OMICS profiling of cardiometabolic diseases

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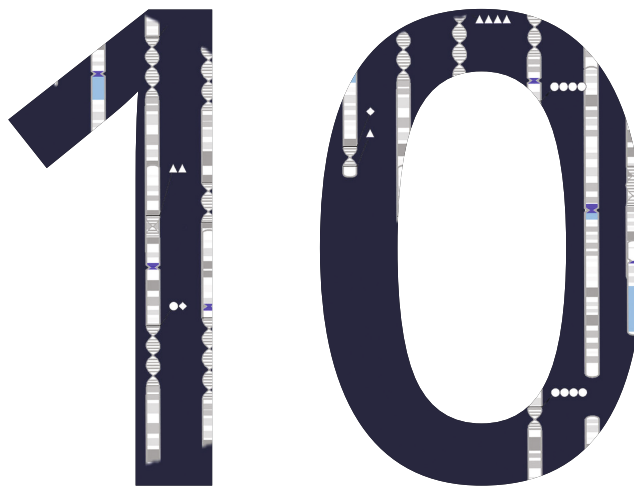
Summary of findings



SUMMARY OF FINDINGS

Clinical application of metabolomics measures requires in depth insight in the validity and reliability of these measurements. In this thesis, we focused on two commercially available targeted platforms, the Biocrates Absolute*IDQ*™ p150 assay, a MS-based metabolomics platform and Nightingale, a NMR-based metabolomics platform (1). Applying the Biocrates AbsoluteIDQ™ p150 assay in a subset of the NEO study, we developed prediction models for the risk of type 2 diabetes (T2D) using fasting and postprandial state metabolites separately. We used these models to stratify pre-diabetic individuals into high- and low-risk of developing to T2D. As described in **Chapter 2**, the results suggested that the model performance for stratification of pre-diabetic individuals into high- and low-risk of developing T2D using postprandial metabolites was similar to the model performance using fasting metabolites. Moreover, postprandial metabolites exhibited enhanced signals (i.e., four postprandial metabolites achieved the same prediction performance as the model composed of 12 fasting metabolites) for stratification of patients with impaired fasting glycaemia into high risk and low risk of developing T2D. The response to a meal, defined as changes between postprandial and fasting state measures, revealed a completely different metabolite selection in the prediction model than either the fasting or postprandial state, and the stratification performance of the model based on metabolite response was worse than the models developed based on fasting or postprandial metabolites. In **Chapter 3**, we further explored the genetic basis of fasting and postprandial state metabolites measured using the Biocrates Absolute*IDQ*™ p150 assay, by a candidate single nucleotide polymorphisms (SNP) approach. Of 38 gene-fasting metabolite concentration associations reported previously, 31 were replicated with postprandial metabolite concentrations, implying highly overlapping genetics of fasting and postprandial metabolite levels.

Using the Nightingale NMR-based platform, we systematically quantified the biological variability of 148 metabolites in both fasting and postprandial states. Both short- (<6 months) and long-term (>3 years) repeated measures were analysed in **Chapter 4**. Looking at short-term repeated measurements, postprandial metabolite concentrations after a liquid meal showed better biological reproducibility than fasting measures. Long-term repeated measurements, i.e., approximately 3 years between measurements, showed similar variability for postprandial and fasting metabolite concentrations. This indicates that postprandial metabolites measured after a liquid mixed meal are robust biomarkers for research. In **Chapter 5**, we performed a hypothesis-free GWAS on all the fasting and postprandial metabolite concentrations in the NEO study, as well as the metabolite meal response derived from the fasting and postprandial metabolite measures. In agreement with the findings in **Chapter 3**, the genetics of 148 fasting metabolite concentrations are overlapping substantially with

the genetics of postprandial metabolite measures. We next exploited two different methods to model the metabolite meal response taking baseline variation into account, i.e., the residuals of an orthogonal nonlinear least squares (OrNLS) and a linear mixed model (LMM). Overall, the genetic architecture of metabolite response revealed a distinctly different pattern from either fasting or postprandial state GWAS results. From both methods, rs10830963 in the melatonin receptor 1B (*MNTR1B)* gene was consistently found to be a genetic determinant of the postprandial glucose response. Since melatonin plays an important role in sleep and circadian rhythmicity, this suggests a role for these processes in the glucose response to a meal. In **Chapter 6**, we analysed the genetics of the early phase insulin response. By means of a GWAS, followed by functional analyses *in vitro*, we demonstrated that rs505922 located in the blood group determining *ABO* gene is associated with early phase insulin secretion. This finding might explain the previously identified elevated risk of T2D with carriers of rs505922:C allele in the general population.

Hyperglycaemia and dyslipidaemia are common risk factors for atherosclerotic cardiovascular diseases (CVD), whereas their roles in the risks for venous thrombosis (VT) are controversial. In **Chapter 7**, we studied the association between increased levels of fasting glucose in non-diabetic individuals as well as self-reported diabetes and the risk of a first VT in a large population-based VT case-control study. Neither fasting glucose nor self-reported diabetes were associated with the risk of a first VT, after adjustment for a large number of potential confounders. Inhibition of cholesteryl ester transfer protein (CETP) reduces plasma low-density lipoprotein cholesterol (LDL-C) concentration and elevated high-density lipoprotein cholesterol (HDL-C), suggesting its potential to prevent cardiovascular disease (CVD). Previous studies also showed the associations between CETP Taq1B genotype and the risk of a first VT. In **Chapter 8**, we performed a GWAS on plasma CETP concentrations in the NEO study, and identified three genetic variants that are strongly associated with CETP concentrations. To further assess causality of plasma lipid levels with VT, we adopted a two-sample Mendelian randomization (MR) approach, by using genetic variants associated with plasma CETP concentration identified from the NEO study in **Chapter 8**. In **Chapter 9**, the association between genetically determined CETP concentrations and 22 haemostatic factors as well as the risk of a first VT was assessed in the MEGA study, a population-based case-control study with the aim of studying the aetiology of VT. We showed that genetically determined CETP concentration revealed a weak negative association with factor VII activity. However, this did not translate to an association between genetically determined CETP concentrations and the risk of a first VT.