Project Details	
Project Code	MRC22PHSEx Barroso
Title	Genetic approaches to study obesity, mental health and neurodevelopmental multimorbidity
Research Theme	Population Health Sciences
Summary	Obesity, mental health and neurodevelopmental disorders co-occur frequently and have complex aetiology. This interdisciplinary project uses cutting edge genetics and data science to study cohorts of different age and ancestry to better elucidate this multimorbid cluster. The student will join a large multidisciplinary MRC funded team, the LIfespaN multimorbidity research Collaborative (LINC), a new initiative representing studies and expertise needed for this work.
Description	Obesity and/or variable levels of adiposity often co-occur with other mental health (anxiety, depression, schizophrenia) and neurodevelopmental disorders. This multimorbid cluster represents a clinically important co-occurrence of diseases which have complex aetiological underpinnings. For example, it is well known that adiposity/obesity can be influenced by rare, large effect variants [1, 2], as well as a multitude of common small effect variants [3]. Recently, variants which lie in a continuum of causality with rare allele frequencies and intermediate effects, have been shown to influence risk of severe childhood obesity [4]. Importantly, several genes harbouring rare highly penetrant mutations causal of severe obesity with additional developmental features have been identified [4, 5]. In addition, there is strong evidence of shared genetic aetiology between obesity, anxiety, depression and schizophrenia (e.g. [6, 7]). Identifying both the genetic loci and the shared mechanisms/ pathways and architecture of genetic effects that contribute to these comorbidities is important. It will help us identify early markers of these conditions as well as identify individuals that may benefit from preventative intervention strategies. This interdisciplinary PhD project aims to utilise cutting edge genetics and data science approaches to better understand this multimorbid cluster – considering both pleiotropic and shared biological pathways contributing to the observed outcomes in population-based datasets. The success of this project will be enhanced by using genetic data from cohorts and studies with differing epidemiological characteristics – from birth/family centred cohorts (like www.bristol.ac.uk/alspac, https://borninbradford.nhs.uk) to large-scale studies with deep “omic” and health data collections (like www.genesandhealth.org and www.ukbiobank.ac.uk). Participants in these collections vary across a range of ages and ancestries and have a uniquely rich collection of data to explore this fascinating problem and a total sample size ~608,000. As a mark of cohesion and as an illustration of the true GW4 character of this proposal, the student will join a large multidisciplinary MRC and NIHR funded team, the LIfespaN multimorbidity research Collaborative (LINC). This newly funded initiative lies across multiple centres (representing the studies and expertise needed for this work), but crucially includes Exeter (Barroso), Cardiff (Van den Bree) and Bristol (Timpson). This project is ideally suited to candidates with quantitative skills wishing to expand their knowledge of genetics and data science as they apply to population health, mental health and multimorbidity.

	There is opportunity for the successful applicant to shape the project to suit their interests both in terms of type of genetic variant to explore in detail (e.g. copy number variant -CNV or polygenic risk scores -PRSs), as well as the particular phenotype overlap (adiposity/obesity and mental health or adiposity/obesity and developmental disorders). [1] Wade et al., 2021. Loss-of-function mutations in the melanocortin 4 receptor in a UK birth cohort. Nat Med 27, 1088–1096; [2] Van Der Klaauw & Farooqi, 2015. The hunger genes: pathways to obesity. Cell 161, 119-132; [3] Yengo et al., 2018. Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. HMG 27, 3641–3649; [4] Marenne et al., 2020. Exome sequencing identifies genes and gene-sets contributing to severe childhood obesity, linking PHIP variants to repressed POMC transcription. Cell Metab 31, 1107-1119; [5] Forsythe & Beales, 2013. Bardet–Biedl syndrome. Eur J Hum Genet 2, 8–13; [6] Gonzaléz et al., 2020. Polymorphic Inversions Underlie the Shared Genetic Susceptibility of Obesity Related Diseases. AJHG 106, 846-858; [7] Morris et al., 2019. Genetic variation in CADM2 as a link between psychological traits and obesity. Sci Rep 9, 7339.
Supervisory Team	
Lead Supervisor	
Name	Professor Inês Barroso
Affiliation	Exeter
College/Faculty	College of Medicine and Health
Department/School	Medical School
Email Address	ines.barroso@exeter.ac.uk
Co-Supervisor 1	
Name	Professor Marianne Van den Bree
Affiliation	Cardiff
College/Faculty	MRC Centre for Neuropsychiatric Genetics and Genomics
Department/School	School of Medicine
Co-Supervisor 2	
Name	Professor Nicholas Timpson
Affiliation	Bristol
College/Faculty	Population Health
Department/School	Medical School
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	