NUTRIM

NUTRIM Self-Assessment (2015-2020)

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

Maastricht University
Maastricht UMC+

Preface

The NUTRIM school of Nutrition and Translational Research on Metabolism is one of the graduate schools of the Faculty of Health Medicine and Life Sciences of Maastricht University. During the previous assessment (2009-2015), NUTRIM was part of National Graduate School VLAG, together with Wageningen University. Thereafter, as of 2016, NUTRIM continued as separate graduate school.

In 2017, NUTRIM was reorganised from four research lines into three interconnected disease-driven divisions. All NUTRIM divisions share the joint NUTRIM vision, mission, overall objectives and strategy as we strongly believe that a shared strategy increases synergy and efficiency. Therefore, the core of the self-assessment is based on the graduate school level and shows relevant accomplishments on the school and division level (part A). A small scale division-specific self-assessment is added as part B.

Contents self-evaluation

Part A

NUTRIM Self-assessment over the period 2015-2020 at graduate school level

1. Introduction

The NUTRIM school of Nutrition and Translational Research in Metabolism aims to contribute to health maintenance and personalised medicine by unravelling lifestyle and disease-induced derangements in metabolism and by developing targeted nutritional, exercise and drug interventions. This is facilitated by a state-of-the-art research infrastructure and close interaction between scientists, clinicians, PhD and master students. NUTRIM is one of the graduate schools of the Faculty of Health Medicine and Life Sciences (FHML) of Maastricht University (UM). From 1998 to 2016, NUTRIM was part of National Graduate School VLAG, together with Wageningen University. As of 2016, NUTRIM continued as a separate graduate school.

1.1 Positioning of NUTRIM within Maastricht University

Maastricht University (UM) was founded in 1976 and is the youngest university of the Netherlands. UM is characterized by its multidisciplinary and thematic approach to research and learning. UM was the first Dutch university to set internationalisation as a top priority and earned the Certificate for Quality in Internationalisation, awarded by the European Consortium for Accreditation in higher education. UM has extensive international partnership networks and encourages international collaborations. Over 50% of students and 40% of academic staff come from abroad. UM stands out for its innovative approach to learning, and is renowned for its problem-based learning (PBL). With almost 16,000 students and 4,000 staff, UM offers a wide choice of bachelor, master and PhD programmes. Education and research at UM is organised in six faculties: 1) Faculty of Health, Medicine and Life Sciences (FHML); 2) Faculty of Law (LAW); 3) School of Business and Economics (SBE); 4) Faculty of Science and Engineering (FSE); 5) Faculty of Arts and Social Sciences (FASoS); 6) Faculty of Psychology and Neuroscience (FPN).

FHML[1] is UM's largest faculty, comprising 65% of the total staff and budget of UM. FHML has officially existed since January 1st, 2007, after a merger of the former faculties of Health Sciences and Medicine. The FHML houses the following graduate Schools: CAPHRI[2]- Care and Public Health Research Institute; CARIM[3] - School for Cardiovascular Diseases; GROW[4] - School for Oncology and Developmental Biology; MHENS[5] - School for Mental Health and Neuroscience; NUTRIM[6] - School of Nutrition and Translational Research in Metabolism; and SHE[7] - School of Health Professions Education. There are also two research institutes: The Maastricht MultiModal Molecular Imaging Institute (M4I)[8] and the Maastricht Institute for Technology-Inspired Regenerative Medicine (MERLN)[9]. Within FHML, the Institute for Education is responsible for the organisation of the educational programmes.

Maastricht UMC+ (MUMC+) is a partnership between Maastricht Academic Hospital and UM's FHML. MUMC+ provides basic healthcare for the city of Maastricht and environs. The mission of MUMC+ is '*To provide the best possible care and improve health in the region by integrating patient care, research and education*' under the motto: Healthy Living. This includes a strong focus on integrated care and prevention of disease. MUMC+ has developed the 'Circle of Innovation©', to reflect the circular process of knowledge, innovation and societal impact. This shows how our researchers and specialists acquire new knowledge and put it into practice, create value and stimulate healthy living. This also stimulates collaboration between Schools/institutes, the hospital, regional healthcare, patient organisations and other knowledge institutes, governmental organisations and industry.

[1] https://www.maastrichtuniversity.nl/about-um/faculties/faculty-health-medicine-and-life-sciences
[2] https://www.maastrichtuniversity.nl/research/school-caphri-care-and-public-health-research-institute
[3] https://www.maastrichtuniversity.nl/research/school-cardiovascular-diseases
[4] https://www.maastrichtuniversity.nl/research/school-oncology-and-developmental-biology
[5] https://www.maastrichtuniversity.nl/research/school-mental-health-and-neuroscience
[6] https://www.maastrichtuniversity.nl/research/school-nutrition-and-translational-research-metabolism
[7] https://www.maastrichtuniversity.nl/research/school-health-professions-education
[8] https://www.maastrichtuniversity.nl/research/maastricht-multimodal-molecular-imaging-institute-0
[9] https://www.maastrichtuniversity.nl/research/institute-technology-inspired-regenerative-medicine

For the valorisation process, the UM and MUMC+ bring their business development activities in the field of Health and Life Sciences to the Brightlands Maastricht Health Campus[10]. As such, the campus is responsible for the entire process, from developing ideas or inventions through financing and guiding new businesses.

1.2 NUTRIM Organization

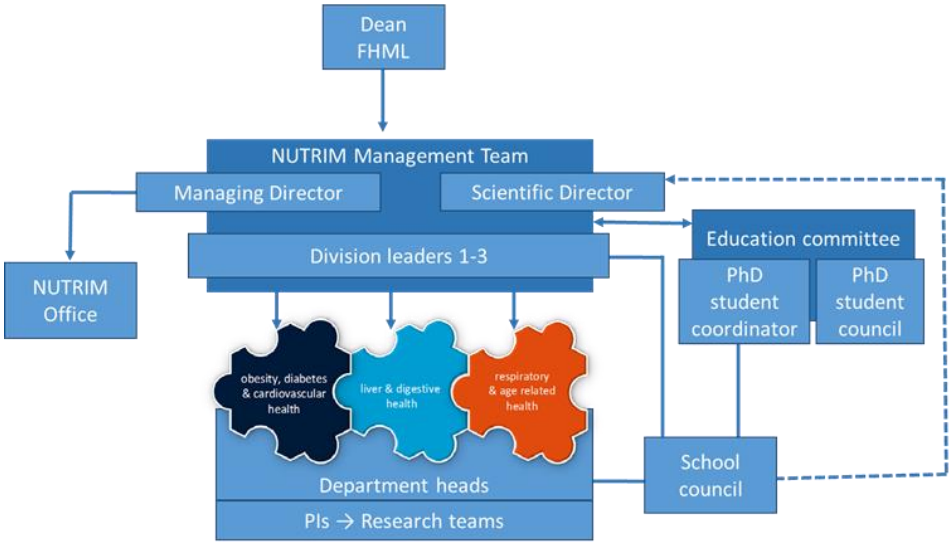
Originally, NUTRIM was organised in four research lines (1. Metabolic syndrome, 2. Gut-liver homeostasis, 3. Chronic inflammatory disease and wasting and 4. Gene-environment interactions). To optimize synergy, minimize redundancy and provide ample critical mass, per 2017, three new disease-driven multidisciplinary divisions were implemented: I) Obesity, diabetes & cardiovascular health; II) Liver & digestive health; III) Healthy aging & chronic disease progression. A further description of the research area and strategy of NUTRIM and the current divisions is provided in Chapter 2.
Each division includes researchers from various departments and is led by two leaders of different departments. The discipline specific departments form the basic infrastructure of NUTRIM, each headed by a chair, who is responsible for the quality of the discipline related education and research. For clinical departments, the chair is also responsible for the discipline related patient care. In a matrix organisation, departments house the human resources: support staff, PhD students and scientific staff. Tasks are provided through labelling in the School (*e.g*. NUTRIM) and educational programs. For the research labelling, the policy as from 2016 is that direct government funding research labelling for all tenured research staff is maximised at 0,5 fte.

1.3 NUTRIM Governance, staff and financing

The **scientific director**, who has final responsibility for the School and reports to the board of FHML, manages NUTRIM. The **managing director** is responsible for the accounting within the School and heads up the NUTRIM Management Office. Together with the division leaders, they form the **NUTRIM Management Team (MT)**, which meets monthly. The NUTRIM education committee (EC) coordinates and advices on the PhD programme and consist of the **PhD coordinator** (Dr. Roger Godschalk; chair) and the **PhD Council**. The latter consists of six PhD students from the different divisions supported by the PhD Coordinator and a member of the NUTRIM management office. The thematic needs and expertise of the disciplinary departments is attuned every three months within the **School Council** consisting of the MT, the PhD coordinator and all department heads. See also figure 1 on the NUTRIM organisational structure.

The Scientific Director is a full professor appointed for 0,5 fte. Since September 2020, Daisy Jonkers holds this position (from 2006-2020 held by Prof. A. Schols). D. Jonkers is actively involved in scientific research as PI for the remaining 0,5 fte. The Scientific Director is assisted by the **NUTRIM Office**, which is exclusively active for the NUTRIM society. It supports the scientific director in the daily school management, and the NUTRIM community with all legal and financial-administrative tasks related to *e.g.* grant proposals, granted projects, appointments, and (inter)national collaborations (*e.g.* contracts, material/data sharing). The NUTRIM Office tries to diminish as much as possible the financial-administrative burden for researchers, so that they can focus as much as possible on research.
The NUTRIM Office consists of the managing director (From April 2020: Drs. Rob Levels (1,0 fte); 2016-2020 Drs. Pascal Stevens), management Information officer (0,45 fte), office manager (1,0 fte), legal representative (0.2 fte), marketing and communication officer (0,2 fte), and a funding advisor (0,4 fte). Furthermore, a financial controller (0,7 fte), contract research expert (0,2 fte) and financial consultants (3,0 fte) are from the UM Finance Department, but hold their workplace at the NUTRIM Office. They are paid directly by FHML. The other fte's are mainly (80%) financed by the yearly government funding the School receives from FHML and partly by the NUTRIM community from the overhead charged on research contracts and grants obtained by NUTRIM researchers. The annual budget for the NUTRIM Office amounts to 350K €.

[10] https://www.brightlands.com/



Departments involved (* clinical departments)	
Div 1	Bioinformatics Endocrinology* Health promotion Human biology Nuclear medicine & radiology* Nutrition & movement sciences Ophtalmology* Pediatrics*
Div 2	Anatomy & Embryology Gastroentrology & hepatology* Genetics & cell biology Intensive care* Medical microbiology Plastic surgery* General surgery*
Div 3	Central diagnostic lab* General surgery* Human biology Nephrology* Nutrition & movement sciences Pharmacology & toxicology Respiratory medicine*

Figure 1: Organisational structure NUTRIM

2. Mission, ambitions, overall objectives and strategy

All NUTRIM divisions share the joint NUTRIM vision, mission, overall objectives and strategy to create optimal synergy and efficiency.

2.1 Vision, mission and objectives

Vision: NUTRIM strongly believes in connecting and integrating different disciplines to create novel scientific insights and innovative health solutions for society. NUTRIM focuses on biomedical research to capitalize on its unique strengths, with a strong link to health promotion. NUTRIM actively maintains a local, national, and international network to contribute to solutions for global health concerns. In our vision, an excellent educational infrastructure plus an innovative and challenging research environment together with pro-active talent and career policy, are crucial for the academic development of young and mid-career researchers and for their ability to acquire skills and expertise.

Mission: NUTRIM promotes translational research on chronic metabolic and inflammatory disorders with a high societal burden that will contribute to personalized lifestyle and medicine approaches. In its PhD programme, NUTRIM aims to meet the demand for scientists who are acquainted with novel fundamental research concepts and are equipped to optimize the translation from science to the clinic and public health.

https://maastrichtuniversity.bbvms.com/p/default_videoteam/c/2874047.html

Objectives: The NUTRIM mission is implemented by the following objectives:

1. To enable an excellent research programme that encompasses the entire spectrum of fundamental, clinical and population based translational research, which leads to novel insight, diagnostic markers, preventive tools and treatment options. Such research provides NUTRIM with a distinct international health science profile that optimally fits within the MUMC+ vision and organization.
2. Availability of unique patient cohorts and biobank as well as an internationally distinct, state of the art infrastructure for metabolic and inflammatory phenotyping allowing a network-based approach linking tissue, organ systems and host outcomes within chronic metabolic disorders and taking inter-individual variation into account.
3. To mentor scientists at various stages of their academic career.
4. To facilitate the sharing of knowledge and expertise within UM and MUMC+, and by collaboration with other universities, research institutes, national and international networks to various stakeholders.

2.2 Research area and strategy

The research area of NUTRIM covers the whole spectrum from maintenance of a healthy lifestyle and disease prevention to disease management, with a strong focus on prevalent chronic metabolic and inflammatory disorders across the lifespan. The research in metabolic diseases is centered on the metabolic syndrome with obesity as key feature and diabetes and cardiovascular disease as prevalent comorbid diseases. Chronic inflammatory disorders are positioned around the respiratory tract, gastrointestinal (GI) tract and the liver, including also tissue degenerative processes, carcinogenesis, and (muscle) wasting.

The three divisions of NUTRIM focus on health and disease models to disentangle disease-specific and lifestyle-induced denominators in disease onset and progression. Furthermore, our aim is to establish targeted therapeutic and preventive strategies, which is enabled by a combination of *in vitro* and *ex vivo* models (including *e.g.* organoids, primary cell cultures), animal studies, (complex) human intervention and cohort studies in healthy and high-risk volunteers and patients. This is supported by the Metabolic Research Unit Maastricht (MRUM) encompassing 20 metabolic rooms (including 5 air-tight respiration chambers, 10 subject-bound calorimeters) and a Metabolic Imaging Unit (*e.g.* PET, MRS, CT), the Human Performance Lab, the recently built Clinical Research Unit (CRU), animal facilities, analytical pipelines for *e.g.* metabolomics, the Maastricht Proteomics Centre, the Stable Isotope Research Centre (SIRC) and the close connection with the clinic. Research innovation is further facilitated by the ultra-high-field MRI centre Scannexus, the advanced microscopy CORE lab, mass spectrometry based molecular imaging institute M4I, the institute for Technology-inspired regenerative medicine MERLN, the Euregional Microbiome Centre and collaborations with the Maastricht Centre for Systems Biology (MaCSBio).
NUTRIM's organisation within three interconnected disease-driven divisions facilitate the translational and integrated approach and optimises synergy within and between research themes. A short description of the research area of each division is given below.

Division 1: Obesity, diabetes and cardiovascular health
(leaders: Prof. Dr. Stef Kremers & Prof. Dr. Jogchum Plat)
https://maastrichtuniversity.bbvms.com/view/um/2874048.html
We try to understand how lifestyle, including diet, physical activity and novel factors like cold exposure and circadian rhythmicity and pharmacological interventions, can improve metabolic health, by performing detailed, deep-phenotype human intervention studies and investigating the underlying mechanisms in humans, animal and *in vitro* models. Specific focus is on skeletal muscle, liver and (brown) adipose tissue metabolism. The knowledge gathered is applied in developing strategies that allow making healthy choices easier, assist people in changing their lifestyle in order to improve their quality of life and disease outcomes, and to reduce public health impact of obesity, diabetes and cardiovascular health.

Division 2: Liver and digestive health
(Leaders: Prof. Dr. Steven Olde Damink & Prof. Dr. Ronit Sverdlov)
https://maastrichtuniversity.bbvms.com/view/um/2874050.html
We intend to provide novel insights into the pathophysiological processes of the gut and liver and to translate these findings to the clinic and the general population. Central disorders investigated include *e.g.* inflammatory bowel disease, functional GI disorders, GI cancer and associated cachexia, intestinal and liver failure, cholestasis and non-alcoholic steatohepatitis. While the main research focus lies within the gut-liver axis, the enterohepatic circulation and the gut microbiome, a secondary research goal of this division is to extrapolate research findings to related organ systems such as the cardiovascular and central nervous system, and to address the inter-organ cross talk and bidirectional interactions with lifestyle.

Division 3: Respiratory and age related health
(Leaders: Prof. Dr. Luc van Loon & Prof. Dr. Frederik-Jan van Schooten)
https://maastrichtuniversity.bbvms.com/view/um/2874049.html
We aim to increase our understanding of the human ageing process in various tissues and understand the onset of respiratory disease related to age and lifestyle. We study the impact of detrimental changes experienced during life in lifestyle (smoking, physical (inactivity), (mal)nutrition) and the environment (*e.g.* air pollution, microplastics) and their interaction with our genetic background. We focus on early

identification of people with an enhanced risk for disease onset and progression and hospitalisation due to sarcopenia and cachexia and on developing effective strategies to modify chronic disease progression and support healthy aging.

2.3 Local, regional, national and international collaborations

NUTRIM has a strong collaboration with the Academic Hospital Maastricht and is part of the hospital/FHML partnership Maastricht UMC+ (MUMC+). All **NUTRIM research themes are linked to the MUMC+ strategy** to ensure optimal alignment for high quality translational research. In 2015-2020, NUTRIM was successfully positioned as innovation platform on 'Metabolism and nutrition' within MUMC+ to contribute to the academic position of major disease clusters and to strengthen the MUMC+ profiling on 'Healthy living'. Additionally, NUTRIM has a strong collaboration with other FHML graduate schools/institutes and UM faculties (*e.g*. via the interfaculty platform EatWell and Campus Venlo).

In the region, UM has joined forces with other institutes as part of 'Knowledge axis 2.0' in a 10-year strategic program of the province Limburg to strengthen the socioeconomic structure and to stimulate a healthy and vital population, and is part of the open innovative community Brightlands. Brightlands comprises four campuses: Maastricht Health Campus (of which NUTRIM is part of), Chemelot Campus, Smart Services Campus and Campus Greenport Venlo.

Nationally, NUTRIM collaborates within various Dutch governmental and public private initiatives including: the National Genomics Initiative; the Parelsnoer Biobank Initiative of the Dutch University Medical Centres in the Health RI network (topics: Multiple Neuroendocrine Neoplasia, IBD, Liver tumours, Pancreatic cancers); National top institutes (TI) including TI Food & Nutrition (TIFN) (Theme Nutrition & health), the TI Pharma (topic: COPD), the Centre for Translational Molecular Medicine (topic: Diabetes) and research infrastructural programs (BBMRI, Elixir and X-omics). Furthermore, we are involved in the NWO Carbohydrate Competence Centre (CCC), various consortia in the Top Sector Life Sciences (Health~ Holland) and Top Sector Agri & Food, and have collaborations with several Dutch universities and knowledge institutes.

Internationally, strengthened by its geographical location in Europe, NUTRIM has a close collaboration with RWTH (Rheinisch-Westfälische Technische Hochschule) Aachen University Hospital, Universities and hospitals in Leuven, Liege and Hasselt, and the German Diabetes Center in Dusseldorf, and amongst others with the University of Copenhagen, University College London, University of Birmingham, University of Oslo, University of Exeter, INSERM Toulouse, Institute Pasteur Lille, and Ecole Polytechnique Fédérale de Lausanne. Longstanding collaborations outside Europe include *e.g.* the National Institute of Ageing, Darmouth College, McMaster University, Harvard Medical School, Renal Research Institute New York, University of Vermont, University of Sao Paulo, St. John's Research Institute and National Academy, Bangalore, India. Additionally, NUTRIM collaborates with various **national and global companies,** such as Danone Research, Philips, Nestle SA, DSM NV, Unilever and GlaxoSmithKline. Key (inter)national collaborations are also presented in Annex 1 Figure 1.5.

2.4 Personnel policy, training and education

An important part of our mission is to mentor scientists in different stages of their careers to ensure scientific and personnel development. This is achieved through several activities, which are discussed in more depth below:

For PhD candidates

- General courses offered *e.g.* by FHML, UM Staff Career Centre, Language Centre and UM Library
- Discipline specific courses organised by PIs of NUTRIM
- Master classes and Capita Selecta organised by the PhD-coordinator and PhD-council of NUTRIM
- Awarding the NUTRIM certificate and Nutritional Scientist certificate to PhD candidates
- Contributing to a wide variety of bachelor and master programs within Medicine, Biomedical Sciences and Health Sciences

General:

- UM/FHML policies on Reward and Recognition and Career Policy

- The NUTRIM PhD Graduate Program, the MUMC+ Kootstra fellowship program, Tenure Track Program and Top Talent Program for talented and promising, early and late stage researchers.
- Regular meetings and lectures within departments and divisions and the Annual NUTRIM symposium
- Contributing to several Bachelor's and Master's programmes
- Attending (inter)national scientific meeting and presenting scientific work (posters, orals)

Diversity: In line with the UM Strategic Programme 'Community at the Core' with **inclusivity** as important goals, NUTRIM continuously strives to increase its PhD candidates and staff **diversity** in terms of gender, age and ethnicity and specifically want to address the issue of equality. We believe that with a differentiated HR policy, all community members should be able to flourish and work to their highest potential. By its geographic position and the international orientation of UM, NUTRIM attracts researchers and students from all over Europe. At present, over 24 PhD candidates and 60 staff members can be identified as coming from abroad. NUTRIM actively supports exchange programmes for foreign PhD-candidates (*e.g.* with China, Saudi-Arabia and India) and joint PhD's (*e.g.* with Birmingham, Leuven, Aachen). Within NUTRIM, ~50% of staff and 20% of professors is female.

Talent policy: MUMC+/FHML aims to create an environment that enables talents to excel with an overall talent policy aiming at identifying and supporting talented (PhD) students and staff at all levels. Examples of specific programs include the Honours program and Marble for Bachelor students, Premium for Master students, and the internal MUMC+ Kootstra Talent Fellowship for last year PhD candidates in their transition to postdoc positions. Each year, about 3 NUTRIM PhDs receive a **Kootstra Fellowship**, which aims to facilitate talented researchers to develop their own research ideas and to increase their chances of obtaining prestigious personal grants. By the **NUTRIM PhD Graduate Program**, each year 2-3 talented students receive a grant for a PhD trajectory for which they propose their own topic, research proposal and supervisors. Talented postdoc researchers can be offered a **Tenure Track Program**, by which they are given the opportunity for a permanent position as Assistant Professor when meeting certain criteria based on output, an independent attitude, acquired funding, impact, personal development and leadership, and scientific recognition. Candidates are supported by their PI, department head and NUTRIM scientific director and are assessed by an independent committee. The number of places is limited and depending on funding available. The MUMC+ based **Top Talent Program** is aiming to scout **potential professors** and to offer them a Professorship with a specialised remit ('Profileringsleerstoel'), with the prospect of moving on to a Structural Chair after assessment of their performance and professional growth potential. The track towards a professorship includes agreements on scientific and personnel development and leadership potential, as well as an accompanying course on the latter two aspects. Every 2-3 years, 2 NUTRIM candidates are selected based on a Top Talent review by NUTRIM and the faculty. Furthermore, UM offers **management development programs** for future leaders and those who have recently started on a management position.

PhD training and education: NUTRIM attracts high quality PhD candidates by vacancies posted at the Dutch main website (Academic Transfer) and by recruitment via (inter)national networks. NUTRIM has about ~250 PhD-candidates, ~40% being internal PhD candidates. Of these, around 60% followed an UM master program. Furthermore, ~60% are external PhD candidates, *e.g.* clinical fellows, those employed by collaborating institutes or who contact NUTRIM themselves (sometimes with scholarships). About one third of our total PhD population comes from abroad.
To contribute to the development of PhD candidates, NUTRIM aims to provide an environment that stimulates their further development, deepens scientific understanding and the development of a broad society oriented perspective. In the first three months, PhD candidates together with their supervisory team compose a **Personal Research plan (PRP) and a Training and Supervision Plan (TSP)**, to be approved by the supervisors and PhD coordinator (and HR for internal PhDs). PhD candidates are offered the NUTRIM PhD program, including the PhD introduction days, lectures, workshops and courses. There are no compulsory courses, but each **training trajectory is tailored** to the individual's personal wishes, project and career path. Many general courses are paid for by FHML. Other educational and conference expenses are paid by the supervisory team (from the PhD incentive payments and/or grants received).

Professors, and since 2019 also tenured associated professors, have the *ius promovendi* that gives them the ability to act as first promotor. Each **supervisory team** consists of at least two promotors, as laid down by the MU Regulation governing the attainment of doctoral degrees, 2020. Supervisors have a PhD degree and come from Dutch or international institutes or hospitals. Within NUTRIM, about 40% of the PhD candidates has supervisors from different departments, Schools or Institutes, illustrating the multidisciplinary character. Since 2017, FHML offers a highly appreciated **course Competence Development for supervisors** of PhD candidates. The quality of the supervision is monitored by the online **PhD-track system.** The **PhD-coordinator** receives a notification in case the supervisory performance warrants further action. PhD candidates can also contact the PhD-coordinator, HR or a confidential counsellor any time for advice or help. The **progress of PhD-candidates** is assessed every 6 months in the PhD-track system, which further monitors the workload, training, and supports the candidates and supervisors for having **annual appraisals**. Internal PhD candidates are formally assessed at the end of every PhD-year according to the Dutch Collective Labour Agreement (CAO). A go/no go interview in month 10, in the presence HR, determines whether the appointment will be extended for the next three years. The PhD-track system also provides a registration of all PhD candidates and supervisory teams that are embedded in the NUTRIM departments and divisions.

2.5 Academic culture and knowledge dissemination

NUTRIM stands for high quality research, with rules for ethically and socially responsible conduct in science as provided in 'The MUMC+ Research Code'. Each researcher has to comply with the **Declaration of Scientific Research Integrity** according to the Netherlands Code of Conduct for Research Integrity and the UM Integrity Code of Conduct. The UM counsellor for scientific integrity can be contacted for questions or complaints and will try to mediate. Eventually, a complaint can be filed with the Committee for Scientific Integrity, who will advise the UM executive board. In 2018, the MUMC+/FHML Platform Scientific Integrity is installed to create awareness and a safe and approachable environment to discuss the topic (NUTRIM contact: Dr. Anke Oenema).
In NUTRIM, many studies involve human subjects and are performed in line with national and EU regulations, the revised version of the declaration of Helsinki and have to be approved by the MUMC+ Medical Ethics Committee. Running and supervising such studies is only allowed in possession of a valid BROK/GCP-WMO certificate. Animal studies are assessed by the Animal Ethics Committee (UM-DEC) and performed by those possessing an article 13 certificate.

NUTRIM considers research integrity very important, especially also given the extensive collaborations with corporate partners, and favours an open culture to discuss research findings and integrity. To further ensure high quality research, we consider it also very important to manage data with care and to ensure reuse and verification of research data following **principles of FAIR and Open Science**, as also defined in the UM Research Data Management Code of Conduct. Submitting a data management plan is a prerequisite for obtaining consent for human studies. Data management is supported by the Clinical Trial Centre Maastricht, the FHML 'Centre for Data and Information Management' MEMIC and the MUMC+ 'DataHub'. In 2019, UM approved the policy "Open Science @ UM" to endorse the principles of open science and to support bringing these into practice, making science 'as open as possible, as closed as necessary'. This is further promoted by an Open Science Ambassador and the Open Science Community (OSC). Omics datasets are generally deposited in public databases. For more sensitive data, NUTRIM is open for requests and collaborations in line with the GDPR and approval obtained. We stimulate open access publications, which is also supported by contracts of the UM library with publishers (Golden Open Access, Hybrid and Green Open Access) and tools developed to stimulate open science. Furthermore, since 2017, publications are posted in the public UM research database PURE (Elsevier).

NUTRIM has a pro-active attitude for **sharing of knowledge and expertise** to various stakeholders by a number of activities:

- Organisation of scientific events with and for national and international partners
- Up-to-data and informative NUTRIM website and Periodic Electronic Newsletter
- Stimulating and initiating national and international collaborations

- Publication of research findings, presentations for various stakeholders and media exposure (see also examples given in chapter 5 and annex 1).

3. Strategy (including the strategic process) of the past six years

In line with the NUTRIM strategy (chapter 2), several actions were taken in the past six years (2015-2020). Most of these were taken at the NUTRIM level as we strongly believe that a shared strategy increases synergy and efficiency.

3.1 Research area and strategy

The original four research lines (1. Metabolic syndrome; 2. Gut-liver homeostasis; 3. Chronic inflammatory disease and wasting; 4. Gene-environment interactions) were **re-organised into three more disease-driven divisions** to provide ample critical mass, a clear focus and to strengthen the multidisciplinary translational research. Using a bottom up approach, we optimised the fit for each PI group in one of the divisions. The new structure was implemented in 2017. In line with the new division structure, **NUTRIM sharpened its mission, vision and its overall and division specific objectives and renewed its website** to improve its visibility. Each division has planned activities for educating researchers, informing peers and facilitating discussions and collaborations. To further stimulate interactions, division 2 and 3 each awarded seeding grants for research that bridge between groups in order to obtain pilot results to attract future funding.

NUTRIM has invested in **new research positions/labelling**, amongst others within the theme of prevention and for research clinicians in MUMC+ and CIRO Horn (Expert centre for the treatment of people with respiratory failure), **to further strengthen the unique position of NUTRIM, synergy with the clinic and new initiatives**. This is further supported by activities in the interfaculty program EatWell, the increasing embedment of nutrition and lifestyle in clinical research, and by joint meetings.
We increasingly perform research that leads to large and complex data sets. NUTRIM has prepared a Multivariate Statistics Support Inventory to anticipate on new needs and to join forces in **"big data" handling**, and made it a central theme of the annual NUTRIM symposium 2016 ('What's hidden in your data'). Advanced modelling and statistics are increasingly applied, but the expertise in NUTRIM is now scattered over a few groups. Recently, a virtual core group of data-scientists was assembled to meet, exchange approaches, collaborate and make use of each other's expertise. This will further strengthen and maximise the use of our high quality data.

In 2016, the **NUTRIM Electronic Newsletter** was implemented to inform the NUTRIM community on aspects of human resources, FHML policy, grant opportunities, research highlights, etc. In 2017, a **dedicated NUTRIM grants advisor was appointed,** who pro-actively monitors grants opportunities, provides career and grants advice and support in the application phase (such as for prestigious personnel grants (*e.g.* VENI, VIDI, VICI, ERCs, *etc.*) and otherwise (*e.g.* FP7/H2020, NWO, ZonMW, TKI)).

3.2 Collaborations and strategic partnerships

In the past years, we have taken a proactive attitude towards **other Graduate Schools** by opening our Graduate Program for collaborative projects and stimulating joint scientific research initiatives and PhD trajectories. Within the **interfaculty** program EatWell and Campus Venlo, we have established fruitful collaborations with the Faculty of Psychology and Neuroscience and the Faculty of Science and Engineering. **Bottom up collaborations have been strengthened** with Universities of Liege, Hasselt, Leuven and Aachen by joint research projects and PhD-trajectories. NUTRIM PIs have double appointments at NUTRIM and RWTH Aachen and the German Diabetes Centre in Dusseldorf. Between 2015-2020, **new collaborations** have been set up amongst others with Leiden University, University of Birmingham, University of Melbourne, Monash University, Bonn University, Gladstone institutes USA, University of Gothenburg, University of Pecs, Darthmouth College of Bonn and University of Alberta. A **strategic alliance** was established with Danone Nutricia Research and NUTRIM with the appointment of Dr. A. van Helvoort; the Netherlands Food and Consumer Safety Authority (NVWA) with Prof. A. Opperhuizen, and the Netherlands organisation for Applied Scientific research (TNO; Unit Science of Circular Economy and Environment) with an honorary appointment

of Dr. I. Kooter. Collaborative PhD projects have been set up conjunction with the National Institute for Public Health and the Environment (RIVM).

3.3 Infrastructure

In 2019, an application was submitted as part of the 'National roadmap for Large-Scale Research Infrastructure' to expand the high-end **Metabolic Research Unit Maastricht (MRUM)** by building amongst others, high quality circadian rooms for studying 24-hour metabolism (with state-of-the art technology in the field of light and temperature regulation), a metabolic ward for long-term stays of study participants and an elaborated combination with further developments in non-invasive imaging technology and a Clinical Metabolic Research Unit. The proposal was not granted. Meanwhile, in collaboration with the Academic Hospital Maastricht and as part of the Euregional INTERREG project PROOF, the NUTRIM **Clinical Research Unit (CRU) has been built** in the hospital for research on nutrition and metabolism in and for patients. This will further strengthen the integration between basic scientists and the clinic and NUTRIM's translational research. The CRU will officially open mid-2021 and will closely collaborate with MRUM to align assessments and to provide a continuum of human studies in health and disease.
In 2018, Prof. Honing was given the assignment to evaluate the Mass Spec (MS) analytics within NUTRIM. In his SWOT, a weakness was that equipment is scattered within the institute and sometimes outdated. Furthermore, a threat is limited internal funding and lack of FHML-wide investment policy together with ad-hoc funding by external funding systems (NWO, ET). Based on this report a NUTRIM workgroup made a plan towards a quantitative MS **analytical NUTRIM facility**, which is currently on hold awaiting FHML infrastructural discussions in a broader context, but will be continued in the very near future.

3.4 Human Resources Policy, including PhD policy and training

As of 2016, NUTRIM continued as local graduate school, independent from VLAG/Wageningen University and has set up a NUTRIM PhD-introduction, training and education program (see also par. 2.4). PhD-candidates students are stimulated to follow courses, lectures, research meetings, workshops, and symposia, and to meet with experts to broaden their knowledge and skills for top-level research. Involvement in teaching does further expand their skills and future career opportunities. The training, progress and supervision of PhD-candidates is monitored via the PhD-track system.
The PhD coordinator and PhD-council have **regular meetings to discuss needs and suggestions for improvements of current and initiate new activities**. Quarterly, this is attuned with the scientific director. The PhD-council also organises social events for PhD-candidates (the NUTRIM networking café), career events (*e.g.* speed-dates) and has implemented a buddy system (2020), by which senior PhD candidates provide advice and share experiences with junior candidates. The PhD council receives an annual budget for organizing activities and the coordinator has 0,1 fte dedicated NUTRIM labelling.

From 2020, the **PhD graduate program** as well as the **annual NUTRIM equipment fund** was **temporarily put on hold** to guarantee a future-proof financial position of NUTRIM. End 2020, **the Research Talent program** has been implemented (together with CAPHRI) for high potential junior researchers to strengthen their academic CV, grant writing skills and to further develop their own research ideas to increase their chances of obtaining personal grants. Since 2017, the course on competence development for PhD supervisors is actively offered to Tenure Track candidates, Assistant and Associated Professors.
In 2015-2020, 11 talented post-docs were offered **a tenure track position,** of which five completed their track**.** In addition, six senior scientists were selected for the **Top Talent Program,** three of which have been appointed professor (Prof. M. Spruit (D3), Prof. R. Sverdlov (D2), Prof. D. Jonkers (D2)). At the same time, NUTRIM aims to attract the best globally when positions are available. During 2015-2020, two external professors have been appointed (Prof. K. Venema D1) and Prof M. Spruit (D3). Additionally, six leading scientists (Prof. W. van Gemert (D2), Prof. E. Köhler (D2), Prof. S. Olde Damink (D2), Prof. N. Bouvy (D2), Prof. M. Poeze (D3), Prof. G. Haenen (D3)) have been appointed professor.

3.5 Open science and academic culture

NUTRIM actively stimulates the implementation and practice of **Open Science.** This is facilitated *e.g*. by posting NUTRIM publications in the public UM research database PURE, the UM policy "Open Science @ UM" (2019), the instalment of an 'Open Science Community (OSC)' and 'Open Science Ambassador', and the University Library supporting and assisting researchers. To promote the relevance of open science, the annual NUTRIM symposium 2020 was dedicated to this topic. Combined, this resulted *e.g.* in an increasing number of open science publications (Figure 1.2) and use of NUTRIM datasets (see also par 5.1).

The NUTRIM community pursues a high standard for Scientific Integrity (in line with the National and UM Codes of Conduct). New researchers receive relevant information by HR and as of 2020, every PhD candidate has to confirm a statement on scientific integrity by taking a public oath at their PhD-defence. The relevance of scientific integrity is also addressed during the PhD-introduction days. The supervisory team and NUTRIM PIs serve as role models and aid in knowledge utilisation and valorisation. To further stress the relevance, each thesis has to comprise an **Impact Paragraph**, where candidates reflect on the **scientific and societal impact** of their findings.

4. Reaction on and follow up of the recommendations of the previous assessment committee

This NUTRIM reaction and follow up is based on recommendations by the External Review Committee (ERC) of the National Graduate School VLAG (2009-2015) and the decision by Wageningen University and UM not to continue as one National Graduate School. A point-to-point reply is given below. Division-specific recommendations are addressed in part B.

- ***The PhD training and education program*** *was judged very positively, but needed to be adapted since NUTRIM as of 2016 continued as local Graduate School no longer being part of VLAG.*

The NUTRIM PhD council and the PhD coordinator took the lead for a new NUTRIM PhD program, including the new NUTRIM PhD introduction days, lectures, workshops, courses and social activities (see also par 3.4).

- *The committee was impressed by the* ***overall excellence,*** *but identified variation between groups.*

We understand this judgement, but think that there was some discrepancy between the self-assessment and the interviews in highlighting specific strengths of the research lines as the ERC could only meet with a limited number of PIs. Nevertheless, we do think that the adaption of the research structure from four research lines into three divisions with ample critical mass and a good balance between depth and breadth does lead to better positioning of NUTRIM within and outside Maastricht. Pillars of the division structure are established research teams with excellent past performance.

- *The ERC advises to be* ***innovative*** *and to remain at the cutting edge.*

We agree and want to build from our own strength and distinct position in translational metabolic and chronic inflammatory research, with a strong focus on prevention. We increasingly adopt tailored and personalized medicine and prevention as well as holistic approaches, in line with the large phenotype heterogeneity and multifactorial origin of various chronic disorders.
In the original research line 4 (Gene-environment interactions), we wanted to bundle our strengths and visibility in genetic epidemiology, bioinformatics and -omics, anticipating on a systems approach towards chronic diseases. In view of recent developments within and outside NUTRIM (*e.g.* strengthening of the Dept. of Bioinformatics and instalment of expertise for big data analysis (Chair in Clinical Data Science (Prof. A. Dekker); Institute of Data Science (Prof. M. Dumontier); Maastricht Centre for Systems Biology (MaCSBio)), this expertise has now been repositioned and integrated in the more “disease oriented” divisions. NUTRIM has also prepared a Multivariate Statistics Support Inventory to anticipate on new needs and to join forces in “big data” handling, and formed a virtual core group to share expertise and maximise the use of our high quality data (see also par 3.1).
Most leading NUTRIM scientists have a balanced research portfolio allowing investments in high-risk initiatives. The ERC indicates that the infrastructure investments (*e.g.* M4I) will facilitate innovative leading-edge research programmes. Several NUTRIM groups (esp. dept. of Surgery) already share manpower and infrastructure with M4I, and they and others explore how to strengthen grant proposals by incorporating this new technology. A NUTRIM PI is the formal M4I clinical liaison to link their work to the clinic. We will further stimulate collaborations with M4I and MERLN. An application to extend our metabolic facilities at MRUM was filed as part of the Dutch NWO Roadmap on large-scale infrastructure. Furthermore, supported by an interregional INTERREG grant, we have built the NUTRIM Clinical Research Unit for research on nutrition and metabolism in patients.

- *The ERC stresses that the* ***recruitment strategy*** *needs to attract the best globally.*

We certainly intend to do so, but it remains difficult to attract established scientists from abroad. Since in the past years NUTRIM has installed (as part of the MUMC+ Top Talent Program) a substantial number of personal chairs, new positions in 2015-2020 were mostly filled at the assistant professor level in order to deal with the high teaching load and to facilitate talented clinicians to combine research and clinical work. In total, 11 talented postdocs were offered a tenure track position. Furthermore, based on a systematic

analysis of performances, vacancies within some departments and strategic considerations, NUTRIM has assigned 1,3 fte extra in 2015-2020 for labelling 6 scientists, embedded in 5 different departments.

- *The **overall quality** of the scientific performance of the **research staff** was seen as impressive and the ERC advice on career planning for individual staff members and succession plans is in line with ongoing procedures (i.e. FHML/MUMC+ Career Policy).*
- *Regarding **future funding**, the ERC questions if NUTRIM is in line with the changing landscape of the national priorities/Top Sectors.*

We notice that our strategic interaction with several companies facilitates TKI-benefit. We are well positioned with PI-roles in new TIFN-TKI and TIFN-NWO initiatives, the Carbokinetics program (www.cccresearch.nl), ZonMW and Health~Holland consortia (tables 1.7/1.10). We are also increasingly successful in the Euregion (*e.g.* Interreg-Oncocare Project, Interreg-PROOF, EIT health) and EU funded projects (table 1.8). Our research fits also well with the Dutch Research Agenda (NWA) and its routes related to Health and Disease. In the NWA-programme it is important to build consortia that contain the whole knowledge chain and to valorise research findings into societal breakthroughs. The multidisciplinary and applied approach of NUTRIM research is perfectly equipped to meet this ambition.

- *The ERC comments that **food companies** are shifting their focus eastwards.*

We do not have the impression that for human and clinical (proof of concept) nutrition research, companies tend to shift their focus eastwards, as our key partners did not change over time. We nevertheless continuously explore opportunities for extending collaborations and building new relationships.

- *The evaluation committee endorses the general strategic aims of NUTRIM within VLAG and recommends strengthening of existing links between **Maastricht and Wageningen**. The ERC also suggests that both universities may wish to explore opportunities for strategic alliances to enhance their international competitiveness.*

In addition to several bottom up collaborations, examples of joining forces by the Universities include the 2016 NWO Gravity application entitled “Turnover”, the 2020 NWA-ORC application “Virtual Human Platform” and “PisTache”, at a European level the KIC “FoodNexus” and intercontinentally the combined ZonMW/Health Holland/CHIR application “RT2T2D”. Additionally, an ESFRI application (‘Towards a pan-European Food Nutrition and Health Research Infrastructure”) is filed, the NUTRIM director is board member of the Top Institute Food and Nutrition (TIFN) and member of the Dutch Academic Platform Food (DAPF). Furthermore, together with Wageningen the foundation Nutrition in Transition was founded, which now is an official working group within the Federation of European Nutrition Societies (FENS) focusing on ‘Standards in Nutritional Sciences’ (headed by Prof. Calder). NUTRIM further strengthened its international position by strategic collaborations within the EU-region (*e.g.* joined positions and joined PhD-trajectories with RWTH Aachen, Univ. of Hasselt) and new collaborations with international partners (see also par. 3.2).

The ERC has also noted several strengths, including:

- *The ERC indicates that NUTRIM is successful in **attracting excellent PhD students** and nurturing their training and development. Supervision of master students is seen as a good management experience.*

Coordination of the multiple tasks in parallel during the PhD trajectory asks for competences that are rare but valuable. We have taken the advice from the ERC to better communicate these activities and competences as they prepare for a position in industry as well. Furthermore, we notice in the PhD-track that an increasing number of PhD candidates value the opportunity to do the Basic Qualification Teaching (BQT)-course to broaden their skills and career perspectives. Last but not least, we stimulate flexibility and the possibilities to move around in the Dutch or international research environment.

- *The ERC concluded that NUTRIM provides a **sound basis for both academic and industrial careers** as illustrated by professional positions of our students after completion of their PhD (see also fig. 2.1).*

This has further been strengthened by new strategic “theme based” collaborations with Global Companies, SME’s and other scientific and healthcare institutions worldwide and by evaluating existing collaborations.

- *The ERC concluded that PhD's and members of the institute expressed their satisfaction with the research environment and facilities and that the "**corporate identity**" was high.*

The distinct NUTRIM identity has been strengthened further by continuing as local Graduate School and the new division structure.

- *The ERC was confident that the NUTRIM's focus on **prevention** helps to make the MUMC+ theme of Healthy Living a reality.*

NUTRIM Investments in new research positions, the connection with the interfaculty program EatWell and broad implementation of lifestyle in clinical research has strengthened the theme. Recently, the dean of FHML (aka vice-chair of executive Board of MUMC+) started an initiative to stimulate the theme 'Lifestyle and the living surrounding' as one of the MUMC+ spearheads. The relationship with the *Netherlands Food and Consumer Safety Authority* and the TNO Unit Science Circular Economy and Environment have been intensified to further promote human health.

- *The ERC judged the **integration of clinicians and basic scientists** within research lines and the bridging of clinical and more basic research as impressive*.

This internationally distinct feature of NUTRIM has further been strengthened by investments in new clinical research formation at several MUMC+ departments and CIRO Horn and by the recently built Clinical Research Unit. To anticipate optimally on healthcare developments and initiatives in MUMC+, clinical scientists from different specialties share their research activities and join forces together. Clinicians involved have also taken the lead in annually organizing a meeting to inform PhD candidates and nonclinical scientists of important healthcare developments within their specialty.

- *The ERC indicates that NUTRIM is in a **strong position to create synergy** with other groups in MUMC+.*

Indeed the placement of NUTRIM in the heart of the MUMC+ strategy with positioning of the strategic program "Healthy living" and embedding of various clinical researchers in NUTRIM, allows for optimal synergy with disease profiles. During the past years, we have taken a proactive attitude towards other Graduate Schools by a) opening the NWO-NUTRIM Graduate Program for collaborative projects and b) stimulating joint scientific research with *e.g.* CAPHRI, CARIM and GROW. There is limited though increasing collaboration with Graduate school MHeNs, and within the interfaculty program EatWell there is excellent alignment of research initiatives and opportunities between NUTRIM and FPN. We foresee that this, also stimulated by the European Centre of Excellence in Ultra-High-Field MRI (Scannexus), could develop further in the near future. Furthermore, we actively explore opportunities with other faculties (*e.g*. FPN, SBE) of UM and are strengthening the collaboration with campus Venlo.

5. Accomplishments/results during the past six years

Due to NUTRIM's reorganisation implemented in 2017, the accomplishments are presented for the three divisions over the period 2017-2020 and for the graduate school as a whole over the period 2015-2020. Representative examples are presented for each division with a more detailed overview in Annex 1.

A division-specific self-assessment is given in part B.

In each division, a **combination of fundamental, clinical and population-based research** contributes to novel insight, diagnostic markers, preventive and treatment strategies for prevalent chronic metabolic and inflammatory disorders and cancer. This translational approach is illustrated for example by case studies 01, 03, 05 (div 1), 06, 08, 10 (div 2), and 11-13 (div 3). Various case studies (02, 05-07, 10, 12, 13) show the **collaboration with the clinic** and linkage to the theme 'healthy living' (01, 02, 04, 05, 07). The **health science profile** and strong focus on **prevention and health promotion** is guaranteed by the department of Health promotion (case study 04), but is included in several projects, such as the Coach project for children with obesity (case study 02) and the holistic approach in IBD (case study 07). During the past six years, various **novel concepts** were taken up by NUTRIM researchers, such as*:*

Division 1:

- The relevance of circadian rhythm on host metabolism
- Personalised approaches to nutrition and metabolism
- Effects of lifestyle on brain vascular function and cognitive performance
- The role of sedentary behaviour on metabolism
- Systemic approaches to the prevention of obesity

Division 2:

- Unravelling mechanisms related to cancer-induced cachexia using host-derived organoids
- Value-based healthcare and integrated patient monitoring; towards personalised medicine
- Identifying molecular mechanisms at the bridge between lipids and inflammation
- The impact of an interrupted entero-hepatic cycle on gut and liver homeostasis
- Establishment of the gut microbiome in new-borns

Division 3:

- Host physiology of plant-derived proteins
- Breathomics for disease diagnosis and monitoring
- Integrated microbiome-metabolome analysis (with division 2)
- Personalized management of sarcopenia in COPD
- Effects of tobacco smoke and regulation of tobacco products (incl. new devices)

5.1 Research quality, use of research products and marks of recognition by peers

Refereed articles and PhD theses are included as scientific performance indicators. The average **number of thesis** is 38.9 per year and showed a peak in 2017 (in line with a prior peak in external funding) and decreased thereafter (table 2.5 annex 2). The overall number of publications within NUTRIM has remained rather stable and high over the years 2015-2020, with a high average number of ~800 publications per year (total number of publications is 4789 of which 3283 Wi-1 (SCI/SSCI journal) in the period 2015-2020, table 1.1, Annex 1). Several NUTRIM researchers have also contributed to **books or book chapters** (n=44) or conference papers (n=17). In line with the pro-active FHML and NUTRIM policy, the number of **open access publications** is increasing over time (figure 1.2), reaching over 30% in 2020.

The **high impact of the NUTRIM publications** is reflected by the fact that on average 19.2% of the publications belong to the top 10% and 2.6% to the top 1% (table 1.2) based on the 'category normalised citation impact' (CNCI, *i.e.* normalised for publications in the same area, over the same years and document type) and supports the use by peers. Numbers are based on InCites, which covers 98% of the NUTRIM's dominant research output. Publications originating from 2019 and 2020 are excluded as normalized citation impact data are most reliable 24 months after publication. With an overall CNCI of 1.7, NUTRIM publications are cited 70% more often than the expected average citation rates of publications in the same areas, over the same years and document types. NUTRIM topics that stand out in terms of number of publications and

citation impact include amongst others COPD, obesity, adiponectin, sarcopenia, physical activity and gut microbiota (see also figure 1.3; citation topic normalised citation impact (CTNCI) above 1 (range 1.26-2.77)). Examples of articles highly cited by peers as based on the CNCI are given in table 1.3. That the research of the NUTRIM community is highly appreciated by peers can also be observed by a high number of invited lectures given (see representative examples in table 1.4) and various (associate) editorships (table 1.5). Both tables show the involvement of not only associate and full professors, but also of assistant professors of each division, illustrating that NUTRIM also has leading scientists at the mid-career level.

NUTRIM strongly acknowledges the strength of **collaborations** between disciplines and with **other Schools/Institutes and faculties, with MUMC+** and with **national and international academic and corporate partners**. This is illustrated by figures 1.5 and 1.6, showing the high numbers of highly cited joint publications for the most frequent partners. The top five most frequent collaborators in terms of documents published together are University of Amsterdam, Free University Amsterdam, Utrecht University, Erasmus University and University of Groningen as national academic partners; RWTH Aachen, Hasselt University, KU Leuven, University of Copenhagen, and University of Birmingham as international academic partners; and GlaxoSmithKline, Danone Nutricia, Philips, Nestlé SA and DSM NV as corporate partners. Overall, the food industry is well represented. Although pharmaceutical companies are also among the frequent collaborators, the nature of the collaboration may (partly) also be in food and nutrition. The world map does show NUTRIM's international connectedness overall (figure 1.4). Collaborations within FHML are characteristic of NUTRIM's research output, with 43% of publications being co-authored by at least one other School. CAPRHI, GROW and CARIM are the most frequent collaborators (figure 1.6).

NUTRIM researchers are recognized by their peers. **Individual research prizes** have been awarded to young and established researchers from all divisions (table 1.6). Examples of **personal grants** obtained by individual researchers include two ERC starting grants, two VIDI and four VENI grants (see table 1.9 for a full overview of prestigious personal grants). NUTRIM also managed to achieve **19 European projects** over the period 2015 – 2020 (table 1.8), with in particular a very strong track record for division 1. Examples of **large grants over 500K €** (*e.g*. Top sector Health Holland /AgriFood, ZonMW, EU) and a categorized overview of strategic projects are given in table 1.10 and 1.7., respectively.
The expertise of NUTRIM PIs is also illustrated by (**honorary) appointments**, *e.g*. at the Australian Catholic University, Free University of Brussels (Prof. L. van Loon), King's College London (Dr. D. Keszthelyi) and secondary appointments, *e.g.* at RHTH Aachen (Prof. S. Olde Damink), University Dusseldorf (Dr. V. Schrauwen-Hinderling) and Hasselt University (Prof. M. Spruit, Dr. S. Langie); **memberships of prestigious scientific committees or councils** (*e.g.* VENI or VIDI committee, ZonMW, Dutch health council and various scientific advisory boards; see also table 1.11 and 1.12).
Functions of NUTRIM community members in the UM Platform Research Ethics and Integrity (Prof. M. Zeegers, chair), the national committee to promote Open Science (Dr. E. Willighagen) and the VSNU committee Responsible Management of Research Information and Data (Prof. N. de Vries), as well as programming of the topics research integrity and open science at annual NUTRIM symposia, PhD introduction days and workshops, show the relevance of these topics for NUTRIM.

Various **databases are available** to other researchers and **have resulted in** international collaborations and use, such as in H2020/DIScOVERIE (Maastricht IBS biobank cohort, div. 2), FP7/SysmedIBD (IBDSL biobank cohort, div. 2), Universities of Gothenburg and Londrina (COPD study, div. 3) or by biomedical research community worldwide (the DiOGeneS Dataset, div. 1; the doubly labelled water database, div. 3).
Various tools have been developed and used by peers, such as WikiPathways with 1.7K downloads each month (div. 1), the pathway editor and analysis tool PathVisio and the Cytoscape app for network extensions CytargetLinker (div. 1), the Experience Sampling Method App for symptom monitoring and identification of triggers in IBS (MEASURE, div. 2), the telemonitoring tool for disease and lifestyle monitoring in IBD (myIBDcoach, div. 2), and various genetically modified skeletal muscle cell lines (div. 3). Furthermore, NUTRIM is involved in commercialization of a clinical activity monitor (MOX, div. 3), respiration rooms and other indirect calorimetric systems by Maastricht Instruments, a high-tech company developed by MUMC+ and located at the Brightlands Health Campus, in collaboration with division 1. Further examples of scientific products and its use by peers is given in table 1.13.

Information on the research quality for each division in included in the tables in Annex 1. A division-specific self-assessment is presented in part B.

5.2 Relevance to society: research products, their use and marks of recognition by societal target groups

We are present in several **governmental advisory bodies in the Netherlands** (such as the Dutch Health Council and committees of the National Institute for Public health and Environment (RIVM), see also table 1.11 and 1.17), fulfil **relevant functions in various professional organisation** (*e.g*. the Dutch Academy of Nutritional Sciences, Dutch Society of Gastroenterology (NVGE), Dutch Society of Hepatology (NVH), Netherlands / European Respiratory Society, Dutch Society of Movement Sciences, Dutch Chemometrics Society, Dutch Society of Toxicology) and are strongly **involved in several patient organisations and foundations** (such as Foundation MyIBDcoach, Netherlands Lung Foundation, Diabetes Fund Netherlands, Kidney Foundation, European Lung Foundation, and the Dutch Gastroenterology and Hepatology Foundation MLDS; table 1.17).

NUTRIM scientists also frequently participate in national and European debates and media, which allows the direct communication of insights, findings and opinions towards a broader audience. An overview of representative **media contacts** is given in table 1.18. The majority of these take place in the Netherlands with over 1500 exposures between 2015 and 2020, but a substantial number also takes place in foreign media (*e.g*. US, UK, Belgium, Germany, Spain and Italy (with 929, 186, 140, 110, 61 and 60 exposures, resp.).

Research directly finds its way into **national organisations** as the Netherlands Food and Consumer product safety authority (NVWA), the Netherlands Health Council and the RIVM. Furthermore, NUTRIM researchers are also involved in development of **(inter)national guidelines** (such as Nutritional guidelines by the Dutch Nutrition Council; clinical guidelines for functional dyspepsia, for faecal incontinence by the United European Gastroenterology Society; for Irritable Bowel Syndrome by Dutch Society for Gastroenterologists and Hepatologists; for Quality of care standards for IBD by the European Crohn and Colitis Association; for Ankle fractures by the Dutch Society of Surgery; for COPD by the KNGF (Quality Registry for Physiotherapists)); **position statements and advisory reports** (see also table 1.19). Furthermore, during 2015-2020, seven spin-off companies (table 1.20) were started and several patents (table 1.21) were filed.

NUTRIM researchers were widely involved in teaching within **FHML bachelor and master programs**, but also in setting up or revising masters and specialisations (*e.g.* Sport and Nutrition; Nutrition, Physical Activity and Metabolism, Health Food Innovation Management) and coordinating masters (Physician-Clinical Researcher; Biomedical Sciences) and the participating on behalf of FHML in the Dutch Federation of University Medical Centres (NFU) and the Young Universities for the Future of Europe.
Information on the societal relevance for each division in included in the tables in Annex 1. A division-specific self-assessment is presented in part B.

5.3 Case studies

Fourteen case studies have been selected demonstrating relevant aspects of NUTRIM and representing different topics (see also Annex 3).

Number	Title case study (Name PI)	Division	Reason(s) for selection, exemplifying amongst others
01	Advancing nutrition research with novel technologies and innovative approaches	1	Translational research, societal impact, nat./ internat. collaboration, disease prevention
02	COACH Childhood obesity; consequences, prevention and treatment	1	Health promotion, link with clinic, societal impact, lifestyle
03	Obesity, impaired cardiometabolic health and COVID-19: a pivotal role of the renin-angiotensin system	1	Translational research, nat./ internat. collaboration, mechanistic, actuality

04	Prevention in the basic health insurance: The Combined Lifestyle Intervention in the Netherlands	1	Health promotion, lifestyle intervention, inter-department collaboration, national relevance
05	Physical Activity Matters!	1 + 3	Translational research, Inter-division collaboration, lifestyle, tool-development
06	Small lysosomes, Big problems, Great solutions: Lysosomes in control of metabolic diseases	2	Translational research, targeted intervention, biomarkers, patent applications
07	Real world data to prevent flares and improve health of patients with IBD	2	Link with clinic, E-health, lifestyle, personalized medicine, disease prevention and management
08	Cancer Cachexia: the impact of a tumour on the body of patients	2	Translational research, link with clinic, organoid models, living biobank
09	On the origins of species: Host-Microbiome-Diet interactions in early life	2	Fundamental-epidemiological research, joined PhD with RWTH Aachen, integrative multi-omics
10	Enterohepatic cycle disturbances in surgical patients	2	Translational research, biomarker, intervention, collaboration RWTH Aachen and M4I
11	Monitoring of disturbed gut by smelling!	2+3	Inter-division collaboration, biomarker identification, mechanistic insight, metabolomics, advanced data analysis
12	How to solve a traumatic bone defect: insights in metabolism of fracture healing and non-union	3	Translational research, link with the clinic, collaboration MERLN, intervention, new concept printed bone
13	The application of intrinsically labelled milk protein in human nutrition research	3	Stable isotope expertise, link with clinic, link nutrition - physical activity
14	Pulmonary epithelial cells as central players in chronic lung disorders	3	Fundamental, impact environment, inter-department collaboration, targeted intervention

5.4. Trends regarding research staff, funding and the duration/success rates of the PhD programme (School and Research lines/Divisions)

In Annex 2 tables 2.1-2.7, the annual figures are presented at NUTRIM level (for 2015-2020) and at the division level (for 2017-2020 because of the new division structure implemented in 2017).

Staff: Per December 2020, NUTRIM employs in total 190,9 fte consisting of 34,3 fte scientific staff (university and hospital), 18,5 fte postdocs, 92,9 fte internal PhD candidates and 45,3 fte support staff (table 2.1). The total research staff is appointed in 17 different departments and includes 77,3, 30,1 and 38,3 fte for division 1, 2 and 3, respectively (table 2.2). Apart from the direct funding from FHML, NUTRIM receives approximately 6,5 fte research capacity free of charge per year from the clinical departments in the University Hospital Maastricht. In addition, 157 external PhD candidates are registered at NUTRIM per December 2020. The enrolment of internal PhD candidates is rather stable over time, while the number of external candidates is increasing (table 2.1 and 2.2). This is merely a result of the close cooperation with the hospital and external partners. This increase in external PhD candidates is more pronounced for division 2 as compared to division 1 and 3 (table 2.2), which is likely related to their stronger link to the clinic.
In 2020, NUTRIM employs 39 full professors (see also table 1.14) and one endowed professor (Prof. A. Opperhuizen from the Dutch Food and Consumer Product safety Authority NVWA)). Strategic alliances are ongoing with a global nutrition company and with TNO (the Netherlands Organization for Applied Science Research), which may lead to endowed chairs in the near future.

Funding: The total funding from external sources is higher in the first half of the evaluation period due to a peak in contract research in 2016-2017. Overall, the average funding obtained by research grants and contract research amounts 10M € per year over the period 2015-2020, and has stabilized in the second half

towards 8.5M € per year. For 2017-2020, the average annual external funding obtained by division 1, 2 and 3, was 5.9M €, 1.6M € and 3.0M €, respectively.
The direct funding is dependent on the number of PhD graduations and is primarily used for paying tenured (research and support) staff. NUTRIM managed to increase its direct funding on which research staff is labeled from 31,7 fte in 2015 to 33,9 fte in 2020 and its labeling on research funds (mainly NWO, ZonMW) from 17,7 fte in 2015 to 26,5 fte in 2020. Due to a peak in contract research (*i.e.* research funding obtained by external organizations, such as industry, governmental ministries, European organizations and charitable organizations) in the first half of the evaluation period, the overall research staff which is labeled on contract research has decreased from 117 fte in 2015 to 78,8 fte in 2020. Information on funding at the school and division level is presented in table 2.3 and 2.4, respectively.

Success of the PhD-program: The mean annual number of PhD graduates is 38.9, showing a small decline over time (table 2.5). Over 2017-2020, the total number of PhD graduations was 41,4, 59,9 and 51,4 for division 1, 2 and 3, respectively. Of the PhD candidates that started during the period 2011-2016, about half of them obtained their degree within five years (see table 2.6 and 2.7 for further details). These figures are not corrected for various personal circumstances or the interval period between approval of the manuscript and the date of public defence. In total, 93% of the enrolled PhD candidates did graduate and only a small number of candidates stopped their PhD-trajectory, mostly due to personal reasons and/or choosing another career. The career prospects for our alumni is excellent, with 91% having a first position in research (37%), healthcare (46%) or industry (8%). In total, 13% of the graduates finds work abroad (figure 2.1).

A reflection on the division-specific trends is included in the division-specific self-assessments in part B.

6. Strategy for the next six years

Most actions will be taken at the NUTRIM level as we strongly believe that a shared strategy increases synergy and efficiency. Division-specific actions are included in chapter 7.

6.1. SWOT analysis

A SWOT analysis was performed by each division as well as by the PhD-student council. The input is combined in the SWOT below.

Strengths

- Profound cross-disciplinary interaction between fundamental, translational, clinical and prevention researchers.
- An excellent, state of the art research infrastructure to carry out (non-)invasive *in vivo*, combined with mechanistic *ex vivo* and *in vitro* metabolic research in healthy volunteers and patients.
- Integrated research programs with strong regional collaborations for maximum synergy and truly innovative connections.
- Clinical and societal highly relevant research themes.
- A strong portfolio in research funds and contracts with a balanced mixture between fundamental, clinical preventive and applied sciences.
- Alignment of research and healthcare strengthens translational research and stimulates career opportunities for talented scientists and clinicians.
- Internationally unique positioning of the strategic program “Healthy living” and the research theme “Metabolism and nutrition” within Maastricht UMC+.
- Attractive environment for strategic collaborations with other knowledge institutes, global companies and SMEs.
- Internationally leading scientists and talented young researchers with strong (inter-)national networks.
- Highly dedicated support staff on financial management, legal issues and human resources.
- Profound embedding in various (bio)medical bachelor and master programs with a strong international character.

Weaknesses

- The nationally eccentric position of Maastricht complicates the recruitment of researchers and clinicians to this area in comparison with the more central part of the Netherlands.
- Less successful in obtaining personal grants at the top level (*i.e.* VICI, ERC consolidator and advanced grants).
- Limited possibilities for long-term positions for technical and support staff positions with specific knowledge due to the ‘flexwet’.

Opportunities

- All themes within NUTRIM are international priorities; the sectors involved are innovative and accept the concept of open innovation.
- In house expertise for big data analysis and systems medicine approaches for optimal use of data sets and integrated analyses.
- Further usage of the research infrastructure at the Brightlands Campuses and linkage to the newly established institutes (MERLIN and M4I).
- Strengthening collaborations and alignment with other UM faculties and graduate schools, the multidisciplinary clinical centers at Maastricht UMC+, and regionally, including the universities of Aachen, Hasselt and Liege, to extend the research portfolio and (inter-)national position of NUTRIM.

- Increasing the visibility of NUTRIM's research and its impact locally, nationally and internationally.
- Creation of a network of collaborating institutes throughout Europe to generate a wider network of courses, open up new research areas and stimulate and facilitate new and more coordinated actions.

Threats

- Increasing pressure on the financial situation by limited central resources and limited and/or competitive funding budgets may impact high quality innovative research initiatives and risk the maintenance of state of the art infrastructure and technical support.
- High workload and pressure experienced by young and established research staff.
- Limited possibilities and means to create continuity for young research talents.
- The growing interest for lifestyle by other national institutes puts pressure on NUTRIM to remain in the front and distinctive, though also increases awareness, funding opportunities and possible collaborations.

6.2 Strategic plan for the next six years

6.2.2 Research area and strategy

NUTRIM has established a leading position in the field of 'Nutrition and Metabolism' in the Netherlands with internationally renowned PIs and focusing on highly relevant clinical and societal themes. NUTRIM will continue its current strategy, which will be evaluated annually to stay aligned with the changing landscape. We strongly believe that our translational and multidisciplinary research benefits from synergistic collaborations and strategic partnership.

The central positioning of the theme 'Nutrition and Metabolism' and 'Lifestyle and prevention' in the updated 'MUMC+ vision 2025' supports the international profile of NUTRIM and provides a strong position to create **synergy with the clinic as well as other graduate schools and faculties**. We will strengthen the collaboration and alignment with MUMC+ care centres by setting up inter-graduate school theme-based collaborative platforms to optimise networking, joint initiatives and (inter)national visibility. We also participate in the recently OECI accredited Maastricht Comprehensive Cancer Centre. Together with the recently built NUTRIM Clinical Research Unit, this will boost research on Nutrition and Metabolism in chronic diseases and cancer.

NUTRIM strongly supports a follow-up of the interfaculty **EatWell program**, and will explore new initiatives with other faculties and in the region. We are currently analysing the added value of **Greenport Campus Venlo** to ensure optimal alignment and synergy. Prevention of disease onset and progression by lifestyle and environmental factors is an important theme of **MUMC+** and the national knowledge agenda (NWA). NUTRIM is perfectly equipped to strengthen its position on this theme and towards personalised strategies, and aims to increase national and international visibility. We will **pro-actively strengthen (inter)national collaborations and strategic partnerships** (with *e.g.* NVWA, TNO, relevant companies and knowledge institutes). Nationally, we are represented in the Top Institute Food and Nutrition, Food Nexus and the Dutch Academic Platform Food, though it should be noted that better alignment of these is needed for joint positioning of the Netherlands in the domain of Food and Nutrition. Internationally, NUTRIM PIs are involved in various international consortia. Combined, the above provides excellent opportunities for public private funding initiatives (*e.g*. for Top Sectors 'Agri & Food' and 'Life Sciences & Health', NWO crossover and NWA calls, H2020, EIT Health, EIT Food).
Intensification of bottom up and strategic **EUregional collaborations** with universities of Aachen, Liege and Hasselt will further boost innovative high-end research and international profiling of NUTRIM. As an example, in May 2021, the Euregional Microbiome Centre was opened, where researchers of UM and MUMC+, Uniklinik RWTH Aachen and the University of Liege have joined forces to enhance microbiome research. Together with the Collaborative Research Center 1382 (The Gut-Liver Axis of the Deutsche Forschungsgemeinschaft), these are excellent examples of symbiotic partnerships. We aim to extend the strategic collaboration with the technical university RWTH Aachen and also explore integration of educational activities and technical facilities. We are currently also discussing further collaborative initiatives with the University of Liege.

6.2.3 Infrastructure

We have to join forces within NUTRIM and with other graduate schools/institutes, to collaborate and develop a collective strategy to **maintain a cutting edge infrastructure** (from basic research to prevention programs and clinical healthcare) for ground-breaking research. We have built a Clinical Research Unit to further strengthen our translational research with the clinic, and have installed a NUTRIM core group to share expertise and provide advice on big data analyses. The latter will also facilitate interaction with in house expertise for data science and Systems Biology (*e.g.* DataHub, MaCSBio). Positioning at the national NWO Roadmap implies recognition that our metabolic research infrastructure (MRUM) has a high priority for science in the Netherlands. We will submit a new Roadmap application for innovations in MRUM and we are bundling expertise on analytical and imaging facilities and model systems. Currently, NUTRIM is involved in the European Strategy Forum on Research Infrastructure (ESFRI) application 'Towards a pan-European Food Nutrition and Health Research Infrastructure" led by Wageningen University via the NL node (Dish.nl) of Eurodish.

6.2.4 Human Resources Policy, including PhD policy and training

To further improve **NUTRIM personnel and career development** and foster researchers and support staff in various stages of their career, we installed the NUTRIM Career and Personnel development committee (Feb 2021) to receive feedback, identify points of attention and start supporting initiatives. Additionally, we will monitor the PhD policy and culture on a regular basis (*e.g.* with the PhD-council and by questionnaires) to take action when necessary. The PhD-TRACK system is used by the whole university and is continuously being improved for optimal guidance of PhD students.
We consider it very important to provide opportunities to young talents. We will provide more support with acquiring personal grants, re-open our graduate program as soon as possible and broaden training activities and networking for PhD-candidates and young researchers. For example, we are implementing NUTRIM Short Training Missions (NSTM) allowing students to become trained in specific techniques or tools, organise speed dates with senior researchers and making their networks available. Together with the Grants Office, we are preparing a more pro-active strategy **to support prestigious personal grant applications and large consortium initiatives**. We are also implementing lectures and workshops on *e.g.* **open science, scientific integrity** (including the dilemma game) and **knowledge utilisation and valorisation**. Given the increasing relevance of societal impact, this will be included in the forthcoming annual NUTRIM symposium and will become part of the annual evaluation (Planning and Control) meetings with departments.

6.3 Viability

The number of NUTRIM PhD-candidates has slightly decreased over the last years, with a future prospect of 38 PhD-graduations each year. The higher numbers in the first three years of this evaluation period were related to a peak in contract research granted in the period 2015-2017. The NUTRIM high quality research portfolio in line with the funding landscape, the internationally leading PIs, the extensive collaborative network and involvement in various (inter)national consortia and societies, is expected to guarantee the preservation of earning power and influx of PhD-candidates. We do, however, acknowledge that the observed downward trend in the number of PhD candidates warrants close attention. This has also been addressed in the School Council and annual evaluations with the departments and PIs, and includes active steering for new PhD positions, completion, and timely graduation of PhD-candidates.

At present, the potential impact of COVID-19 on future funding opportunities and financial prospect of corporate partners is not yet clear and also warrants close monitoring. However, the realised earning power 2020 is in line with the previous years 2018-2019 and there are no concrete signals to expect a lower level of contract revenues in the upcoming year 2021. In addition, NUTRIM continuously aligns the staff capacity with the available funding by monitoring the NUTRIM overall finances as well as the individual research portfolios of the NUTRIM PIs.

We have appointed several assistant, associate, and full professors in various departments, which guarantees the sustainability of the current research themes as well as new initiatives in line with the

NUTRIM mission, vision and objectives. Although many of them are still active within or for NUTRIM, we acknowledge that with the retirement of some top researchers, we also have to invest in their successful themes. We further note that attracting established leading scientists, in particular clinicians with research interest, can sometimes be challenging given the eccentric geographic position in the Netherlands. We feel that this is, however, largely balanced by our attractive position in the EU-region and the international profile of our university.

The instalment of various committees (*e.g.* on 'personnel and career development', 'analytical infrastructure', 'metabolic infrastructure' and 'big data analysis') and dedicated officers (*e.g*. on grant acquisition, marketing, finance, scientific integrity and open science) will guarantee actions to maintain the high quality and motivated NUTRIM staff and high-end innovative infrastructure for high quality research.

Division-specific aspects on viability are included in the divisions-specific self-assessments (part B).

7. Summary

NUTRIM School of Nutrition and Translational Research in Metabolism aims to contribute to health maintenance and personalised medicine by unravelling lifestyle and disease-induced derangements in metabolism and by developing targeted nutrition, exercise and drug interventions. We cover the whole spectrum from maintenance of a healthy lifestyle and disease prevention to disease management, with a strong focus on prevalent chronic metabolic and inflammatory disorders across the lifespan. This is facilitated by a combination of fundamental, interventional, clinical and population based translational research, a state-of-the- art infrastructure and close interactions between scientists, clinicians, PhD and master students. NUTRIM, embedded in the faculty of Health Medicine and Life Sciences, has a strong collaboration with the clinic, as part of the strategic partnership Maastricht UMC+, and with the (EU-)region, and various (inter)national academic and corporate partners.

After the previous external review (200902015), NUTRIM and Wageningen University decided not to continue as one National Graduate School VLAG. Further, in 2017, NUTRIM's 4 research lines were re-organized in 3 disease-driven divisions (1. Obesity, diabetes and cardiovascular health; 2. Liver and digestive health; 3. Respiratory and age-related health) to provide ample critical mass and optimise synergy. We also strengthened our link and alignment with the clinic and with the theme of Health Promotion, prepared an inventory on 'big data handling' and started a core group sharing expertise, and increasingly adopt tailored and personalised approaches. It is our mission to mentor scientists at various stages of their academic career, facilitated *e.g.* by Kootstra fellowships, the Tenure Track and Top Talent Program, and a dedicated grants officer and support staff. The NUTRIM PhD council and PhD coordinator took the lead to develop a new NUTRIM PhD program, including introduction days, lectures, courses and social activities. In addition to the high end Metabolic Research Unit and analytical facilities, a Clinical Research Unit was built and collaborations were strengthened with other school/institutes and within the EU-region.

The NUTRIM research portfolio is well balanced with an average funding of 10M € (2015-2020) and is in line with the funding landscape, as notified by our strategic interaction with several companies facilitating TKI-benefit and the involvement in various EU-funded project. In 2020, NUTRIM employed 190,9 fte and has ~250 PhD candidates. Of these, about 60% are external PhD candidates, merely due to the close collaboration with the hospital. Our research results in about 39 PhD-graduations each year and a CNCI of 1.7, showing that NUTRIM publications are cited 70% more often as compared to publications in the same area, over the same years and document types. In line with a pro-active policy, the number of open access publications is increasing and various databases and tools developed are used by others. That the NUTRIM community is highly appreciated can also be observed by a high number of invited lectures given and media attention, various editorship, and relevant roles in scientific, professional and societal organisations. The involvement of assistant, associate and full professor, illustrates that NUTRIM also has leading scientists at the mid-career level.

The next six years, we will continue the current strategy to maintain our leading position on Nutrition and Metabolism, amongst others by further joining forces with the clinic, other schools/institutes and in the region and will pro-actively strengthen international collaborations and strategic partnerships. The slight downward trend in PhD candidates and financial prospect warrants close attention, also given COVID-19, but we have no concrete signals to expect lower levels of funding in the upcoming period. It is important to maintain a cutting edge infrastructure, to further improve our personal and career development policy and to provide support in prestigious personnel grant and large consortia applications.

Part B

NUTRIM division-specific self-assessments over the period 2015-2020

B1. Division 1: Obesity, diabetes & cardiovascular health

Leaders: Prof. Dr. Stef Kremers & Prof. Dr. Jogchum Plat

1.1 Reaction to recommendations of the previous assessment

The research of current division 1 overlaps to some extent with prior research line 1. The 2009-2014 ERC assessment was:

- Research quality 1
- Relevance to society 1
- Viability 1

The ERC recommends the strong emphasis and excellence on physiology to be emphasized in its aims and mission.

Reaction:
With the implementation of the new division structure, our mission and objectives have been reformulated. The excellence of division 1 in understanding the physiology of lifestyle and metabolism has been strengthened and was further emphasized for example by the fact that the Metabolic Research Unit MRUM is now mentioned on the national Roadmap for large infrastructures as national expertise center for metabolic health within the Netherlands. This aligns with the current aims and ambitions of NUTRIM.

1.2 Research area

Within division 1, we try to understand how lifestyle including diet, physical activity, and novel factors like sedentary behavior, environmental temperature (cold exposure) and circadian rhythmicity, but also by applying pharmacological interventions to influence specific pathways, can improve metabolic health. To do so, we perform detailed, deep-phenotype human intervention studies and investigate the underlying mechanisms. Specific focus is on physiology of skeletal muscle, liver, (brown) adipose tissue and the peripheral and brain vasculature. The knowledge gathered in these detailed human intervention studies is applied in developing strategies that allow to make healthy choices easier, to assist people in changing their lifestyle in order to improve their quality of life and to reduce the public health impact of obesity, diabetes and cardiovascular disease. For the mechanistic studies, the group is equipped with a ”state of the art” metabolic research unit in which twenty rooms are present conforming to the latest quality standards regarding safety, climate and research infrastructure. Here, the emphasis is on the axis molecular biology - physiology- function and health. Basic research is completed by clinical collaborations, for example in the context of bariatric surgery (exploration of physiological changes associated with novel bariatric procedures), childhood obesity (COACH), and metabolism associated liver diseases. We translate this knowledge into behavior change intervention by systematically designing, implementing and evaluating health promotion interventions for various target populations, with a specific focus on children, adolescents, parents and low-socioeconomic status communities.

1.3 Staff, funding and accomplishments

End 2020, the research staff consisted of 111 persons (77,3 fte) and 55 internal PhD-candidates (see also table 2.2. Annex 2). The overall staff and number of internal PhD-candidates was rather stable over the previous years. The number of external candidates showed a pronounced increase (from 28 to 38). The staff is mainly based at the Departments of Human Biology, Health Promotion, Nutrition and Movement Sciences, Radiology, Pediatrics, Internal Medicine, and Bioinformatics, ensuring impressive complementary expertise.

Division 1 has a well-established international reputation and is considered one of the leading units in many aspects of (behavioral) nutrition and metabolism in relation to *e.g.* obesity, diabetes and cardiovascular disease prevention. The group has established many collaborations with prestigious partners within the

Netherlands and on the international scale, such as the UNESCO Chair for Education & Health, National resources for network biology (NRNB), European Reference Networks (ERNs), and the Carbohydrate Competence Center. We have attracted major funding from public (EU in particular) and private sources, with an average of 5.9M € annually (2017 11.3M €; 2018 4.9M €; 2019 3.8M €; 2020 3.5M €). The number of PhD-graduations did decrease over time, from 12.5 in 2017 to 7.3 in 2020, which warrants attention.

The scientific output in terms of publications and citation is outstanding. About 190 refereed articles are published every year, of which 18.1% are within the top 10% and 3.1% are within the top 1% most cited publications in their field based on the CNCI (*i.e.* normalized for research area, year and document type, see also table 1.2 Annex 1). The overall CNCI over the years 2017-2018 is 1.7. Key topics, e.g. obesity, brown adipose tissue and adiponectin, rank among the top 20 most frequent NUTRIM citation topics (fig. 1.3).

Examples for relevant publications with motivation

- *Circadian misalignment induces fatty acid metabolism gene profiles and compromises insulin sensitivity in human skeletal muscle. Proc Natl Acad Sci U S A, 2018: 115(30): 7789-7794. PMID 29987027*

This paper represents the complex, highly controlled human interventions studies we do in the unique NUTRIM infrastructure, including metabolic chambers and the ability for invasive and non-invasive deep metabolic phenotyping. By smartly designing the study, we managed to induce transient disruption of the biological clock to mimic *e.g.*, shift work or jet-lags. Using an array of physiological measurement (*e.g.,* energy and substrate metabolism, sleeping metabolic rate, insulin sensitivity, lipid handling and transcriptomics in muscle biopsy samples) we were able to show that the (inverted) behavioral cycle was no longer aligned with the molecular circadian clock in muscle. Transcriptome analysis revealed the human PPAR pathway as a key player in the disturbed energy metabolism upon circadian misalignment, these changes were paralleled by induction of processes known to predispose to type 2 diabetes development and increased cardiovascular risk.

- *Subcutaneous Adipose Tissue and Systemic Inflammation Are Associated With Peripheral but Not Hepatic Insulin Resistance in Humans. Diabetes, 2019; 68(12): 2247-2258. PMID: 31492661.*

This paper illustrates work within division 1 on characterization of metabolic phenotypes as a basis for personalized nutrition strategies. It is increasingly clear that 'one size does not fit all' and that a more personalized nutritional approach based on metabolic phenotypes may optimize intervention outcome. The severity of insulin resistance (IR) may vary between organs and these different IR phenotypes may respond differentially to dietary macronutrient composition. This paper illustrates that genes related to inflammation in adipose tissue as well as systemic inflammatory profile were upregulated in individuals with more pronounced muscle IR as compared to liver IR. The characterization of these distinct phenotypes towards diabetes is a first step, followed by a currently ongoing proof-of-the-concept study to show that these phenotypes respond differentially to dietary intervention

- *Effects of the KEIGAAF intervention on the BMI z-score and energy balance-related behaviors of primary school-aged children. Int J Behav Nutr Phys Act, 2020; 17 (1): 105. PMID 32807194*

This paper is exemplary for the work in the Division around the prevention of excessive weight gain in children. Based on insights from theory, evidence and bottom-up contextual input, we design intervention approaches for distinct target populations. We tend to evaluate not only on outcome (BMI change), but also on intermediary outcomes (behavior, motivation) and output (environmental change, policy change and sustained intervention implementation). We are one of the leading research groups worldwide in the area of implementation and evaluation of obesity prevention interventions in complex systems.

Relevance to Society

Understanding the etiology of metabolic disorders is of clear societal relevance. The metabolic syndrome as phenotypic exposure of overweight and obesity, is a major public health problem contributing to the steep rise in Type 2 diabetes and cardiovascular disease incidence. Besides understanding the origin and role of the underlying physiological metabolic aberrations, also the treatment and prevention of obesity and its comorbidities, particularly in the area of health promotion is one of the main research areas of the Division. Of course, this brings the data directly to society and the population. Members of the Division are involved in various committees and organizations that provide advice on the role of nutrition and exercise in the prevention and treatment of obesity and diabetes, such as the Dutch Health Council, WHO and RIVM.

Further examples, including scientific and societal impact and use are given in Annex 1 and in case studies 01-05 (Annex 3).

1.4 Strategy and viability

Strategy for the coming 6 years

The strategy is aimed at maintaining the current research expertise and focus of the division, while strengthening the possibilities for interdisciplinary collaboration within the division. We have formed PI teams, and each of the teams has appointed a PI team leader. The PI team leaders meet on a regular basis to share current developments and improve the chances to identify opportunities for collaboration. Regarding training and education of PhD students, we are exploring the re-introduction of division wide research meetings to create awareness of the full thematic research in the division. For the MRUM we are preparing a new roadmap application to keep the facilities as updated and innovative as possible. The innovations in the MRUM that we aim for are in line with trends in research, *i.e.* respiration chambers equipped to do circadian rhythm research and a metabolic ward. Moreover, division 1 finds it highly important and is therefore actively involved in trying to set up long term sustainable infrastructure plans.

Viability

Members of division 1 are leading international experts in physiology, metabolism and health promotion. The publication record is strong and the number of papers appearing in prestigious high impact journals is increasing. Significant funding has been obtained and maintained over the years. However, a drop in the number of PhD-graduates has been observed within the division. In 2020, the division had 7.3 PhD graduates, in contrast to the average of 10 per year in recent years. This trend has our continuous attention. The drop can be partly attributed to postponed defenses due to COVID limitations in 2020. An inventarisation for the first 6 months of 2021 shows already 7.5 defenses, confirming the COVID effect on the lower number of PhD graduations in this Division.
Our SWOT analysis highlights the difficulty in recruiting excellent researchers from outside the Maastricht area, a problem that is further complicated by the necessity to undertake intervention studies in Dutch speaking participants. The division can improve further by cross-departmental collaborations within the division. Furthermore, it remains challenging to establish large infrastructural initiatives. After a peak in 2017, we acknowledge a decrease in financial support by both governments and industry, but this division appears sufficiently established to compete for major sources of support and has a strong track record in public-private partnerships grants.

B2. Division 2: Liver & digestive health

Leaders: Prof. Dr. Steven Olde Damink & Prof. Dr. Ronit Sverdlov

2.1 Reaction to recommendations of the previous assessment

The research of current division 2 largely overlaps with prior research line 2. The 2009-2014 ERC assessment was:

- Research quality 2
- Relevance to society 1
- Viability 2

The ERC noted the remaining need for more high-impact papers. Furthermore, they indicated that the strategy and organisation of the prior research line 2 was not clear, and may need reconsideration and prioritisation. Finally, the strategy to translate the important topics to society could be made clearer.

Reaction:
To improve the strategy and organization, we have implemented regular monthly meetings with representative PIs from the different departments. Furthermore, PhD and young PIs from the division present their work in plenary meetings and are given the opportunity to receive funding in order to obtain preliminary data for innovative research that will connect between different departments within the division. These actions enabled us to acquire a clearer overview about the different topics, infrastructure and methodology that is used in our division and thereby to improve the internal interactions between the different departments, increase the quality and impact of our research (as indicated by an overall CNCI of 1.8) and focus on translation aspects (see also Annex 1).

2.2 Research area

Within division 2, we intend to provide novel insights into the pathophysiological processes of the gut and liver and to translate these findings to the clinic and the general population. Central disorders investigated include disorders of gut-brain interaction; intestinal and liver failure, especially related to inflammatory bowel disease, intestinal ischaemia-reperfusion, hepatic inflammation, disruption of the entero-hepatic circulation and cancer cachexia. While the main research focus lies within the gut-liver axis, the enterohepatic circulation, and the gut microbiome, a secondary research goal of this division is to extrapolate findings to related organ systems such as the cardiovascular and central nervous system, and to address the inter-organ cross talk and multidirectional interactions with lifestyle and other environmental risk factors as well as genetics. To do so, we cover the entire spectrum from mechanistic *in vitro* and *in vivo* models to deeply phenotyped patient cohort studies (*e.g.,* IBD South Limburg Cohort, Maastricht IBS Cohort, NAFLD cohort) and intervention studies. Our division moreover has several state-of-the art research infrastructures, such as a platform for microbiome analyses, patient derived organoids and related cell culture and a mass spectrometry lab that focusses on gut and liver derived metabolites.

Division 2 is internationally renowned for its clinical translational research centered around both bed-and bench site originating hypotheses. This led to several patent applications (table 1.21 Annex 1) and the coordination of multiple completed and ongoing clinical trials. The strong collaboration between clinical, translational and basic science researchers is fueled by highly attended monthly lunch symposia. Furthermore, division 2 has many collaborations with prestigious partners within the Netherlands and internationally. There is especially a strong link with university medical centers in our Euregion (*e.g.,* with the Euregional Microbiome Center and the Collaborative Research Center 1382: The Gut-Liver Axis of the Deutsche Forschungsgemeinschaft), but also strong national collaboration in clinical research, such as the Initiative on Crohn and Colitis; task force Neurogastroenterology and Motility and the NAFLD study group.

2.3 Staff, funding and accomplishments

The research staff in 2020 consisted of 55 persons (30,1 fte) including 17 Scientific Staff members at FHML and 14 at the academic hospital (4,9 and 3,5 fte, respectively), 6 post-docs (3,7 fte) and 18 internal PhD candidates (see also table 2.2 Annex 2). In addition, 70 external PhD-candidates, a large part of them being connected to the hospital, are linked to division 2. The staff is mainly based at the Depts. of Surgery, Plastic Surgery, Internal Medicine Div. Gastroenterology-Hepatology, Molecular Genetics and Medical Microbiology. Division 2 has attracted major funding from public (EU in particular) and private sources including personal and consortia grants (tables 1.8-1.10), with an average of 1.6 M€ (2017 1.9M €; 2018 1.4M €; 2019 1.8M €; 2020 1.3M €).

The scientific output in terms of publications and citation is, particularly relative to the number of staff, outstanding. About 150-200 refereed articles are published every year, of which 23.3% are within the top 10% and 3.4% are within the top 1% of most cited publications in their field based on the CNCI (*i.e*. normalized for topic, year and document type). The overall CNCI over the years 2017-2018 is 1.8. The average number of PhD-graduations is 15 per year (with lower numbers in 2018 and 2019 and an increase towards 17.3 in 2020). Key topics, such as sarcopenia, gut microbiota, rectal cancer and NAFLD, rank among the top 20 most frequent NUTRIM citation topics (figure 1.3).

Examples for relevant publications with motivation

- *Detection of localized hepatocellular amino acid kinetics by using mass spectrometry imaging of stable isotopes. Angew Chem Int Ed Engl; 2017, 12;56(25):7146-7150. PMID 28493648,*

This paper presents a novel and reproducible Mass Spectrometry Imaging method to explore the dynamic chemical changes of complex biological samples, allowing, for the first time, the detection of co-localization of hepatocellular $^{13}C_6$-Phenylalanine and amino acid kinetics. The method enabled the detection of over 60 endogenous metabolites, providing a visual map of liver function and facilitating translation of molecular kinetics to morphology for a wide variety of tissues. It allows differential kinetics between healthy and diseased tissue or altered amino acid metabolism in tumor cells and their microenvironment to be followed.

- Several new translational models using patient derived organoids (PDO) were developed.

Intestinal organoid culture model is a valuable system to study epithelial barrier function in IBD. Gut, 2018; 67(10):1905-1906: PMID 29208677 introduces a PDO model to study epithelial barrier function in IBD.
Generation and initial characterization of novel tumour organoid models to study human pancreatic cancer-induced cachexia. J Cachexia, Sarcopenia and Muscle 2020; 11(6): 1509-1524: PMID 33047901 introduces the concept of a 'living biobank' for cachexia-research by generating tumor PDO from cancer patients who are deeply phenotyped for cachexia-related parameters.
Proteomics analysis of human intestinal organoids during hypoxia and reoxygenation as a model to study ischemia-reperfusion injury. Cell Death Dis. 2021;12(1):95. PMID 33462215 introduces a PDO model to study intestinal ischemia-reperfusion injury and related it to an in-vivo human model.

- *Plasma cathepsin D activity is negatively associated with hepatic insulin sensitivity in overweight and obese humans. Diabetologia 2020 Feb;63(2):374-84. PMID 31690989*

In this paper we demonstrated the link between hepatic insulin resistance and plasma Cathepsin D (CTSD) activity. This paper led us to hypothesize that insulin is regulated by the catalytic activity of CTSD in plasma and that extracellular CTSD may be casually involved in regulation of risk factors for metabolic diseases.

- *The influence of a conjugated pneumococcal vaccination on plasma antibody levels against oxidized low-density lipoprotein in metabolic disease patients: a single-arm pilot clinical study. Antioxidants. 2021 Jan 18;10(1):129. PMID 33477615*

This paper reports the results of a single-arm pilot clinical study which examined the influence of a conjugated pneumococcal vaccination on plasma antibody levels against oxidized low-density lipoprotein in metabolic disease patients. It is an example for the translational research in division 2 as it is based on mechanisms, which we observed earlier in mice.

- *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(6):1620-1629. PMID 31075790*

This paper details about the influence of an interrupted entero-hepatic cycle on gut and liver homeostasis in patients with a short bowel function on home total parental nutrition. It presents the Model of End Stage Intestinal Failure (MESIF score) that integrated functional readouts of intestinal and hepatic metabolic processes that were collected over a 20 years period of follow-up and intense monitoring. The model predicts survival without intestinal transplantation in patients with short bowel function.

- *Efficacy and safety of peppermint oil in a randomized double-blind trial of patients with Irritable Bowel Syndrome. Gastroenterol 2020 Jan;158(1):123-136. PMID31470006*

A multicenter clinical randomized controlled trial in IBS patients led by researchers within the division, which was based on multiple previous pilot studies and translational research on the pathophysiology of IBS, which have led to a strong research hypothesis and the set-up of the trial. This trial shows the high scientific and societal impact that can be reached in field, based on thorough and dedicated basic and preclinical research.

- *Telemedicine for management of inflammatory bowel disease (myIBDcoach); a pragmatic multicenter randomized controlled trial. Lancet 2017 Sep 2;390(10098):959*-968. PMID 28716313

An innovative concept based on the implementation of telemedicine in daily clinical practice has been developed and tested in a multicenter setting in IBD patients, showing excellent results, leading to improvement of patient care, eventually reducing health care costs and potentially changing health care approaches.

- *Bile acids drive the newborn's gut microbiota maturation. Nat. Comm. 2020; 11: 3692. PMID 32703946.*

This paper is joint effort between our group at Medical Microbiology and the Microbiology Institute of RWTH Aachen and also involves other collaborators within our division (General Surgery). By combining *in vitro* and *in vivo* experiments and the use of multi-omics approaches, this paper describes the causal role of host metabolites, in particular bile acids, in the maturation of microbiome during early life.

Relevance to Society

Liver and digestive health are central in healthy conditions as well as in multiple chronic diseases. Our aim is to explore the impact of nutrition on our digestive system and the direct link between the gut and the liver to numerus metabolic disorders in order to provide a better diagnostic tool and novel interventions to prevent and treat chronic inflammatory and metabolic diseases. We focus on common diseases which are a major burden to our society (*i.e.* IBD and IBS, cancer, metabolic syndrome) as well as rare metabolic diseases which have a huge impact on an individual level (*i.e.* NPC1, familial partial lipodystrophy). The combination of basic scientists and clinician as well as our strong collaborations and state of the art approach enable us to translate our research into the society in a fast and effective manner.

Members of division 2 fulfill key roles in regional, national and international advisory boards and government organisations, such as the Dutch Society of Gastroenterology (NVGE) and the Dutch Society of Hepatology (NVH through which they are involved in set up of collaborations and new research lines. Moreover, members of the division 2 are also involved in the development of new clinical and scientific guidelines (see also table 1.19). Additionally, there are strong collaborations with patient organisations, such as the Dutch patient organisation for IBS (PDSB), IBD (Crohn & Colitis NL) and liver diseases (Leverpatiënten Vereniging). Scientists of division 2 are also involved in several foundations (*e.g.* Foundation MyIBDcoach and the Dutch Gastroenterology and Hepatology Foundation (MLDS)). Patients are involved in the formulation of research questions and study set up, trough patient focus groups, interviews and through interaction with patient organisations.

With regard to media and visibility (table 1.18), the researchers present new findings and studies through classical media, but are also involved in social media and new means of communication, through which a broader audience is reached and the division is positioned as an organisation harbouring outstanding expertise in the research in gut and liver, from basic science, through translational research to clinical studies and implementable results. The societal impact is noticeable as well, through teaching within FHML bachelor and master programs, but also in setting up or revising masters and specialisations.

Further examples, including scientific and societal impact and use are given in Annex 1 and in case studies 06-11 (Annex 3).

2.4 Strategy and viability

Strategy for the coming 6 years

In the coming six years, we aim to increase the collaborative projects between different departments within the division and to apply for a collaborative departmental research grant that will combine the complementary expertise of the different members of the department. Furthermore, we aim to further develop the collaboration with the research institutes M4I and MERLN and within the two other NUTRIM divisions by implementing internal research meetings among the junior and senior staff members.
Finally, we aim to centralize the infrastructure and to invest in big data analysis in order to build permanent European connections with partners for grants and to strengthen our existing collaboration in the region.

Viability

Division 2 is based on daily shared work between the basic scientists and the clinic and mixtures between international students from the Biomedical Science and Medicine program. The number of PhD students is highest in this division, also in relation to staff, partly as a result of the close cooperation between the clinic and external partners. Taking into account the increase in the number of external PhD students, it will be a challenge to ensure that the quality of the theses will keep the high standard. Due to the multidisciplinary and complementary expertise, the number of doctoral candidates supervised by PI's from different departments, between different research schools and joint PhDs with other Universities is also increasing.

The strong international network of staff members in division 2 are reflected by prestigious international research initiatives (*e.g*., the scientific advisory board of the International Human Microbiome Concentration and Support Action and steering board of the Million Microbiomes of Humans Project) and by organisation of conferences, commissioned reports etc. (*i.e.* the Dutch Liver Retreat (DLR) and the European Fatty Liver Conferences). The contribution of division 2 to society is also reflected by multiple collaborative grants and projects (*i.e*. Horizon 2020 YUFE Alliance, H2020 DISCoVERIE, EIT Food4Heath, Interreg and Deutsche Forschungsgemeinschaft). These projects demonstrate our position as an excellence European centre for digestive health and our shared dedication and ambition to help address today's challenges.

B3. Division 3: Respiratory & Age-related Health

Leaders: Prof. Dr. Luc van Loon and Prof. Dr. Frederik-Jan van Schooten

3.1 Reaction to recommendations of the previous assessment

The research of current division 3 overlaps to some extent with prior research lines 3 and 4. The 2009-2014 ERC assessment was:

RL3:	Research quality 1	RL 4:	Research quality 2
	Relevance to society 1		Relevance to society 2
	Viability 2		Viability 3

As part of RL3, The ERC noted that the relevance of systemic manifestations in relation to healthy ageing are less clear. Statements on societal relevance were considered to be very broad. They also noted the lack of interventions showing the potential of personalized approaches and the importance to keep focus and prevent dilution. As part of RL4, the ERC noted that this research line was very broad, of high quality, but not internationally leading, but with potentially world-leading topics. They advised to reconsider the strategic direction with a clear focus and sustainable critical mass.

Reaction:
Following the midterm evaluation division 3 has succeeded in defining the core beliefs and research themes of the division and is now working to further increase interaction between research leaders within the division. The present focus on lung and musculoskeletal tissue, and its degeneration from endogenous and exogenous factors, and aging, is a common ground that covers most of the research. The degenerative processes in these tissues go further than just local as they have pronounced systemic effects.

3.2 Research area

Researchers from Respiratory medicine, Internal medicine, Toxicology, Human biology, Nutrition and movement sciences and Complex genetics join forces in division 3, coined around Respiratory & Age Related Health. In this division, we share a great interest in human physiology and how this knowledge can be applied to develop effective strategies to add life to our years instead of years to our lives. The capacity to perform fundamental research in a clinical setting expands the barriers for human metabolic research and allows direct translation to the patient population, lowering both morbidity and mortality.
This division studies the aging process and related metabolic and functional impairments hampering recovery from acute or chronic disease. The division specifically focuses on respiratory diseases such as COPD and lung cancer that become more prevalent with an advancing age due to changes in lifestyle (*e.g.* smoking, physical inactivity or malnutrition) or the environment interacting with our genetic background. Comparative research between different chronic diseases such as COPD and chronic kidney disease provides new insights in mechanisms of accelerated aging. Healthy aging is within our capacity and in this division we aim to increase our understanding of the human aging process (from *in utero* to old age).
Part of the research is etiological with the aim to understand the onset of disease with age and to identify those people with an enhanced risk for disease and hospitalization. The translational research in this division is performed from bench to bedside, ranging from the study of *in vitro* cell and animal models to clinical intervention studies with hospitalized patients, in a rehabilitation setting or with older aged people in the community. Translating insights from muscle biology to personalized nutrition and exercise interventions is used to reverse or slow down the aging process and increase health and well-being, in all disease phases. Early development of chronic metabolic disorders can be prevented by more active, healthy living.

3.3 Staff, funding and accomplishments

End 2020, the research staff of division 3 consisted of 68 persons (38,3 fte) and 27 internal PhD-candidates (see also table 2.2 Annex 2). The overall staff and number of internal PhD-candidates showed a small decrease over time. The number of external candidates showed a pronounced increase (from 38 to 49). The

staff is mainly based at the Departments of Human Biology, Respiratory Medicine, Nutrition and Movement Sciences, Toxicology, and Internal Medicine.

Division 3 has well-established international leading researchers in the field of COPD, chronic kidney disease, healthy aging, biomechanics and breathomics. The groups have established many collaborations with prestigious partners within the Netherlands and on the international scale. Examples are collaborations within consortia as the Bladder cancer Epidemiology and Nutritional Determinants study (BLEND), and taskforces within the International Association Breath Research (IABR), The European Respiratory Society (ERS), Netherlands Respiratory Society (NRS) and the European College of Sports Science (ECSS). They have attracted major funding from public (the EU in particular) and private (about half of its funding) sources, with an average of 3.0 M€ annually (2017 4.1 M€; 2018 1.1 M€; 2019 2.8 M€; 2020 3.9 M€). The number of PhD-graduates has shown a decrease over time, from 16.2 in 2017 to 11.5 in 2020 (table 2.5 Annex 2).

The scientific output in terms of publications and citation is outstanding. About 230 refereed articles are published every year, of which 18.0% are within the top 10% and 1.8% are within the top 1% most cited publications in their field based on the CNCI (table 1.2 Annex 1). The overall CNCI over the years 2017-2018 is 1.5. Key topics, such as COPD, sarcopenia and physical activity, rank among the top 20 most frequent NUTRIM citation topics (figure 1.3).

Examples for relevant publications with motivation

- *Cachexia in chronic obstructive pulmonary disease: new insights and therapeutic perspective. J Cach. Sarc. Muscle 2016 7(1):5-22. PMID: 27066314*

This review discusses the implications of new molecular insights for personalizing the clinical management of COPD-induced cachexia. It shows how the mechanistic work carried out in our division on the disrupted energy balance as a driver of cachexia can lead to improvements in COPD patient care.

- *A European Respiratory Society technical standard: exhaled biomarkers in lung disease. Eur. Resp. J.2017 49: 1600965; PMID 28446552*

In this paper a Task Force from clinicians and researchers with expertise in exhaled biomarkers describe their consensus on standardization of breath sampling, analyzing and reporting of data. Further, suggestions are given for research to cover gaps in knowledge and how to overcome hurdles for implementation of breath biomarkers in the clinic practice. This paper illustrates our active involvement in international consortia to facilitate translational breath research.

- *Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med. 2017 43: 380-398. PMID 28168570.*

This paper presents the results of the European Society of Intensive Care Medicine (ESICM) Working Group on Gastrointestinal Function to provide evidence-based guidelines for early enteral nutrition (EEN) during critical illness. It is an example for the translational research in division 3 with clinical impact in the ICU.

- *IOC Consensus Statement: Dietary Supplements and the High-Performance Athlete. Int J Sport Nutr Exerc Metab. 2018 28 (2);* 104-125. PMID 29589768

This review summarizes the issues faced by high-performance athletes and their support team (coach, trainer, nutritionist, physician) when considering the use of supplements, with the goal of providing information to assist them to make informed decisions. It is obvious that protection of the athlete's health and awareness of potential health risks are paramount before embarking on supplement use. This contribution shows the high scientific and societal impact that can be reached in the sports field, based on the basic research performed in our division.

- *Protein content and amino acid composition of commercially available plant-based protein isolates. Amino Acids. 2018 50: 1685-1695. PMID 30167963.*

This paper provides information on the quality of plant-based and animal-based proteins and their subsequent properties to stimulate skeletal muscle protein synthesis. This basic research provides the basis for the identification of plant-based proteins with a high anabolic potential and for defining new plant-based protein blends that provide a complete spectrum of essential amino acids similar to most animal-based protein sources.

- *Cigarette Filter Ventilation and Smoking Protocol Influence Aldehyde Smoke Yields. Chem Res Toxicol. 2018: 31: 462-471. PMID 29727173.*

This paper shows that smoking strong ventilated cigarettes ("light" cigarettes) leads to increased exposure to toxic substances compared to regular cigarettes. This has attracted a lot of media attention, initiated the Public Prosecution Service to consider a lawsuit against the tobacco industry, and prompted actions by the Ministry of Health, Welfare and Sport towards the EU to work more intensively on new regulations. This illustrates that our collaborations with the Food and Consumer Product Safety Authority (NVWA) and the National Institute for Public Health and the Environment (RIVM) has high scientific and social impact.

- *Diet and Fighting Bladder Cancer 1st Edition. Author: Maurice Zeegers. eBook ISBN: 9780128146781.*

In this book "Diet and Fighting Bladder Cancer" (link) the definitive results on the relationship between bladder cancer and dietary factors are presented. These results are obtained in a WCRF funded project from a world-wide consortium on bladder cancer epidemiology studies covering over half a million participants. This contribution shows the impact of our research in the arena of disease prevention and public health.

- *Impact of fluid status and inflammation and their interaction on survival: a study in an international hemodialysis patient cohort. Kidney Int. 2017 May;91(5):1214-122. PMID 28209335*

In this paper we show that, in a large cohort of patients on hemodialysis, next to inflammation, even mild disturbances in fluid status are related to an increased mortality. This paper is based on an international collaboration (MONDO consortium, including over 100.000 dialysis patients), in which MUMC+ has an important role. This paper also has relevance for other chronic diseases in which a combination of inflammation and fluid overload, albeit less pronounced, are also observed.

3.4 Strategy and viability

Relevance to Society

The translation of basic research towards clinical relevance provides insight in the identification of those at risk of developing chronic diseases, allowing early diagnosis, and better treatment strategies. The research within the division aims to bridge the gaps between academia and medicine, thereby providing enormous valorization potential. The chronic diseases studied represent a rapidly increasing financial and societal burden, underlying the societal impact of the research topics that are addressed. Studying the increased risks for disease due to changes in our modern lifestyle and living environment generates leads to more effectively prevent disease and to support healthy aging. In the local Maastricht region the quality of the living environment is under pressure because of demographic changes (aging population), poor lifestyle (unhealthy food choices) and pollution (poor air quality). The increased incidence of COPD and IBD in our province further underlines the relevance to understand the link between environment, lifestyle, health, and disease.
Members of division 3 are involved in the numerous national and international committees and organizations that consult on the role of environment, nutrition, physical activity, and exercise in the prevention and treatment of chronic diseases to support more active, healthy aging.

Further examples, including scientific and societal impact and use are given in Annex 1 and in case studies number 05 and 11-14 (Annex 3).

Strategy for the coming 6 years

The decline in the number of PhD students is a matter of concern. In part this is related to the fact that the Dutch Top Institute Food and Nutrition ended. Another explanation is the financial and mental effort that must be made to acquire and subsequently supervise PhD students, together with the high teaching load (at least 50% of the time). We will explore the possibilities to spread these responsibilities more equally over staff members and use the full Divisions capacity. Another aspect is that for various reasons some successful researchers choose to hire postdocs instead of PhD students on their grants.
To promote collaborations, 4 start-up grants (40k €) were awarded to young scientists to bridge research between groups while obtaining pilot results for future funding. Collaborations and the focus in research is discussed during division meetings and is anticipated to deliver synergy in coming 6 years. We will organize 4 division meetings per year with the main aim to stimulate intra-division collaborations
After an inventory of the available Mass Spec technology within NUTRIM, plans are in progress to achieve quick wins and to use mutual MS tools and expertise from other RLs and M4I. At faculty and MUMC+ level, a more long-term strategy for purchasing expensive equipment needs to be made.

Viability

Division 3 houses research groups with an established international reputation and is considered one of the leading units in many aspects of lifestyle, disease and healthy aging, and the groups have a wide network of academic and industrial partners, both national and international. Productivity in terms of Wi-1 publications with scientific, clinical and societal impact is high with a CNCI of 1.5 meaning that papers are 50% more cited compared with expected citation rates for papers in the same field with the same document type, year of publication. The research groups within the division have secured significant funding from public, private and hybrid sources. Although the research contracts from external organizations, such as industry, governmental ministries, EU and charitable organizations is relatively high (55-70% of total funding; Table 2.4), at present the funding obtained in national scientific competition is relatively low (6-12%). To continuously compete for these fundings in the larger initiatives, collaborations between divisions and beyond will be sought and strengthened. Our position is strong when we look at the themes of lifestyle and healthy aging in the national and EU research agendas. At the moment, there are enough young and middle career scientists present within the division to fill positions of seniors who will retire in the coming years. It is a constant challenge for staff to find the right balance between teaching and research tasks, and the upcoming initiative of *recognition and reward* will be helpful in this regard.

Annex 1: Factual Evidence (at graduate school and division level)

Research quality: tables

Table 1.1: NUTRIM publications at school and division level

	2015	2016	2017	2018	2019	2020
Wi-1 publications (SCI/SCCI)						
Division 1*			189	180	190	198
Division 2*			179	153	194	183
Division 3*			230	238	242	230
NUTRIM	529	547	561	535	563	548
Other output**						
Division 1*			98	87	92	113
Division 2*			93	95	93	70
Division 3*			123	107	150	119
NUTRIM	97	235	303	273	314	284

**) Based on the new division structure implemented 2017.*

***) including e.g. doctoral thesis, (Wi-1) editorials, letter to the editor, Wi-2 publications, book contributions, reports, etc.*

Notes: Publications can be part of more than one division. Therefore, the sum of the divisions is not equal to NUTRIM total
The research output for 2020 is subject to change as the official values are set by the board of FHML in June 2021. The current values are based on the publications available in the PURE database on April 21, 2021.

Table 1.2: Number of publications (2017-2018)[1] and citation impact based on CNCI[2] for division 1-3

	NUTRIM		Division 1		Division 2		Division 3	
	Number	%	Number	%	Number	%	Number	%
Total publications in PURE	1434		483		435		603	
Total publications in PURE & InCites (articles +reviews)2	1159	100	387	100	352	100	494	100
Top 1%	30	2.6	12	3.1	12	3.4	9	1.8
Top 10%	223	19.2	70	18.1	82	23.3	89	18.0
Top 25%	466	40.2	152	39.3	155	44.0	193	39.1
CNCI	1.7		1.7		1.8		1.5	

General note: the sum of the division output is higher than the total NUTRIM output because of joint publications between divisions

1) *Publications originating from 2019 and 2020 are excluded form citation impact analyses, because normalized citation impact data is most reliable 24 months after publication. 2015-2016 are not included because of the new division structure implemented in 2017.*
2) *CNCI (category normalised citation index) analysis is performed on the PURE articles and reviews that are covered in InCites. InCites does not track raw citation counts but uses the citation counts of the Web of Science to calculate the so-called normalised citation indicators that can be used to evaluate research output. The normalised indicators taken into account that: citation frequencies differ per discipline; older publications have more citations; and that document types differ in citation frequency (e.g. reviews get more citations compared to primary research articles). This normalization makes is possible to compare the citation impact of a document set to other document sets, to the world average(s) of InCites 'complete dataset, or to those of universities and countries.*

Table 1.3: Overview of representative examples of top 1%* publications regarding citation impact and compared to publications of the same age, document type and subject area for each division** in the period 2017-2018

Title, authors***, journal	CNCI	Times Cites
Division 1		
Radiomics: the bridge between medical imaging and personalized medicine. F.M. Mottaghy, J.E. Wildberger, Nature Reviews Clinical Oncology	27.17	617

WikiPathways: a multifaceted pathway database bridging metabolomics to other omics research. S.L. Coort, F. Ehrhart, C.T. Evelo, E.L. Willighagen, Nucleic Acids Research	18.73	175
Improvement of Insulin Sensitivity after Lean Donor Feces in Metabolic Syndrome Is Driven by Baseline Intestinal Microbiota Composition. E.E. Blaak, F.G. Schaap, S.W.M. Olde Damink, Cell Metabolism	15.34	207
Cold-Induced Thermogenesis Depends on ATGL-Mediated Lipolysis in Cardiac Muscle, but Not Brown Adipose Tissue. J. Hoeks, P. Schrauwen, Cell Metabolism	7.64	103
Protein content and amino acid composition of commercially available plant-based protein isolates. L.B. Verdijk, L.J.C. van Loon, Amino Acids	7.39	69
Division 2		
Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicenter randomized trial. C. Dejong, The Lancet	16.93	147
Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicenter cohort study. J. Penders, The Lancet	14.91	149
Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast. R.R.W.J. van der Hulst, JAMA Oncology	12.49	119
Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. M. Pierik, Gastroenterology	9.56	83
Low skeletal muscle radiation attenuation and visceral adiposity are associated with overall survival and surgical site infections in patients with pancreatic cancer. C.H.C. Dejong, S.W.M. Olde Damink, S.S. Rensen, R.M. van Dam, Journal of Cachexia, Sarcopenia and Muscle	7.46	76
Division 3		
IOC consensus statement: dietary supplements and the high-performance Athlete. L.J.C. van Loon, British Journal of Sports Medicine	21.49	113
A European Respiratory Society technical standard: exhaled biomarkers in lung disease. A.W. Boots, F.J. van Schooten, European Respiratory Journal.	18.13	200
Early enteral nutrition in critically ill patients: ESICM clinical practice Guidelines. M. Poeze, Intensive Care Medicine.	13.72	186
DNA methylation in childhood asthma: an epigenome-wide meta-analysis, L. Chatzi, The Lancet.	9.21	69
Protein content and amino acid composition of commercially available plant-based protein isolates. S.H.M. Gorissen, J.M.G. Senden, J.J.R. Crombag, L.B. Verdijk, .L.J.C. van Loon, Amino Acids	7.39	69

Maximum 5 publications are shown per division
**) based on the CNCI: category normalised citation index (i.e. normalised for of publications in the same areas, over the same years and document types)*
***) The publication is shown for the division of the first author in case of co-authors from two divisions*
****) Only key authors with NUTRIM labelling are shown*

Table 1.4: Representative examples of invited lectures given by NUTRIM staff (2015-2020, per division)

Scientist	Title lecture	Meeting
Division 1		
Goossens G. (Assoc. Prof.)	Pathophysiology of obesity-related insulin resistance: Is adipose tissue to blame?	2020, European Association for the Study of Obesity (EASO), New Investigators United Winter School.
Oenema A. (Assoc. Prof.)	Food4Thought. 'Wat weten we over de relatie tussen voeding en psychische gezondheid?'	2020, Orthica digital symposium. Amsterdam, NL
Gubbels J. (Assist. Prof).	'De invloed van de kinderopvang op het eten en bewegen van kinderen'	2019, Preschool@healthyweight symposium. Amsterdam, NL
Joris P. (Assist. Prof.)	Update on health effects of different dietary saturated fatty acids	2019, European Nutrition Conference (FENS). Dublin, Ireland

Meertens R. (Assoc. Prof.)	'Slapen en de volksgezondheid'	2019, Health Council of the Netherlands. Den Haag, NL
Schrauwen P. (Prof.)	Human Skeletal Muscle Mitochondrial function and Insulin Sensitivity	2019, Keystone Symposium on Mitochondrial Biology in Heart and Skeletal Muscle. Keystone, Colorado, USA
Hesselink M. (Prof.)	Day-night rhythm in mitochondrial network morphology in human skeletal muscle.	2019, Keystone Symposium on Mitochondrial Biology in Heart and Skeletal muscle. Keystone, Colorado, USA
Bongers B. (Assist. Prof.)	"Pre- and postoperative outcomes of physical functioning"	2018, Prehabilitation World Conference 2018. Eindhoven, NL
Meex R. (Assist. Prof.)	Hepatokines in insulin resistance	2018, EASO New Investigators United autumn course. Mallorca, Spain
Savelberg H. (Prof.)	To exercise or not to sit	2018, Attitude Prevention, Federation de l'Assurance. Paris, France
Mensink R. (Prof.)	Saturated fat: harmful or harmless?	2017, 39th ESPEN Congress on Clinical Nutrition and Metabolism. The Hague, NL
Summer-Kutmon M. (Assist. Prof.)	From pathways to networks - WikiPathways and Cytoscape	2017, Network analysis seminar Pasteur Institute. Lille, France
Venema K. (Prof.)	Journal of Applied Microbiology Lecture: Probiotics and the gut microbiota	2017, SfAM Annual Conference 2017. Gateshead, UK
Willighagen E. (Assist. Prof)	Making open science a reality, from a researcher perspective	2017, AgreenSkills+ Annual Meeting. Paris, France
Canfora E. (Assist. Prof.)	Short-chain fatty acids affect intracellular lipolysis in a human adipocyte model	2016, European Congress on Obesity. Gothenburg, Sweden
Plat. J. (Prof.)	Plant sterols and stanols: novel dietary modulators of immune function in asthma patients	2016, 3st International Conference on Food Bioactives and Health. Norwich, UK
Blaak E. (Prof.)	Targeting fat metabolism by diet to improve metabolic health in adults	2015, 12th European Nutrition Conference (FENS). Berlin
Coort S. (Assoc. Prof.)	"The Science of Big-Data Analytics and Visualization"	2015,eScience Meeting on the Science of Bid Data Analytics and Visualization, Utrecht, NL
Division 2		
Dejong C. (Prof.)	Surgical treatment of non-colorectal liver metastasis	2018. AUGIS Meeting, Edinburgh, UK
Pierik M. (Assoc. Prof.)	How to implement a digital clinic	2020, ECCO annual conference. Copenhagen , Denmark
Rensen S. (Assoc. Prof.)	Pancreatic tumor organoids to study cancer cachexia	2020 Alpine Liver and Pancreatic Surgery Meeting. Madonna di Campiglio, Italy
Penders J. (Assoc. Prof.)	Does our microbiome travel well	2019, International Human Microbiome Congress. Istanbul, Turkey
Houben T. (Assist. Prof.)	Lysosomes and hepatic inflammation: a key role the lysosomal enzyme cathepsin D?	2018, 8th joint diabetes and metabolism research symposium. Maastricht, NL
Keszthelyi D. (Assist. Prof.)	State-of-the-arts lecture: Clinical trials in functional lower GI disorders	2017, UEG Week. Barcelona, Spain
Jonkers D. (Prof.)	Diet, microbiota and GI function	2016, UEGW. Vienna
Lenaerts K. (Assoc. Prof.)	Intestinal Ischemia Reperfusion Injury	2016, 3rd International Meeting on Ischemia Reperfusion Injury in transplantation (IMIRT2016). Poitiers, Fr.
Olde Damink S. (Prof.)	The role of cancer cachexia in outcome of patients with pancreatic cancer	2019, International Forum of Pancreatic-Biliary Surgery, Wuhan, China
Schaap F. (Assist. Prof.)	Bile salts and intestinal failure	2016, 38th ESPEN Congress on Clinical Nutrition & Metabolism. Copenhagen, Denmark
Shiri-Sverdlov R. (Prof.)	Lysosomal lipid accumulation and non-alcoholic steatohepatitis	2015, European Association for the Study of the Liver Conference 2015. Vienna, Austria

Division 3		
Franssen F. (Assoc. Prof.)	The importance of keeping the patient active: Reducing risk and improving	2020, ERS annual conference, Vienna, Austria
McCrum C. (Assist. Prof.)	A Trip to Remember: Assessing and Improving Walking Stability in Older Adults	2020, VvBN Annual Conference. Online
Kooman J. (Prof.)	Physical activity and malnutrition in dialysis	2019, Oxford University- Ghent Summer School. Oxford
Langen R. (Assoc. Prof.)	Sarcopenia in COPD and its therapy	2019, Society on Cachexia and Wasting Disorders Annual International Conference. Berlin, Germany
Loon, van L. (Prof.)	Nutritional strategies to compensate for the anabolic resistance of aging	2019, EuGMS. Krakow
Meijer K. (Assoc. Prof.)	Innovations with CAREN	2019, ESMAC congress. Prague 24-9-2018
Poeze. M. (Prof.)	From fracture to recovery, setting the stage in the geriatric fracture epidemic	2019, From fracture to recovery, setting the stage in the geriatric fracture epidemic. Krakow, PL
Remels A. (Assist. Prof.)	Mitochondrial dysfunction in COPD: Role for aldehydes	2019, Environmental Protection Agency (EPA): Invited talk. EPA: Durham (NC) USA
Smolinska A. (Assist. Prof.)	Use and abuse of data analysis	Breathomics 2019. Manchester, UK
Spruit M. (Prof.)	Changes in physical activity and mortality in severe chronic lung disease	2019, AIPO congress. Firenze, Italy
Schooten, van F. (Prof.)	Volatile metabolites in breath as markers of health and disease	2018, 46th European Environmental Mutagenesis and Genomics Society (EMGS). Potsdam, Germany
Plasqui G. (Assist. Prof.)	Man and machine variability in calorimetric studies	2017, RACMEM conference. Fribourg, Switzerland
Schols A. (Prof.)	Metabolic and nutritional aspects in relation to disease development in chronic lung diseases	2017, The Lancet summit: COPD and lung cancer. Perth, Australia
Snijders T. (Assist. Prof.)	Protein nutrition: comparing plant and animal based proteins for a better health	2017, Bridge2Food 10th Protein summit. Reims, France
Gosker H. (Assoc. Prof.)	Molecular mechanisms of loss of skeletal muscle oxidative metabolism in COPD	2016, Symposium 'Targeting Skeletal Muscle Oxidative Metabolism to Treat Human Disease'. London, UK
Langie S. (Assist. Prof.)	A child's spit epigenome can reveal its respiratory allergy risk	2016, 45th European Environmental Mutagenesis and Genomics Society (EEMGS) meeting. in Copenhagen, August 2016
Verdijk L. (Assoc. Prof.)	Protein synthesis and regulation of muscle mass and function	2016, Annual Meeting of the Scandinavian Physiological Society. Oslo, Norway
Blokhuis, T. (Assoc. Prof.)	The Diamond Concept: cost-effective or expensive like diamonds?	2015, Annual European Society for Trauma and Emergency Surgery. Amsterdam, NL

Maximum one example is shown per associate, assistant or full professor

Table 1.5 Representative examples of journal editorships in the period 2015-2020

Scientist (div)	Role	Journal
Division 1		
Adam J. (Assoc. Prof.)	Associate editor Editorial board	Journal of Cognition Human Movement Sciences
Adam T. (Assoc. Prof.)	Section Editor Editorial board	Physiology & Behavior Nutrients
Blaak E. (Prof.)	Guest editor Associate Editor Chief Editor Special Issue	Special issue Biomedicines Journal of Clinical Endocrinology and Metabolism Frontiers in Nutrition specialty Nutrition and Metabolism
Coort S. (Assist. Prof.)	Editorial Board	Genes

Evelo C. (Prof.)	Editorial Board	Genes & Nutrition
Goossens G. (Assoc. Prof.)	Editorial Board	European Medical Journal Diabetes International Journal of Diabetes
Gubbels J. (Assist. Prof.)	Guest editor Associate Editor Associate Editor	Nutrients BMC Obesity BMC Public Health
Jocken J. (Assist. Prof.)	Editorial Board	International Journal of Obesity
Joris P. (Assist. Prof.)	Editorial Advisory Committee	Voeding NU
McCrum C. (Assist. Prof.)	Associate editor Editorial Board	Journal of Applied Biomechanics European Review of Aging and Physical Activity
Meex R. (Assist. Prof.)	Editoral board	Biomed Research International
Mensink R. (Prof.)	Editorial board	Nutrients
Plat J (Prof.)	Editor Guest editor	Nutrients Atherosclerosis
Schrauwen P. (Prof.)	Associate Editor Associate Editor Associate Editor Editorial board Editorial board	Molecular metabolism Obesity Diabetologia Scientific Reports Nutrition and Diabetes
Venema K (Prof.)	Editor Chief Editor Editor	Journal of Applied Microbiology Beneficial Microbes Probiotics and Antimicrobial Proteins
Vries de N. (Prof.)	Editorial board	Psychology and Health
Willighagen E. (Assist. Prof.)	Editor-in-Chief	Journal of Cheminformatics
Division 2		
Keszthelyi D. (Assist. Prof.)	Editorial board	Neuro-Gastroenterology and Motility
Penders J. (Assoc. Prof.)	Associate Editor	BMC Infectious Diseases
Dejong, C. (Prof.)	Editor Associate Editor Editoral board	British Journal of Surgery Nederlands Leerboek Chirurgie HBP, Clinical Nutrition, World Journal of Surgery
Schaap F. (Assist. Prof.)	Editorial board	Journal Clinical and Translational Research World Journal of Hepatology
Sverdlov R. (Prof.)	Editorial Advisory Board Editor Co-editor Editorial board	BioMolecular Concepts Biomedicines LEVER magazine Journal of Gastroenterological Sciences
Division 3		
Blokhuis T. (Assoc. Prof.)	Associate Editor Editor	European Journal of medical research Dutch Journal of Trauma Surgery
Boots A. (Assist. Prof.)	Guest Editor	Antioxidants special issue Redox balance in IPF
Franssen F. (Assoc. Prof.)	Deputy Editor/Associate editor Editorial Board Editorial Board	Respirology Breathe Pulmonology
Haenen G. (Prof.)	Editor in Chief	International journal of Molecular Sciences, Molecular Toxicology
Kooman J. (Prof.)	Editorial board Editorial board Editorial board	American Journal of Physiology International Nephrology Urology European Dialysis Transplant Associations

Langen R. (Assoc. Prof.)	Co-editor	Journal of Cachexia, Sarcopenia and Muscle Wasting – Rapid Communications
Langie S. (Assist. Prof.)	Guest Editor Editorial board	Toxicology Letters Mutagenesis
Loon van L. (Prof.)	Associate Editor Section Editor Associate Editor	European Journal of Sports Science Amino Acids Int. J. of Sport Nutrition and Exercise Metabolism
Meijer K. (Assoc. Prof.)	Section Editor Editorial board	Human Movement Sciences PlosOne
Plasqui G. (Assist. Prof.)	Editorial board	Sensors
Poeze M. (Prof.)	Editor Associate Editor	Dutch Journal of Trauma Surgery Trauma
Schols A. (Prof.)	Section Editor Associate Editor Associate Editor Associate Editor	Current Opinion of Clinical Nutrition and Metabolic care Journal of Applied Physiology Journal of Cachexia, Sarcopenia and Muscle Journal of COPD Frontier in Nutrition
Schooten van FJ (Prof.)	Editorial board Associate Editor Editorial board Associate Editor	Journal of Breath Research Toxicology Research Mutation Research Reviews Chemosphere
Smolinska A. (Assist. Prof.)	Editorial board Editorial board Associate Editor	Journal of Breath Research Scientific Reports Analytical Science Advances
Snijders T. (Assist. Prof.)	Associate Editor	Applied Physiology in Nutrition and Metabolism
Spruit M. (Prof.)	Associate Editor Associate Editor Associate Editor	Breath ERJ Open Research Chronic Respiratory Disease
Zeegers M. (Prof.)	Chief Editor Chief Editor	Diet and Fighting bladder cancer Leerboek Epidemiology

Table 1.6: Examples of scientific prizes awarded, ranked by year (2015-2020)

Scientist (division)*	Year	Awarded by
Dr. J. Jocken (div 1)	2015	European Association for the Study of Obesity (EASO); Young Investigators Award
Prof. P. Schrauwen (div 1)	2015	European Association for the study of Diabetes (EASD): 51st Minkowski Award of the EASD
Dr. C. McCrum (div 3)	2016	European Group for Research into elderly and Physical Activity; Young Researcher Award
Dr. J. Penders (div 2)	2016	European Society of Clinical Immunology and Infectious Diseases; ESCMID Research Grant Awardee
Prof. A. Schols (div 3)	2015	European Respiratory Society (ERS); First Gold Medal in COPD
Dr. A. Smolinska (div 3)	2016	Metabolomics Society Conference: Young Researchers Metabolomics Award
Prof. K. Venema (div 1)	2017	Society for Applied Microbiology; sFAM award
Dr. T. Houben (div 2)	2017	Brightlands Science Forum; Inventor NPC1 patent
Prof. R. Sverdlov (div 2)	2017	Brightlands Science Forum; Inventor NASH patent

Prof. L. van Loon (div 3)	2018	New England ACS<; Howard Knuttgen lecture award
Dr. L. Verdijk (div 3)	2018	European College of Sports Science; Young Investigator Award
Drs. R. Vaes (div 2)	2019	Society on Sarcopenia, cachexia and Wasting Disorders; Young Investigators award
Prof. M. Spruit (div 3)	2019	American Association of Cardiovascular and Pulmonary Rehabilitation; Thomas L. Petty Distinguished Pulmonary Scholar Award
Dr. E. Canfora (div 1)	2019	European Association for the Study of Obesity (EASO); Rising Star Award
Dr. M. Pierik (div 2)	2019	Federatie Medische Specialisten; FMS science and innovation prize

*****_Maximum one scientific award per scientist is presented. Prizes for thesis and best abstracts are not included_

Table 1.7: Overall overview of projects awarded (2015-2020, arranged by project type)

	2015		2016		2017		2018		2019		2020		Total	
	#	Value (in k€)	#	Value (in k€)	#	Value (in k€)	#	Value (in k€)	#	Value (in k€)	#	Value (in k€)	#	Value (in k€)
NWO / ZonMW														
NWO			2	500	2	500					1	725	**5**	**1.725**
NWO ASPASIA	2	400							1	200			**3**	**600**
NWO CCC			1	261	1	250							**2**	**511**
NWO VENI			1	250									**1**	**250**
ZonMW	4	1.284	6	2.377	4	1.684	12	2.714	6	1.264	6	2.002	**38**	**11.325**
International non-profit														
EU	2	228	1	224	2	1.766	6	2.041	2	708	3	896	**16**	**5.863**
Eurostars			1	299	1	246			1	245	3	637	**6**	**1.427**
INTERREG					1	323	1	69	1	545			**3**	**937**
EIT									1	114			**1**	**114**
EJP Rare							1	625					**1**	**625**
Top institutes														
TIFN	1	594	4	2.357	1	1.526							**6**	**4.477**
TKI Health Holland			1	909	5	2.111	1	434	5	1.010	4	1.032	**16**	**5.496**
TKI Agri&Food					1	1.267					2	1.027	**3**	**2.294**
TKI UE					1	42	1	306					**2**	**348**
National non-profit														
CVON	1	1.771			1	348	1	50					**3**	**2.169**
DFN	2	275	2	600			2	411	1	275			**7**	**1.561**
EFSD	1	100			1	100	1	66	2	275			**5**	**541**
KWF							1	75					**1**	**75**
Longfonds					2	918					2	66	**4**	**984**
MLDS			1	250	1	250	2	266	1	150			**5**	**916**
NVWA	1	207							1	239			**2**	**446**
RIVM											1	94	**1**	**94**
RVO									1	201			**1**	**201**
Profit organisations														
AstraZeneca					1	1.500	1	454					**2**	**1.954**
Danone/Nutricia	1	50	1	357	3	919							**5**	**1.326**
InSiTe											1	727	**1**	**727**
MedImmune									1	496			**1**	**496**
Tessenderlo Group NV											1	520	**1**	**520**
Unilever	2	446	1	63									**3**	**509**
Other														
Other	12	1.291	19	3.186	12	1.934	7	1.448	12	2.688	9	1.013	**71**	**11.560**
Total	**29**	**6.646**	**41**	**11.633**	**40**	**15.684**	**37**	**8.959**	**36**	**8.410**	**33**	**8.739**	**216**	**60.071**

Table 1.8: Overview of European projects awarded, ranked by year (2015-2020)

Short description of project	Project leader (division)	Year	Project value NUTRIM (in k€)
TKI HHT ECSEl Moore4Medical	MCG van de Poll (div 2)	2020	121
H2020 / Discoverie	DMAE Jonkers (div 2)	2020	316
EIT Olde Damink	SWM Olde Damink (div 2)	2019	114
H2020 / SbD4Nano	EL Willighagen (div 1)	2019	343
H2020/ FNS Cloud	CTA Evelo (div 1)	2019	365
EJP rare diseases	CTA Evelo (div 1)	2018	625
H2020 / RiskGONE	EL Willighagen (div 1)	2018	221
EUToxRisk	CTA Evelo (div 1)	2018	257
H2020 / Fairplus	CTA Evelo (div 1)	2018	258
H2020 Nanocommons	EL Willighagen (div 1)	2018	299

H2020 / NanoSolvelT	EL Willighagen (div 1)	2018	407
H2020 / Sweet	EE Blaak (div 1)	2018	599
EU MC IF LiSDMA	RCR Meex (div 1)	2017	166
H2020 ERC Starting Grant	VB Schrauwen-Hinderling (div 1)	2017	1.600
H2020 / Mobistyle	WD van Marken Lichtenbelt (div 1)	2016	224
ELISIR – Excelerte	CTA Evelo (div 1)	2016	132
EU FP7 IBD-BIOM	MJ Pierik (div 2)	2015	51
H2020-JTC ABC Cancer	FJ van Schooten (div 3)	2016	977
EUMC IIF 2015 Churchward-Venne	LJC van Loon (div 3)	2015	178

Table 1.9: Overview of prestigious personal grants, ranked by year (2015-2020)

Prestigious personal grants NUTRIM 2015 - 2020				
Division	**Year**	**Name**	**Department**	**Grant**
2 - Liver & Digestive Health	2015	J. Penders	Medical Microbiology	ZonMW VIDI
3 - Respiratory & Age-related Health	2015	L. Blanchet	Pharmacology & Toxicology	ERC Starting Grant
1 - Obesity, Diabetes & Cardiovascular Health	2015	P. Schrauwen	Nutrition and Movement Sciences	KNAW van Leersum beurs
1 - Obesity, Diabetes & Cardiovascular Health	2015	T. Adam	Nutrition and Movement Sciences	NWO Aspasia
2 - Liver & Digestive Health	2015	K. Lenaerts	General Surgery	NWO Aspasia
3 - Respiratory & Age-related Health	2015	N. Ubags	Respiratory Medicine	Kootstra (PD)
1 - Obesity, Diabetes & Cardiovascular Health	2015	E. Canfora	Human Biology	Kootstra (PD)
2 - Liver & Digestive Health	2015	M. Uittenboogaart	General Surgery	Kootstra (PhD)
3 - Respiratory & Age-related Health	2016	A. Smolinska	Pharmacology & Toxicology	VENI
1 - Obesity, Diabetes & Cardiovascular Health	2016	V. Schrauwen - Hinderling	Nutrition and Movement Sciences	ERC Starting Grant
1 - Obesity, Diabetes & Cardiovascular Health	2016	V. Schrauwen - Hinderling	Nutrition and Movement Sciences	ZonMW VIDI
3 - Respiratory & Age-related Health	2016	A. Holwerda	Human Biology	Kootstra (PD)
2 - Liver & Digestive Health	2016	A. Jongen	General Surgery	Kootstra (PhD)
2 - Liver & Digestive Health	2016	T. Avery	General Surgery	Kootstra (PhD)
3 - Respiratory & Age-related Health	2017	L. Lindeboom	Respiratory Medicine	VENI
1 - Obesity, Diabetes & Cardiovascular Health	2017	E. Phielix	Nutrition and Movement Sciences	DFN Senior fellowship
3 - Respiratory & Age-related Health	2017	L. Lindeboom	Nutrition and Movement Sciences	DFN Junior fellowship
3 - Respiratory & Age-related Health	2017	B. van Hooren	Nutrition and Movement Sciences	Kootstra (PD)
3 - Respiratory & Age-related Health	2018	T. Snijders	Human Biology	VENI
2 - Liver & Digestive Health	2018	T. Hendrikx	Genetics & Cell Biology	VENI
2 - Liver & Digestive Health	2018	B. Benedikter	Medical Microbiology	Kootstra (PD)
2 - Liver & Digestive Health	2018	T. Houben	Genetics & Cell Biology	Kootstra (PD)
3 - Respiratory & Age-related Health	2018	A. Kneppers	Respiratory Medicine	Kootstra (PD)
3 - Respiratory & Age-related Health	2018	R. Beijers	Respiratory Medicine	Kootstra (PD)
2 - Liver & Digestive Health	2018	J. Verbeek	Internal Medicine	MLDS grant
2 - Liver & Digestive Health	2018	D. Keszthelyi	Internal Medicine	MLDS grant
3 - Respiratory & Age-related Health	2019	I. Kouw	Human Biology	Rubicon
3 - Respiratory & Age-related Health	2020	J. Trommelen	Human Biology	Kootstra
2 - Liver & Digestive Health	2020	N. van Best	Medical Microbiology	Kootstra
3 - Respiratory & Age-related Health	2020	LJ. Jie	Nutrition and Movement Sciences	Kootstra

Table 1.10: Overview of major projects awarded over 500k€ (2015-2020)

Subsidizer	Acronym	Project leader	Title	Year	Contract Value (in k€)
Division 1: Obesity, diabetes and cardiovascular health					
CVON	ENERGISE	P.A.J. Schrauwen	Targeting energy metabolism to comBAT cardiovascular disease	2015	1.771
TKI Health Holland	LF CVD	P.A.J. Schrauwen	Liver fat, insulin sensitivity and diabetes/cardiovascular risk: roads towards prevention and treatment	2016	909
TIFN	MitoHeallth	P.A.J. Schrauwen	Nutritional approaches to preserve and improve physical function in the elderly (Mitochondrial health)	2016	741
EU	MRS in diabetes	V.B. Schrauwen - Hinderling	Novel methods in Magnetic Resonance Spectroscopy to investigate mechanisms underlying metabolic disease	2017	1.600
TIFN	Perceivable benefits	E.E. Blaak	Unravelling the biology behind perceivable consumer benefits	2017	1.526
Astra Zenica	Dapagliflozin	P.A.J. Schrauwen	A Double-blind, Randomized Phase IV, Mechanistic, Placebo-controlled, Cross-over, Single-center Study to Evaluate the effects of 5 weeks Dapagliflozin Treatment on Insulin Sensitivity in Skletal Muscle in Type 2 Diabetes Mellitus Patients	2017	1.500
TKI Agri&Food	WoW	D.M.A.E. Jonkers	A War On modern bread Wheat	2017	1.267
TKI Health Holland	NASH-ID	J. Plat	To prevent hepatic inflammation as part of the obesity epidemic by a targeted dietary intervention	2017	896
ZonMW	Cold acclimation therapy	W.D. van Marken Lichtenbelt	An innovative cold acclimation therapy to treat type 2 diabetes	2017	600
EU	EJP RD	C.T.A. Evelo	European Joint Programme on Rare Diseases	2018	625
EU	SWEET	E.E. Blaak	Sweeteners and sweetness enhancers: Impact on health, obesity, safety and sustainability	2018	599
MedImmune	MEDI0382	P.A.J. Schrauwen	An Exploratory Phase 2, Randomised, Double-blind, Placebo-controlled, and Open-label Active Comparator Study to Evaluate the Effect of MEDI0382 on Hepatic Glycogen Metabolism in Overweight and Obese Subjects with Type 2 Diabetes Mellitus	2019	496
ZonMW	RT2T2D	P.A.J. Schrauwen	Restoring 24-hour substrate rhythmicity to improve glycemic control by timing of lifestyle factors	2020	738
NWO	Carbosupport	E.E. Blaak	Defining carbohydrate formulations to steer gut microbiota and colonic fermentation processes to support metabolic, immune and mental health	2020	725
NWO - NWA	VHP	C.T.A. Evelo	The Virtual Human Platform for Safety Assessment	2020	1.142
Division 2: Liver and digestive health					
ZonMW	AFT	R.R.W.J. van der Hulst	Autologe Vettransplantatie (AFT) bij borstreconstructies na borstkanker; de techniek van de toekomst bij borstreconstructies ontvangen	2015	545
ZonMW	Unwanted souvenirs	J. Penders	Unwanted souvenirs: the application of amulti-layered metagenomic epidemiological approach to study theemergence and dissemination of antrmicrobíal resistance	2016	800
ZonMW	CoCROS	M.J. Pierik	Control Crohn Safe with episodic adalimumab monotherapy as first line treatment trial	2018	500
ZonMW	Napoleon Trial	S.O. Breukink	cost-effectiveness and effectiveness of rubber band ligation versus sutured mucopexy versus haemorrhoidectomy in patients with recurrent haemorrhoidat disease	2019	641
Division 3: Respiratory & age-related health					
TIFN	Muscle Health 101	L.J.C. van Loon	Caseïn and Recovery	2015	594
TIFN	Plant Based Proteins	L.J.C. van Loon	Anabolic properties of plant-based proteins	2016	1.060
TKI Health Holland	Food for thought	A.M.W.J. Schols	Food for thought and active lifestyle in COPD	2017	618
TKI Health Holland	Quark	L.B. Verdijk	Anabolic responsiveness to fermented dairy ingestion	2019	552
INTERREG	PROOF	A.M.W.J. Schols	Platform for Research Oriented towards persOnalised Food	2019	545
TKI Agri&Food	Cow art	L.J.C. van Loon	The impact of protein glycation on dairy protein digestion and post-prandial amino acis absorption kinetics in vivo in humans	2020	942
Chemelot InSciTe	WISE	M. Poeze - van Bokhoven	Wrist Implants Made by Rapid Tooling Using Stereolithography with Injection Mold Engineering	2020	727
Tessenderlo Group NV		L.J.C. van Loon	Collagen ingestion as a means to stimulate myofibrillar and connective tissue protein synthesis rates at rest and during recovery from exercise in vivo in humans	2020	520
TKI Health Holland	Oxygen	A.M.W.J. Schols	Precision Medicine for more Oxygen	2020	994

Table 1.11: Representative examples of functions in scientific committees, councils and organisations in the period 2015-2020

Scientist (division)	Organisation	Function/role
Division 1		
Assema P. (Assoc. Prof.)	National Institute for Public health and Environment (RIVM), recognition committee Interventions Smart Food Intake public-private collaboration Dutch journal for Nutrition and dietetics	Member Subcommittee 4 Health promotion for adults and elderly Scientific advisory board Scientific advisory board
Blaak E. (Prof.)	Dutch Health Council Top Institute Food and Nutrition (TFN) Neth. Organization for Scientific Research (NWO) Eur. Association for the Study of Obesity (EASO) ILSI Europe	Member committee Nutrition Project leader Member VENI committee Secretary Chair expert group on SCFA & metabolic health
Bongers B. (Assist. Prof.)	Neth. Society of Human Movement Sciences (VvBN)	Board member
Canfora E. (Assist. Prof.)	Eur. Association for the Study of Obesity ILSI Europe (expert group SCFA)	Board member of New Investigators Unit Member
Evelo C.	ELIXIR	Co-leader Interoperability Platform

(Prof.)	IMI TransQST project NuGO EdgLeap B.V. Micelio (Belgium)	Advisor Board member Advisor Advisor
Goossens G. (Assoc. Prof.)	Eur. Association for the study of Obesity (EASO) Eur. Congresses on Obesity Neth. Association for the Study of Obesity (NASA)	Chair Scientific Advisory Board Member of International Scientific Committee President
Gubbels J. (Assist. Prof.)	Dutch Health Council; committee Nutrition recommendations for pregnant women Dutch Health Council; committee Physical activity recommendations 0-4 years old ZonMW program Mental Health care; Diet and mental health- Knowledge synthesis Eur. Childhood Obesity Group	Invited committee member Invited committee member Grant committee member International Scientific Committee
Joris P. (Assist. Prof.)	Dutch Academy of Nutritional Sciences (NAV) ILSI Europe Young Health council (jongGR)	Vice-chair Task force member Member
Kremers S. (Prof.)	National working group on Dietary Habits Dutch health council; Standing committee Healthy Nutrition ZonMW program Parenting and Education NFU committee Health in the Region UNESCO Chair for Education and Health	Chair Member Grant committee member Committee member Member of the scientific board
Meertens R. (Assoc. Prof.)	Dutch Health Council; standing committee on public health National Institute for Public health and Environment (RIVM)	Member Member steering committee Research on Crop protection and local residents
Mensink R. (Prof.)	NWO Crossover Program ILSI Europe Dutch health council; Standing committee Healthy Nutrition Supervisory & assessment committee Nutritional Sciences	Member review committee Expert group member; Sc. Advisory task force Member Chair
Oenema A. (Assoc. Prof.)	Working group on Dietary Habits	Vice-chair
Plat J. (Prof.)	Nutrition in Translation	Secretary
Schrauwen P. (Prof.)	EASD Eur. Foundation for the Study of Diabetes (EFSD) Diabetes Fond Nederland Neth. Heart Institute Eur. Association for the Study of Obesity (EASO) Annual Dutch Translational Metabolism Meeting KNAW	Member EASD Minkowski Prize Committee Member review committee Member Scientific Advisory board Member Science Forum Member Award committee Organizer and Funder Organizer KNAW symposium
Summer-Kutmon M. (Assist. Prof.)	ISMB Network Biology COSI WikiPathways	Abstract chair Architect
Venema K. (Prof.)	ILSI Europe Beneficial Microbes Conference Series	Member Prebiotics Expert group Member taskforce alternative for animal testing working group Organizer, president of scientific committee
Vries de N. (Prof.)	Scientific Foundation for Health promotion ZonMW committee Research in Mental health ZonMW committee Care for Refugees Worldwide University Network; steering committee Public Health VSNU-committee Responsible Management of Research Information and Data NFU committee COVID research	President Committee member Committee member Committee member Committee member Committee member

	Scientific Foundation of Health promotion	President
Willighagen E. (Assoc. Prof.)	H2020 anoFabNet project NanoSafety Cluster Data Working Group Foundation 'Chemische congression 6' LIPID MAPS project GO FAIR Chemistry Implementation Network National Plan Open Science Open Knowledge Foundation EU meeting/Amst. call for Action on Open Science	Advisor Chair Board member Advisor Advisor, co-founder Advisor, member working group Responsible for Open Science NL mailing list Active contributor on invitation
Division 2		
Dejong C. (Prof.)	IHPBA Scientific committee ZonMW Translational Research ZonMW Clinical Fellowship	Member Committee member Member Advisory Committee
Jonkers D. (Prof.)	NWO VIDI committee NVGE (Gastroenterology Society) Research award NVGE, Section Experimental Gastroenterology	Member Member/chair jury Board member
Keszthelyi D. (Assist. Prof.)	NVGE, Neurogastroenterology section NVMDL, Taskforce Neurogastroenterology	Board member/chair Board member
Kohler E. (Prof.)	NWO Rubicon	Assessor
Lenaerts K. (Assoc. Prof.)	ZonMW Off Road International Meeting on Ischemia Reperfusion Injuries in Transplantation NVGE, Section Experimental Gastroenterology	Committee member Scientific Council Member Board member
Olde Damink S. (Prof.)	Eur. African Hepato-Pancreato-Biliary Association (E-AHPBA) Intern. Hepato-Pancreato-Biliary Association (IHPBA) Eur. Surgical Association (ESA)	Member Scientific and Research Committee Member Scientific and Research Committee Member
Penders J. (Assoc. Prof.)	NWO-TIFN World Universities Network In VIVO Planetary Health Million Microbiome of Humans Project	Panel member Co-director Steering Committee Member
Pierik M. (Assoc. Prof.)	Epidemiology Committee European Crohn and Colitis Organization (ECCO) NVGE, IBD section Dutch Initiative on Crohn and Colitis (ICC) SMART IBD network	Member/Chair Board member Board member Founder
Savelkoul P. (Prof.)	Roche Global Advisory Committee Euregional Microbiome Center InBiome bv Microbe&Lab bv, Artpred bv	KOL Board member Scientific Advisory Board, board member Scientific Advisory Board
Masclee A. (Prof.)	NWO VIDI committee	Committee member
Sverdlov R. (Prof.)	Dutch Society of Hepatology ZonMW VIDI committee ZonMW Off road committee	Board member/vice president Committee member Committee member
Division 3		
Blokhuis T. (Assist. Prof.)	Osteosynthesis and Trauma Care Foundation (OTC)	Chair educational committee
Boots A. (Assist. Prof.)	European Respiratory Society (ERS) Breath Summit 2018	Member International Planning committee, member Education Council, expert panel, leader group 3 of Assembly, chair Early career member committee Program committee member

Franssen F. (Assoc. Prof.)	Lancet COPD commission European Respiratory Society KCCL Expert Group of Dutch Lung Centers	Member Chair Scientific group Rehabilitation and Chronic care; member Long Range Planning committee; member committee Standardization of Cardiopulmonary Exercise Testing in Chronic Lund Diseases Member
Godschalk R. (Assoc. Prof.)	Dutch Health Council Health and Environmental Safety Institute (HESI) Dutch Society of Toxicology	Member committee Evaluation Carcinogenicity of Substances Member Genetic Toxicology Technical Comm. Board member Section Genetic Toxicology
Kooman J. (Prof.)	Neokidney / Dutch Kidney Foundation	Advisory board member
Langen R. (Assoc. Prof.)	Society on Sarcopenia, Cachexia and Wasting Disorders	Conference program organizer
Langie S. (Assist. Prof.)	Eur. Environmental Mutagenesis and Genomics Society (EEMGS) COST-hCOMET Molecular Epidemiology Group of UKEMS	Vice-president/secretary Management committee, WG leader Committee member
Loon van L. (Prof.)	Eur. College of Sports Science Dutch Health Council IOC diploma in Sport Nutrition Steering group undernutrition University of Applied Sciences Arnhem & Nijmegen	Scientific board member Advisor Advisory board member Member of the scientific advisory council Lector
Meijer K. (Assoc. Prof.)	Society for Motion Analysis Laboratories in the Lower Lands Dutch Biomedical Engineering Society Academic Board PhD program Technology for Health, Univ. Brescia Italy International Conference for activity monitoring and physical activity measurement 2019	Chair Board member Board member President
Plasqui G. (Assoc. Prof.)	Dutch Academy of Nutritional Sciences ICAMPAM	Treasurer Co-chair
Poeze M. (Prof.)	Dutch Society for Intensive Care Medicine European Society of Intensive Care Medicine National Network Acute Care	Member Guidelines Committee Member Research Award Committee Scientific Advisory Council
Remels A. (Assist. Prof.)	NRS Task Force Support for young researchers NRS Young Investigators symposium	Board member/chair Board member
Schols A. (Prof.)	NWO program Healthy Nutrition Eur. Clinical Research Infrastructure network (ECRIN) Top Institute Food and Nutrition Neth. Respiratory Society NWO Hestia Committee UK Nutrition Research Partnership for health and disease (UK NRP) Niels Stensen Foundation	Committee member Member Board member President Member Core member Member
Schooten van FJ. (Prof.)	International Association Breath Research Programme Committee Breath Summit 2018 Joint committee Dutch Health council/WRR/COGEM	Board member Chair Member
Simons S. (Assist. Prof.)	NVALT	Chair section COPD NVALT
Smolinska A. (Assist. Prof.)	Dutch Chemometrics Society International Association Breath Research Metabolomics Society	Treasure Board member Member
Spruit M. (Prof.)	Netherlands Respiratory Society ZonMW Knowledge Synthesis Fatigue in Chronic Diseases Prof. Advisory Committee Eur. Lung Foundation	Treasurer, Head Assembly 9 Co-chair Board member

Verdijk L. (Assoc. Prof.)	Dutch Society for Movement Sciences VvBN ECSS	Board member Review Panel
Zeegers M. (Prof.)	European Epidemiology Association Netherlands Association for Preventive Health Care	Vice chair Board member

Table 1.12: Representative examples of functions in UM/MUMC+ (outside NUTRIM) in 2015-2020

Scientist (division)	Organisation	Function/role
Goossens G. (div 1)	Maastricht UMC+ Scientific Committee (WMUMC+)	Member/vice-chair
Oenema A. (div 1)	Scientific Integrity Platform	Counselor Scientific Integrity
Summer-Kutmon M (div 1)	Maastricht Systems biology forum	Organizer
Vries de N. (div 1)	FHML/UM Maastricht University Medical Center +	Vice-dean Board member
Willighagen E. (div 1)	Open Science Community Maastricht	Co-founder / guest lectures
Penders J. (div 2)	Graduate school CAPHRI	Scientific Advisory Board
Olde Damink S (div 2)	Research institute M4I MUMC+	Clinical Liaison Head HBP Surgery
Jonkers D. (div 2)	Maastricht Comprehensive Cancer Center+	Advisory Board
Loon van L. (div 3)	Stable Isotope Research Center (SIRC)	Scientific coordinator
Poeze M. (div 3)	UM MUMC+	Decentral Selection Committee Medicine Head Trauma Unit
Schols A. (div 3)	UM Interfaculty program EatWell FHML/UM	Initiator and chair Dean
Wessellius A. (div 3)	Maastricht Study	MT member
Zeegers M. (div 3)	UM Platform Research Integrity FHML Platform Research Integrity	Chair Chair

Table 1.13: Representative examples of research products used by others (2015-2020, per division)

Scientist (division)	Type	Used by
Division 1		
Assema P. (Assoc. Prof.)	Manual, intervention materials and website	Digitale handreiking Integrale aanpak voor Gezondheid ZonMW
Blaak E. (Prof.)	DiOGeneS Dataset	Many scientists
Coort S. (Assist. Prof.)	Dataset (Micronutrient pathways Portal WikiPathways)	NuGo and other nutrition organisations
Ehrhard F. (Assist. Prof.)	Rare disease portal on portal WikiPathways Datasets on 60 human and machine readable pathways for data analysis; on genetic variants of MECP2; Gene-Rare diseases-provenance dataset	Many scientists Biomedical research community worldwide
Gubbels J. (Assist. Prof.)	Manual, intervention materials and website : SuperFIT overweight prevention for preschools and parents	**Many childcare organisations and preschools in the Netherlands**
Joris P. (Assist. Prof.)	Vascular function measurements	Metabolic research scientists; users MRUM

Summer-Kutmon M. (Assist. Prof.)	WikiPathways – pathway database PathVisio – pathway editor and analysis tool CyTargetLinker – Cytoscape app for network extension COVID19 pathway collection (WikiPathways + COVID10 Disease Map project)	Biomedical research community worldwide
Willighagen E. (Assoc. Prof.)	Tools: Chemistry Development Kit; BridgedDB (ELIIR Recommended Interoperability Resource) Datasets: NanoWiki; BridgeDb metabolite ID mappings; Blau Book Metabolic Rare Diseases Pathways	Academic, **industrial, clinical** European Union Observatory for Nanomaterials; biomedical research community worldwide, **incl. industry**
Depts. Human Biology/ Nutrition & Movement Sciences	Metabolic rooms (base or advanced)	Universities (Warwick, Singapore, Shanghai, Antwerp, Beijing)
Division 2		
Jonkers D. (Prof.)	Maastricht IBS biobank cohort	H2020/DisCOVERIE; many researchers
Pierik M. (Assoc. Prof.)	IBD-South Limburg biobank cohort Microscopic colitis registry myIBDcoach disease monitoring eHealth tool ICC-drug registration	FP7/Sysmed/BIOM/Character; many researchers Many researchers in Europe **Over 14 hospitals in the Netherlands** **IBD-specialists in the Netherlands**
Kohler E. (Prof.)	Anatomytool (international website for teachers and students of anatomy)	Biomedical researchers worldwide
Keszthelyi D. (Assist. Prof.)	Measure: Experience Sampling Method app for IBS symptoms and triggers	H2020/DisCOVERIE
Penders J. (Assoc. Prof.)	R package Microviz (with MacsBio): Software extension for Microbiome analyses	Biomedical researchers worldwide
Olde Damink S. (Prof.)	Living biobank	Biomedical researchers worldwide
Division 3		
Blokhuis T. (Assist. Prof.)	Muscle Analyzer tool Dataset Biomimetic peptides	**MUMC+ clinic** Many researchers, **Cerapedics**
Franssen F. (Assoc. Prof.)	Dataset COPD	University of Londrina; University of Gothenburg; University Utrecht
Meijer K. (Assoc. Prof.)	Wearables for physical activity monitoring (MOX)	Various European and Dutch University and **regional hospitals**
Kooman J. (Prof.)	Dataset MONDO initiative	Mondo consortium
Langen R. (Assoc. Prof.)	Genetically modified skeletal muscle cell lines	Many international researchers
Langie S. (Assist. Prof.)	Illumina Methylation 450K BeadChip datasets	Openly accessible via Gene Expression Omnibus
Plasqui G. (Assoc. Prof.)	The International Atomic Energy Agency Internal Doubly labelled Water Database	Many researchers
Poeze M	LoBoDe Registry National Trauma registration Trauma Triage App; Smart Sock for customized weight bearing	AO/AOTK National network Acute Care **TAPP; (societal use)** **AO/Sensoria (societal use)**
Zeegers M	App for calculating genetic susceptibility of Sports performance	**Dutch Elite Sport Teams (societal use)**

Note: presented in bold when use by others also includes societal use

Table 1.14: Overview of active NUTRIM Full Professors (active 2015-2020)

Division 1			Division 2			Division 3	
Name	**Department**		**Name**	**Department**		**Name**	
Evelo C.	Bioinformatics		Sverdlov R.	Genetics & Cell Biology		Zeegers M.	Genetics & Cell Biology
Kremers S.	Health promotion		Masclee A.	Internal medicine/ Gastroenterology		Kooman J.	Internal medicine/Nephrology
Vries N.	Health promotion		Jonkers D.	Internal medicine/ Gastroenterology		Bergh J. van den	Internal medicine
Mariman E.	Human Biology		Savelkoul P.	Medical Microbiology		Haenen G.	Pharmacology & Toxicology
Blaak E.	Human Biology		Hulst van der R.	Plastic Surgery		Bast A.*	Pharmacology & Toxicology
Venema K.	Human Biology		Dejong C.	Surgery		Schooten FJ. Van	Pharmacology & Toxicology
Schrauwen P.	Nutrition & Movement Sciences		Bouvy N.	Surgery		Opperhuizen A.	Pharmacology & Toxicology
Mensink R.	Nutrition & Movement Sciences		Olde Damink S.	Surgery		Schols A.	Pulmonology
Hesselink R.	Nutrition & Movement Sciences		Gemert W. van	Surgery		Wouters M.*	Pulmonology
Marken Lichtenbelt W. van	Nutrition & Movement Sciences		Stassen L.	Surgery		Spruit M.	Pulmonology
Plat J.	Nutrition & Movement Sciences		Köhler E.	Anatomy & Embryology		Poeze M.	Trauma- Surgery
Zimmermann L.	Pediatrics		Zandvoort M. van	Genetics & Cell Biology		Loon van L.	Human Biology
Savelberg H.	Nutrition & Movement Sciences		Gemert van W.	Surgery		Bekers O.	Medical Microbiology / CDL

**) currently retired (Wouters 2019, Bast 2020)*

Note: Brouns F., Westerterp-Plantinga M., Westerterp K., Blaak M., Saris W. (D1), and Wouters M., Bast A. (D3) are retired but still registered and active in NUTRIM

Table 1.15: Overview of active NUTRIM Associate Professors (active 2015-2020)

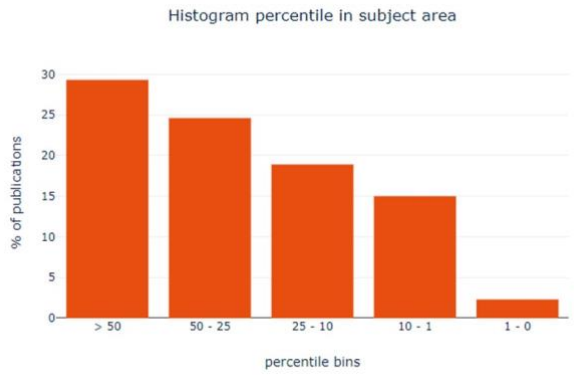
Division 1			Division 2			Division 3	
Name	**Department**		**Name**	**Department**		**Name**	
Oenema A.	Health promotion		Koek G.	Internal medicine/Gastroenterology		Verdijk L.	Human Biology
Assema van P.	Health promotion		Troost F.	Internal medicine/Gastroenterology		Meijer K.	Nutrition and Movement Sciences
Meertens R.	Health promotion		Pierik M.	Internal medicine/Gastroenterology		Godschalk R.	Pharmacology and Toxicology
Goossens G.	Human Biology		Penders J.	Medical Microbiology		Gosker H.	Pulmonology
Savelberg H.	Nutrition & Movement Sciences		Lenaerts K.	Surgery		Langen R.	Pulmonology
Adam J.	Nutrition & Movement Sciences		Renssen S.	Surgery			
Hoeks J.	Nutrition & Movement Sciences						
Adam T.	Nutrition & Movement Sciences						
Vreugdenhil A.	Pediatrics						
Schrauwen-Hinderling V.	Radiology /Nutrition & Movement Sciences						

Table 1.16: Overview of active NUTRIM Assistant Professors (active 2015-2020)

Division 1			Division 2			Division 3	
Name	**Department**		**Name**	**Department**		**Name**	
Coort S.	Bioinformatics		Poll van de M.	Intensive care		Damoiseaux J.	Central Diagnostic Lab
Willighagen E.	Bioinformatics		Stassen F.	Medical Microbiology		Menheere P.	Central Diagnostic Lab
Gubbels J.	Health promotion		Wolffs P.	Medical Microbiology		Wodzig K.	Central Diagnostic Lab
Jocken J.	Human Biology		Cramer T.	Surgery		Gielen M.	Genetics and Cell Biology
Renes J.	Human Biology		Schaap F.	Surgery		Wesselius A.	Genetics and Cell Biology
Meex R.	Human Biology		Houben T.	Genetics and Cell Biology		Snijders T.	Human Biology
Havekes B.	Internal medicine					Christiaans M.	Internal Medicine
Phielix E.	Nutrition and Movement Sciences					Plasqui G.	Nutrition and Movement Sciences
Joris P.	Nutrition and Movement Sciences					Boots A.	Pharmacology and Toxicology
Lindeboom L.	Radiology/ Nutrition and Movement Sciences					Hageman G.	Pharmacology and Toxicology
Well van G.	Pediatrics					Hartog den G.J.	Pharmacology and Toxicology
Waardenburg D.	Pediatrics					Smolinska A.	Pharmacology and Toxicology
Straetemans S.	Pediatrics					Langie S.	Pharmacology and Toxicology
Baumgartner S.	Nutrition and Movement Sciences					Remels A.	Pharmacology and Toxicology
Buitinga M.	Nutrition and Movement Sciences					Berendsen B.	Nutrition and Movement Sciences
Kutmon M.	BioInformatics					McCrum C.	Nutrition and Movement Sciences
Bongers B.	Nutrition and Movement Sciences					Simons S.	Pulmonology
Canfora E.	Human Biology					Reynaert N.	Pulmonology
Ehrhard F.	Bioinformatics						

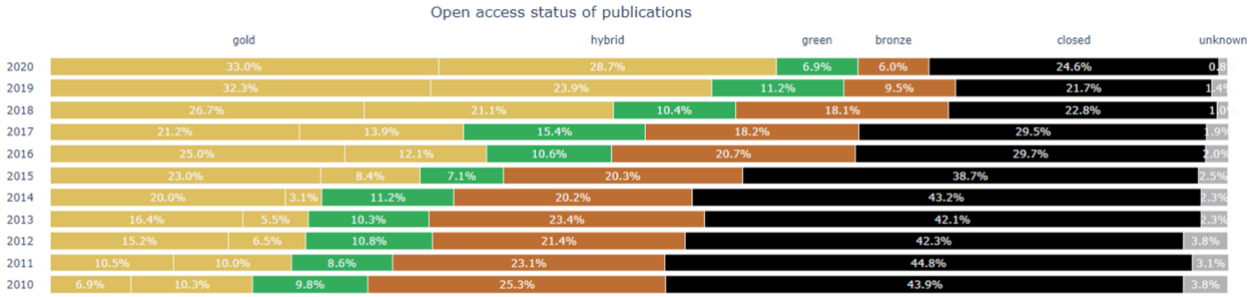
Research quality: figures

Figure 1.1: NUTRIM publication percentile in subject area based on the CNCI (2017-2018)*



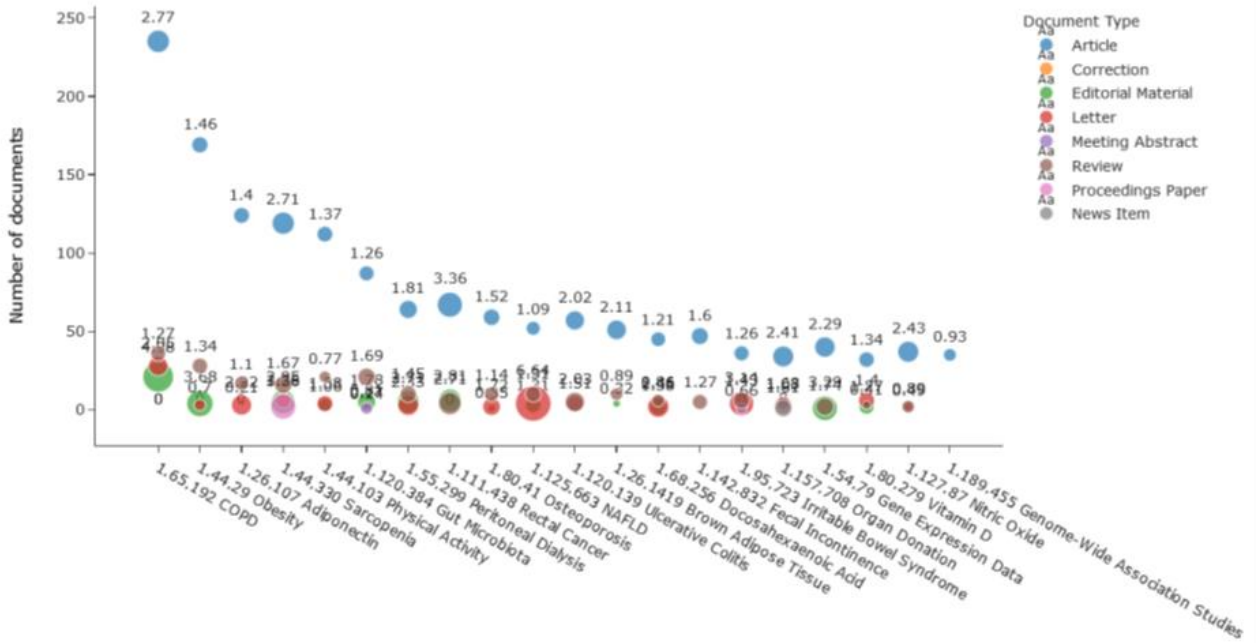
*Percentile of NUTRIM publications in top 1%, top 10% etc, based on the CNCI (i.e. normalised for publications in the same area, over the same years and document types); *) Based on new division structure implemented in 2017.*

Figure 1.2: The percentage of NUTRIM publications in Open Access journals over time



Note: Percentage of NUTRIM open access publications based on the definitions used by the Unpaywall database:
Gold: Free under an open license on the publisher site, published in a fully-OA journal; Hybrid: Free under an open license on the publisher site, published in a toll-access journal; Bronze: Free to read on the publisher page, but without an open license for re-use; Green: Toll-access on the publisher page, but there is a free copy in an OA repository. Most green access publication do not have an open license; Closed: Everything else

Figure 1.3: Top 20 most frequent NUTRIM citation topics with document type and CTNCI (2010-2018)



The number of publications is set out against the citation topics. The color of bullets indicates the document type as assigned by InCites. The size of the bullet corresponds with the Citation Topic Normalized Citation Impact (CTNCI) and is also shown in numbers

above of the bullets. The CTNCI indicates a relative comparison versus the average expected citations of publications with the same age, document type and citation topic.

Figure 1.4: World map of NUTRIM collaboration (2010-2020). The colour of a country indicates the number of publications published together with an affiliations residing in that country.

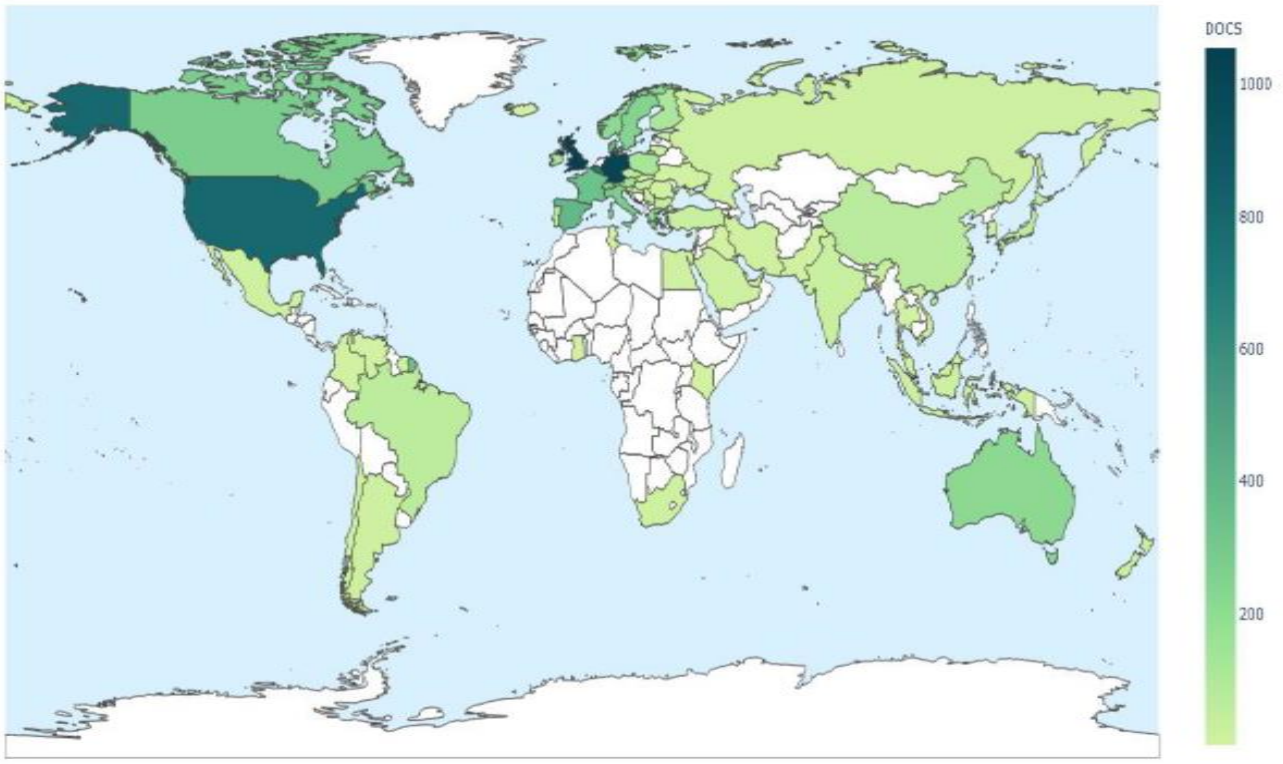
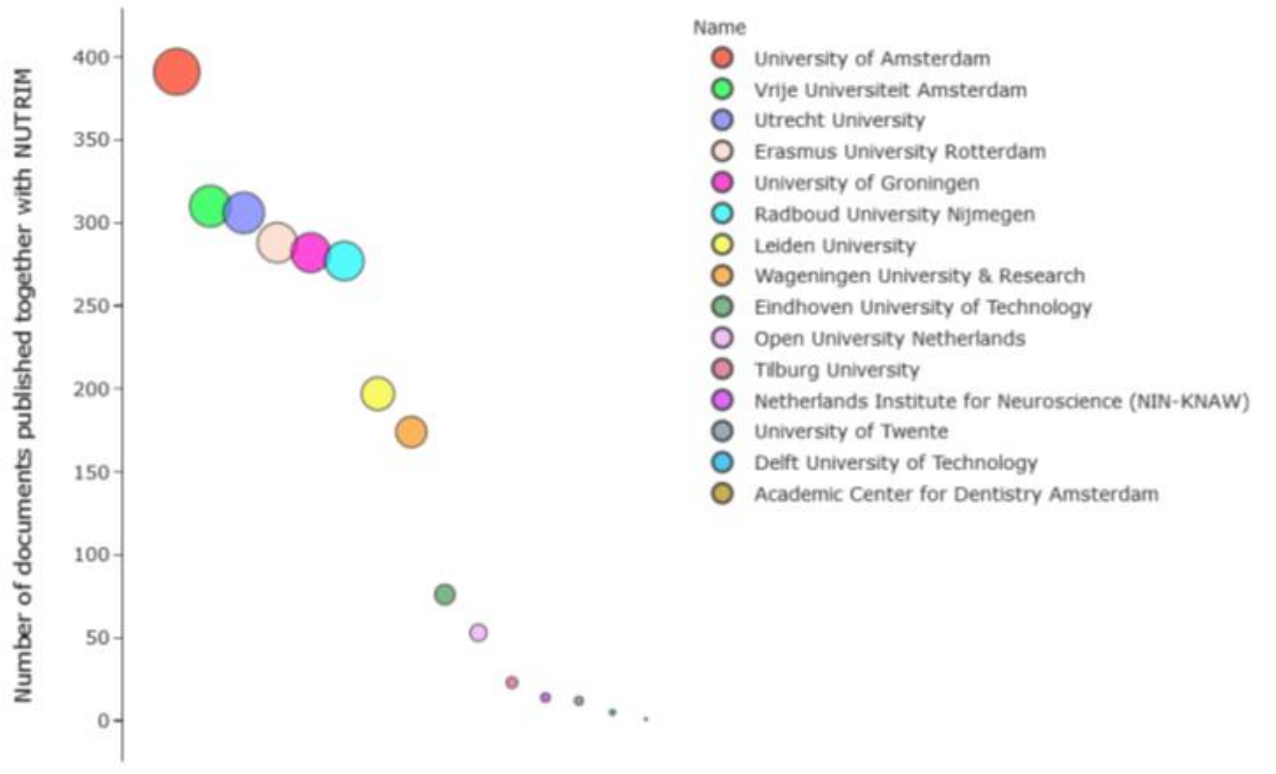
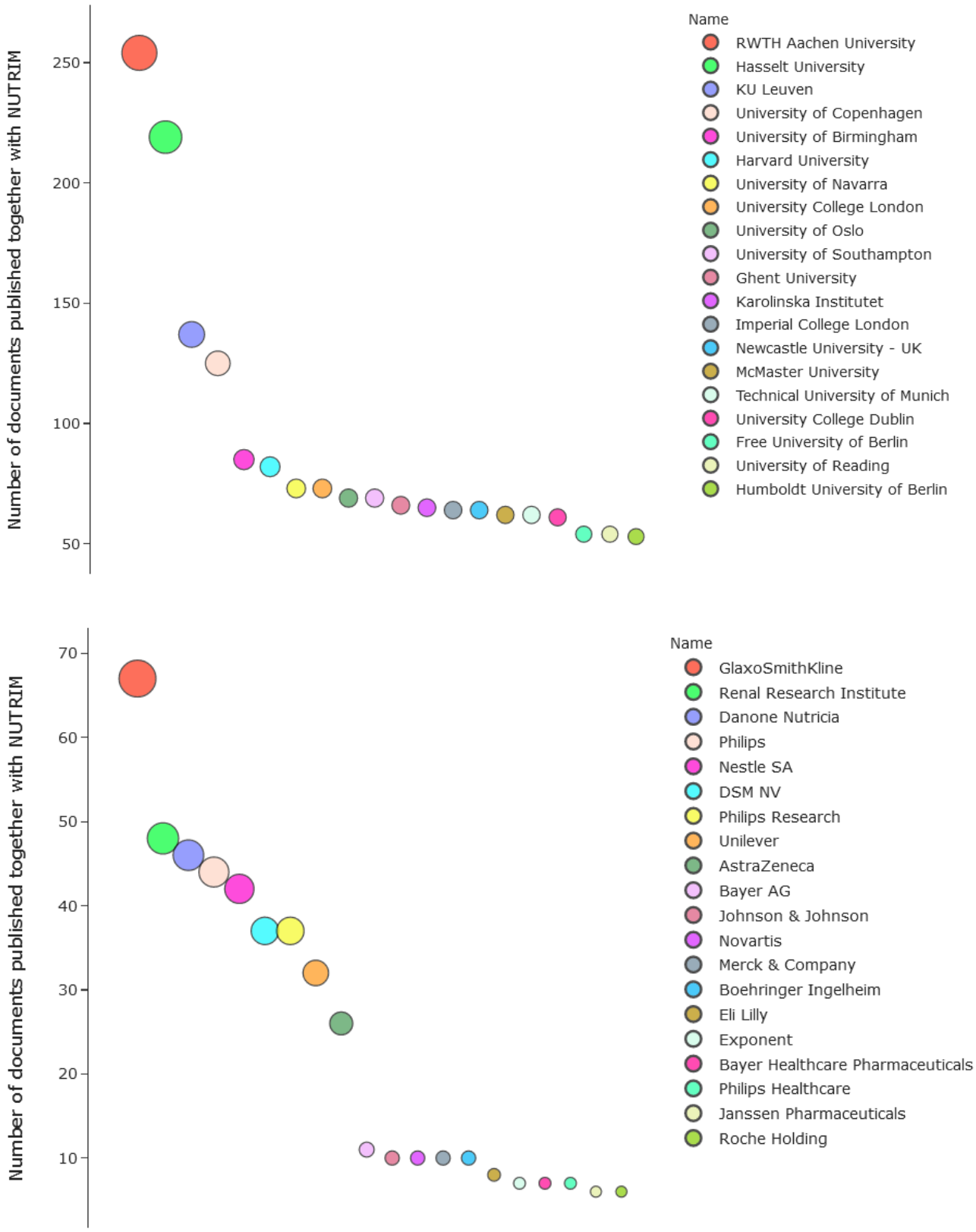


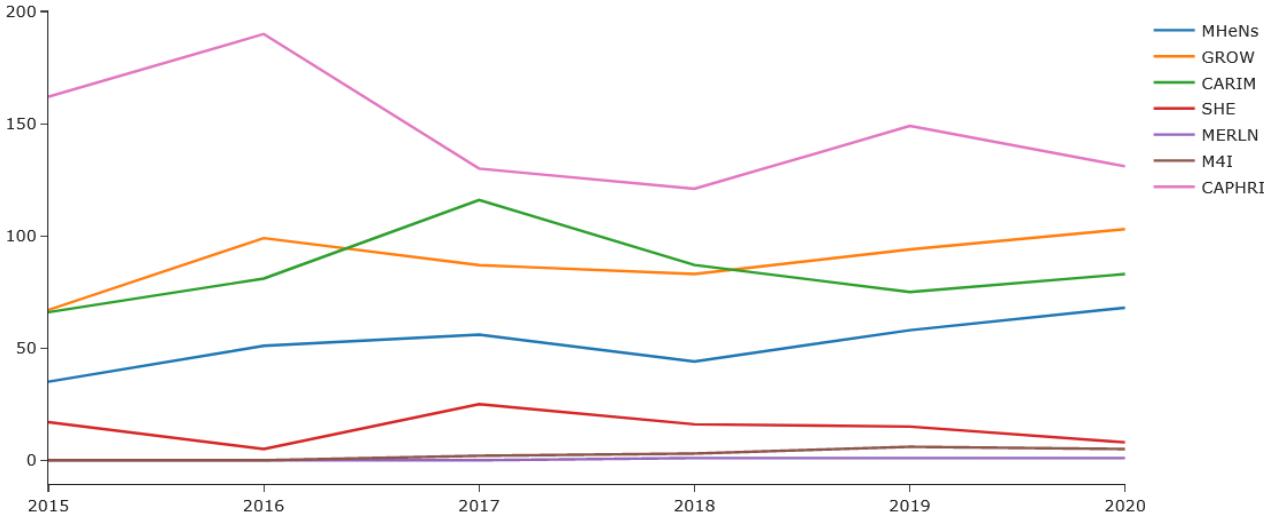
Figure 1.5: Most frequent collaborations of NUTRIM with national academic (panel A), international academic (panel B) and (global) corporate partners (panel C) based on the Incites organization type





Presented is the number of documents published with the most frequent partners in the period 2015-2020, with national academic (panel A), international academic (panel B) and (global) corporate partners (panel C) based on the Incites organization type.

Figure 1.6: NUTRIM collaborations with FHML graduate schools and institutes over time based on the number of joined publications per year


200
150
100
50
0
2015
2016
2017
2018
2019
2020
MHeNs
GROW
CARIM
SHE
MERLN
M4I
CAPHRI

Relevance to society: tables

Table 1.17: Representative examples of functions in professional societal organisations (2015-2020)

Scientist (division)	Organisation	Role
Division 1		
Assema van P.	Smart Food Intake (public-private initiative)	Scientific Advisory Board van Smart Food Intake
Blaak E.	Dutch Health Council	Member committee Nutrition of the Dutch Health Council
Gubbels J.	Knowledge Centre Sports and Physical activity	Invited grant committee member
Meertens R.	IDVO ('Stichting Innovatie Distributie Voorlichting Orgaandonatie')	Board member
Oenema A.	KBO Limburg	Board member
Plat J.	Foundation FIVES	Chair Supervisory board
Savelsberg H.	Committee 'Duurzaam Docentschap' Comenius Netwerk	Chair
Vries de N.	Foundation DIEP (supporting chronic care and self-management) Dutch National Conference of Public Health Advisory Group LIME (Limburg Meet, measurement issues in health care) Program committee Meer Veerkracht, Langer Thuis (resilience projects for the elderly); FNO	President President Advisory group Chair and committee member
Division 2		
Dejong C.	Dutch Liver Working group E-AHPBA Dutch Society of Gastroenterology Dutch Hepatobiliary Audit E-AHPBA	Chair Council member Vice President Chair Secretary-General
Jonkers D.	MLDS	Chair/ Scientific advisory board MLDS
Keszthelyi D.	Network of IBS knowledge centers Nat. Healthcare Institute, Zinnige Zorg Spijsvertering PDSB, Medical Advisory Board PDS (IBS) Therapist, Medical Advisory Board	Chair Advisor Board member Board member
Pierik M.	'Onze zorg van de toekomst': Data2Care care paths Foundation MyIBDCoach NFU committees 'Methode en management' en 'Waarde gestuurde zorg'	Project leader Founder/board member Member
Savelkoul P.	Neurobibromatosis society ESCMID EU Guideline committee for blood stream infections Dutch Society of Medical Microbiology	Advisory Board Member Member Board member
Masclee A.	Neth. Soc. Gastroenterologists & Hepatologists (NVMDL)	President
Olde Damink S.	National Guideline Perioperative Nutrition Policy	Chair
Sverdlov R.	Dutch Gastroenterology Foundation MLDS	Advisory Board member
Division 3		
Fransen F.	Long Range Planning Committee Foundation 'Astma Bestrijding' Expert Group of Dutch Lung Centers; KCCL	Member; ERS Board member; SB Member
Godschalk R.	Dutch Health Council	Member Committee Carcinogenicity of Substances
Loon van L.	Dutch Health Council IOC diploma in Sport Nutrition	Advisor Advisory board member

Poeze M.	National Network Acute Care Network Acute Care Limburg National Network Acute Care Regionaal overleg acute zorg (ROAZ)/GGD	Medical director Limburg Acute Care Member National Committee Trauma Centers Chairman Limburg Traumachirurgisch Genootschap Crisis managementteam
Schooten van FJ	Dutch Health Council	Member
Spruit M.	Professional Advisory Committee, European Lung Foundation	Board Member
Verdijk L.	VvBN - Dutch Society for Movement Sciences	Board member
Zeegers M.	Netherlands Association for Preventive Healthcare	Board member

Table 1.18: Representative examples of media exposure (2015-2020)

Scientist (division)	Year	Topic (media type)
Division 1		
Mariman E.	2015	Kwestie van de lange adem: Afvallen. Complementjes komen pas na verlies van ruim 6 kilo (Newspaper De Telegraaf)
Hoeks J.	2015	5th joint Diabetes and Metabolism Research Symposium (Live event; Public engagement event)
Schrauwen P.	2015 2016	Warming Up to brown fat (Internet: The-scientist.com) Dag-nachtritme in spierstofwisseling ontdekt (Internet: VoedingNU, Nieuwsbank.nl, Nationale Zorggids)
Blaak E.	2016 2017	Obesitas is iet de norm (Interview newspaper De Limburger) Internet: http://www.roomcalorimeters.com/2017/01/19/wanted-all-over-the-world-the-respiration-chambers-designed-in-maastricht/ and https://www.youtube.com/watch?v=D6pFam3d3E0 (Internet)
Gubbels J.	2018	Eating speed of children (Newsletter Trouw) Physical activity at childcare (internet: www.allesoversport.nl)
Willighagen E.	2018	Open Access (Magazine C2W)
Hesselink M.	2019	Energieverspilling ten behoeve van gezondheid (Public event: Pleasure Art and Science Festival)
Canfora E.	2019 2020	EASO spotlight interview Emanuel Canfora (EASO blog) Zoeken naar het juiste vezeldieet (Magazine Dialoog)
Assema van P.	2020	Gezonde basisschool van de toekomst (Various newspapers: https://www.degezondebasisschoolvandetoekomst.nl/nieuws/)
Bongers B.	2020	Prevalidatie in onderzoek en in de praktijk (Newsletter World Cancer Research Fund)
Goossens G.	2020	Obesity and COVID (Newspaper The Times) World obesity day (NPO radio 1, Newspapers Algemeen Dagblad, De Limburger)
Kutmon M.	2020	COVID pathway curation (https://www.mumc.nl/actueel/nieuws/moleculaire-routekaart-van-het-coronavirus-ontwikkeld)
Division 2		
Lenaerts K.	2015	ACSM blog Oral Citrulline to Circumvent Splanchnic Hypoperfusion and Gut Injury in Athletes (Active Voice)
Penders J.	2016	Antimicrobial resistance and Travel (RTL News; Newspaper De Telegraaf)
Hartog den GJ	2016	Artificial sweeteners (Television: Broodje Gezond)
Jonkers D./Penders J.	2017	Meer inzicht in de ziekte van Crohn. (Interview Newspaper De Limburger)
Pierik M.	2017	Darm patiënt heeft baat bij digitale monitoring (Newspaper De Telegraaf0
Savelkoul P.	2017	Avondgasten L1 TV (TV Interview)
Houben T.	2018	CTSD in NASH (Internet: Atlas of Science)
Jonkers D.	2018	IBD and Microbiome (Brochure MLDS, News site nu.nl)
Langie S.	2018	Science communication reel: “How can you give your baby the best start in life?” (YouTube)
Keszthleyi D.	2019	Digestive function (Radio interview NPO Radio 1) Irritable Bowel Syndrome (Magazine GezondNU)
Penders J.	2020	Fecal transplantation upon Cesarean Section delivery (Science Magazine)
Pierik M.	2020	Zinnige Zorg Nederland (Television NOS journal)

Savelkoul P.	2020	Testen, testen, testen, maar bij de laboratoria is het (nog) niet druk (Television RTL news)
Sverdlov R.	2020	Plasma CTSD activity in type 2 diabetes (LEVER Magazine; Internet HashtageScishare)
Division 3		
Gielen M.	2015	Let op vetzuren tijdens zwangerschap (Newspaper De Telegraaf)
Zeegers M.	2015	Too much fish during pregnancy increases a child's obesity risk (CNN)
Bast A.	2017	Onder de invloed van voeding op onze gezondheid: is vlees allen maar ongezond? Rubriek 'Beter eten'(Newspaper De Volkskrant)
Loon van L.	2017	Onder de invloed van voeding op onze gezondheid. Deze week: is het zinnig om zonder ontbijt te gaan sporten? (Newspaper De Volkskrant)
Kooman J.	2017	De ontwikkeling van de draagbare kunstnier van kleiner en flexibeler naar echt draagbaar (NEMO Kennislink)
Schooten van FJ/Opperhuizen A.	2017	Nederlandse sjoemelsigaret veel schadelijker dan Europese meetmethode laat zien (Newspaper De volkskrant)
Verdijk L.	2018	Bietensap en sportprestaties (Magazine Gezond Idee; Internet NEMO Kennislink)
Haenen G.	2018	Traditional Chinese Medication (Radio-television Interview RTV Maastricht)
McCrum C.	2019	Trainen met bewegingsapparaat kan mogelijk valrisico ouderen verkleinen (Internet zorg.nu)
Loon van L.	2019	TV episode 'Spieren' on muscle disuse and exercise training (Television AVRO/TROS Dokters van Morgen)
Schooten van FJ./Smolinska A.	2019	ABC Cancer project (Internet: Health Europa Quarterly)
Poeze M	2020	3D printer voorkomt amputatie (Television RTL News; Radio BNR) 3D-geprint implantaat voorkomt amputatie van onderbeen (Internet ICT&Health)
Blokhuis T.	2020	Opening van een non-union-poli voor complexe botbreuken (Internet: 1limburg.nl)
Franssen F.	2020	COPD: zo is het te behandelen (Newspaper: De Telegraaf) Redefining the diagnostic criteria for COPD (Internet Nature)

Table 1.19: Representative examples of NUTRIM input in guidelines and advisory reports (2015-2020)

Scientist (division)	Organisation/Occasion (year)	Topic
Division 1		
Blaak E. (div. 1)	Dutch Nutrition Council (2016) EASO position statement (2019) Advisory report EASO (2017)	Nutritional guidelines The ABCD of obesity: position statement on diagnostic term with clinical and scientific implications To improve the ICD-11 Diagnostic criteria for Obesity
Goossens G. (div 1)	Position Statement EASO (2020) Position paper WHO (2020)	Global COVID-19 pandemic Obesity during and after the COVID-19 data revolution
Oenema A. (div 1)	Knowledge synthesis (2019)	Nutrition and mental health during life
Meertens R. (div 1)	Dutch Health Council (2020)	Gespoten PUR schuimisolatie en gezondheid
Plat J. (div 1)	Consensus document/guideline EAS (2015)	Plant sterols and plant stanols in the management of dyslipidemia and prevention of cardiovascular diseases
Willighagen E. (div 1)	VSNU, NOW, KNAW, ZonMW (2017)	National plan open science
Division 2		
Keszthelyi D. (div 2)	Guideline UEG, ESNM Guideline NVMDL (2020) Guideline NVVH (2020) Guideline NVVA (2020)	Functional dyspepsia, Fecal incontinence, Gastroparesis Guideline NVMDL (2020) Guideline NVVH (2020) Guideline NVVA (2020)
Penders J. (div 2)	Expert panel European Center for Disease Prevention and Control (2016)	Antimicrobial resistance in travelers

Pierik M. (div 2)	Guideline European Crohn and Colitis Organization (2019) Guideline Dutch Initiative on Crohn's and Colitis (2017)	Quality of care standards in IBD Guideline IBD
Masclee A. (div 2)	NVMDL	Implementation population screening Colorectal cancer
Olde Damink S. (div 2)	Dutch Society of Anesthesiology	Peri-operative Nutrition Policy
Division 3		
Blokhuis T. (div 3)	Guideline Zorginstituut Nederland (2015)	Plaatjesrijk plasma bij een tenniselleboog
Franssen F. (div 3)	Report: LAN (2020)	Treatment and coaching of post-COVID-19 patients
Kooman J. (div 3)	Guideline K-DIGO (2019) Int. Soc. Periton. Dialysis (2016)	Hypertension & fluid overload in end stage renal disease Cardiovascular risk in peritoneal dialysis
Poeze M. (div 3)	Guidelines Dutch Soc. Surgery (2019) AO foundation reports (2020)	Ankle fractures Foot and Ankle Trauma; Tips and Tricks to use RIA-2
Schooten van FJ. (div 3)	Scientific Council for governmental policy (WRR) (2016)	Trend analysis Biotechnology
Simons S./ Spruit M. (div 3)	Guideline KNGF (2020)	COPD
Spruit M. (div 3)	Eur. Resp. Society Statement (2019)	Standardization of cardiopulmonary exercise testing in chronic lung disease

Table 1.20: Overview of spin-offs started between 2015 and 2020

Company	Title	Researcher (and division)	Registered	KvK-nr	CEO
Microsure	Plastic microsurgery	Van der Hulst (Div 2)	1-2-2016	65436849	Deckers
Dutch Screening Group	Drug analytics; CRO	Heeren/Vreeken/Olde-Damink (Div 2)	5-10-2018	72757604	Depondt
TOF	Organoid technology platform	Olde-Damink (Div 2)	4-1-2019	73564672	Depondt
HDX (subsidiary of DSG)	Hair analysis	Olde-Damink (Div 2)	4-10-2018	72757604	Depondt
Adjutec	Pancreatic cancer vaccine	Olde-Damink (Div 2)	20-6-2017	96006105	vd Brekel
Synmabtix	Production of Antibodies to decrease inflammatory diseases	Olde-Damink (Div 2)	20-10-2017	69766215	Graus
MyBasePair B.V.	Cutomized DNA-tests and advanced analytics to the Health and Fitness Industries	Zeegers M. (Div.3)	2017	68418132	Zeegers

Table 1.21: Overview of patents filed (2015-2020)

Patent	Researcher (division)	Priority date
Compounds for the treatment of Niemann-Pick disease type C	Sverdlov (Div 2)	25032016
Exosomal microrna in serum as an indicator for the activation of brown and beige fat tissue (bat)	V Marken Lichtenbelt (Div 1)	28092015

Dietary fiber compositions for curative or prophylactic treatment of obesity and other conditions	Blaak (Div 1)	08032018
Methods of promoting hepatic regeneration.	Olde Damink (Div 2)	21092015
Method for the diagnosis of biliary tract diseases (2018).	Olde Damink (Div 2)	27032018*
Method for the diagnosis of biliary tract diseases (2018).	Olde Damink (Div 2)	27032018*
Method for the diagnosis of airway disease inflammation subtype (2015)	Schooten van (Div 2)	21092015 *
Methods for the treatment of non-alcoholic steatohepatitis (2017)	Sverdlov (Div 2)	22122017*
Methods and compounds for the treatment of Niemann-Pick Disease Type C1	Sverdlov (Div 2)	25032016*
Method for treating non-alcoholic steatohepatitis (2016)	Sverdlov (Div 2)	22022016*

**) filing abandoned*

Table 1.22: Examples of public/societal prizes awarded (2015-2020)

Scientist (division)*	Year	Awarded by
Dr. M. Pierik (div. 2)	2016	Vintura; Vintura Health Care Innovation Award
Drs. M. de Jong (div. 2)	2017	Value Based Care PPrize
Prof. M. Poeze (div. 3)	2020	Allgemeinschaft fur Osteosynthesenfragen (AO); 2020 AO Technical Commission Innovation Prize
Prof. L. Kohler (div. 2)	2020	Wynand Wijnen Award
Drs. J. Ceelen (div. 3)	2016	Nationale Longdagen (NRS/Lung fund); Publiekprijs

**Maximum one prize per scientist is included*

Annex 2: Research staff, funding and the duration/success rates of the PhD programme

Table 2.1 Research staff at NUTRIM level (2015-2020)

NUTRIM - Total	2015		2016		2017		2018		2019		2020	
	fte	#	fte	#	fte	#	fte	#	fte	#	fte	#
Scientific Staff FHML[1]	26,0	74	26,4	70	26,5	70	26,2	72	27,6	72	27,8	75
Scientific Staff academic hospital	6,8	32	6,7	34	6,7	33	6,5	32	6,5	32	6,5	32
Post Docs[2]	27,1	45	19,8	30	21,0	30	23,9	39	23,3	33	18,5	27
Internal PhD-students[3]	115,4	129	110,6	122	105,8	117	101,6	116	97,3	101	92,9	99
Total Research Staff	**175,3**	**280**	**163,5**	**256**	**160,1**	**250**	**158,2**	**259**	**154,7**	**238**	**145,6**	**233**
Support Staff (research)[4]	44,8	54	36,9	51	43,7	56	44,9	66	37,5	12	38,8	55
Support Staff (managerial)[5]	5,9	7	5,8	7	5,5	6	6,5	8	6,5	8	6,5	8
Total Support Staff	**50,7**	**61**	**42,7**	**58**	**49,2**	**62**	**51,4**	**74**	**44,0**	**20**	**45,3**	**63**
Total Staff incl academic hospital	**226**	**341**	**206,2**	**314**	**209,3**	**312**	**209,6**	**333**	**198,7**	**258**	**190,9**	**296**
Total Staff excl academic hospital	**219,2**	**309**	**199,5**	**280**	**202,5**	**279**	**203,1**	**301**	**192,2**	**226**	**184,4**	**264**
External PhD students[6]	93		119		116		108		148		157	
Honorary professor[7]	nb		nb		nb		nb		nb		nb	
Visiting fellows/professors[8]	nb		nb		nb		nb		nb		nb	

#: Number of persons active on the research unit research activities on 31-dec of any year/average MYE (men year equivalents)
fte: Sum of actual fte-factors (in fulltime equivalents) labelled on the research unit research activities on 31-dec on any year/average
Note 1: Comparable with WOPI-categories HGL, UHD and UD; tenured and non-tenured staff appointed at the FHML.
Note 2: Comparable with WOPI-category 'Onderzoeker' (1, 2, 3, 4), with completed PhD, not belonging to scientific staff (with WOPI-categories HGL, UHD and UD)
Note 3: Standard PhD (employed)
Note 4: All support staff working on research (research assistants, lab technicians, and other support staff not working at the management office)
Note 5: Support staff working at the School's management office including the scientific director
Note 6: External PhD (externally or internally funded but not employed)
Note 7: Scientific staff, employed unpaired professor
Note 8: Visiting fellows are researchers/professors who visit the School for a period of typically one week up to three months to work with Schools staff members.

Table 2.2 Research staff at division level (2015-2020)

Division 1: Obesity, Diabetes & Cardiovascular Health	2017		2018		2019		2020	
	fte	#	fte	#	fte	#	fte	#
Scientific Staff FHML[1]	11,2	28	11,6	34	12,1	34	12,8	32
Scientific Staff academic hospital	2,2	10	2,0	9	2,0	9	2,0	9
Post Docs[2]	12,4	17	14,8	23	13,1	18	10,7	15
Internal PhD-students[3]	47,4	50	51,4	54	53,2	57	51,9	55
Total Research Staff	**73,2**	**105**	**79,8**	**120**	**80,4**	**118**	**77,3**	**111**
Support Staff (research)[4]	19,9	29	22,1	35	18,9	30	18,6	30
Support Staff (managerial)[5]	1,8	5	2,2	8	2,2	8	2,2	8
Total Support Staff	**21,7**	**34**	**24,2**	**43**	**21,0**	**38**	**20,7**	**38**
Total Staff incl academic hospital	**94,9**	**139**	**104,0**	**163**	**101,4**	**156**	**98,0**	**149**
Total Staff excl academic hospital	**92,7**	**129**	**102,0**	**154**	**99,4**	**147**	**96,0**	**140**
External PhD students[6]	**28**		24		41		38	
Honorary professor[7]	nb		nb		nb		nb	
Visiting fellows/professors[8]	nb		nb		nb		nb	

Division 2: Liver & Digestive Health	2017		2018		2019		2020	
	fte	#	fte	#	fte	#	fte	#
Scientific Staff FHML[1]	5,4	18	4,4	14	4,9	14	4,9	17
Scientific Staff academic hospital	3,6	15	3,5	14	3,5	14	3,5	14
Post Docs[2]	3,8	6	4,2	7	5,2	6	3,7	6
Internal PhD-students[3]	20,6	23	18,1	26	20,4	25	18,0	18
Total Research Staff	**33,4**	**62**	**30,2**	**61**	**34,0**	**59**	**30,1**	**55**
Support Staff (research)[4]	11,6	15	10,6	16	8,0	12	8,9	14
Support Staff (managerial)[5]	1,8	5	2,2	8	2,2	8	2,2	8
Total Support Staff	**13,4**	**20**	**12,8**	**24**	**10,2**	**20**	**11,1**	**22**
Total Staff incl academic hospital	**46,8**	**82**	**42,9**	**85**	**44,2**	**79**	**41,1**	**77**
Total Staff excl academic hospital	**43,2**	**67**	**39,4**	**71**	**40,7**	**65**	**37,6**	**63**
External PhD students[6]	45		48		58		70	
Honorary professor[7]	nb		nb		nb		nb	
Visiting fellows/professors[8]	nb		nb		nb		nb	

Division 3: Respiratory & Age-related Health	2017		2018		2019		2020	
	fte	#	fte	#	fte	#	fte	#
Scientific Staff FHML[1]	9,9	24	10,2	25	10,7	26	10,2	26
Scientific Staff academic hospital	0,9	8	1,0	9	1,0	9	1,0	9
Post Docs[2]	4,8	9	5,0	9	5,0	7	4,1	6
Internal PhD-students[3]	37,8	40	32,1	36	23,7	28	23,1	27
Total Research Staff	**53,4**	**81**	**48,2**	**79**	**40,3**	**70**	**38,3**	**68**
Support Staff (research)[4]	12,3	19	12,3	17	10,7	16	11,3	18
Support Staff (managerial)[5]	1,8	5	2,2	8	2,2	8	2,2	8
Total Support Staff	**14,1**	**24**	**14,4**	**25**	**12,8**	**24**	**13,4**	**26**
Total Staff incl academic hospital	**67,5**	**105**	**62,6**	**104**	**53,1**	**94**	**51,7**	**94**
Total Staff excl academic hospital	**66,6**	**97**	**61,6**	**95**	**52,1**	**85**	**50,7**	**85**
External PhD students[6]	38		36		50		49	
Honorary professor[7]	nb		nb		nb		nb	
Visiting fellows/professors[8]	nb		nb		nb		nb	

#: Number of persons active on the research unit research activities on 31-dec of any year/average MYE (men year equivalents)
fte: Sum of actual fte-factors (in fulltime equivalents) labelled on the research unit research activities on 31-dec on any year/average
Note 1: Comparable with WOPI-categories HGL, UHD and UD; tenured and non-tenured staff appointed at the FHML.
Note 2: Comparable with WOPI-category 'Onderzoeker' (1, 2, 3, 4), with completed PhD, not belonging to scientific staff (with WOPI-categories HGL, UHD and UD)
Note 3: Standard PhD (employed)
Note 4: All support staff working on research (research assistants, lab technicians, and other support staff not working at the management office)
Note 5: Support staff working at the School's management office including the scientific director
Note 6: External PhD (externally or internally funded but not employed)
Note 7: Scientific staff, employed unpaired professor
Note 8: Visiting fellows are researchers/professors who visit the School for a period of typically one week up to three months to work with Schools staff members.

Table 2.3 Funding at NUTRIM level (2015-2020)

NUTRIM	2015		2016		2017		2018		2019		2020	
	fte[5]	%	fte	%	fte	%	fte	%	fte	%	fte	%
Funding												
-Direct funding[1]	31,7	19	33	21	36,2	23	36,3	24	36,3	24	33,9	24
-Research funds[2]	17,7	11	25,8	17	21	13	23,7	16	26	17	26,5	19
-Contract research[3]	117	70	95,5	62	99,4	63	92,6	61	86,8	58	78,8	57
-Other	0	0	0	0	0	0	0	0	0	0	0	0
Total funding (excl. hospital)[4]	**166,4**	**100**	**154,3**	**100**	**156,6**	**100**	**152,6**	**100**	**149,1**	**100**	**139,1**	**100**
	k€	**%**	**k€**	**%**	**k€**	**%**	**k€**	**%**	**k€**	**%**	**k€**	**%**
Expenditure												
-Personnel costs	12.165	74	11.650	71	12.298	72	12.701	71	13.152	70	12.655	75
-Other costs	4.303	26	4.874	29	4.764	28	5.181	29	5.757	30	4.280	25
Total expenditure	**16.468**	**100**	**16.524**	**100**	**17.062**	**100**	**17.882**	**100**	**18.909**	**100**	**16.935**	**100**

Note 1: Direct funding by FHML/ Maastricht University ('basis financiering' / lump sum budget).
Note 2: Research grants obtained in national scientific competition (e.g. grants from NWO, ZonMw and KNAW)
Note 3: Research contracts for specific research projects obtained from external organisations, such as industry, governmental ministries, European organisations, including ERC, and charitable organisations
Note 4: Funds that do not fit into the other categories.

Note 5: The funding in fte includes the total research staff but excludes the academic hospital-staff

Table 2.4 Funding at division level (2015-2020)

Division 1: Obesity, Diabetes & Cardiovascular Health	2017		2018		2019		2020	
	fte	%	fte	%	fte	%	fte	%
Funding								
-Direct funding[1]	11,7	17	14,7	19	13,5	17	14,1	19
-Research funds[2]	9,8	14	13,4	17	14,3	18	15,0	20
-Contract research[3]	49,0	70	49,7	64	50,5	64	46,3	61
-Other	0	0	0	0	0	0	0	0
Total funding (excl. hospital)[4]	**70,4**	**100**	**77,8**	**100**	**78,3**	**100**	**75,3**	**100**
	k€	**%**	**k€**	**%**	**k€**	**%**	**k€**	**%**
Expenditure								
-Personnel costs	5.333	73	6.076	70	6.525	67	6.375	77
-Other costs	1.927	27	2.573	30	3.201	33	1.895	23
Total expenditure	**7.260**	**100**	**8.649**	**100**	**9.727**	**100**	**8.270**	**100**

Division 2: Liver & Digestive Health	2017		2018		2019		2020	
	fte	%	fte	%	fte	%	fte	%
Funding								
-Direct funding[1]	7,0	22	10,5	39	9,2	31	8,0	30
-Research funds[2]	8,3	26	7,3	27	8,7	29	7,0	26
-Contract research[3]	16,7	52	9,4	35	12,1	40	11,6	44
-Other	0	0	0	0	0	0	0	0
Total funding (excl. hospital)[4]	**31,9**	**100**	**27,2**	**100**	**30**	**100**	**26,6**	**100**
	k€	**%**	**k€**	**%**	**k€**	**%**	**k€**	**%**
Expenditure								
-Personnel costs	2.298	66	2.242	68	2.451	70	2.528	76
-Other costs	1.187	34	1.069	32	1.069	30	787	24
Total expenditure	**3.485**	**100**	**3.311**	**100**	**3.520**	**100**	**3.315**	**100**

Division 3: Respiratory & Age-related Health	2017		2018		2019		2020	
	fte	%	fte	%	fte	%	fte	%
Funding								
-Direct funding[1]	17,6	32	11,2	23	12,1	31	11,8	32
-Research funds[2]	3,0	6	3	6	3	8	4,5	12
-Contract research[3]	33,8	62	33,5	70	24,2	62	20,9	56
-Other	0	0	0	0	0	0	0	0
Total funding (excl. hospital)[4]	**54,4**	**100**	**47,7**	**100**	**39,3**	**100**	**37,2**	**100**
	k€	**%**	**k€**	**%**	**k€**	**%**	**k€**	**%**
Expenditure								
-Personnel costs	4.039	71	4.171	72	3.798	71	3.485	69
-Other costs	1.666	29	1.621	28	1.524	29	1.573	31
Total expenditure	**5.705**	**100**	**5.792**	**100**	**5.322**	**100**	**5.058**	**100**

Note 1: Direct funding by FHML/ Maastricht University ('basis financiering' / lump sum budget).
Note 2: Research grants obtained in national scientific competition (e.g. grants from NWO, ZonMw and KNAW)
Note 3: Research contracts for specific research projects obtained from external organisations, such as industry, governmental ministries, European organisations, including ERC, and charitable organisations
Note 4: Funds that do not fit into the other categories.
Note 5: The funding in fte includes the total research staff but excludes the academic hospital-staff

Table 2.5: PhD defences for NUTRIM and the divisions (2015-2020)

Year	1 - Obesity, Diabetes & Cardiovascular Health	2 - Liver & Digestive Health	3 - Respiratory & Age-related Health	Total
2015				39,47
2016				41,10
2017	13,87	16,34	16,16	46,37
2018	11,50	13,00	10,38	34,88
2019	8,50	12,50	14,40	35,40
2020	12,33	10,25	13,50	36,08
Total	**46,20**	**52,09**	**54,44**	**233,30**
Average per year	**11,55**	**13,02**	**13,61**	**38,88**

Table 2.6: Graduation rates of internal PhD candidates (at NUTRIM level)

Enrolment				Success rates					
Starting year	**Enrolment Male**	**Female**	**Total (M+F)**	**Graduated in year 4 or earlier**	**Graduated in year 5**	**Graduated in year 6**	**Graduated in year 7 or later**	**Not yet finished**	**Discon-tinued**
2011 (T-9)	9	14	23	0 / 0%	10 / 43%	7 / 30%	3 / 13%	2 / 9%	0 / 0%
2012 (T-8)	11	10	21	4 / 19%	9 / 43%	4 / 19%	1 / 5%	2 / 10%	1 / 5%
2013 (T-7)	14	17	31	5 / 16%	13 / 42%	5 / 16%	3 / 10%	2 / 6%	3 / 10%
2014 (T-6)	12	18	30	4 / 13%	10 / 33%	4 / 13%	1 / 3%	9 / 30%	2 / 7%
2015 (T-5)	7	20	27	3 / 11%	12 / 44%	2 / 7%	- / -	7 / 26%	3 / 11%
2016 (T-4)	16	16	32	1 / 3%	8 / 25%	1 / 3%	- / -	19 / 59%	3 / 9%
Total	**69**	**95**	**164**	**17 / 10%**	**62 / 38%**	**23 / 14%**	**8 / 5%**	**41 / 25%**	**12 / 7%**

(1) Standard PhD-candidate with employee status and conducting research with primary aim/obligation to graduate; (AiO, promovendus)

(2) T= last year of the evaluation period

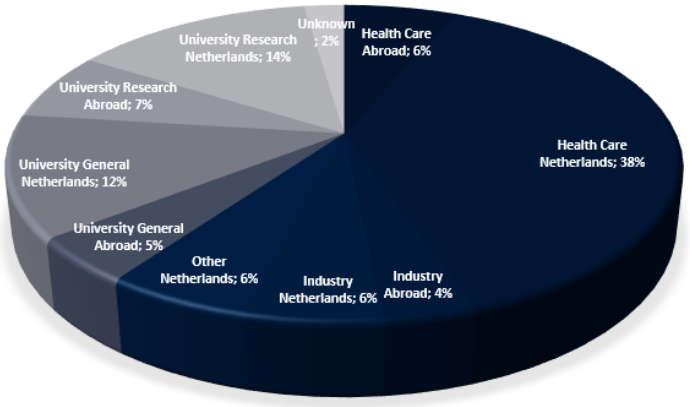
Table 2.7: Graduation rates of external PhD candidates (at NUTRIM level)

Enrolment				Success rates					
Starting year	**Enrolment Male**	**Female**	**Total (M+F)**	**Graduated in year 4 or earlier**	**Graduated in year 5**	**Graduated in year 6**	**Graduated in year 7 or later**	**Not yet finished**	**Discon-tinued**
2011 (T-9)	2	3	5	0 / 0%	1 / 20%	0 / 0%	2 / 40%	2 / 40%	0 / 0%
2012 (T-8)	6	9	15	1 / 7%	6 / 40%	2 / 13%	4 / 27%	1 / 7%	1 / 7%
2013 (T-7)	15	7	22	6 / 27%	10 / 45%	0 / 0%	5 / 23%	1 / 5%	0 / 0%
2014 (T-6)	10	10	20	0 / 0%	4 / 20%	3 / 15%	3 / 15%	8 / 40%	2 / 10%
2015 (T-5)	17	6	23	7 / 30%	3 / 13%	3 / 13%	1 / 4%	9 / 39%	0 / 0%
2016 (T-4)	26	19	45	7 / 16%	6 / 13%	0 / 0%	- / -	28 / 62%	4 / 9%
Total	**76**	**54**	**130**	**21 / 13%**	**30 / 18%**	**8 / 5%**	**15 / 9%**	**49 / 30%**	**7 / 4%**

(1) PhD-candidate without employee status and conducting research with primary aim to graduate;

(2) T= last year of the evaluation period

Figure 2.1: First job of PhD candidates after graduation 2015-2020



Category	Netherlands	Abroad	Total
Health Care	38%	6%	45%
Industry	6%	4%	9%
University General	12%	5%	17%
University Research	14%	7%	21%
Other	6%	0%	6%
Unknown	-	-	2%
Total	76%	22%	100%

Annex 3: Case studies

DIVISION 1

01 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.

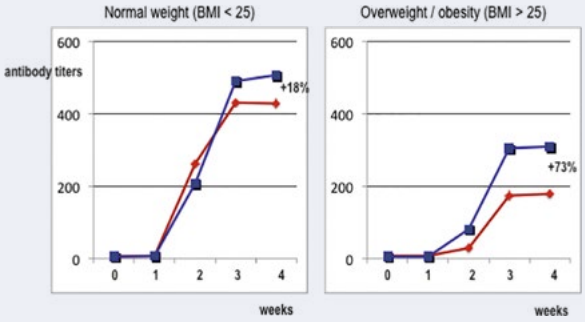
Our research group is internationally well-recognized for their contributions to the complete spectrum of research approaches (nutrients - whole foods - dietary patterns). We apply innovative technologies (such as vascular parameters in periphery and brain, fundus analysis, markers for cholesterol absorption 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.

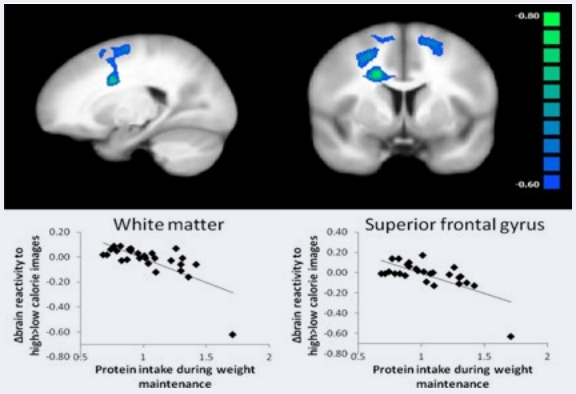


Our recent studies also showed that in LDL-receptor knockout mice plant sterols and stanols inhibited liver inflammation, as induced by a high-fat, high- cholesterol diet (collaboration with Prof. R. Shiri-Sverdlov, division 2). This was shown by lower CD68 staining and a lower number of Kupffer cells, 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.
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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.

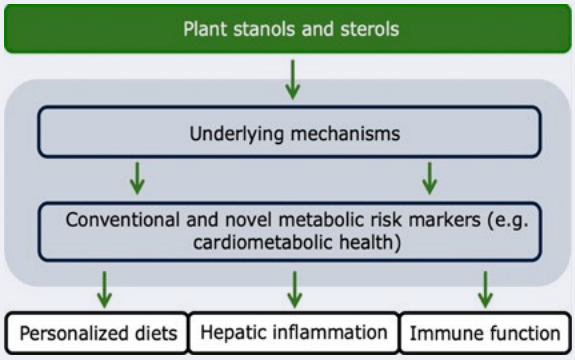
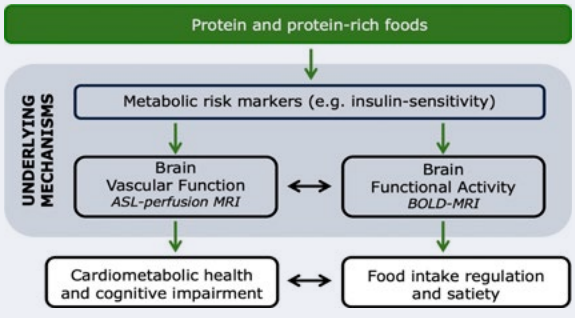


Figure 4: Ongoing longer-term intervention studies in the field of proteins and protein-rich foods.



02 COACH Childhood obesity; consequences, prevention and treatment

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

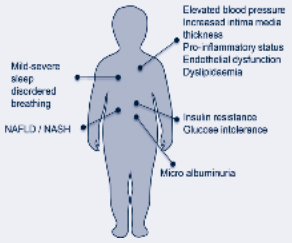
Background

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.

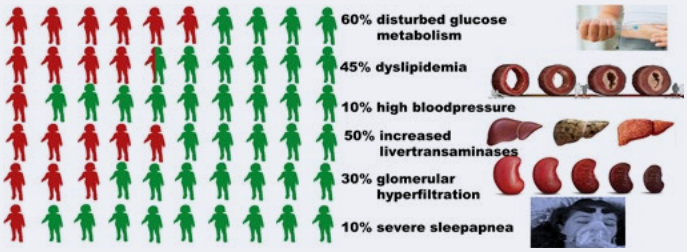
Major breakthroughs

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



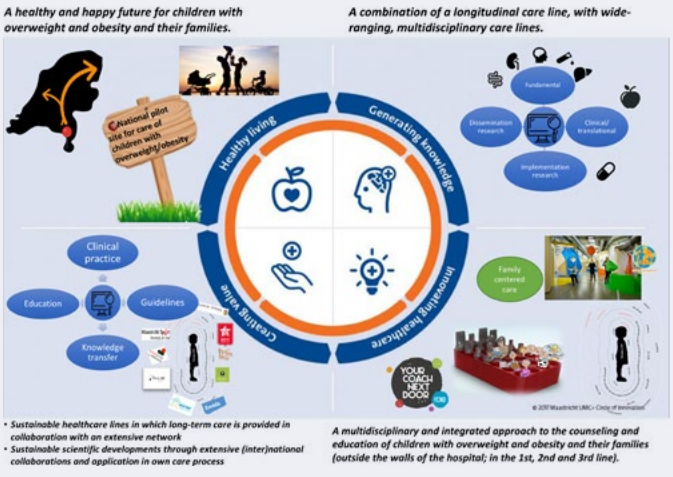
Early stages of chronic diseases in children with overweight/obesity in Limburg



>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



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

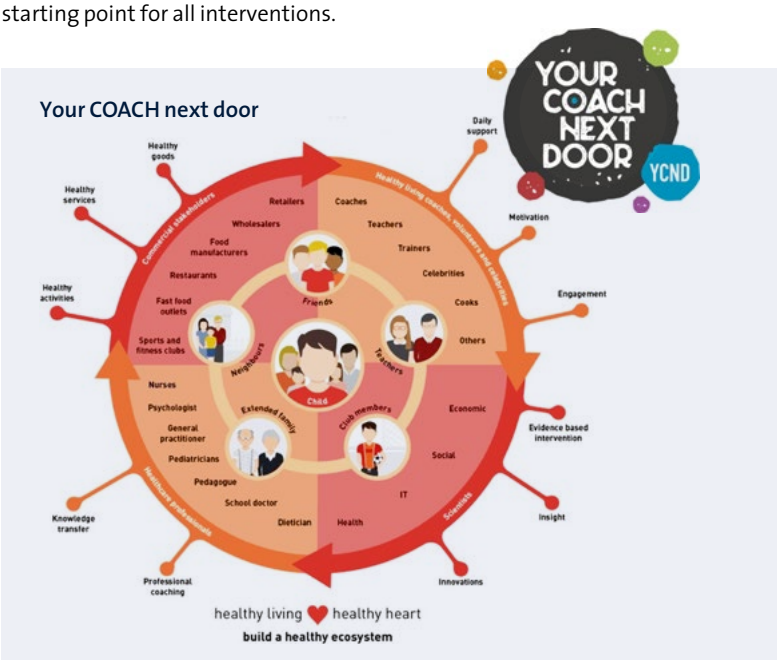
With our research data, we generate knowledge and insights on new methods and markers to early recognize children with a specific high risk for metabolic derangement, diabetes mellitus, cardiovascular disturbances and liver pathology. In addition, insight is gained on the interrelationship of anthropometric 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

Funfilled activities (COACH FOOD)

Policy makers

Funfilled activities (COACH SPORTS)

03 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

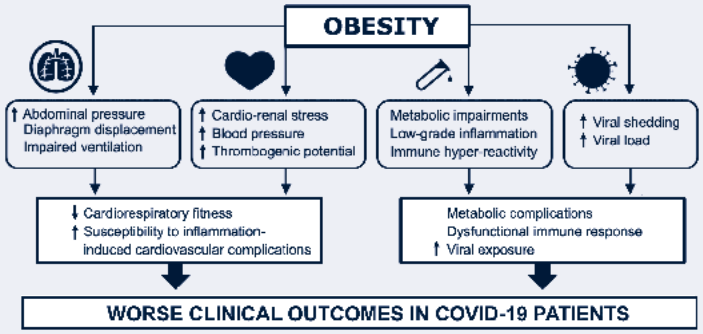
Our research efforts have mainly focused on the metabolic implications of adipose tissue dysfunction in people with obesity. We investigated the metabolic and hemodynamic effects of the renin-angiotensin system (RAS) in obesity for more than 15 years, showing that angiotensin II (Ang II), the main effector 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.

Major Breakthroughs

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

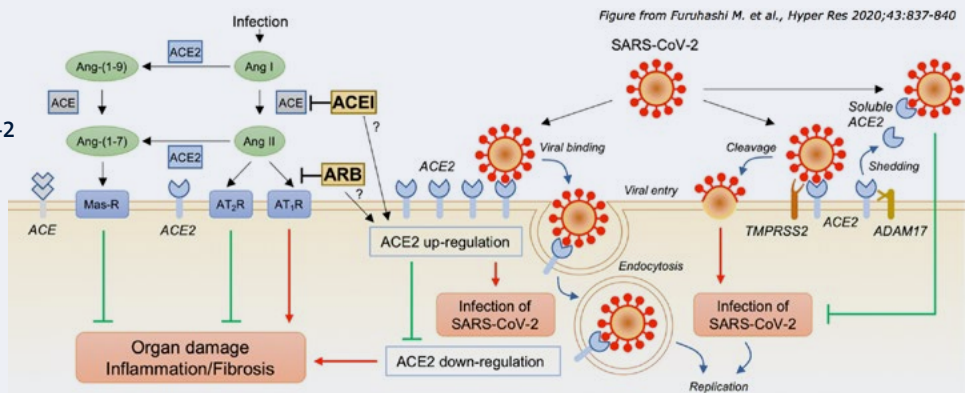
Obesity not only increases the risk of many non-communicable diseases such as type 2 diabetes and cardiovascular diseases, but also seems to impact communicable diseases.

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



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.
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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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10. Moran CS, Biros E, Krishna SM, Wang Y, Tikellis C, Morton SK, et al. Resveratrol Inhibits Growth of Experimental Abdominal Aortic Aneurysm Associated With Upregulation of Angiotensin-Converting Enzyme 2. Arterioscler Thromb Vasc Biol. 2017;37:2195-2203.
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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.

04 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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Berendsen, B.A.J., Kremers, S.P.J., Savelberg, H.H.C.M., Schaper, N.C., Hendriks, M.R.C. (2015). The implementation and sustainability of a combined lifestyle intervention in primary care: mixed method process evaluation. BMC Family Practice, 16, 37

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.
2. AVLEG: Resultaten pilot met CZ en Universiteit Maastricht positief!
3. Van Rinsum, C.E., Gerards, S.M.P.L., Rutten, G.M., Van de Goor, L.A.M., Kremers, S.P.J. (2018). Coaching op Leefstijl (CooL): Eindrapportage van een implementatie- en monitoringstudie. Maastricht University.
4. Algemeen Dagblad, 16-4-2018. Patiënten leren zelf te beslissen over gezondere leefstijl.
5. Johannesma, M., Van de Goor, I., Kremers. S. Leefstijl-interventies onderdeel van verzekerde curatieve zorg. Advisory letter sent to Tweede Kamer, 21-5-2018.
6. Kamerbrief over basispakket zorgverzekeringswet.
7 ZonMw - 20 jaar preventie. Interview Stef Kremers, Maastricht University: 'Gezond gedrag volhouden is lastiger dan een paar kilo's kwijtraken'
8. Zorginstituut Nederland: Standpunt gecombineerde leefstijlinterventie (GLI) bij overgewicht en obesitas.
9. Helmink, J.M.H., Raaijmakers, L.G.M., Rutten, G.M., Kremers, S.P.J., De Vries, N.K. (2013). Gecombineerde Leefstijl-interventies in Nederland: Ervaringen uit de BeweegKuur. Tijdschrift voor Gezondheidswetenschappen, 91, 88-90.
10. Van Rinsum, C., Gerards, S., Rutten, G., Van de Goor, I., Kremers, S (2018). Coaching op Leefstijl: de leefstijlcoach als spin in het web? Tijdschrift voor gezondheidswetenschappen, 96, 189-193.

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.

05 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.
- Ten Hoor GA, Rutten GM, Van Breukelen GJP, Kok G, Ruiter RAC, Meijer K, Kremers SPJ, Feron FJM, Crutzen R, Schols AMJW, Plasqui G. Strength exercises during physical education classes in secondary schools improve body composition: a cluster randomized controlled trial.
- McCrum C, Karamanidis K, Grevendonk L, Zijlstra W, Meijer K. (2020) Older adults demonstrate interlimb transfer of reactive gait adaptations to repeated unpredictable gait perturbations. GeroScience. 42(1): 39-49. doi: 10.1007/s11357019-00130
- Berkel AE, Bongers BC, Kotte H, Weltevreden P, de Jongh FH, Eijsvogel MM, Wymenga AN, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NL, Klaase JM. Effects of community-based exercise prehabilitation for patients scheduled for colorectal surgery with high risk for postoperative complications: results of a randomized clinical trial. Ann Surg. In press.
- 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

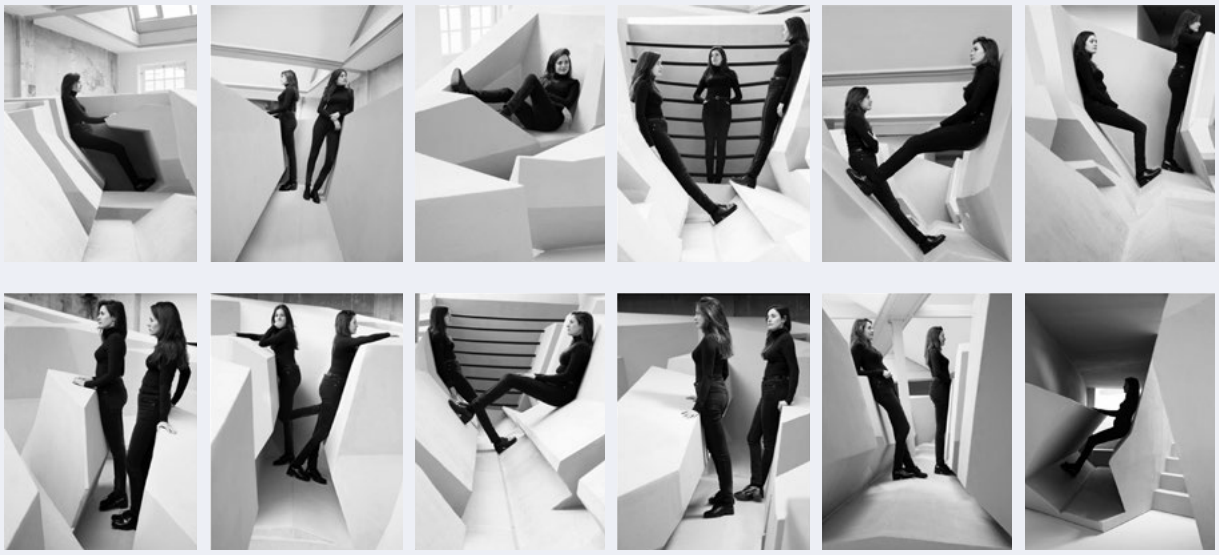
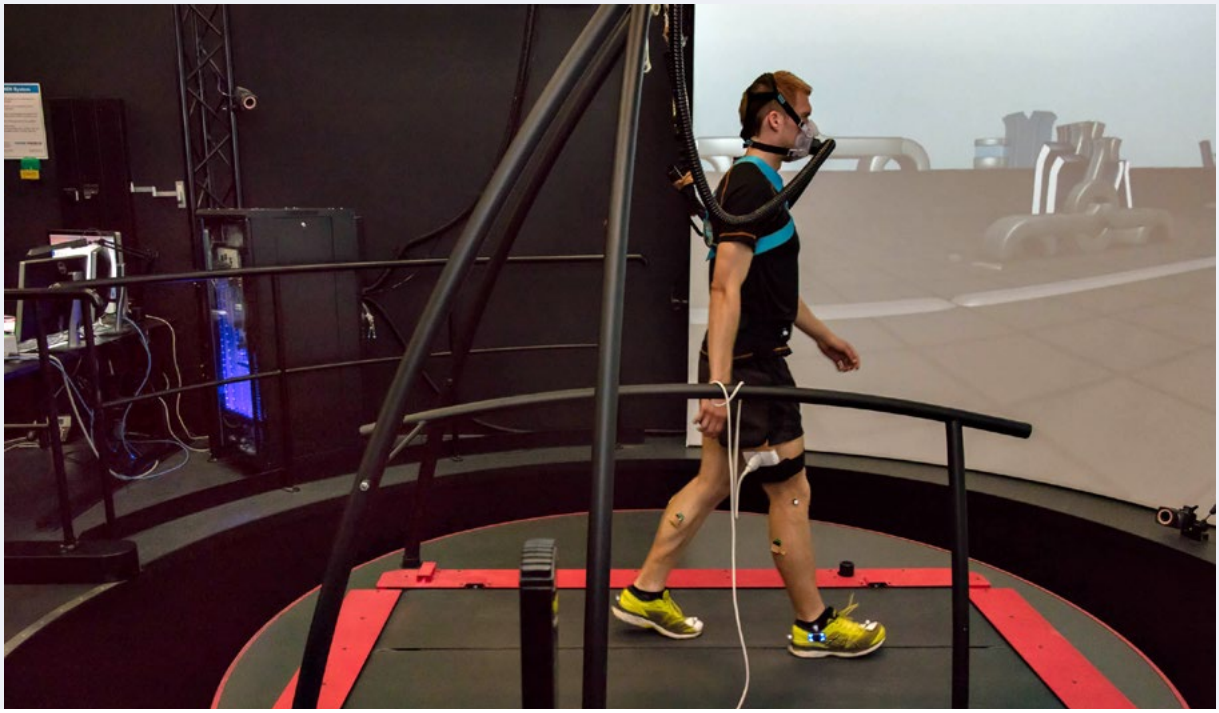


Figure 2
Snapshot of the CAREN system, one of the high-end facilities at the human performance lab. It includes a virtual environment, 3D motion capture, an instrumented treadmill and our in-house developed Omnical setup for indirect calorimetry.



06 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.

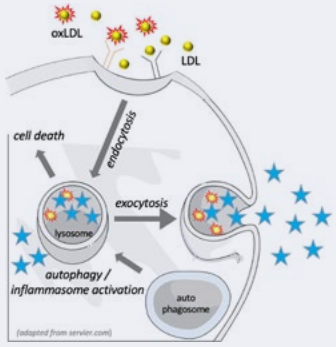
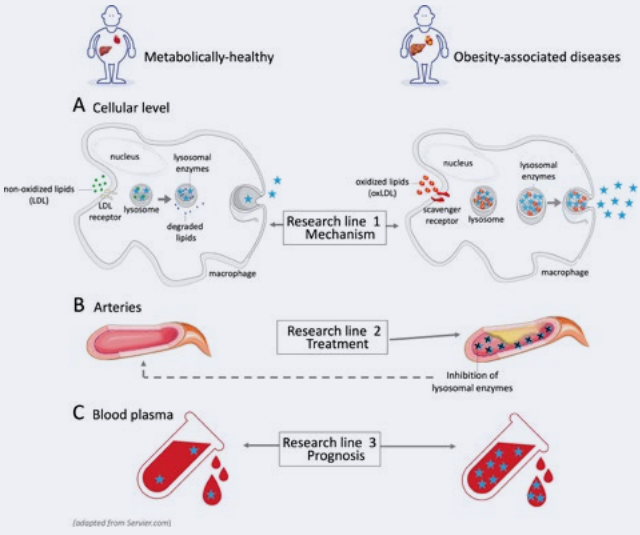


Figure 2: Research focus
Our research consists of three different lines:

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.



07 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

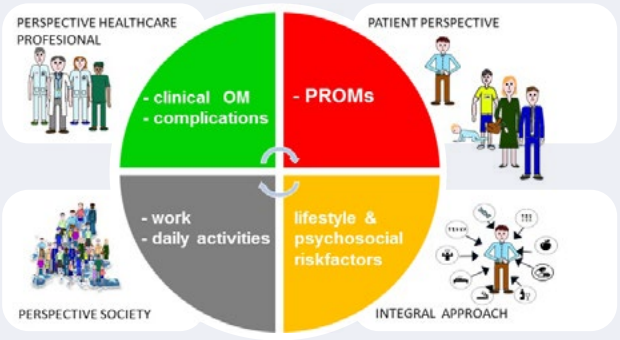


Figure 2: Data2Care Model

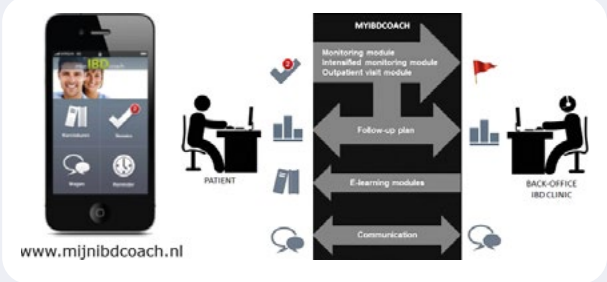
Referred patients from the regional care network are triaged to the optimal care path based on standardized data. During the first outpatient, patients are asked for permission to reuse data for multiple purposes. Standard sets of clinical outcome measures and process outcomes are registered during the 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:

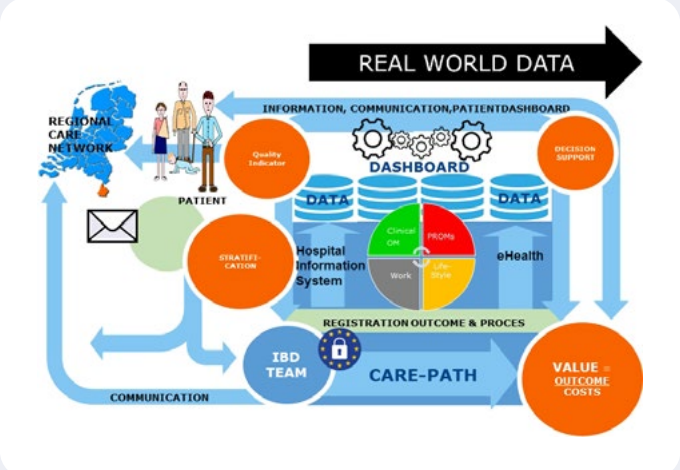
- Shared decision-making in the consultation room with the aid of a patient dashboard and decision support tools.
- Patient group dashboards for evaluation and continuous improvement of the care path. Monitoring the balance between outcomes and costs.
- Communication within the regional care network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

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.





08 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

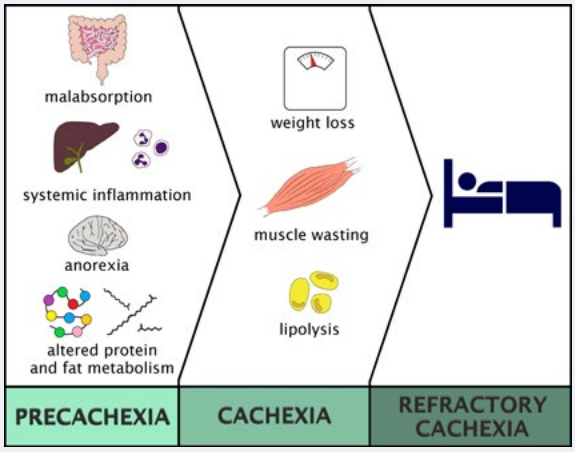
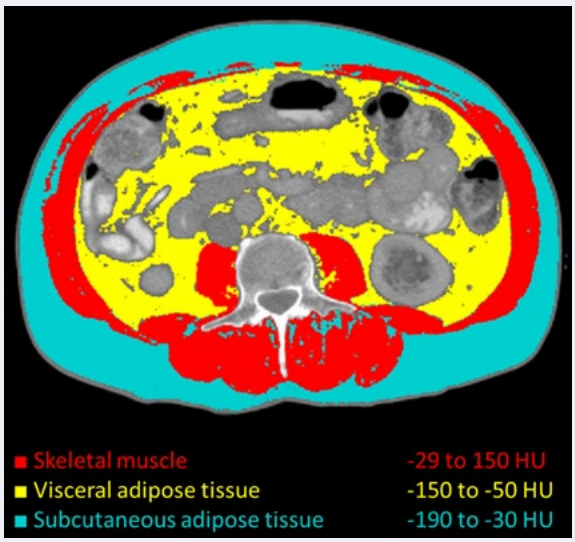


Figure 2



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.

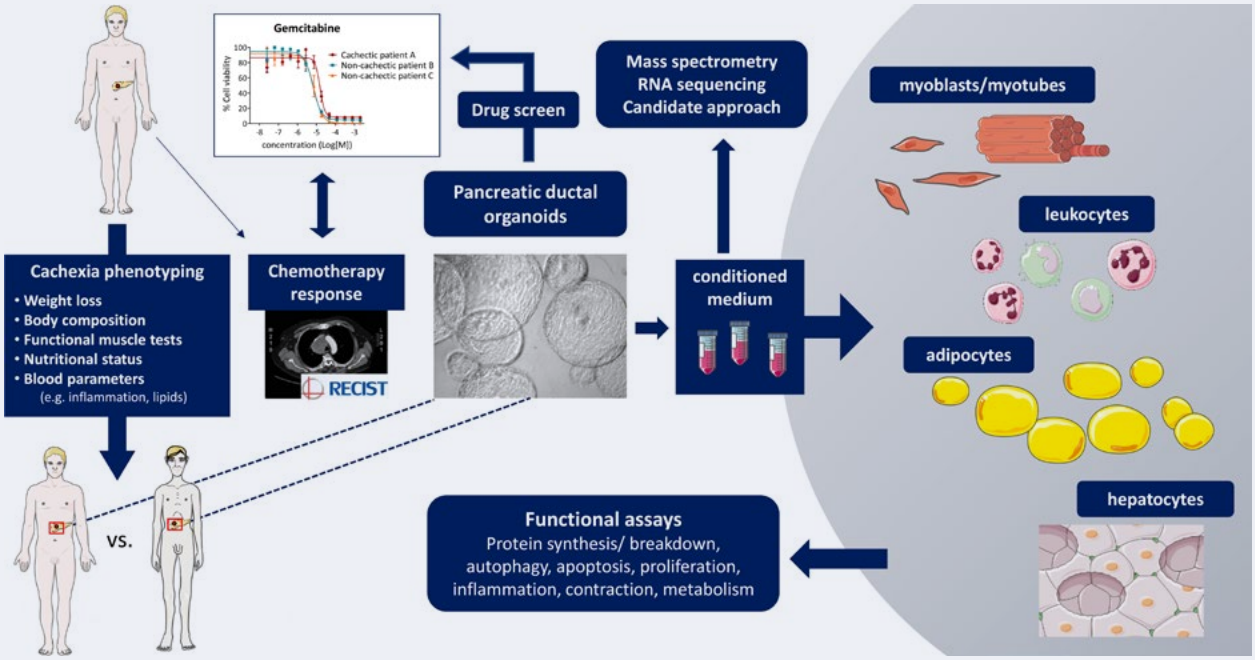
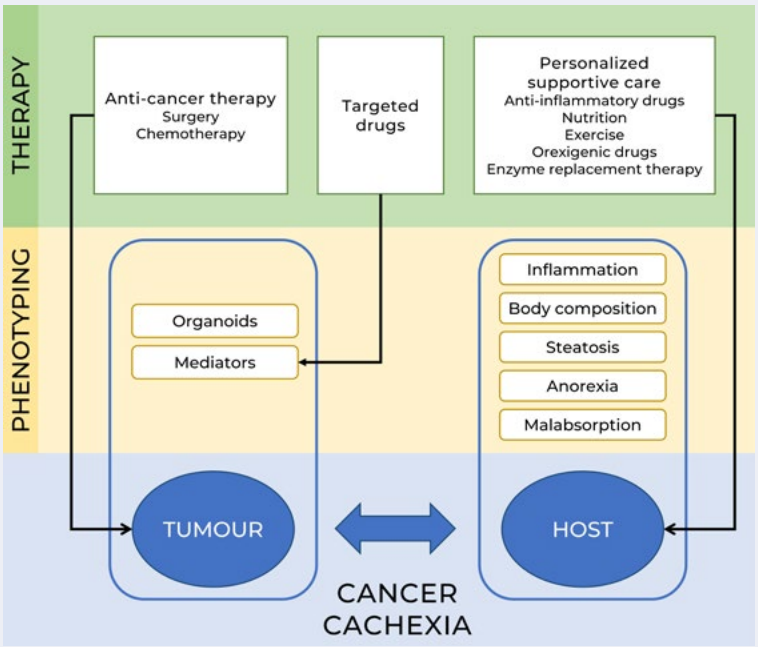


Figure 4
Our research is the result of a true team effort where input from surgeons, oncologists, nurse practitioners, basic researchers, laboratory technicians, and PhD students is integrated in translational studies with a close eye on ultimate clinical benefit for patients.



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.

09 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
HEALTHY MICROBIOME FOR A HEALTHY LIFE
PUBLIC-PRIVATE PARTNERSHIPS
TRAINING AND EDUCATING

10 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.

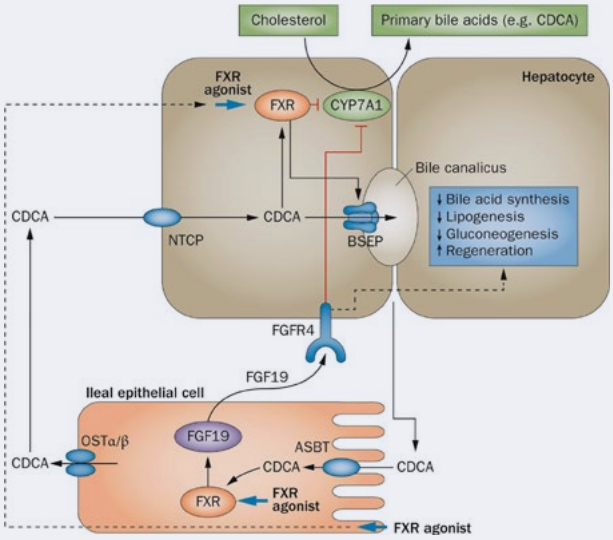


Figure 2: TGR5-expressing tissues and targets
TGR5 signalling in skeletal muscle and brown adipose tissue results in local activation of the deiodinase D102 that generates active thyroid hormone (13), an important regulator of metabolism and energy homeostasis. Bile acids in the intestinal lumen activate 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).

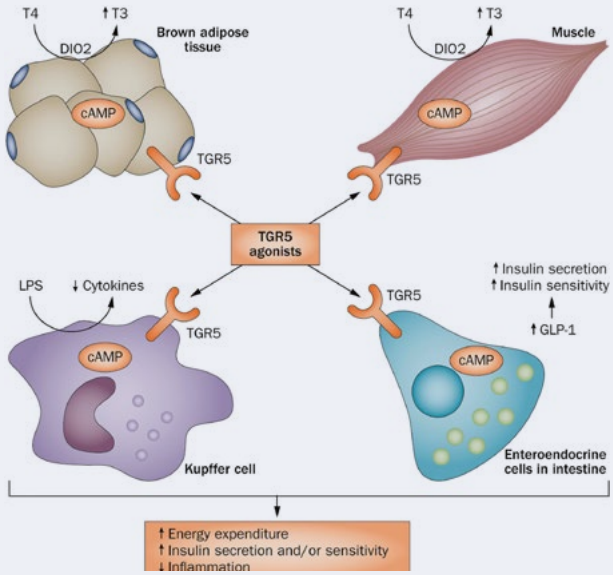
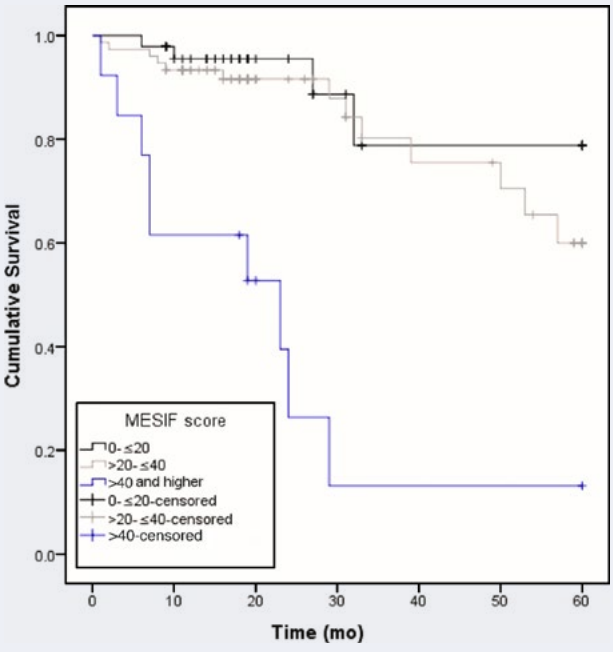


Figure 3: Kaplan-Meier curves for patients with low, intermediate, and high MESIF scores.
Patients with high MESIF scores (> 40) had a significantly lower 5-y survival rate than patients with low (scores between 0 and 20) or intermediate (scores between 20 and 40) MESIF scores (log-rank test, $P < 0.0001$). 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.

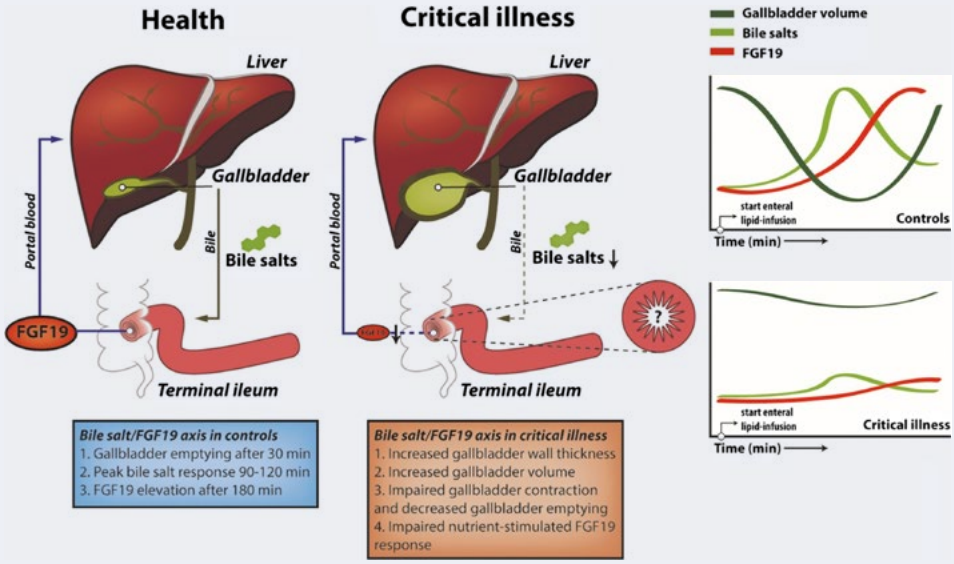


Figure 5: Bile salts appear to be more important than FGF19 in the early phase of human LR.

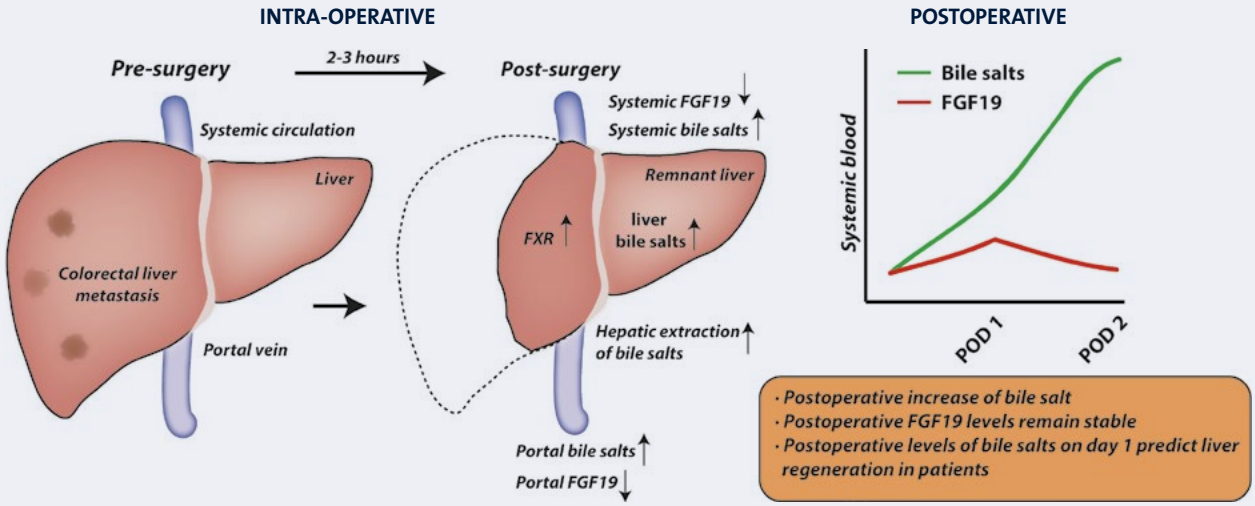
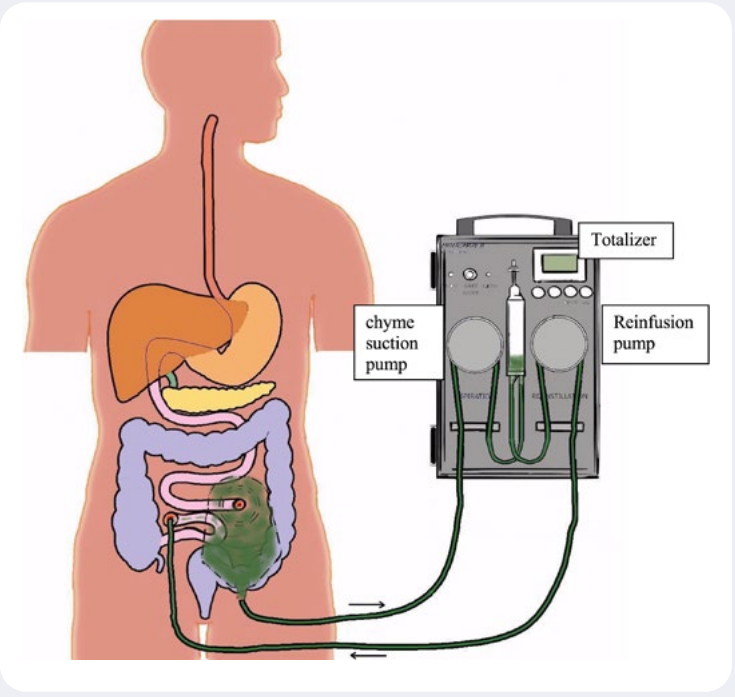


Figure 6: Automated chyme reinfusion in intestinal failure patients with a temporary double enterostomy restores intestinal function and protects against liver injury via increased plasma FGF19 and decreased C4 levels, indicating restored regulation of bile salt synthesis.



11 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 appear 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.

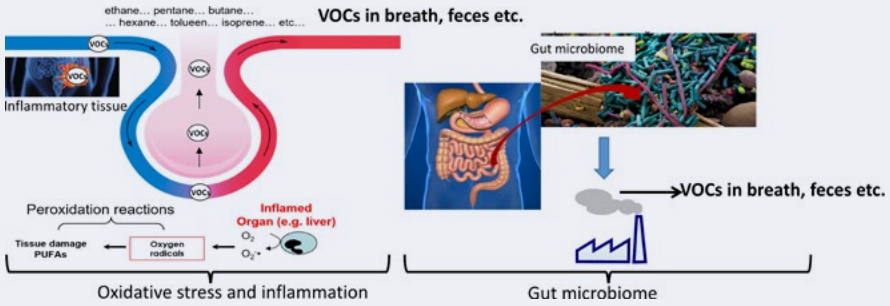


Figure 1. Volatile organic compounds in exhaled breath, feces, blood or urine can be produced as the product of oxidative stress and inflammation or as results of gut microbiome metabolism.

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.

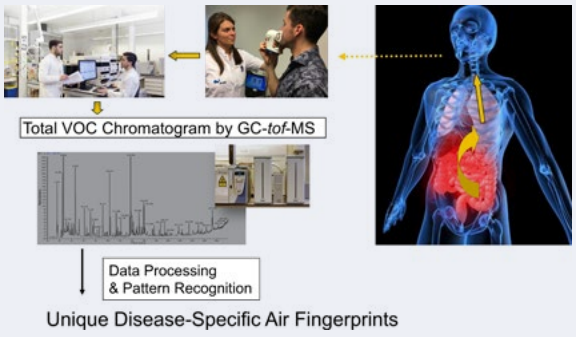


Figure 3: Examples of studies using the VOCS platform; clinical, headspace of bacteria and cells and an in house developed mouse breath sampling device.

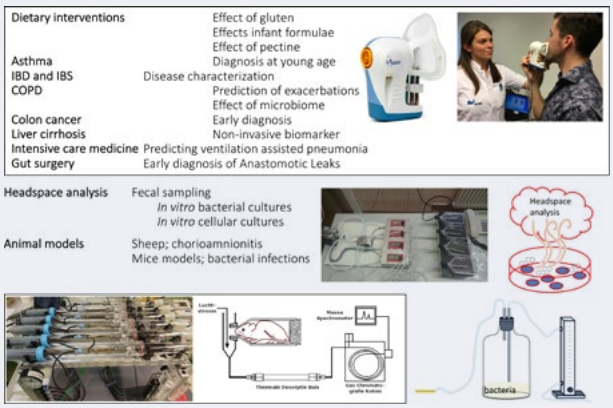
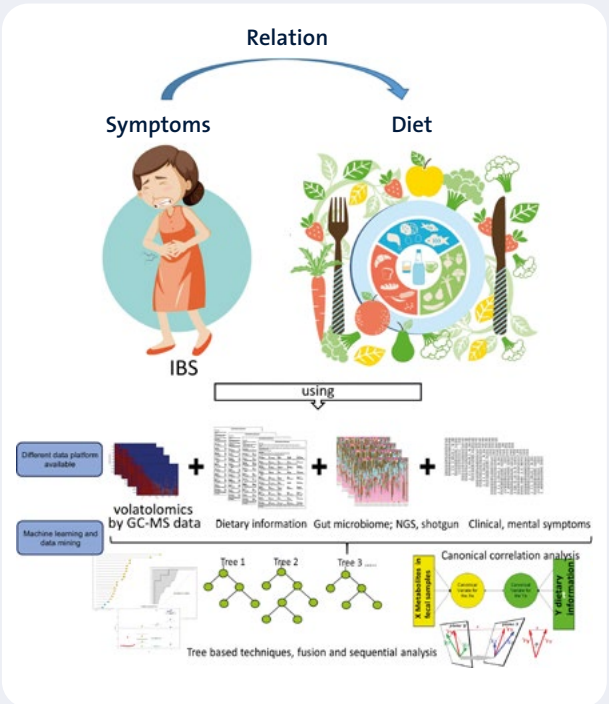


Figure 4: Multidisciplinary approach to find the relation between symptoms in patients and diet. The volatolomics will be combined with microbiome, diet questionnaires and clinical metadata using machine learning and data mining.



12 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.

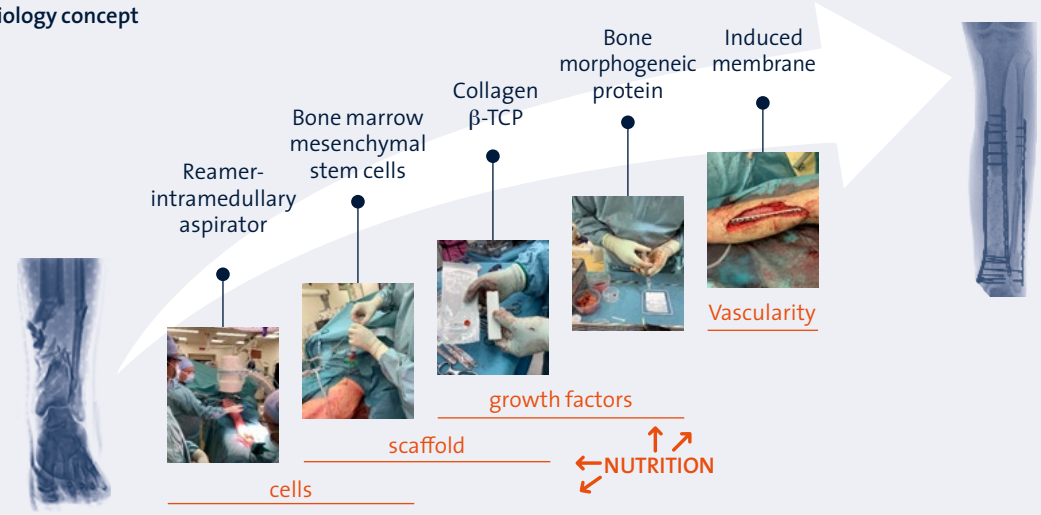
Who is involved?

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

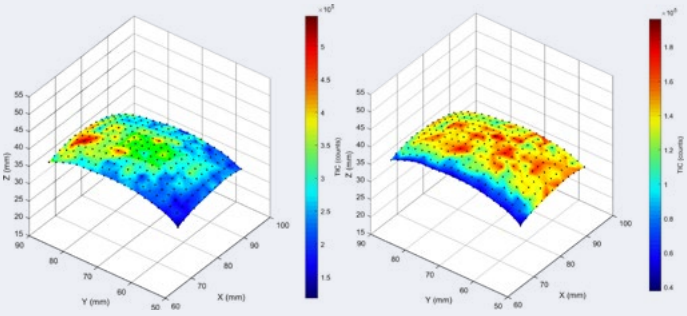


Users and collaborations

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

13 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.

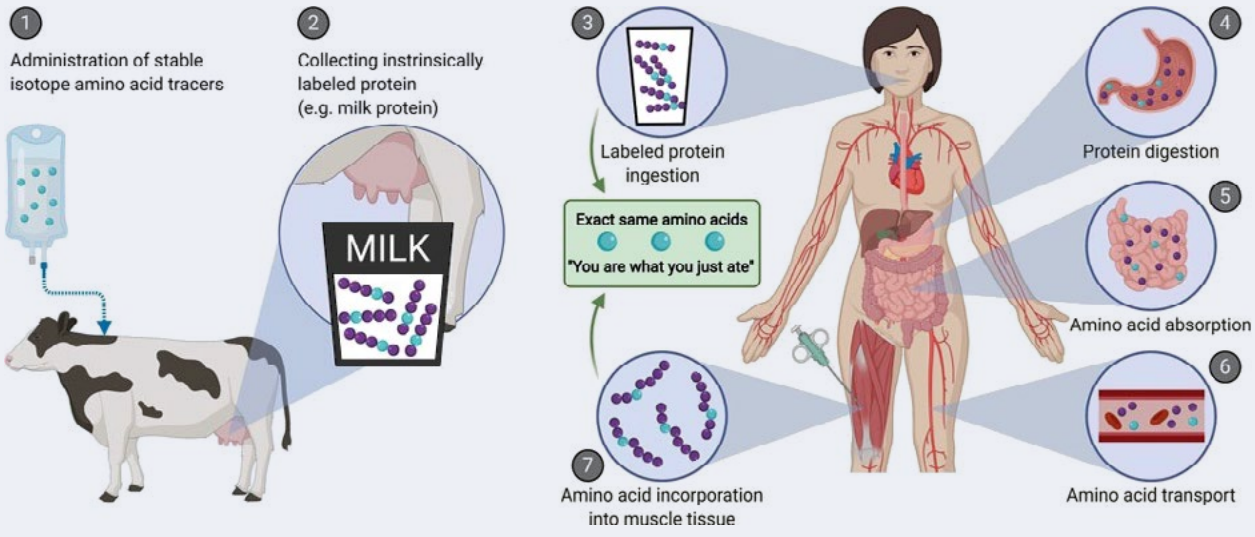
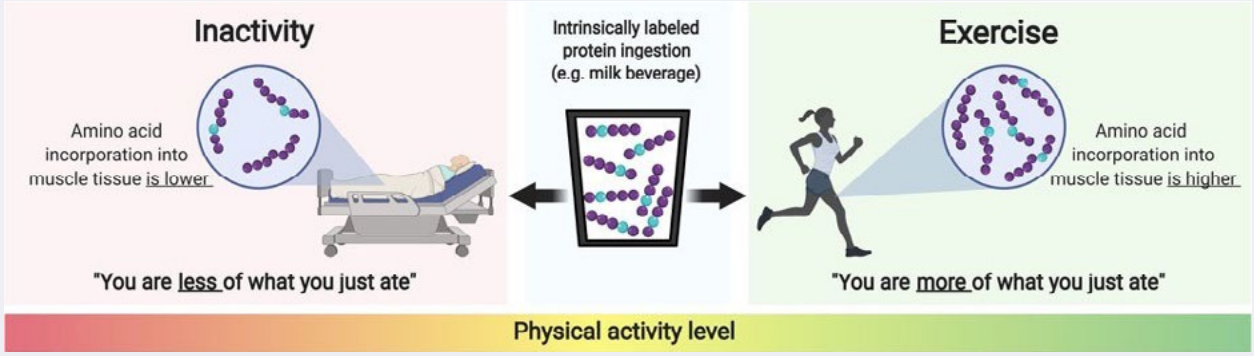


Figure 2: Schematic representation of the impact of physical (in)activity on the incorporation of dietary protein-derived amino acids into skeletal muscle protein.



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.

14 Pulmonary epithelial cells as central players in chronic lung disorders

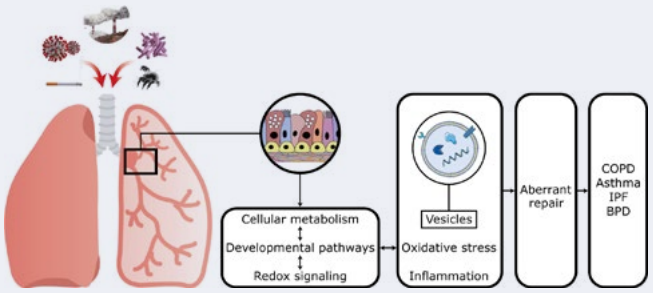
Division 3: Respiratory & Age-related Health
Department of Respiratory Medicine
Department of Pharmacology and Toxicology
Department of Medical Microbiology

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.
4. Proteomic analysis reveals procoagulant properties of cigarette smoke-induced extracellular vesicles. Benedikter, B. J., Bouwman, F. G., Heinzmann, A. C. A., Vajen, T., Mariman, E. C., Wouters, E. F. M., Savelkoul, P. H. M., Koenen, R. R., Rohde, G. G. U., van Oerle, R., Spronk, H. M. & Stassen, F. R. M., 1 Jan 2019, In: Journal of Extracellular Vesicles . 8, 1, 16 p., 1585163.
5. Cigarette smoke extract induced exosome release is mediated by depletion of exofacial thiols and can be inhibited by thiol-antioxidants. Benedikter, B. J., Volgers, C., van Eijck, P. H., Wouters, E. F. M., Savelkoul, P. H. M., Reynaert, N. L., Haenen, G. R. M. M., Rohde, G. G. U., Weseler, A. R. & Stassen, F. R. M., Jul 2017, In: Free Radical Biology and Medicine. 108, p. 334-344 11 p
6. van de Wetering C, Aboushousha R, Manuel AM, Chia SB, Erickson C, MacPherson MB, van der Velden JL, Anathy V, Dixon AE, Irvin CG, Poynter ME, van der Vliet A, Wouters EFM, Reynaert NL, Janssen-Heininger YMW. Pyruvate Kinase M2 Promotes Expression of Proinflammatory Mediators in House Dust Mite-Induced Allergic Airways Disease. J Immunol. 2020.15;204(4):763-774
7. Rutten E, Gopal P, Wouters E, Franssen F, Hageman G, Vanfleteren L, Spruit M, Reynaert N. Various mechanistic pathways representing the ageing process are altered in COPD. Chest. 2016 149(1): 53-61
8. P.Gopal, N.L. Reynaert, J.L.J.M.Scheijen, L. Engelen, C.G.Schalkwijk, F.M.E.Franssen, E.F.M. Wouters, E.P.A. Rutten. Plasma AGEs and skin autofluorescence are increased in COPD. ERJ 2014; 43(2): 430-438.
9. Ine Kuipers, Catherine Moermans, Renaud Louis, Mieke A Dentener, Yvonne Charles Irvin, Christopher Brightling, Yvonne MW Janssen-Heininger, Emiel FM Wouters, Niki L Reynaert. Increased glutaredoxin 1 and decreased protein S-glutathionylation in sputum of asthmatics. ERJ 2013;41(2):469-72.

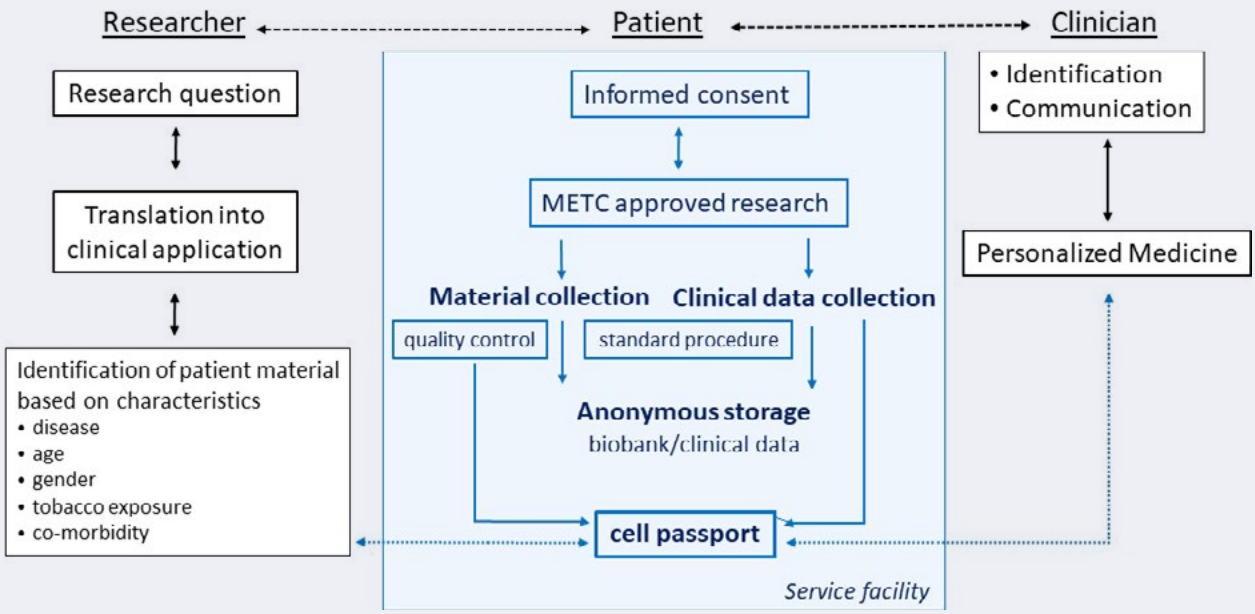
10. Leermakers PA, Remels AHV, Langen RCJ, Schols AMWJ, Gosker HR. Pulmonary inflammation-induced alterations in key regulators of mitophagy and mitochondrial biogenesis in murine skeletal muscle. BMC Pulm Med 2020;20(1):20
11. Aghapour M, Remels AHV, Pouwels SD, Bruder D, Hiemstra PS, Cloonan SM, Heijink IH. Mitochondria: at the crossroads of regulating lung epithelial cell function in chronic obstructive pulmonary disease. Am J Physiol Lung Cell Mol Physiol 2020;318(1):L149-L164

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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