Abstract book

2024

NASO Scientific Spring meeting

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Abstracts

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Boon MR[1,2], Mohseni M[1,2], Welling MS[1,2], Lambermon P[1,2], van der Valk ES[1,2], van Rossum EFC[1,2].

The SWEET study: prolonged effects of sweeteners and sweetness enhancers consumption on the human gut microbiome and other safety outcomes.
Pang MD[1], Bastings JJAJ[1], Maurer-Sost M[2], Umanets A[2,3], Kjølbæk L[4], Martínez JA[5,6], Manios Y[7,8], Navas-Carretero S[5,9], Reppas K[7], Lam T[10], Moshoyiannis H[11], del Álamo M[12], Feskens EJM[13], Harrold JA[14], Halford JCG[14,15], Adam TCM[16], Goossens GH[1], Raben A[4,17], and Blaak EE[1]

Do obesity-associated MRAP2 variants modulate MC4R signaling?
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Unravelling the relationship between head circumference and MC4R deficiency in children: a case-control study
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van Deuren T.[1], van Kalkeren C.[1], Venema K.[2], Blaak E.E.[1]

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Van der Velden, MAM[1], Van Tilborg-Den Boeft, M[1], Buis, S[1], Jansen, W[2,3], Bindels, PJE[1], Van Middelkoop, M[1].

Development of a neighborhood obesogenic built environment characteristics index for the Netherlands
Lam TM[1], Wagtendonk AJ[1], den Braver NR[1], Karssenberg D[2], Vaartjes I[3], Timmermans EJ[3], Beulens JWJ[1,3], Lakerveld J[1].

Long-term preservation of lean mass and loss of fat mass after intensive lifestyle intervention in older adults with obesity and type 2 diabetes
Memelink RG[1,2,3], Hijlkema A[1], Valentin B[1], Streppel MT[1], Pasman WJ[4], Wopereis S[4], De Vogel-Van den Bosch J[5], Tieland T[6], Schoufour JD[1], Bautmans I[3,7,8,9], Weijs PJM[1,2,10]

Mitochondrial uncoupling with BAM15 prevents weight gain, lowers plasma cholesterol and attenuates atherosclerosis development in APOE*3-Leiden.CETP mice.
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Bensi, EAB[1a], Sizoo, D[1b], Ong, L[2c], Witteveen, J[1d], van Dijk, P[3e], Wilhelm, E[2f], van Beek, A[3g], Emous, M[1h]

Why we struggle to make progress in obesity prevention, and how we might overcome policy inertia. Lessons from the complexity and political sciences.

Luc L. Hagenaars*[1,2], Laura A. Schmidt[2], Joost Oude Groeniger[3,4], Marleen P.M. Bekker[5], Fleur ter Ellen[3], Evelyne de Leeuw[6], Frank J. van Lenthe[3,7], Karen M. Oude Hengel[3,8], Karien Stronks[1]

FIRST CONSULTATION FOR KNEE COMPLAINTS IN PEOPLE WITH OVERWEIGHT: INDICATIVE OF EARLY-STAGE KNEE OSTEOARTHRITIS?

Nuria EJ Jansen1, Dieuwke Schiphof1, Jos Runhaar1, Edwin HG Oei2, Sita MA Bierma-Zeinstra1, Marienke van Middelkoop1

The impact of the combination of inulin and exercise on MASLD amelioration and gut-liver crosstalk.

Kovynev A[1,2], Charchuta MM[1,2], Begtasevic A[1,2], Ducarmon QR[3,4], Rensen PCN[1,2] and Schönke M[1,2]

Exploring differences in glucocorticoid receptor sensitivity between obesity vs. lean individuals through a novel in vitro bioassay

Lengton R[1,2], Iyer AM[1,2], Mohseni M[1,2], Dik WA[3], Visser JA[1], Boon MR[1,2], van Rossum EFC[1,2]

Interorgan cross-talk between muscle and liver in individuals with overweight/obesity.

Meshkat K[1], Meex R.C.R[1], Blaak EE [1]

Low muscle mass and sarcopenic obesity and their relation to comorbidities in a population with class II/III obesity: a study on the diagnostic criteria of the EASO/ESPEN consensus guidelines.

Sizoo D[1,2], de Heide LJM[1], van Zutphen T[2], Emous M[1], van Beek AP[3]

Partial replacement of maltodextrin with galactose in a post-weaning diet improves body composition and energy metabolism in early life in a mouse model.

Sun P[1], Rakhshandehroo M[2], Bekkenkamp-Grovenstein M[1], Schipper L[2], Harvey L[2], Keijer J[1], and van Schothorst EM[1]*

A leptin-melanocortin pathway-based polygenic risk score contributes to common obesity

Vlaming P[1]. Sedaghati-Khayat B[1], van Meurs JBJ[1], van Rooij JGJ[1], Visser JA[1]

Early childhood dietary trajectories and the effect on later childhood weight status in Dutch children

Yang J[1], Navis G[2], Mars M[3], Corpeleijn E[1]

11-Oxygenated androgens inhibit brown adipose tissue differentiation and function

Yuan Y, Steenbergen J, Goulart A, Sabaté Pérez A, Visser JA

The following abstracts were selected based on ranking as either oral presentation, or as pitch . They appear in order of presentation.

Title:	**Resting energy expenditure and muscle strength are preserved after weight loss induced by liraglutide or naltrexone/bupropion in patients with obesity**
Authors:	Boon MR[1,2], Mohseni M[1,2], Welling MS[1,2], Lambermon P[1,2], van der Valk ES[1,2], van Rossum EFC[1,2].
Affiliations	[1]Department of Internal Medicine, Division of Endocrinology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands. [2]Obesity Center CGG, Division of Endocrinology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands.
Abstract: (max 300 words)	**Introduction:** Weight loss in obesity is associated with a reduction in resting energy expenditure (REE), which predisposes to weight regain. In recent years, several pharmacological agents, such as the GLP-1 analogue liraglutide or naltrexone/bupropion, have been approved for treatment of obesity. The aim of the current study was to unravel the effects of these agents on REE and body composition in patients with obesity. **Methods:** We evaluated 72 adults with obesity who were treated with liraglutide 3.0 mg (n=47, mean BMI 42.4 ± 8.3 kg/m^2) or naltrexone/bupropion 32/360 mg (n=25, mean BMI 38.9 ± 6.2 kg/m^2). At baseline and at 12 weeks after reaching maximum or highest tolerated dose, anthropometrics, body composition using bio-electrical impedance, and maximal grip strength (kg) were measured. Predicted REE was calculated using the Harris & Benedict equation and REE was measured using indirect calorimetry. **Results:** After Liraglutide body weight and BMI were significantly reduced (-6.8 ± 4.5% and -2.8 ± 1.9 kg/m^2, respectively), with a reduction in fat mass and fat-free mass after 12 weeks (all p<0.001). Hand grip strength remained unaltered compared to baseline. After Naltrexone/bupropion also significant weight loss (-4.8 ± 4.0%) and decrease in BMI (-1.9 ± 1.6 kg/m^2) was observed, with a reduction in fat mass (all p<0.001), but not fat-free mass, and unaltered hand grip strength. While predicted REE decreased after both treatment regimens (both p<0.01), measured REE remained equal after both treatments, independent of changes in fat-free and fat mass. For liraglutide, this resulted in an increased ratio between measured and predicted REE (P=0.033). **Conclusion:** In adults with obesity, after 12 weeks of liraglutide or naltrexone/bupropion treatment significant weight loss was observed. Interestingly, REE was preserved, independent of changes in fat-free mass, and muscle strength. 1. **Conflicts of interest:** None disclosed. 2. **Funding:** EFCvR is supported by a Vidi grant from the Netherlands Organization of Scientific Research NWO (grant number: 91716453) and the Elisabeth Foundation.

Title:	**The SWEET study: prolonged effects of sweeteners and sweetness enhancers consumption on the human gut microbiome and other safety outcomes.**
Authors:	Pang MD[1], Bastings JJAJ[1], Maurer-Sost M[2], Umanets A[2,3], Kjølbæk L[4], Martínez JA[5,6], Manios Y[7,8], Navas-Carretero S[5,9], Reppas K[7], Lam T[10], Moshoyiannis H[11], del Álamo M[12], Feskens EJM[13], Harrold JA[14], Halford JCG[14,15], Adam TCM[16], Goossens GH[1], Raben A[4,17], and Blaak EE[1]
Affiliations	[1]Department of Human Biology, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University Medical Centre+, Maastricht, The Netherlands. [2]Centre for Healthy Eating & Food Innovation (HEFI), Maastricht University-Campus Venlo, Venlo, The Netherlands. [3]Chair Group Youth Food and Health, Faculty of Science and Engineering, Maastricht University-Campus Venlo, Venlo, the Netherlands. [4]Department of Nutrition, Exercise and Sports, University of Copenhagen, Frederiksberg C, Denmark. [5]Center for Nutrition Research, University of Navarra, Pamplona, Navarra, Spain. [6]IMDEA Food Institute, Madrid, Spain. [7]Department of Nutrition and Dietetics, Harokopio University of Athens, Athens, Greece. [8]Institute of Agri-food and Life Sciences, Hellenic Mediterranean University Research Centre, Heraklion, Greece. [9]CIBER Fisiopatología Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III, Madrid, Spain. [10]NetUnion sarl, Lausanne, Switzerland. [11]International Reference Laboratory Services, Bioiatriki SA, Athens, Greece. [12]European Clinical Research Infrastructure Network, Paris, France. [13]Division of Human Nutrition and Health, Wageningen University, Wageningen, Netherlands. [14]Department of Psychology, Institute of Population Health, University of Liverpool, Liverpool, UK. [15]School of Psychology, University of Leeds, Leeds, UK. [16]Department of Nutrition and Movement Sciences, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, The Netherlands. [17]Department for Clinical and Translational Research, Copenhagen University Hospital – Steno Diabetes Center Copenhagen, Herlev, Denmark.
Abstract: (max 300 words)	**Introduction:** The long-term effects of sweeteners and sweetness enhancers (S&SEs) on gut microbial composition remain elusive, with few prior studies showing inconsistent results. In the multi-centre SWEET project, we investigated the effect of S&SEs as a replacement of sugar on gut microbial composition and safety outcomes in adults with overweight or obesity in four European countries (The Netherlands, Greece, Spain, and Denmark). **Methods:** In this randomized controlled trial (RCT), 341 participants (age 18-65 yrs and BMI≥25 kg/m^2) underwent a 2-month weight loss (WL) phase, followed by a 10-month weight-maintenance (WM) phase during which they adhered to a healthy ad libitum diet (<10 energy-% added sugar) either with or without S&SEs products (S&SEs group vs. sugar group). Fecal samples were analyzed by 16S rRNA sequencing from a subgroup of 137 completers at baseline (month (M)0), after WL (M2), M6 and M12 to determine gut microbial composition. Liver fat content was assessed in a subgroup of 29 participants using proton-magnetic resonance spectroscopy at M0, M2 and M12. Adverse events and changes in medication use were monitored throughout the study. **Results:** The S&SEs group demonstrated lower weight regain (change M12-M2: 3.4±0.7 vs. 5.6±0.8 kg, *P*=0.011) and lower energy intake compared to the sugar group. Distinct shifts in microbial communities were observed between groups, with a higher abundance of taxa related to short-chain fatty acid (SCFA) and methane production in the S&SE group compared to the sugar group (q≤0.05). The S&SEs group reported more gastrointestinal symptoms, including abdominal pain, loose stools, and excess gas than the sugar group. Liver fat and concomitant medication use were not different between groups. **Conclusion:** The S&SE group altered gut microbial composition towards a higher abundance of SCFA and methane-producing species compared to the sugar group during a 10-month weight maintenance phase, which was accompanied by more gastrointestinal symptoms. **1. Conflict of interest:** AR has received honoraria from Nestlé, Unilever, and the International Sweeteners Association. JCGH and JH have received project funds from the American Beverage Association. **2. Funding:** The work was supported by the Horizon 2020 project “SWEET” (http://www.sweetproject.eu, 2018–2023, Grant Agreement ID 774293) according to Program H2020-EU.3.2.2.2.

Title:	**Do obesity-associated MRAP2 variants modulate MC4R signaling?**
Authors:	Rodríguez Rondón A.V.[1,2], Prins K.[1,2], Volker F.[1,2], Welling M.S.[1,2,3], de Groot C.[1,3], van Haelst M.M.[4], van den Akker E.L.T.[1,3], van Rossum E.F.C.[1,2], Delhanty P.J.D.[1,2], Visser J.A.[1,2]
Affiliations	*[1]Obesity Center CGG, Erasmus MC, Rotterdam, the Netherlands; [2]Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands; [3]Department of Pediatrics, Division of Endocrinology, Erasmus MC-Sophia Children's Hospital, University Medical Center, Rotterdam, the Netherlands; [4]Department of Human Genetics, Amsterdam University Medical Center, Amsterdam, the Netherlands*
Abstract: (max 300 words)	**Introduction:** Melanocortin 2 receptor accessory protein 2 (MRAP2) is a membrane-bound protein expressed on hypothalamic neurons that modulate the function of appetite-regulating receptors, including melanocortin-4 receptor (MC4R). While *MRAP2* variants are associated with obesity, the mechanism by which MRAP2 modulates MC4R is still unclear. The aim of this study is to investigate the functional impact of wildtype (WT) MRAP2 and MRAP2 variants on MC4R signaling. **Methods:** Four *MRAP2* variants (S80F, R125C, P167A and Q174X) in patients with obesity were identified by obesity gene panel analysis. The functional effects of these variants were analyzed by co-transfecting HEK293 cells with expression plasmids encoding WT or variant *MRAP2* and WT *MC4R*. Endpoints analyses include MC4R cell surface expression, and α-MSH-induced cAMP response, β-arrestin-2 recruitment, and internalization. **Results:** WT MRAP2 significantly decreased basal MC4R cell surface expression by 68.1±4.3% ($p<0.001$). MC4R internalization is induced by α-MSH in the absence of MRAP2. However, in the presence of WT MRAP2, MC4R cell surface expression was increased by 89.4±6.9% upon α-MSH stimulation ($p<0.001$). Furthermore, in the cells expressing MC4R with WT MRAP2, the maximal α-MSH-induced cAMP and β-arrestin-2 recruitment responses were increased by 29.8±5.2% and 81.3±4.2% respectively ($p<0.001$), compared with those lacking MRAP2. Analyzing the MRAP2 variants for these endpoints showed that they did not significantly differ from the WT MRAP2 in modulating MC4R signaling. **Conclusion:** Our results indicate that WT MRAP2 enhances the cAMP response by increasing MC4R cell membrane expression upon α-MSH stimulation. The MRAP2 variants assessed in this study behaved as WT MRAP2 in α-MSH-induced MC4R signaling, suggesting that these may be benign variants. However, since MRAP2 can modulate multiple receptors, we cannot rule out that these *MRAP2* variants affect other appetite-regulating receptors and thereby influence body weight regulation via other pathways. **1. Conflict of interest: None** **2. Funding: None**

Title:	**Unravelling the relationship between head circumference and MC4R deficiency in children: a case-control study**
Authors:	Van der Walle EPL[1], de Groot CJ[1], Welling MS[1], Kleinendorst L[2 3], van Haelst MM[2 3], van den Akker ELT[1]
Affiliations	*[1]Obesity Center CGG, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands; [2]Department of Clinical Genetics, Amsterdam University Medical Center, the Netherlands; [3]Emma Center for Personalized Medicine, Amsterdam University Medical Center, the Netherlands*
Abstract: (max 300 words)	**Introduction:** MC4R deficiency is the most common cause of monogenetic obesity. Other forms of genetic obesity, like 16p11.2 deletion syndrome, are associated with increased head circumference (HC). Little is known about HC in pediatric patients with MC4R deficiency. **Methods:** This study included patients (0-19 years) with a homozygous or heterozygous pathogenic or likely pathogenic (class 4 or 5) MC4R variant. Patients were matched 1:1 to a control with obesity and no genetic diagnosis. HC, height, weight and body-mass index (BMI) were measured and SD-scores were calculated. HC SDS of the patients was compared to the reference population (Dutch National Growth charts) and control group using one-sample t-tests, unpaired t-tests and linear regression analysis. **Results:** MC4R patients (n=61, mean age 10.19 years, 51% female) had a significantly larger mean HC of 1.68 SDS (1.12 SD) compared to the reference population (p-value <0.001) and controls (HC 1.28 SDS, 95% CI -0.78 to -0.03, p-value 0.034). 41% of the patients were classified as macrocephalic (HC ≥2 SDS), compared to 26% of the controls (p-value 0.086). MC4R patients had a significantly larger mean height compared to controls (1.00 SDS and 0.45 SDS respectively, p-value 0.024), but similar mean BMI (4.00 SDS and 3.74 SDS respectively, p-value 0.149). Patients with homozygous (n=3) variants tended to have a larger HC compared to heterozygous (n=58) variants (2.84 SDS and 1.62 SDS respectively, 95% CI -2.53 to 0.08, p-value 0.066). An association was found between HC SDS and height SDS (R^2 0.22, p-value <0.001), but not between HC SDS and BMI SDS (R^2 0.03, p-value 0.22). **Conclusion:** Children with MC4R deficiency present with a larger HC compared to the reference population and controls. HC measurement should be included in the diagnostic work-up of children suspected for genetic obesity, since it can be a clue for MC4R deficiency. **1. Conflict of interest:** no disclosures **2. Funding:** no funding

Title:	**Examining the effects of galactose on energy metabolism and Small Intestine gene expression: the Fatty acid oxidation paradox.**
Authors:	Fos-Codoner FS., Keijer J, van Schothorst EM.
Affiliations	*Human and Animal Physiology, Wageningen University, Wageningen, The Netherlands*
Abstract: (max 300 words)	**Introduction:** Replacement of part of the dietary glucose by galactose, reflecting extended lactose intake during the early post-weaning phase, has substantial beneficial effects on short- and long-term physiological parameters such as body weight, body composition, insulin sensitivity, and hepatic health in mice. Since intestines are the first organ in contact with the nutrients, we hypothesized that this organ might be the primary target organ underlying the observed effects. **Methods:** We investigated the effects of a 3-weeks galactose vs. glucose intervention in young weaned mice (n=13) on whole-body metabolism (indirect calorimetry) , and tissue transcriptomics (proximal small intestine RNAseq, liver qPCR), and intestinal permeability (non-digestible sugar test). **Results:** Feeding dietary galactose versus glucose showed lower 24-hour respiratory exchange ratio (RER) ($p<0.009$), reflecting increased fatty acid oxidation (FAO) and reduced carbohydrate oxidation at the whole-body level, without differences in energy expenditure. Surprisingly, the small intestine displayed a consistently lower expression of transcripts involved in FAO, which contrasts with the systemic effects of galactose on substrate utilization at whole-body level. Interestingly, the liver, the canonical organ involved in galactose metabolism, lacked effects in lipid catabolism, leaving the door open for other organs to be responsible for the lower RER levels. Additionally, all intestinal cytoplasmic NADPH-producing, also showed lower expression. This was accompanied by a lower expression of the main antioxidant enzymes, suggesting a possible reduction in oxidative stress. At the functional level, no differences in intestinal permeability were observed, indicative of good intestinal functionality in both groups. **Conclusion:** Replacing part of the dietary glucose by galactose during postweaning mimicking prolonged lactose exposure has profound effects on energy metabolism at both systemic and tissue-specific level. These changes in substrate utilization and cellular energy pathways might be the key to understanding the positive effects of galactose consumption on metabolic health. **1. Conflict of interest:** the authors declare no conflict of interest **2. Funding:** TKI-top sector Agri and Food 4163007300

Title:	**The associations of sugar intake and its food sources in early childhood with children's body weight**
Authors:	Zou J[1], Soedamah-Muthu SS[2 3], Corpeleijn E[1]
Affiliations	*[1]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands;* *[2]Center of Research on Psychological Disorders and Somatic Diseases (CORPS), Department of Medical and Clinical Psychology, Tilburg University, Tilburg, The Netherlands;* *[3]Institute for Food, Nutrition and Health, University of Reading, Berkshire, UK.*
Abstract: (max 300 words)	**Introduction:** Excessive sugar intake is considered as a significant risk factor for childhood overweight and obesity, but less is known about that in very young children. Moreover, children are advised to consume less sugar-rich foods, but are encouraged to eat more fruits and unsweetened dairy products which contain abundant intrinsic sugars. It may imply that in addition to the amount of sugar consumed, its food source is also crucial. **Methods:** In the GECKO Drenthe birth cohort, dietary intake was derived from the food frequency questionnaire which was filled in by parents when children were 3 years old. Both the sum of daily sugar intake and daily sugar intake in 13 different food groups were calculated. BMI Z-score, the change in BMI Z-score between 3 and 10/11 years, and weight status (overweight/obesity) were derived from the height and weight measured by trained nurses. Weight status was defined by International Obesity Task Force 2012 criteria. **Results:** 936 children were included in the analytical sample. The mean daily sugar intake was 112±34 grams (mean±SD), which related to 32.2 energy percent (en%) of total energy intake (1390±293 kcal). At 10/11 years of age, 149 children had overweight/obesity. Total sugar intake was not related to the observed outcomes. A higher intake of sugar from sugary snacks was related to a higher BMI Z-score (β=0.015(0.006,0.025)) and higher risk of developing overweight/obesity (OR=1.024(1.001,1.048)). While a higher daily sugar intake from fruits was related to a lower BMI Z-score (β =-0.009(-0.017, -0.002)) and less weight gain (β=-0.011(-0.017,-0.004)) but not weight status at 10/11 years. Also a higher sugar intake from dairy products was related to a lower odds for overweight/obesity (OR=0.983(0.968,0.999)). **Conclusion:** Overall, the type of sugar-containing product consumed seems more important than sugar intake itself in relation to the development of overweight in early childhood. **1. Conflict of interest:** None Disclosed. **2. Funding:** JZ is supported by a joint fellowship from the China Scholarship Council and University of Groningen (no. 202307720064). The GECKO Drenthe birth cohort was funded by an unrestricted grant of Hutchison Whampoa Ltd, Hong Kong and supported by the University of Groningen, Well Baby Clinic Foundation Icare, Noordlease, Paediatric Association Of The Netherlands, Youth Preventive Health Care Drenthe, the European Union's Horizon 2020 research and innovation programme (LIFECYCLE, grant agreement No 733206, 2016), and Foundation Vrienden Beatrix Kinderziekenhuis, Groningen, The Netherlands.

Title:	**Long-term Hair Cortisone and Long-term Psychological Stress are Associated with Long-term Hedonic Eating Tendencies in Patients with Obesity**
Authors:	Kuckuck S[1,2,3], van der Valk ES[1,2], Lengton R[1,2], Kavousi M[3], Boon MR[1,2], van den Berg SAA[1,4] & van Rossum EFC [1,2]
Affiliations	[1] Department of Internal Medicine, Division of Endocrinology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. [2] Obesity Center CGG, Erasmus MC, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands. [3] Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. [4] Department of Clinical Chemistry and Department of Internal Medicine, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands.
Abstract: (max 300 words)	**Introduction:** Long-term biological stress, reflected in hair cortisol and cortisone levels, predicts future weight gain and metabolic deterioration. This is likely at least partially mediated by glucocorticoid-induced increases in hedonic overeating. Yet, the relationship between long-term biological stress and long-term hedonic eating tendencies remains to be elucidated. **Methods:** We included N=108 adults with lifestyle-induced obesity (91 women, median body mass index=38.4 kg/m2) to investigate cross-sectional associations between long-term hair glucocorticoid levels (cortisol and cortisone measured in the first 3 cm of scalp hair using liquid chromatography-mass spectrometry) and self-reported long-term hedonic eating tendencies (emotional and external eating, 'Dutch Eating Behavior Questionnaire', and trait food craving, 'Food Craving Questionnaire-Trait'). Additionally, we investigated the role of long-term psychological stress (Perceived Stress Scale-14 score) in determining the relation of hair glucocorticoid levels and hedonic eating tendencies. **Results:** Higher hair cortisone levels were associated with more food cravings after adjustment for sex and age, and also after additional adjustment for psychological stress (all $p<0.05$). Psychological stress correlated positively with food craving and hedonic eating ($p<0.05$), and, in trend, with external eating ($p<0.1$). Dummy-coding of stress groups (high vs. low psychological stress in addition to high vs. low biological stress) suggest potential additive effects of different stress measures, with food cravings and emotional eating being highest in the group with high-psychological-stress combined with high-hair-cortisone ($p<0.05$). **Conclusion:** The positive association between hair cortisone levels and food cravings suggests that patients with obesity may be more susceptible to long-term hedonic eating tendencies if they have higher long-term hair cortisone levels or long-term psychological stress. Long-term psychological and biological stress relate to hedonic eating tendencies in different ways with potentially adverse additive effects on clinical features of obesity.

Title:	**Muscle and liver insulin resistance have distinct plasma protein profiles; a proteomics analysis using the Diogenes cohort**
Authors:	Kemper EJ (1), Blaak EE (1), Adriaens M (2), Meex RCR (1)
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Abstract: (max 300 words)	**Introduction:** Insulin resistance (IR) is a hallmark of type 2 diabetes and can manifest in a tissue-specific manner in adipose tissue, skeletal muscle or liver. Previous research from our lab has shown that different tissue-specific IR phenotypes display different metabolic, plasma lipidome and adipose tissue transcriptome profiles. Hence, this study aimed to determine if muscle and liver IR phenotypes also have distinct plasma protein profiles. **Methods:** We used SomaLogic plasma proteomic profiles from participants with overweight or obesity that previously participated in the Diet, Obesity and Genes (DiOGenes) study (n = 594). A linear regression analysis in R was applied to identify the proteins associated with muscle or liver IR (p-value < 0.05). Subsequently, we used these differentially expressed proteins in a pathway enrichment analysis, utilizing the KEGG and WikiPathways databases. **Results:** In total, we identified 1129 proteins in plasma. Of these, 148 were associated with muscle IR and 69 were associated with liver IR, of which only 12 proteins overlapped between these phenotypes. Pathway enrichment analysis showed 133 enriched pathways for muscle IR, while liver IR was associated with 21 enriched pathways. Muscle IR is associated with a number of significantly enriched pathways, including focal adhesion and PI3K-Akt signaling pathways. Furthermore, muscle IR is characterized by a clear inflammatory profile, including pathways related to proinflammation and profibrotic mediators, chemokine signaling, the complement system, and IL-6 signaling. In liver IR, however, only a limited number of pathways were found to be enriched, which were mainly related to the complement system. **Conclusion:** This study shows that muscle and liver IR have a clear distinct plasma protein expression profile. Muscle IR was in particular associated with several inflammatory pathways, while liver IR was found to be associated with fewer pathways, mostly related to the complement system. **1. Conflict of interest:** None **2. Funding:** The project is supported by an Aspasia grant (NWO) awarded to RCR Meex. The Diogenes project is funded by a grant under the Food Quality and Safety Priority of the Sixth Framework Programme for Research and Technological Development of the European Union (2005-2009), through the Directorate-General for Research of the European Commission.

Title:	**Identifying a Complex Carbohydrate Mixture in Context of a High-Protein Diet That Is Able to Steer Microbial Fermentation to Improve Metabolic Health: The DISTAL Study**
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Abstract: (max 300 words)	**Background**: Short-chain fatty acids (SCFAs) are proposed to largely contribute to improvements in metabolic health associated with dietary fiber (saccharolytic) fermentation. Nevertheless, towards the distal colon, fermentable carbohydrates become depleted, and gut bacteria switches towards proteolytic fermentation. This yields a diversity of metabolites including branched-chain fatty acids (BCFAs), often considered detrimental to metabolic health. More pronounced metabolic health effects may be observed by switching from proteolytic to saccharolytic fermentation in the distal colon. Hence, we aimed to identify a complex carbohydrate mixture capable of inducing such a microbial substrate switch. **Methods**: The TIM-2 model was used to mimic colonic fermentation *in vitro*. TIM-2 was inoculated with standardized pooled microbiota from individuals with overweight/obesity and disturbed glucose homeostasis. After an overnight adaptation period, pre-digested proteins were added and thereafter, either separately or in combination, potato fiber, native inulin from chicory, pectin from sugar beet, or no fibers (control) were administered. Samples of the lumen and dialysate were taken at various time points and assessed for proximal (0–8 h) and distal (8–24 h) SCFA and BCFA levels. **Results**: Of all the tested combinations, combining potato fiber and pectin resulted in the highest distal SCFA production (26.3 vs 6.4 mmol) and SCFA:BCFA ratio (13.3 vs 2.2) compared to the protein control. **Conclusion**: The combination of potato fiber and pectin was best able to increase distal SCFA production in pooled microbiota of individuals with overweight/obese. To assess whether these results translate to improvements in metabolic health, we are currently conducting a 12-week double-blind placebo-controlled randomized study. 44 individuals who are overweight/obese and have a disturbed glucose homeostasis are randomized to supplementation with a potato fiber/pectin mixture or placebo (maltodextrin) while consuming an eucaloric high protein diet (25 E% protein). The primary outcome will be the change in peripheral insulin sensitivity. **1. Conflict of interest:** The authors declare no conflict of interest. **2. Funding:** This study was funded by NWO the Netherlands Organization of Scientific Research (the ENW-public private partnership fund) and the Carbohydrate Competence Center (CCC). Industrial partners within this partnership included: Avebe, Sensus, Nuscience, and Agrifirm.

Title:	**Development of a tool for general practitioners to signal, address and refer children with overweight and obesity: a Delphi study.**
Authors:	Van der Velden, MAM[1], Van Tilborg-Den Boeft, M[1], Buis, S[1], Jansen, W[2,3], Bindels, PJE[1], Van Middelkoop, M[1].
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Abstract: (max 300 words)	**Introduction:** There is a noticeable increase in the number of children with overweight and obesity worldwide. General practitioners (GPs) recognize that they could play a role in signalling, addressing and referring these children but still experience different barriers and are in need of supportive tools. The aim of this study was to establish consensus among Dutch GPs about the content of a supportive tool to signal, address and refer children with overweight and obesity in general practice. **Methods:** A Delphi study was conducted. A concept of a supportive tool was constructed based on literature, the Dutch Obesity guideline for GPs and insights from focus group interviews with GPs, practice nurses and parents of children with and without overweight and obesity. GPs were identified as experts and invited to participate. Through a two-round consensus process, experts evaluated statements on the components of the tool in terms of content and usability. All statements were rated on a 5-point Likert scale and consensus was set at ≥70% of respondents agreeing with the statements. Components and subcomponents were iteratively refined, added or removed until consensus was reached. **Results:** In round one, 31 of 33 experts who consented to participate completed the survey (93.9% response rate), followed by 29 of the 31 experts in round two (93.5% response rate). The experts agreed that the supportive tool for GPs must consist of a child's specialized BMI-calculator; examples to initiate and to continue weight-related conversations with parents and children; a map including available interventions and referral options; background information and resources about health risks of overweight and obesity during childhood. **Conclusion:** The supportive tool for GPs to signal, discuss and refer children with overweight and obesity was successfully determined through a consensus-driven process with GPs. Further validation and assessment are required through a feasibility and implementation study. **1. Conflict of interest:** No. **2. Funding:** Stichting Theia.

Title:	**Development of a neighborhood obesogenic built environment characteristics index for the Netherlands**
Authors:	Lam TM[1], Wagtendonk AJ[1], den Braver NR[1], Karssenberg D[2], Vaartjes I[3], Timmermans EJ[3], Beulens JWJ[1,3], Lakerveld J[1].
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Abstract: (max 300 words)	Objective: Environmental factors that drive obesity are often studied individually, whereas obesogenic environments are likely to consist of multiple factors from food and physical activity (PA) environments. This study aimed to compose and describe a comprehensive, theory-based, expert-informed index to quantify obesogenicity for all neighbourhoods in the Netherlands. Methods: The Obesogenic Built Environment CharacterisTics (OBCT) index consists of 17 components. The index was calculated as an average of componential scores across both food and PA environments and was scaled from 0 to 100. The index was visualized and summarized with sensitivity analysis for weighting methods. We are currently developing an interactive dashboard to showcase the index to interested stakeholders and researchers. Results: The OBCT index for all 12,821 neighbourhoods was right-skewed, with a median of 44.6 (IQR = 10.1). Obesogenicity was lower in more urbanized neighbourhoods except for the extremely urbanized neighbourhoods (>2500 addresses/km^2), where obesogenicity was highest. The overall OBCT index score was moderately correlated with the food environment (Spearman $\rho = 0.55$, $p < 0.05$) and with the PA environment ($\rho = 0.38$, $p < 0.05$). Hierarchical weighting increased index correlations with the PA environment but decreased correlations with the food environment. The pitch includes a small demo of the interactive dashboard. Conclusions: The novel OBCT index and its comprehensive environmental scores are potentially useful tools to quantify obesogenicity of neighbourhoods. **1. Conflict of interest:** Lam TM, den Braver NR and Timmermans EJ received funding from the Netherlands Organization for Scientific Research (NWO) under the Exposome-NL consortium. Lakerveld J & Wagtendonk AJ received funding from Netherlands Organization for Health Research and Development (ZonMw) to collect and process environmental data used in this study. The other authors declared no conflict of interest. **2. Funding:** The Geoscience and hEalth Cohort COnsortium (GECCO) was financially supported by the Netherlands Organization for Scientific Research (NWO), the Netherlands Organization for Health Research and Development (ZonMw), and Amsterdam University Medical Centers.

Title:	**Long-term preservation of lean mass and loss of fat mass after intensive lifestyle intervention in older adults with obesity and type 2 diabetes**
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Abstract: (max 300 words)	**Introduction:** Lifestyle interventions combining caloric restriction with resistance exercise have the potential to preserve lean mass during weight loss. Additional protein intake can further improve lean mass.[1] However, it is unclear whether these effects are sustained over time after completion of the intervention. This study aimed to evaluate the long-term effect of a 3-month lifestyle intervention, with or without supplementation of a protein drink, to preserve lean mass in older adults with obesity and type 2 diabetes at 6 months post-intervention. **Methods:** Adults (n=123) aged ≥55 years with obesity and type 2 diabetes were enrolled in a 3-month intensive lifestyle intervention with hypocaloric diet, resistance exercise and high-intensity interval training. Participants were randomised to either receive a leucine and vitamin D-enriched protein drink or isocaloric control drink. The 3-month intervention was followed by a 6-months phase without intervention. At baseline, 3 and 9 months (follow-up), body composition, physical functioning, and quality of life were assessed. Statistical analysis was performed using a linear mixed model. **Results:** Body weight loss was largely sustained at follow-up (-2.1 kg compared to baseline, 95% CI -2.8 to -1.5), and comprised a sustained loss of fat mass (-2.6 kg, 95% CI -3.2 to -2.0) with simultaneous gain of lean mass (+0.7 kg, 95% CI +0.2 to +1.2). Improvements in 400m walk speed (+0.05 m/s, 95% CI +0.03 to +0.08) and chair stand test time (-1.5 s, 95% CI -1.9 to -1.1) were sustained at follow-up. There were no differences in these changes between the protein supplementation group and the control group at follow-up. **Conclusion:** Older adults with obesity and type 2 diabetes preserved their lean mass, their loss of fat mass, and their improvements in physical functioning, 6 months after completion of a 3-month intensive lifestyle intervention. Protein supplementation during the intervention did not affect outcomes at follow-up. **1. Conflict of interest:** Author JdV-vdB is an employee of Danone Nutricia Research. Authors WP and SW are employees of the Netherlands Organisation for Applied Scientific Research (TNO), which is a not-for-profit research organization collaborating in several public-private partnerships or business-to-business research projects that receive funding from companies. All other authors declare no conflicts of interest related to this research. **2. Funding:** Research relating to this abstract was funded by Topsector Agri & Food, the Netherlands; the Dutch Research Council (NWO); Danone Nutricia Research.

Title:	**Mitochondrial uncoupling with BAM15 prevents weight gain, lowers plasma cholesterol and attenuates atherosclerosis development in APOE*3-Leiden.CETP mice**
Authors:	Jamie I. van der Vaart[1,2], Christopher L. Axelrod[3], Patrick C.N. Rensen[1,2], Robin van Eenige[1,2], Sander Kooijman[1,2]
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Abstract: (max 300 words)	**Introduction:** The global obesity pandemic has led to a high prevalence of obesity-associated diseases including atherosclerotic cardiovascular disease (asCVD). A century ago, 2,4-dinitrophenol (DNP) was developed as an effective weight loss strategy, as it increases energy expenditure through mitochondrial uncoupling. However, DNP was rapidly banned due to adverse effects, hyperthermia and even mortality. Recently, BAM15 was identified as a mitochondria-targeted small molecule protonophore, with wider tolerability *in vitro*, and potency to reverse diet-induced obesity in mice (Axelrod, EMBO Mol Med 2020). Here, we investigated the effects of BAM15 on body weight gain, dyslipidemia and asCVD in APOE*3-Leiden.CETP mice, a well-established model for human-like cardiometabolic diseases. **Methods:** Female APOE*3-Leiden.CETP mice were fed a Western-type diet (containing 16% fat, 0.15% cholesterol) with or without 0.1% w/w BAM15. Body weight, body composition, and 4h-fasted plasma total cholesterol (TC) and triglyceride (TG) levels were monitored. Very-low-density lipoprotein (VLDL) production and VLDL catabolism were assessed, and atherosclerotic lesion size was quantified within the aortic valve area. **Results:** In all experiments, BAM15 attenuated body weight gain (-1.9 g) by preventing fat accumulation (-40%). BAM15 consistently lowered plasma TC levels (approx. -50%), as explained by a lowered VLDL production (-52%), without affecting plasma TG levels. BAM15 increased VLDL-TG-derived fatty acid uptake by subcutaneous and gonadal white adipose tissue (+36% and +85%, respectively), in line with increased uncoupled respiration and heat production. Likely as a compensatory effect, BAM15 decreased fatty acid uptake by subcapsular and interscapular brown adipose tissue (-46% and -36%, respectively). Collectively, BAM15 decreased atherosclerotic lesion size (-34%) and improved lesion stability. **Conclusion:** BAM15 attenuates atherosclerosis development in APOE*3-Leiden.CETP mice by lowering circulating cholesterol, without the typical adverse side effects of DNP. We therefore anticipate that BAM15 is a promising therapeutic tool to combat obesity and asCVD in humans in the future.

The following abstracts were selected to be included in the abstractbook based on their ranking.
They appear in alphabetical order of first author.

Title:	**Continuous glucose monitoring in patients with symptoms of hypoglycemia after bariatric surgery: a retrospective study.**
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Abstract: (max 300 words)	**Introduction:** Hypoglycemia or late dumping syndrome is a known long-term complication after bariatric surgery. Yet, no consensus exists regarding the best diagnostic approach and treatment for these patients. Since 2019, in our bariatric center, patients complaining of hypoglycemic symptoms after bariatric surgery underwent continuous glucose monitoring (CGM) for 7 days whilst concomitantly logging complaints. This study retrospectively analyses this data with the aim to better understand patient complaints in relation to glucose variations. **Methods:** All patients who received GCM due to hypoglycemic complaints after bariatric surgery were included. Demographic data was extracted from the electronic patient files, as well as details regarding surgical history, comorbidities, weight loss and treatment of post-bariatric surgery hypoglycemia. **Results:** Of the 247 cases analysed, 89,5% were female with a mean age of 47 (± 13) years and a mean BMI of 30,1 (± 6,4) at the time of CGM. Glucose values below 3.0 mmol/L were present in 59,5% of these patients, with a median of 1 event [0 – 3] and 5 minutes [0 – 35] spent below this value over 7 days. Within this group 85,8 % received only lifestyle advice and 17,8% of patients received additional pharmacological treatment, resulting in 55,1% improvement. 29% of all patients did not have hypoglycemia during the CGM and yet still experienced postprandial pseudo-hypoglycemic symptoms. The occurrence of values <3.0 mmol/L was significantly associated with the absence pre-operative diabetes type 2 (P=0,04). **Conclusion:** CGM analysis of post-bariatric patients with hypoglycemic symptoms gives relevant insights regarding the occurrence of hypoglycemia. The presence of postprandial pseudo-hypoglycemic symptoms, without measured hypoglycemia, suggests that the development of symptoms has a different aetiology in this patient group. Further analysis of our data on eating behaviour, glucose variability and slope declines shall give valuable information herein. **1. Conflict of interest: none** **2. Funding: none**

Title:	Why we struggle to make progress in obesity prevention, and how we might overcome policy inertia. Lessons from the complexity and political sciences.
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Abstract: (max 300 words)	**Introduction**: Despite evidence for the effectiveness of policies that target obesogenic environments, their adoption remains deficient. We explore why this is the case and how this can be overcome. **Methods**: Drawing on the Punctuated Equilibrium Theory from the political sciences and a literature review of studies about obesity and nutrition policy processes, we developed three systems maps to explain the current policy inertia in addressing obesogenic environments, leverage points for breaking free from inertia, and the system elements required to sustain a focus on obesogenic environments. We analyzed the system maps with Stock-and-Flow analysis to identify self-reinforcing feedback loops that amplify change in a vicious or virtuous cycle, and balancing feedback loops that block or reverse change in the system. **Results**: We found numerous self-reinforcing feedback loops that buttress the assumption that obesity is an individual problem, strengthening the biomedical and commercial weight-loss sectors' claim to 'ownership' over solutions. I.e., improvements in therapies for individuals with obesity reinforces policymakers' reluctance to target obesogenic environments. Random events that focus attention on obesity (e.g., celebrities dismissing soda) could disrupt this cycle, when actors from outside the medical and weight-loss sector (e.g., anti-weight stigma activists) successfully reframe obesity as a societal problem, which requires robust and politically relevant engagement with affected communities prior to such events taking place. Sustained prioritization of policies targeting obesogenic environments requires shared problem ownership of affected communities and non-health government sectors, by emphasizing co-benefits of policies that target obesogenic environments (e.g., ultra-processed food taxation for raising revenue) and solutions that are meaningful for affected communities. **Conclusion**: Prioritization of policies targeting obesogenic environments requires timely advocacy efforts to reframe obesity as a societal issue, and sustained engagement of affected communities and non-health government sectors in shared problem ownership. **1. Conflict of interest:** The authors do not have conflicts of interest from funding or affiliation-related activities. **2. Funding:** This study was funded by a research grant from the Netherlands Organization for Health Research and Development (ZonMw; project number 55.500.2033). LH is supported by a Harkness Fellowship in Healthcare Policy and Practice, funded by the Commonwealth Fund.

Title:	**FIRST CONSULTATION FOR KNEE COMPLAINTS IN PEOPLE WITH OVERWEIGHT: INDICATIVE OF EARLY-STAGE KNEE OSTEOARTHRITIS?**
Authors:	Nuria EJ Jansen1, Dieuwke Schiphof1, Jos Runhaar1, Edwin HG Oei2, Sita MA Bierma-Zeinstra1, Marienke van Middelkoop1
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Abstract: (max 300 words)	**Introduction:** Overweight is a known risk factor for knee osteoarthritis (KOA). Early-stage interventions, like weight loss, are crucial to reduce the disease burden and prevent long-term disability. However, early diagnosis poses a challenge, particularly because the disease trajectory of KOA in the early stages among individuals with overweight is not well understood. This study aimed to describe clinical and structural features of people with overweight within two years after their first consultation for knee symptoms, while exploring differences in the duration of knee complaints. **Methods:** This study used baseline data from a randomized trial assessing the effectiveness of a lifestyle intervention for people presenting with knee complaints and overweight in primary care. Baseline assessments included a questionnaire, clinical assessment, and MRI of the most symptomatic knee. Differences in OA features on MRI among groups with varying durations of knee complaints (<12, ≥12-<24, ≥24 months) were evaluated. **Results:** Participants (N=218, 65% female, mean age 59±7 years, mean BMI 31.9±4.5 kg/m²) had a median knee complaint duration of 14 months. 46% reported their symptoms as unacceptable. Besides KOA and overweight, participants, on average, presented with two other conditions. Structural MRI-defined KOA was observed in 71% of knees. No statistically significant differences were found in the clinical or structural features between the different durations of knee complaints. **Conclusion:** Within two years of their first consultation, more than two thirds of participants displayed structural KOA on MRI and nearly half reported unacceptable symptoms. No association was found between the duration of knee complaints and symptoms severity or structural KOA presence. The high prevalence of structural KOA, even among those with complaints for less than a year, might be explained by overweight accelerating structural KOA progression. These findings emphasize the importance of identifying early KOA diagnostic features beyond complaint duration, especially in individuals with overweight. **1. Conflict of interest:** The authors have declared no conflicts of interest. **2. Funding:** The work was supported by the Netherlands Organisation for Health Research and Development (ZonMW) (50-55515-98-004) and the Dutch Arthritis Society (ReumaNederland) (ZNW 20-501).

Title:	**The impact of the combination of inulin and exercise on MASLD amelioration and gut-liver crosstalk**
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Abstract: (max 300 words)	**Background and aims**: Lifestyle interventions are currently the only available therapies against the obesity comorbidity metabolic dysfunction-associated steatotic liver disease (MASLD). We demonstrated earlier that exercise training late in the active period of mice was associated with fat loss and the enrichment of fiber-digesting gut bacteria, so we now aimed to study the impact of the combination of late exercise training and a fiber-rich diet on the MASLD amelioration. **Methods**: Male APOE*3-Leiden.CETP mice were fed a high fat-high cholesterol diet with or without the addition of 10% inulin and exercise trained on a treadmill 5 days a week for 1 hour at ZT22 for 8 weeks, or remained sedentary. **Results**: Exercise training alone or in combination with fiber reduced fat mass gain. Only the combination of fiber and exercise training, however, also decreased plasma triglyceride and glucose levels compared to sedentary mice. Exercise training with and without fiber had a similar ameliorating effect on the MASLD score compared to sedentary controls (3.3±1.4 and 4.1±1.8 vs. 5.7±1.3, respectively). Both interventions remodeled the gut microbial composition. Exercise and fiber enriched fat-lowering *Anaerostipes hadrus*, while exercise training alone or in combination with fiber decreased the abundance of the MASLD-promoting *Alistipes* genus. Finally, exercise training increased the levels of short-chain fatty acids in the portal vein, with the combination of exercise and fiber leading to the highest levels which correlated with the lowest levels of plasma triglycerides. **Conclusion**: The combination of exercise training and dietary fiber decreases fat mass and restores glucose homeostasis, but does not have an additional positive effect on liver health compared to exercise training alone, despite the shift of the gut microbiota towards a healthier, short-chain fatty acids-producing profile. **1. Conflict of interest:** none **2. Funding:** Grant W223065-2-GSL by the Leiden University Fund and the Gratama Stichting to Schönke M.

Title:	**Exploring differences in glucocorticoid receptor sensitivity between obesity vs. lean individuals through a novel *in vitro* bioassay**
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Abstract: (max 300 words)	**Introduction:** Mounting evidence points to an association between increased glucocorticoid (GC) action and weight gain. The response to GCs is not only determined by GC serum concentrations, but also by differences in GC sensitivity at tissue level. The extent to which individual differences in GC sensitivity may influence development of obesity, or vice versa, is poorly understood. In this study we applied a glucocorticoid sensitivity bioassay to determine the relation between GC sensitivity and obesity. **Methods:** Peripheral blood mononuclear cells (PBMCs) were isolated from 23 patients with obesity (all female, average BMI=41 kg/m^2), and 8 lean individuals (4 females) and stimulated with phytohemagglutinin (PHA) and incubated with increasing dosages of dexamethasone (DEX; 0.33 up to 1000nM), for 4 hours. The half maximal effective concentration of DEX, mediating the transactivation (EC50) of the responsive genes GC-induced leucine zipper (GILZ) and FK506 binding protein 5 (FKBP5) and the transrepression (IC50) of the responsive genes interleukin (IL)-2 and IL-6 was used as a measure of GC sensitivity. **Results:** Reference ranges for GC sensitivity (mean ± 1SD) were calculated on the basis of EC50 for GILZ and FKBP5, and IC50 for IL-2 and IL-6 responses of the lean individuals (5.6±2.0nM, 5.9±2.6nM, 4.8±3.1nM and 5.7±1.9nM, respectively). In patients with obesity, the average IC50 of DEX-mediated transrepression of IL-6 (3.4±2.9nM) was borderline significantly lower from the average response in the lean individuals (p=0.05). There were no significant differences in the other GC-responsive genes between lean individuals and patients with obesity. **Conclusion:** This study suggests that patients with obesity are more sensitive to GC-mediated transrepression of IL-6, compared to lean individuals. Further analysis of the data is in progress to verify these results in a larger cohort and determine whether these differences are also related to differences in anthropometrics. 1. **Conflicts of interest:** All authors declare that they have no conflict of interest. 2. **Funding:** EFCvR is supported by a Vidi grant from the Netherlands Organization of Scientific Research NWO (grant number: 91716453). EFCvR is also funded by the Elisabeth Foundation.

Title:	**Interorgan cross-talk between muscle and liver in individuals with overweight/obesity**
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Abstract: (max 300 words)	**Introduction:** Adipose tissue (AT) dysfunction is frequently associated with the development of AT, liver and/or skeletal muscle insulin resistance (IR). Interestingly, it was recently reported that AT-IR and whole-body IR, as reflected by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), not always coincide. The aim of the present study is to investigate, in a well-defined group of individuals with overweight, the presence and proportion of individuals who are discordant for IR in their AT and their muscle (i.e. in whom the AT is resistant to insulin, while muscle is not, or vice versa), and characterize their clinical and metabolic features. **Methods:** Data of male and female individuals in the PERSON study (n=229) were analyzed. Based on the 50th percentile of the AT-IR index and muscle insulin sensitivity (IS) index (using the oral glucose tolerance test), participants were categorized into four groups. The groups include muscle-IS/AT-IS (n=66) as the reference group, discordant muscle-IS/AT-IR (n=48), discordant muscle-IR/AT-IS (n=49), and muscle-IR/AT-IR (n=66). **Results:** Of all participants, 42% were discordant for IR in AT and muscle. Furthermore, we found that AT-IR associated with a worsened systemic cardiometabolic profile, as reflected by higher FFA, fasting insulin, and triglycerides, independent of muscle-IR. In participants with muscle-IR/AT-IS, cardiometabolic risk parameters were not different compared to the reference group, but liver fat and hepatic IR were found to be increased. **Conclusion:** This study shows that individuals can develop muscle-IR independent of AT-IR, and can be muscle-IS despite the presence of AT-IR, challenging the traditional understanding of IR development. Importantly, individuals with muscle-IR in the presence of AT-IS showed no disturbances in systemic cardiometabolic profile but were characterised by elevated liver fat and liver-IR. These findings contribute to a deeper understanding of metabolic dysregulation in obesity and underscore the need for tailored interventions targeting specific tissue IR phenotypes. **1. Conflict of interest: None** **2. Funding:** This project is organized by and executed under the auspices of TiFN, a public-private partnership on precompetitive research in food and nutrition. Funding for this research was obtained from the industry partners DSM Nutritional Products, FrieslandCampina, Danone Nutricia Research, AMRA Medical AB, and the Top-sector Agri&Food.

Title:	**Low muscle mass and sarcopenic obesity and their relation to comorbidities in a population with class II/III obesity: a study on the diagnostic criteria of the EASO/ESPEN consensus guidelines.**
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Abstract: (max 300 words)	**Introduction:** In sarcopenic obesity (SO), sarcopenia (low muscle mass/function) coincides with obesity, leading to a distinct condition. SO has been associated with an increased risk of comorbidities such as type 2 diabetes and hypertension. Recently, a ESPEN/EASO consensus on SO has been published.1 This study aimed to assess the prevalence of low muscle mass and SO using these diagnostic criteria. **Methods:** This prospective cross-sectional study included participants with a BMI above 35 kg/m² and an age between 18 and 65 years. Study measurements included handgrip strength (HGS) and a dual-energy X-ray absorptiometry (DXA) scan to define sarcopenia and SO. The prevalence of SO is studied as well as differences in participants with or without low muscle mass, and with and without SO-related comorbidities. **Results:** The prevalence of SO was 0 – 1.2%, depending on cut-off levels for HGS. Using only DXA-derived estimates of SO, the prevalence of low muscle mass was 54.8%. Participants with low muscle mass were older (49 vs. 43 years), had a higher HbA1c (40.5 vs. 36 mmol/mol), a higher fat percentage (45 vs. 41%) and a lower hand grip strength (42 vs. 32 kg) compared to those with normal-to-high muscle mass. Participants with SO-related comorbidities were older (52 vs. 44 years), had a higher HbA1c (42 vs. 37 mmol/mol), larger waist circumference (127 vs. 119 cm), lower fat percentage (41 vs. 45%), higher estimated visceral adipose tissue (931 vs. 797 grams) and more sleep apnoea (29 vs. 5%). **Conclusion:** The diagnostic ESPEN/EASO criteria showed a very low prevalence of SO, while a low muscle mass, solely based on DXA, was highly prevalent in this population. Moreover, the presence or absence of SO-related comorbidities did not identify low muscle mass but rather visceral adiposity as the driving force in hypertension and/or diabetes in patients with class II/III obesity. **1. Conflict of interest: None disclosed** **2. Funding: No funding to report**

Title:	Partial replacement of maltodextrin with galactose in a post-weaning diet improves body composition and energy metabolism in early life in a mouse model.
Authors:	Sun P[1], Rakhshandehroo M[2], Bekkenkamp-Grovenstein M[1], Schipper L[2], Harvey L[2], Keijer J[1], and van Schothorst EM[1]*
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Abstract: (max 300 words)	**Introduction:** Early-life nutrition has long-lasting effects on metabolic health in later life. Maltodextrin has been widely used as a substitute for lactose in low lactose/lactose-free follow-on formulas. It is unclear whether partly replacing maltodextrin with galactose, the monosaccharide bound to glucose in lactose, in early life has beneficial effects on long-term metabolic health. **Methods:** Female and male C57BL/6JRccHsd mice were divided into three groups and fed different isocaloric diets; CON: 39 energy% (en%) maltodextrin and 8 en% glucose; GAL: 31 en% maltodextrin and 16 en% galactose; or lactose-mimic (LM): 15 en% maltodextrin, 16 en% galactose and 16 en% glucose, from postnatal day (PN)21 to PN42. From PN42, all mice were given the same high-fat diet (HFD) till PN105 before being sacrificed. In female mice, energy metabolism was assessed by indirect calorimetry from PN40 to PN42, and an oral glucose tolerance test was performed at PN83. **Results:** Body weight, fat mass, and lean mass were significantly lower in GAL and LM groups in both males and females at PN42 (all $p < 0.01$). Energy expenditure was significantly lower and respiratory exchange ratio indicated higher % fat oxidation in GAL and LM versus CON (all $p < 0.05$). Glucose tolerance in adulthood was not affected. At PN105, expression of hepatic insulin-like growth factor 1 (*Igf1)* appeared significantly lower in GAL and LM versus CON (both $p < 0.05$), and the serum IGF1 concentrations tended to be lower in GAL versus CON ($p = 0.07$) in females. **Conclusion:** In early life, body weight, body composition, and energy metabolism were significantly different in GAL and LM versus CON. After nine weeks of HFD, the differences in body weight and body composition were normalized, however, galactose substitution resulted in significantly lower levels of liver *Igf1* mRNA in female mice, suggesting a potential programming effect. The implications of this programming effect remain for further investigation. **1. Conflict of interest:** MR, LS, and LH are employees of Danone Nutricia Research B.V., Utrecht, The Netherlands. All authors declare no conflict of interest. **2. Funding:** Danone Nutricia Research and TKI- Agri & Food (project ID LWV20.100) contributed to the funding of this study. P Sun is funded by the China Scholarship Council (grant ID 202003250074).

Title:	**A leptin-melanocortin pathway-based polygenic risk score contributes to common obesity**
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Abstract: (max 300 words)	**Introduction:** Obesity is a major global health issue arising from a combination of environmental factors and genetic predisposition. Research highlights the significance of the leptin-melanocortin pathway in monogenic obesity; rare early-onset (age <5 years) obesity caused by a single variant. Genome-wide association studies (GWAS) suggest that the same genes play a role in common polygenic obesity. This study investigates the impact of the cumulative effect of variants within this pathway, in form of a polygenic risk score (PRS). We analysed how the PRS influences Body Mass Index (BMI), Waist Circumference (WC), and overall obesity prevalence in the general population. **Methods:** We used the population-based cohort from the Rotterdam Study (n=8081). BMI is measured in kg/m2, WC in cm and obesity is defined as BMI>30 with subclasses; class 1 (≥30BMI<35), class 2 (≥35BMI<40) and class 3 (BMI>40). From the summary statistics of the 2018 GIANT BMI GWAS, 16 out of 941 variants were mapped to 8 genes of the leptin-melanocortin pathway (LEPR, SH2B1, PCSK1, NPY, MC4R, GNB1, ADCY3, BDNF), which were used to calculate the weighted PRS (LMP-PRS). All models were adjusted for age and sex. **Results:** LMP-PRS was associated with BMI (β=0.22, P=2.4e-6), explaining 0.3% of the BMI variance compared to 3.9% by the full PRS, consisting of 941 variants. In addition, the LMP-PRS was significantly associated with WC (β=0.43, P=5.5e-4) and an increased risk of obesity (OR=1.14, P=2.5e-5). Stratification for the obesity subclasses showed that the LMP-PRS yielded the highest risk for OCIII (OCI: OR=1.12, P=1.4e-3: OCII: OR=1.21, P=1.5e-3; and OCIII: OR=1.51, P=6.4e-4). **Conclusion:** Our results suggest that the leptin-melanocortin pathway also plays a role in common obesity, explaining 7% of the total variance explained of BMI by genetic variants. Studies are ongoing to determine whether carriers of the LMP-PRS also have an increased risk of obesity-associated comorbidities. **1. Conflict of interest:** none **2. Funding:** none

Title:	**Early childhood dietary trajectories and the effect on later childhood weight status in Dutch children**
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Abstract: (max 300 words)	**Introduction:** This study assesses dietary trajectories of healthy and unhealthy food consumptions at preschool age, and their relationship to overweight/obesity at 10/11 years, and explores the role of siblings in these relations. **Methods:** Data of 2,523 Dutch children from the GECKO cohort were analyzed. Height, weight and waist circumference were measured by nurses. Dietary trajectories were identified with latent class analyses on food intake/preference reported by participants' parents through seven time-points questionnaires between ages 7 months and 3 years. Associations with weight status at 10/11 years were explored using Chi-square test (overweight/obesity) or One-way ANOVA (BMI Z-score and waist circumference). **Results:** Three dietary trajectories were identified: "Mainly white(n=48)," "Mainly brown(n=1568)," and "Mainly wholegrain(n=176)" for bread-type, and "(Relatively) Poor intake", "(Relatively) Moderate intake", and "(Relatively) High intake" for fruit, vegetable, sugar-sweetened beverages (SSB), "pizza, pancakes, and French fries" (PPP), savory snacks, and sweet snacks. Over time, consumption of healthy foods declined while unhealthy foods increased. Compared with "Poor intake", "Moderate intake" fruit trajectory was associated with higher BMI Z-score (+0.17, *P*=0.03), overweight/obesity risk (+5.3%, *P*=0.03), and increased waist circumference (+1.5cm, *P*=0.01). "Moderate intake" vegetable trajectory correlated with higher BMI Z-score (+0.20, *P*=0.04) compared to "High intake". "Moderate intake" savory snacks trajectory linked to higher BMI Z-score (+0.22, *P*=0.02) compared to "Poor intake". Siblings presence influenced early feeding practices, with stronger associations between fruit and vegetable trajectories observed in children with siblings at birth. A trend for "High intake" sweet snacks trajectory with higher BMI Z-score became significant in those with siblings. The association between "High intake" savory snacks trajectory with the highest BMI Z-score was strongest in those without siblings. **Conclusion:** Children's dietary trajectories show a decline in healthy and an increase in unhealthy food consumption. The trajectories of fruit, vegetable and savory snacks were related to future BMI and/or overweight. **1. Conflict of interest:** The authors declare to have no conflict of interest. **2. Funding:** The GECKO Drenthe birth cohort was funded by an unrestricted grant of Hutchison Whampoa Ltd, Hong Kong and supported by the University of Groningen, Well Baby Clinic Foundation Icare, Noordlease, Paediatric Association Of The Netherlands, Youth Preventive Health Care Drenthe, the European Union's Horizon 2020 research and innovation programme (LIFECYCLE, grant agreement No 733206, 2016), and Foundation Vrienden Beatrix Kinderziekenhuis, Groningen, The Netherlands.

Title:	11-Oxygenated androgens inhibit brown adipose tissue differentiation and function
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Abstract: (max 300 words)	**Introduction:** Reduced brown adipose tissue (BAT) activity is considered to contribute to obesity development. BAT activity is decreased in both women with PCOS and PCOS animal models, possibly due to androgen excess. In addition to ovarian androgens, women with PCOS also have elevated adrenal 11-oxygenated androgens. Here we aim to unravel whether 11-oxygenated androgens, also known as 11-keto-androgens, affect BAT metabolism. **Methods:** The mouse brown adipocyte cell line T37i was treated with increasing concentrations (0.1-10uM) of testosterone (T), dihydrotestosterone (DHT), 11-keto-testosterone (KT) or 11-keto-dihydrotestosterone (KDHT) during or after differentiation. Adipocyte differentiation was assessed by lipid accumulation and gene expression. In addition, female mice received a single injection of vehicle, DHT, KT or KDHT (0.1mg). BAT was collected 24 hours later for RNAseq analysis to identify differentially expressed genes (DEGs) and enriched pathways by Gene Set Enrichment Analysis (GSEA). **Results:** T, DHT, KT and KDHT treatment during differentiation dose-dependently reduced lipid droplet accumulation and inhibited mRNA expression of Ucp1, Prdm16 and Pgc1a by almost 2-fold (all $P<0.05$). Similar results were obtained in mature T37i cells. RNAseq analysis of DHT-exposed BAT identified 374 DEGs, of which 46 were downregulated and 328 were upregulated. KT and KDHT treatment resulted in only 100 and 166 DEGs respectively, with a 50% distribution in up- and downregulated genes. Intriguingly, of these DEGs, only 4 genes related to adipogenesis were shared between DHT, KT and KDHT treatment. DHT and KDHT treatment resulted in 49 shared DEGs, which were involved in inflammation. GSEA revealed downregulation of oxidative phosphorylation and fatty acid metabolism pathways upon DHT or KT treatment, while KDHT-induced DEGs were enriched in proliferation-related pathways. **Conclusion:** Our results demonstrate that 11-oxygenated androgens inhibit differentiation and function of brown adipocytes in vitro. The in vivo effect of 11-oxygenated androgens on BAT transcriptomics appeared to differ from DHT. **1. Conflict of interest: None** **2. Funding: None**