Public summary of PhD-thesis of Yvonne Rozendaal
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Two clinical subtypes revealed of Metabolic Syndrome

The worldwide increase in overweight and obesity co-occurs with the development of various other abnormalities, like diabetes and cardiovascular diseases. The cluster of health issues associated with obesity is known as the Metabolic Syndrome (MetS). The main characteristic of MetS is obesity and the distorted fat and carbohydrate regulations. It is a progressive disease that develops slowly and over long timescales. Many organs and tissues are involved, which makes it complex to study and to develop appropriate treatments for. Since it is also very heterogeneous in its clinical presentation, Yvonne proposed to use a systems biology approach. By making use of systems biology, she systematically studied the long-term development of MetS. She did this by integrating prior knowledge of the biology, with experimental data of various biomarkers measured in mice, into a mathematical model. This work was conducted within the interdisciplinary EU research program RESOLVE (FP7-HEALTH-305707).

Yvonne developed a dedicated mathematical model that describes carbohydrate and fat regulation in a whole-body perspective: MINGLeD (Model Integrating Glucose and Lipid Dynamics). This model was simulated using a pre-existing computational technique (ADAPT; Analysis of Dynamic Adaptations in Parameter Trajectories) to describe change in metabolic status over time.

Since the development of MetS may take as long as a decade in humans, a preclinical mouse model was used. This mouse was genetically modified such that it shows human-like fat regulation. Male mice (APOE*3-Leiden.CETP) were fed a high-fat, high-cholesterol diet for three months to induce human-like MetS symptoms: obesity, glucose intolerance (dysregulation of carbohydrate regulation), and dyslipidemia (dysregulation of fat regulation). In addition, the mice also developed a fatty liver and diabetes, both of which are classical disease outcomes of MetS.

The data included blood and liver samples at various points in time and were integrated in MINGLeD. Her model calculated the full timespan from a healthy state, onset and progression towards full MetS development. It revealed the emergence of two distinctly different clinical subtypes of MetS: those with a severely impaired fat regulation, and those with only minor imbalance of fat regulation. Computational analysis of the underlying model predictions showed two mechanisms that differentiate these different clinical subtypes. Those with severely impaired fat regulation have a more active liver, whereas those with only minor impairment have a decreased uptake of dietary cholesterol from the intestine.

The model not only describes the long-term development of MetS, but it can also be utilized to simulate possible treatment strategies. The constant excess of energy is, in general, considered to be the central cause of MetS. Current treatment of MetS is therefore aimed at lifestyle modification with both diets and physical activity regimens, but this remains insufficient to deal with the growing incidence of MetS. Yvonne explored the effects of increasing energy expenditure in different *virtual* patients. She showed that enhanced energy expenditure led to a direct decrease of cholesterol and fat storages, indicating its potential to improve MetS. This can be translated to clinical practice by considering the contribution of Brown Adipose Tissue, or brown fat, in heat production. Brown fat can be activated for a short period of time by exposure to a colder environment, and can be used support

current treatment strategies in reducing the deregulations of fat and carbohydrate in MetS. In the end, this will also reduce the risk for the development of diabetes and cardiovascular diseases.

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