Project Details	
Project Code	MRC22NMHBr Khandaker2
Title	Novel immunologic mechanisms and treatment targets for depression
Research Theme	Neuroscience & Mental Health
Summary	Emerging evidence implicates low-grade systemic inflammation in depression, but therapeutic advance will depend on identifying and validating immune proteins/pathways that are causally related to illness risk. This PhD will apply population and clinical randomised approaches, e.g., Mendelian randomization analysis and existing data/samples from clinical trials of immunotherapies, to examine the role of NLRP3 inflammasome and related biomarkers in depression.
Description	Background: Inflammation is implicated in pathogenesis of depression, with circumstantial evidence pointing to a role of the NLRP3 inflammasome pathway and related cytokines. For instance, infection is associated with risk of depression. Depressed cases have higher levels of inflammatory proteins such as IL-1b, TNF-a, IL-6, CRP in blood/CSF compared with controls. In rodents, glucocorticoid-driven NLRP3 inflammasome activation in hippocampal microglia has been reported to mediate chronic stress-induced depression-like behaviour. Currently, an industry-led RCT is testing inhibition of the NLRP3 pathway as a potential treatment for depression. However, evidence from humans for a causal role of the NLRP3 inflammasome pathway in depression is scarce. Aim: To examine the role of NLRP3 inflammasome pathway in depression by testing whether its activators (e.g., infection) and its constituent/down-stream biomarkers (e.g., caspase-1, IL-1b, IL-18, TNF-a, IL-6) are causally related to depression using genetics and clinical trials. Hypothesis: 1) NLRP3 inflammasome biomarkers are causally associated with depression. 2) Immunotherapies improve mood symptoms in depressed patients by decreasing levels/activity of NLRP3 inflammasome pathway proteins. Methods: 1) Mendelian randomization (MR): a method using genetic variation to evaluate causal effects of exposures on outcomes, in this case exposures will be variation in DNA methylation and proteins in the NLRP3 inflammasome pathway and the outcome will be depression. 2) Experimental medicine trials: Existing data and samples from two RCTs of immunotherapies (anti-IL-6R and anti-TNF monoclonal antibodies) in patients with depression/inflammatory disease will be used to test whether improvement in mood symptoms are mediated by decreased levels/activity of NLRP3 inflammasome pathway proteins. Statistical Analysis: 1) MR: Two-sample MR analyses will use summary statistics from published genome-wide association studies (GWAS) of relevant biomarkers (e.g., caspase-1, IL-1b, IL-18, TNF-a, sIL-6, sgp130 and gene promoter DNA methylation) and outcomes (i.e., depression) associations from existing large-scale genome-wide and epigenome-wide association studies (GWAS, EWAS). 2) Experimental medicine: Data and biological samples from two RCTs will be used. (i) a proof-of-concept RCT of patients with depression (n=40) treated with tocilizumab or placebo, called the Insight study (Chief Investigator, Khandaker). (ii) a RCT of anti-TNF treatment in patients with hepatitis C (Chief Investigator, Harrison). These patients have provided clinical data (e.g. mood, anxiety symptoms, cognition) and blood samples that will be analysed for relevant biomarkers, e.g., inflammasome pathway proteins

	and epigenetic changes in targeted cytokine/immune genes. Feasibility: MR relies on the use of existing GWAS and EWAS for immune proteins and depression which are already available. The RCT of tocilizumab (Insight study) is now nearing completion, and so data and samples will be ready for use when the PhD starts in autumn 2022. The second RCT is ongoing and will complete data collection in the early stages of this PhD. Significance: The proposed PhD will provide vital evidence regarding causal effects of the NLRP3 inflammasome pathway in depression. This work would inform the development of larger definitive RCTs testing the efficacy of immunotherapies for depression targeting this pathway, and/or help to explain mechanism of effect for current immunotherapy trials for depression. Given 1 in 3 people with depression do not respond to currently available treatment, this will represent a significant advance in psychiatric therapeutics. Training and development opportunities: This PhD will provide an excellent training opportunity in genetic/epigenetic epidemiology, immunology, biostatistics, and novel therapeutics, which would be helpful for future career in academia or industry.
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