Project Details	
Project Code	MRCNMH26Ex Ruth
Title	Genomics, oestrogen and the brain
Research Theme	NMH
Project Type	Dry lab
Summary	We will use 'big data' genomic analyses to investigate the genetics and neuroscience underlying oestrogen-related traits. For example, lower oestrogen following menopause is thought to affect cell signalling in the hypothalamus causing menopausal symptoms, and has also been linked to cognitive decline. The student will investigate the genetic basis and biological mechanisms of oestrogen-related traits by integrating experimental cellular multi-omics data with cutting-edge whole genome sequencing analyses in population-based cohorts of 100,000s of people. The genes identified will be used in genetic epidemiological approaches to test relationships between oestrogen and brain-related health conditions, providing aetiological insights.
Description	**Background** Oestrogen is thought to have protective effects on the brain, with the fall in oestrogen at menopause linked to higher rates of dementia in women than men, poorer cognitive function and also mental health conditions. Oestrogen has key functions in controlling the behaviour of cells and which genes are active, but the underlying biological pathways linking oestrogen levels to health conditions are not well understood. By performing genome-wide analyses, we can provide insights into the specific genes and mechanisms that are responsible, potentially leading to new treatments. For example, low oestrogen levels at menopause are thought to cause menopausal hot flushes by increasing the amount of signalling through the NK3R receptor in the hypothalamus region of the brain. While an effective treatment for hot flushes works by reducing NK3R signalling, our previous genetic studies have raised questions about the biological mechanism; We found that rare genetic variants that should reduce NK3R signalling are not associated with a lower risk of having menopausal hot flushes as would be expected. Our future work aims to resolve such uncertainty. Up to 80% of women going through menopause experience symptoms other than menstrual irregularities, which can impact on all areas of daily life and include hot flushes, night sweats, sleep disturbance and mood change. While oestrogen replacement is an effective treatment, the aetiology of symptoms is poorly understood, partly due to issues of confounding in observational studies. Symptoms related to lower oestrogen levels are often interrelated, for example, women often report hot flushes, night sweats and sleep problems concurrently. However, the direction of the relationship between symptoms is unclear, e.g. whether hot flushes cause or are caused by sleep problems, or whether they are linked due to other risk factors that are common to both. Menopausal symptoms have also been identified as risk factors for other postmenopausal health conditions including depression and cognitive decline. By using genetic epidemiological approaches, the studentship will provide robust causal evidence into the relationships between oestrogen and brain-related health conditions. These insights will benefit population health by providing a robust evidence base to

	advise women, health professionals, the academic community and the public. **Aim** The overarching aim of the project is to investigate how oestrogen affects menopausal symptoms and is linked to brain-related health conditions such as insomnia, mental illnesses and cognitive decline. This will be achieved through 'big data' genomic analyses allowing the student to learn the latest methods in genome-wide analyses and genetic epidemiology, including advanced bioinformatics, statistical and data analysis skills. **Objectives** 1. Conduct analyses of oestrogen-related traits using whole genome sequencing data from large-scale population based cohorts. The student will use the latest computational pipelines to identify novel genetics causing oestrogen-related traits. These powerful methods allow testing of rare variants in the regions of the genome that contain regions responsible for gene regulation, which has been little tested. The student will conduct analyses in 500,000 people in UK Biobank, as well as other similar cohorts (e.g. 'All of Us', 'Our Future Health'). We will include traits such as oestrogen levels at various timepoints over life, duration of hormone exposure and those thought to be caused by changes in oestrogen levels (e.g. menopausal symptoms). 2. Integrate multi-omics and genetics data to identify novel genes and biological pathways. Mapping regulatory regions of the genome to specific genes and pathways is challenging, but the student will do this by integrating multi-omics resources into their genetic analyses. Such data will provide information on which regions of the genome are active at different life stages and in which cells, and also which versions of a gene are produced. We will include data for relevant regions of the brain and also the ovary (a key oestrogen producing organ) to identify specific biological pathways and mechanisms. 3. Identify causal relationships between oestrogen and brain-related health conditions. By using genetics linked to oestrogen-related traits, the student will explore the likely health effects of manipulating treatment targets, generating robust causal inferences. They will test the effects of oestrogen on brain-related health outcomes, including conditions linked to menopause such as insomnia and depression, and those relating to cognitive function and dementia. Using robust methods in genetic epidemiology, they will generate causal evidence relating to the role of oestrogen in health and the direction of such relationships. **Ownership** The student will direct the focus of the analyses towards particular oestrogen related phenotypes, e.g. specific menopausal symptoms, measured oestradiol. There will be scope to direct the brain-related health conditions towards particular outcomes, e.g. mental health, cognitive outcomes. They will also have the opportunity to analyse new and varied datasets, including data from questionnaires, assessment centre measures, electronic health records and multi-omics data. The

	student will also be able to tailor their skills towards statistical genetics, genetic epidemiology, 'omics or a combination of all of these.
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