Sleep and Alzheimer's Disease: Shared Genetic Risk Factors, Drug Targets, Molecular Mechanisms, and Causal Effects

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Research Article

Keywords: Alzheimer's disease, sleep-related phenotypes (SRPs), genetic etiology, cytotoxicity pathways

Posted Date: September 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-853181/v1>

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Abstract

Background: Alzheimer's disease (AD) was associated with sleep-related phenotypes (SRPs). Whether they share common genetic etiology remains largely unknown. We explored the shared genetics and causality between AD and SRPs by using high-definition likelihood (HDL), cross phenotype association study (CPASSOC), transcriptome wide association study (TWAS), and bidirectional Mendelian randomization (MR) in summary-level data for AD ($n = 79145$) and summary-level data for seven SRPs (sample size ranges from 345552 to 386577).

Results: AD shared strong genetic basis with insomnia ($r_g = 0.20$; $P = 9.70 \times 10^{-5}$), snoring ($r_g = 0.13$; $P = 2.45 \times 10^{-3}$), and sleep duration ($r_g = -0.11$; $P = 1.18 \times 10^{-3}$). CPASSOC identifies 31 independent loci shared between AD and SRPs, including four novel shared loci. Functional analysis and TWAS showed shared genes were enriched in liver, brain, breast, and heart tissues, and highlighted the regulatory role of immunological disorders, very-low-density lipoprotein particle clearance, triglyceride-rich lipoprotein particle clearance, chylomicron remnant clearance and positive regulation of T cell mediated cytotoxicity pathways. Protein-protein interaction analysis provided three potential drug target genes (*APOE*, *MARK4* and *HLA-DRA*) that interacted with known FDA-approved drug target genes. CPASSOC and TWAS demonstrated three regions 11p11.2, 6p22.3 and 16p11.2 may account for the shared basis between AD and sleep duration or snoring. MR showed AD had causal effect on sleep duration ($\beta_{IVW} = -0.056$, $P_{IVW} = 1.03 \times 10^{-3}$).

Conclusion: Our findings provide strong evidence of shared genetics and causation between AD and sleep, and advance our understanding the genetic overlap between them. Identifying shared drug targets and molecular pathways can be beneficial to treat AD and sleep disorders more efficiently.

What Are The New Findings?

- The strongest negative genetic correlation was observed between Alzheimer's disease and sleep duration; the strongest positive genetic correlation was observed between Alzheimer's disease and insomnia.
- Cross-trait meta-analysis identifies 31 independent genomic loci shared between Alzheimer's disease and three sleep-related phenotypes (including insomnia, sleep duration and snoring), four of which is novel.
- Implicated genes suggest potential treatment targets and signaling pathways for Alzheimer's disease and sleep disorders.
- Mendelian randomization analysis provided strong evidence in support of higher risk of Alzheimer's disease causally reducing sleep duration.
- Cross-trait meta-analysis and transcriptome-wide association studies support the role of three regions 11p11.2, 6p22.3 and 16p11.2 may account for the shared causes between Alzheimer's disease and sleep duration or snoring.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive memory loss and overall cognitive decline[1] and is highly heritable (heritability 58–79%)[2]. Growing evidence indicates that AD patients frequently have sleep disorders, implying common causes of these complex phenotypes. Emerging epidemiological studies suggest that AD is associated with a significantly increased risk of sleep disorders, and vice versa[3–6]. Furthermore, neuropathological studies showed that extracellular levels of both A β and tau fluctuate during the normal sleep-wake cycle[7]. In animal models, sleep disturbance and increased arousal lead to increased A β production and decreased A β clearance, while chronic increased arousal promotes A β aggregation and deposition, thus leading to sleep disturbance[7]. Importantly, amyloid β and tau protein, core hallmarks of AD, can exacerbate sleep disorder in AD person by orexin A and adenosine A (1) receptor[8]. Taken together, we hypothesized that there might be a shared genetic basis underlying these connections between AD and sleep disorders.

Genome-wide association studies (GWAS) have yielded new insights into the genetics of AD[9, 10] and SRPs[11–14]. Despite the large sample sized GWAS cohorts, the identified genome-wide loci account for only a small portion of the variance of AD and sleep disorders[15]. The combined effects of whole genome SNPs, including those that do not reach genome-wide significance[16] and shared genetic architecture are expected to account for the missing heritability. However, no cross-trait genome-wide study has been conducted to quantify the level of genetic overlap and identify the shared loci between AD and sleep disorders.

Therefore, to improve our understanding of genetic overlap and causality and to identify genomic loci shared between AD and sleep disorders, we conducted a large-scale cross-trait GWAS study to explore genetic correlations and shared genetic components among these complex phenotypes using data from Psychiatric Genomic Consortium (PGC) and Complex Trait Genetics lab (CTGlab). We further compared shared genes between AD and insomnia with known target genes of AD and insomnia medication using the protein-protein interaction analysis which may provide insights into potential target genes for identifying drug targets.

Results

Genetic correlations of AD with SRPs

There was a positive overall positive genetic correlation of AD with insomnia ($r_g = 0.20$; $P = 9.70 \times 10^{-5}$) and snoring ($r_g = 0.13$; $P = 2.45 \times 10^{-3}$) and negative genetic correlation with sleep duration ($r_g = -0.11$; $P = 1.18 \times 10^{-3}$) using HDL (Table 1). No significant genetic correlations of AD with daytime dozing, ease of getting up in the morning, morningness, and daytime napping were observed. Annotation-specific genetic correlation analyses showed that shared effects were concentrated in some chromosomes with the strongest positive genetic correlation at chr16 ($r_g = 0.63$; $P = 1.24 \times 10^{-4}$) between AD and insomnia and at chr4 ($r_g = 0.62$; $P = 1.48 \times 10^{-4}$) between AD and snoring (Fig. 2.A). We also observed a stronger genetic correlation at open chromatin, histone modification,

and TFBS regions between AD and insomnia (Fig. 2.C). Figure 2.B and Fig. 2.D exhibits consistent results with GNOVA estimate, with evidence of positive genetic correlation at bone, breast, brain, heart, gastrointestinal, muscle, pancreas, adipose, skin, fetal, lung and embryonic stem cell tissues between AD and insomnia.

Table 1

Genetic Correlation of Alzheimer's disease With Related Sleep-related phenotypes, Estimated by High-Definition Likelihood method and linkage disequilibrium score regression

Method	Trait	rg	rg, SE	rg, 95%CI	pvalue	h ² (SE)
HDL	Dozing	0.10	0.066	-0.03 to 0.23	1.49E-01	0.01(0.001)
	Gettingup	-0.02	0.038	-0.09 to 0.05	6.61E-01	0.07(0.003)
	Insomnia	0.20	0.052	0.10 to 0.30	9.70E-05	0.04(0.002)
	Morningness	0.00	0.035	-0.07 to 0.07	9.67E-01	0.11(0.003)
	Napping	0.16	0.067	0.03 to 0.29	1.61E-02	0.02(0.001)
	Sleepdur	-0.11	0.035	-0.18 to -0.04	1.18E-03	0.07(0.002)
	Snoring	0.13	0.042	0.05 to 0.21	2.45E-03	0.06(0.002)
LDSC	Dozing	0.12	0.096	-0.07 to 0.31	2.26E-01	0.01(0.001)
	Gettingup	-0.05	0.051	-0.15 to 0.05	3.15E-01	0.07(0.003)
	Insomnia	0.22	0.077	0.07 to 0.37	5.00E-03	0.05(0.002)
	Morningness	-0.03	0.045	-0.12 to 0.06	5.64E-01	0.11(0.004)
	Napping	0.17	0.086	0.00 to 0.34	4.52E-02	0.02(0.002)
	Sleepdur	-0.12	0.051	-0.22 to -0.02	2.15E-02	0.07(0.003)
	Snoring	0.10	0.058	-0.01 to 0.21	7.80E-02	0.06(0.003)

Note: Summary statistics for each trait were merged with Hapmap3 SNPs excluding the HLA region to estimate rg. pvalue < 0.05/7. Dozing: Daytime dozing; Gettingup: Ease of getting up in the morning; Sleepdur: Sleep duration

The local genomic regions around individual AD loci from GWAS showed signals of genetic overlap with related SRPs. Accounting for correction, there was genome-wide significant local genetic correlation between AD and SRPs at three regions (chr16:29036613–31382943 harboring previous AD locus *GDPD3* for AD with insomnia and snoring; chr19:4348967–5811852 harboring previous AD locus *APOE* for AD and insomnia; and chr2:201576284–202818637 harboring previous migraine locus *CDK15* for AD and sleep duration) using SuperGnova ($P_{\text{SuperGnova}} < 1.0 \times 10^{-4}$).

Cross trait meta-analysis between AD and SRPs

In total, we identified 31 independent loci shared between AD and three genetically correlated SRPs ($P_{\text{meta}} < 1.67 \times 10^{-8}$ and single-trait $P < 1 \times 10^{-3}$) (Table 2). The credible set of SNPs for each of these shared loci was also identified (Supplementary Table 6–8). Among the 31 independent shared loci, 2 colocalized at the same candidate causal variant within each variant (rs12292911 and rs3121427) (Supplementary Table 9).

Table 2
Cross-trait meta-analysis results between Alzheimer's disease and sleep-related phenotypes (Pmeta < 1.67×10⁻⁸ and single-trait P < 1.67×10⁻⁸)

Model	Index.SNP	CHR	Genome position	pos	Effect.allele	Reference.allele	P1	P2	Pmeta value	Genes within 100kb
AD_Insomnia	rs11234556	11	11q14.2	chr11:85664234..85860305	T	C	3.92E-17	3.75E-03	8.706E-17	[PICALM]
	rs150567157	19	19q13.32	chr19:45622320..45622320	T	C	6.51E-21	9.43E-03	1.11E-20	[PPP1R37]
	rs186110295	19	19q13.32	chr19:45233503..45233503	T	G	4.45E-11	5.56E-03	1.583E-11	[BCL3]
	rs2249152	19	19p13.3	chr19:5034179..5088080	T	C	9.43E-05	2.55E-06	9.532E-09	[KDM4B]
	rs606757	19	19q13.32	chr19:45707532..45711733	C	A	4.16E-12	7.34E-03	1.193E-11	[MARK4]
	rs6857	19	19q13.32	chr19:45392254..45427125	T	C	0	4.48E-03	0	[APOC1,APOE,P
	rs9268428	6	6p21.32	chr6:32340236..32587090	T	G	1.24E-09	1.41E-03	3.194E-11	[BTNL2,HCG23,FHLA-DRB1,H
AD_Sleepdur	rs1081105	19	19q13.32	chr19:45386634..45421204	C	A	1.16E-232	4.73E-03	8.459E-241	[APOC1,APOE,P
	rs11672748	19	19q13.32	chr19:45448036..45522732	G	A	7.25E-24	3.24E-03	1.013E-23	[APOC2,APOC4,APOC2,CLPTM1
	rs12292911	11	11p11.2	chr11:47346940..47462140	A	G	1.25E-06	6.27E-05	1.511E-09	[MADD,MYBPC3RAPS,SLC39A1
	rs12972970	19	19q13.32	chr19:45387596..45422946	A	G	0	9.38E-03	0	[APOC1,APOE,P
	rs1633096	6	6p22.1	chr6:29696657..30038352	T	G	2.02E-03	3.49E-09	3.32E-09	[HCG4,HCG4B,HHLA-A,HLA-F,HLA-AS1,HLA-G,HLA-IFITM4,PLOC554RNF39,ZNRD1,Z
	rs1979377	19	19q13.32	chr19:45259002..45279340	C	A	4.56E-10	4.59E-03	9.751E-11	[BCL3,MIR8085]
	rs2310752	1	1p31.3	chr1:66390808..66470206	A	G	1.37E-04	5.35E-07	3.68E-09	[PDE4B]
	rs3121427	10	10q23.33	chr10:94139014..94159701	G	A	7.19E-05	4.76E-06	1.024E-08	[MARK2P9]
	rs359539	3	3q25.31	chr3:155271825..155401669	A	G	1.15E-07	1.04E-03	3.182E-09	[PLCH1]
	rs4727449	7	7q21.1	chr7:99641490..100089739	T	C	3.29E-08	2.59E-03	3.187E-09	[AP4M1,C7orf43CNPY4,COPS6,GATC,GPC2,LAMMCM7,MEPCE,MIR106B,MIR46MIR6840,NYAP1PILRA,PILRB,PMPPP1R35,PVRIGSPDYE3,STAG3,STAG3L5P-PVRIPIILRB,TAF6,TSCZCWPW1,ZNF3,
	rs56249331	1	1p35.2	chr1:31393417..31569231	A	G	1.02E-03	1.38E-07	8.476E-09	[PUM1,SNORD8,SNORD103B]
	rs858502	7	7q21.1	chr7:99776272..99843353	T	C	2.36E-09	4.43E-03	3.684E-10	[GATS,PVRIG,ST
AD_Snoring	rs1004173	6	6p12.3	chr6:47440565..47590476	T	C	5.64E-09	5.92E-03	8.448E-10	[CD2AP]
	rs11100203	4	4q32.1	chr4:159857539..159867342	G	A	4.13E-06	2.93E-05	2.563E-09	[C4orf45]

Note: **P1** is the Alzheimer's disease single-trait P value, **P2** is the sleep-related phenotypes (insomnia, sleep duration, and snoring) single-trait P value, and **Pmeta** analysis P value. Chr: chromosome; AD: Alzheimer's disease; Genes in blue are the nearest genes to this locus.

Model	Index.SNP	CHR	Genome position	pos	Effect.allele	Reference.allele	P1	P2	Pmeta value	Genes within clu
	rs11642303	16	16p11.2	chr16:30820866..31155458	A	C	7.71E-06	2.04E-09	5.513E-13	[BCKDK,BCL7C,C FBXL19-AS1,HSI LOC101928736,I ORAI3,PRSS8,PF PRSS53,SETD1A STX4,VKORC1,Z
	rs147188206	19	19q13.32	chr19:45552587..45552587	C	T	2.62E-14	2.89E-03	8.251E-15	[CLASRP]
	rs204911	19	19q13.32	chr19:45456103..45466335	A	T	6.58E-10	6.66E-03	1.757E-10	[CLPTM1]
	rs28469095	19	19q13.32	chr19:45592238..45655333	C	T	1.07E-38	3.14E-03	4.176E-39	[GEMIN7,NKPD1
	rs3098882	8	8q13.3	chr8:71940094..71940094	T	C	7.02E-03	2.27E-09	7.917E-09	[RP11-326E22.1]
	rs429358	19	19q13.32	chr19:45411941..45427125	C	T	0	7.73E-03	0	[APOC1,APOE]
	rs439401	19	19q13.32	chr19:45414451..45416478	T	C	7.70E-167	2.21E-03	1.862E-172	[APOC1]
	rs61597598	2	2q24.1	chr2:156992261..157173800	A	G	6.00E-03	4.52E-14	8.298E-14	[AC093375.1]
	rs62402786	6	6p22.3	chr6:22299046..22337756	G	C	2.89E-07	1.67E-03	7.991E-09	[PRL]
	rs7514002	1	1p31.3	chr1:62604065..62619960	A	G	8.02E-04	1.43E-07	8.921E-09	[PATJ]
Note: P1 is the Alzheimer's disease single-trait P value, P2 is the sleep-related phenotypes (insomnia, sleep duration, and snoring) single-trait P value, and Pm analysis P value. Chr: chromosome; AD: Alzheimer's disease; Genes in blue are the nearest genes to this locus.										

Table 3
Causal Inference Between Alzheimer's disease and Sleep-related Phenotypes Using Two-sample MR

Outcome	Direction	Method	N_snp	Causal_Effect_Size*	SE	p_value
Insomnia	Forward	Simple median	30	-0.102	0.068	1.35E-01
	Forward	Weighted median	30	0.002	0.052	9.68E-01
	Forward	MR Egger	30	-0.042	0.058	4.75E-01
	Forward	Inverse variance weighted	30	-0.028	0.042	5.03E-01
	Forward	MR-RAPS	30	-0.032	0.040	4.26E-01
	Forward	MR-PRESSO	30	-0.028	0.042	5.08E-01
	Reverse	Simple median	13	-0.024	0.026	3.42E-01
	Reverse	Weighted median	13	-0.023	0.026	3.61E-01
	Reverse	MR Egger	13	-0.034	0.068	6.28E-01
	Reverse	Inverse variance weighted	13	-0.020	0.020	3.27E-01
	Reverse	MR-RAPS	13	-0.021	0.019	2.76E-01
	Reverse	MR-PRESSO	13	-0.020	0.020	3.47E-01
Sleepdur	Forward	Simple median	30	-0.038	0.032	2.27E-01
	Forward	Weighted median	30	-0.063	0.025	1.15E-02
	Forward	MR Egger	30	-0.064	0.029	3.46E-02
	Forward	Inverse variance weighted	30	-0.056	0.017	1.03E-03
	Forward	MR-RAPS	30	-0.057	0.017	1.11E-03
	Forward	MR-PRESSO	30	-0.056	0.013	2.12E-04
	Reverse	Simple median	47	-0.013	0.031	6.73E-01
	Reverse	Weighted median	47	-0.010	0.034	7.58E-01
	Reverse	MR Egger	47	-0.122	0.095	2.06E-01
	Reverse	Inverse variance weighted	47	-0.011	0.024	6.64E-01
	Reverse	MR-RAPS	47	-0.011	0.021	6.01E-01
	Reverse	MR-PRESSO	47	-0.011	0.024	6.66E-01
Snoring	Forward	Simple median	30	0.046	0.069	5.03E-01
	Forward	Weighted median	30	-0.101	0.052	5.02E-02
	Forward	MR Egger	30	-0.138	0.065	4.20E-02
	Forward	Inverse variance weighted	30	-0.083	0.049	9.11E-02
	Forward	MR-RAPS	30	-0.101	0.041	1.39E-02
	Forward	MR-PRESSO	30	-0.070	0.040	9.35E-02
	Reverse	Simple median	33	0.025	0.018	1.52E-01
	Reverse	Weighted median	33	0.025	0.018	1.70E-01
	Reverse	MR Egger	33	-0.014	0.082	8.67E-01
	Reverse	Inverse variance weighted	33	0.024	0.015	1.07E-01
	Reverse	MR-RAPS	33	0.025	0.013	4.68E-02
	Reverse	MR-PRESSO	33	0.033	0.012	8.74E-03

Note: *The causal effect size was the beta coefficient from linear or logistic regression models for corresponding outcome. Sleepdur: sleep duration; MR: Mendelian randomization; Direction: Forward means the causal effect size of Alzheimer's disease on sleep-related phenotypes, Reverse means the causal effect size of sleep-related phenotypes on Alzheimer's disease; N_snp: number of instrumental variables; The threshold of significance was at the Bonferroni-adjusted level P-value < 0.0083 (0.05/6). Abbreviations as in Table 1.

We identified 7, 12 and 12 independent loci shared between AD and insomnia, sleep duration, and snoring, respectively (Table 2). Notably, we identified one novel loci (10q23.33, index SNP: rs3121427, mapped gene: *MARK2P9*, $P_{\text{meta}} = 1.02 \times 10^{-8}$) shared between AD and sleep duration and three novel loci (4q32.1, index SNP: rs11100203, mapped gene: *C4orf45*, $P_{\text{meta}} = 2.56 \times 10^{-9}$; 6p22.3, index SNP: rs62402786, mapped gene: *PRL*, $P_{\text{meta}} = 7.99 \times 10^{-9}$; 1p31.3, index SNP: rs7514002, mapped gene: *PATJ*, $P_{\text{meta}} = 8.92 \times 10^{-9}$) shared between AD and snoring. *MARK2P9* (microtubule affinity regulating kinase 2 pseudogene 9)

is a pseudogene and its function is unknown. However, this gene is adjacent to *IDE* gene, which encodes a zinc metallopeptidase, an enzyme whose preferential affinity for insulin results in the inhibition of beta-amyloid degradation by insulin. The defective function of *IDE* gene is therefore associated with AD and type 2 diabetes[17, 18]. *C4orf45* (chromosome 4 open reading frame 45), an uncharacterized protein-coding gene, has been shown to be associated with self-reported educational attainment and cognitive function[19]. *PRL* (prolactin) encodes the anterior pituitary hormone prolactin and is involved in the regulation of many signaling pathways, including amyloid fibril formation, prolactin signaling, growth hormone receptor signaling, cytokine signaling in the immune system and protein metabolism pathway[20, 21]. Prolactin, a pleiotropic hormone, has many functions in the brain, such as maternal behavior, neurogenesis, and neuronal plasticity, among others[22]. Recently, it has been reported to have a significant role in neuroprotection against excitotoxicity[22]. *PATJ* encodes a protein with multiple PDZ domains and plays a role in the cell junction organization, tight junction, hippo signaling pathway. The missense variant in *PATJ* has a stronger association with daytime napping than any previously studied sleep-related phenotypes[23]. Research has found colocalization of the daytime napping loci with daytime sleepiness, snoring, BMI and chronotype at *PATJ*, suggesting an obesity-hypersomnolence pathway[24].

A specific region at 19q13.32 is the strongest shared signal between AD and insomnia (index.SNP: rs6857, $P_{\text{meta}} = 0$), sleep duration (index.SNP: rs12972970, $P_{\text{meta}} = 0$) and snoring (index.SNP: rs429358, $P_{\text{meta}} = 0$). These three loci map to the *APOE* and *APOC1* genes which are well known to be major genetic risk factors for AD[25–27]. In addition, ten loci shared between AD and SRPs were also mapped to the 19q13.32 region. Excluding this strongest signal region, there are some additional loci of interest.

Index SNP rs2249152 (19p13.3, $P_{\text{meta}} = 9.53 \times 10^{-9}$, mapped gene: *KDM4B*) was shared between AD and insomnia. *KDM4B* (Lysine Demethylase 4B) is a protein coding gene and engaged in chromatin organization, chromatin modifying enzymes and DNA double strand break response. Studies showed that *KDM4B* overexpression leads to inflammation and mental retardation[28, 29]. Index SNPs rs12292911 (11p11.2, $P_{\text{meta}} = 1.51 \times 10^{-9}$, mapped gene: *PSMC3*), rs2310752 (1p31.3, $P_{\text{meta}} = 3.68 \times 10^{-9}$, mapped gene: *PDE4B*), rs359539 (3q25.31, $P_{\text{meta}} = 3.18 \times 10^{-9}$, mapped gene: *PLCH1*) and rs56249331 (1p35.2, $P_{\text{meta}} = 8.48 \times 10^{-9}$, mapped gene: *PUM1*) were shared between AD and sleep duration. *PSMC3* (proteasome 26S subunit, ATPase 3) encodes one of the ATPase subunits, a member of the triple-A family of ATPases that have chaperone-like activity and is associated with AD[30]. *PDE4B* encodes a protein that specifically hydrolyzes cAMP, altered activity of this protein has been associated with schizophrenia and bipolar disorder[31, 32]. It has also recently been found to modulate cognition, as reduction in *PDE4B* activity improves memory and long-term plasticity in mouse models, possibly supporting further therapeutic applications[33]. Findings suggest that brief sleep deprivation disrupts hippocampal function by increasing PDE4 activity that interferes with cAMP signaling[34]. Therefore, drugs that enhance cAMP signaling may provide a new therapeutic approach to counteract the cognitive effects of sleep deprivation[34]. *PLCH1* encodes phospholipase C- η enzymes which have recently been implicated in the modulation and amplification of Ca^{2+} signals and are known to be expressed in neuronal regions of the brain associated with cognition and memory[35]. *PUM1* (pumilio homolog 1) encodes a member of the PUF family and may be involved in translational regulation of embryogenesis, and cell development and differentiation. Study has demonstrated the importance of *PUM1* for human neurological development and function and has described its role in neurodegenerative and neurodevelopmental disorders[36]. In addition, we observed other common loci shared between AD and insomnia, sleep duration or snoring, these results were in line with previous studies[11, 13, 14, 37].

Tissue-specific enrichment analysis

We identified 2, 6 and 2 independent tissues that demonstrated significantly enriched expression of cross-trait-associated genes shared between AD with insomnia, sleep duration and snoring, respectively (Fig. 3). The main strongly enriched tissues were part of the endocrine system, digestive system, integumentary system, and musculoskeletal system (including liver, testis, breast, skin, appendix, skeletal muscle, and heart muscle tissue).

Functional enrichment analysis

Our results showed that genes shared between AD and insomnia in the KEGG pathways were significantly enriched in immunological disorders such as asthma (adjusted $P = 1.45 \times 10^{-5}$), inflammatory bowel disease (adjusted $P = 1.74 \times 10^{-5}$), allograft rejection (adjusted $P = 2.37 \times 10^{-5}$) and type I diabetes (adjusted $P = 2.47 \times 10^{-5}$), indicating the role in pathways related to immune regulation (Fig. 4). Additionally, in GO terms, the genes shared between AD and sleep duration were enriched in very-low-density lipoprotein particle clearance (adjusted $P = 4.66 \times 10^{-10}$), triglyceride-rich lipoprotein particle clearance (adjusted $P = 1.53 \times 10^{-7}$), chylomicron remnant clearance (adjusted $P = 1.53 \times 10^{-7}$) and positive regulation of T cell mediated cytotoxicity (adjusted $P = 1.91 \times 10^{-5}$), implicating that processes involving immunity and lipid metabolism may account for shared causes. Evidence of ClueGO log and enrichment results were provided in supplementary material (Supplementary Table 10–11) (Supplementary Results).

Potential drug target genes and Protein-protein interaction (PPI) analysis

Disease-related genes are natural candidates for drug development in complex diseases[38, 39]. We further compared shared genes between AD and insomnia identified from CPASSOC with known target genes of AD and insomnia medication using the TTD. Overall, eight FDA approved drugs were found for AD and correspond to 11 target genes. 28 FDA approved drugs were found for insomnia and correspond to 36 target genes (Supplementary Table 12). None of them were included in the shared genes we identified. We queried the STRING database for the interactions between the 47 drug target genes and the 15 shared genes (Fig. 5). We observed three shared genes had medium confidence (> 0.40) in interaction with nine drug target genes: *APOE* (shared gene) interacting with *ACHE*, *BCHE*, *ESR1*, *IL1B*, *MPO*, *DRD2* and *CHRNA4* (drug target), *MARK4* (shared gene) interacting with *GRIK4* (drug target) and *HLA-DRA* (shared gene) interacting with *CA2* (drug target). These gene interactions provide some insights into potential target genes for identifying drug targets from multi-omics datasets.

Causal inference

We then used bi-directional MR analysis to test the causality between AD and SRPs. Forward MR showed significant negative instrumental effects per doubling odds of AD on sleep duration ($\beta_{\text{IVW}} = -0.056$, $P_{\text{IVW}} = 1.03 \times 10^{-3}$), but not insomnia ($\text{OR}_{\text{IVW}} = 0.97$, $P_{\text{IVW}} = 5.03 \times 10^{-1}$) and snoring ($\text{OR}_{\text{IVW}} = 0.92$, $P_{\text{IVW}} =$

9.11×10^{-2}). There were no significant instrumental variable estimates from SRPs to AD. All heterogeneity P-values were nonsignificant ($P_{\text{heterogeneity}} > 0.01$) indicating at worst only subtle heterogeneity among retained instruments (Supplementary Table 13). Sensitivity analysis for the main MR analysis using weighted median, simple median, MR-RAPS, MR-Egger and MR-PRESSO suggested there was no systematic bias due to pleiotropy (all $P_{\text{MR-Egger}} > 0.05$) (Supplementary Table 13). MR-Steiger results showed that all the causal estimates were oriented in the intended direction (all $P_{\text{MR-Steiger}} < 0.05$). Taken together, the instrumental analysis suggested a potential causal role of increased risk of AD on reduced sleep duration.

Single-trait TWAS and shared genetics between AD and SRPs from TWAS

We next went down to the gene level to examine the shared TWAS genes between AD and related SRPs. In total, 2108 gene-tissue pairs were found across 48 GTEx tissues to be significantly associated with AD after BH correction, in addition to 551, 2227, and 3313 gene-tissue pairs with insomnia, sleep duration, and snoring, respectively (Supplementary Fig. 4).

We identified 9, 8, and 77 TWAS-significant genes shared between AD with insomnia, sleep duration, and snoring, respectively (Supplementary Table 14–16), most of which were observed at tissues from the immune system, cardiovascular system, endocrine system, digestive system and nervous system (Fig. 6). Restricting this list to shared genes with independent signals, we identified 30 genes that were TWAS significant for both AD and at least one of the SRPs traits from tissues including liver, brain, thyroid, skin, heart, and muscle (Supplementary Table 14–16). Intriguingly, highly consistent with the results from CPASSOC, some loci were shared among AD and related SRPs. For example, the *PTPMT1* gene, located at 11p11.2, was co-independently TWAS significant for AD, insomnia and sleep duration and was simultaneously prominent shared locus among AD and sleep duration. *PTPMT1* is a lipid phosphatase that dephosphorylates mitochondria proteins, which in turn regulates mitochondrial membrane integrity. Its expression is highly correlated in human brains and this correlation is lost in AD brains[40]. *PTPMT1* was previously thought to have a role in the rhythmicity of sleep cycle[41]. Notably, we found *KAT8* (16p11.2) was co-significant for AD and snoring and was also the most enriched and significant gene in 48 tissues. *KAT8* (lysine acetyltransferase 8) encodes a member of the MYST histone acetylase protein family. Study indicated that aberrant expression patterns of *KAT8* might be associated with AD progression[42].

Discussion

Our study has five main findings. First and foremost, we provided evidence that AD shared genetic basis with insomnia, snoring, and sleep duration. Second, cross-trait meta-analysis identified independent shared loci between AD and insomnia, snoring, or sleep duration and functional analysis highlighted that those shared loci were mainly enriched in liver tissue and lipid metabolic system as well as immune inflammatory system, and were involved in immunological disorders, very-low-density lipoprotein particle clearance, triglyceride-rich lipoprotein particle clearance, chylomicron remnant clearance and positive regulation of T cell mediated cytotoxicity pathways. Third, PPI analysis identified three potential drug target genes that interact with known FDA-approved drug target genes. Fourth, TWAS identified genes that were shared between AD and sleep phenotypes at tissue from immune system, cardiovascular system, endocrine system, digestive system and nervous system. Fifth, bi-directional MR suggested that higher risk of AD was causally related with shorter sleep duration. Our findings advance our understanding of the genetic contribution of AD and sleep pattern, provide insights into the potential regulatory role of shared inheritance whose function warrants follow-up, and elucidate the etiology and mechanisms underlying the co-morbidity of AD and sleep disorders.

Circadian rhythm disturbances have been suggested as biomarkers for clinical stage AD[43]. The findings of our genetic analyses were highly consistent, generally supporting the observational positive associations between AD with insomnia[3] and snoring[44], and the negative associations with sleep duration[45]. We also observed AD was positively associated with napping ($r_g = 0.16$, $p = 1.61 \times 10^{-2}$), but this significance disappeared after Bonferroni correction. However, recent longitudinal studies had shown that men with longer napping duration had greater cognitive decline and higher risk of cognitive impairment after adjustment for all covariates[46]. Mechanisms for this association between AD and napping were unknown; it might be partially explained by daytime napping is a result of the erosion of the area of the brain responsible for wakefulness by toxic tau proteins, the accumulation of which ultimately leads to AD, however such a putative causal mechanism needs further experimental validation[46].

Meanwhile, 31 independent SNPs from CPASSOC as well as 30 genes from independent TWAS signals of both AD and three SRPs suggested potential functions relevant to AD. The loci identified in both CPASSOC and TWAS analysis revealed potential shared biological mechanisms in AD progress and SRPs regulation involving immunological disorders, very-low-density lipoprotein particle clearance, triglyceride-rich lipoprotein particle clearance, chylomicron remnant clearance and positive regulation of T cell mediated cytotoxicity pathways. Consequently, we highlighted the potentially interesting functions of the novel associations for *PRL*(6p22.3) between AD with snoring, as well as focused *PTPMT1*(11p11.2) and *KAT8*(16p11.2) region shared between AD with insomnia or sleep duration.

Shared genes associated with AD and SRPs were enriched for expression in most liver and brain tissue, indicating that these disorders might be caused by malfunction of the endocrine system and nervous system. For example, *PRL* can influence sleep structure, and *PRL* deficient mice display less rapid eye movement (REM) sleep than wild-type mice[47]. Molina-Salinas et al. have shown that *PRL* can inhibit glutamate excitotoxicity through the AKT and STAT5 pathways, thereby protecting neuronal cells and decreasing the progression of Alzheimer's disease[22]. Evidence has suggested that somatostatin expression is down-regulated in early aging brains in snoring samples, leading to a progressive decrease in *PRL* and neprilysin activity and resulting in amyloid b (Ab) peptide accumulation in AD patients[48]. Additionally, *PTPMT1* is localized to mitochondria via an N-terminal signaling sequence and is found anchored to the stromal surface of the inner membrane. Study shows that activation of protein tyrosine phosphatase (PTP) hastens the progression of AD[49]. W. Lutz et al. identified *PTPMT1* as a common signal in AD and major depressive disorder, which showed consistent moderate expression in brain tissues[50]. A highly promising candidate gene is *KAT8*, as the dominant SNP at 16p11.2 is located within the third intron of *KAT8* and multiple important variants within this locus affect the expression or methylation levels of *KAT8* in multiple brain regions, including the hippocampus[51]. The chromatin modifier *KAT8* is regulated by *KANSL1*, a gene associated with AD deficient in Apoε4. A study on Parkinson's disease reported that *KAT8* is a potentially causal gene based on GWAS and

differential gene expression, implying that *KAT8* may have a common role in the neurodegeneration of AD and Parkinson's disease[52]. While previously reported information on gene function may be of great value, it is best to consider all implicated genes as putative causal factors to guide potential functional follow-up experiments.

Our MR analysis provided strong evidence that AD is associated with shorter sleep duration ($\beta_{IVW} = -0.056$, $P_{IVW} = 1.03 \times 10^{-3}$). However, our findings don't support a causal effect of sleep duration on AD risk. Notably, growing evidence suggests a J-shaped association between sleep duration and AD, suggesting that the causal effect in the long-sleeper group was larger than the short-sleeper group[53, 54]. Apparent inconsistencies between our finding and previous MR studies may be partly due to different definitions, diagnostic criteria and forms of characterization of AD (such as cognitive impairment, memory loss, reaction time and so on)[53], different types of data (individual-level data or summary-level data)[53], different MR methods (linear MR or non-linear MR)[53], or different statistical analysis methods (genetic risk score)[54]. In addition, we found no causal relationship between AD and insomnia, whereas a recent MR study conducted by Huang et al. found that higher risk of AD was associated with lower risk of insomnia (OR: 0.99, $P_{IVW} = 7 \times 10^{-13}$)[55]. Given the consistency in population, sample size and statistical methods between the study by Huang et al. and the present study, we consider that the difference in results is due to Huang et al. adopted F-statistic > 10 to filter exposure-related SNPs to reduce the weak instrumental bias of using genotype data[55]. Finally, there was little evidence to support a causal effect of insomnia, sleep duration and snoring on AD risk, this finding is consistent with recent researches[55, 56]. Our findings add to previous evidence that AD pathology leads to increased wakefulness and high sleep fragmentation in transgenic mouse models[57], and results in neuronal loss of the suprachiasmatic nucleus (SCN), the master circadian clock of mammals, and the locus coeruleus that are essential for maintaining normal wakefulness[58]. Mechanisms underlie the causality between AD and SRPs remain to be elucidated.

Our study has notable strengths. Specifically, we used data from the largest GWAS available for each trait or disorder, and we explored a wide range of SRPs. Second, we leveraged SuperGnova and Gnova to assess the local genetic correlation and annotation-specific genetic correlation between AD and seven SRPs, respectively. SuperGnova has stronger statistical performance compared to HESS, and GNOVA provides more accurate genetic covariance estimates and

powerful statistical inference than LDSC. Third, the identification of potential target genes through PPI analysis provides a new perspective on shared structure. Fourth, we conducted cross-trait meta-analysis using CPASSOC, which is robust to heterogeneous effects and overlap samples between two phenotypes. Nevertheless, there are several potential limitations of our study. First, although TWAS increased the power to detect significant expression trait associations, the relatively smaller sample size for metabolic traits and GTEx reference panels in certain tissues may be inadequate in detect signals with small to moderate effect. Second, despite the large sample sizes of the consortium-based meta-analysis studies, there were differences in sample size and number of SNPs among different studies. Therefore, the enrichment of SNPs with potential common effects may be lower for traits with relatively few loci and samples in the source studies.

Third, some of the observed associations may not be due to independent effects of the same locus on AD and SRPs, but rather to correlations of traits in the causal pathway or through other unmeasured traits. Fourth, our study was limited to European ancestry, and the shared genetics in other ethnic groups are uncertain. Therefore, future research in other ethnic groups are encouraged. More work is needed to identify individual cell types and more detailed molecular mechanisms with the goal of developing potential therapeutic strategies.

In conclusion, our study provides strong evidence of genetic correlations and causality between AD and sleep pattern, identifies of genetic loci associated with both AD and SRPs risk, thus providing therapeutic opportunities to improve sleep quality and lower the risk of AD. Our results further advance our understanding of AD, and provide insight into the shared etiology for comorbid AD and sleep disorders.

Methods

Study design, data source, and study population

Our overall study design is shown in (Fig. 1). We used the most recent GWAS summary-level data from Complex Trait Genetics lab (CTGlab) for AD and seven SRPs[9, 11](Supplementary Table 1). The AD meta-analysis summary statistics combined 24087 cases and 55058 controls from 3 cohort level GWASs including Alzheimer workgroup initiative of the Psychiatric Genomic Consortium (PGC-ALZ), International Genomics of Alzheimer's Project (IGAP) and Alzheimer's Disease Sequencing Project (ADSP)²⁷. Whereas the SRPs meta-analysis summary statistics combined ~ 1331000 participants from the UKB and 23andMe²⁸. In the original GWASs, AD cases were diagnosed according to the recommendations from the National Institute on Aging–Alzheimer's Association (NIAAA) criteria, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria or the International Classification of Diseases (ICD-10) criteria²⁷. Details of the definition of each self-reported SRPs are present in (Supplementary Table 2). All participants were of European ancestry with no overlapping samples (Supplementary Methods).

Genetic correlation analysis

To evaluate genetic correlation (r_g) between AD and SRPs, we used conventional cross-trait linkage disequilibrium score regression (LDSC)[59] and the more recent High-Definition Likelihood (HDL) method[60]. As HDL method yields more precise estimates of genetic correlations than LDSC, we choose HDL method as the main result. HDL method use the LD reference computed from 335265 Genomic British individuals in the United Kingdom Biobank (UKB)[60].

Annotation-specific genetic correlation

We calculated annotation-specific genetic correlation using genetic covariance analyzer (GNOVA) software[61]. As with LDSC, GNOVA is able to statistically correct for any sample overlap between two different sets of GWAS summary statistics. Compared to LDSC, GNOVA provides greater statistical power and higher estimation accuracy, especially in the case of moderate correlations[61]. We estimated the genetic correlation across ~ 5 million well-imputed SNPs in

the 1000 Genomes Project and partitioned the estimates among categories of SNPs defined by 20 functional categories implicated in open chromatin, histone modification and transcription factor binding site (TFBS)[62], 22 autosomes annotations[62], ten broadly-defined tissue types annotations[63], and 66 epigenetic cell types annotations[63]. Using 0.5 as the cutoff, we converted continuous annotation scores into binary annotation scores (i.e. 0,1). Detailed description of these different subdivisions can be found in the supplementary material (Supplementary Table 3–5).

Local genetic correlation

We estimated local genetic correlations between AD and related SRPs in 1703 pre-specified LD-independent segments with super genetic covariance analyzer (SuperGnova)[64]. This method is designed to identify small contiguous regions of the genome where genetic associations are locally consistent with two traits. SuperGnova quantifies the local genetic correlation and P -values ($P_{\text{SuperGnova}}$) between pairs of traits at local regions. SuperGnova has stronger statistical performance compared to Heritability Estimation from Summary Statistics (HESS)[64], which is not robust to incorrectly specified overlapping sample sizes and is subject to type I error inflation when inaccurate overlapping sample sizes and phenotypic correlation values are provided. AD and SRPs were considered to have genetic correlation at local region if $P_{\text{SuperGnova}}$ was significant after correcting for suggestive P -value ($P_{\text{SuperGnova}} < 1.0 \times 10^{-4}$).

Cross trait meta-analysis

We conducted pairwise cross-trait meta-analysis using Cross Phenotype Association (CPASSOC). CPASSOC combines effect estimates and standard error of GWAS summary statistics to test the hypothesis of association between a SNP with two traits.[65] We used the heterogenous version of cross-phenotype association (SHet) that is based on a sample size-weighted, fixed-effect model and is more powerful when there is a heterogenous effect present between studies[66]. The cross-trait meta-analysis was not inflated (Supplementary Figs. 1–3, Supplementary Methods).

Fine-mapping credible set analysis

For each of the shared loci between AD and SRPs that meet the cross-trait meta-analysis significance criteria, we extracted variants within 500 kb of the index SNP and then identified a 99% credible set of causal SNPs using the Bayesian likelihood fine-mapping algorithm (FM-summary)[67].

Co-localization analysis

We extracted summary statistics for variants within 500 kb of the index SNP at each of the shared loci between AD and SRPs and used R 'coloc' package to perform genetic colocalization analysis which calculated the probability that the two traits shared a common genetic causal variant. In our study, we considered loci with probability (H4) greater than 0.4 to be co-localized[68].

Tissue-specific enrichment analysis

To test if shared gene sets identified from cross-trait meta-analysis were highly enriched or specific expressed in tissues, we conducted tissue-specific enrichment analysis (TSEA) by using R 'TissueEnrich' package[69]. The p value was corrected by Benjamini–Hochberg program.

Functional enrichment analysis

To obtain biological insights for identified shared genes ($P_{\text{meta}} < 1.67 \times 10^{-8}$) from cross-trait meta-analysis, we used the plug-in ClueGO (version: 2.5.7) of Cytoscape (version: 3.8.2) tool to access enrichment of the gene sets in the Gene Ontology (GO) biological process (18483 terms\pathways with 17972 available unique genes) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (328 terms\pathways with 8024 available unique genes) displayed the relationship between genes and GO\KEGG terms[70, 71]. Bonferroni procedure was used to account for multiple testing (False Discovery Rate < 0.05).

Drug target gene enrichment analysis

We queried the Therapeutic Target Database (TTD) to identify Food and Drug Administration (FDA) approved drugs that were used for AD and Insomnia[72]. Meditation target genes for AD and Insomnia were extracted from the DrugBank 5.0 database[73], respectively.

Protein-protein interaction (PPI) analysis

We searched the STRING (version: 11.0) database to identify protein-protein interactions (PPIs) among AD drug target genes, Insomnia drug target genes and identified AD and Insomnia shared genes from CPASSOC[74]. We selected Homo sapiens as the organism and considered total scores above 0.40 (medium confidence) that correspond to the combination of the following 3 different scores: co-expression, experimental, and text mining.

Mendelian randomization analysis

To examine evidence for potential causal relationships between AD and genetically associated SRPs, we conducted instrumental variable analysis using bi-directional Mendelian randomization (MR) implemented in two-sample MR (TSMR, version: 0.5.6), and used inverse-variance weighted (IVW) as primary method[75]. Further, as horizontal pleiotropy is an important confounder that could bias the estimates and often results in an inflated test-statistic in MR analysis, we use MR-Egger regression[76] and MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) methods[77] to detect horizontal pleiotropic. P -values were corrected for multiple testing using Bonferroni ($P < 0.05/6$). We conducted sensitivity analyses using weighted median, simple median, MR-Steiger, and MR-Robust Adjusted Profile Scores (MR-RAPS). We applied MR-Steiger to assure that the causal direction between the hypothesized exposure and outcome was correctly assigned[78]. Considering the measurement error in SNP-exposure effects, MR-RAPS is unbiased when there are many weak instruments, and is robust to systematic and idiosyncratic pleiotropy[79]. Heterogeneity test was also performed to determine that each SNP has the same effect on the results. If exposure is a binary variable, we interpreted the causal estimates as the average change in outcome per doubling (two-fold increase) in the odds of exposure, which could be obtained by multiplying the causal estimate by 0.693 ($\log_e 2$)[80].

Transcriptome-wide association studies

To identify shared genes revealing the shared mechanisms of genetic correlations between AD and SRPs, we next traced down to the gene level to evaluate tissue-specific expression-trait associations and the shared expression-trait associations between AD and each genetically correlated SRPs using transcriptome-wide association studies (TWAS)[81]. Benjamini-Hochberg (BH) procedure was applied to identify significant expression-trait associations adjusted for multiple comparisons for all gene-tissue pairs tested for each trait (~ 230,000 gene tissue pairs in total, significant expression-trait associations were defined as $P_{BH} < 0.05$). We further tested for conditional relationships among the shared genes to identify an independent set of gene-based genetic models using an extension of TWAS that leverages previous methods for joint/conditional tests of SNPs using summary statistics[82] (Supplementary Methods).

Abbreviations

SRPs: Sleep-related phenotypes

HDL: High-definition likelihood

LDSC: Linkage disequilibrium score regression

GNOVA: Genetic covariance analyzer

SuperGnova: super genetic covariance analyzer

CPASSOC: Cross phenotype association study

TSEA: Tissue-specific enrichment analysis

MR: Mendelian randomization

TWAS: Transcriptome wide association study

SNP: Single nucleotide polymorphism

GTEx: Genotype-tissue expression portal

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Publicly available summary statistics GWAS for Insomnia, Morningness, Sleep duration, Ease of getting up in the morning, Daytime napping, Dozing, Snoring, and AD were downloaded from the online resource CTGLab (https://ctg.cncr.nl/software/summary_statistics);

Competing interests

The authors declare that they have no competing interests.

Funding

The study was supported by grants from the National Key Research and Development Project (2019YFC2003400). The funding organization had no role in the preparation of the manuscript

Authors' contributions

JJ and TH conceived and designed the study. DC performed the data preparation and analysis, DC performed the result demonstration. DC wrote the manuscript. All authors have read, edited, and approved the current version of the manuscript.

Acknowledgements

Not applicable.

Data availability

Code availability

Custom **R** scripts used to generate results in this study can be made available upon request

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

URLs

PLINK, <https://www.cog-genomics.org/plink2>

LDSC, <https://github.com/bulik/ldsc>

HDL, <https://github.com/zhenin/HDL>

CPASSOC, <http://hal.case.edu/~xxz10/zhu-web/>

Two-sample MR, <https://github.com/mrcieu/TwoSampleMR>

TWAS, <http://gusevlab.org/projects/fusion/>

MR-PRESSO, <https://github.com/rondolab/MR-PRESSO>

TissueEnrich, <https://www.bioconductor.org/packages/release/bioc/vignettes/TissueEnrich/inst/doc/TissueEnrich.html>

FM-summary, <https://github.com/hailianghuang/FM-summary>

Coloc, <https://github.com/chr1swallace/coloc>

ClueGo, <http://apps.cytoscape.org/apps/cluego>

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Figures

Figure 1

Workflow of the study.

Figure 3

Tissue enrichment for the consensus set. (A). Tissue enrichment analysis result of shared genes between AD and insomnia; (B). Tissue enrichment analysis result of shared genes between AD and sleep duration. (C). Tissue enrichment analysis result of shared genes between AD and snoring. The vertical axis illustrates the logarithm of fold change after Benjamini–Hochberg correction. The horizontal axis illustrates 35 independent tissue types.

Figure 4

Functional enrichment for the consensus set. Functional enrichment analysis results using the ClueGO method in Cytoscape (Bindea et al., 2009). (A). Functional enrichment analysis results of AD and insomnia in KEGG pathways. (B). Functional enrichment analysis results of AD and sleep duration in GO terms. Each dot represented a gene or a GO term or a KEGG pathway. Dots in the same color were considered from the same functional group by ClueGO annotation. Gene names were highlighted in red. Each edge indicated the gene was a component gene of the linked GO term or KEGG pathway.

Figure 5

Protein-protein interaction subnetworks identified by Markov cluster algorithm. The protein-coding genes shared between AD and insomnia and the FDA approved AD and insomnia drug target genes were used to construct a functional similarity network of genes (see the Methods section). Nodes are colored to show association. The thickness of lines connecting nodes indicates the strength of the association between nodes.

Figure 6

Numbers of Significant Genes Related With Insomnia, Sleepdur and Snoring, and the Number of Shared Genes With AD. Significant genes were identified by PBH < 0.05. GTEx = genotype-tissue expression project; GWAS = genome-wide association studies; TWAS = transcriptome-wide association study; NSTSGR = Number of Shared TWAS Significant Genes with AD; AD: Alzheimer's disease; Sleepdur: sleep duration (A): No. of TWAS Significant Genes for Insomnia and No. of Overlapped Genes with AD (B): No. of TWAS Significant Genes for Sleepdur and No. of Overlapped Genes with AD (C): No. of TWAS Significant Genes for Snoring and No. of Overlapped Genes with AD

Supplementary Files

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