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Summary of research

Key words: Diabetes, CAD, Risk factors, Genotype

1a: Our aim is to discover novel risk factors for cardiovascular disease (CVD) in diabetic individuals. The study population will be defined by all individuals with diabetes at baseline.

1) We will assess the association of lifestyle, anthropometry, socio-economy and blood pressure in individuals with diabetes with the development of CVD.

2) Investigate the predictive value of biomarkers for development of CVD and differences in risk in a population with established diabetes and in a population with occult diabetes.

3) Identify novel genetic markers for the development for CVD in diabetic individuals using the imputed genotype data.

1b: Being one of the most common chronic diseases in the world diabetes is a major cause of premature illness and death in most countries and exerts a heavy economic burden on society. We aim to use the UK Biobank

data to discover novel risk factors for diabetic CVD. This could provide improved predictive power in asymptomatic subjects such that available preventative measures can be more appropriately targeted and new leads to the biological understanding of the disease. Such information is of high societal interest.

1c: Data from questionnaires, clinical examination, blood measurement, genetic information, death register and hospital admissions from all individuals in the UK Biobank population that reported having diabetes in the verbal interview will be stored on a secure server. Associations between biomarkers, environmental, behavioural and genetic risk factors and the development of CVD will be assessed. The results will be compiled and interpreted using epidemiological methods, summarized in two-three academic papers and submitted for publication.

1d: Aim 1: The study population for the first investigation of lifestyle and anthropometry variables for association with CVD all participants that reported having diabetes in the verbal interview at the assessment centre (~ 27,000 individuals) (Category 100071, Field ID 20002).

Aim 2 and 3: When available (Q3 2016 according to timeline) we would like to add all individuals with a random HbA1 $\geq 6.5\%$ (approximately $\frac{1}{2}$ of the diagnosed individuals, i.e. 13,000) and use this larger population for the biomarker study and the genetic study. When available, we also would refine the self-reported diagnosis with adjudicated diabetes outcomes.

Project extension:

The aim of the proposal is to discover novel risk factors for cardiovascular disease (CVD) in diabetic individuals. The study population is defined by all individuals with diabetes at baseline.

The original application states the following aims:

- 1) We will assess the association of lifestyle, anthropometry, socio-economy and blood pressure in individuals with diabetes with the development of CVD.*
- 2) Investigate the predictive value of biomarkers for development of CVD and differences in risk in a population with established diabetes and in a population with occult diabetes.*
- 3) Identify novel genetic markers for the development for CVD in diabetic individuals using the imputed genotype data.*

We would now like to expand the study to identify genetic variants for CVD risk factors in this population and assess their effect on CV phenotypes of interest in a Mendelian Randomization framework. We therefore would like to amend the following analyses to the study protocol:

- 1) Identification of genetic variants for CVD risk factors and their association with other CV phenotypes and outcomes in type 2 diabetes patients.*

We would also like to add all-cause and CVD mortality as outcomes. We do not need to add any new variables to the data set to perform these studies.

Here is the summary of cardiovascular (CV) risk factors, phenotypes and outcomes. We will apply the proposed analysis to:

1) CV risk factors (identification of genetic variants in diabetic population, candidate + GWAS approach):

Blood lipids: LDL-C, HDL-C, total cholesterol

Anthropometry: BMI, Waist-to-hip ratio

Blood pressure: SBP, DBP

Inflammatory markers: CRP, IL-6

Glycemic traits: Glucose, HbA1c

2) CV phenotypes (here we assess the association of genetic variants for anthropometry/glucose SNPs with phenotypes):

Blood lipids: LDL-C, HDL-C, total cholesterol

Blood pressure: SBP, DBP

Inflammatory markers: CRP, IL-6

Glycemic traits: Glucose, HbA1c

3) Outcomes (here we assess the association of genetic variants for CV risk factors with outcomes):

Heart failure

Coronary heart disease

Stroke

CV mortality

All-cause mortality