Abstract book

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Abstracts

Title:	**Unexpected significant improvement in carotid intima media thickness in patients after bariatric surgery after 1 year follow up: Report from the ASSISI study.**
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Abstract:	**Introduction:** Obesity is a major risk factor for cardiovascular disease. Carotid Intima Media Thickness(cIMT) is a good predictor of severity of cardiovascular disease in obese patients. Our aim was to determine the effects of weight loss after bariatric surgery on intima media thickness. **Methods:** We prospectively collected data of patients undergoing bariatric surgery between 2015-2017 and having had an cIMT-measurement pre-operatively and 1 year postoperatively. Patients were divided into 'progressors', 'regressors' and 'consistent' based on increase or decrease of one standard deviation of the mean difference in cIMT after 1 year. We analyzed data on gender, surgery type, preoperative laboratory values, medical history of diabetes mellitus or hypertension and difference in BMI after 1 year, using one-way ANOVA, Chi2 and Mann-Whitney tests. **Results:** Data on cIMT was available for 134 out of 200 patients. 34 (25.4%) patients had a significant regression of cIMT with a mean decrease of 0.1 mm [-0.24 to -0.06]; 10 patients (7.5%) were progressors with a mean increase of 0.1 mm [0.07 to 0.30] and 90 patients (67.2%) had no significant difference (Figure 1). 3 out of 10 progressors (30%) had diabetes mellitus in contrast to 2 out of 32 regressors(6%) (p=0.035). Furthermore, progressors more often had hypertension (7/10, 70%) than regressors (10/24, 42%) (p=0.020). Other variables did not predict the IMT changes 1 year postoperatively. **Conclusion:** An unexpected significant improvement in cIMT after only 1 year of follow up was established in a quarter of all patients undergoing bariatric surgery. Only a small percentage had a greater cIMT deterioration than expected, and the vast majority showed stabilization. We found that patients with hypertension and diabetes mellitus had a higher likelihood of progression in cIMT after 1 year. Long term follow up is of great importance to assess the impact of the cIMT on cardiovascular disease. **1. Conflict of interest:** None **2. Funding:** None

Title:	**Gut microbiota play a key role in the induction of beneficial effects of butyrate on host energy metabolism**
Authors:	Li Z[1,2], Zhou E[1,2], Yildiz S[1], Kooijman S[1,2], Berbée JFP[1,2], Willems van Dijk K[2,3], Rensen PCN[1,2], Wang Y[1,2]
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Abstract:	**Introduction:** We recently showed that dietary butyrate reduces food intake and improves energy expenditure by activating brown adipose tissue (BAT) as dependent on vagus nerve signalling and related to the change of composition and diversity of gut microbiota (Li, Gut 2017). Since gut microbiota can induce vagus nerve activity, in the present study we aimed to investigate the role of gut microbiota in the beneficial effects of butyrate on energy metabolism. **Methods:** Conventional or gut microbiota depleted APOE*3-Leiden.CETP mice, a well-established translational model for developing diet-induced human-like metabolic syndrome, were fed a high-fat diet (HFD) with or without sodium butyrate (5% w/w). After 7 weeks of intervention, mice received triacylglycerol-rich lipoprotein (TRL)-like emulsion particles labelled with glycerol tri[^{3}H]oleate by intravenous injection, and plasma clearance and organ uptake of [^{3}H]oleate were determined. **Results:** In conventional mice, butyrate reduced food intake and completely prevented the HFD-induced increase in body weight gain. Butyrate administration reduced BAT pad weight and intracellular lipid content within BAT pad, suggesting enhanced BAT thermogenic capacity. Accordingly, butyrate accelerated the clearance of glycerol tri[^{3}H]oleate from plasma, accompanied by increased uptake specifically by BAT, confirming that butyrate enhances plasma triglyceride clearance by activating BAT. In contrast, depletion of gut microbiota by antibiotics completely abolished the satiety effects of butyrate. In addition, gut microbiota depletion also impaired the ability of butyrate to activate BAT, as the intracellular lipid content within BAT pad as well as the uptake of [^{3}H]oleate by BAT were unaffected. As a result, butyrate only partially prevented HFD induced body weight gain in gut microbiota depleted mice. **Conclusion:** Gut microbiota play a key role in the beneficial effects of butyrate on host energy metabolism with respect to reducing appetite, activating brown adipose tissue, and preventing HFD-induced obesity. **1. Conflict of interest:** None **2. Funding:** Chinese Scholarship Council Fellowship to Li Z.

Title:	**Genetic causes of early onset obesity are frequently identified in a tertiary pediatric obesity cohort**
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Abstract:	**Introduction:** Obesity is predominantly considered a multifactorial disorder. In unselected patient cohorts, an underlying genetic diagnosis can be established in only a minority of cases. They typically present with early-onset, severe obesity. Establishing a genetic diagnosis can lead to personalized treatment, reduce stigma and support reproductive decision-making. This study provides an overview of obesity-associated mutations and copy number variations (CNV's) identified in this selected, tertiary pediatric population. **Methods:** In 174 obese children, referred to the pediatric obesity center Centrum Gezond Gewicht between 2012 and 2017, diagnostic sequencing of 52 obesity-associated genes and CNV detection by SNP-microarray analysis were performed to identify genetic causes of obesity. On clinical suspicion, specific additional diagnostics (e.g. Prader-Willi diagnostics, whole exome sequencing) were performed. **Results:** The median age at intake was 10.3 years (range 0.7–18 years); 105 patients were female (60.3%). In 28 patients (16.1%), an underlying genetic cause was identified, leading to a diagnosis of genetic obesity. Fourteen different genetic diagnoses were established, most frequently *MC4R*-associated obesity (5 heterozygous patients, 2 homozygous), leptin receptor deficiency (5 patients) and 16p11.2 deletion syndrome (3 patients). In an additional 22 patients (12.6%), a novel CNV or sequence variant of unknown clinical significance (VUS) was shown in obesity-associated genes, for which the role in the phenotype has yet to be confirmed. **Conclusion:** A definitive diagnosis of genetic obesity was made in 16.1% of our patients with childhood obesity. This may increase, if follow-up studies in patients with VUS confirm a causal role for their variants. Our results indicate that 'genetic obesity' reflects a heterogeneous group of conditions, with 14 different genetic diagnoses made in this pediatric cohort. This diagnostic yield is relatively high compared to similar studies and shows that genetic testing can be highly relevant in selected obese patients, especially when personalized treatment becomes available in the near future. **1. Conflict of interest: none declared.** **2. Funding: n/a.**

Title:	**Metabolite Profiles Associated with Variation in Visceral Fat Distribution: Results from the Netherlands Epidemiology of Obesity Study**
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Abstract:	**Introduction:** Excess visceral adipose tissue (VAT) is associated with an increased cardiometabolic disease risk. Metabolomics might allow for easier quantification of visceral fat, instead of imaging studies or approximations such as waist circumference. Here, we related metabolites to VAT to identify potential biomarkers of VAT. **Methods:** In this cross-sectional analysis of the Netherlands Epidemiology of Obesity study we quantified metabolites using the Nightingale NMR metabolomics platform. VAT was quantified with magnetic resonance imaging in 2,569 middle-aged men and women. We examined associations between metabolites and VAT with linear regressions, adjusting for demographic and lifestyle variables. We additionally adjusted for fasting glucose and triglyceride concentrations, and waist circumference to examine which metabolites contribute above these factors. We use a false discovery rate method to correct for multiple comparisons. **Results:** In the multivariate model, 165 of 225 metabolites were significantly associated with VAT, including positive associations of very large, intermediate and low-density lipoprotein measures, as well as glycoprotein acetyls, alanine, isoleucine, leucine, valine, phenylalanine, tyrosine and lactate. Conversely we observed negative associations of most high density lipoprotein (HDL) measures, as well as glutamine. In our final model, 30 metabolites remained significantly associated. This included most extra-large and large HDL measures from -4.5 (95% CI: -6.9, -2.2) to -3.0 (95% CI: -4.8, -1.1) cm^2 per SD, as well as glycoprotein acetyls, isoleucine, leucine, valine and phenylalanine from 3.1 (95% CI: 1.4, 4.8) to 6.2 (95% CI 3.3, 9.1). **Conclusion:** Even after adjusting for fasting glucose and triglyceride concentrations, and waist circumference, we observed associations of HDL measures, glycoprotein acetyls and amino acids with VAT. These observations may provide insight in the pathophysiology of obesity and provide interesting candidates for potential non-invasive quantification of VAT, but first need replication in other cohort studies. **1. Conflict of interest:** None **2. Funding:** CVON2014-02 ENERGISE

Title:	**The effect of mild intermittent hypoxia exposure on tissue-specific insulin sensitivity in obese humans**
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Abstract:	**Introduction:** Adipose tissue (AT) dysfunction and impairments in skeletal muscle (SM) metabolism contribute to the pathophysiology of cardiometabolic diseases. Recent studies suggest that mild hypoxia exposure (MIH) may improve glucose homeostasis. Here, we investigated the effects of MIH exposure on AT and SM oxygenation, skeletal muscle mitochondrial respiration, inflammation, substrate metabolism and insulin sensitivity in obese individuals. **Methods:** Eight overweight/obese (BMI>28 kg/m2) men participated in an ongoing randomized, single-blind, placebo-controlled, cross-over study. Subjects were exposed to 1) MIH (15% O_2; equivalent to ~3000m above sea level) and 2) normoxia (21% O_2) for 7 consecutive days (3 cycles of 2h exposure/d in a normobaric room) in a randomized fashion, separated by a 4 week wash-out period. We determined AT and SM oxygen tension (pO_2) (day 6), substrate metabolism (day 7, high-fat mixed-meal), and insulin sensitivity (day 8, hyperinsulinemic-euglycemic clamp under normoxic conditions). AT and SM biopsies were collected for gene/protein expression analyses, *ex vivo* mitochondrial respiration and cell culture experiments. **Results:** MIH reduced systemic oxygen saturation (SpO_2: 92.3±0.7 vs. 97.8±0.2 $\%O_2$, $p<0.001$), AT pO_2 (18.2±1.9 vs. 37.0±2.7 mmHg, $p=0.001$) and SM pO_2 (11.4±1.8 vs. 6.4±2.1 mmHg, $p=0.04$) as compared to normoxia exposure. Moreover, carbohydrate oxidation increased and fat oxidation decreased under fasting and postprandial conditions during MIH, resulting in an increased respiratory quotient. MIH increased fasting and postprandial lactate concentrations, while circulating glucose and lipid concentrations remained unchanged. Fasting and insulin-stimulated respiratory quotient remained elevated one day after MIH (d8). MIH did neither affect *ex vivo* mitochondrial respiration nor insulin sensitivity. **Conclusion:** These preliminary data demonstrate that MIH decreased AT and SM oxygenation, and induced a shift in substrate metabolism towards increased carbohydrate oxidation in obese individuals but did not alter insulin sensitivity. **1. Conflict of interest:** None **2. Funding:** Dutch Diabetes Research Foundation (Senior Fellowship to G.H Goossens 2016)

Title:	**The effect of long term Arabinoxylan-oligosaccharide supplementation on gastrointestinal functioning and metabolic parameters: A randomized controlled trial**
Authors:	Müller, M.[1]; Hermes, G.[2]; Canfora, E.E.[1]; Holst, J.J.[3]; Zoetendal, E.G.[2]; Smidt, H.[2], Troost, F.[4]; Lenaerts, K.[5]; Masclee, A.A.M.[4]; Blaak,E.E.[1]
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Abstract:	**Introduction:** Prebiotic fibers may induce shifts in gastrointestinal transit time and gut microbiota composition which may contribute to improved gut functionality and metabolic health. Here, we investigate long- term effects of the prebiotic Arabinoxylan-Oligosaccharide (AXOS) on gastrointestinal transit time, gut microbiota, and metabolic profile in healthy participants with delayed gastrointestinal transit. **Methods:** Forty-eight healthy participants (BMI 19,7-30,2 kg/m^2) with a slow whole gut transit time (>35h) were included in this double-blind, placebo-controlled study. The participants were randomly allocated to a daily intake of 15g AXOS or placebo (maltodextrin) for 12 weeks. Before and after intervention, gastric emptying rate (^{13}C-octanoic acid breath test), small intestinal transit (hydrogen breath test), whole gut transit (radio-opaque markers), gut permeability (multi-sugar assay), stool consistency (Bristol stool chart (BSC)) and fecal microbiota composition were assessed. Energy expenditure, substrate oxidation, glucose, insulin and Glucagon-like peptide 1 (GLP-1) were measured after a standardized meal. **Results:** After intervention, the abundance of fecal *Bifidobacterium spp.* increased in both groups, with a tendency towards a more pronounced increase with AXOS compared to placebo intake (8,5-fold change and 4,3-fold change respectively, NS). This was accompanied by a reduced microbial richness compared in the AXOS group (inverse Simpson index, P<0.001). Gastric emptying, small intestinal and whole gut transit were not affected but BSC types significantly changed towards softer stool consistency after AXOS intake (BSC type 2.7±0.19 to 3.3±0.19, P<0.01). Postprandial fat oxidation (iAUC, P=0.073) increased and early GLP-1 response decreased after AXOS intake ($AUC_{0\text{-}60min}$, P=0.005). Metabolic parameters and gut permeability were not affected. **Conclusion:** Long-term AXOS supplementation tended to increase fecal *Bifidobacterium* abundance, did not affect gastrointestinal transit time but normalized stool consistency. Postprandial fat oxidation tended to increase after AXOS, whilst early postprandial GLP-1 was decreased. The mechanisms by which AXOS induces these effects require further study. **1. Conflict of interest:** The authors declare no conflict of interest. **2. Funding:** The research is funded by TI Food and Nutrition, a public private partnership on pre-competitive research in food and nutrition. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Title:	**Vitamin D and tissue specific insulin sensitivity in overweight/obese humans**
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Abstract:	**Introduction:** Vitamin D deficiency in obesity has been suggested to be related with indices of insulin resistance. However, data on the association between plasma 25-dihydroxyvitamin D (including active metabolite and active/inactive ratio) and tissue specific insulin sensitivity in overweight/obese humans is rather limited. This study was to investigate to what extent plasma vitamin D metabolites (inactive, active, including its ratio) as well as AT VDR expression may associate with tissue-specific insulin sensitivity in overweight/obese individuals. **Methods:** This cross-sectional analysis included 92 adult overweight and obese (BMI range 25-35 kg/m^2, age range: 19-69) men (n=72) and women (n=20). A two-step hyperinsulinemic-euglycemic clamp with a [6,6-2H_2]-glucose tracer was performed to measure peripheral, hepatic and adipose tissue insulin sensitivity. Abdominal subcutaneous AT mRNA expression of genes involved in vitamin D metabolism (VDR, CYP) was determined by qRT-PCR. Liquid chromatography mass spectrophotometry (LC-MS) was used to quantify plasma 25OHD_3 and 1.25OH_2D_3 concentrations. **Results:** BMI and age were associated with plasma 25OHD3 concentration (std ß= -0.274, P=0.011; std ß= 0.321, P=0.012; respectively) but not with plasma 1.25OHD3 nor plasma vitamin D ratio. Plasma vitamin D metabolites and its ratio were not associated with tissue specific insulin sensitivity (P>0.05 for all). Interestingly, higher SAT VDR mRNA was negatively associated with adipose tissue (AT) insulin sensitivity (std ß= -0.207, P=0.025) independent of BMI, age, and sex. **Conclusion:** Neither plasma 25(OH)D nor 1,25(OH)D nor its ratio were related to tissue specific insulin sensitivity. However, expression of VDR in SAT was negatively associated with AT insulin sensitivity of overweight/obese individuals. The underlying mechanisms needs to be investigated more detail in future studies. **1. Conflict of interest:** The authors declare no conflict of interest. **2. Funding:** The first author is supported by Indonesia Endowment Fund for Education (LPDP) to conduct his PhD

Title:	**Anthropometric measurements and metabolic syndrome in relation to glucocorticoid receptor polymorphisms in (local) corticosteroid users**
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Abstract:	**Introduction**: Corticosteroids are amongst the most prescribed drugs and their use has been linked to (cardiometabolic) adverse events including weight gain and abdominal adiposity. Since an essential role in the pathway of glucocorticoid (GC) action is reserved for the glucocorticoid receptor (GR), it could be proposed that GC sensitivity altering polymorphisms could affect the vulnerability for adverse effects. We therefore assessed the relationships between functional GR polymorphisms with anthropometric measurements and metabolic syndrome (MetS) in users of corticosteroids. **Methods**: We included 10,619 adult participants in the population-based Lifelines cohort study. Genotyping was performed for GR polymorphisms associated with a relatively increased (Bcl*I* and N363S) or decreased (ER22/23EK and 9β) GC sensitivity. Analyses were performed between nonusers (genotypes combined) and users (specified) and were adjusted for various covariates. **Results**: Overall corticosteroids use was associated with a significantly higher BMI and waist circumference (WC) in GC hypersensitive (BMI: mean difference +0.67 kg/m^2; WC: +2.09 cm, both P<0.001), and wild type users (BMI: +0.57 kg/m^2, P=0.04; WC: +1.90 cm, P<0.01) but not in GC resistant users. In particular, the use of inhaled corticosteroids was associated with similar findings in GC hypersensitive users (BMI: +1.68 kg/m^2; WC: +4.72 cm, both P<0.001), and wild type users (BMI: +1.07 kg/m^2, P=0.01; WC: +3.53 cm, P<0.01). In regard to MetS, again only GC hypersensitive (odds ratio (OR) 1.23 (95% CI, 1.01-1.50)) and wild type users (OR 1.43 (1.06-1.93)) were more likely to have MetS in comparison to nonusers. This was predominantly found in users of only inhaled corticosteroids. **Conclusion**: Corticosteroid users, in particular of inhaled corticosteroids, have an increased BMI, WC and more often MetS in comparison to nonusers. These relationships are significantly evident in carriers of GR genotypes associated with GC hypersensitivity or the wild type genotype, but not in users harboring GC resistant polymorphisms. **1. Conflict of interest:** None. **2. Funding:** EFCvR is funded by a Vidi grant from The Netherlands Organization of Scientific Research NWO (grant number: 91716453).

Title:	**Timing of Feeding Behavior Affects Daily Rhythms in Body Temperature and Muscle Mitochondrial Metabolism**
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Abstract:	**Introduction:** The prevalence of people with type 2 diabetes mellitus (T2DM) has increased markedly over the last decades. The current best strategy for prevention of T2DM is increasing physical exercise combined with reducing caloric intake. Both exercise and caloric intake affect mitochondrial capacity of skeletal muscle, the most important tissue for glucose uptake. Indeed, recent work suggests that targeting muscle mitochondrial functioning could prevent and treat T2DM. Furthermore, recently it has been suggested that mitochondrial functioning is under control of the biological clock. In this regard it is not unexpected that epidemiological studies found an increased risk of obesity and T2DM in night-shift workers. **Methods:** To characterize the effects of night-shift work on (whole body) metabolism, rats were subjected to ad libitum (AL) feeding or time-restricted feeding (TRF) during the night- (nTRF) or daytime (dTRF) whilst body temperature was measured using temperature loggers. Additionally, we measured mitochondrial metabolism in permeabilized skeletal muscle fibers (soleus) ex vivo using high-resolution respirometry (Oroboros) at 4 different time-points along the light/dark cycle. **Results:** We show that dTRF phase-advances the daily rhythm of subcutaneous body temperature by 6 hours when compared to AL conditions (p=0.02). Interestingly, mean body temperature of dTRF animals was also lowered by 0.2°C (p=0.02). nTRF did not alter body temperature measures. Furthermore, we demonstrate that muscle mitochondrial metabolism shows both a time of day as well as a TRF effect for both maximal coupled and uncoupled mitochondrial respiration (i.e. state 3 and state 3U respiration). Finally, average daily mitochondrial respiration was lowest for dTRF animals and did not differ between nTRF and AL-fed animals. **Conclusion:** Ongoing experiments should reveal whether these differences in mitochondrial respiration result from altered mitochondrial abundance, altered mitochondrial morphology or can be attributed to specific components of the respiratory system and whether these changes translate in functional changes (i.e. glucose tolerance). **1. Conflict of interest:** The authors declare no conflict of interest. **2. Funding:** This work was supported by a grant from the Netherlands Organisation for Scientific Research (NWO; TOP grant number 40-00812-98-14047, 2015).

Title:	**The role of circulating acetate in human insulin sensitivity**
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Abstract:	**INTRODUCTION**: Microbially produced acetate has reported positive effects on metabolic health through effects on satiety, energy expenditure and substrate utilization. However, whether this translates into beneficial effects on insulin sensitivity in humans remains unknown. Of note, there are indications from cross-sectional studies that the gut microbiome may be associated to insulin sensitivity in a sex-specific manner. Here, we investigated the association between sex-specific changes in fasting plasma acetate concentrations and changes in insulin sensitivity indices during weight loss by a low-calorie diet (LCD) and during weight maintenance on diets varying in protein content (P) and glycemic index (GI) in the DiOGenes study. **METHODS:** First, 692 subjects (BMI >27 kg/m^2) underwent a LCD (800 kcal/d) for 8 weeks. Thereafter, 447 successful participants were randomly allocated to diets varying in P and GI: high P/LGI (HP/LGI), HP/high GI (HP/HGI), low P/LGI (LP/LGI), LP/HGI and a control diet for 6 months. A linear mixed model was used to investigate the associations between changes in acetate with changes in insulin resistance (HOMA-IR), insulin sensitivity (Matsuda index) and circulating fasting levels of glucose and insulin. This model was adjusted for center (random factor), age, weight loss, fat free mass and the mean acetate concentration. The model for the weight maintenance period was additionally adjusted for weight regain. Variables not normally distributed were Ln-transformed and changes (deltas) were calculated by the difference between before and after intervention. **RESULTS:** At baseline, acetate showed higher levels in men than women (1.35 ± 1.39 vs. 1.13 ± 0.97 mmol/L, respectively Independent T test *P*=0.030). However, a cross-sectional analysis did not show associations between acetate and insulin sensitivity indices. LCD increased acetate (without differences between men and women; 1.35±1.39 to 1.45±1.16 and 1.13±0.97 to 1.25±1.03 mmol/L, respectively, *P*=0.852) and improved insulin sensitivity more in men than in women (Matsuda index units: 4.20±2.54 to 7.02±3.78 vs 5.78±3.40 to 7.40±3.60, *P*=0.001, respectively). Interestingly, we observed positive associations between delta values of acetate and HOMA-IR (stdß 0.130, *P*=0.033) and insulin levels (stdß0.119, *P*=0.051) in women, but not in men (stdß -0.072, *P*=0.310 and stdß -0.066, *P*=0.359, respectively). In weight maintenance, no associations were found and acetate levels did not change as compared to after LCD on all diets. **CONCLUSION:** These results suggest an association of acetate and insulin resistance in women, but not in men. Exact mechanisms behind this sex-specific relationship with acetate remain to be elucidated.