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Article

Causal relationship between Alzheimer's disease and obstructive sleep apnoea: Insights from a biomechanics-oriented bidirectional mendelian randomization study

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Abstract: Background: The latest observational studies revealed a possible association between Alzheimer 's disease (AD) and obstructive sleep apnoea (OSA). In AD, the accumulation of amyloid-beta plaques and tau tangles disrupts the normal structure and function of neurons in the brain. These pathological changes can affect the mechanical properties of neural tissues, altering their elasticity and stiffness. Such alterations might extend to the neural circuits responsible for regulating sleep and respiration, potentially influencing the occurrence of OSA. We used bidirectional Mendelian randomization approach to analyze causalities between OSA, its typical symptoms (snoring and daytime sleepiness) and AD in European populations. **Methods:** Single nucleotide polymorphisms of AD and OSA, snoring, daytime dozing were selected as instrumental variables. Preliminary MR analysis was inverse-variance weighted (IVW) method. The Cochran Q test, MR-Egger analysis, 'leave-one-out' test were used to verify the data robustness. Results were adjusted for Bonferroni correction thresholds. **Results:** Results from IVW demonstrated a suggestive correlation between AD and higher risks of sleep apnoea (OR 1.0008, 95%CI 1.0000–1.0016, p = 0.044) after Bonferroni correction. However, reverse MR analysis showed no association of genetically primed sleep apnoea towards AD (p = 0.294). No causal effect was detected between genetic AD and snoring, daytime dozing. From a biomechanical perspective, the positive correlation between AD and increased risk of sleep apnoea could be due to the fact that the structural changes in the brain caused by AD might lead to changes in the biomechanical forces exerted on the brainstem regions that control breathing during sleep. **Conclusions:** The findings of the MR study support that AD might increase the risk of OSA. Therefore, individuals with AD should strengthen sleep monitoring, sleep hygiene and develop a regular sleep-wake pattern. Understanding these underlying biomechanical mechanisms could provide valuable insights for developing targeted interventions to mitigate the risk of OSA in AD patients and potentially improve their overall sleep quality and disease management.

Keywords: Alzheimer's disease; obstructive sleep apnoea; snoring; Mendelian randomization; biomechanical mechanisms

1. Introduction

Alzheimer's disease (AD) is a serious and debilitating condition that has a significant impact on global health. It is primarily responsible for causing dementia, which unfortunately ranks as the sixth leading cause of death around the world at present [1,2]. This is a concerning situation that demands our attention, especially considering the projections indicating that the number of AD cases could escalate to a staggering 152 million by 2050 [3]. In light of this looming threat, AD clinical

guidelines have been developed to guide healthcare professionals in dealing with the disease. These guidelines advocate for an integrated approach that combines various strategies. One key aspect is the management of symptoms, as AD patients often experience a range of distressing manifestations like memory loss, confusion, and difficulties in performing routine tasks. Additionally, controlling the controllable risk factors is equally important. By addressing these factors, there's hope to slow down the progression of the disease or even prevent it in some cases [4]. The relationship between sleep and AD has become a hot topic in the scientific community. There's a hypothesized bidirectional causality between them [5,6]. This implies that not only might sleep problems contribute to the development or worsening of AD, but also that AD itself could potentially disrupt normal sleep patterns. Among the different sleep-related factors, Sleep-Disordered Breathing (SDB) has drawn substantial scientific attention as a modifiable risk factor [7,8].

It presents an opportunity for intervention and management, which could potentially have implications for AD. Obstructive sleep apnoea (OSA) is a particularly significant manifestation of SDB in the general population. People with OSA usually display several characteristic symptoms. Snoring is a common and often quite noticeable sign, which can be loud and persistent during sleep. Daytime sleepiness is another prevalent issue. Those affected often struggle to stay alert during the day and feel constantly fatigued, despite having what seems like an adequate amount of sleep at night. This can greatly affect their daily lives, from work performance to social interactions [9]. Observational studies have shed some light on the connection between OSA and AD. They have emphasized that the incidence of OSA tends to be higher among individuals with mild to moderate AD [10]. This finding suggests a possible link between the presence of AD in its earlier stages and an increased likelihood of developing OSA. Moreover, when it comes to severe OSA, there's a concerning association with a higher risk of AD. The relative risk (RR) has been calculated as 1.66, with a 95% confidence interval (CI) ranging from 1.03 to 2.68 [11,12]. This indicates that those with severe OSA face a significantly elevated risk of developing AD compared to those without such severe sleep-breathing problems. In addition, a meta-analysis has provided another interesting piece of evidence. It has shown that long-term use of continuous positive airway pressure (CPAP), a common treatment for OSA, can be linked to cognitive improvement in patients with AD [13]. This suggests that effectively managing OSA might have a positive impact on the cognitive abilities of AD patients. Furthermore, evidence from real-world scenarios has also confirmed that OSA is independently associated with a markedly increased risk of AD incidence. The adjusted hazard ratio (HR) is 2.12, with a 95% CI of 1.27 to 3.56 [14].

However, despite all these findings that seem to point towards a connection between AD and OSA, the causality between them has not been systematically investigated and firmly established in the existing scientific research. Current observational studies have their limitations. They are affected by confounding factors, which are additional variables that can interfere with the true relationship between OSA and AD. For example, lifestyle factors like diet, exercise habits, and smoking status could potentially influence both the occurrence of OSA and the risk of developing AD. Reverse causality is also a problem. It's possible that AD, due to its effects on the brain and neurological functions, could lead to changes that result in

OSA, rather than the other way around. Moreover, observational studies have inherent flaws. Small sample sizes mean that the results might not be representative of the larger population, reducing the generalizability of the findings. The high cost of conducting these studies restricts the scale of research, making it difficult to include a large number of participants. And the lengthy processing times involved in collecting, analyzing, and interpreting the data slow down the progress of understanding the true relationship. All these aspects combined make it hard to clearly explain the causality between AD and OSA using just observational studies [15]. This is where Mendelian randomization (MR) comes into play. MR is a statistical technique that utilizes genetic variations to examine whether the observational association between an exposure (like OSA) and an outcome (such as AD) actually represents a causal effect [16,17]. It has shown great potential in overcoming the constraints faced by conventional epidemiological investigations. Its high statistical power enables more precise analysis of data, helping to detect even subtle causal relationships that might be missed in traditional studies. The timing priority of genetic variations is an advantage too. Since these variations are present from birth, they can offer a perspective before the onset of the disease or exposure, allowing for a purer exploration of causal links without the interference of factors that develop later in life. The random distribution of genetic variation further enhances the validity of MR. It helps to ensure that the associations being studied are not influenced by biases or external factors that commonly affect observational studies. Due to these remarkable features, numerous medical research fields have made extensive use of MR. It provides a valuable tool for delving deeper into causal relationships and holds the promise of helping to clarify the connection between AD and OSA, which could have significant implications for understanding the disease and developing better preventive and treatment strategies [18]. Numerous medical research fields have made extensive use of it for its high statistical power, timing priority, and random distribution of genetic variation.

2. Methods

2.1. Study design

Single nucleotide polymorphisms (SNPs) were used as instrumental variables (IVs) for Mendelian analysis. Since the data were from the GWAS database, no ethical approval was required. In the forward-direction MR analysis, AD was used as "exposure", while self-reported sleep apnoea, snoring and daytime dozing were used as "outcome". The IV used for two-sample Mendelian randomization (TSMR) must strictly comply with 3 assumptions: (1) it must be closely related to the exposure; (2) it must not be correlated to potential confounders; (3) it must not be able to impact the outcome by factors rather than the exposure [19]. Our research design is shown in **Figure 1**.

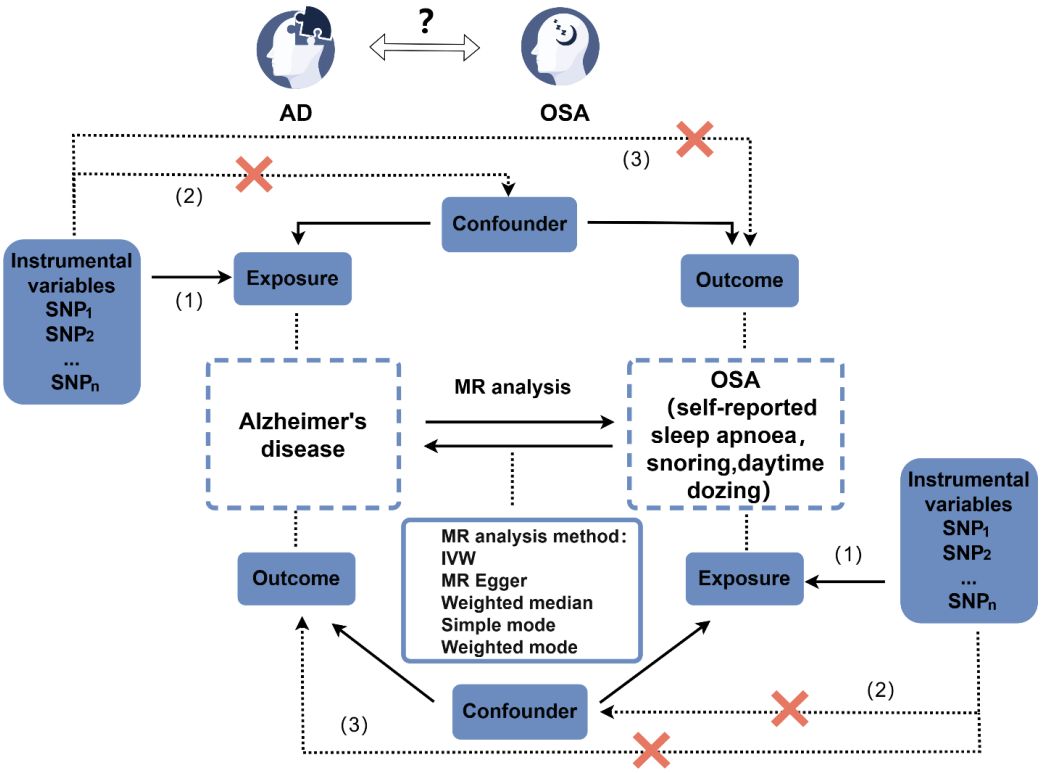

Figure 1. The overall research design (by Figdraw).

All individuals are of European ancestry. AD, Alzheimer's disease; OSA, obstructive sleep apnoea; SNP, single nucleotide polymorphism.

2.2. Data sources

As listed in **Table 1**, Genetic variants of "Alzheimer disease" were extracted from the FinnGen database [20], enlisting 412182 individuals (10521 cases and 401661 controls) of European ancestry. Phenotypes of three sets comprising "Non-cancer illness code, self-reported: sleep apnoea", "Snoring" and "Daytime dozing/sleeping (narcolepsy)" were extracted from IEU GWAS database [21–23] and evaluated. Pooled statistics for "self-reported: sleep apnoea" and "snoring" included 1510 and 270,007 cases; and 461,423 and 160,431 controls respectively. Summary-level data for "daytime dozing" involved 460,913 participants.

Table 1. Inform ation of the included samples.

Traits	Source	Year	Population	Sample size (cases/controls)	GWAS ID
Alzheimer disease	FinnGen	2023	European	10521/401661	NA
Non-cancer illness code, self-reported: sleep apnoea	MRC-IEU	2018	European	1510/461,423	ukb-b-9155
Snoring	MRC-IEU	2018	European	270,007/160,431	ukb-b-17400

2.3. Instrumental variable selection

In the context of our study, with regard to the first crucial hypothesis that Instrumental Variables (IVs) must be associated with the exposure variable, we implemented a stringent screening process. Single Nucleotide Polymorphisms (SNPs)

that exhibited a significant correlation with the exposure were selected at a *p*-value less than 5×10^{-6}. Additionally, we enforced a linkage disequilibrium (LD) parameter of $r^2 < 0.001$ and a clump window greater than 10,000 kb. Subsequently, the exposed SNPs and the outcome SNPs were carefully harmonized, and any incompatible and palindromic alleles with intermediate allele frequencies were removed. To ensure the independence assumption was met, the Phenoscanner database was utilized to guarantee that the filtered IVs were not related to commonly recognized confounding factors.

Moreover, for the evaluation of potential weak IV bias in the chosen SNPs, the F-statistics [R2 $(N - 1 - k)/(1 - R^2)$ k] were calculated [24]. Here, R^2 denotes the proportion of SNP that accounts for the exposure, N represents the sample size of the exposure factors, and k stands for the number of SNPs employed in the MR analysis. An F value greater than 10 suggests that the IV is capable of predicting the exposure, thus mitigating the risk of weak IV biases [25].

2.4. Statistical analysis

We used the "Two Sample MR" package in R (version 4.3.2) in all analyses. In bidirectional MR study, inverse variance weighted (IVW) is considered as a commonly used method of statistics for estimating the causal effect [19]. However, it assumes that all variants are valid. Therefore, MR Egger, Weighted median, Simple mode, and Weighted mode were complementally adopted based on different underlying assumptions. Moreover, the invalid IVs, Weighted median and MR-Egger methods can improve the robustness of causal estimation [26,27]. Sensitivity analysis was performed using the 'leave-one-out 'test to estimate the potential biases introduced by a specific SNP locus [28]. Cochran's Q test and MR-Egger analysis were conducted to evaluate heterogeneities ($p < 0.05$ indicated heterogeneity) and horizontal pleiotropy ($p < 0.05$ indicated horizontal pleiotropy), respectively [29,30].

In addition, the Bonferroni correction method was used to establish rigorous causality. Associations with $p < 0.0167$ (0.05/3) were defined as statistically significant, while $0.0167 < p < 0.05$ were considered as suggestive in correlation.

3. Results

3.1. Information on IVs

The numbers of IVs varied for AD, self-reported sleep apnoea, snoring, and Daytime dozing. There were 6, 13 and 14 AD-related genome-wide loci for MR forward analysis, respectively, and changes in F-statistic was 60.68–130.56. In reverse analysis, comprising of two independent SNPs for self-reported sleep apnoea, F-statistic was 21.93. And 152 SNPs were screened as IVs for snoring, F-statistic was 28.61. 101 SNPs were selected as IVs for daytime dozing, F-statistic was 29.65. Overall, All F-statistics were greater than the conventional value of 10, suggesting strong IVs. Therefore, it has been considered sufficient to mitigate the effect of potential bias. The complete information of IVs and *F* values is shown in Supplementary materials **Table S1**.

3.2. Causal effect of AD on OSA

Results from IVW demonstrated that AD was associated with increased OSA risks (OR 1.0008, 95%CI 1.0000–1.0016, p = 0.044). Whereas, the AD occurrence was not associated with snoring (OR 1.0010, 95%CI 0.9964–1.0056, p = 0.663) and daytime dozing (OR 0.9981, 95%CI 0.9948–1.0014, p = 0.251). The Cochran Q test indicated no apparent heterogeneity (p = 0.651, 0.698, and 0.598, respectively). MR-Egger intercept analysis revealed no horizontal pleiotropy (Intercept = 6.17E-05, p = 0.746; Intercept = −2.62E-04, p = 0.743; Intercept = −2.29E-04, p = 0.728). No obvious outliers among the SNPs were found in the leave-one-out test. (**Figure 2**, Supplementary materials **Figures S1–S9**, Supplementary materials **Tables S2–S3**).

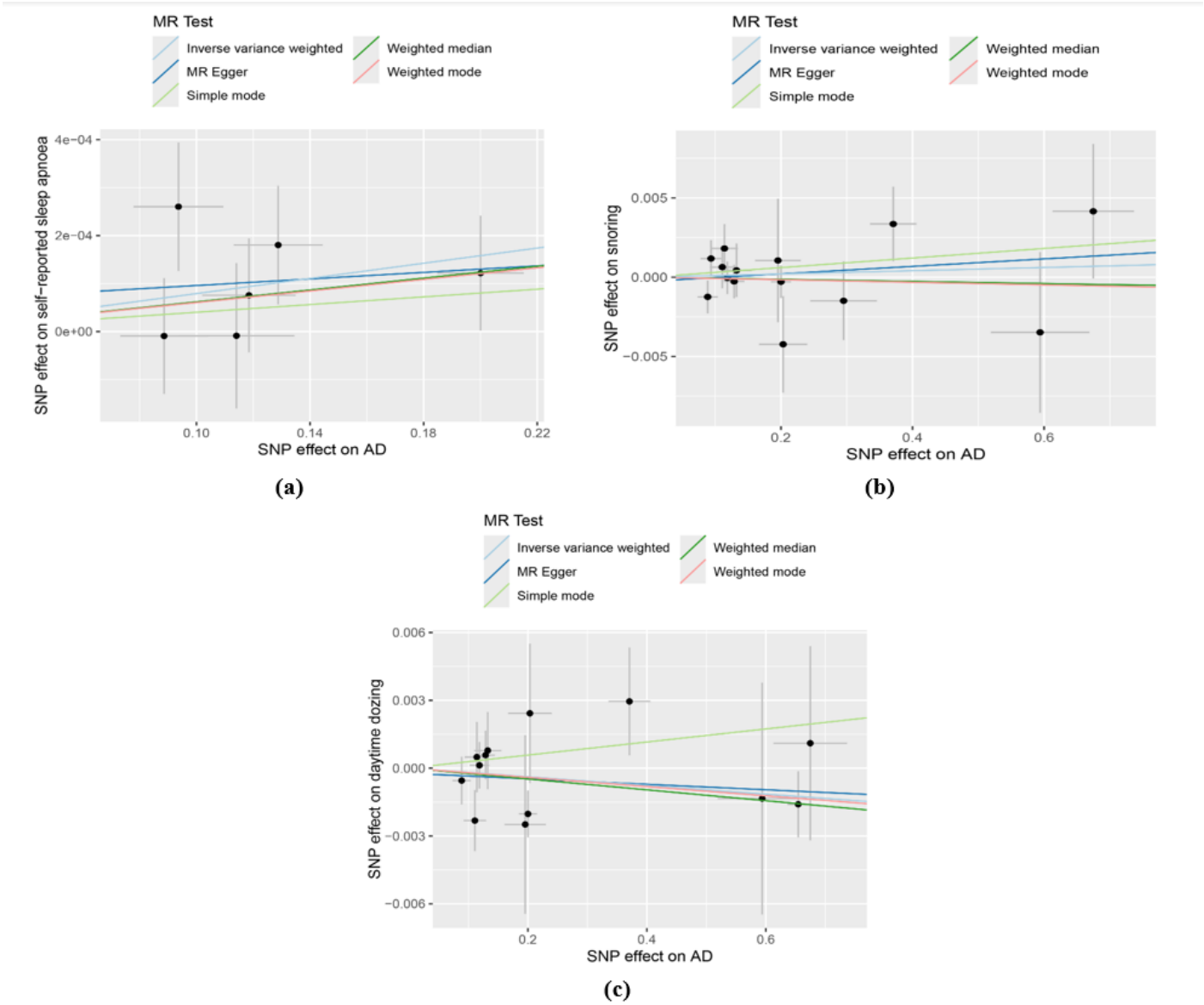

Figure 2. Causal effect of AD on OSA. **(a)** Causal estimates for AD on self-reported sleep apnoea; **(b)** Causal estimates for AD on snoring; **(c)** Causal estimates for AD on daytime dozing.

3.3. Causal effect of OSA on AD

The Inverse MR analysis for the causal role of OSA (exposure factor) on AD (outcome) had the following results: (snoring → AD: OR= 1.1232, 95%CI 0.7170–

1.7594, $p = 0.612$; Daytime dozing → AD: OR= 1.0259, 95%CI 0.5972–1.7623, $p = 0.926$). Two SNPs were significantly found to be associated with sleep apnoea (rs10460162 and rs6539116). The IVW results indicated that sleep apnoea had no causality on AD ($p = 0.294$). (**Figure 3**, Supplementary materials **Figures S10–S17**, Supplementary materials **Tables S2–S3**).

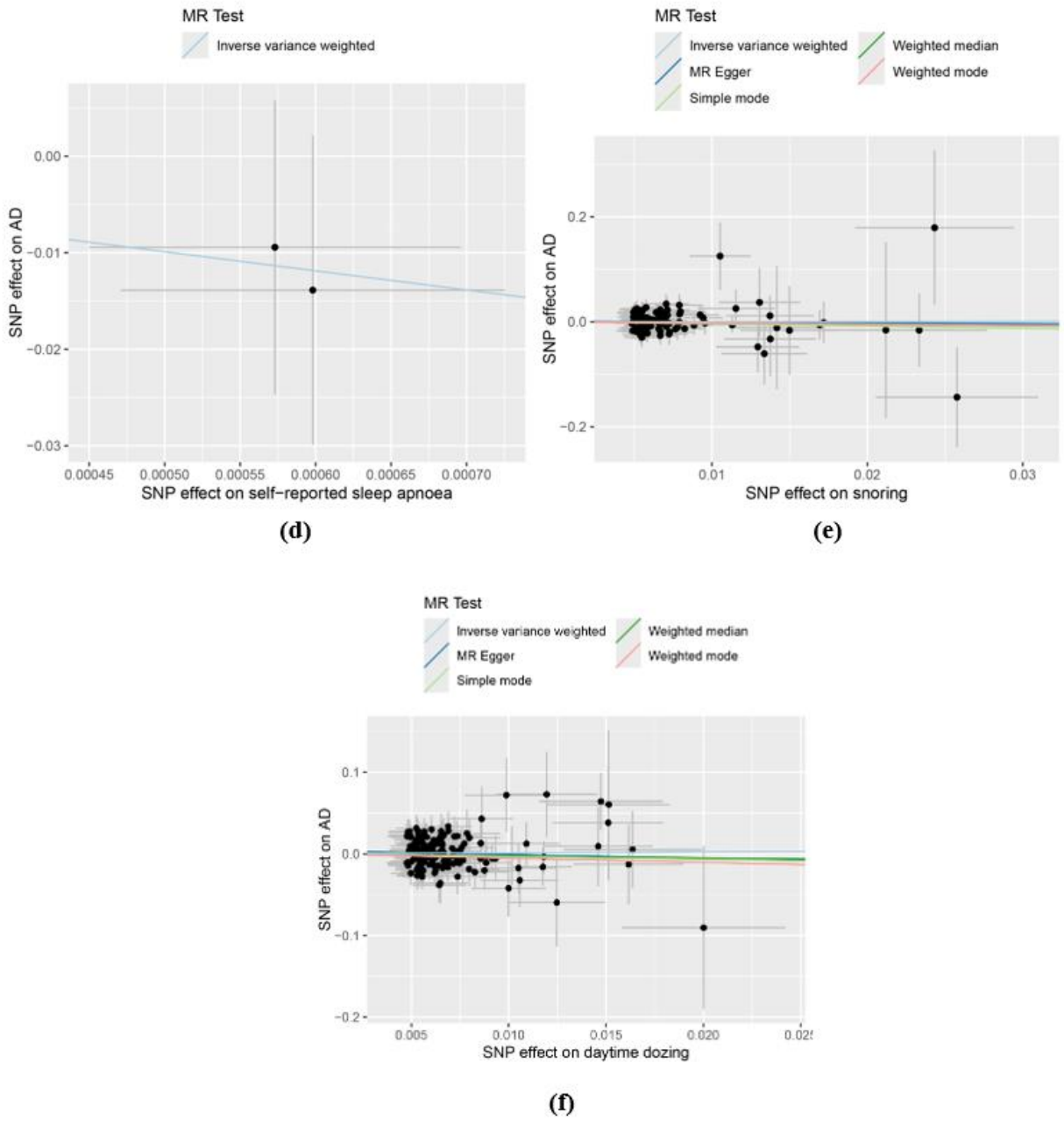

Figure 3. Causal effect of OSA on AD. **(d)** Causal estimates for self-reported sleep apnoea on AD; **(e)** Causal estimates for snoring on AD; **(f)** Causal estimates for daytime dozing on AD.

The horizontal axis depicts impacts of the SNP on exposure as OSA is the exposure variable. The vertical axis illustrates effects of the SNP on the outcome when AD is the outcome variable. (d) Exposure: Non-cancer illness code, self-reported: sleep apnoea, outcome: AD; (e) Exposure: Snoring, outcome: AD; (f) Exposure: Daytime dozing/sleeping (narcolepsy), outcome: AD.

4. Discussion

In the realm of scientific research, this particular work undertook a significant endeavor. We harnessed the power of Genome-Wide Association Studies (GWAS) data to delve into the complex relationship and potentially unearth the causality that exists between Alzheimer's Disease (AD) and several sleep-related factors, namely Obstructive Sleep Apnoea (OSA), snoring, and daytime dozing. This was not a simple task, as it required a high level of precision and scrutiny. All the genetic instruments utilized in our study were subjected to a strict and comprehensive screening process by the advanced tool, PhenoScanner. This ensured that only the most reliable and relevant genetic markers were considered for our analysis. After meticulous data processing and analysis, the Mendelian randomization (MR) studies we conducted led us to infer some suggestive causal effects. Specifically, our findings pointed towards the possibility that AD might contribute to a higher risk of self-reported sleep apnoea.This discovery has the potential to open up new avenues for understanding the disease and its associated factors. The results obtained from our forward-direction MR analysis were quite interesting as they provided support to a previous observational study [10]. According to this earlier research, patients afflicted with AD commonly encounter OSA in different degrees. The proportions of mild to severe OSA among these patients were noted to be 22.7% and 28.9% respectively. [10]. This alignment of our findings with the previous study adds weight to the growing body of evidence suggesting a connection between AD and sleep disorders. However, the scientific landscape is often filled with contrasting viewpoints. In contrast to our results, there was a study that employed four GWAS summary statistics and arrived at the conclusion that there was no causal effect of AD on OSA risk [31]. But it is crucial to approach such contradictory findings with caution. The results of this particular study might be influenced by certain biases. For instance, the sample size might have been insufficient to capture the true nature of the relationship. Incomplete phenotype information could have also led to an inaccurate representation of the participants' characteristics. Moreover, the missing data on exposure factors, which were likely not corrected, could have skewed the results and led to an incorrect conclusion. Existing research in this area has also highlighted a significant gap. There is a lack of well-powered evidence when it comes to evaluating the efficacy of sleep interventions in subjects with mild cognitive impairment (MCI) or mild AD [32]. This is an area that requires further investigation, as understanding the impact of such interventions could potentially offer new strategies for managing and even preventing the progression of AD. Although the slight increase in the effect of relative risk after the Bonferroni correction might seem inconsequential at first glance, it actually holds great significance. In the context of early intervention and disease management, even the smallest of changes can have a profound impact. There have been studies that demonstrated significant neurocognitive improvements in areas such as memory, attention, and executive function after OSA treatment [33]. When combined with previous research on the use of Continuous Positive Airway Pressure (CPAP) in AD [34–36], our current study further bolsters the case for the application of sleep intervention management in AD patients [37]. This could potentially improve the

quality of life and cognitive abilities of those affected by this debilitating disease, and offers hope for more effective treatment strategies in the future.

In the course of our research, the reverse Mendelian randomization (MR) analysis yielded an interesting result. We discovered that when looking at it from a genetic prediction perspective, OSA did not exhibit a causal effect on the risk of developing AD. This finding was at odds with a previous discovery [38]. The scientific community has been actively exploring the relationship between sleep disorders and AD, and the existing body of research presents a somewhat complex picture. A recent comprehensive systematic review brought to light that individuals with Sleep-Disordered Breathing (SDB) or OSA had an elevated likelihood of experiencing all-cause cognitive impairment or dementia. The hazard ratio (HR) was calculated to be 1.52, with a 95% confidence interval (CI) ranging from 1.32 to 1.74 [39]. In a similar vein, a meta-analysis involving a vast number of 1,333,424 patients concluded that the presence of sleep apnoea significantly increased the risk of AD, with an HR of 1.28 and a 95% CI of 1.16 to 1.41 [40]. However, it's important to note that other Mendelian randomization analyses have reached the same conclusion as our study [31,41], which further adds to the intrigue and complexity of this research area. There are several possible explanations for this situation. Firstly, the strict screening process of instrumental variables (IVs) might have led to a limitation in statistical power. This means that the data we were able to analyze might not have been extensive enough to capture all the nuances and potential causal relationships. Secondly, the overall GWAS data that we extracted for this study did not stratify according to age, gender, and the specific characteristics of OSA. This lack of stratification could be a significant factor, as the heterogeneity of OSA is well-known. The prevalence, related comorbidities, and phenotypic manifestations of OSA can vary greatly depending on age. For example, in older individuals, the symptoms and underlying mechanisms of OSA might be different compared to younger patients, and this age differentiation could have had an impact on our outcome [42]. Finally, it's also possible that OSA affects AD through various other factors such as hypertension, coronary heart disease, acute myocardial infarction, heart failure, obesity, and type 2 diabetes. Previous studies have suggested these potential pathways [31,43,44], and they could be contributing to the complex relationship between OSA and AD that we are trying to understand.

Sleep disorders, in general, are widely acknowledged as one of the inducing factors for AD. There is evidence indicating that the sleep interruption and intermittent hypoxia associated with OSA can lead to an increase in serum tau protein and β-amyloid levels [45]. These proteins are closely related to the development and progression of AD. However, despite these findings, the precise mechanism underlying the connection between OSA and AD remains somewhat unclear. The factors that are believed to contribute to the development of AD in the context of OSA include, but are not limited to, sleep fragmentation, inflammation, oxidative stress, and intrathoracic pressure fluctuations [46,47]. Additionally, as AD progresses in the elderly, the gradual accumulation of amyloid plaques and neurofibrillary tangle (NFT) may also cause changes in the sleep pattern, further complicating the relationship between the two conditions. This complex web of interactions requires further in-depth research to fully understand and potentially develop more effective preventive and treatment strategies for AD.

In the realm of this particular study, there exist a series of both advantages and limitations that are worthy of detailed consideration. The Mendelian randomization (MR) research employed in this study offers a distinct advantage. It capitalizes on the genetic data sourced from large-scale Genome-Wide Association Studies (GWAS). By doing so, it delves into the causality between Alzheimer's Disease (AD) and Obstructive Sleep Apnoea (OSA) at the genetic level. This approach effectively overcomes the longstanding issues of confounding factors and reverse causality that have plagued traditional observational studies. The utilization of a large sample size, along with robustly correlated single nucleotide polymorphisms (SNPs), proves to be highly beneficial. It enables a high-precision detection of causal effects. For instance, the calculated F statistics for both AD and OSA demonstrate relatively strong statistical power, enhancing the reliability and significance of our findings. Our data was drawn from the Finn Gen database and the UK Biobank (UKB) database. In this process, we deliberately did not consider the sample overlap problem, which could have otherwise introduced unnecessary complexity and potential biases. Additionally, the participants in the GWAS data were solely from European ancestry. This homogeneity avoided the bias that could have arisen from population heterogeneity, ensuring that the results were not muddled by the diverse genetic backgrounds and characteristics of multiple ethnic groups. However, despite these strengths, several limitations must be acknowledged. Firstly, considering the problem of population stratification, even though our sample was limited to a specific ancestry, there remains a possibility that this could cause some deviations in the estimated values. The question of whether our findings can be extrapolated and applied to other races is still open and requires further investigation. Given that our study was based on European databases, the conclusions drawn cannot be generalized to other ethnicities without caution. This inherently restricts the generalizability of our results, limiting their broader application in a global context. Another limitation is that horizontal pleiotropy, a phenomenon where a genetic variant influences multiple traits, cannot be fully evaluated even with the implementation of multiple sensitivity analyses. This lack of comprehensive assessment means that there could be hidden factors at play that we have not been able to fully account for, potentially affecting the accuracy of our understanding of the relationship between AD and OSA. Moreover, due to the absence of individual-level information, we were unable to conduct further stratified analyses of the population, such as by gender or different age groups. This inability to dissect the data in a more granular way means that we might have missed important nuances and differences that could exist within these subgroups. Finally, in our analysis, we opted to use a more lenient threshold to evaluate the results. While this approach enabled us to more comprehensively assess the potentially strong association between AD and OSA, it also carried the risk of increasing the number of false positives. Additionally, only two SNPs were found to be significantly and independently associated with self-reported sleep apnoea. This scarcity of significant SNPs meant that certain advanced analyses, such as MR-Egger, could not be performed. Consequently, the reverse causality between OSA and AD still remains an area that requires further in-depth exploration to fully understand the complex relationship between these two conditions.

5. Conclusion

This bidirectional MR investigation has yielded substantial evidence that suggests a potential causal relationship, wherein Alzheimer's disease (AD) may exert a causative influence on self-reported occurrences of apnoea. However, despite thorough examination, we were unable to find evidence that would support a causal role of self-reported obstructive sleep apnoea (OSA) as a precursor to AD, which implies that the observed associations between OSA and AD might be explained by reverse causation, where AD could lead to the development of OSA. Furthermore, our study did not uncover any evidence of causal relationships between AD and snoring, nor between AD and the tendency to doze off during the daytime. We need more clinical studies to corroborate our findings and provide a better theoretical basis for clinical research.

Supplementary materials: Figures S1–S17: Supplementary funnel plot, leaveoneout plot and forest plot; **Table S1**: Selected instrumental variables for MR analysis and the calculation of *F* values; **Table S2**: The main results of MR analysis; **Table S3**: The results of Sensitivity Analysis (The Cochran Q test, MR-Egger intercept analysis, 'leave-one-out'test).

Author contributions: Conceptualization, LY, TP, CK and EA; methodology, LY, TP and ZZ; software, LY; formal analysis, LY, CK, EA and ZZ; writing—original draft preparation, LY; writing—review and editing, WZ, TP and EA; supervision, WZ and CK. All authors have read and agreed to the published version of the manuscript.

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