



# Association between depression and sleep apnoea: a Mendelian randomisation study

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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

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## 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 the UK Biobank, including 456 736 patients with sleep apnoea and 766 964 controls. For Mendelian randomisation (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** Out 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 (OR 1.004, 95% CI 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 characterised 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 between 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 multidirectional 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 randomisation (MR) has become a novel epidemiological tool. This approach uses genetic variants as instrumental variables 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 the information of 361 194 individuals from the UK Biobank with linked genetic data. Our approach provides 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 met the Diagnostic and Statistical Manual of Mental Disorders IV or International Classification of Diseases (ICD)-10 criteria for MDD [15]. Detailed description is provided on the FinnGen research project website ([www.finnngen.fi/en](http://www.finnngen.fi/en)). In total, 135 458 patients with MDD and 344 901 controls were analysed in the meta-analysis. 44 single-nucleotide polymorphisms (SNPs) have been reported to be significantly associated with MDD ( $p < 5 \times 10^{-8}$ , linkage disequilibrium  $r^2 < 0.01$ ; supplementary 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] ([www.nealelab.is/uk-biobank](http://www.nealelab.is/uk-biobank)). 2249 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, 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. 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 instrumental variables 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.

## 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% 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

TABLE 1 Details of the genome-wide association studies (GWAS) included in Mendelian randomisation

	Consortium	Participants	PubMed ID/websource
Major depressive disorder	A meta-analysis of GWAS	480 359	29700475
Sleep apnoea	Neale lab consortium	361 194	www.nealelab.is/uk-biobank
Body mass index	A meta-analysis of GWAS	681 275	30124842
Daytime dozing/sleeping (narcolepsy)	Neale lab consortium	336 082	www.nealelab.is/uk-biobank
Hypertension	Neale lab consortium	361 194	www.nealelab.is/uk-biobank
Type 2 diabetes	A meta-analysis of GWAS	70 127	29358691
Cigarettes per day	GWAS and Sequencing Consortium of Alcohol and Nicotine Use	337 334	30643251
Alcoholic drinks per week	GWAS and Sequencing Consortium of Alcohol and Nicotine Use	335 394	30643251
Sleeplessness/insomnia	Neale lab consortium	336 965	www.nealelab.is/uk-biobank

heterogeneity tests using the MR-Egger and IVW methods were 0.876 and 0.902, respectively, which suggests that 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 summarises the association of depression with these potential risk factors. The MR results indicate that a 1-SD increase in the duration of depression was associated with a 16% higher odds of smoking. A 1-SD increase in the duration of depression was also associated with an 8% higher odds of insomnia.

#### 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

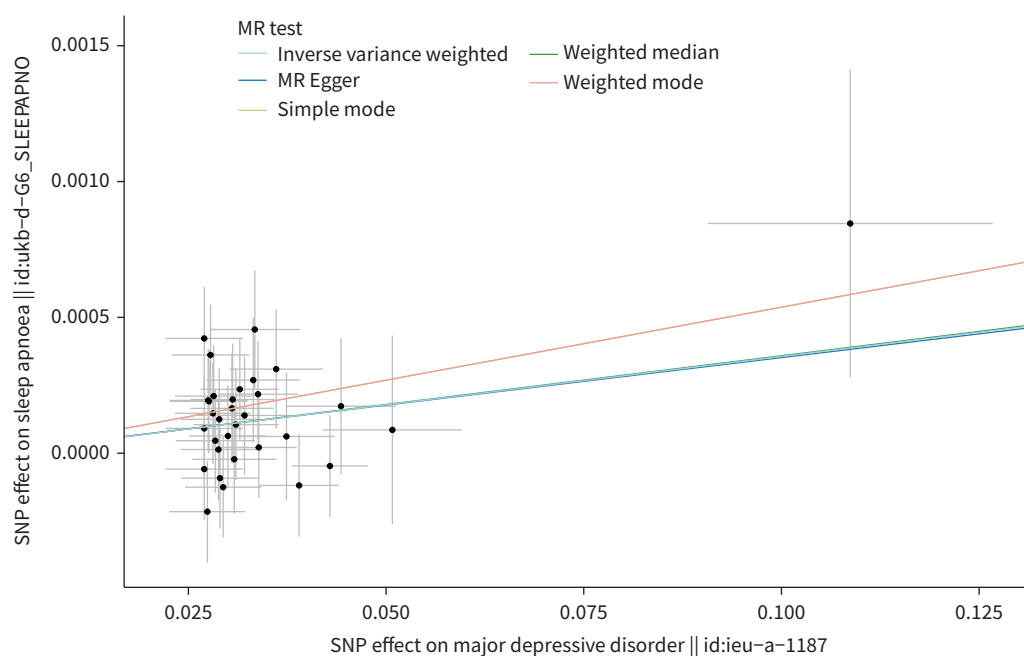


FIGURE 1 Scatter plot of the effect of single-nucleotide polymorphisms (SNPs) on major depressive disorder and sleep apnoea. MR: Mendelian randomisation.

**TABLE 2** Relationship between major depressive disorder predicted by genetic data and potential risk factors for sleep apnoea

	SNPs, n	OR (95% CI)	p-value
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.

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 depression significantly promoting sleep apnoea in previous clinical studies.

The present results support those of prior underpowered and inconsistent studies, and also provide stronger evidence for the role of depression in sleep apnoea. In a European multicountry cooperative study, 18 980 participants were interviewed by telephone [9]. 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 *et al.* [19] found a dose–response relationship between sleep apnoea and depression in a cohort study, suggesting a causal relationship between the two disorders. Unfortunately, that study did not control for a common risk factor, namely, weight gain. In a large clinical cohort study by KENDZERSKA *et al.* [20] that controlled for confounders, sleep apnoea symptoms and severity were not found to be related to the risk of hospitalisation owing to depression. 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 discuss several possible explanations. Although some antidepressants can alleviate sleep apnoea, and decrease the amount of rapid eye movement sleep [21, 22], attention must be paid to drug side-effects. Studies have shown that sedative antidepressants and adjunct treatments for depression may aggravate sleep apnoea [23]. Some antidepressants may reduce the muscle tone of upper airway dilator 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 [24, 25]. SMITH *et al.* [26] noted that selective serotonin reuptake inhibitor antidepressants and tricyclic antidepressants may decrease sleep efficiency in patients with sleep apnoea. 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 [27]. 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 [28]. 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 [29, 30]. Some of these are involved in the regulation of food intake and may lead to obesity [31]. Obesity is a risk factor for both sleep apnoea and depression [32].

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 [33, 34]. Depression is generally considered to be a risk factor for insomnia [35], and insomnia is the most common (up to 88%) subjective sleep complaint among patients with MDD [36]. KHAZAEI *et al.* [37] reported a bidirectional link between insomnia and depression. An MR study found that transcription factor 4 plays an important role in the interaction between MDD and insomnia [38]. 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 [39–42] 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 generalised 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% (95% CI 6–11%), whereas there are only five SNPs associated with sleep apnoea ( $p < 5.0 \times 10^{-8}$ ), including three SNPs in UK Biobank [43].

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.

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**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.

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**Conflict of interest:** None declared.

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