Project Details	
Project Code	NMH27Ex Walker
Title	Investigating molecular mechanisms underlying resilience to dementia and age-related disorders: A multi-omic analysis of large human biobanks
Research Theme	Neuroscience & Mental Health
Project Type	Dry lab
Summary	Why do some people remain cognitively healthy despite being at high genetic risk of dementia? This project will use cutting-edge genetic and molecular data from large human biobanks to identify molecular factors that help protect against dementia and co-occurring age-related conditions. The student will work at the intersection of dementia research, genetics, epidemiology and data science, gaining experience in the analysis of large-scale population datasets and molecular biomarkers. Findings from this project could reveal new targets for dementia prevention and provide insights into the biology of healthy ageing.
Description	Dementia is a leading cause of disability in older adults. As the world's population ages, the prevalence of dementia is expected to increase to 150 million by 2050[1]. Most currently available dementia treatments offer symptomatic relief without affecting the underlying disease pathology. As such, the development of interventions to prevent or delay dementia onset remains a priority. Risk for dementia is determined, in part, by genetic factors; however, genetic susceptibility does not inevitably result in disease. Some individuals maintain cognitive health despite substantial genetic risk, indicating the presence of biological mechanisms conferring resilience. Understanding these mechanisms may reveal novel pathways involved in maintaining brain health, and identify opportunities for dementia prevention. Importantly, dementia rarely occurs in isolation. Older adults frequently experience multiple age-related conditions simultaneously – a phenomenon known as multimorbidity. Many of these conditions, including stroke and cardiovascular disease, share common genetic and biological risk factors with dementia. Studying resilience across multiple conditions provides an opportunity to identify biological mechanisms that promote healthy ageing more broadly, as well as mechanisms specific to dementia risk. Genetic risk factors exert their effects through a range of downstream biological processes that affect the function of cells and tissues, and, ultimately, health. These biological processes can be assessed by measuring molecular traits, including levels of proteins and metabolites, and the presence of epigenetic modifications (chemical modifications that regulate gene expression without altering the underlying genetic code). These molecular traits act as a point of convergence between genetic and environmental influences, capturing biological processes through which risk factors ultimately affect disease development. Importantly, molecular factors may modify the impact of genetic susceptibility. Identifying molecular signatures of resilience could therefore reveal biological pathways that support healthy brain ageing and protect against dementia, while also highlighting shared

	mechanisms that may reduce vulnerability to multiple age-related conditions. Through this project, the student will address the question: Which molecular factors confer resilience to genetic risk for dementia, and do these resilience mechanisms represent shared biological pathways that protect against multimorbidity in later life? This question builds on previous work from the supervisory team, which has identified multi-omic signatures of risk for dementia and related phenotypes[2-4], identified causal links between blood iron levels and dementia risk[5], and built 'omics-based models to predict complex trait and disease outcomes[6]. The student will address this overall question through at least some of the following objectives, with the student contributing to both the choice of objectives and methods used. Objective 1: Define genetic risk and brain health outcomes relevant to dementia. The student will define measures of dementia genetic susceptibility and identify relevant brain health outcomes in large cohort studies, including UK Biobank and the Alzheimer's Disease Neuroimaging Initiative (ADNI). Outcomes may include cognitive function, neuroimaging measures, and prevalent and incident dementia-related outcomes. Objective 2: Characterise conditions that commonly co-occur with dementia. The student will characterise age-related conditions that frequently co-occur with dementia. The selection of conditions will be informed by a literature search, and, potentially, engagement with people affected by dementia and their caregivers. Objective 3: Identify molecular modifiers of genetic risk for dementia. The student will investigate whether molecular traits, including proteins, metabolites, and epigenetic modifications, modify associations between genetic risk and dementia-related outcomes. Objective 4: Determine whether molecular resilience mechanisms are shared across age-related conditions. The student will investigate whether molecular factors that modify genetic risk for dementia also influence resilience to other age-related conditions identified in Objective 2. These analyses will determine whether resilience reflects shared biological pathways that promote healthy ageing broadly, or mechanisms that are specific to dementia risk. Objective 5: Develop and evaluate multi-omic biomarkers of resilience. The student will investigate whether molecular factors identified in previous objectives can be combined into composite biomarkers of resilience predictive of healthy brain ageing. Objective 6: Explore the translational potential of identified resilience mechanisms. The student will investigate whether the identified molecular markers of resilience likely play a causal role in disease outcomes, and whether they might be modifiable by pharmacological or lifestyle intervention. The student will be encouraged to shape the project in line with their scientific interests and emerging findings. They will contribute to decisions regarding how genetic resilience is defined, the selection of molecular traits and health outcomes for investigation, and the

	analytical approaches used. Depending on their interests, the student may place greater emphasis on dementia, multimorbidity, epigenetics, proteomics, biomarker development, causal inference, or machine learning-based prediction. 1. Nichols, E., et al., The Lancet Public Health, 2022. 7(2) 2. Walker, R.M., et al., Alzheimers Dement (Amst), 2020. 12(1) 3. Walker, R.M., et al.,Transl Psychiatry, 2024. 14(1) 4. Walker, R.M., et al., Genome Med, 2021. 13(1) 5. Casanova, F., Q., et al., Neurobiol Dis, 2024. 197 6. Shakeel, A., et al., npj Digital Medicine, 2026. 9(1)
Can be completed part time?	Yes
Supervisory Team	
Lead Supervisor	
Name	Dr Rosie Walker
Affiliation	Exeter
College/Faculty	Health and Life Sciences
Department/School	Psychology
Email Address	r.walker4@exeter.ac.uk
Co-Supervisor 1	
Name	Dr Luke Pilling
Affiliation	Exeter
College/Faculty	Health and Life Sciences
Department/School	Clinical and Biomedical Sciences
Co-Supervisor 2	
Name	Dr Paul Yousefi
Affiliation	Bristol
College/Faculty	Bristol Medical School
Department/School	Department of Population Health Sciences
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	