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To

The Editor
Dr. Rona Strawbridge

Special Issue "Genetic Studies of Mood Disorders and Comorbidities"

Dear Editor,

Please find with this letter our attached manuscript, entitled "A causal web between chronotype and metabolic health traits" in response to the call for the special issue, "Genetic Studies of Mood Disorders and Comorbidities."

In this article, we exploited GWAS study statistics and MR analyses related to chronotype in an effort to identify causal relationships between exposure to chronotype and several cardiometabolic and mental health related traits. Circadian processes are known to impact susceptibility to psychiatric disorders from bipolar to depression, as well as impact risk for diabetes and other metabolic outcomes. Using existing MR repositories, we identified 10 significant chronotype – mental/metabolic associations that, on re-analysis, hold up to multiple testing. These were influenced by 111 potential confounders, 52 intermediates, 18 reverse intermediates, and 31 colliders. These influences affect the relationship between chronotype and commonly reported cardiometabolic traits. Additionally, we have observed potential relationships between chronotype and one cardiac medication, and found a potential mediator between chronotype and bipolar disorder. Our findings could form the basis for combinations of multivariate and multi-stage analyses for further exploratory analysis, including mechanistic studies.

We believe that our work would be of relevance and value to the Genes audience as well as to the wider biomedical community offering a systematic approach to explore causal relationships between exposure to chronotype and several cardiometabolic and mental health related traits

We can confirm that this submitted manuscript is not under review at any other publication, nor has it been the subject of other previously published manuscripts.

We look forward to hearing from you and hope that you find our article of interest.

With kindest regards

John Williams (On behalf of other authors)

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