Project Details	
Project Code	MRCPHS26Br Sanderson
Title	Understanding early and midlife causes of cardiovascular disease through genetics
Research Theme	PHS
Project Type	Dry lab
Summary	Cardiovascular disease is a major cause of ill health in later life. However, development of this disease is likely to be influenced by traits throughout life. This project will use genetic epidemiology to explore methods to estimate how traits at different ages affect long-term disease risk. The project will make use of novel data on the association of genetic variants with traits at specific ages and trait trajectories. The student will gain experience with large-scale genetic data and develop skills in causal inference, statistical genetics, and population health, while addressing important questions in lifecourse epidemiology and chronic disease prevention.
Description	Cardiovascular disease (CVD) is a major cause of ill health in later life, but its development is likely influenced by factors acting across the lifecourse, not just in the period immediately preceding disease onset. Identifying which traits act on disease earlier in life and when can improve prevention strategies by targeting interventions where they are most effective. For example, lowering blood pressure and cholesterol later in life through commonly prescribed inexpensive drugs is a well-established way to lower the risk of cardiovascular disease. If this approach in mid-life would also lower the risk of disease later in life this would provide a cost-effective public health intervention, however if the effects are short lived then resources could be better focused on later life. Randomised controlled trials are the gold standard approach to estimating the effects of such treatments. However, given the timeframe involved, trials to assess the effect of traits in early/mid adulthood on later life outcomes would need to run for potentially 30 – 40 years before they could provide reliable evidence. Conventional epidemiological approaches using observational data could also be used to estimate which traits have a causal effect on later disease outcomes; however, these approaches may be biased by unobserved confounding. An alternative approach to causal effect estimation is to use genetic epidemiological approaches such as Mendelian randomization (MR). MR uses random genetic variation between individuals within an instrumental variable framework for causal effect estimation. This approach reduces the risk of bias from unobserved confounding by relying on an alternative set of assumptions. As an individual's genetic variants are fixed throughout their lifetime, effect estimates obtained from MR have traditionally been interpreted as representing lifetime effects. However, recent methodological developments have aimed to uncover time-specific effects. To date, MR approaches exploring age-specific effects on traits have been largely confined to distinguishing the effects of childhood and adulthood adiposity. Increasingly, though, the availability of age-specific genome-wide data is providing new opportunities to estimate age-specific effects of a range of traits. Similarly, recent GWAS studies have begun to

	identify variants associated with trajectories of a trait across a range of ages. This novel data provides an opportunity to identify early and mid-life casual risk factors for later life disease by extending MR methodology. However, implementing such approaches raises several questions regarding how such estimation should be conducted – issues that are critical for generating robust and reliable effect estimate estimation, yet remain largely unaddressed. **Key research questions:** - How should age- and trajectory-specific GWAS results be incorporated into Mendelian randomization studies to estimate lifecourse effects? - How can interaction effects between different ages, or different characteristics of a trajectory be identified using GWAS summary statistics? - What is the causal effect of early and mid-life traits on cardiovascular disease risk later in life? **Specific objectives:** 1. To conduct a simulation study to assess which causal effects can be estimated by integrating novel age-stratified data with current MR methodologies. This will include identifying which MR methods are most appropriate as well as characterising the specific effects that can be estimated with each approach and data type. This objective will also evaluate the limitations and assumptions of each method. 2. To develop a method for estimation of the effect of interactions between different time periods, or characteristics of a trajectory (such as the slope and intercept) using summary statistics. Methods to estimate interactions in MR are available for individual-level data however the application of these methods is not relevant for lifecourse studies. In this objective the student will develop a method to estimate interactions using GWAS summary statistics. 3. Develop an R package for lifecourse MR estimation. This will incorporate all of the methods considered in both objectives 1 and 2 and will will be made openly available to other researchers to estimate lifecourse effects with GWAS summary statistics. 4. Estimation of the causal effect of a range of traits in early and mid-life on cardiovascular disease in later life. This will incorporate the methodological work produced earlier in the PhD into the estimation of causal effects of a range of traits, determined by the student but including blood pressure and cholesterol measures, on cardiovascular disease later in life. The student will be encouraged to take ownership of the PhD and steer the projects according to their research interests throughout. During Objective 1 they will be supported to determine the scope of the simulation studies and which methods should be included. The later objectives are particularly structured to allow the student to take increasing independence in planning the analysis and so steer the study based on their findings in the earlier parts of the PhD and their own interests as the project develops.

Supervisory Team	
Lead Supervisor	
Name	Dr Eleanor Sanderson
Affiliation	Bristol
College/Faculty	Health and Life Sciences
Department/School	Population Health Sciences, Bristol Medical School
Email Address	eleanor.sanderson@bristol.ac.uk
Co-Supervisor 1	
Name	Professor Rachel Freathy
Affiliation	Exeter
College/Faculty	Health and Life Sciences
Department/School	Department of Clinical and Biomedical Sciences
Co-Supervisor 2	
Name	Dr Grace Power
Affiliation	Bristol
College/Faculty	Health and Life Sciences
Department/School	Population Health Sciences, Bristol Medical School
Co-Supervisor 3	
Name	Professor Gibran Hemani
Affiliation	
College/Faculty	Health and Life Sciences
Department/School	Population Health Sciences, Bristol Medical School