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Summary of research

Key words: Diabetes, Genetics, BMI, obesity, insulin, heart disease

1a: Our research question is "what are the genetic factors that predispose individuals to type 2 diabetes and what are the genetic factors that mean some diabetic individuals' condition progresses faster than others?".

We aim to use the UK Biobank to identify genetic factors that:
i) predispose some individuals to type 2 diabetes. We will include genetic analyses of the traits that are associated with T2D.
ii) predipose some individuals to deteriorate quicker than others. We will use the time it takes an indvidual to progress to insulin treatment or those who develop heart disease as measures of diabetes disease progression.

1b: Our proposed research will address a fundamental health question - why do some individuals develop type 2 diabetes in today's obesogenic environment whilst others do not? There is very strong evidence that genetic factors account for some of these differences between individuals and yet we have not identified a large component of the genetic heritability of type 2 diabetes. We also know little about the genetic factors that may lead to some type 2 diabetic individuals requiring insulin or having heart attacks earlier than others.

1c: Our proposal will proceed in two phases.
In phase 1 we will analyse all the genetic variants measured in the approximately 150,000 individuals that will be genotyped by the end of 2014. We will analyse the approximately 800,000 genetic variants against intermediate traits, type 2 diabetes status in all individuals, and within the type 2 diabetic individuals, against time to insulin, treatment, measures of macro and micro vascular disease and age at diagnosis of diabetes.

In phase 2 we will repeat these analyses but using the full dataset of 500,000 individuals and HBA1C measures.

1d: In phase 1 the 150,000 with genotype data at end 2014 and in phase 2 the full 500,000. We estimate that the full 500,000 includes 14,000-20,000 type 2 diabetic cases depending on the use of HBA1C criteria and how type 1 diabetes is excluded. Some of our secondary-questions such as time to insulin and micor and macro vascular status are applicable only to those we have classified (at baseline) as type 2 diabetic. See Tyrrell et al, IJE our publication on parental diabetes and birth weight.

- Extension details: We would like to perform genetic studies of albumin creatinine ratio and glomerular filtration rate, as derived from serum and urine creatinine and albumin levels. We are interested because these traits are important markers of vascular, especially microvascular function. Microvascular complications such as those in the kidney, eye and periphery are important complications of type 2 diabetes - the main disease trait that is the subject of application 9055.

Project Extension July 2016:

This project is based around understanding the basis of diabetes, obesity and growth. We'd like to expand the scope of this project to look at the epidemiology and genetics of autoimmune diseases and the overlap with these traits. There are known epidemiological links between autoimmune diseases and diabetes, obesity and growth. We will first develop and test the most predictive genetic risk scores for autoimmune diseases (e.g. type 1 diabetes, Celiac, Crohn's, autoimmune thyroid disease) in UK Biobank and other collaborating studies. Subsequently we will use these genetic risk scores to determine whether there is a causal association with diabetes, obesity or growth using techniques such as Mendelian Randomisation.

Project Extension May 2017:

This project is based around understanding the basis of obesity and growth. We'd like to expand the scope of this project to look at the epidemiology and genetics of gastrointestinal diseases and the overlap with these traits. There are known epidemiological links between gastrointestinal diseases and diabetes, obesity and growth, for example, obesity is correlated with several gastrointestinal diseases including diverticular disease. We will first identify new variants associated with gastrointestinal diseases and traits, and develop genetic risk scores for these diseases (e.g. Celiac, Crohn's, diverticular disease) in UK Biobank and other collaborating studies. Subsequently we will use these genetic risk scores to determine whether there is a causal association with diabetes, obesity or growth using techniques such as Mendelian Randomisation.