

Friday, November 15, 2013

8:00 AM – 10:15 AM

**Ethan Sims Finalists' Presentations and Lilly Award Presentation and Lecture****T-49-OR****In Utero Undernutrition Programs Metabolic Adaptations in Skeletal Muscle Associated with Obesity and Weight Loss Resistance in Adult Mice**

Brittany Beauchamp, Michael W. Dysart *Ottawa, Canada*; Sujoy Ghosh *Singapore City, Singapore*; Alphonse Chu, Alexandre Blais, Karunanithi Rajamanickam, Eve C. Tsai *Ottawa, Canada*; Mary-Elizabeth Patti *Boston, MA*; Mary-Ellen Harper *Ottawa, Canada*

**Background:** Maternal undernutrition is associated with increased risk for type 2 diabetes and obesity in the adult lives of offspring. We hypothesize that predisposition to metabolic disease is, in part, due to low oxidative capacity and dysfunctional mitochondrial energetics in skeletal muscle. **Methods:** We used an experimental mouse model system of maternal undernutrition during late pregnancy to examine female offspring from undernourished dams (U) and control offspring from ad libitum fed dams (C). Weight loss of 10 wk old offspring on a 4 week 40% calorie restricted diet was also followed. **Results:** U had reduced birth weight, rapid catch up growth, increased adiposity and impaired glucose tolerance compared to C, confirming previous studies. There was decreased expression in muscle of genes involved in PPAR $\alpha$ /RXR $\alpha$  and RAR activation; fatty acid metabolism; and NRF2-mediated oxidative stress response in U vs. C. Muscle mitochondria from U had decreased coupled (state 3) and uncoupled (state 4) respiration but increased maximal respiration compared to C. After calorie restriction, U lost half as much weight as C, mirroring previously reported weight loss variation in highly diet-adherent obese women in an intensively supervised behavioral weight loss program at the Ottawa Hospital. Muscle from calorie restricted U had decreased oxidative fibers and mitochondrial content as compared to calorie restricted C. Findings have been complimented with energetic studies in permeabilized muscle fibers. Primary muscle cells were isolated from U and C at 3 wk of age. Oxygen consumption of myotubes from U was decreased in the presence of glucose but unaltered in the presence of oleate compared to C. **Conclusions:** Findings suggest that suboptimal nutrition in utero programs adaptations in skeletal muscle that are associated with altered metabolism and weight loss resistance.

**T-50-OR****A Bayesian Meta-Analytic Study of Whether Rigorous Control Conditions Diminish Treatment Effects in Weight Loss Randomized Controlled Trials**

John A. Dawson, Kathryn A. Kaiser, Olivia Affuso, Gary Cutter, David B. Allison *Birmingham, AL*

**Background:** A common question asked by investigators, regulators, industry and federal funding agencies when planning a randomized controlled trial (RCT) of drugs, dietary supplements or other treatments for weight loss (WL) concerns how intense the background intervention given to both the control and intervention groups should be. Some advocate using the minimum background intervention that is ethically acceptable, so as not to diminish treatment effects; others advocate using the maximum background intervention that is practical, as such an approach may be considered more clinically sound, among other reasons. **Methods:** We perform a meta-analysis of 239 WL RCTs using an approach formulated by McIntosh that models the structural and observational aspects of the association between strength of background intervention and magnitude of expected treatment effect. Model parameters are estimated via an Expectation-Maximization (EM) algorithm and the variability associated with these estimates is quantified through a supplemented EM (SEM). We also assess the severity of violations of the assumed model to interrogate the robustness of our results. **Results:** We find that rigorous control conditions diminish expected treatment effects, so that an increase in control group WL of one kilogram corresponds with an expected shrinkage of the treatment effect by 0.309 kilograms [95% C.I. (-0.480, -0.138),  $p=0.0008$ ]; this result is found to be robust against the observed violations of the model assumptions. **Conclusions:** Our results confirm the intuition of some investigators that more rigorous background interventions do 'steal' some efficacy from the studied treatment, but do so only

in part. This recognition allows researchers to obtain more accurate estimates of treatment effects a priori, in order to design adequately powered investigations.

**T-51-OR****Validation of the Thr6Lys+Val81Ile Human Melanocortin 3 Receptor (MC3R) Variant as a Cause of Obesity Using Knock-In Mice**

Bonggi Lee *Bethesda, MD*; Jashin Koo *Rockville, MD*; Oksana Gavrilova, Yongjun Lee, Diane C. Adler-Wailes, Faye C. Chen, Ryan Gardner, Dezmound Taylor-Douglas, Robin Roberson, Jack A. Yanovski *Bethesda, MD*

**Background:** We have previously reported that children who were homozygous for a pair of missense MC3R variants (Thr6Lys+Val81Ile) that decrease MC3R signaling had significantly greater BMI and fat mass than control children. **Methods:** To characterize the effects of these mutations, we generated two novel knock-in mouse models replacing the murine MC3R with either wild type human MC3R (hWT) or Thr6Lys+Val81Ile human MC3R (hMU). **Results:** On both chow and high fat diets, homozygous hMU mice had significantly greater body weight and body fat mass but significantly decreased fat-free mass compared to homozygous hWT. However, as observed for heterozygous Thr6Lys+Val81Ile MC3R children, heterozygous hMU mice did not exhibit any differences in body composition. Homozygous hMU mice had increased energy intake, increased feeding efficiency, and a slight reduction in energy expenditure only at thermoneutrality. Energy intake decreased after leptin injection (1  $\mu\text{g/g b.w.}$ ) equally in homozygous hMU and hWT, suggesting that altered leptin sensitivity does not explain the greater energy intake of homozygous hMU mice. Serum adiponectin was notably increased in homozygous hMU mice ( $p<0.01$ ) and despite their greater fat mass, there was no increase in adipose tissue inflammatory cell infiltration. Homozygous hMU mice had similar insulin sensitivity to lean hWT mice. **Conclusions:** These data suggest that homozygosity for the human MC3R sequence variant Thr6Lys+Val81Ile alters energy homeostasis in mice at least partially by increasing food intake. In addition, despite their higher fat mass hMU mice appear to have white adipose tissue that is metabolically healthier. Further studies examining how such mutations affect peripheral tissue metabolism and how increased adiponectin may affect food intake may further reveal mechanisms through which MC3R affects energy homeostasis.

**T-52-OR****Amylin and Leptin Interact in the Ventral Tegmental Area to Reduce Food Intake**

Elizabeth G. Mietlicki-Baase, Brianne A. Jeffrey, Diana R. Olivos, Matthew R. Hayes *Philadelphia, PA*

**Background:** Amylin, a pancreatic  $\beta$ -cell-derived neuropeptide, suppresses food intake by activating CNS amylin receptors. When amylin is delivered systemically with leptin, an adipose-derived anorectic hormone, the food intake and body weight suppressive effects are greater than those of either peptide alone. Investigations of the CNS nuclei mediating this interaction have been restricted to the area postrema and hypothalamus. Given the recent finding that amylin receptor activation in the ventral tegmental area (VTA) is physiologically involved in the control of food intake, and that VTA leptin receptor activation reduces food intake, it is possible that the VTA may be mediating in part the amylin-leptin interaction. **Methods:** We delivered different dose combinations of amylin and leptin to the VTA of male rats and measured subsequent food intake. We also measured feeding and body weight gain in response to VTA leptin after VTA amylin receptor blockade. **Results:** Low doses of intra-VTA amylin (0.04 $\mu\text{g}$ ) and leptin (0.1 $\mu\text{g}$ ) that alone had no effect on 24h chow intake, suppressed food intake when coadministered. Similarly, moderately suprathreshold doses of amylin (0.4 $\mu\text{g}$ ) and leptin (0.3 $\mu\text{g}$ ) delivered to the VTA reduced feeding individually, while the combination of these doses further suppressed food intake compared to either drug alone. Meal pattern analyses suggest that these effects may be mediated by reductions in meal size. Further evidence supporting the VTA as a physiologically relevant site of interaction for amylin and leptin signaling was provided by the finding that VTA amylin receptor blockade with AC187 (0.3 $\mu\text{g}$ ) attenuated the anorectic and body weight-suppressive effects of intra-VTA leptin (0.6 $\mu\text{g}$ ). **Conclusions:** These findings highlight the VTA as an important CNS structure mediating the cooperative effects of leptin and amylin. DK96139, DK97954.

## T-53-OR

**How Plant-Based Do We Need to Be to Achieve Weight Loss? Results of the New Dietary Interventions to Enhance the Treatments for Weight Loss (New DIETs) Study**

Brie Turner-McGrievy, Ellen Wingard, Charis Davidson, Morgan Taylor, Sara Wilcox *Columbia, SC*

**Background:** Several epidemiological studies have examined differences in health-related outcomes by dietary pattern (vegan, vegetarian (veg), pescovegetarian (pesco), semi-vegetarian (semi), or omnivorous (omni) diets), finding vegans have the lowest BMIs, prevalence of Type 2 diabetes, and risk of certain cancers. Vegans also gain significantly less weight as they age as compared to the other dietary patterns. No randomized trials have explored the effects of adopting these dietary patterns on weight loss. **Methods:** We conducted an 8-wk pilot weight loss trial among overweight and obese adults (n=63; 21% black, 27% male). Participants were randomized to follow one of the 5 dietary approaches, all emphasizing low-fat and low-glycemic index foods without caloric restriction, and attended weekly meetings to learn about their diet. **Results:** Using an intention-to-treat analysis, mean % weight loss ( $\pm$ SD) was significantly different among the 5 groups (vegan:  $-4.8\pm 2.1\%$ , veg:  $-4.8\pm 3.2\%$ , pesco:  $-4.3\pm 1.8\%$ , semi:  $-3.7\pm 2.3\%$ , omni:  $-2.2\pm 2.0\%$ ;  $F=2.62$ ,  $p<0.05$ ). Post-hoc analysis revealed a trend towards a difference between the vegan and omnivorous groups ( $p=0.054$ ). All macronutrients (% kcal) were significantly different (ANOVA,  $p<0.05$ ) among the five groups with the vegan group having a greater decrease in saturated fat than other groups. Study participants will complete a 6-mo follow-up assessment to determine longer-term adherence, and those findings will also be presented. **Conclusions:** Plant-based eating styles have public health appeal, promoting both significant weight loss and dietary improvements. Compared to standard weight loss approaches, which focus on reducing energy intake, plant-based dietary approaches do not require dietary self-monitoring, which can be burdensome. Plant-based diets are a promising strategy for weight loss independent of caloric restriction.

1:30 PM – 3:00 PM

**Oral Abstracts Track 1 - Muscle and Mitochondrial Energetics**

## T-54-OR

**Cellular and Molecular Basis of Modulation of ACSL5 Expression as Pertained to Obesity**

Abishankari Rajkumar, Jessica Chan, Daniel Soong, Pierrette M Bolongo, Kristi Adamo, Éric Doucet, Denis Prud'Homme, Frederique Tesson *Ottawa, Canada*

**Background:** Fatty acid transport is reported to influence the success of weight reduction. The transmembrane Acyl-CoA Synthetase Long Chain 5 (ACSL5) protein involved in fatty acid uptake and metabolism, is localised in both mitochondria and endoplasmic reticulum. Alternative splicing of ACSL5 generates a long and short isoform, regulated by an upstream and downstream AUG respectively. The single nucleotide polymorphism rs2419621 in ACSL5 gene, located 12 nucleotides upstream of the second transcription site, is associated with weight loss. Skeletal muscle in carriers of the rare allele have higher ACSL5 mRNA levels. This functional polymorphism creates a new E-box recognized by transcription factor MyoD, increasing transcription of the downstream reporter gene. We hypothesize that the short isoform expression is regulated by rs2419621 and is predominantly located in the mitochondria where it plays a role in fatty acid  $\beta$ -oxidation. **Methods:** C2C12 myoblast cells were transfected with ACSL5 long and short cDNA containing vectors. Subsequently, colocalisation analysis of ACSL5 isoforms in subcellular organelles was carried out using confocal microscopy and fluorescence-based imaging with determination of Mander's coefficients. **Results:** Mander's coefficient values were 0.421 and 0.706 for long and short isoforms in mitochondria, respectively. Meanwhile, Mander's coefficients for the long and short isoforms in endoplasmic reticulum (ER) were 0.835 and 0.735, respectively. All findings were significant ( $p<0.0001$ ). Although, short and long isoforms are both found in ER, the short isoform appeared to be predominantly localized in the mitochondria, in comparison to the long isoform. **Conclusions:** Carriers of the rare allele might present increased ACSL5 short isoform levels in the mitochondria, leading to increased fatty acid  $\beta$ -oxidation as compared to non-carriers.

## T-55-OR

**Skeletal Muscle Mitochondrial Respiration Is Lower in African American Compared to Caucasian Women and Is Associated with Resting Metabolic Rate and Cardiorespiratory Fitness**

James P. DeLany, Giovanna Distefano, Paul M. Coen, Frederico G.S. Toledo, John J. Dube, Maja Stefanovic-Racic, Bret H. Goodpaster *Pittsburgh, PA*

**Background:** The prevalence of obesity is greater in African American women (AAW) compared to Caucasian women (CW). Lower energy expenditure, particularly lower resting metabolic rate (RMR) is observed in AAW. This low RMR may play a role in the greater obesity in AAW, but reasons for this difference are not known. **Methods:** We examined skeletal muscle mitochondrial respiration, cardiorespiratory fitness (VO<sub>2</sub> peak), and RMR in young (23.8 $\pm$ 4.8 y) healthy women. We present data from 20 AAW (22.7 $\pm$ 4.0 kg/m<sup>2</sup>, 62 $\pm$ 9 kg) and 22 CW (22.7 $\pm$ 3.1 kg/m<sup>2</sup>; 63 $\pm$ 9 kg) matched for BMI and weight. Percutaneous biopsies of the vastus lateralis were obtained following an overnight fast. Mitochondrial respiratory properties were determined in permeabilized muscle fiber bundles by high-resolution respirometry. RMR was measured by indirect calorimetry, and VO<sub>2</sub> peak was determined during a graded exercise test. **Results:** Basal (State 4; 67 $\pm$ 16 vs. 82 $\pm$ 18 pmol O<sub>2</sub>/sec/mg;  $p<0.015$ ), maximal coupled (State 3; 320 $\pm$ 68 vs. 422 $\pm$ 65 pmol O<sub>2</sub>/sec/mg;  $p<0.001$ ) and uncoupled (State U; 354 $\pm$ 76 vs. 483 $\pm$ 69 pmol O<sub>2</sub>/sec/mg;  $p<0.001$ ) respiration were lower in AAW compared to CW. This corresponded with lower RMR (1259 $\pm$ 185 vs 1383 $\pm$ 178 kcal/day;  $p<0.01$ ) and VO<sub>2</sub> peak (2007 $\pm$ 428 vs 2320 $\pm$ 491 ml/min;  $p<0.03$ ) in AAW. When combining groups, State 4, State 3 and State U respiration correlated positively with RMR ( $r=0.44$ ,  $p<0.01$ ;  $r=0.39$ ,  $p<0.03$ ;  $r=0.40$ ,  $p<0.02$ ) and VO<sub>2</sub> peak ( $r=0.54$ ,  $p<0.001$ ;  $r=0.48$ ,  $p<0.002$ ;  $r=0.48$ ,  $p<0.003$ ). **Conclusions:** In summary, RMR and VO<sub>2</sub> peak were lower in these young, lean AAW compared with matched CW. Skeletal muscle mitochondrial respiration was also lower in AAW and was associated with RMR and VO<sub>2</sub> peak. These data suggest that differences in skeletal muscle mitochondrial respiration are related to the lower metabolic rate in AAW and may be related to the increased risk of weight gain in AA women.

## T-56-OR

**Increased Muscle Mitochondrial Respiration in Obese Diet Sensitive Compared to Obese Diet Resistant Humans**

Brianne Thrush, Ghadi Antoun *Ottawa, Canada*; Robert Boushel *Copenhagen, Denmark*; Éric Doucet, Pascal Imbeault, Jean-Francois Mauger, Ruth McPherson, Robert Dent, Mary-Ellen Harper *Ottawa, Canada*

**Background:** Differences in skeletal muscle oxidative capacity and mitochondrial function may contribute to weight loss variability in humans. We previously showed that obese diet sensitive (ODS) have a higher proportion of oxidative fibers and mitochondrial proton leak in quadriceps muscle compared to obese diet resistant (ODR) women. It was hypothesized that skeletal muscle from ODS would demonstrate higher rates of mitochondrial respiration prior to and following a high fat meal (HFM). **Methods:** Diet adherent women who completed the Ottawa Hospital Weight Management Program (OHWMP) and demonstrated the highest (ODS) and the lowest (ODR) rates of weight loss participated in this study. V. lateralis biopsies were obtained from ODS (n=8, 52 $\pm$ 2yrs; 95.8 $\pm$ 1.8 kg; 36.3 $\pm$ 1.7 kg/m<sup>2</sup>) and ODR (n = 6, 46 $\pm$ 2yrs; 101.5 $\pm$ 8.9kg; 36.8 $\pm$ 2.7kg/m<sup>2</sup>) before and 6 h post a HFM. The HFM was 35% of total daily caloric requirements with 60% of calories from fat (50% saturated fat). Mitochondrial metabolism was assessed in permeabilized muscle fibers with high resolution respirometry. **Results:** Fatty acid supported respiration (1.5mM malate (M), 200  $\mu$ M octanoyl carnitine (OC), 5mM ADP) was significantly increased in ODS compared to ODR prior to (ODR vs. ODS; 8.6  $\pm$  1.3 vs. 11.4  $\pm$  1.6 pmol/s/mg wet wt,  $p<0.05$ ) and 6 h post (ODR vs. ODS; 12.1  $\pm$  2.7 vs. 18.4  $\pm$  2.5 pmol/s/mg wet wt,  $p<0.05$ ) the HFM. OXPHOS (M, OC, 2mM pyruvate, 10mM glutamate, 10mM succinate, 10mM ADP) was also significantly increased in ODS compared to ODR prior to (ODR vs. ODS; 52.8  $\pm$  1.4 vs. 65.2  $\pm$  5.0 pmol/s/mg wet wt) and 6 h post (ODR vs. ODS; 53.4  $\pm$  5.6 vs. 71.8  $\pm$  6.1 pmol/s/mg wet wt) a HFM. **Conclusions:** This research demonstrates that muscle mitochondrial function is different between ODS and ODR. Future research will further investigate links between mitochondrial function, oxidative stress and weight loss.

**T-57-OR****Exercise Resistance in Obese Individuals with Type 2 Diabetes**

Lauren M. Sparks, Hui Xie *Orlando, FL*; Neil M. Johannsen, Timothy Church *Baton Rouge, LA*; Steven R. Smith *Orlando, FL*

**Background:** Exercise benefits most, but not all, individuals. We found that 9 months of supervised exercise failed to improve muscle metabolism in ~20% of a cohort of obese individuals with type 2 diabetes (T2D). Exciting new evidence indicates that some individuals with insulin resistance have impaired early gene responses to acute exercise. We hypothesized that those individuals with T2D who did not metabolically improve after exercise have a transcriptional signature of their skeletal muscle distinct from those who did respond favorably. **Methods:** Forty-two individuals (57.5 + 7.6y, 34.8 + 5.7kg/m<sup>2</sup>) with T2D [and balanced in age, BMI, sex] were randomized to 9 months of supervised exercise. All participants underwent a DXA scan, blood draw and biopsy of v. lateralis before and after intervention. Mitochondrial DNA (mtDNA) copy number was assessed by qPCR. RNA was isolated from baseline muscle tissue for Illumina transcriptome analyses. **Results:** A 'responder' was defined a priori as: 1) decrease in HbA1c, 2) increase in mtDNA, 3) decrease in %fat, 4) decrease in BMI. We performed a principal components analysis to distinguish 'non-responders' from 'responders' based on the changes in those 4 outcomes. Two distinct groups (n=9 each) were found based on eigenvalue. We generated a 'hit list' of 192 genes that were significantly different between the two groups. An unsupervised two-way cluster analysis [with R2 index = 0.50] clearly distinguished two groups by the mRNA expression levels. 'Non-responders' displayed a significant down-regulation of ~70% and an up-regulation of ~30% of genes, while 'responders' displayed a reciprocal expression pattern. **Conclusions:** This exciting new data indicates there is a unique basal expression pattern in skeletal muscle tissue which may predict an individual's exercise response in clinical outcomes.

**T-58-OR****CB1 Antagonist Increased Irisin and Genes Related to Energy Expenditure in Fat-Fed Dog**

Morvarid Kabir, Malini Iyer, Qiang Wu, Darko Stefanovski, Orison O. Woolcott, Stella P. Kim, Cathryn M. Kolka, Viorica Ionut, Joyce M. Richey, Richard N. Bergman *Los Angeles, CA*

**Background:** The expression of genes related to energy expenditure, especially irisin, the novel hormone secreted by muscle and fat has not been evaluated with CB1 antagonist rimonabant (RIM). We demonstrated in the dog that RIM improves deleterious effects of high fat diet (HFD) by reducing body fat, and increasing insulin sensitivity. The current study examines the longitudinal effects of HFD and RIM on irisin, uncoupling protein 1, 2, 3 (UCP1,2,3) and PPAR $\gamma$  coactivator 1 alpha (PGC1- $\alpha$ ) in muscle, fat and liver. **Methods:** Animals were fed a HFD (52% fat) for 6 weeks followed by an additional 16 weeks of fat feeding with either HFD + placebo (PL) (n=9) or HFD + RIM (1.25 mg/kg per day; n=11). Biopsies from muscle, subcutaneous (SC) and visceral (VIS) fat and liver were obtained for gene expression: before HFD (Pre-fat) and after 16 weeks of HFD +/- RIM. **Results:** Irisin expression decreased in muscle by 50% (P<0.05) and in SQ fat by 56% (P<0.05) by HFD, RIM restored irisin expression in muscle and increased the expression of this gene 3 fold in SQ and VIS fat (P<0.05). The same trend was observed for PGC1- $\alpha$  and UCP1 in the VIS and SQ fat depots. Interestingly, UCP2 and UCP3 expression decreased by 85% and 65% (P<0.05) after 22 weeks of HFD in PL group, but was completely restored to pre-fat levels by RIM. **Conclusions:** Thus, irisin and genes related to energy expenditure increased significantly by CB1 antagonist.

**T-59-OR****Sarcoplipin Is the Novel Regulator of Thermogenesis and Protects Against Obesity by Increasing Energy Expenditure**

Santosh K. Maurya, Naresh C. Bal, Danesh H. Sopariwala, Sana A. Shaikh, Meghna Pant, Leslie A. Rowland *Columbus, OH*; Sanjeeva A. Goonasekera, Jeffery D. Molkenkin *Cincinnati, OH*; Muthu Periasamy *Columbus, OH*

**Background:** Skeletal muscle, which constitutes 40% of total body mass is considered to be important for heat generation and whole-body energy metabolism. However, the detailed mechanisms are not well defined. **Methods:** We surgically ablated intrascapular brown adipose tissue (iBAT) in a set of wild-type (WT) and SLN-knockout mice (Sln-/-). Acute cold exposure of

mice to 4 °C, and measurement of oxygen consumption, was performed in the CLAMS (Columbus Instruments Inc, Columbus, OH,) set up, which is temperature controlled. Sln-/- mice were bred with SLN-overexpression mice (Sln-OE) to re-introduce SLN (Sln-/-/OE mice.). For weight gain and obesity studies, WT, Sln-/-, and Sln-OE mice were fed with high fat diet (HFD, 45% calories from fat) for 12 weeks. **Results:** Here, we show that sarcoplipin (SLN), a newly identified regulator of the sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPase (Serca) pump, plays critical role in the maintenance of body temperature and whole-body energy homeostasis. Mice, lacking SLN, (Sln-/-) were unable to maintain their core body temperature (37 °C), when challenged with acute cold (4°C). Surgical ablation of iBAT and functional knockdown of uncoupling protein (UCP1) allowed us to highlight the role of SLN in thermogenesis. Reintroduction of SLN in the Sln-/- mice fully corrected the defective muscle-based thermogenesis. In addition, we show that Sln-/- mice are susceptible to weight gain and developed massive obesity when fed with HFD. In contrast, mice overexpressing SLN are resistant to HFD-induced obesity, implicating SLN as a regulator of muscle metabolism. **Conclusions:** Our data suggest that SLN/SERCA pump activity is an important mediator of muscle thermogenesis, metabolism and whole-body energy homeostasis. Therefore, SLN could serve as a potential target to enhance energy expenditure and treat metabolic-overload-induced obesity.

1:30 PM – 3:00 PM

**Oral Abstracts Track 3 - Appetite****T-60-OR****Activation of Intestinal Taste Receptors Augmented Oral Glucose Stimulated GLP-1 and PYY in Healthy Humans**

Steven R. Smith *Orlando, FL*; Rudolph Leibel *New York, NY*; Terri H. Kim, Colleen Burns, Alain D. Baron, Mark S. Fineman *San Diego, CA*

**Background:** Whether activation of enteroendocrine cell taste receptors (TR) leads to gut hormone release is controversial. Previous studies only examined the effects of sweet tastants in the fasting state, or did not consider the confounding effects of activating lingual and stomach TRs. **Methods:** We tested whether activation of sweet, and to a lesser extent umami and bitter TR activation in the intestine could modulate plasma levels of anorexiant hormones GLP-1 and PYY in humans. We made tablets (LC001) combining 1600 mg of sweet (sucralose, stevia, rebaudioside A), 200 mg of umami (glutamine) and 8 mg of bitter (quinine). The tablets were enterically coated to release at pH  $\geq$ 5.5, thus eliminating taste and exposure in the stomach. 12 healthy subjects (7 males, mean age 50 y, fasting glucose 90 mg/dL, and BMI 29.5 kg/m<sup>2</sup>) were studied under 3 meal conditions in a blinded, randomized crossover design. Following a 12h fast, LC001 or placebo was administered orally 60 minutes prior to: an extended fast (6 hours); 75 g oral glucose (OG); or 273 mL Ensure Plus (EP). **Results:** LC001 had no effect on fasting or post EP GLP-1 and PYY concentrations. In contrast, LC001 augmented post OG GLP-1 and PYY concentrations relative to the pre-meal values: AUC<sub>0-5h</sub> 38% and 23%; Cmax 60% and 26%, respectively, p<0.05 for all. LC001 also led to a 6% reduction in glucose AUC<sub>0-5h</sub> (p<0.05) with no change in concurrent insulin concentrations. **Conclusions:** Gut TR activation did not modulate gut hormone release in the absence of calorie intake. LC001 augmented GLP-1 and PYY following OG but not EP. Because LC001 was composed predominantly of sweet tastants, the data suggest that activation of sweet TR requires a critical amount of the cognate fuel (carbohydrate) to modulate hormone release. TR activation beyond the stomach could have beneficial effects on body weight and glucose tolerance.

**T-61-OR****Effects of PYY3-36 and GLP-1 on Energy Intake, Energy Expenditure and Appetite in Overweight Men**

Schmidt B. Julie, Anders Sjödin, Nikolaj T. Gregersen *Frederiksberg C, Denmark*; Jens J. Holst *Copenhagen, Denmark*; Arne Astrup, Sue D. Pedersen, Johanne L. Arentoft, Christian Ritz *Frederiksberg C, Denmark*; Thue W. Schwartz *Copenhagen, Denmark*

**Background:** Aim: To examine the effects of GLP-1 and PYY3-36, separately and in combination, on energy intake, energy expenditure, appetite sensations, glucose and fat metabolism, ghrelin and vital signs in overweight men. **Methods:** 25 male subjects participated in this randomized, double-blinded, placebo-controlled 4-arm crossover study. On separate test days they received a 150 min intravenous infusion of either a) 0.8pmol/kg/min PYY3-

36, b) 1.0 pmol/kg/min GLP-1, c) 0.8pmol/kg/min PYY3-36 + 1.0pmol/kg/min GLP-1 or d) placebo. Ad libitum energy intake was assessed during the final 30 min. Measurements of subjective appetite sensations, energy expenditure and fat oxidation, vital signs and blood variables were collected throughout the infusion period **Results:** No effect on energy intake was found by monoinfusions of PYY3-36 (-4%) or GLP-1 (-3%). However, the combined infusion reduced energy intake compared to placebo (-30%) and was more than the sum of the monoinfusions, demonstrating a synergistic effect. Combined infusion slightly increased sensation of nausea, but this effect could not explain the effect on energy intake. A decrease in plasma ghrelin was found after all active treatments compared to placebo (all  $P < 0.05$ ); however, infusions of GLP-1+PYY3-36 resulted in an additional decrease compared to the monoinfusion **Conclusions:** Co-infusion of GLP-1 and PYY3-36 exerted a synergistic effect on energy intake. The satiating effect of the meal was enhanced by GLP-1 and PYY3-36 in combination compared to placebo. Co-infusion was accompanied by slightly increased nausea and a decrease in plasma ghrelin, but neither of these factors could explain the reduction in energy intake

### T-62-OR

#### Baseline Slow Wave Sleep Negatively Relates to Weight Gain and Increased Caloric Intake During Sleep Restriction in Healthy Adults

Andrea M. Spaeth, Namni Goel, David F. Dinges *Philadelphia, PA*

**Background:** We have recently shown that sleep restriction (SR) leads to increased caloric intake and weight gain. However, not all subjects respond to SR to the same degree (some gain a significant amount of weight while others maintain or lose weight). The amount of time spent in sleep stages 3 or 4 (slow-wave sleep [SWS]) is stable and trait-like within individuals but highly variable between individuals. The current study examined if individual differences in baseline SWS associated with energy balance responses to SR.

**Methods:** N=31 healthy subjects (33.6±8.4 y, 25.6±2.8 BMI, 15 f) participated in a laboratory protocol including 2 baseline nights (BL1-2; 10-12h time in bed [TIB]/night) followed by 5 consecutive SR nights (4h TIB/night). Polysomnography was recorded on BL2 and scored using standard criteria. Duration of each sleep stage was calculated as a percent of total sleep time (%TST). Weight was measured at protocol admittance and discharge.

Food/drink consumption was ad libitum and recorded daily. Partial correlations controlling for age, gender and BMI were used for analyses. **Results:** Subjects gained 0.50±1.5 kg during the study and consumed 21% more calories during SR than during BL. Baseline SWS ranged from 1.6-28.8% of TST and was negatively correlated with weight gain ( $r = -0.46$ ,  $p = 0.015$ ) and with increased caloric intake during SR ( $r = -0.53$ ,  $p = 0.004$ ). Sleep onset latency, sleep efficiency and rapid eye movement sleep were not related to weight gain or SR caloric intake ( $ps \geq 0.29$ ). Stage 2 %TST was not significantly related to weight gain ( $r = 0.31$ ,  $p = 0.11$ ) but was positively associated with increased caloric intake during SR ( $r = 0.40$ ,  $p = 0.036$ ). **Conclusions:** Adults with less slow-wave sleep may be more vulnerable to weight gain and increased caloric intake during sleep restriction. [NIH R01 NR004281, F31 AG044102; CTRC UL1RR024134; ONR N00014-11-1-0361]

### T-63-OR

#### Role of Child Weight Status and the Relative Reinforcing Value of Food in Children's Response to Portion Size Increases

Tanja V. Kral, Adriane Remiker *Philadelphia, PA*; Erin M. Rauh *Fort Collins, CO*; Renee H. Moore *Raleigh, NC*

**Background:** The portion size (PS) of food has been identified as an important determinant of energy intake in children. It remains to be established if children's susceptibility to overeating when served large food portions may depend on their weight status or how reinforcing they find food to be. The aim of this study was to compare the effects of increasing the PS of all foods and beverages served at a fast-food style meal on energy intake in normal-weight (NW) and obese (OB) 8- to 10-year-old children and to test if children's response to PS increases was affected by their relative reinforcing value of food (RRVF). **Methods:** In a cross-over design, 50 children (25 NW, 25 OB) were served dinner once a week for 3 weeks. Across conditions, the same dinner was served, but the PS of all foods and the sugar-sweetened beverage varied (100%, 150%, 200%). Children's RRVF was assessed using a computerized behavioral choice task. **Results:** There was a significant main effect of PS ( $P = 0.003$ ) and child weight status ( $P = 0.0005$ ) and a non-significant

trend for a PS-by-weight status interaction ( $P = 0.108$ ) on energy intake. Mean intakes across conditions (100%, 150%, 200%) were 801 ± 57, 964 ± 58, and 873 ± 57 kcal for NW children and 1041 ± 57, 1129 ± 57, and 1210 ± 57 for OB children, respectively. Neither the main effect of children's RRVF status (high/low) nor the PS-by-RRVF status interaction was significant ( $P > 0.48$ ). **Conclusions:** Obesogenic food environments that offer large portions of energy-dense foods affect all children's energy intake irrespective of their weight status or how reinforcing they find food to be.

### T-64-OR

#### Targeted Prevention of Excess Weight Gain and Eating Disorders in High-Risk Adolescent Girls with Loss of Control (LOC) Eating: A Randomized, Controlled Trial

Marian Tanofsky-Kraff *Bethesda, MD*; Lauren B. Shomaker *Ft. Collins, CO*; Denise E. Wilfley *St. Louis, MO*; Jami Young *New Brunswick, NJ*; Tracy Sbrocco, Mark Stephens, Lisa Ranzhofer, Camden Elliott, Sheila M. Brady, Rachel Miller, Anna Vannucci, Edny J. Bryant, Robyn Osborn, Sarah Berger, Cara Olsen, Merel Kozlosky, James C. Reynolds, Jack A. Yanovski *Bethesda, MD*

**Background:** LOC eating, which comprises both objective and subjective binge eating episodes, predicts excess weight gain and exacerbated disordered eating in youth. Interpersonal psychotherapy (IPT) reduces binge eating and induces weight stabilization in obese adults with binge eating disorder (BED). It is unknown whether IPT prevents excess weight gain and eating disorder (ED) onset in at-risk youth. **Methods:** We randomized 113 girls (12-17y) with BMI 75th-97th %ile and LOC eating ( $\geq 1$  episodes/month) to a 12-wk group of IPT for the prevention of weight gain (IPT-WG; n=55) or health education (HE; n=58) to examine program efficacy for preventing excess weight gain and EDs over a 1-y follow-up interval. Analyses accounted for age and race. **Results:** Girls attended more IPT-WG than HE sessions (85 vs. 78%,  $p = .05$ ). Retention through 1-y follow-up was 89% for IPT-WG and 85% for HE ( $p = .47$ ). Groups did not differ in percentage that gained more than expected BMI at 1-y follow-up (IPT-WG 30 vs. HE 41%,  $p = .26$ ). Despite similar percentages of non-overweight (IPT-WG 4 vs. HE 3%) and overweight (IPT-WG 49 vs. HE 52%) at baseline ( $p = .96$ ), 0% of girls in IPT-WG compared to 10% in HE increased their weight status and became overweight or obese by 1-y ( $p = .02$ ). About half of girls in each group ceased LOC eating by 1-y (IPT-WG 51 vs. HE 48%,  $p = .76$ ), but fewer girls in IPT-WG reported objective binge eating at 1-y (4 vs. 17%,  $p = .04$ ) despite no difference in baseline episodes. Girls in IPT-WG were 2.6 times less likely to have a partial/full-syndrome ED during the 1-y follow-up than girls in HE ( $p = .07$ ). **Conclusions:** A specialized IPT program designed to reduce excess weight gain in high-risk adolescent girls by targeting LOC eating, relative to usual care, reduces classic binge eating patterns that characterize BED and the development of overweight/obesity in at-risk girls.

### T-65-OR

#### Changes in Taste Perception and Eating Behavior After Bariatric Surgery-Induced Weight Loss in Women

M. Yanina Pepino, David Bradley, J. Christopher Eagon, Shelby Sullivan, Nada A. Abumrad, Samuel Klein *St. Louis, MO*

**Background:** Roux-en-Y gastric bypass (RYGB) surgery causes greater weight loss than laparoscopic adjustable gastric banding (LAGB). The mechanism responsible for this difference is not known, but could be related to changes in taste perception, which would influence eating behavior. We tested the hypothesis that RYGB has weight loss-independent and diet-independent effects on sweet taste perception and eating behavior in obese people. **Methods:** A total of 27 obese subjects were studied before and after 20% weight loss induced by RYGB (n=17, BMI=46±8 kg/m<sup>2</sup>) or LAGB (n=10, BMI=49±11 kg/m<sup>2</sup>). After surgery, all subjects participated in a supervised weight management program to enhance consumption of a similar energy-deficit diet and achieve the target weight loss within 4-6 months. The following outcomes were evaluated: 1) taste sensitivity (at threshold and above-threshold sucrose and glucose concentrations); 2) sucrose preferences; 3) sweetness palatability; and 4) eating behavior. **Results:** Weight loss induced by both procedures caused the same decrease in: 1) preferred concentration of sucrose (-12±10%), 2) perceived sweetness of sucrose (-7±5%), 3) frequency of cravings for sweets (-22±5%), and 4) influence of emotions (-27±5%) and external food cues (-30±4%) on eating behavior (all P-values

<0.05). Neither RYGB nor LAGB affected taste detection thresholds. RYGB, but not LAGB, shifted sweetness palatability from pleasant to unpleasant when repetitively tasting sucrose ( $P=0.05$ ). **Conclusions:** Both LAGB and RYGB are associated with similar alterations in eating behaviors, when weight loss is matched. These changes in eating behavior are not associated with changes in taste sensitivity, suggesting other, as yet unknown, mechanisms are involved.

1:30 PM – 3:00 PM

### Oral Abstracts Track 3 - Surgery

#### T-66-OR

#### Gastric Bypass Surgery vs. Highly Intensive Lifestyle and Medical Intervention to Manage Type 2 Diabetes: The CROSSROADS Randomized Clinical Trial

David E. Cummings, David E. Arterburn, Emily O. Westbrook, Jessica N. Kuzma, Skye D. Stewart, Chun P. Chan, Steven N. Bock, Jeffrey T. Landers, Mario Kratz, Karen Foster-Schubert, David R. Flum *Seattle, WA*

**Background:** Randomized trials of bariatric surgery vs lifestyle/medicines likely enroll highly motivated subjects, limiting generalizability of findings. We addressed this problem while comparing Roux-en-Y gastric bypass (RYGB) to the most rigorous lifestyle-medical intervention for type 2 diabetes (T2DM) yet studied in such an RCT. **Methods:** Using a population-based, Shared Decision Making recruitment strategy, we screened 1808 adults with T2DM and BMI 30-45 kg/m<sup>2</sup>. Of these, 43 were randomized to RYGB or a highly intensive lifestyle & medical intervention (ILMI) involving  $\geq 45$  min of aerobic exercise, 5 d/wk for 1 yr, largely supervised by exercise physiologists in a research gym. Using frequent in-person contact, nutritionists directed a weight- and glucose-lowering diet, with daily nutrition & exercise logs. Optimal T2DM medical treatment was provided. **Results:** The groups were equivalent at baseline for age, gender, ethnicity, anthropometrics, fitness, glycemia, dyslipidemia, and hypertension. However, the RYGB group had longer T2DM duration (11.4 $\pm$ 4.8 vs 6.8 $\pm$ 5.2 yr,  $P=0.009$ ). Weight loss at 1 yr was 25.8 $\pm$ 14.5 vs 6.4 $\pm$ 5.8% after RYGB vs ILMI, respectively ( $P<0.001$ ). The ILMI exercise program was successful, yielding a 30.1 $\pm$ 16.9% increase in VO<sub>2</sub>max, but an even greater 46.3 $\pm$ 16.7% increase followed RYGB ( $P=0.005$ ). Diabetes remission (HbA1c<6.0% off diabetes medicines) at 1 yr was 60% with RYGB vs 6% with ILMI ( $P=0.002$ ), even though surgical patients had longer T2DM duration. HbA1c decline over 1 yr was only modestly more after RYGB than ILMI (from 7.7 $\pm$ 1.0 to 6.4 $\pm$ 1.6% vs 7.3 $\pm$ 0.9 to 6.9 $\pm$ 1.3%, respectively,  $P=0.04$ ). However, this drop occurred with fewer medications after RYGB. No life-threatening complications occurred. **Conclusions:** Compared to the most rigorous ILMI yet tested vs surgery in an RCT, RYGB yielded greater T2DM remission in mild-moderately obese patients.

#### T-67-OR

#### A Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes: The Triabetes Study

Anita P. Courcoulas, Bret H. Goodpaster, Jessie K. Eagleton *Pittsburgh, PA*; Wei Lang *Winston-Salem, NC*; Melissa A. Kalarchian, Frederico G. Toledo, Steven Belle, John M. Jakicic *Pittsburgh, PA*

**Background:** Determine feasibility of a randomized controlled trial (RCT) and compare initial outcomes of gastric bypass, gastric banding, and a structured weight loss program for treating type 2 diabetes mellitus (T2DM) in grade 1 and 2 obese participants. **Methods:** A 3-arm RCT with 69 participants age 25-55 years, BMI 30-40 kg/m<sup>2</sup> with T2DM undergoing Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric band (LAGB), or an intensive lifestyle weight loss intervention (LWLI). Primary outcomes on the intention to treat (ITT) cohort were feasibility and effectiveness measured by weight loss and improvements in glycemic control. **Results:** 667 potential participants were screened of whom 69 (10.3%) were randomized, 30 (43.5%) with grade 1 obesity. Mean age was 47.3 $\pm$ 6.4 years, 81% were women, and mean glycated hemoglobin was 7.9 $\pm$ 2.0. After randomization, 7 (10%) participants refused to undergo their allocated intervention (3 RYGB, 1 LAGB, 3 LWLI) and 1 RYGB was excluded for current smoking. Twenty subjects underwent RYGB, 21 LAGB, and 20 LWLI with retention at 12 months of 90%, 86%, and 70%, respectively. RYGB participants had the greatest weight loss compared to LAGB and LWLI with average weight loss of 27%, 17%, 10% from baseline, respectively ( $p<0.0001$ ). Partial/complete

remission of diabetes was 50%/17% in RYGB, 27%/23% in LAGB and 0%/0% in LWLI ( $p=0.0005/0.047$ , partial/complete). **Conclusions:** Preliminary results show that RYGB was the most effective treatment followed by LAGB for both weight loss and diabetes outcomes at one year. This study also highlights several potential challenges to successfully completing a larger RCT for diabetes and obesity treatment in those with BMI 30-40 kg/m<sup>2</sup>, including the difficulties associated with recruiting and randomizing patients to surgical versus non-surgical interventions.

#### T-68-OR

#### Baseline Insulin Levels Predict the Effects of Bariatric Surgery on Serious Events Over 20 Years in the Swedish Obese Subjects Study

Lars Sjöström, Lena M. Carlsson, Markku Peltonen *Gothenburg, Sweden*

**Background:** Bariatric surgery improves survival and reduces the incidence of myocardial infarction, stroke and cancer in obese patients. However, to identify clinically useful predictors of the treatment benefit, the total effect on all serious events needs to be considered. The long-term effects of bariatric surgery on a composite endpoint, consisting of CV events, cancer and mortality of any cause, was therefore examined in the non-randomized prospective controlled Swedish Obese Subjects (SOS) study. **Methods:** The effect of bariatric surgery on the time to the first serious event (death, myocardial infarction, stroke or cancer) was analyzed in 2010 obese subjects who underwent gastric bypass (13%), banding (19%) or vertical banded gastroplasty (68%), and 2037 contemporaneously matched obese controls receiving usual care. Age was 37-60 years and BMI was  $\geq 34$  kg/m<sup>2</sup> in men and  $\geq 38$  kg/m<sup>2</sup> in women. Follow-up time was up to 20 years. **Results:** During follow up, 518 controls and 453 surgery patients had at least one serious event. Bariatric surgery reduced the incidence of serious events (HR=0.84, 95% CI, 0.74 to 0.96,  $p<0.007$ ). The effect of surgery was greater in subjects with high baseline insulin levels compared to patients with low insulin (HR=0.76, 95% CI, 0.64-0.89 and HR=0.85, 95% CI, 0.69-1.04, respectively, interaction- $p$ -value=0.005). Baseline BMI did not influence the treatment benefit (interaction- $p$ -value=0.499). **Conclusions:** Bariatric surgery reduces the incidence of serious events in obese patients. The treatment benefit is increased in patients with high baseline insulin levels, while the degree of obesity does influence the effect of surgery.

#### T-69-OR

#### Association of Gastric Bypass on Gestational Weight of Children Born Before and Following Gastric Bypass Surgery

Ted D. Adams, Ahmad O. Hammoud, Lance E. Davidson, Alison M. Fraser, Rodrick McKinlay, Steven C. Simper, Sherman Smith, Ken R. Smith, Steven C. Hunt *Salt Lake City, UT*

**Background:** Interaction between maternal obesity, intrauterine environment, and adverse clinical outcomes of newborns has been described. This retrospective, matched control cohort study explored the birth weights of paired offspring of women before and after gastric bypass (GBP) surgery that were also compared to birth weights of paired offspring of matched obese control women without bariatric surgery. **Methods:** Using birth certificate data, 237 women who had given birth to a child before and after GBP surgery were matched to 237 women without GBP surgery and with at least 2 live births. Women were individually matched by age, race, parity, birth years of the child born just prior to and the child born just following GBP surgery, and mother's BMI group (30-34.9; 35-39.9 and  $\geq 40$  kg/m<sup>2</sup>). Using repeated-measures ANOVA, the birth weights were compared between children born to women of each group at the two deliveries. Differences in birth weights (preminus post-surgery deliveries in the same mother) were also compared. **Results:** Birth weights at pre-surgery delivery were 3533g and 3562g for GBP and non-GBP, respectively ( $p=0.49$ ) and at post-surgery delivery 3164g and 3412g ( $p<0.0001$ ) for GBP and non-GBP, respectively. Declines in birth weight from the pre- to post-surgery deliveries were 369g and 150g for GBP and non-GBP mothers, respectively ( $p<0.0001$ ). The decrease in birth weight from pre- to post-surgery deliveries in the GBP group represented a 7.3% lower birth weight than controls at post-surgery delivery. **Conclusions:** Birth weight of children born to mothers after GBP was significantly lower when compared to birth weight of siblings born before GBP and also to birth weight of the 2nd child born to non-GBP mothers. Biological reasons for as well as clinical relevance of these findings are yet to be determined.

## T-70-OR

**Does Gastric Bypass Influence Aging?**Natalia Leva, Trit Garg, John M. Morton *Stanford, CA*

**Background:** Telomeres are a well-known marker of aging. Current evidence suggests a link between aging, obesity and inflammation. In this longitudinal study, our goal is to show the relationship between telomere length (TL) and surgical weight loss. **Methods:** Preop and 3, 6, and 12 month postop telomere length, demographic and serologic data were prospectively collected on 51 bariatric surgery patients. Telomere length was assayed with quantitative PCR for a T/S ratio which is proportional to mean telomere length. Data were compared using Students t-tests and regression analyses. **Results:** Average preop demographics were: age (48.6), BMI (44.3), % female (76.5). By 12 mos postop, percent excess weight loss was 71% and declines were seen for hs-CRP (8.3 to 3.6) and fasting insulin (24 to 6). Telomere length (shorter is associated with aging) for the entire cohort did not change significantly (.9867 to .9822). However, when stratifying by preop CRP and LDL, significant changes were seen. Postop, high LDL patients had significant telomere lengthening in comparison to low LDL patients:  $-0.0271$  (low LDL) vs.  $+0.0227$  (high LDL),  $p=0.0387$ . Postop, high CRP patients had significant telomere lengthening in comparison to low CRP patients:  $-0.02294$  (low CRP) vs.  $+0.04125$  (high CRP),  $p=0.005$ . In the high CRP group, there was a significant positive correlation between weight loss and telomere length ( $r=.8787$ ,  $p=.0498$ ). In the high baseline CRP group, postop HDL increase was correlated with increase in telomere length,  $r=0.842$ ,  $p=0.0176$ . **Conclusions:** This is the first study to demonstrate surgical weight loss leading to decreased aging by increasing telomere length. Patients with high preoperative CRP and LDL sustained the greatest increases in telomere length. In addition to weight loss, HDL increase was significantly and positively correlated with telomere length increase.

## T-71-OR

**Bariatric Surgery & Gestational Diabetes: A Population-Based Study of 2199 Pregnancies**Kari Johansson, Sven Cnattingius, Nathalie Roos, Olof Stephansson, Martin Neovius *Stockholm, Sweden*

**Background:** Many women of reproductive age undergo bariatric surgery. The objective of this study was to compare the risk of gestational diabetes in women with versus without bariatric surgery history. **Methods:** After excluding women with diabetes the year before pregnancy, we identified 1,231,419 singleton pregnancies in the Swedish Medical Birth Register between 1998 and 2010. To each post-surgery pregnancy ( $n=2199$ ; 50% gastric bypass, 19% gastric banding, 29% vertical-banded gastroplasty, 3% other), 5 control pregnancies were matched by age, early pregnancy BMI, parity, smoking, education, and delivery year. To compare women with bariatric surgery history with women eligible for bariatric surgery, a secondary control cohort was sampled from women with a  $BMI \geq 35$  and matched for the same factors except BMI. Gestational diabetes information was retrieved from the Medical Birth Register and the National Patient Register. Odds ratios (OR) were estimated conditioned on the matching factors. **Results:** Compared to all pregnancies without bariatric surgery history ( $n=1,229,220$ ), post-surgery pregnancies showed higher maternal age, smoking prevalence and mean BMI, but lower education level and parity (all  $P < .001$ ). Lower risk for gestational diabetes was seen in post-surgery pregnancies than in matched control pregnancies (1.7% vs 3.6%; conditional OR 0.45; 95%CI 0.32-0.66;  $P < .001$ ). In the secondary analysis, comparing post-surgery pregnancies with matched control pregnancies in women with  $BMI \geq 35$  the difference increased (1.7% vs 6.6%; conditional OR 0.34; 95%CI 0.20-0.59;  $P < .001$ ). **Conclusions:** Women with bariatric surgery history had lower risk of gestational diabetes than matched controls, particularly compared to matched controls eligible for bariatric surgery.

1:30 PM – 3:00 PM

**Oral Abstracts Track 4 - Maternal Influences: From Conception to College**

## T-72-OR

**Macrosomia Prevention by Normalizing Prepregnancy Weight among Overweight/Obese Women: Findings from a National Pre-Birth Cohort**Xiaozhong Wen, Leonard H. Epstein *Buffalo, NY*

**Background:** Prepregnancy overweight/obesity is associated with macrosomia. We aimed to examine the extent to which macrosomia can be reduced by normalizing prepregnancy weight among overweight/obese women.

**Methods:** We analyzed data of 7,700 mothers with repeated pregnancies enrolled in U.S. Collaborative Perinatal Project (CPP). We stratified mothers into 4 groups with different trajectories of self-reported prepregnancy weights: Group 1, normal prepregnancy weight for both 1st and 2nd CPP pregnancies ( $N=5,122$ ); Group 2, normal prepregnancy weight for 1st pregnancy but overweight before 2nd pregnancy ( $N=668$ ); Group 3, overweight before 1st pregnancy but normal weight before 2nd pregnancy ( $N=293$ ); Group 4, overweight before both 1st and 2nd pregnancies ( $N=1,617$ ). Macrosomia was defined as measured birth weight 4,000 g or higher. We fit multivariable logistic regression for risk of macrosomia in 2nd pregnancy, adjusting for socio-demographic confounders. **Results:** The risk of giving birth to macrosomia babies for 2nd pregnancy was 4.3% for Group 1 mothers who were stable normal weight, but the risk doubled in Group 2 mothers who went from normal weight to overweight status (8.4%) or Group 4 mothers who were overweight before both pregnancies (9.8%). Interestingly, Group 3 mothers who were overweight for their 1st pregnancy but normal weight for 2nd pregnancy, had a reduced risk of macrosomia births (5.8%). In comparison to Group 1 mothers, there was no significant difference in risk of macrosomia for Group 3 mothers (adjusted odds ratio, 1.53 [95% confidence interval, 0.93 to 2.52];  $P = 0.09$ ), whereas Group 2 (2.08, [1.50 to 2.89];  $P < 0.001$ ) and Group 4 (2.59, [2.03 to 3.30];  $P < 0.001$ ) mothers had much higher risk. **Conclusions:** The elevated risk of macrosomia among overweight/obese women may be largely reduced by normalizing their weight before pregnancy.

## T-73-OR

**The Association between Exclusive Breastfeeding and Lower Obesity Prevalence in a WIC Cohort**Mary Ann Chiasson, Sally Findley *New York, NY*; Jackson Sekhobo *Albany, NY*; Roberta Scheinmann *New York, NY*; Lynn S. Edmunds *Albany, NY*; Natasha McLeod, Diana Hartel *New York, NY*

**Background:** USDA-mandated changes to WIC - adding vegetables, fruits, whole grains and breastfeeding (BF) peer counseling (new WIC) - were implemented in New York State (NYS) in January 2009. This study was conducted to assess the effect of these changes on the prevalence and predictors of obesity ( $BMI > 95$ th percentile) among infants enrolled in WIC and followed until age 2 years. **Methods:** NYS WIC Statewide Information System (WICSIS) data which included BF data from parent interview by WIC staff at certification visits were used. All infants enrolled between July-December 2009 were exposed to new WIC, while unexposed were enrolled between July-December 2008 before new WIC. Children with birthweight (BW)  $< 2,500$  gms were excluded from this analysis. **Results:** 20,923 new WIC exposed and 20,188 unexposed children were similar by race/ethnicity (R/E): 40.5% Hispanic, 28% White, 24.1% Black and 7.4% Asian. At age 2 years, 19.4% of those with  $BW > 4,000$  gms (macrosomic) were obese compared to only 11.5% of those  $> 2,500-3,999$  gms ( $OR=1.85$ ). In multivariable logistic regression controlling for R/E and gender, no difference in obesity was seen by WIC exposure status; those macrosomic were more likely ( $OR=1.86$ ) to be obese; and those exclusively BF at enrollment were less likely to be obese ( $OR=0.46$ ) than those partially BF ( $OR=0.84$ ) compared to no BF (all  $p < 0.001$ ). **Conclusions:** In this cohort of NYS WIC participants, no difference in obesity prevalence at age 2 years was seen for those exposed to the new WIC food package. The greatly reduced odds of obesity in those exclusively BF is encouraging and merits further study as the cohort ages.

## T-74-OR

**Maternal Mental Health and Toddler Temperament Impact How Toddlers Are Fed: A Sample of Low-Income Mothers Participating in WIC**Jennifer S. Savage, Leann L. Birch *University Park, PA*

**Background:** Maternal depression and anxiety have been shown to affect child well-being; depressed mothers tend to be less sensitive and more reactive to a negative or fussy child (i.e. less responsive parenting). However, little is known about how these factors impact dimensions of feeding (i.e., controlling feeding practices compared to creating a structured feeding environment which may be protective against excessive weight gain.) **Methods:** A cross-sectional study of 210 low-income WIC mothers with a toddler aged 12 to 36 months. Mothers completed the Toddlers Need Feeding Questionnaire to assess food to soothe, Early Child Behaviors Questionnaire (ECBQR) to measure toddler temperament, the Center for Epidemiological Studies Depression Scale (CES-D) and an author developed scale to assess dimensions of parental structure and control when feeding toddlers. **Results:** 42% of mothers were obese and 37% of toddler were overweight (BMI > 85th %). Clinical depression was identified in 28% of mothers. Mothers who reported exposing toddlers to a more structured feeding environment tended to perceive their toddlers to be less fussy (negative) and to have higher self-regulation (effortful control) scores. In contrast, use of food to soothe toddler distress was positively associated with maternal depression, maternal anxiety, and toddler negativity (fussiness). Lastly, use of food to soothe toddler distress was positively associated with the practice of using the TV/radio to soothe a crying/fussing toddler. **Conclusions:** The proportion of mothers who were clinically depressed was high among these WIC mothers and was associated with more controlling and less structured feeding practices. To encourage responsive feeding, interventions may need to be individually tailored to address maternal mental health and perceptions of toddler temperament.

## T-75-OR

**Mom Feeds Us Differently: Differential Restrictive Feeding Is Associated with Differential BMI and Caloric Compensation among Male and Female Twins**Gina Tripicchio *Chapel Hill, NC*; Kathleen L. Keller *University Park, PA*; Cassandra Johnson *Chapel Hill, NC*; Angelo Pietrobelli *Verona, Italy*; Moonseong Heo *Bronx, NY*; Myles Faith *Chapel Hill, NC*

**Background:** Restrictive feeding by parents is linked to childhood overeating and obesity; however these could be spurious associations due to other factors that drive children to overeat and parents to restrict (eg, child genetics, other home environmental factors). Using a pediatric twin design, we tested whether differences in restrictive feeding within families is associated with differences in twins' weight status and caloric compensation ability. **Methods:** Sixty-four same-sex twin pairs, ages 4-7 years old, were studied with their mothers. Feeding styles towards each twin were assessed by the Child Feeding Questionnaire (CFQ). Child caloric compensation ability (COMPX%) was assessed using an established laboratory preloading protocol. Child BMI was assessed by directly measured weight and height; waist circumference and %body fat (from DXA) were also assessed. Within each family, we calculated within-twin pair differences in CFQ feeding measures, COMPX%, anthropometric/body fat measures. **Results:** Within-pair differences in restriction were associated with within-pair differences in child COMPX% ( $r=-0.25$ ,  $p<0.05$ ) and BMI z-score ( $r=0.31$ ,  $p=0.01$ ). Specifically, mothers were more restrictive towards the more poorly compensating and heavier twin. Also, within-pair differences in parental pressure to eat were associated with differences in BMI z-score ( $r=-0.40$ ,  $p<0.001$ ), percent body fat ( $r=-0.38$ ,  $p<0.05$ ) and waist circumference ( $r=-0.37$ ,  $p<0.05$ ). Parents were more pressuring towards the thinner twin. **Conclusions:** Parents feed their children differently, even same-sex twins pairs, which could drive differences in adiposity. Future research needs to elucidate cause-and-effect, and intervention implications.

T-76-OR<sup>DT</sup>**The Effect of Mother-Daughter Relationship Quality, Adolescent Depression and Race on the Physical Activity Trajectories of Young Women from Adolescence to Early Adulthood**Danielle E. Schoffman, Katrina M. Walsemann *Columbia, SC*

**Background:** Physical activity (PA) levels are low among all US children, but markedly lower for females than males, and for black females than white females. Low PA has been cited as a contributor to rising rates of pediatric obesity. While most research has focused on socioeconomic disadvantage in understanding the racial disparity in PA, the family environment and individuals' psychological functioning, may also play a role in the establishment of health behaviors and the perpetuation of disparities in PA across the life course. **Methods:** To examine the impact of mother-daughter relationship quality and daughter's depressive symptoms on PA trajectories, we analyzed 4 waves of restricted data from the National Longitudinal Study of Adolescent Health using 3-level linear growth models. Analyses were restricted to female respondents living with a mother figure ( $n=7,416$ ). We excluded respondents with missing data on indicators included in our analysis, resulting in a final analytic sample of 7,367 (4,189 whites; 1,619 blacks; 1,216 Hispanics; 323 Asians). **Results:** Black respondents consistently engaged in less PA from adolescence to early adulthood than whites. PA declined through early adulthood, regardless of race. Better mother-daughter relationship quality was associated with higher PA at age 21, the median age of the sample, but the effect on PA diminished as respondents aged. Depressive symptoms were associated with lower PA. Mother-daughter relationship quality accounted for 9.4% of the white-black PA disparity at age 21, whereas depressive symptoms accounted for 4.9% of the disparity. **Conclusions:** Interventions targeted at reducing racial disparities in PA and related chronic disease like obesity, should consider factors beyond individual PA behaviors, such as family communication between mothers and daughters and positive psychological functioning.

## T-77-OR

**Maternal Work Hours Predict Girls' BMI from 5 to 15y, Even After Adjusting for Frequency of Food Eaten Away from Home and Daily Hassles**Julia A. Bleser *University Park, PA*; Brandi Y. Rollins, Leann L. Birch *State College, PA*

**Background:** Maternal work hours is a hypothesized risk factor for childhood obesity. However, it is unclear whether work hours or other variables related to employment (e.g. increased daily hassles or food away from home) may explain this relation. **Methods:** In this study, 167 White, middle-income girls and their mothers were followed from 5-15y. Measures included girls' BMI and food eaten away from home (FAFH), mothers' work hours, BMI, and severity and frequency of daily hassles. **Results:** At 5y, 36% of mothers reported working full-time. Maternal work hours was positively associated with FAFH at 5y, but no relation was observed between work hours and frequency of daily hassles. In addition, maternal work hours was associated with an increased risk for girls' overweight (OR=1.03) at 5y, after adjusting for demographics. However, severity of daily hassles was found to be a greater risk factor for girls' overweight (OR=2.39) at 5y. No relation was observed for FAFH and girls' BMI at 5y. By 15y, 71% of mothers reported working full-time. Using growth curve analyses, a main effect for maternal work hours was observed on girls' BMI z-score from 5 to 15y, even after adjusting for daily hassles and FAFH, suggesting that working more hours outside the home was consistently associated with higher BMIs in girls. No main effect for daily hassles or FAFH was found on girls' change in BMI from 5y to 15y. **Conclusions:** This study suggests that the relation between maternal work hours and girls' weight status may be present in early childhood and persist into adolescence. Research exploring mediators of relations between work hours and child weight status is needed to identify possible childhood obesity prevention strategies. Our results expand upon previous findings by using 10y of longitudinal data and including contextual measures hypothesized to be associated with work hours.

5:15 PM – 6:15 PM

**Oral Abstracts Track 1 - Gestational Environment and Metabolic Health****T-78-OR****Maternal Low Protein Diets Decrease Skeletal Muscle Growth, PGC-1 $\alpha$  mRNA Expression and Mitochondrial Oxidative Respiration and Increase Obesity and Insulin Resistance in Obesity Prone Sprague-Dawley Rats**Kate Claycombe, James Roemmich, Eric Uthus, William T. Johnson *Grand Forks, ND*

**Background:** Malnutrition during the fetal growth period followed by postnatal catch-up growth results in obesity and the development of type 2 diabetes (T2D). **Methods:** To determine whether a prenatal low protein diet followed by postnatal high fat diet increase offspring's propensity to obesity and T2D, obese-prone female Sprague-Dawley rats were fed 8% (low protein; LP) or 20% protein (normal protein; NP) diets 3 weeks prior to mating. Dams were fed the same diet during pregnancy and lactation. Postnatally, male offspring were fed 10% (normal fat; NF) or 45% (high fat; HF) diets for 12 weeks. **Results:** Maternal LP and postnatal HF diets resulted in offspring obesity and increased insulin resistance. Recent studies showed that reduction in peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) increases T2D risk due to decreased mitochondria biogenesis and oxidative metabolic function. No studies have tested whether maternal LP and postnatal HF diets influence muscle PGC-1 $\alpha$  expression, mitochondria biogenesis, and mitochondrial oxidative respiratory functions. Current data showed that skeletal muscle PGC-1 $\alpha$  mRNA expression and mitochondrial oxygen consumption rate is decreased by maternal LP while postnatal HF diets had no effect. Mitochondria biogenesis, mRNA expression of mitochondrial biogenic factors including nuclear respiratory factor 1 (NRF1) and cytochrome c oxidase 1 and 4 (COX-1 and 4) were unaffected by maternal LP and postnatal HF diets. Interestingly, skeletal muscle size was 12-17% smaller in the maternal LP group compared to NP group with corresponding decreases in insulin-like growth factor 1 and 2 (IGF-1 and 2) mRNA expression. **Conclusions:** Taken together these data suggest that maternal LP and postnatal HF diets increase risk for T2D by decreasing skeletal muscle growth, PGC-1 $\alpha$  expression, and oxidative metabolic function.

**T-79-OR****Energy Intake, Not an Adaptation in Energy Expenditure, Is a Strong Determinant of Gestational Weight Gain**L. Anne Gilmore *Baton Rouge, LA*; Nancy F. Butte *Houston, TX*; Eric Ravussin, Hongmei Han, Leanne Redman *Baton Rouge, LA*

**Background:** There is little understanding how energy intake and energy expenditure contribute to gestational weight gain (GWG). We tested the hypothesis that women who gain weight above the 2009 Institute of Medicine (IOM) guidelines ('high-gainers') will have increased energy intake, but no change in energy expenditure adjusted for GWG, when compared to women who gained weight according to the guidelines ('normal-gainers'). **Methods:** The energy intake and energy expenditure of 61 pregnant women (BMI < 20; n=15; BMI: 20-24.9, n=32; BMI > 25, n=14) were estimated at 9 and 36 weeks of gestation. Energy intake was measured as the sum of total energy expenditure (TEE) measured by doubly labeled water and energy deposition by a 4-compartment body composition model. Basal metabolic rate (BMR) was measured by indirect calorimetry during an overnight stay in a room calorimeter. **Results:** Energy intake was significantly higher in 'high gainers' versus 'normal gainers' overall (p=0.0002) and within each prepregnancy BMI group (BMI < 20: 3211 vs. 2550 kcal/d; BMI 20-24.9: 3393 vs. 2755 kcal/d; BMI  $\geq$  25: 3504 vs. 2617, kcal/d), however no significant difference in energy intake within 'high gainers' or 'normal gainers' was evident across BMI groups (p= 0.234). BMR increased in proportion to GWG; however, BMR adjusted for GWG (BMR residuals) was not significantly different between 'high gainers' and 'normal gainers' (146 vs. 135 kcal/d; p=0.803). **Conclusions:** Weight gain above the IOM guidelines was achieved by an increased energy intake and not a conservational adaptation in energy expenditure.

**T-80-OR<sup>DT</sup>****Gestational Stress and Obesity: Cortisol and Gonadal Steroids in the Maternal-Fetal Unit**Gregory Grimberg, Laura Dhariwal, Sushila Arya, Mudar Dalloul, Vijaya Nacharaju, John G. Kral *Brooklyn, NY*

**Background:** Obesity and stress are associated with multiple risks to mother, fetus and child. Environmental stressors are common in our Caribbean Black population with high prevalence of obesity comorbidities. We found an inverse relationship between maternal BMI and placental 17- $\beta$  (OH) steroid dehydrogenase (HSD) activity, a regulator of maternal steroid passage to the fetus associated with impaired conversion of estradiol (E2) to estrone. To assess effects of gestational stress and obesity we studied 40 uncomplicated singleton births in unselected mothers aged 17-45 with mean BMI  $\pm$  SD = 35  $\pm$  6 (range: 24-49) and 18% with gestational diabetes (GDM). **Methods:** Placental weight and HSD activities (by GC/MS/MS). Obstetric record analyses. Cord serum cortisol, E2, estrone, DHEA, 5-AD and insulin (by ELISA). Socio-environmental stress questionnaire. **Results:** Mean cord serum levels: cortisol, 40.0  $\pm$  11  $\mu$ g/dl; estradiol, 3180  $\pm$  690 pg/mL; insulin 28.6  $\pm$  6.74  $\mu$ U/mL. Mean birthweights: 3110  $\pm$  590 g (1710-4625) unrelated to maternal BMI, correlated strongly with cord cortisol (r= 0.65; p<0.0001). Maternal BMI, inversely related to gestational age (r=-0.49; p<0.0035), was unrelated to cord E2, DHEA and surprisingly insulin. Cord E2 and insulin levels were inversely correlated (r= -0.53, p=0.0014) mainly attributable to female sex but unrelated to GDM. E2 conversion was inversely related to BMI with 17- $\beta$  HSD 2 activity inversely related to cord E2. **Conclusions:** Estradiol is protective of pancreatic  $\beta$ -cell function which might explain the relative absence of hyperinsulinemia and macrosomia, whereas impaired placental steroid metabolism with reduced inactivation of estradiol and high cortisol levels may contribute to the dysmetabolic diathesis in offspring.

**T-81-OR****Greater Physical Activity Levels During Pregnancy Are Associated with Lower Inflammation and Insulin Resistance in Obese Women**Aline Andres, Jennifer Faske, Kartik Shankar, Thomas M. Badger *Little Rock, AR*

**Background:** Compared to lean pregnant women, obese women develop greater insulin resistance and systemic inflammation during pregnancy. Identifying lifestyle factors that can reduce the metabolic effect of obesity during pregnancy is critical to protect both the mother and the fetus from insulin resistance and inflammation. **Methods:** We prospectively investigated the association between physical activity and serum levels of insulin, glucose and C-reactive protein (CRP) at gestation week 30 and birth in 33 lean and 18 obese women. Total body fat mass (FM) was obtained using air displacement plethysmography (BodPod®). Physical activity was monitored using an accelerometer (Actical®, Phillips, Andover, MA) worn for 2 weekend days and 2 week days to derive total daily activity counts (AC). Serum analyses were conducted using standard ELISA and colorimetric assays on fasted serum samples at gestation week 30 and on umbilical cord serum at birth. **Results:** Homeostatic model assessment of insulin resistance (HOMA-IR) indexes computed from insulin and glucose levels were negatively associated with AC in obese women at gestation week 30 (r=-0.588, P=0.01, N=18) and at birth (r=-0.542, P=0.07, N=13). Similarly, CRP levels were negatively associated with AC in obese women (r=-0.523, P=0.03) at gestation week 30. There were no significant associations of HOMA-IR indexes or CRP levels with AC in lean women. **Conclusions:** These data suggest that physical activity interventions during pregnancy may be beneficial to the mother and the offspring by increasing maternal and fetal insulin sensitivity and reducing maternal inflammation in obese pregnant women. Funded by USDA-ARS CRIS # 6251-51000-005-03S.



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## Oral Abstracts Track 2 - Human Brain Imaging

## T-82-OR

**Brain Activation in Stress-Responsive Regions Is Associated with Actual Food Intake in the Laboratory in Overweight Girls**

Sarah Berger, Marian Tanofsky-Kraff, Eric Nelson, Johanna M. Jarcho, Adrienne Romer *Bethesda, MD*; Lauren B. Shomaker *Ft. Collins, CO*; Sara Field, Amber B. Courville, Sheila M. Brady, Anna Vannucci *Bethesda, MD*; Scott G. Engel *Fargo, ND*; Daniel S. Pine, Jack A. Yanovski *Bethesda, MD*

**Background:** Difficulties in social functioning and emotion regulation are commonly reported by overweight youth and are associated with reported episodes of disinhibited eating. In theory, socially stressful situations lead to negative affective states, which in turn, trigger excessive food consumption. This theoretical mechanism can be elucidated by studying how actual food intake relates to activation of brain regions linked to social stress (e.g., amygdala) and emotion regulation (e.g., prefrontal cortical regions) that modulate the hypothalamic control of energy intake. **Methods:** Eighteen overweight (BMIz:  $1.86 \pm 0.41$ ) adolescent ( $15.78 \pm 1.59$  y) girls underwent fMRI during a simulated virtual chatroom paradigm during which youth were exposed to peer evaluation. Immediately after the fMRI session, girls consumed lunch ad libitum from a 10,934-kcal laboratory buffet test meal array with the instruction to “let yourself go and eat as much as you want.” **Results:** Girls’ greater relative activity in the right amygdala when contemplating feedback from peers they rejected (versus those they selected) was positively associated with total energy consumption ( $p < .01$ ). Further, girls’ activation in the ventromedial prefrontal cortex, anterior cingulate cortex, and hypothalamic areas when both anticipating and receiving peer feedback was inversely correlated with energy intake ( $ps < .005$ ). **Conclusions:** In overweight girls, activation of brain regions involving social stress and emotion regulation appear to be linked to actual food intake. While amygdala activation was positively associated with energy consumption, findings suggest that failure to engage prefrontal regulatory regions may lead to overeating in order to cope with negative affect due to social stress. These data support the role of social-emotional neurological underpinnings for overeating in susceptible youth.

## T-83-OR

**The Effects of Energy Imbalance and Obesity Propensity on the Neuronal Response to Food Cues**

Marc-Andre Cornier, Kristina McFadden, Elizabeth A. Thomas, Jamie L. Bechtell, Daniel H. Bessesen, Jason R. Tregellas *Aurora, CO*

**Background:** The mechanisms responsible for the propensity to weight gain are poorly understood. How short-term energy imbalance impacts the neuronal response to food cues in obesity resistant (OR) or obesity prone (OP) individuals is also unclear. **Methods:** Here we report findings of a study designed to examine differences in neuronal response to visual food cues during energy imbalance in healthy adults recruited as either OR or OP based on self-identification, BMI, and personal/family weight history. 26 OR and 28 OP individuals were studied in underfed (UF) and overfed (OF) as compared to eucaloric (EU) conditions in a randomized crossover design. Each study period included a 3 day run-in diet, 1 day of controlled feeding (basal energy needs for EU, 40% above/below basal energy needs for OF/UF), and a test day. On the test day fMRI was performed in the acute fed state (30 minutes after a test meal) while subjects viewed images of foods of high hedonic value and neutral non-food objects. **Results:** Overall UF was associated with significantly increased activation of inferior visual cortex. Most interestingly, UF was associated with significantly greater activation of the insula, inferior prefrontal cortex (PFC), somatosensory cortex and dorsolateral PFC in the OR as compared to OP. While OF was associated with reduced activation of inferior visual cortex overall, no group interaction was seen with OF.

**Conclusions:** These findings suggest that individuals resistant to weight gain and obesity are more sensitive to short-term energy imbalance particularly with UF than those prone to weight gain. The inability to sense or adapt to changes in energy balance may represent an important mechanism contributing to excess energy intake and risk for obesity.

## T-84-OR

**Challenging the Reward Hypofunction Theory of Human Obesity: Brain Dopamine D2/D3 Receptor Binding Potential Is Positively Correlated with BMI and Body Fat**

Juen Guo *Bethesda, MD*; W. Kyle Simmons *Tulsa, OK*; John E. Ingeholm, Bernard V. Miller, Alex Martin, Kevin D. Hall *Bethesda, MD*

**Background:** Brain dopamine plays an important role in determining incentive salience of food stimuli and ‘wanting’ of food rewards. An early positron emission tomography (PET) study found that 10 morbidly obese subjects had lower dopamine D2/D3 receptor binding potential in the brain reward region called the striatum (comprising the caudate, putamen, and nucleus accumbens) compared to 10 lean controls following a 17-19 hour fast (Wang et al., *Lancet* 2001). This finding led to the reward hypofunction theory of human obesity where increased food intake results from an attempt to counter depressed striatal dopamine signaling. However, this theory is controversial and few human follow-up studies have been performed to validate this now classic finding. **Methods:** We investigated striatal dopamine binding potential in 37 subjects (18M/19F) ranging in BMI from 17.9-44.5 kg/m<sup>2</sup>. All subjects were inpatients and fed an energy-balanced diet on the day prior to a 4 hour resting PET study that occurred 2 hours after a standard breakfast and immediately following an intravenous infusion of 5 mCi <sup>18</sup>F fallypride, a high-affinity D2/D3 radioligand. We aligned and co-registered the PET images to high resolution MRI scans to identify striatal regions of interest and tracer kinetics were quantified using the cerebellum as a reference. **Results:** In contrast to previous findings, D2/D3 receptor binding potential was positively correlated with BMI in the caudate ( $r=0.5, p<0.002$ ) and putamen ( $r=0.48, p<0.003$ ), but not in the accumbens area. Similar positive correlations were observed with percent body fat as determined by DEXA. **Conclusions:** In contrast to the reward hypofunction theory, obese individuals may have greater dopamine signaling potential in brain reward regions resulting in greater ‘wanting’ for food and a correspondingly increased energy intake.

## T-85-OR

**Brain Function Changes Following Diet Intervention in Successful and Unsuccessful Obese Dieters Compared to Healthy Weight Controls**

Florence J. Breslin, Trisha M. Patrician, Joshua Powell, Rebecca J. Lepping, Anthony M. Lynch, Laura E. Martin, Joseph E. Donnelly, Cary R. Savage *Kansas City, KS*

**Background:** Although obese, formerly obese, and healthy weight individuals show differences in brain activation to food cues, little is known about intervention-related functional brain changes. **Methods:** Sixty-nine obese participants were scanned using fMRI before (BL) and after (3M) a 3-month group-based diet intervention, while 21 healthy weight controls (HW) were scanned twice, three months apart. During scanning, participants viewed food and nonfood images before (pre-meal) and after (post-meal) eating a standardized 500 kcal meal. Hunger and fullness ratings were obtained before each scanning session. Successful dieters (Suc: >7% weight loss) were compared to unsuccessful dieters (UnS) and HW. **Results:** Whole brain analysis using random effects GLM FWE corrected and 3-way Image Type  $\times$  Time-point  $\times$  Group ANOVA run separately for pre-meal and post-meal conditions revealed significant interactions ( $p < .01$ ) in a priori regions, including dorso-lateral prefrontal cortex and hippocampus pre-meal and left anterior insular cortex (AIC) post-meal. Although groups did not show differential activation in AIC at BL, UnS showed deactivation in AIC from BL to 3M, whereas Suc and HW groups showed no change. **Conclusions:** The AIC is implicated in consciousness and emotional processing, and AIC activation has been correlated with increased anxiety (Simmons et al., 2012) and subjective feelings of fullness (Craig, 2009). The deactivation over 3M in the UnS may indicate that they were less aware of internal cues of satiety. Furthermore, the Suc but not the UnS group demonstrated a significant increase (BL to 3M,  $p < .05$ ) in fullness after eating. Results suggest that diet failure may be associated with decreased activation in brain networks required for subjective awareness of satiety. Support: R01DK080090, meals for diet provided by Health Management Resources.

## T-86-OR

**CBT for Weight Loss Alters Network Connectivity in Obesity: A Resting State fMRI Pilot Study**

Kasey O'Neil- Ferreira, Janet Ng *Hartford, CT*; Feroze Mohamed, Eunice Y. Chen, Gary D. Foster *Philadelphia, PA*; Godfrey D. Pearlson *Hartford, CT*

**Background:** Several studies have examined resting state network connectivity in obesity (Tregellas et al, 2011; Kullman et al, 2012; Garcia, 2012); however, none has tested differential effects of treatment. **Methods:** Participants were 12 obese (mean body mass index [BMI] = 35.9, SD= 3.3) adults (10 women; mean age= 40.3 years, SD 11.5) that completed a 12-week CBT group weight loss program. Participants completed an fMRI, eyes open, resting state task within 1 week before beginning CBT and 12 weeks post. Images were collected on a Siemens 3T Allegra scanner using a T2-weighted gradient single-shot echo sequence (TR/TE=2000/30msec; flip angle=90°; FOV=220 mm; matrix=64; slice thickness=5 mm). SPM8 was used for all preprocessing and data were analyzed using the GIFT independent component toolbox to identify components reflecting distributed networks (Laird et al., 2011) to examine activation change across time. Results were significant at  $p < 0.05$ , uncorrected. **Results:** Functional connectivity strength differed before and after CBT. Prior to treatment, participants showed more connectivity strength in the medial prefrontal cortex of the default mode network (DMN), BA24 of the ACC-OFC network, and the Rolandic operculum and insula of the insula-frontal operculum network. After treatment, connectivity within networks showed increased strength in BA32, BA39, BA21, IFG/BA46, superior parietal regions, and middle temporal gyrus. **Conclusions:** Results indicate obese individuals showed increased connectivity in networks responsible for emotion processing, gustation, and reward encoding. After weight loss, there was greater connectivity in regions responsible for inhibitory control, cognitive reasoning and preference for delayed discounting. Collectively, findings suggest that weight loss CBT alters resting state network connectivity previously obesity.

## T-87-OR

**Differences in Cortical Thickness and Striatal Volume Associated with Increased Body Mass Index and Waist Circumference in Late Adolescence**

Kristin N. Javaras *Chapel Hill, NC*; Gregory R. Kirk, Cory A. Burghy, Diane E. Stodola, Marjorie H. Klein, Marilyn J. Essex, Richard J. Davidson *Madison, WI*

**Background:** Despite evidence of adiposity-related differences in cortical and striatal function during response inhibition and food-reward tasks, respectively, few studies have examined associations between cortical thickness and adiposity or subcortical volumes and adiposity in late adolescence. **Methods:** We investigated the cross-sectional relationship between cortical thickness and adiposity and between striatal volume and adiposity in late adolescence. Participants ( $n = 99$ ; 54.5% female; 18-19 years old) were selected from among a cohort of individuals followed longitudinally from gestation to late adolescence. T1-weighted structural images (1 mm<sup>3</sup> voxels) were acquired using a 3T MRI scanner. Cortical thickness and subcortical volumes were calculated using the FreeSurfer image analysis suite (v5.1.0). Height, weight, and waist circumference were measured by a staff member during a laboratory visit prior to the scanning session. **Results:** Greater adiposity was associated with reduced cortical thickness in posterior regions (including inferior and superior parietal cortex and lateral occipital cortex). However, greater adiposity was not associated with reductions in cortical thickness in prefrontal regions implicated in response inhibition. In addition, greater adiposity was positively associated with mean (left and right) volume of the nucleus accumbens area and the putamen. **Conclusions:** Results suggest that greater adiposity in late adolescence is associated with increased volume of the nucleus accumbens and putamen, as well as reduced cortical thickness in posterior regions. Additional research will be required to determine whether these differences are antecedents or consequences of increased adiposity.