ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original research article

Association between depression and sleep apnoea: a Mendelian randomisation study

Gui Chen, Junyang Xie, Weixing Liu, Tianhao Liang, Xiao Liao, Wenjing Liao, Lijuan Song, Xiaowen Zhang

Please cite this article as: Chen G, Xie J, Liu W, *et al*. Association between depression and sleep apnoea: a Mendelian randomisation study. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00394-2021).

Association between depression and sleep apnoea: a Mendelian randomization study

Contributing Authors: Gui Chen, MD; Junyang Xie, MD; Weixing Liu MD; Tianhao Liang, MD; Xiao Liao, MD; Wenjing Liao, PhD; Lijuan Song, PhD; Xiaowen Zhang *, MD, PhD

Address: State Key Laboratory of Respiratory Disease, Department of Otolaryngology-Head and Neck Surgery, First Affiliated Hospital, Guangzhou Medical University, Guangzhou 510120, China.

*These authors contributed equally

Corresponding author

Dr. Xiaowen Zhang, MD, PhD

State Key Laboratory of Respiratory Disease, Department of Otolaryngology-Head and Neck Surgery, The First Affiliated Hospital, Guangzhou Medical University

#151 Yanjiangxi Road, Guangzhou, Guangdong 510120, P.R. China

Tel.: +86 20 83062236; Fax: +86 20 83177207; Email: entxiaowen@163.com

ABSTRACT

Background Studies have reported a close relationship between depression and sleep apnoea, yet it is unknown whether these are causally related. Thus, we aimed to determine whether depression is associated with the aetiology of sleep apnoea.

Methods We used publicly available genetic summary data from two large consortia, the Psychiatric Genomics Consortium, with data from 36 single-nucleotide polymorphisms (SNPs) closely associated with major depressive disorder (MDD) and UK Biobank, including 456,736 patients with sleep apnoea and 766,964 controls. For Mendelian randomization (MR) analysis, we used the inverse-variance weighted method, weighted median method, MR-Egger regression, MR pleiotropy residual sum, and outlier test to retrieve summary data. Analyses were performed using the 'TwoSampleMR' package in R.

Results Of the 36 SNPs associated with MDD, we found statistically significant evidence of a potential causal effect of MDD on the risk of sleep apnoea (odds ratio 1.004, 95% confidence interval: 1.001−1.006, P = 0.001). Similar results were obtained using the MR-Egger and weighted median methods. Additionally, we found no heterogeneity or pleiotropy.

Conclusions Our findings suggest that depression slightly increases the risk of sleep apnoea. Further investigation of the potential biological mechanisms is necessary.

INTRODUCTION

Sleep apnoea is a common sleep-disordered respiratory disease that affects nearly every system in the body, resulting in an increased incidence of neurocognitive disease, cardiovascular disease, and altered immune function [1]. Major depressive disorder (MDD) is a debilitating condition characterized by depressed mood, diminished interest, impaired cognitive function, and vegetative symptoms [2]. The incidence and prevalence of these two diseases has increased in recent years,becoming a global health concern [3-6].

Studies examining the relationship between sleep apnoea and depressive symptoms have reported a significant association between these two conditions [7]. Observational studies have shown that patients with depression have a high prevalence of sleep apnoea [8], and those with severe depression are five times more likely to develop sleep apnoea than the general population [9]. According to clinical studies, the prevalence of sleep apnoea among patients with depression ranges from 20% to 40% [10-11]. Differences and inconsistencies among studies may reflect differences in definitions of sleep apnoea and depression, research methods, sample sizes, and misclassification caused by overlapping symptoms of these two disorders. Indeed, studies have shown that the high prevalence of coexisting depression and sleep apnoea may be owing to shared symptomatology and common underlying risk factors [12]. It has also been speculated that sleep apnoea and depression may have a multi-directional causal relationship, including the effects of sleep fragmentation, biological disorders, metabolic syndrome, mental diseases of the central nervous system, and the effects of some psychotic drugs [13]. However, the current evidence does not support a causal relationship between sleep apnoea and major depression [14]. In addition, researchers believe that depressive symptoms are more likely to be a consequence, rather than a cause of sleep apnoea. Altogether, there is no convincing evidence as to whether sleep apnoea causes depression or depression causes sleep apnoea. Therefore, whether a causal relationship exists between depression and sleep apnoea needs further investigation.

With an increasing number of genome-wide association studies (GWAS), Mendelian randomization (MR) has become a novel epidemiological tool. This approach uses genetic variants as instrumental variables (IVs) to investigate potential causal relationships among different human traits. To examine the possibility of a causal effect of depression on sleep apnoea, we performed a two-step MR analysis using information of 361,194 individuals from UK Biobank with linked genetic data. Our approach will provide clinicians and researchers with up-to-date information on the relationship between depression and sleep apnoea.

METHODS

Genetic variants associated with MDD

The main genetic instruments used were from a GWAS meta-analysis of MDD, and included seven MDD cohorts The participants was met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or International Classification of Diseases-10 (ICD-10) criteria for MDD.[15] Detailed description is provided on the FinnGen research project website (https://www.finngen.fi/en). In total, 135,458 patients with MDD and 344,901 controls were analysed in the meta-analysis. A total of 44 single-nucleotide polymorphisms (SNPs) have been reported to be significantly associated with MDD ($P < 5 \times 10^{-8}$, linkage disequilibrium $r^2 < 0.01$; Table S1). These associated SNPs account for 0.23% of

the variation in MDD. The F statistic in our study was 156, which is considerably larger than the standard value of 10, indicating that the instruments used can strongly predict MDD [16]. Additionally, there was no evidence to support the existence of unbalanced pleiotropy within the genetic instruments used for examining the SNPs associated with sleep apnoea ($P < 10^{-8}$).

GWAS summary data for sleep apnoea

The GWAS summary data for sleep apnoea, determined by ICD-10, were obtained from the Neale Lab [17] (http://www.nealelab.is/uk-biobank). A total of 2,249 patients with sleep apnoea and 358,945 controls were included. In total, 44 SNPs associated with MDD were retrieved from the UK Biobank. SNPs rs1363104, rs34215985, and rs62099069 were removed from as they were palindromic with intermediate allele frequencies. A further five SNPs were removed because the result set lacked the information needed for MR analysis. The inverse-variance weighted (IVW) method was used to examine the relationship between MDD and risk of sleep apnoea. Effect estimates (equivalent to beta coefficients) were calculated and then transformed to odds ratios (ORs). The weighted median and MR-Egger method were also used to examine the effect. A heterogeneity test was applied to determine the variability in effect estimates obtained for each SNP. However, as many IVs are associated with multiple traits (pleiotropy), this may impact the validity of MR analysis. Therefore, MR-Egger regression was also performed to examine horizontal pleiotropy. To determine the robustness of significant results, a leave-one-out sensitivity analysis was performed, whereby the analysis was reduced by one SNP at a time to determine whether the estimates in IVW analysis could be biased by a single SNP. All MR analyses were performed using R version 4.0.3 with the 'TwoSampleMR' package [18].

GWAS summary data for sleep apnoea risk factors

To determine the mediating effect of depression on sleep apnoea through other risk factors, an IVW analysis was performed to examine the association between MDD and other known risk factors for sleep apnoea. Well-known risk factors include body mass index, insomnia, daytime sleeping, hypertension, type 2 diabetes, smoking, and alcohol consumption. GWAS summary data for these phenotypes were extracted from the Neale Lab Consortium, GWAS and Sequencing Consortium of Alcohol and Nicotine Use, and meta-analysis of GWAS. Details of all GWAS included in our study are provided in Table 1.

Table 1. Details of the genome-wide association studies included in Mendelian randomization

Phenotype	Consortium	Participants	PMID/Web source
Major depressive disorder	A meta‐analysis of GWAS	480359	29700475
Sleep apnoea	Neale Lab Consortium	361194	http://www.nealelab.is/uk‐biobank
Body mass index	A meta‐analysis of GWAS	681275	30124842
Daytime dozing / sleeping (narcolepsy)	Neale Lab Consortium	336082	http://www.nealelab.is/uk‐biobank
Hypertension	Neale Lab Consortium	361194	http://www.nealelab.is/uk‐biobank
Type 2 diabetes	A meta‐analysis of GWAS	70127	29358691
Cigarettes per Day	GWAS and Sequencing Consortium of Alcohol and Nicotine use	337334	30643251
Alcoholic drinks per week	GWAS and Sequencing Consortium of Alcohol and Nicotine use	335394	30643251
Sleeplessness / insomnia	Neale Lab Consortium	336965	http://www.nealelab.is/uk‐biobank

GWAS, genome-wide association studies.

RESULTS

Effect of MDD on sleep apnoea

Using 36 SNPs associated with MDD, we found evidence for a potential causal relationship, with a statistically significant association between MDD and risk of sleep apnoea (OR = 1.004, 95% confidence interval [CI]: 1.001–1.006, P = 0.001). Additionally, the weighted median method was statistically significant (OR = 1.004, 95% CI: 1.000–1.008, P = 0.019). Similar risk estimates were obtained using the MR-Egger method (OR = 1.004, 95% CI: 0.993–1.014, P = 0.511), although the correlation was not significant (Figure 1). The P-values for heterogeneity tests using the MR-Egger and IVW methods were 0.876 and 0.902 respectively, which suggests there is no heterogeneity. There was no significant interception (intercept = 0.000; SE = 0.000, P = 0.991), indicating no horizontal pleiotropy. Furthermore, the funnel plot was symmetrical, confirming no pleiotropy. In the sensitivity analysis, there was no fundamental impact on sleep apnoea (all lines were on the right side of 0), regardless of which SNP was removed, suggesting that the MR result was robust .

Effect of MDD on potential sleep apnoea risk factors

To identify potential risk factors for the association between depression and sleep apnoea, we used IVW analysis to investigate the relationship between depression and several sleep apnoea risk factors including smoking, insomnia, daytime sleeping, hypertension, type 2 diabetes, alcohol consumption, and body mass index. Table 2 summarizes the association of depression with these potential risk factors. The MR results indicate that a one standard deviation increase in the duration of depression was associated with a 16% higher odds of smoking. A one standard deviation increase in the duration of depression was also associated with an 8% higher odds of insomnia.

Table 2. Relationship between major depressive disorder predicted by genetic data and potential risk factors of sleep apnoea

Outcomes	SNPs, n	**OR**	**95%CI**	**P**
Body mass index	27	1.022	0.917, 1.140	0.689
Daytime dozing / sleeping (narcolepsy)	32	1.019	0.999,1.040	0.068
Hypertension	32	1.000	0.998, 1.002	0.884
Type 2 diabetes	32	1.031	0.854, 1.244	0.753
Cigarettes per Day	31	1.166	1.033, 1.316	0.013
Alcoholic drinks per week	31	1.000	0.955, 1.048	0.992
Sleeplessness / insomnia	32	1.089	1.045, 1.134	<0.001

SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

DISCUSSION

In this study, we used two-sample MR methods to comprehensively examine the relationship between depression and the aetiology of sleep apnoea in European populations. MR analysis showed that depression slightly increased the risk of sleep apnoea. It should be noted that although we found statistically significant evidence that there is a potential causal relationship between the 36 SNPs associated with MDD and the risk of sleep apnoea, this is different from such a strong relationship in previous clinical studies.

The present results support those of previous underpowered and inconsistent studies, and also provide stronger evidence for the role of depression in sleep apnoea. In a European multi-country cooperative study, 18,980 participants were interviewed by telephone [19]. Of these, 17.6% of patients with sleep apnoea had a diagnosis of MDD and 18% of patients with MDD also met the diagnostic criteria of sleep apnoea. Additionally, only 4.3% of patients with MDD had no sleep breathing symptoms. Although the sample size of that study was relatively large, it was a cross-sectional telephone survey. In 2006, Peppard found a dose–response relationship between sleep apnoea and depression in a cohort study, suggesting a causal relationship between the two disorders [20]. Unfortunately, that study did not control for a common risk factor, namely, weight gain. In a large clinical cohort study by Kendzerska that controlled for confounders, sleep apnoea symptoms and severity were not found to be related to the risk of hospitalization owing to depression [21]. However, those authors did not rule out a potential link between sleep apnoea and mild depression.

The mechanisms underlying the association between sleep apnoea and depression are still unclear, however, we will discuss several possible explanations. Although some antidepressants can alleviate sleep apnoea, and decrease the amount of Rapid-eye-movement (REM)-sleep [22-23], drug side effects need to be paid attention. Studies have pointed out that sedative antidepressants and adjunct

treatments for depression may aggravate sleep apnoea [24]. Some antidepressants may reduce the muscle tone of upper airway dilatator muscles; these stimulate the body’s wake-up response to hypoxia and hypercapnia, and increase the wake-up threshold for apnoea events, thereby increasing the number and duration of apnoea events [25-26]. Smith et al. noted that selective serotonin reuptake inhibitor antidepressants and tricyclic antidepressants may decrease sleep efficiency in patients with sleep apnoea [27]. Additionally, the use of antidepressant medication is often accompanied by weight gain and subsequent worsening of sleep apnoea. Patients with sleep apnoea who have depressive symptoms showed significant areas of neural injury [28]. Compared with healthy controls, people with MDD showed structural and functional defects in the hippocampus, anterior cingulate gyrus, amygdala, and frontal cortex. However, patients with sleep apnoea may also have structural and functional defects in these anatomical regions [29]. Moreover, depression is associated with several neuroendocrine and metabolic changes that have been linked to sleep apnoea, including altered glucocorticoids, adipokines, insulin, leptin, and inflammatory signalling [30-31]. Some of these are involved in the regulation of food intake and may lead to obesity [32]. Obesity is a risk factor for both sleep apnoea and depression [33].

It should be noted that the relationship between depression and sleep apnoea may be mediated by many intermediate phenotypes. Because smoking can relieve the symptoms of depression, the ‘self-medication’ hypothesis suggests that depression can lead to smoking behaviour [34-35]. Depression is generally considered to be a risk factor for insomnia [36], and insomnia is the most common (up to 88%) subjective sleep complaint among patients with MDD [37]. Khazaie et al. reported a bidirectional link between insomnia and depression [38]. An MR study found that transcription factor 4 plays an important role in the interaction between MDD and insomnia [39]. Our analysis confirms that the longer the duration of depression symptoms, the higher the risk of smoking and insomnia. Given that smoking and insomnia are established causes of sleep apnoea [40-43] and are clearly related to depression, these may be key intermediate factors in the depression –sleep apnoea pathway. Reasonably, there may be a confounding effect between depression and sleep apnoea. However, given the nature of the data used, it was not possible to conduct a stratified analysis based on smoking and insomnia, and we cannot separate depression from confounding factors.

Our study has many methodological advantages. First, multiple samples were used to examine the relationship between depression and risk of sleep apnoea. Second, a strict framework was applied. All 44 SNPs associated with MDD were identified in GWAS from European populations and replicated in our samples. Third, these results were confirmed in sensitivity analysis and pleiotropic testing. Limitations should also be considered when interpreting the results. First, whether the findings described here can be generalized to other populations remains to be studied. Second, greater attention is needed to the diversity of patients with sleep apnoea. Depression may have a causal relationship with sleep apnoea in some populations. More extensive studies, including sleep apnoea subgroups, should

be considered in the future. Third, we attempted to examine the relationship between sleep apnoea and depression in a population using MR. However, studies have reported sleep apnoea heritability estimates of 8.3% (0.06–0.11), whereas there are only five SNPs associated with sleep apnoea ($P < 5.0 \times 10^{-8}$), including three SNPs in UK Biobank [44].

The results of this study show that depression has a potential causal relationship with a higher risk of sleep apnoea, providing evidence for the role of depression in sleep apnoea. According to our results, greater attention should be given to the potential risk of depression as a cause of sleep apnoea. Sleep apnoea screening should be performed in people with MDD, with polysomnography and physical examination carried out when necessary. Future research should focus on mechanisms of the relationship between depression and sleep apnoea.

Acknowledgements

We express our gratitude to the participants and research teams from UK Biobank and FinnGen that have made the GWAS results publicly accessible. We thank Rachel James, PhD, from Liwen Bianji (Edanz) (www.liwenbianji.cn/) for editing the English text of a draft of this manuscript.

Contributors

(I) Conception and design: Gui Chen, Junyang Xie, and Xiaowen Zhang; (II) Administrative support: Xiaowen Zhang; (III) Data analysis and interpretation: Weixing Liu, Tianhao Liang, Xiao Liao, Wenjing Liao, and Lijuan Song; (IV) Manuscript writing: All authors; (V) Final approval of the manuscript: All authors.

Declaration of interests

All authors declare that they have no competing interests.

Ethical considerations

No ethical approval was required for this research as no patients were involved in the development of the research question or its outcome measures. Only secondary analyses were performed using published GWAS summary statistics available in the public domain.

Figure Legends

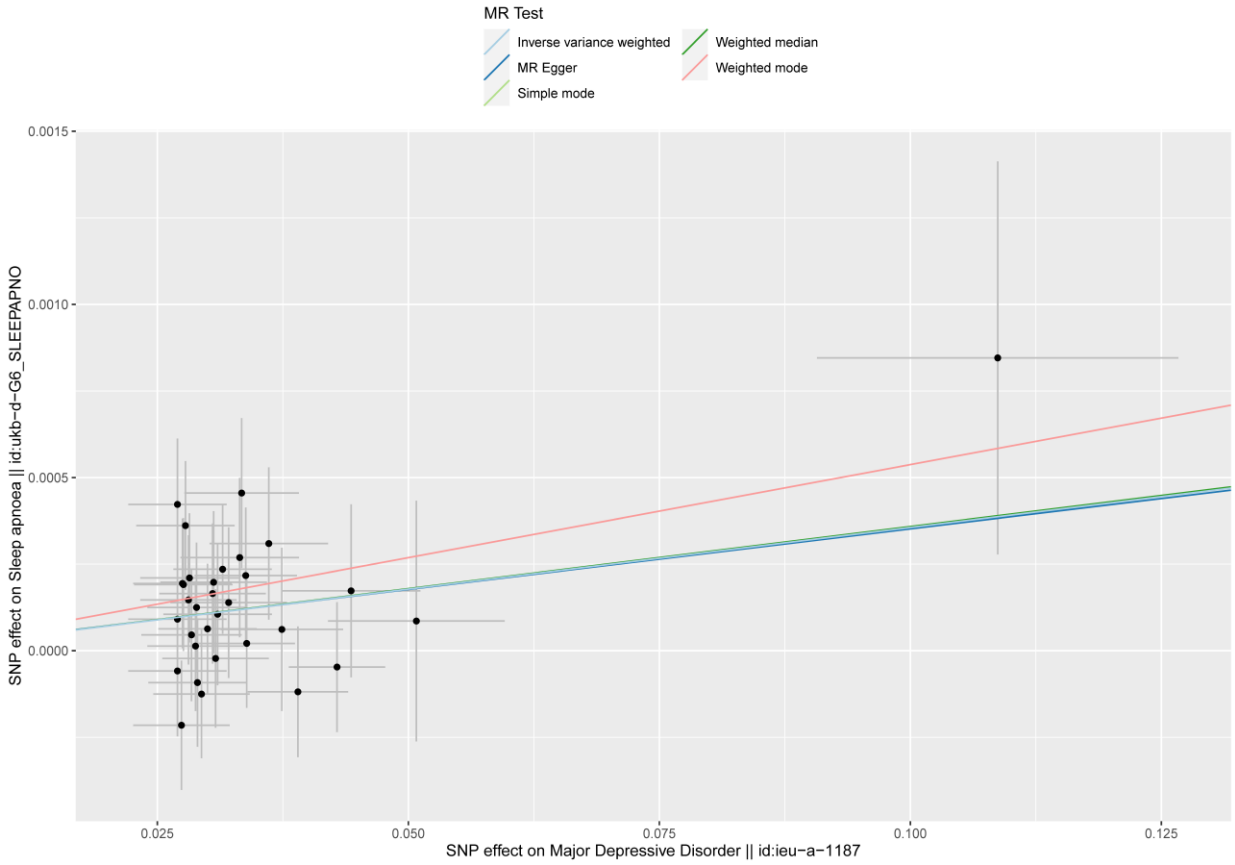

Figure 1. Scatter plot of the effect of SNPs on major depressive disorder and sleep apnoea.

SNP, single-nucleotide polymorphism; MR, Mendelian randomization.

References

[1] Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. JAMA. 2020 Apr 14;323(14):1389-1400.

[2] Otte C, Gold SM, Penninx BW, et al. Major depressive disorder. Nat Rev Dis Primers. 2016 Sep 15;2:16065.

[3] Grote L. The global burden of sleep apnoea. Lancet Respir Med. 2019 Aug;7(8):645-647.

[4] Garbarino S, Magnavita N, Sanna A, et al. Estimating the hidden burden of obstructive sleep apnoea: challenges and pitfalls. Lancet Respir Med. 2020 Jan;8(1):e1.

[5] Gliklich RE, Leavy MB, Cosgrove L, et al. Harmonized Outcome Measures for Use in Depression Patient Registries and Clinical Practice. Ann Intern Med. 2020 Jun 16;172(12):803-809.

[6] Malhi GS, Mann JJ. Depression. Lancet. 2018 Nov 24;392(10161):2299-2312.

[7] BaHammam AS, Kendzerska T, Gupta R, et al. Comorbid depression in obstructive sleep apnea: an under-recognized association. Sleep Breath 2016; 20: 447–456.

[8] Stubbs B, Vancampfort D, Veronese N, et al. The prevalence and predictors of obstructive sleep apnea in major depressive disorder, bipolar disorder and schizophrenia: A systematic review and meta-analysis. J Affect Disord. 2016 Jun;197:259-67.

[9] Ohayon MM. The effects of breathing-related sleep disorders on mood disturbances in the general population. J Clin Psychiatry. 2003;64:1195–1200.

[10] Harris M, Glozier N, Ratnavadivel R, et al.Obstructive sleep apnea and depression. Sleep Med Rev 2009; 13: 437–444.

[11] Basta M, Lin HM, Pejovic S, et al. Lack of regular exercise, depression, and degree of apnea are predictors of excessive daytime sleepiness in patients with sleep apnea: sex differences. J Clin Sleep Med 2008; 4: 19–25.

[12] Ejaz SM, Khawaja IS, Bhatia S, et al. Obstructive sleep apnea and depression: a review. Innov Clin Neurosci 2011; 8: 17–25.

[13] Gupta MA, Simpson FC. Obstructive sleep apnea and psychiatric disorders: a systematic review. J Clin Sleep Med 2015; 11: 165–175.

[14] Bixler EO, Gaines J, Vgontzas AN. Obstructive sleep apnoea and depression: is there an association? Eur Respir J. 2017 Jun 1;49(6):1700858.

[15] Wray NR, Ripke S, Mattheisen M, et al. Genome‐wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50(5):668–681.

[16] Burgess S, Thompson SG; CRP CHD Genetics Collaboration. Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol. 2011 Jun;40(3):755-64.

[17] Campos AI, García-Marín LM, Byrne EM, et al. Insights into the aetiology of snoring from observational and genetic investigations in the UK Biobank. Nat Commun. 2020 Feb 14;11(1):817.

[18] Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife. 2018 May 30;7:e34408.

[19] Ohayon MM. The effects of breathing-related sleep disorders on mood disturbances in the general population. J Clin Psychiatry. 2003 Oct;64(10):1195-200; quiz, 1274-6.

[20] Peppard PE, Szklo-Coxe M, Hla KM, et al. Longitudinal association of sleep-related breathing disorder and depression. Arch Intern Med. 2006 Sep 18;166(16):1709-15.

[21] Kendzerska T, Gershon AS, Hawker GA, et al. Obstructive sleep apnoea is not a risk factor for incident hospitalised depression: a historical cohort study. Eur Respir J 2017; 49: 1601361.

[22] Brownell LG, West P, Sweatman P,et al. Protriptyline in obstructive sleep apnea: a double-blind trial. N Engl J Med. 1982;307(17):1037-1042.

[23] Hanzel DA, Proia NG, Hudgel DW. Response of obstructive sleep apnea to fluoxetine and protriptyline. Chest. 1991;100(2):416-421.

[24] Schröder CM, O'Hara R. Depression and Obstructive Sleep Apnea (OSA). Ann Gen Psychiatry. 2005;4:13. Published 2005 Jun 27.

[25] Miles LE, Dement WC. Sleep and aging. Sleep. 1980;3:1–220.

[26] Guilleminault C. Benzodiazepines, breathing, and sleep. Am J Med. 1990;88:25S–28S.

[27] Smith SS, Dingwall K, Jorgenson G, et al. Associations between the use of common medications and sleep architecture in patients with untreated obstructive sleep apnea. J Clin Sleep Med. 2006;2(2):156-162.

[28] Cross RL, Kumar R, Macey PM, et al. Neural alterations and depressive symptoms in obstructive sleep apnea patients. Sleep. 2008;31(8):1103-1109.

[29] Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A meta-analytic study of changes in brain activation in depression. Hum Brain Mapp. 2008;29:683–95.

[30] Hryhorczuk C, Sharma S, Fulton SE. Metabolic disturbances connecting obesity and depression. Front. Neurosci. 2013;7:177.

[31] Vicente E, Marin JM, Carrizo SJ, et al. Upper airway and systemic inflammation in obstructive sleep apnoea. Eur Respir J. 2016 Oct;48(4):1108-1117.

[32] Reeves GM, Postolache TT, Snitker S. Childhood Obesity and Depression: Connection between these Growing Problems in Growing Children. International journal of child health and human development: IJCHD. 2008;1(2):103–14.

[33] Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry. 2010;67(3):220–9.

[34] Carceller-Maicas Natàlia,Ariste Santiago,Martínez-Hernáez Angel et al. [Smoking as a form of self-medication for depression or anxiety in young adults: results of a mixed-methods study].[J] .Adicciones, 2014, 26: 34-45.

[35] Chaiton, M.O., Cohen, J.E., O'Loughlin, J. et al. A systematic review of longitudinal studies on the association between depression and smoking in adolescents. BMC Public Health 9, 356 (2009).

[36] Fang H, Tu S, Sheng J, Shao A. Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment. J Cell Mol Med. 2019;23(4):2324-2332.

[37] Yates WR, Mitchell J, Rush AJ, et al. Clinical features of depressed outpatients with and without co-occurring general medical conditions in STAR*D. Gen Hosp Psychiatry. 2004;26(6):421-429.

[38] Khazaie H, Veronese M, Noori K, et al. Functional reorganization in obstructive sleep apnoea and insomnia: A systematic review of the resting-state fMRI. Neurosci Biobehav Rev. 2017 Jun;77:219-231.

[39] Cai L, Bao Y, Fu X, et al. Causal links between major depressive disorder and insomnia: A Mendelian randomisation study. Gene. 2021 Feb 5;768:145271.

[40] Amiri S, Behnezhad S. Smoking and risk of sleep-related issues: a systematic review and meta-analysis of prospective studies[J]. Canadian journal of public health. Revue canadienne de santé publique, 2020, 111(5).

[41]Esen AD, Akpinar M. Relevance of obstructive sleep apnea and smoking: Obstructive sleep apnea and smoking. Fam Pract. 2021 Mar 29;38(2):181-186.
[42] Grandner MA, Malhotra A. Connecting insomnia, sleep apnoea and depression. Respirology. 2017 Oct;22(7):1249-1250.
[43] Humer E, Pieh C, Brandmayr G. Metabolomics in Sleep, Insomnia and Sleep Apnea. Int J Mol Sci. 2020 Sep 30;21(19):7244.
[44] Strausz S, Ruotsalainen S, Ollila HM, et al. Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health. Eur Respir J. 2021 May 6;57(5):2003091.

Supplementary Table 1. Forty-four SNPs associated with major depressive disorder

SNP	Chromosome	Position	Effect allele	Other allele	Frequency	Beta	Se	P	Sample size
rs12129573	1	73768366	A	C	0.3671	4.00E-04	0.0083	0.9568	140,254
rs1432639	1	72813218	A	C	0.6187	-0.0027	0.0083	0.746	140,254
rs159963	1	8504421	A	C	0.5671	0.0051	0.0085	0.5495	140,254
rs2389016	1	80799329	T	C	0.2744	4.00E-04	0.0096	0.9632	140,254
rs4261101	1	90796053	A	G	0.3543	-0.0036	0.0086	0.6699	140,254
rs9427672	1	1.98E+08	A	G	0.2187	-0.018	0.0101	0.07444	140,254
rs11682175	2	57987593	T	C	0.5333	-0.0178	0.008	0.02626	140,254
rs1226412	2	1.57E+08	T	C	0.7859	-0.005	0.01	0.6207	140,254
rs9862324	3	44433910	T	C	0.669	-0.0085	0.0086	0.326	140,254
rs7430565	3	1.58E+08	A	G	0.5674	0.0027	0.008	0.7403	140,254
rs34215985	4	42047778	C	G	0.2135	-0.0179	0.01	0.07425	140,254
rs27732	5	87992576	A	G	0.4167	-0.0081	0.0083	0.3302	140,254
rs2018142	5	1.04E+08	A	C	0.5229	-0.0085	0.0081	0.2922	140,254
rs116755193	5	1.24E+08	T	C	0.3786	-0.0193	0.0085	0.02314	140,254
rs11135349	5	1.65E+08	A	C	0.4504	0.0207	0.0083	0.01254	140,254
rs4869056	5	1.67E+08	A	G	0.6311	-5.00E-04	0.0089	0.9554	140,254
rs115507122	6	30737591	C	G	0.172	-0.0526	0.0106	7.09E-07	140,254

rs9402472	6	99566521	A	G	0.2222	-0.006	0.0099	0.5395	140,254
rs10950398	7	12264871	A	G	0.4074	0.011	0.0081	0.1762	140,254
rs12666117	7	1.09E+08	A	G	0.4652	-0.0034	0.008	0.6718	140,254
rs1354115	9	2983774	A	C	0.6308	0.0092	0.0089	0.3049	140,254
rs10959913	9	11544964	T	G	0.765	-0.0231	0.0098	0.01801	140,254
rs7856424	9	1.2E+08	T	C	0.2896	0.0087	0.0091	0.3379	140,254
rs7029033	9	1.27E+08	T	C	0.0796	-0.0189	0.0151	0.2121	140,254
rs61867293	10	1.07E+08	T	C	0.206	0.0127	0.0099	0.2009	140,254
rs1806153	11	31850105	T	G	0.225	-1.00E-04	0.0099	0.9951	140,254
rs4074723	12	23947737	A	C	0.401	-0.0168	0.0091	0.06559	140,254
rs4143229	13	44327799	A	C	0.9189	-0.0093	0.0148	0.5284	140,254
rs12552	13	53625781	A	G	0.4329	0.0051	0.0084	0.5459	140,254
rs4904738	14	42179732	T	C	0.555	-0.009	0.0082	0.2716	140,254
rs915057	14	64686207	A	G	0.4302	-0.0163	0.0083	0.05126	140,254
rs3742786	14	75373011	A	G	0.4488	0.0242	0.0079	0.002278	140,254
rs10149470	14	1.04E+08	A	G	0.4949	-0.0213	0.008	0.007901	140,254
rs8025231	15	37648402	A	C	0.5519	0.0041	0.0083	0.6174	140,254
rs8063603	16	6310645	A	G	0.6568	-0.0047	0.0089	0.6002	140,254
rs7198928	16	7666402	T	C	0.6256	-0.0049	0.0084	0.5638	140,254
rs7200826	16	13066833	T	C	0.2605	-0.0089	0.0096	0.3528	140,254
rs11643192	16	72214276	A	C	0.4027	-0.0234	0.0082	0.004284	140,254
rs17727765	17	27576962	T	C	0.9147	-0.012	0.015	0.4247	140,254

rs62099069	18	36883737	A	T	0.4246	-0.0097	0.0084	0.2505	140,254
rs11663393	18	50614732	A	G	0.4713	0.0079	0.008	0.3242	140,254
rs1833288	18	52517906	A	G	0.7116	0.0192	0.0095	0.04256	140,254
rs12958048	18	53101598	A	G	0.3223	-0.0151	0.0086	0.07798	140,254
rs5758265	22	41617897	A	G	0.2832	0.0173	0.0089	0.05145	140,254

SNP, single-nucleotide polymorphism.