Genetic and environmental determinants of cardiometabolic health

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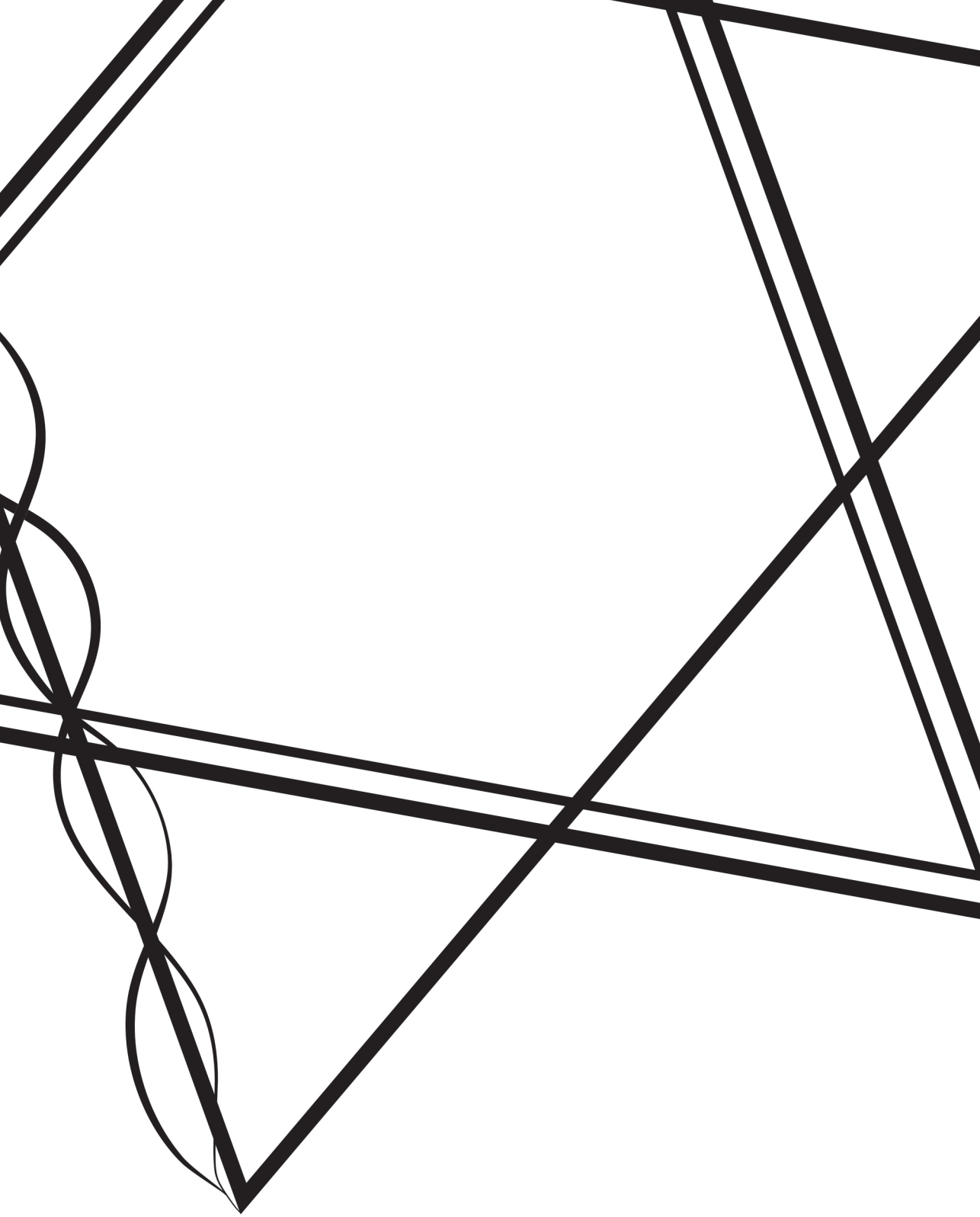

CHAPTER 7.1

English summary

ENGLISH SUMMARY

As a consequence of increased ageing of the population, age-related diseases have vastly increased. Cardiovascular disease is the leading cause of death. Moreover, a steep increase in the prevalence of type 2 diabetes mellitus is observed worldwide. In addition to obesity, being one of the main risk factors, there are multiple genetic and nongenetic factors that jointly determine the risk of developing cardiometabolic diseases. Therefore, it is important in research to focus on a better understanding of those factors that are (causally) associated with cardiometabolic diseases. This thesis aims to study the interplay between non-modifiable factors (genetics) and modifiable lifestyle factors (e.g. sleep, nutrition, physical activity) with cardiometabolic and cardiovascular health.

In chapter 2, we aimed to identify plasma metabolites associated with different indices of early disturbances in glucose metabolism and insulin sensitivity. In 233 non-diabetic individuals from the Leiden Longevity Study, we tested whether we could find associations between metabolites and measures of glucose metabolism and insulin resistance. We repeated these analyses in another cohort (the Netherlands Epidemiology of Obesity study) in individuals without diabetes to replicate our findings. Next, we investigated the significant findings in individuals with diabetes mellitus to validate these findings. We identified 12 metabolites to be associated with measures of glucose metabolism. Moreover, five of these metabolites, tyrosine, alanine, valine, tryptophan, and alpha-ketoglutaric acid levels, had a higher mean level in blood in individuals with diabetes mellitus compared to individuals without diabetes mellitus. These results may improve the understanding of the mechanisms involved in disease etiology and thereby may contribute to improved diagnostics of the early metabolic disturbances preceding diabetes mellitus.

In chapters 3.1, 3.2 and 3.3, we studied the association of sleep traits with cardiometabolic outcomes. It is known that both a short and long sleep duration and a poor sleep quality may affect glucose metabolism as well as serum and hepatic lipid levels. Therefore, we aimed to study the association between sleep duration and quality with serum and hepatic lipid content in chapter 3.1, and with glucose metabolism and insulin sensitivity in chapter 3.2. These studies were performed in the Netherlands Epidemiology of Obesity study. Self-reported sleep duration and quality were assessed using the Pittsburgh Sleep Quality Index questionnaire and outcomes were measures of the lipid profile, hepatic triglyceride content and glycemic traits. Compared with participants with medium sleep (7.0 hours of sleep per night), participants with the shortest sleep (5.0 hours sleep per night) had higher levels of blood lipids and hepatic triglyceride content, and higher insulin resistance. Bad sleep quality as compared with good sleep

quality was associated with higher levels of triglycerides in the blood and higher insulin resistance. However, when we adjusted our analyses for body mass index and the risk of sleep apnea, all these associations disappeared. In addition, we performed a Mendelian Randomization analysis to test for a potential causal relationship of sleep duration with glucose metabolism and diabetes, and we did not find evidence these associations were based on causality. Therefore, we concluded that previously observed cross-sectional associations of shorter sleep duration and poorer sleep quality with an adverse lipid profile and higher insulin resistance, may be explained by body mass index and the risk of sleep apnea, rather than by a direct effect of sleep itself. Therefore, in chapter 3.3, we aimed to elucidate the biological pathways of an adverse lipid profile for both short and long sleepers. We performed short- and long-sleep-SNP interaction analyses in over 125,000 individuals in a large collaborative setting (participating in the gene-lifestyle working group of the Cohorts for Heart and Ageing Research in Genomics Epidemiology) to obtain novel insights in the biological background of sleep duration-associated adverse lipid profiles. A total of 59 novel loci were identified in relation to lipid traits and we identified sleep-interactions for known lipid loci. For short sleep, the loci were previously described in relation to adiposity and inflammation and for long sleep in relation to neuropsychiatric traits. These results contribute to our understanding of the biological mechanisms that underlie sleep-associated adverse health outcomes.

Candidate gene studies and genome-wide association studies found that genetic variation in *APOE* is robustly associated with multiple cardiometabolic diseases and age-related phenotypes. However, large differences in the deleterious effects of this gene occur. In chapter 4.1, we described how a higher intake of fish and polyunsaturated fatty acids (e.g. omega-3 fatty acids) and a higher level of physical activity may be beneficial in preventing cognitive decline and heart disease onset in carriers of the risk *APOE ε4* allele. In chapter 4.2, we tested this hypothesis in the large UK Biobank, and we aimed to investigate the presence of a gene-environment interaction between physical activity, fish intake and polyunsaturated fatty acid intake and *APOE* on incident cardiovascular heart disease. In a population comprised of 344,092 European participants with no history of cardiovascular disease at study inclusion, we observed that a higher level of physical activity and a higher intake of oily fish was associated with a lower risk of new onset cardiovascular disease. This association was similarly observed in both APOE genotype carriers (risk and nonrisk). A higher intake of polyunsaturated fatty acids was only associated with a lower risk of cardiovascular disease in carriers of the risk allele. We did not find evidence for a formal gene-environment interaction on a multiplicative scale on cardiovascular disease onset. These results indicate that a better lifestyle might be similarly effective across all APOE isoform carriers in reducing new cardiovascular disease onset.

Increasing evidence suggests an association between levels of thyroid hormone and insulin resistance, and diabetes mellitus. In chapters 5.1 and 5.2, we aimed to investigate the potential causal association of thyroid hormone status with glucose metabolism and diabetes mellitus. Genetic variants were used in Mendelian Randomization analyses to assess these associations relatively free of residual confounding and/or reverse causation. Genetically-determined thyroid hormone status was not associated with glucose metabolism nor with diabetes mellitus in the study described in chapter 5.1. In chapter 5.2, we used a new study population and a more recent set of genetic instruments. Similar as in chapter 5.1, thyroid hormone status was not associated with diabetes mellitus. However, in a group with a genetically-determined lower body mass index, higher thyroid stimulating hormone (TSH) level was causally associated with a lower risk of diabetes mellitus. This indicates that there might be a causal association between thyroid hormone status and diabetes mellitus, however, only in individuals with a lower body mass index. These findings suggest a potential protective effect of TSH in individuals with a low body mass index.

This thesis has provided novel insights in several associations that are potentially important for cardiometabolic health. However, we should keep in mind that cardiometabolic diseases are very complex and multiple pathways act together in order to maintain cardiometabolic health. This extraordinary level of complexity calls for more sophisticated approaches in order to deepen our understanding of the mechanisms that underlie cardiometabolic health and disease. For example, by using more advanced data modelling techniques, several types of data (e.g. clinical and omics) may be analyzed simultaneously. When these methods are then used to predict individual risks for disease onset, this may be of value in personalized medicine. In the future, these efforts may lead to a healthcare system in which the risk for an individual (or group of individuals) for certain diseases can be estimated more precisely. Eventually, preventive strategies may be implemented, specifically tailored to an individual's genetic and/or metabolomics profile to more effectively prevent and treat cardiometabolic diseases. This may thereby result in a decrease of the burden of cardiometabolic disorders and age-related diseases on the patient and the society as a whole.