Abstract book

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Abstracts

Contents; first 10 abstracts are presented in order of presentation, remainder in alphabetical order of first author

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Title:	**A novel successful therapeutic option after a journey of treatment failures in a patient with heterozygous *melanocortin-4 receptor* deficiency**
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Abstract:	**Introduction:** As lifestyle interventions often fail in patients with genetic obesity disorders, additional anti-obesity pharmacotherapy may be needed. In this case report, we describe the therapeutic journey of a patient with early-onset obesity and hyperphagia due to heterozygous *melanocortin-4 receptor* deficiency. **Case presentation:** A 33-year-old woman came to the outpatient clinic with severe early-onset obesity and hyperphagia. After regular lifestyle treatment without sufficient effect, a gastric bypass was performed at the age of 26 years leading to -40 kg weight loss, but eventually in greater weight regain. At the age of 27 years, genetic testing revealed a heterozygous pathogenic variant in the *melanocortin-4 receptor* gene, explaining her phenotype. Glucagon-like peptide-1 receptor agonist (GLP-1 RA) treatment, liraglutide 3mg, was started which resulted in -7.3 kg of weight (-3.8%, baseline weight 193.5kg) and sustained hyperphagia after 5 months of treatment. GLP-1 RA treatment was therefore terminated and metformin treatment was started at a daily dosage of 1500mg, without any effects on weight or hyperphagia. Additionally, naltrexone-bupropion treatment was initiated. In 6 months of naltrexone-bupropion treatment, she lost -29.5 kg of weight (-15.8%, baseline weight 186.4kg), of which -27.9 kg (-7.3%) was fat mass. Most importantly, her subjectively reported hyperphagia and quality of life improved. **Discussion:** To our knowledge, this case report is the first to describe that naltrexone-bupropion has beneficial effects on weight, hyperphagia, and quality of life in a patient with genetic obesity. This extensive journey shows that in patients with genetic obesity various anti-obesity agents can be initiated and when ineffective terminated and substituted to other anti-obesity agents to find the most efficient treatment with regard to weight loss, hyperphagia, and quality of life. It also demonstrates that genetic screening should be considered in patients with early-onset obesity and hyperphagia prior to bariatric surgery. **No conflicts of interest** **No funding**

Title:	**Higher Glucocorticoid Receptor Sensitivity is Associated with Less Favorable Body Composition in Patients with Obesity**
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Abstract:	**Background:** Mounting evidence suggests an association between increased glucocorticoid (GC) action and weight gain. However, the response to GCs is also determined by individual differences in tissue-specific sensitivity. The extent to which differences in GC sensitivity may influence development of obesity, or vice versa, is poorly understood. Here we investigate the relation between GC sensitivity and obesity. **Methods:** Anthropometric data and peripheral blood mononuclear cells (PBMCs) were obtained at baseline (T0) and completion of 10 weeks of treatment (T1) from 16 patients with obesity (BMI≥30 kg/m2) undergoing a multidisciplinary combined lifestyle intervention. The half maximal effective concentration of dexamethasone (DEX), mediating the transactivation (EC50) or transrepression (IC50) of responsive genes GC-induced leucine zipper (GILZ) or interleukin (IL)-2 and IL-6 respectively in PBMCs, was used as a measure of GC sensitivity. The associations of EC50 and IC50 with anthropometrics were analysed using linear regressions. **Results:** A lower IC50 of DEX-mediated transrepression of IL-6 at inclusion was associated with higher dual-energy X-ray absorptiometry (DXA) fat mass (% of total body mass) (β=-0.52, 95%CI=-0.86 to -0.19) and lower DXA lean mass (% of total body mass) (β=0.52, 95%CI=0.18 to 0.86). Interestingly, the lower the IC50 for DEX-mediated transrepression of IL-6 at inclusion, the higher the weight loss in the first 10 weeks of lifestyle intervention (T1, β=0.32, 95%CI=0.04 to 0.60). Similar, but non-significant, associations were observed for IL-2. However, there were no associations between EC50 (GILZ) and any of the anthropometrics variables. **Conclusion:** Our results suggest that increased sensitivity to GC-mediated transrepression is associated with less beneficial body composition in patients with obesity. Although increased GC sensitivity at baseline was associated with weight loss at T1, further analysis of the data is in progress to determine whether this seeming contradiction is related to changes in GC sensitivity after lifestyle intervention. **1. Conflict 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 and BvdV are also funded by the Elisabeth Foundation.

Title:	**Imaging the GLP-1 receptor in human by using radiolabeled exendin-4 PET/CT**
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Abstract:	**Introduction:** The hormone glucagon-like peptide-1 (GLP-1) and its analogues are thought to have an important role in several pathways associated with obesity and related diseases. For example, GLP-1 and GLP-1 analogues induce satiety and results of bariatric surgery can partly be explained by increased GLP-1 levels. However, the localization of its receptor (GLP-1R) is not completely understood in humans and has never been studied *in vivo* yet. Radiolabelled exendin-4 has been developed to target beta cells via GLP-1R. In this study we aimed to determine the whole body distribution of this radiotracer in participants of ongoing studies. **Methods:** Sixty-two participants were included from ongoing studies into insulinoma, type 1 diabetes, obesity and type 2 diabetes (T2D) and post-bariatric outcomes. All participants received 75-100 MBq ^{68}Ga-exendin-4 (4-7 µg peptide) and underwent PET/CT one hour after administration. Abdominal imaging was performed in all participants (n=62), chest and head imaging in n= 57 and n=41, respectively. Radiotracer distribution was assessed visually and quantitatively. **Results:** Clear radiotracer uptake was observed in the pancreas and duodenum in all participants. The majority of participants showed uptake in salivary glands (95%) and pituitary gland (78%). Other structures in the brain did not show any uptake. Additionally, accumulation in cardiac tissue was observed in four participants (7%) and half of the female participants had uptake in glandular breast tissue (47%) and uterus and ovary (4 out of 8). **Conclusion:** These results demonstrated uptake of ^{68}Ga-exendin-4 in several extrapancreatic locations and most observations matched with previously described GLP-1R expression. Except from the pituitary, no uptake was observed in the brain, although GLP-1R expression is known in, for example, hypothalamic nuclei. To conclude, exendin-4-PET imaging is a promising tool to visualize GLP-1R expression *in vivo* and may be a valuable for studies into obesity and related diseases and treatment response. **1. Conflict of interest: none** **2. Funding:** *M.B. and M.G. received funding from ZonMw and Diabetes Fonds under project number 459001019 ('iPave').*

Title:	**Sociodemographic characteristics as an effect modifier of the causal impact of classical cardiovascular risk factors on atherogenic cardiovascular disease: a Mendelian Randomization study**
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Abstract:	**Introduction:** Low socioeconomic status (SES) increases both the risk factors as well as the risk of coronary artery disease (CAD). Here, we tested the hypothesis that SES is an effect modifier of the association between classical cardiovascular risk factors and CAD. We tested this hypothesis by performing stratified one-sample Mendelian Randomization (MR) studies based on SES in European-ancestry participants from the UK Biobank population (N=446,485). **Methods:** Individual-level genetic risk scores (GRS) were calculated for the risk factors body mass index (BMI), blood pressure, LDL cholesterol, and triglycerides based on independent lead variants (p-value<5e-8) that have been previously identified in genome-wide association studies in which the UK Biobank did not contribute. Participants in the UK biobank were stratified by Townsend deprivation index (TDI) scores as a measure of SES and logistic regression models were used to investigate the associations between the different GRS's and CAD. Effect modification was tested by introducing an interaction term between TDI and the GRS in the logistic regression model. **Results:** In line with previous literature, all studied risk factors were associated with increased risk for CAD. In addition, the risk for CAD per s.d. increase in genetically determined BMI was highest in the group with the highest TDI (OR: 1.081, 95% CI: 1.059 to 1.103 in low TDI; OR: 1.126, 95% CI: 1.106 to 1.145 in very high TDI. p-value for interaction = 0.0014). The risk for CAD per s.d. increase in genetically determined blood pressure, LDL cholesterol, and triglyceride were similar between the different SES groups (p-value for interaction = 0.37, 0.32, and 0.072, respectively). **Conclusion:** These findings indicate that CAD risk attributable to BMI is not homogenous and could be modified by SES, and furthermore suggest that tailor-made approaches for CAD risk reduction need to be considered. **1. Conflict of interest:** None. **2. Funding:** This work was supported by the VELUX Stiftung [grant number 1156] and the Dutch Heart Foundation [grant number 2019T103]

Title:	**Resting energy expenditure and body composition in children and adolescents with genetic, hypothalamic, medication-induced or multifactorial severe obesity**
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Abstract:	**Background:** Pediatric obesity is a multifactorial disease. In rare cases, it is caused by underlying medical disorders arising from disruptions in the hypothalamic leptin-melanocortin pathway, which regulates satiety and energy expenditure. **Aim:** To investigate and compare resting energy expenditure (REE) and body composition characteristics of children and adolescents with severe obesity with or without underlying medical causes. **Methods:** This study included pediatric patients who were evaluated for non-syndromic and syndromic genetic, hypothalamic, and medication-induced causes of obesity at our academic centre. REE was assessed by indirect calorimetry; body composition by air displacement plethysmography. The ratio between measured REE (mREE) and predicted REE, REE%, was calculated, as well as the ratio between mREE and fat-free-mass (FFM). **Results:** We included 292 patients, of which 218 (75%) had multifactorial obesity and 74 (25%) an underlying medical cause: non-syndromic genetic (n=29), syndromic genetic (n=28), hypothalamic (n=10), and medication-induced (n=7) obesity. Mean age was 10.8 ± 4.3 years, 59% were female, mean BMI SDS was 3.8 ± 1.1. Mean REE% was higher in children with non-syndromic genetic obesity (107.4% ± 12.7) and lower in children with hypothalamic obesity (87.6% ± 14.2) compared to multifactorial obesity (100.5% ± 12.6, both $p<0.01$). mREE was ≥10% decreased in 60 (21%) patients and ≥10% elevated in 69 (24%) patients. Mean mREE/FFM was 46.5 ± 10.6 kcal/day/kg FFM and did not differ between patients with underlying medical causes compared to multifactorial obesity (all $p>0.05$). **Conclusions**: In this cohort of children with severe obesity due to various etiologies, large inter-individual differences in mREE were found. Almost half of patients had decreased or elevated mREE. This knowledge is important for patient-tailored treatment, e.g. personalized dietary and physical activity interventions and consideration of pharmacotherapy affecting central energy expenditure regulation. Moreover, we are the first to describe REE in Temple syndrome and 16p11.2-deletion syndrome. **1. Conflict of interest:** None. **2. Funding:** Elisabeth Foundation.

Title:	**Run for your live(r): Exercise training at different times of day differentially modulates hepatic inflammation in early NAFLD**
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Abstract:	**Introduction:** Exercise effectively prevents obesity-related disorders, but it is unclear whether the beneficial health effects of exercise are restricted to unique circadian windows. We recently showed that late exercise training over four weeks reduces atherosclerosis and body fat mass whereas early training did not prevent fat mass gain, suggesting a greater improvement of hyperlipidemic and inflammatory diseases with late training. Therefore, we now aimed to study whether timing of exercise training differentially modulates obesity-related NAFLD development and progression. **Methods:** We used male APOE*3-Leiden.CETP mice that were fed an obesogenic (high fat-high cholesterol) diet to induce NAFLD. These mice were endurance-trained on a treadmill for eight weeks (5x per week, 1 hour) either in the early (ZT13) or in the late (ZT22) active phase. Subsequently, NAFLD score (histology), hepatic inflammation (FACS) and inflammatory genes expression (qPCR) were compared to sedentary mice. **Results:** Exercise training prevented an increase in body fat mass (+1.13 g and +1.06 g with early and late training) vs sedentary mice (+3.67 g) and fasting plasma glucose 7.0 mM and 6.9 mM in early and late training, compared to 7.7 mM in sedentary mice). Neither early nor late training affected liver triglyceride or cholesterol content compared to sedentary mice, likely due to a very early stage of hepatic steatosis. In line, hepatic expression of *de novo* lipogenesis genes (e.g., *Fasn*, *Srebp1c*) was similarly downregulated by early and late training. However, exercise had a distinct time-dependent effect on hepatic inflammation, as only early training promoted an influx of neutrophils and monocytes into the liver paired with increased expression of the pro-inflammatory cytokines (e.g. *Tnfa*, *Il1b*). **Conclusion:** Timing of exercise is a critical factor for the positive effect in obesity and cardiometabolic disease management. We currently investigate the effect of timed training on the development of advanced stages of NAFLD/NASH. **1. Conflict of interest:** There is no conflict of interests **2. Funding**: Novo Nordisk Foundation grant NNF18OC0032394 to Milena Schönke

Title:	**Gut microbiome profiling in tissue-specific insulin resistance: A cross-sectional analysis of the PERSON study**
Authors:	Jardon KM[1,2], Umanets A[3,4], Venema K[3], Gijbels A[1,5], Trouwborst I[1,2], Hul GB[1,2], Afman LA[1,5], Goossens GH[1,2], Blaak EE[1,2] and the PERSON Study consortium
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Abstract:	**Introduction:** Obesity-related insulin resistance (IR) may develop to a different extent in key metabolic organs as the liver (LIR) or muscle (MIR), characterized by distinct cardiometabolic profiles. In addition, gut microbiome disturbances may impact host metabolism, yet the link between the gut microbiome and tissue-specific insulin resistance is still poorly understood. **Objective:** To determine whether tissue-specific IR is characterized by distinct gut microbial composition and circulating concentrations of the gut microbiota-derived short-chain fatty acids (SCFAs) and branched-chain fatty acids (BCFAs) in individuals with overweight/obesity. **Methods:** The PERSON study is a two-center, randomized-controlled 12-week intervention study examining the effects of targeted diets on glucose homeostasis in individuals with either LIR or MIR. The current preliminary cross-sectional analysis included a subset of 82 individuals (BMI 25-40 kg/m^2, age 40-75y). The hepatic insulin resistance index (HIRI) and muscle insulin sensitivity index (MISI) were determined by a 7-point oral glucose tolerance test. Plasma SCFA and BCFA concentrations were determined using liquid chromatography–mass spectrometry. Fecal samples were collected to determine gut microbiota composition and diversity using Illumina MiSeq sequencing of the V3-V4 region of the 16S rRNA gene. **Results:** Distance-based redundancy analysis revealed a significant differentiation between overall composition of microbial communities in the MIR and LIR phenotypes ($p<0.01$). HIRI correlated positively with circulating 2-methyl valeric acid ($r=0.280$, $p=0.024$), isovaleric acid ($r=0.289$, $p=0.020$) and valeric acid ($r=0.352$, $p=0.004$) concentrations. MISI correlated negatively with circulating valeric acid concentration ($r=-0.312$, $p=0.012$). Several SCFAs and BCFAs were positively correlated with HbA1c and fasting glucose levels, while an inverse correlation was found between acetic acid and fasting glucose ($r=-0.256$, $p= 0.023$). **Conclusion:** These preliminary data reveal that tissue-specific IR is characterized by differential gut microbial characteristics. Implementing these findings in future research could lead to advancements in the field of precision nutrition and improving cardiometabolic health. 1. **Conflict of Interest:** None to disclose. 2. **Funding:** The 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 DSM Nutritional Products, FrieslandCampina, Danone Nutricia Research, the Netherlands Organisation for Scientific Research and the Top-sector Agri&Food.

Title:	**Hair cortisol, obesity and the immune system: Results from a 3 year longitudinal study**
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Abstract:	**Objectives** Higher long-term glucocorticoid levels, measured in scalp hair (HairGC), are associated with obesity. This may represent the state of obesity (perhaps interrelated with chronic immune activation), but could also promote further weight gain. We studied whether hair cortisol (HairF) and hair cortisone (HairE) predict changes in body mass index (BMI) and waist circumference (WC) over time, and assessed the association between HairGC and common immune parameters. **Methods** We measured HairGC in 1604 participants of the Netherlands Study of Depression and Anxiety (NESDA), and investigated their associations to BMI, WC, and immune parameters (interleukin-6 (IL-6), C-reactive protein (CRP), and leukocyte subsets). Also, we assessed whether baseline HairGC predict changes in BMI and WC at follow-up (three years later). **Results** In cross-sectional analyses, HairF and HairE were positively associated to BMI (β = 2.06 kg/m2, 95% confidence interval (CI)= 1.22–2.90 kg/m2) and β = 2.84 kg/m2 (95%CI 1.75–3.93 kg/m2) respectively) and WC (β = 5.36 cm (95%CI 3.09–7.62 cm) and β = 8.54 cm (95%CI 5.60–11.48 cm) respectively, all $p < 0.001$). HairF was also positively associated to IL-6 (β = 0.15 (95%CI 0.003–0.292) $p < 0.05$) and leukocyte count (β = 0.57 (95%CI 0.234–0.909), $p < 0.01$), and HairE to IL-6 (β = 0.21 (95%CI 0.016–0.399), $p < 0.05$).In the longitudinal analyses, higher HairF was associated with yearly increases in BMI (β = 0.58% BMI change per year (95%CI 0.14–1.01%), p = 0.009) and higher HairE with increases in WC (β = 0.84% WC change per year (95%CI 0.02–1.69%), p = 0.049). Adjusting for baseline IL-6 or leukocytes did not change the found associations between HairGC and WC or BMI change. **Conclusions** HairGC levels are positively associated to BMI, WC, IL-6 and leukocyte numbers in cross-sectional analyses, and to increases in BMI and WC in longitudinal analyses. Although causality is yet to be proven, higher long-term glucocorticoid levels could represent a relevant risk factor for the development of obesity. **1. Conflict of interest: none** **2. Funding: Elisabeth Foundation; Netherlands Organization of Scientific Research NWO, Vidi Grant/ Award Number: 91716453.**

Title:	**Fibroblast growth factor 21 potently protects against diet-induced obesity, atherosclerosis and NASH development**
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Abstract:	**Introduction:** Fibroblast growth factor 21 (FGF21) is a key regulator of energy metabolism acting on adipose tissue and liver that is currently evaluated in humans for treatment of obesity. However, its role in lipoprotein metabolism in relation to cardiometabolic diseases including atherosclerotic cardiovascular disease and NASH remains elusive. **Methods:** By using APOE*3-Leiden.CETP mice, a well-established mouse model mimicking human-like cardiometabolic diseases, we investigated the role of FGF21 in obesity, atherosclerosis and NASH development via administration of a recombinant FGF21 and an AAV8 vector encoding murine-optimized FGF21, respectively. **Results:** FGF21 largely lowered diet-induced weight gain and plasma cholesterol within lipoprotein remnants. Mechanistically, FGF21 promoted brown adipose tissue (BAT) activation and white adipose tissue (WAT) browning, thereby increasing fatty acid oxidation and enhancing the selective uptake of fatty acids from triglyceride-rich lipoproteins into these tissues, consequently accelerating the clearance of the cholesterol-enriched remnants by the liver and largely reducing atherosclerotic lesion area and severity. FGF21 also improved adipose tissue function, accompanied by alleviated insulin resistance. Moreover, FGF21 abolished hepatic steatosis, and largely alleviated hepatic inflammation as evidenced by decreased crown-like structures, Kupffer cell activation, infiltrated monocytes and lipid/scar-associated macrophages, correlating with less liver fibrosis as demonstrated by reduced collagen accumulation. **Conclusion:** FGF21 largely increases fatty acid oxidation in thermogenic tissues and in the liver, thereby reducing obesity, improving lipid metabolism, and attenuating development of atherosclerosis and all features of NASH. Our data provide a strong experimental basis for the clinical development of FGF21 to treat both atherosclerotic cardiovascular disease and NASH in the context of obesity. **Conflict of interest:** KW, ND, AP, SO, YI and X-RP are employees of AstraZeneca **Funding:** This work was supported by the Dutch Diabetes Research Foundation (2015.81.1808 to MRB); Novo Nordisk Foundation (NNF18OC0032394 to MS); CVON-GENIUS-2 (PCNR); the Netherlands Heart Foundation (2009T038 to PCNR).

Title:	**Angiopoietin-like 4 dictates the day-night rhythm of metabolic brown adipose tissue activity**
Authors:	van Eenige R[1,2] & In het Panhuis W[1,2], Schönke M[1,2], Kersten S[3], Rensen PCN[1,2], Kooijman S[1,2]
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Abstract:	**Introduction:** Thermogenic activity in brown adipose tissue (BAT) protects from obesity and related disorders as BAT takes up large amounts of triglyceride (TG)-derived fatty acids (FAs) for oxidation. Interestingly, this process shows a strong day-night rhythm (Van den Berg, Cell Rep 2018). The aim of the present study was to elucidate the molecular mechanisms underlying this diurnal rhythm, in order to identify novel strategies to optimally activate BAT. **Methods:** BAT was collected from chow-fed male C57BL/6J mice at 3-hour intervals throughout a 24-hour period. RNA-sequencing and lipidomics were performed, and oscillating genes and lipid species were identified by JTK. Mice were injected with glycerol tri[^{3}H]oleate labeled TG-rich lipoprotein-like particles at the onset of the light or dark phase, and BAT was collected to determine the uptake of [^{3}H]oleate. **Results:** Out of the 13,547 expressed genes and 1,941 measured lipid species, 5,486 genes and 430 lipids were oscillating. Expression of lipoprotein lipase (*Lpl*), encoding the enzyme responsible for the liberation of FAs from TGs, showed the largest diurnal amplitude in synchrony with metabolic BAT activity, which translated into a superimposing rhythm in FA and monoacylglycerol content within the tissue. Transcription factor enrichment analyses revealed a central role for PPARγ in the regulation of diurnal gene expression with the LPL-modulator angiopoietin-like 4 (*Angptl4*) as prime target. Subsequent kinetic experiments revealed that diurnal rhythm in LPL activity and [^{3}H]oleate uptake by BAT was flattened in *Angptl4* engineered mice, with persistent high uptake in *Angptl4* knockout mice and low uptake in *Angptl4* overexpressing mice. **Conclusion:** Our findings highlight a crucial role of ANGPTL4 in mediating the day-night rhythm of TG-derived FA-uptake by BAT, and implicate that timing of administration of currently developed ANGPTL4 inhibitors is crucial when aiming at maximizing metabolic BAT activity throughout the day in the treatment of obesity and related disorders. **1. Conflict of interest:** The authors declare no competing interests. **2. Funding:** SKO is supported by the Dutch Heart Foundation (2017T016).

Title:	**How can national government policies improve *food* environments in the Netherlands?**
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Abstract:	**Introduction:** Government policies are essential to create food environments that support healthy diets and prevent overweight, obesity and non-communicable diseases (NCDs). The aims of this study were 1) to benchmark the implementation of Dutch government policies influencing food environments, and 2) to identify and prioritize actions to improve food environments in the Netherlands. **Methods:** The Healthy Food Environment Policy Index (Food-EPI) was applied. The Food-EPI includes 46 indicators of food environment policy and infrastructure support. Independent experts (n=28) rated the extent of implementation on these indicators against international best practices, and formulated and prioritized policy and infrastructure support actions to improve food environments. **Results:** Most policies with a direct influence on healthy food environments (e.g. food marketing) were rated as having a low (50% of the indicators) or very low (41% of the indicators) level of implementation. Infrastructure support indicators that facilitate policy development and implementation (e.g. funding) were rated as having a fair (42%) or medium (42%) level of implementation. In total, 18 policy and 11 infrastructure support actions were recommended in order to improve food environments in the Netherlands. Highly prioritized actions included, for example, to ban all forms of unhealthy food marketing aimed at children (<18 years old), to increase the prices of unhealthy foods and to develop a government-wide national prevention policy and implementation plan. **Conclusion:** There is large potential for the Dutch national government to strengthen its policy action and infrastructure support in order to improve the healthiness of food environments in the Netherlands that support healthy diets and prevent overweight, obesity and NCDs. **1. Conflict of interest:** The authors declare that there are no conflicts of interest. **2. Funding:** The authors declare that this study received funding from The Netherlands Organization for Health Research and Development (ZonMw), project number 529051020.

Title:	**Plasma FGF21 levels are not associated with weight loss or improvements in metabolic health markers upon 12 weeks of energy restriction in abdominally obese subjects**
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Abstract:	**Introduction:** Fibroblast growth factor 21 (FGF21) is a hormone that regulates metabolic homeostasis. Recent studies suggest that circulating FGF21 may be a marker of metabolic health status. The aim of this study was to investigate the effects of two energy-restricted (ER) diets on fasting and postprandial plasma FGF21 levels in abdominally obese individuals, as well as to explore associations of plasma FGF21 with metabolic health markers, (macro)nutrient intake and sweet preference. **Methods:** We performed a secondary analysis of a 12-week randomized controlled trial. Abdominally obese subjects aged 40-70 years (n=110) were randomized to one of two 25% ER diets or a control group. Before and after the 12-week intervention, markers of metabolic health were assessed. Plasma FGF21, glucose, insulin and lipids were measured in the fasting state, as well as after a high-fat mixed meal (HFMM). Intrahepatic lipid content (IHLC) and abdominal fat distribution were determined by proton magnetic resonance spectroscopy and magnetic resonance imaging, respectively. Habitual dietary intake at baseline was assessed by a food frequency questionnaire. **Results:** Both ER diets resulted in weight loss and accompanying improvements in metabolic health markers, but did not affect fasting or postprandial plasma FGF21 levels. At baseline, fasting plasma FGF21 was not associated with markers of metabolic health including intrahepatic lipid content and abdominal fat distribution, (macro)nutrient intake or sweet preference. The postprandial FGF21 response after a high-fat mixed-meal was positively correlated with fasting plasma glucose and insulin, HOMA-IR, VAT, and the liver enzyme ASAT. Diet-induced improvements in metabolic health markers were not accompanied by changes in plasma FGF21 levels. **Conclusion:** In this study, we found no clear evidence that circulating FGF21 is a marker for metabolic health status. Circulating FGF21 dynamics in response to a metabolic or nutritional challenge may reflect metabolic health status better than fasting levels. **1. Conflict of interest: None to disclose.** **2. Funding: This study was funded by the Division of Human Nutrition and Health, Wageningen University, The Netherlands.**

Title:	**Physiological**, **Psychological and Behavioural Improvements in Patients with Obesity After a Combined Lifestyle Intervention With Cognitive Behavioural Therapy**
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Abstract:	**Introduction:** Obesity (BMI ≥ 30 kg/m^2) is associated with various metabolic, mental and behavioural comorbidities. Lifestyle interventions are generally considered effective if they induce weight loss ≥5% which promotes significant improvements in cardio-metabolic health. However, the heterogeneous nature of the disease may necessitate a more comprehensive approach in assessing the effects of obesity treatment. Here, we describe changes in physiological, psychological and behavioural health outcomes in response to a multidisciplinary combined lifestyle intervention (CLI). **Methods:** Data were collected from 97 adult patients with obesity (74 women), recruited via the Obesity Center CGG, Rotterdam, The Netherlands. The 1.5-year CLI comprised a healthy normocaloric diet, physical activity and cognitive behavioural therapy. We compared physiological health (anthropometrics, endocrine, metabolic and immune parameters), psychological health (a. o. IWQoL-Lite, HADS, PSS), eating behaviour (e.g. DEBQ, EDE-Q) and physical activity (IPAQ) before and after treatment. **Results:** Moderate 5.1% weight loss was accompanied by a 6.1% decrease in waist circumference, a 9.8% decrease in fat mass (all p<.001) and no change in fat free mass. In addition, we saw significant improvements in metabolism (e.g. Hba1c (-2.6%)), hormonal status (e.g. normalization of hypogonadism in men (p<.05)) and immune parameters (e.g. sIL2R (-10.9%)). Moreover, we observed decreased psychopathology (e.g. HADS p<.001), decreased disordered eating (e.g. DEBQ emotional eating (p<.01)), increased quality of life (IWQoL-Lite (p<.001)), and increased physical activity (p<.05). Weight loss correlated with most metabolic changes (e.g. Hba1c (p<.05)), but not most psychological and behavioural changes (except IWQoL-Lite, PSS, and EDE-Q, all p<.05). **Conclusion:** We observed a broad variety of physiological, psychological and behavioural improvements in response to a CLI, even though weight loss was rather moderate. Interestingly, most beneficial changes in psychological and behavioural health outcomes occurred irrespective of the amount of weight loss. Future research should assess the precise mechanisms promoting these favourable and long-lasting effects. **1. Conflict of interest:** Nothing to disclose. **2. Funding:** EFCvR is funded by a Vidi grant from the Netherlands Organization of Scientific Research NWO/ZONMW (grant number: 917164R is financially supported by

Title:	**Psychological improvements are related to changes in fat mass, but not lean mass, after a combined lifestyle intervention with cognitive behavioural therapy in patients with obesity**
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Abstract:	**Introduction**: Obesity is a chronic relapsing disease, which is characterized by an excess of body fat mass and is associated with impairments in psychological well-being and quality of life. Lifestyle interventions are considered one of the cornerstones of obesity treatment. Here we aim to study changes in psychological parameters and quality of life in relation to body composition after a multidisciplinary combined lifestyle intervention program with cognitive behavioural therapy (CLI). **Methods**: Data were collected from 43 adults with obesity (mean BMI 39.7 kg/m^2; 76.7% women, mean age 42.3 years), recruited at the Obesity Center CGG, Erasmus MC, Rotterdam, The Netherlands before and after 1.5 years of CLI at the end of the program. Psychological well-being was assessed via different questionnaires, including the Perceived Stress Scale (PSS), Hospital Anxiety Depression Scale (HADS), the Fear of Negative Appearance Evaluation (FNAES) as well as the Impact of Weight on Quality of Life-Lite questionnaire (IWQoL-Lite). In addition, we assessed body composition using Dual-Energy X-Ray Absorptiometry scans. **Results**: Between baseline and 1.5 years of treatment, there were significant decreases in body weight (- 5.5%, p<.001) and fat mass (-9.7%, p<.01), whereas lean mass was roughly maintained (-1.5%, p>.05). Decreases in fat mass were associated with improvements in psychological well-being: increased quality of life (r=-.483, p=.001), decreased fear of negative appearance (r=.374, p=.017), decreased perceived stress (r=.276, p=.092), decreases depression and anxiety scores (r=.220, p=.170). However, there were no associations with changes in lean mass (p>.05). **Conclusion**: Lifestyle-induced reductions in fat mass are associated with significant improvements in psychological well-being and quality of life. Our results suggest that in weight loss studies, distinct measurements of body composition should be considered. Future studies should investigate the exact mechanisms behind this observation such as potential endocrine or inflammatory changes which are known to accompany loss of fat mass.

Title:	**The effect of weight-loss on whole-body and tissue-specific insulin sensitivity and intrahepatic lipid content and composition – a SWEET sub-study.**
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Abstract:	**Introduction:** Weight loss improves intrahepatic lipid (IHL) content and insulin sensitivity (IS) in individuals with overweight or obesity. Interestingly, recent evidence suggests that the fatty acid composition rather than total IHL content is related to hepatic IS. We investigated the effects of weight loss on whole-body and tissue-specific IS, IHL content and hepatic fatty acid composition in individuals with overweight or obesity. Secondly, the association between weight loss-induced changes in whole-body and tissue-specific IS and alterations in the content and fatty acid composition of IHL were determined. **Methods:** 50 adults (18-65 yrs) with overweight or obesity (BMI≥25 kg/m^2) followed a low-energy diet (LED) for two months (800-1000 kcal/day). Measurements were performed at baseline and after the LED. Body composition was assessed by Dual-Energy X-ray Absorptiometry. The content and fatty acid composition of IHL was determined using advanced proton magnetic resonance spectroscopy (^{1}H-MRS). Whole-body IS (Matsuda-index), muscle IS index (MISI), and hepatic insulin resistance index (HIRI) were derived from a 7-point oral glucose tolerance test. **Results:** The LED reduced body weight, waist and hip circumferences, body fat percentage, and visceral fat mass (all P<0.001). Analyses of preliminary data revealed a 29.3% improvement in whole-body IS as reflected by Matsuda-index (n=15; P=0.012), whereas no significant improvements were found in HIRI (n=15; P=0.107) and MISI (n=14; P=0.246). The LED reduced IHL content by 56.5% (n=34; P<0.001) and the fraction of hepatic saturated fatty acids changed from 41.0% to 36.6% (n=12; P=0.039). Significant associations were found between the change in IHL content and change in HIRI (n=13; *r* = 0.598, P=0.031). **Conclusion:** These preliminary findings suggest that a LED significantly reduces body weight, (visceral) fat mass, IHL content, and the hepatic saturated fatty acid fraction and increased whole-body IS in individuals with overweight and obesity. The weight-loss induced reduction in IHL content was associated with improved hepatic IS. 1. **Conflict of Interest:** None Disclosed 2. **Funding:** Research relating to this abstract was funded by European Commission Horizon 2020

Title:	**Galactose in the post-weaning diet programs improved circulating adiponectin concentrations and skeletal muscle insulin signalling**
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Abstract:	**Introduction:** Post-weaning nutritional interventions can result in long lasting beneficial effects in later life. This study aims to assess whether partial replacement of glucose by galactose in the post-weaning diet -which showed previously direct effects on liver inflammation- programs body weight, body composition and insulin sensitivity at adult age. **Methods:** Three-week-old female C57BL/6JRccHsd mice were fed a diet with glucose + galactose (GAL; 16 energy% (en%) each) or a control diet with glucose (GLU; 32 en%) for three weeks, and switched to the same high fat diet (HFD) afterwards. After five weeks HFD, an oral glucose tolerance test was performed. After nine weeks HFD, energy metabolism was assessed by indirect calorimetry and fasted animals were sacrificed fifteen minutes after a glucose bolus, followed by serum and tissue analyses. **Results:** Body weight and body composition were not different between the post-weaning dietary groups, neither during the post-weaning period, nor during the HFD period. Glucose tolerance and energy metabolism in adulthood were not affected by the post-weaning diet. Serum adiponectin concentrations were significantly higher (P=0.02) in GAL-fed mice while insulin, leptin and insulin-like growth factor-1 concentrations were not. Simultaneously, expression of *AdipoQ* was significantly higher in gonadal white adipose tissue (gWAT) (P=0.03), while its receptors in liver and extensor digitorum longus (EDL) muscle remained unaffected. However, insulin receptor *Irs2* expression was significantly lower in EDL muscle (P=0.01), but not in gWAT, nor was *Irs1* expression in both tissues. Gene expression of inflammatory markers in gWAT and liver were also not affected. **Conclusion:** Galactose in the post-weaning diet significantly improved circulating adiponectin concentrations and reduced EDL muscle *Irs2* expression in adulthood without alterations in fat mass, glucose tolerance and inflammation. **1. Conflict of interest:** AO is employee at DNR; all other authors declare no conflict of interest. **2. Funding:** PS is funded by the China Scholarship Council (grant ID 202003250074) and this project was funded by the Dutch Technology Foundation STW (13509).

Title:	**Systemic and abdominal subcutaneous adipose tissue immune cells are associated with hepatic- but not with muscle insulin resistance in people with overweight and obesity**
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Abstract:	**Introduction:** Alterations in adipose tissue and systemic immune cell population may be an important link between adiposity, systemic low-grade inflammation, and insulin resistance. Insulin resistance can develop separately in the liver, skeletal muscle, and adipose tissue, representing different etiologies towards obesity-related metabolic complications. Here, we investigated the relationship between adipose tissue and systemic immune cell populations, and tissue-specific insulin resistance. **Methods:** The present study was part of a randomized, double-blind, parallel, 12-week personalized dietary intervention study (PERSON study). Eighty individuals with overweight or obesity underwent a 7-point oral glucose tolerance test to calculate the hepatic insulin resistance index (HIRI) and the muscle insulin sensitivity index (MISI) to estimate hepatic and skeletal muscle insulin sensitivity, respectively. Furthermore, an abdominal subcutaneous adipose tissue (aSAT) biopsy was collected. Immune cell populations (expressed as % of live cells) in fresh whole-blood and in aSAT were identified using flow cytometry, and aSAT gene expression was determined with qPCR. This preliminary analysis includes data from 50 individuals (62% women; BMI: 30.7±3.4 kg/m^2; age: 60.4±7.9 yrs). Data from the total study population will be presented during the congress. **Results:** Multiple linear regression analyses revealed that classical monocytes and NK cells in blood, and CD11C-CD206+ macrophages in aSAT were positively associated with HIRI, while blood granulocytes were negatively associated with HIRI after adjustment for age, sex and BMI (std. β's between 0.318-0.488, all *p*-values<0.05). None of the blood and aSAT immune cells were associated with MISI (all *p*-values >0.05). **Conclusion:** These preliminary findings demonstrate that systemic classical monocytes and NK cells, and aSAT CD11C-CD206+ macrophages were associated with hepatic but not skeletal muscle insulin resistance, suggesting that hepatic, but not muscle insulin resistance, is linked to the detrimental effects of altered systemic and subcutaneous immune cell populations in people with overweight and obesity. 1. **Conflict of Interest:** None disclosed. 2. **Funding:** Research relating to this abstract is organized by and executed under the auspices of TiFN, a public -private partnership on precompetitive research in food and nutrition.

Title:	**Weight Loss, Visit-to-Visit Body Weight Variability and Cognitive Function in Older Individuals**
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Abstract:	**Introduction:** Higher variability in LDL-cholesterol and systolic blood pressure, known markers of unstable homeostasis, are associated with worsened cognitive function. Whether higher variability and loss of body weight also signal prodromal cognitive decline, remains unclear. **Methods:** We aimed to investigate the association between variability and loss of body weight with cognitive performance in participants of the PROSPER study (PROspective Study of Pravastatin in the Elderly at Risk), a multicentre trial with participants from Scotland, Ireland and the Netherlands. Body weight was measured every three months for 2.5 years. Weight loss was defined as average slope across all weight measurements and as ≥5% decrease in baseline weight during follow-up. Visit-to-visit variability was defined as the SD of weight measurements (kg) between visits. Four tests of cognitive function were examined: Stroop test, Letter-Digit Coding test, immediate and delayed Picture-Word learning tests. Two tests of daily living activities, Barthel Index (BI) and instrumental activities at daily living (IADL), were also examined. All tests were performed at month 30 of follow-up. **Results:** Both larger visit-to-visit body weight variation and loss of ≥5% of baseline weight were independently associated with worse scores on all cognitive tests, but minimally with BI and IADL. Compared to participants who maintained stable weight, participants with significant weight loss scored 5.87 seconds (95%CI 3.78; 7.96) slower on the Stroop test, coded 1.74 digits less (95%CI -2.33; -1.14) on the Letter-Digit Coding test, and remembered 0.71 less pictures (95%CI -0.93; -0.49) on the delayed Picture-Word Learning test. **Conclusion:** Weight loss and increased body weight variability are independent risk-factors for worse cognitive function. **1. Conflict of interest:** None. **2. Funding:** Michelle H. Zonneveld was supported by Young Talent Award from the Netherlands Cardiovascular Research Initiative funded project ENERGISE (CVON2014-02). The original PROSPER clinical trial was funded by an investigator-initiated grant from Bristol-Myers Squibb, USA.