

Project Details	
Project Code	MRC21PHBr Anderson
Title	The immune system and risk of Alzheimer's disease
Research Theme	Population Health
Summary	The effect of immune dysfunction on risk of Alzheimer's disease is poorly understood. This PhD will use genetic and observational epidemiology to understand if and how immune parameters such as complement proteins, cytokines and antibodies, as well as immune disorders such as rheumatoid arthritis and Multiple Sclerosis alter risk of Alzheimer's disease and cognitive decline
Description	<p>Alzheimer's disease (AD) is a late-onset neurodegenerative disorder, constituting the majority of dementia cases. It affects 46 million people worldwide and its prevalence is expected to double in the next 20 years(1). The immune system has long been implicated as a key factor in the development of AD. Over the last decade attention has been drawn to the interplay between the central nervous system and immune responses (i.e. neuroinflammation)(2) in the pathogenesis of AD, mostly due to evidence stemming from observational studies suggesting that inflammatory disorders (e.g. rheumatoid arthritis)(3) and chronic inflammation (e.g. periodontitis)(4) are associated with a higher risk of AD. Many observational studies have also examined the association between cytokine concentrations and the risk of AD(5). However, deciphering the role of immune and inflammatory markers in the pathogenesis of AD in observational studies is challenging because of the potential for bias due to reverse causation (i.e. inflammation being a consequence of, rather than a cause of, the disease) and unmeasured or residual confounding (i.e. common causes of both inflammation and AD). Recently, causal inference methods such as Mendelian Randomization (MR) have been developed to help overcome such biases. MR is a method that uses genetic variants as instrumental variables for environmental exposures (such as cytokines and complement proteins). Identifying causal risk factors for AD is imperative for informing successful prevention strategies and identifying appropriate targets for drug trials. This PhD will examine whether (i) autoimmune disorders and (ii) specific immune parameters effect risk of AD and rates of cognitive decline. The specific objectives are to: 1) Conduct a systematic review of existing evidence for associations between autoimmune disorders and AD risk 2) Examine associations between immune parameters (including complement proteins and cytokines), autoimmune disorders (e.g. Rheumatoid Arthritis, Multiple Sclerosis and Lupus) and risk of AD/AD proxies using genetics (two-sample MR summary statistics from genome-wide association studies, and polygenic risk score analysis in the UK Biobank and DPUK cohorts with relevant data) 3) Interpret existing immune-relevant parameters and measure plasma levels of specific immune-relevant analytes identified from the genetic studies in objectives 1 and 2. The Morgan Lab will provide support and training for this objective. The type of assay(s) will be dictated by the nature of the implicated analyte(s) but are likely to include commercial and in-house ELISA that are already established in the lab 4) Examine observational associations of various antigens (including fungal; protozoan; herpes viruses; common colds; measles;</p>

	<p>bacteria and dietary antigens) with cognitive function in both children (Avon Longitudinal Study of Parents and Children [ALPSAC]; 5, 7, 11 and 15 years) and adults (Caerphilly Prospective Study [CaPS], mean age at baseline 53 years), and with mild cognitive impairment and dementia in adults only (CaPS). References 1) https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf 2) Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. <i>Lancet Neurol.</i> 2015;14(4):388-405. 3) Chou RC, Kane M, Ghimire S, Gautam S, Gui J. Treatment for Rheumatoid Arthritis and Risk of Alzheimer's Disease: A Nested Case-Control Analysis. <i>CNS Drugs.</i> 2016;30(11):1111-20. 4) Leira Y, Dominguez C, Seoane J, Seoane-Romero J, Pias-Peleteiro JM, Takkouche B, et al. Is Periodontal Disease Associated with Alzheimer's Disease? A Systematic Review with Meta-Analysis. <i>Neuroepidemiology.</i> 2017;48(1-2):21-31. 5) Shen XN, Niu LD, Wang YJ, Cao XP, Liu Q, Tan L, et al. Inflammatory markers in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review of 170 studies. <i>J Neurol Neurosurg Psychiatry.</i> 2019;90(5):590-8.</p>
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