**Application number/Title:** 35327 - Dissecting genetic relationships between type 2 diabetes, depression, and related phenotypes

**Applicant PI:** Dr Zhanna Balkhiyarova

**Applicant institution:** Imperial College London, London, UK

**Collaborator:** Professor Arie Nouwen, Middlesex University, London, UK

**Keywords provided by the Applicant PI to describe the research project:** biomarkers, depressive-disorders, diabetes, genetics, mendelian-randomisation, mri

**Application Lay Summary:**

Rationale: People with diabetes have an increased risk of developing depression, while people with depression have an increased risk of developing diabetes. Although the exact underlying mechanisms are still unknown, both conditions are believed to share a number of psychosocial (e.g. stress, life-style, burden of diabetes) and physiological (obesity, high blood pressure, inflammation, brain function, genetic) factors. Most epidemiological studies have found support for a direct effect of psychosocial factors in the development of depression in diabetes. However, the physiological factors, and notably genetic factors, may play a more indirect role and interact with the psychosocial factors.

The study aims to elucidate shared mechanisms of depression and type 2 diabetes (T2D) and to identify genetic factors contributing to their comorbidity using a high dimensional multi-omics framework.

The project main questions:

1) To identify common genetic determinants of depression and T2D using large-scale multi-phenotype genome-wide association study approach based on the UK Biobank data.

2) To identify genetic markers for white and gray matter reductions associated with T2D and depression and their role as possible moderators in the relationship between these two conditions.

3) To dissect causality and direction of the relationship between depression and T2D using bi-directional Mendelian randomisation (MR) approach.
The results of the project will elucidate shared mechanisms underlying the development of T2D and DD that can be used for development of preventative and treatment approaches for people with both conditions. The identified biomarkers of T2D and depression can be used as targets for therapy aimed at normalising the glycaemic profile and psychological state of patients, ultimately leading to the improvement of their subjective well-being and quality of life, and reduce the risk of diabetes complications. The innovative analytical multi-phenotype approach introduced in this project has a potential of changing public health standards within the next decade. This project will use modern robust high-dimensional data analysis approaches to analyse large-scale genetic data along with a statistical (Mendelian randomization) approach to establish the causal relationships between diabetes and depression. We wish to study the full cohort.

The duration of the project will be 36 months.