Targeting obesity and metabolic health

S U M M A R Y

Obesity is a complex chronic disease of which its prevalence has been steadily increasing worldwide. Besides posing challenges to public health, obesity raises the risk of other chronic diseases, including type 2 diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease. To improve health of individuals living with obesity and reduce the global burden of associated diseases, comprehensive strategies are needed, including lifestyle interventions promoting balanced nutrition and physical activity, as well as supportive environments. Understanding the underlying mechanisms of obesity-related metabolic health risks and exploring innovative prevention or treatment approaches are crucial for effectively addressing this global health challenge. Therefore, the main objective of this thesis was to investigate different strategies to tackle obesity and improve metabolic health. The different strategies comprised the use of a low-energy diet to induce weight loss in adults with overweight or obesity, the use of sweeteners and sweetness enhancers (S&SEs) in replacement of sugar in adults with overweight or obesity, and a family-based approach to improve or maintain weight after weight loss in adults with overweight or obesity and their children. To accomplish this, different human intervention studies were performed and lined up in the different chapters of this thesis.

The most effective approach to target obesity and the associated metabolic risks is weight loss. In **Chapter 2**, we investigated the effect of weight loss, by use of a low-energy diet, on whole-body and tissue-specific insulin sensitivity and hepatic lipid content and composition in adults with overweight or obesity. Data from the European SWEET project (S&SEs: Impact on health, obesity, safety and sustainability) was used. We observed improvements in whole-body and tissue-specific insulin sensitivity, as well as, intrahepatic lipid (IHL) content, and more specifically, a reduction in hepatic saturated fatty acid fraction following weight loss in individuals with overweight or obesity without hepatic steatosis (defined as >5% IHL content). The decrease in IHL content was associated with improved hepatic insulin sensitivity in individuals with overweight or obesity. In **Chapter 6** and **Chapter 7**, we extended our investigation to a larger population of the SWEET-study, building upon the findings observed in **Chapter 2**. Consistent with **Chapter 2**, we demonstrated improvements in whole-body insulin sensitivity after weight loss, not only within the same research center (**Chapter 7**) but also multi-center across different

countries in Europe, including The Netherlands, Denmark, Spain, and Greece (**Chapter 6**). These findings not only confirm the initial observations but also highlight the robustness and generalizability of the improvements in metabolic health following weight loss.

Despite the observed beneficial effects of weight loss in **Chapter 2**, weight loss may pose challenges in long-term maintenance in both adults and children. In **Chapter 3**, we investigated the efficacy of a weight-maintenance family-based approach in adults with overweight or obesity and their children following weight loss. Data from the European Diet, Obesity, and Genes (DiOGenes) study was used to assess the efficacy of a family-based dietary approach in eight different countries through Europe. We found that better weight maintenance in parents after a period of weight-loss was associated with less increase in BMI Z-score of their children. Importantly, this approach proves beneficial regardless of the child's initial weight status. The findings support family-based approaches and the inclusion of parents for weight management of their children throughout eight different countries in Europe, including The Netherlands, Denmark, United Kingdom, Greece, Germany, Spain, Bulgaria, and The Czech Republic

One common approach to improve energy balance and thereby body weight control is to refrain from sugars by replacing them with S&SEs. In **Chapter 4** and **Chapter 5**, we provide an overview of the current literature on the physiological effects of S&SEs on body weight control, glucose homeostasis, and food intake behavior. We explained that the majority of clinical studies performed thus far report no effects or beneficial effects of S&SEs on body weight and glycemic control. Furthermore, it is evident that extrapolation of the metabolic effects of a single S&SE to all S&SEs is not appropriate due to differences in pharmacokinetics of different S&SEs. In **Chapter 4** and **Chapter 5**, the importance of long-term human dietary intervention studies investigating the impact of S&SEs on metabolic health, and especially the underlying physiological mechanisms, was highlighted.

In **Chapter 6** and **Chapter 7**, we described the outcomes of the SWEET-study in which we investigated the long-term effects of S&SEs, as a replacement for sugar in the

context of a healthy diet, on body weight control, gut microbiota composition, markers of adipose tissue function, and metabolic health in individuals with overweight or obesity. In **Chapter 6**, we demonstrated that long-term S&SE-intake improves body weight control and other parameters of body composition in adults with overweight or obesity across different countries in Europe. One possible mechanism, as shown in **Chapter 7**, may relate to the alterations in the expression of adipose tissue genes involved in lipid metabolism, including lower expressions of lipoprotein lipase (*LPL*) and comparative gene identification-58 (*CGI-58*), leading to reduced adipose tissue lipid turnover. It can be speculated that the latter findings may lead to reduced adiposity and improved body weight control, thereby contributing to the beneficial effects of S&SEs. Furthermore, in **Chapter 6**, we found that long-term S&SE-intake can affect energy balance by reducing energy intake (rather than affecting energy expenditure). Additionally, no alterations were found in the expression of the sweet taste receptor, *TAS1R3*, upon S&SE-intake, thereby suggesting that the intake of S&SEs does not disrupt metabolic signaling pathways in adipose tissue involving the sweet taste receptor.

Moreover, in **Chapter 6** we showed that the S&SEs group shifted their gut microbial composition towards a higher abundance of short-chain fatty acid (SCFA) and methane (CH_4)-producing taxa compared to the sugar group. This was accompanied by more gastrointestinal symptoms in the S&SEs group, possibly due to the higher abundance of CH_4-producing taxa. Since SCFA are associated with positive metabolic effects, it can be speculated that the higher abundance of taxa related to SCFA production influenced the observed effects on body weight control or reduced energy intake by potential effects on energy expenditure or satiety. Although no effects were found in circulating incretin levels, more research is warranted to investigate the functionality of the human gut microbiome and brain reward upon long-term S&SE-intake.

Although positive effects were observed on body weight control upon long-term S&SE-intake, no significant effects were found on metabolic health, including insulin sensitivity (whole-body and muscle-or liver) and IHL content, in adults with overweight or obesity (as discussed in **Chapter 6** and **Chapter 7**). This suggest that the potential reduction

in adipose tissue lipid turnover and the shift in microbial composition, as well as the observed improvements in body weight control following prolonged S&SE-intake do not translate into alterations in metabolic health.

In conclusion, the work described in this thesis demonstrated different approaches that are effective in targeting obesity and/or metabolic health. The main findings are that weight loss improves insulin sensitivity and IHL content and composition, family-based approaches are effective in the weight management of children, and that long-term S&SE-intake improves energy balance and body weight control, with no effect on cardiometabolic health. Furthermore, we showed altered adipose tissue lipolytic gene expression and gut microbial composition changes upon long-term S&SE-intake, indicative of possible beneficial health effects. However, while our findings provide valuable insights, further studies are warranted for further mechanistic deepening of S&SE-induced alterations on microbial composition and their broader implications for body weight management and metabolic health. Overall, our findings contribute valuable knowledge to the fields of obesity research, metabolic health, and dietary interventions, highlighting the potential of S&SEs to not only support body weight control but also foster beneficial shifts in microbial composition, thereby offering a promising approach to target obesity and improve overall health outcomes.