Sleep duration and cognition:

Application of linear and non-linear Mendelian randomization in UK Biobank

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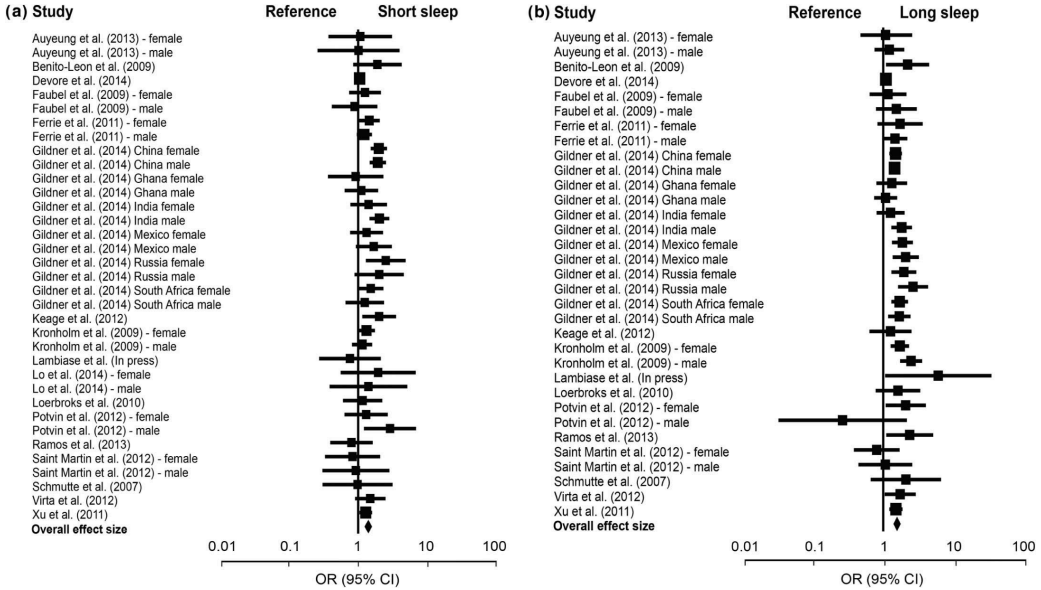
Short and long sleep duration have been associated with poorer cognition in observational studies



Lo JC, *et al.* (2016)

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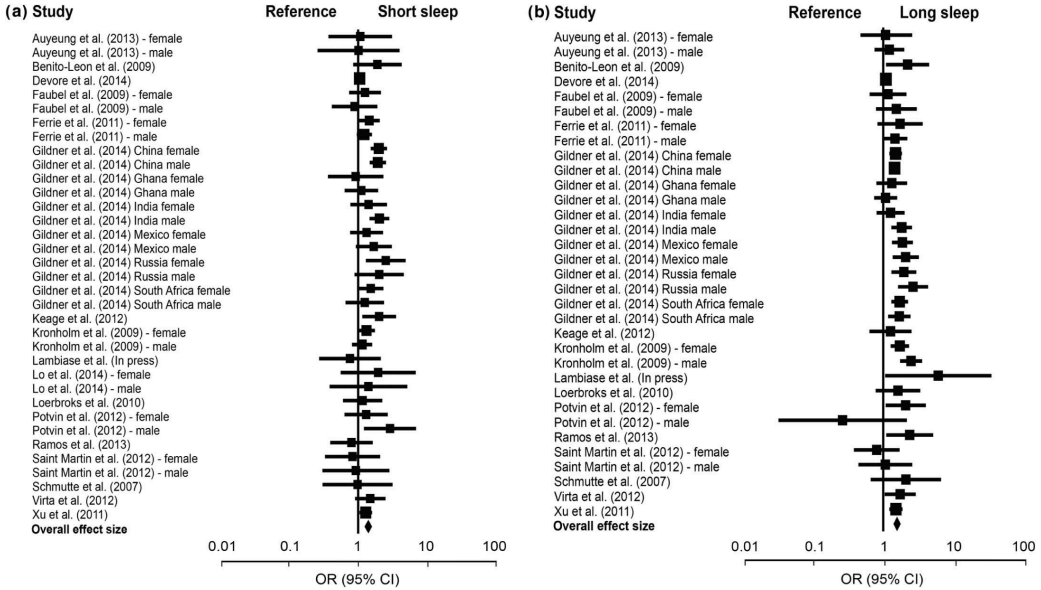

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Confounding factors?

Reverse causation?

Randomized trial is not practical

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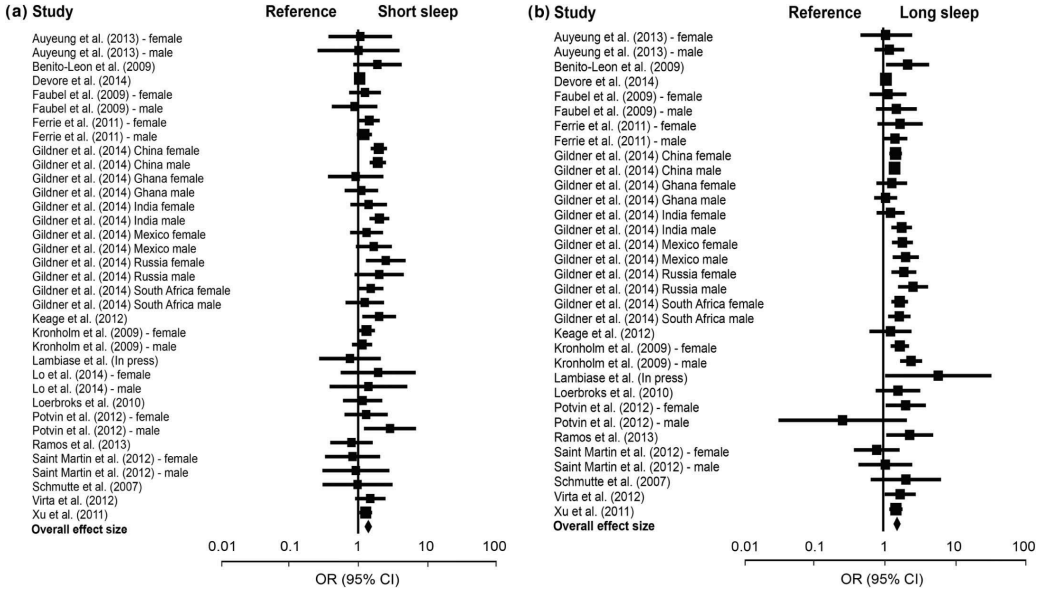

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Non-linear relationship?

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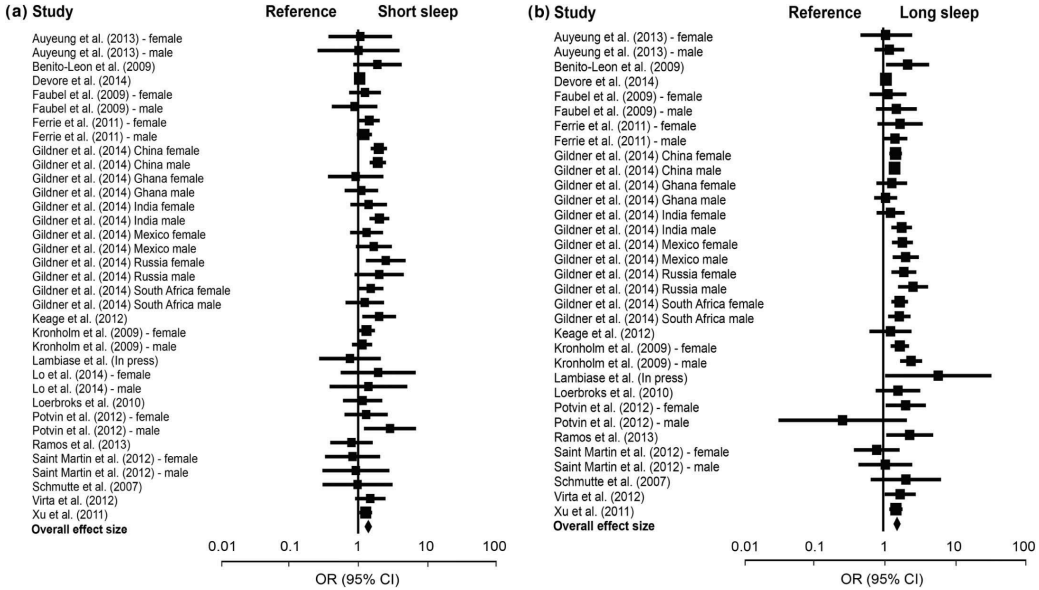

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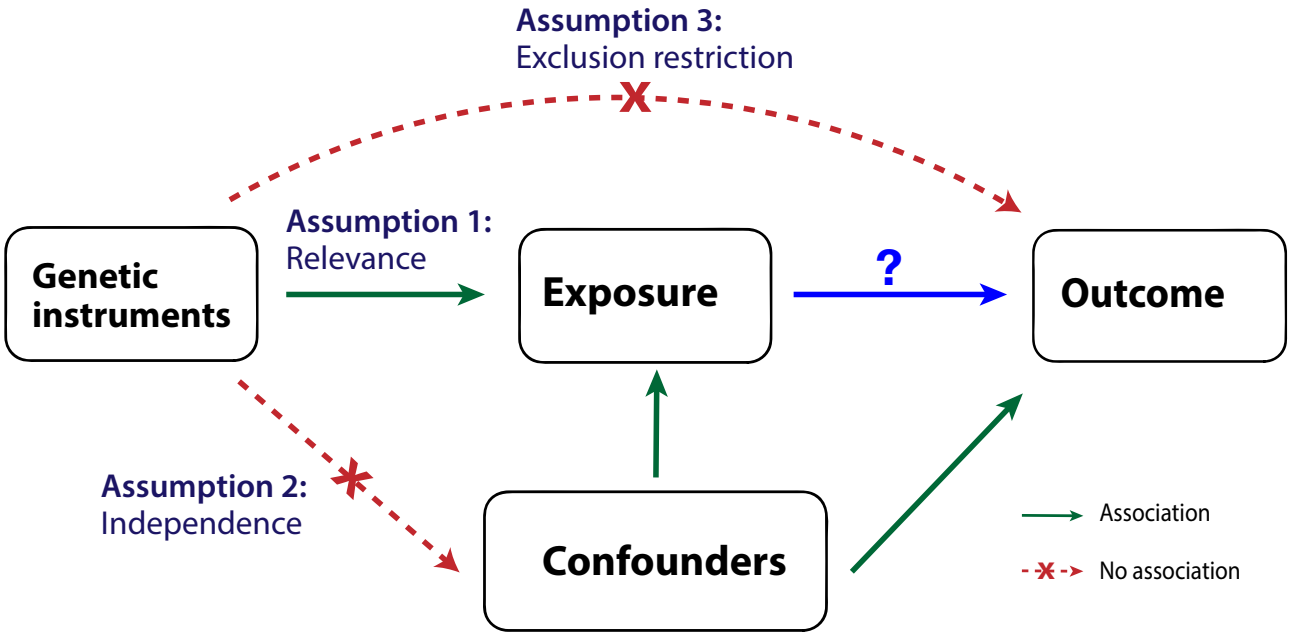
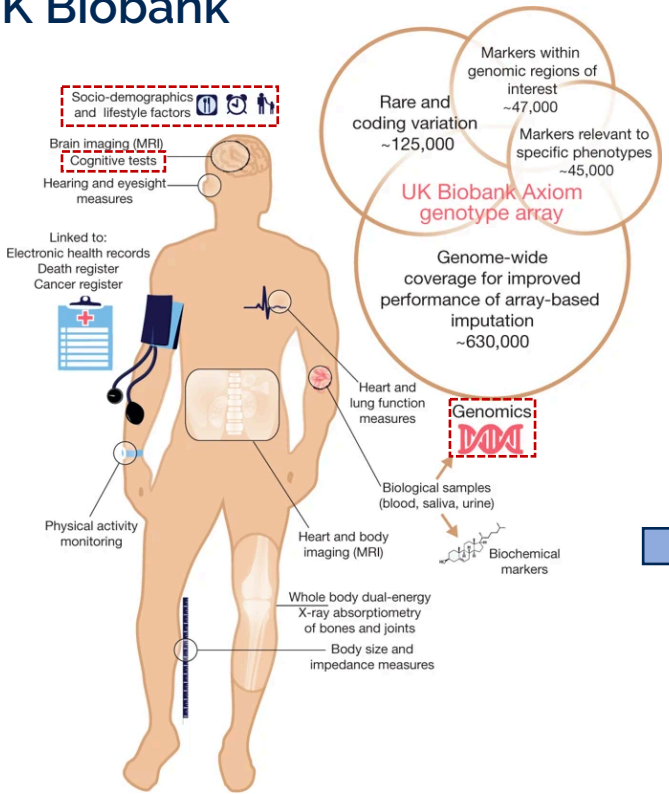
Can we answer with Mendelian randomization?

Mendelian randomization



Study design

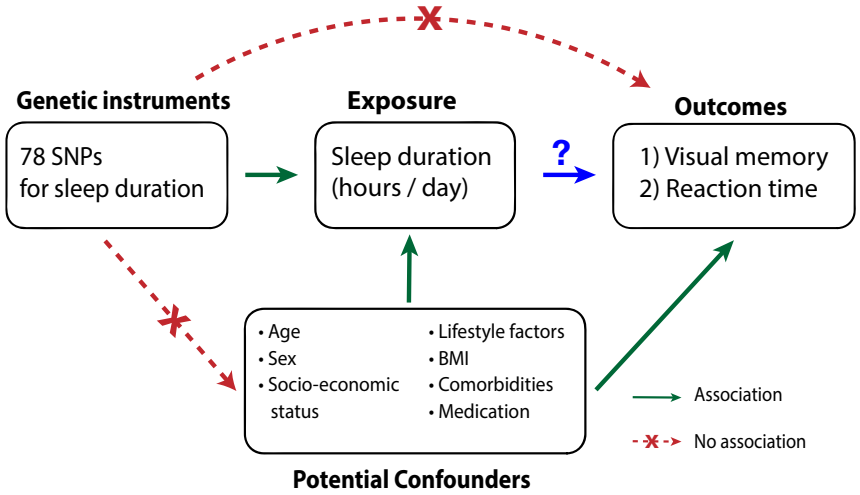
UK Biobank



Bycroft C, *et al.* (2018)

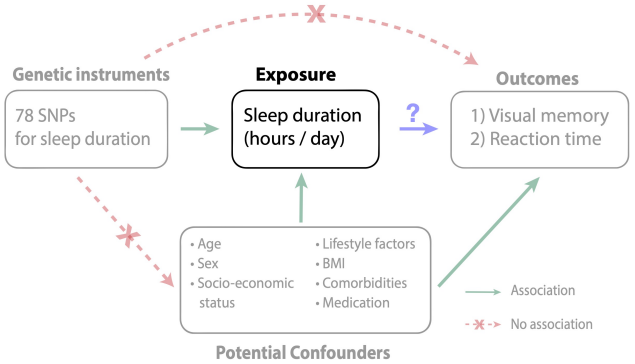
Present study:

- N = 395 803
- European ancestries
- Mean age = 56.9 ± 8 years
- 54% Female



Sleep duration

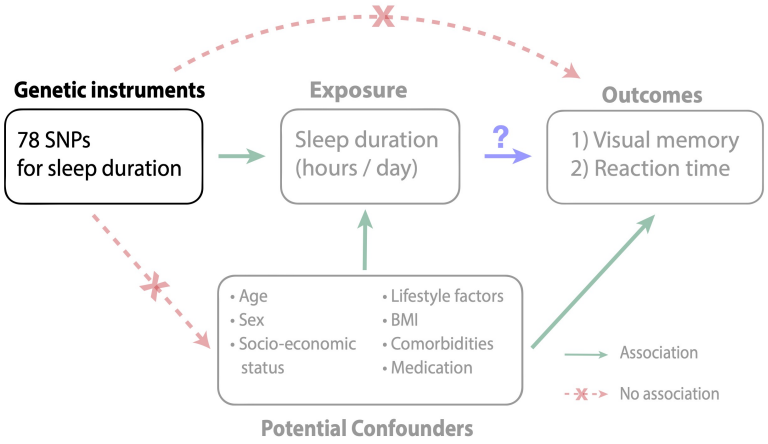
- Baseline self-reported average hours of sleep (including naps) in every 24 hours
- Excluding sleep duration <2 hrs/day and >12 hrs/day
- Avg. = 7.17 hrs/day (1.07 SD)

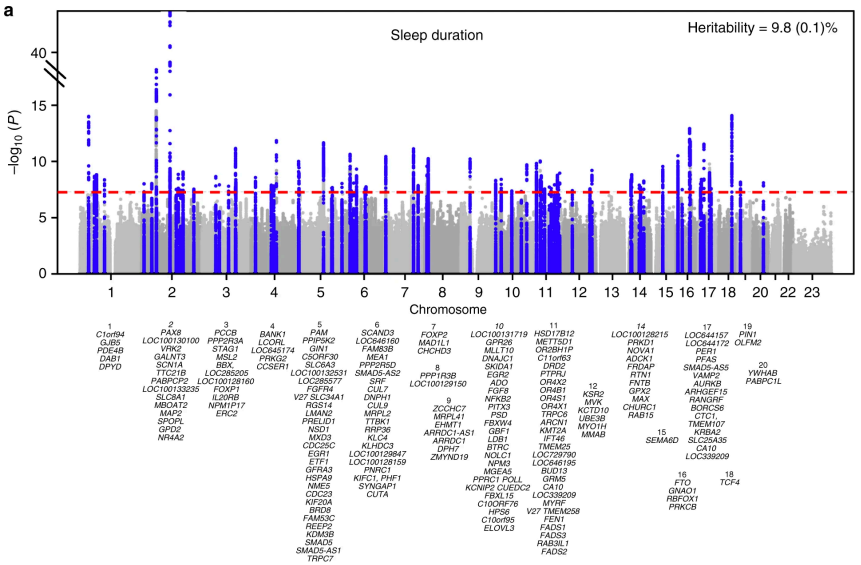


≤5 hrs/day	6 hrs/day	7 hrs/day	8 hrs/day	9 hrs/day	≥ 10 hrs/day
N **= 19 926**	***N*** **= 73 813**	***N*** **= 155 333**	***N*** **= 116 573**	***N*** **= 23 536**	***N*** **= 6622**
(5.0%)	**(18.7%)**	**(39.3%)**	**(29.5%)**	**(6.0%)**	**(1.7%)**

Genetic instruments

- 78 SNPs associated with self-reported sleep duration ($P < 5 \times 10^{-8}$)
- 0.69% variance explained
- Avg. effect per allele = 1.04 min (0.34 SD)
- *PAX8* has largest effect = 2.44 min (0.16 SE)





Dashti HS, *et al.* (2019)

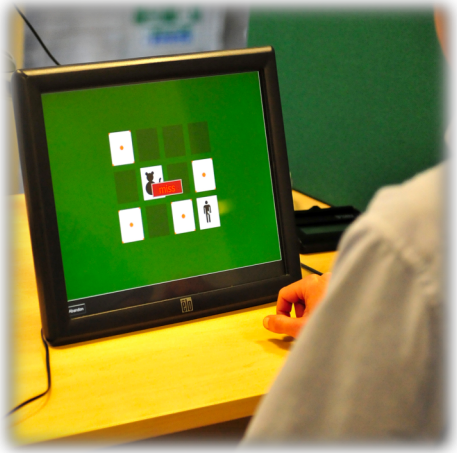
Outcomes

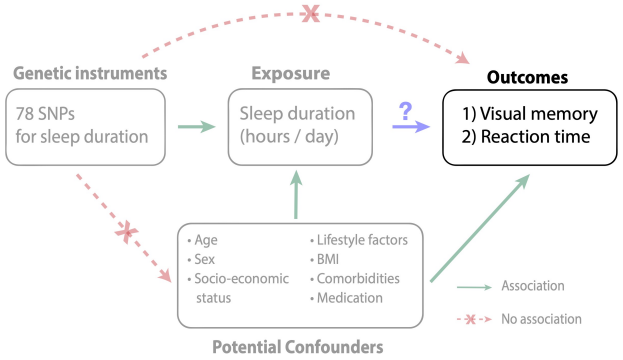
Visual memory

- Number of errors made in pairs-matching test
- **Higher value → poorer visual memory**

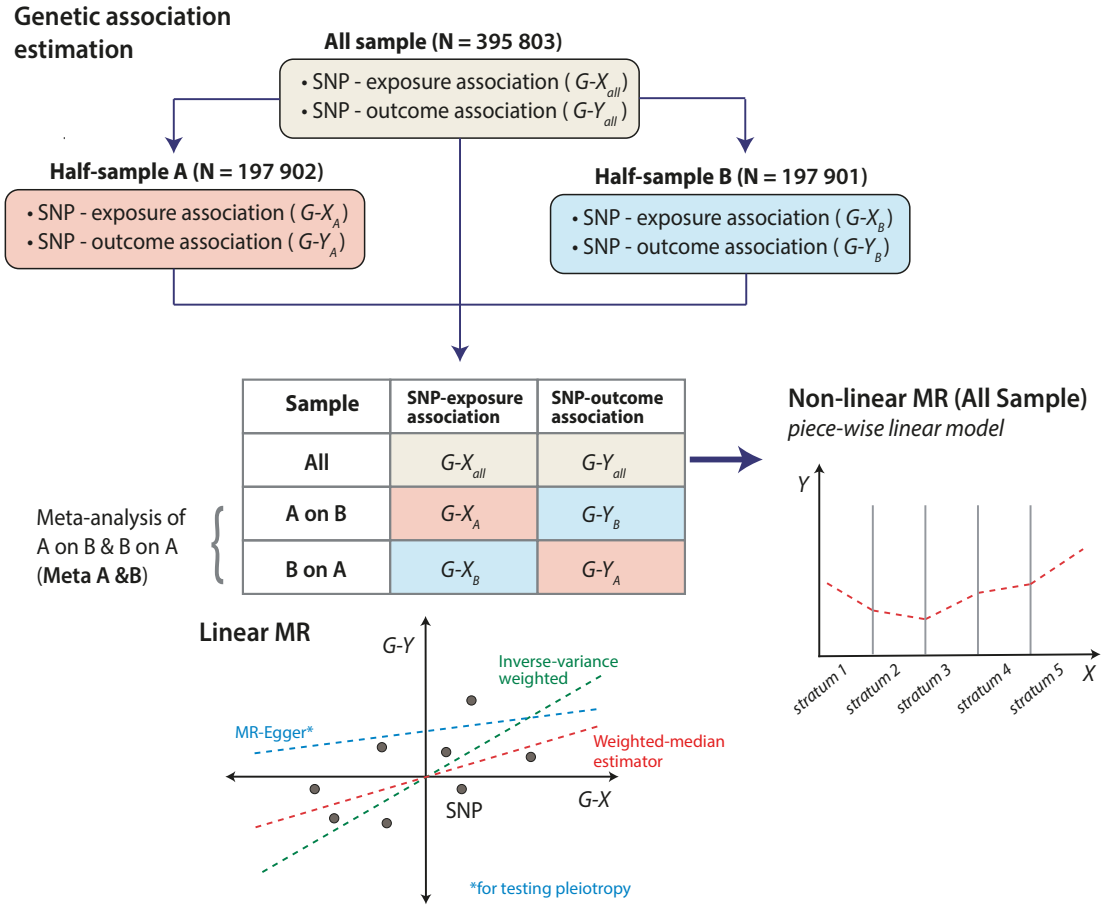
Reaction time

- Mean duration to first press of snap-button summed over rounds in which both cards matched
- **Higher value → poorer (slower) reaction time**

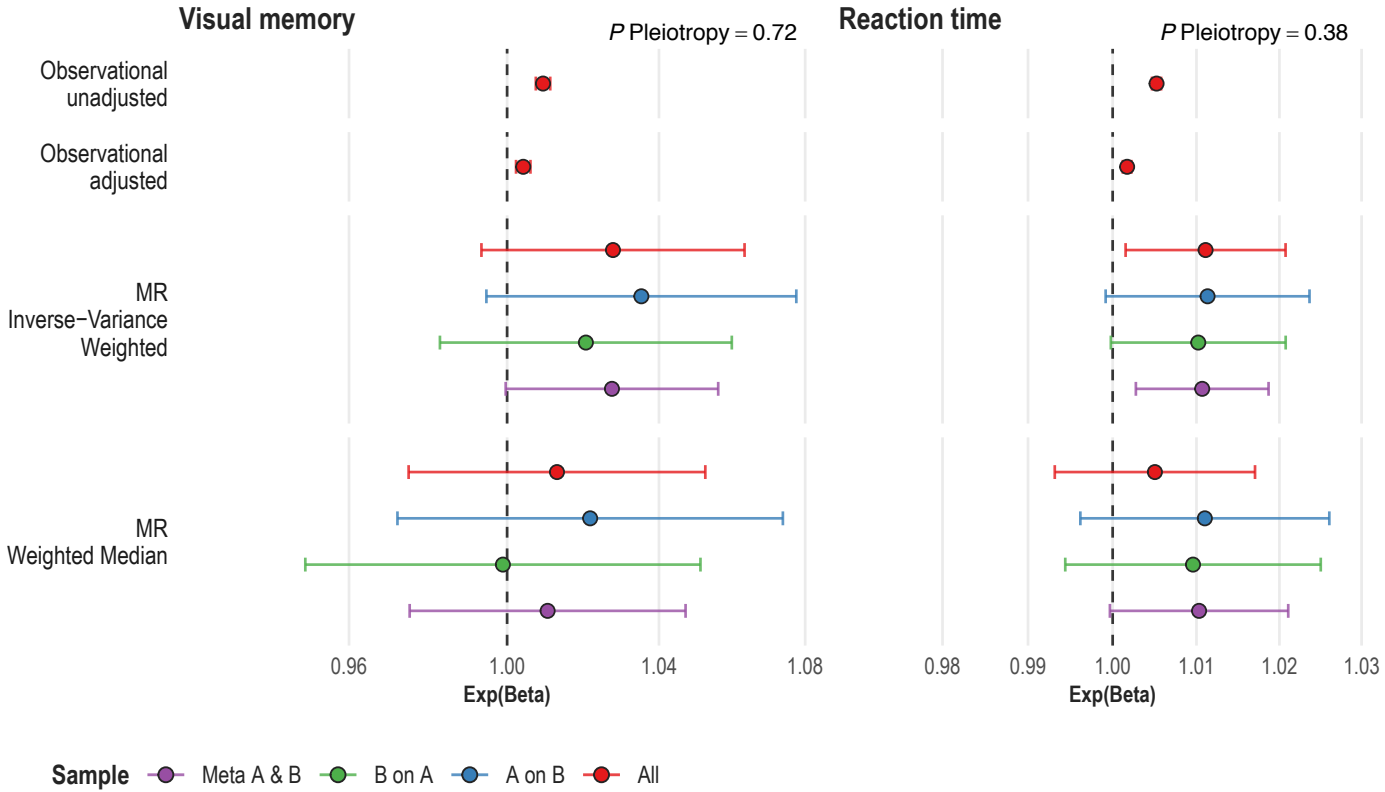




Study design: Linear and Non-linear MR



Results: Linear MR



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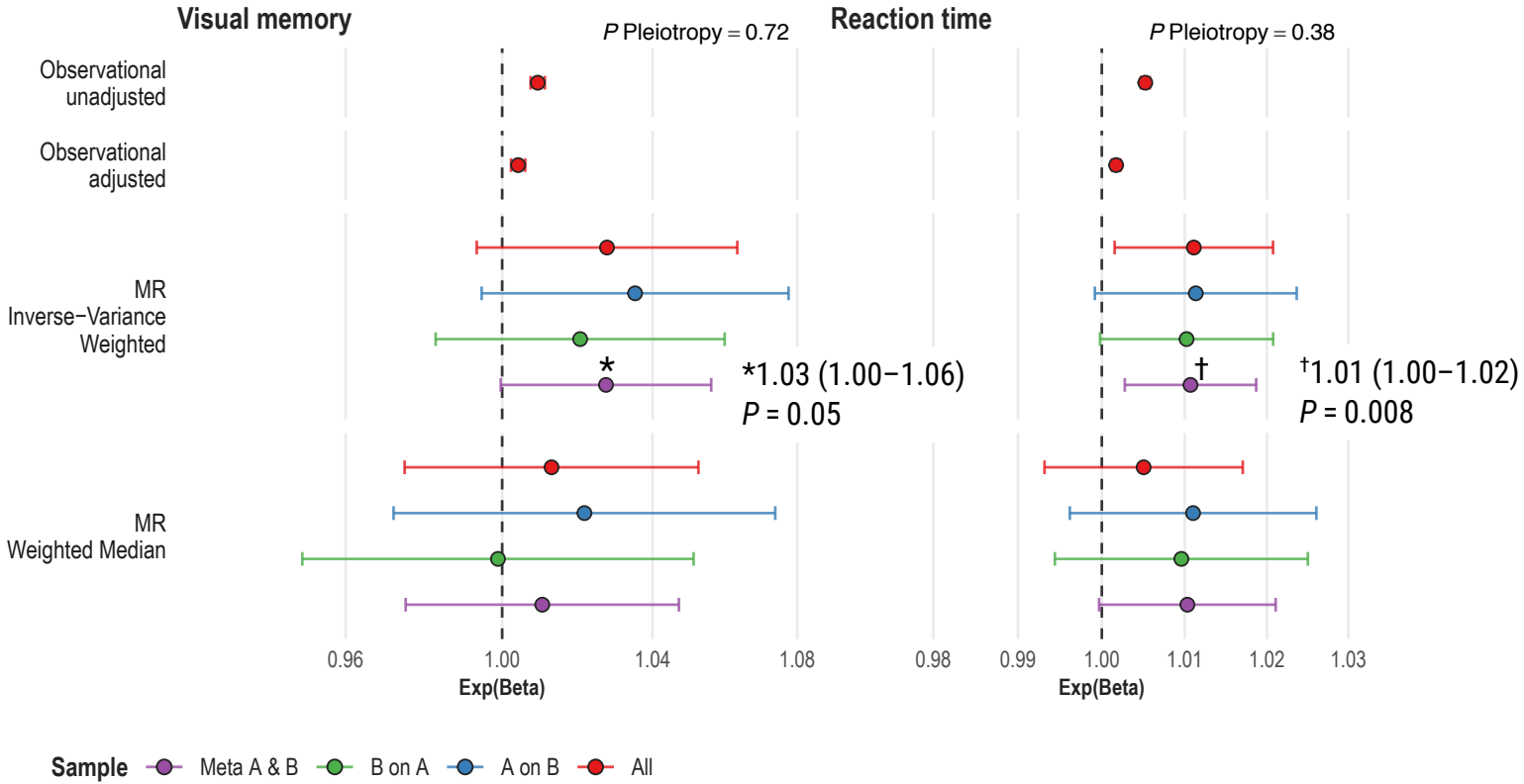

Non-linear MR with piecewise linear model

Staley JR, Burgess S. *Genet Epidemiol*. (2017)

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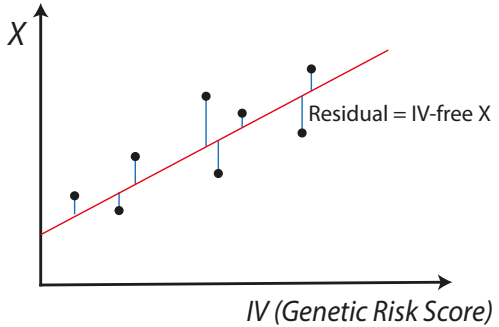
- Derive IV-free exposure



Non-linear MR with piecewise linear model

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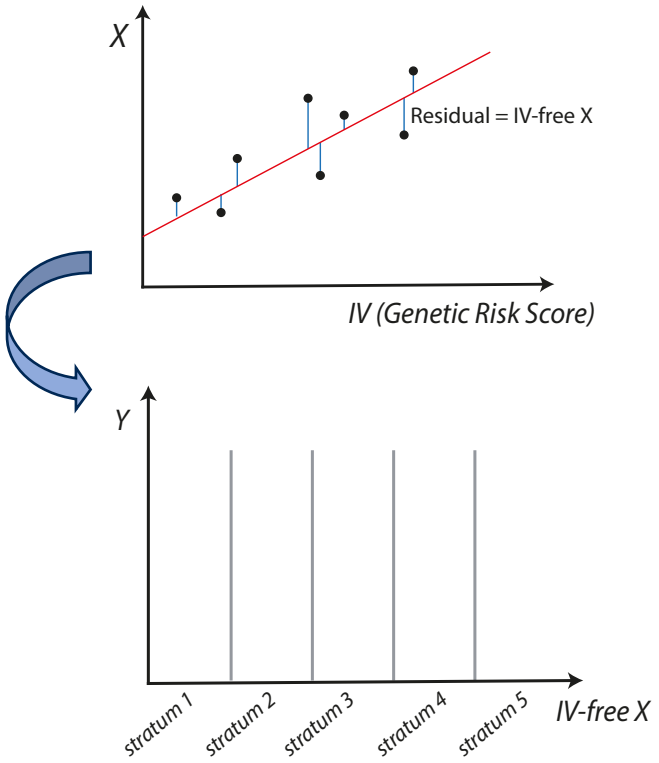
- Derive IV-free exposure
- Stratify on the IV-free exposure



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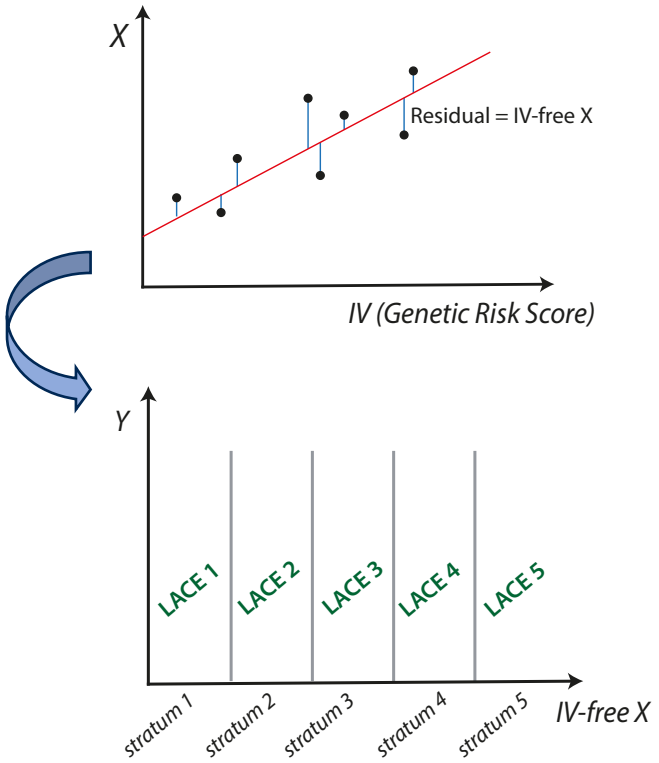
- Derive IV-free exposure
- Stratify on the IV-free exposure
- Estimate *localized average causal effect* (LACE) in each stratum

$$LACE = \frac{coef\ Y \sim IV_{stratum}}{coef\ X \sim IV}$$

- Test of non-linearity (*Cochran's Q* or quadratic)



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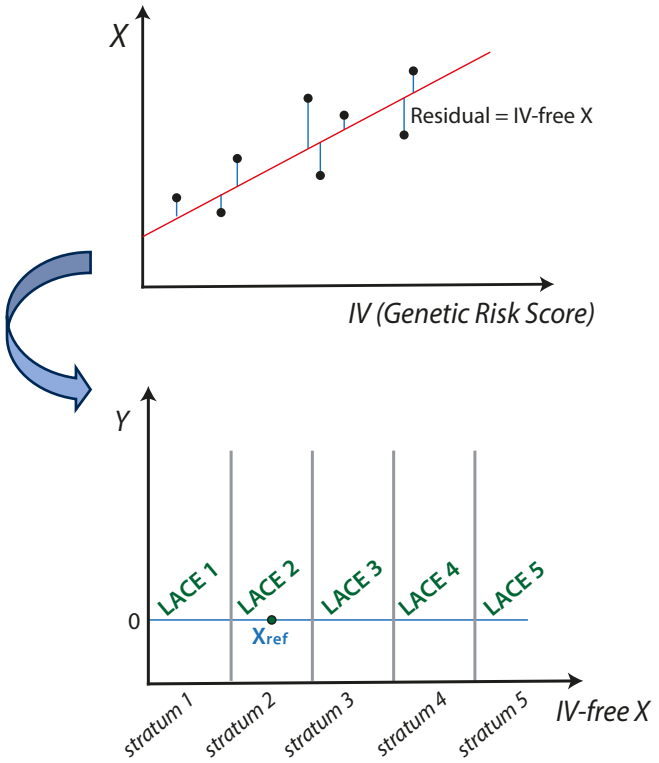

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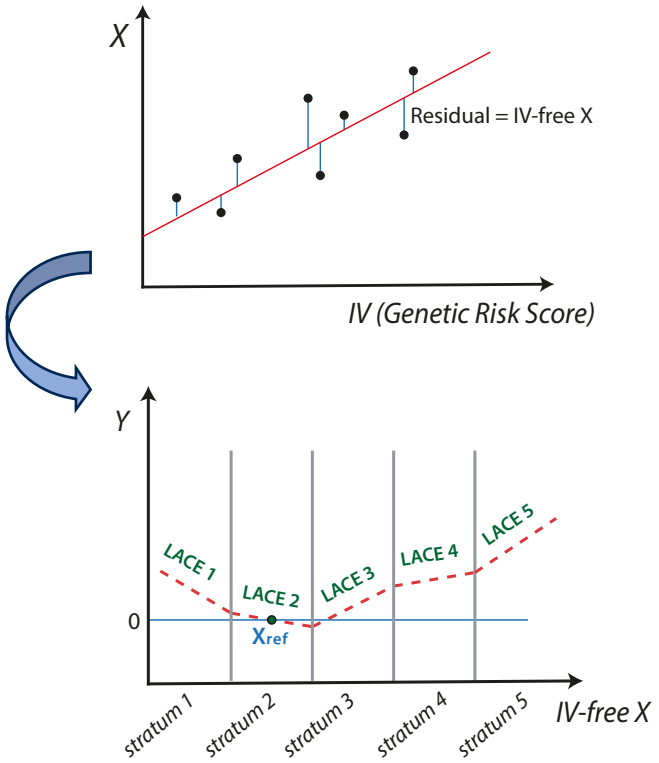
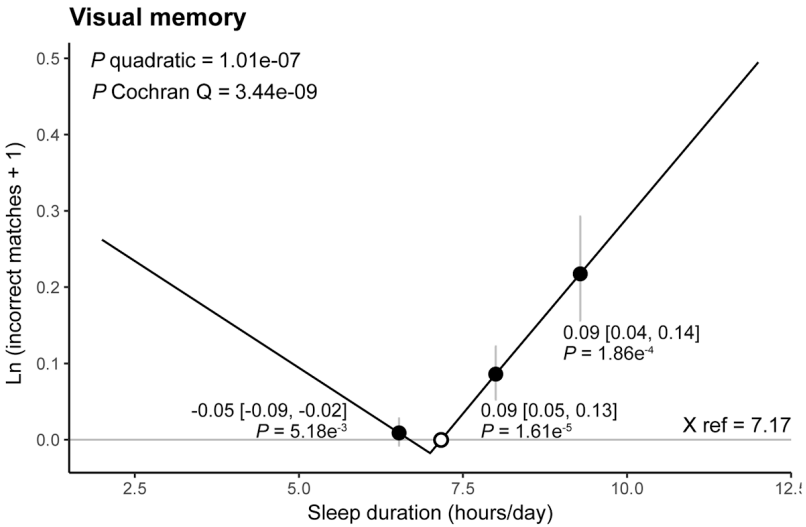
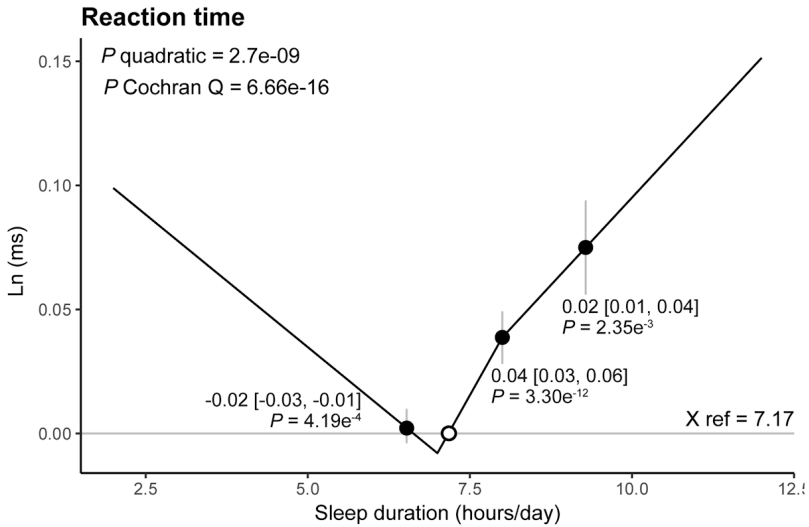
- Test of non-linearity (*Cochran's Q* or quadratic)
- Set overall intercept as a reference point, e.g. at *Mean X*
- Fit semiparametric piecewise linear model



Results: Non-linear MR

Piecewise linear model with 3 strata





<~7 hrs/day: 5% poorer visual memory
>~9 hrs/day: 9% poorer visual memory

<~7 and >~9 hrs/day:
2% slower reaction time

Limitation of piecewise linear model

- Three strata is not ideal
- It is not possible to fit the model on a discrete exposure with a few distinct values
- *Workaround*:

  Add a small random noise to de-discretise sleep duration and re-run the analysis with 10 strata

  ….

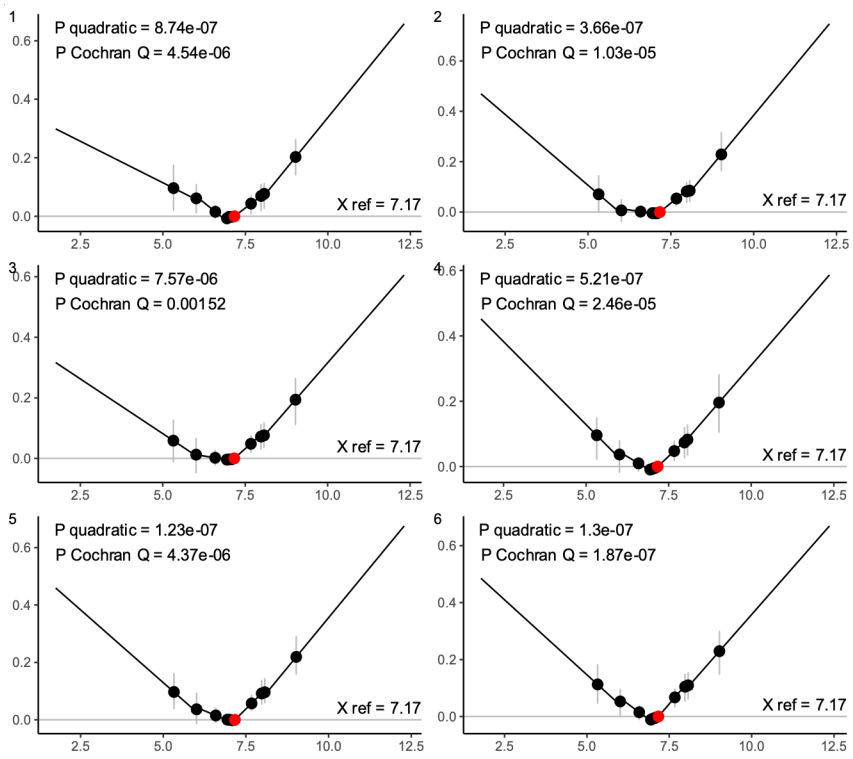
  Repeat 10 times

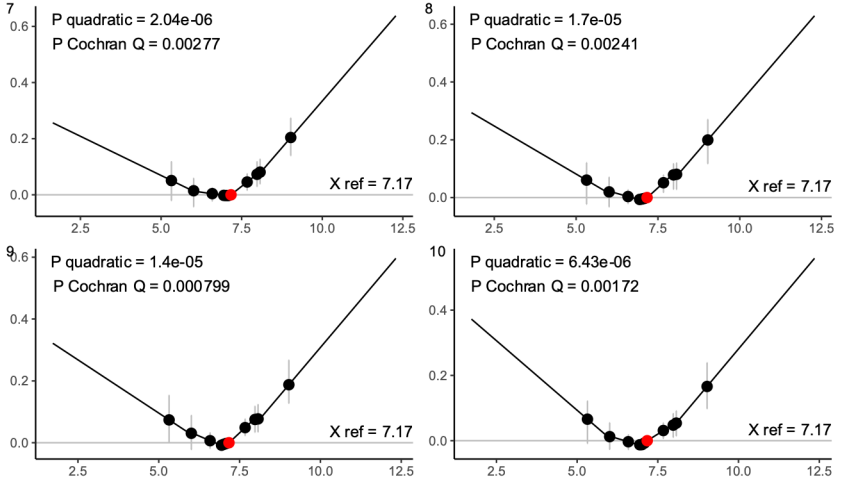
Participant	Sleep duration (hrs/day)	X1	X2	X3	…	X10
1	7	6.99	7.05	6.94		6.97
2	6	6.10	5.90	6.03		6.00
3	8	8.02	7.94	7.93		8.01
4	7	6.97	7.06	7.07		6.92
…						
395 803	9	9.02	9.05	9.03		9.09

Fit piecewise linear MR model with 10 strata in each of the 10 de-discretised X values

Results: Visual memory

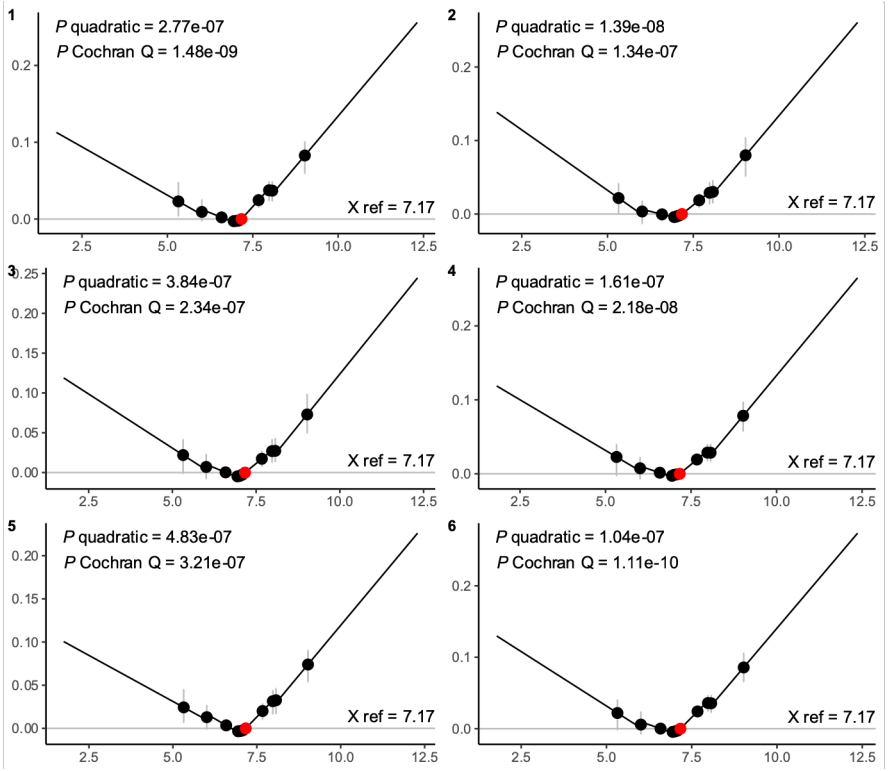
Non-Linear MR with 10 strata + de-discretised sleep duration

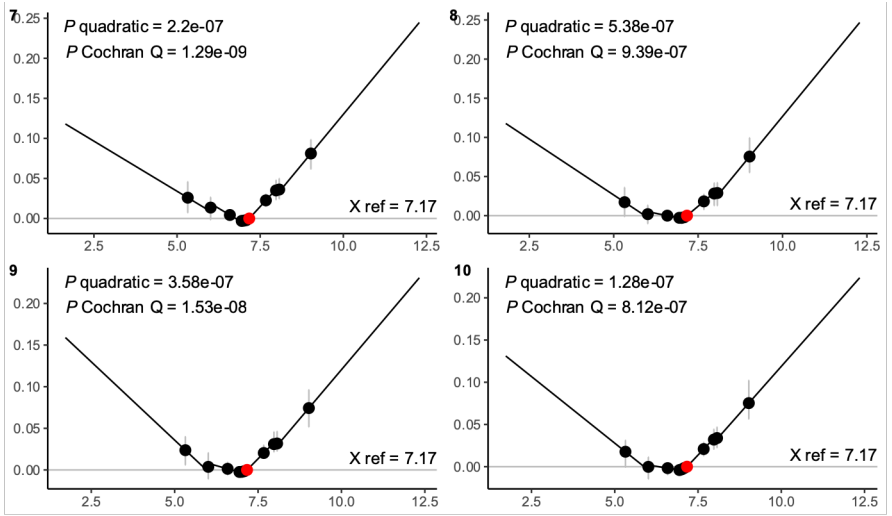




Results: Reaction time

Non-Linear MR with 10 strata + de-discretised sleep duration





Summary

- Observational and MR analysis results are consistent
- A linear increase in sleep duration is associated with poorer reaction time and visual memory with small effect size
- Non-linear (J-shaped) association is likely, hence the small linear effect size
- Improving sleep habits within the general population might be useful as a potential therapeutic target to improve cognition

For curious minds …

The relationship between sleep duration, cognition and dementia: a Mendelian randomization study

Albert Henry, Michail Katsoulis, Stefano Masi, Ghazaleh Fatemifar, Spiros Denaxas, Dionisio Acosta, Victoria Garfield, Caroline E Dale Author Notes

International Journal of Epidemiology, Volume 48, Issue 3, June 2019, Pages 849–860, https://doi.org/10.1093/ije/dyz071

SCAN ME!

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