Lifestyle Genomics

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Abstracts

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Oral Presentations

1
The Need for Precision Nutrition, Genetic Variation and Resolution in Covid-19 Patients

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The health of the individual and the population in general is the result of interaction between genetics and various environmental factors, of which diet/nutrition is the most important. The focus of this presentation is on the association of high n-6 PUFA or low n-3 PUFA due to genetic variation and/or dietary intake, with changes in specialized pro-resolving mediators (SPMs), cytokine storm, inflammation-resolution and Covid-19. Present day humans have two common FADS haplotypes that differ dramatically in their ability to generate long-chain fatty acids. The more efficient, evolutionary derived haplotype increases the efficiency of synthesizing essential long-chain fatty acids from precursors and could have provided an advantage in environments with limited access to dietary long-chain fatty acids ARA, EPA and DHA. African Americans and Latino populations have increased susceptibility to Covid-19 and higher death rates than whites. These populations are characterized by increased numbers of persons (about 80%) that are fast metabolizers, leading to increased production of ARA, as well as poor intake of fruits and vegetables. In vitro and human studies show that the specialized pro-resolving mediators (SPMs) produced from the n-3, EPA and DHA influence the resolution of inflammation, allowing the tissues to return to function and homeostasis. The nutritional availability of dietary n-3 fatty acids from marine oils enriched with SPMs intermediate precursors, along with increasing local biosynthesis of SPMs to functional concentrations may be an approach of value during SARS-CoV2 infections, as well as in prevention, and shortening their recovery from infections. It is evident that populations differ in their genetic variants and their frequencies and their interactions with the food they eat. Nutritional science needs to focus on Precision Nutrition, genetic variants in the population and a food supply composed of Nutrients that have been part of our diet throughout evolution, which is the diet that our genes are programmed to respond to.

2
Knowledge translation in nutritional genomics: Where are we now and where do we go from here?

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Background: Precision nutrition is a scientific approach used to develop nutrition recommendations relevant to both individuals as well as populations. Nutrigenetic testing has become increasingly available to the public as a method for guiding nutrition recommendations based on genetic variation. The scientific validity of such recommendations is, however, debated.

Content: Population-based nutrition recommendations are developed based on the highest level of evidence available. Several approaches exist to evaluate scientific validity, such as the GRADE approach which is often used in the fields of nutrition as well as genetics. However, the evaluation of scientific validity for various gene-diet associations using these existing approaches is limited. Two systematic reviews with evidence grading for nutrigenetic associations have been completed thus far, both identifying associations/interactions with moderate to strong scientific evidence. Moreover, nutritional genomics is a unique field with specific considerations that may not be relevant when evaluating scientific validity in the fields of nutrition or genetics individually. Given this, researchers have developed an evidence evaluation tool that was specifically designed for evaluating the evidence of the effects of genes and environments on cancer. This is an example of a framework that should be applied to determine the scientific validity of gene-diet associations and various health outcomes.

Conclusions: Moving from research to practice recommendations requires consideration of analytic validity, clinical utility and ethical/legal/social considerations in addition to clinical (scientific) validity. Once scientific validity is determined, researchers should aim to develop clinical practice guidelines that incorporate these various factors, especially for nutrigenetic associations with moderate and strong scientific evidence.

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Nutrition and cardiovascular diseases: what is the role of TMA and TMAO?

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Nutrition represents a key factor able to impact health through modulation of gene expression and gut microbiota responses. Gut microbiota can produce various metabolites from food; trimethylamine (TMA) and its oxidized product trimethylamine-N-Oxide (TMAO) have been considered secondary metabolites to be studied for their potential role as triggers of cardiovascular diseases (CVDs). TMA is produced by gut bacteria from dietary choline, betaine and L-carnitine contained in animal food or from the catabolism of vegetarian products such as ergothioneine present in mushrooms and beans. TMA is absorbed and carried by portal circulation into the liver where it is oxidized to TMAO. Exogenous TMAO also derives from fish consumption. TMA and TMAO circulating levels vary according to the host's gut microbiota composition (i.e., abundance of TMA-producing bacteria), genetic variability (i.e. enzymes involved in TMA and TMAO metabolism), and nutrition (i.e., intake of dietary precursors of TMA and TMAO). Considering that it is not clear whether TMA or TMAO is the key risk factor for CVDs, the aim of the present study was to investigate how plasma TMA and TMAO levels change in a cohort (n=547) of CVD patients and control, and whether gender differences and other risk factors for CVD can be correlated to the circulating levels of these proposed biomarkers. Results on TMA and TMAO will be discussed considering gender differences in oxidative blood biomarkers and mitochondrial DNA copy number.

4

Genome-Wide Association Study of Food Preference

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Background: Preference to groups of foods of each individual is one of the key factors to be taken into consideration for the practice of precision nutrition. Many studies have revealed some genetic variations which are associated with dietary habits and food preference.

Methods: In collaboration with a personal genome service company, Genequest Inc., we have been investigating such associations using ~300,000 SNPs data and internet questionnaire obtained from over 10,000 Japanese population.

Results: We identified and reported loci and SNPs associated with preference to sweet taste, frequencies of the intakes of coffee, black tea, and fish in Japanese, which were mostly unique to Asian populations. Since the 12q24 locus was associated with the intakes of them we further performed a phenome-wide analysis (Phe-WAS) and found that the locus correlates with various dietary behaviors and preferences.

Conclusions: Combination of data of genetic testing service and internet questionnaire is highly effective for genome- and phenome-wide association studies of dietary behaviors and preferences.

5

Exercise genomics: role of genetic factors in the response to exercise training

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Background: There is overwhelming evidence that the response to exercise training, or trainability, varies considerably among individuals and that genetic factors play an important role in explaining the adaptation to exercise training for a wide variety of health-related fitness traits.

Aim and methods: The objective of this presentation is to provide a brief overview of the role of genetic factors in cardiorespiratory fitness and cardiometabolic risk factors responses to exercise training. The most important study documenting the extent of interindividual differences in the response to exercise in undoubtedly the HERITAGE Family Study.

Results: This study and results from other twin and family studies suggest that 20-50% of the variation in trainability could be accounted for by genetic factors. Candidate gene studies and genome-wide screening approaches have been used to identify genomic markers of trainability. Despite the large number of genetic variants that have been associated with the response to exercise training, only a few have been replicated in independent studies.

Conclusions: Although the results are promising, more research is needed to unravel the molecular basis of trainability and to be able to use genetic markers to predict performance or to discriminate between high- and low-responders to exercise training.

6

Rationale for Nutrigenetic Guideline Development

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Responses to specific nutrition factors and foods can be substantially different between individuals due to numerous characteristics including gender, body size and composition, age, and health status. An increasing number of both rare and common genetic variants are now reliably known to modify individual

responses in a highly predictable fashion. For example, several hundred rare variants of the PAH gene, sometimes in conjunction with variants in additional genes, reliably predict phenylketonuria (PKU) in response to phenylalanine intake and how to best treat individual patients. At the same time, we now also know about many common genetic variants that can help to predict individually different outcomes, though typically with more complex interactions than the rare monogenic inborn errors of metabolism. Examples include the effects of caffeine and sodium intake on blood pressure, fats and cholesterol on the blood concentrations of atherogenic lipoproteins, abdominal discomfort in response to high lactose and sucrose intake, and individual requirements of choline and other essential nutrients. For a significant minority of identifiable individuals, standard dietary recommendations are ineffective due to their particular genetic disposition, sometimes even detrimental. Great care must be taken not to confuse patients and the general public about the proper application of nutrigenetic guidelines. Some genotype-specific guidelines differ from guidelines for the general public by design without contradicting them. Just like patients with PKU-causing variants need different dietary guidance than unaffected individuals, elevated LDL levels of patients with two APOE4 alleles are typically responding better to genotype-specific dietary guidance than patients without APOE4 alleles. Physicians and other health professionals have to learn to work with such differing standards, depending on what they know and do not know about their patients. They also have to know how nutrition advice for the general public often differs from individual treatment regimes and be able to explain the difference.

7
The physiology of salt sensitivity of blood pressure and the impact of genetic variants

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Background: The pathophysiology of hypertension, which affects over 1 billion individuals worldwide. Critically, the salt sensitivity of blood pressure increases hypertension risk and associated adverse cardiovascular outcomes. The kidney, which governs sodium excretion via several mechanisms including pressure natriuresis and the actions of renal sodium transporters, is central to long term blood pressure regulation and the salt sensitivity of blood pressure. The impact of the salt sensitivity of blood pressure in health and hypertension is a critical public health issue owing to the excess of dietary salt consumed globally. However, given that the majority of genome-wide association studies (GWAS) are not conducted in identified salt-sensitive versus resistant populations, the identification of specific genes or markers of the salt-sensitivity of blood pressure has been challenging.

Methods: This presentation will cover selected recent advances that provide genetic mechanism-based insight into the salt-sensitivity of blood pressure, including our recent studies investigating that GNAI2 SNPs are associated with salt sensitivity of BP in humans.

Results: GNAI2 SNP (rs10510755) positively associates with salt sensitivity of BP in the Genetic Epidemiology of Salt Sensitivity dataset (Continuous Phenotype P=0.049, Case-Control Phenotype P=0.039; N=968), independent of subject sex or age.

Conclusions: Multiple recently identified mechanistically relevant genes, including genotyping at GNAI2, may lead to the identification of new biomarkers to identify individuals at risk for developing the salt sensitivity of blood pressure or in identifying salt sensitivity within the hypertensive population.

8
Gene-gene interaction and salt sensitivity of blood pressure

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The salt sensitivity of blood pressure, whether it occurs in hypertensive or normotensive subjects, is associated with increased cardiovascular risk and overall mortality. Organ to organ communication is important in the maintenance of fluid and electrolyte balance and blood pressure (BP) homeostasis. The gastrointestinal tract and the kidney are major organs involved in this process. When the excess sodium that is ingested is not excreted by the kidney and compensatory mechanisms fail, hypertension develops. The impaired renal sodium handling in essential hypertension and salt sensitivity is caused by aberrant counter-regulatory natriuretic and antinatriuretic pathways. One of the natriuretic pathways is afforded by dopamine. Renal tubule-selective inhibition of dopamine production in mice causes salt-sensitive hypertension. Extrarenal mechanisms are also important because global germline deletion of any of the five dopamine receptor genes, *Drd1*, *Drd2*, *Drd3*, *Drd4*, and *Drd5*, in mice results in hypertension that may be salt-sensitive. *DRD1 rs4532* is associated with hypertension in some ethnic groups but variants of other dopamine receptor genes are not associated with essential hypertension. Therefore, genes with products that interfere with renal dopamine receptor function must be involved. G protein-coupled receptor kinase 4 (GRK4) regulates dopamine D_1 receptor (D_1R) and angiotensin type 1 receptor (AT_1R) function. The *GRK4* locus (4p16.3) is linked to human essential hypertension. In humans, the odds of hypertension increase as the number of *GRK4* single nucleotide polymorphisms (*GRK4γ65L*, *GRK4γ142V*, and *GRK4γ486V*) increases. Germline deletion of *Grk4* in mice decreases blood pressure and prevents the salt sensitivity of blood pressure. *GRK4γ486V* transgenic mice have salt-sensitive hypertension while *GRK4γ142V* transgenic mice have salt resistant hypertension. *GRK4γ65L* transgenic mice are also salt-sensitive. *GRK4γ65L* interacts with the sodium bicarbonate exchanger 2 gene, *SLC4A5*, and its variants are associated with salt sensitivity in humans with hypertension. *GRK4γ65L* alone, or in association with *SLC4A5* intronic variants,

increases the expression of SLC4A5. SLC4A5 is expressed in the luminal membrane of renal proximal tubule cells and its variants increase luminal sodium bicarbonate cotransport. Increased renal expression of wild-type *SLC4A5* exacerbates the increased blood pressure of *GRK4γ65L* transgenic mice fed 4% NaCl diet. These studies suggest that GRK4 is critical in the prevention of hypertension and salt sensitivity and that *GRK4γ65L* and *SLC4A5* variants interact to cause a higher state of salt-sensitive hypertension. This insight into the complexity of sodium regulatory pathways will enable selective personalized therapeutics for this deadly and costly chronic disease.

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Integrating genetic predictors of salt sensitivity into dietetics practice

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Nutritional, pharmacological, and lifestyle interventions can help reduce elevated blood pressure to prevent, treat, and manage cardiovascular disease progression. Focusing on sodium intake and ensuring it is within recommended levels is one nutritional approach in the management of elevated blood pressure. Reducing sodium intake is especially important given that sodium consumption around the world exceeds recommended levels. There is variation in how individuals respond to changes in sodium intake—blood pressure changes are observed in salt sensitive individuals when there are changes in sodium intake while blood pressure changes are not observed in salt resistant individuals when there are changes in sodium intake. The salt sensitivity phenotype can be useful clinically in identifying individuals who would benefit from more restrictive sodium intake (e.g., aiming for sodium intake closer to the adequate intake level rather than the upper limit level) given that salt sensitive individuals who are normotensive or hypertensive are at higher risk of cardiovascular disease and mortality. Salt sensitivity is impacted by numerous factors, including genetics. Many genetic variants have been associated with this phenotype, including genetic variants in the *GRK4* and *SLC4A5* genes. Using a genetic screening tool is a promising approach in identifying individuals who are salt sensitive and has the potential to enable sodium intake recommendations to be tailored further. A salt sensitivity screening tool can be especially important for salt sensitive patients who have resistant or refractory hypertension where uncontrolled hypertension persists despite the use of multiple antihypertensive agents.

10

The genetics of food choices

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The considerable differences in individuals' overall food intake, as well as in the intake of particular foods or specific nutrients, are partly explained by genetic variation. The magnitude of genetic effects typically ranges from about 20% to 40%. Environmental determinants of food choices include food availability and accessibility, as well as the social and cultural environment, but also several economic factors. Individual biological predispositions depend on several mechanisms, which are responsible for the regulation of appetite as well as taste and sensory sensitivity. Taste is considered as one of the most important determinants of food choice. Several genes have been tested for their association with food choices. One group of genes includes those encoding taste receptors, e.g. *TAS2R38*, which accounts for bitter taste sensitivity The so called PAV/AVI polymorphism of *TAS2R38* has been associated with vegetable and coffee intake. The *CD36* gene encodes fatty acid translocase and its rs1761667 polymorphism affects its expression, and thus the fatty acid detection threshold. Associations of this polymorphism with fatty food choices and preference have also been shown. Moreover, the *OPRM1* gene, which encodes a receptor expressed in the brain's reward system, has also been associated with fat intake. *OPRM1* genotype (rs1799971) and hedonic hunger may interact to affect fast-food intake. Unraveling the relations between genetic variation and food choices still needs more research. However, several good examples of such associations have already been found.

11

Nutrigenetics in Non-Alcoholic Fatty Liver Disease

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Background: Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases that affects about 25% of the world population. Nonalcoholic steatohepatitis (NASH) is a form of NAFLD, where hepatic steatosis, hepatocyte injury and inflammation coexist and can progress to advanced fibrosis, liver cirrhosis and hepatocellular carcinoma. Until now, there is no approved and safe therapy for NAFLD/NASH, with lifestyle modifications, such as weight loss and increased physical activity being recommended.

Methods: Mastiha Treatment for Obese with NAFLD Diagnosis (MAST4HEALTH) is an EU-funded project designed to explore the effectiveness of Mastiha as a nonpharmacological intervention in NAFLD. We designed a multicenter, randomized, double-blinded, and placebo-controlled clinical trial where the effect of Mastiha on NAFLD/NASH was investigated through MRI, biochemical, and multi-omic analyses. Also, we explored

gene-diet interactions and more specifically the potential personalized activity of the Mastiha, and how genetic variants might modulate its effect on antioxidant markers and markers of inflammation in NAFLD patients.

Results: The main finding of MAST4HEALTH was the improvement in liver inflammation and fibrosis as depicted in MRI parameters assessed by MRI scanning and the sensitive LiverMultiScan. More specifically, severely obese patients with NAFLD/NASH showed an improvement in cT1 and LIF in Mastiha versus Placebo. Furthermore, Mastiha increased dissimilarity of gut microbiota, as shown by the Bray-Curtis index, downregulated Flavonifractor, a known inflammatory taxon and decreased phospholipids and cholic acid plasma levels compared to Placebo. Regarding gene-by-Mastiha interactions, several novel gene-by-Mastiha interaction associations with levels of cytokines and antioxidant biomarkers have been identified. Some of the identified genetic loci are implicated in the pathological pathways of NAFLD, including the lanosterol synthase gene (LSS), the mitochondrial pyruvate carrier-1 gene (MPC1) and the sphingolipid transporter-1 gene (SPNS1) associated with hemoglobin levels, the transforming growth factor-beta-induced gene (TGFBI) and the micro-RNA 129-1 (MIR129-1) associated with IL-6 and the granzyme B gene (GZMB) associated with IL-10 levels.

12

Role of CHDH-PNPLA3 Gene-Gene Interactions in predicting Insulin Resistance in Children with Obesity

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Background: Insulin resistance plays a major role in the metabolic syndrome and is recognized as the most common risk factor for non-alcoholic fatty liver disease. Identifying predictors for insulin resistance could optimize screening and prevention.

Purpose: To evaluate the contribution of multiple Single Nucleotide Polymorphisms across genes related to non-alcoholic fatty liver disease and choline metabolism, in predicting insulin resistance in children with obesity.

Methods: 153 children with obesity (73 girls), aged 7-18 years, were evaluated within the NutriGen Study (ClinicalTrials.gov,NCT02837367). Insulin resistance was defined by Homeostatic Model Assessment for Insulin-Resistance cut-offs that accommodated pubertal and gender differences. Several anthropometric, metabolic, intake-related variables, and 55 Single Nucleotide Polymorphisms related to non-alcoholic fatty liver disease and choline metabolism were evaluated. Gene-gene interaction effects were assessed using Multiple Data Reduction Software.

Results: Sixty percent (93/153) of participants showed insulin resistance (58.7% of boys, 63% of girls). Children with insulin resistance presented significantly higher values for standardized body mass index, triglycerides, transaminases and plasma choline, when compared to those without insulin resistance. Out of 52 Single Nucleotide Polymorphisms analyzed, the interaction between genotypes *CHDH* (rs12676) and *PNPLA3*(rs738409) predicted insulin resistance. The model presented a 6/10 cross-validation consistency and 0.58 testing accuracy. Plasma choline levels and alanine aminotransferase modulated the gene interaction effect, significantly improving the model.

Conclusion: The interaction between genotypes in *CHDH* and *PNPLA3* genes, modulated by choline and alanine aminotransferase levels, predicted insulin resistance status in children with obesity. If replicated in larger cohorts, these findings could help identify metabolic risk in children with obesity.

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A comparison of a Ketogenic Diet with a LowGI/Nutrigenetic Diet over 6 months for Weight Loss and 18-month Follow-up

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Background: Obesity and its related metabolic disturbances represent a huge health burden on society. Many different weight loss interventions have been trialed with mixed efficacy, as demonstrated by the large number of individuals who regain weight upon completion of such interventions. There is evidence that the provision of genetic information may enhance long-term weight loss, either by increasing dietary adherence or through underlying biological mechanisms.

Methods: The investigators followed 114 overweight and obese subjects from a weight loss clinic in a 2-stage process. 1) A 24-week dietary intervention. The subjects self-selected whether to follow a standardized ketogenic diet ($n = 53$), or a personalised

low-glycemic index (GI) nutrigenetic diet utilising information from 28 single nucleotide polymorphisms ($n = 61$). 2) After the 24-week diet period, the subjects were monitored for an additional 18 months using standard guidelines for the Keto group vs standard guidelines modified by nutrigenetic advice for the low-Glycemic Index nutrigenetic diet (lowGI/NG) group.

Results: After 24 weeks, the keto group lost more weight: -26.2 ± 3.1 kg vs -23.5 ± 6.4 kg ($p = 0.0061$). However, at 18-month follow up, the subjects in the low-GI nutrigenetic diet had lost significantly more weight (-27.5 ± 8.9 kg) than those in the ketogenic diet who had regained some weight (-19.4 ± 5.0 kg) ($p < 0.0001$). Additionally, after the 24-week diet and 18-month follow up the low-GI nutrigenetic diet group had significantly greater ($p < 0.0001$) improvements in total cholesterol (ketogenic -35.4 ± 32.2 mg/dl; low-GI nutrigenetic -52.5 ± 24.3 mg/dl), HDL cholesterol (ketogenic $+4.7 \pm 4.5$ mg/dl; low-GI nutrigenetic $+11.9 \pm 4.1$ mg/dl), and fasting glucose (ketogenic -13.7 ± 8.4 mg/dl; low-GI nutrigenetic -24.7 ± 7.4 mg/dl).

Conclusions: These findings demonstrate that the ketogenic group experienced enhanced weight loss during the 24-week dietary intervention. However, at 18-month follow up, the personalised nutrition group (lowGI/NG) lost significantly more weight and experienced significantly greater improvements in measures of cholesterol and blood glucose. This suggests that personalising nutrition has the potential to enhance long-term weight loss and changes in cardiometabolic parameters.

14

Maternal nonalcoholic fatty liver disease and dietary choline intake modify lifelong gene expression profile in rat offspring

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Background: Both maternal metabolic status and nutrition during pregnancy and lactation may have programming effects on offspring's metabolism. The aim of the study was to examine the role of dietary choline supply during pregnancy and lactation in rat dams suffering from nonalcoholic fatty liver disease (NAFLD) on lifelong expression of selected transcription factors: *Nr1h4*, *Srebf1*, *Pparg*, *Egr1* in their progeny.

Methods: The Wistar rat groups included the offspring of: 1. healthy dams receiving choline during pregnancy and lactation (the control group); 2. NAFLD dams receiving choline during pregnancy and lactation (NN); 3. NAFLD dams receiving choline during pregnancy as well as a choline-deficient diet during lactation (ND); 4. NAFLD dams receiving a choline-deficient diet during pregnancy as well as a supply of choline during lactation (DN); and 5. NAFLD dams receiving a choline-deficient diet during both pregnancy and lactation (DD). The relative expressions were assessed by real-time PCR (qPCR) on day 3, 24, 90 and 12 month of offspring life.

Results: At day 24, expression of *Nr1h4* and *Egr1* was the highest in the NN group. A similar non-significant trend was observed for expression of *Srebf1* and *Pparg*. At day 90 expression of *Nr1h4 Egr1* and *Srebf1* was higher in the ND group compared to the DD and DN, and *Pparg* the expression was the highest in the DN group. At 12 months, expression of *Srebf1* was higher in the NN group compared to the DN and control and expression of *Egr1* was higher in the DN group compared to the DD and control.

Conclusions: Maternal NAFLD and choline deficient diet during pregnancy can modify lifelong gene expression profile in rat progeny. Differential expression of *Nr1h4* and *Egr1* is much more pronounced in youth (24 d) and adulthood (90 d), while differential expression of *Srebf1* and *Pparg* only in adulthood (90 d).

The project was financed by the National Science Centre, Poland (2016/21/D/NZ9/00360).

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From plant to human body: the long and tortuous journey of dietary polyphenols

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Polyphenols are the most abundant family of bioactive compounds present in our diet. Their major sources are fruit, vegetables, legumes, as well as beverages, tea, coffee, wine. The polyphenol family is composed of more than 8,000 compounds which have a common phenolic structure, and they are grouped on the basis of the several different substituents on it. Among the flavonoids, the main classes are flavonols, flavanones, flavan-3-ols, flavones, anthocyanins and isoflavones, while non-flavonoids mainly include phenolic acids, lignans and stilbens. Differently from macro- and micronutrients, polyphenols are not essential for our metabolisms, but they are able to modulate several different pathways, impacting human health. However, several aspects limit the bioaccessibility (i.e. cooking methods, matrix effect) and the bioavailability of such compounds along the gastrointestinal tract. In fact, *in planta* polyphenols are poorly absorbed at the upper gastrointestinal level, and reach almost unmodified the colon tract, where they undergo an extensive gut microbial metabolism, leading to smaller and more polar compounds, such as phenolic acids. Moreover, those formed compounds are objects of the detoxification phases I and II, mainly resulting in sulfated, glucuronidated or methylated forms, which are delivered to tissues and cells by the bloodstream. The aim of this presentation is to give an introduction to the polyphenol compounds *in planta* and an overview of their metabolism once ingested, with a particular focus on the gut microbiota impact on them. This will serve as background for the upcoming presentations about the different biological effects of polyphenols on the human body.

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Metabolism, cardiometabolic health effects and mechanisms of action of dietary polyphenols: a clear example of personalised nutrition.

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Dietary polyphenols are drastically modified after being ingested by humans. They are not well absorbed at the small intestinal level, but are instead vastly degraded by the colonic microbiota, to form smaller and more bioavailable metabolites. These metabolites undergo further phase II conjugation at hepatic level before becoming available to our internal compartments through systemic circulation. These modification steps have been described to be highly variable at the population level, with the intriguing hypothesis that this interindividual variability might become relevant in the framework of the health effects attributed to dietary phenolic substances. This lecture will highlight the basis of these assumptions and report a few cases where the impact of these differences in disposing of polyphenols also corresponded to a difference in physiological response.

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Polyphenols as modulators of gut microbiota composition

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Background: Alterations in gut microbiota (dysbiosis) are associated with chronic metabolic diseases such as obesity, non-alcoholic fatty liver disease or diabetes. Specific dietary patterns and foods may affect the abundance of specific gut bacteria as well as trigger/control intestinal inflammation and permeability, contributing to the onset/development of cardiovascular related diseases. Bioactive polyphenols administration may involve microbiota diversity shifts hypothetically mediating the polyphenol role as antioxidant and anti-inflammatory agents. Moreover, the poor polyphenol bioavailability could result in a prebiotic effect, displaying polyphenol-microbiota interactions.

Aim and Methods: The aim of this presentation is to critically examine the polyphenol-related modulation of gut microbiota composition and accompanying health-related effects. Metagenomic tools were implemented to explore the effects of quercetin, resveratrol and pterostilbene on gut microbiota.

Results: Different trials have reported that resveratrol promotes changes in gut microbiota composition associated with a healthy phenotype. In mice experiments, the administration of resveratrol decreases the *Bacteroidetes/Firmicutes* ratio, while increasing the abundance of *Bacteroides*, *Lactobacillus* or *Bifidobacterium* bacteria. Resveratrol supplementation produced a lower *Firmicutes/Bacteroidetes* ratio and an enhanced occurrence of *Akkermansia muniphila* or *Ruminococcaceae* in high-fat high-sucrose fed animals. In Zucker-obese rats, the administration of pterostilbene (a resveratrol derivative) reduced *Firmicutes* levels, whereas enhanced those of *Akkermansia* and *Odoribacter*, where a negative correlation between *Akkermansia* and body weight was found. The administration of different doses of pterostilbene also resulted in fecal microorganisms changes in *Akkermansia*, *Blautia*, *Ruminococcaceae*, *Faecalitatea*, or *Lactococcus* in rodents fed a fat and fructose enriched diet. Other polyphenols such as quercetin lowered the *Firmicutes*/*Bacteroidetes* ratio and decreased the abundance of bacteria such as *Erysipelotrichaceae, Bacillus* or *Eubacterium cylindroides* in diet-induced obese models. In humans, the intake of pure phenolic compounds and polyphenol-rich sources such as cocoa, tea or wine was effective modulating gut microbiota, mainly by promoting beneficial bacterial strains and excluding pathogenic species. Mediterranean Diet, involving a high intake of fiber, antioxidants and polyphenols, has been reported to beneficially impact gut microbiota by increasing abundances of bacteria such as *Bifidobacterium animalis*, *Roseburia faecis* or *Ruminococcus bromii*. Polyphenols can also blunt the microbial production of pro-inflammatory mediators such as lipopolysaccharide (LPS), alleviating the chronic inflammatory status found in obese and diabetic patients.

Conclusions: The effectiveness of polyphenols as modulators of gut microbiota composition will enable applications in this field by better understanding the precise mechanisms of action linking polyphenol-derived beneficial health effects through dysbiosis management.

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Polyphenols modulate liver miRNAs: a mechanism for their beneficial effects

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Background: mi(cro)RNAs modulate most metabolic pathways and are involved in several metabolic disorders, and thus, can be used as therapeutic targets. Dietary polyphenols have positive effects on metabolic syndrome, including cardiovascular protection at improving lipid homeostasis. Otherwise, our research group has shown that polyphenols can regulate central and peripheral molecular clocks which could mediate their beneficial effects.

Indeed, long term disturbances of the circadian system are linked with an increase of metabolic syndrome prevalence. Thus, we aimed to elucidate whether one of the mechanisms underlying the polyphenols beneficial effects on the dysfunctions associated with the metabolic syndrome are via liver miRNA modulation.

Methods: We approach this general objective through the study of the capacity of polyphenols 1) to modulate and bind liver miRNAs involved in lipid metabolism regulation and 2) to modulate liver miRNAs that regulate the hepatic clock system.

Results: Liver miR-33 and miR-122 regulate the expression of key enzymes and proteins for the lipid metabolism and their deregulation has been associated with the development of metabolic syndrome. We demonstrated that polyphenols regulate miR-33 and miR-122 and their target genes, Abca1 and Fas, in rat hepatocytes *in vivo* and *in vitro*. Polyphenols improve the lipid profile by the repression of these two miRNAs in rat liver of obese dyslipidemic rats. Moreover, using ^{1}H NMR studies we showed *in vitro* that these dietary compounds can directly bind to miR-33 and miR-122. Additionally, we showed that polyphenols can regulate the expression of the hepatic Bmal1 clock gene via mir-27b-3p in rats.

Conclusions: These results indicate that polyphenols regulate liver lipid metabolism and the molecular hepatic clock via miRNAs. Thus, miRNA modulation by polyphenols is suggested as a mechanism that explains their beneficial effects on metabolic syndrome.

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Nutrigenomics and multi-omics in identification of mechanisms of action underlying health properties of polyphenols: a guideline for nutrigenetics?

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Diets and different micro and macronutrients can negatively or positively affect vascular function and consequently induce or prevent the development of associated diseases, such as cardiovascular or neurodegenerative diseases. In recent years, it has been shown that polyphenols play an important role in prevention of these diseases, effects that are dependent on their capacity to exert genomic modifications, such as modulation of expression of genes, proteins and changes in DNA methylation. However, use of targeted approaches and identification of novel types of RNAs, such as microRNAs, long-non coding RNAs and short RNAs, suggests new still unexplored mechanisms of action of these plant food bioactives. Therefore, to decipher as precisely as possible the molecular mechanisms of action of polyphenols, use of integrated multi-omic approach assessing different levels of cellular regulation followed by bioinformatic analyses is essential. This presentation will present novel results of the multi-genomic effects of polyphenols by integrated analyses of genomic data on different types of RNAs, in-vitro and in-vivo. Use of such an approach has revealed that polyphenols can simultaneously modulate different types of RNAs, forming a complex network of cellular regulation. Moreover, multi- omic analysis can also reveal major cellular functions but also genes involved in the genomic action of these bioactives. The results of nutrigenomic modifications of polyphenols will support the future setup up of nutrigenetic studies to study associations between genetic polymorphism of these genes and inter-individual variability in responses to intake of these bioactives and therefore pave the way for individualized dietary recommendations.

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The negative association between Ruminococcus abundance and body mass index could be mediated by the methylation of a differentially methylated region between MACROD2/SEL1L2 genes

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Background: Obesity is a global epidemic and an independent risk factor for several metabolic disorders. Variations in gut microbiota composition and in epigenetics markers have been proposed as key players in the onset and development of obesity and other metabolic diseases. However, the interactions between epigenetics markers and gut microbiome in obesity remains not completely understood.

Objective: To identify differentially DNA methylated genes that could be potentially regulated by gut microbiota in obesity.

Methods: A total of 342 subjects with BMI between 18 and 40 kg/m^2 were included in this study. DNA methylation profiles were performed in buffy coat, through a methylation array (*Infinium Methylation EPIC Bead Chip-Illumina*). Differential methylation regions (DMR) were analyzed using a function of ChAMP (Chip Analysis Methylation Pipeline) in R software. Bacterial DNA sequencing was performed following the Illumina 16S protocol. The hypothesized relations between gut microbiota, DNA methylation, and BMI were tested through structural equation modeling (SEM) using Stata 16.0.

Results: DNA methylation analyses identified a total of 2,648 DMRs associated with BMI. Among the ten bacterial genera associated with BMI, only the abundance of *Ruminococcus* was associated with one BMI-related DMR. The abundance of *Ruminococcus*

was negatively correlated with BMI (σ= - 0.1941; P= 0.003) and the DMR presented a hypermethylation pattern in obesity. This DMR is composed of 7 CpG sites and it is located on chromosome 20 between *MACROD2* and *SEL1L2* genes. Additionally, the mediation test has shown that 19% of the effect of *Ruminococcus* abundance on BMI is mediated by the methylation of the DMR *MACROD2*/*SEL1L2* (P= 0.035).

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From genome to metabolome – examples with relevance for diet-related NCD´s

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Metabolomics is driven by the breathtaking advancements of the NMR- or mass-based techniques providing constantly larger metabolite panels. In addition, new databases for annotation and identification of so far unknown metabolites are created. When metabolite profiling is combined with genetic and molecular tools, identification of the metabolic pathways and mechanisms altered along the health-disease trajectory is enabled as never before. Seemingly unlimited when applied to cells in culture or model organisms, metabolomics in humans however mainly relies on the profiling of plasma and urine samples. When used as a diagnostic tool, changes in the concentrations in metabolites or metabolite ratios are used to discriminate health and disease conditions. However, what usually remains hidden which organ(s) and cell type(s) are the origins of the alterations seen in plasma or urine – in particular when taken into account that each cell type has a distinct metabolite pattern with intracellular concentrations of metabolites exceeding those in plasma in some cases up to 200-fold. Urinary metabolites do in most cases also not reflect plasma levels and the contribution of the intestinal microbiota to the body fluid metabolome remains as well to be defined. Although classical physiological chemistry/biochemistry has created a huge knowledge base, we miss quite often the understanding of metabolite variability and the dynamics of changes of the human metabolome and that needs more dedicated human studies. Metabolomics in total needs a push to advance from a "snapshot science" to an explanatory science and from the "fold-science" to quantification. I shall provide examples from diet-related NCD´s (obesity, non-insulin-dependent diabetes to address all these critical points with the goal to provide the current state of art and science.

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The Internal Exposome in Precision Medicine and Precision Nutrition

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Background: An individual's response to a nutrient or to a diet is related to their inherited genetics and lifetime exposures. Exposures through dietary intake, and use of supplements, natural products, tobacco, alcohol, medications, and drugs of abuse all contribute to an individual's internal exposome. Chemicals that are added to foods and water, used to produce commercial and household products, or derived from environmental contamination and pollution represent additional sources of the internal exposome. The exposome profile of an individual results from their genetics, state of health and wellness, and lifetime exposures.

Methods: Ultra-high performance liquid chromatography coupled with high resolution mass spectrometry (UHPLC-HR-MS) can simultaneously capture tens of thousands of signals for metabolites in biological specimens. The range of analytes that have been identified and annotated on the untargeted UHPLC-HR-MS platform include metabolites derived from host and microbial metabolism, tobacco use, medications and illicit drugs, environmental chemicals, and from ingestion of foods. Yet, most signals in exposome analysis remain unknown. Approaches that are used to identify and annotate these signals include mining against public databases and using clustering motifs to predict unknown structure. Because nutritional dark matter may represent a significant contribution of the unknowns, peak identities have also been expanded using data acquired from controlled feeding intervention studies.

Results: This presentation will describe results from several recent investigations of opium use disorder, hypertensive disorders of pregnancy, osteoarthritis, and fertility.

Conclusions: Exposome research can simultaneously inform the development of biomarkers of health and wellness, and the development of nutritional intervention strategies, while informing needs in exposure reduction.

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Development of personalized nutrition: applications in lactose intolerance diagnosis and management

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Recent discoveries in the "omics" field and the growing focus on preventive health have opened new avenues for personalized nutrition (PN), which is becoming an important theme in the strategic plans of organizations that are active in healthcare, food, and nutrition research. PN holds great potential for individual health optimization, disease management, public health interventions, and product innovation. However, there are still multiple challenges to overcome before PN can be truly embraced by the public and healthcare stakeholders. The diagnosis and management of lactose intolerance (LI), a common condition with a strong inter-individual component, is explored as an interesting example for the potential role of these technologies and the challenges of PN. From the development of genetic and metabolomic LI diagnostic tests that can be carried out in the home, to advances in the understanding of LI pathology and individualized treatment optimization, PN in LI care has shown substantial progress. However, there are still many research gaps to address, including the understanding of epigenetic regulation of lactase expression and how lactose is metabolized by the gut microbiota, in order to achieve better LI detection and effective therapeutic interventions to reverse the potential health consequences of LI.

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Whole blood transcriptome identifies distinct profiles of metabolic responsiveness to raspberry consumption

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Background: Consumption of red raspberries has been reported to exert beneficial effects on human health, especially on immune-metabolic conditions, though these effects and their underlying mechanisms are not well defined yet. In this study, we aimed to investigate the architecture of the interindividual variability of the response to raspberry consumption, by stratifying participants according to their transcriptomic response.

Methods: The 24 participants assigned to the treated arm of a randomized controlled trial, received 280g of raspberries daily for 8 weeks. RNAseq data from whole blood assessed at weeks 0 and 8 were used to identify subgroups of response to raspberry consumption, by using partial least-squares discriminant analysis (PLS-DA) and hierarchical clustering. Changes in metabolic parameters and plasma metabolites were compared between the resulting sub-groups.

Results: Following the clustering approach, 13 participants were defined as responders, and 11 as non-responders based on significant transcriptional changes throughout the intervention. Most discriminant genes were grouped into two major components composed respectively of 100 and 220 genes. A significant decrease in plasma triglycerides, total-cholesterol and C-reactive protein levels, was found in responders, as compared to non-responders following the intervention. Factor analysis revealed that the first metabolomic factor, mostly composed of decreasing triacylglycerols and increasing phosphatidylcholines, was significantly higher in responders, as compared to non-responders.

Conclusions: The discrimination analysis based on transcriptional changes led to the identification of sub-groups with divergent metabolic responses to raspberry consumption. Transcriptomic clustering thus emerges as a promising tool for the understanding of the interindividual variability in response to a nutritional intervention.

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Olfactory influences on appetite and metabolism

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Appetite and smell are closely linked. Smell is important not only for flavor but also for finding and selecting food. The importance of smell is reflected in the fact that the genes encoding olfactory receptors (ORs) constitute the largest mammalian gene family. The OR gene repertoire is largely species-specific, suggesting that it is shaped by the nature and necessity of chemosensory information (e.g. food sources) for survival in each species' niche. Moreover, the gender, health (e.g. obese vs lean), and internal homeostatic state (e.g. hunger vs satiety) of an individual can modulate olfactory performance and sensitivity, which could, in turn, affect food retrieval and consumption. We employ a multidisciplinary strategy to better understand how the various factors outlined in the preceding paragraph shape the olfactory system and, ultimately complex behaviors such as appetite enhancement or suppression. First, we performed RNA-seq of the nose across mammalian species (mouse, rat, dog, marmoset, macaque, and human) to measure the expression of ORs. In studies of human olfactory tissue, we found that ORs sensitive to key food odors were among the most highly expressed. Second, we developed a behavioral assay aiming to identify odorants that modulate food intake in mice. Third, through multiplexed ELISA techniques, we are assessing whether the circulating level of hormones and neuropeptides can be modulated through odor exposure. Finally, we are also investigating the impact of odor exposure and dietary intervention on gene expression across various nervous and digestive system organs. We believe this integrated approach will

contribute to a better understanding of the neural logic underlying odor-induced effects on appetite, food intake and metabolism. Importantly, these studies could provide clues to potential approaches for controlling appetite and ultimately obesity, which is of serious medical concern in our modern society.

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Taste testing in educational and clinical practice

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Individuals differ in the way they are able to detect food flavors and such differences in turn influence food preferences and eating behavior. Bitterness is a taste quality of obvious interest because it will reduce consumption when perceived as unpleasant, but attract to other foods when perceived as a desirable accent. About forty different bitter taste receptors are known and well defined on a molecular level. All of them detect the same bitter taste quality, but respond to distinctly different spectra of ligands. This has the consequence that the same person may strongly perceive the bitterness of Brussel sprouts which contains one kind of bitter-tasting molecules but be oblivious to the bitter tasting compounds in grapefruit. In another individual it may be just the other way around. These individual differences in bitter taste sensitivity are very useful to raise awareness of both newcomers to nutrigenetics and of patients in clinical practice. Few people, even when they are well-trained health professionals, realize such strong differences and how they shape individual food preferences. We have used taste testing in numerous nutrigenetic training courses to emphasize that in dietary counseling such innate propensities should be taken into account. Better understanding of the strong genetic determination of bitter taste perception can help to work around dislikes of healthful foods such as broccoli or Brussel sprouts by demonstrating how to turn an unpleasant perception into a more acceptable one, for instance by roasting or adding small amounts of sugar. There is clearly the potential for adding an element of precision nutrition to counseling and the culinary arts by asking more about what works for the individual patient and consumer instead of assuming that everybody has the same taste buds. Bitter taste addresses only one aspect of our culinary chemosensing systems. Similar efforts are needed to bring into practice better understanding of individual differences in the many other taste and smell qualities that influence our food choices and may be surmountable barriers to desired intake behavior change.

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Chemosensing, genetics and eating behavior

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Understanding the role of taste in food selection and ingestive behavior is important for expanding our understanding of the factors involved in body weight maintenance and the risk of chronic diseases including obesity, atherosclerosis, cancer, diabetes, liver disease, and hypertension. Taste perception influences food intake, and gut related chemosensors relay sensory signals to the brain impacting macronutrient selection and eating behavior. Members of the TAS2R family are expressed throughout the GI tract, where they function as bitter taste receptors, and have roles in prandial, gut-derived hormone release. A bitter insensitive allele has been shown to be significantly associated with increased disinhibited eating behavior and higher BMI, particularly among females in our genetically isolated population.

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Taste nutrigenetics – more than just modulation of preferences

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Various receptors (G-protein coupled receptors and ion channels), and subsequent signalling pathways, are involved in detecting the 5 basic tastes (sweet, bitter, umami, salt and sour). The standard paradigm connecting taste nutrigenetics to health and disease outcomes is via the modulation of taste preferences and therefore dietary habits. However, research attempting to link common diet related outcomes including oral health, diabetes, cardiovascular diseases, and cancers have yielded mixed associations. More recently taste receptor expression has been identified in other organs throughout the human body, including in the stomach, intestines, pancreas, blood vessels, brain and more. This has led to interest in other functional roles for these receptors beyond traditional gustatory functions, including chemosensory functions to modulate gut motility, inflammation, and more, which may explain links between taste receptor nutrigenetics and disease. Investigations into the roles of these receptors, and an extension of the investigations into non-gustatory ligands is progressing with potential future applications to disease prevention and therapeutics, both for pharmaceutical and nutraceutical interventions.

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TAS2R38 haplotype is associated with vegetable consumption in the Canadian Longitudinal Study of Aging

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Background: *TAS2R38* haplotypes have been associated with bitter taste sensitivity and preferences for sweet foods, although associations with dietary intake are inconsistent. However, previous investigations of *TAS2R38* and dietary intake have been limited in sample size. Thus, assessment in a large-scale cohort is warranted.

Objective: To evaluate associations between *TAS2R38* haplotype and dietary intake using baseline data from the Canadian Longitudinal Study on Aging (CLSA), a large-scale representative cohort of middle- and older-aged men and women (45-85 years).

Methods: Genetic (rs1726866 and rs10246939), dietary, anthropometric, and sociodemographic data were obtained from the CLSA (n=26,622). *TAS2R38* haplotype was categorized into non-tasters (VI/VI) (n=7,687), tasters (AV/VI) (n=12,939) and supertasters (AV/AV) (n=5,780). Usual consumption frequency of 36-food items was assessed over the previous 12 months using the Short Diet Questionnaire. Outcome variables included daily consumption frequency (times per day) of vegetable items (green salad, other vegetables (excluded carrots, potatoes and salad), and both combined) and a derived variable for overall consumption frequency of sweet-tasting foods (ice cream, ice milk, frozen yogurt, milk-based desserts, cakes, pies, doughnuts, pastries, cookies, muffins, chocolate bars). General linear models adjusted for sex, age, recruitment province, income, waist circumference, and the first five principal components of ancestry were used to assess associations between haplotype and outcome variables.

Results: Consumption of other vegetables and both vegetable outcomes combined was highest among non tasters (adjusted mean ± standard error times per day: non-tasters 0.69±1.01, tasters 0.67±1.01, supertasters 0.68±1.01, p=0.01, and non-tasters 1.17±1.01, tasters 1.14±1.01, supertasters 1.14±1.01, p=0.04, respectively). There was no association between *TAS2R38* haplotype and sweet tasting foods (0.41±1.01, 0.41±1.01, 0.41±1.02, p=0.79).

Conclusions: Among a large cohort of middle- and older-aged men and women, *TAS2R38* haplotype was modestly associated with daily consumption frequency of vegetables, but not sweet-tasting foods.

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Mission of the Guideline Development Workgroups

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The International Society for Nutrigenetics/Nutrigenomics (ISNN) has undertaken since 2015 to review the scientific evidence for gene variant candidates that impact individual responses to nutrition interventions in a consistent and predictable manner. The goal is to issue genetically particularized guidelines with sufficient clinical utility for everyday practice. The process entails expert review, public presentation and discussion of currently available evidence, publication of the findings, development of draft guidelines, vetting by ISNN members with additional input from the wider scientific and professional community, and finally release of the guidelines subject to continued scrutiny and revisions as warranted by the most current evaluation of the scientific evidence. The first challenge is to agree on well-formulated guideline propositions. The work groups then use a priori criteria to rate the evidence supporting each proposition. The next challenge is then all too often the lack of direct evidence in support of propositions with sufficiently promising clinical utility. Thus, the proposition that carriers of particular genetic variants are likely to benefit from a particular dietary intervention gets only weak support, if at all, from the demonstration of associations in populations. We really need to demonstrate prospective interventional benefits, ideally in well-designed clinical trials of sufficient duration. We also cannot ignore that much of the available trial data fails to ensure ethnic diversity. Finally, while trials with direct answers to questions about the effectiveness of genetically targeted nutritional interventions are rare, replication of trials with the desired outcomes is even less common. This leaves evidence support often at high risk for several types of bias. Such exacting requirements for support of nutrigenetic guidelines may be disheartening. However, the combination of biological plausibility, a multitude of diverse supporting evidence, and the low-risk, high-gain nature of moderate dietary modifications can still add up to a sufficiently strong case.

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Proposed nutrigenetic guidelines for vitamin D

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The current recommendations for vitamin D are typically set with regards to maintaining bone health. However, roles for vitamin D are now being identified in the reduction of risk for a variety of other complex and chronic diseases. Furthermore, population recommendations are set around normal levels and responses, with ranges set to extrapolate to hypothetically accommodate a

large proportion of the population. With a growing body of data on how specific variants of Group-specific Component (GC, encoding vitamin D binding protein, VDBP), vitamin D hydroxylating enzymes (CYPs), and the vitamin D receptor (VDR) influence vitamin D detection and responses, and a growing number of the general public accessing their nutrigenetic information for these genes, it may now be time to adjust recommendations to incorporate known variance. Several common variants have been shown to increase individual risk for deficiency and risk for chronic disease, as well as modulate response to supplementation. It is now time to consider how this information can be incorporated into guidelines for practice. Without this guidance it remains up to each individual nutrigenetic practitioner to adjust needs based on personal data, which poses risks for trust and transparency.

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The ups, downs, and ups again of omega-3 fatty acids as cardioprotective agents

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After the glory of earlier trials with omega-3 fatty acids in cardiovascular disease, culminating in the GISSI-Prevenzione trial in 1999, documenting important effects on cardiovascular mortality and sudden cardiac death in the thrombolytic era of myocardial infarction treatment, skepticism has risen on the reproducibility of those results in current times, with several meta-analyses not being able to re-document significant efficacy. This contrasts however with the consistency of epidemiologic data relating consumption of omega-3 fatty acids with lower cardiovascular risk. Such discrepancy can be largely explained by consideration of the fundamental difference between continuous dietary intake extended for an entire life, as in epidemiological studies, as opposed to relatively short-term intakes occurring in intervention trials. Indeed, the inverse relationship of omega-3 fatty acid intake with cardiovascular events, including myocardial infarction, has been confirmed even recently by studies documenting that incorporation of omega-3 fatty acids in the adipose tissue, a stable and reliable marker of omega-3 fatty acid intake, is inversely related to cardiovascular events even at extended follow-up. Recent data from the REDUCE-IT trial have again boosted the enthusiasm for these agents also in the course of an intervention trial in primary and secondary cardiovascular prevention, probably as the result of doses used, higher than before, and of an accurate selection of the target population. Such data will be discussed in the broad perspective of the history of attempts at using such agents to improve cardiovascular health, and in an attempt of issuing nutritional and pharmacological recommendations.

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Updated nutrigenetic guidelines relating to caffeine

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The effects of caffeine on cardiovascular disease remains controversial. This is due, in part, to genetic differences impacting caffeine metabolism or response. During the 2015 ISNN conference in Chapel Hill, a group of experts convened to evaluate the evidence base for making nutrigenetic recommendations for caffeine, and an ISNN Consensus article was published (De Caterina and El-Sohemy, J Nutrigenet Nutrigenomics 2016;9:106–115). A grading system was used to evaluate the level of evidence for making specific recommendations. Several genes, and their biological function, were assessed, along with various cardiovascular-related outcomes. Four recommendations were made based on the evidence to-date. In the past five years, several additional studies have explored whether common genetic variations modify the effects of caffeine on cardiovascular disease risk. This presentation will review the current state of the science and examine how the current body of evidence impacts the recommendations previously made by the 2016 ISNN Consensus article on nutrigenetic recommendations for caffeine and cardiovascular disease.

Poster Presentations

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Trimethylamine N-oxide (TMAO) modulates the expression of cardiovascular disease related microRNAs and their targets

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Background: Cardiovascular diseases (CVD) are mainly caused by lifestyle, in which diet plays an essential role. Metabolites from diet, regulate microRNAs expression, altering their target genes, related to metabolism and CVD. Choline, betaine, and L-carnitine are nutrients found in animal products and are metabolized into trimetilamine (TMA) by gut microbiota. TMA is oxidized by FMO genes in the liver, to TMAO, which has been associated with CVD. Objective: to investigate TMAO

regulation of CVD-related microRNAs and genes, in liver and peripheral mononuclear cells biological models.

Methods: HepG2, THP-1, mice liver organoids and human primary macrophages were treated with (6μM) TMAO for different time points. HepG2 cells were transfected with anti-miR-30c and syn-miR-30c for the same time points. Proteins and RNA enriched in microRNAs were isolated. Previously selected microRNAs and their target genes were amplified by q-PCR. Proteins were analyzed by western blot.

Results: TMAO increased the expression of miR-21, miR-30c and miR-92a in all biological models tested. miR-30c increased its expression with TMAO even with anti-miR-30c. Expression of target genes selected was analyzed. PER2, target gene of miR-21, miR-92a and miR-30c, decreased its expression at 8h and 24h in HepG2 and organoids, but increased its mRNA expression with TMAO with syn-miR-30c. SERPINE1 increased its mRNA levels at 4h and 24h, and decreased at 8h, but protein levels increased at 8 and 24h. It also increased its expression with TMAO with syn-miR-30c at 4h and 8h. CXCL16, target of miR-30c and miR-92a, increased at 12h and 24h. IL12A target gene of miR-21, also increased at 12h and 24h. Analysis of target genes showed that these microRNAs play a role in lipid metabolism and inflammation.

Conclusions: TMAO modulates the expression of microRNAs related to CVD, having an impact on their target genes. TMAO modulates CVD related genes independently of their microRNAs.

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Impact of Nicotinamide Riboside Supplementation on Metabolite Levels in a Rat Model of Heart Failure

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Background: Nicotinamide riboside (NR), a form of vitamin B3, is a precursor of nicotinamide adenine dinucleotide (NAD), a central regulator of the metabolism. Alterations of NAD homeostasis are widely studied in the context of cardiac diseases including heart failure (HF). NAD stimulation has emerged as a new avenue for the development of metabolic therapy of HF. The aim of this study is to test the impact of NR supplementation on metabolite levels in cardiac tissue in a rat model of HF.

Methods: 40 rats were fed either with a NR supplemented diet or a control diet (CD), following sham or left anterior descending coronary artery ligation surgery mimicking myocardial infarction (MI). Untargeted metabolomics was used to measure metabolite levels in the left ventricular tissue using both hydrophilic interaction (HILIC) and reverse phase (C18) high-performance liquid chromatography coupled with high resolution mass spectrometry. Quality control steps were performed on the metabolomic dataset (n=2917), while unsupervised learning techniques such as UMAP and differential quantification analyses were implemented for highlighting relevant metabolites.

Results: The unsupervised learning analyses show clear separation between NR diet and CD groups and a more subtle separation between sham and MI conditions. A total of 605 and 507 metabolite features were differentially quantified in NR diet compared to CD in MI and sham conditions, respectively. A subset of annotated discriminant metabolites were of interest in the context of heart disease (adenosine, malic acid, citric acid, s lactoylglutathione, creatinine, riboflavin-5-monophosphate, GMP), and NAD metabolism (nicotinamide mononucletide, cyclic ADP-ribose).

Conclusions: We found key differences in the cardiac tissue metabolome following a NR supplementation in rats, which vary according to the disease state. Several metabolites relevant to heart disease were identified and follow up network analyses will bring new insights into metabolic pathways underlying the effects of NR in this model.

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Could gluten free diet improve weight loss in HLA DQ2 or D8 positive subjects?

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Background: Gluten-free dieting has gained considerable popularity in the general population. Our primary purpose was to provide experimental evidence for the effect on weight loss of a gluten-free diet and analyse the potential interactions between genetic factors affecting gluten sensitivity (located at the HLADQ gene) and gender.

Methods: We analysed 221 subjects who were genotyped with a nutrigenetic panel that included the HLA genes (Eurogenetica – NutriGene+). Of 221 patients, 215 were overweight or obese and 69 patients were found to have at least one allele for DQ2 or DQ8. 64 were overweight and were randomly divided into two groups. Both groups were prescribed a 1800 kcal/day diet and one group was gluten free. Patients were monitored, both weight and BIA, at one month, 3 months and 6 months.

Results: The gluten-free group showed a significant weight loss compared to the control group at three and six months (3m: 14% vs 8% and 6m: 25% vs 14%). A gluten elimination diet in patients with at least one risk allele for gluten sensitivity correlated to a significantly more weight loss in patients with weight problems than a standard diet. The negative HLA genotypes were less effective on a gluten free diet, compared to the positive HLA genotypes with at least one risk allele for gluten sensitivity.

Conclusions: There was no difference, on a gluten free diet, between HLA genotype; a gluten-free diet has been shown to be more effective in weight loss than a diet with gluten. We are not sure but we suspect that a gluten free diet reduces inflammation, but other studies are needed in this regard and therefore it is necessary to study the gluten free diet for subjects with risk alleles.

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Molecular mechanisms of the anthocyanin-mediated cardioprotection against Doxorubicin cardiotoxicity

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Background: Doxorubicin (Doxo) is a chemotherapeutic drug, whose efficacy is severely hindered by its severe side effects. Cardiotoxicity is the most important one since symptoms can start 10-15 years after the end of the treatment. It is important to identify compounds that can counteract or prevent Doxo-induced cardiotoxicity without altering its antitumoral efficacy. Anthocyanins (ACNs) are renowned cardioprotective agents thanks to their antioxidant and anti-inflammatory properties. An ACN-rich diet from purple corn (RED diet), which mainly contains cyanidin 3-glucoside (C3G) and its acetylated derivatives, was proved to be effective in reducing the Doxo-induced cardiotoxicity in mice. Aiming at unveiling the molecular mechanisms involved in ACN protection, we decided to consider the FGF21-AMPK-SIRT1-p53 pathway that recently gained interest for its cardioprotective role. FGF21 is mainly secreted by liver and adipose tissue, and involved in cardioprotection through an endocrine mechanism, but it is also expressed and secreted by cardiomyocytes after different cardiac stress stimuli. AMPK is a conserved energy sensor involved in stress response, cellular homeostasis and regulation of SIRT1 activity, a deacetylase involved in stress resistance. SIRT1 activation may protect the heart from Doxo side effects through p53 acetylation.

Methods: HL-1 murine cardiomyocytes were treated with Doxo in presence or absence of purple corn extract (RED). Gene expression, protein and/or activation level of FGF21, AMPK, SIRT1, p53 and its apoptosis related target genes were evaluated in controls and upon Fgf21 or Sirt1 siRNA-induced silencing.

Results: Our results showed that Doxo-induced excessive AMPK activation was restored to control levels by RED. An indirect indication of SIRT1 activity was obtained measuring the NAD/NADH ratio, which is increased by Doxo and maintained at control level by the RED co-treatment, suggesting a SIRT1 activation upon Doxo treatment. P53 acetylation was increased by RED treatment and upon Sirt1 silencing, indicating that p53 acetylation is SIRT1-dependent and suggesting that RED may affect SIRT1 activity through AMPK. Notably, increased P53 acetylation led to decreased levels of cleaved-Caspase 3, and Puma and p21 transcript levels, implying a reduced level of apoptosis.

Conclusion: In conclusion, RED may prevent cardiomyocytes apoptosis through modulation of AMPK and acetylation of p53.

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CYP24A1 genetic variants in the vitamin D metabolic pathway as a prognostic factor in non-small cell lung cancer

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Background: Non-small cell lung cancer (NSCLC) is diagnosed at advanced stage, so the overall survival rate is around 5%. Vitamin-D may influence cancer survival by inhibiting tumor progression, suppressing metastasis, cell proliferation, and angiogenesis, or promoting apoptosis. Little information is available about polymorphisms in *CYP24A1*, which regulates the catabolism of circulating Vitamin-D. The aim of this study was evaluated the influence of polymorphisms in the *CYP24A1* gene on NSCLC survival.

Methods: Retrospective study. Patients diagnosed with NSCLC (non-resected) between 2003-2019, followed-up until December 2020. *CYP24A1* polymorphisms (rs6068816-rs4809957) were analyzed by real-time PCR using TaqMan® probes. Overall survival (OS) and progression-free survival (PFS) were evaluated. Kaplan-Meier method and log-rank test were used to analyze the associations of demographic, clinical and genetic variables with survival.

Results: Patients' mean age was 60.86±10.51 year; 72.7% (106/146) men; 88.9% (129/145) stage IIIB-IV; 66.7% (96/144) adenocarcinoma. The median OS and PFS were 26.8 [15.5-64.2] and 13.7 [6.46-29.9] months, respectively. Patients carrying the TT genotype for *CYP24A1*-rs6068816 gene polymorphism were associated with higher risk of death and progression. The median OS for patients carrying the rs6068816-TT genotype was 12.4 (95% CI=6.47-NR) months, while for the CC/CT genotypes were 23.4 (95% CI=20.1-27.0) and 24.5 (95% CI=16.0-38.9) months, respectively. The median PFS for the rs6068816-TT genotype was 5.43 months (95% CI=4.27-NR), and for the CC/CT genotypes were 11.9 (95% CI=10.1-16.1) and 10.4 (95% CI=6.20-18.7) months, respectively. Multivariate cox regression showed that *CYP24A1* rs6068816 is associated with OS (p=0.0089; HR=3.47; 95% CI=1.37- 8.79; TT *vs* C) and PFS (p=0.0048; HR=8.77; 95% CI=1.94-39.7; TT *vs* C). However, for *CYP24A1* rs4809957 we did not find a statistically significant association.

Conclusions: Our results suggest that *CYP24A1* rs6068816-TT genotype influences OS and PFS in NSCLC (non-resected) patients. Therefore, this polymorphism could be used as a prognostic marker of the disease.

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TNF-alpha plasma concentration and PBMC gene expression in women with metabolic syndrome: relationship with body adiposity parameters

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Background: Chronic inflammation may represent a triggering factor in the origin of metabolic syndrome (MS). Among the inflammatory biomarkers, the tumor necrosis factor-alpha stands out for its involvement in the resistance to insulin action. Thus, we evaluated the plasma concentration and gene expression (mRNA) of TNF-α in peripheral blood mononuclear cells (PBMC) of women with MS and their relationship with body adiposity parameters.

Methods: We enrolled 71 overweight or obese women aged 40.6 ± 1.1 years recruited in the outpatient clinic of endocrinology. The diagnosis of MS was performed according to the criteria proposed by Alberti (2009). To assess body adiposity, we measured the waist circumference (WC) and the percentage of body fat mass (%BF) through an 8-polar bioelectrical impedance. The plasma TNF-α level was performed by the Immunoassay technique. Total RNA from PBMCs was extracted and transcribed into cDNA for further RT-qPCR analysis and expressed as arbitrary units (AU) relative to GAPDH. All results are expressed as median ± IQR.

Results: Thirty-one participants (43.7%) were classified as MS. The level of TNF-α did not differ between MS and non-MS women (2.2 ± 1.8 pg/mL versus 2.1 ± 1.5 pg/mL respectively, P = 0.316). Nevertheless, PBMC gene expression of TNF-α was 43% greater in MS women compared to non-MetS (18.2 ± 13.6 AU versus 12.7 ± 8.3 AU, P = 0.026). There was no correlation between plasma TNF-α concentration and WC (rho = 0.12, P = 0.405) or %BF (rho = 0.15, P = 0.296). TNF-α mRNA also did not show a significant correlation with WC (rho = 0.21, P = 0.131) or %BF (rho= -0.02, P = 0.889).

Conclusion: Our results suggest that there is an increased gene expression of TNF-α in the PBMC of women with MS, regardless of their body adiposity.

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A Berberis microphylla (Calafate) extract promotes thermogenesis and browning in mice with diet induced obesity

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Background: the pro-thermogenic characteristics associated with the consumption of polyphenols have led to position them as possible anti-obesity metabolites. The aim of the present study was to evaluate the effect of a polyphenol-rich Berberis-microphylla extract (Calafate) in obese mice.

Methods: 8-week old C57BL6 mice (n=30) were divided into 4 diets/treatments. Control Diet(C), High-Fat-Diet(HF), High Fat-Diet/Calafate(HFC) and High-Fat-Diet/Calafate/Antibiotics (HFCAB). At 19 weeks, animals of HFCAB were treated with a broad-spectrum antibiotic in the drink for 2 weeks. Then, HFC and HFCAB were treated with a daily dose of 50mg of total-polyphenols/kg-animal-weight, of the Calafate extract for 3 weeks. At 24 weeks, animals were euthanized and interscapular brown-adipose-tissue (BAT) and epididymal (eWAT) and inguinal (iWAT) white-adipose-tissue were obtained. Gene expression of thermogenic markers (Ucp-1, Pgc1-α, Pparα/γ, Prdm16, Sirt1 and Dio2) and beige adipose tissue marker (Tbx1) were analyzed. Transmission-electron-microscopy was used to evaluate mitochondrial morphology and mitochondrial cristae density in BAT. Further, cecal content was extracted to analyze the gut microbiota (GM) by mass sequencing with MiSeq-Illumina. α-diversity of GM was calculated using Shannon index and β-diversity values using principal coordinate analysis. One-way ANOVA and Tukey post hoc was used for comparison between groups.

Results: With respect to thermogenic markers only a higher relative expression of Dio2 was observed in HFC compared to C and HFCAB in both BAT and iWAT. Also, greater expression of Tbx1 was observed in HFC eWAT, which was not observed in HFCAB. HFC presented higher mitochondrial cristae density in comparison to HF and HFCAB. In the GM was observed a lower α-diversity in HFCAB in comparison to C, HF, and HFC. No differences in β-diversity were observed between HF and HFC.

Conclusions: a polyphenol-rich Calafate extract promotes thermogenesis and browning in mice with diet induced obesity. The effects of Calafate disappear when animals are treated with antibiotics.

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Diverse effects of pterostilbene and resveratrol in gastrointestinal physiology after feeding rats a high-fat high-fructose diet

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Background: Obesity and associated comorbidities such as NAFLD are worldwide highly prevalent, being unbalanced diets major contributors to fat deposition. Impaired gut microbiota composition, intestinal integrity or gut bacterial metabolites like fecal SCFA´s have been putatively linked to NAFLD development. Besides energy-restriction diets prescription, phenolic compounds administration is considered allegedly a potential therapeutic tool for managing this liver condition. This study aimed to investigate the effects of a dietary induced steatosis and the preventive role of resveratrol and pterostilbene administration in relation to NAFLD.

Methods: Rats (6-week-old) were fed a standard diet, or a high-fat high-fructose diet alone or combined with pterostilbene (15 or 30 mg/kg/day) or resveratrol (30 mg/kg/day) for 8 weeks. Serum transaminase levels (AST and ALT) were measured spectrophotometrically, faecal gut microbiota composition and SCFA levels were assessed by 16S rRNA gene amplification method and liquid Chromatography with tandem mass-spectrometry, respectively. TNFα and claudin protein expressions were determined by western blot to feature intestinal inflammation and permeability.

Results: High-fat high-fructose feeding induced a significant increase in serum transaminase levels, which were reverted by pterostilbene and resveratrol. Contrariwise, the significant reduction induced in gut microbiota richness by the hypercaloric diet, was not prevented by pterostilbene or resveratrol. Nevertheless, the low pterostilbene dose significantly increased Akkermansia municiphila abundance. Isobutiric and isovaleric acid levels increases induced by the high-fat high-fructose feeding were reduced by resveratrol administration. TNFα protein expression remained unchanged, whereas high-fat high-fructose diet induced claudin expression decrease was partially or totally prevented by pterostilbene and resveratrol intake, respectively.

Conclusions: The high-fat high-fructose feeding produced hepatic damage in rats that is associated with changes in gut microbiota and intestinal integrity. Pterostilbene promoted Akkermansia municiphila abundance which could account for some hepatoprotective effects, whereas that of resveratrol may be linked to changes in SCFA levels and intestinal integrity preservation.

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Associations between genetic variants and sugar intake in a Swedish population-based cohort study

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Background: Hereditary mechanisms are partially responsible for individual differences in sensitivity and preference of sweet taste. Several potential genetic variants associated with sweet preference and sugar intake have been identified using genome wide association scans (GWAS), including single nucleotide-polymorphisms (SNPs) in the *FGF21* and *FTO* genes. Additionally, associations for several SNPs (including a SNP in close proximity to the *FGF1* gene) were recently identified, although they did not reach GWAS significance. The aim of this study was to examine the associations between these SNPs and sugar intake in a middle-aged Swedish population.

Methods: The study population consisted of 22,794 individuals from the Malmö Diet and Cancer Study (45-74 y, 61.4% women). The associations between 10 genetic variants (two SNPs within *FGF21* gene and eight top hits from a previous GWAS study on sugar intake and sugar sensitivity, including a variant within the *FTO* gene) and intakes of total sugar, sugars with sweet taste (i.e monosaccharides and sucrose), and added sugar were studied.

Results: After adjusting for multiple testing, significant associations were observed between three SNPs, all in close relation to the *FGF21* gene (rs838145, rs838133, and rs8103840), and intake of added sugar, total sugar, and sugars with sweet taste ($P<5x10^{-3}$). No associations were found between the rs11642841 within the *FTO* gene in our main analyses (P=0.07), but associations were found among participants with BMI ≥25 ($P= 4.96x10^{-3}$). None of the remaining SNPs investigated could be replicated.

Conclusions: The findings of our study indicate that three SNPs in close relation to the *FGF21* gene are associated with increased intake of sugar in different forms in this population.

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Current knowledge and conceivable interests in nutritional genomics among nutritionists and university-level nutrition students in Mexico: A cross-sectional study

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Background: Technological advancements in genomics are permitting a better understanding about the relationship between genomics and nutrition, thus allowing the prescription of personalized nutritional advice to improve people's health. In the last years, the supply and demand of nutrigenomics services have increased, making access to genomic tests less complicated and more affordable. Therefore, health professionals must have the necessary background to offer genome-based individualized nutrition - with nutritionists being qualified experts to carry out this task. Nevertheless, the current knowledge and interests in nutritional genomics among nutritionists and nutrition students in Mexico have not been deeply evaluated. The aim of this study was to assess the knowledge and interests in nutritional genomics among nutritionists and university-level nutrition students in Mexico.

Methods: A cross- sectional study was conducted through the application of an online open survey. This approach consisted of 56 previously validated questions given to nutritionists and university-level nutrition students in different regions of Mexico. Participants were recruited through the social network Facebook, enrolling 543 participants in order to identify socio-demographic data, academic preparation information, self-reported knowledge, objective knowledge, and interest in the main topics related to nutritional genomics.

Results: The objective knowledge evaluation showed that 69.3% of participants had low or very low knowledge in nutritional genomics, while 73.5% of self-reported participants stated insufficient knowledge. However, about 87.8% of participants showed interest in the subject. The students showed greater interest (90% of students and 86% of nutritionists showed high interest) and less objective knowledge (72% of students and 67.4% of nutritionists had low or very low knowledge). Only 49.9% of respondents had taken nutritional genomics-based courses during their professional formation, and 24.6% had taken update education courses related to this topic.

Conclusions: Our results suggest that most nutritionists are still not properly trained to engage in nutrigenetic and nutrigenomic practices, while the interest of university-level nutrition students and graduated nutritionists in nutritional genomics is high. This information highlights the importance of nutritional genomics in the college curricula, as well as in the development of nutritional genomics-based training education courses.

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Sweet cherry consumption affects metabolic parameters and gene expression depending on the origin and the photoperiod in which it is ingested

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Background: The growing environmental conditions of fruits and vegetables provide a characteristic phytochemical signature, mainly given by polyphenols, which would serve as a signal of metabolic adaptation for the heterotrophs that consume them. Moreover, it is known that biological rhythms have an impact on the bioactivity of these compounds. Therefore, the consumption of fruits from different origins, as well as their intake in different seasons, could have differential effects on health. Thus, the objective of this work was to evaluate the metabolic effect of the consumption of cherries from different geographic origins (Spain and Chile) and in different photoperiods.

Methods: 72 Fisher 344 rats were acclimatized for 4 weeks to different photoperiods. To simulate seasonal differences, they were divided into 3 groups: short (L6), standard (L12) or long (L18), with 6, 12, and 18 hours of light, respectively. In turn, the animals were divided into 3 groups (n = 8) according to supplementation with local cherry (LC), non-local cherry (nLC) or vehicle (VH). Serum parameters and genetic expression of liver enzymes were evaluated.

Results: The photoperiod affected the concentration of triglycerides, plasma NEFAs and gene expression of hepatic enzymes of lipid metabolism (acc1, cpt1, srebp-1c, fas1). Glucose and HDL-c concentration varied between treatments, while insulin and HOMA index were affected by the interaction of photoperiod and treatment. There were no differences neither in the levels of total cholesterol and LDL-c nor in the expression of enzymes Had, Fatp5, cd36.

Conclusions: Cherry consumption was associated with metabolic benefits. Specifically, the concentration of serum triglycerides and hepatic lipogenic enzymes were affected both by the geographical origin of the fruit and by the photoperiod of consumption, possibly due to the different content of bioactive compounds given by the polyphenolic signature of each cultivar.

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Δ5 and Δ6 Desaturase Activities in Young Canadian Adults are Influenced by *FADS1* Genotype but not Dietary Zinc

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Background: Past evidence suggests that dietary zinc intake influences Δ5 and Δ6 fatty acid desaturase enzyme (D5D and D6D) activities. Given that the worldwide prevalence of zinc deficiency is ~17%, this suggests that nearly 1 in 5 individuals may have impaired long-chain polyunsaturated fatty acid (LC PUFA) synthesis. We therefore investigated if Δ5 and Δ6 desaturase activities were influenced by dietary zinc intake in a population of young Canadian adults. We also examined if *FADS1* genotype affected any relationships between zinc intake and desaturase activities.

Methods: We analyzed zinc intake data (food records), % plasma fatty acids (gas chromatography) and the *FADS1* rs174547 polymorphism in a subset of young men and women (n=749) from the Toronto Nutrigenomics and Health Study who were not using zinc-containing supplements. Product-to-precursor fatty acid ratios were used to estimate desaturase enzyme activities (D5D = AA:DGLA; D6D = GLA:LA). Individuals were classified as either zinc deficient or adequate based on sex-specific RDA values (8mg/d women, 11mg/d men), as well as by their rs174547 genotype (TT vs. TC and CC), and data was analyzed by 1-way and 2-way ANOVA.

Results: Fatty acid levels and estimated D5D/D6D activities did not differ between zinc deficient and zinc adequate men or women. Interestingly, the recently proposed biomarker of zinc intake, DGLA:LA, was not different between zinc deficient and adequate individuals. *FADS1* genotype was significantly associated with estimated desaturase activities in men and women ($P<0.0001$), but not zinc status. Specifically, estimated D5D and D6D activities were higher in individuals with the TT genotype compared to TC+CC genotypes irrespective of dietary zinc intake status, except for D5D in zinc deficient women which did not differ between genotypes ($p=0.1$).

Conclusion: The current findings suggest that *FADS1* genotype, but not dietary zinc intake, affects estimated desaturase activity in young adults.

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The association of Lifestyle Score and genetic polymorphisms in a Greek NAFLD case-control study

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Background: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide with many complex processes involved in its development and manifestation. Previous research has studied the distinct effects of both genetic and lifestyle factors in NAFLD, but little is known regarding the synergistic action. Therefore, the present study used data from the Hellenic NAFLD study (129 cases and 210 controls), in order to assess the potential link between a constructed Lifestyle Score (LS) including various lifestyle behaviours, and previously identified single nucleotide polymorphisms (SNPs) associated with NAFLD disease risk.

Methods: LS consisted of 4 variables: the Mediterranean diet score (included nine dietary components: non-refined cereals, potatoes, fruits, vegetables, legumes, fish, red meat & products, poultry and full fat dairy products) (≤ median cut off of 20), Body Mass Index (BMI) (≥ 24.99 kg/m^2), physical activity level (PAL) (≤ median cut off of 1.370) and smoking status (current or non smoker); each being given binary scores of 1 or 2. Higher values of LS indicate unhealthy behaviors. Fifty SNPs were examined for their association with NAFLD, using binary logistic regressions adjusted for age, gender, and LS.

Results: LS was associated with higher prevalence of NAFLD in both the unadjusted model [OR: 1.97, p: 8.38e-08] and the model adjusted for age and gender [OR: 2.20, p: 1.01e-08]. After adjusting for age, gender, and LS, significant associations were found between the YIPF1 rs11206226 (A) [OR:2.22, p: 0.0375], the PNPLA3 rs2896019 (C) [OR: 1.57, p: 0.0381] and NAFLD risk. Also, an inverse association was detected between the OTX2P1-PCSK5 rs12344488 (A) [OR: 0.28, p: 0.00693] and NAFLD.

Conclusions: Higher LS was linked to a higher prevalence of NAFLD, indicating that adopting a healthy lifestyle may be advantageous to liver health. The YIPF1 rs11206226 and the PNPLA3 rs2896019 were also associated with NAFLD risk.

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R230C polymorphism of ABCA1 and its relationship with adipose tissue dysfunctional and atherogenic lipid profile in Mexican women

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Background and Aim: Cardiovascular diseases (CVD) are the primary cause of morbidity and mortality in Mexico and are related with adipose tissue dysfunction (ATD) and atherogenic lipid profile (ALP). Since CVD are associated with the presence of genetic variants, the aim of this study was to analyze the association between R230C variant (rs9282541) of the *ABCA1* gene with ATD and ALP phenotypes.

Methods: Participants were 242 healthy women aged 18-50-years old residents of Monterrey, Nuevo Leon with prior signed informed consent who underwent measurements of body composition, as well as biochemical and DNA extraction analyzes and genotyping by qPCR. ATD phenotype was determined by visceral adiposity index (VAI) and atherogenic lipid profile by NCEP-ATPIII criteria. To test association of the R230C variant with the presence of the phenotypes, we carried out different non-parametric statistical tests using SPSS Statistics 25.

Results: About 23.5% of the total population studied had ATD and 2.47% ALP. The minor allele frequency (MAF) of R230C in the ATD group was A (0.05); interestingly, 100% of the participants on ALP group had ancestral G allele. In the healthy group (without ATD) lower values of total cholesterol (TC) were observed (p=0.048) on participants with GA/AA dominant inheritance model. Moreover, within the ALP group participants with GA/AA on dominant inheritance model showed lower values of total body weight (p=0.042), gynoid fat (p= 0.039), glucose (p=0.039) and TC (p=0.043). There were no associations between R230C variant and phenotypes, which suggests that individuals with GA/AA on dominant inheritance model, had lower values of TC without ATD and lower values of TBW, GF, glucose and TC on the ALP group.

Conclusions: Current findings suggest that ATD and ALP are independent of the presence of R230C variant, but additional studies of R230C variant should be carried to understand its role in the development of CVD.

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Influence of ACE INDEL polymorphism and overweight on biochemical and blood pressure markers in young adults

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Background: The ACE gene insertion and/or deletion polymorphism is a single nucleotide polymorphism that is related to cardiovascular disease risk factors such as hypertension and dyslipidemia. The aim of the study was to investigate the influence of this polymorphism and overweight on biochemical markers and on systolic (SBP) and diastolic (DBP) blood pressure in healthy young adults.

Methods: This is a cross-sectional study with individuals aged 19 to 30 years, carried out in the city of Ouro Preto (MG) in the first half of 2021. Blood collection was performed for biochemical evaluation (total cholesterol and fractions, triglycerides and fasting blood glucose), anthropometric assessment (weight, height and body mass index (BMI)) and blood pressure measurement. Genotyping was performed using the polymerase chain reaction technique. The subjects were categorized regarding to overweight according to the BMI classification and a new categorization of these associated with genotypes was carried out (presence of at least 1 risk allele - D), being DD + ID with overweight (Dwith), DD + ID without overweight (Dwithout), II with overweight (Iwith) and II without overweight (Iwithout). ANOVA and Kruskal Wallis tests were performed, followed by Tukey and Dunn post hoc, according to the normality of the variables.

Results: We evaluated 86 subjects with a mean age of 26 years (±2,54 years old), being 20% homozygous for insertion (II), 29.4% homozygous for deletion (DD) and 50.6% heterozygous (ID). The Dwith group has higher levels of DBP and total cholesterol, compared to Dwithout, and higher levels of triglycerides compared to Dwithout and Iwithout.

Conclusions: It was observed that carriers of at least 1 D allele and overweight have less favorable results in terms of serum levels of total cholesterol, triglycerides, HDL and DBP values.

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Activation of thermogenesis and mitochondrial function by phytochemicals to relieve the metabolic stress and inflammation associated to high fat diet-induced obesity

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Background: Obesity is the epidemic of the 21st century, being associated to metabolic stress, insulin resistance (IR), and dysfunctional adipocytes, which recruit macrophages promoting chronic inflammation. Therefore, urgent therapeutic options are needed, not only by mean of pharmacotherapy but also nutritional-based strategies including diet and nutraceuticals interventions to reverse these alterations. Herein we evaluate the potential of 20 natural extracts (EFSA approved) in the modulation of key targets of lipid and glucose metabolism, inflammation, and mitochondrial function. Of them, 2 extracts were selected to evaluate their potential benefits in a preclinical model of high-fat diet (HFD) induced obesity.

Methods: 20 natural extracts are evaluated in the genetic modulation of genes implicated in energy expenditure, lipid metabolism, and mitochondrial function. Then, the functional relevance of 4 of them is evaluated in the modulation of cell bioenergetics and lipid accumulation in SGBS and HSSM differentiated cell lines. Finally, 2 of them are selected to conduct a preclinical model of obesity after a HFD + extract treatment for 3 months to study their effect on body weight (BW), IR, and molecular effect.

Results: The treatments reported an improvement in adipocyte and muscle mitochondrial function in vitro, significantly increasing oxidative phosphorylation and thermogenic uncoupling. In addition, 3 of them reduced the expression of inflammatory markers such as interleukin 6. Importantly, the 2 extracts analyzed in the preclinical model were able to reduce the metabolic stress associated with HFD induced obesity by distinct mechanisms. Extract A reduced BW and inflammation, while extract B reduced IR and increased body temperature in mice exposed to cold. In addition, both activated browning and improved mitochondrial function in white adipose tissue.

Conclusions: The findings from the current study suggest that these natural extracts could be used as an effective nutrigenomic tool to reduce the metabolic stress associated with obesity.

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CYP1A2 and ADORA2A genotypes and acute effects of caffeine on resistance exercise and jumping performance

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Background: Caffeine is one of the most widely used pre-workout supplements around the world. Yet, large inter-individual variation in response to caffeine is observed. The aim of this study was to evaluate the effect of acute caffeine supplementation on muscular strength, power and endurance and to assess whether response to supplementation depends on *CYP1A2* (rs762551) and *ADORA2A* (rs5751876) gene polymorphisms.

Methods: The study was designed in a randomized double-blinded crossover manner. 27 resistance trained males participated in the study and on two separate occasions ingested either 5 mg/kg caffeine or placebo 60 min before a battery of exercise tests. Saliva samples for caffeine and paraxanthine concentrations were collected pre-ingestion, 60 min post ingestion and post-exercise (~120 min after ingestion). Caffeine and paraxanthine concentrations were measured using high- performance liquid chromatography. DNA was isolated from saliva samples and tested for the rs5751876 and rs762551 single nucleotide polymorphisms in the *ADORA2A* and *CYP1A2* genes.

Results: Fast metabolizers (*CYP1A2* AA homozygotes) had significantly higher paraxanthine concentrations 60 min post-ingestion than slow metabolizers (*CYP1A2* C-allele carriers). Caffeine improved performance, irrespective of genotypes, in jumping velocity and bench press average power, max power and mean velocity in sets 2 and 3. The difference between caffeine and placebo (ΔCAF-PL) was improved in fast metabolizers compared to slow metabolizers in isometric mid-thigh pull force, bench press total repetitions and quality repetitions in set 2. ΔCAF-PL for max mean velocity in set 2, max power in set 1 and total repetitions set 3 was significantly lower for *ADORA2A* TT compared to C-allele carriers.

Conclusions: Caffeine improves lower body jumping power and velocity and bench press performance, irrespective of genotypes. *CYP1A2* AA homozygotes may benefit more from caffeine intake than C-allele carriers. *ADORA2A* TT genotype may be ergolytic in response to caffeine in some performance outcomes, but that interpretation is limited due to very low sample size.

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Choline content in the diet modulates expression of genes related to endogenous choline synthesis and accumulation of lipids in the rat liver

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Background: Numerous studies have revealed that isoflavones may protect against fatty liver. A potential mechanism for this effect may be that soy isoflavones affect the expression of the *Pemt* gene responsible for endogenous choline synthesis, as choline is involved in lipid export from the liver. The aim of our study was thus to test the effect of choline and soy isoflavone content in the diet on the expression of genes related to endogenous choline synthesis and lipid accumulation in the liver.

Methods: Eighty-eight-week old male Wistar rats were divided into eight groups. Four of these consumed the standard AIN93 diet with the addition of the soy isoflavones genistein, daidzein, or soy isoflavone isolate (CD, CD-Gen, CD-Dai, CDD-Iso, respectively). The remaining four groups consumed a modified AIN-93M without choline but with the same additives. The relative expression levels of four selected genes (*Pemt, Fasn, Ppar* γ, and *Srebp1c,* which are involved in lipid synthesis and beta oxidation) was determined in liver samples obtained at the end of this experiment.

Results: The level of *Pemt* gene expression was lower in the groups consuming the diets with the normal choline level than in the groups consuming the diets without choline. The expression level of the *Fasn*, *Pparγ*, and *Srebp1c* genes were higher in the CDD-ISO group than in the CD-ISO.

Conclusions: The Choline content in the diet can modify expression of the *Pemt*, *Fasn*, *Ppar* γ, and *Srebp1c*.

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In vitro Effects of –(-) epicatechin on the transcriptome of Human Umbilical Venous Endothelial Cells (HUVEC) exposed to lipopolysaccharide as Inflammatory Stimulus

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Background: Polyphenols have been extensively studied due to their effects on cardiovascular health. These effects are mediated through complex molecular mechanisms that regulate gene expression involved in inflammatory response, nitric oxide (NO) metabolism and antioxidant activity. The aim of the study was to assess the effect of - (-) epicatechin (EC) on the transcriptome after a pro- inflammatory stimulus with lipopolysaccharide (LPS) in cultured HUVEC cells.

Methods: HUVEC primary cultures were exposed to physiologically achievable concentrations (0.01 μm) of EC during 2 h, followed by stimulation with 1 μg/dL of lipopolysaccharide (LPS) for 2h. Vehicle (DMSO) was used as control. MTT analysis was conducted to assess cytotoxicity. Transcriptome was analyzed using RNAseq. Contrasts included the comparison of EC treatment vs control, LPS vs control, EC+LPS vs control, EC+LPS vs LPS and EC+LPS vs EC. Selected genes for each contrast had a log fold change of 2 and adjusted $p< 0.005$. Pathway analysis was conducted in Metacore. A group of transcripts were measured with qRT-PCR for validation of findings (IL 6, IL-8, P50 NFkB subfraction, E-selectin, SOD2 and eNOS).

Results: Treatments with EC modulated the expression of 383 genes as compared with control. These genes participate in binding and catalytic activities. LPS induced the expression of 853 genes that belong to inflammation- related pathways. The addition of EC before exposure to LPS significantly reduced the expression of 367 genes. Differentially expressed genes belong to the anti-inflammatory IL-10 and angiogenic pathways, among other. The qPCR analysis confirmed that the EC pre-treatment decreased the expression of IL-8, IL-6, E-selectin, and SOD2. No effect of EC was observed on the P50 NFkB and eNOS expression.

Conclusions: EC at the used experimental conditions attenuated the pro-inflammatory effect of LPS in HUVEC cells. This effect may contribute to the protective effects of this polyphenol to endothelial cells.

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Precision Nutrition in Medicine (pNIM): A training program for physicians in clinical practice

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Background: Many medical interventions are less effective when key nutritional aspects are not addressed. Hospital malnutrition is associated with increased readmission rates after many types of surgery, and antihypertensive treatment often fails without correction of nutritional imbalances. Implementation of best nutrition practices in medical care is complicated by inconsistent responses to many nutritional interventions. Often, for nutrition interventions one size does not fit all patients. Health care providers will be more effective when they can anticipate which particular dietary pattern is most likely to achieve the intended outcome for a given patient. To help physicians create effective nutrition prescriptions for their individual patients, we developed a program that teaches how to implement precision nutrition in medical practice.

Methods: We produced a training program with recorded lectures, study materials, instructor-led case reviews, peer-to-peer exercises, and knowledge assessments. We built exercises for groups of three to practice the efficient integration of genetic information into nutrition guidance efforts when there are evidence-supported reasons to do so.

Results: Learners in each group take turns assuming the roles of physician, patient, and observer. The physician receives relevant patient information and the assigned task. The patient gets background details for answering physician questions. The observer gets a clinical skills checklist to rate the physician's performance. After completion of each case there is a brief discussion of the shared experience and then the roles are switched. After finishing all cases, the groups come back for more case discussions with the instructor.

Conclusions: Eight instructor-led sessions during several weeks cover a rich range of knowledge items, clinical skill sets and practical strategies for using precision nutrition guidance in medical practice. Learners get continuous feedback and remedial assignments based on observer ratings and case-based quizzes. The program typically requires about 50 hours of fully engaged study for successful completion.