Human cardiometabolic health

IMPACT

The human studies described in this thesis were centered around two aims: 1) to examine the influence of genetic factors, the circadian system, and macronutrient intakes on endogenous cholesterol synthesis and intestinal cholesterol absorption, and 2) to study the cardiometabolic health effects of various intermittent energy restriction diets. In summary, results showed that multiple genetic variants are associated with endogenous cholesterol synthesis or intestinal cholesterol absorption. Furthermore, we observed that endogenous cholesterol synthesis peaked at night, which agreed with previous findings. We were the first to examine the possible diurnal rhythm of cholesterol absorption, which however was not present. We also showed that this absence of a cholesterol-absorption rhythm was not related to the type of macronutrient that was mainly consumed, at least not in the acute situation. Regarding longer-term dietary interventions, this thesis did not find that intermittent energy restriction diets were superior to continuous energy restriction diets for human cardiometabolic health. This chapter will discuss the potential impact of these findings in terms of societal, economic, and scientific relevance. Then, implications for the translation of the findings into practice will be discussed.

Societal and economic impact

Global disability and death from cardiovascular diseases (CVDs) increased in the previous thirty years (1). The prevalent cases of total CVD increased from 271 million in 1990 to 523 million in 2019, and the number of CVD deaths from 12.1 million to 18.6 million (1). This represented 32% of all global deaths in 2019 (2). In addition, the worldwide disability-adjusted life years (DALYs), years lived with disability (YLDs), and years of life lost (YLLs) due to CVD all increased from 1990 to 2019 (1). The European Society of Cardiology published that high-income countries spent on average four times more money on healthcare than middle-income countries in 2018 (3). Most healthcare costs were due to CVD and accounted for around 16% of the total costs in a selection of high-income European countries in 2016 (3). To add, it was estimated that CVD cost the European economy 210 billion euros in 2015, of which 53% was due to healthcare costs, 26% to loss of productivity, and 21% to the informal care of CVD patients (3). These data highlight the importance of targeting CVD risk factors at early stages to prevent the development of CVD and thereby lower death, disability, and healthcare costs due to this type of disease. Important modifiable CVD risk factors include increased low-density lipoprotein cholesterol (LDL-C) concentrations and overweight or obesity (1, 2).

Various interventions have been developed to lower serum LDL-C concentrations, thereby reducing CVD risk. Next to LDL-C concentrations, attention is paid to other novel risk markers for CVD. High intestinal cholesterol absorption, for example, has been positively associated with CVD (4-6). In addition, a high cholesterol synthesis or a high cholesterol absorption has been related to other diseases and metabolic disturbances (6). It may thus also be interesting to examine other approaches that further reduce CVD risk, including cholesterol synthesis and absorption. To optimize interventions, it is of relevance to clearly understand how various factors influence or are related to cholesterol homeostasis. In this thesis, a relation between different single-nucleotide polymorphisms (SNPs) with cholesterol synthesis and absorption was found, which may be a first

step towards more personalized cholesterol-lowering interventions. In addition, this thesis demonstrates that endogenous cholesterol synthesis has a diurnal rhythm with a nocturnal peak. Information regarding the timing of the endogenous cholesterol synthesis peak may be used for timed administration of cholesterol-lowering diets or drugs to have the largest impact on serum LDL-C lowering. The initial treatment for Dutch individuals with hypercholesterolemia is either atorvastatin, rosuvastatin or simvastatin (7). Of these, the latter has a short half-life time whereas the first two have a long half-life time (8). A recent meta-analysis of randomized controlled trials observed that statins taken in the evening led to a greater reduction in total cholesterol and LDL-C concentrations compared to statins taken in the morning (9). Comparison of short half-life time versus long half-life time statins, however, showed that this benefit of evening intake was only significant for statins with a short half-life time (9). The diurnal rhythm of endogenous cholesterol synthesis may thus be relevant when prescribing statins with a short half-life time but is less important for statins with a long half-life time.

Another important CVD risk factor is overweight or obesity. The global obesity prevalence has almost tripled between 1975 and 2016 and around 40% of adults was overweight and 13% was obese in 2016 (10). In the Netherlands, half of the adult population was overweight of which slightly more than 14% was obese in 2021 (11). Between 1990 and 2019, global deaths due to high body mass index (BMI) increased with 4.9%, DALYs with 18.0%, YLDs with 60.2%, and YLLs with 8.3%, after correction for population growth and aging (1). Results of a cross-sectional analysis showed that the health-related quality of life decreased with an increasing BMI (12). Moreover, loss of work productivity in people who were employed full-time increased with increasing BMI (12). Another study assessed the impact of obesity on life expectancy for 26 European populations and the United states over 1975 to 2012 and reported that the age-standardized obesity-attributable mortality fraction (i.e., the share of mortality caused by obesity) was 11% among men and 10% among women in European countries in 2012 (13). This obesity-attributable mortality fraction increased over time for all countries, but not to the same extent. Furthermore, the estimated potential gain in life expectancy if obesity was eliminated increased in all countries between 1975 and 2012 (13). Overweight or obesity is traditionally based on BMI, but a shift towards alternative measures which take abdominal adiposity into account, such as waist circumference, is observed (14). An increase in abdominal obesity was associated with an increased risk of future CVD events in adult men and women (15). Additionally, waist circumference showed a strong and significant association with the risk of death with and without adjustment for BMI in a large European cohort (16). In agreement, another study that pooled data from 11 prospective cohort studies that included over 650.000 individuals, observed that waist circumference was positively associated with all-cause mortality in men and women with and without adjustment for BMI (17). Each 5 cm increase in waist circumference was associated with a 9% higher mortality risk in women and 7% greater mortality risk in men (17). Finally, intensive care unit patients with abdominal obesity had a significantly higher mortality rate compared to patients without abdominal obesity (18). That study also reported that abdominal obesity was a significantly better predictor of mortality in an intensive care unit setting than a BMI higher than 30 kg/m^2 (18).

These previous paragraphs demonstrate that it is of societal and economic relevance to reduce the prevalence of CVD and overweight or obesity, especially abdominal obesity. It is therefore important that intervention studies are designed that target overweight and obesity and thereby reduce disability and premature death due to CVDs. It is essential to make lifestyle changes to effectively lower body weight, which is often achieved by reducing total energy intake. In this thesis, various types of intermittent energy restriction diets were examined, and results showed that effects of these types of diets on anthropometric and cardiometabolic risk parameters did not substantially differ from those of continuous energy restriction. It can therefore be suggested that intermittent energy restriction diets may be advised as an alternative to continuous energy restriction diets for individuals who are unable to adhere to continuous energy restriction diets on the long-term.

Scientific relevance

The studies included in this thesis provide novel information that is of scientific relevance. First of all, we identified new associations between genetic variants with endogenous cholesterol synthesis and intestinal cholesterol absorption. Most of these associations with SNPs in cholesterol metabolism and circadian clock genes had not been reported in literature before and other associations confirmed findings from previous research. The relation between SNPs in circadian relevant genes with cholesterol synthesis and absorption provides further knowledge on the link between the circadian system and cholesterol homeostasis. Second, this thesis increases our understanding of the diurnal variation in endogenous cholesterol synthesis and intestinal cholesterol absorption. The reciprocal relation between cholesterol synthesis and cholesterol absorption that has been reported before in the fasted state was not observed over 24 hours. Third, a comparison between acute consumption of a meal high in fat, protein, or carbohydrates on endogenous cholesterol synthesis and intestinal cholesterol absorption had not been performed before. The fact that people spend most of the day in the postprandial state instead of the fasted state makes it essential to understand how meals influence cholesterol homeostasis on the short term. The non-significant changes in intestinal cholesterol absorption following meal consumption further suggest that the absence of a diurnal rhythm of cholesterol absorption could not be explained by dietary macronutrient intake during the study. Next to cholesterol homeostasis, intermittent energy restriction, which has become increasingly popular among the public and in science over the previous years, was investigated to better understand the potential health effects of meal timing and a prolonged fasting duration. So far, a large amount of scientific evidence describing the benefits of intermittent energy restriction diets is based on animal studies. The meta-analysis presented in this thesis not only compared intermittent energy restriction diets to continuous energy restriction diets in humans but focused on different types of intermittent energy restriction diets as well. Previous results from animal studies are hopeful, but the results obtained from the meta-analysis based on human intervention studies indicate that intermittent energy restriction is not superior to continuous energy restriction with regards to changes in anthropometric and cardiovascular measures. This suggests that perhaps not the duration of fasting itself produced the health benefits, but that these may have resulted from an overall reduction in energy intake. More human intervention studies should be performed to distinguish between the influence of weight loss and meal timing on the health effects of intermittent energy restriction.

Translation into practice

This thesis includes two studies that presented associations between genetic variants in genes essential in cholesterol metabolism and the circadian clock with cholesterol synthesis and absorption. It has been observed that having a relatively high endogenous cholesterol synthesis or intestinal cholesterol absorption is associated with various health conditions, including CVD. Thus, classifying individuals as high synthesizer or high absorber based on genetic variants may be a promising step towards personalized cholesterol-lowering therapies. It remains, however, important to first replicate those findings in other independent cohorts before these genetic variants can be used for personalized treatment in practice. The information regarding the timing of the endogenous cholesterol synthesis peak is relevant for health care professionals who prescribe cholesterol synthesis inhibitors with a short half-life time to their patients, but does not have to be taken into account for statins with a longer half-life time. In animal studies, intermittent energy restriction diets seemed very promising for improving cardiometabolic health, but it is important to confirm findings from animal studies in human clinical trials before recommendations can be made to the general population. The findings of our meta-analysis, which included trials in healthy overweight/obese individuals, may be relevant for dietitians and other health care workers who want to provide overweight or obese people with advice on possible weight loss diets. In the future, more studies should be performed that measure compliance to different types of intermittent energy restriction diets on the longer term. All studies presented in this thesis have been or will be published in international peer-reviewed scientific journals. Furthermore, the findings have been or will be presented via poster presentations and oral presentations. The knowledge obtained from these studies is therefore available for interested scientists, dietitians, policymakers, and other (para)medical health professionals.

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