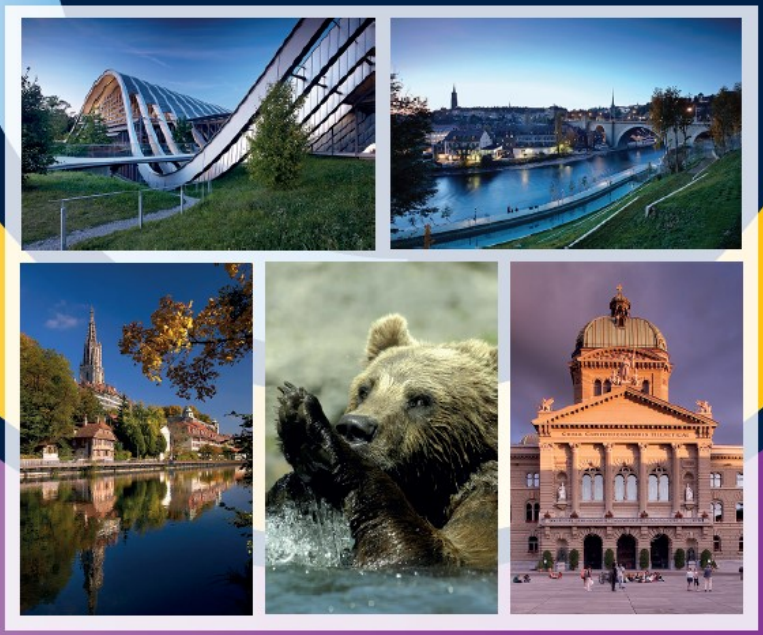
NuGOweek 2019 - 16th edition

9-12 September 2019
Agroscope, Bern, Switzerland



From Foodomics to Nutrigenomics: Translating food composition data into healthy diets

Book of abstracts

In partnership with the National Committee of the International Union of Nutritional Sciences (IUNS) and the Swiss Society for Nutrition (ssn)

NuGO

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Campus Liebefeld
Bern, Switzerland

NuGO is an Association of Universities and Research Institutes focusing on the joint development of the research areas of molecular nutrition, personalised nutrition, nutrigenomics and nutritional systems biology

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Welcome to NuGOweek 2019

Dear NuGOweek participants,

Most of us don't organize our daily lives to optimize our long-term health … yet we do prepare or make decisions about the food we eat every day!

NuGOweek 2019 will emphasize the importance of linking food science to human biology within nutrition research to deliver knowledge that can maintain or even improve health and well-being. The 16th edition of NuGOweek is organized in consecutive sessions addressing the composition, consumption and metabolism of food and diets as well their functional impact on the health of populations and individuals. These topics will be introduced by 7 keynote lectures, each highlighting the important contribution of modern analytical life science technologies to the field of nutrition research. A comprehensive set of 23 oral and 56 poster presentations build the core of NuGOweek 2019 sessions. Among the 145 registered participants, we are particularly pleased that young researchers contribute to a significant proportion of these presentations. The impact of young researchers within the NuGO organization is further underlined in the activities of the early career network (ECN) during NuGOweek.

NuGOweek 2019 will be launched with a timely topic, the impact of climate change on nutrition and health. We warmly invite you to join us on Monday evening for the introductory lecture and a welcome drink with your NuGO colleagues.

During the weekend preceding NuGOweek 2019, 30 young researchers registered to the postgraduate course will follow our course on nutrimetabolomics. This field has emerged during the last decade and has quickly become a key analytical strategy in nutrition science.

NuGO seeks to promote nutrition research on an international scale but this goal is also reached by the local activities of each of the NuGO member institutes. The organization of NuGOweek 2019 by Agroscope in Bern is thus a unique opportunity to promote nutrition research in Switzerland. Notably, a satellite meeting of NuGOweek 2019, set up by the national committee of the International Union of Nutritional Sciences (IUNS) on Thursday afternoon, will bring together more than 90 specialists representing the major stakeholders of the agriculture, food and nutrition sector in Switzerland to address the future of nutrition research. In addition, NuGOweek 2019 highlights will be featured during the annual meeting of the Swiss Society of Nutrition (SSN), which will take place on Friday.

Agroscope is honoured to organize the first NuGOweek in Switzerland. For those visiting the capital city for the first time, you will soon realize that Bern is an accessible city with a beautiful old town registered as a UNESCO World Heritage Site and a stunning landscape marked by the Aare river and surrounding hills. We encourage you to take the opportunity to discover Bern during your stay. We also invite you to participate in the gala dinner on Wednesday evening, which will take place on the Gurten, the Bern local 'mountain'. This will be the chance to discover Bern from above and renew your connections with fellow NuGO participants while walking to the farm-restaurant or sharing a drink!

The organization committees welcome you in Bern and wish you a productive and entertaining NuGOweek 2019.

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Scientific programme

Session 3 - Food and diet metabolism and function

Theatre

Poster

Session 4 - Nutritional epidemiology

Theatre

Poster

Session 5 - Public health nutrition strategies: towards personalized nutrition?

Theatre

Poster

Impact of Climate Change on Nutrition and Health

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Climate change impacts on physical and mental health through various pathways, including heat waves, floods, droughts, fires, air pollution, and ocean acidification. Nutrition has a central and in fact bidirectional role in the link between climate change and health.
On the one hand, climate change has an impact on the nutritional state of people. The above pathways adversely affect agriculture and fishery and thereby food security. In particular, harvesting yield, biodiversity, micro- and macro-nutrient content of food, microbial content of the diet, and infrastructure for food processing and distribution are altered. This poses a challenge to food access, affordability, and dietary patterns. In addition, an increase in exposure of populations to chemicals can result due to excess pollutants in food, for example due to an increased pesticide use.
On the other hand, how and what people eat has an important impact on climate change. It is estimated that globally the food system accounts for between 19 and 29 % of all greenhouse gas emissions (GHGE). The continuing increase in beef and meat consumption particularly also in middle income countries is a central contributor to global warming. The current fires in Amazon region, resulting from deforestation to make room for grazing land are evidence of the detrimental effects of excess and non-regional meat production. Food processing, food transport, and food waste further add to the problem of global warming.
Populations in low and middle income countries and those in high income countries are not equally affected by the problem of climate change and nutrition. As macro- and micronutrient intake in Western countries is generally far above recommended guidelines, citizens in high income countries are not (yet) affected by the nutritional impact of climate change in a major way. This may not be true for the lowest social class as an increase in prices for healthy food can already be a challenge. Climate change clearly puts citizens of low and middle income countries at risk for undernutrition, and children therefore at risk for stunting. The latter hampers children's development and puts them at higher risk of non-communicable diseases later in life. In fact climate change could stall or even reverse current gains in the reduction of child stunting.
From a health and ecosystem perspective, it is essential that health promotion and environmental policy play hand in hand. In particular, nutritional guidelines are needed that integrate considerations related to greenhouse gas emissions. More research is needed to understand how people in different social and cultural settings adopt these guidelines.

Session 1
Food composition

Theatre

Translating Multicriteria Information on Individual Foods into healthy and sustainable Diets

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The Food and Agriculture Organization defines sustainable diets as nutritionally adequate, safe and healthy, culturally acceptable, economically fair and affordable and with a low environmental impact.
The assessment of diet sustainability needs comprehensive databases compiling relevant food metrics for the four sustainability dimensions (namely health/nutrition, culture, economy and environment. Such databases may provide multicriteria information on nutrient and contaminant content of foods, bioavailability factors, distribution of dietary intakes, portion sizes, food prices, environmental impact (e.g. greenhouse gas emissions or land use) for a list of commonly consumed generic foods.
Once the information is collected and compiled into one single generic database, a tool is needed to translate such multicriteria information on individual foods into healthy and sustainable diets. Hence, designing sustainable diets requires the integration of different dimensions of diet sustainability that may not be compatible with each other. Among multi-criteria assessment methods, diet optimization is a powerful mathematical method to address the fundamentally multifactorial aspects of nutrition and dietetics. Diet optimization is a computational technique that has the capacity to test the feasibility, the practical implications and cost and/or environmental impact of a given set of constraints and to find the solution that best meets simultaneously all the constraints.
The main strength of diet optimization in nutrition lies in the translation of nutrient-based recommendations into concrete and quantified food guidance. It can also be used to test the robustness and nutritional relevance of food-based dietary guidelines in order to improve them. Diet optimization can be used to design low cost nutritious food baskets, to assess the contribution of specific food items to the nutritional adequacy of diets, to optimize the diet of a population or diets of individuals.
Recently, diet optimization has received paramount attention to identify the food choices and the dietary shifts needed to make our diets more sustainable. It can help understand the links between the different dimensions of diet sustainability, and it can be used to design more sustainable diets for population and for individuals.

Session 1
Food composition

Poster

Using new Genetic Sequencing Technologies to increase Food Transparency through Citizen Science

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Everyone remembers the horse-meat lasagna scandal. Our globalized food system means there are often numerous steps between the production of raw material and food being on our plates, often across borders. At each of these steps foods can be modified, either intentionally or accidentally, without the next company or consumer down the line being aware. Common food fraud is substitution, dilution or mislabelling. All plants and animals contain DNA which contains the information necessary for the organism's development. Sequencing this DNA can also be used to identify species. Traditionally requiring a lot of resource, infrastructure and expertise, genetic sequencing is rapidly becoming easier to use and more affordable. We are harnessing this to develop a lab protocol that can be done in a community setting, and on the long-term maybe even at home, to extract and sequence the DNA contained in food. This genetic data, in the form of a sequence like AGGTCTTAG, can then be analysed to identify which plants or animals are present – for example if there is porc, peanuts or natural vanilla in the food, in the format of an ingredient list. On the long run, this would mean that any food put on the market could potentially be sequenced, which is an incentive for all steps in the chain to do regular tests on what they are supplied and provide what they claim to in order to avoid a public outcry.
The project is being piloted in 2019. Several foods have successfully been sequenced in a lab setting, and the first food DNA sequencing workshop was held in a Community Lab near Lausanne. Ten foods were sequenced, some produced good data which we are currently analysing and we are improving the protocol and the workshop in view of doing it again. The raw genetic data will be available on FoodRepo, the first open access and collaborative database of barcoded foods in Switzerland! This database hosts information on foods available is Swiss supermarkets, taking it from the private/commercial domain to the public domain and allowing every citizen to browse. Anyone who wants to create an app can use the data available via an API (link to; https://www.foodrepo.org/api-docs/swaggers/v3). There are currently over 40'600 barcoded products and it's growing every day.
More information about the DNA project is available here: www.foodrepo.org/dna.

NutriOpt: Digital solutions for nutrient optimization in product development

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The current project NutriOpt offers digital solutions for nutrient optimization in product development. We establish product databases containing plants, plant-based powders, and drinks with decisive information about nutrient composition, bioavailability, antinutrients or inhibitory effects. A mathematical model for mixed integer problems allows to combine different products that are approaching a target vector. The target vector is the recommended nutrient composition for a specific target group. It is possible to select different nutrients or to give them more weight. The models were already applied for plant-based protein alternatives to ensure that the protein requirements for amino acids from WHO are guaranteed. In the future, additional effects of processing will be included to be able to combine products for increased nutritive value. Finally, we will like to develop a user-friendly WEB-Software for the operations.

Characterization of grassland based Swiss milk by a metabolomics approach

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Milk nutritional and technological quality is closely related to milk composition, which comprises proteins, lipids and metabolites. Since milk is a biological liquid, it can be assumed that its constituents allow conclusions to be drawn about the milk production process and the cow's state of health. In recent decades, the influence of cow husbandry and feeding conditions on the fat and protein composition of milk has been thoroughly investigated. On the contrary, little is known about the influence of these factors on the milk metabolome. These days, due to progress in “omics” technologies and computational methods for the analysis of high-throughput data, the metabolome of food, even of such a great complexity as milk, can be analysed at reasonable expense. Therefore, in our comprehensive study of the effect of husbandry and herbage feeding on the milk composition, we investigated, in addition to conservative parameters as protein and fat content and specific composition, the somatic cell count, the urea and the acetone body content, the metabolome of the milk of twelve dairy farms, distributed over several regions in Switzerland. For this purpose, methods for untargeted metabolite analysis for semi volatile and soluble metabolites using gas and liquid chromatography-tandem mass spectrometry (LC-MS) were developed. The data was evaluated with Progenesis QI (version 2.3.6198.24128) and SIMCA (version 13.0) using a multivariate analysis of variance, and differences in metabolites between the milk of different dairy farms were assessed using principal component analysis (PCA) and orthogonal partial least squares discriminant analysis (OPLS-DA). As a result, the abundance of certain metabolites, semi volatile as well as soluble ones, correlated well with the proportion of herbage in the diet of the cows. Conclusively, metabolomics offers new opportunities for the dairy industry to gain insights into the complex interplay of husbandry and feeding conditions on the milk composition and thus milk quality.

Differences in the *G*ut *M*icrobiota of *M*ice from different *S*ources

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Mouse as an animal model is increasingly being used for investigating the genetic basis of diseases and potential drug targets. The C57BL/6J mouse was the first strain to have its genomic sequence published, and this strain is considered a gold standard in many research areas.
Although, studies with mice models are performed using genetically identical animals in highly controlled environments, reproducibility of results using mice has increasingly become an area of concern. Evidence exists that highlights differences in size and behavior, such as enhanced anxiety between C57BL/6J mice from different vendors. Recent studies have demonstrated that the gut microbiota of mice can differ significantly depending on the source of the animals and other environmental factors associated with animal husbandry. Thus, it is highly likely that differences in the gut microbiota may play a role in the lack of reproducibility between C57BL/6J mice.
In the present study, we characterized the changes in small intestinal microbiota and bile acid profiles of C57BL/6J mice from two different sources (In-house and Charles River Laboratories UK, CRUK) after 4 weeks feeding with a synthetic semi-purified diet. The microbial analysis data revealed significantly increased abundance of *Akkermansia* and *Ruminococcaceae* in CRUK mice compared to the in-house mice. Moreover, the bile acid analysis shows decreased levels of deoxycholic acid and lithocholic acid and increased levels of muricholic acid, tauro-α-muricholic acid and trihydroxycholic acid in the ileum of CRUK mice. These differences in the microbiota and therefore, individual bile acids could be affected by the environmental variables such as diet, type of caging, type of bedding, and housing density occurring at different vendors.
Our results suggest that more importance should be given to the vendors when publishing research findings and designing future experiments in order to tackle the issue of poor replicability. Our research also highlights the importance of documenting gut microbiota composition for animal-based research and the need for cost effective targeted strategies to address lack of reproducibility.

REFRESH Food Waste Compositional Database – FoodWasteEXplorer

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Introduction: The EU has set a target to reduce food waste by 30% by 2025. However, by considering supply, quality and composition, it is possible for stakeholders to find value in food waste, and build a more sustainable and secure food system.
Objective: As part of the EU-funded project (REFRESH), 'FoodWasteEXplorer' was developed to help identifying the edible and inedible food waste streams most appropriate for valorisation.
Methodology: FoodWasteEXplorer, an online searchable database, provides the composition of food waste streams, so users can explore how food waste might be better managed and identify market opportunities, e.g. animal feeds, textile fibres, bioplastics or biofuels.
Main Findings: More than 25,000 datapoints on 1,264 main food side streams (e.g. orange peel), from a variety of sources, including published peer-reviewed scientific papers, have been added. The structure is based on CEN's standard for food data (EN 16104:2012) with easy to use search and reporting systems and is fully compatible with other information systems (e.g. FoodEXplorer, www.eurofir.org/foodexplorer and Quisper, quisper.eu).
Conclusion: FoodWasteEXplorer is a valuable resource for food waste management, allowing identification of components and potential valorisation for important side streams. It enables use of side streams as new raw materials for a wide range of products, decreasing waste generation, and increasing value and sustainability. Access to FoodWasteEXplorer is free-of-charge at www.foodwasteexplorer.eu.

Session 2
Food and diet intake

Theatre

Modern Tools in the Assessment of Food and Diet Intake

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In the last decade, there has been a wide recognition of the limitations associated with the questionnaire instruments traditionally used for dietary assessment, which has boosted innovation and research in the field. New technology-based tools such as web-based tools, smartphone apps and sensors hold promise to overcome some of the limitations of dietary questionnaires. Rapid progress are being made, however, most of these tools have not been properly validated yet. Furthermore, they still often rely on self-reporting, with its inherent bias. Biomarkers, which allow a more objective measure of dietary intakes, represent another important axis of development. Major achievements for the discovery and validation of dietary biomarkers have been made in the framework of the JPI-HDHL-FoodBAll project, including the proposition of a new classification of dietary and health biomarkers, the BFIRev protocol for identifying candidate biomarkers of food intake (BFIs) though literature search and a validation scheme dedicated to BFIs. A large collaborative effort was undertaken to inventory the candidate BFIs for dozens of foods and to evaluate their level of validation. This work confirmed that very few validated BFIs are available, that are far from covering the variety of food commonly consumed. The chemical composition of foods often shows that some compounds exist, especially in plant-based foods, which have sufficient specificity to be plausible putative BFIs. However, for a vast majority of foods, the appropriate discovery and validation studies have not been conducted.
The efficiency of untargeted metabolomics for the discovery of BFIs, especially when no obvious candidate compounds exist, has been largely demonstrated. Within and beyond FoodBAll, many studies have recently provided new candidate biomarkers, using various study designs and methodological approaches. We learned a lot about methodology and strategies to optimize future studies. Several complementary studies with different designs are clearly necessary to fully validate a BFI.
There are still many challenges ahead, including: 1) developing and validating quantitative methods of analyses and calibration curves for a large range of BFIs, 2) Improving databases and tools for the identification of unknowns in metabolomic profiles, 3) developing new methodological approaches and biomarkers for dietary patterns, 4) implementing methods to comprehensively assess the individual exposure to the hundreds of diet-derived metabolites (plant food bioactives, additives, compounds such Maillard products generated during food processing, contaminants…) 5) developing the metabotyping approach for precision nutrition, 6) Ensure applicability of the new biomarkers and tools for public health and nutrition researchers, clinicians, consumers and other types of end-users.

Identification of milk and cheese intake biomarkers

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The use of biomarkers of food intake in serum or urine has shown great promise for completing traditional dietary assessment tools. Untargeted metabolomics was used here to identify new biomarkers of milk and cheese intake and further explore the metabolic response to the ingestion of such foods. A randomized controlled crossover study was conducted in eleven healthy men and women. Serum and urine samples were taken postprandially up to 6 h and fasting 24 h after a single intake of isocaloric doses of milk, cheese or soy drink (non-dairy control). Untargeted metabolomics was conducted using UHPLC-MS. Biomarkers of intake were first selected in serum by multivariate statistical analysis, their mass distribution and postprandial kinetics were characterized, and their presence in urine was then investigated. Among the 2988 unique metabolites detected in serum, 261 were selected as potential biomarkers of milk, cheese or soy intake. Biomarkers of cheese intake had a significant lower mass distribution than biomarkers of milk or soy intake. The identities of nine compounds were confirmed (5 biomarkers of cheese intake and 4 of milk intake) including saccharides, amino acids, amino acids derivatives and dipeptides. Among them, six were also found in urine. Two oligosaccharides, the blood group H disaccharide and the Lewis a trisaccharide, appeared as clear serum biomarkers of milk intake but with high inter-individual variability. Interestingly, the two oligosaccharides presented opposite trends, *i.e.* after milk intake, subjects showing an increase in blood group H disaccharide did not show any increase in Lewis a trisaccharide, and conversely. This result was confirmed in urine. New biomarkers of milk or cheese intake could be identified using HPLC-MS based untargeted metabolomics, most of them being related to peptides and amino acid metabolism. The observations made for the blood group H disaccharide and the Lewis a trisaccharide first recalls the importance of inter-individual variability when searching for biomarkers of intake, but also encourages further investigations towards the role of the Lewis antigen system and related genotypes in the differential response to milk intake and the potential health outcomes.

Biomarkers of red Meat Intake: are we there yet?

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Background: Biomarkers of red meat intake may clarify the relationship between meat intake and health. While many studies target the discovery of new biomarkers of intake, only a few seek to carefully evaluate their potential for application. Herein, we discover, validate, and evaluate the prediction performance of new and existing biomarkers of meat intake, while aiming to assess consumption of red meat.
Methods and results: We present data from two cross-over meal studies with varying control of background noise, and from a cross-sectional analysis of a lifestyle intervention (PREVIEW study). The metabolic profiles of postprandial and 24h urine samples were explored by uni- and multivariate analysis to discover biomarkers of three types of meat of increased redness (chicken, pork and beef) and a control meal. The candidate meat biomarkers, originating from collagen degradation, meat flavor, muscle breakdown and amino acid metabolism, were then reconfirmed in independent studies and validated for plausibility, time-response, robustness, and prediction performances. Only 30% of the initially discovered biomarkers showed potential as dietary assessment tools after extensive validation. While half of the biomarkers of red meat intake were replicated in independent studies, none showed good prediction performance, neither in the less-controlled meal study, nor in a free-living sub-population of the PREVIEW study. In the absence of specific red meat markers, a three-step strategy was developed to evaluate consumption of red meat by using biomarkers of white and general meat intake. The first two steps are qualitative and aim to indicate if 1) any meat was consumed and 2) if the meat was white or red. Prediction performances of AUROC 0.94-0.97 were obtained using single and combined biomarkers. The third step is a quantitative evaluation to estimate the amount ingested. Carnosine showed a trend for dose-response between non-consumers, low-consumers and high-consumers when red meat and poultry were assessed separately and should be investigated further in dose-response studies. The biomarkers used to qualify and quantify intake of the varying subtypes of meat differed.
Conclusion: It is possible to estimate red meat intake using combinations of previously identified biomarkers for white and overall meat intake, in a step-wise objective assessment strategy. Such an approach offers a solution where not all biomarkers are required to have both qualitative and quantitative characteristics and highlights that quantitation may be easier achieved once the meat source is known.

Syringol Metabolites as new Biomarkers for Smoked Meat Intake

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Background: Processed meat is associated with higher risk of colorectal cancer but the estimation of intake of this heterogeneous food group in epidemiological studies is challenging because of the lack of sufficient details in dietary questionnaires.
Objective: To identify novel biomarkers for processed meat intake using metabolomics. **Design:** An untargeted metabolomic approach based on LC-MS was applied to processed meat products previously digested *in vitro,* and to urine and plasma samples from a randomized cross-over dietary intervention in which 12 volunteers consumed successively 3 processed meat products and two other control foods during 3 days. The identified biomarkers were then measured in urine from 474 subjects from the European Prospective Investigation into Cancer and nutrition (EPIC) cross-sectional study for which a 24h dietary recall and food frequency questionnaires were available. **Results:** Syringol and four derivatives of syringol were found to be characteristic of digests of smoked meat products. The same compounds present as sulfate esters in urine showed increased levels following consumption of smoked meat products in the intervention study. The same syringol sulfates were also positively associated with recent or habitual consumption of smoked meat products in urine samples from participants of the EPIC cross-sectional study. These markers showed good discriminative ability for smoked meat intake with receiver operator characteristic areas under the curve up to 0.86 and 0.79 for short-term and habitual intake, respectively. **Conclusions:** The biomarkers of smoked meat intake identified in this study may be used to improve assessment of smoked meat intake in epidemiological studies.

Session 2
Food and diet intake

Poster

Identification of Plasma and Urinary Volatile Food Intake Biomarkers for Milk, Cheese, and Soy-Based Drink by Untargeted GC-MS in Healthy Humans

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Because of their central importance in determining the organoleptic properties of foods, volatile compounds are the subject of intensive research in food and sensory sciences. However, passed the gastrointestinal system, the metabolic behavior of these compounds has not been evaluated. We hypothesize that the characterization of volatile compounds in biological fluids can be a suitable approach to study the metabolic imprint of foods on the human metabolome, in particular for the identification of biomarkers of food intake (BFIs).
Using a combination of solid phase extraction, dynamic headspace vacuum transfer in trap extraction, and gas chromatography coupled with mass spectrometer we have therefore measured volatile compounds (the “volatilome”) in plasma and urine samples from a randomized controlled crossover intervention study with eleven healthy subjects having ingested milk, cheese, or a soy drink. More than 2800 volatile compounds were detected in plasma and urine samples. A multivariate analysis allowed to select 41 molecules specific to the ingestion of one of the three foods in urine sample and three molecules in plasma samples, of which nine metabolites were specific to the dairy products in urine samples and two in plasma samples. These results show that it is possible to identify candidates BFIs for dairy products using the analysis of the metabolic imprint on the plasma and urinary volatilome following the acute ingestion of food under controlled conditions. This analytical approach will allow for a better understanding of the impact of food fermentation on digestion and metabolic health.

Transcriptomic and metabolomic Effects of Butter or Margarine (with or without Trans fatty acids) enriched Diet in healthy Subjects

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Omics technologies such as transcriptomics and metabolomics provide powerful tools to demonstrate the effects of foods on molecular and metabolic pathways and functions. The current parallel study was designed to test the hypothesis that short-term consumption of alpine-butter or margarine with and without *trans* fatty acids (TFA) differentially alters gene expression, circulating lipids and metabolites in healthy subjects. After a two-week run-in period of margarine without TFA (wTFA), 42 volunteers aged 45 to 69 years, were randomly assigned to three groups (control=wTFA), alpine butter (ruminant TFA (rTFA)) and a margarine containing industrial TFA (iTFA)) for four weeks. Fasting blood samples were collected before and after the four week intervention to assess changes in clinical parameters, blood lipids (high resolution analysis) gene expression of peripheral blood cells (microarray) and metabolome profiles (mass spectrometry (LC-MS, GC-MS)).
None of the TFA interventions had a negative clinical impact on endothelial function measured by brachial artery flow mediated dilation. Also, biomarkers of inflammation, coagulation, and endothelial function were not significantly changed apart from a small but significant increase of total cholesterol and LDL-cholesterol after the rTFA intervention (compared to wTFA). However, after supplementation of the diet with alpine butter for four weeks, significant changes in some blood lipids and 185 metabolites measured by LC-MS were observed (including prostaglandines, piperine, cholic acid, …..), but neither gene expression nor metabolites measured by GC-MS were significantly affected. The effect of TFA was only visible in blood lipids.
In the current analysis the effect of different sources of fat, with and without TFA, from dietary lipids appeared to be best captured via a combination of LC-MS techniques and high-resolution lipid analysis.

Discovery of Urinary Biomarkers of Spinach Consumption using untargeted LC-MS Metabolomics in a Human Cross-over Study

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Background: Spinach, one of the most popular vegetables in the world, may have significant functional properties. Discovery of biomarkers of spinach consumption would allow assessing its intake in observational studies accurately or to facilitate compliance assessment in studies on the potential health effects of spinach in humans.
Objective: we aimed to identify the spinach-derived metabolites present in urine after intake of whole leaf-or minced spinach using untargeted metabolomics and also to investigate their presence in subjects with severely compromised absorption.
Methods: A randomized, controlled cross-over study design was used in a study on 22 volunteers (12 healthy, 10 metabolically stable short bowel patients, gut length140-350 cm), with 2 dietary interventions standardized by carotenoid content: 1) 178 g whole leaf spinach with 7.1 g rapeseed oil, 2) 200 g minced spinach containing 8.0 g rapeseed oil, both served with 400 mL water. Urine samples were collected in 24-hour intervals pre-and post the intervention meal. The samples were analyzed by UPLC-QTOF-MS. The resulting profiles were analyzed by multilevel PLSDA and by paired t-test to select features associated with spinach intake.
Results: Seven features were selected by PLSDA having AUROC between 0.9-1 with an error < 0.1 comparing before and after the treatment. These features were not significantly different in healthy subjects and in patients with a compromised gut. The excretion was also unaffected by spinach processing (mincing). Among the seven features, there are three potentially specific spinach metabolites. One metabolite is a coumaric acid ester with a mass spectrum showing partial similarity to D-malic acid p-coumarate. A second metabolite is an unidentified daughter ion of a compound (most likely a flavonoid) present also in spinach, allowing isolation of larger quantities (mg) of this apparent precursor compound for identification. A third metabolite is an ester of des-amino arginine.
Conclusion: In a highly controlled setting, we have identified three putative biomarkers of spinach intake that seem robust to spinach pre-processing and to gut length. We will now 1) synthesize additional standards to identify the exact structure of the coumaric acid derivative, 2) Identify the other two putative markers by additional syntheses, 3) Investigate whether the samples are robust in a cross-sectional study using 24hr recalls for validation.

Post-myocardial Infarction Patients

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Background: Circulating odd-chain fatty acids pentadecanoic (15:0) and heptadecanoic acid (17:0) are considered to reflect dairy intake. In cohort studies, higher circulating 15:0 and 17:0 were associated with lower type 2 diabetes risk. A recent randomized controlled trial in humans suggested that fiber intake also increased circulating 15:0 and 17:0, potentially resulting from fermentation by gut microbes. We examined the associations of dairy and fiber intake with circulating 15:0 and 17:0 in patients with a history of myocardial infarction (MI).
Methods: We performed cross-sectional analyses in a subsample of 869 Dutch post-MI patients of the Alpha Omega Cohort who had data on dietary intake and circulating fatty acids. Dietary intakes (g/d) were assessed using a 203-item food frequency questionnaire. Circulating 15:0 and 17:0 (as % of total fatty acids) were measured in plasma phospholipids (PL) and cholesteryl esters (CE). Spearman correlations (r_s) were computed between intakes of total dairy, dairy fat, fiber, and circulating 15:0 and 17:0.
Results: Patients were on average 69 years old, 78% was male and 21% had diabetes. Total dairy intake comprised predominantly milk and yogurt (69%). Dairy fat was mainly derived from cheese (47%) and milk (15%), and fiber was mainly from grains (43%). Circulating 15:0 in PL was significantly correlated with total dairy and dairy fat intake (both r_s=0.19, p<0.001), but not with dietary fiber intake (r_s =0.05, p=0.11). Circulating 17:0 in PL was correlated both with dairy intake (r_s=0.14 for total dairy and 0.11 for dairy fat, p<0.001), and fiber intake (r_s=0.19, p<0.001). Results in CE were roughly similar, except for a weaker correlation of CE 17:0 with fiber (r_s=0.11, p=0.001). Circulating 15:0 was highest in those with high dairy intake irrespective of fiber intake, while circulating 17:0 was highest in those with high dairy and fiber intake.
Conclusions: In our cohort of post-MI patients, circulating 15:0 reflected dairy intake but not fiber intake, whereas circulating 17:0 reflected both dairy and fiber intake. These data suggest that cardiometabolic health benefits previously attributed to 17:0 as a biomarker of dairy intake may partly be explained by fiber intake.

Modulation of Gut Microbiome Composition: Effects of Fruits and Vegetables

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Background/Objective: It has been well defined over the last decade that the diet influences the health of an individual, especially plant-based diet has been proposed to improve/maintain people's health. But, it remains unclear until recently is the role of gut microbiome to this effect. So, in this study, we aimed to evaluate the beneficial effects of formulated fruits and vegetables supplementation (FVS) on the gut microbiome composition from healthy population.
Materials and Methods: This study is a randomized, double-blind, placebo-controlled study. This pilot study involves 30 healthy subjects aged 18-65 years, were randomly assigned to the treatment or placebo group, 15 subjects in each group and the duration of FVS supplementation/treatment was 6 weeks. Phenotypes, such as anthropometry, nutritional intake (by 24 hr food recall method), biochemical parameters were recorded before and after treatment. The stool samples were collected before and after treatment. The gut microbial composition was evaluated by 16s rRNA sequencing on Illumina Miseq platform targeting V1-V3 hypervariable region. The short chain fatty acids (SCFA) were estimated using Agilent Gas Chromatography-MS. The anti-oxidant capacity was measured by Oxygen radical absorbance capacity (ORAC) method.
Results: The anti-oxidant level from plasma measured by ORAC was comparatively higher (+21%, p=0.036) in the FVS groups than the placebo group. The FVS group have shown a significant increase in the plasma folic acid level (+59.7%, p=0.0001), and vitamin B_2 (VitB2; +25.6%, p=0.04) compared to placebo group. No significant differences were observed for vitamins A, E, K and serum potassium level. The 16s rRNA sequencing analysis have shown that FVS treatment greatly affects the bacterial lipid metabolism, gluconeogenesis and pentose pathways. In addition, gut microbiome composition positively correlated with butanoic, isobutanoic, and ethanoic acids, and dietary intake of lipids, sugar, VitC and VitB in the FVS treatment group.
Conclusion: The formulated fruits and vegetables supplementation effectively modified gut microbial composition in healthy subjects.

Mon Alimentation Sur-Mesure, a Tailored Nutrition Counselling Web-Application based on Mathematical Diet Optimization

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Background: By definition, messages in *tailored approaches* are built to reach a given person, based on her/his specific characteristics and needs. Tailored dietary behavior change interventions have a small but significant effect on dietary behavior change. The majority of these interventions target a few food groups or nutrients, without evaluating the overall diet. *Diet optimization* is a powerful mathematical method to translate nutrient recommendations into individual-specific food choices. This method is increasingly used in nutrition research, in the fields of public health and diet sustainability.
Objective: The aim was to combine *tailored approaches* and *diet optimization* in a web application of tailored nutrition counselling.
Method and results: The web application, called Mon Alimentation Sur-Mesure, was developed based on behavior changes techniques, such as: self-monitoring, self-regulatory, tailored feedback and engaging communication techniques. In a first feature, based on user's data collected online (including answers to a food frequency questionnaire), the user can obtain a picture of the nutritional quality of her/his diet, the diet cost and the level of physical activity. In a second feature, Mon Alimentation Sur-Mesure suggests to the user a list of tailored dietary advices to get a healthier diet (i.e., a nutritionally adequate diet), adapted to her/his specific needs and food preferences. With the application, the user is actor in her/his own dietary changes: she/he specifies her/his food preferences and; chooses dietary suggestions that she/he considers achievable.
Conclusion: This prototype could be a future online health promotion tool which could help individuals to improve their diet or serve as a decision-support tool for health professionals. The evaluation of the tool (e.g. whether the use of the tool results in changes of dietary habits) is warranted before use on health promotion.

Intake of fatty Fish according to Dietary Recommendations is associated with a beneficial Lipoprotein Subclass Profile among Healthy Adults

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Background: Fish intake is associated with reduced risk of cardiovascular disease. Low density lipoprotein (LDL) cholesterol in the circulation is one of the most important modifiable risk factors for cardiovascular disease. High density lipoproteins (HDL) are responsible for reverse cholesterol transport, and are associated with reduced risk of cardiovascular disease. The aim of this study was to investigate the association between fish intake and lipoprotein subclass particle concentrations and composition.
Methods: We performed a comprehensive plasma lipid profiling in 517 healthy adults, using a commercial high-throughput nuclear magnetic resonance spectroscopy platform. The participants were divided into tertiles for consumption of lean fish and fatty fish, reported through a validated self-reported food frequency questionnaire. The lipoprotein subclass particle concentrations and lipid composition was compared between the participants with lowest and highest tertiles of lean fish consumption and between lowest and highest tertiles of fatty fish consumption.
Results: We show that high (>223 g/week) versus low (<107 g/week) consumers of fatty fish have significantly higher particle concentrations of large and extra-large HDL particles, and significantly higher content of total lipids, phospholipids, total cholesterol and free cholesterol in large and extra-large HDL particles. No significant difference was found in particle concentration of VLDL and LDL between high and low consumers of fatty fish. We found no significant difference in the lipoprotein subclass profile between high (>180 g/week) versus low (<64 g/week) consumers of lean fish.
Conclusions: High consumers of fatty fish seem to have a more beneficial lipoprotein profile compared to low consumers of fatty fish.

More than 80 Sugar Compounds detectable by comprehensive two-dimensional GC-MS Analysis in Human Urine

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Our recently published semi-targeted one-dimensional GC-MS sugar profiling method (Mack et al. 2018) revealed a complex sugar profile in human urine with the detection of 55 sugar compounds. Nonetheless, in these studies, further signals exhibiting mass spectra characteristic for sugar compounds, but with low intensities, were observed. Furthermore, in some cases the separation of stereoisomeric sugar compounds was insufficient.
As a consequence, our aim was an optimization of this method with respect to sensitivity and separation performance. To achieve both an improved sensitivity and separation performance, we transferred the one-dimensional GC-MS method towards a two-dimensional GC×GC-MS approach. Important aspects addressed were: i) column set-up; ii) MS mode; and iii) data processing strategy. An orthogonal column combination was used consisting of a long, unpolar first-dimensional column and a medium polar, short second-dimensional column. For the MS mode, characteristic SIM masses were chosen, to improve both sensitivity and selectivity. An in-house developed workflow for the processing of two-dimensional data using the MS in Scan mode was adjusted to enable the processing of SIM data. The advantage of the two-dimensional GC×GC-SIM-MS sugar profiling method was demonstrated by measuring samples from the FoodBAll acute intervention study (cross-over design) with apple and coke as test foods for intake marker identification compared to water as control.
Overall, as a result of the improved sensitivity and separation performance, as many as 84 sugar compounds could be detected in human urine using the improved method in comparison to the one-dimensional one capturing 55 sugar derivatives. For the majority of the sugar compounds a good method repeatability with intra-day coefficients of variation of less than 15% was achieved in a long measurement series with more than 400 samples. The exemplary data from the FoodBAll-MRI intervention showed several sugar compounds increasing after the interventions with apple and/or coca cola, but not in the water control. Among others, threitol, xylose and a deoxyhexitol increased after apple consumption. In conclusion, the GC×GC-SIM-MS sugar profiling method enables the reliable detection of a large number of sugar compounds in human body fluids, which is a helpful tool to identify markers of food intake or health status and to understand the metabolism of sugar compounds in humans.

Specificity and Kinetics of Markers after Chicken and Beef Consumption using targeted quantitative LC-MS/MS Analysis

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Established methods for the assessment of food intake are known to be error-prone. Attempts to estimate food intake via metabolite biomarkers in blood or urine are challenged by inter-individual variation of uptake, bioconversion and excretion processes. Especially, discovery of intake markers for meat is difficult, since most compounds in meat are also endogenously present in humans at varying concentrations. Within the previous joint action of the JPI HDHL Biomarkers in Nutrition and Health (the FOODBALL-consortium) we aimed to evaluate individual meat markers including dose-dependency, specificity to meat type (chicken versus beef), kinetics of appearance and disappearance and their ability to quantitatively reflect meat intake.
We performed two randomized human interventions in which subjects consumed defined amounts of meat at different doses (0g, 100g and 200g). Concentrations of 108 analytes, including amino acids, amino acid intermediates, acylcarnitines and dipeptides were determined in plasma at different time points up to 24 hours after meat ingestion using a targeted LC-MS/MS approach. The analysis also included 15 of the most-prominently reported biomarkers of meat consumption.
Plasma levels of π-methylhistidine correlated best with the amount of chicken meat administered even after 24 h. Both, anserine and π-methylhistidine showed first-order elimination kinetics with half-lives of 1.4h and 5.9h, respectively, irrespective of meat dose. Surprisingly, π-methylhistidine was also found as best predictor of meat dose after beef consumption, albeit at much lower plasma concentrations. In addition, chicken breast consumption was characterized by a specific increase of dimethylglycine, while beef consumption correlated with intermediates of carnitine, most prominently TMAO. Intermediates of amino acid breakdown, including acylcarnitines, appeared later in plasma compared to their parent compounds. Importantly, π-methylhistidine and anserine where the only two compounds which were completely absent at baseline and remained absent after the control treatment with rice alone. The lack of variation in baseline concentrations is likely the strength of π-methylhistidine to predict meat dose. Nevertheless, considerable variation in the peak heights and areas under the curves could be observed between individuals after consuming equal amounts of meat. The prediction therefore over- or underestimated the dose >20% for some individuals. In conclusion, quantitative assessment of meat intake within 24 hours is most accurate with π-methylhistidine. However, while plasma π-methylhistidine concentrations were best to predict meat dose, both after chicken and beef consumption, TMAO and dimethylglycine best discriminated between chicken and beef.

Session 3

Food and diet: metabolism and function

Theatre

Impact of Diet on Human Health – Microbiome as a Show Case

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The intestinal microbiome is suggested to play an essential role in the regulation of human health and disease susceptibility. Human cohort studies demonstrated changes in gut microbiota composition and function in a variety of different pathologies including obesity and metabolic disorders such as Type 2 diabetes (T2D). Although metagenomic resolution and bioinformatic tools considerably improved, allowing even strain level analysis, the search for microbial risk patterns in human cohorts is often confounded by environmental factors (e.g. medication) and large individual as well as regional variations. In addition, risk profiles partially overlap between a variety of different disorders, including inflammatory bowel diseases (IBD), colorectal cancer and metabolic diseases, questioning the disease-specific prognostic and therapeutic value of the currently available information. To extract functionally and clinically relevant information from microbiome changes in human populations, the combined information of prospective cohort and intervention studies needs to be integrated at a mechanistic level. KORA is a regionally confined and prospectively followed population study with a focus on metabolic health. In an interval of 5-years, we performed microbiota profiling on consecutive stool samples (t_1=1,976 and t_2=701 samples) using high-throughput sequencing of the V3/V4 and V1/V2 regions of 16S rRNA genes. To assess shifts in the microbiota linked to metabolic conditions, individuals were stratified based on body mass index (BMI), impaired glucose tolerance (HbA1c, fasting glucose and OGTT) to discriminate between unaffected (N_1=1340), obese (N_1=558), prediabetic (N_1=353) and Type-2 diabetic individuals (T2D; N_1=283) conditions. In parallel, using samples from a human intervention trial, we performed fecal transfer studies from obese/T2D patients into germ-free mouse models to evaluate disease-conditioning mechanisms. In conclusion, we identified bacterial signatures that improve the diagnostic profiling of T2D patients, however mechanistic links are still lacking. The keynote will give a critical reflection of available data related to the question whether microbiome changes are cause or consequence of metabolic disorders.

Postprandial Transcriptomic Response of Adipose Tissue to High Fat Meals in Middle-Aged Men with Metabolic Syndrome

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Background: Metabolic syndrome (MetS) increases the risk for developing CVD and T2DM. Key physiological changes that drive these pathologies occur in adipose tissue (AT), an endocrine organ that facilitates metabolic homeostasis via cross-talk with other tissues. To further explore adaptations that occur in MetS, we have measured the transcriptomic response of abdominal subcutaneous adipose tissue before and after the consumption of high fat meals.
Method: Twenty men (10 control; 10 MetS) were recruited to participate in a controlled randomised, crossover single meal study. Participants consumed isocaloric soy-based and dairy-based breakfast meals that were matched on % macronutrient contribution but differed in nutrient profile. AT was collected at baseline (0 h), and 4 h following each test meal. Global gene expression profiling was performed (Illumina Human WG-6 v3 microarray). Differentially expressed genes (+/- 1.2-fold, adj-p < 0.05) were analysed in PathVisio software to decipher affected pathways (Z-score > 1.96), and GOElite to investigate gene ontology classes. The network program Cytoscape software was used to integrate the biological processes.
Results: The expression of only 11 genes were significantly different between control and MetS after overnight fasting. Following the meal, the control group consistently demonstrated increased numbers of significantly differentiated genes, compared with the MetS group. Following the dairy meal, control AT exhibited significant changes in expression levels of 2444 genes, compared with 332 genes in MetS AT. There were 299 genes similarly expressed in both groups. After the soy meal, control AT showed significantly changed expression levels of 2367 genes compared with 336 genes in the MetS AT, with 298 genes similarly expressed in both groups. The genes that were similarly expressed between MetS and control participants after both meals were related to inflammation and the immune response, the change in gene expression levels were similar in direction and magnitude between groups. The biological processes that were overrepresented after the dairy meal in control participants but not MetS included gene expression regulation, nucleotide metabolism, and growth. Whereas the biological processes that were overrepresented after the soy meal in control participants but not MetS included stress, cell cycle, growth, and cell differentiation.
Conclusion: Adipose tissue of participants with MetS displays metabolic inflexibility in response to a meal, most likely associated with insulin resistance. Meal composition of the soy and dairy meals differentially affected the transcriptome response of adipose tissue in control participants.

Challenging the Metabolic Fingerprint of normal Weight and Obese Subjects using a Dose Responsive Strategy to a High Fat Meal

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Metabolic disorders, encompassing obesity and type 2 diabetes, have become recurrent health issues contributing to the death of millions of people worldwide. In this context, nutritional metabolomics is an emerging discipline that might contribute to a better characterization of the impact of dietary behaviors on these pathologies.
The current randomized crossover study aimed to evaluate and differentiate the blood serum metabolome of a cohort of 19 normal weight (NW) (BMI: 20-25) and 18 obese men (OB) (BMI: 30-50) after the ingestion of a high-fat meal (HFM). The metabolic equilibrium of these subjects was challenged by administrating, in a randomized crossover design, 3 caloric doses (i.e. 500, 1'000 and 1'500 kcal) of HFM (i.e. 61% of energy from fat, 18% from protein, 21% from carbohydrates). The dose-response of the serum metabolome was then measured by untargeted LC-MS for each individual after 0, 1, 2, 4 and 6 hours.
Among 1'385 features with a postprandial effect, 178 showed a dose-response. Overall, the postprandial metabolome showed a caloric saturation, 1'500 kcal being quantitatively only marginally different from 1'000 kcal, in particular for OB. Seven kinetic clusters of dose-responsive molecules with biological functions ranging from fat adsorption (i.e. bile acids), fatty acids transport (i.e. via carnitine esters derivatives for β-oxidation) to ammonia regulation (i.e. urea cycle), significantly differed between NW and OB. Overall, linear acyl-carnitines ranging from six to twelve carbon atoms (i.e. β-oxidation of fatty acid) inversely responded to both the caloric dose and the carbon number for NW while the inversed trend was observed for short chain and branched fatty acid in OB. These results suggest a better assimilation of long chain fatty acid for NW while OB may be less efficient in the absorption of short chain and branched fatty acids.
Moreover, only OB presented a dose responsive glycogenesis when looking at the uridine diphosphate level. This finding suggests that OB may develop an alternative route for glucose storage. Finally, amino acids catabolism (i.e. ammonia production) and urea cycle (i.e. ammonia regulation) were upregulated and dose-responsive solely for NW except for the branched chain amino acid valine (a bio-marker for obesity), which was dose-responsive uniquely for OB. These final observations may pinpoint a disorder in the ammonia regulation of OB. Taken together these results provide a deeper understanding of the impact of obesity on the metabolic response of men to the ingestion of HFM.

The Role of 3,4-Dihydroxyphenyl-γ-valerolactone, the Gut Microbiota Metabolite of Epicatechin, in reducing Insulin Resistance

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Introductions: Dietary polyphenols are found in natural food sources and (-)-epicatechin (EC) is one polyphenol that has has beneficial effects on health and in particular biomarkers of type-2 diabetes. Gut microbiota-dependent phenyl-γ-valerolactones (DHVL) account for about one third of EC metabolites reaching the peripheral circulation, but little is known of their biological activity.
Aim and Methods: My research therefore has focussed on investigating the effects of EC and (3,4-DHVL) on insulin resistance in a model of type-2 diabetes. A 15-week dietary intervention study on C57BL/6J mice which incorporated 20 mg/kg body weight EC or 3,4-DHVL in combination with a low fat 10%kcal (LF) or high fat 60%kcal (HF) base diet. Plasma insulin and glucose (Glc) levels were recorded at 13 weeks via a fasted glucose tolerance test (GTT). Seven liver samples per group were sent off for RNA-Sequencing and samples analysed on web server Galaxy (Penn State, US).
Results:
The HF diet significantly impaired insulin sensitivity (79% higher Glc AUC compared to the LF diet, $p < 0.05$). The effect of EC-supplementation of the HF diet was to significantly reduce body weight gain (12%, $p < 0.05$) and blood Glc concentration 2 h after IP injection in the GTT ($p < 0.05$). EC supplementation reduced the HOMA-IR by almost 50% compared to mice on the high fat only diet ($p < 0.01$) although still showing IR. In contrast, 3,4-DHVL supplementation did not reduce weight gain and increased the fasting insulin concentration in comparison to the HF base diet, increasing their HOMA-IR ($p < 0.01$) and reducing the GTT Glc AUC with borderline significance.
Hepatic transcriptomic analysis showed clear differences in gene expression between the LF and HF diets and identified several genes where the expression was significantly affected by polyphenol supplemented diets.
Conclusions: EC protected against HF diet induced weight gain and insulin resistance. In contrast, 3,4-DHVL was not able to reduce weight gain and appeared to exacerbate IR, but cryptically was the only treatment reducing GTT Glc AUC. The data from RNASeq analysis of liver will assist with interpreting these somewhat unexpected findings and suggest mechanisms of action.

Postprandial Arteriovenous Analyses of the Metabolome provide new dynamic metabolic Signatures about the Insulin Resistance Condition in the Skeletal Muscle of Minipigs

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The postprandial phase (PP) represents one of the most challenging events in whole-body metabolism, as it must adapt to major changes in blood composition following food intake. This ability to adapt is strongly dependent on the metabolic flexibility of the individual, which is compromised in insulin resistant (IR) conditions, particularly at the skeletal muscle level. Therefore, to detect at the muscle level and as early as possible this condition could be of upmost importance to prevent further progression to diabetes. We applied an untargeted LC/MS-based metabolomics approach to arterial and venous plasma samples across the skeletal muscle before (0) and 1.5, 3 and 6 h after a regular meal in a control or in a model of IR (dexamethasone treated) minipigs. Metabolites fluxes were further calculated by multiplying for each metabolite the arteriovenous (AV) difference by the blood flow (BF): (A-V) x BF. Metabolite fluxes data were complemented by the assessment of the metabolome in muscle biopsies at the same sampling times. Our metabolomics analyses allowed to discriminate the A and the V metabolomes in the control animals. The discrimination was stronger in the IR condition. Among the 2991 variables detected in the plasma samples, 364 of them showed an altered AV profile on the IR animals following the meal. Hierarchical cluster analysis of the AV metabolome showed that the IR muscle did not respond to the meal, which resulted in a blunted response of the exchanged metabolites (reduced uptake vs control condition). Among the annotated metabolites, 33 showed an altered PP flux across the muscle in the IR minipigs. 22 of them were further detected in the muscle biopsies with changes correlated with the observed fluxes. These metabolites participated to pentose phosphate, taurine, biotin, and amino acids (methionine, lysine, alanine, valine) metabolisms, and constituted the dynamic fingerprint across the muscle signing the altered PP response to the meal in the IR condition. This is the first time that high-throughput metabolites fluxes were calculated across IR the muscle, allowing us to obtain an innovative, dynamic and specific muscle signature. We are currently exploring peripheral blood samples (equivalent to clinical blood samples in humans) in order to look for the metabolites found in the IR muscle fluxes signatures. If some of those metabolites appear to be also altered in the systemic circulation they could be potential biomarkers able to sign the IR condition without having access to the skeletal muscle biopsies.

Multi-biofluid Metabolomics as a Tool to Discover Metabolite Biomarkers for Cow's Milk Allergy Diagnosis

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In industrialized nations, food allergies are a growing epidemic and are considered a major thread to our wellbeing. Cow's milk allergy (CMA) is one of the first allergies to occur in early childhood and early life sensitization has been associated with an increased risk to develop the atopic march, including eczema, asthma and other food allergies later in life. As such, more research is urgently needed to gain more insights into this disease. Therefore, this study evaluated a unique multi-biofluid platform for polar metabolic fingerprinting of feces, plasma and urine, applying UHPLC-Q-Orbitrap-HRMS, to determine the optimal biofluid for future research on CMA in children. Plasma is popular for metabolomic analysis, but collection is problematic in young children, while feces and urine are readily available biofluids. All fingerprinting approaches were proven 'fit-for-purpose' through extensive validation, displaying excellent linearity (R^2 > 0.99 or 0.90), recovery and precision (coefficient of variance < 15 or 30%). The effectivity of the platform was demonstrated by subjecting simultaneously collected fecal, urine and plasma samples from 10 healthy volunteers (25 – 41 years old) to metabolic profiling and fingerprinting, yielding respectively 9672, 9647, and 6122 components, with a substantial overlap of the plasma metabolome with that of feces (69.48%) and urine (76.79%). Orthogonal partial least-squares discriminant analysis (OPLS-DA) provided similar results for feces and plasma in gender-discrimination (*p*-value = 0.036), suggesting feces as a promising alternative biofluid to plasma. Additionally, the added value of a multi-biofluid strategy over a single-biofluid platform was evaluated by comparing their fingerprinting abilities, which revealed an increased number of recovered metabolites and improved model predictivity for the multi-biofluid approach. These results were confirmed by a pilot study, subjecting simultaneously collected fecal and urine samples from children, below the age of 5 years, with IgE-mediated CMA (n = 5), non-IgE mediated CMA (n = 3) and their healthy brothers and sisters (n = 5) to metabolic fingerprinting. The established OPLS-DA models for feces and the combination of urine and feces were able to discriminate according to allergy state, except for the model discriminating fecal samples from non-IgE-mediated CMA with the healthy control group. These results indicated that urine as a single-matrix was not equally powerful as compared to feces. However, the combination of urine and feces as a multi-matrix platform improved the power of the final models. As such, the multi-biofluid strategy entails the unprecedented potential to reveal more significant results in food allergy research, including the discovery of biomarkers and unraveling of mechanistic information.

Diurnal Differences in the Transcriptome of Peripheral Blood Mononuclear Cells in Response to a Meal

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Eating at night has been linked to impaired glucose metabolism and dyslipidaemia that is likely a consequence of an underlying disrupted circadian rhythm in metabolic processes. An understanding of the mechanisms causing metabolic disruption after eating at night is important for prevention and management of disease risk factors. The aim of this study was to explore the transcriptomic differences in nutrient metabolism after eating a meal at night compared with the same meal in the morning. In a cross over design, 10 healthy adults fasted for >10 hours and then completed two acute meal challenges at 8am and 8pm on non-consecutive days separated by a wash out. Fasting and postprandial blood samples were collected to assess glucose and insulin responses. For a subset of five participants RNA sequencing was completed on the Illumina NextSeq500. Total RNA was extracted from peripheral blood mononuclear cells at fasting (baseline) and 2 h after the test meal, the quality of all samples was above RIN 8 (AATI Fragment Analyzer). Differential expression analysis was completed using the DESeq2 package. False discovery rate correction was applied at the pathway analysis level, conducted in PathVisio. Postprandial blood glucose was significantly higher at 8pm vs. 8am (208.8(154.1) mmol/L.3 h vs 36.4(99.6) mmol/L.3 h, $p = 0.005$) no concurrent changes in insulin responses were observed ($p = 0.100$). Under fasting conditions, 704 genes were differentially expressed between morning and night, with 60% of these genes being down regulated at night. The meal challenges were associated with changes in gene expression compared with fasting in the morning 552 genes were differentially expressed and 532 genes were differentially expressed in the evening, however only 7% were commonly differentially regulated at both times of day. Pathway analysis of the differentially expressed genes identified that more immune system and signal transduction pathways were enriched after eating at night compared with morning, where as a greater number of pathways involved in lipid metabolism were enriched in the morning. The time of day a meal is consumed has an effect on which genes are differentially regulated in the acute postprandial period, and the biological pathways they are involved in. Investigating the differences in the transcriptomic response to food at night provides a greater understanding of the mechanisms underlying the phenotypic dissimilarities observed in circulating metabolic biomarkers according to the time of day.

Platelet Mitochondrial DNA Methylation and CVD Risk: what is the Role of Trimethylamine-N-oxide and Carnitine Supplementation during Physical Activity?

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Trimethylamine-N-oxide (TMAO), indirect product of specific micronutrient (i.e. carnitine) metabolism, has been positively correlated with an increased risk for cardiovascular disease (CVD). Despite the strict correlation between carnitine and TMAO, a consensus about effects of carnitine supplementation on cardiovascular health has not been achieved yet.
Another interesting biomarker which has been recently associated to cardiovascular health is platelets mitochondrial DNA (mtDNA) methylation.
This study investigates the effects of leucine and carnitine supplementation during 6 months of regular resistance training, on TMAO levels, lipid profile and platelets mtDNA methylation levels in a group of aged women.
All subjects participated in the resistance training program twice a week with no supplementation (control group), 4000 mg L-leucine per day (leucine group) or 1000 mg L-carnitine-L-tartrate in combination with 3000 mg L-leucine per day (leucine+carnitine group). Fasting blood samples were collected and total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and TMAO have been measured. DNA methylation levels in D-loop region and *MT-CO1* mitochondrial gene have been assessed by pyrosequencing analysis.
Data analysis revealed that carnitine supplementation significantly alters TMAO levels and mtDNA methylation at D-loop region but not at *MT-CO1* gene. Increased LDL and TC were positively associated with TMAO, while an improved lipid profile was measured in subjects with higher D-loop methylation levels.
These data suggest that, despite carnitine increases TMAO levels, other triggered pathways could be responsible for the positive effects (which are associated to D-loop methylation levels) on lipid profile affecting CVD risk. Further analyses are warranted to identify mechanistic explanations and clarify the usage of mtDNA methylation levels as CVD biomarker.

Interactions between Anthocyanin Microbial Metabolites, HDL Function and PON1 Genotype

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High HDL quantity and functions are inversely associated with CVD risk. Paraoxonase 1 (PON1) contributes to many atheroprotective functions of HDL such as reverse transport of cholesterol and prevention of LDL from oxidation. PON1 activities are influenced by several factors, most importantly, diet and genetic polymorphism. The results from nutrigenetic observational studies has identified protective genotypes of PON1 that are associated with increased HDL with high anthocyanin consumption. However, the interaction between PON1 and anthocyanin consumption is not understood. Anthocyanins are extensively metabolized suggesting that their metabolites are responsible for their high bioactivity. Most of these metabolites have recently identified and their effects on PON1 are unexplored. Additionally, the effects of anthocyanins on lactonase, the physiologically-relevant activity of PON1, haven't been investigated nor have interactions between anthocyanins and PON1 genetic variants. Therefore, the present study was conducted to investigate the ability of anthocyanins and their metabolites to increase PON1 arylesterase and lactonase activities considering the genetic polymorphism of PON1 *in-vitro* and in human.
In-vitro; two predominant types of anthocyanins and 18 of their recently identified metabolites including the pure synthetic phase II conjugates of metabolites were incubated individually and as mixtures with two isoforms of PON1 that phenotyped for the 192 Q/R polymorphism, RR and QQ, at physiologically relevant concentrations to investigate their effects on arylesterase and lactonase activities. In vivo; 52 of hypercholesterolemic individuals were genotyped for 192Q/R and 55L/M given capsules containing either bilberry extract or black rice extract that providing 320 mg anthocyanins/day for 28 days in three-arms placebo-controlled cross-over intervention. PON1activities, HDL subspecies and other biomarkers associated with HDL function and CVD were assessed in serum.
In-vitro, none of the anthocyanins or their tested metabolites affected PON1 activities in either RR or QQ phenotype except for cyanidin at high concentration which modestly decreased lactonase only with QQ but not RR phenotype ($p \leq 0.001$). In the human intervention, PON1 activities remained unchanged after treatments whatever the genotype which was consistent with the in-vitro result. Additionally, no significant differences were observed in total HDL, HDL2, HDL3, ApoA1 and ApoB1 in humans after anthocyanins consumption. It can be concluded that anthocyanins and their metabolites didn't confer a protective effect toward PON1 and HDL function biomarkers *in-vitro* and *in-vivo*. The lack of effects may be due to the short duration of intervention.

Measuring Polyphenols Metabolism in Mankai Duckweed: a novel aquatic and amino rich Plant Protein Source

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The duckweed Mankai, is based on a specific strain of *Wolffia globosa*, one of the smallest plants on earth, belonging to the family *Lemnaceae*. Mankai is being considered as a high-quality substitute for animal protein, and a potential source of vitamin B_{12} and iron. In fact, it contains all 9 essential amino acids and its protein profile is extremely close to that of egg. Recently, it has been granted GRAS status, and chosen as a test food in a long-term intervention DIRECT-PLUS (ClinicalTrials.gov identifier (NCT number): NCT03020186). Our role will be to determine and compare the metabolic fate of Mankai polyphenols in plasma and urine of 300 volunteers suffering from cardiometabolic disease randomly assigned to physical activity (PA), PA + MED diet, or PA + green-MED diet (enriched with Mankai). However, molecular characterization of phenolic composition of Mankai plant has not previously been reported. Therefore, our initial measurements of total phenolic content determined by Folin-Ciocalteu assay classifies Mankai amongst the foods highest in polyphenols content (8606.7 mg/kg). Then, we characterized the polyphenols profile using an UHPLC-ESI-MS/MS system, identifying 26 different polyphenols. One of the main advantages of Mankai is its hydroponic cultivation that optimizes yield throughout the year. Light source, water and mineral management can influence the composition of phenolic content. Our analysis has been done in 30 different plant batches treated with 5 different treatments to assess how quality of light may play a major role in the accumulation of secondary plant compounds. Notably, led light seems to enhance the glycated form of luteolin and quercetin compared to sunlight and the aglycone form of luteolin and quercetin are higher in sunlight treatment. The present analysis confirms the high polyphenol status of Mankai, profiles its major polyphenol components and provides new information on how production process in terms of light quality determines polyphenol content.

Molecular Mechanisms of Action of β-apocarotenoids and Functional Biomarkers of Plasma Carotenoids

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β-Carotene is the major dietary source of provitamin A. Central cleavage of β-carotene catalyzed by β-carotene oxygenase 1 yields two molecules of retinaldehyde. Subsequent oxidation produces all-trans-retinoic acid (ATRA), which functions as a ligand for a family of nuclear transcription factors, the retinoic acid receptors (RARs). Eccentric cleavage of β-carotene at non-central double bonds is catalyzed by other enzymes and can also occur non-enzymatically. The products of these reactions are β-apocarotenals and β-apocarotenones, whose biological functions in mammals are unknown. We used reporter gene assays to show β-apo-14'-carotenal, β-apo-14'-carotenoic acid, and β-apo-13-carotenone antagonized ATRA-induced transactivation of RARs. Molecular modeling and ligand binding studies confirmed that β-apo-13-carotenone can interact directly with the ligand binding site of the retinoid receptors. Finally, we developed an LC/MS method and found 3-5 nm β-apo-13-carotenone was present in human plasma. These findings suggest that β-apocarotenoids function as naturally occurring retinoid antagonists. The antagonism of retinoid signaling by these metabolites may have implications for the activities of dietary β-carotene as a provitamin A and as a modulator of risk for cardiovascular disease and cancer.

Carotenoids are naturally occurring pigments that function as vitamin A precursors, antioxidants, anti-inflammatory agents or biomarkers of recent vegetable and fruit intake, and are thus important for population health and nutritional assessment. An assay approach that measures proteins could be more technologically feasible than chromatography, thus enabling more frequent carotenoid status assessment. We explored associations between proteomic biomarkers and concentrations of 6 common dietary carotenoids in plasma from 500 6-8 year old Nepalese children. Plasma proteins were quantified using tandem mass spectrometry and expressed as relative abundance. Linear mixed effects models were used to determine the carotenoid:protein associations, accepting a false discovery rate of $q < 0.10$. Relative abundance of 4 proteins were associated with β-carotene, 11 with lutein/zeaxanthin and 51 with β-cryptoxanthin. Carotenoid-associated proteins are notably involved in lipid and vitamin A transport, antioxidant function and anti-inflammatory processes. No protein biomarkers met criteria for association with α-carotene or lycopene. Plasma proteomics may offer an approach to assess functional biomarkers of carotenoid status, intake and biological function for public health application.

Session 3

Food and diet: metabolism and function

Poster

The Maternal Intake of a Cafeteria Diet during Lactation affects not only the Total Amount of Protein Content in Breast Milk but also Changes specific Peptides Concentration

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Background and objective: Maternal consumption of a cafeteria diet throughout lactation in rats affects the macronutrient composition of breast milk and produces lasting effects in the metabolic health of their offspring. We have previously reported that maternal consumption of an obesogenic diet, such as the cafeteria diet, reduce protein content in breast milk. Thus, considering that proteins may exerts a biological role beyond their nutritional role as source of amino acids, we considered of interest to extend our investigations and asses if a maternal cafeteria diet intake during lactation not only reduce the total protein content in breast milk but also affects the composition and levels of specific peptides and proteins present in milk.
Methods: Nursing rats were fed a control diet or a cafeteria diet during lactation (CAF dams) and milk samples were obtained at different time points of lactation (day 5, 10 and 15). At the same time points plasma samples were collected from pups. 15 µl of milk samples at day 15 were separated on one-dimensional sodium dodecyl sulphate- polyacrylamide gel (1D SDS-PAGE) and stained with Coomassie Blue to visualize protein bands. Bands with a different intensity between groups were selected and excised for in-gel digestion and peptide extraction, followed by MALDI-TOF MS and MASCOT protein identification. Results regarding the levels of haptoglobin (one of the identified proteins) were further confirmed by enzyme-linked immunosorbent assay (ELISA). In addition, levels of know proteins present in milk with a biological role in the energy homeostasis (leptin, adiponectin and irisin) were analysed by ELISA in breast milk samples.
Results: The bands that presented a lower intensity in milk samples from CAF dams than control contains some caseins (α-S1-casein, α-S2-casein like B, and β-casein), α-lactalbumin and haptoglobin. Leptin and adiponectin levels were greater in breast milk of CAF dams than control, while levels of irisin and haptoglobin in breast milk were lower. The offspring of cafeteria fed dams presented greater leptin levels during lactation.
Conclusion: This study revealed that the relative concentration of peptides was influenced by maternal diet consumption during lactation. These changes in specific peptides at early stages of life could influence the phenotypic traits of the offspring.

Ageing is Associated with Different Metabolic Postprandial Responses after acute Milk and Yogurt Intake in Men

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Dairy products (DPs) consumption is often recommended through all stages of life due to their nutritional value. However, it is still difficult to evaluate precisely the impact of their consumption on human health because of the variability of the studied populations and milk processing techniques (e.g. fermentation) as well as the difficulty to measure food intake quantitatively, qualitatively and accurately.
To overcome these limitations, a randomized, controlled, cross-over study was established with 2 main objectives: 1) characterize the differential metabolic signatures resulting from the consumption of two specific DPs, milk and yoghurt, in two different aged groups, healthy young (YM, 20-35 yr) and old (OM, 65-80 yr) men; 2) identify candidate dairy intake biomarkers (DIBs, milk and yoghurt intake) which can be an objective measurement tool for food intake; 28 subjects (YM:14, OM:14) were recruited and acutely consumed 600 mL of milk or yoghurt produced from the same raw milk at two different days separated by a wash-out period of 1 week. Serum and urine samples were collected for biochemical and metabolomic analysis during a 6-hour period of sampling.
After both DPs intake, there was no significant difference in the incremental area under the curves (iAUCs) of insulin but the time needed to decrease insulin levels to half of their maxima was significantly longer for OM than YM both after milk (83.2±9.9 vs 59.1±3.0 min, respectively, $p < 0.05$) and yoghurt (117.9±9.7 vs 85.2±10.6 min, respectively, $p < 0.05$). Postprandial glucose excursions, expressed by the difference between the highest (C_{max}) and lowest concentration (C_{min}), were smaller after yoghurt consumption than after milk in both age groups. Glucose excursions were also smaller in OM compared to YM (-0.86±0.11 vs -1.35±0.13 mmol/L, respectively, $p < 0.05$). Triglyceride levels throughout the postprandial period were higher in OM compared to YM (milk iAUC: 72.2±10.7 vs 26.4±15.9 mmol/L*min; yoghurt iAUC: 77.2±9.0 vs 39.9±4.5 mmol/L*min, respectively, $p < 0.05$). The triglyceride response of OM to dairy consumption was also characterized by delayed kinetics. Finally, yoghurt consumption, compared to milk, resulted in higher C_{max} for glucose-dependent insulinotropic polypeptide (GIP) in both age groups while no age-dependent differences were observed.
Overall, ageing and milk fermentation influence the amplitude and dynamics of the postprandial responses to DP consumption. To clarify their precise association as well as underlying mechanisms, metabolomic analyses of the serum and urine samples (GC-MS, LC-MS) are currently being measured. This data will complement the biochemical parameters described above and contribute to the discovery of candidate DIBs.

Role of Dietary derived Propionyl-CoA and Odd-Chain Fatty Acids in Hepatic Lipid Metabolism

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Our data provide evidence for an improvement of diet-induced hepatic steatosis and insulin resistance by propionate (Pr) which is intestinally produced from fermentable fiber. Correspondingly, odd-chain fatty acids (OCFA; pentadecanoic acid: C15:0 and heptadecanoic acid: C17:0) in plasma phospholipids are induced indicating that propionyl-CoA (Pr-CoA) is used for fatty acid synthesis. Beside their consideration as biomarkers for dairy intake, OCFA are related to an improved type 2 diabetes risk. However, causal relationships are not elucidated. Since the detectable amount of OCFA in plasma is low, we hypothesize that beneficial associations are rather a consequence of increased Pr-CoA availability. For drawing causal conclusions we performed dietary intervention studies in mice to identify by which dietary components metabolic Pr-CoA concentrations are increased.
C57BL/6JRj-mice were fed a semi-synthetic high fat diet (HFD; 40 en% of fat) supplemented either with 10% dietary fibers (HFC: 10% cellulose; HFI: 3% cellulose + 7% inulin), milk components (HFMF: 14% milk fat; HFHP: 28% milk protein; HFLP: 14% milk protein), or 5% of BCAA (HFV: valine; HFL: leucine) for one week. Additionally, control diets only supplemented with 5% C17:0 (HFC17) or Pr (HFPr) were used.
As expected, mice showed no differences in food intake or final body weight after 1 week of intervention comparing all groups. However, fat gain was higher in HFLP-fed animals compared to high milk protein group. This is consistent with an increased gonadal adipose tissue weight and reduced liver weight. A high intake of Pr was associated with an increased liver weight, and reduced brown adipose tissue weight. Gene expression analysis in liver showed higher levels of Acyl-CoA synthetase 3 (Acss3, utilizes Pr) and lower expression of Acss2 (utilizes acetate) in HFPr-fed animals. After supplementation of inulin (HFI), high milk protein (HFHP) and leucine (HFL) a reduced expression of hepatic lipogenesis genes (Elovl6, Scd1) can be seen. Furthermore we observed changes in LCFA composition (liver phospholipids). Especially, the formation of OCFA (C15:0 and C17:0) was enhanced after dietary intake of HFI, HFHP, HFMF, HFC17 and HFPr.
The present data show that besides fermentable fiber also milk components can contribute to OCFA formation probably due to increased substrate availability of Pr-CoA. To further analyze if these diets can also lead to metabolic improvements, long-term experiments will be performed to clarify that and elucidate underlying mechanisms. Overall, the project is important to understand how Pr-CoA can change metabolic characteristics and further improve whole body energy metabolism.

The Metagenome of a Microbial Culture Collection Derived from Dairy Environment Covers the Genomic Content of the Human Microbiome

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Background: The diversity of the human microbiome is positively associated with human health. However, this is endangered by Westernised dietary patterns that are characterised by a decreased food variety. This diversity might be improved by promoting dietary patterns rich in microbial species. Various collections of bacterial cultures resulting from a century of dairy research are readily available worldwide and could be exploited to contribute towards this end. To help to achieve this goal, we conducted a functional analysis of the metagenome of 24 strains, each representing one of the species available in the Liebefeld bacterial culture collection composed of 631 sequenced strains (Liebefeld collection) and compared the pathways potentially covered by this metagenome to the intestinal metagenome of four healthy humans.
Results: A comparison of the annotated Enzyme Commission (EC) numbers, which classify chemical reactions catalysed by an enzyme, revealed that the pan-genome of the Liebefeld collection covers 91% of the human gut microbiome pathway functionality. After restricting the number of strains to 24, the pan-genome still covers 89% of gut microbiome functionality.
Conclusions: Microbial culture collections derived from dairy research have the genomic potential to support human microbiome functionality. The ability of these strains to actively establish themselves in the human intestinal environment should therefore be investigated.

Polyfermenthealth – Linking Bacterial Diversity In Fermented Food To Metabolic Health

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Westernized diets (high-fat, high-protein, high-sugar and low-fibre) are associated with a range of chronic diseases, which are themselves accompanied by a reduced genetic and functional diversity of the gut microbiota. As more diseases are linked to the Western microbiota, hence a possible therapeutical target, microbiota reprogramming may need to involve strategies that incorporate dietary corrections as well as taxa not currently present in the gut in Western-like conditions. Fermentation, using lactic acid bacteria producing strains, is a method of natural food preservation resulting in the improvement of the nutritional value of the transformed food. Fermented foods contain live microorganisms that may improve gastrointestinal health and increase the biodiversity of the whole intestinal microbiota.
Polyfermenthealth project intends to demonstrate that the genetic potential contained in collections of lactic acid bacteria can be translated, via fermented food, into diverse and beneficial metabolic profiles *in vivo*. It will employ a combination of genetic screening methods as well as *in vitro* assays for the selection of the bacterial strains from the collection of sequenced bacteria from dairy industry available at Agroscope-Liebefeld. This selection aims at enhanced production of certain metabolites potentially capable of contributing to health and improved function of immune system. Selected strains will be used for the fermentation of cow milk to produce experimental yoghurts.
Subsequently, a combination of *in vivo* techniques will be applied, using axenic animal models, next generation sequencing technologies and 'Omics'-based approaches such as 16S ribosomal sequencing, metagenomics, metatranscriptomics, metabolomics and host RNA sequencing in order to discover new mechanisms involved in the interactions between the beneficial exogenous microbes, the produced yoghurts and the host organism in order to maximize the health properties of these foods.
The results from Polyfermenthealth project will pave the way for the food industry to develop a new generation of products with nutritional claims. In the long term, Polyfermenthealth will contribute to a targeted use of bacterial resources and food matrices to deliver nutrients that contribute to human metabolic health and increase in the added value of dairy products.

The Triple Interaction Diet-Microbiome-Epigenome: A Novel Approach to Type 1 Diabetes (T1D)

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The role of diet and lifestyle in modulating the gene function (epigenetics) and the gut microbiome both in health and diseases are well demonstrated. This study aims to identify the pathways affecting T1D children among both dietary and microbiome metabolites, and its effect on epigenetic markers.
120 pediatric patients are recruited from Sidra Medicine, Qatar, based on major inclusion criteria, (age 6-12 yrs, no antibiotic treatment in the past 3 months, no chronic diseases except T1D and obesity). Anthropometric parameters, clinical biomarkers, treatments, and 24 hrs dietary recalls are collected. Stool and blood samples are collected for microbiome and SCFA analyses (by 16S rDNA-sequencing and gas chromatography) and epigenetics analysis (Illumina DNA-methylation Array and gene expression analysis on QuantoStudio platform). Statistical analysis is performed using logistic regression with two-sided P-value of < 0.05.
Preliminary results from show that kcal intake negatively correlates with TM7 and positively correlates with the genus Enterobacter and Turicibacter. Cholesterol intake had a mixed effect by its positive correlation with the genus Dorea and negatively affecting Lactobacillus. Fiber level in the diet had the most prominent effect with a strong negative correlation towards Halanaerobium and Odoribacter and a significant positive correlation with RF32 family. No significant correlation resulted between biochemical parameters and microbiome composition.
Preliminary results show that diet intake affects gut microbiome composition in T1D patients. The study is on-going, and the epigenetics analysis is in progress.

Cafeteria Diet Consumption during Lactation in Rats, rather than Obesity *per se*, alters miR-222, miR-200a, and miR-26a Levels in Milk

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Introduction: microRNAs (miRNAs) are present in breastmilk and could exert important functions for the mammary gland development and the infant needs. miRNAs regulate metabolic processes, including adipocyte differentiation and glucose/insulin homeostasis, among others, and hence a deregulation of their pathways may be related to the pathogenesis of obesity. Impact of maternal nutrition on specific miRNAs levels in milk is little known. Cafeteria diet feeding during lactation in rats has been shown to have detrimental effects in the offspring, while diet normalization before gestation, while maintaining excess body fat, the so called postcafeteria model, prevents these detrimental effects. Therefore, the aim of the present study is to investigate in nursing rats the impact of cafeteria-diet feeding during lactation (cafeteria dams) on specific miRNA levels in breast milk and to discern them from the effects of maternal adiposity per se (postcafeteria dams).
Methods: Milk samples were collected from control, cafeteria, and postcafeteria dams at three time points of lactation (days 5, 10, and 15) and levels of selected miRNAs (miR-222, miR-203, miR-200a, miR-103, miR-27a, and miR-26a) were determined. The expression of Cdkn1c (a validated target gene of miR-222) was also measured in the liver of the offspring of control, cafeteria and postcafeteria dams after weaning.
Results: Levels in milk of miR-222 rose while miR-103 and miR-27 fell throughout lactation. Moreover, at day 15 of lactation, cafeteria dams presented higher miR-222 and lower miR-200a and miR-26a levels in milk than controls. No differences were found in postcafeteria dams compared with controls. At weaning, the offspring of cafeteria dams, but not the offspring of postcafeteria dams, displayed lower expression levels of Cdkn1c in liver than controls.
Conclusion: Cafeteria diet intake in nursing rats, rather than obesity per se, leads to alterations in specific miRNA levels, which, through the milk supply, may alter expression of target genes and potentially affect offspring phenotype.
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Changes of Gut Microbiota and its Effect on Lipid Metabolism induced by two Weight-loss Diets in Chinese Women

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Increasing evidence has indicated that gut microbiota is closely associated with obesity and related metabolic diseases. However, it is unclear how gut microbiota changes under different weight-loss diets, and how these changes influence host lipid metabolism. We previously reported that a low-carbohydrate (LC) diet resulted in similar weight lost but better lipid profile compared with an energy-restricted (ER) diet in a 12-week full feeding trial among 48 overweight or obese Chinese women. Here, we investigated the diet modified gut microbiota changes, and its association with lipid metabolism by metagenomic sequencing analysis and targeted metabolomics approaches. The results showed that different diets distinctively altered the gut microbial structure despite the similarity of gut microbiota changes associated with weight-loss. The group-specific changes of microbial functions in LC group indicated potential beneficial effects of carbohydrate-restricted diet on cardiometabolic outcomes. Moreover, our data indicated that the diet-induced microbiome alterations could influence blood lipid, especially HDL-cholesterol, thus might play a role in dyslipidemia treatment. Overall, our findings deepened our understanding of the diet-microbiome-host interactions, highlighting the importance of further studies targeting the gut microbiota in clinical interventions of dyslipidemia and related metabolic disorders.

Effects of two *W*eight-*L*oss *D*iets on *F*atty acids and *A*cylcarnitines in Chinese *W*omen

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Obesity has become a major public health challenge with the rapid changes in nutrition and lifestyle. There has been growing preferences for weight loss with low carbohydrate (LC) diets, but the safety and effectiveness of these diets is limited. On the basis of our previous study, we investigated the effect of a LC diet on the improvement of fatty acid (FA) and lipid metabolism among overweight and obese Chinese women compared to an energy-restricted (ER) diet. Targeted metabolomics approach was conducted to identify erythrocyte FAs and plasma acylcarnitines using blood samples collected at both baseline and the end of the intervention. Compared with ER diet, LC diet demonstrated a favorable change in lipid profile. Besides, LC diet significantly suppressed two FAs in the de novo lipogenesis pathway, whereas raised eicosapentaenoic acid. Levels of plasma acylcarnitines generally increased in both groups, and the changes of FAs and acylcarnitines were not strongly correlated with each other. In addition, we found 5 FAs and 6 acylcarnitines contributed to 52.5% and 50.0% of HDL-cholesterol changes, respectively. As for triglycerides, 29.8% and 61.0% changes were attributable to 4 FAs and 16 acylcarnitines, respectively. In conclusion, our data showed group-specific changes of FA profiles in LC group, indicating potential beneficial effects of carbohydrate-restricted diet on cardiometabolic outcomes.

Plasma Lipidomics revealed Protection of Renal Function by traditional Chinese Medicine Herbs for IgAN Patients through Lipid Metabolism

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IgA nephropathy (IgAN) is the most prevalent type of primary glomerular disease (PGD) worldwide. Corticosteroids as anti-inflammatory agents remain a powerful tool for treating patients with IgAN. However, long-term use of corticosteroids can cause a myriad of side effects. Evidences showed that traditional Chinese medicine (TCM) herbs could be of benefit for patients with IgAN, when intake with corticosteroids as food supplements or therapy. In the present work, using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) based targeted lipidomics assay, a total of 545 lipid species from 24 different lipid (sub) classes were measured in plasma of 181 participants, including 104 IgAN patients with either TCM or combined corticosteroids and TCM (CT) treatment, and 77 healthy volunteers. Among them, 70 lipid species belonging to TAG, CE, PE, PC, LPC, and SM classes were significantly ($p < 0.05$) associated with change in estimated glomerular filtration rate (eGFR) between baseline and 12-month follow-up in patients from CT treatment group. Furthermore, a subset of 7 lipid species and 2 demographic variables were selected to generate a simplified model, which can predict the increase in eGFR of 5.0 mL/min/1.73 m^2 or more at 12 months compared to baseline with the area under the ROC curve (AUC) of 0.82 (95%CI, 0.63-0.96). The results were subsequently validated in an independent validation cohort of 35 IgAN patients. Thus, we discovered a distinct panel of lipids, which may allow the prediction of medium-term outcomes of IgAN patients. The protection of renal function by TCM herbs combined with corticosteroids might be through lipid metabolism.

3,4-dihydroxytoluene (DHT), a metabolite of rutin, prevents non-alcoholic fatty liver disease through inhibition of acetyltransferase activity

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Histone lysine acetylation is thought to play a role in regulation the balance between energy storage and expenditure. However, the epigenetic mechanisms by which metabolites of phytochemicals influence metabolic processes in the liver have not been thoroughly investigated. We examined the potential of representative metabolites of rutin as a novel histone acetyltransferase inhibitor (HATi) and demonstrated that 3,4-dihydroxytoluene prevents non-alcoholic fatty liver disease (NAFLD) by inhibiting HAT activity. The anti-HAT activity of metabolites of rutin, 3,4-dihydrophenyl acetic acid (DHPAA), 3-hydroxyphenyl acetic acid (HPAA), 3,4-dihydroxytoluene (DHT), and Homovanillic acid (HPAA), was examined using HAT activity assays. An in vitro NAFLD model was generated by treating oleic and palmitic acids in HepG2 cells, and male ob/ob mice (6 weeks) were used for in vivo validation. Finally, the possibility of interacting p300 and DHT was simulated through computational docking program, and then has been shown via drug affinity responsive target stability (DARTS) assays. We found that DHT suppressed HAT activity both in vitro and in vivo through destabilization of p300, inducing histone deacetylation at lysine residues 9 and 36 of histone H3, and 8, 16 of histone H4 proteins, and consequently inhibiting gene expressions related to lipogenesis and attenuated lipid accumulation. Furthermore, we observed that NAFLD features, including body weight, liver mass, were fat mass were improved by DHT injection through ob/ob mouse tail vein in vivo. Finally, our data showed the possibility that DHT directly binds to bromodomain of p300 through docking simulation and DARTS assay.

Taken together, our findings demonstrate that DHT, one of rutin metabolites, a novel HATi, has potential application for the prevention of NAFLD.

Insights on hepatic glutathione, lipogenesis and branched-chain amino acid pathways from a combined metabolomics and transcriptomics profiling strategy on adult rats born from normal or high fat-fed mothers

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Obesity development involves genetic factors, considered to account for only a small fraction of the overall susceptibility to high fat (HF) feeding, and foetal environment factors, also known to trigger an adaptive response under certain conditions. This involves the further onset of insulin resistance (IR) in certain organs like the liver. Here, we studied the impact of a perinatal and post-weaning exposure to a HF diet on rats liver metabolome and transcriptome.
Pregnant rats were fed a normal fat (NF) or a HF diet during gestation and lactation. After weaning, males from the F1 generation were fed either the NF or the HF diet, until PND142, resulting in 4 groups depending on perinatal and post-weaning diet: NFxNF, NFxHF, HFxNF and HFxHF. ^{1}H-NMR spectroscopy, high resolution mass spectrometry, mRNA levels, protein phosphorylation and enzyme activities analyses were performed on male livers extracts.
Obesity and IR phenotypes were expressed according to post-weaning diet but not according to maternal diet. In contrast, the multivariate models on genes and metabolites were further able to discriminate F1-animals based on maternal feeding.
Several factors involved in glycolysis (glucose levels, PK) and lipogenesis (ACLY, ACC, FAS) showed increased levels in HFxNF animals compared to NFxNF ones, suggesting that under NF-F1 feeding, the maternal exposure to an obesogenic diet could result, in adulthood, in disrupted lipid deposition. Interestingly, when F1 were fed on a HF diet animals showed (irrespectively of the maternal feeding) an increased expression of genes participating to hepatic inflammation and a reduction in oxidative stress protectors, including glutathione and several endogenous molecules involved in its metabolic pathway (betaine, dimethylglycine, glycine, oxoproline). Finally, by comparing the HFxNF and HFxHF groups we observed that the branched-chain amino acid metabolism was altered, with higher leucine levels and further enhanced catabolism (BCAT, BCKDH), which is known to be a marker of IR. The most extreme scenario (NFxNF *vs.* HFxHF) resulted in a worsen deleterious phenotype, as the consequence of the combination of the inflammatory and metabolic features described above.
We conclude that, despite the fact that HF feeding of F1 animals induced similar changes in clinical phenotyping regardless of maternal feeding, the hepatic metabolomics and transcriptomics analyses were further able to discriminate them according to maternal regimen. This provides valuable information on the underlying inflammatory and metabolic processes signing the consequences of different maternal feeding and demonstrates an enhanced susceptibility to develop IR in animals born from HF-fed mothers.

Compared to animal proteins, plant proteins induce metabolic reorientations that ensure protein homeostasis and are associated with a reduced high-fat-induced insulin resistance

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We aimed at studying the metabolic reorientations induced by the ongoing nutritional transition towards more plant (PP) and less animal (AP) proteins for sustainability reasons.
Male Wistar rats were fed 4 isonitrogenous diets, with AP (milk) or PP (50:50 wheat:pea) as protein source and a normal (NF) or high (HF) level of fat and sucrose (AP-NF, AP-HF, PP-NF and PP-HF, n=11 rats each). Body weight, composition (MRI) and insulin resistance (HOMA-IR index) were regularly measured. After 4 months on the diets, rat received an intraperitoneal administration of ^2H_2O to assess tissue protein synthesis. 48h later, blood, intestine, liver and muscles were collected. Tissue protein were isolated and weighted, and the tissue protein synthesis fluxes were calculated from the ^2H enrichment in tissue free and protein-bounded alanine measured by GC-MS. Natural ^{15}N and ^{13}C enrichment in tissue proteins were measured by EA-IRMS to respectively assess the rate of tissue amino acid (AA) metabolic trafficking (by transaminations and deaminations) and the routing of dietary AA to tissue AA (as C in tissue AA originate mainly from dietary AA but can also derive from dietary lipids and carbohydrates).
In HF *vs* NF rats, we observed a 10% higher body weight due to a higher fat mass but similar lean mass, with also similar protein masses and synthesis fluxes in all tissues except the liver where they were slightly higher. Protein intake was similar across groups and the protein source (PP *vs* AP) did not affect body weight, lean mass and the tissue protein masses and synthesis fluxes. Compared to AP, PP induced more AA metabolic trafficking in tissues, and a slightly less routing of dietary AA to tissue AA with a greater contribution of non-protein macronutrients to non-indispensable AA synthesis via β-oxidation and glycolysis. Furthermore, compared to AP, PP alleviated the HF-induced increase in insulin resistance.
To conclude, compared to milk AP, a well-balanced grains and legumes PP blend allows to similarly maintain protein homeostasis via an enhanced AA metabolic trafficking and a stimulation of the intermediate metabolism, which compensate their suboptimal AA profile regarding the metabolic demand. Our results further suggest that these metabolic adaptations could be beneficial to cardio-metabolic health. To clarify the underlying mechanisms, plasma metabolomics (LC-MS) and tissue transcriptomics analyses are underway. These omics data will complement the biochemical and flux data described above and contribute to elucidate the metabolic changes induced by the different protein sources utilization.

Associations of serum indole propionic acid with liver and adipose tissue transcriptome in individuals with high risk for type 2 diabetes

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Diet related changes in serum metabolome reflect food biotransformation in host tissue or microbial degradation by gut microbiota. Many studies in past have identified gut derived systemic metabolites e.g. Branched chain amino acids, Enterolactones, Betaines, Tryptophan derivatives etc. linked with prognosis, pathology or prevention of Type 2 diabetes (T2D). We recently identified, Indole propionic acid (IPA), a microbial metabolite of tryptophan obtained from high fibre diet, to be associated with a lower risk of developing T2D in the Finnish Diabetes Prevention Study (DPS). Other independent studies have also highlighted IPA's role as an anti-inflammatory & neuroprotective agent.
To gain further insight into the mechanisms mediating IPA effects in tissues, the available metabolomics profile of the serum samples of individuals (n = 175) from an ongoing Kuopio Obesity Surgery Study (KOBS) were analysed at the day of the surgery using non-targeted LC-MS. At the same time liver & adipose tissue biopsies were obtained for whole RNA paired end sequencing on Illumina HiSeq platform, depth 40-50 M reads per sample. The aligned reads from all samples were mapped to corresponding genes and ones with >10 reads in at least 80% of samples were included. The gene level quantification was estimated as sum of read counts of all transcripts of a gene. Linear model for association was used to test association of inverse normal transformed IPA levels with tissue specific gene expression levels. WebGestalt was used for pathway enrichment analysis.
When associating the global gene expression and IPA levels expression of 9 genes in liver was significantly associated with serum IPA levels (FDR<0.10; F-test) while no gene was found to be associated in adipose tissue. Next, we restricted the analysis to genes differentially expressed between individuals with and without T2D (FDR<0.05; T-test) because of the hypothesis to identify diabetes-related transcriptomic signals. Based on this analysis expression of 180 genes in the liver and 2 genes in the adipose tissue were significantly associated with serum IPA levels (FDR<0.10; F-test). These 180 genes identified in the liver were significantly enriched in the following pathways: amino acid, tryptophan and fatty acid metabolism, PPAR and PI3K-Akt signalling and ECM receptor pathway.
Based on our results we suggest that IPA may regulate liver than adipose tissue metabolism at the transcriptome level. We will further analyse what are the molecular networks linked with IPA in tissues and aim to verify the underlying mechanisms using human primary cells.

The impact of Varna basin mineral water intake on blood pressure in healthy volunteers

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Sulfur rich mineral waters intake to treat liver, gastrointestinal and metabolic disorders are very popular in European spas. It is considered that dissolved hydrogen sulfide (H_2S) and other sulfur components therein have beneficial effects on health. Varna mineral waters contains hydrogen sulphide and dissolved sulphides with different concentrations. Hydrogen sulfide is recognized as the third signal molecule and together with nitrogen oxide and carbon monoxide it affects a number of physiological and pathological processes related with blood clotting, cardioprotection and atherosclerosis. Other effects are related also with decrement of the blood pressure. The delivery of H_2S in the body by H_2S-based therapeutics is still a big challenge concerning the control of concentration and pharmacokinetics. In this aspect, mineral waters could be considered as natural donors of the molecule in physiological concentration. The aim of present research is to explore whether Varna basin mineral water intake would have any effect on the blood pressure in healthy volunteers. An 8-week intervention with Varna SMW intake, fully characterized physicochemically prior the intervention, was performed with fifty healthy volunteers in age between 40-65 years (females/males=43/7) water. Daily amount of the mineral water intake was 20 ml/kg but not lower than 800 ml/24 hours. Blood pressure was detected before and after the intervention in a sitting and relaxed position. Participants were divided into two groups according to the preferred mineral water sources. In total, 33 participants have used water from Dom Mladost fountain with higher concentration of H_2S (Dom Mladost group), and another 13 participants consumed the water from Aquarium fountain with lower concentration of H_2S (Aquarium group). To explore whether the differences in physicochemical characteristics of both springs would reflect on the changes in the blood pressure, we compared the two groups. Four participants were excluded from this analysis because, according to their diaries, they have consumed water from both fountains. After the intervention, blood pressure difference was observed, with a statistically significant decreasement in the diastole (79 ± 1.55 mmHg vs 72.82 ± 1.50 mmHg, $p < 0.01$) for total group. A tendency of decreasement in the systole was also detected without statistical significance. Similar results were observed in both subgroups according the stratification. Varna SMW might have antihypertensive effect most probably due to the vasodilation properties of hydrogen sulfide and can be used as natural source for hydrogen sulfide donor. Further studies are required to clarify the antihypertensive effect of Varna SMW.

Anti-obesity Effect of Tamarixetin is accompanied by Inhibition of Histone Acetylatransferase

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In our preliminary study, tamarixetin found in *Chrysanthemum coronarium* (crown daisy) strongly inhibited histone acetylation among major bioactive compounds. Thus, we examined whether tamarixetin influence the expression of histone acetyltransferases (HATs) and lipogenesis-related genes in adipocyte differentiation based on our previous result. It was observed that the MDI-induced expression of pCAF (p300/CBP-associated factor), a representative HAT, was down-regulated after tamarixetin treatment, while there was no difference in expression of p300 and CBP (CREB binding protein). It was also expected that tamarixetin binds to the HAT domain, a catalytic pocket of pCAF through computational docking program. Furthermore, it was found that tamarixetin decreased MDI-induced lipid accumulation by significantly attenuating the expression of lipogenic proteins, FAS, PPARγ2, ACLY, LXRα, CEBPα, and DGAT1 at 50μM and 100μM, in a dose-dependent manner. Taken together, our observations suggest that tamarixetin acts as a HAT inhibitor and an anti-obesity agent.

Novel Dietary Biomarker Candidates identified through a combined NMR and LC-MS Metabolomics Approach

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Nutritional biomarkers are biological indicators of nutritional status reflecting the consumption or metabolism of dietary constituents. It is now possible to investigate biochemical markers systematically using metabolomics tools to improve dietary assessment techniques such as food frequency questionnaires and food diaries. The aim of the current project was to discover new dietary biomarkers by performing both NMR and LC-MS-based metabolomics analyses on serum samples collected within NICOLA (Northern Ireland Cohort for the Longitudinal Study of Ageing). Samples and data were provided from a dietary validation subset of NICOLA participants, comprised of 95 individuals. Blood samples from individuals were collected at baseline and with a 6 month follow-up, each with coinciding nutritional information (four-day food diary). Samples were prepared and analysed by two complementary metabolomic platforms. UPLC-MS analysis involved a Waters TQ-S coupled with an Acquity I-class UPLC, used in combination with a targeted metabolomics kit (AbsoluteIDQ p180 kit, Biocrates Life Sciences), with acquired data processed using MassLynx v4.1 and MetIDQ software. NMR analysis involved the use of a Bruker 600 MHz Ascent coupled to a TCI cryoprobe, with acquired spectra analysed using Bayesil software (University of Alberta, Canada). Statistical analysis of quantified metabolites and food consumption was performed using SPSS.
A total of 15 statistically significant ($p<0.05$) food-metabolite correlations were detected after adjusting for age, sex and BMI. Strong correlations between dairy consumption and specific serum glycerophospholipids were detected, and also between fruit and serum levels of acetic acid. Gender-specific associations of dairy consumption and glycerophospholipids were particularly strong. Some of these findings were supportive of previously published dietary biomarkers. This study brings forward new information to assist with the discovery of reliable and reproducible nutritional biomarkers. Further validation studies are required in other cohorts/populations to improve confidence in the discovered biomarkers.

Time-of-Day dependent Effect of bioactive Compounds on white adipose Tissue Metabolism and Expandability in obese Rats

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Bioactive compounds have been described to exert beneficial effects on obesity. Indeed, they may play a role in managing white adipose tissue (WAT) expandability and metabolism. However, the biology of adipose tissue in mammals is synchronized by circadian rhythms and, therefore, the timing of bioactive compounds consumption could influence their beneficial effects in WAT. Thus, the aim of this study was to determine whether the time-of-day at which a bioactive multi-compound (MIX) is consumed influences the metabolism and expandability of epididymal WAT (eWAT) in cafeteria diet-obese rats. Accordingly, we used male Wistar rats (n=32) fed a cafeteria diet for 9 weeks. During the last 4 weeks animals were orally supplemented with MIX when either the lights turned on (ZT0) or turned off (ZT12). Biochemical parameters concentrations in plasma were analysed. Adipocyte size and number were assessed by histological analyses. In addition, gene expression of genes related to lipid and glucose metabolism and thermogenesis was performed by qPCR in eWAT. Interestingly, plasma adiponectin concentrations were higher in ZT0 compared to ZT12. Regarding to the histology, an increase in the adipocyte number and a decrease in the adipocyte size was shown in ZT0, being the opposite in ZT12. In addition, *Adipoq* gene expressions was up-regulated in ZT0. Moreover, expression levels of genes related to lipogenesis (*Acacα* and *Gpat*) were up-regulated in ZT12. In conclusion, circadian rhythms could exert a direct effect on the beneficial properties of our bioactive multi-compound, inducing a healthier expansion and metabolism of WAT to match the surplus energy provided by the cafeteria diet only when it is consumed at ZT0.

Human Caco-2 Cell Line as intestinal Model to study Glucose Diffusion: a Metabolomics Approach

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Since obesity and type 2 diabetes are often caused by an excessive introduction of foods with high sugar concentration, it is crucial to fully understand the dynamics of intestinal absorption to implement nutritional strategies to reduce it. To study intestinal absorption *in vivo* is extremely difficult, and *in vitro* models are a valuable alternative. When properly grown on specific support (transwell) simulating the intestinal lumen and the internal milieu, the Caco-2 cell line is considered a reliable model to study the mechanisms of absorption and release of glucose and other nutrients. The aim of this study was to assess the dynamic of glucose uptake and release in Caco-2 cells. The use of NMR-based Metabonomics allowed monitoring also the flux of other metabolites as amino acids and organic acids. In the basolateral chamber (representing the internal milieu) glucose concentration increased in a time depending manner and was paralleled by the rise in pyruvate, lactate, and alanine content. To some extent, the increased concentration of these metabolites can be ascribed to endogenous synthesis. Results obtained indicate that Caco-2 cells represent a suitable model for studying metabolites transport through the small intestinal epithelium. The observation of the metabolic fingerprint in Caco-2 cells is a feasible technique allowing the detection of metabolic patterns and the generation of hypothesis about the metabolic pathways involved. Overall, to fully understand the absorption and release of nutrients in the intestine could be the driving force for further research aimed to the formulation of innovative food improving the health status of the population through a nutritional approach.

Broccoli-derived Sulfur-containing Metabolites profoundly alter metabolic and transcriptomic Profiles *in vitro,* in a cell-line specific Manner

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Significant epidemiological evidence exists to support the association of a broccoli-rich diet with a reduced incidence of cancer and cardiovascular disease. Experimental evidence from human intervention studies has also shown that a broccoli-rich diet can reduce circulating cholesterol, rebalance anaplerotic/cataplerotic metabolism, and promote the integration of fatty-acid β-oxidation with tricarboxylic acid (TCA) cycle flux. These indicators of improved metabolic health potentially serve as one explanation for the apparent chemopreventative and cardioprotective effects of broccoli. These beneficial effects have largely been attributed to a single class of plant secondary metabolites known as glucosinolates, from which the powerful antioxidant sulforaphane is derived. Whilst the effects of sulforaphane are well characterised, very few studies report upon, or consider, the potential bioactivity of other sulphur-containing plant metabolites such as S-methyl-L-cysteine sulfoxide (SMCSO) which is found in abundance in brassica and allium crops. Here, we report on the bioactivity of SMCSO and its metabolites S-methyl methanethiosulphinate (MMTSI) and S-methyl methanethiosulphonate (MMTSO) in both cancerous and non-cancerous cell lines. Using RNA sequencing technology, we are the first to characterise the effect of SMCSO and its metabolite MMTSO on the transcriptomic profile of cultured cells, revealing a cell-line specific, and glucose dependant effect. In addition, we quantify the capacity of these MMTSO and MMTSI to alter energy metabolism and mitochondrial metabolic capacity at physiological concentrations, through the use of the Seahorse Metabolic Flux Analyzer. Our data suggests that SMCSO-derived metabolites offer a significant yet uncharacterised contribution to brassica-associated health benefits, and further contributes to the mechanistic understanding of metabolic regulation by brassica vegetables. This work also highlights the pitfalls of taking a reductionist approach in identifying single food-derived bioactives when considering the health benefits of food.

In vitro faecal Fermentation of Broccolo di Torbole Ecotype (*Brassica oleracea* var. *botrytis*)

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Introduction: Gut microbiota (GM) is intrinsically connected to host health and metabolism, thanks to its capability to digest and transform dietary compounds, especially the ones that escape human digestion and become available for intestinal bacterial metabolism, such as fiber and plant secondary metabolites. Phytochemicals represent a wide class of dietary molecules principally contained in plant foods with renown beneficial effects on human health, including antioxidant capacity, improved vascular health and brain function. A relationship exists between GM and phytochemicals, since GM is able to biotransform plant secondary metabolites into the derivative metabolites with *in vivo* activity. Similarly, also the GM breaks down complex vegetable dietary fibers with production of short chain fatty acids and gas as main fermentation end products. This study aims to analyze changes in microbial populations and metabolites after *in vitro* faecal fermentation of Broccolo di Torbole (*Brassica oleracea* var. *botrytis*), a broccoli ecotype rich in polyphenols (flavonoids, hydroxycinnamic acids) and glucosinolates, and also dietary fiber (non-starch polysaccharides and other plant components). *In vitro* metabolic impact of Broccolo di Torbole will be preliminary to study *in vivo* metabolism of this plant food in a human feeding study in obese subjects.
Material and methods: Fecal samples were collected from 5 donors (female, age between 20 and 50 years, no antibiotic treatment in the 3 months preceding the experiment), diluted 1/10 (wt/vol) in PBS and used as fermentation inoculum at 1% (wt/vol). As substrates, inulin (positive control), cellulose (negative control) and Broccolo di Torbole (steamed-cooked leaves and fruit in equal proportion), were employed at 1% of the total fermentation volume after *in vitro* upper digestion, were carried out over 24 hours, as previously described. *In vitro* anaerobic batch cultures fermentations were carried out anaerobically at 37°C for 24 hours and at pH between 5.5 and 5.9, to simulate the proximal colon. Samples were collected from each vessel at hour 0, 5, 10 and 24 for microbial 16SrRNA sequencing analysis and MS-based metabolite profiling.
Results and discussion: Faecal fermentation of a local Trentino ecotype of *Brassica oleracea* showed to modulate gut microbial composition over time and these changes will be related to production of *Brassicaceae*-derived microbial metabolites in fermentation supernatants and to systemic metabolites produced after *in vivo* long-term clinical nutrition study in obese subjects.

Sugars and Derivatives in the Human Metabolome: What they can tell us

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Sugar compounds (mono- and disaccharides, polyols and sugar acids) are part of the metabolome. Although numerous sugar compounds occur in nature, mostly only a very few common and well-known compounds are analyzed. Metabolomics often requires a compromise between detecting as many different metabolites and substance classes as possible and satisfactory separation of compounds within each substance class. Sugars with their high structural similarity present a particular challenge with usually insufficient chromatographic and mass spectrometric separation. More comprehensive and highly selective methods to assess the diversity of the human body fluid sugar profile are thus needed. Sugar compounds may serve as markers of dietary intake and may act as reporter molecules of the health status.
We developed a semitargeted GC-MS based sugar profiling method enabling detection of known and unknown sugar compounds in urine and plasma. 24 h urine samples of the observational *Karlsruhe Metabolomics and Nutrition* study with 300 healthy participants were analyzed and markers for dietary intake were identified amongst the sugars, such as mannoheptulose and perseitol for avocado consumption or galactose and lactose for dairy product consumption. In a separate intervention study including an oral glucose tolerance test, plasma samples of healthy, prediabetic and diabetic participants were analyzed using the semitargeted GC-MS sugar profiling method. Next to glucose, a variety of sugars and derivatives with marked postprandial differences dependent on health status were revealed, such as trehalose. In urine samples 55 different sugar compounds and in plasma samples 40 different sugar compounds were detected. Overall, the application of the sugar profiling in these human studies revealed a more complex sugar profile than described or expected so far with potential for finding novel markers for both dietary intake and health status.

A Phenol-enriched Grape-derived decreases Blood Pressure via Sirtuin-1 in spontaneously hypertensive Rats

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Cardiovascular disease (CVD) is the leading cause of death worldwide, and one of the major risk factors for CVD is hypertension (HTN). Available evidence suggests that a vegetable and fruit rich diet, abundant in flavonoids and phenolic compounds, helps to control blood pressure (BP). Grapes are rich in polyphenols and their health effects are well known. In a previous study, the antihypertensive effect and the involvement of nitric oxide (NO) in the BP lowering effect of a phenol-enriched grape-derived product (PGDP) was demonstrated in spontaneously hypertensive rats (SHR). Sirtuin (Sirt-1) is an important NAD-dependent deacetylase that activates endothelial NO synthase (eNOS). Therefore, the aim of this study was to evaluate the role of Sirt-1 in the antihypertensive effect of PGDP. The antihypertensive effect of a single oral administration of PGDP was tested at 125 mg/kg in SHR. Systolic blood pressure (SBP) was recorded before and 2, 4, 6, 8, 24 and 48 h post-administration by the tail cuff method. In other additional experiment, SHR were administered water or 125 mg/kg PGDP. After 4 hours of water or PGDP administration, both groups of rats were divided in 2 different groups and were treated intraperitoneally with saline or 1 mg/kg sirtinol, inhibitor of Sirt-1. SBP was recorded by the tail-cuff method in the rats at 0 and 6 h after oral administration. Results showed that the maximum BP lowering effect of PGDP was at 6 h post-administration. Therefore, this time was fixed to carry out the additional study. Administration of water and saline did not produce changes in SBP. However, as was expected PGDP produced a significant decrease in SBP. Nevertheless, when animals were treated with sirtinol the antihypertensive effect of PGDP was partially abolished. In conclusion, we corroborated that the antihypertensive effect of PGDP is partially regulated by Sirt-1, because the selective Sirt-1 inhibitor sirtinol partially abolished the antihypertensive effect of PGDP.

Grape Seed Proanthocyanidins-mediated Adaptation of seasonal Rhythms after an abrupt Disruption of the Photoperiod in obese Rats

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Seasonal variations in day length trigger clear changes in behavior, growth, food intake, and reproductive status of animals. In this regard, modulating effects on the circadian and seasonal rhythm has been reported for some polyphenols. Specifically, the modulation of clock system in the liver by a grape seed extract rich in polyphenols (GSPE) has been reported by our group. In addition, it has been shown that GSPE presents beneficial effects in rats with hypertension and other cardiometabolic risk factors related to metabolic syndrome.
The aim of this study was to evaluate the effect of GSPE in cafeteria diet (CAF)-fed rats when are transferred abruptly from a standard (12 h light/day, L12) to a long (18 h light/day, L18) or short photoperiod (6 h light/day, L6). Activity, body temperature and blood pressure were recorded by radiotelemetry in 24 CAF-fed Fischer 344 rats for 6 weeks under L12 conditions. After this time, animals were transferred to L18 or L6 and administered vehicle (VH) or GSPE (25 mg/kg) for 1 week.
Results showed the impact of photoperiod change on activity and body temperature. In addition, photoperiod disruption produced a non-dipper pattern, i.e. the lack of blood pressure fall in the sleeping period. GSPE administration resulted in a better adaptation to the new rhythm of light/darkness under L18 condition, as elucidated by a decreased activity during the light hours. However, no differences in the activity were observed between VH and GSPE groups under L6 condition. In addition, adaptation of body temperature to the new photoperiod was better in GSPE than VH groups under both L18 and L6 conditions. Finally, GSPE administration resulted in an attenuation of the non-dipper pattern, maintaining the drop in blood pressure during the light hours, corresponding with the phase of less activity in rats.
Although further research is needed to elucidate the effect of the GSPE in these conditions, these results suggest that the GSPE can modulate seasonal rhythms contributing to the adaptation to the new photoperiod, especially, in L18 condition.

The Study of Enterohormone Secretion in Human Colon is conditioned by the ex vivo experimental Model

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Enteroendocrine cells (EC) are specialized cells in the gastrointestinal (GI) tract that produce different hormones in response to nutrients arrival. ECs are polarized and the distribution of the distinct EC types is different along the GI tract. Their polarization determines their vectorial functionality; they sense apically the content of the intestinal lumen and react to these stimuli producing basolateral enterohormone secretions. *Ex vivo* models are widely used to study enterohormone secretion. They can be vectorial, like Ussing chambers, if they allow the separation between apical and basolateral compartments, or non-vectorial explants. However, it is unclear whether the variety of models offer comparable results. We aimed to evaluate the effect of human colon with different enterohormone secretagogues, i.e. peptone and grape seed proanthocyanidin extract (GSPE), in vectorial and non-vectorial *ex vivo* models. We studied PYY and GLP1 secretion. We used 0.5cm diameter explants as non-vectorial model, and Ussing Chambers as a vectorial model. In the vectorial model, we added the secretagogues treatment apically and collected the secretions of the basolateral compartments. We found that 50 mg/mL peptone increased GLP-1 and PYY secretion in explants, while in Ussing chambers only GLP-1 was increased. When peptone concentration was lowered to 15 mg/mL, the secretion in explants was still observed, but no effects were found in Ussing chambers. We also tested GSPE, which is hypothesized to increase enterohormone secretion through a different mechanism. We observed that 100 mg/L GSPE increased PYY secretion in explants but not in Ussing chambers. GLP-1 was not modified in any of the models. We conclude that non-vectorial studies are not a good model to study basolateral enterohormone secretions in human colon. Therefore, it is important to take into consideration the polarity of ECs to obtain reliable results in enterohormone studies.

Phenotypes of Resveratrol Metabolism in Humans

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Physiological properties of resveratrol (RES) are intensively investigated since decades. Several health-promoting properties like anti-tumor effects, protection against cardiovascular diseases, and promotion of longevity by mimicking caloric restriction are frequently described in various models but also controversially discussed. We hypothesize that conflicting results of in vivo studies may be due to differences in microbial biotransformation of RES into dihydroresveratrol, 3,4'-dihydroxy-trans-stilbene, and lunularin. The latter two entities were recently discovered by our group (Bode et al. 2013, AJCN, 97(2):295-309). However, the significance of those metabolites has not yet been elucidated in a sufficiently large number of subjects. The aim of our study was to provide those valid data and deduce different RES metabolizing phenotypes in humans.
Methods: In a human intervention study healthy volunteers (n=104) ingested a single dose of 1.0 mg trans-RES / kg body weight. Subsequently, urine was collected for 48 h. Quantification of RES and its microbial metabolites was performed by LC-MS/MS. Fecal samples of all participants were analyzed regarding microbial diversities by 16S rRNA gene amplicon high-throughput sequencing. The biological activity of the RES and its metabolites was investigated in HepG2 cells for different end points.
Results: Both, the quantitative relevance and high inter-individual differences of the microbial metabolism of RES in humans were highlighted. Dihydroresveratrol was detected in the 48 h-urine of all volunteers, whereas lunularin was observed in only 48 participants (46.2%). Based on urinary RES metabolite profiles, the 104 volunteers were classified into different RES metabolizing phenotypes by hierarchical clustering. However, those phenotypes were not associated with clusters formed on the basis of fecal microbiomes. The microbial RES metabolites differ in their bioactivity compared to RES.
The different phenotypes of RES metabolism should be considered in clinical studies in the future as they may impact the biological effects of RES in vivo.

Exploring Health Effects of Salmon, Salmon Fishmeal and Beef in obese Mice

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Background: Seafood is known to have beneficial health effects, in part due to the content of marine oils. However, both lean and fatty fish have been shown to have favorable effects in epidemiological studies. Some *in vivo* or *in vitro* studies have indicated that protein and bioactive peptides from fish may influence appetite, lipid- and glucose metabolism and inflammation. On a different note, 40% of the salmon from fish farms are protein rich by-products not used for human consumption. Exploring the health impact of these products may encourage a more sustainable exploitation of resources.
Aims: The study was part of a larger, multidisciplinary study exploring the health effects of fishmeal from salmon by-products in humans, mice and cell cultures. The aim of the current study was to investigate the metabolic effects of salmon filet, salmon fishmeal and beef in mice fed a high fat diet.
Methods: Female C57BL/6 mice were placed on a high fat diet for 10 weeks to induce obesity and impaired glucose tolerance. The animals were then fed a high fat diet supplemented with ~15 w/w% salmon fishmeal, salmon filet or beef from cattle for 10 weeks (n=10 in each group). The diets were isocaloric with equal content of protein, carbohydrates and fat. Metabolic characterization was done by metabolic caging (Phenomaster) and glucose tolerance testing.
Results: Mice fed a high fat diet for 10 weeks developed obesity and glucose intolerance. When placed on a high fat diet supplemented with either salmon, salmon fishmeal or beef, the animals continued gain fat mass. The dietary groups had similar food intake, body weight and body composition. No differences were observed in energy expenditure and glucose tolerance. The groups had similar amounts of visceral adipose tissue and liver weights. Interestingly, mice fed beef had bigger hearts compared to the other groups (11%, p=0.02 compared to fishmeal).
Conclusion: Salmon, fishmeal or beef had similar effects on metabolic health in mice. Mice fed beef had larger hearts, but whether this influenced cardiac health is unknown. More studies are needed to uncover tissue-specific effects of these diets as well as the effects of salmon protein.

Session 4
Nutritional epidemiology

Theatre

The Impact of Epigenetics on Nutritional Epidemiology

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There is now substantial evidence from both human epidemiological studies and animal models that an adverse intrauterine environment induced by a variety of environmental and maternal factors such as diet, body composition or endocrine factors can induce a phenotype in the offspring that is characterized by an increased risk of developing chronic non-communicable diseases in later life. The mechanism by which cues about nutrient availability in the postnatal environment are transmitted to the fetus and the process by which different, stable phenotypes are induced are beginning to be understood and involve the epigenetic regulation of specific genes. Epigenetic processes induce heritable change in gene expression without altering gene sequence. The major epigenetic mechanisms include DNA methylation, histone modification and non coding RNAs. The epigenetic changes induced in response to nutritional cues from the mother may allow the fetus to adjust its developmental programme in order to be better adapted to the future environment, while inappropriate adaptations may predispose an individual to increased risk of a range of non-communicable diseases.
This talk will describe how both maternal and paternal diet can influence the health of the child through the altered epigenetic regulation of genes, how epigenetic changes in early life may be used as predictive markers of future disease risk, and how nutritional interventions in postnatal life may be able to reverse the epigenetic and phenotypic changes induced by an adverse early life environment.

Metabolomics-Based Dietary Biomarkers in Nutritional Epidemiology - current Status and future Opportunities

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Applications of metabolomics in nutrition research has increased in recent years. The applications can be generally be grouped into one of the following: (1) Applications to identify dietary biomarkers for single foods or for dietary patterns (2) Applications to dietary intervention studies to help understand metabolic alterations following certain diets and (3) Applications to diet-related diseases. With respect to dietary biomarkers there has been a proliferation of publications in this field: these biomarkers have the potential to act as objective measures of dietary intake thus overcoming some of the key issues with traditional assessment methods. To date, metabolomic profiling has been successful in identifying a number of putative biomarkers of food intake. Recently, we used an acute study design where participants consumed standardized breakfasts for three consecutive days over three weeks: the quantity of the food of interest was varied over the weeks. Calibration curves were constructed with the urinary proline betaine concentration against the known orange juice intake (g/day). Importantly, we then applied these calibration curves to biomarker measurement in a cross-sectional study and estimated citrus intake. Good agreement with the self-reported data indicated that this approach could be used in large epidemiology studies to estimate intake. Similarly, use of combination of biomarkers can be employed to study dietary patterns. While significant progress has been made in this field a number of challenges remain and will be discussed.

Effects of Obesity and Weight Loss on microRNA Expression in the Human Colorectal Mucosa

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Colorectal cancer (CRC) is the 3rd most common cancer worldwide. Obesity, and its lifestyle determinants, physical inactivity and poor diet, increase CRC risk. However, the effects of weight loss by bariatric surgery on CRC risk are unclear. Epigenetic mechanisms involving microRNAs that lead to dysregulated gene expression may mediate the effects of obesity and weight loss on CRC risk. We hypothesised that microRNAs are i) aberrantly expressed in obese individuals compared with healthy non-obese individuals and ii) modulated by significant weight loss following bariatric surgery. We used data and samples from the Biomarkers of Colorectal Cancer after Bariatric Surgery (BOCABS) Study. Obese patients listed for bariatric surgery and age- and sex-matched healthy non-obese adults (Controls) were recruited at North Tyneside General Hospital. Rectal mucosal biopsies were collected at baseline and six months post-surgery from obese participants and at baseline only from Controls. Using Next Generation Sequencing and bioinformatics analysis, a panel of 8 microRNAs was selected and validated by quantitative PCR in colorectal mucosal biopsies. Data were available for 20 control participants and for 22 obese participants with matched pre- and post-surgery samples. Next Generation Sequencing revealed that compared with non-obese individuals, obese individuals showed differential expression of 112 microRNAs ($p < 0.05$). Roux-en-Y gastric bypass, resulted in differential expression of 60 microRNAs, when compared with expression levels at baseline ($p < 0.05$). A total of 36 microRNAs differed significantly in both i) the obese with non-obese and ii) the pre- and post-surgery comparisons. Validation by quantitative PCR demonstrated that expression of miR-31, miR-215, miR-3196 and miR-4516 was significantly ($p < 0.05$) higher in obese than in non-obese individuals. Weight loss, (mean 28.5 kg) following Roux-en-Y gastric bypass, reduced expression of miR-31, miR-215 and miR-3196 significantly ($p < 0.05$) to expression levels that were comparable with those in Controls. These differentially expressed microRNAs are implicated in pathways linked with inflammation, obesity and cancer. The pattern of microRNA expression in macroscopically-normal human colorectal mucosa differed substantially between obese and non-obese individuals. However, six months after Roux-en-Y gastric bypass, the pattern of microRNA expression was similar to that in non-obese Controls. This suggests that surgically-induced weight loss may normalise microRNA expression in the human colorectal mucosa and so reduce CRC risk.

Finding Genetic Markers of Vitamin D Deficiency from the 2013 Philippine National Nutrition Survey using High-throughput Next Generation Sequencing

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Background: In the Philippines, based on the 2013 National Nutrition Survey, vitamin D deficiency was highest in Benguet at 60.3% and lowest in Cagayan, but still very high, at 19.5%. With vitamin D implicated in a wide range of multiple health outcomes, a fuller understanding of the determinants of vitamin D status is needed and must include consideration of inherited characteristics.
Objective: The study determined the relationship of serum vitamin D levels and genetic variations in 502 lifestyle related genes among adult respondents, age 21 years old and above, from the 2013 Philippine National Nutrition Survey (NNS).
Materials and Methods: The study followed a cross-sectional research design. A total of 1,160 adult respondents of the 2013 NNS and living in Metro Manila, Philippines were included in the study. Anthropometric, biochemical, clinical and dietary data were generated through validated questionnaires, physical examination and laboratory analyses. Total serum 25-hydroxyvitamin D (25OHD3) was determined using electro-chemiluminescence binding assay method. Genomic DNA was used for massively parallel sequencing of 502 lifestyle related genes.
Results: Of the study participants, 56% were classified as having low serum 25OHD3 concentration (< 75 nmol/mL). The data discovered at least six genetic variations show statistically significant differences in serum vitamin D concentration across genotypes. These genes were previously known to have contributed to the risk of developing Type 2 Diabetes Mellitus, Obesity, Iodine Deficiency and a neurodegenerative disorder.
Conclusion and Recommendation: Large-scale analysis of genes associated with lifestyle disease and other determinants of overall health have shown great utility in the discovery of genes and polymorphisms that play a role in vitamin D nutrition. Post – hoc test may be performed to confirm where the differences occurred between groups. It is envisioned that understanding how genetic variations interact with environmental factors, especially nutrition may hold the key to better prevention and management of nutrition-related diseases.

Nutritional Metabolomics – Finding and Validating Biomarkers of Food and Beverage Intake

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Background: Assessing food intake is fundamental to the field of nutritional research but relies on subjective dietary instruments. These include interviews, diaries and 24hr recalls for short-term assessments while food frequency questionnaires or repeated short-term assessments are used for estimating longer-term average intakes. The extent of misreporting is difficult to estimate. Biomarkers of Food Intake (BFIs) may provide an objective alternative to dietary instruments and help to estimate misreporting. Using more than one BFI may help to evaluate sources of error.
Methods: Systematic literature reviews and metabolic profiling of meal studies were used in the FoodBAll project to identify putative BFIs for all major food groups and many single foods. Combined biomarkers were constructed by using patterns of metabolites uniquely associated with specific foods or food groups. Validation of the simple or combined BFIs was performed according to a published standard protocol. Comparisons of candidate BFIs related to intake of alcoholic beverages, some protein-rich foods or fruit with intakes based on 24hr recalls, interviews or diaries/food records were subsequently carried out cross-sectionally in the PREVIEW (New Zealand), NU-AGE (Netherlands) and KarMeN (Germany) studies.
Results: Candidate BFIs were identified for more than 20 foods and food groups. Extended validation studies of fruit (e.g. banana) and some meats indicate good agreement with 24hr recalls with AUROCs >= 0.9. However, 24hr recalls and dietary interviews are not always sufficiently detailed to allow comparison with BFIs for specific foods. For total alcohol intake, the concordance between BFIs and 24hr recalls was lower while concordance between independently measured alcohol markers was high.
Conclusion: The 24hr recall or dietary interviews show high concordance with novel BFIs for recent intake of some well-defined foods. For others such as alcohol, the concordance is lower indicating a particular need for BFIs to support dietary assessment instruments. Additional food intake examples indicate that lack of appropriate biomarker validation as well as misreporting variably contribute to failures in intake assessment.
Further validation of dose-response and inter-laboratory comparisons are still needed for most BFIs.

Identifying and Validating Biomarkers of Fermented Food Intake to Better Understand their Associations with Cardiometabolic Health

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Fermented foods are commonly consumed in diets worldwide and have been associated with beneficial effects on cardiometabolic health. Dietary molecules originating from or enriched by fermentation may impart novel nutritional qualities, and impact diverse metabolic pathways that influence cardiometabolic disease pathogenesis and development. However, as traditional dietary assessment tools are subjective and may not accurately capture the "true" intake of these foods, establishing validated biomarkers of fermented food intake is warranted. The Cardioferment project aims to identify and validate biomarkers of fermented food intake in a prospective cohort study conducted in the Netherlands (NQplus). The study comprised 2,048 participants aged 20-77 years, providing extensive data on dietary intake and cardiometabolic disease risk factors, as well as blood and urine samples. Fermented food intake was identified from food frequency questionnaires (FFQ) and 24-hour recalls. FFQ and 24-hour recall data were compared on the absolute level (percent difference, Bland-Altman) and for their ranking ability (quintile cross-classification, Spearman's correlation) in 809 participants with complete dietary data. Approximately 16-18% of the foods consumed by this population consisted of fermented food items, and a further 9-14% comprised composite dishes with a fermented ingredient. Fermented foods with the highest levels of consumption were coffee (~453 g/day), yoghurts (~88 g/day), wholegrain bread (~81 g/day), wine (~70 g/day), and cheese (~32 g/day). Food groups with acceptable or good relative validity between the FFQ and 24-hour recalls included total fermented beverages, coffee, wholegrain bread, rye bread, fermented dairy, and cheeses (percent difference 0.67-9.73%, correlation 0.204-0.795, same/adjacent quintile cross-classification 57.8-88.5%; Bland-Altman $p > 0.05$). Untargeted and targeted metabolomics analysis using liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS) are being conducted on plasma and urine samples from a subcohort of 535 participants. A targeted panel of 50 candidate biomarkers was selected from the results of a systematic literature search, and includes compounds specific to foods (e.g., 3-phenyllactic acid for cheese), food groups (e.g., heptadecanoic acid for dairy), and dietary pattern (e.g., tyramine for fermented foods). Future associations between dietary patterns of fermented food intake and biomarkers of intake (as determined in the plasma and/or urine metabolome) will be determined in participants stratified by cardiometabolic risk level. In addition to improving the dietary assessment of fermented foods, this project may provide insight into their nutritional quality to help develop fermented food products with beneficial properties, and better influence health/nutritional policy guidelines for inclusion of fermented foods in the diet to promote health.

Metabolic Phenotyping reveals Potential Biomarkers of Diet-modifiable individual Susceptibility to Coronary Heart Disease

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A healthy Nordic diet rich in whole-grain cereals, berries, root vegetables, and fish, has been associated with a lower risk of cardiovascular diseases. A higher Baltic Sea Diet Score (BSDS), as an indicator of higher adherence to the healthy Nordic diet, has been inversely associated with abdominal adiposity and inflammation marker C-reactive protein as risk factors of coronary heart disease (CHD), but the mechanisms remain unclear. Here we present the application of non-targeted metabolite profiling to identify potential endogenous mediators how healthy Nordic diet may benefit cardiovascular health, including the metabolites indicative for differences in dietary response and diet-independent CHD risk. From the population-based Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study, we collected 364 baseline plasma samples in 4 groups: 1) 88 subjects with high BSDS who did not develop CHD during the mean follow-up of 21 years (controls), 2) 94 subjects with high BSDS who develop CHD during follow-up (cases), 3) 93 CHD cases with low BSDS, and 4) 89 controls with low BSDS. Non-targeted metabolite profiling was performed with high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) analysis. The potential predictors of CHD risk included several lipid molecules, whose correlation disappeared after adjustment for age, smoking, systolic blood pressure, LDL cholesterol, and waist-to-hip ratio, except plasmalogen PC(O-16:1/18:2) which was higher in cases. The same metabolite also indicated lower adherence to the healthy Nordic diet, in addition to (oxidized) fatty acids. Conversely, carnitines, proline betaine, indole propionic acid, and pipecolic acid indicated higher adherence to the healthy Nordic diet, even after adjustment for age, waist-to-hip ratio, physical activity, and total cholesterol. The comparison of metabolic profile between cases and controls within groups with high BSDS showed how a higher level of PC(16:0/18:1) in cases might indicate lower sensitivity towards healthy Nordic diet in reducing CHD risk. Similarly, the comparison of metabolic profile between cases and controls within groups with low BSDS may indicate a higher resistance to CHD, independent of their dietary intake. The metabolites that were higher in these “resistant” controls included PC(17:0/18:1), (16:0/18:1), (18:0/22:5), plasmalogens PC(O-16:1/18:2) and PC(O-18:1/20:4), and bilirubin. These findings hence suggest that lipid metabolism may potentially be involved in the link between healthy Nordic diet, individual dietary responses, and susceptibility of CHD.

Session 4

Nutritional epidemiology

Poster

Effects of Obesity and of bariatric Surgery on Human faecal short-chain Fatty Acids: Findings from the Biomarkers of Colorectal Cancer after Bariatric Surgery Study

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Introduction: Obesity is associated with many detrimental effects on health which may be mediated via g ut microbiota dysbiosis and subsequent alterations to short-chain fatty acid (SCFA) concentrations. Whilst bariatric surgery is the most effect treatment for obesity, it has effects on the gut microbiome and consequences for SCFA concentrations are unclear.
The current study investigated the effects of i) obesity and ii) bariatric surgery-induced weight loss on faecal SCFAs in human volunteers. We hypothesised that i) obese individuals have increased SCFA concentrations compared with non-obese and that ii) bariatric surgery reduces faecal SCFAs.
Methods: The Biomarkers of Colorectal cancer After Bariatric Surgery (BOCABS) study recruited 38 bariatric surgery patients and 12 non-obese healthy participants (Controls). Participants were extensively phenotyped and samples including stool were collected at baseline and at 6 months post-surgery. Concentrations of the SCFAs acetate, butyrate, propionate, isobutyrate, isovalerate and valerate were quantified by gas chromatography.
Results: Faecal concentrations of butyrate, propionate, isobutyrate, isovalerate and valerate were significantly greater in obese individuals (pre-surgery) compared with the Control group (non-obese) ($P < 0.05$). The molar proportion of acetate was 12% lower ($P = 0.005$) in obese individuals, whilst molar proportions of butyrate ($P = 0.024$) and of valerate ($P = 0.006$) were increased significantly in the obese participants. At 6 months post-surgery, when bariatric surgery patients had lost mean 28 kg body mass faecal concentrations of acetate ($P = 0.019$) and propionate ($P = 0.014$) were reduced by approximately a third and butyrate ($P = 0.035$) by almost 20% compared with pre-surgery. The proportion of isovalerate was almost four-fold greater post-surgery compared with baseline ($P < 0.001$). Post-surgery SCFA concentrations were similar to Controls except for isovalerate ($p = 0.049$) and valerate ($p = 0.041$) where concentrations remained elevated.
Conclusions: In agreement with the existing literature, faecal concentrations of all SCFAs, bar acetate, were significantly greater in obese compared with non-obese individuals ($P < 0.05$). The findings from this study suggest that weight loss following bariatric surgery tends to normalise faecal SCFAs. We are currently investigating potential mechanisms for these weight loss-related changes in SCFA with a focus on habitual dietary patterns and changes in dietary intake post-surgery as well as the gut microbiota.

Lipopolysaccharide binding protein, inflammatory markers, adipokines, and incidence of hyperuricemia in a cohort study of middle-aged and older Chinese

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Hyperuricemia is associated with obesity and noncommunicable diseases (NCDs), especially cardiovascular disorders. Microbiota-derived endotoxemia and related inflammation are involved in the etiology of metabolic diseases. However, no cohort has investigated the association of endotoxemia with hyperuricemia, while studies examining the role of inflammatory markers in the pathogenesis of hyperuricemia are limited. Therefore, this study aimed to systematically investigated the associations of an endotoxemia-marker (lipopolysaccharide-binding protein, LBP), multiple inflammatory cytokines and adipokines with incident hyperuricemia in a Chinese cohort. A 6-year prospective cohort study was conducted among 1949 community-living Chinese aged 50-70 years with baseline free of hyperuricemia. Baseline LBP, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor receptor 2 (TNFR2), adiponectin, resistin, and retinol-binding protein 4 (RBP4) in plasma were measured. Incident hyperuricemia was defined as the occurrence of plasma uric acid ≥416 μmol/L (7.0 mg/dl) in men or ≥357 μmol/L (6.0 mg/dl) in women by the end of 6-years of follow-up. Log-poisson model was used to assess the associations of markers with hyperuricemia. Mediation analysis was used to examine the mediated effects of inflammatory cytokines on the association between LBP and incident hyperuricemia. In the results, 473 (24.3%) participants developed hyperuricemia over the 6-year period. After controlling for conventional risk factors including body mass index and uric acid at baseline, elevated concentration of LBP and TNFR2 were significantly associated with a higher risk of hyperuricemia, while adiponectin was inversely associated with incident hyperuricemia. Comparing the highest with the lowest quartiles, relative risks of incident hyperuricemia were 1.27 (95% CI:1.01-1.60; P_{trend}=0.032) for LBP, 1.31 (95% CI:1.04-1.64; P_{trend}=0.009) and 0.65 (95% CI:0.49-0.85; P_{trend}=0.001) for adiponectin, respectively. Moreover, mediation analysis showed that the association of LBP with incident hyperuricemia was not explained by the inflammatory cytokines and adipokines. In conclusion, this prospective cohort study shows that elevated levels of LBP and TNFR2, and lower levels of adiponectin, were independently associated with a greater risk of hyperuricemia in middle-aged and elderly Chinese. Moreover, the LBP-hyperuricemia association may be independent of inflammation. Nevertheless, more studies are merited to validate our findings and elucidate relevant mechanisms.

Association of Fish Intake and Omega-3 Fatty Acids with Kidney Function Decline in post-Myocardial Infarction Patients

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Background: Kidney function declines with age, and this decline is accelerated after myocardial infarction (MI). Omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish, may have beneficial effects in the cardiovascular system. Little is known about the role of EPA+DHA in the prevention of kidney function decline in post-MI patients.
Aim: To examine habitual fish intake, EPA+DHA intake and plasma EPA+DHA in relation to kidney function decline in post-MI patients.
Methods: The analysis included 2,055 Dutch post-MI patients (60-80 years, 80% men) from the Alpha Omega Cohort. A validated 203-item food frequency questionnaire was used to collect data on dietary intake at baseline. Non-fasting plasma EPA+DHA concentrations were measured in cholesteryl esters. Glomerular filtration rate, a measure of kidney function, was estimated using the Chronic Kidney Disease Epidemiology equation based on both serum cystatin C and serum creatinine (eGFR). Multiple linear regression was used to study the association of baseline fish and EPA+DHA intake, and plasma EPA+DHA, with annual eGFR change over a period of 41 months, adjusting for confounders, such as age, sex, BMI, diabetes, smoking, alcohol use, physical activity and dietary factors.
Results: Of all patients, median [IQR] fish intake was 13.2 [4.5-17.3] g/day, median [IQR] EPA+DHA intake was 102.7 [41.5-180.0] mg/day and mean ± SD plasma EPA+DHA was 2.0 ± 0.9% of total fatty acids. Spearman correlations of fish and EPA+DHA intake with plasma EPA+DHA were 0.36 ($p<0.001$) and 0.43 ($p<0.001$), respectively. Baseline eGFR was 78.7 ± 18.6 ml/min/1.73m^2. During 41 months of follow-up, eGFR declined by 4.75 ± 13.02 ml/min/1.73m^2, corresponding to an annual decline of 1.39 ± 3.81 ml/min/1.73m^2. Annual change in eGFR was not significantly associated with baseline intake of fish (fully adjusted beta (95% CI): -0.04 (-0.48,0.41) in fish eaters vs. non-fish eaters), intake of EPA+DHA (beta (95% CI): -0.07 (-0.52; 0.37) for >150 vs. ≤50 mg/day) or plasma EPA+DHA (beta (95% CI): -0.14 (-0.55; 0.28) for >2.1% vs. ≤1.5% of total fatty acids).
Conclusion: Habitual fish and EPA+DHA intake, and plasma EPA+DHA, were not related to kidney function decline in post-MI patients. This may be due to a very low fish and EPA+DHA intake in the Dutch population.

Plasma and Dietary Linoleic acid and Risk of type 2 Diabetes after myocardial Infarction: a 3-Year prospective Analysis in the Alpha Omega Cohort

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Background: Plasma linoleic acid (18:2n-6, LA) has been associated with a lower risk of type 2 diabetes mellitus (T2D) in population-based cohort studies, while no consistent associations have been found with dietary LA. The role of plasma and dietary LA in the risk of T2D after myocardial infarction (MI) is unclear.
Objective: To study plasma and dietary LA in relation to incident T2D in post-MI patients.
Methods: We included 3,257 patients (80% males) from the Alpha Omega Cohort aged 60-80 y who had an MI <10 y before study enrollment and were free of T2D. At baseline (2002-2006), plasma LA was measured in cholesteryl esters and dietary LA was estimated with a 203-item food-frequency questionnaire. Incident T2D was ascertained through self-reported physician diagnosis and medication use. Hazard ratios (HR) and 95% confidence interval (CI) for incident T2D by plasma and dietary LA were calculated by using Cox regression models, adjusting for demographic, lifestyle and dietary factors. Dietary LA was analyzed in a theoretical substitution model by isocalorically replacing the sum of saturated (SFA) and trans fatty acids (TFA).
Results: Plasma and dietary LA were weakly correlated (Spearman r= 0.13, p<0.001). During a median follow-up of 41 months, 171 patients developed T2D. Plasma LA was inversely associated with T2D risk in quintiles ($HR_{Q5vsQ1:}$ 0.44; 95% CI: 0.26, 0.75) and continuously ($HR_{per\ 5\%:}$ 0.73, 95% CI: 0.62, 0.86). Substitution of dietary LA for SFA+TFA showed no significant association with T2D risk ($HR_{Q5vsQ1:}$ 0.78; 95% CI: 0.36, 1.72; $HR_{per\ 5\ en\%:}$ 1.18; 95% CI: 0.59, 2.35).
Conclusion: In our cohort of post-MI patients, plasma LA was inversely related to T2D risk whereas dietary LA was not related. Further research is needed to assess whether plasma LA indicates metabolic state rather than dietary LA in this type of patients.

Session 5

Public health nutrition strategies: toward personalized nutrition?

Theatre

The Contribution of Diet to Socioeconomic Inequalities in Health

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A key issue in public health policies is to consider social disparities behind health inequalities. Nutrition being a key determinant of health also presenting a clear social patterning, social disparities have an impact on health in part via unhealthy dietary habits. Diet is known to substantially differ across socio-economic groups. In high income countries, adults with lower socio-economic status (SES) tend to eat less healthy (less fresh fruit, vegetables, whole grains and low-fat dairy products and more sugar-sweetened beverages, salt and sugary energy-dense foods) than adults with higher SES. A similar observation can be made for children and adolescents with respect to parental SES, thereby illustrating the lifecourse component to such inequalities. Social inequalities in diet have also been reported during pregnancy. Given the influence of maternal nutritional status on offspring's health, *in utero* exposure to suboptimal maternal diet may influence the risk of adult-onset chronic diseases.
In particular, socioeconomically disadvantaged people are disproportionally more likely to develop obesity and other obesity-related diseases. Using data from the first national nutrition survey (menuCH, n=1860 adults aged 18 to 75 years), it was shown that, in Switzerland, people with primary or secondary education were two to three times more likely to be obese than people with tertiary education, used as a proxy for SES. A similar observation was made for low versus high income. Counterfactual mediation modelling allowed estimating that 20% to 30% of the association between educational level and obesity (or other metrics of overweight) can be explained by diet quality, when assessed using the Alternate Healthy Eating Index. These findings suggest that a poorer diet quality among individuals with disadvantaged socioeconomic background substantially contributes to socioeconomic inequalities in obesity within the Swiss context.

Personalized Dietary Management of Overweight and Obesity

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During the past several decades, numerous trials have compared various diets for the management of overweight and obesity, assuming that a single dietary strategy would be appropriate for all individuals. These studies have failed to provide strong evidence for the efficacy of any particular diet, and it is likely that different people will have different levels of success on different diets. We have made two such findings: 1) Four years ago we discovered that higher pre-treatment fasting glucose predicted progressively greater weight loss on a diet rich in fibre and whole grain compared to a western diet. This finding prompted our re-analysis of several dietary RCTs to cross-validate this finding. By now, we have re-analysed ten studies and conducted a review. Based on these data, at least three groups of individuals respond differently to different diets. Subjects with normal fasting glucose tend to respond better to low-fat/high-protein diets. Individuals with impaired fasting glucose respond better to diets high in fibre and low in glycaemic index whereas individuals with high fasting glucose (mostly individuals with type-2-diabetes) should also reduce their carbohydrate intake and increase their fat and protein intake. Research indicates that glucose needs to be taken up by the brain to induce satiety, stop eating, and thereby avoid overconsumption of calories. This supports the hypothesis that meals containing carbohydrate may be satiating in insulin-sensitive subjects, but less so in more insulin-resistant individuals and even less in individuals with type-2-diabetes. In the case of insulin-resistant individuals, satiety signals may depend more on other satiety hormones that are released mainly in response to fats and protein, as well as in response to dietary fibre fermentation in the colon. 2) Two years ago we discovered that greater pre-treatment microbial *Prevotella/Bacteroides*-ratio (proxy for enterotype) predicted progressively greater weight loss on a diet rich in fibre and whole grain compared to a western diet. By now, we have cross-validated this finding in another four independent re-analyses of RCTs and conducted a review - one of which successfully link the importance of both pre-treatment glucose and *Prevotella/Bacteroides*-ratio for body weight regulation. *Prevotella* species have been found to produce more short-chain-fatty-acids, especially propionate, compared to *Bacteriodes* species when feeding varies arabinoxylans of which has been suggested to stimulate satiety. Therefore, we will now carry out a 12-week RCT to investigate the hypothesis that subjects with greater pre-treatment *Prevotella/Bacteroides* ratio have a progressively greater weight loss on arabinoxylans.

The Effect of Genetic Variation in *TMPRSS6* (SNP rs855791) on Iron Metabolism and oral Iron Absorption: a stable Iron Isotope Study in Taiwanese Women

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Background: Iron deficiency is considered the most prevalent nutritional deficiency worldwide and one of the leading contributors to preventable disability globally. Several studies have associated the prevalent SNP (allele frequency between 0.4-0.5) *TMPRSS6* SNP rs855791 (2321 C>T with iron status and hepcidin.
Objective: To compare dietary iron absorption using stable isotopes, iron indices and serum hepcidin in subjects homozygotes in the *TMPRSS6* SNP rs855791.
Methods: Healthy nonanemic and iron sufficient females (Haemoglobin (Hb) > 12 g/dL; serum ferritin (SF): 30-120 µg/L) were recruited. Two rice testmeals were administered to fasted subjects on alternate days (day 1 and 3). The meals contained 4 mg of labeled ^{57}Fe, or ^{58}Fe as $FeSO_4$. We measured fractional iron absorption (FIA) as erythrocyte incorporation of Fe stable isotopes on study day 17. Predictors of FIA were assessed by linear mixed model, and stepwise backward regression.
Results: 45 women carrying the TT variant and 35 women carrying the CC variant were enrolled in the study, one participant with the TT variant left the study after day three. There were no significant between-group differences in age, weight, height, inflammation (CRP and AGP) Hb, SF, and soluble transferrin receptor (sTfR). The TT variants had significantly lower transferrin saturation (TS) (TT = 27.7% (25.5, 30.2); CC = 36.5% (33.3, 39.9); $P < 0.001$). Fasting plasma hepcidin (pHep) concentrations were low and did not differ between the variants (TT = 2.06 (1.79, 2.37) nM; CC = 2.10 (1.80, 2.46) nM; P = 0.862). However the ratio of pHep to TS, was lower in CC compared to TT (P = 0.042). The fractional iron absorption of the two test meals was: 7.96% (6.87, 9.22) in the TT variant, and 6.50% (5.54, 7.62) in the CC variant (P = 0.160). In the overall model ($R^2 = 0.484$), when controlled for Hb, TS, sTfR, and menstruation losses, SF ($P < 0.001$), pHep ($P < 0.001$), and genetic variant (P = 0.046) were significant predictors of FIA. When fitting models by genotype, CC had better goodness of fit, ($R^2 = 0.700$), and SF is the only significant predictor ($P < 0.001$). In TT variants, in contrast, a lower goodness of fit was found ($R^2 = 0.422$), and significant predictors were Hb (P = 0.023), TS (P = 0.017), sTfR (P = 0.003), and pHep ($P < 0.001$), but not SF.
Conclusion: Systemic iron homeostasis differs in TT variants, with higher pHep/TS ratio. Presence of TT or CC SNP rs855791 variant significantly affects FIA, and may contribute to the etiology of iron deficiency.

Personalized Responses to a Grape Seed and Bilberry Extract Supplementation in a Human Intervention Study

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Diabetes is linked to elevated blood glucose levels that increase the likelihood of cardiovascular diseases such as strokes, heart attacks and embolism. Furthermore, diabetes is associated with cholesterol abnormalities including raised levels of low-density lipoprotein (LDL) and triglycerides, and decreased levels of high-density lipoprotein (HDL). Evidence from prospective cohort studies and randomized controlled trials has shown the importance of diet in T2DM prevention and management.
We identified, in a systematic review, that bilberry and grape seed extracts demonstrated beneficial effects on blood glucose and cholesterol metabolism in previous human studies (unpublished results). These effects have been attributed to the presence of proanthocyanidins and their metabolites that are formed by the gut microbiota in the large intestine. Inter-individual differences in metabolic enzyme activities, and in gut microbial communities, are believed to underpin differences in the metabolism of proanthocyanidin polymers, and therefore in the responsiveness of individuals to bilberry and grape seed extracts.
In vitro digests were incubated with faecal samples from six healthy donors, to understand the extent to which microbiota variation might influence the bioavailability of active compounds. We observed that the metabolite profiles obtained after incubation were different between donors, indicating that the gut microbiota play a role in individual responses.
We have designed a double-blinded, randomized, crossover designed human intervention study to assess whether a blend of grape seed and bilberry extracts beneficially affects glucose and lipid metabolism in human volunteers at risk of developing Type 2 Diabetes, and whether factors such as bioavailability of proantocyanidins, age, sex, BMI, ethnicity, genetic markers and gut microbiota composition influence individual responsiveness.

Personalized Nutrition & Citizen Science: A Healthy Diet through Algorithms

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We will present a large-scale citizen science research project currently running in Switzerland, called Food & You. The first participants enrolled in January 2019. The preliminary results will be presented at the seminar.
The project is based on a the study which demonstrated high interpersonal variability in postprandial (postmeal) glycemic responses (PPGR) and which developed an algorithm that predicts PPGR and gives personalized diet recommendations. The three major foci of our project are that we are building a “Digital cohort” (a), we developed an app to track dietary intake with the help of machine learning algorithms (b) and that it is designed as a citizenscience project (c).
(a) “Digital cohort” means that the participants of the study are entirely coordinated digitally through the website (no face-to-face interviews or medical appointments are organized). The study material is sent by post and the data are collected via the website and the smartphone app. The aim is to test whether the project can be scaled to tens or hundreds of thousands of people, with low burden on the user and much lower budget requirement than traditional studies in nutrition
(b) A smartphone app, named MyFoodRepo, has been developed to track dietary intakes of cohort participants. Participants simply take photos of their food and drink and the photos are then analyzed by a machine learning algorithm confirmed by human annotation.
(c) There is emphasis on scientific outreach through citizen participation (cohort volunteers) which raises awareness on nutrition and science
The participants of the project have to track their dietary intakes for 14 days as well as their physical activity, their sleep and their glucose level. They also self-collect a stool sample (to identify the microbiome composition), and answer anthropometric, demographic, and health status online questionnaires. With these data, we will build a new algorithm that will predict PPGR with input that is readily available through such a “digital cohort.” The results of this project may have substantial consequences in dietary guidelines, personalized diet and on health conditions related to dietary intake.

@OBEDIS Core Variables Project: A European Expert Proposition on a minimal Core Set of Variables to include in exploratory Clinical Trials of Obesity Interventions

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Obesity is a problem that represents a significant health and economic burden in Europe and throughout the world. The prevalence of obesity in many European countries has tripled in the last several decades (WHO, 2018), making it one the leading public health challenges. A critical part of addressing this global epidemic is to improve the evidence base for more effective, tailored treatments for obesity. Consistently, however, the randomized, controlled trials (RCTs) of obesity interventions find remarkable heterogeneity of responses among adult patients. Most RCTs for obesity interventions include a mixture of patients that, despite meeting the inclusion criteria for the study, vary remarkably when it comes to the medical history of their disease, their associated comorbidities, and many other factors (including lifestyle and environmental factors) that may drive the heterogeneous responses to the same intervention. This emphasizes the need to stratify patients according to precise phenotyping criteria that might predict an individual's response to an intervention: a paradigm shift in individually tailored obesity treatment, going from 'one-size-fits-all' to precision medicine. Even for the largest and most comprehensive published clinical studies, however, stratification leads to subgroup analyses with reduced statistical power. Thus, it is necessary to merge the data from multiple intervention studies—but data pooling is only possible with trials that include a common set of variables measured in similar ways, including samples that are collected using consistent methods.

A group of European obesity researchers convened in 2018 to create a plan for helping shape future studies by identifying the minimal set of variables that should be included in trials of different kinds of obesity interventions, whatever the type and the endpoints of the intervention. The experts intend for this minimal core set to be adopted in future studies while acknowledging that in addition, RCTs or other trials will collect data on additional variables, depending on the specific area of focus. This initiative (@OBEDIS (OBEsity Dietary Intervention Sharing) funded by the JPI HDHL, was created to give the research community a blueprint for designing future RCTs in order to allow the sharing and merging of datasets, and to enable meaningful subgroup analyses. To achieve this, the @OBEDIS experts surveyed the scientific literature, shared their expert opinions on a recommended minimal core set of variables to include in all future trials of adult obesity interventions, and sought to reach consensus on both these variables and the related assessment methods.

Determining Responders and Non-responders to Fish Consumption

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The FISH DISH study examined the effect of eating two portions per week of salmon with either a high (HPUFA) or moderate (SPUFA) content of omega-3 fatty acids, compared with eating no salmon (CONTROL), in healthy volunteers (n = 17/group). We measured 168 outcomes assessing heart health, micronutrient status, inflammation, oxidative stress and gut health after 9 and 18 weeks of intervention. We found that consumption of both salmon types significantly increased participants' Omega-3 Index (O3I) ($p < 0.05$). Consumption of SPUFA salmon also significantly decreased plasma triglycerides ($p < 0.05$). However, we observed considerable variation in responsiveness between individuals in both salmon groups.

We designed and executed an analysis pipeline to consider individual responsiveness to dietary intervention using R software. This analysis investigated whether (1) baseline markers and measures of dietary intake could predict O3I and triglyceride response to intervention using K-means clustering; and (2) we could define "high" and "low" responders to assess whether both groups could be differentiated based on baseline data. Clusters were compared using one-way ANOVA. Responders and non-responders were compared using t-tests. Relationships between variables were analysed using simple and multiple linear regression.

K-means clustering on baseline data did not predict the magnitude of response in the O3I and plasma triglycerides, despite one cluster having a much higher O3I at baseline. However, we found that lower levels of plasma p-Selectin at baseline were linked to a higher decrease in plasma triglycerides over the course of the study in both salmon groups ($p < 0.05$). This suggests that baseline inflammation may affect the individual triglyceride response upon consumption of oily fish. When comparing individual responses in O3I that were either above ("responders") or below the median ("non-responders"), we found that only in the group consuming salmon containing moderate levels of omega-3 fatty acids, those whose O3I increased above the median had a significantly lower energy intake at both the start and end of the study ($p=0.01$). When comparing the top 6 responders with the bottom 6 non-responders in terms of O3I, the 'high responders' were found to have a higher protein intake as % of daily energy intake ($p = 0.02$). This suggests there may be a link between energy/protein intake and response in O3I.

This precision nutrition-style analysis framework has been shown to reveal valuable insights into the main drivers of responsiveness, and may help to evaluate which diet works for whom in future studies.

Session 5

Public health nutrition strategies: toward personalized nutrition?

Poster

Personalized Nutrition and eHealth as New Approaches for the Therapy of Adults with Obesity: Design and Methods of the Lifestyle Intervention Study (LION-Study)

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Background: Due to the increasing prevalence of obesity, methods for a more effective treatment especially in a long term perspective are needed. However, despite standardized intervention strategies, weight loss and weight maintenance show heterogeneous results between people. For this reason, it is difficult to predict the individual success of weight maintenance after weight loss. On this account, it is of great interest to identify factors which may contribute to inter-individual differences and may predict the success of long term weight management.
Objective: The aim of the lifestyle intervention (LION) study is to evaluate the effect of two diets (low carb/low fat) and two digital tools (newsletter/app) on weight maintenance 12 months after weight loss (primary outcome). Moreover, several factors (e.g. genetic, epigenetic, physiological, psychological and lifestyle) that may predict the success of weight loss and weight maintenance will be identified as a secondary outcome.
Methods: Men and women with a body mass index (BMI) between 30.0 and 39.9 kg/m², aged 18 to 65 years, and without severe diseases will be considered eligible. The study starts with a deep phenotyping of the participants (e.g. anthropometry, resting metabolic rate, meal challenges, blood parameters). In the next step, participants will follow a formula-based, low calorie diet for 8 weeks in order to lose weight. Subsequently, 252 participants will be randomized into one of the four intervention groups (low carb/app, low carb/newsletter, low fat/app, low fat/newsletter) for 12-month weight maintenance. The study will be concluded after another 12 months of follow-up. Seven face-to-face visits will take place during the course of the study for data collection.
Future work: This study is funded by the Federal Ministry of Education and Research (BMBF) within the framework of the Junior Research Group „Personalized Nutrition & eHealth (PeNut)“ (FKZ: 01EA1709) of the enable Nutrition Cluster and is expected to start in the middle of 2019. Results should provide indications for personalized nutritional recommendations for weight management.

Providing Insight into what defines Weight Loss Success: A secondary Analysis of Gene Expression Changes in two Weight Loss Interventions

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Obesity rates are rising which brings considerable burden at both the individual and population level. Individuals with obesity are at an increased risk of developing non-communicable diseases. Sustained weight loss can reduce co-morbidities. There are various different ways in which weight loss can be achieved, the question remains whether these methods induce the same physiological changes in all that are successful or whether response is more individual. Peripheral blood mononuclear cells (PBMCs) have been suggested as a tissue type that can reflect whole body changes in gene expression, and as such may help to unravel any systemic changes resulting from weight loss and whether there are differences between high responders and low responders to an intervention. A systematic literature search was undertaken to identify articles that explored the impact of a weight loss intervention on changes in gene expression levels in PBMCs. Repositories were searched and authors contacted to obtain the raw gene expression data. Two papers, one in adolescent males (n=12) the other in adult females (n=17), were identified as meeting the inclusion criteria and provided raw gene expression data with individual weight changes. The raw gene expression data were normalised using robust multiarray averaging through the online tool ArrayAnalysis. Participants in each study were grouped into high and low responders to the weight-loss interventions; high responders lost ≥ 5% body weight over the intervention period. Gene expression levels of high responder (male n=6; female n=7) and low responders (male n=6; female n=10) prior to the interventions were compared to determine differentially expressed genes (+/- 1.2 fold, $p < 0.05$) using the ArrayAnalysis statistical module. PathVisio software was utilised to visualise the differences in gene expression levels between high and low responders on relevant affected pathways. Sixteen pathways were significantly differentiated (Z-score > 1.96) between high and low responders in adolescent males, and 21 significantly differentiated (Z-score > 1.96) pathways in the adult females, with no clearly identifiable common pathways. The genes that were associated with a high versus low weight loss response were different between males and females. The lack of commonality between males and females and with weight loss approach taken in the intervention itself, suggests that there is further complexity, yet to be elucidated. Before we are able to predict weight loss success using transcriptomics, there is much we need to understand about gene expression changes and the affected pathways.

A Diet supplemented with omega 3 Fatty acid decrease IL-6 Expression in Subjects with Obesity

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Background: Obesity is an abnormal accumulation of fat mass that can be harmful to health, interaction of genetics and environmental factors, including diet composition, are related to the development of this pathology. This condition has a high prevalence in Mexico and in the World, and it is related to development of metabolic disorders and the proinflammatory cytokines synthesis. The levels of these cytokines, particularly IL-6, are correlated to low-grade inflammation associated to obesity and its comorbidities; thus, there is evidence that the downregulation of *IL-6* could inhibit inflammatory pathways. Therefore, it has been proposed that the anti-inflammatory properties of omega 3 fatty acid, an essential nutrient, could decrease the low-grade inflammation through its action as a ligand of some transcriptional factors, altering the regulation of gene expression associated to inflammation as IL-6 gene.
Objective: To analyze the effect of omega 3 supplementation on *IL-6* expression in subjects with obesity.
Methods: In a randomized controlled clinical trial a total of 41 subjects with obesity were included. They received an energy-restricted diet supplemented with omega 3 (1.2g) or placebo during 16 weeks. The analyses of diet records were performed by Nutritionist Pro software. Body composition was analyzed by electrical bioimpedance (In Body 3.0). Biochemical measurements were realized by dry chemistry (Vitros 350). The *IL-6* expression was analyzed by real time PCR with Taqman probes using $2^{-\Delta\Delta cq}$ method (LightCycler 96, Roche). Statistical analysis was performed in the SPSS Software (version 20). T-student test and chi-square test were used for quantitative and qualitative variables, respectively. A p-value <0.05 was considered statistically significant.
Results: After the intervention, it was shown a significant reduction in total energy (-695kcal), diet cholesterol (-127mg), trans fatty acid (-0.4g), total sugar (-28g) and sodium (-615mg), and an increase of polyunsaturated fatty acids (6.3g), particularly EPA (80mg) and DHA (150mg). In relation to anthropometric data, the mainly results were a significant decrease in waist circumference (-6.1 and -4.5 cm) in placebo and omega 3 group respectively. Respect to biochemical data, we found a lower LDL-c levels (-8.4 mg/dL *vs* 11.0 mg/dL; $p<0.05$) in omega 3 group than placebo group, respectively. According to expression analysis, the omega 3 group decreased *IL-6* expression in 49% regarding to placebo group ($p<0.05$).
Conclusions: Our results demonstrated the anti-inflammatory effects of diets enriched with omega 3. These findings highlight the importance of design personalized-nutrition strategies to prevention and management of obesity and their comorbidities.

Genetic Risk Score predicts Risk for Overweight and Obesity in Finnish Preadolescents

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Background and objectives: Common genetic variants predispose to obesity with varying contribution by age. We incorporated known genetic variants into genetic risk scores (GRSs) and investigated their associations with overweight/obesity and central obesity in preadolescents. Besides, we compared GRSs with lifestyle factors, and tested if they predict the change in body size and shape in a 4-year follow-up.
Materials and methods: We utilized 1142 subjects from the Finnish Health in Teens (Fin-HIT) cohort. Overweight and obesity were defined with age- and gender-specific BMI z-score (BMIz) according to International Obesity Task Force guidelines, while central obesity by the waist-to-height ratio (WHtR). Background data on parental language, eating habits, leisure-time physical activity (LTPA) and sleep duration were included. Genotyping was performed with the Metabochip platform. Weighted, standardized GRSs were derived including 32 and 30 relevant SNPs for BMI and WHR, respectively.
Results: Of the 11-year old children, 25.5% were at least overweight (BMIz >+1), 13.8% presented with central obesity (WHtR $\geq$ 0.5), 45.6% with had LTPA less than 7 hrs/week and 90.8% had Finnish speaking background. BMI-GRS associated with higher risk [with OR (95% CI)] for overweight 1.39 (1.20;1.60) and obesity 1.41 (1.08;1.83), but not with central obesity. BMI-GRS was weakly associated with the change in BMIz and WHtR in the follow-up. WHR-GRS was not related to any obesity measures at baseline nor in the follow-up. The effect of BMI-GRS is similar to that of low LTPA on overweight. An interaction between parental language and BMI-GRS was noted (p=0.019): BMI-GRS associated more strongly with overweight in Swedish than in Finnish speakers.
Conclusions: In preadolescents, when combined the known genetic predisposing factors induce a risk for overweight comparable to low LTPA. The GRSs were poor in predicting short-term changes in BMI or WHtR from preadolescence to adolescence, but appeared valuable in detecting obesogenic environments in this age group. Genetic predisposing factors are informative in epidemiological studies determining risk or protective factors for overweight and obesity.

Quisper: A digital Solution to enhance Consumer Trust in Personalised Nutrition

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Development of apps, wearables, and web-tools, and implementation of artificial intelligence (AI), which enable personalised nutrition advice for consumers, are growing in number and sophistication. Consumers are increasingly interested in tailor-made recommendations that can help improve health and lifestyle choices. Previous studies have shown the use of technology to deliver personalised nutrition advice can induce greater behavioural changes in consumers for longer. Nevertheless, the lack of solid scientific evidence for personalised services can create doubt about their value and accuracy, undermining consumer trust.
Quisper® (www.quisper.eu), funded EIT-Food (ID 19075), is developing further outputs from past EU-projects (Food4Me, QuaLiFY) with the aim of delivering a digital platform (QSP) that facilitates, for the first time, access to scientifically validated personalised nutrition data, knowledge rules, tools and services (resources). Quisper® is pursuing a business-to-business strategy, where SMEs, companies or research organisations can integrate their resources with QSP to add new information and features or improve existing functionalities.
In addition, small business-to-consumer components will be added to the platform, such as eNutri app, which was developed by the University of Reading (UK) and, currently, is being enhanced for use with mobile technologies. The app delivers personalised food-based dietary advice automatically. During the second half of 2019, eNutri app will be validated in the UK and Germany, and the impact of personalised food recommendations on dietary habits and consumer behaviour examined. This work will also demonstrate whether and how methodologies, such as Diet Quality Scores, can be tailored and applied in different European Member States.
Part of the unique approach of Quisper® is the involvement of an independent scientific advisory board (QuiSAB), which will evaluate the resources linked with QSP. This will ensure the scientific validity of information underpinning services based on QSP. By facilitating access to scientifically validated resources, Quisper® can assist SMEs to improving their offerings and provide consumers with high-quality personalised nutrition services, increasing trust and, eventually, improved health due to long-term sustainable behavioural changes.

Association between Metabolites and Body Composition- the Importance of Consideration of Sex

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Metabolomics and lipidomics have emerged as important tools in nutrition research. Understanding the impact of physiological factors on the profiles is becoming increasingly important to aid interpretation of the data. We examined the associations between metabolomic biomarkers and body composition measures in men and women.
Material and Methods: A total of 214 (100 men and 114 women) healthy adults were recruited. The mean age was 32±10 years for males and 31±11 years for females. Anthropometric measures included body weight, height, waist and hip circumference. Body composition was evaluated by total fat mass, and gynoid and android fat mass using Dual Energy X-Ray Absorptiometry (DEXA). Metabolomics and lipidomics was performed using Biocrates p180 kit. Relationships between parameters were assessed using Spearman correlation analysis.
Results: Valine, Leucine and Tyrosine presented significant associations with BMI and android fat mass in men, while Proline, Valine and Leucine were related to BMI, and android and gynoid fat mass in women. There was no association between gynoid fat mass and amino acids in men. Metabolites specifically related to BMI, and android and gynoid fat mass included diacyl-phosphatidylcholines C38:3 and acyl-alkyl-phosphatidylcholine C34:3 in both sexes. A range of other metabolites were related to one of the parameters only and the relationships differed between the sexes.
Conclusion: The study demonstrated that metabolite- body composition relationships were different in men and women. The site of fat mass accumulation is also important. Future work should consider body composition influences on the metabolic profiles.

Self Health Quantification Blockchain (SHQB)

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Introduction – The blockchain is an incorruptible digital ledger that can be used to record anything. It permits digital information to be distributed without a centralized server. Secure data-blocks are bound by cryptographic principles (chain). Cryptocurrency is the first blockchain use; however, its potential extends far beyond. Block chain technology may offer a reliable, consistent solution to catalogue and share research and personal health data.

Personal health record – The self-health quantification blockchain (SHQB) provides a consistent, private, reliable location for your data you can access easily using a variety of applications. Information will never be too old or impossible to access and stays with you for life. You can approve medical provider access to your information, easily downloadable and augmented by any practitioner.

The SHQB empowers the individual to collect data on symptoms, responses to medications, nutritional therapies, and other lifestyle modifications. Graphs provide easy to read information on trends and changes over time; including a timeline chart that shows how events in your life correspond to changes in your health.

With this information, you may choose personal changes to benefit your health resilience. Health care practitioners are empowered to help you through access to pre-analyzed historical health data.

Research data provision – Consistency in data collection and categorization allows participation in retrospective and prospective research programs. Crypto-tokenization is used for incentivization.

Technology – The SHQB is decentralized, using a peer-to-peer content-addressable-storage to distribute data, and is resilient to network outage. The data is securely chained with a sponge hash-function (SHAKE224) and one-time-signatures.

Consensus between each participating node is obtained with an idempotent merge of recorded data; avoiding costly proof-of-work mechanisms and a large operational network. Interoperability and synchronization with other technologies is straight forward.

De-identification – A one-time-identity tokenization is used to protect user privacy. Real identities are concealed and data elements for individualized data analysis are preserved with asymmetric cryptography and shared secrets.

Security – Data is encrypted. The user grants access to data for certified personal and registered organizations. Private keys are kept local to mitigate data breach risk.

Conclusion – The SHQB integrates fundamental blockchain concepts with decentralization, asymmetric cryptography and de-identification to create an easy to understand technology. The SHQB holds the potential to improve access to and quality of research data, as well as, medical, nutrition and lifestyle care. It empowers users, researchers, and practitioners to collaborate on individualized care, with a secure, permanent data record.

Delivery of Personalised Nutrition advice using a Metabotype Approach

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Introduction: Delivery of personalised nutrition at a group level is referred as targeted nutrition. Metabotypes are groups of individuals defined based on their similarities in metabolic profiles and have been successfully associated with diet-related diseases and differential responses to interventions. Thus, metabotypes provide an opportunity to deliver personalised dietary advice. The objective of the present study is further develop a targeted approach based on metabotypes and compare it to an individualised approach.
Methods: A total of 160 individuals were classified into metabotypes previously defined by four markers (triacylglycerols, total cholesterol (TC), HDL-c, and glucose) in a cross-sectional study with Irish adults and were assigned dietary advice using a targeted nutrition approach. A personalised approach was achieved through the use of the Food4Me decision trees for dietary advice. Agreement between methods was compared and the targeted approach was optimised to incorporate: 1) the most prevalent advice exclusively given by the Food4Me decision trees, and 2) recent guidelines for the dietary management of chronic diseases. The optimised metabotype approach was subsequently tested by comparison with individualised advice manually compiled by a dietitian.
Results: Individuals in metabotype-1 had high average TC (4.9±0.7 mmol/L), while individuals in metabotype-2 had the four biomarkers in normal concentrations. However, metabotype-3 was the unhealthiest cluster with the highest average TC (5.4±0.9 mmol/L), triacylglycerols (2.1±0.9 mmol/L), body mass index (29.5±6.5 kg/m2), and diastolic blood pressure (80.1±12.3 mmHg). As part of the optimised metabotype approach, all individuals were assigned nutrition advice messages which encompassed metabotype characteristics and individuals information. Examples include messages to avoid processed food, moderate alcohol intake, choose lean meats and low-fat dairy, and increase the intake of oily fish and fruits and vegetables, including pulses and green vegetables. In metabotype-3, all individuals received messages to reduce foods high in sugar, 81.8% received messages to reduce high-fat foods and control portions sizes, 18.2% to choose low-salt products and eat more dairy products, and 84.8% to engage in physical activity for >60 minutes/day. The agreement for these messages ranged from 78.8 to 100%. Overall, the optimised metabotype approach presented a good total agreement of 80.3% with the individualised manual approach, especially in metabotype-1 (93.8%) and metabotype-3 (94.3%).
Conclusion: The framework comprising metabotypes and decision trees is a promising model to deliver personalised nutrition. Future work is warranted to demonstrate that this targeted approach is effective in changing behaviours and health outcomes.

Frequency and Diversity of Potential Genetic Markers of Nutrition-Related Diseases Generated from the Next Generation Sequencing (NGS) Panel

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The ubiquity of lifestyle diseases is a challenge in the contemporary health of Filipinos that requires solid and practical answers. To lessen the impact of non-communicable diseases (NCDs) on individuals and society, a comprehensive approach is needed, one that requires careful consideration of all the factors and risks associated with NCDs, as well as promote the interventions to prevent and control them. The study identified and profiled SNPs associated with non-communicable diseases (NCDs) among Filipinos living in the National Capital Region (NCR). The identification of SNPs will help in the assessment of likelihood of developing aforementioned diseases. Whole human blood samples from anonymized selected NCR participants were used for genomic DNA extraction. Genomic DNA was isolated using the QIAamp DNA Blood Mini Kit. About 50 ng of anonymized DNA samples were sequenced using the Ion Torrent Proton (Life Technologies). Data were analyzed using the Ampliseq™ Variant Caller plug-in within the Ion Torrent Suite software (Invitrogen Life Technologies) and annotated using Ion Reporter software version 5.4. The targeted sequencing of 502 published genes and SNPs associated with NCDs and other nutrition-related diseases was achieved by designing multiple primer sets that flank targeted regions of the SNPs. The identification of genes and SNPs underlying common non-communicable diseases and other nutrition-related diseases performed in the Filipino population has tremendously helped determined level of susceptibility of the population towards development of debilitating but preventable diseases such as type II diabetes, cardiovascular diseases, osteoporosis and micronutrient deficiency. Genotyping of published SNP variants that interact with dietary composition to modulate biomarkers and health outcomes can provide a framework for the development of novel foods that are genotype dependent, in addition to the development of personalized dietary recommendations, aimed towards a more individualized/personalized strategy of health promotion, prevention and management of nutrition related diseases.

Improved long- term Weight Management & Compliance using nutrigenetically tailored Diet among Obese Asian Indians

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Studies on gene-environment interactions demonstrate differences in the human metabolic individuality depending upon the genetic variations affecting nutrient absorption, biosynthesis, metabolism and transport. In this study, we examined whether a nutrigenetically tailored diet could improve an individual's compliance & long-term weight management. Similar studies were carried out in several populations, however, there are no such studies, to date, among Asian Indians. In this study, we selected individuals, generally healthy, free- living adults, both men and women with BMI 25- 30 kg/m2 and with previous history of failures at weight loss who visited Geneobe Weight Loss Clinic, based in India & were offered a nutrigenetic test. We included 54 individuals in the intervention group who received personalised dietary advice for weight loss based on the nutrigenetic test and another set of 47 individuals attending the same clinic were selected for comparison based on age, BMI at initial clinic visit. This group did not receive a nutrigenetic test. BMI and waist circumference reduction at 100 days were measured and they were followed up at 180 days. Personalised weight loss motivational messages were sent to individuals in the intervention group based on the nutrigenetic test results, whereas the second group received generic messages through whatsapp, a mobile app used to send messages. After 180 days of follow-up individuals in the nutrigenetic group were more likely to have maintained some weight loss (82%) than those in the comparison group (21%) and motivation and willingness to lose weight were higher than the comparison group. Addition of nutrigenetically tailored diets resulted in better compliance, higher motivation and improved weight loss and long-term weight management.

Plasma Metabolite Profile in Anorexia Nervosa Inpatients in Comparison to Athletes, Overweight, Obese, and Normal Weight Controls

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Introduction: Anorexia nervosa (AN) is a severe psychosomatic disease that affects nutritional status seriously. Severe symptoms of starvation as result of long term metabolic adaptation to caloric restriction are in focus for therapeutic treatment. This metabolomics study of plasma samples from AN inpatients, overweight, obese, athletes and normal weight controls aimed to find characteristic metabolic differences between these subgroups.
Methods: We compared metabolic profiles in a cohort of 107 female participants: Anorexia nervosa patients (n=18), athletes (n=20), normal weight (n=27), overweight (n=22) and obese women (n=20). A non-targeted metabolomics approach utilizing UHPLC-QTOF-MS was performed. Additional to the standard laboratory diagnostics, dermal and plasma carotenoids, leptin, oxidative stress parameters, dietary intakes, body composition, and the gut microbiome were determined.
Results: Increased levels of fatty acids (FA16:1, FA20:4, FA22:4; ($p<0.001$). FA18:1, FA20:3; ($p<0.01$). FA18:2, FA20:2, FA22:5, FA22:6; ($p<0.05$)) and acylcarnitines (AC11:1 ($p<0.001$), AC10:1, AC6:0; ($p<0.01$)) in overweight and obese, especially in contrast to athletes and AN were seen. FA18:0 containing phosphatidylcholines (PC18:0_20:4 ($p<0.001$). PC18:0_20:3, PC18:0_22:6; ($p<0.05$)) and sphingolipids (SMd36:2, SMd34:2; ($p<0.01$)) were increased with obesity and decreased in AN. Branched chain amino acids (isoleucine, leucine ($p<0.001$). valine ($p<0.01$)) were increased in athletes, overweight and obese compared to AN. For many of the observed metabolites, there was an increasing or decreasing trend along the range from AN patients to obese participants. Athletes did not follow this trend and had a more mixed metabolic profile.
Conclusion: These results give good overall view of the effect of weight and active lifestyle to metabolic profiles of women. It gives excellent background for more detailed investigations on different subgroups or for a more large-scale replication in multigroup setting. Overall, the results of the present analysis are robust even though the group sizes are relatively low for a non-targeted metabolomics analysis in human, indicating that the selection of the subjects and collection of the samples has been excellent.

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