Sleep and circadian regulation of cardiometabolic disease

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Project outline

Sleep deprivation is associated with poor general health, and cardiometabolic diseases (obesity and hypertension)[1]. Even acute circadian misalignment, such as the annual transition to Daylight Saving Time in the USA, significantly increases the risk of myocardial infarction over the following three days[2] and a single night of sleep-deprivation or jet lag impairs glucose tolerance by 40%[3]. Two-sample Mendelian randomisation provides insight into the causative role of sleep disturbance, increasing cardiovascular disease, and type 2 diabetes mellitus, among others[4]. In addition, behavioural sleep extension studies in obese adults drives reduction in blood pressure, markers of metabolic health, and energy intake[5].

Chronotype refers to an individual's tendency to be active earlier or later in the day, and there are known interactions between morningness/ eveningness and the risk of cardiometabolic disease or susceptibility to the adverse metabolic effects of circadian misalignment. In current work to understand the mechanistic drivers of chronotype in the human brain we prioritised non-coding SNPs highlighted in chronotype Genome-Wide Association Studies (GWAS). We then used high-resolution chromatin capture to find genes regulated by these putative enhancers. This approach has highlighted over 100 candidate genes, including MAPT, which is associated with Alzheimer's disease, and CRHR1, a GPCR that is part of the HPA axis and linked to stress-mediation and obesity. Most interestingly, the mRNA translation machinery has been implicated multiple contacts to tRNA genes, and genes encoding tRNA processing and ribosomal proteins. This identifies an entirely new biological substrate for chronotype, and associated cardiometabolic disease. We now want to exploit this new understanding to find new approaches for cardiometabolic disease management, prevention, patient stratification, precision medicine, and biomarker development

Project Plan
We will use **UK Biobank data** to explore links between evening light exposure, accelerometer-derived phenotypes, such as chronotype, and cardiometabolic function. We will use this data to investigate genetic associations with susceptibility to circadian disruption and metabolic disorders and to understand the mechanisms explaining the cardioprotective effects of certain chronotypes. We will then use a **human experimental medicine approach using state of the art wearable light monitors** (Condor ActLumus) in people with pre-diabetes, recruited from Oxfordshire primary care networks, with specific lighting interventions to reduce evening light exposure and improve circadian health versus control (Brown et al., 2022), monitoring both circadian/sleep parameters and cardiometabolic

health (blood pressure, heart rate, continuous blood glucose monitoring, serum lipidomics, and BMI). We will also investigate how an individual's chronotype impacts the effectiveness of these interventions.

To understand how candidate genes identified from our chromatin capture experiment drive circadian and cardiometabolic phenotypes, we will **conduct recall by genotype studies on individuals that are homozygous for null variants of candidate genes using the Oxford Biobank**, a resource to which we already have data access. We have already identified OBB people carrying such alleles, and found them to have raised CRP, and serum lipidomic marker changes. Their chronotype will be profiled in depth using the Munich Chronotype Questionnaire (MCQ) and further reproducible device-based measurements from wearables will be used complement and enhance this measurement. Metabolomics, and lipidomics will be conducted to assess how chronotype impacts cardiometabolic markers.

We will further investigate the how perturbation of the mRNA translational system impacts energy metabolism we will use human liver cell assays. Here, we will genome edit the enhancers, or use CRISPR i/a to affect target genes expression. We will include enhancers identified to regulate tRNA expression.

We will interrogate data held by NN on the use of GLP1 mimetics in diabetes and obesity, to identify if genetic risk scores for sleep and circadian phenotypes affect responses. We anticipate convergence between the GLP1 regulated brain networks, and those underpinning sleep/circadian function. In this way we anticipate that responses will vary by circadian phenotype, and indeed the use of the GLP1 mimetics may affect quality of life by directly regulating rhythmic human behaviour. We can pursue this further using wearable devices in patient groups, although this is likely beyond the scope of this fellowship.

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Prof David Ray

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