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ORIGINAL RESEARCH

# Causal Associations of Sleep Apnea With Alzheimer Disease and Cardiovascular Disease: A Bidirectional Mendelian Randomization Analysis

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**BACKGROUND:** Sleep apnea (SA) has been linked to an increased risk of dementia in numerous observational studies; whether this is driven by neurodegenerative, vascular, or other mechanisms is not clear. We sought to examine the bidirectional causal relationships between SA, Alzheimer disease (AD), coronary artery disease (CAD), and ischemic stroke using Mendelian randomization.

**METHODS AND RESULTS:** Using summary statistics from 4 recent, large genome-wide association studies of SA (n=523 366), AD (n=94 437), CAD (n=1 165 690), and stroke (n=1 308 460), we conducted bidirectional 2-sample Mendelian randomization analyses. Our primary analytic method was fixed-effects inverse variance–weighted (IVW) Mendelian randomization; diagnostics tests and sensitivity analyses were conducted to verify the robustness of the results. We identified a significant causal effect of SA on the risk of CAD (odds ratio [$OR_{IVW}$]=1.35 per log-odds increase in SA liability [95% CI=1.25–1.47]) and stroke ($OR_{IVW}$=1.13 [95% CI=1.01–1.25]). These associations were somewhat attenuated after excluding single-nucleotide polymorphisms associated with body mass index ($OR_{IVW}$=1.26 [95% CI=1.15–1.39] for CAD risk; $OR_{IVW}$=1.08 [95% CI=0.96–1.22] for stroke risk). SA was not causally associated with a higher risk of AD ($OR_{IVW}$=1.14 [95% CI=0.91–1.43]). We did not find causal effects of AD, CAD, or stroke on risk of SA.

**CONCLUSIONS:** These results suggest that SA increased the risk of CAD, and the identified causal association with stroke risk may be confounded by body mass index. Moreover, no causal effect of SA on AD risk was found. Future studies are warranted to investigate cardiovascular pathways between sleep disorders, including SA, and dementia.

**Key Words:** Alzheimer disease ■ cardiovascular diseases ■ causal inference ■ coronary artery disease ■ Mendelian randomization ■ sleep apnea ■ stroke

See Editorial by Wolford and Åsvold.

Sleep apnea (SA), a common respiratory disorder in elderly individuals, has been linked to an increased risk of dementia in numerous epidemiologic studies.[1–3] However, the types of dementia associated with SA remain uncertain. Some studies have suggested an association between SA and Alzheimer disease (AD),[1,4,5] whereas others have highlighted a link with vascular dementia.[1,3] Currently, 2 main mechanistic pathways are

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## CLINICAL PERSPECTIVE

### What Is New?

- Our study revealed a significant causal relationship between genetically predicted sleep apnea and higher risk of coronary artery disease, whereas the causal association with stroke risk may be confounded by body mass index.
- Sleep apnea may not have a causal effect on the development of Alzheimer disease.
- In the bidirectional analyses, no causal effects were observed for genetically predicted Alzheimer disease, coronary artery disease, or stroke on the risk of sleep apnea.

### What Are the Clinical Implications?

- These findings suggest a greater role for cardiovascular pathology than Alzheimer disease pathology in the relationship between sleep apnea and all-cause dementia.
- Addressing vascular risk factors and sleep apnea through lifestyle modifications and medical interventions may be an important strategy in reducing the risk of all-cause dementia.
- These findings may also prompt subsequent investigations aimed at exploring therapeutic approaches targeting sleep apnea to prevent cardiovascular risks.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **GWAS-SS** | genome-wide association study summary statistics |
| **IV** | instrumental variable |
| **IVW** | inverse variance weighted |
| **MR** | Mendelian randomization |
| **MVMR** | multivariable Mendelian randomization |
| **SA** | sleep apnea |

hypothesized to explain the SA-dementia association. First, SA may increase dementia risk by promoting AD-related brain changes. Notably, SA has been associated with the accumulation of AD proteins, such as amyloid-β and tau proteins in the brain, potentially attributable to intermittent hypoxia and increased sleep fragmentation induced by SA.[6–8] Second, SA may increase the risk of dementia through its influence on cerebrovascular pathology. Indeed, observational studies have linked SA with an increased risk of numerous cardiovascular diseases (CVDs)[9] and CVD risk factors, which are themselves established risk factors for dementia.[10,11] Potential mechanisms may include oxidative stress, inflammation, endothelial dysfunction, atherosclerosis, or sympathetic activation.[9] However, these hypotheses primarily rely on findings from observational studies, which are limited by biases, including residual confounding and reverse causality. Moreover, it is difficult to differentiate between neurodegenerative and cardiovascular pathways because mixed pathology is often more prevalent than pure forms of AD,[12] especially with increasing age. Clarifying the causality between SA, AD, and CVDs might help in understanding the biological mechanisms underlying the SA-dementia relationship, which is an important research area given the potential of sleep as a modifiable factor to prevent dementia.

Mendelian randomization (MR) is a method that estimates causal effects by leveraging naturally randomized genetic variation. This approach limits confounding bias because of the random assignment of genes at conception and minimizes reverse causality bias because diseases cannot affect an individual's germline genetic variation. In the literature, 2 previous MR studies did not detect a causal effect of SA on AD,[13,14] whereas heterogeneous results have been found for SA and CVD outcomes.[15–20] These studies were limited by use of older genome-wide association study (GWAS) data sets, low-powered genetic instruments for SA,[14] and lack of investigation into potential reverse causal associations.[16–20] Furthermore, SA may also be a consequence of AD and CVDs,[9,21] and so new approaches are needed to better understand the potential bidirectionality of these relationships. Therefore, our goal was to examine the bidirectional causal relationships between SA and the risks of AD and CVDs (coronary artery disease [CAD] and stroke) by performing MR analyses using the most recent GWAS available.

## METHODS

We used the strengthening the reporting of observational studies in epidemiology using Mendelian randomization (STROBE-MR) checklist when writing our report.[22,23] This study used summary results from published research articles with publicly available data. Tables S1 and S2 provide the harmonized single-nucleotide polymorphism (SNP) effects needed to reproduce the results of this analysis, and codes are publicly accessible online (https://github.com/ccavailles/Sleep-apnea-AD-MR; https://github.com/ccavailles/Sleep-apnea-CAD-MR; https://github.com/ccavailles/Sleep-apnea-stroke-MR).

### Study Design and Data Sources

We conducted this MR study using summary-level data obtained from large, recent, and publicly accessible GWASs (Table S3). All GWASs were restricted to European ancestry to minimize potential bias attributable

to population stratification. Ethical approval and informed consent from the participants were granted in original studies.

For the exposure, we obtained GWAS summary statistics (GWAS-SS) from the most recent and largest GWAS on SA (n=523 366 from 5 cohorts, including 25 008 SA cases).[24] This GWAS used a multitrait analysis GWAS approach to enhance statistical power, leveraging the high genetic correlations between SA and snoring. SA cases were identified using the *International Classification of Diseases, Ninth Revision* (*ICD-9*), and *International Classification of Diseases, Tenth Revision* (*ICD-10*), diagnostic codes from electronic health records or self-reported data (either through diagnostic information or answer to the item "stop breathing during sleep"). All cohorts included age, sex, genotype batch (where relevant), and genetic ancestry principal components derived from genotype data as covariates.

Genetic variant association estimates with the risk of late-onset AD, CAD, and stroke were used as the outcomes. For AD, we used GWAS-SS from the largest available GWAS of clinically diagnosed AD, conducted by the International Genomics of Alzheimer's Project (n=94 437).[25] For CAD, GWAS-SS in individuals of European ancestry were taken from the latest GWAS available, combining 8 cohorts with the CARDIoGRAMplusC4D consortium (n=1 165 690).[26] For stroke, we obtained GWAS-SS of European ancestry from the GIGASTROKE consortium, the latest and largest GWAS available (n=1 308 460)[27] (Table S3 and Data S1).

## Selection of Instrumental Variables

To estimate causal effects, MR analysis uses genetic variants as instrumental variables (IVs), which must satisfy 3 core assumptions: (i) the IVs should be associated with the exposure (relevance); (ii) the IVs should not be associated with any confounding factors (independence); and (iii) the IVs should affect the outcome solely through their impact on the exposure (exclusion-restriction).[28] On the basis of these assumptions, we identified IVs as independent SNPs that were significantly associated with SA at a genome-wide level ($P<5\times10^{-8}$). To ensure their independence, we excluded duplicate SNPs and performed linkage disequilibrium clumping ($r^2>0.001$, 10-MB window, using the 1000 Genomes Project as the European reference panel). We calculated the F-statistic for the exposure to evaluate the strength of the IVs, as previously described.[29] Then, we extracted these IVs in each of the 3 outcome GWAS data sets. If a specific SNP was not present, we used a proxy SNP with high linkage disequilibrium ($r^2>0.8$, using a European reference). To ensure consistency, we harmonized the exposure and outcome GWAS data sets so that the effects corresponded to the same alleles. Finally, we applied additional filtering criteria, removing palindromic and ambiguous SNPs (minor allele frequency>0.42) as well as SNPs with incompatible alleles.[28] SNPs showing genome-wide significance for the outcome were also excluded from the analyses.[30] For the analyses involving AD, we further excluded variants located ±250 kb from the *APOE ε4*–defining SNP, rs429358, because of its pleiotropic nature, which represents a violation of the exclusion-restriction assumption.[31]

## Statistical Analysis

We conducted 2-sample MR analyses to estimate the causal effects of genetically predicted SA on the risk of AD, CAD, and stroke. More precisely, given that SA is a binary trait, the MR evaluates the causality between genetic liability to SA on the outcomes, with estimates representing the change in outcome per unit change in SA on the log odds scale.[32] A fixed-effects inverse variance–weighted (IVW) approach was performed as the primary method. To evaluate if the causal estimates were robust to violations of MR assumptions, diagnostic tests were performed. We used the MR-Egger regression intercept test to assess for directional horizontal pleiotropy,[28] whereas the Cochran Q test was used to estimate between-SNP heterogeneity in the estimate of the causal effect. Moreover, the impact of outlier genetic instruments was assessed by 3 methods: (i) we performed leave-one-out analysis (for IVW and MR-Egger approaches), excluding one IV at a time, to explore the contribution of individual SNPs to the overall effects; (ii) we conducted radial-MR analysis ("RadialMR," version 1.1, package) to identify data points with large contributions to global heterogeneity, as quantified by the Cochran Q statistic and using a Bonferroni-corrected significance threshold; and (iii) we implemented the MR Steiger test of directionality to verify that the genetic variants were more valid as instruments for the exposure rather than the outcome. This verification supports their use in this MR analysis rather than in the reverse MR. If the test was nonsignificant (ie, indicating that at least 1 genetic variant might be more valid as instrument for the outcome than the exposure), we used Steiger filtering to identify and filter out these instruments. We used PhenoScanner ($r^2>0.8$, using a European reference) to obtain further information on these SNPs. Detected outliers were removed from the analyses (Figures S1–S6). If diagnostic issues were identified, sensitivity analyses using MR-Egger, weighted median, and weighted mode methods were applied. Random-effects IVW method was also performed in a supplementary analysis. Additionally, if significant causal associations were observed, 3 further sensitivity analyses were performed. First, to address any potential bias from sample overlap between the exposure and outcome data sets,

cross-trait linkage disequilibrium score regression was performed, allowing us to calculate the corrected IVW causal effect estimate using the "MRlap," version 0.0.3, package.[33] Second, considering the well-known associations between obesity and SA[34] and the potential strong confounding effect of obesity in the SA-CVD association (Figure S7), multivariable MR (MVMR) analysis using the IVW approach was conducted, adjusting for genetically predicted body mass index (BMI) (see Table S3 for GWAS-SS details).[35] This method provides insights into the independent causal effects of the 2 exposures (ie, SA and BMI) on the outcome by involving the simultaneous use of both SA and BMI instruments (see Figure S8 for MVMR setup). Moreover, we applied the MVMR-Horse method, a novel Bayesian approach to MR that has demonstrated greater robustness to pleiotropy compared with other MVMR methods.[36] Third, because of weak instrument bias in the MVMR analyses (conditional F-statistics <10), we also assessed the impact of obesity on the results by excluding BMI GWAS variants. This involved the exclusion of SNPs associated with BMI at a genome-wide level ($P<5\times10^{-8}$) in any BMI GWAS data set, after restricting the identification to SNP from European ancestry with an $r^2>0.8$. These SNPs were identified via online PhenoScanner and reported in Table S4. Finally, we explored potential reverse causation by conducting MR analyses in the reverse direction, with the SA phenotype as the outcome and AD and CVDs as the exposures. These analyses were performed using the same methods as in the forward direction, by identifying genetic instruments with AD and CVDs as the exposures. All statistical analyses were performed using R, version 4.3.0, with the "TwoSampleMR," version 0.5.7, package.[28]

## RESULTS

We used 32 genetic variants associated with SA as IVs in this MR analysis. In each analysis involving CAD and stroke, 1 SNP was excluded because of its identification as an outlier. The SNPs used as IVs, their harmonized effects, the identified outliers, and the BMI-associated SNPs are displayed in Tables S1 and S2. Figures S1 through S6 show the results from leave-one-out and radial-MR analyses. Results using the random-effects IVW approach are presented in Table S5 as they were similar to the ones obtained with the fixed-effects IVW method.

### Causal Effects Between SA and AD

Genetically predicted SA did not influence the risk of AD (odds ratio [$OR_{IVW}$]=1.14 per log-odds increase in SA liability [95% CI=0.91–1.43]; Table and Figure 1).

**Table. MR Estimates for the Effect of Genetically Predicted SA on the Risk of AD, CAD, and Stroke, and Their Reverse Causality**

| Exposure | Outcome | SNP | Outlier, N | F-statisitcs | Fixed-effects IVW | | MR-Egger | | Weighted median | | Weighted mode | | Cochran Q test | MR-Egger intercept |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | OR (95%CI) | *P* value | OR (95%CI) | *P* value | OR (95%CI) | *P* value | OR (95%CI) | *P* value | *P* value | *P* value |
| Forward | | | | | | | | | | | | | | |
| SA | AD | 32 | 0 | 41.0 | 1.14 (0.91–1.43) | 0.25 | 0.67 (0.21–2.11) | 0.50 | 1.10 (0.79–1.52) | 0.60 | 1.47 (0.78–2.77) | 0.26 | 0.09 | 0.36 |
| SA | CAD | 31 | 1 | 40.2 | 1.35 (1.25–1.47) | $7.93\times10^{-14}$ | 1.02 (0.58–1.80) | 0.94 | 1.43 (1.25–1.64) | $1.50\times10^{-7}$ | 1.53 (1.16–2.00) | 0.006 | $6.48\times10^{-7}$ | 0.33 |
| SA | Stroke | 31 | 1 | 41.2 | 1.13 (1.01–1.25) | 0.03 | 0.87 (0.55–1.40) | 0.58 | 1.16 (1.01–1.34) | 0.06 | 1.23 (0.93–1.62) | 0.14 | 0.43 | 0.29 |
| Reverse | | | | | | | | | | | | | | |
| AD | SA | 23 | 0 | 56.1 | 1.01 (0.99–1.02) | 0.42 | 0.99 (0.94–1.05) | 0.83 | 1.01 (0.99–1.03) | 0.39 | 1.01 (0.98–1.05) | 0.36 | 0.51 | 0.64 |
| CAD | SA | 159 | 4 | 79.2 | 1.02 (1.00–1.03) | 0.008 | 0.99 (0.96–1.02) | 0.54 | 1.01 (0.99–1.03) | 0.32 | 1.01 (0.98–1.03) | 0.69 | $4.44\times10^{-7}$ | 0.06 |
| Stroke | SA | 22 | 1 | 44.0 | 1.01 (0.98–1.04) | 0.61 | 0.91 (0.71–1.17) | 0.47 | 1.00 (0.95–1.05) | 0.98 | 0.95 (0.85–1.06) | 0.39 | 0.001 | 0.43 |

ORs represent the per log-odds increase in exposure liability on the outcome. AD indicates Alzheimer disease; CAD, coronary artery disease; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; SA, sleep apnea; and SNP, single-nucleotide polymorphism.

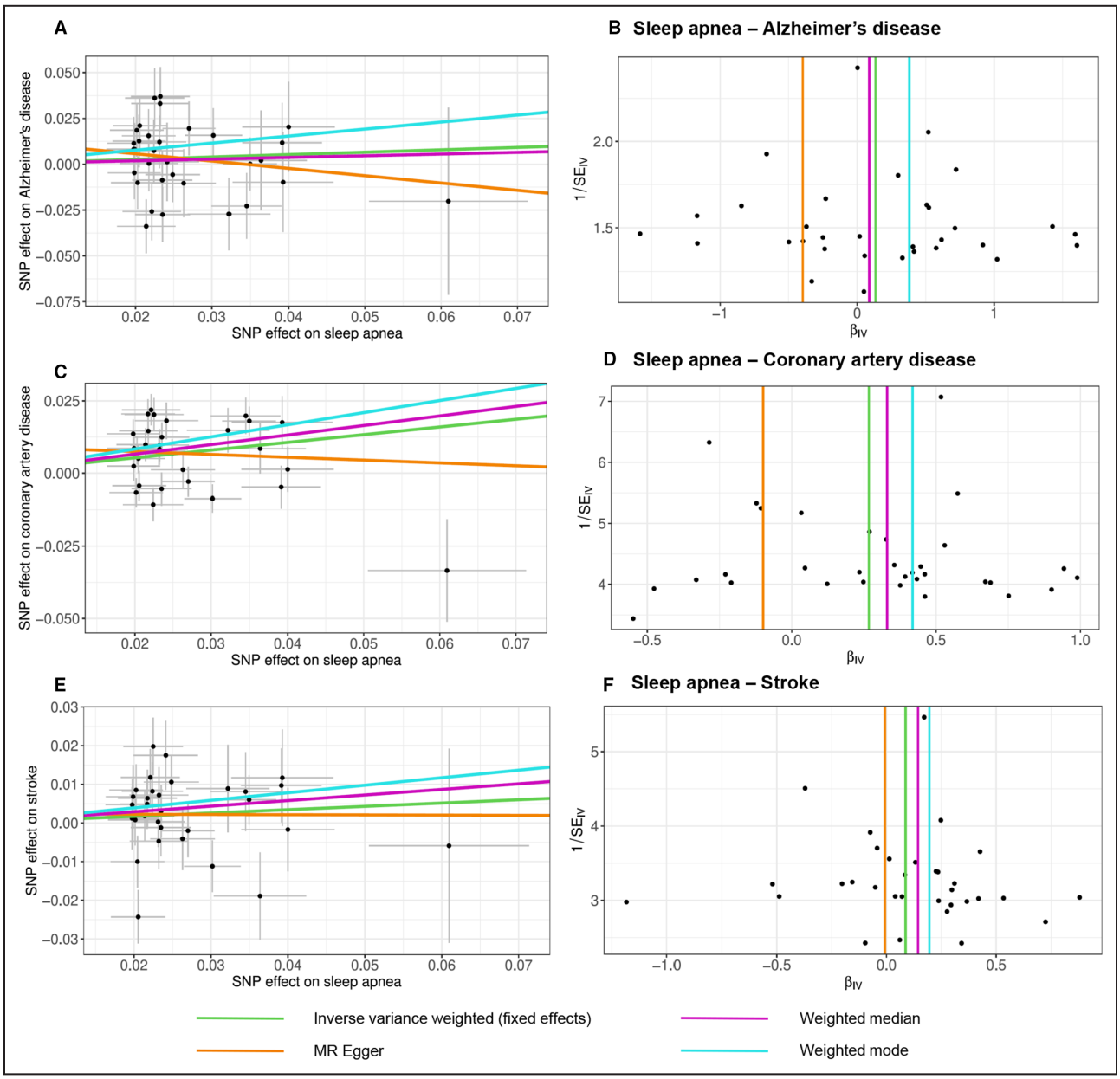


**Figure 1. Scatter and funnel plots for each relationship between sleep apnea and the different outcomes (Alzheimer disease, coronary artery disease, and stroke).**
**A**, **C**, and **E**, Scatterplots () show the sleep apnea variant effect size against the outcome variant effect size and corresponding SEs. **B**, **D**, and **F**, Funnel plots show the Mendelian randomization (MR) causal estimates for each variant against its precision, with asymmetry in the plot indicating potential violations of the assumptions of MR. Regression lines show the corresponding causal estimates: fixed-effect inverse-weighted (green line) meta-analysis; MR-Egger regression (orange line); weighted median-based estimator (purple line); and weighted mode-based estimator (blue line). IV indicates instrumental variable; and SNP, single-nucleotide polymorphism.

There was no evidence of heterogeneity (Cochran Q statistic, *P*=0.09) or pleiotropy (MR-Egger intercept, *P*=0.36) effects. In the reverse direction, genetically predicted AD did not influence the risk of SA ($OR_{IVW}$=1.01 [95% CI=0.99–1.02]; Table and Figure 2). Results from the MR Steiger approach are reported in Table S6. Outliers (ie, SNPs that might have stronger effects on the outcome than the exposure) were identified in the forward direction (*P* value for MR Steiger test of directionality=0.07); however, results after SNP filtering remained similar (Table S6).

## Causal Effects Between SA and CAD

Genetically predicted SA was associated with higher risk of CAD ($OR_{IVW}$=1.35 per log-odds increase in SA liability [95% CI=1.25–1.47]; Table and Figure 1). Heterogeneity was detected (Cochran Q statistic,

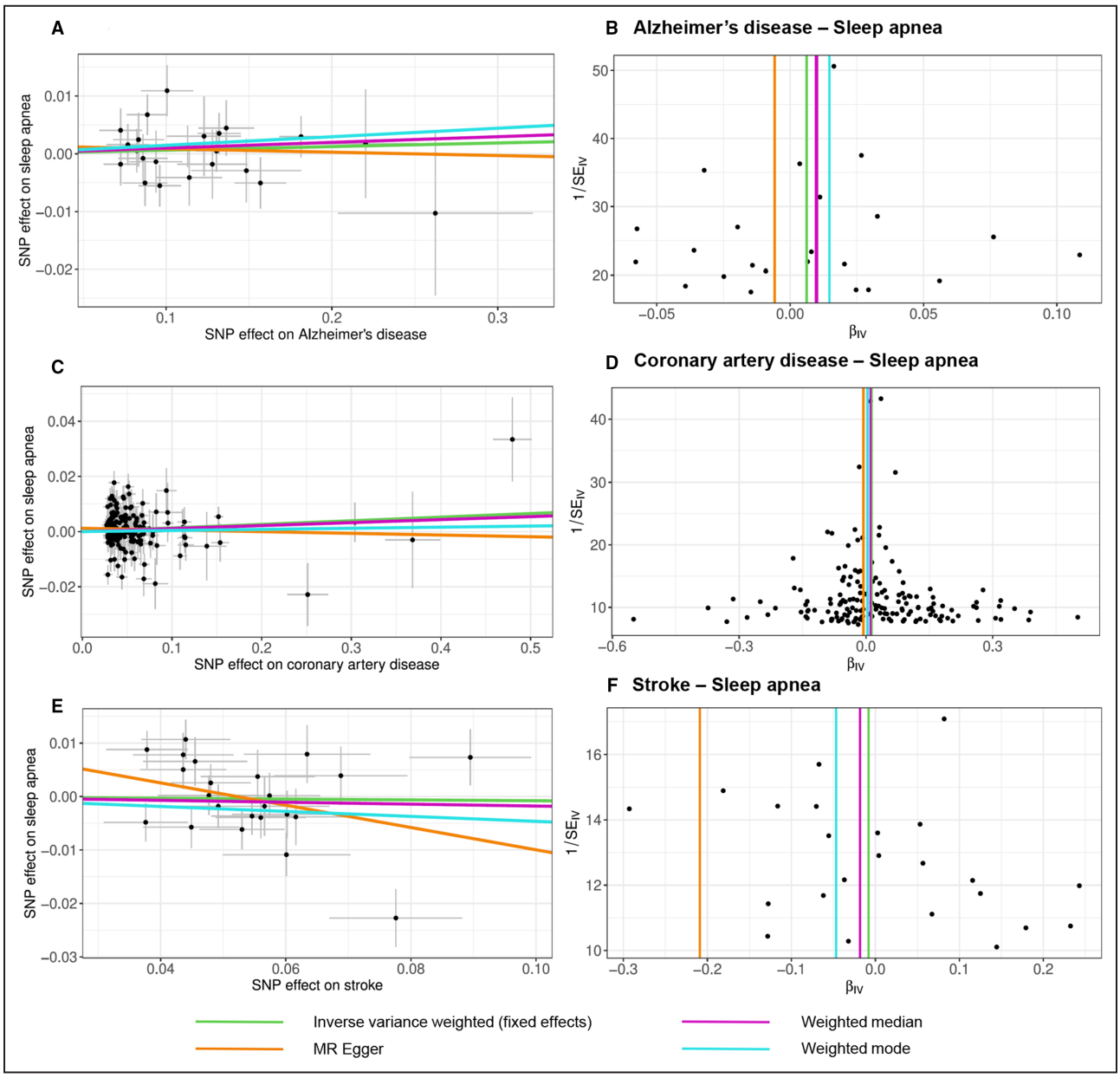


**Figure 2. Scatter and funnel plots for each relationship in the bidirectional analysis between the different exposures (Alzheimer disease, coronary artery disease, and stroke) and sleep apnea.**
**A**, **C**, and **E**, Scatterplots show the exposure variant effect size against the sleep apnea variant effect size and corresponding SEs. **B**, **D**, and **F**, Funnel plots show the Mendelian randomization (MR) causal estimates for each variant against its precision, with asymmetry in the plot indicating potential violations of the assumptions of MR. Regression lines show the corresponding causal estimates: fixed-effect inverse-weighted (green line) meta-analysis; MR-Egger regression (orange line); weighted median-based estimator (purple line); and weighted mode-based estimator (blue line). IV indicates instrumental variable; and SNP, single-nucleotide polymorphism.

$P$=6.48×10$^{-7}$; Figure 1), but MR sensitivity analyses were significant, except for the MR-Egger estimate, and were consistent in effect direction. No pleiotropy effect was detected (Egger intercept, $P$=0.33). A significant difference between observed and corrected effects was found in the analysis correcting for sample overlap. After correction, genetically predicted SA was still significantly associated with higher risk of CAD, although the estimate was somewhat attenuated ($OR_{IVW\text{-}corrected}$=1.13 [95% CI=1.06–1.20]). In the MVMR analysis adjusting for BMI, the causal relationship became nonsignificant ($OR_{IVW}$=1.05 [95% CI=0.92–1.21]; $OR_{Horse}$=1.08 [95% credible interval=0.93–1.22]; Table S7). However, this specific analysis was limited by weak instruments (conditional F-statistics=2.4 for SA and 4.8 for BMI), which represents a violation of the

relevance MR assumption. Therefore, we explored the impact of excluding the BMI-associated SNPs on the results and found that genetically predicted SA still significantly increased the risk of CAD ($OR_{IVW}$=1.26 [95% CI=1.15–1.39]; Table S8). In the bidirectional analysis, a significant causal effect of genetically predicted CAD on SA risk was found using the IVW approach ($OR_{IVW}$=1.02 [95% CI=1.00–1.03]; Table 1 and Figure 2). However, there was evidence of heterogeneity, and all the sensitivity analyses were nonsignificant, suggesting a potential bias in the IVW causal estimate. No genetic variant was identified as potential outlier in the MR Steiger approach (*P* value for MR Steiger test of directionality <0.0001 in the forward and reverse directions; Table S6).

### Causal Effects Between SA and Stroke

We found a significant causal effect of genetically predicted SA on stroke ($OR_{IVW}$=1.13 per log-odds increase in SA liability [95% CI=1.01–1.25]; Table and Figure 1); there was no evidence of heterogeneity (Cochran Q statistic, *P*=0.43) or pleiotropy, as evidenced by the Egger intercept (*P*=0.29). Analysis correcting for sample overlap did not reveal a significant difference between observed and corrected effects, suggesting that the IVW estimates are not biased by sample overlap. In the MVMR analysis adjusting for BMI, the causal relationship became nonsignificant ($OR_{IVW}$=1.03 [95% CI=0.91–1.16]; $OR_{Horse}$=1.02 [95% credible interval=0.87–1.17]; Table S7), suggesting that BMI could confound the association; but this analysis was limited by weak instruments (conditional F-statistics=2.6 for SA and 5.2 for BMI). After excluding the BMI-associated SNPs, the causal effect also became nonsignificant ($OR_{IVW}$=1.08 [95% CI=0.96–1.22]; Table S8). Finally, the bidirectional MR analysis indicated no causal effect for genetically predicted stroke on the risk of SA ($OR_{IVW}$=1.01 [95% CI=0.98–1.04]; Table and Figure 2). No genetic variant was identified as a potential outlier in the MR Steiger approach (*P* value for MR Steiger test of directionality <0.0001 in the forward and reverse directions; Table S6).

## DISCUSSION

Using the most recent GWAS data sets available, this MR study revealed that genetically predicted SA increased the risk of CAD, whereas the causal association with stroke risk may be confounded by BMI. Furthermore, findings do not support evidence of a causal link between genetically predicted SA and AD risk. In the bidirectional analyses, no causal effects were observed for genetically predicted AD, CAD, or stroke on the risk of SA. Taken together, these findings suggest that cardiovascular pathology may play a more important role than AD pathology in the relationship between SA and dementia.

Numerous observational studies have established a link between SA and an increased risk of cognitive impairment and all-cause dementia.[1–3,37] However, it remains controversial which type of dementia is driving this association. Some studies have found an association between SA and AD,[1,4,5] whereas others have not.[38] Moreover, few studies have investigated the association between SA and vascular dementia, also reporting conflicting findings.[1,3,39] These discrepancies might be attributable in part to the limitations of observational studies, which are more prone to several sources of bias (eg, confounder bias and reverse causality). In this study, we used an MR approach to overcome these limitations. We did not yield evidence supporting a causal effect of SA on AD, aligning with the results of the 2 previous MR studies examining this causal relationship.[13,14] However, our findings suggest that cardiovascular pathology would be a more important pathway in the SA-dementia relationship. This is consistent with the well-established vascular risk factors of dementia[10,11,40] as well as the vascular consequences of SA.[9]

Notably, most observational studies, but not all,[41,42] have reported an association between SA and increased risk of CAD and stroke.[43–45] In contrast, previous MR studies did not establish a causal effect of SA on stroke risk,[15–18] whereas results for CAD were mixed.[15,16,19,20] Specifically, SA did not increase the risk of CAD in 2 MR studies,[16,19] whereas a suggestive association was observed in 2 other studies.[15,20] Our findings contribute to the literature by highlighting a significant causal relationship between genetically predicted SA and higher risk of CAD, and by showing that the causal association with stroke risk was confounded by BMI. These differences may be attributable to the use of smaller GWAS data sets for the exposure and/or outcomes in previous MR studies, along with a limited number of valid IVs. For instance, the 2 prior studies that did not observe a causal relationship between SA and CAD relied on 3 and 4 SNPs, respectively, whereas our study involved 31 SNPs.

Given the strong genetic correlation between SA and obesity, accounting for BMI is important as their pathways leading to CVDs may be confounded. Indeed, the role of BMI in the SA-CVD associations remains controversial. In observational studies, some research has shown associations between SA, CAD, and stroke independently of BMI,[41,42,44] whereas some others have not.[41,45,46] Similarly, we found that genetically predicted SA increased the risk of CAD independently of BMI, whereas the causal effect of genetically predicted SA on stroke risk was confounded by BMI. Further studies with higher statistical power are warranted to replicate these results. Although we do not have a clear explanation for

these differences, our results primarily hallmark the important role of BMI and suggest that it may explain the entirety (eg, stroke risk) or only a part (eg, CAD) of the SA-CVD association. SA might impact CVDs through several mechanisms, including, but not limited to, intermittent hypoxia, oxidative stress, inflammation, endothelial dysfunction, white matter lesions, and atherosclerosis.[2,9]

Overall, these findings suggest a greater role for cardiovascular pathology than AD pathology in the relationship between SA and dementia. This observation aligns with mounting evidence involving vascular damage, such as infarcts and white matter changes, as a common feature in various types of dementia.[12,47] Several mechanisms, such as atherosclerotic and inflammation pathways, could be involved. It is also consistent with the importance of vascular cognitive impairment and dementia,[48] underscoring the complex interplay between neurodegenerative and vascular mechanisms. Future studies should investigate these causal relationships using amyloid/tau and cardiovascular phenotypes rather than clinical phenotypes. Although it remains possible that both pathologies contribute to dementia in varying degrees, addressing vascular risk factors and SA through lifestyle modifications and medical interventions may be an important strategy in reducing the risk of dementia.[49,50]

Strengths of our study include a bidirectional MR approach, allowing a better understanding of the direction of the causal effects, the use of large-scale GWAS-SS, a small magnitude of weak instrument bias in the main analyses (F-statistics of the IVs were >10 for all exposures), and multiple sensitivity analyses to confirm the robustness of the results. However, our findings should be interpreted in light of several limitations. First, considering SA is a binary exposure, our estimates represent the average causal effects in "compliers" (ie, individuals for whom SA would be present if they have the genetic variant and absent otherwise).[32] Therefore, estimates should be interpreted as the effect of liability to SA on the outcome, rather than exact causal effect. Second, because SA was evaluated from primary care records or self-reported data, underdiagnosis is possible, which might bias the results of the associations between the genetic variants and SA toward the null. Moreover, we could not conduct the MR analysis on the SA GWAS meta-analysis, before implementation of the multitrait analysis GWAS approach, because of insufficient number of IVs. Results should be thus interpreted with caution, acknowledging that SA and snoring meta-analyses were combined. Third, potential bias toward observational associations might be present when the exposure and the outcome data sets overlap.[51] To address this, we performed a cross-trait linkage disequilibrium score regression analysis to verify the reliability of the identified causal effect of SA on CAD and stroke risks (≈20% overlap for both data sets), and results remained unchanged. Fourth, despite the use of the largest and more recent GWAS data sets available, we were unable to report robust conclusions in the MVMR analyses adjusting for BMI attributable to weak instruments bias. To mitigate this limitation, we applied a novel Bayesian approach to MR, which has been shown to outperform traditional MVMR methods in the presence of weak instruments.[36] Although this approach yielded results similar to those obtained with the MVMR-IVW approach (ie, nonsignificant), it may not significantly enhance the power of the analyses, and results may still be underpowered. Thus, acquiring better GWAS data sets appears to be the most effective strategy to overcome this issue. Furthermore, our additional analysis excluding SNPs associated with BMI at a genome-wide level may not be sufficient to eliminate all confounding effects related to BMI. Consequently, although we have demonstrated a causal relationship between SA and CAD by excluding BMI-related SNPs, it is important to acknowledge the possibility that BMI may still contribute to this association. Further studies are needed to decipher the potential mediating role of BMI in the SA-CVD associations. In addition, we were not able to directly assess vascular dementia as no sufficiently robust GWAS has been published to date. Development of powerful GWASs on the different dementia subtypes has the potential to enhance our understanding of the SA-dementia association. Fifth, competing risks with death and other CVDs cannot be excluded and may lead to false null findings. This limitation is particularly relevant for late-onset diseases, such as AD. Future studies are thus warranted to confirm the current results. Finally, we restricted our analyses to European-ancestry participants, which might limit the generalizability of our findings to other populations.

Among individuals of European ancestry, this MR study supports the hypothesis that genetically predicted SA increased the risk of CAD, whereas the causal effect on stroke risk was confounded by BMI. Furthermore, genetically predicted SA may not have a causal effect on the development of AD. These findings may prompt subsequent investigations aimed at exploring therapeutic approaches targeting SA to prevent CVD risks,[52,53] while also elucidating the role of BMI in these associations. Furthermore, they could lead to additional research investigating cardiovascular mediating pathways between sleep and dementia development, thereby enhancing our comprehension of the biological mechanisms that underlie this association.

## ARTICLE INFORMATION

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## Disclosures

None.

## Supplemental Material

Data S1
Tables S1–S2

## REFERENCES

1. Yaffe K, Nettiksimmons J, Yesavage J, Byers A. Sleep quality and risk of dementia among older male veterans. *Am J Geriatr Psychiatry*. 2015;23:651–654. doi: 10.1016/j.jagp.2015.02.008
2. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, Ancoli-Israel S, Stone KL. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA*. 2011;306:613–619. doi: 10.1001/jama.2011.1115
3. Chang WP, Liu ME, Chang WC, Yang AC, Ku YC, Pai JT, Huang HL, Tsai SJ. Sleep apnea and the risk of dementia: a population-based 5-year follow-up study in Taiwan. *PLoS One*. 2013;8:e78655. doi: 10.1371/journal.pone.0078655
4. Lee JE, Yang SW, Ju YJ, Ki SK, Chun KH. Sleep-disordered breathing and Alzheimer's disease: a nationwide cohort study. *Psychiatry Res*. 2019;273:624–630. doi: 10.1016/j.psychres.2019.01.086
5. Tsai MS, Li HY, Huang CG, Wang RYL, Chuang LP, Chen NH, Liu CH, Yang YH, Liu CY, Hsu CM, et al. Risk of Alzheimer's disease in obstructive sleep apnea patients with or without treatment: real-world evidence. *Laryngoscope*. 2020;130:2292–2298. doi: 10.1002/lary.28558
6. André C, Rehel S, Kuhn E, Landeau B, Moulinet I, Touron E, Ourry V, Le Du G, Mézenge F, Tomadesso C, et al. Association of sleep-disordered breathing with Alzheimer disease biomarkers in community-dwelling older adults: a secondary analysis of a randomized clinical trial. *JAMA Neurol*. 2020;77:716–724. doi: 10.1001/jamaneurol.2020.0311
7. Sharma RA, Varga AW, Bubu OM, Pirraglia E, Kam K, Parekh A, Wohlleber M, Miller MD, Andrade A, Lewis C, et al. Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly. A longitudinal study. *Am J Respir Crit Care Med*. 2018;197:933–943. doi: 10.1164/rccm.201704-0704OC
8. Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. *Lancet Neurol*. 2014;13:1017–1028. doi: 10.1016/S1474-4422(14)70172-3
9. Yeghiazarians Y, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N, Mehra R, Bozkurt B, Ndumele CE, Somers VK. Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;144:e56–e67. doi: 10.1161/CIR.0000000000000988
10. Kuźma E, Lourida I, Moore SF, Levine DA, Ukoumunne OC, Llewellyn DJ. Stroke and dementia risk: a systematic review and meta-analysis. *Alzheimers Dement*. 2018;14:1416–1426. doi: 10.1016/j.jalz.2018.06.3061
11. Deckers K, Schievink SHJ, Rodriquez MMF, van Oostenbrugge RJ, van Boxtel MPJ, Verhey FRJ, Köhler S. Coronary heart disease and risk for cognitive impairment or dementia: systematic review and meta-analysis. *PLoS One*. 2017;12:e0184244. doi: 10.1371/journal.pone.0184244
12. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol*. 2017;134:171–186. doi: 10.1007/s00401-017-1717-7
13. Li J, Zhao L, Ding X, Cui X, Qi L, Chen Y. Obstructive sleep apnea and the risk of Alzheimer's disease and Parkinson disease: a mendelian randomization study OSA, Alzheimer's disease and Parkinson disease. *Sleep Med*. 2022;97:55–63. doi: 10.1016/j.sleep.2022.06.004
14. Cullell N, Cárcel-Márquez J, Gallego-Fábrega C, Muiño E, Llucià-Carol L, Lledós M, Amaut KEU, Krupinski J, Fernández-Cadenas I. Sleep/wake cycle alterations as a cause of neurodegenerative diseases: a mendelian randomization study. *Neurobiol Aging*. 2021;106:320.e1–320.e12. doi: 10.1016/j.neurobiolaging.2021.05.008
15. Wang J, Campos AI, Rentería ME, Xu L. Causal associations of sleep apnea, snoring with cardiovascular diseases, and the role of body mass index: a two-sample mendelian randomization study. *Eur J Prev Cardiol*. 2023;30:552–560. doi: 10.1093/eurjpc/zwad005
16. Li Y, Miao Y, Zhang Q. Causal associations of obstructive sleep apnea with cardiovascular disease: a Mendelian randomization study. *Sleep*. 2023;46:zsac298. doi: 10.1093/sleep/zsac298
17. Li P, Dong Z, Chen W, Yang G. Causal relations between obstructive sleep apnea and stroke: a mendelian randomization study. *Nat Sci Sleep*. 2023;15:257–266. doi: 10.2147/NSS.S398544
18. Titova OE, Yuan S, Baron JA, Lindberg E, Michaëlsson K, Larsson SC. Sleep-disordered breathing-related symptoms and risk of stroke: cohort study and Mendelian randomization analysis. *J Neurol*. 2022;269:2460–2468. doi: 10.1007/s00415-021-10824-y
19. Ding X, Zhao L, Cui X, Qi L, Chen Y. Mendelian randomization reveals no associations of genetically-predicted obstructive sleep apnea with the risk of type 2 diabetes, nonalcoholic fatty liver disease, and coronary heart disease. *Front Psych*. 2023;14:1068756. doi: 10.3389/fpsyt.2023.1068756
20. Titova OE, Yuan S, Baron JA, Lindberg E, Michaëlsson K, Larsson SC. Self-reported symptoms of sleep-disordered breathing and risk of cardiovascular diseases: observational and mendelian randomization findings. *J Sleep Res*. 2022;31:e13681. doi: 10.1111/jsr.13681
21. Emamian F, Khazaie H, Tahmasian M, Leschziner GD, Morrell MJ, Hsiung GYR, Rosenzweig I, Sepehry AA. The association between obstructive sleep apnea and Alzheimer's disease: a meta-analysis perspective. *Front Aging Neurosci*. 2016;8:78.
22. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, VanderWeele TJ, Higgins JPT, Timpson NJ, Dimou N, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomization: the STROBE-MR statement. *JAMA*. 2021;326:1614–1621. doi: 10.1001/jama.2021.18236
23. Skrivankova VW, Richmond RC, Woolf BAR, Davies NM, Swanson SA, VanderWeele TJ, Timpson NJ, Higgins JPT, Dimou N, Langenberg C, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): explanation and elaboration. *BMJ*. 2021;375:n2233. doi: 10.1136/bmj.n2233
24. Campos AI, Ingold N, Huang Y, Mitchell BL, Kho PF, Han X, García-Marín LM, Ong JS, Law MH, Yokoyama JS. Discovery of genomic loci associated with sleep apnea risk through multi-trait GWAS analysis with snoring. *Sleep*. 2023;46:zsac308. doi: 10.1093/sleep/zsac308
25. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, Boland A, Vronskaya M, Van der Lee SJ, Amlie-Wolf A, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet*. 2019;51:414–430. doi: 10.1038/s41588-019-0358-2
26. Aragam KG, Jiang T, Goel A, Kanoni S, Wolford BN, Atri DS, Weeks EM, Wang M, Hindy G, Zhou W, et al. Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants. *Nat Genet*. 2022;54:1803–1815. doi: 10.1038/s41588-022-01233-6
27. Mishra A, Malik R, Hachiya T, Jürgenson T, Namba S, Posner DC, Kamanu FK, Koido M, Le Grand Q, Shi M, et al. Stroke genetics informs drug discovery and risk prediction across ancestries. *Nature*. 2022;611:115–123. doi: 10.1038/s41586-022-05165-3
28. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R, et al. The MR-base platform supports systematic causal inference across the human phenome. *eLife*. 2018;7:e34408. doi: 10.7554/eLife.34408
29. Burgess S, Thompson SG; CRP CHD genetics collaboration. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol*. 2011;40:755–764. doi: 10.1093/ije/dyr036
30. Thompson SB, Simon G. *Mendelian Randomization: Methods for Causal Inference Using Genetic Variants*. 2nd ed. Chapman and Hall/CRC; 2021:240.
31. Watanabe K, Stringer S, Frei O, Umićević Mirkov M, de Leeuw C, Polderman TJC, van der Sluis S, Andreassen OA, Neale BM, Posthuma

D. A global overview of pleiotropy and genetic architecture in complex traits. *Nat Genet*. 2019;51:1339–1348. doi: 10.1038/s41588-019-0481-0
32. Burgess S, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. *Eur J Epidemiol*. 2018;33:947–952. doi: 10.1007/s10654-018-0424-6
33. Mounier N, Kutalik Z. Bias correction for inverse variance weighting mendelian randomization. *Genet Epidemiol*. 2023;47:314–331. doi: 10.1002/gepi.22522
34. Kuvat N, Tanriverdi H, Armutcu F. The relationship between obstructive sleep apnea syndrome and obesity: a new perspective on the pathogenesis in terms of organ crosstalk. *Clin Respir J*. 2020;14:595–604. doi: 10.1111/crj.13175
35. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, Frayling TM, Hirschhorn J, Yang J, Visscher PM, et al. Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. *Hum Mol Genet*. 2018;27:3641–3649. doi: 10.1093/hmg/ddy271
36. Grant AJ, Burgess S. A Bayesian approach to mendelian randomization using summary statistics in the univariable and multivariable settings with correlated pleiotropy. *Am J Hum Genet*. 2024;111:165–180. doi: 10.1016/j.ajhg.2023.12.002
37. Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of sleep-disordered breathing with cognitive function and risk of cognitive impairment: a systematic review and meta-analysis. *JAMA Neurol*. 2017;74:1237–1245. doi: 10.1001/jamaneurol.2017.2180
38. Lutsey PL, Misialek JR, Mosley TH, Gottesman RF, Punjabi NM, Shahar E, MacLehose R, Ogilvie RP, Knopman D, Alonso A. Sleep characteristics and risk of dementia and Alzheimer's disease: the atherosclerosis risk in communities study. *Alzheimers Dement*. 2018;14:157–166. doi: 10.1016/j.jalz.2017.06.2269
39. Elwood P, Bayer A, Fish M, Pickering J, Mitchell C, Gallacher J. Sleep disturbance and daytime sleepiness predict vascular dementia. *J Epidemiol Community Health*. 2011;65:820–824. doi: 10.1136/jech.2009.100503
40. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Copper C, et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. *Lancet*. 2020;396:413–446. doi: 10.1016/S0140-6736(20)30367-6
41. Catalan-Serra P, Campos-Rodriguez F, Reyes-Nuñez N, Selma-Ferrer MJ, Navarro-Soriano C, Ballester-Canelles M, Soler-Cataluña JJ, Roman-Sanchez P, Almeida-Gonzalez CV, Martinez-Garcia MA. Increased incidence of stroke, but not coronary heart disease, in elderly patients with sleep apnea. *Stroke*. 2019;50:491–494. doi: 10.1161/STROKEAHA.118.023353
42. Marshall NS, Wong KKH, Cullen SRJ, Knuiman MW, Grunstein RR. Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the Busselton health study cohort. *J Clin Sleep Med*. 2014;10:355–362. doi: 10.5664/jcsm.3600
43. Carthy CEM, Yusuf S, Judge C, Alvarez-Iglesias A, Hankey GJ, Oveisgharan S, Damasceno A, Iversen HK, Rosengren A, Avezum A, et al. Sleep patterns and the risk of acute stroke: results from the INTERSTROKE international case-control study. *Neurology*. 2023;100:e2191–e2203. doi: 10.1212/WNL.0000000000207249
44. Strausz S, Havulinna AS, Tuomi T, Bachour A, Groop L, Mäkitie A, Koskinen S, Salomaa V, Palotie A, Ripatti S, et al. Obstructive sleep apnoea and the risk for coronary heart disease and type 2 diabetes: a longitudinal population-based study in Finland. *BMJ Open*. 2018;8:e022752. doi: 10.1136/bmjopen-2018-022752
45. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, et al. Obstructive sleep apnea–hypopnea and incident stroke. *Am J Respir Crit Care Med*. 2010;182:269–277. doi: 10.1164/rccm.200911-1746OC
46. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, et al. A prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation*. 2010;122:352–360. doi: 10.1161/CIRCULATIONAHA.109.901801
47. Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med*. 2010;362:329–344. doi: 10.1056/NEJMra0909142
48. Wong EC, Chui HC. Vascular cognitive impairment and dementia. *Contin Minneap Minn*. 2022;28:750–780.
49. Dunietz GL, Chervin RD, Burke JF, Conceicao AS, Braley TJ. Obstructive sleep apnea treatment and dementia risk in older adults. *Sleep*. 2021;44:zsab076. doi: 10.1093/sleep/zsab076
50. Rosenberg A, Ngandu T, Rusanen M, Antikainen R, Bäckman L, Havulinna S, Hänninen T, Laatikainen T, Lehtisalo J, Levälahti E, et al. Multidomain lifestyle intervention benefits a large elderly population at risk for cognitive decline and dementia regardless of baseline characteristics: the FINGER trial. *Alzheimers Dement*. 2018;14:263–270. doi: 10.1016/j.jalz.2017.09.006
51. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample mendelian randomization. *Genet Epidemiol*. 2016;40:597–608. doi: 10.1002/gepi.21998
52. Brown DL, Durkalski V, Durmer JS, Broderick JP, Zahuranec DB, Levine DA, Anderson CS, Bravata DM, Yaggi HK, Morgensstern LB, et al. Sleep for stroke management and recovery trial (sleep SMART): rationale and methods. *Int J Stroke*. 2020;15:923–929. doi: 10.1177/1747493020903979
53. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med*. 2016;375:919–931. doi: 10.1056/NEJMoa1606599