Project Details	
Project Code	MRC22PHSBr Fraser
Title	Variation in placental structure and function, causes and consequences for mothers' and offspring health in pregnancy and across the life course
Research Theme	Population Health Sciences
Summary	The placenta is an essential organ of mammalian pregnancy and has been likened to "a treasure trove", storing a wealth of information on the woman, her fetus and the pregnancy; yet it is poorly understood. The overall aim of this project is to investigate the determinants a consequences of variation in placental morphology, pathology and gene expression using ALSPAC and other cohorts, and by applying cutting edge analytical and bioinformatics methods.
Description	The placenta is an essential organ of mammalian pregnancy, providing transport of oxygen and nutrients to the fetus and hormonal regulation of maternal cardiovascular, metabolic and immunological adaptations to pregnancy.(Burton, Fowden et al. 2016) It has been likened to "a treasure trove that stores a wealth of information on the woman, her fetus, and the pregnancy".(Ananth and Elkind 2019) Yet it also the most under-researched and "least understood human organ".(Guttmacher, Maddox et al. 2014) Placental impairment can result in a range of adverse pregnancy outcomes (APO), including hypertensive disorders of pregnancy (preeclampsia and gestational hypertension; HDP), fetal growth restriction, and preterm delivery.(Brosens, Pijnenborg et al. 2011) APO are a major cause of maternal and neonatal mortality and morbidity. Epidemiological studies have consistently found that APO are also associated with offspring developmental, neurocognitive and psychiatric disorders,(Ursini, Punzi et al. 2018, O'Connor, Miller et al. 2019) and with poorer cardiovascular health in later life in both offspring and mothers.(Crump, Howell et al. 2019, Fox, Kitt et al. 2019) Yet understanding of what constitutes normal and impaired placental structure and function is limited, as are their effects on the long term health of mothers and children. This PhD project offers an opportunity to address these knowledge gaps using novel data and state-of-the-art analytical methods. The overall aim of this PhD is to investigate the determinants and consequences of variation in placental morphology, pathology and gene expression. The following are examples of specific research questions that the student may wish to address as part of their PhD. The student and supervisors will use the prep period to tailor and finalize research plans to reflect the student's interests. 1. Are maternal (and paternal) characteristics and health related behaviours (such as pre-pregnancy BMI, smoking) associated with placental dimensions, weight and number of cotyledons? 2. Are placental traits associated with APO and long term maternal and/or offspring health outcomes, e.g. neurodevelopment in offspring, and cardiometabolic health in mothers and offspring. 3. Are associations identified above likely to reflect a causal effect? This question will be addressed using Mendelian randomization. 4. Are there fetal sex differences in placental structure and function? 5. Can placental pathology and/or gene expression identify homogenous subtypes of APO? 6. What constitutes normal (and impaired) placental gene expression? 7. Can we identify blood based biomarkers of placental

	dysfunction? The student will use data from multiple studies: 1. ALSPAC – existing placental data on a random sample of placentas from the ALSPAC index pregnancies linked to genetic and lifelong health related data on both mother (generation 0; G0) and G1 offspring. 2. ALSPAC – we are in the process of generating RNA-seq data on several hundred placentas collected as part of the ALSPAC-G2 cohort (G1 participants are now adults and are their pregnancies/children are part of the ALSPAC-G2 cohort). 3. MOMI – a clinical dataset including placental pathology on >20K placentas. Prof Fraser has access to these data. 4. Open access gene expression datasets deposited in GEO and publicly available results of genome wide association studies (GWAS)will also be used as appropriate (e.g. Drs Beaumont and Freathy are leading a GWAS that has identified genetic variation associated with placental weight. 5. Access to other relevant datasets will be sought if appropriate, e.g. the Norwegian MoBa cohort (linked with the birth register) and POPS (a Cambridge based pregnancy cohort with placental data). 6. We await funding decisions that would enable us to generate pathology (n=3000) and expression data (n=1000) ALSPAC G0/G1 placentas, see below. However, the PhD project does not depend on this funding.
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