



Application number/Title: 29819 - Mental health risk factors and outcomes: elucidating reciprocal causal relationships

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Keywords provided by the Applicant PI to describe the research project:
brain, causality, genetics, mental-health, risk, substance

Application Lay Summary:

Health Conditions: The project will focus on mental health, including substance use and related outcomes (e.g. hospital self-harm records).

Aim: The aetiology of mental health can be characterised as a network of reciprocal relationships between (i) distinct mental health phenotypes (e.g. depression, substance abuse, and self-harm) and (ii) multiple risk factors (e.g. education, brain structure). Recent advances in genetic epidemiology enable stronger causal inference in observational studies. Building on these techniques, the project will aim to map out the network of causal relationships between those diverse mental health-related phenotypes and multiple relevant risk factors. **Implications:** Establishing the directionality, effect size, and causal status of reciprocal relationships between different mental health phenotypes and between those phenotypes and relevant risk factors, will provide useful information to clinicians for risk assessment. In addition, it will provide new insights to design more targeted public health interventions.

Suitability of the UK Biobank. The project will require assessments of relevant mental health outcomes and risk factors, genome-wide data, and brain structure data. In addition, the methods that will be implemented require a very large sample. Therefore, the UK Biobank matches perfectly the project's requirements. The present project will study the reciprocal relationships between mental health phenotypes (e.g. depression to self-harm) as well as the relationships between those phenotypes and a variety of risk factors. The research will first focus on predefined relationships of interest (examples in methodology). Building on this first step, we will then examine multiple risk factors and mental health outcomes

simultaneously, mapping out the network of their reciprocal relationships.

The methods, described below, are familiar to the PI and collaborators and required analyses will be run on a cluster at the host institution, which already hosts UK Biobank data. Full cohort