Snoring and risk of dementia: a prospective cohort and Mendelian randomization study

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Abstracts

Study Objectives

The association between snoring, a very common condition that increases with age, and dementia risk is controversial. We aimed to investigate the observational and causal relationship between snoring and dementia, and to elucidate the role of body mass index (BMI).

Methods

Using data from 451,250 participants who were dementia-free at baseline, we examined the association between self-reported snoring and incident dementia using Cox proportional-hazards models. Causal relationship between snoring and Alzheimer's disease (AD) was examined using bidirectional two-sample Mendelian randomization (MR) analysis.

Results

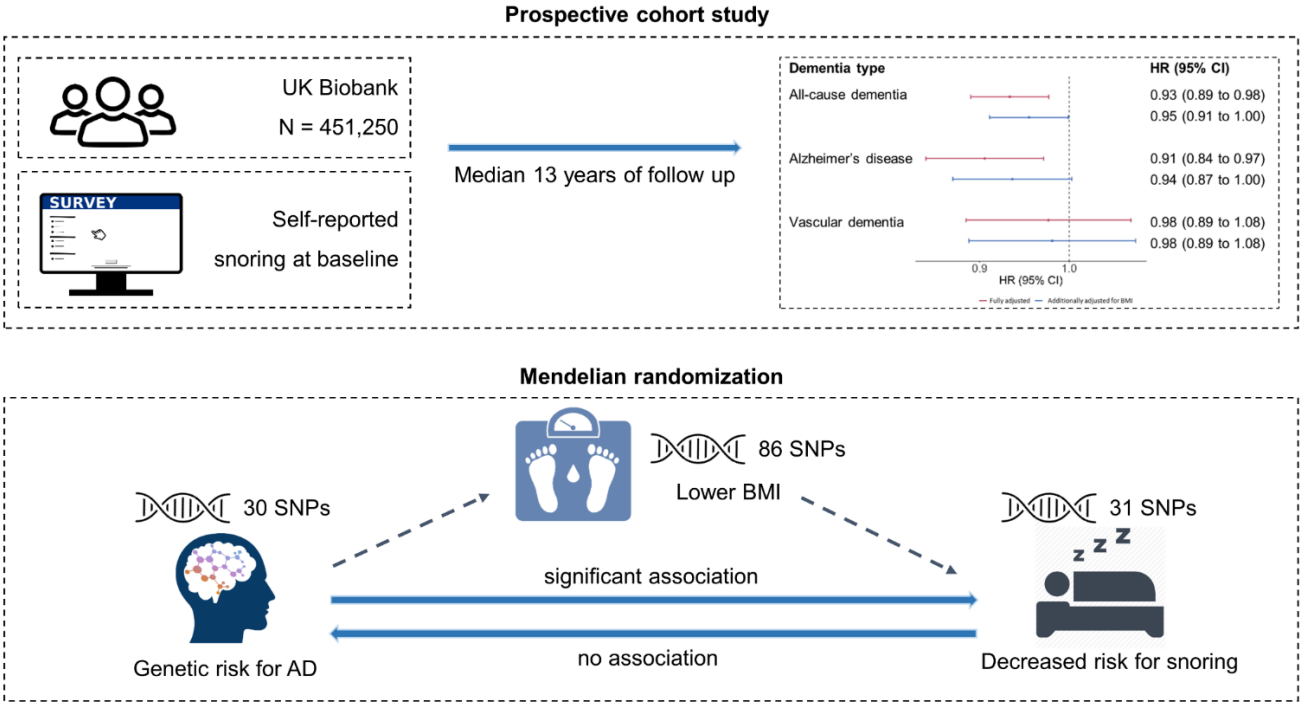
During a median follow-up of 13.6 years, 8,325 individuals developed dementia. Snoring was associated with a lower risk of all-cause dementia (hazard ratio [HR] 0.93; 95% confidence interval [CI] 0.89 to 0.98) and AD (HR 0.91; 95% CI 0.84 to 0.97). The association was slightly attenuated after adjusting for BMI, and was stronger in older individuals, *APOE* ε4 allele carriers, and during shorter follow-up periods. MR analyses suggested no causal effect of snoring on AD, however, genetic liability to AD was associated with a lower risk of snoring. Multivariable MR indicated that the effect of AD on snoring was primarily driven by BMI.

Conclusions

The phenotypic association between snoring and lower dementia risk likely stems from reverse causation, with genetic predisposition to AD associated with reduced snoring. This may be driven by weight loss in prodromal AD. Increased attention should be paid to reduced snoring and weight loss in older adults as potential early indicators of dementia risk.

Keywords: snoring, sleep apnoea, dementia, Alzheimer's disease, vascular dementia, body mass index, prodrome, Mendelian randomization, multivariable Mendelian randomization

Graphical abstract



Statement of Significance

The association between snoring and dementia is controversial, and the underlying mechanisms, including the role of body mass index (BMI) in this relationship, remain unclear. In a large longitudinal cohort of ~500,000 middle- to older-aged adults, we found that snoring was associated with a lower risk of incident all-cause dementia and Alzheimer's disease (AD). These associations were stronger in older adults and *APOE* ε4 carriers and were attenuated with increasing follow-up length, indicating potential reverse causality. Mendelian randomization (MR) analysis confirmed a causal association between AD and reduced snoring. Both observational and MR analyses suggest that this association was driven by decreased BMI as an AD prodrome. Increased clinical attention should be paid to reduced snoring and weight loss in older adults who are at high risk for dementia.

Introduction

Snoring, a very common condition affecting 35-45% of males and 15-28% of females in the general population,(1) is a noise that arises from increased resistance to airflow in the upper airway during sleep and vibrations of the surrounding tissues.(2) Snoring increases with age and body mass index (BMI), and is frequently associated with obstructive sleep apnoea (OSA) and cardiometabolic diseases.(3-5) However, the research evidence regarding the association between snoring and dementia is scarce and controversial.

While a case-control study suggested that demented patients snored twice as frequently as control subjects,(6) two meta-analyses found no association between snoring and risk of dementia,(7, 8) and one study suggested higher cognitive function associated with snoring.(9) There are several explanations for these inconsistent findings. First, a positive association, possibly bi-directional, may exist. Patients with dementia experience exacerbated age-related neuromuscular changes, such as heightened airway collapsibility or reduced airway muscle responsiveness, increasing the likelihood of snoring.(10) Snoring may be associated with OSA and cardiometabolic diseases, which have been suggested as risk factors for dementia.(11-13) Second, snoring is associated with vascular damage, possibly through hypoxia-related inflammation and oxidative stress,(14) as well as pressure waves from snoring vibrations transmitted to the carotid arterial wall.(15) This may contribute to the risk of vascular dementia (VaD) rather than Alzheimer's disease (AD). Therefore, failure to consider the subtypes of dementia or focusing on AD as the outcome may lead to null findings. Third, while obesity is one of the strongest predictors for snoring,(1) low BMI in late life has been associated with an increased risk of AD,(16) which could be due to metabolic alterations and decreased intake in prodromal AD.(17) This may lead to a negative association between snoring and risk of AD, especially in older individuals. Therefore, it is crucial to unravel the causal relationship between snoring and dementia, the direction of the relationship, and the role of BMI in this link.

Mendelian randomization (MR) employs single-nucleotide polymorphisms (SNPs) as genetic instrumental variables for the proposed risk factor that affects health. Therefore, it can be used to address some of the limitations of observational studies, particularly confounding and reverse causation. Multivariable MR (MVMR) estimates the direct effect of the genetic liability of the exposure on the outcome, while adjusting for the genetic liability of a second exposure of interest.(18) MR and MVMR have yet to be applied to snoring, BMI, and dementia, which could help disentangle the causal relationship among these factors.

In this study, we aimed to determine the association of snoring with incident all-cause dementia, AD, and VaD, using a conventional observational study approach in a large longitudinal cohort of over 500,000 middle- to older-aged adults, and a two-sample bi-directional MR design to elucidate the causal relationship between snoring and AD. We also utilized MVMR analyses to examine the role of BMI in the link between snoring and AD.

Methods

Study population

This prospective cohort study used data from UK Biobank, which recruited over 500,000 individuals aged 40 to 69 years from 22 assessment centres across the UK between 2006 and 2010.(19) Baseline assessments included touch-screen questionnaires, verbal interviews, physical measurements, and genotyping blood samples. Follow-up information was obtained through linkage to hospital inpatient records and death registries from national datasets in England, Scotland, and Wales.

For the current study, out of the 502,409 participants initially recruited, we excluded those who self-reported dementia at baseline or had a hospital inpatient record of dementia prior to baseline (n=232). Additionally, participants with missing exposure (n=37,070) or covariate (n=17,452) data were excluded from the main analysis but included through multiple imputation in sensitivity analysis. The final sample size for the main analysis consisted of 451,250 participants.

Assessment of snoring

At baseline, participants provided information on sleep-related traits. Snoring was assessed using a single item (Field-ID: 1210): “Does your partner or a close relative or friend complain about your snoring?” Participants were given the following response options: “Yes,” “No,” “Don't know,” or “Prefer not to answer.” Participants who selected "Don't know", "Prefer not to answer", or left the question blank were categorized as having missing data. They were excluded from the main analysis but included in sensitivity analyses.

Diagnoses of Incident Dementia

Dementia diagnoses were determined by using the UK Biobank-linked hospital inpatient records and death registries, which were documented based on the International Classification of Disease (ICD) codes (e-Table 1). Individuals who received a primary or secondary diagnosis of dementia after the baseline assessment or had dementia identified as an underlying or contributory cause of death were categorized as having incident dementia. The primary outcome of the present study was all-cause dementia, while subtypes of dementia, including AD and VaD, were assessed as secondary outcomes.

Statistical Analysis

Prospective Cohort Study Analysis

We first utilized data from the UK Biobank to assess the longitudinal association between snoring and the subsequent risk of dementia. Participants were followed from baseline until the date of first dementia diagnosis, death, loss to follow-up, or the censor dates for hospital inpatient data (31 October 2022 for England, 31 August 2022 for Scotland, and 31 May 2022 for Wales), whichever occurred first. We applied Cox proportional-hazards models with follow-up time as the underlying time scale, and checked the proportional hazards assumption through the Schoenfeld residual tests. The main model (Model 1) was adjusted for age, sex, ethnicity, education, Townsend deprivation index (TDI) quintiles, smoking status, alcohol consumption, living alone, and histories of depression, diabetes, hypertension, ischaemic heart disease, and stroke; To investigate the role of BMI as the potential mediator, we additionally adjusted for BMI in Model 2. The secondary outcomes (i.e., AD and VaD) were analysed using the same models. Detailed definitions and classifications for covariates and ICD codes used in detecting disease diagnoses are listed in e-Table 1-2.

To examine potential effect modification by factors such as age, sex, genetic susceptibility to dementia (i.e., *APOE* ε4), and history of sleep apnoea, we incorporated interaction terms between snoring and each of these modifiers and conducted stratified analyses.

To examine the robustness of our findings, we performed four sensitivity analyses. Firstly, the analysis was stratified based on the duration of follow-up, including participants who were followed for ≤5 years, 5 to 10 years, and >10 years after the baseline assessment. Secondly, we additionally adjusted for history of sleep apnoea. Thirdly, as previous studies indicate that uncertain responses to questions about snoring ("don't know" or left blank) also have clinical implications,(20) such as a moderate risk for OSA,(21) we included people with

missing snoring data as a separate category and compared their dementia risk with non-snorers and snorers. Fourthly, baseline participants were invited to attend follow-up visits. Of 451,250 baseline participants, 17,497 attended both the baseline and the first repeat assessment visit (conducted in 2012-2013), and 60,802 attended both the baseline and the imaging visit (starting in 2014). During these visits, subjective assessments of snoring were repeated, and we analysed whether changes in snoring status between baseline and follow-up were associated with subsequent dementia risk. Fifthly, we performed multiple imputation to impute missing exposure and covariate data (e-Appendix 1).

MR Analysis

We utilized the latest GWAS summary statistics for snoring, which was derived from self-reported data from over 400,000 individuals from the UK Biobank baseline assessment, including more than 150,000 snorers, and identified 42 loci that were genome-wide significant.(1) We obtained GWAS summary statistics for Alzheimer's disease (AD) from the study based on International Genomics Alzheimer's Project, which reported 20 genome-wide significant loci in a sample of 94,437 individuals.(22) GWAS summary statistics for BMI were obtained from the most recent GWAS meta-analysis, which included association findings for up to 339,224 individuals and had no overlapping sample with the AD GWAS, identifying 97 loci.(23) To identify instruments for each exposure, independent genome-wide significant SNPs were extracted ($p < 5 \times 10^{-8}$) from their respective GWASs. Details for clumping, proxy identification, and harmonization of effect sizes for the instruments on outcomes and exposures can be found in e-Appendix 1. The harmonized datasets are available in e-Table 3.

The primary MR method employed to assess causal association was the fixed-effects inverse variance weighted (IVW) method, which assumes all genetic variants are valid instruments – that is, they don't violate any of the underlying assumptions for MR. We conducted sensitivity analyses using alternative methods known to produce more robust causal estimates in the presence of horizontal pleiotropy but at the cost of reduced statistical power. These methods included MR-Egger regression, Weighted Median Estimator (WME), and Weighted Mode Based Estimator (WMBE). We conducted MVMR analysis to assess whether the causal association remains significant when controlling for the effect of BMI. Diagnostics tests included the MR-Egger regression to evaluate the presence of directional horizontal pleiotropy, Cochran's Q test to evaluate heterogeneity, Radial MR to identify outliers, and F-statistics to evaluate instrument strength. Figure 1 presents the hypothesized pathways examined through univariate and multivariate MR.

Results

Prospective cohort analysis

Among the 484,725 dementia-free participants with complete covariate data, 168,286 (34.7%) reported snoring, 282,964 (58.4%) reported not snoring, and 33,475 (6.9%) had missing data (Table 1). Compared with non-snorers, snorers tended to be older, more often male, and current smokers, had higher alcohol consumption, had higher BMI, were less likely to live alone and carry *APOE* ε4, and were more likely to have a history of depression, hypertension, cardiovascular diseases, and diabetes. Participants with missing data on snoring had lower socioeconomic status, were more likely to live alone, and had a health status comparable to those without missing data.

In a final sample of 451,250 participants (with people with missing snoring data excluded), during a median follow-up of 13.6 years (interquartile range 12.9 to 14.3), we identified 8,325 incident cases of dementia. Among these cases, 3,706 were diagnosed as AD, and 1,801 as VaD. In Cox regression analysis adjusted for sex, age, socioeconomic status, lifestyle factors, and comorbidities, snoring was associated with a lower risk of incident all-cause dementia (hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.89 to 0.98) (Figure 2). Secondary analysis of dementia subtypes revealed that snoring was associated with a lower risk of AD (0.91, 95% CI 0.84 to 0.97), whereas no significant association was found for VaD. The association between snoring and dementia was slightly attenuated after adjusting for BMI (0.95, 95% CI 0.91 to 1.00).

Snoring was related to decreased dementia risk only in older participants (Figure 3). The HRs for dementia were 0.89 (95% CI 0.84 to 0.94) for participants aged 65 years or older, compared to 0.98 (95% CI 0.91 to 1.06) for those under 65 years old ($p_{interaction}$<0.001). Larger magnitude of association was also observed for individuals who were *APOE* ε4 carriers compared to non-carriers (0.94 [95% CI 0.88 to 1.00] vs 0.97 [0.91 to 1.04]; $p_{interaction}$=0.008). Although snoring was linked to dementia risk only in participants without a sleep apnoea diagnosis, not in those with a diagnosis, no significant interaction effect was observed between snoring and history of sleep apnoea or sex ($p_{interaction}$>0.05).

The association between snoring and risk of dementia decreased with increasing length of follow-up, with HRs of 0.83 (95% CIs 0.70 to 0.99), 0.88 (95% CIs 0.81 to 0.95), and 0.98 (95% CIs 0.93 to 1.04) for a follow-up length of ≤5 years, 5 to 10 years, and over 10 years, respectively (e-Figure 1). The associations between snoring

and dementia remained largely unchanged after adjusting for history of sleep apnoea or imputing missing exposure and covariate data (e-Figure 2 and e-Table 4). We did not detect any statistically significant dementia risk related to participants with missing snoring data compared to non-snorers (e-Figure 3). In analyses limited to participants with snoring measured at both baseline and a follow-up, neither snoring at a single time point nor changes in snoring were significantly associated with dementia risk (e-Table 5).

MR analysis

In the forward direction, 31 SNPs were selected as genetic instruments for snoring (mean *F-statistic* is 40.9), with no outliers detected using Radial-MR (e-Figure 4). Genetically predicted snoring was not causally associated with the risk of AD in the IVW and all sensitivity analyses (Table 2). Seven snoring-associated SNPs were also significantly associated with BMI ($p < 5 \times 10^{-8}$) and were excluded in an additional sensitivity analysis, however, the causal association remained non-significant (e-Table 6). In the reverse direction, 30 SNPs were selected as genetic instruments for AD (mean *F-statistic* is 105.2), with no outliers detected using Radial-MR (e-Figure 5). While the IVW analysis was non-significant, diagnostic tests indicated that there was evidence of both heterogeneity and pleiotropy, suggesting that the IVW estimates may be biased. Sensitivity analyses, including MR-Egger (odds ratio [OR], 0.994; 95% CI 0.990 to 0.998), $p = 0.004$), WME (0.995, 95% CI 0.991 to 0.999, $p = 0.013$), and WMBE (0.996, 95% CI 0.992 to 0.999, $p = 0.031$), indicated that increased genetically predicted AD was causally associated with a reduced risk of snoring.

For MVMR, a total of 86 SNPs were selected as genetic instruments for BMI ($N_{SNP} = 67$) and AD ($N_{SNP} = 19$), with conditional *F-statistics* of 45.4 and 13.2 respectively. In the MVMR-IVW analyses, the causal association between genetically predicted AD and snoring was attenuated (Table 2). There was evidence of heterogeneity, and sensitivity analyses indicated that genetically predicted BMI remained significantly associated with an increased risk of snoring (e-Figure 6).

Discussion

In this study, we investigated the longitudinal association between snoring and dementia in 451,250 participants from UK Biobank. Our results showed that snoring is associated with a lower risk of both all-cause dementia and AD, while no significant association was observed with VaD. Furthermore, this association was slightly attenuated after adjusting for BMI, and was stronger in older individuals, *APOE* ε4 allele carriers, and during shorter follow-up periods. We further explored the relationship between snoring and AD using univariate MR analyses, which revealed a potential causal effect of AD on the risk of snoring but no significant evidence for a causal effect of snoring on AD. Our MVMR analyses suggested that the association between AD and snoring was mainly driven by BMI. The results indicate that the phenotypic association between snoring and decreased dementia risk is likely the result of reverse causation, possibly mediated by decreased BMI levels during the preclinical phase of dementia.

Our findings suggest that the association between snoring and all-cause dementia and AD may be attributed to reverse causation. In our study, the median follow-up time was 13.6 years; however, the accumulation of AD pathology in the brain can occur more than 20 years before clinical symptoms onset.(24) Therefore, although we excluded participants with clinically diagnosed dementia at baseline, it is plausible that many remaining individuals are in the prodromal phase of AD, particularly the older individuals and those carrying the *APOE* ε4 allele, in whom we observed a stronger negative association between snoring and dementia. This complements previous studies that found an association between snoring and higher cognitive function among older adults over a shorter follow-up period of 10 years.(9) In contrast, no such association was found in a relatively younger sample (mean 52.3 years) with a longer follow-up of 22.5 years.(25) A previous cross-sectional study of non-demented older adults also found that *APOE* ε4 carriers reported less snoring than non-carriers,(26) consistent with our results showing a slightly higher proportion of *APOE* ε4 carriers among non-snorers than among snorers. In our analysis based on repeated snoring measurements, persistent or new snoring showed a similar dementia risk as stable non-snoring, suggesting that snoring may not be causally associated with decreased dementia risk. However, these findings should be interpreted with caution due to potential biases: follow-up participants were generally healthier, possibly underestimating the effect size.(27) This might explain why snoring measured at a single time point was also not associated with dementia risk in these analyses. The direction of the phenotypic association between snoring and dementia was further supported by our univariate

MR results. Specifically, we identified a one-way causal relationship between AD and a reduced risk of snoring, which survived in multiple sensitivity analyses.

The role of BMI, one of the strongest predictors of snoring,(1) is of significant interest in elucidating the relationship between AD and snoring. Indeed, our observational and MVMR results suggested that the association between AD and snoring was driven by BMI. Specifically, a lower BMI, as frequently observed during the preclinical phase of AD,(16, 28) may lead to a reduced risk of snoring in prodromal AD. Studies have established a dynamic association between BMI and dementia across the life course, known as the "obesity paradox". Obesity in midlife, especially before the age of 50, has been linked to an increased risk of dementia, whereas in late-life, the association between high BMI and dementia often reverses.(29, 30) Prior MR studies have revealed that genetic liability to AD is linked to lower BMI,(31, 32) highlighting the role of late-life weight loss as a prodromal factor for AD. Accumulating evidence suggests that AD pathology leads to impaired functions of the hypothalamic and other brain regions crucial for metabolic regulations, which contribute to weight loss in the early stages of AD.(33, 34) Future research should explore how BMI or change in BMI at different stages of life may influence the association between snoring and risk of dementia.

Notably, snoring is commonly considered as a sign of obstructive sleep apnoea (OSA), with both self-reported and objectively measured snoring correlating with OSA severity.(35, 36) OSA has been extensively studied as a potential risk factor for late-life brain health, with cross-sectional studies consistently linking it to cognitive impairment.(13, 37) Two prospective studies have linked clinically diagnosed OSA with an increased risk of dementia, although with only 5-year follow-up periods.(12, 38) Another study examining the association over a 15-year period found a significant relationship for severe OSA (≥30 vs. <5 apnoea-hypopnea events/hour), which attenuated after controlling for cardiovascular risk factors.(39) However, the cognitive outcomes of snoring has been understudied, despite snoring being more prevalent than OSA and easily detectable and modifiable. We addressed this knowledge gap by conducting the first comprehensive investigation into the observational and causal relationship between snoring and dementia. Contrary to the findings with OSA, our current study suggested an association between snoring and a decreased risk of dementia. There are two plausible, mutually inclusive explanations. First, it is important to note that 60%-80% of snorers do not exhibit apnoea severe enough to warrant an OSA diagnosis, a condition often referred to as "simple snoring".(1) We performed a sensitivity analysis by excluding participants with a history of sleep apnoea at baseline, and the

relationship between snoring and dementia remained unchanged. Therefore, simple snoring and OSA may have distinct clinical implications for dementia. However, one must interpret this finding with caution, as using diagnostic codes to identify OSA cases in administrative data leads to severe underdiagnosis of OSA.(40) In our study, the overall proportion of OSA identified from hospital inpatient data and self-reported diagnoses is 0.7%, significantly lower than the prevalence estimate of 6%-17% from a meta-analysis of studies, mainly conducted in the US and Europe, that screened OSA (defined as ≥15 apnoea-hypopnea events/hour) using laboratory instruments.(41) Moreover, we failed to detect the presumably positive association between snoring and dementia in participants with an OSA diagnosis, suggesting potential inaccuracies in the coded diagnosis of OSA within the UK Biobank. Second, weight loss and neuromuscular changes in the airway during the preclinical phase of AD may also affect the risk of OSA. This is supported by studies showing that the association between obesity and OSA is weaker in older adults compared to middle-aged individuals.(42-44) Notably, one study even found that lower BMI was associated with OSA in older hypertensive patients.(45) Additionally, studies have shown a positive correlation between risk of frailty and OSA in the elderly.(46) The causality and directionality of the relationship between OSA and dementia remain controversial. Prospective evidence suggests an attenuation of this relationship with longer follow-up times,(39) and a recent review suggested that the association between OSA and cognitive function primarily exists in middle-aged adults, rather than in older adults.(47) Additionally, a recent MR study did not find any causal relationship between OSA and AD.(48) Our findings on snoring underscore this controversy and highlight the need for further research into the complex relationship between snoring, OSA, and dementia.

In our MR study, we found no causal association between snoring and risk of AD. It is important to note that snoring, through hypoxia and inspiratory vibrations, may contribute to vascular pathology and thus have a more significant impact on the risk of VaD.(49, 50) Our observational study did not identify an association between snoring and VaD. This lack of association may be attributed to the diagnostic criteria for VaD, which have low sensitivities compared to AD,(51) leading to misclassification that biased estimates towards the null. The limited sample size of VaD cases in most studies also constrained statistical power and the ability to achieve statistical significance.

This study has several limitations. Firstly, self-reported snoring may be subject to recall bias, which could lead to misclassification of snorers and non-snorers and potentially bias the results. Secondly, the snoring phenotype

and genetic loci associated with it reflect snoring tendencies from middle to old age, restricting our ability to assess how snoring at different life stages affects dementia risk. Thirdly, dementia cases were identified using UK Biobank linked hospital inpatient records and death registry. This approach may result in the underestimation of milder forms of dementia. Furthermore, the utilization of these two sources yielded low positive predictive values for VaD (33.3%), compared with all-cause dementia (84.5%) and AD (70.8%).(52) The potential misclassification of dementia, particularly in the case of VaD, should not be disregarded. Fourthly, there is evidence suggesting that sleep disturbances are associated with a higher risk of Lewy body dementia (LBD) compared to AD and VaD.(53) However, our data source, the UK hospital inpatient data, lacks disease-specific ICD codes for LBD, thereby limiting our ability to include it as one of the outcomes in our study. Fifthly, OSA may play a crucial role in the link between snoring and dementia. However, in our study, the diagnosis of OSA is likely severely underreported, as we identified cases only through hospital inpatient data and self-reported diagnoses, rather than through polysomnography-based screening. This limitation restricts our ability to fully elucidate the relationship between snoring and OSA, and to provide accurate estimates of snoring-related dementia risk among OSA patients. Sixthly, the participants for repeated measurements were generally healthier, and the late timing of these measurements led to a shorter follow-up period. Seventhly, the lack of a published GWAS of VaD limited our ability to examine the causal relationship between snoring and VaD.

In our study, we found that snoring, a common condition in older adults, was associated with a lower risk of all-cause dementia and AD, particularly in older individuals and *APOE* ε4 carriers. Our MR analyses suggest potential reverse causation, where genetic liability to AD was associated with reduced snoring, possibly through lower BMI in prodromal AD. Future studies with repeated snoring measures in a representative sample and extended follow-up are warranted to disentangle the temporality of this association. Additionally, there is a need to clarify the causal relationship between snoring and different subtypes of dementia and to elucidate underlying mechanisms. The role of BMI should be carefully considered in research on AD and snoring.

Declarations

Ethics approval

The North West Multi-centre Research Ethics Committee granted approval to UK Biobank, and UK Biobank obtained informed consent from all participants.

Data Availability

The UK Biobank data is accessible online at https://www.ukbiobank.ac.uk for researchers who have received approval for their proposals of data use from the UK Biobank.

Author Contributions

Conception and design of the study: Y.L., S.A., Y.G. Acquisition and analysis of data: Y.G., S.A., Y.L. Manuscript drafting: Y.G., S.A., Y.L. Manuscript editing: Y.G., S.A., Y.L, W.B., C.A.R., K.Y.

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Figure 1. Hypothesized pathways examined through univariate and multivariable Mendelian randomization

MR, Mendelian randomization; MVMR, multivariable Mendelian randomization; SNPs, single nucleotide polymorphisms; BMI, body mass index; IVs, instrumental variables; AD, Alzheimer's disease.

Figure 2. Multivariable-adjusted associations between snoring and incident dementia

IR, incident rate; HR, hazard ratio; CI, confidence interval. Model 1 included age, sex, ethnicity, education, Townsend deprivation index quintiles, smoking status, alcohol consumption, living alone, history of depression, diabetes, hypertension, ischaemic heart disease, and stroke. Model 2 was further adjusted for body mass index.

Figure 3. Subgroup analyses of the association between snoring and incident all-cause dementia

IR, incident rate; HR, hazard ratio; CI, confidence interval. The models were adjusted for age, sex, ethnicity, education, Townsend deprivation index quintiles, smoking status, alcohol consumption, living alone, history of depression, diabetes, hypertension, ischaemic heart disease, and stroke.

Table 1. Baseline characteristics of participants by snoring status

Characteristic	Not snoring	Snoring	Missing data
N	282964	168286	33475
Age (mean (SD))	56.79 (8.28)	57.24 (7.78)	57.74 (7.94)
Female (%)	108818 (38.5)	99450 (59.1)	12311 (36.8)
Townsend deprivation index quintile			
1 (Least deprived)	58283 (20.6)	35387 (21.0)	4477 (13.4)
2	57531 (20.3)	35038 (20.8)	5301 (15.8)
3	57079 (20.2)	34214 (20.3)	6129 (18.3)
4	56385 (19.9)	32990 (19.6)	7672 (22.9)
5 (Most deprived)	53686 (19.0)	30657 (18.2)	9896 (29.6)
Education (%)			
Primary	46545 (16.4)	29590 (17.6)	6717 (20.1)
Secondary	64235 (22.7)	37077 (22.0)	7728 (23.1)
Post-secondary non-tertiary	34249 (12.1)	20284 (12.1)	3936 (11.8)
Tertiary	137935 (48.7)	81335 (48.3)	15094 (45.1)
Non-white (%)	13969 (4.9)	8519 (5.1)	2384 (7.1)
Current smoker (%)	26362 (9.3)	19789 (11.8)	4579 (13.7)
Drinking daily or almost daily (%)	55203 (19.5)	38586 (22.9)	5493 (16.4)
Living alone (%)	51587 (18.2)	19185 (11.4)	19265 (57.6)
Obese (%)	53358 (18.9)	54761 (32.5)	9159 (27.4)
***APOE* ε4 carriers (%)**	72075 (25.5)	42304 (25.1)	8430 (25.2)
Medical history (%)			
Sleep apnoea	912 (0.3)	2211 (1.3)	173 (0.5)
Depression	15893 (5.6)	10747 (6.4)	2887 (8.6)
Ischaemic heart disease	13511 (4.8)	10279 (6.1)	1960 (5.9)
Stroke	4014 (1.4)	2670 (1.6)	629 (1.9)
Hypertension	68159 (24.1)	54098 (32.1)	10107 (30.2)
Diabetes	12122 (4.3)	10411 (6.2)	2109 (6.3)

N, number of participants; SD, Standard deviation; BMI, body mass index.

Table 2. Bi-directional causal estimates between snoring and Alzheimer's disease

	Snoring → AD (Univariate MR)		**AD → Snoring (Univariate MR)**		**AD → Snoring (Multivariable MR)**	
Method	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
IVW	0.838 (0.387 to 1.817)	0.655	0.998 (0.995 to 1.001)	0.114	1.002 (0.994 to 1.011)	0.616
MR-Egger	23.829 (0.255 to 2223.326)	0.181	0.994 (0.990 to 0.998)	0.004	1.004 (0.995 to 1.013)	0.362
WME	1.144 (0.357 to 3.667)	0.821	0.995 (0.991 to 0.999)	0.013	1.000 (0.993 to 1.008)	0.912
WMBE	1.230 (0.147 to 10.268)	0.850	0.996 (0.992 to 0.999)	0.031	1.009 (0.997 to 1.021)	0.132
Diagnostics	**Estimate**	***p***	**Estimate**	***p***	**Estimate**	***p***
F-statistic	40.9	NA	105.2	NA	13.2	NA
Cochran's Q	40.6	0.095	32.9	0.282	252.1	6.04×10^{-19}
MR-Egger Intercept	-0.025	0.151	0.001	0.009	0.001	0.031

AD, Alzheimer's disease; MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted; WME, Weighted Median Estimator; WMBE, Weighted Mode Based Estimator; NA, not applicable.

Figure 1

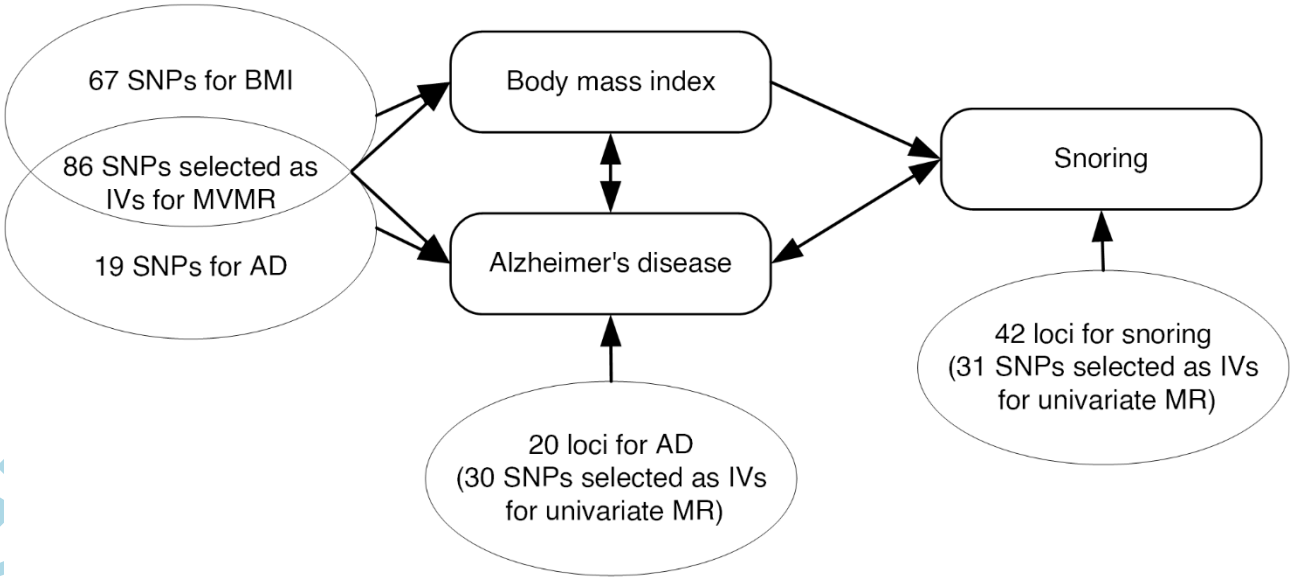

Figure 2

Dementia type	Number of cases/1000 person-years (IR)		HR (95% CI)	*p*
	Snoring	Not snoring		
All-cause dementia	3045/2225.96 (1.37)	5280/3743.21 (1.41)	0.93 (0.89 to 0.98)	0.003
			0.95 (0.91 to 1.00)	0.047
Alzheimer's disease	1298/2230.14 (0.58)	2408/3750.18 (0.64)	0.91 (0.84 to 0.97)	0.005
			0.94 (0.87 to 1.00)	0.062
Vascular dementia	702/2231.42 (0.31)	1099/3753.24 (0.29)	0.98 (0.89 to 1.08)	0.625
			0.98 (0.89 to 1.08)	0.694

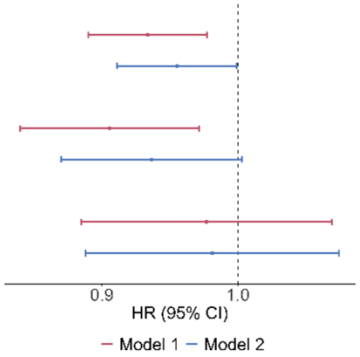

Figure 3

Characteristic	Subgroup	Number of cases/ 1000 person-years (IR)	HR (95% CI)	*p*	*p* for interaction
Age	< 65 years	3132/4769.61 (0.66)	0.98 (0.91 to 1.06)	0.678	<0.001
	≥ 65 years	5193/1199.57 (4.33)	0.89 (0.84 to 0.94)	<0.001	
Sex	Female	3930/3242.79 (1.21)	0.94 (0.88 to 1.01)	0.096	0.500
	Male	4395/2726.39 (1.61)	0.92 (0.87 to 0.98)	0.011	
APOE ε4	Non-carriers	3796/4184.95 (0.91)	0.97 (0.91 to 1.04)	0.414	0.008
	Carriers	4077/1507.70 (2.70)	0.94 (0.88 to 1.00)	0.048	
Sleep apnoea	Yes	101/39.94 (2.53)	0.94 (0.62 to 1.43)	0.775	0.761
	No	8224/5929.23 (1.39)	0.93 (0.89 to 0.97)	0.002