Project Details	
Project Code	MRCPHS25Br Timpson
Title	Metabolomic characterisation of adiposity across the life course
Research Theme	Population Health Sciences
Summary	Adiposity, measured by body mass index (BMI), is linked to a range of health outcomes, but the underpinning biology is less understood. Metabolomics (the large-scale study of small molecules in biological samples) is an approach that can help in understanding the complex mechanism linking BMI to health outcomes. Using a high-throughput metabolomics profiling approach in one of the UK's most well-known birth cohorts, Children of the 90's, this project aims to characterise the metabolomics associated with adiposity in different time periods from childhood to early adulthood, and to understand how these might relate to health outcomes across the life course.
Description	**Background** This project centres around better understanding obesity, a disease whose prevalence continues to rise worldwide despite local, national and international strategies to tackle the epidemic.[1] The global trends of increasing overweight and obesity are important because these are major risk factors for many other diseases.[2] 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.[3] Metabolomics is the large-scale study of metabolites, which are small molecule substrates, intermediates, and products of cell metabolism. Metabolomics data contain information relevant to a wide range of health conditions and can help us to understand the complex link between risk factors, such as BMI, and downstream health outcomes.[4] To date, most metabolomic analyses of BMI have been conducted in cross-sectional designs,[5] using data and samples collected at a single timepoint. Analysing repeated measures across time can provide additional relevant information, especially during important developmental stages such as puberty. **Aims & objectives** The overall aim of this work is to understand how individuals' metabolic profiles change over time, specifically from childhood to early adulthood, how this might vary according to BMI, and the relevance of this to health (and disease) in later life. The main objectives of this project are to: 1) Characterise the metabolic profile from childhood to early adulthood using high-throughput metabolomics. 2) Explore the relationship between BMI and metabolic profile across the life course. 3) Consider the impact of metabolic trajectories at an early age on later life health and disease. **Methods** The focal point for this project is a new longitudinal collection of untargeted metabolomics data in the Avon Longitudinal Study of Parents & Children (ALSPAC, also known as 'Children of the 90's') representing five timepoints between ages 7 and 30 years. The high-throughput metabolomics platform used provides high-quality data across the full

spectrum of molecules found in the circulation. Whilst studies exist elsewhere charting the metabolome of disease, or of adult or mid-to-late age participants, there are few examples of longitudinal metabolomic data in such well characterised individuals and through such a critical point in the life course. This dataset comprises 300 unique individuals each with data from up to five timepoints, giving a total of 1250 samples with >1400 metabolites measured at each. This dataset will be complemented by a similar collection of proton nuclear magnetic resonance (NMR) spectroscopy metabolomics data, which is available for at least 3000 individuals at each of the five timepoints. The NMR platform provides a detailed quantification of circulating plasma lipoprotein lipids, along with a selection of amino acids and carbohydrates.

These metabolomic datasets sit in the context of 30 years of phenotypic data collected on these same participants. Crucially for this study, anthropometric data, including more detailed body composition measures, have been collected throughout the life course, including at timepoints corresponding to the metabolomics samples. Genetic data are also available for most participants including genotype array data, whole exome and whole genome sequence data, and DNA methylation array data.

The student may choose to incorporate a variety of pre-existing adiposity and omics data into their analyses.

This work will require the development of a high throughput quality control and imputation bioinformatics pipeline to deliver an analysis-ready dataset. The student will use statistical approaches to model linear and non-linear trajectories of continuous outcomes (metabolites and adiposity traits). A range of multivariate methods and data reduction techniques may also be deployed to deal with large number of correlated metabolites. Existing bioinformatics tools will be used to provide biological context for and aid interpretation of results.

The student will be encouraged to explore a variety of methodological approaches including supervised and unsupervised multivariate techniques, as well as network analyses and machine learning.

This PhD will be coordinated with a programme of research using the most contemporary and powerful study designs, multiomics data and analytical techniques to explore BMI as a risk factor, and metabolomics as one of the key links between BMI and later health (https://teamtimpson.github.io/). As such, the student will have access to other in-house collections of metabolomic data including under alternative study designs such as clinical trials, as well as the opportunity to access shared resources with relevant disease outcome data at scale, e.g., UK Biobank.

The student will have the option to focus on one or a small number of disease outcomes of their choice and may pursue a range of methods including prospective analyses and Mendelian randomization.

References

1.   Lobstein T, Jackson-Leach R, et al. World obesity atlas 2023. 2023

2.   Sattar N, McMurray JJV, et al. Lancet Diabetes Endocrinol. 2023;11:58-62

	3. Corbin LJ, Timpson NJ. Obesity (Silver Spring). 2016;24:1630-1638
	4. Timpson NJ, Wade KH, et al. BMJ Medicine. 2024;3:1
	5. Cirulli ET, Guo L, et al. Cell Metab. 2019;29:488-500 e482
Supervisory Team	
Lead Supervisor	
Name	Professor Nicholas Timpson
Affiliation	Bristol
College/Faculty	Faculty of Health Sciences
Department/School	Bristol Medical School; MRC Integrative Epidemiology Unit & Population Health Sciences
Email Address	n.j.timpson@bristol.ac.uk
Co-Supervisor 1	
Name	Dr Ana Goncalves Soares
Affiliation	Bristol
College/Faculty	Faculty of Health Sciences
Department/School	MRC Integrative Epidemiology Unit & Population Health Sciences
Co-Supervisor 2	
Name	Dr Rachel Freathy
Affiliation	Exeter
College/Faculty	Faculty of Health and Life Sciences
Department/School	Department of Clinical and Biomedical Sciences
Co-Supervisor 3	
Name	Dr Laura Corbin
Affiliation	Bristol
College/Faculty	Faculty of Health Sciences
Department/School	Bristol Medical School; MRC Integrative Epidemiology Unit & Population Health Sciences