Trajectories of modifiable risk factors and their influences on disease outcomes: using genetics in life course epidemiology

**Supervisors: Stephen Burgess and Jessica Barrett**

Questions about how risk factors influence disease outcomes are fundamental to epidemiology. However, these questions are difficult to answer, as relevant data are usually observational, and thus associations are not necessarily a reliable guide for causal relationships. An approach that has gained traction over the past decade is the use of genetic variants as instrumental variables to make causal inferences from observational data. If we can assume that genetic variants behave as if they are randomly distributed in the population, then individuals with genetic variants predisposing them to high levels of a given risk factor should be similar to those with genetically-predisposed lower levels of the risk factor in all respects other than the distribution of the risk factor itself. Hence any difference in outcomes between these groups can be traced to the risk factor under investigation.

The aim of this project is to extend this idea to consider risk factors that vary across the life course. For example, we know that there are genetic predictors of birth weight, of pubertal timing, and of adult body mass index (BMI). Each of these overlapping sets of variants affects obesity in a different way. However, as an example, increased adult BMI is observationally associated with increased risk of type 2 diabetes, but increased birth weight is observationally associated with decreased risk of type 2 diabetes. How can we use these different genetic variants to answer causal questions about the timings of causal effects? Or to find critical periods in which changes in the risk factor may particularly impact the outcome? This project will consider both theoretical issues grounded in the causal inference literature about how to express these concepts, and applied issues about how to use available genetic information to answer relevant questions about the origins of disease.

The project will be supervised by Stephen Burgess and Jessica Barrett, with input on the applied perspective from Tim Frayling and colleagues at the University of Exeter.

**Start date:** Easter Term (April) or Michaelmas Term (October) 2019

All application queries regarding eligibility should be directed to phdstudy@mrc-bsu.cam.ac.uk

**How to Apply:** Applications should be made on-line via www.graduate.study.cam.ac.uk/applicant-portal selecting course details MDBI22 PhD in Biostatistics

**Deadline for applications:** 3rd January 2019