Application number/Title: 11867 - Dissection of the Genetic Susceptibility of Obesity Traits and their Comorbidities

Applicant PI: Dr Cecilia Lindgren

Applicant institution: University of Oxford
Wellcome Trust Centre for Human Genetics
Roosevelt Drive
Oxford OX3 7BN
United Kingdom

Collaborators:

Dr Eleftheria Zeggini, Professor Naveed Sattar, Professor Ruth Loos, Professor Paul Elliott and Professor Tuomas Kilpelainen

Collaborator institutions:

Wellcome Trust Sanger Institute
Department of Human Genetics
Wellcome Trust Genome Campus
Hinxton
Cambridge CB10 1HH
United Kingdom

University of Glasgow
Cardiovascular and Medical Science
126 University Place
Glasgow G12 8TA
United Kingdom

Icahn School of Medicine at Mount Sinai
Preventive Medicine
One Gustave L. Levy Place
New York NY 10029
United States

Imperial College London
Epidemiology and Biostatistics
School of Public Health
St Mary’s Campus, Norfolk Place
London W2 1PG
United Kingdom

University of Manchester
Manchester Diabetes Centre
Obesity, Adiposity, Fat distribution, Genetics, Environmental, Comorbidities

Application Lay Summary:

1a: Obesity is a heritable and heterogeneous condition that is defined as the accumulation of excess body fat to the extent that it results in long-term adverse health outcomes (psychiatric conditions, osteoarthritis, type 2 diabetes mellitus, hypertension, hyperlipidemia, liver steatosis, cardiovascular disease, subfertility traits and certain types of cancer, amongst others). In this proposal, we propose to dissect the environmental, lifestyle and genetic underpinnings as well as the relationships between an array of obesity traits and their comorbidities in UK Biobank through epidemiological investigations and genome-wide association analyses.

1b: Currently ~50% of the population in the UK is overweight with a further 25-30% that are obese and the socioeconomic cost incurred by obesity and related comorbidities are high. The full spectrum of obesity traits and their underlying causes and links to adverse outcomes is not well characterized. There are also few (cost) efficient treatment strategies for obesity. The identification of risk factors an increased understanding for obesity traits thus fits with the central aim of UK Biobank to improve the prevention, diagnosis and treatment of diseases.

1c: We will conduct epidemiological analyses to identify demographic, disease, environmental and lifestyle factors associated with increased risk of obesity traits. We will then perform genome-wide association analyses of DNA-genotyping data to identify novel genetic variants that increase the likelihood of obesity traits, after accounting for these “epidemiological” risk factors. We will also perform analyses to investigate epidemiological and genetic risk factors for obesity trait-related adverse health outcomes and how they are correlated with, and possibly causing, each other.
1d: For these analyses, we request access to data generated for all individuals in UK Biobank. We request relevant environmental and lifestyle factors potentially associated with obesity traits (activity, diet, etc.) as well as in depth measures of adiposity (anthropometric measures, MRI data etc.), associated risk factors (lipids, HbA1c, etc.) and co-morbidities (prevalent and incident) inclusive of downstream adverse health outcomes (psychiatric conditions, osteoarthritis, T2D, hypertension, hyperlipidemia, liver steatosis, cardiovascular disease, subfertility traits, certain types of cancer). We also request genetic data for all individuals to evaluate association of genetic variants with obesity traits after accounting for lifestyle factors.

Project extension March 2018: “Obesity is a heritable and heterogeneous condition that is defined as the accumulation of excess body fat to the extent that it results in long-term adverse health outcomes (psychiatric conditions, osteoarthritis, type 2 diabetes mellitus, hypertension, hyperlipidemia, liver steatosis, cardiovascular disease, subfertility traits and certain types of cancer, amongst others). In this proposal, we propose to dissect the environmental, lifestyle and genetic underpinnings as well as the relationships between an array of obesity traits and their comorbidities in UK Biobank through epidemiological investigations and genome-wide association analyses. We plan to use the UKBB MRI scans to measure adipose- and muscle-specific phenotypes.

Reason: We plan to use the UKBB MRI scans to measure adipose- and muscle-specific phenotypes. A means of MRI quality control needs to be established. We will then generate a training dataset of MRI scans. Several deep learning approaches have been successful when applied to the task of classifying medical imaging data, exceeding gold standards such as trained radiologists (e.g., convolutional neural networks to diagnose skin cancer (Esteva et al., 2017) and U-nets (Çiçek et al., 2016) to fully segment MRI images into volumetric components). These methods would allow us to extract particular phenotypic information (e.g., amount of visceral fat, gluteal fat, etc) from MRI scans. The majority of algorithms that do such phenotyping are implemented by companies, making the algorithms intellectual property. Such a phenotyping approach would therefore be a tremendous resource not only for our efforts, but for the scientific community. To verify if biological signatures are homogeneous or heterogeneous across the phenotypes extracted, we will use several analytic approaches, including genome-wide association studies of MRI phenotypes, LD Score Regression across these GWAS to identify overlapping genetic signatures and build predictive models based on genetic risk score for a diverse set of fat depots throughout the body.”