Aims and outline of this thesis

Aims

The general aim of this thesis is to explore modifiable risk factors of liver disease in the general population. We examined the role of 1) dietary quality and composition, 2) body composition, and 3) the gut microbiome in relation to liver steatosis and liver stiffness.

Outline

As set forth in the introduction, diet plays a major role in the development and treatment of NAFLD. Furthermore, there is increasing evidence that it is not only dietary quantity, but also dietary quality that is important in promoting liver health. For instance, the consumption of nutraceuticals – foods with a particular health benefit – may promote liver health via various pathways. A well-known studied example of such a nutraceutical is coffee. Together with tea, it is the most consumed beverage worldwide and it has been suggested that coffee could prevent or even reverse hepatic fibrosis. However, studies in the general population are lacking. And although tea and coffee share certain features, such as the constituents caffeine and antioxidant polyphenols, the association between tea and liver health was not well-studied at all. We therefore examined whether coffee and tea were associated with hepatic steatosis and fibrosis in our large community-dwelling population in part II (**Chapter 3**). To further explore the mechanisms underlying the role of coffee in liver health, we conducted a systematic literature search in **Chapter 4**. Specifically, we reviewed experimental models studying the effect of coffee on hepatic steatogenesis, fibrogenesis, and carcinogenesis.

In part III, we studied the role of diet as a whole in relation to NAFLD. Lifestyle modification, generally aimed at weight reduction, is the cornerstone of treatment in NAFLD, but specific evidence-based recommendations on the optimal dietary composition for NAFLD lacked. Therefore, we studied the independent associations between macronutrients and NAFLD in **Chapter 5**. In this study we found in particular that excessive intake of animal protein was associated with higher NAFLD prevalence. To further examine the pathophysiological mechanisms behind this association we conducted a spin-off study on the association between diet-dependent acid load – which is known to be particularly high in animal protein rich diets – and NAFLD in **Chapter 6**. Lastly, to summarize the relation between diet and NAFLD, we conducted a study in which we longitudinally assessed the relation between well-known dietary quality indices, such as the Mediterranean Diet Score, the World Health Organization Score and the Dutch Dietary Guidelines, and risk of NAFLD. We additionally looked at population-specific dietary patterns and NAFLD (**Chapter 7**).

In part IV of this dissertation, we explored the in-depth association between body composition and NAFLD. We know that not every NAFLD patient is obese and that – vice versa – not every obese person has NAFLD. In addition, it is increasingly recognized that BMI is not an all-encompassing measure for adiposity. Asian studies have proposed that low skeletal muscle mass is an important risk factor for NAFLD as well. However, studies using validated tools to measure skeletal muscle mass performed in a Western population were lacking. In addition, the populations studied were rather overweight, so it was not clear whether the association found was an actual reflection of low skeletal muscle mass, or a mere reflection of excess fat mass. In **Chapter 8** we therefore studied the independent association of the different components of the body with NAFLD, stratified by sex and BMI. We were particularly interested in the association between NAFLD and skeletal muscle mass with (sarcopenia) or without (presarcopenia) loss of muscle function. In addition, we compared the various body parameters in relation to NAFLD prevalence. In **Chapter 9** we respond to an interesting prospective study on the lifestyle benefits in lean NAFLD patients. We discuss whether it is weight loss or something else about the lifestyle in this group that causes NAFLD to reverse. In addition, we plead against the use of FLI in the context of assessing body composition, based on additional data analyses performed in our population.

Over the last decade, the role of the gut microbiome in human health has gained global interest. The tight connection between the gut microbiome and the liver is referred to as the 'gut-liver-axis'. Indeed, microbiome-derived metabolites can reach the liver via the portal vein, which constitutes 70% of the hepatic blood inflow. It has even been proposed that ethanol-producing bacteria in the gut microbiome of children contribute to the pathogenesis of steatosis, mimicking alcoholic liver disease. In **Chapter 10** we therefore studied the association between microbial diversity, composition, predicted metagenomics and serum metabolomics with (non-alcoholic) steatosis and steatofibrosis.

Finally, part VI contains a compilation of all correspondence. **Chapter 11 to 13** concern replies to correspondences on studies from **Chapter 3 and 5**. These correspondences reflect the interest and discussion these publications triggered in the field.