# Gastrointestinal transit time, gut microbiota and metabolic health



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## Valorization

The present thesis discusses the potential interaction between the gastrointestinal tract, the gut microbiota and the effect of dietary fiber intake in the context of metabolic health. Further, the future implications and the relevance of the present results will be put into a societal and economical context.

The most recent world health organization (WHO) report indicates that obesity has tripled in the last forty decades with more than 1.9 billion adults being overweight and more than 650 million being obese in 2016. Obesity develops as a result of positive energy balance caused by increased food intake accompanied by declining physical activity, most commonly manifesting in gradient weight gain over years. Further, obesity is a strong risk factor in the onset of other metabolic diseases such as type II diabetes mellitus (T2DM), and is also associated with development of certain cancers, depression and cardiovascular diseases. Thus, despite being a preventable disease, the obesity pandemic and its comorbidities pose a massive challenge to healthcare systems worldwide. Moreover, due to rising childhood obesity, the challenges of the obesity pandemic will only foreseeable accelerate in the future. Current obesity treatment mainly focuses on the counseling of lifestyle adaptions such as caloric restriction and physical activity. These lifestyle adaptions can effectively lead to weight loss and reverse progression to T2DM, but adherence to lifestyle changes is challenging. The lack of implementing a healthy life style in the long term inevitably leads to treatment failure. Hence, there is an urgent need to advance current treatment strategies to tackle the obesity pandemic and obesity-related disorders.

Most recently, much attention has been drawn to the role of the gastrointestinal (GI) tract and especially the gut microbiota in the etiology of obesity. Thus, industry, as well as academia have put much effort into the development and study of dietary components targeting the gut microbiota and specific “beneficial” microbial species in order to improve parameters of human metabolism. However, there are still huge gaps in our understanding of the complex interactions between dietary components, the physiological functions of the GI tract, the gut microbiota and its metabolites in the context of metabolic health. The studies conducted in this thesis have been partly funded by the Top Institute for Food and Nutrition, (TIFN), a public-private partnership on pre-competitive research in food and nutrition combining resources and expertise from both food industry and academia. By using industrial and academic resources, this thesis aimed to elucidate some of these interactions by means of different methodological approaches.

## |Valorization

Our findings indicate that long-term supplementation with a dietary fiber (Arabinoxylan-Oligossacharide, AXOS) that clearly stimulates Bifidobacteria does not translate into beneficial metabolic changes in a healthy, normoglycemic population. Yet, AXOS- stimulated growth of Bifidobacteria may help to improve stool consistency and thus may have potential applications in patients suffering from functional GI disorders. Further, the supplementation of AXOS led to a decreased microbial diversity, which is associated with several GI diseases. Yet, these findings need to be interpreted in a microbiological/ecological context, a perspective that seems to lack in many prebiotic interventional studies. Further, our results show that microbial diversity may also depend on the colonic transit time, thereby adding an important covariate which should be considered in future interventional studies targeting the gut microbiota. Further, the results from this thesis may suggest more careful interpretation of microbial diversity in the context of prebiotic intervention studies. Further large-scale cross-sectional studies including segmental colonic transit are needed to validate our findings. Nevertheless, the results from this thesis elucidate the complex interaction between GI transit, the gut microbiota and dietary fibers in the context of metabolic health and further research, especially in humans is required to identify underlying mechanisms and drivers.

Many human and animal studies emphasize the beneficial potential for microbially produced short-chain fatty acids on the human metabolism. Yet, in order to efficiently target SCFA production, it is important to understand their metabolism and covariates thereof. This thesis gave important insights into the latter, emphasizing that the gastrointestinal transit time is linked to fecal SCFA concentrations, a parameter often used in prebiotic intervention studies to indicate fermentation. Further, we emphasize that rather than fecal SCFA, the measurement of plasma SCFA may be more meaningful in the context of metabolic processes, since only plasma SCFA concentrations associated with several important metabolic markers. These results provide interesting considerations for future studies targeting lifestyle interventions thereby increasing their effectiveness to prevent chronic metabolic diseases.

In this thesis, we report results from a proof-of concept studie funded by a partnership between the Netherlands Organization of Scientific Research and the Carbohydrate Competence Center, a private- public organization aiming to “generate, develop and share high-value knowledge in the field of carbohydrates, to promote innovation worldwide and contribute to healthy and sustainable societies”. The study reported in this thesis gave import insights into the effectiveness of dietary fiber combinations with the approach of directly translating *in vitro* findings into an acute *in* *vivo* human interventional study. We show that a dietary fiber mixture induces beneficial metabolic effects on energy expenditure and postprandial insulin tolerance after one day intake in lean men. These results should encourage further research, especially investigating long-term beneficial effect of dietary fiber mixtures specifically targeting increased distal acetate production as a nutritional strategy to improve or metabolic health. Also, these results may provide direct lead for food industry to develop products with specific (combinations of) dietary fiber(s) which are most effective in counteracting or preventing obesity and type 2 diabetes mellitus.

The studies described in this thesis have been or will be published in scientific journals in the field of nutrition and microbiology and thus will be partly available for the public and scientific community. Industrial partners as well as academic partners have contributed to this project by funding and knowledge exchange during meetings and presentations. Thus, given the interesting implications of this thesis, the development of novel food products such as dietary fiber mixtures may provide an interesting strategy within the existing collaborations between academia and industrial partners and may provide leads for industrial product development. Ultimately, and from the public health perspective, novel recommendations regarding specific fibers and mixtures may be implemented in dietary guidelines to more efficiently prevent development of T2DM and to combat obesity.