Project Details	
Project Code	NMH27Ex Tyrrell
Title	Severe mental illness, inflammation and cardiometabolic health
Research Theme	Neuroscience & Mental Health
Project Type	Dry lab
Summary	This exciting PhD combines big data and genetics to understand the complex relationships between severe mental illness, inflammation, and obesity and other adverse metabolic health outcomes. This research is important as people with severe mental illness are more likely to have adverse metabolic health problems and we don't know why. Preliminary results from the supervisory team suggest inflammation may be a crucial factor. This PhD will test this idea in more detail using novel genetic epidemiological techniques in large global biobanks. The student will train in 3 world leading centres and will gain skills in immunology, statistics and genetic epidemiology.
Description	This interdisciplinary PhD will provide the student with an excellent underpinning in metabolic- and immuno-psychiatry, two rapidly developing fields investigating the shared mechanisms underlying severe mental illness (SMI), metabolic health and immune dysfunction. People with SMI (e.g. schizophrenia, bipolar disorder and severe depression) have high rates of obesity, type 2 diabetes, cardiovascular disease and immune dysfunction. This PhD will test the hypothesis that inflammation could be a common mechanism linking SMI with metabolic conditions, focusing on key systemic inflammatory biomarkers such as interleukin-6 (IL-6) and C-reactive protein (CRP), and key metabolic health measures. The PhD will utilise big data, including genetics, biomarkers, population cohort and electronic health records (EHRs), and methods such as Mendelian randomization (MR) and genetic clustering to improve our understanding of how inflammation contributes to both SMI and adverse metabolic outcomes. Chronic low-grade systemic inflammation is implicated in a range of adverse outcomes including SMI, neurodegeneration and cardiometabolic disease. Elevated inflammatory markers such as IL-6 and CRP have been consistently associated with obesity, depression and schizophrenia. However, the mechanisms underlying these relationships remain complex. Obesity may act as both a driver and consequence of inflammation, while inflammation may independently influence neurodevelopment, neurotransmitter signalling and brain structure and function. Antipsychotic medication, lifestyle factors and socioeconomic disadvantage may also contribute to inflammatory burden among people with SMI. Disentangling these overlapping pathways is a major research priority. Large population health datasets combining genetics, biomarkers and linked EHRs provide an unprecedented opportunity to investigate these relationships. This PhD will build upon emerging evidence suggesting bidirectional relationships between inflammation, obesity and SMI alongside preliminary work from the supervisory team indicating substantial heterogeneity in the effects of CRP genetic variants on BMI. Specifically, the PhD will consist of three work packages (WP):

	WP1: Genetic clustering of inflammatory and adiposity pathways to identify mechanistic variant subsets. Research question: do genetic determinants of inflammation and adiposity influence the same or different biological processes? Here the student will utilise GWAS summary statistics and several clustering approaches (e.g. MR-Clust, MR-AHC, Bayesian approaches) to identify potential clusters of genetic variants linking systemic inflammation (e.g. IL-6, CRP, TNF-□, IL-1b) and adiposity (e.g. BMI and WHR). These potential clusters could include: o Inflammation-driven (BMI-independent) o Adiposity-driven inflammation o Divergent/opposing effects (e.g. ↑CRP, ↓BMI) o Null or pleiotropic clusters Clusters will be replicated using independent datasets, including FinnGen, UK Biobank (UKB), All of Us (AoU) and Our Future Health (OFH). This will enable assessment of cluster stability across ancestries and by sex. The student will functionally characterise the clusters using several approaches including testing associations with key traits (e.g. HbA1c, fasting glucose, metabolites), Functional Mapping and Annotation via FUMA (https://fuma.ctglab.nl) and through collaboration with the Functional Genomics Initiative (e.g. single cell expression data/ATAC seq). This will provide data on tissue/cell-type and pathway enrichment. WP2: Cluster-specific causal effects on SMI and cardiometabolic outcomes Research question: do biologically distinct genetic determinants of inflammation and adiposity casually influence the risk of SMI and cardiometabolic disease? Here, the student will quantify if the different genetic clusters (from WP1) differentially influence SMIs and cardiometabolic outcomes (e.g. T2D, CVD, dyslipidemia) using both summary statistic data and individual level population health study data. The student will be able to tailor the list of outcomes considered and develop endophenotypes using the rich data available. For example, they may wish to derive metrics related to prescribed medications, treatment resistance or augmentation. The student will then perform one- and two-sample MR using the adiposity partitioned inflammation clusters and compare the cluster effects with global effects. Findings will be replicated in diverse cohorts. WP3: Early-life phenotypic footprint of the inflammation and adiposity genetic clusters Research question: How do biologically distinct genetic determinants of inflammation and adiposity influence early-life mental and cardiometabolic health? Finally the student will utilise the Avon Longitudinal Study of Parents and Children (ALSPAC) to test how the derived clusters influence early-life mental and cardiometabolic health using the rich longitudinal data within ALSPAC. This will include but not be limited to BMI trajectories and depression metrics across early-life. The student will gain expertise in several cutting-edge methodologies, including: 1. Statistical analyses: Regression models; mediation analysis; lifecourse epidemiology.

	2. Genetic analyses: genetic correlations, partial LDSC, Mendelian randomisation (MR) in populations with diverse ancestry, clustering. 3. Data science: handing large datasets including EHRs and biomarker data in UKB, OFH, AoU, ALSPAC. 4. Clinical science: psychiatric assessments and cardiometabolic health. The student will be able to tailor their PhD based on areas of interest, for example, focusing on a specific SMI. They will work across disciplinary boundaries, with their supervisors and external collaborators coming from molecular/genetic, epidemiological, psychiatric and physical health, including advanced biostatistical backgrounds. This PhD will provide an excellent platform for a successful scientific career, working at the interface of immunology, metabolic and mental health, a growing area of research interest.
Can be completed part time?	Yes
Supervisory Team	
Lead Supervisor	
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