

Background: Sleep is a known key complex trait associated to metabolic, cardiovascular, musculoskeletal, neurological, and inflammatory diseases. However, it still remains unclear whether sleep duration causally contributes to disease pathways or simply reflects underlying health conditions across a broad spectrum of complex traits. Globally, short sleep duration affects nearly one-third of adults and contributes to the rising burden of chronic diseases. The UK Biobank (UKBB) offers extensive self-reported phenotypes, but such data are still underused in causal inference research. Notably, no Mendelian randomization (MR) study has systematically investigated whether self-reported sleep duration causally influences the wide spectrum of diseases that is self-reported in UKBB. To address this gap, we applied the TwoSampleMR framework using UKBB genetic data.

Methods: We conducted a bidirectional Two-sample Mendelian Randomization (2TSMR) analysis using the TwoSampleMR R package and GWAS summary statistics from the IEU OpenGWAS platform, which hosts harmonized UK Biobank (UKBB) datasets. For the bidirectional design, genetic instruments for self-reported sleep duration were selected from UKBB GWAS ($p < 5 \times 10^{-8}$, $r^2 < 0.001$, $F > 10$), while 57 self-reported complex diseases across nine categories served as outcomes in forward MR and as exposures in reverse MR. Forward MR tested whether sleep duration influenced disease risk, and reverse MR evaluated whether diseases affected sleep duration. Causal estimates were generated using inverse-variance weighted (IVW) MR, with MR-Egger, weighted median, weighted mode, and RAPS for robustness. Sensitivity analyses included Cochran's Q for heterogeneity, MR-Egger intercept for pleiotropy, leave-one-out assessments, and single-SNP MR. Statistical significance was set at $p < 0.05$ (0.05–0.10 considered suggestive).

Results: Forward MR showed that longer sleep duration had significant protective effects against type 2 diabetes (OR=0.995, $p=0.034$), stroke (OR=0.993, $p=0.017$), osteoarthritis (OR=0.962, $p<0.001$), back problems (OR=0.991, $p=0.018$), and asthma (OR=0.976, $p=0.018$). Suggestive associations were observed for osteopenia (OR=0.997, $p=0.093$) and angina (OR=0.990, $p=0.068$). No forward causal effects were detected for thyroid, neurological/psychiatric, gastrointestinal, autoimmune, or reproductive traits. Reverse MR identified disease-to-sleep effects, where several conditions shortened sleep duration, including thyroid problems (OR=0.082, $p=0.034$), gout (OR=0.664, $p=0.021$), hypertension (OR=0.192, $p=0.041$), malabsorption/coeliac disease (OR=0.520, $p<0.001$), pancreatitis (OR=0.158, $p=0.025$), rectal/colon polyps (OR=0.221, $p=0.037$), and gastric ulcers (OR=13.317, $p=0.001$). Several associations replicated previous MR findings (e.g., type 2 diabetes, gout, thyroid dysfunction, skeletal traits), while multiple outcomes, including coeliac disease, chronic sinusitis, rheumatic fever, Meniere's disease, vestibular disorders, uterine prolapse, bladder problems, ovarian cysts, benign breast lumps, diverticular disease, and eye/eyelid disorders, represent novel causal links. Sensitivity analyses showed minimal pleiotropy and acceptable heterogeneity.

Conclusion: Using large-scale UKBB self-reported phenotype data, we showed that longer sleep duration causally protects against several major chronic diseases, while multiple metabolic, endocrine, and gastrointestinal conditions significantly reduce sleep. We also identified several novel causal associations, including coeliac disease, vestibular disorders, and urogenital traits. Overall, sleep duration emerges as both a modifiable protective factor and a sensitive marker of disease burden, highlighting the value of UKBB data.