NUTRIM

Scientific and Societal Impact in Case Studies

Projects | Best Practices | Stories

Faculty of Health, Medicine and Life Sciences
NUTRIM School of Nutrition and Translational Research in Metabolism

Maastricht University Maastricht UMC+

Contents

Advancing Nutrition Research with novel technologies and innovative approaches

Division 1: Obesity, Diabetes & Cardiovascular Health
Department of Nutrition and Movement Sciences

Background

Modern nutrition research

Nutrition research has changed over the past decades. We have therefore enriched our research portfolio from intervention studies focusing on the preventative impact of single nutrients on metabolic health parameters towards studies evaluating effects of nutrients, whole foods and dietary patterns in healthy individuals. Moreover, primary outcome parameters are not only plasma biomarker profiles, but also a wide array of non-invasive *in vivo* functional markers for specific tissues. These novel "functional" markers may be even more important predictors for the development of non-communicable diseases and offer promising opportunities for evidence-based prevention strategies.

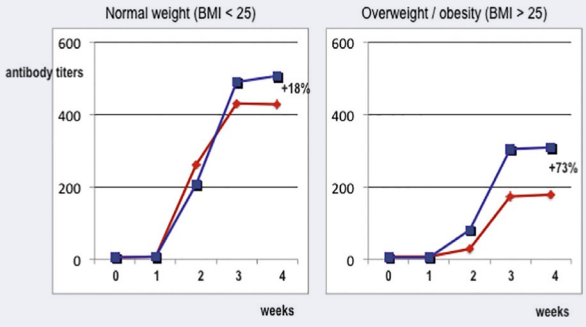
Our research group is internationally well-recognized for their contributions to the complete spectrum of research approaches (nutrients - whole foods - dietary patterns). We apply innovative technologies (such as vascular parameters in periphery and brain, fundus analysis, markers for cholesterol absorption and synthesis, wearables for continuous metabolic monitoring in home settings, clamp techniques, magnetic resonance imaging (MRI)), focusing on functional endpoints (cardio metabolic health, satiety, weight-loss maintenance strategies, and cognition). In our studies, we generate in particular novel "fundamental" data for a certain nutrient / food (pattern). The major aim is to translate that findings ultimately to dietary guidelines and can be used to extend already proven health benefits towards novel areas.

Major breakthroughs

Example 1: Plant sterol and plant stanols

Plant sterols - and their saturated derivative the plant stanols - resemble the molecular structure of the mammalian cholesterol. These plant substances lower the atherogenic LDL-cholesterol concentrations by reducing intestinal cholesterol absorption. These conclusions are based on many studies to which we have contributed substantially. In fact, in the late 90's we were the first group outside Finland to demonstrate the cholesterol-lowering efficacy of plant stanols. This study was the first of many studies addressing effects of consumption frequency, impact of food matrix, mechanistic aspects, and the combined intake with statins and fibres on the LDL-cholesterol lowing effects of these plant-derived functional ingredients. In later studies, we also showed that plant stanols lowered serum triacylglycerol concentrations in subjects with overt hypertriglyceridemia. More recently, additional benefits beyond those on the serum lipoprotein are explored, i.e., effects on immune function and (liver) inflammation. For immune function, we have first shown that plant sterols and stanols can normalize a possible disbalance between the activity of T-helper 1 and T-helper 2 cells *in vitro* via activation of regulatory T-cells via TLR2 activation. Findings were confirmed in a randomized placebo-controlled human intervention trial with allergic asthma patients, in which Th2 cells are overactive. Plant stanol consumption dampened this Th2-activity by activating the Th1 response as shown by boosting the vaccination response to Hepatitis A. Interestingly, this effect was particularly evident in subject with a higher BMI, who clearly have a compromised immune response (Figure 1).

Figure 1: Plant stanols activate the Th1-immune response after a vaccination response especially in subjects with a higher BMI. Blue: Plant stanol group, Red: Control group.

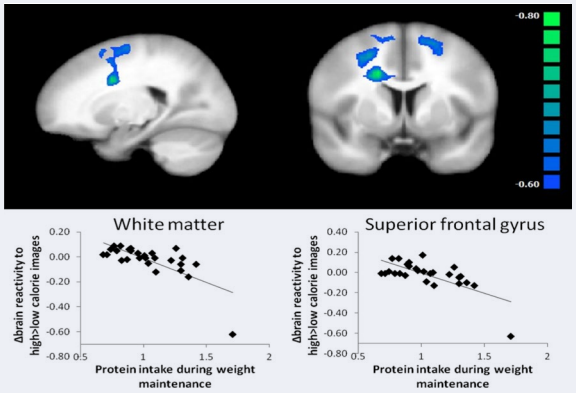


Our recent studies also showed that in LDL-receptor knockout mice plant sterols and stanols inhibited liver inflammation, as induced by a high-fat, high- cholesterol diet (collaboration with Prof. R. Shiri-Sverdlov, division 2). This was shown by lower CD68 staining and a lower number of Kupffer cells, as well as decreased gene expression of inflammatory cytokines TNFα, IL-1β, and MCP-1. Hepatic steatosis did not change.

Example 2: Protein-rich foods and diets

Considering the well-established effect of proteins on satiety, diet-induced thermogenesis and the preservation of fat-free mass during weight loss, proteins are the intuitive nutritional component of a whole food-based intervention for intentional weight loss and weight-loss maintenance. These effects may in part be mediated through an effect on food reward signalling in the brain. In our studies assessing whole food high protein intake we found an inverse relationship with high protein intake and brain reward activity, and a positive association between high protein intake and changes in body weight. The results pose a potential mechanistic link between protein intake and weight maintenance after weight loss (Figure 2). Furthermore, we could establish that this relationship was mediated by changes in insulin sensitivity.

Figure 2: Whole brain contrast map of regions with inverse associations between changes in high>low calorie image brain activation and daily protein intake (g/kg) during weight maintenance.



For longer-term intake of soy nuts, which are not only rich in proteins but also in other potential bioactive ingredients, we observed in older subjects an increased regional cerebral blood flow (CBF), a physiological marker of cerebrovascular function. Psychomotor speed was also improved. In addition, non-invasive markers of the peripheral vasculature changed in a positive way. These effects may be important mechanisms by which protein intake reduces cardiometabolic risk and cognitive decline.

Who is involved?

Dr. Tanja C. M. Adam, Dr. Sabine Baumgartner, Dr. Peter J. Joris, Prof. Dr. Ronald P. Mensink, Prof. Dr. Jogchum Plat, Dr. Herman E. Popeijus.
The research is embedded with the PHuN (Physiology of Human Nutrition) group from the Department of Nutrition and Movement Sciences. Except for the staff members, also PhD-students from both the Netherlands and abroad and supporting personnel are an essential part of our research group.

Users and collaborations

In our research projects, we collaborate with various national and international user and research groups, and industrial partners (ranging from SME to multinational) and receive funding from ZonMw, NWO, TKI-LSH, TTW, several product-related foundations and the EU.

Scientific impact/Research quality

Our studies with plant sterol and stanol esters (Example 1) have contributed to the positioning of products enriched with these nutrients in some (international) dietary guidelines. Moreover, our so-called frequency study demonstrating that a single intake of plant stanols was as effective as the same intake divided over three meals was the basis for the development of the highly successful commercially available one-shot yoghurt mini-drinks. Regarding the studies focusing on the longer-term effects of protein-rich foods and diets (Example 2), findings extended the evidence that these foods and diets prevent age-related health conditions, such as cardiovascular disease and cognitive impairment, due to their beneficial effects on vascular function and metabolic health; not only in the periphery, but also the brain.

Selection of publications

1. Baumgartner S, Ras RT, Trautwein EA, Mensink RP, Plat J Plasma fat-soluble vitamin and carotenoid concentrations after plant sterol and plant stanol consumption: a meta-analysis of randomized controlled trials. Eur J Nutr 2017; 56:909-923.
2. Brüll F, De Smet E, Mensink RP, Vreugdenhil A, Kerksiek A, Lütjohann D, Wesseling G, Plat J. Dietary plant stanol ester consumption improves immune function in asthma patients: results of a randomized, double-blind clinical trial. Am J Clin Nutr 2016; 103:444-453.
3. Drummen M, Heinecke A, Dorenbos E, Vreugdenhil A, Raben A, Westerterp-Plantenga MS, Adam TC. Reductions in body weight and insulin resistance are not associated with changes in grey matter volume or cortical thickness during the PREVIEW study. J Neurol Sci 2019; 403:106-111.
4. Drummen M, Dorenbos E, Vreugdenhil AC, Raben A, Westerterp-Plantenga MS, Adam TC. Insulin resistance, weight and behavioral variables as determinants of brain reactivity to food cues - a PREVIEW Study. Am J Clin Nutr 2019; 109:315-321.
5. Joris PJ, Plat J, Kusters YH, Houben AJ, Stehouwer CD, Schalkwijk CG, Mensink RP. Diet-induced weight loss improves not only cardiometabolic risk markers, but also markers of vascular function: A randomized controlled trial in abdominally obese men. Am J Clin Nutr 2017; 105:23-31.
6. Kleinloog JPD, Mensink RP, Ivanov D, Adam JJ, Uludağ K, Joris PJ. Aerobic exercise training improves cerebral blood flow and executive function: a randomized, controlled cross-over trial in sedentary older men. Front n Aging Neurosci 2019; 11:333.
7. Mensink RP, de Jong A, Lütjohann D, Haenen GR, Plat J. Plant stanols dose-dependently decrease LDL-cholesterol concentrations, but not cholesterol-standardized fat-soluble antioxidant concentrations, at intakes up to 9 g/d. Am J Clin Nutr 2010; 92:24-33.
8. Plat J, Baumgartner S, Vanmierlo T, Lütjohann D, Calkins KL, Burrin DG, Guthrie G, Thijs C, Te Velde AA, Vreugdenhil ACE, Sverdlov R, Garssen J, Wouters K, Trautwein EA, Wolfs TG, van Gorp C, Mulder MT, Riksen NP, Groen AK, Mensink RP. Plant-based sterols and stanols in health & disease: Consequences of human development in a plant-based environment? Prog Lipid Res 2019; 74:87-102.
9. Talbot CPJ, Plat J, Ritsch A, Mensink RP. Determinants of cholesterol efflux capacity in humans. Prog Lipid Res 2018; 69:21-32.
10. Tayyeb JZ, Popeijus HE, Mensink RP, Konings MCJM, Mokhtar FBA, Plat J. Short-chain fatty acids (except hexanoic acid) lower NF-kB transactivation, which rescues inflammation-induced decreased apolipoprotein A-I transcription in HepG2 cells. Int J Mol Sci 2020; 21:5088.

Future Perspectives

For plant sterols and stanols (Figure 3), we are currently examining whether (i) we can make the advice to use plant sterol or stanol-enriched products more personalized, based on genetic profiling (ii) plant sterols and stanols lower hepatic inflammation and (iii) the dampening effect of plant stanol consumption on the Th2 response also translates into less symptoms in a large multi-centre clinical trial in patients with allergic asthma.

For protein and protein-rich foods (Figure 4), the existing knowledge describing effects on (functional) markers in the periphery will be further corroborated with innovative markers in the brain. Ongoing trials focus on effects of whole foods (almonds, mixed nuts) and protein hydrolysates. Innovative non-invasive brain MRI methods are used to investigate brain vascular function and insulin-sensitivity, and functional activation of brain reward areas in response to visual stimuli. For this, MRI scanner facilities and support at the Scannexus are used. Specific focus is on functional outcomes such as cognitive performance and food intake.

Figure 3: Ongoing longer-term intervention studies in the field of plant stanols and sterols.

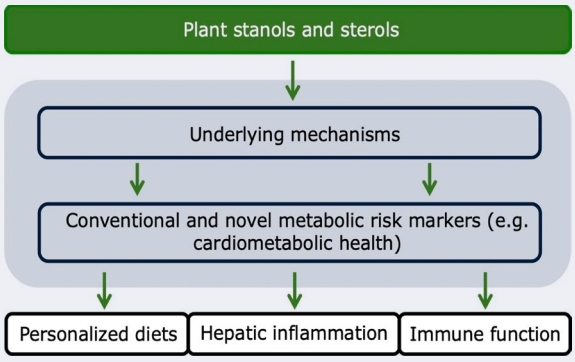
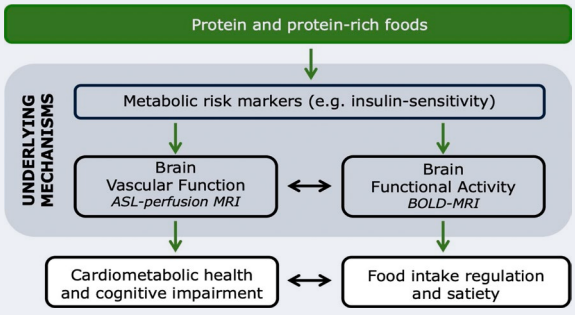


Figure 4: Ongoing longer-term intervention studies in the field of proteins and protein-rich foods.



DIVISION 1

COACH Childhood obesity; consequences, prevention and treatment

Division 1: Obesity, Diabetes & Cardiovascular Health
Department of Pediatrics

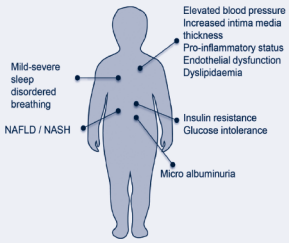
Background

The childhood obesity epidemic is a critical public health challenge facing the 21st century, incurring a significant loss of quality of life, significant health risks that are likely to project into adulthood (chronic diseases, psychological disorders and premature death) and increased costs to society and healthcare systems worldwide. In the Netherlands, half a million children are overweight or obese. Our studies have shown that more than 50% of children with overweight/obesity in our region have one or more weight related comorbidity. This underlines the urgency for effective multi-faceted interventions to achieve initial and long-term health benefits. Dealing with the modifiable lifestyle factors of building a vital community and a healthier environment for children poses a major challenge to healthcare and other authorities.

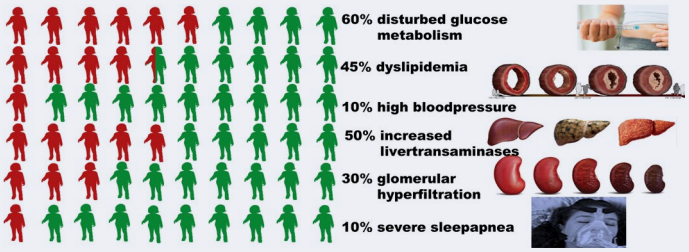
Major breakthroughs

Expertise Centre for overweight adolescent and children's healthcare.
Where research, clinic and society meets
The Centre for Overweight Adolescent and Children's Healthcare (COACH) is a centre for evaluation, integral treatment and monitoring of children with overweight and obesity. This centre has evolved into the academic expertise centre that it is today, with a comprehensive multi-sectoral network of participating partners, multiple research lines with (inter) national collaborations and transfer of knowledge to all levels of society as an important assignment. The interdisciplinary, translational research team initiates basic studies, clinical studies, behavioral impact studies and social and economic impact studies of the interventions in real life practice. Research in COACH continuously seeks better detection of health risks, better coaching and monitoring strategies and better ways to create multilevel multi-stakeholder collaboration with a common aim; a healthy life for every child. The focus of research is lifestyle, overweight and obesity in the perspective of the developing child. Over the past years, a cohort of children with overweight, obesity and morbid obesity was built. The COACH research team searches for 1) new methods and markers to early recognize children with a specific high risk for metabolic derangement and liver pathology (NAFLD), 2) innovative interventions for the treatment of children with overweight and obesity, 3) characteristics of children and families prone for development of overweight and obesity.

Early stages of weight related diseases in childhood



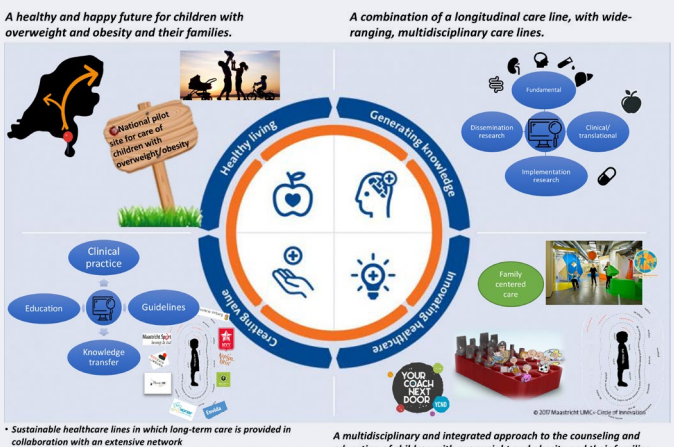
Early stages of chronic diseases in children with overweight/obesity in Limburg



>50% Obese children have ≥1 early stage of chronic disease

COACH Maastricht
For future health
COACH Clinic
COACH Research
COACH Network
COACH Academy

Circle of innovation COACH



- *Sustainable healthcare lines in which long-term care is provided in collaboration with an extensive network*
- *Sustainable scientific developments through extensive (inter)national collaborations and application in own care process*

A multidisciplinary and integrated approach to the counseling and education of children with overweight and obesity and their families (outside the walls of the hospital; in the 1st, 2nd and 3rd line).

Who is involved

PI: Dr. Anita Vreugdenhil and Department of Pediatrics research team

Users and collaborations

From the perspective of "Think globally, act locally" we collaborate with scientists and healthcare professionals within the MUMC+ and around the globe. The urgency to gain more knowledge about development, prevention and treatment of lifestyle related diseases in children is felt all over Europe, which has amongst others resulted in the European Paediatric Non-Alcoholic Fatty Liver Disease (EU-PNAFLD) network, in which physicians and researchers from all over Europe have united. With our research projects in Europe and India, we learn about possibilities to adjust lifestyle in different cultures and in Western and developing countries. Besides, we take action in our own communities, surrounding cities and the South of the Netherlands. This has grown into long-term and close contacts and cooperation with all kind of actors involved in the development of children at the micro-, meso- and macrolevel. In particular, we work together with parents, schools, companies, Youth and Healthcare Divisions, hospitals, municipalities and the Province of Limburg.

Scientific impact/Research quality

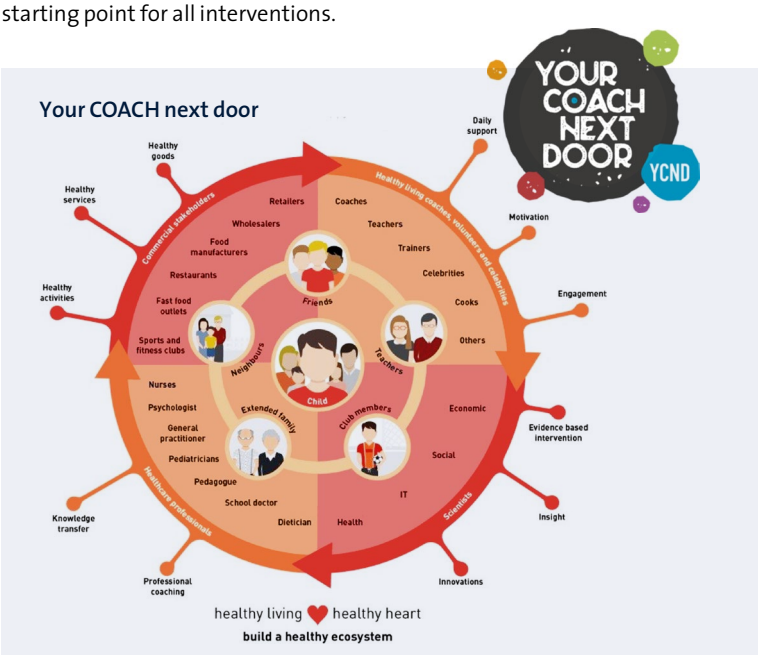
With our research data, we generate knowledge and insights on new methods and markers to early recognize children with a specific high risk for metabolic derangement, diabetes mellitus, cardiovascular disturbances and liver pathology. In addition, insight is gained on the interrelationship of anthropometric measurements, comorbidities, metabolic derangements, cardiovascular measurements and liver parameters. Innovative interventions for the treatment of children with overweight and obesity have already been an important yield of our research work. More and more is known about the recognizing characteristics of children and families prone for development of overweight and obesity.

Societal impact

COACH developed an evidence-based approach for improving healthy living in overweight and obese children. The COACH approach is unique in that it connects the target individuals with other levels of society, stimulates mutual learning and initiates development of innovative nudging activities for the participating families. This approach has proven to be successful in health improvement; a healthier weight and less comorbidities. Our research work and results contribute to changes in policy, financial structures, collaboration between parties, awareness of lifestyle and obesity related consequences for children and next generations.

Future Perspectives

We now expand the COACH approach and network to Your Coach Next Door by including more families, more societal partners, new regions and new methods for engaging all stakeholders in a sustainable financial model. Professionals in primary care provide the program close to home. The YCND program will be further developed, implemented, feasibility tested and the effectiveness and cost-effectiveness of YCND evaluated. This approach can be considered as a 'natural experiment' and a continual improvement process as the research will follow the natural course of the intervention development. Medical and online assessments and online data in YCND will gather an enormous amount of data resulting in a unique possibility to evaluate effects of interventions and, due to its large scale, enable prediction models for personalized successful interventions. From the beginning a nation-wide rollout of the concept was anticipated. Children's voice is the starting point for all interventions.



The outdoor clinic is a playful and interactive world that nudges children and their parents in the direction of a healthy diet and reglar exercise. A motivating and stimulating environment that seems miles away from the world of doctors and hospitals.

Healthcare professionals

diëtheek GEZOND IN VOEDING
Hospitals in the region
youz PG
xonar omdat hulp helpt...
Cirkel - een gezin in balans Voor Ouder & Kind
medisch centrum sint pieter
EURELINGS fysiotherapie • manuele therapie • fysiofitness
Envida
Maastricht UMC+
Zio
GGD Zuid Limburg

Funfilled activities (COACH FOOD)

EXPLORE Educatie | Cultuur | Sport
The MASTERS
KOKKERELLI KIDS UNIVERSITY for cooking
RESTO van Harte Hét recept voor een betere buurt
JUMBO supermarkten
tapijn tuin
SPORTVOEDINGSCOACH.EU ANDRE MOSTARD

Policy makers

provincie limburg
JOGG Jongeren Op Gezond Gewicht
Zorginstituut Nederland
Gemeente Maastricht
C4O
CZ
VGZ
Nederlandse Zorgautoriteit
Ministerie van Volksgezondheid Welzijn en Sport

Funfilled activities (COACH SPORTS)

Fontys Hogescholen
Maastricht Sport beweegt de stad
Stichting Maatschappelijke Projecten Maastricht
BOOSTH activity game
MVV MAASTRICHT
Jeugd Sport Fonds
embedded fitness

Obesity, impaired cardio metabolic health and COVID-19: a pivotal role of the renin-angiotensin system

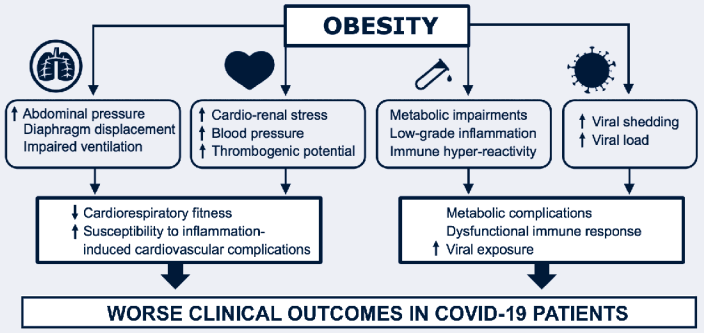
Division 1: Obesity, Diabetes & Cardiovascular Health
Department of Human Biology

Background

The renin-angiotensin system in obesity: metabolic and hemodynamic effects

Our research efforts have mainly focused on the metabolic implications of adipose tissue dysfunction in people with obesity. We investigated the metabolic and hemodynamic effects of the renin-angiotensin system (RAS) in obesity for more than 15 years, showing that angiotensin II (Ang II), the main effector peptide of the RAS, contributes to impairments in adipose tissue and skeletal muscle metabolism and blood flow in humans (1-4), thus contributing to the development of insulin resistance. In several follow-up studies, amongst other findings, we discovered that interference with the RAS, using the angiotensin II type 1 (AT1) receptor blocker (ARB) valsartan, alters adipocyte morphology, lowers adipose tissue inflammation, improves insulin sensitivity and enhances beta-cell function in humans (5, 6). These studies have led to important contributions in our understanding of the contribution of the RAS to obesity-related metabolic perturbations.

Figure 1: Pathways linking obesity to worse clinical outcomes in patients with COVID-19.



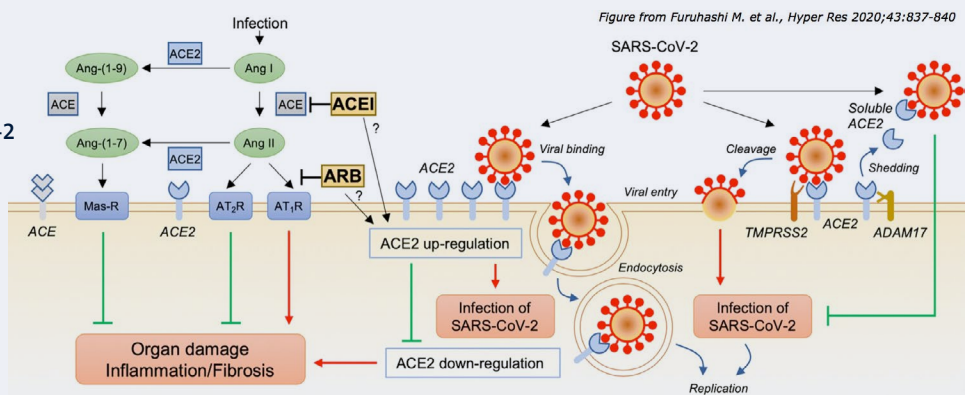
Major Breakthroughs

Obesity and COVID-19: Involvement of the renin-angiotensin system

Obesity not only increases the risk of many non-communicable diseases such as type 2 diabetes and cardiovascular diseases, but also seems to impact communicable diseases.

Recent evidence indicates that obesity is an independent risk factor for worse clinical outcomes in patients with coronavirus disease 2019 (COVID-19) (Figure 1). Adopting a healthy lifestyle and adequate management of obesity and related complications is crucial to lower the risk of SARS-CoV-2 infection and poor outcomes in COVID-19 (7). Angiotensin converting enzyme-2 (ACE2) is the cell-surface receptor enabling cellular entry of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The abundance of ACE2 is high in adipose tissue, rendering adipose tissue a potential SARS-CoV-2 reservoir, thereby contributing to the viral spread and cytokine storm typically observed in COVID-19 patients with obesity (7). ACE2 is part of the RAS.

Figure 2:
The renin-angiotensin system (RAS) plays a pivotal role in SARS-CoV-2 replication/shedding as well as COVID-19 progression, and provides a target for the prevention and treatment of COVID-19.



The RAS not only regulates blood pressure, but also mediates pro-inflammatory signaling, thrombotic processes and fibrosis via the AT1 receptor, thus contributing to pathological changes of organ structure and function. Hence, the ACE2 receptor and other components of the RAS have been suggested to play a pivotal role in SARS-CoV-2 replication/shedding as well as COVID-19 progression and may provide targets for the prevention and treatment of COVID-19 (Figure 2) (7, 8). Animal studies suggest that the polyphenolic compound resveratrol may influence ACE2 expression (9-11). We have recently analyzed tissue biopsies from a previously conducted randomized, placebo-controlled, crossover study, in which healthy obese men received resveratrol supplementation for 30 days (12). We found that resveratrol significantly lowers adipose tissue ACE2 expression. These findings suggest that resveratrol may aid to reduce the risk of severe clinical outcomes following SARS-CoV-2 infection in people with obesity.

Who is involved

A team effort

The research on obesity and the RAS is embedded within the Nutrition, Integrative Metabolism and Obesity NIMO lab, PI's Prof. dr. Ellen Blaak and Dr. Gijs Goossens). We focus on the metabolic inter-organ crosstalk between the gut, adipose tissue, liver and skeletal muscle in the pathophysiology of obesity-related insulin resistance and metabolic complications.

Our team also explores the impact of (precision-based) dietary, exercise and pharmacological interventions, as well as modulation of environmental factors such as oxygen availability, on metabolic health in people with obesity, with healthy ageing as the ultimate goal. This is investigated at the whole-body, tissue and cellular level by integrating innovative human *in vivo* techniques, analyses in adipose tissue and skeletal muscle biopsies, and mechanistic experiments using human primary adipocytes and myotubes.

Users and collaborations

Profs. Marleen van Baak, Ellen Blaak and Wim Saris (Dept. of Human Biology, MUMC+) were closely involved in the studies performed to elucidate the metabolic and hemodynamic effects of the RAS in people with obesity. We investigated metabolic fluxes across adipose tissue and studied the importance of the RAS in adipose tissue blood flow regulation in humans in collaboration with Profs. Keith Frayn and Fredrik Karpe (University of Oxford, UK). Moreover, we explored the effects of ARB treatment on glucose homeostasis with the team of Prof. Michaela Diamant (Amsterdam UMC), and joined forces with Prof. Karine Clément (Paris, France) to unravel ARB effects on inflammation. In parallel, we started a new research line to examine the importance of tissue oxygenation in cardiometabolic health, in collaboration with Dr. Merima Čajlaković (Graz, Austria), and developed/validated a novel technique to continuously monitor tissue oxygen partial pressure *in vivo* in humans (13-15). In addition, as a Chair of the Scientific Advisory Board of the European Association for the Study of Obesity (EASO), Gijs Goossens was actively involved in the writing of several collaborative Opinion/Perspective articles on obesity and COVID-19 with several international experts and EASO colleagues (7, 16, 17). The studies examining the effects of resveratrol and ARB treatment on tissue ACE2 were performed in close collaboration with Dr. Marlies de Ligt and Prof. Matthijs Hesselink (Dept. of Nutrition and Movement Sciences, MUMC+).

Scientific impact/Research quality

For the work our team performed together with our (inter) national collaborators to explore the impact of obesity, the RAS and oxygen partial pressure on glucose homeostasis in humans, Gijs Goosens has received several prestigious awards, including the Young Investigator Award in Clinical Research from the European Association for the Study of Obesity (yearly awarded to most promising young researcher within Europe in the field of obesity) and the Rising Star Award from the European Foundation for the Study of Diabetes (yearly awarded to most promising young researcher within Europe in the field of diabetes). In addition, our recent work on the association between the gut microbiota and host metabolism has had substantial scientific impact.

Selection of publications

1. Goossens GH, Jocken JWE, Blaak EE. Sexual dimorphism in adipose tissue, skeletal muscle and liver metabolism - the impact on cardiometabolic health. Nat Rev Endocrinol 2021; 17: 47-66.
2. Goossens GH, Dicker D, Farpour-Lambert NJ, Frühbeck G, Mullerova D, Woodward E, Holm J-C. Obesity and COVID-19: a Perspective from the European Association for the Study of Obesity on Immunological Perturbations, Therapeutic Challenges and Opportunities. Obes Facts 2020; 13: 439-452.
3. Vogel MAA, Jocken JWE, Sell H, Hoebers N, Essers Y, Rouschop KMA, Cajlakovic M, Blaak EE, Goossens GH. Differences in Upper and Lower Body Adipose Tissue Oxygen Tension Contribute to the Adipose Tissue Phenotype in Humans. J Clin Endocrinol Metab 2018; 103: 3688-3697.
4. Goossens GH, Vogel MAA, Vink RG, Mariman E, van Baak MA, Blaak EE. Adipose tissue oxygenation is associated with insulin sensitivity independent of adiposity in obese men and women. Diabetes Obes Metab 2018; 20: 2286-2290.
5. Vink RG, Roumans NJ, Čajlaković M, Cleutjens JPM, Boekschoten MV, Fazelzadeh P, Vogel MAA, Blaak EE, Mariman EC, van Baak MA, Goossens GH. Diet-induced weight loss decreases adipose tissue oxygen tension with parallel changes in adipose tissue phenotype and insulin sensitivity in overweight humans. Int J Obes 2017; 41: 722-728.
6. Reijnders D*, Goossens GH*, Hermes GD, Neis EP, van der Beek CM, Most J, Holst JJ, Lenaerts K, Kootte RS, Nieuwdorp M, Groen AK, Olde Damink SW, Boekschoten MV, Smidt H, Zoetendal EG, Dejong CH, Blaak EE. Effects of gut microbiota manipulation by antibiotics on host metabolism in obese humans: a randomized double-blind placebo-controlled trial. Cell Metab 2016; 24: 63-74.
7. van der Zijl NJ, Moors CCM, Goossens GH, Hermans MM, Blaak EE, Diamant M. Valsartan improves beta-cell function and insulin sensitivity in subjects with impaired glucose metabolism: a randomized controlled trial. Diabetes Care 2011; 34: 845-851.
8. Goossens GH, Bizzarri A, Venteclef N, Essers Y, Cleutjens JP, Konings E, Jocken JWE, Čajlaković M, Ribitsch V, Clément K, Blaak EE. Increased adipose tissue oxygen tension in obese compared to lean men is accompanied by insulin resistance, impaired adipose tissue capillarisation and inflammation. Circulation 2011; 124: 67-76.

Societal impact

Gijs Goossens highly values the sharing of new insights with scientific colleagues, other health professionals and the general public and has been invited to present their work at many different (inter)national conferences (i.e. European and International Congress on Obesity) as well as at meetings with dieticians, general practitioners and specialists (Jaaroverzicht Obesitas platform, 3 Dec 2020; Werkgroep Deskundigheids-bevordering Huisartsen Limburg, 10 Dec 2020; Kenniscentrum Diëtisten Overgewicht en Obesitas, 12 Oct 2020). Our work has also been widely covered in the (inter)national media.

- Article in The Times (UK): "Call for obese people to be shielded in new outbreaks" (Sept 2020).
- FHML Research Stories: "Obesity and COVID-19" (18 Sept 2020).
- Interview De Telegraaf (7 Nov 2020): "COVID-19 valt zwaar".
- Interview European Association for the Study of Obesity: "Obesity impacts NCDs and Communicable Disease too: ACE2 receptor in human adipose tissue" (12 Nov 2020).
- Broad national media coverage (radio, newspapers, social media) related to the media campaign that I have initiated around World Obesity Day (4 March 2020). This included news items on NPO Radio 1, EenVandaag, RTL Nieuws/Editie NL, and articles in AD, Metro, Zorgkrant, and De Limburger.
- Interview Maastricht UMC+ ('Onze verhalen'): 'Obesitas vergt een aanpak op maat', 3 maart 2020.
- Artikel De Limburger: "Onderzoeker Maastricht UMC+ bepleit aanpak op maat bij obesitas" (3 maart 2020).
- Interview UMagazine (25 Feb 2021): "Obesitas en corona een gevaarlijk duo".

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Future Perspectives

To further explore the putative impact of the RAS in the development and progression of COVID-19. We are currently investigating the effects of long-term treatment with the ARB valsartan on gene expression of RAS components, including ACE2, in human abdominal subcutaneous adipose tissue and skeletal muscle, using biopsies that were collected as part of a randomized, double-blind, placebo-controlled clinical trial that we have previously executed. The outcomes of this study may help to better understand the results of ongoing clinical trials investigating the effects of RAS blockade on clinical outcomes in patients with confirmed COVID-19.

Prevention in the basic health insurance: The Combined Lifestyle Intervention in the Netherlands

Division 1: Obesity, Diabetes & Cardiovascular Health
Department of Health Promotion and the Department of Human Biology and Movement Sciences

Background

Combined lifestyle interventions (CLIs) aim to help people who are overweight or obese to change their physical activity level and dietary behaviors and maintain the new healthier lifestyle. Typically, a lifestyle coach supports overweight or obese clients to prevent chronic lifestyle-related diseases such as Diabetes Type II. To date, many interventions have failed to translate outcomes in controlled research settings to real-world settings, due to unsuccessful or incomplete implementation. Implementation of CLIs benefit from action oriented research, as this provides insight into the implementation process. It also helps to understand the results of the intervention and the success factors influencing both the intervention contents, its implementation and its sustainability.

Major breakthroughs

The research group led by Prof. Kremers was involved in the trajectory to design, implement, evaluate and improve CLI's in the Netherlands from the very beginning. In 2008, Commissioned by the Dutch Ministry of Health, Welfare and Sports (VWS), we participated in the development of a lifestyle intervention called 'BeweegKuur', together with the Netherlands Institute for Sport and Physical Activity (NISB). This led to a series of implementation and evaluation studies that mostly had an action-oriented research design. Dr. Judith Helmink received her PhD for her work in the BeweegKuur. We published nine reports for the Ministry of VWS, two Dutch language papers for Dutch practitioners and ten international peer-reviewed research papers with the purpose to improve the contents of the intervention and to start a sound evidence base for what was later labelled as CLI.

In 2014, we were asked by health insurance company CZ to develop and evaluate a new CLI, based on the results of our previous work. The goal for CZ was to develop an optimal system for the reimbursement of CLIs by health insurance companies, with the ultimate aim of reducing the health care costs in the longer term. We took up the challenge together with Academic Collaborative Center Tranzo in Tilburg. While our pilot study for the intervention labeled Coaching on Lifestyle (CooL) was underway, the Dutch government decided that CLIs will indeed be covered by the health insurance from 2019 onwards. This decision was largely based on the results of the studies that our group performed, led by PhD student Celeste van Rinsum. Since various parties were waiting to see the results of a successfully implemented CLI, the CooL results came at exactly the right time and quickly accelerated practical processes throughout the Netherlands including education of future lifestyle coaches and preparation of local networks of key stakeholders. From 2019 onwards, three Dutch intervention programs qualify as CLIs that are reimbursed by health insurance companies, including both the BeweegKuur and CooL. The two owners of the CooL intervention (N. Philippens and E. Janssen) are currently involved in a PhD trajectory to evaluate the implementation and dissemination of CooL. Nationwide data are gathered to monitor the intervention and potential promoting and hindering factors for optimal implementation.

Who's involved

The team involved works within the departments of Health Promotion (Prof. Dr. Stef Kremers, Dr. Geert Rutten, Dr. Sanne Gerards, Dr. Judith Helmink, Dr. Celeste van Rinsum, Dr. Jessie Meis, Dr. Lieke Raaijmakers, Nicole Philippens, Ester Janssen) and the department of Human Biology and Movement Sciences (Prof. Dr. Hans Savelberg, Dr. Brenda Berendsen, Dr. Marike Hendriks).
The team includes researchers from various backgrounds including psychology, health promotion, movement sciences and physiotherapy and involved two professors, three postdoctoral researchers and seven NUTRIM PhD students (two ongoing).

Scientific impact/Research quality

Our work has been published in high-quality journals such as the International Journal of Behavioral Nutrition and Physical Activity. Action oriented research has become the standard for implementation studies; our group can be viewed as one of the groups that have contributed to the increased adoption of such studies in the field of obesity prevention.

Selection of publications

Helmink, J.H.M., Meis, J.J.M., De Weerdt, I., Visser, F.N., De Vries, N.K., Kremers, S.P.J. (2010). Development and implementation of a lifestyle intervention to promote physical activity and healthy diet in the Dutch general practice setting: the BeweegKuur programme. International Journal of Behavioral Nutrition and Physical Activity, 7, 49.

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Rutten, G.M., Meis, J.J.M., Hendriks, M.R.C., Hamers, F.J.M., Veenhof, C., Kremers, S.P.J. (2014). Does lifestyle coaching of overweight patients in primary care contribute to more autonomous motivation for physical activity and healthy dietary behaviour? Results of a longitudinal study. International Journal of Behavioral Nutrition and Physical Activity, 11, 86.

Societal impact

The studies presented above have been followed closely by implementation institutes (such as Netherlands Institute for Sport and Physical Activity (NISB) (1)), but also by educational institutes for lifestyle coaching (2), health insurance companies (3), the national press (4), the Dutch government (5), the Ministry of Health, Welfare and Sports (6), Netherlands Organisation for Health Research and Development (7), the Dutch Care Institute (Zorginstituut Nederland) (8) and Dutch health promotion practitioners (9, 10).

This resulted in multiple publications for all these stakeholders.

A brief summary is given below.

1. Helmink, J.H.M., Meis, J.J.M., Kremers, S.P.J. (2010). Een jaar BeweegKuur, en dan? Een onderzoek naar de bevorderende en belemmerende contextuele factoren. Universiteit Maastricht.
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Future Perspectives

The national dissemination of the CLI will be monitored by RIVM (the National Institute for Public Health and the Environment). In depth process evaluation and implementation studies will however be executed within NUTRIM by two external PhD students (Nicole Philippens, Ester Janssen), with a specific focus on CooL. The evaluation is aimed at understanding processes of change and improving the implementation of the intervention.

Physical Activity Matters!

Division 1: Obesity, Diabetes & Cardiovascular Health and Division 3: Respiratory & Age-related Health
Department of Nutrition and Movement Sciences

Background

Why does physical activity matter?
Already the ancient Greeks considered physical activity as a lifestyle factor. Physical activity is key to staying healthy as an individual; the key saying being 'use it or lose it'. Physical activity affects many aspects of being, cardio-metabolic health, musculoskeletal performance, cognitive function, resilience, and well-being. For a long time, physical activity was equated with exercise and more precisely the energy expenditure due to exercise. Over the last decennia, the notion has grown that the importance of physical activity for human well-being extends beyond compensating energy intake. Daily behavioral patterns and the exposure to challenging physical activities also play a major role in the health effects. Benefits of physical activity apply over the whole lifespan, in health and disease. Children engaging in physical activity have better weight control and are less likely to develop metabolic disease over time.
In the elderly, mobility is reduced and falls occur more frequently. 'Use it or lose it' also applies here and relatively short interventions can improve balance control. In patients undergoing surgery, it been established that physical conditioning before and after surgery decreases the risk of complications, shortens hospitalization, and leads to a faster recovery of physical functioning.

Major breakthroughs

Do not sit, stay active
Over the last decennium, research in the department of Nutrition and Movement Sciences has shown that the pattern in which daily energy is expended is a key determinant. Cardio-metabolic health is significantly more improved by spreading physical activity over the day in numerous low-intensity bouts, and thus frequently breaking sitting time, than by spending the same amount of energy in a short and single bout of intense physical activity. This insight has considerable impact on interventions targeting lifestyle-related diseases and has been adopted in the recent health guidelines. The challenge is not just to convince the public to exercise, but also to show how low-intense activities can be easily incorporated in daily life to interrupt extended periods of sitting.

Being active over the lifespan, in health and disease
To promote being physically active from young age onwards, our group collaborates with the department of Health Promotion, Pediatrics and the faculty of Psychology to design innovative school-based activity interventions aimed at promoting durable healthy behaviour in children. One of the key factors here is to increase intrinsic motivation to be physically active by focusing on what children want to do not what they need to do.

Our work on fall prevention has shown that a task-specific approach and training specific balance mechanisms result in fast, significant improvements in reactive balance control in a fraction of the time of more typical general exercise interventions. Our work has also demonstrated that these benefits are long lasting - suggesting that an annual or biannual "inoculation" of highly specific balance training could be extremely effective, as well as feasible, for falls prevention. Daily exposure to balance challenging physical activities could prevent falls.

Life-long physical activity and the consequent fitness is a benefit when one prepares for surgery. Patients who have not been successful at keeping their fitness up to par are left with nothing but a high-intensity interval training program to preoperatively improve their aerobic capacity. Persuading these patients to participate is in this case the challenge. To maximize participation rate, adherence, and effectiveness in these high-risk patients, our work demonstrated that a preoperative exercise program must be integrated in the perioperative trajectory and performed in the patient's pre-existent living context.

State of the art infrastructure
Our research is built on state-of-the art facilities, including a Human Performance Lab in which we can study the biophysical and physiological mechanisms that are triggered by physical activities. Moreover, we are actively involved in the development, implementation and validation of wearable health technology and data science. These developments have led to several tailor-made platforms for activity monitoring (www.accelerometry.eu) , that are vital tools for research and coaching of physical activity.

Who is involved?

Key personnel: Jos Adam, Brenda Berendsen, Bart Bongers, Hans Essers, Chris McCrum, Kenneth Meijer, Guy Plasqui, Hans Savelberg, Paul Willems
The impact of our research is reflected in our broad network of clinical and research departments within the Maastricht University Medical Centre. We cooperate with colleagues from the departments of Anesthesiology, Cognitive Neurosciences, Epidemiology, Health Promotion and Education, Internal Medicine, Neurology, Neuropsychology, Neurosurgery, Orthopaedics, Otorhinolaryngology and Head and Neck Surgery, Physical Therapy, Reumatology, Respiratory Medicine, Surgery and pediatrics. Furthermore, we have numerous national and international collaborators; such as University Medical Centre Groningen, the University of Applied Sciences Nijmegen, the London South Bank University, the University of Limerick and the Norwegian School of Sports Sciences. Grants from industries, patient organizations and competitive research grants (ZonMW, TTW, Eurostars) have contributed highly to the success of our team.

Scientific impact/Research quality

- Duvivier BM, Schaper NC, Hesselink MK, van Kan L, Stienen N, Winkens B, Koster A, Savelberg HH. Breaking sitting with light activities vs structured exercise: a randomised crossover study demonstrating benefits for glycaemic control and insulin sensitivity in type 2 diabetes. Diabetologia, 2017;60(3):490-498.
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- Bijnens W, Aarts J, Stevens A, Ummels D, Meijer K. Optimization and Validation of an Adjustable Activity Classification Algorithm for Assessment of Physical Behavior in Elderly. Sensors (Basel). 2019 Dec 4;19(24):5344. doi: 10.3390/s19245344.

Societal impact

Our work on interrupting prolonged sedentary behaviour, is reflected in the last version of Furthermore, beyond our scientific work we contributed to:

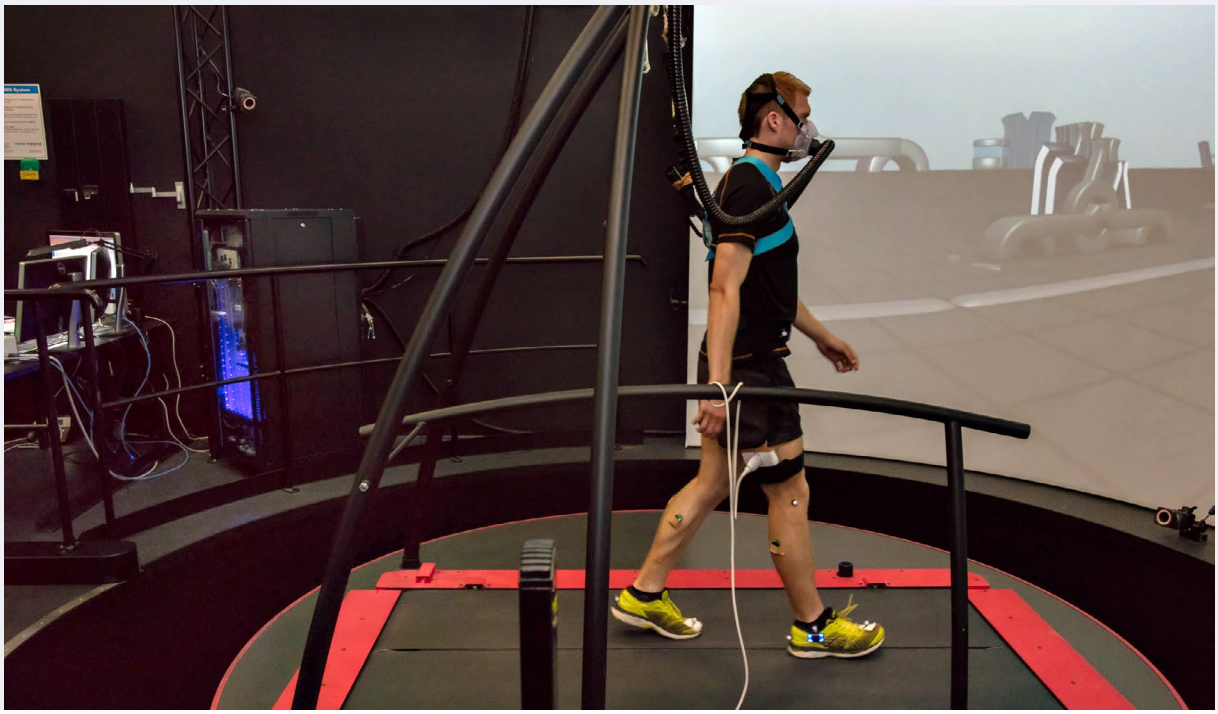
- The Dutch Guidelines for Physical Activity (2017), that advice to limit sitting time.
- The development of the Hospital Fit App, a tool that promotes physical activity in hospital settings. It is currently used by several hospitals.
- Participation in national study groups and expert panels to promote advanced gait analysis (e.g. The GRAIL User group and the Gaitscript study group (standardization of clinical gait analysis)).
- Development and implementation of novel, perturbation based, training regimes to reduce fall risk in elderly subjects.
- Personalized prehabilitation programs that have been adopted by several clinical disciplines (e.g., abdominal (cancer) surgery, cardiac surgery) to accelerate and improve postoperative recovery of physical functioning and reduce (the consequences of) complications and length of stay. This will also lead to a reduction in healthcare costs.
- An approach to measure professional athletes' energy expenditure in the field during competition events in order to optimize their nutritional strategies
- Development of international operating and reporting standards for the assessement of human energy and substrate metabolism using respiration chambers.
- Development of an international standard methodology for human doubly labelled water studies.

Future Perspectives

Physical activity behaviour is characterized by duration, intensity, timing on the day, and frequency of various sort of activities. A future challenge will be to find combinations of these aspects that have beneficial outcomes, not only for cardiometabolic health, but also for other health and performance outcomes (learning, musculoskeletal power, balance control, immunity, preparation for surgery, et cetera). This work will capitalize on technological developments in wearable monitoring and data science to which we contribute via collaboration with technology partners.

Figure 1
New office environments to stimulate physical activity
www.raaaf.nl

Figure 2
Snapshot of the CAREN system, one of the high-end facilities at the human performance lab. It includes a virtual environment, 3D motion capture, an instrumented treadmill and our in-house developed Omnical setup for indirect calorimetry.



DIVISION 2

Small lysosomes, Big problems, Great solutions: Lysosomes in control of metabolic diseases

Division 2: Liver and Digestive Health
Department of Genetics and cell biology, Department of Genetics and cell biology, Laboratory Medicine and Medical University Vienna, Austria

Background

Obesity, accompanied by the characteristics of metabolic syndrome, constitutes the greatest threat to global health, affecting 20-25% of the adult population. These patients are at risk to develop cardiovascular diseases, type 2 diabetes (T2D) and a spectrum of liver diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH). Additionally, obese subjects have increased risk for other complications such as hypertension, dyslipidemia, osteoarthritis, and some cancers. Chronic low-grade inflammation is thought to be the primary cause for the complications. However, while it is clear that the inflammatory response is induced by oxidative stress, the molecular and cellular mechanisms that trigger inflammation in some but not all obese individuals remain unclear. One piece of the puzzle is related to lysosomes and lysosomal enzymes. In the last decade, lysosomes have emerged as a nutrient signalling hub - both sensing and directing metabolic responses. Not surprisingly, lysosomal dysfunction is detrimental, and associated with development of lysosomal storage diseases, neurodegenerative disorders, cancers and a wide range of metabolic diseases. Our scientific ambition is to unravel the function and regulation of lysosomes in metabolic diseases in order to assess patients at risk for developing complications and to develop novel translational approaches for treatment and prevention.

Major breakthroughs

Mechanistically, we have demonstrated that hypercholesteremia leads to increased levels of oxLDL, which accumulates in lysosomes and triggers the development of inflammation. The accumulation of oxLDL in lysosomes initiates lysosomal dysfunction and leads to increased exocytosis of lysosomal enzymes. Based on these studies, we have demonstrated the predictive potential of antibodies against oxLDL for the development of NASH in humans and of the lysosomal enzyme Cathepsin D (CTSD) as an extremely powerful and the earliest non-invasive biomarker for NASH. We have further translated these mechanistic studies to the development of dietary, pharmacological and immunological treatments for combating low-grade inflammation. We showed that targeting dietary cholesterol and immunization against oxLDL are exceptionally efficient tools to prevent NASH. We have also applied these treatments within the context of a rare neurological disease (NPC1) and within cancer. Additional to the direct effect of oxLDL on the lysosomes, we have demonstrated that it leads to increased secretion of CTSD (among other lysosomal enzymes) into plasma of mice and humans with metabolic diseases including NASH, T2D and cancer.

We further demonstrated that increased CTSD in the plasma is a trigger for systemic disturbances in lipid metabolism, altered immune function and disease progression. These latest data suggest that plasma lysosomal enzymes also regulate systemic metabolic and inflammatory pathways independent from their intracellular role. To inhibit CTSD in a non-toxic manner we initiated the development of a novel inhibitor, which specifically targets the extracellular fraction of CTSD (and not the intracellular fraction) (PCT/IB2018/059764). By using this unique and non-toxic compound, we demonstrated decreased steatosis and systemic inflammation as well as reduced plasma insulin levels in rats and hyperlipidemic mice.

Who is involved

Multiple previous PhD students and postdocs contributed to the development of this research line. Our current team includes Prof. Dr. Ronit Shiri-Sverdlov (Principal investigator), Dr. Tom Houben (Assistant professor), Dr. Tim Hendrikx (Principal investigator), Dr. Albert Bitorina (Research assistant), Dr. Dennis Meesters (Lab manager and technician) and five PhD students; Tulasi Yadati, Lingling Ding, Ines Reis, Annemarie Westheim and Mengying Li.
The research was supported by multiple grants including NWO VENI, VIDI, TKI-LSH, CVON, VCK, KWF, CTMM, MLDS, Horizon 2020 and Novo-Nordisk Foundation.

Scientific impact/Research quality

Our data led to nine registered patent applications which received wide interest from industrial partners and led to two clinical trials (1: dietary stanols as a treatment for NASH; 2: antibodies against oxLDL as a treatment for NPC1). Furthermore, it has been presented in multiple international conferences (i.e. ATLAS International Symposium, Denmark; Global NASH Congress, London; Complications of Diabetes

and Obesity Symposium, Dublin, European Association for the Study of the Liver, Vienna; Leading-Edge Research Center for Drug Discovery, Kyungpook, South Korea) and was published in various high impact scientific journals.

Selection recent publications

1. Houben T, Oligschlaeger Y, Hendrikx T, Bitorina AV, Walenbergh SMA, van Gorp PJ, Gijbels MJJ, Friedrichs S, Plat J, Schaap FG, Lütjohann D, Hofker MH, Shiri-Sverdlov R; Cathepsin D regulates lipid metabolism in murine steatohepatitis. Sci Rep 2017 Jun;7(1):3494.
2. Houben T, Magro Dos Reis I, Oligschlaeger Y, Steinbusch H, Gijbels MJJ, Hendrikx T, Binder CJ, Cassiman D, Westerterp M, Prickaerts J, Shiri-Sverdlov R; Pneumococcal immunization reduces neurological and hepatic symptoms in a mouse model for Niemann-Pick Type C1 disease. Front Immunol 2019 Jan;9:3089.
3. Khurana P, Yadati T, Goyal S, Dolas A, Houben T, Oligschlaeger Y, Agarwal AK, Kulkarni A, Shiri-Sverdlov R; Inhibiting extracellular cathepsin D reduces hepatic steatosis in Sprague-Dawley rats. Biomolecules 2019 May;9(5):171.
4. Ding L, Goossens GH, Oligschlaeger Y, Houben T, Blaak EE, Shiri-Sverdlov R; Plasma cathepsin D activity is negatively associated with hepatic insulin sensitivity in overweight and obese humans. Diabetologia 2020 Feb;63(2):374-84.
5. Tom Houben, Albert V Bitorina, Yvonne Oligschlaeger, Mike LJ Jeurissen, Sander Rensen, Eleonore Köhler, Marit Westerterp, Dieter Lütjohann, Jan Theys, Andrea Romano, Jogchum Plat, Ronit Shiri-Sverdlov; Sex-opposed inflammatory effects of 27-hydroxycholesterol are mediated via differences in estrogen signaling. Journal of Pathology 2020 Aug;251(4):429-439.

Societal impact

Our work has been distributed via Layman communication platforms (i.e. Pan European Networks, LEVER, HashtageScishare, Atlas of Science and researchista.com) and involvements with the relevant national societies (i.e. NVH and MLDS).

Future Perspectives

Our aim is to explore the potential of targeting oxLDL and extracellular lysosomal enzymes as prognostic markers for disease severity and as non-toxic targets for treatment and for boosting the immune system in a wide variety of metabolic diseases including hepatocellular carcinoma, cardiovascular diseases, depression, Inflammatory bowel disease and autoimmune diseases.

Figure 1: Rationale
Unlike non oxidized LDL, accumulation of oxLDL in lysosomes can lead to lysosomal dysfunction by interfering with autophagy, by triggering apoptosis or by increasing the secretion of lysosomal enzymes into the plasma.

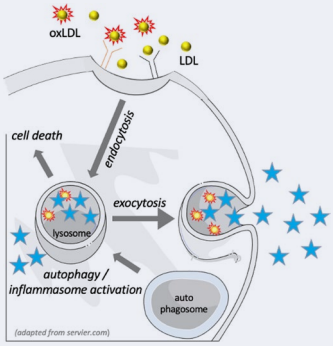
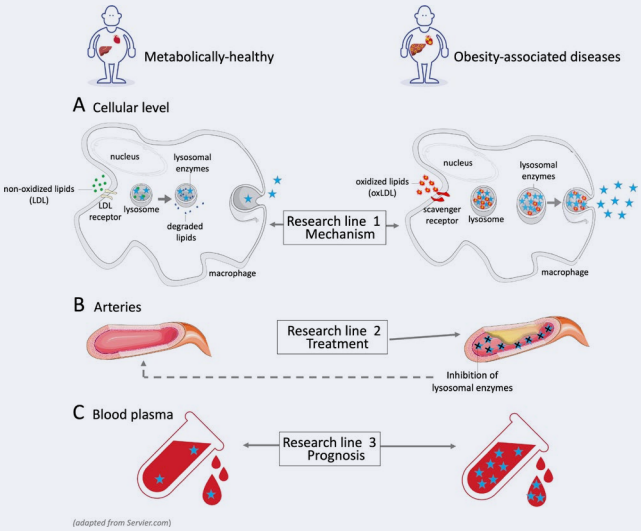


Figure 2: Research focus
Our research consists of three different lines:

1. **Mechanism**
   Investigation of the pathogenic signalling linking lysosomal dysfunction, disturbed lipid metabolism and inflammation.
2. **Treatment**
   Developing novel treatments for obesity-associated diseases, aimed at improving lysosomal function and reducing the activity of circulating lysosomal enzymes.
3. **Prognosis**
   Developing prognostic tools for assessing the risk of developing obesity-associated diseases.



DIVISION 2

Real world data to prevent flares and improve health of patients with IBD

Division 2: Liver and Digestive Health
Department of Gastroenterology - Hepatology, MUMC+

Background

More than half of the people in Western countries have at least one chronic disease. The cause of chronic conditions is in most cases complex and multifactorial. Environmental factors, lifestyle (e.g. nutrition, exercise) and psychosocial factors (e.g. social support, adherence) have a major influence on both the clinical course of the disease and the subjective health of patients, measured with patient reported outcome measures (PROMs). Quality of care is the degree to which the care provided succeeds in improving health. The best possible care provides optimal outcomes for all parties in the health care system; the patient, healthcare professional, regional care network and the society, with the available resources. Therefore, registering and reporting of all outcomes is necessary to measure quality of care and evaluate the effect of interventions (Figure 1). Digitization in healthcare, in particular the introduction of electronic patient files and Telemedicine enables registration of all these outcomes within the primary care process.

The inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis, are chronic conditions characterized by recurrent inflammation of the intestinal mucosa. There are more than 90,000 people with IBD in the Netherlands and the incidence is rising [1]. Like other chronic diseases, IBD has a complex aetiology and a heterogeneous clinical presentation and disease course. There is no curative treatment, no available drug is effective for all patients, and most drugs can cause serious side effects. State-of-the-art clinical stratification does not sufficiently predict the response to drugs and there are no reliable molecular markers. With traditional disease, management based on the treatment of symptoms and a 'step-up trial and error' drug introduction structural bowel damage caused by insufficient control of chronic inflammation is still common and negatively impacts the quality of life [2]. To improve the long-term course, new drugs were developed and new treatment goals and strategies were introduced. It is however unknown how quality of life, disability and quality of care have evolved in parallel with these innovations over the past ten years or if the interventions are cost-effective.
As with other chronic conditions, there frequently is a perception gap between doctors and patients; people with IBD often have disabling complaints, while the doctor believe, the disease is in remission. It is therefore important in addition to monitoring the clinical outcomes; mucosal inflammation and complications to measure the subjective burden to patients. PROMs measure this burden through patient questionnaires. They enable reporting of aspects that matter most to patients like subjective symptoms, quality of life, daily functioning and other aspects of their health and well-being. Finally, mounting evidence shows that lifestyle and psychosocial factors influence the course of the disease measured by classical clinical outcomes, but also the subjective perception of health, and therefore registration and reporting of these factors in every day practice is necessary.
By registration all outcomes and merging and analyzing aggregated data in health care, new insights can arise that support the clinical decision-making process. Converting data into information can result in better management of patient and within the organization. To enable the transformation to data-driven health care, a cross-disciplinary model was developed at the MUMC+ (figure 2). To capture PROMS and psychosocial and lifestyle factors, gastroenterologists and nurses from the Maastricht IBD research group developed the Telemedicine tool "myIBDcoach" in collaboration with the Dutch IBD patient association (Crohn-Colitis NL) [3]. MyIBDcoach supports the healthcare provider in remote monitoring (via periodic questionnaires and a point of care stool test), guiding (via a patient dashboard) and informing and communicating with patients (figure 3). The Online monitor shows red flags if risks are detected, making it possible to monitor patients remotely.

Major breakthroughs

According to the literature and studies of the Maastricht IBD-research group in the IBD-South Limburg cohort, the most important cost drivers for IBD are diagnostics, outpatient clinic visits, hospitalisations, and medication. Based on this information, the classical IBD care-path was adapted into an eHealth care-path. A RCT shows that implementation of the eHealth care-path using myIBDcoach, resulted in a 50% reduction in hospitalisations and a 37% decrease of outpatient visits in one year. Patient reported treatment adherence and quality of life increased and quality of care was similar compared to standard care [4]. A cost–utility analysis shows that implementation of the registration of PROMs with telemedicine resulted in an average annual cost reduction of €547 per patient (95% CI, [€1029, €2143] and an increase in the cost-effectiveness ratio of €707 per patient (95% CI, [1241, 2544]) [5]. Further studies show that psychosocial factors (stress) and lifestyle factors (malnutrition) increase the risk of flares [6,7]. Moreover, an exploratory analysis shows that the predictive value of psychosocial and lifestyle factors for flares is higher than that of the classical clinical classification of IBD [8].

"The doctor of the future will not give medicine, but will interest her or his patient in the care of the human frame, in a proper diet, and in the cause and prevention of disease." Thomas Edison (1847-1931)

Who is involved?

Maastricht IBD-research group, Division 2, NUTRIM Maastricht University and Clinical IBD-team MUMC+: PI: Dr. M.J. Pierik, Prof dr. D. Jonkers , Dr. Z. Mujagic, Dr. J. Haans, Mrs. M. Cilissen, Mrs. I. Sour, Mr. M. Braun, Prof. dr. L. Stassen, Dr. S. Breukink, Dr. J Melenhorst, Dr. F. Kokke, Drs. N. Bevers. DataHub Maastricht University Mr. P. Suppers. MyIBDcoach foundation, SMART-IBD network and Sananet bv.

Scientific impact/Research quality

Selection recent publications

1. Van den Heuvel TRA, Jeuring SFG, Zeegers MP, van Dongen DHE, Wolters A, Masclee AAM, Hameeteman WH, Romberg-Camps MJL, Oostenbrug LE, Pierik MJ, Jonkers DM. A 20-year temporal change analysis in incidence, presenting phenotype and mortality, in the Dutch IBDSL Cohort-can diagnostic factors explain the increase in IBD incidence? J Crohns Colitis. 2017;11(10):1169-79.
2. Jeuring SF, van den Heuvel TR, Liu LY, Zeegers MP, Hameeteman WH, Romberg-Camps MJ, Oostenbrug LE, Masclee AA, Jonkers DM, Pierik MJ. Improvements in the long-term outcome of Crohn's disease over the past two decades and the relation to changes in medical management: results from the population-based IBDSL cohort. Am J Gastroenterol. 2017;112(2):325-36.
3. De Jong M, van der Meulen-de Jong A, Romberg-Camps M, Degens J, Becx M, Markus T, Tomlow H, Cilissen M, Ipenburg N, Verwey M, Colautti-Duijsens L, Hameeteman W, Masclee A, Jonkers D, Pierik M. Development and feasibility study of a telemedicine tool for all patients with IBD: MyIBDcoach. Inflamm Bowel Dis. 2017;23(4):485-93.
4. De Jong MJ, van der Meulen-de Jong AE, Romberg-Camps MJ, Becx MC, Maljaars JP, Cilissen M, van Bodegraven AA, Mahmmod N, Markus T, Hameeteman WM, Dijkstra G, Masclee AA, Boonen A, Winkens B, van Tubergen A, Jonkers DM, Pierik MJ. Telemedicine for management of inflammatory bowel disease (myIBDcoach): a pragmatic, multicentre, randomised controlled trial. Lancet. 2017;390(10098):959-68.
5. de Jong MJ, Boonen A, van der Meulen-de Jong AE, Romberg-Camps MJ, van Bodegraven AA, Mahmmod N, Markus T, Dijkstra G, Winkens B, van Tubergen A, Masclee A, Jonkers DM, Pierik MJ. Cost-effectiveness of telemedicine-directed specialized vs standard care for patients with inflammatory bowel diseases in a randomized trial. Clin Gastroenterol Hepatol. 2020;18(8):1744-52.
6. Spooren CEGM, Wintjens DSJ, de Jong MJ, van der Meulen-de Jong AE, Romberg-Camps MJ, Becx MC, Maljaars JP, van Bodegraven AA, Mahmmod N, Markus T, Hameeteman WM, Masclee AAM, Winkens B, Jonkers DMAE, Pierik MJ. Risk of impaired nutritional status and flare occurrence in IBD outpatients. Dig Liver Dis. 2019;51(9):1265-9.
7. Wintjens DSJ, de Jong MJ, van der Meulen-de Jong AE, Romberg-Camps MJ, Becx MC, Maljaars JP, van Bodegraven AA, Mahmmod N, Markus T, Haans J, Masclee AAM, Winkens B, Jonkers DMAE, Pierik MJ. Novel perceived stress and life events precede flares of inflammatory bowel disease: a prospective 12-month follow-up study. J Crohns Colitis. 2019;13(4):410-6.
8. Lalisang RCA, Adriaans G, de Jong M, Van der Meulen-de Jong A, Romberg-Camps M, Mahmmod N, Markus-de Kwaadsteniet T, Dijkstra G, Haans J, Stamm C, Vanwersch R, Jonkers D, Almeida RJ, Pierik MJ, MyIBDcoach Study Group. Can lifestyle and psychosocial factors predict flares of IBD; an exploratory study using telemedicine. J Crohn's Colitis. 2020;14:S059-60.

Users and collaborations

- The eHealth carepath with myIBDcoach is implmented in routine-care in 20 hospitals in the Netherlands.
- SMART-IBD is a learning network of health-care professionals (gastroenterologists, nurses, dieticians) of all 20 hospitals involved and the patient organisation (www.crohn-colitis.nl) with the aim to optimize care paths through smart registration and reusing outcomes via a Dataplatform (DataHub UM). Developing and evaluating care-paths that focus on interventions on psychosocial and lifestyle risk factors for chronic conditions are given special attention. The aim of the SMART-IBD collaboration is transition from monitoring classical outcomes and treatment of mucosal inflammation alone to improving health from the patient's perspective.

Societal impact

With the myIBDcoach RCT - published in The Lancet in 2017 - the research group won the Wetenschaps- en Innovatieprijs of the Dutch federation for medical specialists (FMS).

The SMART-IBD project was nominated for the Value-Based Health Care Prize and the Zinnige Zorg Award.
By demonstrating that the eHealth care-path for IBD with, continuous monitoring of PROMs and psychosocial and lifestyle factors, is cost-effective compared to standard care, myIBDcoach could be implemented in 20 hospitals in the Netherlands. The data-optimized care paths for IBD are described in detail and shared with the SMART-IBD network. The SMART-IBD school aims to share knowledge regarding the innovative care-paths and organizes 3 monthly webinars for healthcare professionals.

Future perspectives

The SMART-IBD network is an ongoing collaboration using the aggregated data in DataHub UM to create evidence on life style and psychosocial interventions to prevent flares or improve health in IBD. The Maastricht IBD-research group maps myIBDcoach data to the OMOP common data model to enable combined analyses with the ICC-drug registry, PSI-IBD and IBD-SL cohort data to develop decision support tools and improve patient stratification of IBD.

Figure 1: Desired outcomes of different players in the Dutch Health Care system

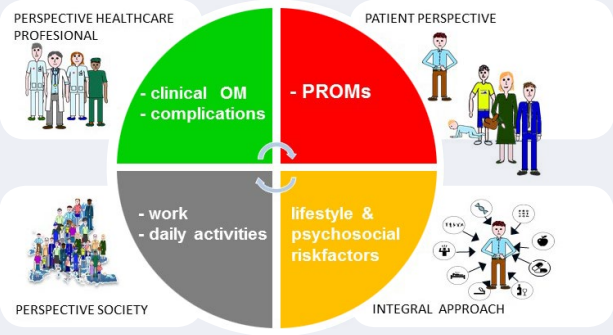


Figure 3: myIBDcoach

Overview of the elements of the telemedicine tool myIBDcoach:

1. Monitoring modules containing PROMS and clinical questionnaires: standard monitoring (every month, or every 3 months when the disease is in remission), intensified monitoring (weekly in case of a flare) and modules to prepare an outpatient clinc-visit.
2. Personal Follow-up plan: Graphical visualisation of clinial outcomes, calprtectin point of care test, PROMs and psychosocial and lifestyle riskfactors in a dashboard for patients and health care professionals
3. E-learning modules: interactive patient-tailored information on topics such as medications, adherence to medication, smoking cessation, (mal)nutrition, methods to prevent or reduce symptoms (self-management), fatigue, work productivity, anxiety and depression.
4. Communication: secure message connection between patient and healthcare providers' back-office.

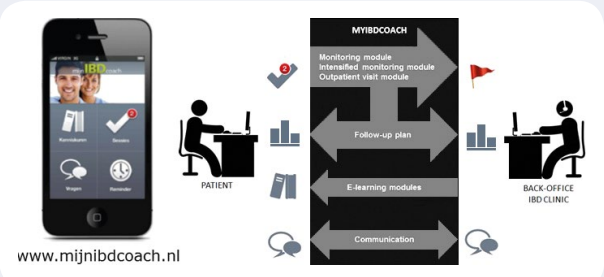
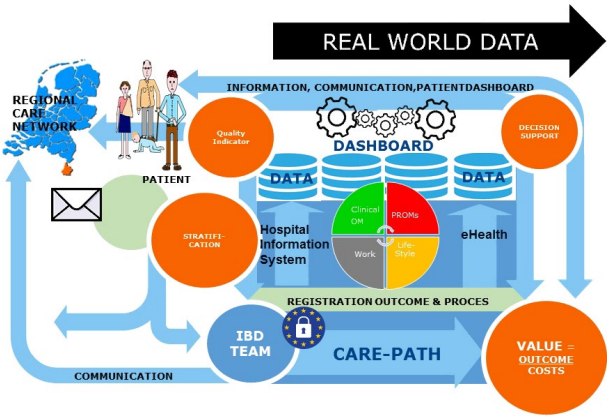


Figure 2: Data2Care Model

Referred patients from the regional care network are triaged to the optimal care path based on standardized data. During the first outpatient, patients are asked for permission to reuse data for multiple purposes. Standard sets of clinical outcome measures and process outcomes are registered during the primary care process in the Hospital Information system. PROMs, PREMs, psychosocial and lifestyle risk factors are registered in the eHealth tool myIBDcoach. Existing ZIBs are used as much as possible. Captured RWD is reused for:

- Shared decision-making in the consultation room with the aid of a patient dashboard and decision support tools.
- Patient group dashboards for evaluation and continuous improvement of the care path. Monitoring the balance between outcomes and costs.
- Communication within the regional care network
- To provide quality indicators for external accountability and transparency.
- Development of decision support tools
- Optimization of patient stratification



Cancer Cachexia: the impact of a tumor on the body of patients

Division 2: Liver and Digestive Health
Department of Surgery, MUMC+

Background

Our research focuses on cancer cachexia, a metabolic syndrome characterized by involuntary weight loss and loss of muscle mass in cancer patients (Figure 1). Cancer cachexia has a severe negative impact on survival and quality of life. Our research starts from relevant observations made in patients and their tissues, which form the basis for mechanistic studies. This involves the development of innovative organoid models of pancreatic cancer and investigation of numerous cachexia-related parameters in patients with pancreatic cancer, breast cancer, ovarian cancer, colorectal cancer or lung cancer to identify common as well as cancer-specific disease drivers. Diagnosing cachexia is challenging because patient reported weight loss is often unreliable. Recent technological advances enable accurate real-time monitoring of weight loss and habitual physical activity. These 'patient-recorded integrated measurements' (PRIMs) help us to establish a more accurate prognosis and support personalization of treatment. We also put effort into body composition assessment focusing on skeletal muscle mass and quality and adipose tissue volume of patients by analysis of CT (Figure 2). Furthermore, we initiated the construction of an advanced clinical research unit where patients can undergo deep phenotyping using state-of-the-art equipment focused on assessment of insulin sensitivity, muscle strength, and exercise capability.

Our specific research aims are to:
1. develop novel tools for objectively assessing cachexia severity;
2. identify host phenotypes of cachectic patients that predispose to adverse outcome;
3. relate tumor organoid characteristics to host phenotypes;
4. identify tumor-derived mediators responsible for tissue loss and dysfunction in cachexia;
5. show the importance of the tumor stroma for the development of cancer cachexia.
6. understand the link between cachexia and chemotherapy resistance;
7. assess smooth muscle dysfunction in cachexia;
8. evaluate the role of gut bacteria in cachexia.

Figure 1

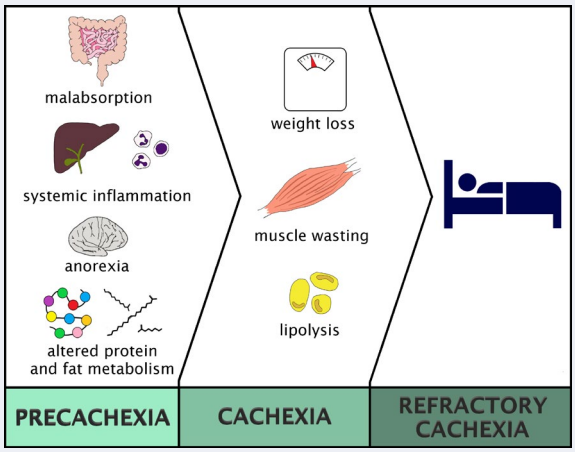
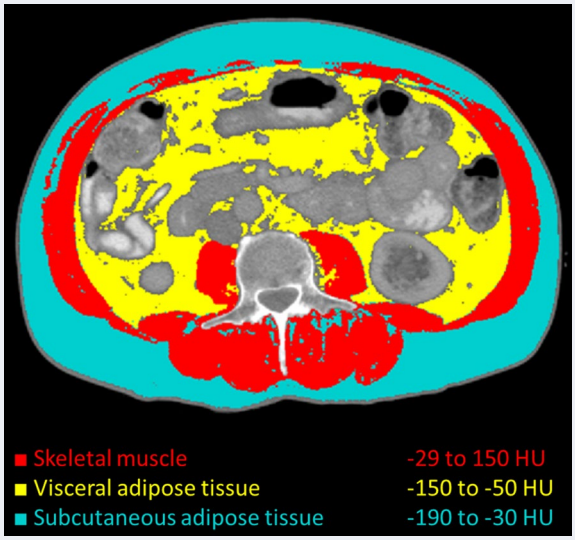


Figure 2



Major breakthroughs

We are the first to apply organoids for identifying novel tumour-derived factors that cause the metabolic aberrations underlying cancer cachexia (Figure 3). In this context, we have developed a living biobank with a uniquely extensive characterization of the patients who contributed the organoids, which is made freely available to other researchers. We have applied these organoids to not only study the impact of tumour factors on skeletal muscle, the traditional focus of cachexia researchers, but also on smooth muscle and immuno metabolism of leukocytes.

Furthermore, we transplanted tumour organoids into mice, providing a novel avatar model of human cachexia. This has provided important novel insights to the field, such as the increased basal respiration in macrophages, the accelerated myogenic differentiation of skeletal muscle cells, and the switch to a synthetic phenotype by smooth muscle cells after exposure to tumour organoid factors.

We have also advanced the body composition analysis field by showing that combining several body composition parameters and information on systemic inflammatory factors is more predictive of patient survival than tumour stage. In addition, we showed that ectopic fat deposition in liver and muscle are independent predictors of survival and infectious complications after surgery. We are actively implementing radiomics and developing automated CT-based body composition algorithms. Furthermore, our analyses of the microbiome of cancer patients in relation to their cachexia status is unique and has yielded the information that is required to develop a prebiotic intervention, which could represent a novel means of nutritional support for cancer patients. Finally, we have applied our long-standing expertise in stable isotope tracing approaches to study protein metabolism in various organs in cachectic cancer patients, showing that tumour protein synthesis is quantitatively lower than protein synthesis of surrounding healthy pancreatic tissue as well as of muscle and adipose tissue.

Who is involved?

P.I.s Steven Olde Damink, Sander Rensen.
Our research is the result of a true team effort where input from surgeons, oncologists, nurse practitioners, basic researchers, laboratory technicians, and PhD students is integrated in translational studies with a close eye on ultimate clinical benefit for patients (Figure 4).

Surgeons Ulf Neumann, Ronald van Dam, Kees Dejong, Marielle Coolsen, Stefan Bouwense, Anjali Roeth, Taco Blokhuis, and Marcel den Dulk as well as oncologists Judith de Vos-Geelen and Liselotte Valkenburg-van Iersel are crucial for inclusion and follow-up of patients and for collection of samples. Lieke Corpelijn and Bart Bongers perform essential functions in the physical and nutritional assessment of patients. Ralph Brecheisen and Leonard Wee are instrumental in applying radiomics and facilitate automated CT-based body composition analysis. A group of talented PhD students and technicians is essential for performing, analysing, and interpreting our clinical and laboratory studies.

These studies are only possible with financial and in-kind support from many sources, including the NWO NUTRIM Graduate Program, the Eurostars Program of EU Horizon 2020, the European Society for Clinical Nutrition and Metabolism, the European Institution of Innovation & Technology (EIT) Food4Health Program, the European Union Interreg fund for cross-border projects, and the Top Consortium for Knowledge and Innovation (TKI).

Users and collaborations

Since the start of this research line in 2012, we have firmly established our position within the cachexia research field. Our work is recognized worldwide as evident from collaborations with many world-class scientists, including Prof. Dave Tuveson (USA) and Dr. Sylvia Boj (NL), the pioneers in the pancreatic tumor organoid field, and with Prof. Vickie Baracos (Canada) and Prof. Paola Costelli (Italy), leading cancer cachexia scientists. Important collaborations in the pancreatic cancer field include those with Prof. David Chang (UK) and Dr. Richard Skipworth (UK). We collaborate closely with Prof. Thorsten Cramer (Germany) in the context of tumour metabolism. We are among the initiators of the newly formed preclinical Dutch Pancreatic Cancer Group, an assembly of

Figure 3
Organoid approaches to study cancer cachexia and its link to chemotherapy resistance.

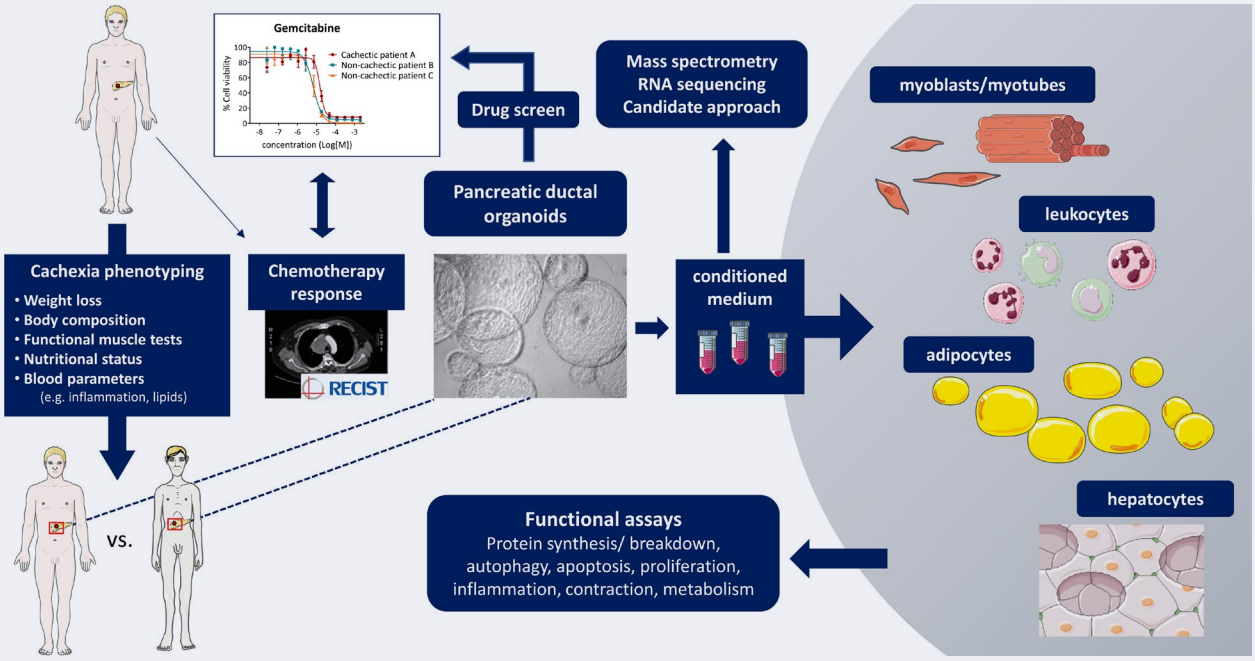
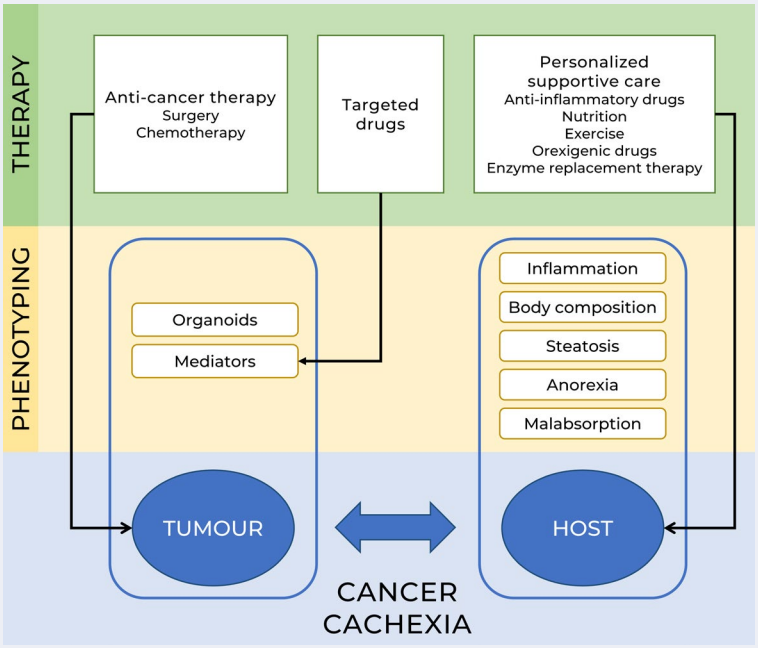


Figure 4
Our research is the result of a true team effort where input from surgeons, oncologists, nurse practitioners, basic researchers, laboratory technicians, and PhD students is integrated in translational studies with a close eye on ultimate clinical benefit for patients.



scientists who perform basic research on pancreatic cancer, embedded in the clinically focused Dutch Pancreatic Cancer Group. Internally, we collaborate actively with groups in other NUTRIM divisions (Annemie Schols/Ramon Langen, Luc van Loon, Patrick Schrauwen). In addition, we have joined forces with Danone Nutricia to assess the role of the gut microbiota in cancer cachexia and to develop a prebiotic intervention for supporting the gut microbiota. Furthermore, we have an active collaboration with Cell Guidance Systems to develop a novel growth factor platform for advancing organoid culture systems.

Scientific impact/Research quality

In the last five years, we have published many studies with high impact in the top journal of our field, the Journal of Cachexia, Sarcopenia, and Muscle (IF ~10). Examples are:

- Vaes RDW, van Dijk DPJ, Welbers TTJ, Blok MJ, Aberle MR, Heij L, Boj SF, Olde Damink SWM, Rensen SS. Generation and initial characterization of novel tumour organoid models to study human pancreatic cancer-induced cachexia. J Cachexia Sarcopenia Muscle. 2020;11(6):1509-1524.
- West MA, van Dijk DPJ, Gleadowe F, Reeves T, Primrose JN, Abu Hilal M, Edwards MR, Jack S, Rensen SSS, Grocott MPW, Levett DZH, Olde Damink SWM. Myosteatosis is associated with poor physical fitness in patients undergoing hepatopancreatobiliary surgery. J Cachexia Sarcopenia Muscle. 2019;10(4):860-871.
- van Dijk DPJ, Horstman AMH, Smeets JSJ, den Dulk M, Grabsch HI, Dejong CHC, Rensen SS, Olde Damink SWM, van Loon LJC. Tumour-specific and organ-specific protein synthesis rates in patients with pancreatic cancer. J Cachexia Sarcopenia Muscle. 2019;10(3):549-556.
- van Dijk DPJ, Krill M, Farshidfar F, Li T, Rensen SS, Olde Damink SWM, Dixon E, Sutherland FR, Ball CG, Mazurak VC, Baracos VE, Bathe OF. Host phenotype is associated with reduced survival independent of tumour biology in patients with colorectal liver metastases. J Cachexia Sarcopenia Muscle. 2019;10(1):123-130.
- van Dijk DP, Bakens MJ, Coolsen MM, Rensen SS, van Dam RM, Bours MJ, Weijenberg MP, Dejong CH, Olde Damink SW. Low skeletal muscle radiation attenuation and visceral adiposity are associated with overall survival and surgical site infections in patients with pancreatic cancer. J Cachexia Sarcopenia Muscle. 2017;8(2):317-326.
- van Dijk DP, van de Poll MC, Moses AG, Preston T, Olde Damink SW, Rensen SS, Deutz NE, Soeters PB, Ross JA, Fearon KCh, Dejong CH. Effects of oral meal feeding on whole body protein breakdown and protein synthesis in cachectic pancreatic cancer patients. J Cachexia Sarcopenia Muscle. 2015;6(3):212-21.

Our PhD students have won multiple prizes presenting this original work on different conferences, e.g. the best presentation award for Rianne Vaes at the 12th Congress of the Society of Sarcopenia, Cachexia and Wasting Disorders in Berlin in 2019, and a fellowship from the Living with Hope foundation for Merel Aberle in 2018.

Societal impact

We consider it very important to communicate our data and insights to fellow researchers and to the broader community. We partner with patient advocate organizations like Living with Hope and Inspire2live to ensure the inclusion of patient opinions in our research projects, thereby adding relevance to our work. We have organized a workshop on the use of organoids in translational research as part of the 11th Congress of the Society of Sarcopenia, Cachexia and Wasting Disorders. Our educational activities also include a recent contribution to the novel Textbook of Pancreatic Cancer Principles and Practice of Surgical Oncology (due March 8, 2021) on The Cachexia Syndrome in Pancreatic Cancer. We are actively working on implementation of our findings in the patient care paths of the Maastricht Comprehensive Cancer Centre.
Recently, our research activities have been picked up by regional and national newspapers, which allowed us to create awareness of the detrimental impact of cancer cachexia on the patient's treatment outcome and quality of life. In addition, we are active in the valorisation of our research insights. We are among the founding members of Adjutec, a start-up that focuses on the development of a novel anti-cancer vaccination platform with an innovative adjuvant that promotes strong immune responses to patient-specific tumour targets.

Future Perspectives

In the near future, we will focus on improving the characterization of cachexia severity in cancer patients by fully integrating the novel equipment and assessment tools that have come available within the clinical research unit into our translational research lines. We will start with an exercise-based intervention study to assess the feasibility of a prehabilitation approach for patients with pancreatic cancer, and determine the effect of training on the fitness of the immune system.

On the origins of species: Host-Microbiome-Diet interactions in early life

Division 2: Liver and Digestive Health
Department of Medical Microbiology

Background

What are - Host-Microbiome-Diet Interactions
"Off to the best start for newborns by giving them a healthy microbiome"

The human gut microbiota is well-known to contribute to health and disease. Our understanding of intestinal microbial ecology, therefore, has a direct impact on our ability to manage and maintain human health. In this respect, early childhood is a critical age-window since diversification and maturation of the microbiota primarily occurs during this period of life and affects metabolism, maturation of the gastrointestinal tract, immune system function, and brain development. Consequently, unraveling the complex host-microbiome-diet interactions during this window-of-opportunity is pivotal to find new leads to prevent the development of non-communicable diseases. Combining epidemiological human birth cohorts, clinical trials, *in vitro* models and murine *in vivo* models, we aim to understand the natural process of the maturation of the microbiota and the impact of host, environmental and dietary factors in this process. We have, for example, recently demonstrated the causal impact of bile acids in neonatal microbiota development (van Best et al., Nature Communications 2020). In addition, the impact of human milk oligosaccharides as well as factors of the host's innate immune system that shape the microbiota composition and thus ensure a beneficial outcome and host-microbial homeostasis after the postnatal period are being investigated. In addition, the role of microbial perturbations in the onset of non-communicable diseases are main topics within our research. This is exemplified a RCT (PROTEA-study) on the prevention of respiratory infections and allergies in premature neonates by administrating bacterial lysates, a study facilitated by a Netherlands Lung Foundation consortium grant that will start shortly.

Major breakthroughs

- We have recently for the first time demonstrated how joint modelling (integration of longitudinal microbiome analysis and survival analysis) can be used to unravel microbial perturbations prior to disease onset (Galazzo et al., Gastroenterology 2020).
- Within our PROTEA-study, we expect to reduce respiratory infections and comorbidities after preterm birth and thereby significantly enhance the quality of life in this vulnerable population.
- By focusing on integrative multi-omics and innovative single cell phenotyping approaches, we strive to markedly deepen the knowledge on the functional development of the infant microbiota and its interaction with the host.

Who is involved?

Dr. J. Penders (PI), Dr. Niels van Best (post-doc, joint-PhD UM-RWTH Aachen), Drs. G. Galazzo (PhD-student), Drs. David Barnett (external PhD-student at Maastricht Center for Systems Biology), Drs. Bich Ngoc (external PhD at Oxford University Clinical Research Unit, Hanoi, Vietnam), Dr. Giang Le (bioinformatician) and Christel Driessen and Mayk Lucchesi (supportive staff).
Our team's research is characterised by a multi-disciplinary approach combining fundamental and applied research to gain insight in early-life microbiome development. Importantly, translation of novel mechanistic insights into diagnostic, prognostic and therapeutic improvement is always pursued. Epidemiological studies (LucKi Birth cohort, KOALA Birth Cohort, Asthma Early Detection study) are conducted in collaboration with clinical (Paediatrics; Obstetrics & Gynaecology) and non-clinical (Epidemiology) departments within our faculty. Moreover, our team is responsible for the microbiome research in birth cohorts and clinical trials conducted at other university medical centres within the Netherlands and abroad (e.g., Erasmus MC, RWTH Uniklinik Aachen and Charité Universitätsmedizin Berlin).
The research is funded by grants from the Joint Programmes Initiative a Healthy Diet for a Healthy Live, a NWO-VIDI grant (to J. Penders), Carbohydrate Competence Center NWO Carbobiotics, a Lung Foundation Consortium Grant, EFSD/Chinese Diabetes Society/Lilly and a Kootstra Talent Fellowship (to N. van Best).

Scientific impact/Research quality

Selection of publications

- van Best N, Rolle-Kampczyk U, Schaap FG, Basic M, Olde Damink SWM, Bleich A, Savelkoul PHM, von Bergen M, Penders J, Hornef MW (2020). Bile acids drive the newborn's gut microbiota maturation. Nature Communications, 11(1), 3692, DOI: 10.1038/s41467-020-17183-8.
- van Best N, Trepels-Kottek S, Savelkoul P, Orlikowsky T, Hornef, MW, Penders, J (2020). Influence of probiotic supplementation on the developing microbiota in human preterm neonates. Gut Microbes, 12(1), 1-16. DOI: 10.1080/19490976.2020.1826747.
- Galazzo G, van Best N, Bervoets L, Dapaah I, Savelkoul PH, Hornef MW, Lau S, Hamelmann E, Penders, J (2020). Gastroenterology, 158(6), 1584-1596, DOI: 10.1053/j.gastro.2020.01.024.
- Fassarella M, Blaak EE, Penders J, Nauta A, Smidt H, Zoetendal EG (2020). Gut microbiome stability and resilience: elucidating the response to perturbations in order to modulate gut health. Gut, DOI:10.1136/gutjnl-2020-321747. Epub ahead of print. PMID: 33051190.
- Zhong H, Penders J, Shi Z, Ren H, Cai K, Fang C, Ding Q, Thijs C, Blaak EE, Stehouwer CDA, Xu X, Yang H, Wang J, Wang J, Jonkers DMAE, Masclee AAM, Brix S, Li J, Arts ICW, Kristiansen K (2019). Impact of early events and lifestyle on the gut microbiota and metabolic phenotypes in young school-age children. Microbiome 7(1):2. DOI: 10.1186/s40168-018-0608-z.

Users and collaborations

Our research on early-life host-microbe-diet interactions is embedded in several ambitious international networks, incl.:

- the Million Microbiomes of Humans Project (J. Penders - member steering committee, https://db.cngb.org/mmhp), which aims to establish a reference catalogue of human microbiomes across age and geography;
- the InViVo Planetary Health Network (J. Penders co-Director, www.invivoplanet.com), which aims to transform personal and planetary health through awareness, attitudes and actions and to have a deeper understanding of how all systems are interconnected and interdependent, and;
- the JPI Knowledge Platform on Food, Diet, Intestinal Microbiomics and Human Health, which aims to standardise, harmonise and share data and knowledge.

We furthermore collaborate with various academic partners (a.o. Uniklinik RWTH Aachen, University of Liège, Wageningen University & Research, McMaster University, Washington University, McMaster University, Charité, DTU Copenhagen, OUCRU Hanoi), as well as industrial partners (a.o. InBiome, Symbiopharm, FrieslandCampina).

Societal impact

Our research is focused on healthy microbiome development in early-life for a healthy life and explicitly multiple stakeholders. The Lucki Gut Birth Cohort (www.luckigut.nl) is, for example, embedded within the Youth Health Care (JGZ) and as such close interactions with stakeholders including paediatricians and nurses of child health clinics, but also midwives, maternity care and lactation specialists is warranted. Research tools (R packages and codes, e.g., MicroViZ) developed within our team are shared with the scientific community via our lab's GitHub. Our team is often invited to present results on the early life microbiome and its role in non-communicable diseases at various (inter)national congresses (e.g., EAACI, ESPEN, International Human Microbiome Congress, German Allergy Congress, Nordic Allergy Symposium, Beneficial Microbes Conference).

Media exposure

Source	Title
Algemeen Dagblad, 20th November 2020	Onderzoek naar voorkomen longontsteking bij te vroeg geboren baby'tjes
www.gutmicrobiotaforhealth.com January 2019	Gut microbiome development continues between 6 and 9 years of age, with pre-school diet and breastfeeding acting as major driving forces
www.limburger.nl 23rd January 2020	Minder allergieën bij jonge kinderen met goede darmflora
Nederlands Dagblad, 21st January 2020	Darmflora van baby's bepalend voor allergieën
Gezond idee, June 2017	Hoe houd je je darmflora gezond?
Gezond idee, October 2016	Bacteriën als slankmakers

Future Perspectives

Our research in the next five years will focus on generating a deeper functional understanding of the developing infant microbiota and its interaction with the host by integrative multi-omics (metabolomics, metagenomics, meta-transcriptomics) as well as single-cell phenotyping approaches. Together this should further unravel the ecological processes of microbiota maturation as well as identify (non)responders to microbiota-targeted interventions. In order to achieve this and maintain a strong international position, we have recently joined forces with partners at Uniklinik RWTH Aachen, the Centre for Healthy Eating & Food Innovation (HEFI) at Campus Venlo and University of Liège to launch the Euregional Microbiome Center (EMC).

By establishing a prestigious training and research climate, initiating joint-PhD projects and exchanging students between EMC partner institutes, we strive to be a breeding ground for the next-generation of leading scientists.

Figure 1


UNRAVEL HOST-MICROBE INTERACTIONS
INTERVENTIONS & CLINICAL PREDICTION
CREATING VALUE
SOCIETAL IMPACT
IN VIVO & VITRO MODELS
LONGITUDINAL BIRTH COHORTS
MICROBIOME-BASED THERAPEUTCIS & DIAGNOSTICS
PUBLIC-PRIVATE PARTNERSHIPS
TRAINING AND EDUCATING
HEALTHY MICROBIOME FOR A HEALTHY LIFE

DIVISION 2

Enterohepatic cycle disturbances in surgical patients.

Division 2: Liver and Digestive Health
Department of Surgery

Background

What are the consequences of disturbances in the enterohepatic circulation?
Bile salts are the prototypical signaling molecules involved in bidirectional communication in the gut-liver axis. Synthesized in the liver, bile salts are secreted in the biliary network for eventual release in the proximal small intestine to aid in digestion and absorption of dietary lipids. Active reclamation of the bulk of bile salts in the terminal ileum along with passive re-uptake of bile salts spilling over into the colon, allow near-complete conservation and return of bile salts to the liver via the portal blood for re-secretion into bile. During their enterohepatic cycle (EHC), bile salts activate dedicated plasma membrane (e.g. TGR5) and nuclear bile salt receptors (e.g. FXR) in the small intestine and liver. Attendant signaling actions are pivotal for maintaining metabolic homeostasis, liver tissue homeostasis, gut barrier integrity and inflammatory control in the intestine and liver (Figures 1 and 2). Disturbances in the EHC result in a loss of these signaling actions, as well as loss of physicochemical actions of bile salts. Consequences of perturbed EHC thus include fat malabsorption and deficiency of fat-soluble vitamins, small intestinal bacterial overgrowth whether or not accompanied by (portal) endotoxemia and hepatic bile salt accumulation and attendant cellular damage and inflammatory sequela. Dysregulated bile salt homeostasis/bile salt toxicity is considered an important etiological factor in liver disease in patients with EHC disturbances. Likewise, it is linked to impaired liver regeneration and post-operative complications in (post)cholestatic patients with hepatobiliary tumors.

What are causes of abrogated enterohepatic circulation?
Clinical scenarios giving rise to defective EHC include obstruction caused by compression of the bile ducts by a tumor mass inside (e.g. perihilar cholangiocarcinoma) or outside (e.g. head of pancreas carcinoma) the liver. This results in impaired flow of bile (i.e. cholestasis) towards the duodenum, hepatic retention and accumulation of bile salts and intestinal bile salt deficiency. In surgical patients with a proximal enterostomy or enterocutaneous fistula, bile and other digestive fluids are lost via the stomal or fistula output. This lack of intestinal continuity can give rise to intestinal failure-associated liver disease. This syndrome also occurs as a consequence of intestinal failure caused by massive resection of intestine resulting from a surgical emergencies. In patients with critical illness, gallbladder dysfunction is a common feature, with impaired expulsion of bile resulting in EHC perturbation. Likewise, patients receiving (total) parenteral nutrition lack the enteral stimuli that induce gallbladder contraction and enterohepatic bile salt cycling.

Major breakthroughs

Low FGF19 levels predict poor survival in adult patients with chronic intestinal failure.
FGF19 is an enterokine that is transcriptionally induced following uptake of bile salts from the intestinal lumen, and mediates negative feedback regulation of bile salt synthesis (Figure 1). Low levels of FGF19 were found in adult patients with chronic intestinal failure, and this correlated with chronic cholestasis and poor survival (Figure 3). Low FGF19 is one of the three predictors incorporated in a risk model of survival termed Model for End-Stage Intestinal Failure (MESIF). The MESIF score may help to identify patients for closer clinical monitoring or earlier referral to intestinal transplantation centers. https://pubmed.ncbi.nlm.nih.gov/31075790

The nutrient-stimulated FGF19 response is abrogated in critically ill patients.
Enteral lipids induce gallbladder emptying and postprandial elevation of the metabolic hormone FGF19. The nutrient-stimulated FGF19 response is impaired in ICU patients (Figure 4), which is mechanistically linked to gallbladder dysmotility in critical illness. This may contribute to disturbed liver metabolism in these patients and has potential as a nutritional biomarker. https://pubmed.ncbi.nlm.nih.gov/30933374

Bile salt levels at post-operative day 1 predict liver regeneration in humans.
In patients undergoing liver resection for colorectal liver metastasis (CRLM), levels of bile salts in the portal circulation were elevated 2-3 hrs after start of liver transection. This was accompanied by elevated hepatic bile salt content and associated with transcriptional induction of genes engaged in priming hepatocyte cell cycle re-entry. Bile salt levels increased in the postoperative trajectory, and levels at post-operative day 1 predicted liver regeneration in these patients (Figure 5). This observation was replicated in an external validation cohort. Strikingly, a divergent postoperative bile salt course was observed in (post)cholestatic patients undergoing resection for perihilar cholangiocarcinoma, in which postoperative complications are far more frequent than in patients with CRLM.

Figure 1: Enterophepatic actions of FXR

Bile acids (exemplified as the primary bile acid CDCA) are produced in the liver by CYP7A1-initiated conversion of cholesterol in primary bile acids. Bile salts are secreted via BSEP into the canalicular lumen. In the ileum, bile salts are reabsorbed via ASBT in terminal ileum enterocytes. Here, they bind and activate FXR and this stimulates the transcription of FGF19, which encodes a protein that is secreted into the portal circulation. In the liver, FGF19 binds to its receptor FGFR4, which activates a signalling pathway involving MAP kinases and causes repression of CYP7A1, thus downregulating bile acid synthesis. After OSTa/13- mediated secretion into the portal circulation, bile acids are taken up by the liver via NTCP, thus, completing the enterohepatic cycle. In the liver, bile acids bind to FXR, which transcriptionally upregulates a protein called SHP (not shown) that interferes with expression of CYP7A1. Oral FXR agonists will affect FXR in both liver and intestine and this strongly downregulates CYP7A1 both by FGF19-dependent and FGF19-independent effects. FGF19 additionally affects lipogenesis, gluconeogenesis and liver regeneration. Abbreviations: ASBT, apical sodium-dependent bile salt transporter; BSEP, bile salt export pump; CDCA, chenodeoxycholic acid; CYP7A1, cholesterol 7-a-monooxygenase; FGF19, fibroblast growth factor 19; FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; NTCP Nattaurocholate cotransporting polypeptide; OST, organic solute transporter; SHP, small heterodimer partner.

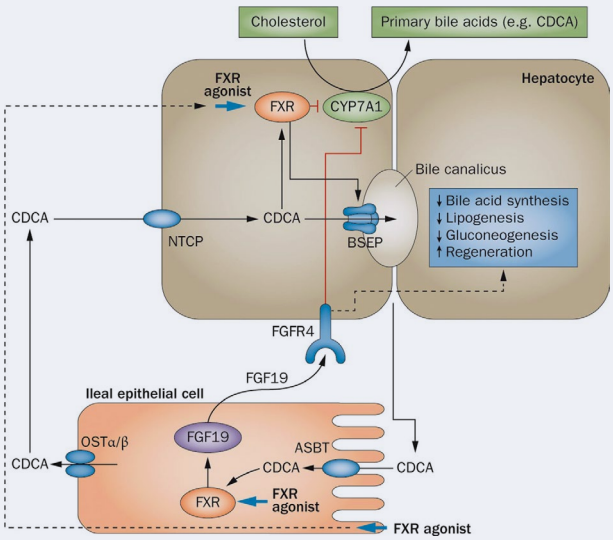


Figure 2: TGR5-expressing tissues and targets

TGR5 signalling in skeletal muscle and brown adipose tissue results in local activation of the deiodinase D102 that generates active thyroid hormone (13), an important regulator of metabolism and energy homeostasis. Bile acids in the intestinal lumen activate TGR5 in enteroendocrine cells, resulting in release of the incretin GLP-1. In Kupffer cells and macrophages, TGR5 activation inhibits LPS-induced cytokine production. Abbreviations: D102, type II iodothyronine deiodinase; GLP-1, glucagon-like peptide 1; LPS, lipopolysaccharide; 13, active thyroid hormone; 14, inactive thyroxine; TGR5, transmembrane G protein-coupled receptor TGR5 (also known as GPBAR1).

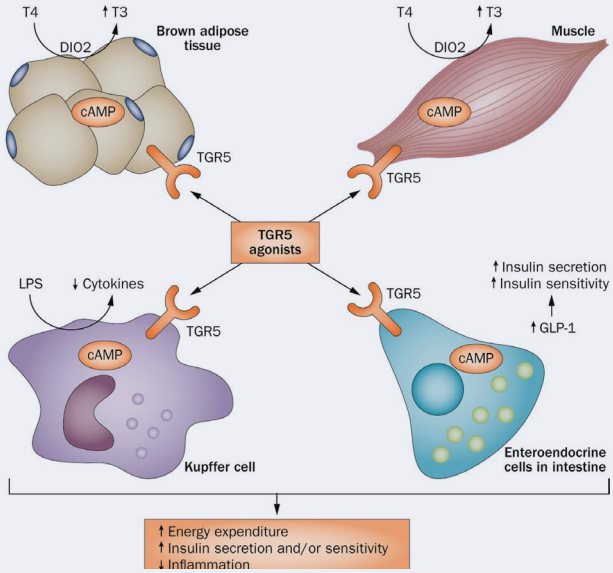
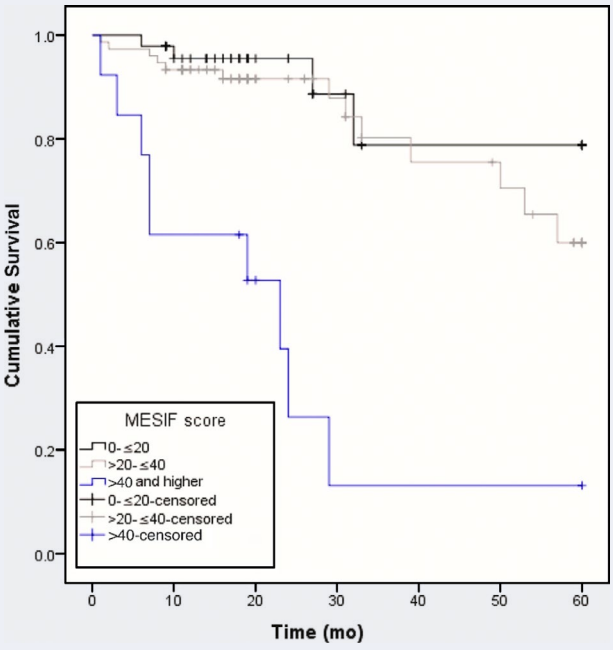


Figure 3: Kaplan-Meier curves for patients with low, intermediate, and high MESIF scores.

Patients with high MESIF scores (> 40) had a significantly lower 5-y survival rate than patients with low (scores between 0 and 20) or intermediate (scores between 20 and 40) MESIF scores (log-rank test, $P < 0.0001$). MESIF, Model for End-Stage Intestinal Failure.



Patients at risk, *n*						
Time (mo)	0	12	24	36	48	60
0 - ≤20	47	38	16	6	6	6
>20 - ≤40	75	60	29	17	16	8
>40 and higher	13	8	3	1	1	1

Chyme reinfusion restores the regulatory bile salt-FGF19 axis in intestinal failure patients.
Automated chyme reinfusion (CR) in intestinal failure patients with a temporary double enterostomy restores intestinal function and protects against liver injury. CR evoked an increase in plasma FGF19 and decreased C4 levels, indicating restored regulation of bile salt synthesis via endocrine FGF19 action (Figure 6). Furthermore, citrulline and albumin levels were gradually rising after CR, while abnormal serum liver tests normalized after CR, indicating restored intestinal function, improved nutritional status and amelioration of liver injury. Beneficial effects of chyme reinfusion are partly mediated by recovery of the bile salt-FGF19 axis and subsequent homeostatic regulation of bile salt synthesis.

Who is involved?

The research team is headed by P.I.s Frank Schaap and Steven Olde Damink and at present consists of five PhD students: Kim van Mierlo, Kiran Koelfat (supported by NWO/ESPEN), Lin Cheng & Xinwei Chang (both supported by Chinese Scholarship Council) and Ümran Ay (supported by the German Research Foundation). A visiting scientist (Dr. Martin Lenicek) was previously supported by a NWO travelling grant and is presently working in our team with support of an EU mobility grant. Staff support is provided by technicians Annemarie Bijnen and Bas Boonen (general lab support) and Dr. Hans van Eijk (analytical support). We are also embedded within the prestigious Sonderforschungsbereich 1382 " Die Darm-Leber-Achse-Funktionelle Zusamenhange und Therapeutische Strategie of the Deutsche Forschunsgemeinschaft as part of a collaboration with the RWTH Aachen.

Users and collaborations

We collaborate locally with Prof. Ron Heeren (M4i) and Dr. Rob Vreeken (M4i) to study spatial localization of bile salts and sulfatides in cholangiopathies, and with Dr. John Penders, Dept. of Medical Microbiology to investigate the interaction between the gut microbiota and bile salts.
National collaborations exist with Dr. Barbara de Koning, Erasmus UMC, Rotterdam (pediatric intestinal failure) and Dr. Geert Wanten, Radboud UMC, Nijmegen, with whom we study acute and chronic intestinal failure in the pediatric and adult population. In collaboration with Dr. Maarten Soeters, Amsterdam UMC we study metabolic consequences of enterohepatic bile salt signaling in human subjects.

International collaborations
With Prof. Mathias Hornef, RWTH Aachen, Aachen, Germany we study the interaction between the gut microbiota and bile salts. Bile salt receptor-based enhancement of liver regeneration in mouse is studied in collaboration with Prof. Isabelle Leclercq, Université Catholique de Louvain, Brussels, Belgium. In a long-standing collaboration, dysregulation of the bile salt/FGF19 regulatory axis and other aspects of bile salt (patho) physiology are studied in patient populations together with Dr. Martin Lenicek, Charles University Prague, Czech Republic. Joint studies with Dr. Espen Melum, Oslo University Hospital/Norwegian PSC Research Center, Oslo, Norway, focus on gaining insight into the role of sulfatides in cholangiocyte biology and the bile duct disorder primary sclerosing cholangitis. Together with Prof. Ronan Thibault, Rennes University Hospital, France, we study adult patients with acute intestinal failure, receiving chyme reinfusion therapy.
We are also embedded within the prestigious Sonderforschungsbereich 1382 "Die Darm-Leber-Achse-Funktionelle Zusamenhange und Therapeutische Strategie" of the Deutsche Forschunsgemeinschaft, where we are collaboration partners in 7 of the 16 projects.

Industrial partners
The effects of an FDA-approved FXR agonist on liver growth after experimental portal vein embolization are studied in collaboration with Dr. Luciano Adorini, Intercept Pharmaceuticals Inc.

Scientific impact/Research quality

Our focus on human translational studies is internationally recognized and well appreciated, as mirrored by publications in high impact journals in the field of hepatology and gastroenterology. Most of the knowledge on bile salt signaling stems from mouse studies, with many aspects of bile salt biology differing between man and mouse, these translational studies are of key importance.

Selection of publications

- Koelfat KVK et al. Chyme reinfusion restores the regulatory bile salt-FGF19 axis in intestinal failure patients. Hepatology, revised manuscript under consideration.
- Koelfat KVK et al. Bile salt and FGF19 signaling in the early phase of human liver regeneration. Hepatol. Commun., in press
- Koelfat KVK, Plummer MP, Schaap FG, Lenicek M, Jansen PLM, Deane AM, Olde Damink SWM. Gallbladder Dyskinesia Is

Associated With an Impaired Postprandial Fibroblast Growth Factor 19 Response in Critically Ill Patients. Hepatology. 2019;70:308-318.
- Koelfat KVK, Huijbers A, Schaap FG, van Kuijk SMJ, Lenicek M, Soeters MR, Wanten GJA, Olde Damink SWM. Low circulating concentrations of citrulline and FGF19 predict chronic cholestasis and poor survival in adult patients with chronic intestinal failure: development of a Model for End-Stage Intestinal Failure (MESIF risk score). Am J Clin Nutr. 2019;109:1620-1629.
- Schubert K, Olde Damink SWM, von Bergen M, Schaap FG. Interactions between bile salts, gut microbiota, and hepatic innate immunity. Immunol Rev. 2017;279:23-35.
- Olthof PB, Huisman F, Schaap FG, van Lienden KP, Bennink RJ, van Golen RF, Heger M, Verheij J, Jansen PL, Olde Damink SW, van Gulik TM. Effect of obeticholic acid on liver regeneration following portal vein embolization in an experimental model. Br J Surg. 2017;104:590-599.
- Schaap FG, Trauner M, Jansen PL. Bile acid receptors as targets for drug development. Nat Rev Gastroenterol Hepatol. 2014;11:55-67.
- Schaap FG, van der Gaag NA, Gouma DJ, Jansen PL. High expression of the bile salt-homeostatic hormone fibroblast growth factor 19 in the liver of patients with extrahepatic cholestasis. Hepatology. 2009;49:1228-1235.

Societal impact

Our PhD students have won multiple prizes presenting this original work on different conferences, e.g. the second (2019) and the first (2020) price for best abstract and oral presentation at the ESPEN congresses. Kiran Koelfat also received an ESPEN Fellowship (2018). We consider it very important to communicate our data and insights to fellow researchers and to the broader community, as exemplified from several recent activities. The findings of chyme reinfusion study have been included in the ESPEN guidelines of treatment of Intestinal Failure and is currently being validated in a large multi-center study in France. Yearly lecture on "bile salts & liver disease" are given (by FGS) to Biomedical Sciences student of UM and in the framework of a course (Lipids in health and disease) for 2nd-3rd year medical students at the RWTH Aachen.

Future Perspectives

Future translational research will focus on improving liver regeneration in the (post)cholestatic patient, typically patients with resectable perihilar cholangiocarcinoma. In pre-clinical models we have explored pharmaceutical activation of FXR as a strategy to accelerate liver regeneration in both non-cholestatic, cholestatic, and post-cholestatic animals. While liver regeneration after partial hepatectomy was not enhanced in any of these groups, FXR agonism was effective in accelerating portal vein embolization-induced liver growth in rabbit. Another spear point will be to study the interaction between the gut microbiota, bile salts and host immunity in the context of liver regeneration.

Figure 4: Schematic overview of the postprandial bile salt/FGF19 axis in healthy participants and critically ill patients.

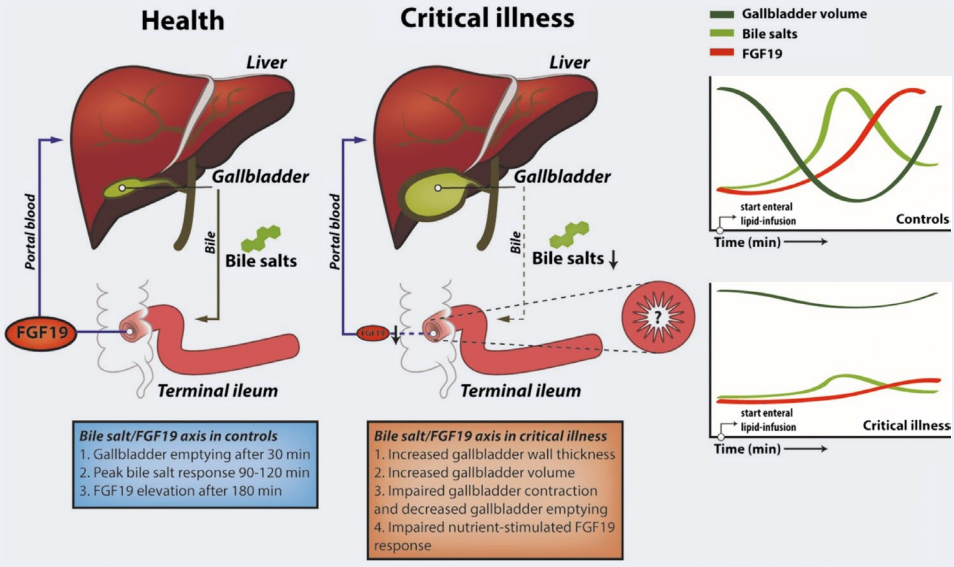


Figure 5: Bile salts appear to be more important than FGF19 in the early phase of human LR.

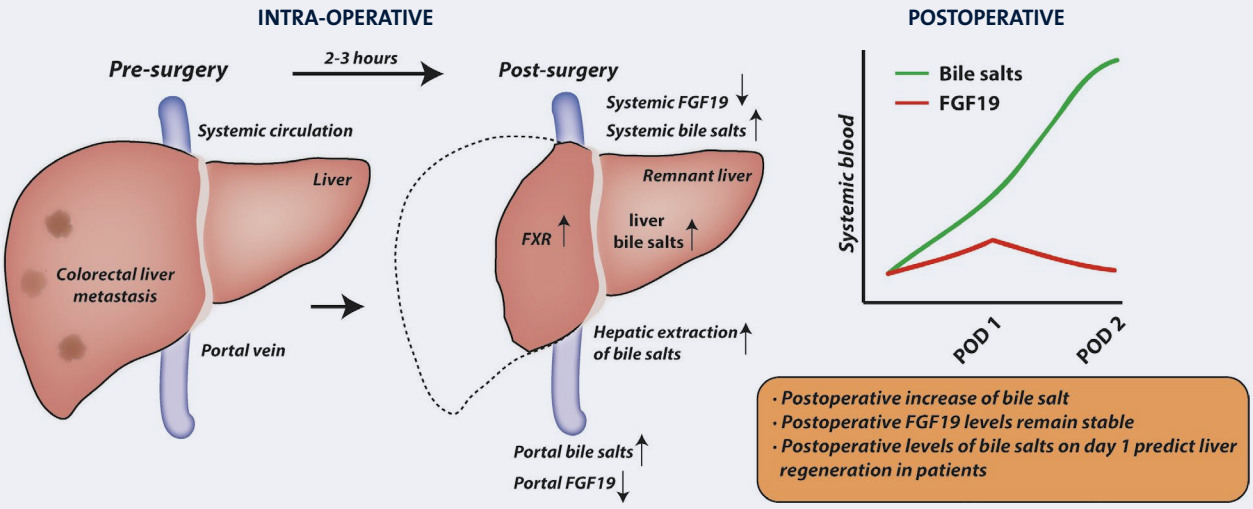
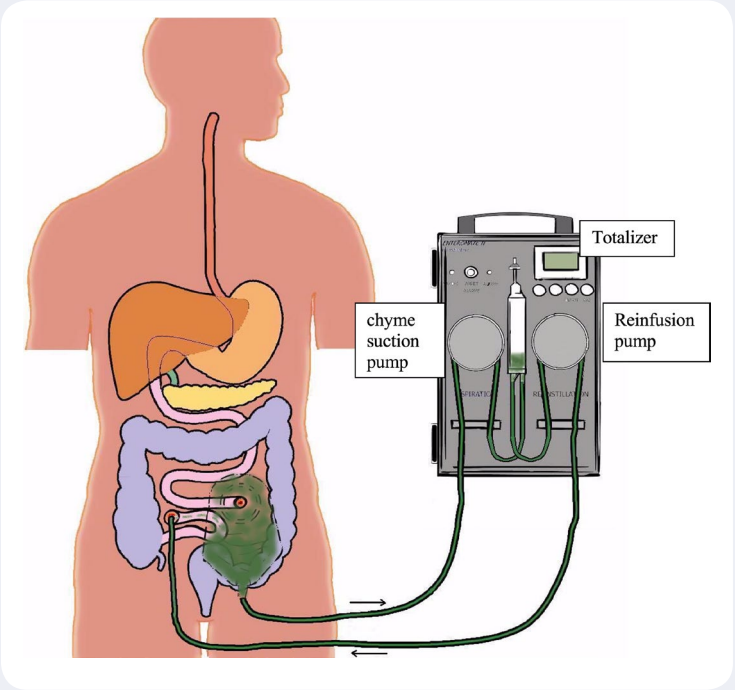


Figure 6: Automated chyme reinfusion in intestinal failure patients with a temporary double enterostomy restores intestinal function and protects against liver injury via increased plasma FGF19 and decreased C4 levels, indicating restored regulation of bile salt synthesis.



Monitoring of disturbed gut by smelling!

Division 2: Liver and Digestive Health and
Division 3: Respiratory & Age-related Health
Department Pharmacology and Toxicology and
Department Internal Medicine

Background

How can odours be an olfactory indication of an individual's metabolic status?

In ancient times, Greek and Chinese physicians already used scents to diagnose diseases since they noted that fetor hepaticus, a fruity smell in exhaled breath, was related to severe liver failure. The reason for this is that a diseased liver generate ketones and sulfurous substances that end up in the bloodstream and make their way to the lungs producing the strong musty smell. The odours released from a body often function as olfactory indications about the psychological or metabolic status of an individual. A broad range of volatile organic compounds (VOCs) emitted via breath, urine, feces or skin are related to inflammatory processes occurring in a body (Figure 1). Emerging advancements within mass spectrometry technology enables the sensitive detection of these volatile metabolites. Emitted VOCs appeare to be promising non-invasive markers of health and various diseases. At present, metabolic profiling (a.k.a. metabolomics) is a powerful complement in both diagnosis and understanding of the molecular mechanisms involved in disease occurrence, growth, remission and recurrence. Similarly, we study whether volatilomics, as a form of metabolomics, can become a non-invasive and rapid monitoring tool of disease.

How to relate VOCs profiles to disease?

Next to different pulmonary disorders, we focus on monitoring of gut and liver related diseases, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), colorectal cancer (CRC), non-alcoholic steatohepatitis (NASH) and primary sclerosing cholangitis (PSC). These studies are conducted in clinical settings in which groups of patients are sampled together with appropriate controls. In these studies we sample exhaled breath with a sophisticated device that captures alveolar air on a sorption carbon tube, of which it's VOCs content is subsequently measured by advanced mass spectrometry technology. This leads to detection of approximately 1000 VOCs which can be indicative of pathology occurring in human body. The disease specific VOCs, diagnostic profiles, are found with the use of sophisticated machine learning approaches (Figure 4).

The important aspect of discovering promising biomarker profiles is the proper validation of the outcomes in independent sampled patient cohorts and checked for their performance in sensitivity and specificity. Along these advanced machine learning lines, the clinical studies are supported with bacterial and cellular *in vitro* models, and experimental animal studies to understand the physiological origin of volatile metabolites (Figures 2-3). Of special interest is the gut microbiome and more specifically the host-microbiome interaction. The microbial composition and function is driven by diet and this can be reflected in VOCs composition in breath and feces.

Major breakthroughs

Numerous external influences hamper the application of breath analysis and standardization of sampling is crucial.
A major breakthrough comes from the ReCVIA sampling device developed for that purpose within the breath-free community and the UK company Owlstone Medical.

Furthermore, we showed the influence of several confounding factors on the exhaled breath composition, including knowledge how diet effects the content of exhaled breath. Further, we show strong correlations between VOCs in exhaled breath and various bacteria in the gut. Certain breath volatiles including SCFAs are explained by the presence of gut bacteria and the interaction with host metabolism. This opens avenues to enhance our understanding of gut disorders and the diet-microbiome-host interaction by combining microbiomics, metabolomics, dietary assessment and clinical manifestation.

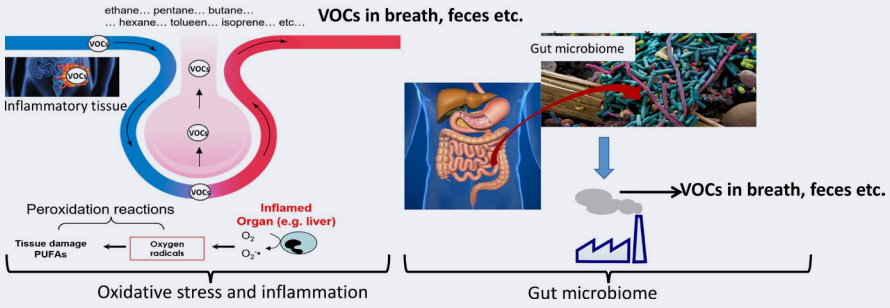


Figure 1. Volatile organic compounds in exhaled breath, feces, blood or urine can be produced as the product of oxidative stress and inflammation or as results of gut microbiome metabolism.

Who is involved?

The VOCs research group within NUTRIM is highly multidisciplinary consisting of clinicians, chemical, biomedical and data scientists. This multidisciplinary approach allows for integration of data and expertise to unravel the complex diet-microbiome-host susceptibility interaction in relation to intestinal health and wellbeing. In that respect, the research is truly a team effort. At present, the team includes totally of two expert technicians, research nurses, and seven PhD students. The research takes full advantage of excellent patient and population cohorts from the Department of Internal Medicine, comprising of IBS and IBD patients, and is a synergistic collaboration with scientists of the Department of Pharmacology and Toxicology with outstanding accomplishments in the field of breath research. Prof. van Schooten and Dr. Smolinska have a multidisciplinary profile in analytical measurements, statistical analysis and biochemical interpretation. Dr. Smolinska's expertise covers breath, fecal and in-vitro headspace analysis by mass spectrometry technology and data mining including machine learning techniques and data fusion strategies. Dr. Mujagic is a clinical researcher highly experienced in IBD and IBS, metabolomics, gut microbiomics and dietary influences on diseases courses. Prof. Jonkers has specific expertise in intestinal health, microbiota and diet, with a strong translational approach. Additionally, the development of the VOCs platform resulted in unexplored collaborative efforts with several clinical groups in the MUMC+ to study VOCs in relation to various diseases (Figure 3), for example Respiratory Medicine, Respiratory Pediatrics, Surgery, Gastro-enterology and Hepatology, Immunology, Medical Microbiology, Human Biology.
The group has been successful in the acquisition of many research funding from international and national institutions, NWO, ZON-MW, Dutch Cancer Society, EU, MLDS, TIFN and NVWA.

Users and collaborations

Because of our expertise and leadership in the field, there are many excellent national and international collaborations, including International association on breath research, Owlstone Medical, Interscience VB, Fraunhofer-Institute for Process Engineering and Packaging IVV (Germany), The Academic Medical Center in Amsterdam, UMC Groningen, University of Antwerp (Belgium), University of Lille (France).

Scientific impact/Research quality

The developed VOCs platform, connected with the preprocessing of the raw data and subsequent data analysis to discover biomarkers of health and diseased organs, is unique in its kind locally and (inter)nationally. Since we started with this research in 2007, many (pre) clinical groups showed interest to collaborate and the applications have been diverse with a high scientific output of more than 50 high-impact peer-reviewed publications (a selection is provided below). Members of the group are active in the International Association of Breath Research (IABR) and in 2018, we organized the IABR Breath Summit in Maastricht. Further, the results of our research have been presented at numerous conferences and received various Young Investigator Awards in the field of breath research.

1. Wilms E, An R, Smolinska A, Stevens Y, Weseler AR, Elizalde M, Drittij MJ, Ioannou A, van Schooten FJ, Smidt H, Masclee AAM, Zoetendal EG, Jonkers DMAE. Galacto-oligosaccharides supplementation in prefrail older and healthy adults increased faecal bifidobacteria, but did not impact immune function and oxidative stress. Clin Nutr. 2021;S0261-5614(21)00002-9. https://pubmed.ncbi.nlm.nih.gov/33509667 [IF:6.4].
2. Smolinska A, Baranska A, Dallinga JW, Mensink RP, Baumgartner S, van de Heijning BJM, van Schooten FJ. Comparing patterns of volatile organic compounds exhaled in breath after consumption of two infant formulae with a different lipid structure: a randomized trial. Sci Rep. 2019;9(1):554. https://pubmed.ncbi.nlm.nih.gov/30679671 [IF:4.6].
3. Smolinska A, Tedjo DI, Blanchet L, Bodelier A, Pierik MJ, Masclee AAM, Dallinga J, Savelkoul PHM, Jonkers DMAE, Penders J, van Schooten FJ. Volatile metabolites in breath strongly correlate with gut microbiome in CD patients. Anal Chim Acta. 2018;1025:1-11. https://pubmed.ncbi.nlm.nih.gov/29801597 [IF:6.0].
4. Blanchet L, Smolinska A, Baranska A, Tigchelaar E, Swertz M, Zhernakova A, Dallinga JW, Wijmenga C, van Schooten FJ. Factors that influence the volatile organic compound content in human breath. J Breath Res. 2017;11(1):016013. https://pubmed.ncbi.nlm.nih.gov/28140379 [IF:2.9].
5. Smolinska A, Bodelier AG, Dallinga JW, Masclee AA, Jonkers DM, van Schooten FJ, Pierik MJ. The potential of volatile organic compounds for the detection of active disease in patients with ulcerative colitis. Aliment Pharmacol Ther. 2017;45(9):1244-1254. https://pubmed.ncbi.nlm.nih.gov/28239876 [IF:7.5].

6. Baranska A, Mujagic Z, Smolinska A, Dallinga JW, Jonkers DM, Tigchelaar EF, Dekens J, Zhernakova A, Ludwig T, Masclee AA, Wijmenga C, van Schooten FJ. Volatile organic compounds in breath as markers for irritable bowel syndrome: a metabolomic approach. Aliment Pharmacol Ther. 2016;44(1):45-56. https://pubmed.ncbi.nlm.nih.gov/27136066 [IF:7.5].

Societal impact

Disorders such as IBD and IBS affect large numbers of people in the general population, severely impact their quality of life, lead to health care costs and indirect societal costs.
The target group, health care providers, the food industry and patient societies, are highly interested, to improve health by dietary adjustments. Defining these adjustments, require biomarker panels able to predict and monitor the response to diet. Furthermore, the results of our developed VOCs platform are of great value to build on diagnostic clinical tools and we are collaborating intensively with the innovative UK Company Owlstone Medical to achieve this goal. We are actively collaborating in projects on colorectal cancer, pediatric asthma, and liver cirrhosis. We are regularly contacted by various groups and journalists who disseminate our research results, unsolicited, illustrating the interest in this topic of the general community.

Future Perspectives

In the future, we aim to get a better understanding of gut health, the interplay between diet, altered microbiota and state-of-the-art metabolomics and volatilomics. To achieve this aim we will make use of the multidisciplinary approach (Figure 4). Additionally, we will make use of our mouse breath sampling device to study in more depth the relation between metabolic pathways, gut microbiome and volatile metabolite.

Figure 2: Procedure how to discover VOCs related to disease.

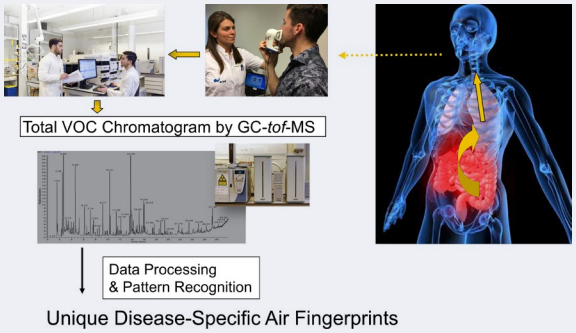


Figure 3: Examples of studies using the VOCS platform; clinical, headspace of bacteria and cells and an in house developed mouse breath sampling device.

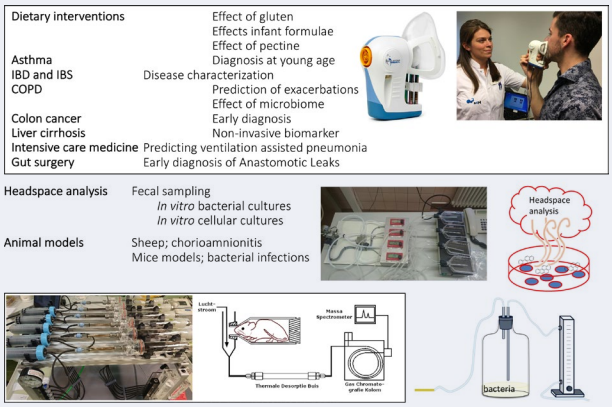
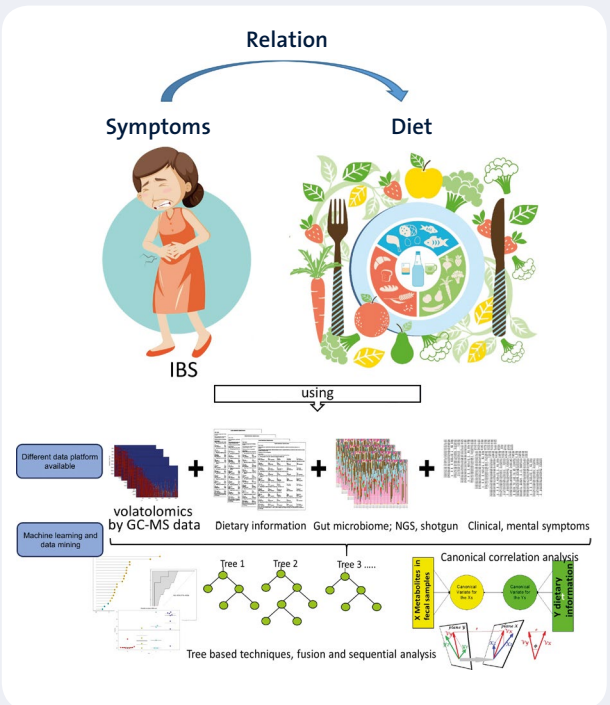


Figure 4: Multidisciplinary approach to find the relation between symptoms in patients and diet. The volatolomics will be combined with microbiome, diet questionnaires and clinical metadata using machine learning and data mining.



DIVISION 3

How to solve a traumatic bone defect

Division 3: Respiratory & Age-related Health
Department of Surgery, section Trauma surgery

Background

Yearly 175.000 persons suffer from a fracture in the Netherlands. Of these patients, 10% have a fracture healing that is halted, leading to a non-healed fracture or non-union. In high-risk patients, this risk can increase up to 46%. This arrested fracture healing, in which a defect between the fracture fragments remains, is the key subject of research of the trauma surgery group. In this defect the regeneration of the interfragmentary tissue is not sufficient. In case of a large critical size bone defect the requirement for these metabolic processes are even higher and the risk of non-union increases parallel to the defect size.

Previously treatment was aimed at the pentagon concept augmenting the non-union tissue during surgery using a combination of five elements: supplementation of bone cells, scaffold and growth factors with optimized mechanical stability and vascularity. The new hexagon model uses nutritional intervention prior to surgery to optimize metabolic conditions of the fracture or non-union tissue for regeneration. This nutritional intervention is designed a short-term nutritional intervention using a combination of specific amino acids, electrolytes and vitamins. The concept to boost the bone biology is to use nutrition to optimize each metabolic component important in fracture healing; mesenchymal stem cells and osteoblasts, collagen bone stroma as scaffold, growth factors and vascularity.

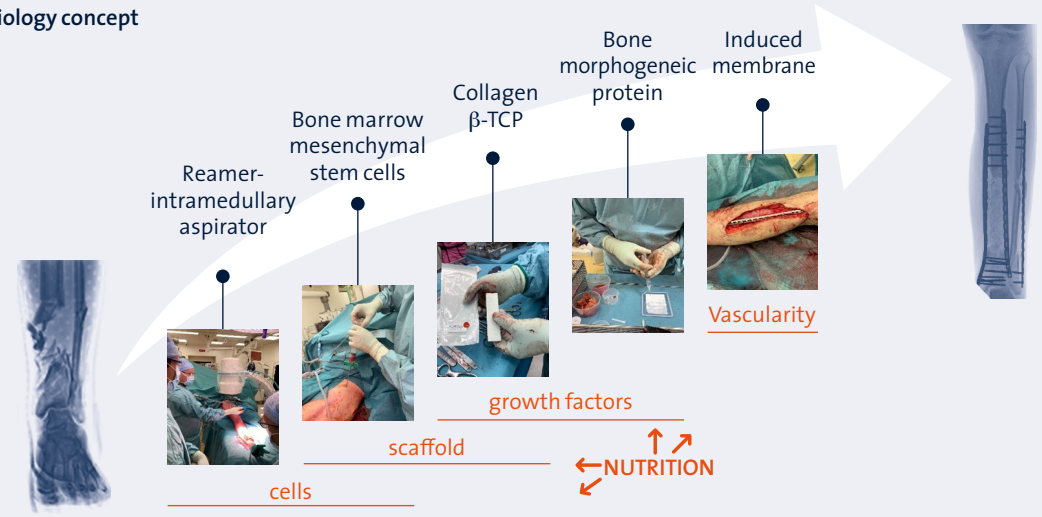
Who is involved?

The NUTRIM research team of the traumasurgery group consists of two P.I.s (Taco Blokhuis and Martijn Poeze), together with 2 postdoctoral researchers and 16 PhDs.

Major breakthrough

A key finding is the discovery that nutritional supplementation of specific amino acids is indeed able to increase the fracture regenerative capability with a reduced risk of non-union [1-5] in a validated murine delayed fracture healing model [2]. Previous studies in patients indicate a decreased availability of amino acids both in the non-union tissue and also in the bone marrow distant from this non-union site, as marker of nutritional depletion of the bone marrow [9]. In other mechanistic studies citrulline was found to be a more important amino acid than arginine for increasing vascularity and regeneration during conditions of increased inflammation [10,11]. Finally, the inflammatory phase of the fracture hematoma was demonstrated to be key in the sequential steps of regeneration of bone [12-15].

Boosting the bone biology concept

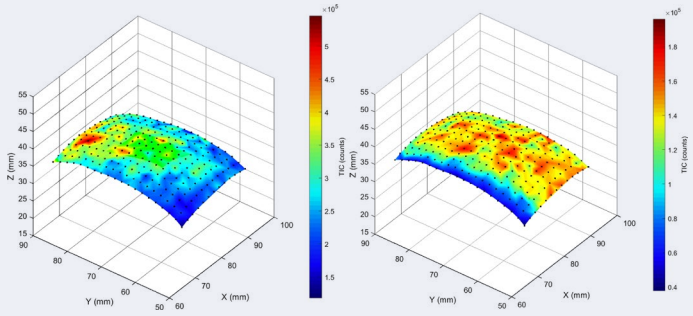


Users and collaborations

Together with the cBITE group (head Prof. dr. Martijn van Griensven) of the MERLN institute, a newly developed 3D printed bone defect cage (with polycaprolactone and tricalciumphosphate) was successfully implanted in a first-in man study in patients with critical size defects (see picture above) together with bone marrow stem cell concentrate and autologous bone graft. These cages can be used for increased bone regeneration capabilities, thereby increasing the maximum size of the defect that can be treated (example above demonstrating a 15-cm bone defect). Further evaluation of fracture healing is performed using high-resolution quantitative CT scanning together with the group of Prof. dr. Joop van den Bergh. Within the Chemelot InScite consortium, the WISE project aims at developing an interponate for posttraumatic arthritis. Together with the department of movement sciences (Dr. Kenneth Meijer) a number of studies are carried out on gait kinematic abnormalities in patients after foot- and ankle-trauma, as clinically relevant outcome parameter.

3D visualization of m/z distributions

Together with the M4I institute (head Prof. dr. Ron Heeren) techniques for intra-operative evaluation of bone vitality using laser-assisted mass spectrometry are developed (see figure displaying intensity of two different molecular masses (m/z value) using 3D robotic surface scanning and metabolic profiling).



Scientific impact/Research quality

The scientific quality of the research is apparent from the publications in relevant and high impact journals (see below selection of papers), including review articles [4,15], as well as research grants obtained (ZonMW doelmatigheidsubsidies (4x), Horizon 2020 grants: Eurostars, EITHealth; and a Chemelot Inscite grant).

Selection of publications

01. Meesters DM, et al. Enhancement of fracture healing after citrulline supplementation in mice. Eur Cell Mater. 2020 Mar 20;39:183.
02. Gröngröft I, et al. Development of a novel murine delayed secondary fracture healing *in vivo* model using periosteal cauterization. Arch Orthop Trauma Surg. 2019;139(12):1743.
03. Hofman M, et al. Effect of neurokinin-1-receptor blockage on fracture healing in rats. Sci Rep. 2019;9(1):9744.
04. Meesters DM, et al. Malnutrition and Fracture Healing: Are Specific Deficiencies in Amino Acids Important in Nonunion Development? Nutrients. 2018;10(11):1597.
05. Meesters DM, et al. Deficiency of inducible and endothelial nitric oxide synthase results in diminished bone formation and delayed union and nonunion development. Bone. 2016;83:111.
06. Wijnands KA, et al. Citrulline Supplementation Improves Organ Perfusion and Arginine Availability under Conditions with Enhanced Arginase Activity. Nutrients. 2015;7(7):5217.
07. Hofman M, et al. Improved fracture healing in patients with concomitant traumatic brain injury: proven or not? Mediators Inflamm. 2015;2015:204842.
08. Hannemann PF, et al. The effects of low- intensity pulsed ultrasound and pulsed electromagnetic fields bone growth stimulation in acute fractures: a systematic review and meta-analysis of randomized controlled trials. Arch Orthop Trauma Surg. 2014;134(8):1093.
09. Wijnands KA, et al. Impaired fracture healing associated with amino acid disturbances. Am J Clin Nutr. 2012;95(5): 1270.
10. Wijnands KA, et al. Citrulline a more suitable substrate than arginine to restore NO production and the microcirculation during endotoxemia. PLoS One. 2012;7(5):e37439.
11. Luiking YC, et al. Reduced citrulline production in sepsis is related to diminished de novo arginine and nitric oxide production. Am J Clin Nutr. 2009;89(1):142.
12. Bastian OW, et al. Neutrophils Inhibit Synthesis of Mineralized Extracellular Matrix by Human Bone Marrow-Derived Stromal Cells *In Vitro*. Front Immunol. 2018;9:945.
13. OW Bastian et al. Neutrophils contribute to fracture healing by synthesizing fibronectin+ extracellular matrix rapidly after injury. Clin Immunol, 201612;164:78.
14. R van der Bel, et al. Increased osteogenic capacity of Reamer/Irrigator/Aspirator derived Mesenchymal Stem Cells. Injury, 2014;45:2060.
15. Bastian O, et al. J Systemic inflammation and fracture healing. Leukoc Biol. 2011;89(5):669.
16. Fracture fixation in the operative management of hip fractures (FAITH): an international, multicentre, randomised controlled trial. Fixation using Alternative Implants for the Treatment of Hip fractures (FAITH) Investigators. Lancet, 2017;15;389(10078):1519.

Societal impact

We have established intense cooperation with two worldwide international trauma care societies (AO (Allgemeinschaft fur Osteosynthesenfragen) Foundation and OTC (Osteosynthesis and Trauma Care) Foundation) for implementing specific trauma related products.

For our work on autografting techniques we received for example the 2020 Innovation Award of the AO Foundation

We established an outpatient clinic for patients with a non-union with nationwide reach.
www.1limburg.nl/nieuwe-poli-mumc-voor-botbreuken-die-niet-genezen?context=default

In addition, our work together with MERLN on the 3D printed bone cage attracted nationwide attention with interviews on RTL news and BNR news radio.

Since most of our work is clinically oriented, patient participation is of utmost importance. Patient councils are involved in our studies and symposia aimed at improving involvement in trauma after care.
www.nazl.nl/actueel/nieuws/20-jaar-traumacentrum

The application of intrinsically labeled milk protein in human nutrition research

Division 3: Respiratory & Age-related Health
Department: Department of Human Biology

Background

Food ingestion plays an important role in maintaining muscle mass and strength. Ingestion of protein provides us with amino acids that we require as building blocks for our own muscle tissue. However, amino acids can also act as signaling molecules, directly activating molecular pathways that stimulate muscle growth and repair. The capacity of a dietary protein to stimulate protein synthesis largely depends on its protein digestion and amino acid absorption kinetics. These processes have proven difficult to study in an *in vivo* human setting. To study the process of protein digestion, amino acid absorption, and the subsequent incorporation in skeletal muscle tissue we developed a novel method for which we produced intrinsically, stable isotope labeled milk protein. By infusing a large amount of stable isotope labeled amino acids in a lactating cow, collecting its milk, and extracting the protein we managed to produce a protein source that we could follow throughout the human body, from ingestion all the way to its use for human tissue protein synthesis (Figure 1).

Major breakthroughs

The application of intrinsically labelled protein has revealed that dietary protein-derived plasma amino acid availability can be strongly modulated by numerous nutritional and non-nutritional factors. This is of important clinical relevance, since dietary protein-derived amino acid availability is the main determinant driving the post-prandial increase in skeletal muscle protein synthesis rates. Intrinsically labelled protein is now frequently being applied to investigate how muscle protein synthesis rates are modulated by the various aspects of post-prandial protein handling. It has contributed largely to our understanding how nutrition and physical (in) activity interact in determining muscle quality in both health and disease (Figure 2).

The use of intrinsically labelled proteins will facilitate our efforts to understand the impact various nutritional and non-nutritional factors have on post-prandial protein handling and, as such, how they can modulate muscle quality in both health and disease.

Figure 1: Schematic representation of the production of intrinsically labelled protein to assess various aspects of post-prandial protein handling. Here, the production of intrinsically labelled milk: (1) stable isotope amino acid tracers are administered to lactating cows, (2) the cow produces milk with the amino acid tracer incorporated into the milk protein matrix. Application of intrinsically labelled protein: (3) the collected intrinsically labelled milk protein is consumed by participants, (4) dietary protein is digested into amino acids, (5) dietary protein-derived amino acids are taken up in the gastrointestinal tract, (6) dietary protein-derived amino acids are released into the circulation and (7) dietary protein-derived amino acids are taken up and incorporated into tissues, such as skeletal muscle.

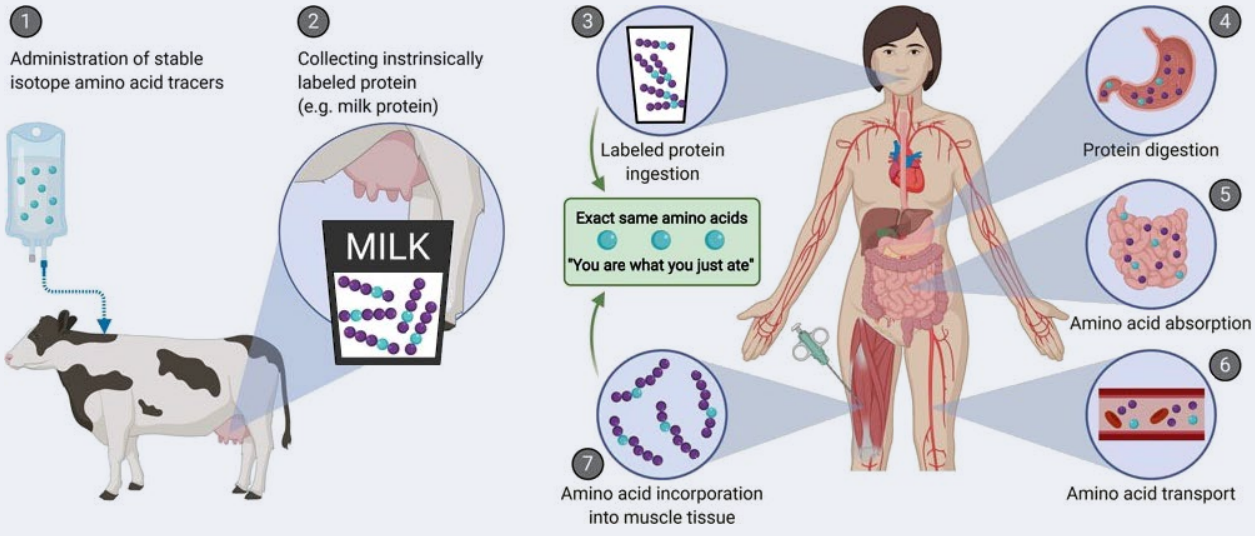
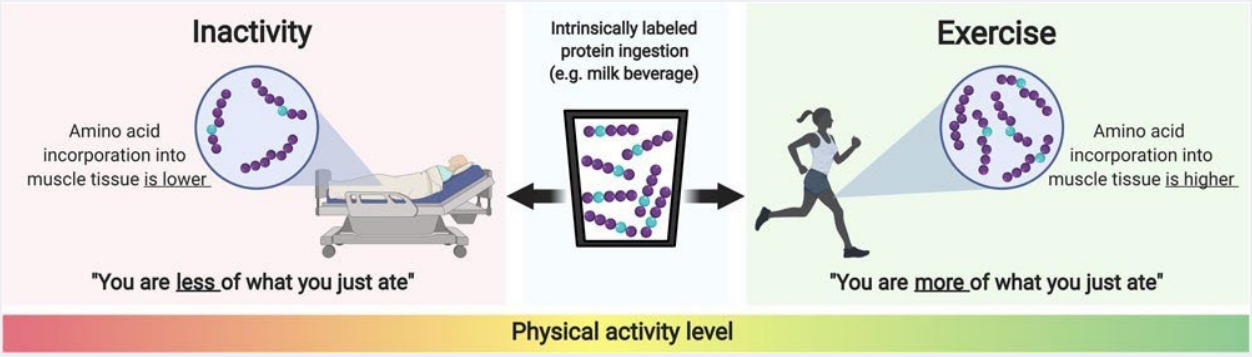


Figure 2: Schematic representation of the impact of physical (in)activity on the incorporation of dietary protein-derived amino acids into skeletal muscle protein.



Who is involved?

The M3-research unit is part of the Department of Human Biology and includes 4 expert technicians, 3 post-doctoral fellows, and more than 12 PhD students, supervised by Dr. Tim Snijders (assistant professor), Dr. Lex Verdijk (associate professor) and Dr. Luc van Loon (professor). The research group specialises in *in vivo* human metabolic research, with skeletal muscle metabolism, exercise metabolism, sports and clinical nutrition, and aging as the main fields of interest. The group has been successful in the acquisition of more that 25 M€ of research funding, mainly through building large public-private partnerships. The stable isotope analytical facilities at Maastricht University Medical Centre are provided by the Stable Isotope Research Centre (SIRC).

Users and collaborations

The work leading up to the development of the method, the application in human nutrition research, and the subsequent use of these insights in education, healthcare and product research and development represents a team effort including both academic, medical, and industry partners.
Academic and medical collaborators include: Université Clermont Auvergne, Wageningen University, INRA, University of Exeter, Karolinska Institutet, Royal Adelaide Hospital, Australian Catholic University, University of Birmingham, Virga Jessa Hospital and the University Medical School in Nottingham. Industrial partners include DSM, Friesland Campina, Danone/Nutricia, Kellogg, Syral, Cargill, Pepsico, and many more. Top Institute Food and Nutrition and the Dutch TKI have been instrumental in bringing all parties together. The list of partners will continue to grow as we strive for even more fruitful collaborations.

Scientific impact/Research quality

The scientific output based upon the described method and its application has been extensive, with more than 50 high-impact, peer reviewed publications (a selection is provided below) and at least 10 successful PhD theses. Besides the publication record, the method and the insights it has provided have been presented at numerous conferences and received various Young Investigator Awards in different fields of research.

Selection of publications

1. Gorissen SHM, Trommelen J, Kouw IWK, Holwerda AM, Pennings B, Groen BBL, Wall BT, Churchward-Venne TA, Horstman AMH, Koopman R, Burd NA, Fuchs CJ, Dirks ML, Res PT, Senden JMG, Steijns J, de Groot L, Verdijk LB, van Loon LJC. Protein type, protein dose, and age modulate dietary protein digestion and phenylalanine absorption kinetics and plasma phenylalanine availability in humans. J Nutr. 2020. www.ncbi.nlm.nih.gov/pubmed/32069356 [IF:4.423] [Altmetric score: 43].
2. Horstman AMH, Kouw IWK, van Dijk JW, Hamer HM, Groen BBL, van Kranenburg J, Gorissen SHM, van Loon LJC. The muscle protein synthetic response to whey protein ingestion is greater in middle-aged women when compared with men. J Clin Endocrinol Metab. 2019;104(4):994–1004. www.ncbi.nlm.nih.gov/pubmed/30423113 [IF:6.215] [Altmetric score: 41].
3. Trommelen J, Kouw IWK, Holwerda AM, Snijders T, Halson SL, Rollo I, Verdijk LB, van Loon LJC. Presleep dietary protein-derived amino acids are incorporated in myofibrillar4-protein during post-exercise overnight recovery. Am J Physiol Endocrinol Metab. 2018;314(5):E457-E67. www.ncbi.nlm.nih.gov/pubmed/28536184 [IF:4.248] [Altmetric score: 136].
4. Gorissen SH, Horstman AM, Franssen R, Kouw IW, Wall BT, Burd NA, de Groot LC, van Loon LJC. Habituation to low or high protein intake does not modulate basal or postprandial muscle protein synthesis rates: a randomized trial. Am J Clin Nutr. 2017;105(2):332-42. www.ncbi.nlm.nih.gov/pubmed/27903518 [IF:7.506] [Altmetric score: 17].
5. Wall BT, Dirks ML, Snijders T, van Dijk JW, Fritsch M, Verdijk LB, van Loon LJC. Short-term muscle disuse lowers myofibrillar protein synthesis rates and induces anabolic resistance to protein ingestion. Am J Physiol Endocrinol Metab. 2016;310(2):E137-47.www.ncbi.nlm.nih.gov/pubmed/26578714 [IF:4.248] [Altmetric score: 38].
6. Wall BT, Gorissen SH, Pennings B, Koopman R, Groen BB, Verdijk LB, van Loon LJC. Aging Is accompanied by a blunted muscle protein synthetic response to protein ingestion. PLoS One. 2015;10(11): e0140903. www.ncbi.nlm.nih.gov/pubmed/26536130 [IF:3.394] [Altmetric score: 22].
7. Gorissen SH, Burd NA, Hamer HM, Gijsen AP, Groen BB, van Loon LJC. Carbohydrate co-ingestion delays dietary protein digestion and absorption but does not modulate postprandial muscle protein accretion. J Clin Endocrinol Metab. 2014;99(6):2250-8. www.ncbi.nlm.nih.gov/pubmed/24628553 [IF:6.215] [Altmetric score: 28].
8. Wall BT, Snijders T, Senden JM, Ottenbros CL, Gijsen AP, Verdijk LB, van Loon LJC. Disuse impairs the muscle protein synthetic response to protein ingestion in healthy men. J Clin Endocrinol Metab. 2013;98(12): 4872-81. www.ncbi.nlm.nih.gov/pubmed/24108315 [IF:6.215] [Altmetric score: 14].
9. Groen BB, Res PT, Pennings B, Hertle E, Senden JM, Saris WH, van Loon LJC. Intragastric protein administration stimulates overnight muscle protein synthesis in elderly men. Am J Physiol Endocrinol Metab. 2012;302(1):E52-60. www.ncbi.nlm.nih.gov/pubmed/21917635 [IF:4.248] [Altmetric score: 78].
10. Pennings B, Koopman R, Beelen M, Senden JM, Saris WH, van Loon LJC. Exercising before protein intake allows for greater use of dietary protein-derived amino acids for de novo muscle protein synthesis in both young and elderly men. Am J Clin Nutr. 2011;93(2):322-31.www.ncbi.nlm.nih.gov/pubmed/21084649 [IF:7.506] [Altmetric score: 30].

Societal impact

The applied method and its application have provided us with a more comprehensive insight in the digestion and absorption of protein from our diet and its subsequent impact on muscle protein synthesis. Moreover, it has provided us with a more holistic view on how physical activity and nutrition can modulate health. Such a comprehensive assessment of the various processes involved in post-prandial protein handling facilitates the transfer of our research output towards the general public. Besides many interviews, podcasts and lectures, several popular scientific instruction videos have been made by the University of the Netherlands to educate the general public on the fact that we can actually show that 'you are what you eat'.
www.youtube.com/watch?v=huTlXfKHtVQ
www.youtube.com/watch?v=mCRzi1tObe0

Future Perspectives

This novel approach will further extend the use of stable isotope tracers in nutrition research as other research groups are now applying the method extensively and its application will continue to grow among researchers in the field. Further innovations include the recent successful production and application of intrinsically labeled insects. There is a growing interest in insects as an alternative source of dietary protein for human consumption that may be produced on a more viable and sustainable commercial scale and, as such, will contribute to ensuring global food security. We have successfully produced intrinsically labeled insects allowing us to evaluate the bioavailability and functional properties of this protein source following their consumption *in vivo* in humans.

DIVISION 3

Pulmonary epithelial cells as central players in chronic lung disorders

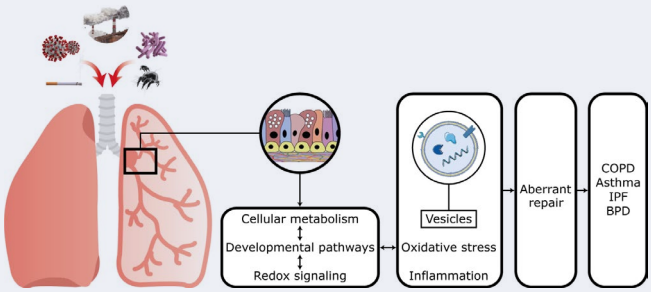
Division 3: Respiratory & Age-related Health
Department of Respiratory Medicine
Department of Pharmacology and Toxicology
Department of Medical Microbiology

Background

According to estimates from the WHO and the Global Burden of Disease study, a staggering number of 500-600 million people worldwide suffer from chronic lung/airway diseases such as Chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), asthma and bronchopulmonary dysplasia (BPD). Chronic and repetitive exposure of the lungs and airways to insults such as noxious particles, allergens and infectious agents is considered the most important risk factor for developing these diseases.

Our overall aim is to obtain insight in the underlying causes of maladaptive responses of respiratory epithelial cells to these insults from a molecular, cellular and whole tissue perspective with the ultimate goal of developing novel therapeutic strategies to reverse or halt disease progression. We focus on the following triggers: (components of) cigarette smoke, emissions from novel tobacco products (i.e. heated tobacco products), microplastics and wood smoke, allergens and infectious agents (Figure 1). Our experimental models include state-of-the art human *in vitro* and *ex vivo* models as depicted in Figure 2, as well as primary human and murine stem cells, and precision cut lung slices. The Primary Lung Culture facility (PLUC) developed at the MUMC+ is essential for deployment of these models as it provides a unique biobank of well-characterized primary bronchial stem cells, alveolar stem cells, peripheral human lung tissues and primary fibroblasts (Figure 3). Clinical evidence is obtained from these materials and, in addition, systemic biomarkers that can be used to monitor pulmonary processes are examined in clinical samples (mostly from the circulation and urine) which are available via our collaboration with the pulmonary rehabilitation center CIRO (Horn, the Netherlands). In addition, we use an extensive array of experimental animal models of disease and exposures mainly through our large network of collaborators (see below). An important read-out in our models is cellular metabolism (including glycolysis and mitochondrial function) as it is a key regulator of critical cellular processes and responses. We furthermore focus on the mediating role of redox signalling, the extracellular matrix (ECM), and intercellular communication via secreted factors such as extracellular vesicles (EVs)(Figure 1). Importantly, new therapeutic strategies, including pharmacological or cell-based therapies are tested.

Figure 1

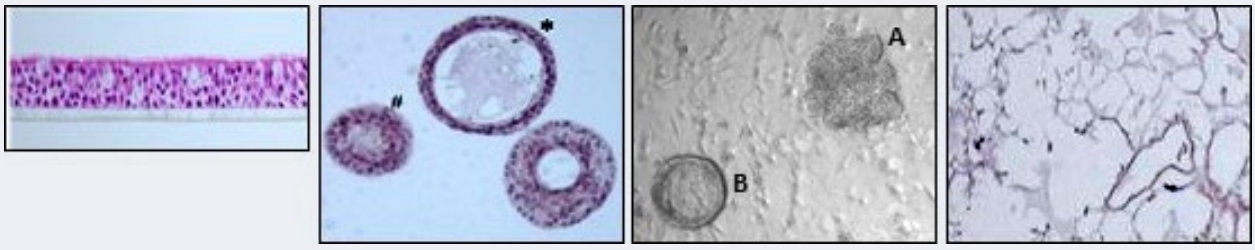


Major breakthroughs

Cellular metabolism
Using peripheral lung tissue as well as primary human bronchial epithelial cells (PBECs) isolated from COPD and non-COPD donors, we have identified abnormalities in mitochondrial biogenesis and mitophagy in COPD likely induced by exposure of these cells to cigarette smoke (components). Furthermore, as a step towards future regulation of specific chemicals in cigarette smoke by governmental bodies, we have identified aldehydes, a harmful class of chemicals formed during the combustion and pyrolysis of tobacco, as compounds responsible for smoke-induced mitochondrial dysfunction in these cells. We are also working on extending these studies to include new, currently non-regulated, tobacco products such as heated tobacco products and are directing research efforts to explore the potential negative impact of inhaled microplastics and wood smoke (from woodstoves, a large contributor to airborne particulate matter in the Netherlands). In addition to these findings, we have identified abnormalities in the glycolysis pathway in animal models and clinical samples of asthmatics, and have demonstrated its crucial role in the pathogenesis of allergic airways disease by increasing IL-1β-induced proinflammatory signaling.

Redox signaling
We have shown the importance of redox regulation in general, and of the redox-based post-translational modification S-glutathionylation in particular, in modulating inflammation, cellular metabolism, and innate epithelial responses in relation to the diseases mentioned above.

Air-liquid interface | Bronchail organoids | Bronchail (B) & Alveolar (A) organoid | Lung tissue scaffold



Importantly, we focus on modifiable redox events, offering the possibility to be (personalized) therapeutically targeted. In IPF, emphasis lies on the role of the pulmonary ROS-producing enzyme NOX4 and the redox-sensitive Src kinase family. Additionally, we study the effect of the only two FDA-approved anti-IPF drugs on the market hereon, as well as new treatment options including kinase inhibitors and dietary antioxidants, supported by comprehensive genomic and gene expression profiling of IPF lungs. Finally, we examine the potential use of volatile organic compounds (VOCs) as biomarkers of disease diagnosis, progression and response to therapy in both *in vitro* systems and *in vivo* in naïve patients suffering from IPF and other ILDs.

Extracellular matrix (ECM)

We have identified an important role for epithelial cells in ECM remodeling *in vitro*, in animal models and in COPD patients. The contribution of this remodeled ECM to the hostile micro-environment to lung repair in emphysema is currently being examined. Of particular attention are the contribution of elastin degradation and its modulation by vitamin K, and the shifted metabolism of the glycosaminoglycan hyaluronan.

Extra-cellular vesicles

In another (related) research line, we investigate the role of secreted factors, particularly extracellular vesicles (EVs), in mediating lung inflammation. We have demonstrated that cigarette smoke extract (CSE) induces increased release of EVs as well as changes in their proteomic composition. Specifically, CSE-induced EVs were enriched in proteins related to hemostasis and could promote activation of coagulation factor X and thrombin generation. Like mitochondrial dysfunction, induction of procoagulant EVs was mediated by reactive aldehydes and furthermore preventable by antioxidants such as glutathione. Currently, we work with patient materials to investigate whether and how procoagulant EVs contribute to lung inflammation and comorbid cardiovascular disease in patients with COPD. Finally, we showed that EVs contribute to innate immunity during infections with respiratory pathogens and are currently investigating whether this defense mechanism is impaired in COPD.

Early origins of lung disease

Importantly, aberrant lung outcomes faced in later life can have their origins already before birth. Therefore, in a clinically-relevant large animal model of chorioamnionitis, we are examining the impact of BPD on lungs on the long term, and the therapeutic potential of stem cells. We recently demonstrated negative effects of chorioamnionitis on lung resident epithelial progenitor cells and are now examining whether their progenitor functions can be preserved using stem cells.

Who is involved?

This research is conducted in a collaborative fashion between the departments of Respiratory Medicine (Niki Reynaert & Mieke Dentener), Pharmacology and Toxicology (Alex Remels & Agnes Boots) and Medical Microbiology (Birke Benedikter & Frank Stassen), with a total of 8 PhD students and 4 support staff.

Users and collaborations

We work closely with a large number of local, (inter)national, governmental and academic partners. State-of-the art *in vitro* models are developed in collaboration with the MERLN institute (Maastricht University; Prof. Truckenmuller), Leiden University, Groningen University, the Hubrecht Institute, and University of Pittsburgh. For exposure studies, we work with the Dutch National Institute for Public Health and the Environment (RIVM), the Netherlands Organisation for applied scientific research (TNO), the Environmental Protection Agency (USA), University of Louisville, Purdue University and Brown University, and for regulatory implications with the RIVM, the Netherlands Food and Consumer Product Safety Authority (NVWA) and the Study group Tobacco Regulation of the WHO. Studies into redox biology and animal models of asthma are performed within the context of our long-standing collaboration with Prof. Janssen-Heininger and Prof. van der Vliet (University of Vermont, USA). Early origins of lung diseases are studied together with the Dept of Pediatrics at Maastricht University (Prof. Kramer/Dr. Wolfs). Research on extracellular vesicles and models of viral and bacterial infections are performed in close collaboration with the extracellular vesicle core facility of Philipps University Marburg, Germany. In addition to our internal collaborations with the clinical staff of the Depts of Respiratory Medicine and Pathology at the MUMC, and with Prof, Spruit/Dr. Franssen at the Pulmonary rehabilitation center CIRO, clinical centers of expertise provide patient materials and data (St Antonius Hospital Nieuwegein, Erasmus University Rotterdam, University of Liege (Belgium), KU Leuven (Belgium), University of Frankfurt (Germany), INSERM (France), Thorax Klinik Heidelberg (Germany)). BigCaT and the Norwegian University of Science and Technology (Norway), support our research with expertise in bio-informatics and systems biology. The PLUC facility provides cells with a passport and other lung tissue specimens for research to Maastro, Dept of Toxicogenomics, MERLN and the RIVM.

Scientific impact/Research quality

The scientific quality of the research is apparent from publications in relevant and high impact journals (see below selection of papers), as well as research grants from NWO/ZonMW, National Institute for Public Health and Environment, Dutch Lung Foundation, Wijerhorst Foundation, European Respiratory Society, and Chiesi Pharmaceuticals.

Selection of publications

1. Profibrotic epithelial TGF-β1 signaling involves NOX4-mitochondria cross-talk and redox-mediated activation of the tyrosine kinase FYN. Veith C, Hristova M, Danyal K, Habibovic A, Dustin CM, McDonough JE, Vanaudenaerde BM, Kreuter M, Schneider MA, Kahn N, van Schooten FJ, Boots AW, van der Vliet A. Am J Physiol Lung Cell Mol Physiol. 2020 Dec 16
2. SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. Lukassen S, Chua RL, Trefzer T, Kahn NC, Schneider MA, Muley T, Winter H, Meister M, Veith C, Boots AW, Hennig BP, Kreuter M, Conrad C, Eils R.EMBO J. 2020;39(10):e105114.
3. Redox Imbalance in Idiopathic Pulmonary Fibrosis: A Role for Oxidant Cross-Talk Between NADPH Oxidase Enzymes and Mitochondria. Veith C, Boots AW, Idris M, van Schooten FJ, van der Vliet A. Antioxid Redox Signal. 2019;31(14):1092-1115.
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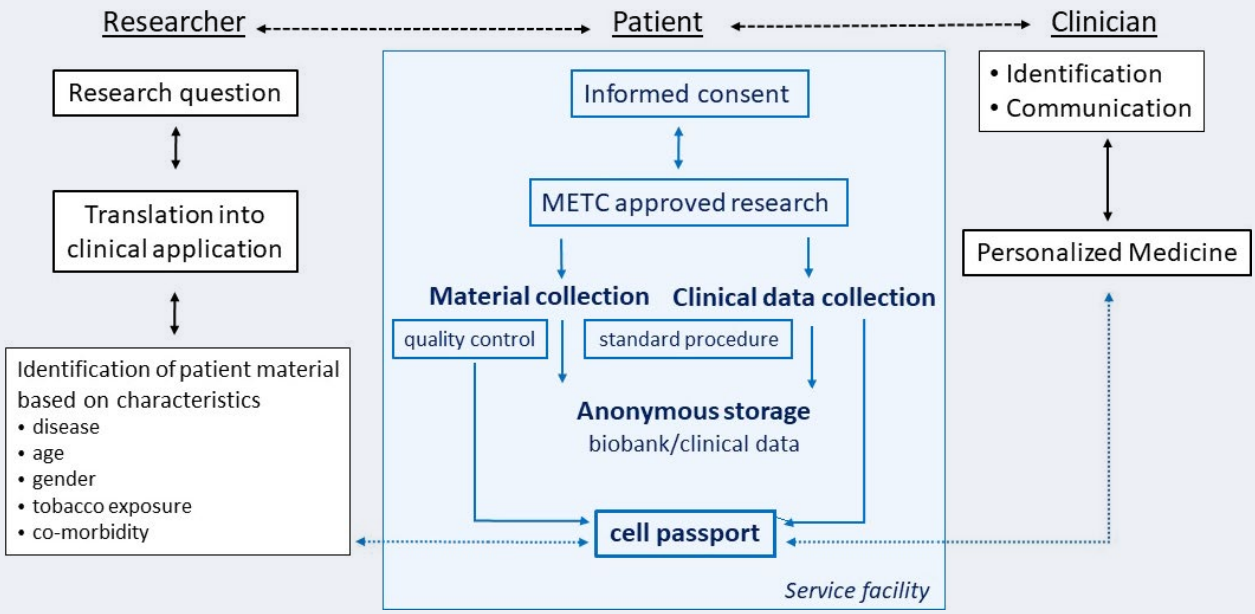
Societal impact

Patents have been obtained on the detection of S-glutathionylated proteins and Glutaredoxin-based treatments (NR). The application hereof in pulmonary disorders is currently examined in collaboration with Prof. Janssen-Heininger at the University of Vermont.

Future Perspectives

Flow chart: Cell transport



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