Project Details	
Project Code	MRCNMH25Br Khandaker
Title	Examining risk factors for cognitive dysfunction in serious mental illness
Research Theme	Neuroscience & Mental Health
Summary	Cognitive problems (e.g., impaired memory/attention) are a core yet often overlooked feature of serious mental illness (SMI). Currently, little is known about what contributes to the development of these problems and who is most at risk of experiencing them. Using patient- and population-based data, this PhD would examine genetic and non-genetic risk factors for cognitive problems in psychosis and depression. This work would provide valuable insights into the underlying mechanisms of cognitive dysfunction and could drive the development of new treatments for patients. Training gained in data science, multi-omics, causal inference, and risk prediction would help future career in academia/industry.
Description	**Background** Cognitive dysfunction (e.g., problems with memory and attention) is an integral part of psychosis, depression, and other serious mental illness (SMI). Current treatments for cognitive dysfunction are largely inexistent, making it an unmet clinical need. However, little is known about what contributes to the development of these problems. Understanding the bio-psycho-social mechanisms contributing to the development and maintenance of cognitive problems is critical for the development of novel effective treatments. **Aims** The aim of this PhD is to advance our understanding of the aetiology of cognitive dysfunction in SMI to help inform the development of effective treatments in the future. Specific Objectives and Methods This PhD would provide an excellent opportunity to develop skills in data science (especially, multi-omics and causal inference), and to apply these skills to patient- and population-based datasets for addressing clinically important questions. Datasets required for this PhD are already available or in development and would not require new data collection by the PhD student. With regards to specific studies to be carried out, below we provide an outline of proposed studies. However, the supervisors anticipate that these ideas would be developed further and finalised in collaboration with the student. 1) Examining genetic and non-genetic risk factors for cognitive problems in people with psychosis and depression: Using existing data from large cohorts (e.g., UK Biobank) and patient samples, this study would examine the associations of known risk factors for depression and psychosis with cognitive function in people with these conditions. Risk factors would include biological, psychological, and social factors such as sociodemographic factors, developmental factors (e.g., early-life trauma/adversity), blood immunological and metabolic biomarkers, and genetic predisposition for schizophrenia and major depressive disorder. Cognitive outcomes examined would include a variety of measures including general cognitive ability, attention, executive function, processing speed, and memory. In addition, using

	longitudinal data this study will examine effect of risk factors on longitudinal trend in cognitive function over time. World leading expertise in psychiatric epidemiology and genetics available at the Universities of Bristol, Bath and Cardiff University would be a great advantage for this project. 2) Interrogating evidence for causality using genomics: For this study, the student will learn and apply Mendelian randomization (MR) analysis, a genetic causal inference method designed to examine whether the association between a risk factor and an outcome is likely to be causal or could instead be explained by confounding or reverse causation. MR analysis will help assess whether associations between risk factor(s) and cognitive problems identified in Study 1 are likely to be causal. This analysis will use summary statistics from existing genome-wide association studies which are publicly available. In addition, genetic colocalization analysis will be carried out to test whether identified risk factor(s) and a specific cognitive problem share common genetic aetiology. Establishing evidence of causality using MR and other methods is valuable because causal factors could be new treatment targets. The student would be based within the MRC Integrative Epidemiology Unit (IEU) at the University of Bristol, a world leading centre for genetic epidemiology (developing MR methods particularly) and population-based research. The student would also benefit from supervision from their supervisors in Bath and Cardiff, who are leading internationally leading research into neuropsychiatric genetics and genomics. **Feasibility, importance and skill gain** Proposed projects are feasible because datasets necessary for the work are already available or are currently being curated by the supervisors. Genetic analysis would use existing publicly available data. The student would benefit from excellent expertise available in supervisors' groups in proposed epidemiological and genetic analysis including blood biomarker and omics data analysis. Relevant training courses are available in Bristol, Bath and Cardiff. For example, Bristol has an excellent menu of short courses in various aspects of epidemiology, genetics (including MR), and other statistical methods which are free for PhD students (three free courses per year). The proposed project would provide training and skills in data analysis including omics, blood biomarkers, MR, and other causal inference methods, as well as neurocognitive aspects of SMI. These skills are invaluable for a future career in the academia or industry.
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