VALORIZATION

SOCIAL RELEVANCE
Obesity is a worldwide increasing problem, warranting for new prevention and treatment strategies to reduce the risk on developing chronic diseases related to excess body weight. According to the 2016 report of the World Health Organization (WHO) the prevalence of obesity is still increasing worldwide, with 39% of adults aged 18 years and older being overweight (> 1.9 billion adults) and 13% being obese (>600 million adults) (1). It is especially alarming that 41 million children under the age of 5, and 340 million children and adolescents aged 5-19 were overweight and obese in 2016 (1). Overweight and obesity are major risk factors for the development of type 2 diabetes mellitus (T2DM). Just like obesity, the prevalence of T2DM has been steadily increasing over the past few decades. T2DM is associated with various comorbidities, including cardiovascular diseases and non-alcoholic fatty liver disease as well as an increased mortality risk. The WHO underscores in their global report on diabetes the enormous scale of the diabetes problem, and also the potential to reverse current trends (2). It has also been pointed out by the WHO that obesity is preventable (1). Furthermore, T2DM is one of the four priority noncommunicable diseases (NCDs) targeted by world leaders in the 2011 Political Declaration on the Prevention and Control of NCDs (2). These reports and declarations highlight the importance of the prevention and treatment of obesity and T2DM worldwide.

The fundamental causes of obesity and T2DM include a high caloric diet and insufficient physical activity. Effective tools are available to prevent obesity and T2DM and to improve disease management to reduce the risk of complications. Promoting physical activity is considered one of the most potent strategies to prevent and treat T2DM. World leaders agreed that one of the global targets for the prevention of T2DM (and other NCDs) to be attained by 2025 is a 10% relative reduction in the prevalence of insufficient physical activity (2). Other effective strategies for the prevention and treatment of obesity and T2DM include a healthy diet low in calories. Existing strategies that stimulate physical activity and promote a healthy diet are effective in reducing body weight and improving glucose homeostasis in patients with obesity and T2DM. However, these strategies seem to be challenging to adhere to on the long term for the people at risk. Therefore, it is important to investigate other strategies to prevent and treat obesity and T2DM. The present thesis describes three novel approaches that could lead to novel prevention and treatment strategies for people with obesity and obesity-related comorbidities such as T2DM and cardiovascular diseases.
Supplementation with the NAD+ precursor nicotinamide riboside has been investigated in this thesis as the first novel approach. Nicotinamide riboside can be easily added to the normal diet, which would enhance the compliance for the general public in contrast to low compliance rates for exercise training or a rigorous diet. Although it has been shown that nicotinamide riboside had many metabolic benefits including improvements in insulin sensitivity in animal models, these effects could so far not be translated to humans, as also shown in this thesis. However, since a relative short intervention period was applied in this thesis, future research should investigate whether long term supplementation with nicotinamide riboside could have metabolic benefits in humans to prevent or treat obesity and T2DM. The second novel approach that was investigated in this thesis was non-shivering cold acclimation. From this thesis we conclude that non-shivering cold acclimation for ten days at 16-17 °C does not have major beneficial health effects in humans with T2DM. However, it could be suggested that mild shivering induced by cold environmental temperatures, either indoor or outdoor, could be a novel way to improve metabolic health for the general public. More research is needed to quantify the amount and intensity of shivering that is needed to contribute to the prevention and treatment of obesity and T2DM, and the practical applicability in daily life. As a third novel approach we investigated whether replacing sitting time with low-intensity physical activities would have the same metabolic benefits compared to replacing sitting time with a single moderate-to-vigorous exercise bout per day. In this thesis we demonstrated that low-intensity physical activities such as standing and walking are similar effective in improving insulin sensitivity compared to a single moderate-to-vigorous exercise bout per day. Taken together, investigating novel approaches that have beneficial health effects and that can be implemented in daily life are of great social relevance to prevent and treat obesity, T2DM and other metabolic diseases.

**ECONOMIC RELEVANCE**

Obesity, T2DM and related comorbidities are a major economic burden for national health care systems, as well as for the patients and their families. In the Netherlands, total health care costs for T2DM (including comorbidities) were 1.6 billion euro’s in 2017 (3). Preventing obesity and T2DM via inexpensive and easy to access strategies such as the ones presented in this thesis can contribute to a reduction in global economic burden. Increasing physical activity by standing and walking is not only freely accessible and inexpensive for the general public, it does also contribute to a reduction in transportation use and costs. Food supplements, such as nicotinamide riboside, can be an inexpensive and easy addition to a healthy diet. Furthermore, lowering indoor temperatures and thereby challenging the body to deal with cooler environments, cannot only could improve human health but can also could reduce
heating costs of homes, offices and buildings. Above all, a reduction in transportation and heating contributes to less emission of greenhouse gases. Scientific evidence exists that warming of the climate system is unequivocal and that greenhouse gases emitted by human activities are the primary driver (4). The Paris Agreement signed in 2016 by 195 countries, states that by 2050 the emission of greenhouse gases has to be reduced by 95% in comparison to the level in 1990 (5, 6). As obesity and T2DM is an increasing problem and at the same time climate change is an urgent matter, the investigation of novel health promoting strategies to prevent and treat obesity and T2DM that are at the same time climate-friendly are of great economic relevance.

**ACTIVITIES AND PRODUCTS**
All studies described within this thesis were executed at the Department of Nutrition and Movement Sciences at Maastricht University within the Diabetes and Metabolism Research Group. The Diabetes and Metabolism Research Group investigates the mechanisms underlying the pathogenesis of T2DM and related metabolic diseases by performing translational research. The studies presented in this thesis were performed in close collaboration with the Department of Radiology and Nuclear Medicine of Maastricht University Medical Centre. This collaboration between scientists and the clinic allowed us to use non-invasive techniques like MR and a PET-CT scanning. Furthermore, research presented in this thesis is part of a large consortium (CVON ENERGISE 2014-02) between Amsterdam Medical Center, Leiden University Medical Center, Wageningen University and Maastricht University. Being part of such a consortium enhances collaborations between the different centers and thereby improves translational research.

The results presented in this thesis are or will be published in original scientific articles in international well-recognized peer-reviewed journals. Importantly, articles will be available online and can be assessed by scientists or other interested people worldwide. Furthermore, results from the studies described in this thesis are communicated and presented to the scientific community on (inter)national conferences and symposia via oral presentations and posters. Via this way, research knowledge was spread within the scientific community to facilitate new research ideas and hypotheses and to promote future research.

**INNOVATION**
The study results presented in this thesis are obtained in humans by state-of-the-art methods and techniques. When human clinical trials are performed, it is of great importance that reliable results are obtained in the most non-invasive way possible. In this thesis, we applied relatively new MRS techniques developed by our research
group to examine among others lipid accumulation in the muscle and muscle acetylcarnitine dynamics in a non-invasive way. In the past, these outcomes could only be studied and quantified with the use of tissue biopsies. Furthermore, we used stable isotope tracers during the hyperinsulinemic-euglycemic clamps and during the assessment of brown adipose tissue activity in combination with PET scanning. We also used a metabolic chamber to assess sleeping metabolic rate upon NR supplementation and to control the indoor environment with a stable temperature during the cold acclimation study period. Collaborations within the ENERGISE consortium allowed us to use additional technologies, such as metabolomics, to obtain more results from the valuable muscle tissue samples. The combination of these advanced techniques can only be performed in a few research departments worldwide and leads to innovative translational research data.

Furthermore, many research has been performed on classic intervention strategies such as exercise training (endurance training, resistance training, high intensity interval training or a combination) and reducing caloric intake with various diets (such as low carbohydrate diet, high protein diet, low fat diet, low glycemic load diet, Mediterranean diet, paleo diet, intermittent fasting or a combination). These intervention strategies share a common goal: increasing energy expenditure and reducing energy intake resulting in a low cellular energy status. A low cellular energy status activates metabolic pathways that lead to metabolic adaptations which are favorable for human health, such as an increase in insulin sensitivity. The research presented in this thesis describes the investigation of novel approaches to improve insulin sensitivity by targeting the same metabolic pathways as are activated by exercise training and caloric restriction, but then with novel strategies: supplementation with the food supplement nicotinamide riboside, non-shivering cold acclimation, and replacing sitting time by low-intensity physical activities.
REFERENCES