Project Details	
Project Code	MRCPHS25Br Wade
Title	Investigating the role of the microbiome in obesity-driven colorectal cancer development
Research Theme	Population Health Sciences
Summary	Alarmingly, the incidence of early-onset colorectal cancer (EOCRC) is increasing rapidly in the UK. This rise may be, in part, attributable to obesity but exactly how obesity might impact CRC is largely unknown. There is therefore an urgent need to understand this relationship to identify novel targets for prevention to reduce the burden of CRC, and particularly EOCRC, worldwide. This project is about understanding how changes to the microbiome, driven by obesity, might be driving CRC 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 Accounting for more than 10% of all cancers, colorectal cancer (CRC) is the second leading cause of cancer-related deaths and the third most common cancer globally[1]. Over 54% of CRC cases are estimated to be preventable through manipulation of known risk factors including aspects of diet (e.g., eating high amounts of processed meat) and related lifestyle factors (e.g., obesity)[2]. The incidence of CRC has been steadily declining worldwide, particularly in high-income countries due early diagnostic and screening efforts[1]. However, rates of early-onset CRC (EOCRC; <50 years of age) are rapidly increasing, with incidence expected to double by 20303. Whilst this increasing incidence of EOCRC is thought to largely mirror rises in obesity from early life, the mechanisms by which higher adiposity influences CRC are largely unknown[4]. Given the lack of effective prevention strategies and treatments coupled with the fact that most EOCRC cases are often diagnosed in advanced stages with worse prognosis, there is an urgent requirement to fully understand this relationship and identify novel diagnostic biomarkers and preventative targets to reduce the burden of CRC, and particularly EOCRC, in the population. Growing research has highlighted a likely complex relationship between adiposity and the gut microbiome[5], as well as the wide-ranging potential for these microbes to play a role in oncogenic processes including host metabolism, inflammation and immune response[6]. However, there are uncertainties within these relationships, particularly with regards to the direction of causality and underlying biological mechanisms, that limit the current utility of the gut microbiome as a possible biomarker or preventative target for CRC. The integration of human genetics within population health sciences has proved successful in facilitating improved causal inference and characterising inherited susceptibility to health outcomes. The former exploits properties of human genetic variation to estimate the causal effect of a trait on health outcomes (i.e., the gut microbiome on CRC) and the latter uses aggregate genomic information to predict those at risk of a health outcome (e.g., CRC). AIM

	Adopting a powerful interdisciplinary approach, the proposed project aims to assess the causal role of changes in the human gut microbiome, driven by adiposity, on CRC (and EOCRC) risk and progression. DESIGN This interdisciplinary PhD project will use a unique combination of epidemiological and causal inference analyses applied to large-scale population-based observational and trial data with mechanistic in-vitro research with cellular colorectal tumour models to understand the relationships between and mechanisms explaining adiposity-driven changes in the gut microbiome and CRC aetiology. RESEARCH AIMS Aim 1: Describe associations between adiposity and the microbiome. The student will use epidemiological techniques to identify putative causal effects of adiposity on the gut microbiome. Firstly, the student will mine literature to assess the existing evidence for these relationships. Secondly, the student will conduct conventional observational epidemiological analyses in combination with, thirdly, established genetic epidemiological techniques (predominantly Mendelian randomization [MR]) to appraise causality in these relationships. Finally, the student will investigate changes in the microbiome using data from a weight-loss intervention trial in overweight individuals. Triangulation across these approaches will allow for inclusive understanding of how the microbiome is altered by adiposity. Aim 2: Identify associations between the microbiome, altered by adiposity, and CRC. The student will identify putative causal effects of the gut microbiome (altered by adiposity) on CRC aetiology by literature mining and undertaking conventional observational and established genetic epidemiological approaches. Aim 3: Examine the mechanistic role of the microbiome, altered by adiposity, in CRC development. The student will use established colorectal tumour cell lines and human colorectal organoid models to further explore the mechanisms underlying relationships between the gut microbiome and CRC. The student will determine the effect of bacteria on colorectal tumour cell phenotypes (including growth, proliferation, survival, morphology, migration and metabolism). Finally, the student will determine the impact of bacterial co-culture on gene expression using RNA-sequencing. Following identification of genes differentially expressed upon exposure to bacteria, the student will construct genetic instruments for use in MR analyses to understand the role played by gene expression (driven by adiposity-related microbial variation) in CRC aetiology. IMPACT This novel and interdisciplinary research has the potential to highlight if and how changes in the gut microbiome driven by adiposity can be modified for the diagnosis, prevention and treatment of CRC and EOCRC. Ultimately, this work will contribute to understanding whether we can help prevent CRC by altering the gut microbiome and how or whether the gut microbiome can be used as an early diagnostic biomarker for CRC and EOCRC, the latter of which is rising at an alarming rate. This project will allow a junior scientist to undertake a PhD in a novel and

	exciting field, specialising in bowel research and learning essential interdisciplinary skills. References 1.WHO.Colorectal cancer. 2023. 2.CRUK. Bowel cancer statistics. 3.Saraiva. World J Gastroenterol. 2023;29:1289-1303. 4.Timpson. BMJ Medicine 2024;3:1. 5.Garrett. Science 2015;348:80-6. 6.Visconti. Nat Commun. 2019;10:4505.
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