Snoring-AD MR analysis

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## Abstract

**Introduction:**

**Methods:** We used bidirectional two-sample Mendelian randomization (MR) to investigate the bidirectional causal effects of Snoring and Alzheiemr’s disease; and the causal effect of sleep apnea on AD. Summary statistics for genome-wide association studies of AD (n = 94,437; cases = 35,274), Snoring (n ~ 408,000; snorers ~ 152,000), and a multi-trait GWAS of sleep apnea and snoring (n = xxx). Genetic instruments were obtained by selecting independent genome-wide significant SNPs (p < 5e-8, r2 = 0.001, window = 10Mb) for each exposure and harmonizing their effects with each outcome. Fixed-effects inverse-variance weighted (IVW) meta-analysis was the primary method for estimating causal effects, with MR-Egger, Weighted mode, Weighted median, radial-MR, estimators used as sensitivity analyses. LHC-MR was further used to investigate birectional effects accounting for potential heritable confounders. Multivariable MR was used to estimate direct of AD on snoring independent from BMI. Heterogeneity was assessed using Cohcrans Q test, and pleiotropy using the MR-Egger intercept.

**Results:** No causal effect of snoring (OR [95%CI] = 0.84 [0.39, 1.8], p = 0.65) or sleep apnea (OR [95%CI] = 1.1 [0.83, 1.3], p = 0.67) on Alzheimer’s disease was observed. In the reverse direction, no-significant effect of AD on snoring was observed using IVW (b [se] = -0.0022 [0.0014], p = 0.11) and LHC-MR (b [se] = 0.005 [0.02], p = 0.85), however, suggestive causal effects were observed in the MR-Egger (b [se] = 0.006 [0.002], p = 0.004), Weighted mode (b [se] = 0.004 [0.002], p = 0.03), and Weighted Median (b [se] = 0.004 [0.002], p = 0.01) sensetivity analyses. There was no evidence of heterogenity, but evidence of pleiotropic effects (MR-Egger Intercept: b [se] = 0.001 [0.0003], p = 0.009). Multivariable MR indicated that the effect of AD on snoring was likely driven by BMI.

**Conclusion:**

## Datasets

Exposure: Snoring

* Campos, A. I. et al. Nat Commun 11, 817 (2020).
* Genome-wide association study on snoring (n ~ 408,000; snorers ~ 152,000) using data from the UK Biobank. Identified 42 genome-wide signiﬁcant loci, with an SNP based heritability estimate of ~10% on the liability scale
* Also Snoring adjusted for BMI

Exposure: Sleep Apnea + Snoring

* Campos, A. I. et al. Sleep (2022).
* genome-wide association study (GWAS) meta-analysis of sleep apnoea across five cohorts (NTotal=523,366), followed by a multi-trait analysis of GWAS (MTAG) to boost power, leveraging the high genetic correlation between sleep apnoea and snoring. Replicated top findings in 23andMe. 49 Signficant loci, with twenty nine replicated in 23andMe

Exposure: BMI

* Lock et al Nature 2015
* To understand the genetic basis of obesity better, here we conduct a genome-wide association study and Metabochip meta-analysis of body mass index (BMI), a measure commonly used to define obesity and assess adiposity, in up to 339,224 individuals. This analysis identifies 97 BMI-associated loci, 56 of which are novel.

Outcome: Alzheimer’s disease

* Kunkle, B. W. et al. Nat Genet 51, 414–430 (2019).
* Genome-wide association study on Alzheimer’s disease (n = 94,437) using data from the International Genomics Alzheiemr’s Project. Identified 20 genome-wide signiﬁcant loci

## Methods

Harmonization

* LD Clumping: r^2 = 0.001; 10mb window
* p-value theshold: 5e-8
* Proxy SNPs using EUR reference, r^2 > 0.8
* palindromic SNPs: Removed (no allele frequency info for exposure)
* no snps in APOE region or GWS for outcome

TwoSampleMR (Foward)

* Primary analysis: Fixed effect Inverse Weighted Analysis
* Sensitivity analysis: Weighted median, Weighted mode, MR-Egger
* Heterogeneity and Pleiotropy:
  + MR-Egger Intercept
  + Cochrans Q test
  + Radial MR

TwoSampleMR (Reverse)

* Primary analysis: Fixed effect Inverse Weighted Analysis
* Sensitivity analysis: Weighted median, Weighted mode, MR-Egger
* Heterogeneity and Pleiotropy:
  + MR-Egger Intercept
  + Cochrans Q test
  + Radial MR

LHC-MR

Multivariable MR

## Results (Foward)

No significant effect of snoring or sleep apnea on AD.

| **exposure** | **method** | **nsnp** | **or** | **ci** | **pval** |
| --- | --- | --- | --- | --- | --- |
| SnoringBMIadj | Inverse variance weighted (fixed effects) | 26 | 1.30 | 0.55, 3.1 | 0.560 |
| MR Egger | 26 | 140.00 | 1.4, 14000 | 0.046 |
| Weighted median | 26 | 1.50 | 0.45, 5 | 0.510 |
| Weighted mode | 26 | 3.70 | 0.42, 32 | 0.250 |
| Snoring | Inverse variance weighted (fixed effects) | 31 | 0.84 | 0.39, 1.8 | 0.650 |
| MR Egger | 31 | 24.00 | 0.26, 2200 | 0.180 |
| Weighted median | 31 | 1.10 | 0.36, 3.7 | 0.820 |
| Weighted mode | 31 | 1.20 | 0.15, 10 | 0.850 |
| SAsnoring | Inverse variance weighted (fixed effects) | 29 | 1.10 | 0.83, 1.3 | 0.670 |
| MR Egger | 29 | 0.79 | 0.4, 1.6 | 0.500 |
| Weighted median | 29 | 0.98 | 0.7, 1.4 | 0.900 |
| Weighted mode | 29 | 0.76 | 0.42, 1.4 | 0.380 |

Figure 1: Scatter Plot showing MR causal estimatesFigure 1: Scatter Plot showing MR causal estimates

No significant heterogenity

| **exposure** | **outcome** | **method** | **Q** | **Q\_df** | **Q\_pval** |
| --- | --- | --- | --- | --- | --- |
| SnoringBMIadj | AD | MR Egger | 13.08697 | 24 | 0.96 |
| AD | Inverse variance weighted | 17.21038 | 25 | 0.87 |
| Snoring | AD | MR Egger | 37.72636 | 29 | 0.13 |
| AD | Inverse variance weighted | 40.55547 | 30 | 0.095 |
| SAsnoring | AD | MR Egger | 27.11118 | 27 | 0.46 |
| AD | Inverse variance weighted | 27.91981 | 28 | 0.47 |

No significant pleiotropy

| **exposure** | **outcome** | **egger\_intercept** | **se** | **pval** |
| --- | --- | --- | --- | --- |
| SnoringBMIadj | AD | -0.0350 | 0.0170 | 0.054 |
| Snoring | AD | -0.0250 | 0.0170 | 0.15 |
| SAsnoring | AD | 0.0076 | 0.0085 | 0.38 |

Figure 2: Funnel Plot showing heterogeneityFigure 2: Funnel Plot showing heterogeneity

no significant outliers from LOO or Radial MR

Figure 3: Leave-one-out Plot showing effect of individual SNPs on causal etimateFigure 3: Leave-one-out Plot showing effect of individual SNPs on causal etimate

Figure 4: Radial Plot showing potential outliersFigure 4: Radial Plot showing potential outliers

## Results (Reverse)

### Causal estimates

| **exposure** | **outcome** | **method** | **nsnp** | **b** | **se** | **pval** |
| --- | --- | --- | --- | --- | --- | --- |
| AD | SnoringBMIadj | IVW | 30 | -0.00013 | 0.0013 | 0.92 |
| MR Egger | 30 | -0.00360 | 0.0023 | 0.12 |
| Weighted median | 30 | -0.00280 | 0.0019 | 0.15 |
| Weighted mode | 30 | -0.00260 | 0.0019 | 0.19 |
| Snoring | IVW | 30 | -0.00220 | 0.0014 | 0.11 |
| MR Egger | 30 | -0.00610 | 0.0020 | 0.0042 |
| Weighted median | 30 | -0.00490 | 0.0019 | 0.013 |
| Weighted mode | 30 | -0.00440 | 0.0019 | 0.031 |
| BMI | SnoringBMIadj | IVW | 67 | -0.02600 | 0.0053 | < 0.001 |
| MR Egger | 67 | -0.11000 | 0.0270 | < 0.001 |
| Weighted median | 67 | -0.04600 | 0.0099 | < 0.001 |
| Weighted mode | 67 | -0.07700 | 0.0150 | < 0.001 |
| Snoring | IVW | 65 | 0.04400 | 0.0055 | < 0.001 |
| MR Egger | 65 | -0.04600 | 0.0260 | 0.082 |
| Weighted median | 65 | 0.01800 | 0.0099 | 0.071 |
| Weighted mode | 65 | -0.00027 | 0.0140 | 0.98 |

Figure x: Scatter Plot showing causal estimates of AD/BMI onto Snoring

### Heterogenity

| **exposure** | **outcome** | **method** | **Q** | **Q\_df** | **Q\_pval** |
| --- | --- | --- | --- | --- | --- |
| AD | SnoringBMIadj | MR Egger | 38.92486 | 28 | 0.082 |
| Inverse variance weighted | 45.29738 | 29 | 0.028 |
| Snoring | MR Egger | 25.00289 | 28 | 0.63 |
| Inverse variance weighted | 32.89441 | 29 | 0.28 |
| BMI | SnoringBMIadj | MR Egger | 201.46821 | 65 | < 0.001 |
| Inverse variance weighted | 235.80269 | 66 | < 0.001 |
| Snoring | MR Egger | 160.79858 | 63 | < 0.001 |
| Inverse variance weighted | 196.00094 | 64 | < 0.001 |

### Pleiotropy

| **exposure** | **outcome** | **egger\_intercept** | **se** | **pval** |
| --- | --- | --- | --- | --- |
| AD | SnoringBMIadj | 0.00089 | 0.00042 | 0.041 |
| Snoring | 0.00100 | 0.00036 | 0.009 |
| BMI | SnoringBMIadj | 0.00250 | 0.00075 | 0.0014 |
| Snoring | 0.00260 | 0.00070 | < 0.001 |

Figure x: Funnel Plot showing heterogeneity of AD/BMI onto Snoring

Figure 2: Funnel Plot showing outliers in AD/BMI onto Snoring

## LHC-MR

Parameters

* pi(x|y): polygenicity
* h2(x|y): heritability
* t(x|y): confounding effect
* axy: causal effect of exposure on outcome (fwd)
* ayx: causal effect of outcome on exposure (rev)
* iXY: cross-trait intercept (LDSC)

| **parameters** | **piX** | **piY** | **h2X** | **h2Y** | **tX** | **tY** | **axy** | **ayx** | **iXY** | **iX** | **iY** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Parameter estimates | 0.00058 | 0.0000016 | 0.055 | 0.061 | 0.0680 | 0.16000 | -0.11 | 0.0054 | 0.0024 | 1.1 | 1.1 |
| SE-JK |  |  | 0.0045 | 0.035 | 0.0220 | 0.04300 | 0.16 | 0.0280 | 0.0180 |  |  |
| Pval |  |  | < 0.001 | 0.086 | 0.0019 | 0.00012 | 0.48 | 0.8500 | 0.8900 |  |  |

## Multivariable MR

| **exposure** | **outcome** | **nsnp** | **b** | **se** | **pval** |
| --- | --- | --- | --- | --- | --- |
| AD | Snoring | 19 | 0.0022 | 0.0043 | 0.62 |
| BMI | Snoring | 67 | 0.0510 | 0.0093 | < 0.001 |

Figure x: RMVMR results for AD (exp1) and BMI (exp2) on Snoring

| **Exposure** | **Outcome** | **method** | **b** | **se** | **p** |
| --- | --- | --- | --- | --- | --- |
| AD | Snoring | MRMV-IVW | 0.00220 | 0.0043 | 0.62 |
| BMI | Snoring | MRMV-IVW | 0.05100 | 0.0093 | < 0.001 |
| AD | Snoring | MRMV-Egger | 0.00360 | 0.0056 | 0.53 |
| BMI | Snoring | MRMV-Egger | 0.05100 | 0.0094 | < 0.001 |
| AD | Snoring | MRMV-WME | 0.00042 | 0.0039 | 0.91 |
| BMI | Snoring | MRMV-WME | 0.04200 | 0.0100 | < 0.001 |
| AD | Snoring | MRMV\_WBE | 0.00260 |  | 0.17 |
| BMI | Snoring | MRMV\_WBE | 0.02000 |  | < 0.001 |