

Investigating causal relationships between sleep phenotypes and metabolites: a two-sample Mendelian randomization study

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Background

- Insomnia, short sleep duration and having a preference for evenings (rather than mornings) have all been associated with a wide-range of health outcomes including adverse cardiometabolic health, some cancers and mental ill health; MR suggests causal effects for some of these
- Effects of sleep patterns of multiple metabolic paths may underly these
- Our aim was to determine the causal effect of insomnia, sleep duration and chronotype on metabolic traits.

Methods

- We used two-sample MR, using summary data from the following genome wide association studies (GWAS):
 - Exposures (sample 1)
 - ❖ Insomnia (comparing any symptoms to none) [1]
 - ❖ Sleep duration (in 1 hour units) [2]
 - ❖ Chronotype (comparing morning to evening preference) [3]
 - Outcomes (sample 2)
 - ❖ 123 NMR assessed metabolic traits (mostly lipids/lipoproteins and fatty acids, with some glycolysis related traits, amino acids and ketone bodies (in standard deviation (SD) units) [4]
- We used inverse-variance weighted (IVW) for the main analyses and explored possible directional horizontal pleiotropy (violation of exclusion restriction assumption) using weighted medians (WM) and MR-Egger regression

Results

- Figure 1 shows the IVW results for each of the three exposures with all outcomes, using the novel visualisation tool 'MR-Viz' [5]
- Of 369 associations assessed there was some evidence (based on a p-value <0.05) of a possible causal effect for 29. These suggest:
 - ❖ Inverse effects of insomnia symptoms on medium and large HDL (sections 18 and 14, respectively)
 - ❖ Positive effects of morning preference on small LDL (section 24) and several fatty acids (section 7)
 - ❖ Positive effects of longer sleep duration on very large VLDL (section 27)
- IVW effect estimates for these were consistent with those from sensitivity analyses using WM and MR-Egger (Figure 2 (a)-(c)).

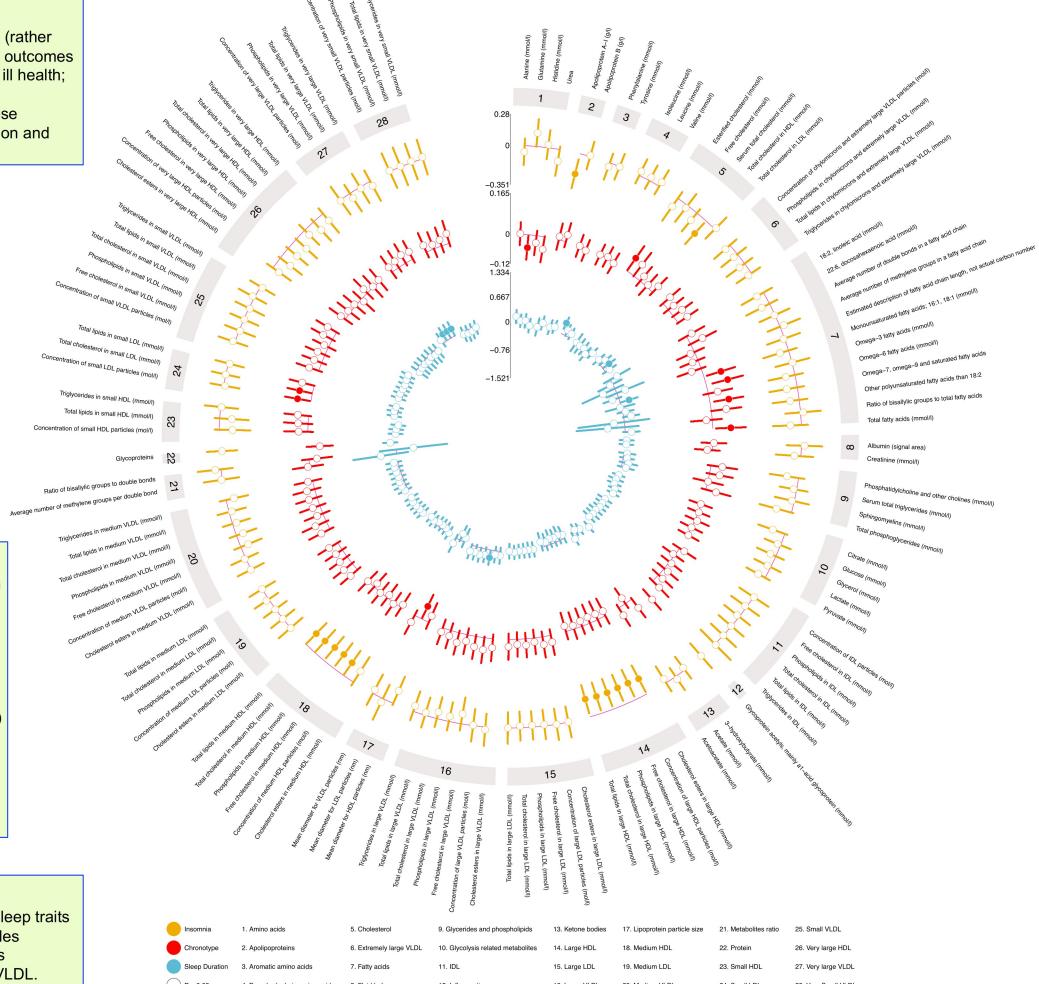


Figure 1. Circos plot: Mendelian randomization analysis results using an IVW model of three exposures (insomnia, chronotype and sleep duration) and 123 NMR derived metabolites, with 95% confidence interval (CI). Units: 1-SD increase in exposure (i.e. between those with and without insomnia, between morning and evening person and per hour of sleep duration) per SD increase in mean metabolite concentrations.

Conclusions

- These findings do not suggest widespread metabolic disruption by sleep traits
- Insomnia symptoms lead to lower levels of cholesterol in HDL particles
- For morning preference there is a shift towards smaller LDL particles
- The longer the sleep duration the worse the lipid profile in terms of VLDL.

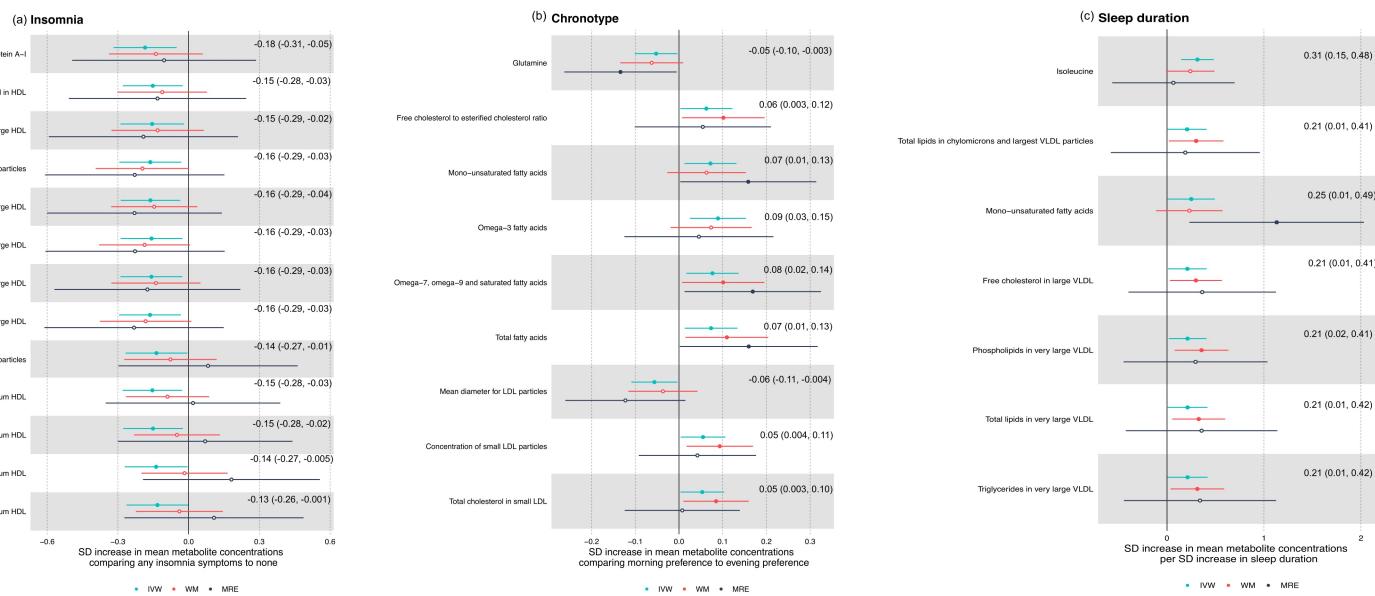


Figure 2. Forest plots of sensitivity analyses using WM and MR-Egger for each exposure (insomnia (a), chronotype (b) and sleep duration (c)), for where IVW p-value <0.05, with 95% CIs. IVW estimates (with 95% CIs) on right-hand side of each plot.

Reference list: [1] Lane, J. M. Biological and clinical insights from genetics of insomnia symptoms. *Nat. Genet.* 51, (2019). [2] Dashti, H. S. et al. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nat. Commun.* 10, 1100 (2019). [3] Jones, S. E. et al. Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. *Nat. Commun.* 10, 343 (2019). [4] Kettunen, J. et al. Genome-wide study for circulating metabolites identifies 62 loci and reveals novel systemic effects of LPA. *Nat. Commun.* 7, 11122 (2016). [5] <http://bristol-medical-stat.bristol.ac.uk:3838/MR-Viz/>