Project Details	
Project Code	MRCPHS24Br Vincent
Title	Investigating the role of dietary fructose in the development of early-onset colorectal cancer
Research Theme	Population Health Sciences
Summary	Alarmingly, the incidence of early-onset colorectal cancer (EOCRC) is increasing rapidly in the UK. Because of this, there is a critical need to understand more about it and how it is different to late-onset disease. This project is about understanding how dietary fructose might be driving EOCRC development. The student will develop and use an interdisciplinary skill set in genetic epidemiology and cancer cell biology to investigate this research question.
Description	IMPORTANCE This project will investigate the role of fructose in the development of colorectal cancer (CRC) in adults <50 years (early-onset CRC, EOCRC). Alarmingly, the incidence of EOCRC in the UK is increasing rapidly and people are more likely to present with advanced disease and respond poorly to treatment. Because of this, defining and understanding the differences in EOCRC compared to late-onset CRC (LOCRC) is a question of critical importance. We are currently unable to prevent, predict or optimise treatment for people with EOCRC for the simple reason that we do not understand the etiological factors and the biology of this disease completely. As EOCRC incidence has risen across successive birth cohorts since the 1960s, it suggests that environmental, behavioural, and dietary factors may be driving higher incidence rates. Indeed, there is strong evidence that dietary factors affect CRC risk and nutritional prevention of CRC continues to hold much promise. Drinking sugar sweetened beverages (SSBs) has been implicated in risk of developing EOCRC. Consistent with this, fructose, a major constituent of SSBs, has itself been implicated in CRC development and metastasis. The mechanisms underlying how fructose may drive CRC remain poorly understood, however, there is accumulating evidence that they may be mediated by altering chromatin accessibility and epigenetic modifications in colon tissue. This could result in changes in gene expression driving the biology of a developing tumour. Importantly, changes in chromatin accessibility are known to play an integral role in CRC and studies in EOCRC have highlighted differences in chromatin accessibility in comparison to LOCRC. RESEARCH AIMS The aim is to understand how exposure to dietary fructose might influence EOCRC development through its impact on chromatin accessibility and downstream gene expression. This is an interdisciplinary project using techniques in both genetic epidemiology and laboratory-based cell biology. As such, upon completion of this PhD, the student will possess a highly desirable and versatile interdisciplinary skill set. Aim 1. Determine whether genes involved in fructose metabolism play a causal role in the development of EOCRC. Training in genetic epidemiological techniques, such as Mendelian randomization, will allow the student to determine whether expression of fructose metabolism genes can influence EOCRC development. The student will also investigate LOCRC for comparison. The student will use the largest genetic dataset of human EOCRC available and receive training at the word leading MRC Integrative Epidemiology Unit at the University of Bristol and the

	International Agency for Research on Cancer in Lyon, France. Aim 2. Determine whether fructose alters tumour cell phenotype and chromatin accessibility. Training in techniques in cancer cell biology will allow the student to determine how exposure to fructose alters tumour cell phenotype using both cell lines and state-of-the-art patient derived organoids models. The student will undertake training in conducting the assays of transposase-accessible chromatin with sequencing (ATAC-Seq) and proteomics experiments. Analysis will determine how fructose alters chromatin accessibility and gene expression. Here, the student will also use ATAC-Seq and 'omics datasets from a pre-collected EOCRC patient cohort. Aim 3. Investigate whether changes downstream of fructose exposure are causal for EOCRC development. Here, the student will use the training they have received across the first two aims to shape and steer their project. Data collected will guide and inform further studies using genetic epidemiological techniques. For example, gene expression changes downstream of fructose exposure identified in cellular models can be investigated for a causal role in EOCRC development in a population using Mendelian randomization and validated in EOCRC patient datasets.
Supervisory Team	
Lead Supervisor	
Name	Dr Emma Vincent
Affiliation	Bristol
College/Faculty	Health
Department/School	Translational Health Sciences
Email Address	emma.vincent@bristol.ac.uk
Co-Supervisor 1	
Name	Dr Adam Chambers
Affiliation	Bristol
College/Faculty	Life Sciences
Department/School	Cellular and Molecular Medicine
Co-Supervisor 2	
Name	Professor Adele Murrell
Affiliation	Bath
College/Faculty	Life Sciences
Department/School	Biology and Biochemistry
Co-Supervisor 3	
Name	Professor Ann Williams
Affiliation	Bristol
College/Faculty	Life Sciences
Department/School	Cellular and Molecular Medicine