



Exploring Causal Links Between Sleep And Cognitive Performance: Evidence From Twin-based Mendelian Randomization



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INTRODUCTION

Poor sleep quality (SQ) is associated with diminished cognitive performance, and both are linked to elevated risk for Alzheimer’s disease and related dementias.¹⁻³

Determining whether these associations are causal is critical for evaluating sleep as a modifiable target for preserving cognitive health and reducing dementia risk.

METHOD

Participants

Participants included 798 men (230 Monozygotic Twin Pairs, 169 Dizygotic Twin Pairs) from the Vietnam Era Twin Study of Aging (VETSA)⁴: Age: $M = 67.34$ years ($SD = 2.50$), Range = 61.37 – 73.25 years

Sleep Measures

- Sleep Quality: Global Pittsburgh Sleep Quality Index⁵ Score (PSQI) $M = 5.53$ ($SD = 3.73$)
- Sleep Duration
 - A single component within the PSQI: “During the past month, how many hours of actual sleep did you get at night?” $M = 6.80$ ($SD = 1.33$)

Polygenic Scores (PGS)

- Sleep Health PGS, Habitual Sleep Duration PGS, and General Cognitive Ability PGS were used as instrumental variables

Instrument strength reflects how well each PGS predicts its target phenotype; stronger instruments improve power to distinguish causal effects from shared genetic liability.

- Sleep Health-PGS moderately predicted SQ
 - $F(1,957) = 7.17$, $p < 0.01$
- Sleep-Duration-PGS strongly predicted sleep duration
 - $F(1,957) = 24.57$, $p < 0.001$
- GCA-PGS strongly predicted all six cognitive measures
 - $F = 14.57\text{--}50.96$.

Cognitive Measures

- General Cognitive Ability (GCA) and domain factor scores: executive function, visual-spatial ability, verbal fluency, episodic memory, and processing speed

RESULTS

Advantages of the MR-DoC2 Method

- MR-DoC2 combines twin-based Direction of Causation (DoC) modeling with Mendelian Randomization (MR).
- Extends traditional MR by accounting for unmeasured genetic and environmental confounding.
- Tests bidirectional causal effects while controlling for shared familial influences.

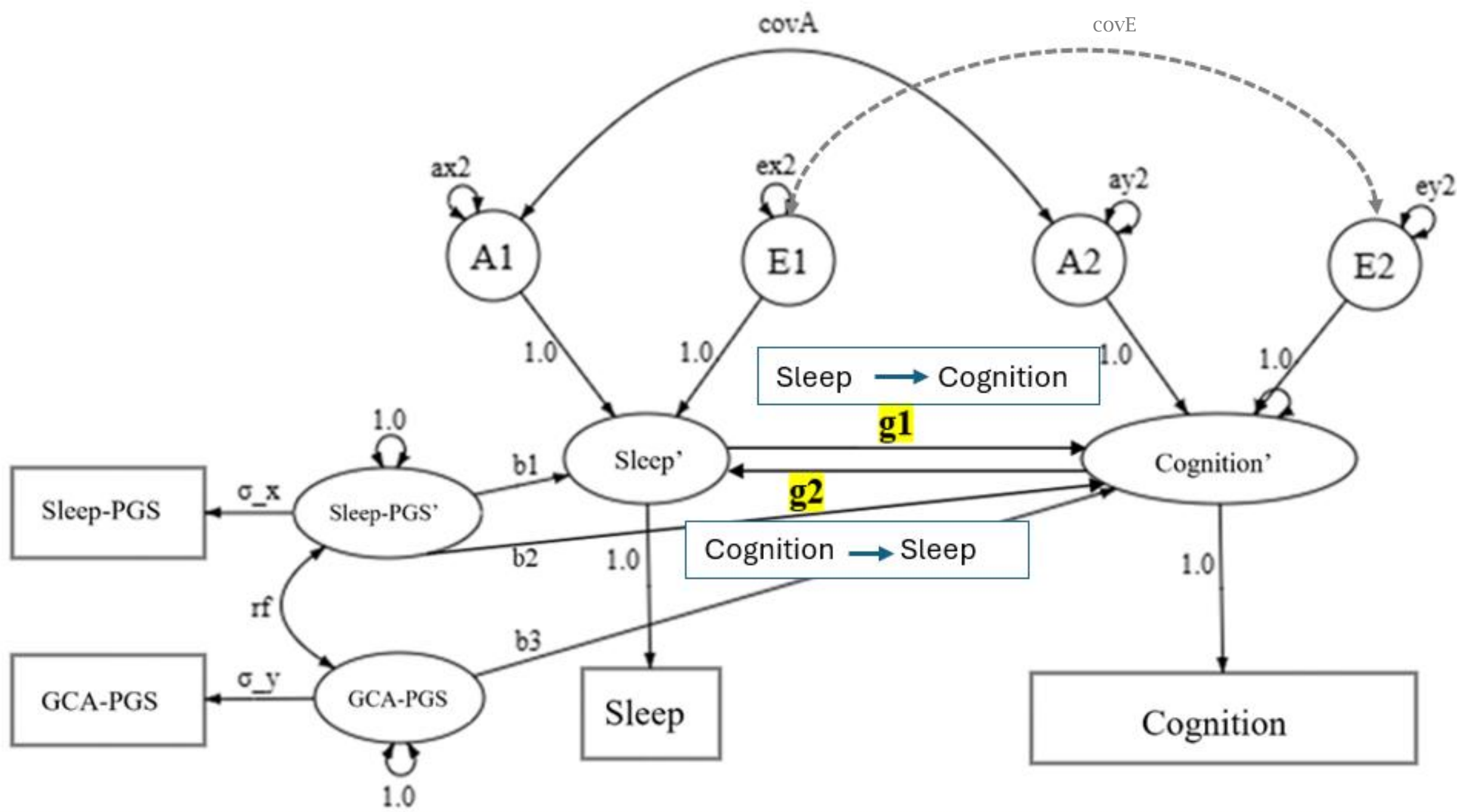


Figure 1. Conceptual MR-DoC2 Model

Table 1. Paths examined in MR-DoC2

Path	Description
Directed	
g1 (Sleep → cognition)	Causal pathway from sleep to cognition
g2 (Cognition → Sleep)	Causal pathway from cognition to sleep
b1	Effect of a sleep PGS on measured sleep phenotype
b2	Effect of a sleep PGS on cognition
b3	Effect of the GCA PGS on the measured cognitive phenotype
Undirected	
covA	Genetic covariance between sleep and cognition
covE	Nonshared environmental covariance between sleep & cognition
rf	Correlation between the PGSs

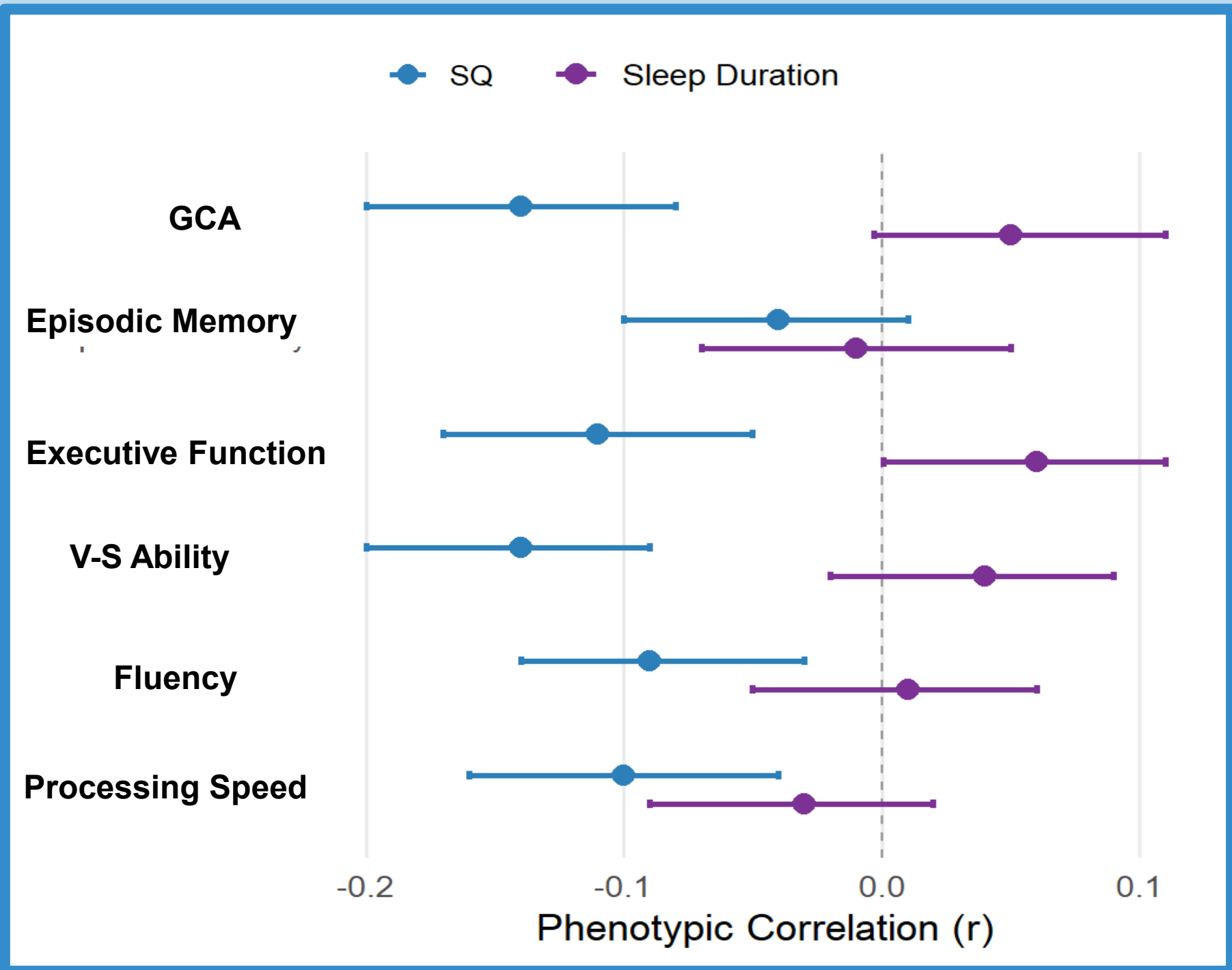


Figure 2. Sleep and Cognition Phenotypic Correlations

Table 2. Sleep → cognition parameter estimates from best-fitting models

Cognitive Measure	g1 (sleep → cognition)
GCA	-0.09 (0.04)*
Executive Function (Sleep Quality)	-0.09 (0.05)
Executive Function (Sleep Duration)	0.07 (0.04)
V-S Ability	-0.09 (0.03)*
Fluency	--
Processing Speed	-0.13 (0.04)*

Note. Except for fluency, the best-fitting models fixed the cognition → sleep path (g2) to zero, leaving the sleep → cognition path (g1) freely estimated

Evidence for bidirectional causal effects (SQ ↔ Cognition)

- Removing both the SQ → cognition path (g1) and cognition → SQ path (g2) significantly worsened model fits for SQ with:
 - GCA: $\chi^2(2) = 6.90$, $p = 0.03$
 - Visual-spatial ability: $\chi^2(2) = 7.50$, $p = 0.02$
 - Processing speed: $\chi^2(2) = 9.43$, $p = 0.01$
- Best-fitting models generally favored SQ → cognition** over cognition → SQ effects for:
 - GCA, visual-spatial ability, and processing speed.
 - Effect sizes were modest (SQ → cognition: $d \approx -0.18$ to -0.26 ; small effects)

CONCLUSION

- Modest, potentially bidirectional effects between sleep quality and cognition for GCA, visual-spatial ability, and processing speed.**
- No causal associations were observed between sleep duration and cognitive performance.**
- Sleep quality—rather than duration—may be a promising target for preserving cognitive functioning, as it is more amenable to intervention.**

