**Single Nucleotide Polymorphisms Associated With Fasting Blood Glucose Trajectory And Type 2 Diabetes Incidence: A Joint Modelling Approach**

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To detect association between a SNP and a biomarker, genome-wide association study (GWAS) is still the main approach used, and has contributed to the identification of over a hundred SNPs associated with type 2 diabetes (T2D) or fasting glucose (FG). In published GWAS, the oft-used approach is predominantly a cross-sectional one. But many cohorts collect longitudinal data with repeated measurements at predetermined time points for many biomarkers, along with other covariates measured at baseline. It might be of interest to take into account the trend and/or temporal variation over time of these measurements. This could lead to improved statistical techniques for detecting novel genetic loci associated to T2D and/or FG, or help in refining signals in loci already reported in the literature.

In these observational cohorts with multiple measurements of a biomarker, time until a certain event of interest occurs is commonly reported. In many cases, a biological relationship is well documented and known to exist between the biomarker and the event of interest. Here, we propose a joint model approach specifically designed to efficiently estimate statistical parameters involved in both the time at onset of a given event and the temporal trajectory of a biomarker. Time at onset is modelled through a survival model, whereas the longitudinal biomarker trajectory is described using a linear mixed model.

First, using genotypes assayed with the MetaboChip DNA arrays (Illumina) from about 4,500 subjects recruited in the French cohort D.E.S.I.R. (Data from an Epidemiological Study on the Insulin Resistance Syndrome), we assessed the feasibility of implementing the joint modelling approach in a real high-throughput genomic dataset. Second, through simulated estimations of statistical power, we compared the joint model approach to the more traditional approach employed in GWAS. In our work, the event of interest was the reported onset of T2D diagnostic, and the longitudinal biomarker repeatedly measured over time was plasma FG level.

To the best of our knowledge, joint models have never been applied into a genetic epidemiology context and could help to identify novel loci sharing biological effects on both glycaemic traits and T2D.