Project Details	
Project Code	MRCPHS26Br Corbin
Title	Use of network analysis to understand the molecular footprint of body mass index
Research Theme	PHS
Project Type	Dry lab
Summary	This project aims to better understand obesity, a disease whose prevalence continues to rise worldwide despite local, national and international strategies to tackle the epidemic. Adiposity, measured by body mass index (BMI), is linked to a range of health outcomes, but the underpinning biology is complex with many causes. Metabolomics (the large-scale study of small molecules in biological samples) is a data source with the potential to link the complex mechanisms behind BMI to health outcomes. In this research, network analysis of metabolomics data will be used to understand the impact of adiposity on human health and disease.
Description	**Background** This project centres around better understanding obesity, a disease whose prevalence continues to rise worldwide despite efforts to tackle the epidemic. Of 204 countries studied in an analysis of the Global Burden of Disease 2019, none saw a decline in the proportion of the population with high BMI in the past decade (https://doi.org/10.1016/S0140-6736(20)30752-2). These trends of increasing overweight and obesity are important because they are potent risk factors for many other diseases, prompting clinicians to call for action (https://doi.org/10.1016/S2213-8587(22)00317-5). Whilst there is evidence that adiposity, measured by body mass index (BMI), causally influences a range of health outcomes, there is little understanding of the biological mechanisms driving BMI effects (https://doi.org/10.1002/oby.21554). Furthermore, there is increasing recognition of the limitations of BMI as a measure, including new clinical recommendations relating to definition and diagnosis of obesity (https://doi.org/10.1016/S2213-8587(24)00316-4). Metabolomics is the large-scale study of metabolites (small molecule substrates, intermediates, and products of cell metabolism). Current approaches in the field of metabolomics enable the measurement of hundreds of metabolites from low-volume samples. These data contain information relevant to a wide range of health conditions and can help understand the complex link between risk factors and downstream health outcomes (https://doi.org/10.1136/bmjmed-2023-000787). We have conducted a series of metabolome-wide association studies (MWAS) for BMI using different study designs (https://doi.org/10.1007/s00125-023-06019-x, https://doi.org/10.1002/oby.23441). However, this univariate MWAS approach of identifying individual metabolites associated with a given exposure or outcome without any consideration of the interrelationships between metabolites is likely a sub-optimal approach. We propose that by using a network analysis approach applied to metabolomics data we can identify biological signals relevant to BMI and its impact on downstream health outcomes.

	Aim: To integrate data from various study designs and to use network analysis and/or machine learning methodologies, to elucidate the molecular footprint of body mass index. **Methods:** This project will make use of metabolomics datasets from two complementary commercial platforms. Firstly, Metabolon's mass spectroscopy-based platform that delivers high quality semi-quantitative data for more than 1400 metabolites from a single sample, providing excellent coverage across the full spectrum of molecules found in the circulation. Secondly, Nightingale Health's proton nuclear magnetic resonance (NMR) spectroscopy platform that provides a detailed quantification of circulating plasma lipoprotein lipids and a selection of amino acids and carbohydrates. Studies include (but are not limited to): 1) The Diabetes Remission Clinical Trial (DiRECT) (https://doi.org/10.1016/S0140-6736(17)33102-1) 2) The By-Band-Sleeve Trial (https://doi.org/10.1002/oby.23746) 3) The Avon Longitudinal Study of Parents and Children (ALSPAC) including data from age 7 to age 30. The student will be able to select which studies to work with as well as which variables from within those studies to use. Objective 1: Characterise the properties of metabolites and metabolic profiles relating to BMI within studies To integrate metabolomics data across multiple study designs, there needs to be a good understanding of the properties of the metabolites and their interrelationships and how these vary within and between studies. The aim in this part of the work is to develop an analytical pipeline to characterise metabolites in a multivariate framework. Work might include, for example, an assessment of the extent to which relationships (profiles) between metabolites are consistent and reproducible across different datasets. Methods to compare Gaussian graphical models (https://doi.org/10.1093/ije/dyy119) could provide a starting point. Objective 2: Apply network analysis and/or machine learning methods to integrate and to compare metabolomic signatures of BMI across interventions and population-based analyses Here profiles or networks of metabolites and their relationship with BMI will be compared with a view to identifying more biologically meaningful patterns of association than those from univariate statistics. Methods developed for multi-omics data integration will be reviewed and potentially adapted to the current application. Two reviews of integration methods (focused on metabolomics) have been published providing a useful starting point (https://doi.org/10.1016/j.aca.2020.10.038, https://doi.org/10.3390/metabo9040076). The student will also consider adaptation of cutting-edge methods from AI and Machine Learning such as Graphical Neural Networks (https://arxiv.org/abs/2405.19230; ICLR 2025) to omics. Taking forward the best identified method, the second step will be to modify and test the efficacy of the method when applied to our research question and datasets. Based on their critical review, the student will select their method of choice or develop novel methodologies uniquely appropriate to multi-

	study single omics integration. This work could be extended to incorporate proteomics data. Objective 3: Explore the relevance of findings to BMI-associated health outcomes Taking the learning from Objective (2), the student will consider how the metabolomic profile of BMI relates to relevant health outcomes utilising additional cohort data, for example, UK Biobank. Initially the focus will be on endometrial cancer where findings will be considered in the context of results from alternative approaches applied by the supervisory team, e.g. Mendelian randomization studies (https://doi.org/10.1101/2024.04.18.24305987). To supplement the work in endometrial cancer, the student will be able to choose other disease outcomes according to their interests.
Supervisory Team	
Lead Supervisor	
Name	Dr Laura Corbin
Affiliation	Bristol
College/Faculty	Health and Life Sciences
Department/School	Bristol Medical School (Population health Sciences)
Email Address	laura.corbin@bristol.ac.uk
Co-Supervisor 1	
Name	Dr Daniel Lawson
Affiliation	Bristol
College/Faculty	Science and Engineering
Department/School	School of Mathematics
Co-Supervisor 2	
Name	Dr Vanessa Tan
Affiliation	Bristol
College/Faculty	Health and Life Sciences
Department/School	Bristol Medical School (Population Health)
Co-Supervisor 3	
Name	Professor Inês Barroso
Affiliation	Exeter
College/Faculty	Clinical and Biomedical Sciences
Department/School	Exeter Medical School