibility for the data, the analyses and interpretation, and the conduct of the research. The authors had full access to all of the data and have the right to publish any and all data separate and apart from any sponsor.

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Ethics approval and consent to participate

The present study is a secondary analysis of publicly available data. Ethical approval was granted foreach of the original GWAS studies. In addition, no individual-level data were used in this study.Therefore, no new ethical review board approval was required.

Data availability statement

All data used in the present study were obtained from genome-wide association study summary statistics which were publicly released by genetic consortia. The authors confirm that all data underlying the findings are either fully available without restriction through consortia websites, or may be made available from consortia upon request. Insomnia GWAS dataset is available at https://gwas.mrcieu.ac.uk/datasets/finn-b-G6_SLEEPAPNO/; Coffee intake, alcohol intake and family income GWAS datasets are available at https://gwas.mrcieu.ac.uk; Gestational diabetes GWAS dataset is available at https://risteys.finregistry.fi/endpoints/O15_PREG_DM.

CRediT authorship contribution statement

Minne Liu: Writing – original draft, Investigation, Data curation. **Xianfeng Yu:** Supervision, Resources, Data curation. **Jie Shi:** Writing – original draft, Visualization, Validation. **Jiahui Su:** Visualization, Supervision. **Min Wei:** Supervision, Software, Investigation. **Qingshuang Zhu:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not Applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33638.

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