Project Details	
Project Code	MRCPHS26Br Nivard
Title	Shining a light on the un-common to identify novel health risk-factors
Research Theme	PHS
Project Type	Dry lab
Summary	Complex traits such as body mass index and height are influenced by a mixture of genetic and environmental factors. By first predicting what an individual's BMI or height should be, based on their genetics (the heritable part of the trait), we can identify those individuals whose measured value is different from expected. The aim of this project is to use this deviation from expectation to identify novel environmental, genetic and interaction contributions to these traits and related health outcomes.
Description	**Background:** Complex traits such as body mass index (BMI) and height are influenced by a multitude of genetic and environmental factors. High-powered genome-wide association studies (GWAS) have delivered estimated effect sizes for millions of genetic variants across the genome. Whilst individually these common genetic effects have only a very small influence on the target trait, combining them into a polygenic score (PGS) is an effective way of capturing the trait variance that is due to common additive genetic variation, also known as the narrow sense heritability. If we remove this portion of variance, what remains is trait variance due to environmental factors and non-additive genetic effects, as well as the interaction between them (plus measurement error). The aim of this project is to investigate the non-additive genetic contribution to BMI and height variance with a view to identifying additional causal determinants. One way to remove the additive genetic variance component is to residualise the measured trait on the PGS for the trait. The residuals from this model indicate the extent to which an individuals' measured phenotype deviates from expectation based on their PGS. The potential for this approach to identify both environmental (https://jech.bmj.com/content/77/6/384) and rare genetic factors (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9934696/) influencing height and disease has been demonstrated. Using a similar approach focused on residualisation on PGS, the student will explore the non-additive genetic contribution to BMI and height variance. Key research question: Can removing the common additive genetic component of complex traits aid the identification of novel environmental, genetic and interaction contributions? **Methods:** This project requires access to large scale cohort data with genetic and phenotypic (BMI and height) data. Initially, the student may use data from: (1) UK Biobank (UKB), a large-scale biomedical database and research resource containing de-identified genetic, lifestyle and health information and biological samples from half a million UK participants; (2) the All of Us study, a large-scale database similar to UKB, but based in the USA with a considerably more diverse ancestral makeup; (3) the Avon Longitudinal Study of Parents and Children (ALSPAC), a world-

	leading birth cohort study based at University of Bristol; (4) the Netherlands Twin Register, a national register in which twins, multiples and their parents, siblings, spouses and other family members participate; (5) The HUNT study, a representative large population based sample from Norway. The student will be able to select which of these data-rich cohort studies to work with as well as which variables from within those studies to use. Further studies can be incorporated into the work as required. The first step is to generate PGS scores for all cohort individuals for both height and BMI using summary statistics (genetic variant effect estimates) from existing GWAS. Tools such as PRSice, a software for calculating, applying, evaluating and plotting the results of PGS analyses, could be used for this stage. The properties of the PGS will be investigated including its relationship with non-genetic factors (e.g., indicators of socioeconomic position) and its performance across different sampling frames (e.g., across the life course). The student will be encouraged to explore a variety of methodological approaches for generating PGS including Bayesian approaches. The second step is to residualise the measured phenotype (as the dependent variable) against the PGS, delivering a new trait value for every individual, with the identified additive genetic component removed. The properties of this residual component will be explored and compared to those of the PGS. The final step is to decompose the residual component further with a view to identifying causal factors for the target trait and for outcomes related to the target trait. The assumption is that the residuals will capture trait variation due to environmental factors, genetic variation not captured by the PGS and measurement error. Environmental effects could include nutritional challenges, and exposure to infection and disease. Genetic variation not captured in the PGS will be a mixture of rare variants, marginal common variant associations, non-additive effects (including gene-by-gene and gene-by-environment interactions) and indirect genetic effects, e.g., variation related to parental or sibling genetics. These effects can be explored by running a GWAS on the residuals themselves. As an extension to this work, the student will have the option to extend analyses across the life course and/or in populations with differing social, environmental and ancestral backgrounds. This approach, which the student will develop in relation to height and weight, could be applied to many phenotypes. The PhD could usher in a new methodology in population based genetically informed epidemiology, that will have considerable future traction. The student may choose to extend the work to focus on other traits of interest to them.
Supervisory Team	
Lead Supervisor	
Name	Professor Michel Nivard
Affiliation	Bristol
College/Faculty	Health and Life Sciences
Department/School	Bristol Medical School (Population Health)

Email Address	m.g.nivard@bristol.ac.uk
Co-Supervisor 1	
Name	Dr Laura Corbin
Affiliation	Bristol
College/Faculty	Health and Life Sciences
Department/School	Bristol Medical School (Population Health)
Co-Supervisor 2	
Name	Dr Gareth Hawkes
Affiliation	Exeter
College/Faculty	
Department/School	Exeter Medical School
Co-Supervisor 3	
Name	Professor George Davey Smith
Affiliation	Bristol
College/Faculty	Health and Life Sciences
Department/School	Bristol Medical School