Project Details	
Project Code	MRC21PHBr Stergiakouli
Title	Understanding psychiatric outcomes in children born with cleft lip and/or palate using genetics
Research Theme	Population Health
Summary	Cleft of the lip and/or palate is a common birth defect which can affect appearance, speech, hearing, dentition and mental health. This PhD will investigate risk of mental health outcomes in cleft and their genetic and non-genetic causes and provides the opportunity to develop into one of few experts globally with in-depth understanding across cleft, genetics, genetic epidemiology and psychiatry.
Description	Cleft of the lip and/or palate is a common birth defect worldwide and occurs at a rate of one in 650 live births in the UK. Being born with cleft places a significant burden on children, their families and the health system as they require surgery (multiple times depending on cleft type), and other interventions to improve appearance, speech, hearing, dentition and other adverse outcomes. They are also at increased risk of psychological, psychiatric and cognitive problems [1]. There are several possible mechanisms underlying these associations that may be operating alone or together. First, they may reflect the psychological, developmental and social impacts of clefting and its treatment. Second, they may reflect genetic factors either as pleiotropic outcomes of genetic susceptibility to clefting or as independently inherited genetic risk. The UK-based Cleft Collective is a unique resource comprising the world's largest cohort study of individuals affected by cleft and their families [2]. Rich longitudinal information is collected on the children's mental health, parental, prenatal and early life factors as well as genetic data, providing unique opportunities to study genetic as well as environmental influences on risk of development of mental health conditions over time. The aetiology of both cleft and of psychiatric disorders is complex, with common risk alleles [3] [4] of individually small effects as well as rare genetic mutations of large effect and environmental factors playing roles. One group of rare mutations of large effect are Copy Number Variants (CNVs), referring to deletion or duplication of a part of the genome leading to differences between individuals in the number of copies of genes within the affected region. CNVs are known to increase risk of neurodevelopmental disorders (ND-CNVs), such as ADHD and autism, as well as mental health disorders but the presence and the impact of CNVs have not been studied in cleft [5]. The PhD project will provide the first detailed description of neurodevelopmental and mental health outcomes in children with cleft and examine the contributions of genetic and environmental factors. We will use two unique genetically informative clinical cohorts of children; the University of Bristol Cleft Collective and the Cardiff University longitudinal ExperiencCes of people witH cOpy number variants (ECHO) study. Control samples will consist of the Avon Longitudinal Study of Parents and Children (ALPSAC) and the Millennium cohort which are deeply-phenotyped cohorts of typically developing children. The aims of the study are: 1) To improve understanding of risk of neurodevelopmental and mental health outcomes in children born with cleft. This will be achieved by comparing children born with cleft to

	those at high genetic risk of neurodevelopmental and mental health outcomes but without cleft (children with ND-CNV from the ECHO study) and typically developing children. 2) To improve understanding of the causes of neurodevelopmental and mental health outcomes in children born with cleft. This will be achieved by determining in children born with cleft the contribution of: a) composite genetic (polygenic) risk scores for neurodevelopmental and psychiatric disorders and b) rare genetic mutations. Causally informative designs will also be used to test the causal link between cleft and mental health problems. 3) To improve understanding of non-genetic factors, the project will also examine contributions of early developmental problems, family socio-economic status, family relationship quality, and traumatic experiences to risk of childhood psychiatric disorders in children born with cleft. [1] doi: 10.1016/j.jaac.2018.06.024 [2] http://www.bristol.ac.uk/dental/cleft-collective/ [3] doi: 10.1038/s41380-020-0654-3 [4] doi: 10.1371/journal.pgen.1007501 [5] doi: 10.1016/S2215-0366(19)30123-3
Supervisory Team	
Lead Supervisor	
Name	Dr Evie Stergiakouli
Affiliation	Bristol
College/Faculty	MRC IEU, PHSI
Department/School	Bristol Medical School
Email Address	e.stergiakouli@bristol.ac.uk
Co-Supervisor 1	
Name	Professor Marianne van den Bree
Affiliation	Cardiff
College/Faculty	Division of Psychological Medicine and Clinical Neuroscience
Department/School	School of Medicine
Co-Supervisor 2	
Name	Professor Michael Owen
Affiliation	Cardiff
College/Faculty	Division of Psychological Medicine and Clinical Neuroscience
Department/School	School of Medicine
Co-Supervisor 3	
Name	Dr Sarah Lewis
Affiliation	Bristol
College/Faculty	MRC IEU, PHSI
Department/School	Bristol Medical School
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	