frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 07 February 2024
DOI 10.3389/fneur.2024.1321216

OPEN ACCESS

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RECEIVED 17 October 2023
ACCEPTED 11 January 2024
PUBLISHED 07 February 2024

CITATION
Zhang RY, Li FJ, Zhang Q, Xin LH, Huang JY and Zhao J (2024) Causal associations between modifiable risk factors and isolated REM sleep behavior disorder: a mendelian randomization study. *Front. Neurol.* 15:1321216. doi: 10.3389/fneur.2024.1321216

Causal associations between modifiable risk factors and isolated REM sleep behavior disorder: a mendelian randomization study

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Objectives: This Mendelian randomization (MR) study identified modifiable risk factors for isolated rapid eye movement sleep behavior disorder (iRBD).

Methods: Genome-wide association study (GWAS) datasets for 29 modifiable risk factors for iRBD in discovery and replication stages were used. GWAS data for iRBD cases were obtained from the International RBD Study Group. The inverse variance weighted (IVW) method was primarily employed to explore causality, with supplementary analyses used to verify the robustness of IVW findings. Co-localization analysis further substantiated causal associations identified via MR. Genetic correlations between mental illness and iRBD were identified using trait covariance, linkage disequilibrium score regression, and co-localization analyses.

Results: Our study revealed causal associations between sun exposure-related factors and iRBD. Utilizing sun protection (odds ratio [OR] = 0.31 [0.14, 0.69], $p = 0.004$), ease of sunburn (OR = 0.70 [0.57, 0.87], $p = 0.001$), childhood sunburn occasions (OR = 0.58 [0.39, 0.87], $p = 0.008$), and phototoxic dermatitis (OR = 0.78 [0.66, 0.92], $p = 0.003$) decreased iRBD risk. Conversely, a deep skin color increased risk (OR = 1.42 [1.04, 1.93], $p = 0.026$). Smoking, alcohol consumption, low education levels, and mental illness were not risk factors for iRBD. Anxiety disorders and iRBD were genetically correlated.

Conclusion: Our study does not corroborate previous findings that identified smoking, alcohol use, low education, and mental illness as risk factors for iRBD. Moreover, we found that excessive sun exposure elevates iRBD risk. These findings offer new insights for screening high-risk populations and devising preventive measures.

KEYWORDS

mendelian randomization, isolated REM sleep behavior disorder, risk factors, causal association, genetic correlation

1 Introduction

Isolated rapid eye movement behavior disorder (iRBD) is defined as parasomnia characterized by the absence of muscle atonia during rapid eye movement (REM) sleep, often accompanied by dream enactment behavior (1, 2). Patients frequently display aggressive behaviors such as shouting, punching, or striking during sleep, leading to sleep disturbances and potential harm to themselves or their bed partners (3–5). Furthermore, previous studies have shown that iRBD is most importantly a potential preclinical sign of neurodegenerative synucleinopathies, with more than 80% of patients with iRBD eventually develop Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA), (6–9). Therefore, identifying risk factors, especially those amenable to intervention, is crucial for screening high-risk populations and reducing the incidence of iRBD.

Numerous studies have suggested that increased sun exposure can reduce the incidence of PD (10–12), but its effect on iRBD is still uncertain. Previous observational studies have identified various risk factors for iRBD including lifestyle factors (smoking, alcohol consumption, coffee and tea intake, and low physical activity), low education levels, agricultural work, pesticide exposure, head injuries, mental illness, and antidepressant use (13–20). However, substantial contradictions and debates persist regarding these factors. In a multicenter case–control study, Postuma et al. found that patients with iRBD (diagnosed using polysomnography [PSG]) were more likely to report smoking, low educational levels, head injuries history, occupational pesticide exposure, and farming work (16). Additionally, a Canadian Longitudinal Study on Aging (CLSA) with a sample size of 30,097 individuals found mental illness and antidepressant use could also serve as risk factors for possible RBD (pRBD, diagnosed via an RBD single-questionnaire) (19). However, a study from Beijing conducted by Zhang et al. involving 7,225 individuals found no association between education levels, occupation, antidepressant treatment, and the incidence of pRBD (diagnosed using the RBD Questionnaire-Hong Kong) (20). Furthermore, a community-based study led by Jian-Fang Ma involving 3,635 individuals failed to identify the relationships between smoking, depression and the risk of pRBD (diagnosed by the RBD screening questionnaire) (15). These findings demonstrate the complexity and ongoing uncertainty that is encountered in the field of iRBD research.

Discrepancies between studies could be attributed to several factors. First, prior studies used traditional observational research designs, which are susceptible to confounding factors and reverse causation. Second, the inadequate sample sizes of some studies limit statistical power, increasing the likelihood of false-negative results and diminishing the generalizability of study conclusions. Finally, the low specificity of questionnaires used may have led to selection bias. Therefore, addressing limitations of prior studies and conducting further research using more robust study designs and larger sample sizes will be needed to obtain reliable and definitive conclusions.

Mendelian randomization (MR) is a statistical method that employs genetic variations as instrumental variables in the appraisal of causal associations between risk factors and particular diseases. The evidence level of MR is second only to randomized controlled trials (21–23). As genetic variations are randomly allocated to offspring through allelic randomization (24), results of MR studies are less likely to be affected by confounding factors and reverse causality, common limitations of traditional observational research (25). Furthermore, the genome-wide association study (GWAS) data on iRBD utilized in our MR analysis included a large sample, with each patient being diagnosed through PSG. This significantly enhances the credibility of our research findings.

Our study classified 29 potential modifiable risk factors into the following eight categories: anthropometric traits, metabolic traits, smoking, beverage consumption patterns, physical activity, education levels, mental illness, and sun exposure-related factors. We performed the MR approach to evaluate the causality between these factors and iRBD, providing more perspectives and evidence for screening and early intervention in at-risk populations.

2 Materials and methods

2.1 Study design

We conducted a systematic review of articles in the PubMed database to identify potential risk factors for iRBD. After selecting 29 modifiable factors, they were classified into the following eight categories: anthropometric traits, metabolic traits, smoking behavior, beverage consumption patterns, physical activity, education levels, mental illness, and sun exposure-related factors (Figure 1).

MR method employs genetic variations as instruments for exposure, so we assessed the causality between 29 modifiable factors and iRBD risk based on genetic variants strongly linked to these factors. The design of this MR study is illustrated in Figure 1. First, we conducted a two-sample MR analysis to evaluate the causality between these factors (as exposure) and iRBD (as outcome) in both the discovery and replication stages. Second, co-localization analyses of causal associations identified in MR study were performed to further explore whether the relationships depended on shared driver genes. Subsequently, reverse MR analysis was used to evaluate the possibility of reverse causality. Finally, since numerous previous studies have supported the connection between several common mental illness and iRBD; we explored their genetic correlations using trait covariance, linkage disequilibrium score regression (LDSC), and co-localization analyses.

MR research must satisfy the following three core assumptions: relevance, independence, and exclusivity. First, genetic variants should be highly correlated with an exposure. Second, genetic variation should not be associated with confounding factors. Lastly, genetic variants should not affect an outcome via a pathway other than that of the exposure (26, 27).

The GWAS summary datasets used in this study were derived from publicly available databases previously receiving ethical approval and all participants of each GWAS data provided informed consent. Our research strictly followed Strengthening the Reporting of Mendelian Randomization Studies (STROBE-MR) guidelines (28).

2.2 Data sources

The GWAS data for exposure factors in discovery and replication cohorts primarily originated from various datasets available on the

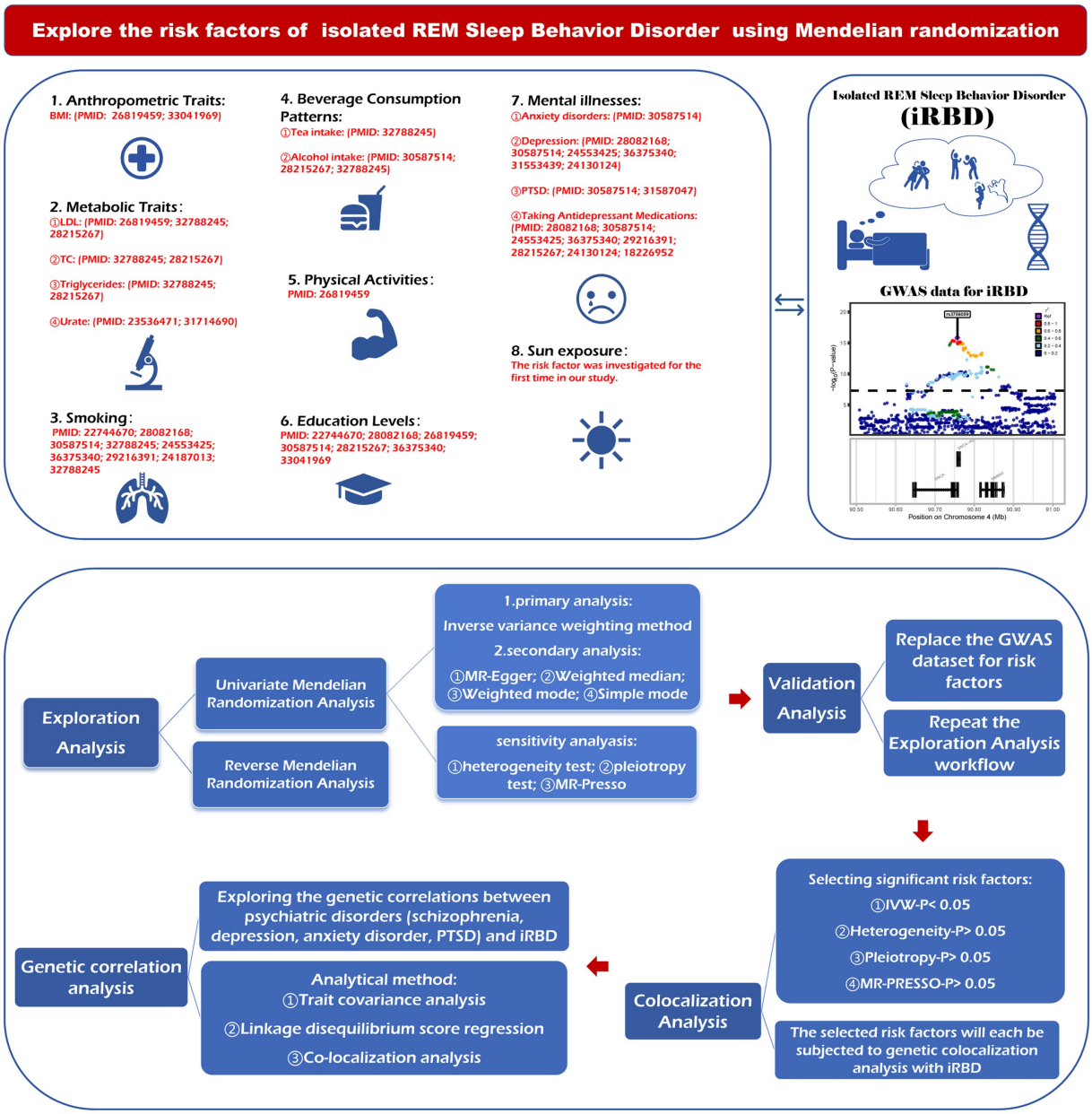

FIGURE 1
The figure outlines the steps of the research design. BMI, body mass index; LDL, low density lipoprotein; TC, total cholesterol; PTSD, post-traumatic stress disorder; MR, Mendelian randomization; GWAS, genome-wide association studies; MR-PRESSO, Mendelian randomization pleiotropy residual sun and outlier.

IEU Open GWAS project website.[1] Moreover, data on anxiety disorders in the discovery cohort; along with replication cohort data including urate levels, strenuous sports or other exercises, and years of schooling were sourced from the GWAS catalog.[2] Data on PTSD (PMID:31594949) in the discovery cohort and schizophrenia (PMID:35396580) in the replication cohort were obtained from the Psychiatric Genomic Consortium (PGC).[3] Detailed information is provided in Tables 1, 2.

Outcome data for iRBD were obtained from the International RBD Study Group involving approximately 9,447 individuals of European ancestry (1,061 cases and 8,386 controls) (29). This iRBD cohort included large cohorts of French, French Canadian, Italian and British origins, and smaller cohorts from different European populations. The cases were aged 68 +/− 9 years (standard deviation) on average and

1 https://gwas.mrcieu.ac.uk
2 https://www.ebi.ac.uk/gwas
3 https://pgc.unc.edu

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TABLE 1 The risk factors for iRBD in the discovery phase.

Exposure	ID	NSNP	Sample	R^2 (%)	F	Power	PMID or Consortium
Anthropometric traits							
Standing height	ukb-b-10787	724	461,950	8.55%	30.9	1.00	MRC-IEU
Weight	ukb-b-11842	470	461,632	5.01%	33.6	0.38	MRC-IEU
Body mass index	ukb-b-19953	426	461,460	5.33%	41.7	1.00	MRC-IEU
Basal metabolic rate	ukb-b-16446	517	454,874	3.51%	20.6	1.00	MRC-IEU
Trunk fat-free mass	ukb-a-292	394	331,030	3.38%	19.7	1.00	Neale Lab
Whole body fat-free mass	ukb-a-266	391	331,291	3.28%	19.1	1.00	Neale Lab
Trunk fat percentage	ukb-b-16407	365	454,613	3.66%	34	0.99	MRC-IEU
Whole body water mass	ukb-b-14540	527	454,888	3.36%	18.5	1.00	MRC-IEU
Metabolic traits							
HDL-C	ebi-a-GCST008035	15	17,751	>100%	9817.4	0.06	31217584
LDL-C	ebi-a-GCST90002412	290	431,167	11.00%	46.7	1.00	32493714
Total cholesterol	ieu-a-301	81	187,365	8.53%	75.1	0.15	GLGC
Triglycerides	ieu-b-111	267	441,016	8.24%	43.3	0.88	UK Biobank
Hypertension	ebi-a-GCST008036	7	21,936	2.47%	69.3	0.23	31217584
Urate levels	ebi-a-GCST001791	25	110,347	9.04%	123.3	0.99	23263486
Smoking							
Current tobacco smoking	ukb-a-16	9	337,030	0.04%	12.7	0.30	Neale Lab
Past tobacco smoking	ukb-b-2134	93	424,960	1.40%	56.5	1.00	MRC-IEU
Beverage consumption patters							
Coffee intake	ukb-b-5237	36	428,860	0.36%	21.3	1.00	MRC-IEU
Tea intake	ukb-b-6066	39	447,485	0.55%	37.1	1.00	MRC-IEU
Alcohol intake frequency	ukb-b-5779	94	462,346	2.32%	76.2	0.21	MRC-IEU
Physical activity							
Number of days/week of vigorous physical activity 10+ minutes	ukb-b-151	11	440,512	0.37%	136.9	1.00	MRC-IEU
Education levels							
Years of schooling	ieu-a-1239	299	766,345	2.14%	44.6	0.95	SSGAC
Mental illness							
Schizophrenia	ieu-b-5099	202	320,404	27.12%	201.2	1.00	PGC
Anxiety disorder	GWAS catalog: GCST90043712	46	456,348	1.86%	161.5	1.00	UK Biobank
Depression	GWAS catalog: ebi-a-GCST003769	11	180,866	0.20%	19.8	0.06	NA
PTSD	PMID:31594949	4	206,605	1.31%	551.5	1.00	PGC
Sun exposure-related factors							
Ease of sunburn	ukb-b-533	120	453,065	13.08%	51.4	1.00	MRC-IEU
Childhood sunburn occasions	ukb-b-13246	76	346,955	3.52%	36.9	1.00	MRC-IEU
Skin color	ukb-b-19560	135	456,692	5.20%	18.9	1.00	MRC-IEU
Use of sun/uv protection	ukb-b-7422	47	459,416	0.92%	29.2	1.00	MRC-IEU

NSNPs, number of single nucleotide polymorphism; R^2, phenotype variance explained by genetics; F, F statistic; PMID, the publication ID in PubMed; HDL-C, High density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; PTSD, post-traumatic stress disorder; MRC-IEU, Medical Research Council Integrative Epidemiology Unit; GLGC, Global Lipids Genetics Consortium; SSGAC, the Social Science Genetic Association Consortium; PGC, Psychiatric Genomic Consortium; GIANT, Genetic Investigation of Anthropometric Traits; GSCAN, the GWAS and Sequencing Consortium of Alcohol and Nicotine use.

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TABLE 2 The risk factors for iRBD in the replication phase.

Exposure	ID	NSNP	Sample	R^2 (%)	F	Power	PMID or Consortium
Anthropometric traits							
Standing height	ieu-a-89	356	253,288	12.10%	59.2	1.00	GIANT
Weight	ieu-a-107	10	73,137	0.92%	64.3	0.82	GIANT
Body mass index	ieu-b-40	482	681,275	5.05%	52.7	1.00	GIANT
Metabolic traits							
HDL-C	ieu-b-109	295	403,943	8.24%	40.5	0.05	UK Biobank
LDL-C	ieu-b-110	141	440,546	5.42%	59.5	1.00	UK Biobank
Total cholesterol	met-c-933	20	21,491	8.46%	63	0.12	27005778
Triglycerides	ieu-a-302	53	177,861	5.44%	54.4	0.88	GLGC
Hypertension	finn-b-I9_HYPTENS	51	218,734	9.71%	371.6	0.77	NA
Urate levels	GWAS catalog: GCST90014015	226	389,404	4.09%	32.7	1.00	UK Biobank
Smoking							
Cigarettes smoked per day	ieu-b-142	20	249,752	3.31%	152.3	0.95	GSCAN
Beverage consumption patters							
Alcoholic drinks per week	ieu-b-73	30	335,394	0.61%	39.4	0.46	GSCAN
Physical activity							
Strenuous sports or other exercises	GWAS catalog: GCST006100	8	350,492	0.42%	109.3	0.31	UK Biobank
Education levels							
Years of schooling	GWAS catalog: GCST90029013	206	461,457	46.62%	853.5	0.97	UK Biobank
Mental illness							
Schizophrenia	NA	146	130,644	24.69%	188.8	0.06	35396580
Anxiety disorder	finn-b KRA_PSY_ANXIETY	5	218,792	0.70%	379.5	0.84	NA
Major Depressive Disorder	ieu-a-1187	30	480,359	1.28%	196.9	1.00	PGC
PTSD	finn-b-F5_PTSD	3	199,213	11.56%	6192.1	0.56	NA
Sun exposure-related factors							
Sunburn easily	finn-b-L12_NONIONRADISKIN	8	218,281	17.00%	377.8	1.00	NA
Phototoxic dermatitis	finn-b-L12_ RADIATIONRELATEDSKIN	7	218,792	18.27%	2327.4	1.00	NA

were 81% male, and the controls were aged 58.5 +/− 9 years on average, 68% male. Isolated RBD cases were diagnosed according to criteria outlined in the International Classification of Sleep Disorders (2nd or 3rd Edition), which includes video polysomnography findings. To ensure that case and control groups were comparable, principal components were employed to adjust for population substructure, taking factors such as sex and age into account.

2.3 Instrumental variable selection

A series of quality control measures were used to select appropriate instrumental variables. Single nucleotide polymorphisms (SNPs) were selected based on strong associations with the exposure ($p < 5 \times 10^{-8}$) and a minor allele frequency (MAF) > 0.01. To eliminate linkage disequilibrium (LD), SNPs were clumped based LD threshold ($r^2 < 0.001$) and distance (10,000 kb). If SNPs were unavailable, high-LD proxies were selected for evaluation based on index SNP ($r^2 > 0.8$) per LD link or SNIPA guidelines (30, 31). Instrument strength was evaluated using the F-statistic, with an F-statistic >10 designated to mitigate potential bias arising from weak instruments (32, 33).

2.4 Statistical analysis

For the primary MR analysis, the inverse variance weighted (IVW) method (34) was used to evaluate causality. In addition, MR-Egger regression (35), weighted-median estimation (36) and weighted-mode (37) methods were used to supplement IVW findings. IVW analysis is sometimes susceptible to instrumental bias and multiple effects. Therefore, sensitivity analyses were used examine the

validity and robustness of IVW results. Cochran's Q statistic was used to assess heterogeneity among estimated IVW values. The MR-Egger intercept and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) methods were used to detect horizontal pleiotropy. The MR-PRESSO method is useful for detecting outlier values. The analysis was conducted after all other MR analyses, after excluding aberrant SNPs (38). Leave-one-out sensitivity analysis was performed to validate the impact of each SNP loci.

All statistical analyses were performed using two-tailed Student's t-tests. The effect estimates were presented as odds ratios (ORs) to more intuitively indicate the relationship between potential risk factors and iRBD. Values of $p < 0.05$ were considered statistically significant. Finally, we interpreted findings based on statistical significance and consistency (via a comparison between discovery and validation cohorts). The mRnd was used to calculate the statistical power for Mendelian randomization.[4] Statistical analyses were performed using the R statistical software (version 4. 2. 3) and relevant R packages.

2.5 Trait covariance, LDSC and co-localization analyses

The bivariate LDSC method was used to assess the genetic correlations between mental illness and iRBD (39–42). Trait covariance analysis was performed using the metaCCA package (43). We employed co-localization analysis using the Coloc R package (version 5.1.0.1) to further probe shared genetic underpinnings (44). The variant with the lowest value of p designated via MR analysis was most strongly associated with an exposure and selected as a reference. We included variants within 50 kb of the reference variant. The 1,000 Genomes v3 European ancestry dataset was used as an LD reference panel. In Bayesian co-localization analysis, five posterior probabilities are provided to determine whether two traits share the same variation. A posterior probability of hypothesis 4 greater than 0.8 indicates the presence of shared causal variants.

3 Results

Following the exclusion of SNPs in linkage disequilibrium, the number of SNPs analyzed in our study ranged from 3 to 724, with corresponding explained variances with diverse distributions ranging from 0.04 to 100% (Tables 1, 2). Notably, all included SNPs had F-statistics that surpassed the empirically determined threshold of 10, indicating the absence of any potential bias arising from weak instrumental variables, which confirms the credibility of our findings.

3.1 Results based on the discovery cohort

In the discovery phase, we identified seven genetically determined factors across two categories that were causally associated with iRBD (Figure 2A). Their impacts on iRBD incidence were presented as odds ratios (ORs) with their corresponding 95% confidence intervals (95%CIs). Specifically, among anthropometric traits, trunk fat-free mass (OR: 1.54 [1.03, 2.31]; $p = 0.036$), whole-body fat-free mass (OR: 1.60 [1.06, 2.42]; $p = 0.027$), and whole-body water mass (OR: 1.61 [1.06, 2.45]; $p = 0.025$) emerged as risk factors. Within the category pertaining to sunlight exposure, factors such as ease of sunburn (OR: 0.70, 95% CI: 0.57–0.87; $p = 0.001$), childhood sunburn occasions (OR: 0.58, 95% CI: 0.39–0.87; $p = 0.008$), use of sun protection (OR: 0.31, 95% CI: 0.14–0.69; $p = 0.004$) were associated with a reduced risk of iRBD, while a deeper skin color (OR: 1.42, 95% CI: 1. 04–1. 93; $p = 0.026$) was linked to an increased incidence. Our study did not find evidence supporting causal associations between other factors and iRBD. Reverse MR analyses revealed that iRBD significantly increased drinking risk (Supplementary Figure S13).

Study conclusions were supported by weighted-median estimation, weighted-mode, and MR-Egger methods (Supplementary Table S2). Cochran's Q statistic indicated no significant heterogeneity in SNP effects ($p > 0.05$). No evidence of potential horizontal pleiotropy was detected for the seven factors identified ($p > 0.05$). To further assess the robustness of the results, we conducted MR-PRESSO tests on the included SNP loci. In addition, a leave-one-out sensitivity analysis was conducted to assess the influence of each SNP on the overall causal relationship. The results demonstrated that systematically removing individual SNPs and repeating the MR analysis did not reveal significant differences in the observed causal relationships (Supplementary Tables S3–S5).

3.2 Results based on the replication cohort

Sunburn easily (OR: 0.82 [0.70, 0.96]; $p = 0.015$) and phototoxic dermatitis (OR: 0.78 [0.66, 0.92]; $p = 0.026$) were confirmed to be protective factors for iRBD using replication phase data (Figure 2B). Furthermore, similar effect estimates were observed after applying weighted-median, weighted-mode, and MR-Egger methods (Supplementary Table S7). In sensitivity analyses, no heterogeneity or pleiotropy was observed, indicating the robustness of results (Supplementary Tables S8, S9). However, given that the data used regarding trunk and whole-body fat-free mass, and whole-body water mass were originated from a single source, we were unable to confirm the causal relationship between these factors and iRBD in the replication stage.

3.3 Co-localization analysis

To further investigate whether causal associations identified in discovery and validation phases were driven by shared genes, we conducted co-localization analysis. The results were as follows (Figure 3; Supplementary Table S17): ease of sunburn [coloc. Abf-posterior probability of hypothesis 4 (PPH4) = 0.057], childhood sunburn occasions (coloc. Abf-PPH4 = 0. 441), sun/ultraviolet (UV) protection (coloc. Abf-PPH4 = 0.426), and a deeper skin color (coloc. Abf-PPH4 = 0.039), sunburn easily (coloc. Abf-PPH4 = 0.301), and phototoxic dermatitis (coloc. Abf-PPH4 = 0.437). In general, a PPH4 exceeding 80% is considered indicative of robust colocalization evidence. However, in our research, the PPH4 values ranged from 3 to 44%. Additionally, there was no observed genetic overlap between

4 https://cnsgenomics.shinyapps.io/mRnd/

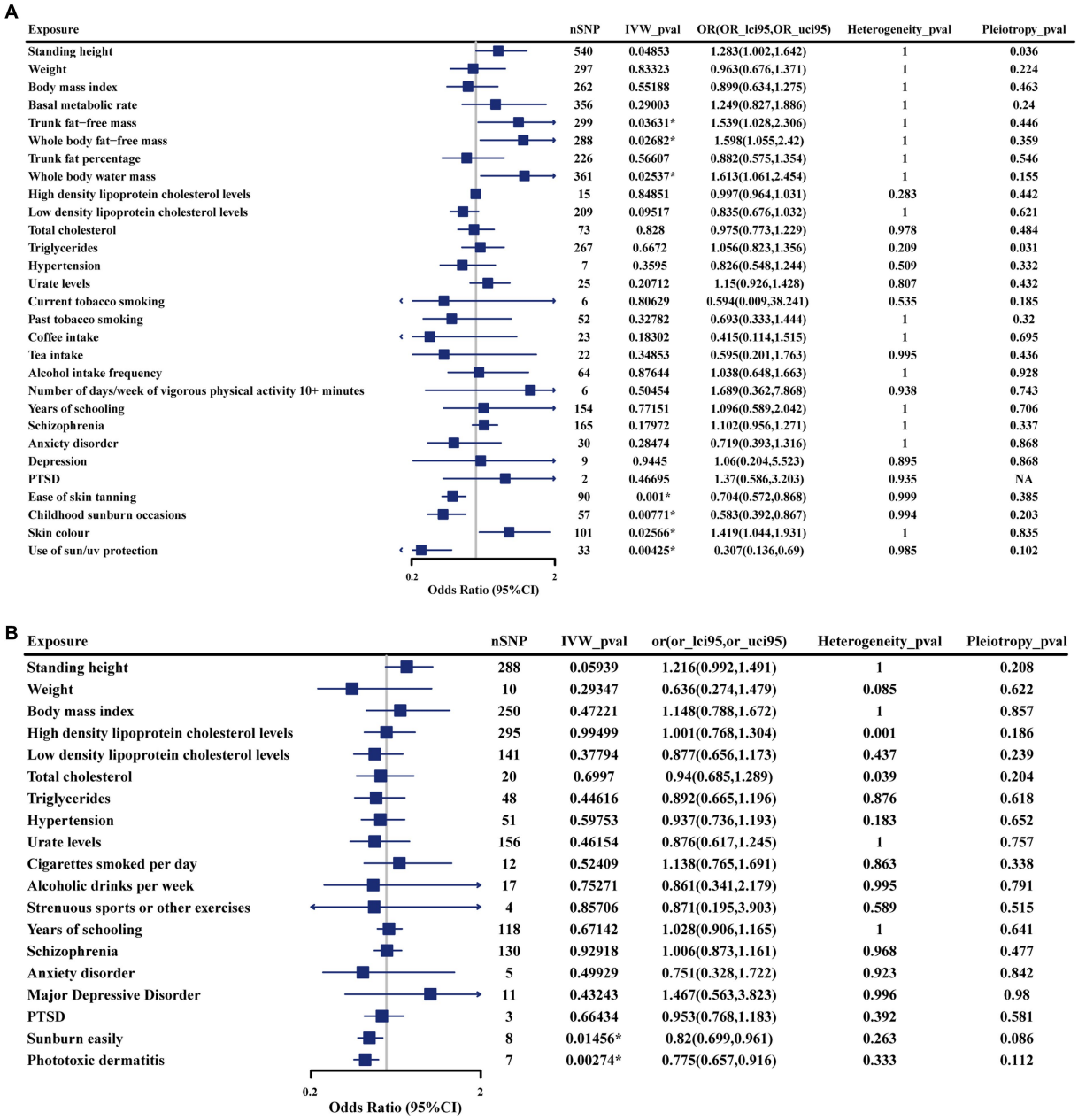


FIGURE 2
Forest plot illustrates the causal estimates of modifiable risk factors on iRBD using the inverse variance-weighted method. **(A)** Results from the discovery cohort. **(B)** Results from the replication cohort. SNP, singlenucleotide polymorphism; IVW: Inverse variance weighted; OR, odds ratio; 95%LCI, lower limit of 95% CI; 95%UCI, upper limit of 95% CI. Statistics significant. *$p < 0.05$.

three exposure factors (trunk fat-free mass, whole-body fat-free mass, and whole-body water mass) and iRBD occurring within a range of 50 kb of their respective lead SNPs.

3.4 Genetic correlation between common mental illness and iRBD

In this study, we identified a genetic correlation between iRBD and anxiety disorders using the LDSC method ($r = 0.2719$, $p = 0.0098$) and trait covariance analysis (covariance = 0.0096). Moreover, co-localization analysis of iRBD (exposure) and anxiety disorders (outcome) identified a shared driver gene located within 50 kb of rs7822441 (Figure 4). However, no evidence supported a genetic correlation between schizophrenia, depression, PTSD, and iRBD.

4 Discussion

Considering the prevailing ambiguity surrounding risk factors for iRBD, our investigation marks the pioneering utilization of MR analysis to systematically assess the causality between 29 potential

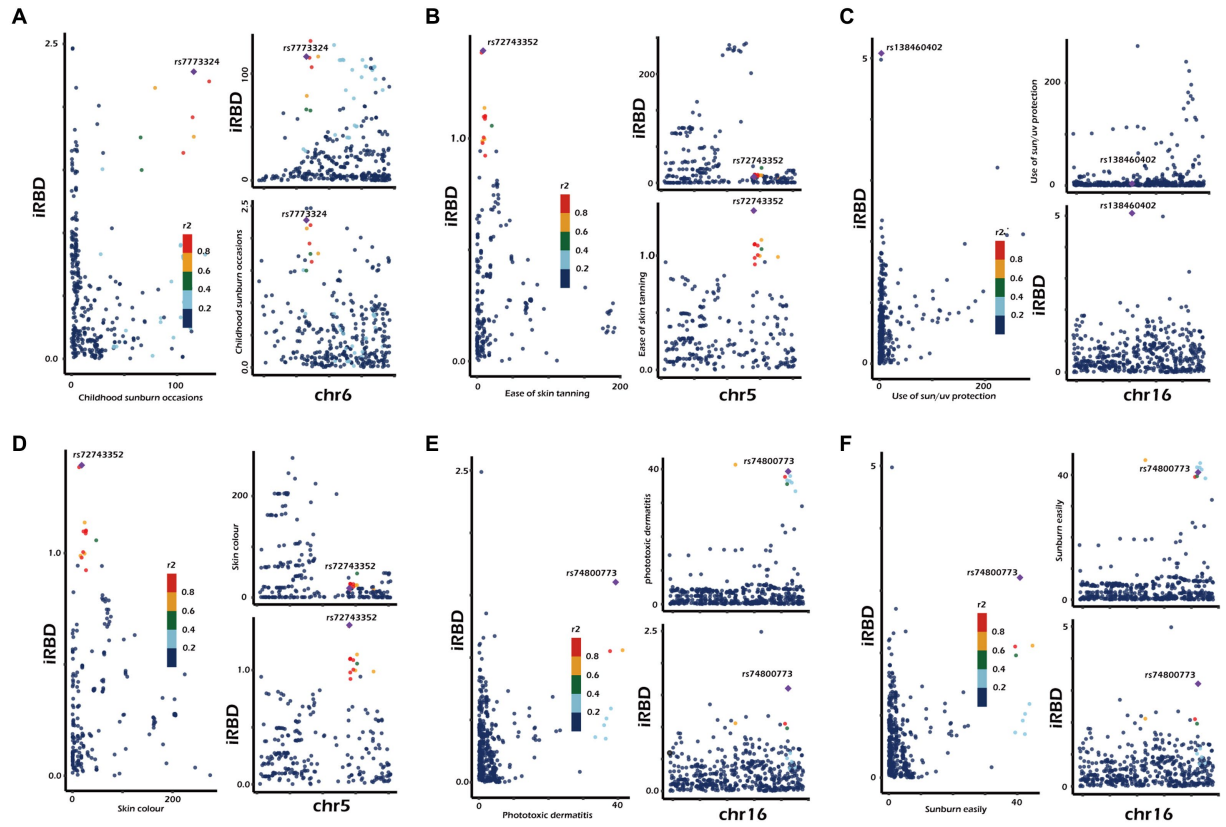


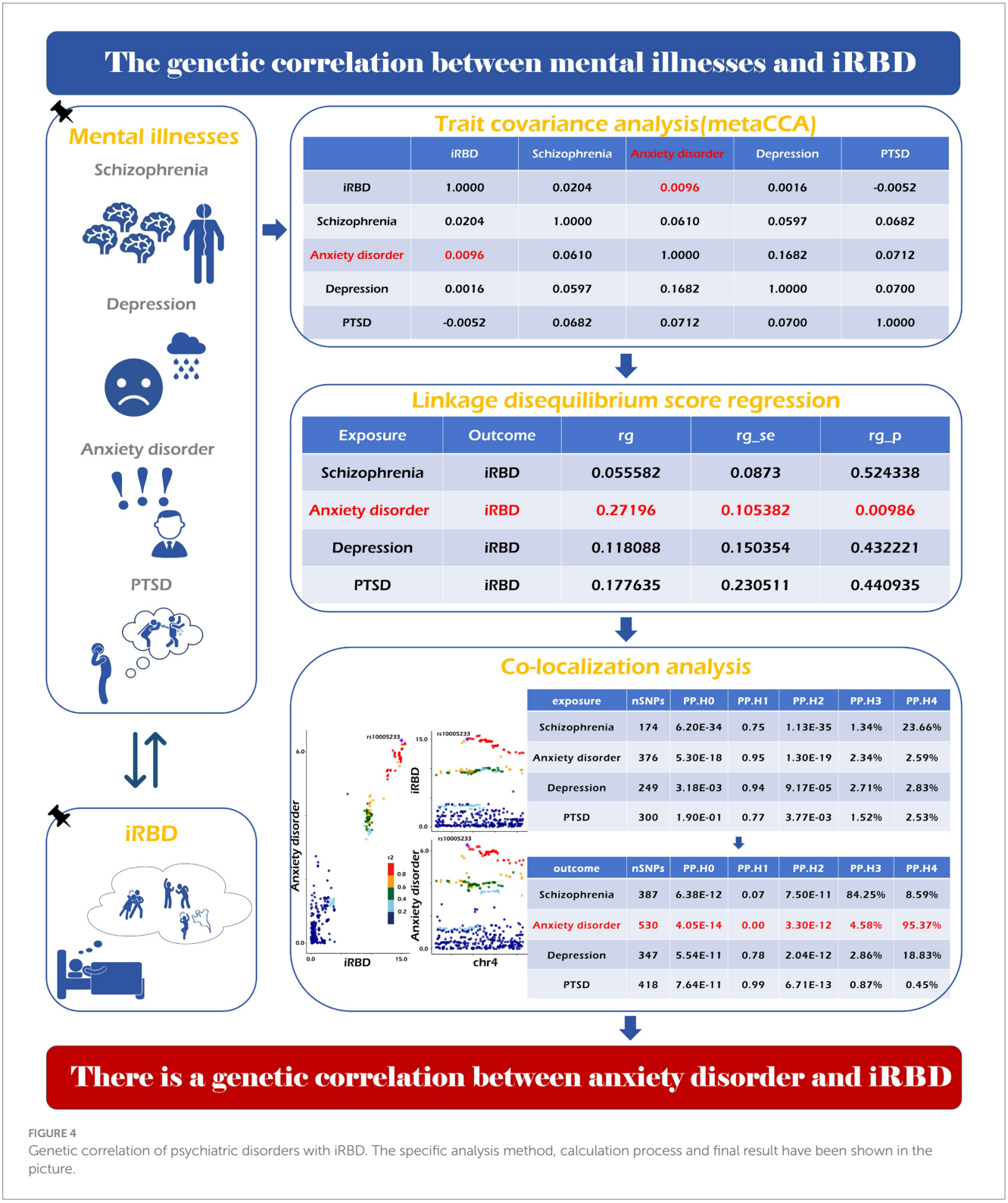
FIGURE 3
Genetic correlation of sun exposure-related factors with iRBD. Results were derived from co-localization analysis. chr, chromosome. The presented data are available in Supplementary Table 2.

determinants and iRBD. Our study identified a causal relationship between sunlight exposure the incidence of iRBD. Specifically, utilizing sun protection, and ease of sunburn, childhood sunburn occasions, and phototoxic dermatitis may reduce risk of iRBD. In contrast, individuals with a deep skin color are at increased iRBD risk. Furthermore, our research revealed no causal associations between smoking, coffee consumption, alcohol intake, educational attainment, mental illness, and other risk factors previously identified through observational studies and iRBD. A genetic correlation between anxiety disorders and iRBD was observed.

Previous researches have demonstrated that increasing exposure to sunlight can diminish risk of PD by elevating levels of 25-hydroxyvitamin D (10, 11, 45–47). IRBD, as a prodromal stage of α-synucleinopathies, is also the strongest predictor of PD onset. However, there is currently a lack of research exploring the relationship between sunlight exposure and iRBD. Therefore, we selected several factors related to sun exposure to investigate whether they were causally associated with iRBD. Surprisingly, we found that individuals who were prone to sunburn, had a childhood history of sunburn and phototoxic dermatitis, and took sun protection measures tended to have a reduced risk of developing iRBD. Conversely, individuals with a deep skin color were at increased risk of developing the disease. At first glance, these results seem to contradict each other. However, upon closer examination, intriguing connections emerge.

In our discovery cohort, four consistent MR methods initially demonstrated that sun protection measures decrease iRBD incidence, underscoring the reliability of our findings. It is well-documented that personal protective behaviors play a significant role in moderating UV exposure (48), suggesting that excessive sun exposure could pose a risk for iRBD. Deep skin color emerged as an iRBD risk factor, a conclusion reinforced by both IVW and MR-Egger methods. Prior researches have indicated that individuals with deeper skin tones often exhibit reduced sunlight sensitivity, possibly leading to less frequent use of sun protection and heightened sun exposure (49–53). Data from both our discovery and replication cohorts, sourced from FinnGen and the UK Biobank, revealed that those more prone to sunburn experience a lower iRBD incidence. According to Fitzpatrick's photo-type classification, sunburn-susceptible individuals are viewed as UV-sensitive and typically limit their sun exposure (48, 54–58). Moreover, our research identified childhood sunburn history and photosensitive dermatitis as protective factors against iRBD. As phototoxic dermatitis is UV radiation-related, those afflicted often adopt enhanced sun protection, thereby reducing their overall sun exposure relative to the general population (59). Earlier studies also highlight that childhood sunburn experiences can prompt increased sun protection use (60). Collectively, our data indicate that excessive sun exposure elevates iRBD risk, but vigilant sun protection can diminish this risk (Figure 5). This insight is notable, especially given past findings linking farmers, who typically have heightened sunlight exposure (61–63) with a higher iRBD risk (13, 16, 17, 20). Identifying this ubiquitous and modifiable iRBD risk factor carries profound public health significance.

Sunlight exposure has opposite effects on the incidence rates of iRBD and PD, indicating that despite the tendency of iRBD patients to progress



	iRBD	Schizophrenia	Anxiety disorder	Depression	PTSD
iRBD	1.0000	0.0204	0.0096	0.0016	-0.0052
Schizophrenia	0.0204	1.0000	0.0610	0.0597	0.0682
Anxiety disorder	0.0096	0.0610	1.0000	0.1682	0.0712
Depression	0.0016	0.0597	0.1682	1.0000	0.0700
PTSD	-0.0052	0.0682	0.0712	0.0700	1.0000

Exposure	Outcome	rg	rg_se	rg_p
Schizophrenia	iRBD	0.055582	0.0873	0.524338
Anxiety disorder	iRBD	0.27196	0.105382	0.00986
Depression	iRBD	0.118088	0.150354	0.432221
PTSD	iRBD	0.177635	0.230511	0.440935

exposure	nSNPs	PP.H0	PP.H1	PP.H2	PP.H3	PP.H4
Schizophrenia	174	6.20E-34	0.75	1.13E-35	1.34%	23.66%
Anxiety disorder	376	5.30E-18	0.95	1.30E-19	2.34%	2.59%
Depression	249	3.18E-03	0.94	9.17E-05	2.71%	2.83%
PTSD	300	1.90E-01	0.77	3.77E-03	1.52%	2.53%

outcome	nSNPs	PP.H0	PP.H1	PP.H2	PP.H3	PP.H4
Schizophrenia	387	6.38E-12	0.07	7.50E-11	84.25%	8.59%
Anxiety disorder	530	4.05E-14	0.00	3.30E-12	4.58%	95.37%
Depression	347	5.54E-11	0.78	2.04E-12	2.86%	18.83%
PTSD	418	7.64E-11	0.99	6.71E-13	0.87%	0.45%

FIGURE 4
Genetic correlation of psychiatric disorders with iRBD. The specific analysis method, calculation process and final result have been shown in the picture.

to PD, there are still differences in the pathogenesis of the two diseases. The decline in melatonin levels may explain the increased incidence of iRBD caused by excessive sun exposure. Melatonin, known as the chemical expression of darkness, is a sunlight-dependent indole compound primarily released by the pineal gland, which is crucial for regulating the human biological clock and sleep cycle (64, 65). Sun exposure significantly influences melatonin levels. Previous observational studies have noted that during sunnier summer months, melatonin levels are lower and last for shorter periods compared to winter (66, 67). From the poles to the equator, with increasing sunlight intensity and duration, melatonin secretion decreases (68, 69). This phenomenon is biochemically explained by excessive sunlight suppressing the activity of key enzymes in the synthesis pathway (70, 71), while also activating melanopsin produced by retinal ganglion cells, thereby suppressing the synthesis and release of melatonin

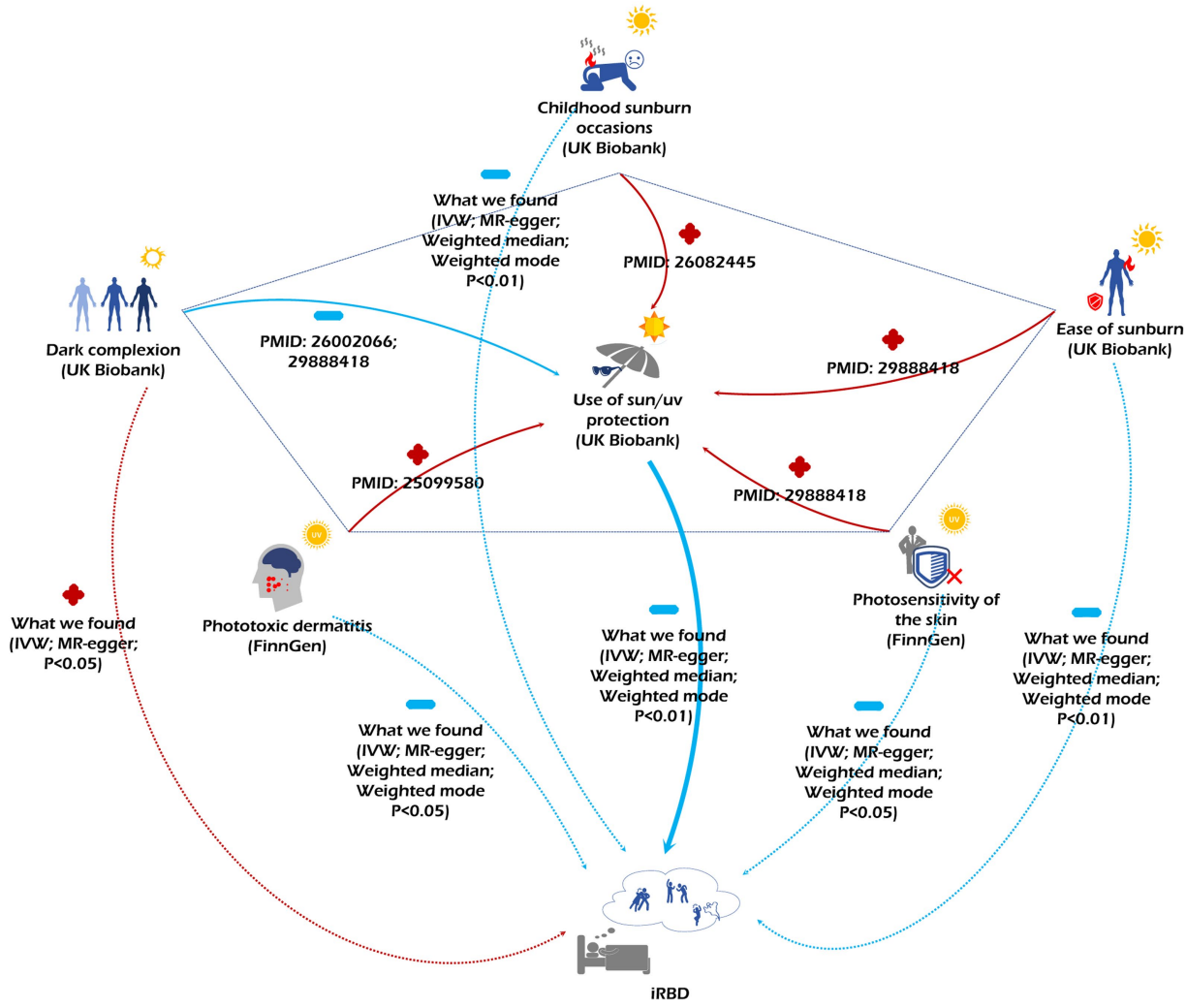


FIGURE 5
The figure depicts the relationships among various sun exposure-related factors and their associated risks for iRBD. Red arrows accompanied by a "+" indicate a promoting effect, while blue arrows paired with a "-" signify an inhibitory effect.

in the pineal gland (70, 72, 73). Experimental researches have also confirmed the negative correlation between light exposure duration and intensity and melatonin production (74–78).

Melatonin might have a protective effect against the onset of iRBD. Firstly, impaired glycine and GABA neurotransmission could be potential mechanisms underlying iRBD (79–81). Studies have demonstrated that melatonin can potentiate the action of GABA on $GABA_A$ receptors located on motoneurons, directly augmenting tonic $GABA_A$ transmission (80, 82, 83). This action ultimately triggers REM sleep atonia, thereby improving iRBD symptoms. Secondly, the α-synuclein accumulation in the brainstem is also a mechanism contributing to the pathogenesis of iRBD. Melatonin can reduce the aggregation of α-synuclein and exerts neuroprotective effects by scavenging free radicals (84, 85), stimulating glutathione synthesis (86, 87), enhancing antioxidant enzyme synthesis, and inhibiting the production of pro-oxidant enzymes (88, 89), thus alleviating α-synuclein's mitochondrial toxicity (90, 91). Thirdly, studies have reported that inflammation plays a role in the pathogenesis of iRBD (92, 93). Melatonin can exert anti-inflammatory effects by acting as an antioxidant, modulating the expression of inducible nitric oxide synthase, and influencing inflammatory signaling pathways and the production of inflammation-related cytokines (94–97). Finally, previous case–control and randomized controlled trials have confirmed that melatonin can improve symptoms of RBD (75, 98–107). Thus, excessive sun exposure may lead to melatonin levels reduction in patients, consequently diminishing its neuroprotective, antioxidant, and anti-inflammatory effects. This could potentially explain the correlation between increased sun exposure and a higher incidence of iRBD.

A community-based study demonstrated that having a low BMI may increase risk of iRBD (17). This study did not identify a causal relationship between BMI and iRBD risk. However, we found that increased trunk and whole-body fat-free mass were associated with in increased risk of iRBD. Compared to BMI, Fat-free mass, which represents trunk non-adipose tissue mass (trunk mass after subtracting the mass of fat tissue), provides an accurate depiction of body composition and serves as a valuable diagnostic tool for obesity (108–110). Although the mechanisms underlying these indicators remain unclear, they offer valuable guidance for identifying populations at high risk of developing iRBD.

Previous studies of the relationship between lifestyle factors (such as smoking and alcohol consumption) and iRBD have been fraught with contradictions and controversies. Studies have suggested that

smoking (13, 14, 19, 20, 111, 112), alcohol consumption (19, 20), and tea consumption (20) increase risk of iRBD. However, other researches have failed to establish causal associations between the factors and iRBD (15–17). Our study did not support the notion that smoking, coffee consumption, or tea consumption are risk factors for iRBD. With a statistical power of 1, these findings are highly robust. Inconsistency in results of observational studies may arise from the possible presence of confounding factors such as socioeconomic status, which may have obscured the true relationship between lifestyle factors and iRBD. Furthermore, our reverse MR analysis indicated that iRBD increased alcohol consumption, suggesting that the relationship between alcohol use and iRBD that was identified in previous observational studies may have been due to reverse causation.

Some studies have suggested that individuals low education levels are at increased risk of iRBD development (13, 15, 18, 113). However, in our study, we did not find a causal association between years of schooling and iRBD. Socioeconomic status can influence educational experiences, living conditions, and medical services accessed by individuals. These factors may affect the incidence of various diseases. This suggests that socioeconomic status may confound the relationship between education and iRBD in observational studies. This was supported by findings of a CLSA population-based cohort study that demonstrated that the association between education and iRBD was diminished after adjusting for socioeconomic level (19). In addition, we should not overlook the influence of education levels on a patient's willingness to seek medical care, a phenomenon that may contribute to selection bias in observational studies.

Previous studies have reported a close association between some mental illnesses and iRBD, indicating that anxiety, depression, psychological stress, and PTSD may be risk factors for iRBD (13, 14, 19, 113–116). Nevertheless, we found no causality between mental illness and iRBD in both discovery and replication phases of our study. The discrepancies between prior studies and our findings can be elucidated from several perspectives: (1) overexposure: individuals with mental illness are more likely to report sleep problems (117, 118), leading to an increased frequency of sleep evaluations, which could inflate the detection rate of sleep disorders. Such overexposure may result in an overestimation of the association between mental illness and iRBD. (2) Misdiagnosis: depression and anxiety disorders often coexist with obstructive sleep apnea (OSA) (119, 120), a condition that shares many clinical presentations with iRBD. Distinguishing between the two without PSG is challenging (2). Observational studies using scales to screen for iRBD patients may overstate its association with mental illness. (3) Genetic Correlation: our research identified a genetic correlation between anxiety disorders and iRBD. This makes the concurrent occurrence of both conditions more probable, potentially obscuring their genuine relationship. It is worth noting that while our study does not support a causal relationship between depression and iRBD, the limited statistical power (0.06) of the instrumental variable for depression may lead to false-negative results. Further studies are needed to better understand the link between depression and iRBD. Conducting additional family-based, genetic association, and molecular genetic studies are essential for exploring genetic links between mental illness and iRBD.

Our MR study had several strengths. First, it is the first MR study to investigate modifiable risk factors associated with iRBD, aiming to substantially reduce bias due to the presence of confounding factors and reverse causality commonly encountered in observational studies. Second, to evaluate the relationships between exposure factors and iRBD, we utilized the most extensive GWAS datasets available. In both the discovery and replication stages, separate exposure datasets were leveraged to ensure result consistency. Our analysis incorporated a range of methods, including MR, LDSC, trait covariance, and colocalization analyses, to probe potential associations. When MR failed to pinpoint a connection, we assessed the power to ensure result reliability. These strategies significantly bolstered the reliability and validity of our conclusions. Third, our findings revealed that excessive sun exposure increases the risk of iRBD, while sun protection acts as a potent preventive measure. Identifying this prevalent and modifiable risk factor in daily life is pivotal for devising effective preventive strategies, holding substantial public health significance.

Despite its strengths, our study has several limitations. First, our study showed discrepancies with past observational studies, possibly due to potential confounding bias and reverse causality in previous researches, or our limited iRBD data sample size, restricting the wide applicability of our findings. Thus, we advocate for stricter observational study designs and the application of larger GWAS data in MR analyses to clarify these issues more distinctly. Second, although our discovery cohort identified potential causality among trunk fat-free mass, whole-body fat-free mass, whole-body water mass and iRBD, the GWAS data for these exposure factors were exclusively sourced from the UK Biobank. Future research utilizing different datasets is warranted to validate our findings. Third, we identified the causal associations between sun exposure-related factors and iRBD using MR analysis. However, further observational studies will be needed to confirm our findings. Furthermore, as the statistical power of the depression data is insufficient, higher quality GWAS data are required. In addition, there is a lack of GWAS datasets on antipsychotic drugs to further investigate the causality between antipsychotic medications and iRBD.

5 Conclusion

In this study, we discovered that excessive sun exposure increase the risk of iRBD. However, Our research does not corroborate the findings from previous observational studies that identified alcohol consumption, smoking, mental illness, and low education levels as risk factors for iRBD. Interestingly, we did observe a genetic correlation between anxiety disorders and iRBD. These insights offer fresh perspectives for screening high-risk populations and devising preventive measures.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

R-YZ: Conceptualization, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. F-JL: Conceptualization, Data curation, Software, Supervision, Validation, Visualization, Writing – review & editing. QZ: Investigation, Resources, Writing – review & editing. L-HX: Software, Writing – review & editing. J-YZ: Software, Writing – review & editing. JZ: Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We extend our gratitude to everyone who participated in and collaborated on this research. We would like to thank Editage (www.editage.cn) for English language editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1321216/full#supplementary-material

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