

Targeting obesity and metabolic health

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IMPACT

This thesis described different strategies to tackle, prevent and reduce the risk of obesity and its related metabolic complications. We investigated the effect of weight loss on metabolic health in adults with overweight or obesity and the effectiveness of a family-based approach on body weight control and metabolic health in both adults with overweight or obesity and children. In addition, we determined whether sweeteners and sweetness enhancers (S&SEs) in replacement of sugar improves body weight control and metabolic health, including whole-body and tissue-specific insulin sensitivity, intrahepatic lipid (IHL) content, gut microbial composition, and markers of adipose tissue function. In this section, the impact of the work described in this thesis will be discussed in terms of societal, economic, scientific and public relevance. Further implications and applications of approaches as a potential therapeutic strategy to improve adiposity and metabolic health will be highlighted.

Social and economic impact

Over the past few decades, overnutrition and obesity have surged as global health concerns due to factors like globalization and dietary shifts. Since 1970, dietary habits have shifted towards an increase in energy intake, greater consumption of energy-dense foods, and reduced fiber intake (1, 2), all contributing to the rise of non-communicable diseases, including obesity. By 2016, over 1.9 billion adults were overweight and 650 million were obese, illustrating a global prevalence of 13% (3). This issue spans ages, with a 28% increase in the prevalence in infants (0-5 years) from 1990 to 2016 and a 14% increase in children and young adolescents (5-19 years) from 1976 to 2016 (4). Obesity is associated with increased risk for the development of cardiovascular disease, type 2 diabetes, and several types of cancer (5). In addition, compared to individuals with normal weight, the total mortality was 22% higher in individuals with obesity (5).

Furthermore, obesity is estimated to be the cause of more than 4% of Years of Life Lost (YLL) and 4% of Disability-Adjusted Life Years (DALYs) all around the world (6). Besides the clear clinical effects, obesity carries a substantial burden in personal life by possible reduction in daily functioning and quality of life, thereby affecting mental and social health (7-9). Economically, the burden is significant, with obesity and its comorbidities straining

healthcare systems and affecting families. In the Netherlands, yearly societal costs for those with overweight or obesity is on average nearly €11.500 (including healthcare, patient and family, and other costs) per person, of which productivity losses make up the biggest share (9). This underscores the urgency for effective strategies, interventions, and treatments to tackle the prevalence of overweight and obesity and the related metabolic consequences.

However, the maintenance of weight loss proves to be more challenging than achieving initial weight loss, with most individuals regaining weight over time (10-12). Research has demonstrated that weight regain may lead to a worsening of cardiometabolic complications compared to a previous period of obesity (13-15). The efforts to maintain weight loss have not been overly successful in adults as well as in children. In this thesis, we demonstrated that the use of S&SEs, in replacement of sugar, can improve body weight maintenance following initial weight loss. Moreover, we highlighted the importance of adopting a family-based approach to address childhood obesity effectively. Our findings suggest an effective approach to improve obesity and, subsequently, a possible reduction in obesity-related societal costs. Those well-defined strategies for body weight control and prevention of obesity should be a priority on the political health agenda, improving individual well-being and the burden on healthcare systems. Besides personal health gains, these actions will contribute to a healthier population and thereby a more productive workforce and robust economy.

Scientific and public impact

Conducting research with the goal of managing or preventing overweight or obesity has profound implications for science, public health, and policy development. In scientific terms, the research detailed in this thesis uncovers underlying mechanisms and enhances our understanding of how different approaches interact with the body metabolism and processes to improve body weight control and metabolic health. On a public level, research can drive informed decision-making and behavioral change within communities. Additionally, research insights shape evidence-based policies guiding comprehensive obesity interventions and promoting societal health.

Energy-restricted approach

One key strategy for preventing or managing obesity involves an energy-restricted approach to reduce weight. This approach has demonstrated reductions in IHL content and improvements in whole-body insulin sensitivity in individuals with overweight or obesity. Notably, our research contributes novel insights by also demonstrating a reduction in the fraction of saturated fatty acids after weight loss. This study, utilizing proton-magnetic resonance spectroscopy, was the first to explore changes in hepatic fatty acid composition before and after low-energy-diet-induced weight loss in individuals with overweight or obesity. These findings contribute to a better understanding of the interplay between IHL content, hepatic fatty acid composition, and whole-body and tissue-specific insulin sensitivity, paving the way for more effective strategies to manage obesity-related health issues. Additionally, our exploration of tissue-specific insulin sensitivity offers insights into responsive tissues or pathways after weight loss, guiding the development of targeted therapies for personalized and effective treatments of metabolic disorders.

Family-based approach

Obesity has a significant impact on public health, with its influence stretching beyond adulthood to affect the well-being of younger generations. Recent increases in childhood obesity prevalence highlight the urgency of addressing this issue (16). Offspring of overweight parents are at higher risk of developing weight-related problems (17). Furthermore, parental obesity more than doubles the likelihood of adult obesity in children aged under 10, regardless of their own weight status (18, 19). Since parents are a key mediator for driving the obesogenic environment at home, the parental involvement in weight management and lifestyle interventions targeting childhood obesity is important. Nevertheless, successful long-term weight management in children is hard to achieve and drop-out rates in family-based long-term weight management programs are often high.

In this thesis, we provide evidence supporting the effectiveness of incorporating parents into family-based dietary approaches for weight management of their children across eight distinct European countries. Importantly, this approach proves beneficial regardless of the child's initial weight status. These evidence-based insights can guide

policymakers, healthcare experts, and researchers in developing more impactful approaches for managing childhood obesity in Europe. Furthermore, this information resonates with parents and caregivers who are seeking ways to support their children's health, potentially fostering the adoption of healthier lifestyles including eating habits within families.

Sweeteners and sweetness enhancers

Excessive sugar consumption is a major factor contributing to the surplus of energy leading to the development of obesity (20). According to the World Health Organization (WHO) guidelines free sugar consumption should be less than 10% of the daily energy intake in order to prevent obesity (20). In the Netherlands, sugar intake surpasses recommendations with a total/free sugar intake of 14% of total daily energy intake by the Dutch population as confirmed by the Dutch National Food Consumption Survey (21). One common strategy to reduce sugar intake is to replace sugar by S&SEs. Recent WHO guidelines advise against the use of non-sugar sweeteners for body weight control or reduce the risk of noncommunicable diseases due to inconclusive evidence (22). While observational evidence hints at potential negative associations, short-term studies show neutral or positive effects. However, the short-term nature of these RCTs raises concerns about comprehensively understanding the long-term impact of S&SEs on human health, emphasizing the need for further long-term well-controlled studies.

The European SWEET project, outlined in this thesis, pioneers the exploration of the long-term effects of S&SEs in replacement of sugar, in the context of a healthy diet, on body weight control, the gut microbiota, and metabolic health, including IHL content and markers of adipose tissue function. The novel findings presented in this thesis challenges existing claims by demonstrating that the use of S&SEs, as a replacement for sugar, is not detrimental but rather beneficial for body weight control and dietary energy content, without having any effects on glycemic control. This is line with the majority of clinical studies performed thus far, reporting no effects or beneficial effects of S&SEs on body weight and glycemic control (23). Moreover, our research shows downregulation of genes in adipose tissue that are associated with adipose tissue lipid turnover, thus deepening our understanding of the potential metabolic impact of S&SEs. Interestingly, we were able to

demonstrate altered gut microbial composition towards a higher abundance of short-chain fatty acid and methane-producing taxa in the S&SEs group compared to the sugar group during a 10-month weight maintenance phase, which was accompanied by more gastrointestinal symptoms. Since SCFA concentrations have been associated with beneficial health effects in humans (24), it remains to be investigated whether the higher abundance of taxa related to SCFA production in the S&SEs group influenced the observed effects on body weight control or reduced energy intake by potential effects on satiety.

Hence, the described studies in this thesis showed effective approaches to improve body weight control and/or metabolic health. We not only validate the efficacy of weight loss and the positive impact of parental involvement in childhood weight management but also challenge existing WHO guidelines (25). In this thesis, we showed that the use of S&SEs in replacement of sugar is beneficial for body weight control without affecting glycemic control, prompting a reconsideration of the WHO guideline (25, 26). Additionally, these insights hold the potential to promote healthier lifestyles and alleviate the global burden of obesity and its related health issues.

Dissemination and exploitation

Communication of the research findings is key in order to achieve the intended impact. Therefore, for the SWEET project, a dissemination and exploitation plan was made to share these groundbreaking findings with the scientific community, healthcare professionals, policymakers, and the public. By strategically disseminating this knowledge, we aimed to contribute to the ongoing discussions in the field and encourage further exploration into the implications of substituting sugar with S&SEs. This plan aligned with our commitment to advancing scientific understanding and promoting evidence-based practices in the pursuit of better health outcomes. This strategic dissemination included the project website (<https://sweetproject.eu>), our research group's website (<https://www.nimolab.nl>), social media platforms (including Twitter, Youtube, and LinkedIn), leaflets and factsheets, press releases, and stakeholder workshops and meetings. Furthermore, a decision-support tool was developed for industry use, facilitating the implementation of the project's interventions and outcomes, leading to

APPENDIX

post-project commercial opportunities. For scientific communication, findings are disseminated to the research community via the European Association for the Study of Obesity (EASO) network of experts throughout Europe (e.g. by use of newsletters), European and International workshops at congresses (i.e. the European Congress on Obesity (ECO) and the Federation of European Nutrition Societies (FENS)), and open-access publications. Finally, Innovation Advisory Panel meetings and workshops were given for external stakeholders to provide updates, fostering collaborations and exploring exploitation opportunities.

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