How sleep genes affect cognition:
a Mendelian randomisation study in UK Biobank

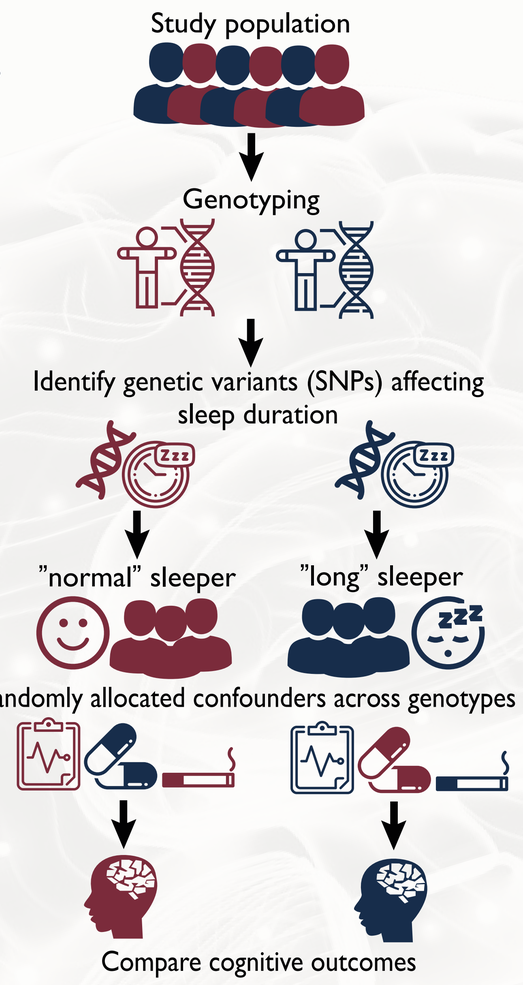
Henry A[1]✉, Masi S[2], Fatemifar G[1], Mena DA[1], Danaxas S[1], Garfield V[1], Dale CE[1]
[1]Farr Institute of Health Informatics Research, University College London
[2]Institute of Cardiovascular Science, University College London
✉albert.henry.16@ucl.ac.uk

Background

Short and long sleep duration have been linked with poorer cognitive outcomes, but it remains unclear whether this association is causal. To investigate this issue, we performed the first Mendelian randomisation (MR) analysis using 34 genetic variants for sleep duration in 108,760 UK Biobank participants. We further perfomed MR analysis for Alzheimer's disease (AD) using summary statistics from the International Genomics of Alzheimer's Project (IGAP).

What is Mendelian randomisation?

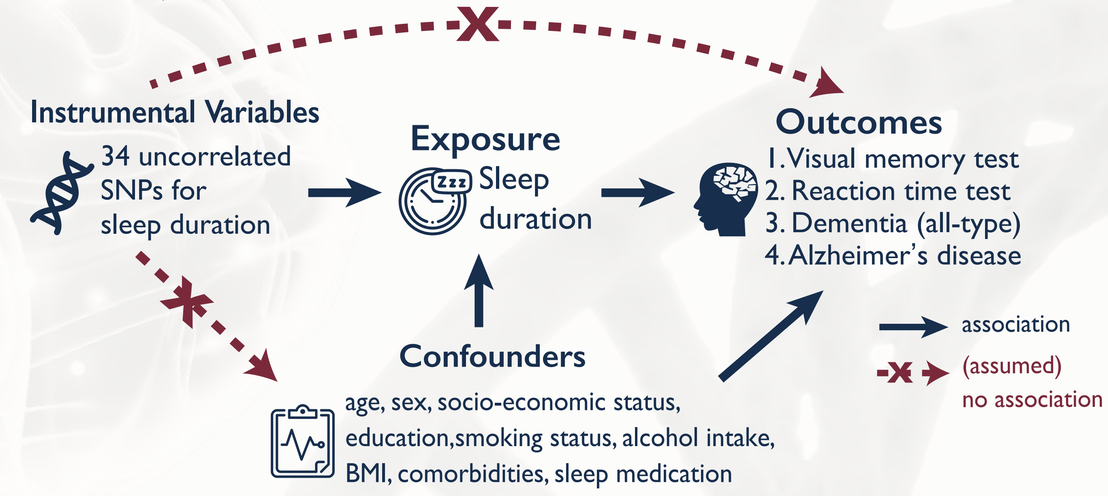
Mendelian randomisation (MR) study uses genetic variants (single-nucleotide polymorphisms - SNPs) as instrumental variables to investigate the causal effect of the exposure (phenotype) on the outcome of interest. Due to random assortment of genes at conception, MR is more robust to confounding and reverse causation than observational studies. This concept is equivalent to that of randomised trial, with respect to confounders being randomly allocated across exposure groups and exposure preceding the outcome – allowing for causal inference.



Methods

Study Participants

We used individual-level data of 108,760 participants of European ancestry from the UK Biobank cohort, a large prospective study comprising health and genetic data of UK-based individuals aged 40-73 years. For AD, we used summary statistics data from meta-analysis in the IGAP stage I, a large consortium based upon genome-wide associatio studies (GWAS) on individuals of European ancestry consisting of 17,008 AD cases and 37,154 controls.



Variable Ascertainment

- *Sleep duration* was based on self-reported data (hours/day).
- *Visual memory test* was measured at baseline as number of errors in a pairs-matching test with 6-pairs-of-card.
- *Reaction time test* was measured at baseline as mean time (in milliseconds) to correctly identify matches from 12 rounds of 'Snap' card game.
- *Dementia (all-type)* was derived from hospital records based on ICD-10 codes.
- *Alzheimer's disease* was estimated using IGAP summary statistics.
- The *34 SNPs for sleep duration* were identified from 3 GWAS with proportion of variance explained (R^2) of 0.57%

Statistical Analyses

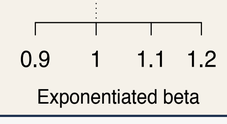
- *Observational analysis;* performed with two linear / logistic regression models: (1) *unadjusted* and (2) *adjusted* for age, sex, socioeconomic status, education, smoking status, alcohol intake, BMI, comorbidities, and use of sleep-inducing medication.
- *MR analysis;* performed with four methods: (1) *unweighted genetic score*, (2) *weighted genetic score*, (3) *inverse-variance weighted*, and (4) *weighted median estimator*. For ease of interpretation, only results with lowest P-value were presented.

Results

Visual memory test

N = 108,760

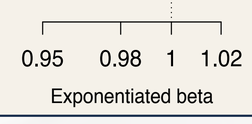
Analysis method	Exp(Beta) [95% CI]
Obs (Unadjusted)	1.01 [1.01, 1.02]
Obs (Adjusted)	1.01 [1.00, 1.01]
MR analysis	1.09 [1.04, 1.14]



Reaction time test

N = 108,760

Analysis method	Exp(Beta) [95% CI]
Obs (Unadjusted)	1.01 [1.00, 1.01]
Obs (Adjusted)	1.00 [1.00, 1.00]
MR analysis	0.99 [0.98, 1.00]



Effect of sleep duration on...

Dementia

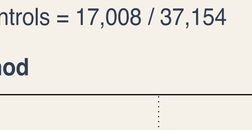
N cases / N total = 380 / 86,096

Analysis method	OR [95% CI]
Obs (Unadjusted)	1.04 [0.95, 1.13]
Obs (Adjusted)	0.96 [0.88, 1.04]
MR analysis	5.86 [1.04, 33.04]

Alzheimer's Disease (IGAP Dataset)

N cases / N controls = 17,008 / 37,154

Analysis method	OR [95% CI]
MR analysis	1.05 [0.79, 1.39]



Exp(beta) = exponentiated beta; *OR* = odds ratio; *CI* = confidence interval, *N* = number of observations; *Obs (Unadjusted) / (Adjusted)* = observational analysis without / with adjustment for confounders; *MR analysis* = Mendelian randomisation (instrumental variable) analysis

For visual memory and reaction time tests, higher Exp(beta) represents poorer performance (more errors and slower reaction). Value represents multiplicative effect size, e.g. Exp(beta) = 1.09 indicates 9% poorer performance and OR = 1.05 indicates 5% increased risk, per 1 hour/day increase in genetically-instrumented sleep duration.

Discussion

- **Non-linear association**
  The presented estimates only represent linear effect, while the true causal association could be U-shaped / J-shaped.
- **Other sleep characteristics**
  Sleep duration may be associated with other sleep characteristics, e.g. long sleep may indicate poor sleep quality, which may have important effects on cognition
- **Different effect across cognitive domains**
  Sleep disturbances may have more effect on certain brain functions; e.g. prefrontal cortex and dopaminergic pathways in visual memory function.
- **Findings in UK Biobank vs IGAP dataset**
  Compared to the IGAP dataset, the UK Biobank data included all-type dementia and had a younger population. Positive association in UK Biobank but not in IGAP implies that certain dementia subtypes, particularly those with early onset, may be more susceptible to sleep disturbances.
- **Limitations**
  Limitations include bias due to sample overlap in two-samples MR setting, limited understanding of the genetic variants function, non-standard cognitive tests, and low statistical power in MR analysis due to weak instrument and lack of dementia cases in UK Biobank.

What are the main findings?

Longer sleep duration adversely affects visual memory and potentially increases the risk of all-type, early-onset dementia, but has no effect on reaction time and Alzheimer's disease risk.

How much sleep do we need?

We suggest to stick with the recommended 7-9 hours of sleep / day, but individuals with prolonged sleep duration may benefit from further assessment of sleep quality, sleep-related problems, and cognitive functions.

What are the next steps?

Further research should investigate non-linear association, other sleep parameters, dementia subypes, and validity of the genetic instruments.

References

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