A metabolically healthy lifestyle

Impact

What is the main objective of the thesis, and what are the most important results and conclusions?

The main objective of this thesis is to examine if re-aligning the timing of physical activity and food intake with the natural biological rhythm, as well as reinforcing the eating-fasting cycle, has the potential to improve metabolic health. **Chapter 2** explains the working mechanisms of the biological rhythm and provides an assembly on current evidence on the potential of timed lifestyle interventions to improve metabolic health. Although the current body of evidence on beneficial metabolic effects of timed interventions is promising, there is still only a limited amount of human intervention studies that addresses timed interventions, and also the understanding of underlying mechanisms is lacking. More specifically, from this review it became clear that there is little knowledge in humans about the health effects of performing physical activity at a specific time-of-day. Therefore, **chapter 3** assessed the relationship between the amount and timing of moderate-to-vigorous physical activity (MVPA) on subjective sleep quality and -duration. Sleep was chosen as outcome variable since it is both related to metabolic health and regulated by the internal biological rhythm. This study found that performing a higher amount of MVPA was associated with a lower odds of fatigue-related dysfunction during daytime. Additionally, performing most MVPA in the morning was associated with fewer sleep disturbances compared to similarly distributing MVPA over the day. The subsequent **chapters 4** and **5** were devoted to investigate the effects of advancing dinner time and thereby prolonging the overnight fast on metabolic health. **Chapter 4** shows that acutely prolonging the overnight fast from 9.5 hours to 16 hours resulted in a higher overnight fat utilization in both middle-aged volunteers with a non-alcoholic fatty liver (NAFL) as well as in middle-aged healthy lean controls. However, even during the 16-hour fast, nocturnal fat utilization did not reach the same level in the volunteers with NAFL compared to that observed

in the control volunteers, even when the control volunteers were fasted for a shorter amount of time. Thus, although prolonged fasting improves fat oxidation in adults with NAFL, it does not result in a normalization of fat oxidation. Furthermore, in both groups, hepatic glycogen utilization did not change in response to the longer time fasting. In **chapter 5** the metabolic efficacy of a time restricted eating (TRE) regime was tested in adults with type 2 diabetes. The main finding of this study was that limiting food intake to a 10-hour daily time window for a period of 3 weeks resulted in lower fasting- and 24-hour glucose levels as compared to the control condition, in which volunteers spread their habitual food intake over at least 14 hours per day. In addition, volunteers spent significantly more time in the normal glucose range with TRE. Importantly, it was found that eating within 10 hours during daytime was safe and feasible to follow for adults with type 2 diabetes.

In **chapter 6**, a pharmacological approach was used to create a more pronounced fasted state by studying the diabetes medication dapagliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i), in adults with insulin resistance. This medication blocks the resorption of glucose in the proximal renal tubules resulting in a higher urinary glucose excretion. Two weeks of dapagliflozin resulted in lower 24-hour glucose levels, higher 24-hour FFA levels, and lower nocturnal levels of beta-hydroxybutyrate as compared to the placebo. In addition, maximal mitochondrial oxidative capacity was higher with dapagliflozin. No changes were found in hepatic glycogen and -lipid content.

To gain more insight into the physiological mechanisms that underlie the fasting response, **chapter 7** looks into the acute effects of a 60-hour fast versus fed condition on energy metabolism and -rhythmicity in healthy young male volunteers. This study showed a rapid switch to fat oxidation during the prolonged fast, and fat oxidation kept increasing gradually during the 60h fast. Carbohydrate oxidation decreased to a minimum during the fast, although it scarcely became zero. Inspection of the day-night rhythm of energy metabolism showed that particularly the rhythms in substrate

oxidation were driven by food intake, whereas the rhythm in energy expenditure remained unaltered with fasting.

What is the contribution of the research results to science and society?

For the last couple of centuries, society is struggling with an increasing burden of chronic diseases, including obesity and type 2 diabetes. According to the WHO, global deaths that could be attributed to diabetes increased with a staggeringly 70% from the year 2000 to 2019. In addition, during the recent COVID-19-pandemic it became painfully clear that the societal burden of chronic diseases does not only consist of increasing healthcare costs. During this pandemic, people with a disturbed metabolism were inflicted the most, and hospitals were overflowing. This illustrates that the current medical facilities are poorly equipped for the current disease load and emphasizes the need for improvement of metabolic health.

Although human lifestyle intervention studies generally have a limited effect on societal health, they can have an impact on health at the individual level. Importantly, human intervention studies are capable of unravelling cause-and-effect relationships which can be used as a foundation for policy makers to adjust health care recommendations or to implement measures that are able to improve metabolic health on a large scale. Poor diet and low levels of physical activity have traditionally been viewed as the most important lifestyle behaviours that underlie the development of obesity and type 2 diabetes. Studies in this thesis add to the change in this vision by highlighting that the timing of eating and being active also impacts metabolic health. Results of this thesis build on the existing body of evidence that indicates that eating and being active at the wrong time-of-day, as with night-shift work, is related to poor metabolic outcomes such as weight gain and an increased risk of developing type 2 diabetes.

Not only night-shift work disturbs the natural day-night rhythm, also flying across continents (experienced as jetlag) and going to bed late and sleeping in during the weekend as compared to work days (societal jetlag) disturbs the internal rhythm. Moreover, current 24-hour society facilitates eating around the clock, with omnipresent food availability, and thereby discourages the abstinence of food intake resulting in a disturbed feeding-fasting rhythm. Studies have indeed shown that most people spread their food intake over the larger part of the day. Consequently, people are still eating in the evening and night, when the body is less prepared to handle the nutrient load. Results in this thesis emphasize the importance of a pronounced fasting state during the night for metabolic health.

A large part of the society also suffers from sleep problems. This is concerning, since sleep affects both mental- as well as physical health, including metabolic health. Indeed, a good quality of sleep is important for the prevention of type 2 diabetes but has been long overlooked in most previous metabolic studies. Importantly, the preferred treatment for sleep problems is behavioural intervention, since sleep medication generally has negative side effects and a short-lasting effectivity. The day-night rhythm largely determines sleep quality. Therefore, re-aligning the timing of food intake and activity with the internal rhythm may also affect sleep. In this perspective, exercise is seen as an effective behavioural intervention to improve sleep. Since it can be challenging for people to implement exercise in their daily lives, in this thesis it was explored if an association exist between being generally more active (so not exercise per se) and sleep. Furthermore, it was investigated if there existed an association between the time-of-day at which participants were most active and sleep outcomes. Although association studies are not able to unravel cause-and-effect relationships, they do provide information if there could exist a relationship between two parameters. The study conducted in this thesis did, however, not show strong evidence of an association between the amount and timing of moderate-to-vigorous physical activity, and sleep. Thus, it does not appear that being active in general and/or being more active on a certain time-of-day is related to sleep.

To whom are the research results relevant?

The internal day-night rhythm is present in virtually all cells and tissues, and thereby affects whole-body physiology. Therefore, the research results discussed in this thesis are relevant to a wide public. First of all, the studies performed in this thesis investigated a range of mechanisms underlying the metabolic benefits of restoring the fasting-feeding cycle, but also revealed gaps in knowledge that need to be addressed in future studies. As such, academics could use the results found in this thesis to give direction to the development of future studies. Important to note is that the effects of reinforcing the internal rhythm via timed interventions could extend beyond metabolic health. Indeed, rhythmicity can be found in the whole body and disturbances of the internal rhythms do not only affect metabolism. For example, sleep deprivation and disruption of the day-night rhythms are also implicated in the development of Alzheimer's disease, which is the third leading cause of death in America and Europe. Conversely, people with Alzheimer's disease also exhibit disruptions in their internal rhythm. Thus, an interesting future research direction could be the effect of re-aligning the internal rhythm with the external rhythm via time restricted eating on the prevention or management of Alzheimer's disease.

Secondly, the studies performed in this thesis could be relevant to the field of medicine. In this perspective, it has long been known that some medication work better when taken at a specific time-of-day, termed chronotherapy. However, there are still a lot of knowledge gaps in the field of chronotherapy when it comes to metabolism. Currently, there are agents on the market that are able to partly mimic the effects of exercise and/or fasting by targeting the same metabolic pathways. Results in this thesis support the notion that altering the timing of the intake of these agents may enhance their efficacy. Thus, in this thesis is was showed that creating a more fasted state during the night resulted in beneficial metabolic outcomes, such as a higher fat oxidation and improved glucose homeostasis. Therefore, timing the intake

of exercise/fasting mimetics so that they are effective at night time may confer the maximal metabolic benefit.

Ultimately, it is not unlikely that the timing of food intake and physical activity could also be combined with medical treatment to gain the maximal metabolic benefit. Thus, in the future, medicine and lifestyle may join forces to achieve the highest treatment efficacy. Furthermore, results in this thesis may not only be relevant for medical research, but also for daily medical practice. The current modus operandi for assessing the medical status of a patient is the examination of the patient during only one medical visit. However, studies in this thesis show that fasting time as well as the time-of-day at which the measurement takes place can affect its outcome. Twenty-four-hour measurements, performed over multiple days, could give a better indication of the health status of a patient as compared to a single measurement at one time point. With the introduction of devices that are able to measure glucose every 15 minutes for multiple days, the development of devices that are able to also measure other metabolites for multiple days seems within arm's reach.

Thirdly, when looking at health from a broader perspective, the studies discussed in this thesis may be interesting for the public health sector as well. An important take home message from our results is that a long fasting period during the night positively affects metabolism, which could be implemented into a healthcare recommendation that is easy to understand. Given that fasting does not require any resources, the recommendation of prolonging the fasting period also fulfils the societal demand for sustainability.

Finally, a lot of media attention was gained for the TRE study, indicating that the results in this thesis are not only relevant for professionals working in the field of healthcare and type 2 diabetes, but that also the general population expresses an interest in these findings.