Project Details	
Project Code	MRCPHS26Ex Freathy
Title	The role of fetal insulin in preeclampsia and maternal cardiovascular disease: a missing piece of the puzzle?
Research Theme	PHS
Project Type	Dry lab
Summary	Preeclampsia is a serious and life-threatening, but poorly understood pregnancy disease that affects 1 in 50 pregnancies. Women who experience preeclampsia have a two-fold risk of later-life cardiovascular disease. Much research focuses on the mother's risk factors, but this project takes a novel approach, aiming to define the critical, but under-researched contributions of the fetus and placenta to preeclampsia. It will focus on the role of fetal insulin, a key growth factor. This PhD will address knowledge gaps by analysing comprehensive datasets to elucidate disease mechanisms. The student will receive full training and support to publish their work.
Description	**Background** Although much pregnancy research is focused on maternal characteristics, the fetus and placenta may make important contributions to maternal health in pregnancy. For example, placental dysfunction, a fetally-derived organ, is central to the pathophysiology of preeclampsia, a serious and life-threatening, but poorly understood pregnancy disease. Preeclampsia affects 2-4% of pregnancies globally and accounts for 25% of maternal deaths in Africa. It is characterised by high blood pressure (hypertension) and damage to other systems and organs such as the kidneys, and women who develop it in pregnancy have a higher risk of later cardiovascular diseases (CVD) including coronary artery disease and stroke. Yet, critical gaps remain in our understanding of its causes and its links with later life cardiovascular health. Filling these gaps is necessary to inform future antenatal and postnatal care, for example by risk stratification or new therapies. Diabetes is a key risk factor for preeclampsia and is characterised by higher circulating glucose levels. High maternal glucose levels cause the fetus to produce insulin, which acts as a key growth factor for both the fetus and placenta. Fetal insulin is particularly important for growth in the third trimester of pregnancy and accounts for half of human birth weight at term. We recently observed that a fetal genetic predisposition to a larger placenta raises the risk of preeclampsia in the mother. In addition, we have preliminary evidence that placental size provides a causal link between raised maternal glucose levels and a mother's risk of preeclampsia. This evidence supports the hypothesis that a faster growing fetus and placenta contribute to preeclampsia. However, there are critical gaps in our understanding. We hypothesise that the effect of maternal glucose on placental size is mediated by fetal insulin, but this has not been tested directly. Furthermore, it is not known whether fetal and placental contributions to a mother's risk of preeclampsia also contribute to her later risk of cardiovascular disease. This PhD will address these critical gaps. **Key research question** How do fetal and placental growth contribute to a mother's risk of preeclampsia and later cardiovascular disease?

	Specific objectives The student will be encouraged to develop the project according to their research interests and particular gaps that they wish to explore. The following are potential projects that will provide the student with experience using a range of analytical methods and datasets. 1. To identify fetal factors associated with preeclampsia risk. These could include levels of fetal insulin measured in cord blood, placental weight, and placental sFlt (a marker of preeclampsia usually measured in the circulation). A multivariable model will also include established maternal risk factors (e.g. pre-pregnancy BMI, age, maternal glucose, early pregnancy blood pressure). Interactions will be examined between maternal and fetal factors in their associations with preeclampsia. Data could be analysed from multiple birth cohort studies, including ALSPAC, EFSOCH, BiB and HAPO. 2. To investigate evidence of causal relationships between maternal glucose, fetal insulin, placental growth, fetal growth and preeclampsia/preeclampsia markers. This part of the project will use ALSPAC data in one-sample Mendelian randomization (MR) analyses and data from the largest available genome-wide association studies (GWAS) of maternal glucose in pregnancy, birth weight, placental weight and umbilical cord insulin in two-sample MR. Insights may also be gained here from studying pregnancies where the fetus has hyperinsulinism, a rare genetic condition linked with fetal overgrowth. 3. To investigate the associations of established maternal CVD risk factors and fetal/placental growth with mother's CVD disease risk. Evidence will be examined of maternal and fetal/placental effects that are independent (of each other), as well as potential interactions between them in their relation to long term cardiovascular health. One hypothesis is that fetal/placental factors could influence maternal long-term health via primary effects on cardiovascular health in pregnancy. Methods will include multivariable regression using ALSPAC data, and genetic techniques such as polygenic risk score association analyses, analyses of GWAS summary statistics, and Mendelian randomization. Rich datasets are available for these analyses, including several birth cohorts and open data sets containing the results of GWAS. The supervisory team have leading roles in large GWAS consortia which will identify new associations with birth weight, placental weight, diabetes in pregnancy and cord insulin as the project progresses, all of which will directly enhance the PhD. For the final objective, the student will lead the design of the analysis, identifying the data to be used and defining the analysis scope.

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