Project Details	
Project Code	CMD27Ex Jones
Title	Understanding the causes, and best treatment, of type 2 diabetes in people who are not overweight.
Research Theme	Cardiometabolic Disease
Project Type	Dry lab
Summary	Many people think of type 2 diabetes as being a condition that affects people with high body weight, but millions of people with type 2 diabetes worldwide are lean. We do not know the cause of diabetes in these people or how to treat them. The successful applicant will work with experts in diabetes, data science, and genetics, and use detailed existing studies of hundreds of thousands of people with diabetes, to understand what is causing apparent type 2 diabetes in those who are thin and how they can be best treated.
Description	Background Lifestyle interventions and medications that improve body fat and insulin resistance are the cornerstone of type 2 diabetes management. However many people developing apparent type 2 diabetes are not overweight (8% of those living with Type 2 diabetes in the UK, and up to 40% in some countries). The cause of type 2 diabetes in those without overweight and obesity is poorly understood. This has critical importance for both treatment and prevention. If diabetes is unrelated to excess body fat and insulin resistance then interventions targeting these pathologies may not be effective for either prevention or treatment, and other approaches to management may be needed. Recent work by the supervisory team and collaborators has already demonstrated a new form of non-autoimmune diabetes in young thin Africans (Katte Lancet Diabetes 2025), discovered new forms of monogenic diabetes, and (in preliminary data) demonstrated that a striking high proportion of newly diagnosed non-overweight type 2 diabetes in the UK appear to be misclassified. Research questions Does the cause of apparent type 2 diabetes differ in those who are not overweight in comparison to those who are overweight, and does their response to weight loss differ? Hypothesis Non-overweight type 2 diabetes is predominantly driven by genetically determined beta cell failure, and will have reduced glucose response to weight loss in comparison to overweight/obese type 2 diabetes. Objectives 1. To determine whether patients diagnosed with non-overweight Type 2 diabetes in the UK and USA have evidence of misclassified type 1 and monogenic diabetes, and whether this differs by ethnicity. 2. To use partitioned genetic risk scores to compare the genetic aetiology of type 2 diabetes in the non-overweight and overweight, and determine the proportion of cases attributable to specific aetiology 3. To determine whether exercise and macronutrient intake is associated with the development of non-overweight type 2 diabetes.

	4. To explore the metabolomic and proteomic signatures associated with development of non-overweight type 2 diabetes, and whether these differ from those living with overweight and obesity. 5. To determine whether glycaemic response to weight loss differs between those with non-overweight and overweight type 2 diabetes. Overview In this project the successful applicant will work together with experts in clinical medicine, genetics and statistical analysis, and use data from large population cohorts with intensive phenotyping and genetic data (the UK Biobank and US Geisinger Cohort) to investigate the cause and treatment of non-overweight type 2 diabetes. Phenotyping of these cohorts includes recent measurement of diabetes classification biomarkers (C-peptide and/or islet autoantibodies, led by Jones/Patel), that will for the first time allow robust exclusion of type 1 diabetes. They will be supported by a large team with an international reputation in subclassification and phenotyping of diabetes, and work alongside African researchers undertaking related research in lean Africans (NIHR Global Health Group– PI Jones) with extensive opportunities for collaboration. A wide range of analysis can be undertaken in this project, which can be steered by the applicant. We have included a summary of key potential analysis below but this will be tailored to the applicants interests and progress. The applicant will analyse data from non-overweight (BMI <25kg/m2 or ethnicity specific equivalent) type 2 diabetes and compare them to matched controls of similar BMI without diabetes, and to classical type 2 diabetes with raised BMI. They will assess frequency of misclassified autoimmune and monogenic diabetes. After excluding misclassified participants they will use previous published genetic risk scores to determine whether those with non-overweight type 2 diabetes have genetic evidence of specific aetiology including islet autoimmunity, ectopic fat, beta cell failure and insulin resistance, and whether these differ from the overweight/obese. They will use a genetic epidemiology technique, developed by the Exeter team (Thomas Lancet Diabetes 2018) to estimate the proportion of cases attributable to specific aetiology, and examine for biomarker evidence of these pathologies, including data from UK Biobank metabolomic and proteomic panels. This will build on recent work that has identified novel protein markers for subtyping of adult-onset diabetes (Patel, in review). They will have the opportunity to progress the work in further areas including: 1. Contribution of diet and exercise to development of non-overweight type 2 diabetes using data derived from 24 hour dietary recall and accelerometery in UK biobank (in collaboration with Prof Rob Andrews, Exeter). 2. Whether response to weight loss (and potentially pharmacological therapy and long term outcomes) differs from the obese, using healthcare record data from over 300,000 people with type 2 diabetes (Clinical Practice Research Datalink, working with the Exeter led MRC Mastermind consortium on precision treatment of type 2 diabetes. 3. How aetiology differs by ethnicity.

	The end result of this research will be crucial information to understand the cause of apparent type 2 diabetes in those without obesity, to inform future prevention and treatment.
Can be completed part time?	Yes
Supervisory Team	
Lead Supervisor	
Name	Professor Angus Jones
Affiliation	Exeter
College/Faculty	Health and Life sciences
Department/School	Clinical and Biomedical Sciences
Email Address	angus.jones@exeter.ac.uk
Co-Supervisor 1	
Name	Professor Kashyap Patel
Affiliation	Exeter
College/Faculty	Health and Life Sciences
Department/School	Clinical and Biomedical Sciences
Co-Supervisor 2	
Name	Professor Beverley Shields
Affiliation	Exeter
College/Faculty	Health and Life Sciences
Department/School	College of Clinical and Biomedical Sciences
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	