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ORIGINAL RESEARCH

Circadian Biology and Gynecological Diseases: Genetic Mechanisms and Potential Therapeutic Targets Underlying the Causal Link Between Insomnia and Ovarian Cysts

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Background: Although circadian disruption has been implicated in gynecologic malignancies, genetic evidence for a causal relationship between insomnia and ovarian cysts remains lacking. The biological pathways linking sleep disturbance to ovarian pathology are therefore poorly understood, limiting mechanistic insights and therapeutic development.

Methods: We employed a two-sample Mendelian Randomization (MR) framework using large-scale Genome-Wide Association Study (GWAS) datasets of European ancestry to examine the effects of seven sleep-related traits on five gynecologic outcome types. We further conducted transcriptomic analyses using Gene Expression Omnibus (GEO) datasets (GSE208668 and GSE7305) and performed molecular docking with 288 drug-like compounds to explore therapeutic targets.

Results: MR identified a strong, unidirectional association between insomnia and increased ovarian cyst risk, with no evidence of reverse causality. Other sleep traits showed mixed effects across gynecologic outcomes. Single-nucleotide polymorphism (SNP)-mapped gene enrichment revealed involvement of neuronal signaling, circadian rhythm, and immune pathways. Three core genes (GFRA1, SORCS2, RASGRF2) were identified through overlap with ovarian cyst differentially expressed genes (DEGs) and were further supported by in silico docking with favorable predicted binding energies. Shared DEGs between insomnia and ovarian cyst samples were enriched in leukocyte activation, oxidative stress, and developmental processes.

Conclusion: This multi-omics study provides genetic and molecular evidence that insomnia may contribute to ovarian cyst formation through circadian, synaptic, and immune mechanisms. The identified hub genes and druggable targets suggest circadian-aligned therapeutic strategies (chronotherapy), including sleep optimization, rhythm-timed pharmacotherapy, and melatonin-related modulation, as potential avenues for prevention and intervention.

Keywords: insomnia, ovarian cyst, Mendelian randomization, circadian rhythm, transcriptomics, molecular docking, gynecologic outcomes

Introduction

Circadian rhythms orchestrate essential physiological processes-including metabolism, immune function, hormone secretion, and cell proliferation-via a highly conserved network of clock genes and transcriptional feedback loops.[1,2] The core circadian clock machinery, composed of genes such as CLOCK, BMAL1, PER1-3, and CRY1-2, produces rhythmic gene expression patterns that maintain physiological homeostasis across diverse organ systems.[3] Mounting evidence indicates that disruption of circadian rhythms is implicated in tumorigenesis, particularly in hormone dependent cancers of the female reproductive system.[4,5]

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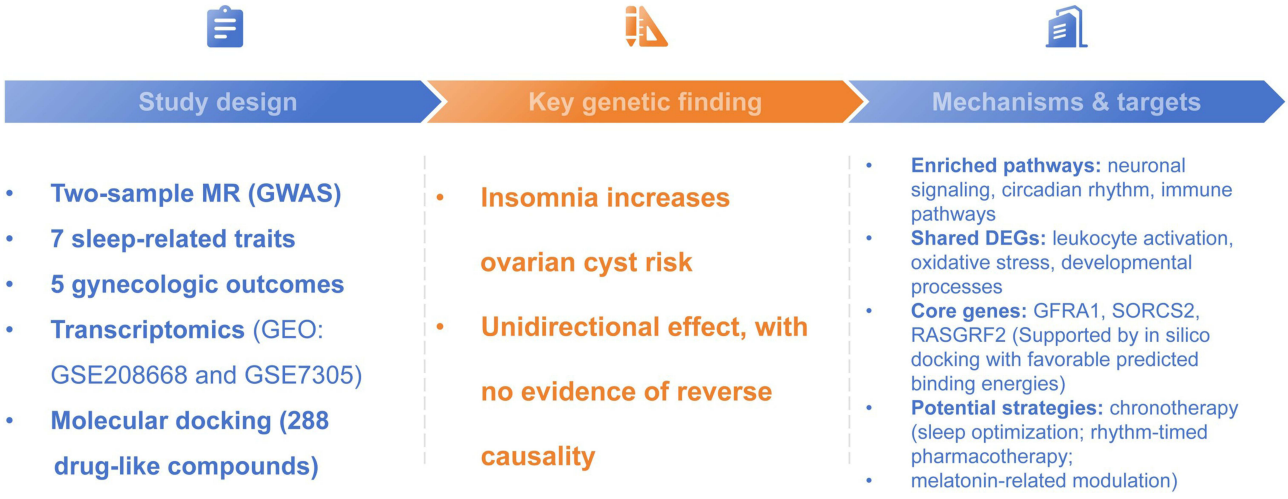
Graphical Abstract



MR, Mendelian Randomization; GWAS, Genome-Wide Association Study; GEO, Gene Expression Omnibus

Epidemiological studies have shown that circadian misalignment-arising from shift work, chronic sleep disturbances, or genetic variation in clock genes-may increase the risk of ovarian, endometrial, and cervical cancers.[4–6] However, these associations from observational research are inherently limited by confounding, reverse causality, and selection bias, making it difficult to establish definitive causal relationships. Mechanistically, circadian disruption can affect multiple cancer relevant pathways, including cell cycle progression, DNA damage repair, apoptosis, hormone signaling, and immune regulation.[7–9] For example, aberrant expression of PER and CRY genes can reduce apoptotic capacity and promote unchecked cellular proliferation, while dysregulation of CLOCK and BMAL1 alters oncogenic signaling cascades involving tumor suppressors and protooncogenes such as p53, MYC, and NF-κB.[7,10,11] Furthermore, circadian control of hormone biosynthesis and receptor signaling-particularly estrogen pathways-plays a crucial role in gynecologic tumorigenesis.[12,13]

To overcome the inherent limitations of observational designs, MR provides a robust genetic epidemiological tool for causal inference, leveraging single nucleotide polymorphisms (SNPs) as instrumental variables for circadian related traits. Because these genetic variants are randomly allocated at conception and largely immune to confounding and reverse causality, MR allows for more reliable assessment of causality than traditional epidemiologic approaches.[14–16] Although MR has been widely applied to metabolic, cardiovascular, and neurodegenerative disorders, its application in gynecological diseases remains limited. Notably, existing MR studies have focused almost exclusively on malignant gynecologic outcomes, whereas benign gynecological conditions—despite their high prevalence and substantial impact on women's reproductive health—have received little attention. This gap is particularly evident for ovarian cysts, a common benign ovarian disorder closely linked to hormonal regulation and ovarian physiology.[17,18]

In this study, we implemented a comprehensive two-sample MR framework to systematically evaluate the potential causal effects of circadian related traits-including insomnia, sleep duration, snoring, daytime dozing, excessive sleep, and chronotype-on the risks of ovarian cancer, endometrial cancer, cervical cancer, ovarian cysts, and hydatidiform mole. We used summary statistics from largescale genome wide association studies (GWAS) to ensure statistical power and broad genetic coverage. Our MR analyses incorporated methods such as inverse variance weighting (IVW), MR-Egger regression, weighted median estimation, and MR-PRESSO to rigorously test instrument strength, horizontal pleiotropy, and heterogeneity.

To gain further mechanistic insight, we mapped insomnia associated SNPs to target genes and performed Metascape pathway enrichment analyses to identify dysregulated biological processes. We additionally analyzed differential gene expression in ovarian cyst tissues (GSE7305) and integrated these results with in silico molecular docking to predict the interactions of drug-

like compounds with candidate proteins. This multipronged approach enabled us to interrogate not only causal relationships but also to identify potential therapeutic targets related to circadian disruption and gynecologic tumorigenesis.

By integrating genetic epidemiology, transcriptomic profiling, pathway enrichment, and molecular docking, our study seeks to elucidate whether circadian disruption contributes causally to the development of gynecologic diseases. Importantly, by including ovarian cysts as a primary outcome, we extend the application of MR beyond malignant tumors to a common benign gynecologic condition, thereby addressing an important and underexplored gap in the circadian-reproductive health literature.

Methods

Study Design

This study did not involve any clinical trial or interventional study in human participants. All analyses were based on publicly available datasets. Therefore, clinical trial registration was not required.

Figure 1 outlines the overall study framework.

Module 1. Genetic Causality (Left, Pink Panel)

Large European-ancestry GWAS datasets for seven sleep phenotypes (insomnia, sleep duration, snoring, daytime dozing, hypersomnia, sleep disorder, and chronotype) and five gynecologic outcomes (ovarian cysts, ovarian cancer, endometrial cancer, cervical cancer, and hydatidiform mole) were interrogated using two-sample MR. Inverse-variance weighting with complementary sensitivity analyses demonstrated a pleiotropy-free, unidirectional effect of insomnia on ovarian cyst risk, which was further supported by bidirectional MR analyses.

Module 2. Potential Application (Upper Right, Yellow Panel)

Risk SNPs from the insomnia-ovarian cyst MR were mapped to genes and enriched to identify key regulators. Intersection with ovarian cyst DEGs (GSE7305) yielded three core targets (GFRA1, SORCS2, and RASGRF2), which

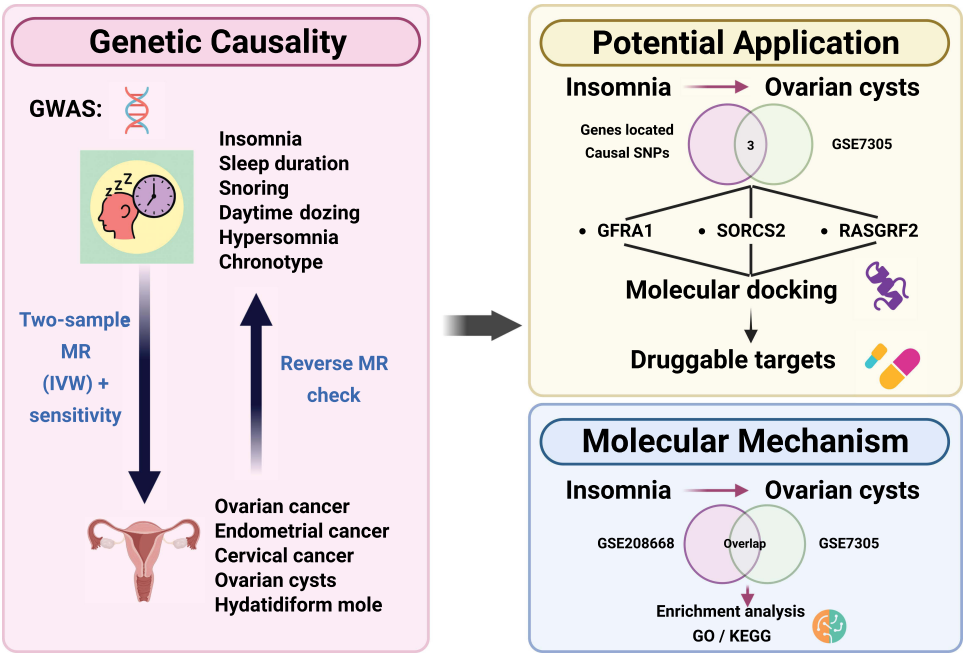


Figure 1 Integrative analysis framework uncovering the causal link and molecular mechanisms between insomnia and ovarian cysts. The left panel illustrates the two-sample Mendelian randomization (MR) strategy assessing the causal relationship between sleep-circadian traits (insomnia, sleep duration, snoring, daytime dozing, hypersomnia, chronotype) and gynecological outcomes (ovarian cancer, endometrial cancer, cervical cancer, ovarian cysts, hydatidiform mole), with reverse MR analysis performed for validation. The upper right panel depicts potential translational applications, where intersection analysis between insomnia-associated causal SNP-located genes and ovarian cyst transcriptomic data (GSE7305) identified three candidate genes (GFRA1, SORCS2, RASGRF2) subjected to molecular docking for druggable target prediction. The lower right panel illustrates molecular mechanism exploration through transcriptome overlap analysis between insomnia (GSE208668) and ovarian cysts (GSE7305) datasets, followed by GO and KEGG enrichment analyses to reveal biological pathways underlying the insomnia-ovarian cyst connection.

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were subsequently docked against 288 drug-like ZINC compounds in AutoDock Vina, revealing high-affinity, sleep-related ligands (eg., ZINC27546400 and ZINC72352778) and highlighting potential druggable nodes for chronotherapy.

Module 3. Molecular Mechanism (Lower Right, Blue Panel)

To elucidate downstream biology, whole-blood insomnia transcriptomes (GSE208668) were compared with ovarian cyst tissue profiles (GSE7305). Overlapping genes were subjected to GO (Gene Ontology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment, revealing convergent immune activation, metabolic stress, cell adhesion, and developmental pathways that may mechanistically connect circadian disruption to ovarian cyst formation.

Data Sources

In this two-sample MR study, we systematically evaluated the causal effects of circadian rhythm traits on the risk of gynecologic outcomes. Exposure data for seven circadian related phenotypes-including chronotype, insomnia, snoring, sleep duration, daytime dozing, hypersomnia, and sleep disorders-were obtained from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/). Specifically, the following GWAS datasets were used: chronotype (ieu-b-4861, ieu-b-4862, ieu-a-1087, ebi-a-GCST003837), insomnia (ukb-b-3957, ukb-a-13), snoring (ukb-b-17400, ebi-a-GCST009760, ebi-a-GCST009761, ukb-a-14, ebi-a-GCST009763, ebi-a-GCST009762), sleep duration (ukb-b-4424, ukb-a-9, ieu-a-1088, ebi-a-GCST003839), daytime dozing (ukb-b-5776, ukb-a-15), hypersomnia (UKB "sleeping too much", ukb-d-20534), and sleep disorders (ukb-d-SLEEP).

Outcome data for five gynecological conditions were also sourced from the IEU Open GWAS database, including ovarian cysts (ebi-a-GCST90018889, finn-b-N14_OVARYCYST), cervical cancer (ebi-a-GCST90018817, ieu-b-4876), endometrial cancer (ebi-a-GCST90018838, ebi-a-GCST006464), ovarian cancer (ebi-a-GCST90018888, ieu-b-4963), and hydatidiform mole (finn-b-O15_PREG_HYDAT).

All selected GWAS datasets were derived from European ancestry populations to minimize potential confounding due to population stratification. Detailed characteristics of each dataset are summarized in Table 1. Detailed MR estimates for circadian rhythm traits across ovarian cyst, cervical cancer, endometrial cancer, ovarian cancer, and hydatidiform mole are provided in Tables S1A–E.

Table 1 Characteristics of Selected GWAS Data

Trait	ID	Sample Size	nSNP	Population
Exposure				
Chronotype	ieu-b-4861 ieu-b-4862 ieu-a-1087 ebi-a-GCST003837	244,207 205,527 128,266 127,898	11979082 17070463 17032431 16832291	European European European European
Insomnia	ukb-b-3957 ukb-a-13	462,341 336,965	9851867 10894596	European European
Snoring	ukb-b-17400 ebi-a-GCST009760 ebi-a-GCST009761 ukb-a-14 ebi-a-GCST009763 ebi-a-GCST009762	430,438 408,317 407,066 314,449 218,346 189,971	9851867 10707662 10707669 10894596 10707574 10707886	European European European European European European
Sleep duration	ukb-b-4424 ukb-a-9 ieu-a-1088 ebi-a-GCST003839	460,099 335,410 128,266 127,573	9851867 10894596 16761226 16570056	European European European European

(*Continued*)

Table 1 (Continued).

Trait	ID	Sample Size	nSNP	Population
Daytime dozing	ukb-b-5776 ukb-a-15	460,913 336,082	9851867 10894596	European European
Sleeping too much	ukb-d-20534	45,540	13149723	European
Sleep disorders	ukb-d-SLEEP	361194	11120383	European
Outcome				
Ovarian cyst	ebi-a-GCST90018889 finn-b-N14_OVARYCYST	218,469 79817	24100412 16377648	European European
Cervical cancer	ebi-a-GCST90018817 ieu-b-4876	239,158 199,086	24138337 8506261	European European
Endometrial cancer	ebi-a-GCST90018838 ebi-a-GCST006464	240,027 121,885	24135295 9470555	European European
Ovarian cancer	ebi-a-GCST90018888 ieu-b-4963	246,520 199,741	24137758 9822229	European European
Hydatidiform mole	finn-b-O15_PREG_HYDAT	89548	16378810	European

Selection Criteria for Instrumental Variable

To evaluate the causal relationships between circadian rhythm traits and gynecological diseases, we selected SNPs as instrumental variables (IVs) for both exposures and outcomes. This approach reduces confounding and reverse causation, analogous to random allocation in randomized controlled trials.

SNPs were selected using a genome-wide significance threshold of $P < 5\times10^{-6}$. To minimize linkage disequilibrium (LD), we excluded correlated variants with $r^2 > 0.001$ within a 10,000 kb window. Instrument strength was assessed using the F-statistic, and SNPs with $F < 10$ were removed to avoid weak instrument bias.

The same selection criteria were applied consistently to forward and reverse MR analyses to ensure methodological comparability across all exposure-outcome pairs. Only SNPs meeting all criteria were retained for final causal estimation.

Although the conventional threshold is $P < 5 \times 10^{-8}$, we adopted $P < 5\times10^{-6}$ because several sleep-related traits, and ovarian cysts in particular, yielded few genome-wide significant SNPs. This approach is widely used in MR studies when combined with strict LD clumping and F-statistic screening. This strategy balances statistical power and instrument availability while maintaining robustness through multiple sensitivity analyses. The characteristics of instrumental SNPs used for each gynecological outcome, including SNP counts and effect allele information, are listed in Tables S2A–E.

All selected instruments were further evaluated using MR-Egger, weighted median, and MR-PRESSO to detect horizontal pleiotropy. For traits with fewer than three valid SNPs, results were interpreted cautiously and supported primarily by sensitivity analyses. Sensitivity analyses for the associations between circadian rhythm traits and each gynecological outcome are presented in Tables S3A–E.

Functional Annotation and Enrichment Analysis

Causal SNPs were first mapped to their corresponding or nearby genes using the Ensembl Genome Browser. The mapped gene lists for each insomnia GWAS-ovarian cyst outcome pair are provided in Box S1A-D. Differential expression analysis was performed on the GSE208668 (insomnia) and GSE7305 (ovarian cyst) datasets using $|\log2FC| > 1$ and $P < 0.05$, yielding 2,222 upregulated and 1,620 downregulated genes for insomnia, and 1,038 upregulated and 811 downregulated genes for ovarian cysts. Overlapping DEGs between conditions were identified using Venn diagrams.

All variant mapped and shared DEGs were subjected to functional enrichment analysis using Metascape (https://metascape.org/), which integrates GO, KEGG, Metascape, and other canonical pathway databases. Enrichment

significance was determined by cumulative hypergeometric testing with Benjamini-Hochberg adjustment (adjusted $P < 0.05$). Enrichment results were visualized with bubble plots, Sankey diagrams, and dot plots generated by Metascape and Bioinformatics (http://www.bioinformatics.com.cn/), providing systematic insight into the key biological processes and pathways associated with insomnia and ovarian cysts.

GWAS Harmonization

Exposure and outcome summary statistics were harmonized using the TwoSampleMR pipeline to ensure consistent strand orientation and allele coding across datasets. Specifically, effect alleles were aligned between exposure and outcome GWAS, and palindromic SNPs with intermediate allele frequencies (minor allele frequency between 0.42 and 0.58) were removed to avoid strand ambiguity. When necessary, alleles were flipped to match a common reference orientation prior to MR analysis.

Statistical Analysis

MR analysis was the principal statistical approach used to assess the causal effects of circadian rhythm traits on gynecological disease risk, with genetic variants serving as instrumental variables. All analyses were performed in R (version 4.2.2), utilizing the "Two-sample MR", "Variant Annotation", and "ieugwasr" packages to implement the two-sample MR framework.

Five complementary estimators were applied: inverse variance weighting (IVW, primary), MR Egger, weighted median, simple mode, and weighted mode. Statistical significance was defined as $P < 0.05$. Causal estimates are presented as odds ratios (ORs), with $OR > 1$ indicating increased risk and $OR < 1$ indicating a protective effect.

Instrument heterogeneity was evaluated using Cochran's Q statistic and the MR-PRESSO global test; $P > 0.05$ was interpreted as no significant heterogeneity. Horizontal pleiotropy was assessed via the MR-Egger intercept (an intercept close to zero and $P > 0.05$ indicating no evidence of directional pleiotropy). Leave one out sensitivity analysis was performed by iteratively excluding each SNP to identify influential variants and confirm the robustness of results.

Scatter plots, funnel plots, and leave one out forest plots were generated to visualize the consistency, symmetry, and reliability of SNP effects. To correct for multiple testing across different circadian rhythm traits and tumor outcomes, we applied the Benjamini-Hochberg false discovery rate (FDR) correction, with FDR adjusted $P < 0.05$ considered statistically significant.

Molecular Docking

Small molecule compounds with Log $P < 5$ and molecular weight < 500 Da were retrieved from the ZINC database and processed using Python 2.5, resulting in a library of 288 unique ligands, each stored as a single conformer PDBQT file. Protein structures for GFRA1 (PDB ID: 6Q2N), SORCS2 (PDB ID: 1WGO), and RASGRF2 (AlphaFold model: AFO14827F1model_v4) were downloaded, with water molecules and bound ligands removed in PyMOL v2.5. Proteins were protonated and assigned Gasteiger charges using AutoDock Tools 1.5.7, then converted to PDBQT format.

Docking grids (search spaces) were centered on the coordinates of native ligand-binding sites or predicted functional pockets. The grid box parameters (in Å) were set as follows: SORCS2 center = (−5.513, −1.032, 1.613), size = (40×58×34); GFRA1 center = (117.694, 117.665, 119.086), size = (118×206×70); and RASGRF2 center = (−1.459, 12.769, −8.768), size = (156×132×148). These boxes were defined to fully encompass the functional pocket while minimizing irrelevant search space, and num_modes was set to 9.

AutoDock Vina v1.1.2 (default parameters) was used to perform molecular docking of each receptor against all 288 ligands. The top five compounds with the lowest predicted energy of binding (kcal/mol) for each target protein were selected for further analysis, and their binding poses were visualized in PyMOL. Additionally, these hit compounds and their structural analogs were queried in PubChem for chemical information and in PubMed to investigate potential links to sleep regulation or circadian pathways.

Results

Instrument Strength and Data Quality

After linkage-disequilibrium pruning ($r^2 < 0.001$ within 10,000 kb), all selected SNP instruments had F-statistics > 10, indicating strong instruments for both forward and reverse MR analyses.

MR results

As shown in Table 2, forward MR using the IVW method revealed a significant causal association between insomnia and increased ovarian cyst risk.

All odds ratios reported in Tables 2–3 were evaluated together across all tested pairs with FDR (adjusted P values) using the Benjamini-Hochberg procedure; associations were interpreted as statistically robust only when both nominal significance and FDR-adjusted significance were satisfied, whereas borderline findings were supported primarily by sensitivity analyses (MR-Egger, weighted median, MR-PRESSO, and leave-one-out tests).

Insomnia (ukb-a-13; nSNP=112) increased risk of ovarian cyst (ebi-a-GCST90018889): OR 1.645 (95% CI 1.263–2.142), P < 0.001.

Insomnia (ukb-b-3957; nSNP=157) increased risk of ovarian cyst (finn-b-N14_OVARYCYST): OR 1.794 (95% CI 1.315–2.446), P < 0.001.

Insomnia (ukb-a-13; nSNP=110) increased risk of ovarian cyst (finn-b-N14_OVARYCYST): OR 2.137 (95% CI 1.577–2.897), P < 0.001 (Table S4A).

Cervical cancer (Table 2 Cervical cancer):

Daytime dozing (ukb-b-5776; nSNP=113) was inversely associated with cervical cancer (ebi-a-GCST90018817): OR 0.281 (95% CI 0.081–0.975), P = 0.045.

Snoring (ebi-a-GCST009762; nSNP=46) was inversely associated with cervical cancer (ieu-b-4876): OR 0.992 (95% CI 0.985–0.999), P = 0.018 (as detailed in Table S4B).

Endometrial cancer (Table 2 Endometrial cancer):

Snoring (ebi-a-GCST009763; nSNP=77) was inversely associated with endometrial cancer (ebi-a-GCST90018838): OR 0.366 (95% CI 0.155–0.864), P = 0.022.

Sleep duration (ukb-a-9; nSNP=132) was inversely associated with endometrial cancer (ebi-a-GCST90018838): OR 0.618 (95% CI 0.394–0.971), P = 0.037.

Snoring (ebi-a-GCST009760; nSNP=135) increased risk of endometrial cancer (ebi-a-GCST006464): OR 1.747 (95% CI 1.056–2.891), P = 0.030 (as presented in Table S4C).

Ovarian cancer (Table 2 Ovarian cancer):

Chronotype (ieu-a-1087; nSNP=77) increased risk of ovarian cancer (ebi-a-GCST90018888): OR 1.462 (95% CI 1.005–2.127), P = 0.047.

Snoring (ebi-a-GCST009763; nSNP=72) showed a borderline association with ovarian cancer (ieu-b-4963): OR 1.008 (95% CI 1.000–1.017), P = 0.060.

Excessive sleep (ukb-d-20534; nSNP=8) showed a borderline inverse association with ovarian cancer (ieu-b-4963): OR 0.988 (95% CI 0.975–1.001), P = 0.072 (Table S4D).

Hydatidiform mole (Table 2 Hydatidiform mole):

Sleep duration (ukb-a-9; nSNP=127) was inversely associated with hydatidiform mole (finn-b-O15_PREG_HYDAT): OR 0.171 (95% CI 0.030–0.958), P = 0.045 (Table S4E).

These findings suggest that insomnia phenotypes causally increase ovarian cyst risk, while various sleep behaviors (daytime dozing, snoring, sleep duration, chronotype) exhibit differential causal effects across gynecological outcomes. Detailed MR estimates for all sleep-related traits across different analytical methods are summarized in Tables S1A–E.

Although several associations showed P values in the range of 0.060–0.072, these findings should be interpreted cautiously. Given the multiple comparisons across sleep traits and gynecologic outcomes, such borderline results are best considered suggestive rather than definitive and require validation in independent cohorts.

Table 2 Mendelian Randomization (MR) Results for Sleep-Circadian Traits and Gynecological Outcomes

Exposure	Outcome	nSNP	Method	pval	FDR	or	or_lci95	or_uci95
Insomnia (ukb-b-3957)	Ovarian cyst (ebi-a-GCST90018889)	163	IVW	0.002361718	0.002361718	1.486271687	1.151221908	1.918833816
Insomnia (ukb-a-13)	Ovarian cyst (ebi-a-GCST90018889)	112	IVW	0.000223755	0.000298339	1.644594884	1.262738908	2.141925235
Insomnia (ukb-b-3957)	Ovarian cyst (finn-b-N14_OVARYCYST)	157	IVW	0.00022253	0.000445059	1.793552501	1.315290338	2.445719002
Insomnia (ukb-a-13)	Ovarian cyst (finn-b-N14_OVARYCYST)	110	IVW	9.9326E-07	3.97304E-06	2.137168314	1.57657143	2.897102099
Daytime dozing (ukb-b-5776)	Cervical cancer (ebi-a-GCST90018817)	113	IVW	0.045452364	0.045452364	0.280977898	0.081001067	0.974660979
Snoring (ebi-a-GCST009762)	Cervical cancer (ieu-b-4876)	46	IVW	0.017565046	0.035130092	0.991956808	0.98536687	0.998590819
Sleep duration (ukb-a-9)	Endometrial cancer (ebi-a-GCST90018838)	132	IVW	0.036672436	0.036672436	0.618499481	0.394094746	0.970684363
Snoring (ebi-a-GCST009760)	Endometrial cancer (ebi-a-GCST006464)	135	IVW	0.02982307	0.044734605	1.747281364	1.056086678	2.890853781
Chronotype (ieu-a-1087)	Ovarian cancer (ebi-a-GCST90018888)	77	IVW	0.047259717	0.044623231	1.461645527	1.00459544	2.126634823
Sleep duration (ukb-a-9)	Hydatidiform mole (finn-b-O15_PREG_HYDAT)	127	IVW	0.044623231	0.044623231	0.170556478	0.030350696	0.958446307

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Table 3 Reverse Mendelian Randomization (MR) Analysis of Gynecological Outcomes on Sleep-Circadian Traits

Exposure	Outcome	Method	nSNP	pval	FDR	or	or_lci95	or_uci95
Ovarian cyst (ebi-a-GCST90018889)	Insomnia (ukb-b-3957)	IVW	25	0.879658384	1.05559006	1.001010585	0.98800651	1.014185819
Ovarian cyst (ebi-a-GCST90018889)	Insomnia (ukb-a-13)	IVW	25	0.849313314	1.455965681	1.001379062	0.987243466	1.015717054
Ovarian cyst (finn-b-N14_OVARYCYST)	Insomnia (ukb-b-3957)	IVW	16	0.105782206	0.634693234	1.00868688	0.998169849	1.019314722
Ovarian cyst (finn-b-N14_OVARYCYST)	Insomnia (ukb-a-13)	IVW	16	0.084873689	1.018484262	1.010807371	0.998523087	1.023242782
Cervical cancer (ebi-a-GCST90018817)	Daytime dozing (ukb-b-5776)	IVW	13	0.879206616	1.172275488	1.000237861	0.997174533	1.003310601
Cervical cancer (ieu-b-4876)	Snoring (ebi-a-GCST009762)	IVW	13	0.955032585	0.955032585	0.955951603	0.199712958	4.575784545
Endometrial cancer (ebi-a-GCST90018838)	Sleep duration (ukb-a-9)	IVW	14	0.67467143	2.02401429	0.998472353	0.991369845	1.005625746
Endometrial cancer (ebi-a-GCST006464)	Snoring (ebi-a-GCST009760)	IVW	40	0.892918561	0.974092976	1.000423491	0.994274976	1.006610028
Ovarian cancer (ebi-a-GCST90018888)	Chronotype (ieu-a-1087)	IVW	18	0.424723835	1.69889534	0.995549927	0.984707208	1.006512036
Hydatidiform mole (finn-b-O15_PREG_HYDAT)	Sleep duration (ukb-a-9)	IVW	3	0.81156921	1.62313842	1.000264536	0.998091753	1.002442049

Sensitivity Analyses

We conducted horizontal pleiotropy testing (MR-Egger intercept), Cochran's Q heterogeneity test, and the MRPRESSO global and outlier tests. No evidence of directional pleiotropy or heterogeneity was detected (all $P > 0.05$), indicating that circadian rhythm SNPs influence gynecological disease risk exclusively via the intended pathway (Tables S3A–E).

Leave one out analysis further demonstrated robustness: sequentially omitting each SNP in turn produced IVW effect estimates highly consistent with those obtained using the full SNP set. Point estimates remained on the same side of the null line (OR = 1), and none of the confidence intervals crossed the null, confirming that no single variant unduly drove the results (Figure S1).

Reverse MR

We then inverted the analysis to test whether gynecological traits causally influence sleep phenotypes, again using the IVW method. No reverse causal effects were observed for any tested pair (all $P > 0.05$; Tables S5A–E), including ovarian cysts on insomnia, cervical cancer on daytime dozing (also referred to as daytime napping)/snoring, endometrial cancer on sleep duration/snoring, ovarian cancer on chronotype, and hydatidiform mole on sleep duration.

Enrichment Analysis of SNP-Mapped Genes

To uncover molecular pathways through which insomnia SNPs influence ovarian cyst risk, we first mapped 163 ukb-b-3957 and 112 ukb-a-13 insomnia-associated variants to 154 and 97 genes, respectively, for the ebi-a-GCST90018889 cyst phenotype, and 157 ukb-b-3957 and 110 ukb-a-13 variants to 146 and 95 genes for the finn-b-N14_OVARYCYST dataset (Box S1A-D). Enrichment analysis of these gene sets (adjusted $P < 0.05$) highlighted overrepresented processes in neuronal and synaptic signaling (Neuronal System, Transmission across Chemical Synapses, Neurotransmitter receptors and postsynaptic signal transmission, and Activation of NMDA receptors and postsynaptic events), circadian-epigenetic control (Circadian entrainment HDAC6 interactions in the central nervous system), immune-inflammatory cascades (FCERI-mediated NF-κB activation, Cytokine Signaling in Immune System, and Interleukin-4 and Interleukin-13 signaling), core signal transduction hubs (MAPK signaling, MAPK1/MAPK3 signaling, RAF/MAP kinase cascade, Ras signaling, G alpha (q) signalling events, and Platelet activation, signaling and aggregation), disease-linked modules (Neuroinflammation and glutamatergic signaling, Pathways in cancer, Huntington disease, Alcoholism, and Amyotrophic lateral sclerosis, please see Figure 2A (upregulated genes) and 2B (downregulated genes). Sankey-style network plots further pinpointed twelve hub genes STAT6, TCF4, MEF2C, DAB1, PTPRD, KCNJ12, ARHGEF10L, SLC6A3, NUPR1, KSR2, TTBK1, and RASGRF2 that bridge circadian regulation, neuronal development, transporter function, and small GTPase signaling, suggesting these interconnected pathways mediate insomnia's causal impact on ovarian cyst formation (Figure 2C and D).

Differential Gene Expression Analysis

Differential gene expression analysis of the GSE7305 ovarian cyst dataset identified 1,038 upregulated and 811 downregulated genes ($|\log FC| > 1$, $P < 0.05$). Intersection of these DEGs with insomnia associated SNP mapped genes revealed a small set of overlapping candidates, among which GFRA1 (rs12769612), SORCS2 (rs6833329), and RASGRF2 (rs7710039) were consistently highlighted (Figure S2 and S3). These genes may serve as core mediators linking the genetic architecture of insomnia to ovarian cyst pathogenesis.

Briefly, GFRA1 is a co-receptor for glial cell line-derived neurotrophic factor and regulates neuronal survival and axonal signaling; SORCS2 participates in synaptic plasticity and endocytic trafficking; and RASGRF2 acts as a guanine nucleotide exchange factor controlling intracellular signaling cascades. These functions provide biological plausibility for their involvement in sleep-circadian regulation and ovarian physiology.

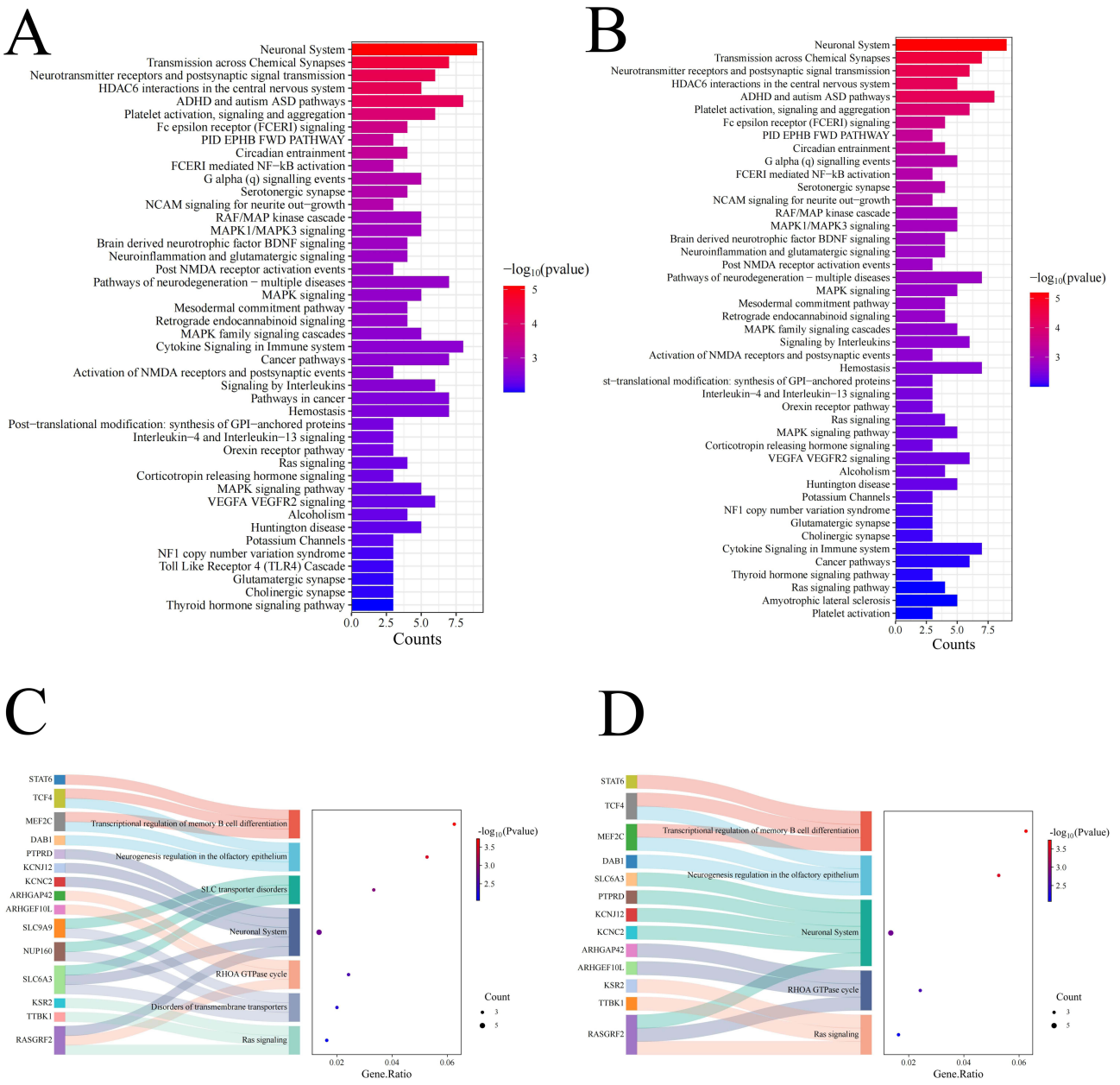

Figure 2 Pathway enrichment of genes mapped from insomnia SNPs linked to ovarian cysts. (**A** and **B**) Bar plots show top enriched pathways, mainly involving neuronal signaling, synaptic transmission, and immune processes. (**C** and **D**) Sankey plots display key genes and representative pathways. These results suggest shared neural and immune mechanisms may underlie the genetic link between insomnia and ovarian cyst risk.

Molecular Docking Screening and Sleep-Related Compound Identification

To identify potential small molecule modulators of key proteins linking insomnia and ovarian cyst risk, we screened 288 drug-like compounds from the ZINC database (Log P < 5, molecular weight < 500 Da). All compounds were processed using Python 2.5 to generate single conformer PDBQT files compatible with AutoDock Vina.

Three target proteins GFRA1 (PDB: 6Q2N), SORCS2 (PDB: 1WGO), and RASGRF2 (AlphaFold: AFO14827F1model_v4) were prepared for docking. Protein structures were preprocessed in PyMOL to remove water molecules and bound ligands, then hydrogenated and charged using AutoDock Tools 1.5.7 to generate receptor PDBQT files. Docking boxes were defined based on native ligand sites or predicted functional pockets.

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Each protein was docked against all 288 compounds using AutoDock Vina. The top five binding compounds for GFRA1, SORCS2, and RASGRF2 were ranked by energy of binding and are listed in Table S6. Figure S4A–C shows the molecular docking poses of the top 5 candidate compounds with three key genes linking insomnia and ovarian cysts.

To assess the biological relevance of these compounds, we conducted additional PubChem and PubMed searches to evaluate structural similarity and literature evidence of involvement in sleep regulation.[19–22] Notably, for each protein, one of the top five ligands was found to be sleep-related: ZINC27546400 for both GFRA1 and RASGRF2, and ZINC72352778 for SORCS2.

Detailed docking results for these three sleep associated compounds are presented in Figure 3A–C and Table 4, including their energy of binding and key interaction residues. ZINC27546400 exhibited strong binding to GFRA1 (−9.6 kcal/mol) through three hydrogen bonds with Glu136 and Arg77, and also bound to RASGRF2 (−8.5 kcal/mol) via a key interaction with Tyr1157. ZINC72352778 docked to SORCS2 with a predicted energy of binding of −7.9 kcal/mol, forming stable hydrogen bonds with Thr80, Gln5, and Gly57. Hydrogen bonds are shown as dashed lines in the inset views. These results highlight potentially druggable targets that may inform future therapeutic intervention.

These findings support the potential of insomnia associated ligands to modulate circadian and neuronal pathways via key target proteins in ovarian cyst pathogenesis.

Differential Gene Expression and Functional Enrichment Linking Insomnia and Ovarian Cyst

Differential expression analysis of GSE208668 (insomnia) and GSE7305 (ovarian cyst) datasets identified 2,222 upregulated and 1,620 downregulated genes for insomnia, and 1,038 upregulated and 811 downregulated genes for ovarian cysts. Venn analysis (Figure 4A) revealed 92 genes were commonly upregulated and 57 genes were commonly downregulated in both conditions (Box S2A-B).

For upregulated overlaps, GO and pathway analyses (Figure 4B) showed enrichment in cell-cell adhesion, leukocyte activation, oxidative stress response, prostaglandin signaling, and ferroptosis. For downregulated overlaps (Figure 4C), terms included gland and organ development, cell cycle regulation, and tissue morphogenesis. These results indicate that insomnia and ovarian cysts share transcriptomic changes involving immune activation, metabolic stress, cell adhesion, and developmental pathways providing molecular evidence for their potential mechanistic connection.

Discussion

In this multi-omics MR study, we evaluated the potential causal relationship between genetic liability to insomnia and ovarian cyst risk using large-scale GWAS data. We further explored plausible molecular pathways by integrating transcriptomic profiling with hypothesis-generating in silico docking. Collectively, our findings support insomnia as a potential causal risk factor and nominate candidate biological modules and targets warranting further experimental validation.

The MR analyses revealed a consistent and significant causal effect of genetically predicted insomnia on increased ovarian cyst risk across both the ebi-a-GCST90018889 and finn-b-N14_OVARYCYST datasets. Effect sizes were substantial (ORs ranging from 1.486 to 2.137) and statistically robust (all $P < 0.001$). The magnitude of the estimated effects should be interpreted in the context of MR assumptions and phenotype definitions, as differences in case definitions across GWAS sources and potential residual biases (eg., weak-instrument related bias or winner's curse in discovery GWAS) may influence effect size estimates even when directionality is consistent. Sensitivity analyses (MR-Egger intercept, Cochran's Q, and MR-PRESSO) did not reveal significant horizontal pleiotropy or heterogeneity, reinforcing the specificity of the observed associations. Leave-one-out analyses further supported result stability, reducing concern that any single SNP disproportionately drove the findings. Importantly, MR estimates reflect the effect of genetic liability to insomnia rather than short-term or clinically diagnosed insomnia episodes.

These results align with accumulating epidemiological evidence that sleep disturbance adversely affects female reproductive health. Observational studies have linked poor sleep quality and insomnia with higher risks of menstrual disorders,[23] infertility,[24] and polycystic ovary syndrome.[25] However, such studies are vulnerable to confounding and reverse causality. By leveraging genetic variants as instrumental variables, MR strengthens causal inference. Potential mediating pathways may include metabolic traits (eg., BMI/insulin resistance), HPG-axis hormone dynamics, and stress-related neuroendocrine signaling, which could be tested explicitly using multivariable or mediation MR frameworks.

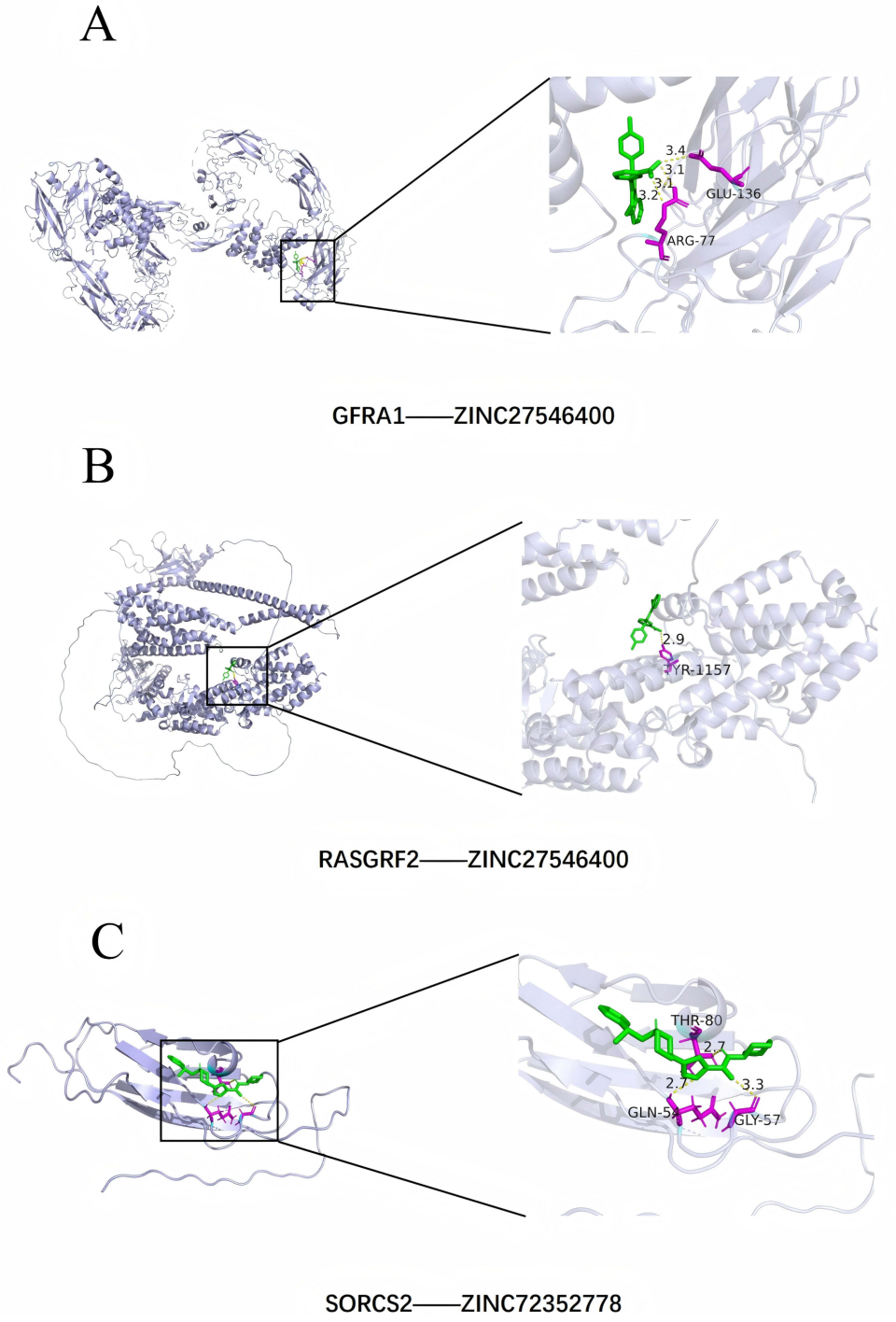

Figure 3 Molecular docking of candidate compounds with key genes linking insomnia and ovarian cysts. (**A**) Docking model of GFRA1 with ZINC27546400. (**B**) Docking model of RASGRF2 with ZINC27546400. (**C**) Docking model of SORCS2 with ZINC72352778.

Bidirectional MR analyses did not support reverse causality, which is consistent with a predominant direction from insomnia liability to ovarian cyst development rather than the reverse.

To investigate biological underpinnings, we conducted SNP mapping and pathway enrichment analyses for insomnia-associated variants relevant to ovarian cyst risk. These analyses indicated interconnected biological modules, including neuronal and synaptic signaling, circadian rhythm regulation, immune-inflammatory processes, and key signal transduction pathways.

Table 4 Physicochemical Properties and Energy of Binding of Candidate Compounds Targeting Key Genes

Gene	Zinc_ID	Hydrogen Acceptors	Hydrogen Donors	Rotatable Bonds	LogP	Molecular Weight	TPSA	Energy of Binding (kcal/mol)
GFRA1	ZINC27546400	3	0	3	4.736	382.443	51	−9.6
RASGRF2	ZINC27546400	3	0	3	4.736	382.443	51	−8.5
SORCS2	ZINC72352778	3	2	6	4.72	395.547	59	−7.9

Neuroendocrine/neuronal signaling was a primary enriched module, implicating HPG-axis dysregulation. Enrichment of neuronal pathways (eg., neurotransmitter receptor activity, NMDA receptor activation, and glutamatergic signaling) highlights the potential role of neuroendocrine axes in ovarian function. Beyond central regulation, ovarian follicular physiology is shaped by local crosstalk between neuronal and immune signals. Neurotrophic factors acting through GFRA1 and SORCS2 can modulate granulosa-theca communication, steroidogenesis, and follicular survival, while RASGRF2-mediated small GTPase signaling may influence cytoskeletal dynamics and ovulatory rupture.[26,27] In parallel, resident macrophages and T cells within follicles produce cytokines and prostaglandins that regulate follicle selection, atresia, and corpus luteum formation.[28] Our enrichment results are compatible with a model in which altered neuro-immune signaling may contribute to a pro-inflammatory and oxidative microenvironment in the ovary.[27,29] These processes, including ferroptosis-related pathways identified in transcriptomic integration, could plausibly promote cyst persistence.[30,31] However, direct mechanistic links require experimental validation.

Circadian regulation was also strongly enriched, suggesting a clock-mediated pathway. The circadian system, orchestrated by transcriptional feedback loops involving CLOCK, BMAL1, PER, and CRY genes,[11] governs reproductive hormone secretion[32] and follicular dynamics.[33] Experimental studies have demonstrated that circadian disruption impairs ovulation and promotes ovarian pathology.[34,35] Thus, genetic predisposition to insomnia may contribute to ovarian cyst risk via circadian dysregulation.

Immune-inflammatory signaling (notably NF-κB/cytokines) was also enriched. Chronic low-grade inflammation is increasingly recognized as a shared pathogenic mechanism underlying both sleep disturbance[36] and gynecological disorders.[37–39] Finally, ferroptosis and oxidative stress signatures aligned with transcriptomic overlaps. Ferroptosis, a regulated cell death program linked to lipid peroxidation, was identified through transcriptomic integration as a shared molecular process between insomnia and ovarian cysts, consistent with evidence implicating ferroptosis in ovarian pathology.[40,41]

By integrating SNP-mapped genes with ovarian cyst tissue transcriptomics (GSE7305), we identified GFRA1, SORCS2, and RASGRF2 as overlapping candidate genes potentially bridging insomnia and ovarian cyst pathogenesis. These genes regulate neurotrophic signaling, synaptic plasticity, and small GTPase signaling, all relevant to ovarian function and follicular development.[42] Docking suggested that sleep-related small molecules (eg., ZINC27546400 and ZINC72352778) have favorable predicted binding to GFRA1, RASGRF2, and SORCS2, respectively. These findings provide preliminary in silico support for target tractability and motivate functional studies to assess whether modulating shared neurotrophic and small GTPase-related pathways could be therapeutically relevant for both sleep regulation and ovarian physiology.[43,44] Accordingly, the docked compounds should be interpreted as putative pleiotropic modulators of common signaling nodes, rather than as independent "sleep drugs" acting directly on ovarian tissue.[45]

Such dual effects are biologically plausible because GFRA1, SORCS2, and RASGRF2 function in neuronal signaling, and related neurotrophic/MAPK and small GTPase-related pathways also contribute to ovarian folliculogenesis and luteal function.[46] Nonetheless, whether these compounds can meaningfully affect sleep or ovarian pathology in vivo requires experimental validation. Docking results should also be interpreted cautiously: although GFRA1 binds the endogenous ligand GDNF, SORCS2 and RASGRF2 are not classical small-molecule targets and are mainly regulated by protein-protein interactions and intracellular signaling. Thus, docking here serves to explore potential tractability rather than native ligand binding and should be viewed as hypothesis-generating.[47–49]

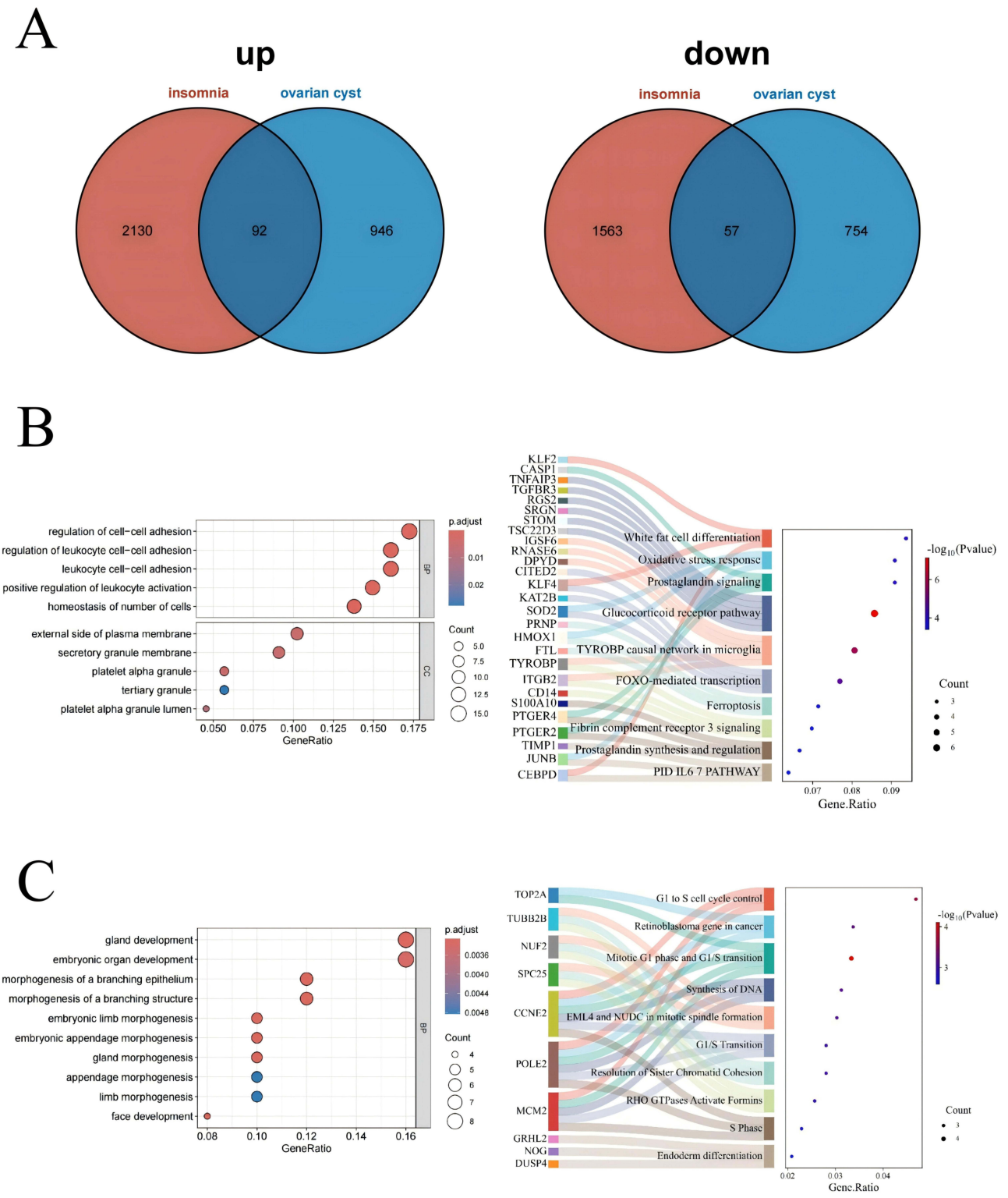

Figure 4 Intersection and functional enrichment analysis of differentially expressed genes (DEGs) from insomnia and ovarian cyst GEO datasets. (**A**) Venn diagrams showing the overlap of upregulated (left) and downregulated (right) DEGs between insomnia (GSE208668) and ovarian cyst (GSE7305) datasets. (**B**) GO and pathway enrichment of overlapping upregulated genes. Bubble plots and Sankey diagrams highlight enrichment in cell adhesion, leukocyte activation, and immune-related pathways. (**C**) GO and pathway enrichment of overlapping downregulated genes, mainly involved in gland development, embryonic morphogenesis, and cell cycle regulation. These results suggest shared biological pathways that may mediate the link between insomnia and ovarian cyst pathogenesis.

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Differential expression analyses of insomnia (GSE208668) and ovarian cyst (GSE7305) further supported a molecular connection between these conditions: 92 upregulated and 57 downregulated genes were shared across both datasets. Enrichment analyses indicated that shared upregulated genes were involved in immune activation, oxidative stress responses, prostaglandin signaling, and ferroptosis, whereas shared downregulated genes were enriched in developmental processes and cell cycle regulation. These overlaps reinforce the hypothesis that insomnia and ovarian cysts converge on inflammation, metabolic dysregulation, and impaired tissue development. Recent transcriptomic and proteomic studies similarly highlight immune activation[50,51] and ferroptosis[52,53] as central features of both sleep disorders and ovarian disease.

This study has several strengths, including well-powered independent GWAS datasets, bidirectional MR to reduce concerns about reverse causality, comprehensive sensitivity testing, and multi-layered omics integration. The nomination of candidate targets and ligands via docking adds a translational dimension that is rarely explored in prior work.

Several limitations should be noted. First, despite rigorous pleiotropy testing, undetected pleiotropy cannot be fully excluded. Second, transcriptomic analyses relied on public datasets with inherent heterogeneity. Third, docking predictions require cellular and animal validation to establish biological relevance. Lastly, while we focused on ovarian cysts, other sleep traits showed variable associations with gynecological outcomes and warrant further study. In addition, GWAS instruments were predominantly derived from European-ancestry cohorts, limiting generalizability to other populations. Transcriptomic comparisons between GSE208668 and GSE7305 may be influenced by batch effects and platform differences despite standardized preprocessing, and ovarian cyst tissue transcriptomics likely reflect both causal drivers and downstream consequences, constraining strict causal interpretation.

Taken together, our integrative strategy combining MR, transcriptomics, and structure-based docking provides a framework for uncovering genetic links between sleep disorders and benign gynecological conditions while nominating candidate targets and compounds for downstream functional and translational evaluation.

Conclusion and Future Directions

In conclusion, our integrative genetic and molecular investigation provides the first comprehensive evidence supporting a causal role of insomnia in ovarian cyst susceptibility. The elucidation of neuronal, circadian, immune-inflammatory, and ferroptosis-related pathways, coupled with the identification of druggable target genes, opens new avenues for mechanistic exploration and therapeutic intervention.

Future research should focus on functional validation of candidate genes and pathways, experimental assessment of sleep-related compounds in ovarian models, and exploration of whether improving sleep quality could mitigate ovarian cyst risk. Moreover, investigating the broader impact of sleep traits on female reproductive health, using multi-omics and experimental approaches, represents a promising direction for advancing precision medicine in this field.

Data Sharing Statement

All the data supporting the findings of this study are included in this article and its supporting information.

Ethics Approval and Consent to Participate

This study did not involve any direct interaction with human participants, clinical interventions, or access to identifiable personal information. All analyses were conducted using publicly available, de-identified summary-level GWAS data (IEU Open GWAS) and public transcriptomic datasets from the GEO.

According to Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (issued February 18, 2023, People's Republic of China), research that uses legally obtained, publicly available, and anonymized human data, and does not involve new sample collection or intervention, may be exempt from additional Institutional Review Board (IRB) approval. Therefore, this study was exempt from ethical review by the local ethics committee.

The original studies contributing data to the public databases were conducted in accordance with the Declaration of Helsinki and had obtained ethical approval and informed consent from their respective institutional review boards.

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Disclosure

The authors declare no conflicts of interest in this work.

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