JOURNAL OF WOMEN'S HEALTH
Volume 22, Number 10, 2013

DOI: 10.1089/jwh.2013.ab02

Abstracts from the

NIH Office of Research on Women's Health

Tenth Annual Interdisciplinary Women's Health Research Symposium October 24, 2013

JOURNAL OF WOMEN'S HEALTH
Volume 22, Number 10, 2013

Tenth Anniversary NIH Interdisciplinary Women's Health Research Symposium October 24, 2013

Joan Davis Nagel, MD, MPH

The Office of Research on Women's Health (ORWH) initiated its signature research and career development programs in women's health based on a paradigm that views interdisciplinary approaches as essential to moving forward the science associated with women's health and to increasing understanding of the contributions of sex and gender factors to human health and disease. From the beginning it was hoped that supporting interdisciplinary research efforts and building a cadre of interdisciplinary women's health researchers would help to reduce the fragmented approach to women's health issues and encourage more comprehensive, integrated approaches to women's health and new ways of evaluating those who conduct such research. ORWH supports innovative ways to encourage collaborative, interdisciplinary research that is team based to improve women's health through two major initiatives, the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program and the Specialized Centers of Research (SCOR) on Sex Differences. The BIRCWH program was first funded in 2000, and the SCOR center was first funded in 2002. Both programs were expanded in fiscal year 2012 as part of the implementation of the 2010 National Institutes of Health (NIH) Strategic Plan for Women's Health Research, A Vision for 2020 for Women's Health Research (http://orwh.od.nih.gov/resources/policyreports/index.asp).

BIRCWH Program

The BIRCWH is a mentored institutional research career development program, designed to support and foster the interdisciplinary research careers of junior faculty who are conducting research in women's health. The program pairs junior faculty with senior investigators in women's health. BIRCWH is built around three pillars: strong mentoring, interdisciplinary research, and career development. Programs accomplish these goals by ensuring that mentors represent diverse disciplines needed to carry out interdisciplinary projects that will bridge training with research independence for BIRCWH scholars. In fiscal year 2012, the BIRCWH program awarded over $11 million to participating academic institutions; over the past 13 years, the program has provided over $88 million in support to sites across the country with funds from ORWH, other NIH Institutes, and other federal agencies. To date, 77 BIRCWH awards have been made to 39 institutions in 25 states, and over the course of the program's existence, 539 individuals have participated as scholars. While the BIRCWH program is open to both women and men, 80 percent of the BIRCWH scholars were women and 20 percent were men. Twenty-nine programs are active as of 2013 and the majority of BIRCWH scholars have gone on to receive independent funding from Federal and other sources, including academic, foundation, and industry grants.

SCOR Center

The Specialized Centers of Research (SCORs) on Sex Differences represent an innovative interdisciplinary research program focusing on sex differences and major medical conditions affecting women. The SCORs program supports accomplished scientists who conduct research that integrates basic, clinical, and translational research. SCOR centers are designed to increase the transfer of basic and clinical research findings into clinical practice. In fiscal year 2012, ORWH provided over $9 million in funding to the SCOR. Over the course of the program's existence, financial support has also been provided by several NIH Institutes and the Food and Drug Administration. Research from the SCOR centers has provided numerous insights into the sex differences observed in pain, including visceral pain and pelvic floor dysfunction; mental health disorders, including depression, the stress response, and sex differences in the brain's response to drug cues; and new potential therapeutic targets for recurring urinary tract infections.

Interdisciplinary Symposium

This year, 2013, marks the 10th Anniversary of the NIH Annual Interdisciplinary Women's Health Research Symposium, which brings together early stage scholars from the BIRCWH program with established researchers from the SCOR center. The symposium is designed to showcase the latest interdisciplinary research findings as presented by both groups and to allow for productive interaction among investigators at differing stages of their scientific careers. The 10th Annual NIH Interdisciplinary Women's Health Research Symposium will be held on October 24, 2013 on the NIH Bethesda campus. The research presented at the symposium represents the breadth of women's health topics, from the progress made in some research areas and remaining research challenges. The Symposium will include plenary talks on women's health across the lifespan including the influence of early adverse life events on the development of chronic pain syndromes, how drug treatment for type 2 diabetes mellitus

Office of Research on Women's Health, National Institutes of Health, Bethesda, Maryland.

modifies fibroid risk, and the examination of novel targets for gender-sensitive treatment of tobacco dependence. In addition, other talks will look at such topics as the intersection of reproductive health with other aspects of health and disease, nicotine addiction in women, eating disorders and the role of loading mechanics in sex differences that are seen in knee osteoarthritis. A poster session is also planned spanning a variety of women's health topics.

Abstracts from both oral and poster presentations are presented in the special journal edition. We hope that they enhance your appreciation of the value of interdisciplinary approaches to studying the role of sex and gender factors in health and disease.

Address correspondence to:
Joan D. Nagel, MD, MPH
Office of Research on Women's Health
National Institutes of Health
Bethesda, MD 20817

E-mail: ORWHINFO@mail.nih.gov

JOURNAL OF WOMEN'S HEALTH
Volume 22, Number 10, 2013

BIRCWH and SCOR Poster Abstracts

P-1: Predictors of Neonatal Neurologic Birth Depression and Intraventricular Hemorrhage in Preterm Premature Rupture of Membranes

Jennifer Armstrong-Wells (presenting author)

University of Colorado, Denver

Background and Objective: Preterm birth is a major cause of adverse perinatal outcomes, including birth depression and intraventricular hemorrhage (IVH). Both contribute to lasting neurological disability; however, the role of maternal characteristics in contributing to these outcomes have not been well defined. We sought to determine predictors of these adverse outcomes in pregnancies complicated by early preterm premature rupture of membranes (PPROM).

Methods: We performed a retrospective cohort study of all singleton pregnancies with early PPROM less than 32 weeks gestational age (GA) and delivery greater than 22 weeks GA at University of Colorado Hospital (UCH) from January 1, 2007, to December 31, 2011. Adverse perinatal outcomes were defined as Apgar of less than 7 at 1 and 5 minutes, or clinically significant IVH (grade III or IV). To determine independent predictors of each outcome, we created a multivariate model including all univariate covariates with $P \leq .10$.

Results: In our cohort (n = 229), there were no independent predictors of poor 1 minute Apgar. Female gender was the only independent predictor of poor 5 minute Apgar (OR = 2.3 CI 1.06–5.28, $P = .04$). When adjusted for non-white race, younger maternal age and increased BMI were independent predictors of clinically significant IVH (OR = 1.4 CI 1.04–1.79, $P = .03$; OR 1.2 CI 1.04–1.33, $P = .01$, respectively).

Conclusions: In our cohort, female newborns had a two-fold greater risk of poor 5 minute Apgar. Infants born to younger mothers or mothers with higher BMI appear to be at increased risk for clinically significant IVH. Larger studies are warranted to examine maternal risk factors associated with adverse neurological outcome in pregnancies complicated by early PPROM.

P-2: Detecting Endometrial Cancer Using the Common Tampon

Jamie N. Bakkum-Gamez (presenting author),[1]
Nicolas Wentzensen,[2] Matt Maurer,[1] Karl Podratz,[1]
Mark Sherman,[2] and Viji Shridhar[1]

[1]*Mayo Clinic and* [2]*Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute*

Background and Objective: Endometrial cancer (EC) is the most common gynecologic cancer in the United States. Survival is improved in earlier stage disease and when precancerous lesions exist. A screening test for endometrial cancer does not exist. The objective was to determine whether genes commonly methylated in EC can be detected in the lower genital tract secretions of women with EC.

Methods: A pilot study of women with biopsy-proven endometrial cancer and women undergoing hysterectomy for benign conditions underwent collection of the lower genital tract secretions via intravaginal tampon and endometrial brushings with a Tao brush prior to hysterectomy. DNA methylation status of RASSF1A was determined in tampon and Tao brush samples. Thirty-seven women with endometrial cancer and 29 women undergoing hysterectomy for presumed benign conditions (benign endometrium [BE]) were prospectively enrolled.

Results: Methylation of RASSF1A was first determined via direct sequencing for four subjects (1 EC, 3 BE). No methylation was observed in the three BE cases; methylation of the same sites in DNA from both tampon and Tao brush was observed in the EC case. Larger scale pyrosequencing of tampon DNA revealed significantly higher methylation among all 16 RASSF1A CpG sites within the EC cohort compared to the BE cohort. RASSF1A is hypermethylated in EC (compared to BE), and this DNA alteration can be detected in the lower genital tract fluid via intravaginal tampon among women with EC.

Conclusions: Combining a well-accepted collection technique with sensitive DNA analyses may lead to a screening test for EC.

P-3: Sex Differences in Autonomic Support of Blood Pressure: Complicated by Aging

Jill N. Barnes (presenting author)

Mayo Clinic

Background and Objective: Young women regulate blood pressure differently than young men, yet this changes dramatically after menopause. Additionally, in young women, tonic autonomic nervous system activity contributes less to resting blood pressure than that in young men. There are also age-related increases in the level of autonomic support of blood pressure in men. However, it is unknown whether the autonomic support of blood pressure increases similarly in postmenopausal women. Therefore, we examined the effect of autonomic blockade on blood pressure and how this relates to baseline muscle sympathetic nerve activity (MSNA) in women.

Methods: Twelve young (25 ± 3 years) and 12 older (61 ± 6 years) women were examined before and during autonomic blockade using trimethaphan camsylate (TMP) and were retrospectively compared to older men.

Results: MSNA burst frequency and burst incidence were higher in older women (33 ± 3 vs. 16 ± 1 bursts/min; 57 ± 5 vs. 25 ± 3 bursts/100 hb, respectively; $P < .05$). Older women had a greater drop in mean arterial pressure (MAP; −29 ± 2 vs. −9 ± 2 mmHg; $P < .01$) and total peripheral resistance (TPR; −10 ± 1 vs. −5 ± 1 mmHg/L/min; $P < .01$) during autonomic blockade. In contrast to older men, who demonstrated a decrease in cardiac output and a small reduction in TPR, older women had an 8% increase in cardiac output to mediate the 30% decrease in MAP and 36% decrease in TPR. MSNA bursts were abolished by TMP within minutes. Baseline burst frequency and burst incidence were associated with the decrease in MAP during autonomic blockade ($r = -0.67$, $r = -0.73$, respectively; $P < .05$).

Conclusions: Autonomic blockade reduces MAP to a greater extent in older women, and this decrease in blood pressure is associated with resting levels of MSNA. Our results suggest that autonomic support of blood pressure is greater in older women compared to young women. Elevated sympathetic nerve activity may explain the increased incidence of hypertension after menopause.

P-4: Gender Differences in the Effects of Sleep Disruption on Pain—A Pilot Study

Kelly S. Barth (presenting author), Jeffrey Borckardt, and Kathleen Brady

Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina

Background and Objective: Females are more likely to suffer with both chronic pain disorders and sleep disturbances than males. The reasons for these gender differences are not understood. As poor sleep and pain are strongly interrelated, one possible explanation is that females may be more sensitive to the effects of sleep disturbance on pain. This pilot study explored gender differences in the role of sleep disruption on laboratory measures of pain in 4 healthy men and women. The purpose of the pilot study was to inform the application for a larger grant using this protocol in 52 subjects.

Methods: Utilizing a within-subjects design, we examined pain laboratory measures in 4 subjects (2 male and 2 female) before and after 1 night of sleep disruption. The method of sleep disruption was unique and imitates sleep disturbances seen in those with chronic pain.

Results: Preliminary data analysis reveals that pain inhibition (measured by the Descending Noxious Inhibitory Control Index) was decreased in female subjects after sleep disruption, while it was slightly increased in male subjects after sleep disruption.

Conclusions: These preliminary findings suggest that females may be more likely than males to demonstrate a breakdown of central pain inhibition mechanisms following sleep deprivation. This data will inform a larger study that will measure gender differences in pain, somatic symptoms, and stress reactivity following sleep disruption. This data will ultimately inform the study of gender-specific treatment interventions for those that suffer with painful conditions that are more prominent in females, such as fibromyalgia.

P-5: Variation in Circulating miRNA Across Physiologic Traits: Implications for Biomarker Studies

Alicia Beeghly-Fadiel (presenting author), Ryan J. Delahanty, Hui Cai, Jie Wu, Wei Zhang, and Qiuyin Cai

Vanderbilt University

Background and Objective: Numerous studies have evaluated circulating microRNA (miRNA) as potential disease biomarkers. Naturally occurring variation of circulating miRNA in healthy individuals has not been studied. The objective was to evaluate associations between circulating miRNA and normal physiologic traits, including age, sex, menopausal status, body mass index (BMI), height, and systolic blood pressure.

Methods: Genome-wide expression profiling (Human Genome V2.0 Complete RT2 miRNA PCR Array; Qiagen) was conducted on purified miRNA from 200 μl of plasma from 44 healthy Chinese adults. Correlations with continuous traits were evaluated with the Pearson correlation coefficient. Associations with dichotomous traits were evaluated with *t*-tests. Statistical significance was defined by $P < .01$.

Results: Of 752 miRNA assayed, 307 were detectable. No miRNA were correlated with age (mean, 59.8 years). Twenty-five miRNA were associated with sex; of these, 14 had higher levels among women (N = 30) than men (N = 14). No miRNA were found to differ between pre- (N = 12) and postmenopausal (N = 18) women. Thirteen miRNA were correlated with BMI (mean 24 kg/m^2); of these, 9 were positively associated. Six miRNA were positively correlated with height (mean 161.9 cm); levels of these miRNA were also higher among men. Four miRNA were correlated with systolic blood pressure (mean 128 mmHg); of these, 3 were positively associated. With the exception of height and sex, no miRNA were associated with more than 1 physiologic trait.

Conclusions: This pilot study indicates that circulating miRNA can vary across physiologic traits. To avoid spurious associations, researchers must consider this variability during either study design or analysis.

P-6: Regenerative Polymer Therapeutics: Next-generation Osteoporosis Therapies

Danielle S.W. Benoit (presenting author),[1] Deborah Cory-Slechta,[2] J. Edward Puzas,[2] Christopher Schmitt,[1] Amanda Chen,[1] and Ian Marozas[1]

[1]*University of Rochester and* [2]*University of Rochester Medical Center*

Background and Objective: Targeting drugs specifically to bone will provide novel, specific, efficacious, and safe therapies for osteoporosis, a debilitating and costly musculoskeletal disorder. We aim to exploit peptide-targeting to selectively deliver bone anabolic drugs to resorption surfaces. By combining peptides that bind to resorption sites with high affinity and drugs to enhance bone production, we aim to improve bone regeneration selectively at the sites of resorption to treat osteoporosis.

Methods: Polymers were formulated with controlled, radical polymerizations and tested for specific bone affinity using surface plasmon resonance. Drug tethering and release was achieved using incorporation of hydrolytically degradable bonds, as analyzed using liquid chromatography.

Results: We synthesized multivalent, highly controlled peptide-based polymer architectures that home to bone with high affinity.

Conclusions: We have demonstrated simple and reproducible incorporation and controlled Wnt/β-catenin agonist drug release to enhance osteoblast bone production. Future studies focus on identifying appropriate doses and dosing regimes and testing the efficacy of drug delivery in osteoporosis models. Successful completion of this research will significantly advance our ability to treat osteoporosis specifically through rejuvenation of osteoblasts and, more broadly, develop bone-specific drugs. The proposed work possesses great transformative and translational potential based on the wide applicability of drug delivery systems developed in this study.

P-7: Angiotensin Converting Enzyme Inhibitors (ACEI) and Doxorubicin (DOX) Pharmacokinetics in Women Undergoing Chemotherapy for Breast Cancer

Anne Blaes (presenting author),[1] Ryan Shanley,[2] Heather Beckwith,[1] David Potter,[1] Douglas Yee,[3] Kinjal Sanghavi,[4] and Pamala Jacobson[4]

[1]*Division of Hematology/Oncology/Transplantation,* [2]*Biostatistics Core,* [3]*Masonic Cancer Center, and* [4]*College of Pharmacy, University of Minnesota*

Background and Objective: Doxorubicin (DOX) chemotherapy can cause cardiac complications in breast cancer survivors. Angiotensin converting enzyme inhibitors (ACEI) may protect against these complications. We performed a pharmacokinetics study to determine whether DOX exposure is altered in breast cancer patients receiving DOX concurrently with ACEI.

Methods: Women with locally advanced breast cancer prescribed DOX and cyclophosphamide every 14 days were randomized to receive enalapril 10 mg daily or no enalapril during DOX chemotherapy. Blood samples for pharmacokinetics (DOX and doxorubicinol levels) were drawn at baseline, 0.5, 1.0, 2.0, 4.0, 24.0, and 48.0 hours after infusion with and without enalapril. Correlative laboratories were also obtained. Pharmacokinetic data was analyzed using noncompartmental methods and DOX and doxorubicinol area under the curve (AUC) 0 to infinity, Cmax, and half-life were estimated. Paired *t*-tests, two tailed, were used to determine whether DOX and its metabolite were altered with the use of enalapril ($P < .05$).

Results: Nine women (median age, 41 years) with no cardiac history received 60 mg/m^2 DOX every 2 weeks for 4 cycles. Mean (SD) AUC 0 to ∞ for DOX and doxorubicinol with enalapril exposure was 1235 (168.1) hr*ng/mL and 954.6 (219.6) hr*ng/mL, respectively. AUC 0 to ∞ for DOX and doxorubicinol without enalapril was 1238 (193.2) hr*ng/mL and 984.4 (219.9) hr*ng/mL, respectively. There appears to be no interaction between DOX ($P = .97$) or doxorubicinol ($P = .78$) and enalapril. Enalapril was well tolerated (33% grade 1 dizziness).

Conclusions: ACEI, enalapril, does not appear to alter the pharmacokinetics of DOX chemotherapy. Ongoing efforts to determine the effectiveness of ACEI as a cardioprotective agent in women receiving DOX chemotherapy should be continued.

P-8: Utility of Thrombophilia Screening in Children Awaiting Kidney Transplantation: Sex Does Not Associate With Thrombophilia-related Thromboembolic Events

Margret E. Bock (presenting author),[1] Amy E. Bobrowski,[1] and Rukhmi Bhat[2]

[1]*Division of Kidney Diseases and* [2]*Division of Hematology, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University*

Background and Objective: Vascular thrombosis is a common cause of early allograft loss in children after kidney transplantation (KTx). Screening for acquired/ inherited thrombophilia is controversial. We posited that universal pretransplant screening for thrombophilia had low predictive value, and did not differ by sex, for postoperative outcomes.

Methods: We reviewed 84 children, 1 to 18 years old, who underwent comprehensive thrombophilia evaluations (protein C, S, anti-thrombin 3 [AT], homocysteine, antiphospholipid antibody, lupus anticoagulant; factor V Leiden [FVL], prothrombin, and MTHFR gene mutations) prior to KTx.

Results: Pre-operative screening demonstrated thrombophilia in 91% (76/84) of patients. In 10/84 (12%) children, a bleeding (5/84, 6%) or clotting (7/84, 8%) event occurred after KTx. A pre-KTx thromboembolic event occurred in 8/84 patients (10%). Post-operative events were associated with history of pre-KTx thromboembolic events ($P = .019$), FVL mutation ($P = .002$), and low AT ($P = .016$). History of a pre-KTx thromboembolic event and FVL mutation were associated with poorer graft survival at 3 years and 3 months, respectively ($P < .0001$ for both); low AT levels were associated with poorer graft survival at 1 and 3 years ($P < .0001$ for both). Two of 84 grafts were lost to thrombosis. Sex was not associated with pre- or post-KTx thromboembolic events; neither were age or race.

Conclusions: Analysis of long-term follow-up data demonstrates that the value of comprehensive thrombophilia evaluation before KTx is low. Focused universal investigation, however, with more detailed testing in those with a previous thrombosis, may be advisable, as these patients may benefit from perioperative anticoagulation.

P-9: Fetal Growth Restriction and Maternal Obesity: Shared or Competing Processes?

Janne Boone-Heinonen (presenting author)[1] and Lynne C. Messer[2]

[1]Department of Public Health and Preventive Medicine, Oregon Health & Science University; and [2]School of Community Health, Portland State University

Background and Objective: Maternal obesity increases risk for both small and large birth size. Despite ongoing research on the causes and effects of fetal growth restriction, little is known about the drivers of small birth size among obese mothers. The objective was to estimate interactive effects of maternal pre-pregnancy body mass index (BMI) with risk factors for fetal growth restriction on birth size in a population-based sample.

Methods: We used data from the Oregon Pregnancy Risk Assessment Monitoring System (2004–2007; n = 6,302) and linked birth records. Using multinomial logistic regression, we estimated interactive effects of prenatal smoking and gestational hypertension with pre-pregnancy BMI (underweight, normal weight, overweight, obese class I, obese class II-III) on small, appropriate, or large for gestational age (SGA, LGA, AGA). Models excluded women with gestational diabetes or multiple births and controlled for pregnancy weight gain, parity, and sociodemographic characteristics.

Results: Non-obese women who smoked or had gestational hypertension exhibited the highest risk of SGA [Odds Ratio (OR) (95% CI) range: 2.6 (1.4, 4.5) to 5.1 (2.6, 10.0)]. Gestational hypertension combined with class II or III obesity was also associated with elevated SGA risk [OR (95% CI): 4.4 (1.9, 10.2)] compared to normal weight, non-smoking, or non-hypertensive women. Increased LGA risk with greater BMI was not apparent in the presence of prenatal smoking or gestational hypertension.

Conclusions: Extreme maternal obesity and gestational hypertension may induce common processes leading to SGA, while competing fetal under- and over-growth may be involved in LGA. Investigation of inflammatory and other mechanisms that underlie these associations is needed.

P-10: Neuroimaging of Goal-directed Behaviors in Overweight Women

Kelly Bosak (presenting author)

University of Kansas Medical Center

Background and Objective: Health behaviors have been widely studied; however, the neurophysiological mechanisms underlying adherence and maintenance of these behaviors have received little research attention. The objectives of this study were to validate a goal-directed decision task as a proxy measure of goal-directed behavior; and characterize the associated brain activations in overweight (OW) women, and healthy weight (HW) age-matched controls.

Methods: Non-diabetic, midlife women (aged 47–55 years) were assigned to the OW (body mass index [BMI] 25–40 kg/m^2) group (n = 16) or the HW (BMI 18.5–25 kg/m^2) comparison group (n = 16). Participants underwent functional MRI while completing a decision task in the scanner. The decision task used is quite complex. Participants received training prior to the scan and a follow-up survey to test the validity of the protocol.

Results: Both groups showed similar ability to use feedback to respond appropriately to stimuli during training. Behavioral results from the decision task were consistent with neuroimaging findings. Compared with HW women, OW women showed greater activation in the dorsolateral prefrontal cortex associated with planning and self-regulation.

Conclusions: Compared with HW women, OW women appeared to be sensitive to goals, but may have difficulty transforming goals into action. Both groups had similar self-regulation responses to this general test of goal-directed behavior. Future study is needed to test goal-directed and habitual behavior as it relates to specific aspects of energy balance.

P-11: Maternal High-fat Diet Adversely Affects Offspring Skeletal Muscle Metabolism

Kristen E. Boyle (presenting author), Margaret J. Heerwagen, and Jacob E. Friedman

Department of Pediatrics, University of Colorado, Denver

Background and Objective: The intrauterine environment is increasingly recognized as an important contributor to increased offspring adiposity as a result of maternal obesity. However, little is known about the effects of maternal obesity on offspring metabolic tissues, such as skeletal muscle. We hypothesized that a maternal high-fat diet (HFD) would lead to reduced lipid oxidation and increased oxidative stress in skeletal muscle of the offspring, and these outcomes would be exacerbated by offspring consumption of HFD.

Methods: Female C57BL/6J mice were fed a control diet (CD) or HFD for 8 weeks before mating and maintained throughout pregnancy (maternal diet [MD]). Male offspring were weaned to CD or HFD (offspring diet [OD]) yielding 4 groups (MD-OD): CD-CD, CD-HFD, HFD-CD, HFD-HFD. At 16 weeks, offspring skeletal muscle was harvested and lipid oxidation (LipOx), muscle triglyceride content (IMTG), and oxidative stress markers (GSH:GSSG) were measured. We tested the effect of MD, OD, or interaction using 2x2 ANOVA.

Results: MD significantly impacted all offspring parameters, including body weight, where HFD-CD and HFD-HFD gained more weight, had 75% reduced LipOx, increased oxidative stress (-45% GSH:GSSG), and 75% increased IMTG than CD-CD and CD-HFD ($P < .05$ for all measures). Only body weight and IMTG showed additional effects of OD, where CD-HFD and HFD-HFD gained more weight and had increased IMTG than CD-CD and HFD-CD, respectively ($P > .05$).

Conclusions: Maternal HFD adversely affects skeletal muscle LipOx and related parameters, indicating that intrauterine exposure to HFD leads to long-term impairments in offspring skeletal muscle lipid metabolism, which is likely a major contributor to the developmental programming of obesity and metabolic syndrome.

P-12: Maternal Smoking and the Impact on Infant Weight at 9 Months

Susan Braid (presenting author)

University of Maryland, Baltimore

Background and Objective: Maternal smoking during pregnancy is associated with lower birth weight (LBW) and overweight status in childhood. Both LBW and in utero exposure to tobacco have been associated with childhood obesity, but it is unclear whether in utero exposure to tobacco is independently associated with infant weight or if the association is attributable to catch-up growth in infants born

LBW. Infant feeding practices may also confound the association. The objective was to examine the independent association between maternal smoking during pregnancy and the z-score of infants aged 9 months in a nationally representative sample of infants.

Methods: This is a secondary data analysis of a nationally representative sample of children born in the United States from the 2001 Early Childhood Longitudinal Study, Birth Cohort (ECLS-B). Data were collected on 8,300 singleton infants without major congenital anomalies. Multiple linear regression was conducted to analyze the independent effect of smoking on the 9 month z-score of infants.

Results: Z-scores at 9 months were significantly higher in infants whose mothers smoked during the last 3 months of pregnancy versus non-smokers or those who did not smoke during this time period ($P = .03$) after adjusting for infant gestational age, birth weight, age-adjusted size, feeding practices, maternal factors, and socioeconomic factors.

Conclusions: Exposure to tobacco in utero is independently associated with higher z-scores at 9 months. The mechanisms for this association are unclear and may be due to epigenetic changes from tobacco exposure during fetal development.

P-13: Animal Studies of Sex Differences and Hormonal Influences on Positive and Negative Effects of Drug Abuse and Its Treatment

Marilyn E. Carroll (presenting author), Nathan A. Holtz, and Natalie E. Zlebnik

University of Minnesota

Background and Objective: An aim of our SCOR grant is to compare the effects of pharmacological treatments in male and female rats. The first study involved the effects of progesterone and atomoxetine on reinstatement (relapse) of cocaine seeking. These data and background data from other related studies will be presented. Very little data exists in animals or humans regarding the effects of behavioral or pharmacological treatments for drug abuse. This work was conducted as Project 3 of the University of Minnesota SCOR project. The work was conducted with graduate and postdoctoral students supported by the grant.

Methods: We hoped to examine this question in rats self-administering cocaine or nicotine that were treated with progesterone and atomoxetine (for cocaine) and varenicline (for nicotine) in a model of relapse.

Results: With single treatment (e.g., atomoxetine or progesterone) females responded better than males to treatment. However, with combined treatments (atomoxetine and progesterone), males had greater reductions in cocaine relapse behavior.

Conclusions: It is important to recognize that the effectiveness of treatments for drug abuse may vary in males and females. Furthermore, when treatments are combined they are more effective than when offered alone, and there are sex differences in the effects of combined treatments.

P-14: Sex-based Imaging Biomarkers of Carpal Bone Motion and Shape in Hand Osteoarthritis

Abhijit J. Chaudhari (presenting author),[1] Anand A. Joshi,[2] Richard M. Leahy,[2] Nancy E. Lane,[3] Ramsey D. Badawi,[1] and Michael H. Buonocore[1]

[1]Department of Radiology, UC Davis School of Medicine; [2]Signal and Image Processing Institute, University of Southern California; and [3]Department of Medicine, UC Davis School of Medicine

Background and Objective: Hand osteoarthritis (HOA) prevalence in women is more than double that in men across all ages. Our hypothesis is that joint motion and bone shape will differ by sex and will contribute differently to the development of HOA in each sex. The objective was to develop imaging approaches (real-time MRI during active hand motion, morphometric analysis) to understand better the sex-specific shape and motion-related variations for components of the hand.

Methods: The MRI data acquisition protocol was based on balanced steady-state free precession. Magnetic susceptibility artifacts that are usually introduced during motion were mitigated by the use of a wrist harness and susceptibility pads attached to the carpal region of the hand. Two healthy men and 2 healthy women were scanned using the imaging protocol. Carpal bone shapes obtained from a publicly-available database for women (n = 10) and men (n = 10) without HOA were analyzed using spectral theory (2D-Helmholtz equation and the Laplace-Betrami operator) and finite element modeling. This shape analysis approach was independent of scale and bone orientation.

Results: We were able to track the carpal bones and soft tissue components during different hand maneuvers for the initial 2 healthy men and women. Sex-based comparisons based on morphometric analysis for the 10 healthy men and 10 healthy women showed statistically significant shape differences ($P < .05$) between the sexes.

Conclusions: Women and men appear to differ in carpal bone motion metrics and shape. Our future work will validate the imaging approaches and start to determine if the derived imaging metrics correlate with HOA risk.

P-15: Evaluate Perineal Body Property in Vivo Using Ultrasound Elastography Technique: Method Development and Preliminary Results

Luyun Chen (presenting author)

University of Michigan

Background and Objective: Previous research have shown that, during the second state of labor, the pubovisceral muscle is stretched to 3.2 times its original length, thereby placing it at greatest risk for stretch-induced injury of the levator ani muscle (Lien et al., 2004). This injury is highly associated with the common problem of pelvic organ prolapse later in a woman's life. Ashton-Miller & DeLancey (2009)'s "fusible link" hypothesis suggests that, due to the location of the perineal body [in series (i.e., "end-to-end") with the pubovisceral muscle], the more elastic ("stretchy") the perineal body, the more it will stretch during the second stage and the less the pubovisceral muscle has to stretch, thereby reducing its risk for injury. The knowledge gaps are that there are no measurements of (a) perineal tissue properties in humans, (b) whether or not they vary systematically (i.e., "soften") during the second stage, or (c) whether they systematically differ between individuals enduring greater risk of levator ani muscle injury during second stages of labor. The objective of this study is to develop a technique to evaluate the perineal body property in vivo and report the preliminary finding of the perineal body property in a group of normal non-pregnant women.

Methods: A custom-made polyvinyl chorlide plastisol (PVCP) standoff pad was used as a common reference for the comparison between different women. An UltraSONIX RP500 ultrasound system running elastography software was used to measure the strain ratio between the perineal body and the standoff pad. The transducer was perpendicular to the skin surface of perineal body region and was pressed by free-hand manipulation with an up-and-down, cyclic motion of approximately 2 Hz. The relative elasticity of perineal body compared with that of the reference was indicated by a strain ratio. The measurements were performed 4 times, and the mean and standard deviation (SD) were calculated in each of ten nulliparous women.

Results: The standoff pad has a compressive modulus of 8.41 kPa at 12%/sec stain rates. The strain ratio between the standoff pad and perineal body is 0.93 ± 0.16.

Conclusions: The initial pilot data suggest that ultrasound elastography with standoff pad reference could be a valid method to evaluate perineal body property in vivo.

P-16: Cytochrome P4502C9 Activity Is Unaffected by Oral Contraceptive Use Among Obese Women

Ganesh Cherala (presenting author)[1] and Alison Edelman[2]

[1]Department of Pharmacy Practice, Oregon State University/Oregon Health & Science University; and [2]Department of Obstetrics & Gynecology, Oregon Health & Science University

Background and Objective: Variability in drug metabolism is a critical contributor to inter-individual variability in drug response.

Cytochrome-P4502C9 (CYP2C9) metabolizes 15% to 20% of prescribed drugs. Obesity and contraceptive use were identified as independent contributors to variability in CYP2C9. While obesity was shown to increase CYP2C9 activity, contraceptive use decreases activity in normal body mass index (BMI) women. However, there is a lack of knowledge about the status of CYP2C9 among obese women who are also contraceptive users. This is important to understand, given that about 50% of reproductive-aged women are either obese or overweight. We have determined the status of CYP2C9 activity in obese women before and after the use of oral contraceptives.

Methods: Institutional review board approval was obtained. Obese women (BMI > 30 kg/m^2; n = 34) were consented, and CYP2C9 status was determined pre- and post- oral contraceptive regimen (daily dose of 100μg of levonorgestrel per 20 μg of ethinylestradiol for 21 days). Tolbutamide (125 mg tablet) was administered, single blood sampled at 24 hours, and plasma concentrations measured using liquid chromatography and mass spectrometry. Plasma concentration at 24 hours is a measure of CYP2C9 activity. Analysis was performed with a paired *t*-test.

Results: Tolbutamide levels were unchanged before and after oral contraceptive use (pre: 1.98 ± 1.50 μg/mL, mean ± S.D.; post: 1.90 ± 1.30 μg/mL).

Conclusions: Unlike in normal BMI women, oral contraceptive use did not alter CYP2C9 activity in obese users. These results are reassuring that the use of oral contraceptives in obese women may not interfere with other pharmacotherapies metabolized through similar pathways. We speculate that the effects of obesity and contraceptive use counteract each other, and, hence, lack of alteration is seen in CYP2C9 activity.

P-17: Association of Tamoxifen Use and Ovarian Aging in Patients with Invasive or Pre-invasive Breast Cancer

Amy Jo Chien (presenting author), Erin Duralde, Chia-Ning Kao, Charles McCulloch, Michelle Melisko, and Mitchell Rosen

University of California, San Francisco

Background and Objective: The impact of long-term endocrine therapy for breast cancer treatment and prevention on ovarian aging are not known. Understanding these effects will help breast cancer patients of reproductive age make more informed and empowered decisions regarding their treatment. The aim of this study was to explore the relationship between tamoxifen therapy and age onset of menopause in women diagnosed with invasive or pre-invasive breast cancer.

Methods: We conducted a retrospective cohort study in patients identified through the UCSF Cancer Registry. Subjects were premenopausal at diagnosis and could not have received systemic chemotherapy. The primary analysis compared age onset of menopause, as assessed through surveys, between subjects who received tamoxifen for any duration and control subjects who never received tamoxifen.

Results: A total of 227 subjects were included in the final analysis (110 tamoxifen, 117 no tamoxifen). The median age onset of menopause was 50.94 and 51.34 for the tamoxifen and no tamoxifen groups, respectively (hazard ratio 1.077, $P = .6917$). No association ($P = .55$) was found between the duration of tamoxifen use and the age onset of menopause, and there was no significant difference ($P = .93$) in age onset of menopause between subjects who initiated tamoxifen prior to age 45 and those who initiated at age 45 or older.

Conclusions: These data suggest that tamoxifen alone is not associated with an earlier age onset of menopause in patients with preinvasive or invasive breast cancer, and that tamoxifen use, in the absence of systemic chemotherapy, is unlikely to significantly accelerate ovarian aging.

P-18: Bladder Exfoliation Response to *E. coli* Infection Exposes New Receptors Bound by FmlD: Multi-phasic Colonization Maintains Chronic UTI

Matt S. Conover (presenting author), Michael E. Hibbing, Henry Schreiber IV, and Scott J. Hultgren

Center for Women's Infectious Disease Research, Washington University in St. Louis

Background and Objective: Uropathogenic *Escherichia coli* (UPEC) is the primary etiological agent of more than 85% of community acquired urinary tract infections (UTI). These painful and economically costly infections affect approximately 50% of women at least once in their lifetime. UPEC has been shown to utilize highly conserved type 1 pilus, a prototypical chaperone/usher pathway (CUP) pilus to establish UTI. However, all UPEC isolates encode numerous CUPs, some of which are conserved across UPEC. A recent sequencing analysis of clinical UPEC isolates revealed that one CUP locus, fml, was conserved in 97% of strains. Given the high level of conservation, we sought to determine whether fml had an important role in UPEC's pathogenesis.

Methods: We deleted the predicted fmlD adhesin gene in the pyelonephritis isolate CFT073 and determined pathogenic phenotypes in mouse models.

Results: We found a competitive chronic, but not acute, colonization defect when fmlD is deleted, suggesting that it is not necessary for the establishment of cystitis, but is involved in persistence. Additionally, we found that those strains that did not have a complete fml operon had a highly adaptive allele of the type 1 pilus adhesin, fimH. Swapping this fimH into CFT073 fmlD resulted in a rapid out competition of the original CFT073 strain.

Conclusions: These results suggest that fmlD is important for the maintenance of chronic cystitis in UPEC strains and that this locus is evolutionarily linked to the pathoadaption of fimH.

P-19: Greater Pancreatic Beta-cell Mass in Female Compared With Male Organ Donors May Be Associated With a Lower Propensity for Pancreatic Apoptosis and Viral-mediated Destruction in Females

Kirstie K. Danielson (presenting author),[1] Enza Marchese,[1] Jan Jensen,[2] and Jose Oberholzer[1]

[1]*Division of Transplant Surgery, University of Illinois, Chicago, and* [2]*Department of Stem Cell Biology and Regenerative Medicine, Cleveland Clinic*

Background and Objectives: Pancreatic insulin-producing beta cells proliferate during pregnancy, but the influence of sex on the maintenance and regulation of beta-cell mass independent of pregnancy is unknown. Such data could provide insight into why type 1 diabetes (T1D), caused by destruction of beta cells, is the only autoimmune disorder not more prevalent in females. The objectives were to determine whether beta-cell mass differs between female and male pancreas organ donors, and if so, whether inflammatory genes mediate the sex difference.

Methods: Nondiabetic cadaveric organ donor (n = 12 female, n = 15 male; mean age 48.9 ± 12.8 years) pancreatic biopsies were assessed using immunohistochemistry and enumeration for the proportion of beta cells. Microarray analysis included 11 inflammatory genes selected a priori. Donor data (e.g., age, body mass index, cause of death, biochemical profiles) were obtained from medical records. Multivariable linear regression and mediation analyses were conducted.

Results: The proportion of beta cells was greater in females than males (74.8% vs. 69.0%, $P = .09$). The difference was confounded only by donor white blood cell count; after adjustment, the greater proportion in females was more pronounced (75.9% vs. 67.7%, $P = .03$). Mediation analysis revealed that lower pancreatic gene expression of interleukin (IL)-24 and higher IL-28 receptor alpha (Ra) in females, compared to males, explained 70% of this sex difference.

Conclusions: Greater beta-cell mass in females was associated with lower IL-24, which can promote pancreatic cell apoptosis, and with higher IL-28Ra, recently found to protect beta cells during viral infection. These factors may lessen the T1D risk in women, particularly in light of evidence that viral infection precipitates T1D onset.

P-20: Subjective and Physiological Responses to IV Nicotine: Effects of Sex and Menstrual Phase

Elise E. DeVito (presenting author),[1] Aryeh I. Herman,[2] and Mehmet Sofuoglu[1,2]

[1]*Department of Psychiatry, Yale University School of Medicine; and* [2]*VA Connecticut Healthcare System*

Background and Objective: Sex differences are widely documented in the population rates, clinical characteristics, and treatment-responsiveness of addictive behaviors, including nicotine-dependence. Gonadal hormones (progesterone, estradiol) are neuroactive and interact with addiction-relevant neurotransmitter receptors while also differing by sex and fluctuating across the menstrual cycle. Therefore, the study of cycle phase effects on nicotine response may elucidate the biological mechanisms contributing to sex differences in nicotine-dependence. The objective was to investigate sex and menstrual cycle phase effects on abstinence-related withdrawal and both subjective and physiological responses to nicotine.

Methods: Following overnight abstinence, nicotine-dependent adults received 2 intravenous (IV) doses of nicotine (0.5 and 1.0 mg/70 kg) and IV saline (placebo). Subjective drug-effects ratings and physiological measures were collected throughout the session. Nicotine withdrawal symptoms were assessed at baseline and end-of-session. Serum progesterone levels confirmed women's menstrual cycle phases. Analyses addressed sex (49 women, 111 men) and menstrual cycle phase (26 follicular, 18 luteal) differences.

Results: Follicular phase women reported more withdrawal symptoms than luteal-phase women following overnight abstinence. Following IV nicotine administration, women demonstrated greater increases in heart rate, yet less robust subjective nicotine-effects than men. Luteal phase women reported dampened subjective nicotine-effects relative to follicular phase women.

Conclusions: Phase-related fluctuations in nicotine response may contribute to sex differences. Phase-related fluctuations in nicotine-response, perhaps accounted for by gonadal hormones, may have important clinical implications. That luteal-phase women experienced less withdrawal and diminished subjective nicotine-reactivity may partially explain previous reports of greater success amongst women initiating quit-attempts in the luteal rather than the follicular phase.

P-21: Ovarian Hormone Suppression in Premenopausal Women Reduces Fat-free Mass and Resting and 24-hour Energy Expenditure

Kathleen M. Gavin (presenting author),[1] Ellie Gibbons,[1] Anne Stavros,[1] Kate Lyden,[2] Karen L. Shea,[1] Pam Wolfe,[1] Edward L. Melanson,[1,2] and Wendy M. Kohrt[1]

[1]Division of Geriatric Medicine, [2]Division of Endocrinology, Metabolism, and Diabetes, University of Colorado Anschutz Medical Campus

Background and Objective: Compelling evidence from animal studies suggests that estradiol (E_2) deficiency disrupts energy balance and causes excess weight gain, but the effects of sex hormone suppression in women have not been well studied. The objective was to compare the effects of ovarian hormone suppression with add-back of placebo (PL) or E_2 therapy in premenopausal women on body composition, resting energy expenditure (REE), and 24-h energy expenditure (EE).

Methods: Forty-five premenopausal women underwent 5 months of gonadotropin releasing hormone agonist therapy ($GnRH_{AG}$, monthly injections of leuprolide acetate 3.75 mg) to suppress ovarian hormones, with add-back of transdermal E_2 (0.075 mg/d, $GnRH_{AG}$ + E_2, n = 21) or placebo patch ($GnRH_{AG}$ + PL, n = 24). At study entry (mean ± SD): age, 35 plus or minus 8 years; body mass index (BMI), 27.1 plus or minus 6.2 kg/m^2.

Results: $GnRH_{AG}$ + PL caused a decrease in fat-free mass (FFM; −0.5 ± 0.2 kg, $P = .02$; mean ± SE) with no change in fat mass (FM; −0.2 ± 0.4 kg, $P = .65$). E_2 prevented the decrease in FFM (0.5 ± 0.3 kg, $P = 0.11$), but FM increased (0.8 ± 0.3 kg, $P = .02$). $GnRH_{AG}$ + PL resulted in decreases in REE (-57.3 ± 21.9 kcal/d, $P = .02$) and 24-h EE (-128 ± 42 kcal/d, $P = .005$); the decrease in REE was attenuated by E_2 (-4.2 ± 16.5 kcal/d, $P = .80$) but 24-h EE was not (-100 ± 30 kcal/d, $P = .003$).

Conclusions: Ovarian hormone suppression led to decreases in FFM, REE, and 24-h EE. E_2 add-back therapy had a favorable effect on some, but not all, bioenergetic changes resulting from chronic suppression of ovarian hormones. Loss of ovarian function at menopause may influence metabolism in a way that reduces energy expenditure.

Support: NIH R01 AG018198, P30 DK048520, UL1 TR000154

P-22: Dosage Effect of Prenatal Home Visiting on Pregnancy Outcomes in At-risk, First-time Mothers

Neera K. Goyal (presenting author), Eric S. Hall, Jareen K. Meinzen-Derr, Robert S. Kahn, Judith B. Van Ginkel, and Robert T. Ammerma

Department of Pediatrics, University of Cincinnati College of Medicine

Background and Objective: Home visiting programs seek to support prenatal services for women at high risk of preterm birth (<37 weeks gestation); however, previous studies demonstrate inconsistent results. The objective was to examine the association between dosage of prenatal home visiting and pregnancy outcomes.

Methods: A retrospective cohort study of women in southwest Ohio with a singleton pregnancy enrolled in home visiting prior to 26 weeks gestation. Vital statistics and hospital discharge data were linked with home visiting data from 2007 to 2010. Program eligibility required at least 1 of 4 risk factors: unmarried, low income, younger than 18, or suboptimal prenatal care. Logistic regression tested the association of gestational age at enrollment and number of home visits before 26 weeks with preterm birth. Proportional hazards analysis tested the association of total number of home visits with small-for-gestational-age (SGA) status.

Results: Among 441 participants enrolled by 26 weeks, 10.9% delivered preterm; 17.9% of infants were born SGA. Mean gestational age at enrollment was 18.9 weeks, and mean number of prenatal home visits was 8.2. In multivariable regression, completion of at least 8 visits by 26 weeks compared with at least 3 visits was associated with an odds ratio of 0.38 for preterm birth (95% CI 0.16, 0.87), while having at least 12 total home visits compared with at least 3 visits was significantly associated with a hazards ratio 0.32 for SGA (95% CI 0.15, 0.68).

Conclusions: Among at-risk, first time mothers enrolled prenatally in home visiting, higher dosage of intervention is associated with reduced likelihood of adverse pregnancy outcomes.

P-23: Gender Modifies the Effect of HHV6 IgG Response on Relapse Rate in Children With Multiple Sclerosis

Jennifer Graves (presenting author),[1] Judith James,[1] Lauren Krupp,[2] Anita Belman,[3] and Emmanuelle Waubant[3]

[1]Adult and Pediatric MS Center, University of California, San Francisco; [2]Oklahoma Medical Research Foundation, Oklahoma City; and [3]National Pediatric MS Center, Stony Brook, New York

Background and Objective: Antibody responses against herpes viruses are associated with the risk of multiple sclerosis (MS). Women have a higher risk of MS (3:1), but men have a higher risk for severe MS. We sought to determine if the effects of herpes virus antibody responses on MS relapse rate (RR) were modified by gender. Pediatric MS patients are an ideal population for study, as they are closer to the age of primary exposure to herpes viruses.

Methods: Batched ELISA IgG assays (EBV, CMV, HSV-1) and IgG immunofluorescence assay (HHV6) were performed for patients from two Pediatric MS Centers. Genotyping of strongest MS genetic risk factor, HLA-DRB1*1501, was performed by Taqman assay. Patients were followed prospectively for relapses. Repeated events models adjusted for disease-modifying therapy, demographic variables, and vitamin D level.

Results: For 171 subjects, 416 relapses were captured over 516 patient-years of follow-up. High levels of HHV6 responses were associated with increased hazard for relapse compared with lower response levels (HR 1.54, 95% CI 1.15–2.05; $P = .003$). Girls constituted 64% of all cases and 89% of those with high HHV6 responses. The effect of HHV6 response was modified by gender (P interaction = .07) and DRB1*1501 status ($P = .05$). The magnitude of effect on relapse hazard was stronger in men (OR 2.27, 95% CI 1.39–3.71, $P = .001$) than in women (OR 1.47, 95% CI 0.95–2.26, $P = .08$). No association was seen for other viruses.

Conclusions: Elevated HHV6 IgG responses are associated with higher relapse rates in children with MS. This effect varies by gender and genetic background.

P-24: Altered Th1/Th2 Cytokines in Pregnancy and Risk for Postpartum Anxious Depression

Constance Guille (presenting author),[1] Leah Fryml,[2] Roger Newman,[3] Neill Epperson,[4] and Laura Goetzl[5]

[1]*Department of Psychiatry and Behavioral Sciences,* [2]*College of Medicine, and* [3]*Department of Obstetrics and Gynecology, Medical University of South Carolina;* [4]*Department of Psychiatry, University of Pennsylvania; and* [5]*Department of Obstetrics and Gynecology, Temple University*

Background and Objective: Alterations in Th-1/Th-2 cytokine represent a promising biomarker for risk of major depression, but findings have been inconsistent due to disease heterogeneity. Further, cross-sectional studies preclude inference regarding directionality of cytokines and depression. Depression with comorbid anxiety is common during the postpartum period and likely represents a distinct subclass of depressive symptoms (anxious depression). Moreover, the postpartum period can be anticipated, allowing prospective assessment of cytokine levels. The objective was to determine if cytokines in pregnancy are associated with subsequent postpartum anxious depression (ppAD).

Methods: Medical records were reviewed to identify cases of depression and anxiety during pregnancy and the year postpartum in participants in a prospective study of cytokines in pregnancy. Signature Th-1/Th-2 cytokines (7 in total) were measured at 34 to 42 weeks' gestation. Logistic regression methods were used to assess the relationship between individual cytokines and ppAD.

Results: A total of 231 women with a complete cytokine profile were included in the analysis. After controlling for potentially confounding variables, women were more likely to experience ppAD with lower *interferon gamma* (IFN-γ) (OR 0.78; 95% CI 0.61–0.99), higher interleukin (IL) 6 (OR 1.6; 95% CI 1.002–2.79) and higher IL-10 (OR 1.2; 95% CI 1.01–2.79).

Conclusions: We report a novel temporal relationship between an altered Th-1/Th-2 cytokine profile in pregnancy and subsequent risk of ppAD. One therapeutic mechanism of selective-serotonin reuptake inhibitors is upregulation of IFN-γ; therefore our finding of an association between lower IFN-γ and increased ppAD has biologic validity. Higher IL-6/IL-10 levels suggest that maternal inflammatory response to pregnancy may mediate mood and/or anxiety symptoms. Further prospective evaluation of these relationships are needed.

P-25: Association Between Perceived Implementation of School Wellness Policies and Health Behaviors Among Middle School Girls

Erin Hager (presenting author),[1] Nicole O'Reilly,[2] Donna Harrington,[2] and Maureen Black[1]

[1]*Department of Pediatrics and Department of Epidemiology and Public Health, University of Maryland School of Medicine; and* [2]*University of Maryland School of Social Work*

Background and Objective: Childhood obesity disproportionately effects African American (AA) adolescent girls. School wellness policies are federally mandated but are effective only if implemented. Few studies have examined perceived implementation of school wellness policies. The objective was to examine how perceived school wellness policies relate to health behaviors (diet and physical activity [PA]) among AA adolescent girls.

Methods: Adolescent girls were recruited from urban schools serving low-income, predominantly AA neighborhoods. Questionnaires on diet (food frequency [FFQ], summarized with Healthy Eating Index [HEI] and My Pyramid Equivalents [MPE]) and food/physical activity policies (F/PA-P, scales and individual items) were used. A subset of participants wore an accelerometer for *at least* 7 days (minutes/day moderate-vigorous PA [MVPA]). We measured height/weight converted to gender-specific body mass index (BMI)-for-age z-scores. Multi-level regression was used to determine associations adjusting for within-school clustering and BMI-for-age z-scores.

Results: Recruitment yielded 789 girls in 22 schools: Over half (54.2%) were 6th graders, mean age was 12.2 ± 0.72 years; 90.4% were AA; 51.1% were overweight/obese; mean HEI-2005 score was 60.8 ± 7.7. Mean minutes/day spent in MVPA was 42.0 ± 28.7 (n = 560). F/PA policies scales were not associated with MVPA or diet. Access to the school for PA on weekends (26.6% endorsed) was associated with MVPA (β = 7.7, P = .008); access to water at school (58%) was marginally associated with HEI (β = 0.38, P = .096); teachers rewarding with food (35.3%) was associated with added sugar (β = 1.60, P < .001).

Conclusions: Three individual policies (school access for weekend PA, access to school water, and unhealthy reward mechanisms) are associated with diet and PA among low-income, urban, AA adolescent girls. The relationship between wellness policy implementation (perceived and real) needs further examination to inform policymakers of strategic and effective approaches to promoting school wellness.

P-26: Long-acting Reversible Contraception for Adolescents: Addressing the Provider Barrier

Sadia Haider (presenting author),[1] Cynthia Stoffel,[2] and Rebecca Cohen[1]

[1]*College of Medicine, Department of Obstetrics and Gynecology, and* [2]*College of Nursing, University of Illinois at Chicago*

Background and Objective: Implantable and intrauterine contraception (IUD) methods, also known as long-acting reversible contraception (LARC), are highly effective but under-utilized by adolescent women. Research on barriers to LARC use among adolescents has focused primarily on family physicians' and obstetrician gynecologists' knowledge and practices. To more fully understand barriers to use, it is important to include a broader range of providers, especially pediatricians—who provide care to a substantial proportion of adolescents. The objective was to compare contraception-related knowledge, attitudes, and practices across provider specialties and describe perceived barriers to LARC provision.

Methods: A cross-sectional study of family physicians, pediatricians, obstetrician gynecologists, and certified nurse midwives from Chicago-area hospitals was conducted. An online, electronic mail survey, with up to four reminders, was sent to 211 providers, and 77 surveys were received (34% response rate). Analyses were conducted using cross-tabs and ANOVA.

Results: Despite reporting similar numbers of adolescent visits, pediatricians were less likely than other providers to ask adolescents about contraception (P = .01). Knowledge about adolescents' eligibility for LARC was high and did not differ by specialty. However, only one-half (51%) and one-third (36%) of providers recommended IUDs or implants to adolescents, respectively. Compared with other providers, pediatricians reported less LARC-specific knowledge (P < .05) and comfort (P < .05) with counseling. Although cost and time were not identified barriers, perceived lack of patient interest was the most commonly reported (54%) barrier to providing LARC.

Conclusions: Provision of LARC to adolescents remains low. Interventions should address providers' attitudes and focus on patient-provider communication. Efforts that target pediatricians are particularly needed.

P-27: The Effect of Mental Health Symptoms on Young Women's Risk of Unintended Pregnancy

Kelli Stidham Hall (presenting author),[1] Yasamin Kusunoki,[2] Heather Gatny,[1] and Jennifer Barber[1]

[1]*Institute for Social Research, University of Michigan; and* [2]*Department of Obstetrics and Gynecology; Institute for Social Research, University of Michigan*

Background and Objective: Depression and stress have been linked with poor contraceptive behavior, but whether existing mental health symptoms influence women's subsequent risk of unintended pregnancy is unclear.

Methods: We prospectively examined the effect of depression and stress on young women's 1-year unintended pregnancy risk. We used panel data from a longitudinal study of 992 U.S. women ages 18 to 20 years, 97% of whom reported a strong desire to avoid pregnancy. Weekly journals measured relationship, contraceptive, and

pregnancy outcomes. We examined 27,572 journals from 940 women over the first year. Our outcome was self-reported pregnancy. At baseline, we assessed moderate/severe depression (CESD-5) and stress (PSS-4) symptoms. We estimated the effect of baseline mental health symptoms on pregnancy risk with discrete-time, mixed-effects, proportional hazard models using logistic regression.

Results: At baseline, 24% and 23% of women reported moderate/severe depression and stress symptoms, respectively. Ten percent of women became pregnant during the study. Rates of pregnancy were higher among women with baseline depression (14% vs. 9%, $P = .04$) and stress (15% vs. 9%, $P = .03$) compared to women without symptoms. In multivariable models, the risk of pregnancy was 1.6 times higher among women with stress compared to those without stress (RR 1.6, CI 1.1–2.7); the risk was even higher among women with comorbid stress and depression symptoms (RR 2.1, CI 1.1–3.8).

Conclusions: Women with stress and especially comorbid mental health symptoms had an elevated risk of unintended pregnancy over 1 year. We are further investigating women's time-varying mental health symptoms throughout their unintended pregnancy experiences.

P-28: Sex Differences in Estrogen Receptor/LOX-1 Signaling in Mouse Aortic Smooth Muscle Cells

Milton H. Hamblin (presenting author), and Habib R. Ansari

Tulane University School of Medicine

Background and Objective: Mortality rates for CV disease differ between men and women in that although declining for men, they do not seem to be declining for women. Unfortunately, very few studies have directly examined sex differences in vascular estrogen receptor signaling in atherosclerosis and CV disease. The objective of this study is to determine the impact of estrogen receptor alpha (ERα) activation on total lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) expression in both male and female aortic smooth muscle cells.

Methods: Mouse aortic smooth muscle cells from 8- to 12-week-old mice were isolated from other vascular cells and then collected. First, mouse aortas were incubated with collagenase and then flushed with warm collagenase. Following the collection of endothelial cell-containing elutes, the remaining aorta was further incubated with fresh collagenase for an additional 2 hours to obtain aortic smooth muscle cells. The cells were plated on a 6-well plate at 37°C until confluence was reached and passaged.

Results: The results from our studies indicate that ERα activation decreased total LOX-1 expression in male aortic smooth muscle cells. In contrast, ERα activation increased LOX-1 expression in female aortic smooth muscle cells.

Conclusions: The present study is an important step in exploring the sex-related contribution of ERα-mediated signaling in mouse aortic smooth muscle cells and its potential role in atherosclerosis and cardiovascular complications. There is a great need to further examine other sex-specific differences in vascular estrogen receptor signaling for improving cardiovascular outcome in women.

P-29: Examining Direct and Indirect Pathways Between Psychological, Physical, and Sexual IPV Victimization, Avoidance Coping, and Mental Health and Substance Use Problems Among Women Experiencing Bidirectional IPV

Julianne C. Hellmuth (presenting author),[1] Véronique Jaquier,[1] Nicole Overstreet,[1] Suzanne C. Swan,[2] and Tami P. Sullivan[1]

[1]*Yale University School of Medicine; and* [2]*Department of Psychology, University of South Carolina*

Background and Objective: Mental health and substance use problems are highly prevalent and frequently co-occur among women who experience intimate partner violence (IPV). This population of women frequently has limited treatment options and access to resources. Investigating avoidance coping strategies, which are often malleable through intervention and are known to influence mental health outcomes among women who experience IPV, is one underrepresented avenue to inform potential pathways for treatment for this large population of women. This study examined the direct and indirect relationships between psychological, physical, and sexual IPV victimization and post-traumatic stress, depression, and alcohol and drug use problems through avoidance coping.

Methods: Our sample was composed of 362 community women who reported both physical IPV victimization and use of physical IPV in their current intimate relationship. Four separate path models were examined, one for each outcome variable.

Results: Unique direct and indirect pathways were found between each type of IPV victimization and each mental health and substance use outcome.

Conclusions: Findings highlight the differential effects of psychological, physical, and sexual IPV on avoidance coping and on mental health and substance use outcomes among women. Findings also suggest that avoidance coping is a critical factor for researchers and clinicians to consider in future research efforts and in the development and delivery of mental health treatments for women experiencing IPV.

This manuscript is the result of work supported, in part, by resources from the National Institutes on Drug Abuse (T32DA019426), the National Institute of Mental Health (T32MH020031), the National Institute of Justice (NIJ2001-WT-BX-0502) the Swiss National Science Foundation (PBLAP1-140055 and PBLAP1-145873), and the University of South Carolina Research Foundation.

P-30: Plasminogen Activator Inhibitor-1 (PAI-1) Deficiency Protects Against Hepatic Steatosis in a Murine Model of Steatohepatitis

Anne Henkel (presenting author), Shantel Olivares, and Douglas Vaughan

Northwestern University

Background and Objective: Cirrhosis secondary to nonalcoholic steatohepatitis (NASH) disproportionately affects women. Patients with NASH have increased hepatic expression of PAI-1 yet the role of PAI-1 in the pathogenesis of NASH is poorly understood. Interestingly, the prevalence of NASH in women escalates after menopause paralleling a rise in serum PAI-1 levels. We aim to determine the role of PAI-1 in the pathogenesis of murine steatohepatitis.

Methods: PAI-1 deficient (PAI-1-/-) and C57BL/6 control mice were fed a methionine- and choline-deficient (MCD) diet, a well-established murine model of steatohepatitis, for 8 weeks.

Results: Liver histology demonstrated reduced hepatic steatosis in PAI-1-/- mice compared with WT controls. Quantification of hepatic lipids confirmed protection from hepatic triglyceride accumulation in PAI-1-/- mice (19.1 ± 9.0 vs. 38.3 ± 9.6 mg trig/g liver in WT, $P < .01$). Hepatic expression of key genes governing lipogenesis were suppressed to a greater degree in PAI-1-/- than WT controls in response to MCD feeding (72% and 58% suppression of SREBP-1c and fatty acid synthase in PAI-1-/- relative to WT, $P < .05$). PAI-1-/- and WT mice showed no significant difference in serum ALT elevation (301 ± 189 vs. 289 ± 129 U/L in PAI-1 vs. WT, NS) or hepatic inflammation histologically in response to MCD feeding.

Conclusions: Loss of PAI-1 in mice protects against MCD diet-induced hepatic triglyceride accumulation but does not protect against hepatic inflammation. The protection against hepatic steatosis in PAI-1-/- mice may be due in part to enhanced suppression of hepatic lipogenesis in response to MCD diet-induced hepatic lipid accumulation.

P-31: Positive Selection Analysis Identifies a Role for Arginine Metabolism in Chronic Bladder Colonization by Uropathogenic *E. coli*

Michael E. Hibbing (presenting author),[1] Swaine Chen,[2] and Scott J. Hultgren[1]

[1]*Department of Molecular Microbiology and The Center for Women's Infectious Disease Research, Washington University in Saint Louis; and* [2]*Department of Medicine, National University of Singapore and Genome Institute of Singapore*

Background and Objective: Urinary tract infections (UTIs) caused by uropathogenic *Escherichia coli* (UPEC) account for more than 85%

of community acquired UTIs, affecting 50% of women during the course of their lifetime. Understanding the molecular basis of UTIs has proven difficult due to severe population bottlenecks, abrogating the feasibility of generic screens in vivo. sTo better understand the bacterial mechanisms needed for development of UTI, we used whole-genome in silico positive selection analysis of clinical UPEC isolates that identified 29 genes under positive selection. We sought to determine the role of these positively selected genes in UPEC pathogenesis.

Methods: We made isogenic mutants in each of the 29 genes in the prototypical UPEC isolate, UTI89, and assessed their ability to cause acute and chronic UTIs in mouse models.

Results: Mutations in 7 positively selected genes demonstrated competitive colonization defects in our murine UTI models, including genes with functional roles in outer membrane permeability, small molecule efflux, iron uptake, DNA repair, protein localization, tRNA modification and arginine metabolism. Specifically, the ornithine transcarbomylase gene *argI*, necessary for arginine biosynthesis, demonstrated a strong competitive colonization defect, suggesting a role for arginine metabolism in urinary tract colonization. Further mutational analysis of the gene in both the arginine anabolic and catabolic pathways revealed roles for both the synthesis and breakdown of arginine in successful bladder colonization.

Conclusions: These results reveal that positive selection analysis effectively identifies genes with critical roles in UPEC UTIs and that arginine metabolism is critical for competitive chronic colonization of the bladder.

P-32: Gender Differences in Tuberculosis Rates Among Older Adults in the United States

Natasha S. Hochberg (presenting author)[1]
and C. Robert Horsburgh, Jr.[2]

[1]Department of Epidemiology, Boston University School of Public Health; and [2]Department of Medicine, Section of Infectious Diseases, Boston University School of Medicine

Background and Objective: Older adults (≥65 years) are at increased risk for tuberculosis disease (TB). There are 40% more older women than men in the U.S., and about 75% of long-term care facility (LTCF) residents are women. The objective of the study was to examine rates and identify risk factors for TB among older adults in the U.S.

Methods: Average rates and rate ratios (RR) for TB by gender, age group, and LTCF residence were calculated using Centers for Disease Control and Prevention TB case reports and Census Bureau data.

Results: Older adults accounted for 21.9% of TB cases in the U.S. between 1993 and 2008. Rates per 100,000 declined from 11.8 in 1993 to 4.5 in 2008 in older women and from 26.3 to 9.0 in older men. Over the 16 years, older men had higher TB rates than older women (RR 2.1; 95% CI, 2.1–2.2). Adults at or over 85 years of age had higher rates per 100,000 than those aged 65 to 74 (9.5 and 6.5 in women and 25.6 and 13.4 in men, respectively). Older people in LTCFs are also at higher risk for TB than those in the community (RR 2.3; 95% CI 2.2–2.3).

Conclusions: Although rates are declining, elimination of TB in the U.S. will require addressing the substantial burden of disease among older people, including older women and those in LTCFs. Studies are needed to determine whether the gender differences in TB rates reflect dissimilar rates of latent TB infection or biological factors that promote reactivation of latent TB in men.

P-33: Factor Analysis of the Longitudinal Maternal Immune Response to Pregnancy

Shernan Holtan (presenting author),[1] Douglas Creedon,[2]
Wendy Nevala,[1] Alexey Leontovich,[1] and Svetomir Markovic[1]

[1]Mayo Clinic; and [2]Oregon Health & Science University

Background and Objective: The maternal immune response to pregnancy is increasingly recognized as a dynamic phenomenon. Few studies have used a high-throughput, longitudinal approach to identifying the key immune components associated with and possibly responsible for the dynamic changes.

Methods: To better understand which cytokines and growth factors exhibit patterns of fluctuation during pregnancy, we tested thawed longitudinal serum samples from 16 healthy primigravidas on multiplex cytokine arrays. We determined protein levels of 42 cytokines and growth factors, using the Millipore® MILLIPLEX MAP Human Cytokine/Chemokine Kit. An average of 18 samples, from the first trimester through parturition, were tested in this study. To incorporate within-subject correlation and to identify those factors demonstrating a change in concentration over time, we normalized the data by (log(1 + fold change from baseline value)). We identified two "factors" (independent clusters of variables that can help identify physiologic relationships) consisting of 3 cytokines each that could explain 80% of the variance in the data.

Results: Factor 1 accounted for 43.2% of the variation and consisted of proteins important for myeloid homeostasis—VEGF, fractalkine, and GM-CSF. Factor 2 consisted of IL-1b, IL-15, and IL-13—cytokines important for Th1/Th2 homeostasis.

Conclusions: Factor analysis helps to reduce dimensionality of data without a priori assumptions about relationships and can assist in hypothesis generation for testing of previously unobserved interconnectedness of variables. In our longitudinal study of 16 healthy primigravidas, we identified a potential regulatory network involving VEGF, GM-CSF, and fractalkine, which appears to be independently affected by the pregnancy state.

P-34: Up-regulation of Fas Expression in Human Breast Carcinomas Treated With Preoperative Radiation

Janet K. Horton (presenting author),[1] Jen-Tsan Ashley Chi,[2]
Jeff Groth,[3] Yingchun Zhou,[1] Chen-Ting Lee,[2] and Joseph Geradts[2]

Departments of [1]Pathology, [2]Radiation Oncology, and [3]Molecular Genetics, Duke University

Background and Objective: Clinical data suggest that breast cancer subtypes respond differently to therapeutic radiation. We previously identified a link between subtype-specific radiation-induced gene expression and radiation sensitivity. Here we extend our initial cell culture findings and evaluate a potential biomarker of radiation sensitivity in tissue from early stage breast cancer patients treated on a novel clinical trial evaluating preoperative radiation.

Methods: Annexin V/PI staining was used to evaluate the downstream impact of radiation-induced Fas induction on tumor cell apoptosis in a subset of breast cancer cell lines. Immunohistochemistry (IHC) was performed using a Fas antibody (Santa Cruz sc715) on human breast cancer tissue before and after radiation. A histoscore was created using the average membrane and cytoplasmic staining intensity multiplied by the percentage of positive cells. Paired Fas expression data was available for 16 of 32 cases.

Results: Apoptosis was significantly increased in response to radiation for 3 of the 4 cell lines tested. The degree of induction and percent cell death appear to correlate with radiation sensitivity. Furthermore, IHC confirmed the up-regulation of Fas after radiation in human tumor tissue. The mean combined post-treatment histoscore was about twice as high as the mean pre-treatment score. Six of 16 paired cases showed significant Fas up-regulation after radiation.

Conclusions: Apoptotic cell death is increased after radiation to a greater extent in cell lines known to exhibit Fas induction. We have previously linked this induction to radiation sensitivity in cell culture and now confirmed that this phenomenon exists in breast cancer patients.

P-35: Association Between Phthalate Metabolites in Pregnancy and Risk of Gestational Diabetes

Tamarra James-Todd (presenting author),[1] Aditi Saxena,[1]
Florence Brown,[1] John Meeker,[2] Thomas McElrath,[3]
and Janet Rich-Edwards[1]

[1]Brigham and Women Hospital and Harvard Medical School; [2]Joslin Diabetes Center and Harvard Medical School; and [3]University of Michigan School of Public Health

Background and Objective: Studies show higher phthalate levels are associated with increased type 2 diabetes risk, likely through binding and activation of peroxisome proliferator-activated

receptors. Yet, few have examined the association between phthalate metabolites and gestational diabetes (GDM) risk. The purpose of the study was to evaluate the associations between urinary phthalate metabolites and GDM risk, as well as pre- pregnancy weight (PPwt), gestational weight gain (GWG), and glucose levels.

Methods: We analyzed 350 women who participated in the Predictors of Preeclampsia cohort study. Seven urinary phthalate metabolites were measured at 4 points throughout pregnancy and divided into quartiles (reference lowest concentration). GDM was defined by Carpenter-Coustan criteria. PPwt, GWG and glucose levels were categorized as less than vs. greater than the median. We used logistic regression to calculate odds ratios and 95% confidence intervals adjusting for maternal age.

Results: Phthalate concentrations remained similar throughout pregnancy; however, they varied by race/ethnicity ($P < .003$). Women with the highest first trimester levels of mono-(3-carboxypropyl) phthalate had 2 times the odds of greater-than-median PPwt (95% CI: 1.09–3.71). Women in the second quartile of monobenzyl phthalate (MBzP) had 2.32 times the odds of greater-than-median GWG and 1.62 times the odds of greater glucose (95% CI: 1.17–4.59 and 0.78–3.36, respectively). Higher MBzP levels were associated with four-fold increased odds of GDM (95% CI for fourth quartile: 0.52–36.37).

Conclusions: Certain phthalates were associated with PPwt, GWG, and glucose levels, with some indication of elevated GDM risk. If replicated, lowering exposure to certain phthalates may reduce GDM risk and potentially women's future type 2 diabetes risk.

P-36: Bisphenol A in Pregnancy and Risk of Gestational Diabetes

Tamarra James-Todd (presenting author),[1] Aditi Saxena,[1] John Meeker,[1] Thomas McElrath,[2] and Janet Rich-Edwards[1]

[1]Brigham and Womens Hospital; and [2]University of Michigan School of Public Health

Background and Objective: Studies show a positive association between Bisphenol A (BPA) and type 2 diabetes, likely through its ability to bind to estrogen-related receptor and peroxisome proliferator–activated receptor. Yet, few have evaluated the association between BPA and gestational diabetes (GDM). The objective of this study was to evaluate the association between BPA levels during pregnancy and risk of high pre-pregnancy weight, gestational weight gain, and GDM.

Methods: A total of n = 298 women who delivered at term and were participants of the Predictors of Preeclampsia study had BPA measurements and had data on GDM diagnosis. BPA was divided into quartiles. Pre-pregnancy weight was measured using weight at first trimester (8–10 weeks gestation). Gestational weight gain was measured as the difference between weight at delivery and pre-pregnancy weight. Both were categorized as less than or as greater than or equal to the median. GDM was defined using the Carpenter-Coustan criteria. We used logistic regression to calculate odds ratios and 95% confidence intervals, adjusting for maternal age.

Results: BPA levels remained similar across the first 2 trimesters of pregnancy. Women who had higher first trimester BPA levels were twice as likely to have greater-than-or-equal-to-median pre-pregnancy weight (95% CI for second quartile, 1.14–3.93). There was no association between BPA and gestational weight gain. However, women with the high first trimester BPA levels had over 5-fold increased odds of GDM (OR for fourth quartile: 5.92; 95% CI, 1.28- 27.60).

Conclusions: BPA was associated with increased odds of high pre-pregnancy weight and GDM, but not with gestational weight gain. If these findings are replicated, women may benefit from reductions in BPA exposure before and during pregnancy to reduce risk of GDM.

P-37: In Women With Normal Glucose Levels on Fasting 75-g Oral Glucose Tolerance Tests, Excessive Gestational Weight Gain Was Not Associated With Increased Neonatal Adiposity

Jami L. Josefson (presenting author),[1] Dinah M. Zeiss,[2] Mary J. Kwansy,[3] and Boyd E. Metzger[4]

[1]Department of Pediatrics, [2]Northwestern Comprehensive Center on Obesity, [3]Department of Preventive Medicine, and [4]Department of Medicine, Northwestern University Feinberg School of Medicine

Background and Objective: Excessive gestational weight gain (GWG) among American women has steadily increased over the past 20 years, in parallel with the increasing prevalence of maternal obesity. Evidence suggests that newborns with increased adiposity have increased risk of childhood obesity. Whether excessive GWG is associated increased neonatal adiposity requires further study. The objective was to determine whether weight gain above Institute of Medicine–recommended amounts in an ethnically diverse obstetric population is associated with increased neonatal adiposity.

Methods: Women carrying singleton pregnancies with normal glucose levels on 2-hour fasting 75-gram oral glucose tolerance tests (OGTT) who delivered full term were enrolled. Gestational weight gain was calculated from weights measured at first and last prenatal visits. Neonatal adiposity was measured by air displacement plethysmography at 24 to 72 hours of life.

Results: Preliminary analysis of 100 participants (BMI categories: 3% underweight, 58% normal weight, 21% overweight, and 18% obese) demonstrated no difference in body fat of neonates born to mothers who met (34%) or exceeded (44%) GWG guidelines. The 22% of women who gained less than GWG guidelines had neonates with significantly lower median body fat (8.3%) compared with neonates of mothers who met (11.1%, unadjusted $P = .01$) or exceeded guidelines (11.2%, unadjusted $P < .01$). Mean glucose levels (sd) on 75-gram OGTT were as follows: fasting: 76.3 (5.8); 1 hour: 115.8 (27.1); 2 hours: 101.3 (19.5) mg/dL, all lower than thresholds of 92, 180, and 153 mg/dL, respectively, recommended by the International Association of Diabetes and Pregnancy Study Groups.

Conclusions: In this cohort of women with normal 75-gram oral glucose tolerance tests, excessive GWG was not associated increased neonatal adiposity.

P-38: Inhibition of Peroxisome Proliferator Gamma (PPARγ): A Potential Link Between Chronic Maternal Hypoxia and Impaired Fetal Growth

Colleen Julian (presenting author),[1] Ivana Yang,[1] Enrique Vargas,[1] Brent Pedersen,[2] Lorna Moore,[1] and David Schwartz[3]

[1]Department of Medicine, University of Colorado Denver; [2] Bolivian Institute of High Altitude Biology; and [3]Department of Obstetrics and Gynecology, University of Colorado Denver

Background and Objective: Chronic maternal hypoxia impairs fetal growth and increases the incidence of intrauterine growth restriction (IUGR). To identify the mechanisms underlying these hypoxia-related effects, we evaluated whether exposure to chronic hypoxia during pregnancy alters maternal gene-expression patterns relative to normoxic pregnancy and, if so, to define the dominant genes and pathways involved.

Methods: Gene expression profiles were generated using NimbleGen Human Gene Expression microarrays for 79 peripheral blood mononuclear cell samples collected from 43 women residing at high (n = 25, 3600–4300 m) or low (n = 18, 300 m) altitude in the non-pregnant state or during pregnancy (20 or 36 weeks). Transcriptional differences between altitudes were detected using Limma, Lme4, and Car packages in R; the relationship of such differences to biological processes and pathways was assessed in IPA.

Results: Gene expression differed at high versus low altitude in the non-pregnant state (43 genes), at 20 weeks of pregnancy (59 genes) and at 36 weeks of pregnancy (985 genes). Several genes of known pathologic significance for IUGR varied between altitudes during pregnancy but not in the non-pregnant state. Among the pathways enriched by these genes was the peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathway. Transcriptional changes were consistent with the negative regulation of PPARγ at high versus low altitude during pregnancy, but not in the non-pregnant state.

Conclusions: Pregnancy magnifies the influence of environmental hypoxia on gene expression in ways that may be related to fetal growth. Given its involvement in the regulation of inflammation, vascular function, and glucose metabolism, we consider PPARγ to be an important candidate for future study.

P-39: Transcriptomic Analysis of Amniotic Fluid for Insight Into Fetal Maturation: A Pilot Study

Beena Kamath-Rayne (presenting author), Maria Hughes, Erin Wagner, Ardythe Morrow, Jeffrey Whitsett, and Yan Xu

University of Cincinnati

Background and Objective: Amniotic fluid (AF) is an underutilized resource for learning more about fetal development and timing of parturition, as it both reflects and contributes to fetal well-being. Systems biology analysis of AF mRNAs may provide insights into genes, processes and transcriptional networks regulating organ maturation and the relationships among gestation, organ maturation, and timing of parturition. Our aim was to test the hypothesis that mRNA transcriptomic analysis of AF will identify fetal organ maturation providing insight into processes influencing normal and pathologic pregnancy.

Methods: To identify the tissue-specific gene expression patterns in AF, RNA sequencing was performed on RNA isolated from the AF of 2 infants born at 39 weeks by elective Cesarean section. Genes abundantly expressed in full-term AF (>90% in distribution analysis) were then mapped to the mouse expression data from the GNF Gene Expression Atlas to estimate the relative expression of these AF genes across 61 tissues.

Results: The between-sample correlation was 0.973, indicating little individual variation across full term AF samples. Stomach, lung, and epidermis ranked as the top 3 tissue resources of genes from full-term AF. Many of the tissue signature genes were functionally involved in epithelial cell differentiation, suggesting that tissue-specific epithelial cell differentiation will provide tissue-specific markers useful in monitoring fetal well-being and maturation, and provide insight in the biologic processes regulating human fetal development.

Conclusions: Transcriptomic analysis of AF can provide information regarding functional organ maturity and may possibly improve upon our current methods of fetal lung maturity testing. Further work is under way to compare AF samples from term and preterm infants in normal and abnormal pregnancies in order to identify the transcriptional networks influencing preterm birth.

P-40: Associations Among Domains of Maternal Physical Activity and Lipid Levels During Pregnancy

Lanay M. Kazmirzack (presenting author)[1] and Jean Kerver[2]

[1]*Department of Kinesiology and* [2]*Department of Epidemiology and Biostatistics, Michigan State University*

Background and Objective: High and low lipids during pregnancy are associated with poor birth outcomes. Higher physical activity (PA) has been related to lower lipids in early pregnancy, but these relations have not been examined later in pregnancy, when lipids naturally increase. The objective was to examine associations between PA domains and lipids among pregnant women in the 2nd and 3rd trimesters.

Methods: Women completed the Pregnancy PA Questionnaire. Percentages of total MET-min/wk (%PA) spent in Household, Work, and Exercise domains were calculated. A fingerstick blood sample determined non-fasting levels of total (TC), high- (HDLc), and low-density-lipoprotein cholesterol (LDLc) and triglycerides (TG). Partial correlations examined relations among %PA in each domain and lipids, controlling for total MET-min/wk. Multiple linear regression examined relations among tertiles of %PA in all domains and TC.

Results: There were 69 participants (2nd trimester, n = 40; 3rd trimester, n = 29). No significant relations were observed among 3rd-trimester women. Among 2nd-trimester women, Household accounted for 49%; Work, 19%; and Exercise, 2% of total PA, on average. Household %PA ($r = -0.39$) and Work %PA ($r = 0.42$) were related to TC ($P < .05$). No significant relations were found for other lipids. In regression analyses including all %PA domains, only tertiles of Household %PA was associated with significantly lower TC ($\beta = -27.5$, $P < .05$, adj$R^2 = 0.21$).

Conclusions: In this sample of low-income women, Household %PA accounted for most of the total PA and was associated with lower TC levels in the 2nd trimester. Pregnancy-related increases in lipids in the 3rd trimester may overwhelm any effect of PA.

P-41: A Need for Culturally Tailored Group Prenatal Programs for Obese Minority Women to Meet Gestational Weight Gain Recommendations

Michelle Kominiarek (presenting author),[1] Franklin Gay,[1] and Nadine Peacock[2]

[1]*University of Illinois at Chicago; and* [2]*University of Chicago*

Background and Objective: Interventions have not been effective in assisting obese women to meet gestational weight gain (GWG) recommendations. Culturally tailored prenatal programs may be needed. The objective of the study was to investigate minority women's perceptions about obesity and GWG and their motivations and barriers to improving health behaviors during pregnancy.

Methods: Sixteen primarily non-Hispanic black pregnant women with a pre-pregnancy body mass index greater than 30 kg/m^2 receiving prenatal care at an inner-city hospital–based clinic participated in focus groups. Discussion topics included GWG goals, body image, health behaviors, stress management, and group prenatal care.

Results: Women frequently stated a target GWG of greater than 20 pounds. They expressed fear of gaining weight, but also frustration when told to restrict weight gain. Women described a body image not in line with clinical recommendations: "200 pounds is not that big"; "[to] maintain my weight between 250 and 245 would be good." They avoided the term "obese" and more commonly used "thick." They were interested in learning more about nutrition and in culturally specific healthy cooking resources. Women stated they would enjoy massage and exercise in a group setting, though definitions of "exercise" varied. There were mixed feelings about support systems; family members could be helpful, but generational differences posed challenges (grandmothers would "curse them out" for exercising during pregnancy). As a result, most felt the need to "encourage myself" and "do this for me and the baby."

Conclusions: Culturally tailored programs that use acceptable terms for obesity, provide education regarding healthy eating and safe exercise, and encourage appropriate support from social networks may be effective in addressing GWG in obese minority women.

P-42: Born Too Soon: Trends in Childbirth Before 39 Weeks Gestation Without Medical Indication, 1995–2009

Katy B. Kozhimannil (presenting author),[1] Michelle Macheras,[2] and Scott A. Lorch[2]

[1]*Division of Health Policy and Management, University of Minnesota School of Public Health; and* [2]*The Children's Hospital of Philadelphia*

Background and Objective: Childbirth is the most common and costly reason for hospitalization in the U.S. There is increasing clinical and policy attention to labor induction and cesarean delivery occurring without medical indication between 37 and 39 weeks of completed gestation ("early term" deliveries). The objective was to measure prevalence, change over time, and individual characteristics associated with early term nonindicated delivery.

Methods: We conducted a retrospective, longitudinal analysis using linked hospital discharge and birth certificate data for all 7,296,363 full-term, uncomplicated births that occurred between 1995 and 2009 in 3 states: Missouri, California, and Pennsylvania. The primary outcome is early term nonindicated delivery, either medical induction of labor or cesarean delivery, and calculated among all uncomplicated deliveries between 37 and 44 weeks gestation. Gestational age is from birth certificates, and medical procedures and indications are from hospital discharge records. Secondary outcomes include infant prolonged length of stay and respiratory distress.

Results: Across all uncomplicated births, the rate of early term nonindicated delivery was 3.18%, increasing from 2.12% in 1995 to 3.74% in 2009. After controlling for clinical, sociodemographic, and hospital factors, the risk of having a nonindicated delivery before 39 weeks was 78% higher in 2009 compared with 1995 (hazard ratio (HR) = 1.78; 95% CI [1.73–1.82]). Factors associated with greater odds of early term nonindicated delivery included advanced maternal age, white race, higher education levels, private health insurance, and delivering at smaller volume or nonteaching hospitals. There were

racial/ethnic differences in the risk of early term nonindicated birth by mode of delivery, with nonwhite women having substantially lower rates of nonindicated induction, compared with white women; however, black women had higher rates of nonindicated cesarean delivery (HR = 1.26 [1.23–1.29]) compared with white women. Early term nonindicated delivery was associated with 25% greater odds of prolonged length of stay (AOR = 1.25 [1.23–1.27]) and with 52% greater odds of respiratory distress (AOR = 1.52 [1.49–1.56]).

Conclusions: Early term nonindicated delivery has increased over the past 15 years. In 2009, nearly 4% of all full term infants without complications were born too soon in the U.S., with no medical indication, and these births were associated with adverse infant outcomes.

P-43: Sex, Strain, and Regional Differences in the Colonic Epithelial Response to Repeated Water Avoidance Stress (rWAS)

Muriel Larauche (presenting author), Ganna Tolstanova, Million Mulugeta, and Yvette Tachè

Specialized Center for Neurovisceral Science and Women's Health and CURE: DDRC

Background and Objective: Irritable bowel syndrome (IBS), a stress-sensitive disorder characterized by recurrent abdominal pain and altered bowel habits, is more common in women. The mechanisms underlying this sex difference in prevalence remain unclear. A subset of IBS patients shows a compromised colonic epithelial barrier function. While studies in male rodents demonstrated that chronic stress is associated with increased colonic permeability, potential sex differences in the colonic epithelial response to stress have not been reported. The objective of the study was to determine the influence of sex on stress-induced colonic mucosal function alterations.

Methods: Male and female Wistar and Wistar-Kyoto (WK) rats (7–11 wks) were used. Naïve or stressed (rWAS, 1 h/day, 4 days) rats were euthanized 5 h after the last stress session. Proximal and distal colon segments were collected. After seromuscular stripping, the mucosa was mounted in Ussing chambers containing oxygenated Krebs Ringer's buffer. The conductance (G, paracellular permeability) and short circuit current (Isc, transmembrane ion exchanges) were measured. In both strains, rWAS increased the Isc in females, but not males, in the proximal colon.

Results: In the distal colon, both male and female Wistar rats displayed an increase in Isc following rWAS while female and male WK rats showed a decreased Isc. Females, but not males, of both strains exhibited an increase in G exclusively in the proximal colon following rWAS.

Conclusions: Female rats show an increased susceptibility to develop colonic epithelial disturbances during repeated psychological stress which is conserved among different strains. This altered colonic response may contribute to the greater prevalence of visceral hypersensitivity and IBS symptoms in women.

P-44: Preferences of Breast Cancer Survivors for Traditional and New Media Delivery of Health Promotion Interventions

Elizabeth J. Lyons (presenting author)[1], Karen Basen-Engquist,[2] Janice Blalock,[3] Cindy L. Carmack,[3] and Wendy Demark-Wahnefried[3]

[1]*University of Alabama;* [2]*University of Texas Medical Branch; and* [3]*University of Texas M.D. Anderson Cancer Center*

Background and Objective: Internet-delivered health promotion interventions are increasingly implemented among breast cancer survivors, but little is known about their acceptability and uptake. This questionnaire study assessed cancer survivors' interest in health promotion interventions delivered in clinics, by telephone, or by computer or smartphone.

Methods: Cancer survivors (breast, colorectal, and prostate) were sent a brief survey by mail. Of 1,871 who received the survey, 1,053 completed and returned it. Interest in health promotion interventions using various delivery methods (clinic, telephone, computer, and smartphone) was assessed. Frequencies and chi squared tests were used to investigate differences across cancer sites.

Results: Participants were mean 63 (11, SD) years old and 4.6 (3.1, SD) years from diagnosis; 55% were female. Most (50.1%) were breast cancer survivors; 39.8% were prostate and 10.1% colorectal cancer survivors. Breast cancer survivors were more interested in all intervention modalities than were survivors of other cancers ($P < .001$ for clinic, telephone, and computer; $P = .016$ for smartphone). Their interest was highest for computer-based interventions (37% extremely or very interested); 25% were extremely or very interested in clinic-based programs, and 23% were extremely or very interested in telephone-based programs. Smartphone-based interventions produced the least interest, with only 12%.

Conclusions: Breast cancer survivors are interested in technology-mediated interventions but prefer computers to smartphones. Further investigation is needed to determine whether greater reported interest leads to improved uptake or behavior change.

P-45: Air Pollution Exposures and Incident Infertility in the Nurses' Health Study II

Shruthi Mahalingaiah (presenting author)

Department of Obstetrics and Gynecology, Boston Medical Center and Boston University School of Medicine

Background and Objective: Second-hand smoke (SHS) exposure has been previously associated with impaired fertility. Air pollution (AP) is composed of similar constituents as SHS, although few studies have examined the impact of AP on infertility. This study's purpose was to examine the associations of distance to road (a measure of traffic exposure) and particulate matter air pollution and incidence of infertility.

Methods: The study included Nurses' Health Study II subjects who were alive, aged 45 or younger, premenopausal, not using contraceptives (surgical or medical), not diagnosed with infertility prior to 1993, who had at least one address from 1993 to 2007 geocoded to the street segment level, and who were not lost to follow-up. Proximity to major roadways and outdoor levels of particulate matter (PM10, PM10-2.5, PM2.5) were determined for all residential addresses for 18,887 women from 1989 to 2007. Infertility was defined as attempted conception for 1 year or longer without success since the previous questionnaire administration. Multivariable-adjusted time-varying Cox proportional hazard models were used to estimate the relation between distance to road and PM exposures and infertility risk.

Results: Over 107,197 person-years, there were 894 incident cases of infertility. Living close to a major road was associated with an increased risk of infertility, adjusted hazard ratio (aHR) of 1.12 (95% confidence interval (CI) 0.97–1.28). Each 10 $\mu g/m^3$ increase in 2-year average, 4-year average, or cumulative average exposures to PM10-2.5 were associated with small increased risks, aHR 1.14 (95% CI 0.98–1.32), aHR 1.18 (95% CI 0.99–1.40), aHR 1.15 (95% CI 1.00–1.31), respectively.

Conclusions: Long-term exposures to traffic and PM10-2.5 may be associated with a modest increased risk of infertility.

P-46: Placental Neutrophil Extracellular Traps (NETs) in Pregnancies Complicated by Preeclampsia and Systemic Lupus Erythematosus

Wendy Marder (presenting author)

University of Michigan

Background and Objective: Neutrophil extracellular traps (NETs) have been identified in renal and skin tissue from patients with systemic lupus erythematosus (SLE). NETs have also been identified in placental intervillous space in preeclampsia (PE), but not in normal pregnancies. We hypothesized that intervillous NET formation is a feature of SLE pregnancy, in which adverse obstetric outcomes (intrauterine growth restriction, preeclampsia, eclampsia) are significantly increased compared to non-lupus pregnancies.

Methods: Cases were identified by ICD-9 search for deliveries complicated by PE and SLE. Formalin-fixed, paraffin-embedded placental tissue blocks were retrieved and cut sections stained with myeloperoxidase immunohistochemical stain. Neutrophils were

counted in 10 consecutive fields of intervillous space at 60x, and defined as "intact" (myeloperoxidase staining confined within cell cytoplasm with a multi-lobulated nucleus), "not intact" or NETted (extracellular myeloperoxidase staining), or "indeterminate." Wilcoxon rank sum test was used to compare NETs between PE and SLE groups. Placentas from 8 SLE and 9 PE pregnancies were reviewed.

Results: Numbers of total neutrophils were not significantly different, but greater variability was observed among SLE (median 26.5 [IQR 52.5–178]) versus PE pregnancies (median 95 [IQR 69–105]). NETted neutrophils were comparable between SLE vs PE (median 14.5 [IQR 3.5–35.5] vs. 12 [11–29]) respectively, as was percentage of NETs/total neutrophils (median 17 [IQR 12–31] vs. 19 [IQR 11–30]).

Conclusions: In this pilot study, comparable numbers of intervillous NETs in PE and lupus placentas suggest a common pathologic process, and comparison with control pregnancies is planned. Whether NETs are causative or result of inflammatory vasculopathy frequently observed in these pregnancies is currently unknown.

P-47: Personality Traits Elucidate Sex Differences in Attention-Deficit/Hyperactivity Disorder Comorbidity

Michelle M. Martel (presenting author)

Psychology Department, University of Kentucky

Background and Objective: Attention deficit/hyperactivity disorder (ADHD) is highly comorbid with other childhood disorders, and there are striking sex differences in this comorbidity, particularly during early childhood. For example, boys with ADHD are more likely to exhibit comorbid disruptive behavior and neurodevelopmental disorders, compared with girls, during early childhood. Yet explanations for these well-established sex differences remain in short supply. The current study evaluated the novel hypothesis that personality traits may serve as intermediate phenotypes that help explain sex differences in common ADHD comorbidity profiles during early childhood.

Methods: Study participants were 109 children between the ages of 3 and 6 and their primary caregivers and teachers/daycare providers, recruited from the community and over-recruited for ADHD-related problems. Primary caregivers completed the Child Behavior Checklist, and teachers/daycare providers completed the Teacher Report Form as a measure of child behavior problems. Examiners completed the California Q-Sort as a measure of child personality traits.

Results: Moderated mediation analyses suggested that personality traits explain associations between ADHD and oppositional-defiance, aggression, and language problems in a sex-specific manner. While high neuroticism mediated associations between ADHD and oppositional-defiance in girls, disagreeableness mediated associations between ADHD and aggression and low conscientiousness mediated associations between ADHD and neurodevelopmental language problems in boys.

Conclusions: Sex differences in trait-psychopathology associations may help explain sex differences in comorbidity profiles with possible implications for child assessment and personalized early intervention.

P-48: Neurobiology of Resilience—Personality and Functional Connectivity of the Default Mode and Salience Networks

Joshua Istrin and Emeran Mayer (presenting author)

University of California, Los Angeles

Background and Objective: Increased resilience may be associated with better health outcomes and reduced morbidity in response to physical or psychological perturbations of homeostasis. The NEO Personality Inventory has been used to capture a resilient personality profile (NEO PI- R), and correlations between individual personality traits and resting state (RS) brain networks have previously been reported. However, only recently have biological correlates of resilience been investigated. The objective of the study was to identify possible correlations between personality traits of resilience and RS networks.

Methods: Seventy-seven healthy subjects (53 female, 24 male) from the Pain and Interoception imaging Network repository (PAIN) completed a resting fMRI scan and NEO PI-R. Independent components analysis was used to identify RS networks. Partial Least Squares was performed to examine relationships between RS networks and NEO personality profiles.

Results: A relationship between a pattern of personality traits previously associated with resilience and default mode network (DMN) functional connectivity was demonstrated. Low resilience was associated with increased DMN functional connectivity of lateral parietal, posterior, and anterior cingulate cortices. In addition, male subjects demonstrated a relationship between a resilience personality profile and functional connectivity within a salience/executive control network (SAL). For males but not females, low resilience was associated increased SAL functional connectivity of anterior insula and dorsolateral prefrontal cortex.

Conclusions: This is the first study to identify correlations between RS-fMRI and a measure of personality-related resilience. Identification of the neurobiology of resilience may have future implications for identifying individuals at high risk for developing adverse health consequences when faced with perturbation of homeostasis.

P-49: HIV and GBV in Nyanza Province, Kenya: Mental Health Care Needs Among Women

Susan M. Meffert (presenting author)

University of California, San Francisco

Background and Objective: HIV-positive (HIV+) women face extraordinary rates of gender-based violence (GBV). The study's objective was to assess the mental health care needs of HIV+ women affected by GBV (HIV+GBV+) at the UCSF-KEMRI HIV treatment site in Nyanza Province, Kenya, a location with very high rates of HIV infection and GBV. Data from this study will be used to inform development of a locally delivered, sustainable mental health treatment for HIV+GBV+ women.

Methods: We used 30 key informant interviews and 4 focus groups with HIV+ female patients, health care providers, community health workers, and local leaders to investigate four domains: (1) violence against HIV+ women in Nyanza Province; (2) mental and physical health problems among HIV+GBV+ women; (3) current coping methods; (4) barriers to and preferences for mental and physical health care.

Results: Despite the fact that male partner infidelity is the source of most female HIV infections, GBV is typically perpetrated against HIV+ women by male partners and male partners' families, based on the accusation that women brought the infection into the family. GBV leads to "stress," "fear," "unhappiness," "hopelessness," and appetite and weight loss, which affect HIV health. Coping methods include support from other HIV+ women. Fear of HIV disclosure, associated stigmatization from community members, and GBV from male partners and their families are barriers to health care.

Conclusions: Mental health care for HIV+GBV+ women is greatly needed in order to alleviate emotional suffering and associated impact on HIV health. Treatment should build on current interpersonal coping methods women and prioritize privacy.

P-50: Guanfacine Has Antidepressant-like Effects and Potentiates Nicotinic-based Antidepressants

Yann S. Mineur (presenting author), Margreet Platenga, and Marina R. Picciotto

Yale University School of Medicine

Background and Objectives: Women are 3 times more likely to relapse to smoking than men after short-term abstinence, and nicotine replacement therapies may be less effective for women. Further, higher stress reactivity also has a greater negative impact on smoking cessation in women than in men. In order to develop gender-based treatments for smoking cessation it would be important to identify the neurobiological basis for these sex differences. There are sex differences in brain structures involved in stress reactivity, such as the amygdala. Both norepinephrine (NE) and acetylcholine (ACh)

regulate the amygdala-prefrontal cortex circuit and are modulated by stress and substance abuse. We hypothesize that there might be sex differences in NE and ACh regulation of the amygdala that could contribute to the neurobiological basis of nicotine relapse.

Methods: To address this issue, we investigated the effect of guanfacine, an α2-adrenergic autoreceptor agonist that decreases NE release, in a test of antidepressant efficacy in both male and female C57BL/6J mice.

Results: Guanfacine induced a dose-dependent antidepressant-like effect in both male and female mice, although there was greater immobility in female at baseline. Further, a sub-threshold dose of guanfacine greatly potentiated the antidepressant-like effects of the nicotinic ACh antagonist mecamylamine, but only in females. Both guanfacine and mecamylamine show efficacy in aiding with smoking cessation under specific conditions, and both have potential antidepressant effects.

Conclusions: These data therefore suggest that targeting the noradrenergic and cholinergic systems could be useful in aiding women with smoking cessation, particularly if these individuals have depressive symptoms.

P-51: Gender Differences in Subjective Responses to Yohimbine Administration Between Cocaine-Dependent Men and Women

Megan M. Moran-Santa Maria (presenting author), Aimee L. McRae-Clark, Nathan L. Baker, and Kathleen T. Brady

Medical University of South Carolina

Background and Objective: There are significant gender differences in the risk factors associated with cocaine craving and relapse. For example, cocaine-dependent (CD) women are more likely to report stress prior to a relapse episode than CD men. Although dysregulation in the noradrenergic system (NAS) has been associated with elevated stress and anxiety during drug withdrawal, surprisingly little is known about the role of the NAS in contributing to the gender differences in the risk factors associated with relapse. The objective of the study was to compare the impact of pharmacological provocation of the NAS on subjective responses to cocaine cues between CD men and women.

Methods: CD men (n = 32), CD women (n = 30), control men (n = 32), and control women (n = 25) received either the alpha-2 adrenergic receptor antagonist yohimbine (21.6 mg) or placebo before each of 2 cocaine-cue exposure sessions. Participants were tested under both conditions in a counter-balanced, double-blind fashion. Subjective data were collected at baseline, immediately after (T0), T5, T15, T30 and T60-minutes after the cues.

Results: Significant gender by condition interactions were found for craving at T5 ($P < .01$) and anxiety at T0 ($P < .05$) and T5 ($P < .05$), indicating that CD women reported significantly greater cue-induced craving and anxiety in response to yohimbine than CD men. There was a significant condition effect on stress at T0 ($P < .001$) and at T5 ($P < .01$). There were no condition effects or condition by gender interactions on subjective responses in the control subjects.

Conclusions: Sex differences in noradrenergic dysregulation may be a critical neurobiologic factor that underscores gender differences in stress-induced relapse.

P-52: The Impact of Worry on Error-related Brain Activity and Behavioral Performance Is Moderated by Hormonal Contraceptive Use

Jason Moser (presenting author), Hans Schroder, and Tim Moran

Michigan State University

Background and Objective: Chronic worriers, "individuals characterized by repetitive, uncontrollable anxious thoughts," show enhanced brain activity to errors, suggesting they invest greater neural resources to bounce back from mistakes. Recently, we showed that the relationship between worry and enhanced error-related brain activity is several times greater in women than men, consistent with other behavioral research indicating that worry may have a disproportionately negative impact on women. Together, these findings suggest that female-specific factors may contribute to the impact of worry on error-related brain activity and behavioral performance. The objective of the study was to test the hypothesis that endogenous ovarian hormone fluctuations contribute to the impact of worry on error-related brain activity and performance.

Methods: Twenty-seven undergraduate women not taking hormonal contraceptives and 13 undergraduate women taking hormonal contraceptives performed a standard reaction time task while error-related brain activity was recorded. Following the task, they completed the Penn State Worry Questionnaire to measure worry levels.

Results: Women not taking hormonal contraceptives showed the expected associations such that higher worry scores were related to enhanced error-related brain activity ($r = .45$) and poorer behavioral performance ($r = -.55$). Importantly, women taking hormonal contraceptives did not demonstrate significant associations between worry and error-related brain activity ($r = .22$) or worry and behavioral performance ($r = .29$).

Conclusions: Findings from the current study suggest that the effect of worry on error-related brain activity and performance may depend on naturally fluctuating ovarian hormones. Hormone therapy may be one viable option for reducing the negative impact of worry on cognitive functioning.

P-53: Transcriptional Control of the Response to Diet by Nuclear Hormone Receptors

Laura Musselman (presenting author)

Washington University

Background and Objective: The health of women can be adversely affected by excess calorie intake and by hormonal imbalance, with both factors increasing the incidence of diseases such as diabetes, breast cancer, and cardiovascular disease. Transcriptional mechanisms of nuclear hormone receptors (NHRs), in part, control the ability to accommodate changes in hormone concentrations and caloric intake. The purpose of this study was to define the roles of NHRs in nutrient metabolism in the fat body.

Methods: Flies offer a rapid, genetically dissectible system in which to study conserved metabolic pathways in a tissue-specific manner. We studied the transcriptional response to a high sugar diet, which induces hyperglycemia and insulin resistance, in the Drosophila fat body, a liver- and adipose-like tissue. A transgenic RNA interference strategy was used to dissect the functions of NHRs.

Results: Tissue-specific, loss-of-function studies reveal a role for several NHRs in maintaining metabolic homeostasis in the fat body during high-sugar diet feeding. The NHRs EcR, E75, and E78 all function to alleviate hyperglycemia, whereas βFTZ-F1 is essential in the fat body for survival on a high-sugar diet. Another NHR, Seven-up, is critical for modulating hyperglycemia and insulin sensitivity in the fat body, possibly by controlling ER stress.

Conclusions: Our studies reveal potential mechanisms by which NHRs might function in the adipose-like *Drosophila* fat body. Most NHRs act protectively, suggesting that their target pathways improve the ability to cope with the caloric overload. Future work will test the pathways downstream of these receptors to identify conserved RNA and lipid mediators of diabetes-like pathophysiology in this organ.

P-54: 17β-estradiol Increases IL-17A Protein Expression From Mouse CD4+ Th17 Differentiated Cells

Dawn C. Newcomb (presenting author), Jacqueline-Yvonne Cephus, Madison G. Boswell, Kasia Goleniewska, and R. Stokes Peebles, Jr.

Department of Medicine, Vanderbilt University Medical Center

Background and Objective: Th17 cells have increased IL-23/IL-23 receptor (R) signaling, leading to increased IL-17A and IL-17F protein expression. Th17 cells are associated with severe asthma, multiple sclerosis, and lupus. After puberty, women have a higher prevalence of these diseases, suggesting a role for sex hormones, but the mechanisms by which sex hormones affect Th17 cell cytokine production remain unknown. The objective was to determine the role of sex hormones in expression of IL-23R, IL-17A, and IL-17F in Th17 cells from prepubescent and adult mice.

Methods: Naïve CD4+ T cells from female, male, and ovariectomized mice ages 3 weeks (prepubescent) or 8 to 10 weeks (adult) were isolated and differentiated into Th17 cells. Placebo, 17β-estradiol (E2), progesterone, or 5α-dihydrotestosterone (5α-DHT) pellets were implanted into ovariectomized mice 21 days prior to naïve T cells isolation. IL-23R mRNA expression was measured by qPCR, and IL-17A and IL-17F protein expression was measured by ELISA.

Results: In prepubescent mice, IL-23R mRNA expression and IL-17A and IL-17F production were decreased by approximately 50-fold in Th17 cells from female compared with male mice. In adult mice, IL-23R mRNA expression and IL-17A and IL-17F production was increased by about 50-fold in Th17 cells from females compared with male and ovariectomized mice. In vivo administration of 17β-E2, but not progesterone or 5α-DHT, significantly increased IL-17A and IL-17F production by Th17 cells by 2.5-fold compared with ovariectomized mice receiving placebo pellets.

Conclusions: In vivo 17β-E2 increases Th17 cell differentiation and provides a biological mechanism to explain the switch in prevalence of Th17-mediated diseases at puberty.

P-55: A New Murine Model of Urinary Tract Infection Identifies Sex Differences in Pathogenesis

Patrick D. Olson (presenting author)[1] and David A. Hunstad[1,2]

[1]*Department of Pediatrics and* [2]*Department of Molecular Microbiology, Washington University School of Medicine*

Background and Objective: Between the ages of 2 and 60 years, community-onset urinary tract infection (UTI) occurs almost exclusively in females, a sex predilection attributed solely to anatomical differences. Technical challenges in catheterizing male mice have heretofore precluded extensive study of male UTI and sex differences in these model hosts. The objective was to develop a model of UTI to infect both male and female mice and define sex differences contributing to sexual disparity in UTI.

Methods: We developed a novel mini-surgical inoculation technique that yields reliable infection of the upper and lower urinary tract by uropathogenic *Escherichia coli* (UPEC), without peritonitis or systemic complications. Following infection, outcomes were analyzed by tissue bacterial load and other measures.

Results: Male C57BL/6 mice developed significantly higher UPEC titers in the kidney at 24 hours post-infection (hpi) and 2 weeks post-infection (wpi) compared with females. Following resolution of acute infection, female C57BL/6 showed significantly more bacteria in chronic reservoirs in the bladder (a seed for recurrent UTI). In the C3H/HeN background, male mice had higher bladder titers than females at 6 hpi and 2 wpi. By LacZ staining and confocal microscopy, there was no difference in the number or structure of intracellular bacterial communities in the bladder between males and females. Most striking, males showed significantly higher renal bacterial loads at all time points examined, and a much higher incidence of renal abscesses.

Conclusions: Our mini-surgical model of UTI will be useful in identifying and characterizing sex differences in pathogenesis, host responses, and susceptibility to these common infections.

P-56: Intraperitoneal Drug Delivery to Improve Efficacy of Targeted Therapies in Mouse Models of Epithelial Ovarian Cancer

Harsh B. Pathak (presenting author)

University of Kansas Medical Center

Background and Objective: Intraperitoneal (IP) drug delivery of existing chemotherapy for the treatment of patients with advanced epithelial ovarian cancer (EOC) is gaining recognition and is currently being evaluated in two large multi-centric prospective Phase 3 clinical trials designed to evaluate IP vs. intravenous drug delivery. Given the increased bioavailability of drugs when administered IP and the improvement by 19% to 25% in overall survival of patients with EOC as observed by performing meta-analyses on retrospective Phase 3 clinical trial data, it is likely that IP drug delivery will be a part of the standard of care provided to these patients in the near future. The purpose of the study was to improve efficacy of targeted therapies which have shown limited response in patients with EOC in Phase 2 clinical trials by reformulating for IP delivery.

Methods: As a proof of principle, nanomicelle formulations of dasatinib, an SRC kinase inhibitor, were prepared and then evaluated using mouse models of EOC.

Results: In pilot studies using mice bearing intraperitoneal ovarian tumors, IP delivery of dasatinib, either as a free drug or as a nanomicelle preparation, reduced tumor growth by 39% to 48%. The same drug given at the same dose via its typical oral route using the oral formulation to mice bearing ovarian tumors had absolutely no effect on tumor growth.

Conclusions: The dasatinib nanomicelle formulation is currently being evaluated using an orthotopic mouse model of ovarian cancer. Efficacy of targeted therapies such as dasatinib can be improved by reformulating its delivery. Other failed targeted therapies should be similarly evaluated.

P-57: Use of Supplemental Calcium Is Associated With Brain Lesion Volumes in Older Adults

Martha E. Payne (presenting author),[1] Cortnee W. Pierce,[2] Douglas R. McQuoid,[2] David C. Steffens,[2] and John J. B. Anderson[3]

[1]*Department of Nutrition, University of North Carolina;* [2]*Department of Psychiatry and Behavioral Sciences, Duke University; and* [3]*Department of Psychiatry, University of Connecticut Health Center*

Background and Objective: Ischemic brain lesions promote several catastrophic conditions, including depression, stroke, and dementia, in older adults. Arterial calcification and dietary calcium intakes have been associated with brain lesions. Use of calcium supplements has been linked to negative cardiovascular outcomes. The objective of the study was to investigate the association between use of calcium-containing dietary supplements and brain lesion volumes in older adults.

Methods: Food and supplemental calcium intakes were assessed, using a Block 1998 food frequency questionnaire, in 227 older adults who were participating in a study of depression. Participants with supplemental calcium intakes above zero were categorized as supplement users. Total brain lesion volume was determined from magnetic resonance imaging (1.5 Tesla), using a semi-automated segmentation technique. Subjects were aged 60 or older.

Results: An analysis of covariance model showed that supplement users had greater lesion volumes than non-users, even after controlling for dietary food calcium, age, sex, race, education, energy intake, depression, and hypertension (calcium supplement use: â = 0.34; SE = 0.10; F9,217 = 10.98, P = .0011).

Conclusions: This study indicates that the use of calcium-containing dietary supplements, even low dose supplements, by older adults may be associated with greater lesion volumes. Longitudinal studies are warranted to determine if this relationship is a causal one. Potential adverse effects of high intakes of calcium need to be elucidated.

P-58: Oxytocin Differentially Decreases Methamphetamine Intake and Reinstatement to Methamphetamine Seeking in Male and Female Rats

Carmela M. Reichel (presenting author), Brittney M. Cox, Amy B. Young, and Ronald E. See

Department of Neurosciences, Medical University of South Carolina

Background and Objective: Sex differences exist in methamphetamine (meth) addiction patterns; however, meth effects and potential therapeutic treatments are typically studied in males. We determined whether oxytocin impacted motivation for meth and sucrose self-administration, as well as its efficacy at reducing reinstatement in males and females.

Methods: Rats self-administered meth or sucrose pellets. Following stable daily intake, rats were tested on a progressive ratio after acute oxytocin (1 mg/kg) or saline. Lever responding was then extinguished and rats underwent a series of conditioned cue, meth, and yohimbine primed reinstatement tests with oxytocin (1 mg/kg) or saline.

Results: On the progressive ratio test, females had higher lever responding, drug infusions, and break points relative to males. Oxytocin effectively decreased responding on these measures in females. Sucrose intake in males and females did not differ on any measure, nor did oxytocin impact responding. Females reinstated more than males to meth-conditioned cues, and oxytocin decreased this responding. Females had greater meth-primed reinstatement, and oxytocin decreased meth seeking in both sexes. Oxytocin did not affect reinstatement of sucrose seeking under any conditions.

Conclusions: The combined pattern of results suggests that oxytocin may be a potential treatment for prevention of relapse in meth addiction for males and females, with more extensive benefits in females.

These studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, as adopted and promulgated by the National Institutes of Health. This research was supported by NIH grants P50DA016511, K12HD055885.

P-59: HIV-associated Mucosal Dysfunction Is Augmented by Deregulation of Estrogen Receptor Expression

Sumathi Sankaran-Walters (presenting author),[1] Anne Fenton,[1] Irina Grishina,[1] Jason Flamm,[1] Thomas Prindiville,[2] and Satya Dandekar[1]

[1]University of CA, Davis; and [2]Kaiser Permanente, Sacramento, CA

Background and Objective: HIV disease progression correlates with immune activation, which is higher in women compared to men, in the blood and gut. Compromised mucosal integrity allows for increased microbial translocation in women, which stimulates systemic immune activation. Estradiol (E2)–estrogen receptor β (ER-β) interaction plays an important role in the maintenance of mucosal integrity. The effects of HIV infection on this process are unknown. The objective of the study was to determine if HIV infection is associated with decreased ER-β levels in the epithelial monolayer of the gut mucosa.

Methods: Plasma E2 levels in HIV positive (HIV+; n = 13) and HIV negative (n = 13) healthy women were measured using ELISA, gut epithelial ER-β levels by Real-time PCR assay and in vitro epithelial integrity by analysis of the trans-epithelial resistance.

Results: In vitro, epithelial integrity was decreased by 25% in the presence of SIV/HIV. No significant differences were observed in the plasma E2 levels between HIV+ women and age-matched healthy controls. However, a significant decrease in ER-β levels (25%) was observed in HIV+ women and a further decrease to 50% of normal was observed in women on HAART (n = 7). A similar decrease was observed in vitro in epithelial cells grown in the presence of SIV/HIV, and topical application of exogenous E2 protected the intestinal mucosa from loss of integrity and restored expression of ER-β.

Conclusions: These preliminary data suggest that HIV infection is associated with decreased ER-β levels in the gut epithelium and increased microbial translocation. Low levels of exogenous E2 may help overcome the HIV-associated decline in epithelial integrity in women.

P-60: Association of Urinary Phthalate Levels With Metabolic Syndrome Among Women and Men in NHANES 1999-2008

Aditi Saxena (presenting author), Tamarra James-Todd, and Ellen Seely

Harvard Medical School

Background and Objective: Increased exposure to certain phthalates is associated with increased risk of diabetes and insulin resistance; however, association with metabolic syndrome, a harbinger of future cardiovascular disease, has not been examined. The purpose of the study was to conduct an exploratory analysis evaluating associations between urinary phthalate metabolites with the presence of metabolic syndrome and its components, with focus on sex differences.

Methods: We analyzed men and women aged 20 to 80 years, in NHANES 1999-2008 (n = 2611). Logistic regression assessed the relationship individually between 8 urinary phthalate metabolites and presence of metabolic syndrome (yes/no), controlling for urinary creatinine and age. Stratified analyses provided sex-specific estimates of association.

Results: Both MEP and MiBP were associated with increased risk of metabolic syndrome, whereas MBzP, MnBP, MCPP and ÓDEHP were not. In the overall population, both MEP and MiBP conferred increased risk of metabolic syndrome, OR 1.44 (1.10, 1.89), $P = .008$ for MEP, and OR 1.27 (1.004, 1.61), $P = .045$ for MiBP, though odds varied by sex and levels of exposure. Men in the highest quartile of exposure to MEP had significantly greater odds of metabolic syndrome (OR 1.52, [1.07, 2.18], $P = .02$). In women, MEP exposure was not associated with metabolic syndrome. Conversely, MiBP exposure was associated with increased risk of metabolic syndrome in women, OR 1.58, (1.10, 2.27), $P = .01$, but not in men.

Conclusions: Urinary phthalate metabolites are associated with metabolic syndrome, but the strength of association varies by specific phthalate exposure and sex. Metabolic syndrome portends future cardiovascular risk. Mechanisms linking phthalate exposure to cardiovascular disease require further investigation.

P-61: Maternal Intake of Supplemental Iron and Risk for Autism Spectrum Disorders

Rebecca J. Schmidt (presenting author),[1] D. J. Tancredi,[1] Davis R. L. Hansen,[2] Davis S. Ozonoff,[2] and Irva Hertz-Picciotto[3]

Departments of [1]Public Health Sciences, [2]Pediatrics, and [3]Psychiatry and Behavioral Sciences, Medical Investigation of Neurodevelopmental Disorders (MIND) I, University of California, Davis

Background and Objective: Iron deficiency affects 40% to 50% of pregnancies. Iron is critical for early neurodevelopmental processes, including ones that are dysregulated in autism spectrum disorders (ASD). Our objective was to examine maternal supplemental iron intake in relation to ASD risk.

Methods: Children enrolled in the CHARGE population-based case-control study from 2003 to 2009 with diagnoses of ASD (n = 510) or typical development (TD, n = 341) confirmed at the UC Davis MIND Institute using standardized clinical assessments were included. Mean daily iron intake was quantified based on dose, brands, and frequency of use reported in parental interviews for prenatal vitamins, multivitamins, iron-specific supplements, other supplements, and cereal for each month from 3 months before through the end of pregnancy and during breastfeeding (index period). Associations with ASD were evaluated using logistic regression.

Results: Compared to mothers of TD children, mothers of children with ASD were significantly less likely to report taking iron-specific supplements any time during the index period after adjustment for confounders (OR = 0.62, 95% CI 0.4, 0.9; $P = .01$). Mean (SD) daily iron intake was also lower for mothers of children with ASD (51.7 [34.0] versus 57.1 [36.6] mg/d, $P = .04$). Odds of ASD declined as iron intake increased (Ptrend = .02). Compared to the lowest quintile of iron intake (<30 mg/d), the highest quintile (86 + mg/d) was associated with significantly lower adjusted ASD risk (OR = 0.55, 95% CI 0.34, 0.89).

Conclusions: This is the first study to show a protective association between maternal supplemental iron and ASD. Further studies of this association and potential prevention strategies are warranted.

P-62: A Next Generation Sequencing (NGS) Method to Identify HPV16 Integration Sites in Human Cervical Cancer

Julie Schwarz (presenting author),[1] Eric Duncavage,[3] and Ramachandran Rashmi[2]

[1]Department of Radiation Oncology and [2]Department of Pathology, [3]Washington University School of Medicine

Background and Objective: Human Papilloma Virus (HPV) DNA can integrate in the tumor genome and cause mutagenesis. Current methods to detect HPV integration sites in human DNA are labor intensive. The study's objective was to design an NGS assay to determine HPV16 integration sites with single nucleotide accuracy.

Methods: DNA was obtained from four pretreatment cervical biopsies and assessed for HPV16 viral copy number using RT-PCR.

Sample DNA was prepared and ligated to standard Illumina sequencing primers and then hybridized with synthetic 120 bp oligonucleotide HPV16 capture probes designed to span the entire 8 kb of the HPV16 genome (NC_001526.2). Captured DNA was indexed by limited-cycle PCR and sequenced on a single HiSeq2000 lane using 2x101bp reads. The resulting sequencing data was aligned to the human genome (hg19) and the HPV16 genome. Integration sites were identified by chimeric read pairs that spanned both the HPV and the human genomes using ClusterFASTQ. Average HPV16 sequence coverage was >30,000x in all cases.

Results: HPV16 viral genome deletions in the E1 and L1 regions were identified in 2 of 4 cases, suggesting inactive virus. A viral integration site was identified in 1 of 4 cases and mapped to the SPDYE3 gene on chromosome 7. This region included a ~7 kb deletion of exonic and intronic human (host) sequence.

Conclusions: Here we show that HPV16 integration sites can be rapidly identified using a combination of next generation sequencing and informatics. Large-scale studies of the HPV genome and viral integration sites in tumor DNA may identify new mechanisms of HPV-associated carcinogenesis.

P-63: Risk Factor Differences for Female Adolescent Iron Deficiency as Defined by Body Iron and Ferritin Models

Deepa Sekhar (presenting author),[1] Laura Murray-Kolb,[2] Allen Kunselman,[1] and Ian Paul[1]

[1]Penn State College of Medicine and [2]Pennsylvania State University

Background and Objective: Body iron (BI) has been proposed as an alternative to the traditional ferritin model (FM) for diagnosis of iron deficiency. The objective was to examine risk factors for iron deficiency by BI versus FM among females 12 to 18 years old using data from the National Health and Nutrition Examination Survey (NHANES), 2003–2006 (n = 1,747).

Methods: Iron deficiency by FM is defined as having 2 of 3 laboratory values (transferrin saturation, ferritin, erythrocyte protoporphyrin) out of range. BI measures iron deficiency with a formula involving transferrin receptor and ferritin. Bivariate analyses examined associations between social and behavioral risk factors from NHANES and a diagnosis of iron deficiency by BI versus FM, based on NHANES laboratory data.

Results: Older age (OR 1.17, 95% CI 1.05–1.29, $P = .003$), non-white race (1.92, 1.24–2.99, $P = .004$), more physical activity (2.01, 1.05–3.87, $P = .036$), and Spanish vs. English language of interview (1.94, 1.19–3.18, $P = .008$) increased the odds of iron deficiency measured by FM. Less food consumption in the FM was protective (0.43, 0.23–0.80, $P = .008$). In contrast, older age (1.22, 1.07–1.39, $P = .004$), non-white race (1.75, 1.04–2.95, $P = .035$), and a past pregnancy (4.08, 1.14–14.62, $P = .031$) increased the odds of iron deficiency measured by BI. In both models, use of Depo-Provera was protective.

Conclusions: Risk factors for female adolescent iron deficiency vary by the method of measuring iron deficiency, complicating the identification of high-risk individuals for screening. Future work will assess which combination of risk factors better predicts clinically relevant iron deficiency.

P-64: Sex Differences in Lung Gene Expression in Response to Ozone Exposure: Role of MicroRNAs

Patricia Silveyra (presenting author), Susan DiAngelo, Noe Cabello, Judie Howrylak, and Joanna Floros

Penn State College of Medicine

Background and Objective: Women are more susceptible to inflammatory lung diseases induced by air pollution, including ozone, and show worse adverse pulmonary health outcomes than men. The mechanisms involved in these gender differences remain unknown. Our hypothesis is that microRNAs, a new class of regulatory small non-coding RNAs, mediate gender-specific host responses to environmental toxins by modulation of pulmonary gene expression. The goal of this study was to identify sex differences in microRNA regulation of lung gene expression in response to oxidative stress caused by ambient ozone in an animal model.

Methods: Adult male and female mice were exposed to ozone (2 ppm) or filtered air (control) for 3 hours (n = 6 per group). Lung tissue was collected 4 hours post-exposure, and the mRNA levels of inflammatory mediators were compared among groups. The online software TargetScan was used to predict microRNA binding to these targets.

Results: Exposure to ozone significantly induced mRNA expression of pro-inflammatory cytokines (TNFα, IL-6), chemokines (MCP-1, MIP-1, MIP-2), and other immunity mediators (GM-CSF, TLR4) in mouse lungs. Levels of TNFα, MIP-1, MIP-2, and IL-6 were differentially affected in males and females. In silico analysis revealed several microRNA binding sites in regulatory regions of these transcripts.

Conclusions: Sex differences exist in the mouse lung gene expression profile of inflammatory mediators in response to ozone. Further experimentation will confirm a role of microRNAs in this response. MicroRNAs may regulate the molecular mechanisms involved in the increased susceptibility to pollution-induced pulmonary disease observed in women versus men.

P-65: Mechanosensitivity in the Upper Limb Following Breast Cancer Treatment

Betty Smoot (presenting author),[1] Benjamin Boyd,[2] Nancy Byl,[3] and Marylin Dodd[2]

Departments of [1]Physiological Nursing and [2]Physical Therapy and Rehabilitation Science, University of California, San Francisco; and [3]Department of Physical Therapy, Samuel Merritt University

Background and Objective: Nerve injury may result from breast cancer (BC) treatment (i.e., positional traction, forceful retraction, laceration, or contusion during surgery; or entrapment/compression from fibrosis and scarring). Peripheral nerves may become "sensitized" when subjected to trauma and become less tolerant to movement, resulting in pain and limited mobility. The goal of the study was to evaluate neural mechanosensitivity through elbow extension range of motion (ROM) during upper limb neurodynamic testing (ULNT) post BC treatment.

Methods: 145 women post BC treatment and 25 healthy controls (HC) participated. Bilateral ULNT elbow ROM was measured and symptoms assessed. The BC group was further divided by presence or absence of pain (+/-PAIN) and lymphedema (+/-LYMPH). T-tests, ANOVA, chi-square, and non-parametric tests were used to test for significance of differences.

Results: ULNT elbow extension ROM for the BC group was 6.9° less on the unaffected limb compared to the dominant limb of the HC group (95% CI 1.2°, 12.6°) and 8.8° less on the affected limb compared to the non-dominant limb of the HC group (95% CI 2.9°, 14.6°). Compared to the HC group, ULNT elbow extension ROM was 12.8° less for the unaffected limb ($P = .004$) and 16.6° less in the +PAIN/+LYMPH group for the affected limb ($P < .001$). Symptoms were more frequent and more intense in the affected limb compared to the unaffected limb in women with BC ($P < .05$).

Conclusions: Women with lymphedema and pain post BC treatment have greater alterations in neural mechanosensitivity and limited ULNT elbow extension. Neural mechanosensitivity should be assessed following BC treatment, particularly for women with pain and lymphedema.

P-66: Compared With Aspartame, Consumption of High Fructose Corn Syrup– and Sucrose-sweetened Beverages Increases Triglycerides, Cholesterol, Non-HDL cholesterol, Apolipoprotein-B, and Uric Acid in Young Men and Women

Kimber Stanhope (presenting author),[1] Andrew Bremer,[1] Valentina Medici,[2] Nancy Keim,[1] and Peter Havel[3]

[1]Univerisity of California, Davis; [2]Vanderbilt University; and [3]United States Department of Agriculture, Western Human Nutrition Research Center

Background and Objective: The risk of cardiovascular disease is higher in men than in pre-menopausal women; however, the etiology of this is unclear.

Methods: We compared lipid responses in young men and women who consumed beverages sweetened with high fructose corn syrup (HFCS), sucrose, or aspartame for 2 weeks. In a parallel, double-blinded study, young adults (18–40 years of age) were assigned to

beverage groups matched on sex, BMI, and fasting triglycerides. During inpatient baseline testing over 3.5 days, participants consumed energy-balanced diets containing 55% of energy requirements (EReq) as complex carbohydrates. For 12 outpatient days they consumed usual diets and 3 servings/day of HFCS-, sucrose- (providing 25% EReq), or aspartame-sweetened beverage (n = 24/group). Participants then consumed energy-balanced diets, which included the experimental beverages, during inpatient testing.

Results: HFCS and sucrose sweetening increased plasma levels of triglycerides, cholesterol, apolipoprotein B, apolipoprotein CIII, and uric acid compared with aspartame. These sugar-induced increases of fasting triglycerides (men: 18% ± 3%; women: 7% ± 5%, $P < .05$ for sex difference) and mean triglycerides from 32 samples collected over 24 hours (men: 16% ± 3%; women: 9% ± 4%, $P < .05$) were significantly higher in men than women. Postprandial cholesterol (men: 18% ± 4%; women: 11% ± 2%, $P = .13$ for sex difference), non-HDL-cholesterol (men: 19% ± 6%; women: 12% ± 3%, $P = .14$), apolipoprotein B (men: 13% ± 3%; women: 13% ± 3%, $P = .75$), apolipoprotein CIII (men: 22% ± 3%; women: 20% ± 3%, $P = .62$), and uric acid (men: 13% ± 2%; women: 11% ± 2%, $P = 96$) were not significantly higher in men than women.

Conclusions: Except for triglycerides, risk factors for metabolic disease were comparably increased in young men and women consuming 25% EReq as sucrose- or HFCS- sweetened beverages for 2 weeks.

P-67: Factors Associated With Change in Activities of Daily Living Dependence in Older Long-Stay Nursing Home Residents

Kristine M. C. Talley (presenting author), Kay Savik, Hong Zhai, and Jean F. Wyman

School of Nursing, University of Minnesota

Background and Objective: Understanding change in activities of daily living (ADL) dependence in long-stay nursing home residents may help identify when to intervene to delay its progression. The goal of the study was to describe change in ADL dependence among long-stay nursing home residents and identify associated factors.

Methods: Longitudinal analysis of nursing home Minimum Data Set data linked to the 2004 National Nursing Home Survey using a sample of 7,735 residents, aged 65 years or older without terminal illness living in 1,097 nursing homes for at least 6 months. Linear mixed models estimated change in ADL dependence over 18 months.

Results: Most residents were non-Hispanic white (88.9%) females (75.4%) with a mean age of 84.8 ± 8.0 years and mean length-of-stay of 3.3 years living in urban (52.24%) for-profit (59.2%) nursing homes. Only 60% of the sample remained at 18 months. On average, ADL dependence increased 1.5 points (12.4%) over 18 months. Age, gender, and length-of-stay did not predict ADL change. Baseline cognitive impairment levels were associated with increasing rates of ADL change. Residents with no baseline cognitive impairment had no change in ADL dependence, those with the mean level of impairment (2.4) increased 1.8 points (11.1%), and those with the highest level of impairment (6.0) increased 3.2 points (15.8%).

Conclusions: Older women comprise 75% of long-stay nursing home residents, who experience increasing ADL dependence throughout their residency. The greatest ADL change occurred with higher levels of cognitive impairment. Interventions to maintain ADL function should be developed for residents with cognitive impairment and be provided throughout a resident's entire stay.

P-68: Adult Smoking Initiation Is on the Rise in the U.S., But Among Whom? Smoking Initiation by Age, Race, and Gender From 2002 to 2010

Azure B. Thompson (presenting author), Jacob K. Tebes, and Sherry A. McKee

Department of Psychiatry, Yale University School of Medicine

Background and Objective: The number of adolescents who become smokers has declined over the past decade, but the number of adults who become smokers has nearly doubled (623,000 to 1.1 million). We know little about adults who start smoking. Knowledge on the demographic trends in adult initiation during the 2000s is necessary to target prevention resources effectively, particularly among women and racial/ethnic minorities who have high rates of adult relative to adolescent initiation and are vulnerable to tobacco-related disparities. The goal of the study was to investigate by age, race, and gender temporal trends in prior-year first cigarette use and transition into daily smoking.

Methods: We analyzed data from the 2002 to 2010 National Survey of Drug Use and Health, cross-sectional surveys of the U.S. civilian population 12 years of age and older.

Results: During the 2000s, prior-year first cigarette use and transitions into daily smoking increased among young adults between the ages of 18 and 21. Among all other age groups (12–14, 15–17, 22–25), these behaviors declined or were stable. Analysis indicates that there was an increase in the ratio of adult relative to adolescent initiation behaviors among white men. Adult relative to adolescent initiation remained high but stable among racial/ethnic minority men and all racial/ethnic groups of women. Increases in initiation were most concentrated among 18- to 21-year-olds.

Conclusions: Tobacco control efforts should focus on the development of interventions and policies targeting young adults, particularly young adult men. One such policy may include increasing the minimum legal age to purchase cigarettes to 21.

P-69: Prospective Association Between Mitochondrial Copy Number and Stage of Breast Cancer

Bharat Thyagarajan (presenting author),[1] Renwei Wang,[2] Heather Nelson,[1] Helene Barcelo,[1] Woon-Puay Koh,[3] and Jian-Min Yuan[2]

[1]University of Minnesota; [2]University of Pittsburgh; and [3]Duke-National University of Singapore

Background and Objective: Mitochondrial DNA (mtDNA) copy number in peripheral blood is prospectively associated breast cancer risk when blood was collected within 3 years of diagnosis. Results from a previous retrospective study suggests that breast cancer stage can influence mtDNA copy number in peripheral blood. We evaluated the prospective association between mtDNA copy number in peripheral blood and breast cancer at different stages.

Methods: We utilized data from a previously reported nested case-control study of 88 breast cancer cases with pre-diagnostic blood samples and 252 individually matched controls among participants of the Singapore Chinese Health Study in whom blood was collected within 3 years of breast cancer diagnosis to evaluate the association between mtDNA copy number and breast cancer stage.

Results: Conditional logistic regression analyses showed that a positive association between mtDNA copy number and breast cancer risk only among women with advanced breast cancer (stages III and IV); OR (95% CIs) for 2nd and 3rd tertile of mtDNA copy numbers were 2.41 (0.71–8.13) and 4.28 (1.23–14.83), respectively, compared with the 1st tertile ($P_{trend} = .02$). There was no association between mtDNA copy number and breast cancer risk among women with localized breast cancer (stages I and II) ($P_{trend} = .50$).

Conclusions: This study supports a prospective association between increased mtDNA copy number and breast cancer risk that is dependent on the stage of breast cancer. Future studies are warranted to confirm these findings and evaluate the utility of mtDNA copy number as a biomarker for early detection of breast cancer.

P-70: Preliminary Evidence for a Psychobiological Model for Adolescent Eating Disorders

Abbigail M. Tissot (presenting author), Jennifer B. Hillman, Laurie Mitan, and Jenny Tong

Cincinnati Children's Hospital Medical Center

Background and Objective: Though both biological and psychological mechanisms are known to promote eating disorders (EDs) in adolescents, no research has yet established a formal psychobiological model. This study aimed to evaluate biological (hormonal) and psychological profiles of newly diagnosed ED in adolescent females. Profiles were then evaluated for key associations (i.e., psychobiological associations). Psychobiological associations for ED girls were

compared with patterns of associations identified among healthy adolescent females to advance a psychobiological model of ED.

Methods: Quasi-experimental procedures included Meal Tolerance Tests with serial blood draws and ecological momentary assessment. Girls were recruited from the inpatient unit (ED) and community (controls).

Results: Despite the small sample ($N = 30$), preliminary analyses revealed that biological profiles differed between the ED ($n = 15$) and control groups ($n = 15$) at a small to medium magnitude (Cohen's d's = 0.2–0.5). Psychological profiles of also differed by group, but with greater magnitude (medium to large; Cohen's d's = 0.5–2.0). Psychobiological associations differed by variable pairing but generally supported that associations were strongest shortly after meal consumption (15 to 30 minutes) and at 120 to 150 minutes post-meal. Overall, controls showed fewer significant psychobiological associations than girls with ED. Moreover, compared with controls, psychobiological associations for ED girls were stronger, differently timed, and varied by hormone.

Conclusions: Results support the presence of psychobiological processes in girls with newly diagnosed EDs; these associations are qualitatively different from those of healthy controls. Psychobiological mechanisms may underlie ED treatment resistance. Specifically, psychobiological feedback may promote a positive feedback loop that amplifies ED pathology. Though preliminary, results warrant further investigation.

P-71: Managing the Competing Demands of Low-wage Employment and Breast Cancer Treatment

Robin C. Vanderpool (presenting author)[1] Jennifer E. Swanberg,[1] Mary K. Webster,[2] and Nicolas Coomer[1]

[1]*University of Kentucky and* [2]*University of Maryland*

Background and Objective: Low-wage employment, ever more prevalent in today's economy, offers women minimal autonomy, schedule inflexibility, limited paid time off, minimal health benefits, and economic insecurity. Indeed, these workplace characteristics become even more significant in the event of a breast cancer diagnosis. The goal of the study was to understand how breast cancer survivors employed in low-wage jobs manage treatment within the context of work.

Methods: In-depth, semi-structured interviews were conducted with 24 women in Kentucky who were who were diagnosed with a new, primary breast cancer in the past 3 years and who were employed in low-wage positions (<$15.00/hour) at the time of diagnosis.

Results: At the time of diagnosis, the mean hourly wage was $11.25 (SD = 2.18); 18 of the 24 (75%) women had household incomes of less than $40,000. Retail, healthcare, social assistance, manufacturing, and food services were the most commonly represented industries (n = 19). Over half of the women (n = 13, 54%) continued working during treatment due to financial stress, fiscal necessity, lack of paid time off, and fear of health insurance loss. Women provided detailed explanations of how they managed the competing demands of work and treatment, concurrent with medical and economic challenges. Access to paid time off, Family Medical Leave, and short-term disability; understanding of health insurance benefits; and work environments with supportive supervisors and co-workers influenced treatment-related behaviors.

Conclusions: Management of breast cancer treatment and employment may be complex for women who work low-wage jobs. Future research should focus on employment and healthcare system supports that help women successfully complete breast cancer treatment and maintain employment.

P-72: Systematic Review of Cancer-associated Lymphedema Risk Factors

Lisa D. VanHoose (presenting author),[1] Electra D. Paskett,[2] Philip Twasami-Ankrah,[3] Kandis M. Smith,[4] Ausanee Wanchai,[4] Jason M. Green,[4] Bob R. Stewart,[4] and Jane M. Armer[4]

[1]*Physical Therapy and Rehabilitation Science, University of Kansas Medical Center;* [2]*College of Medicine, Ohio State University;* [3]*Preventive Medicine and Public Health, University of Kansas Medical Center; and* [4]*Ellis Fischel Cancer Center, Sinclair School of Nursing, University of Missouri*

Background and Objective: Lymphedema is a chronic state of progressive extracellular accumulation with an insidious onset. Cancer-associated lymphedema accounts for the majority of lymphedema cases in the U.S., with incidence rates up to 75% depending on tumor type. The body of knowledge is shifting from interventions to risk reduction strategies and modeling. This systematic review was conducted to determine the strength of evidence regarding patient-related, disease-related, and treatment-related risk factors of lymphedema for various cancer types over the past decade (2003 to 2012).

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 framework was utilized for the systematic review. Multiple databases, including PubMed, CINAHL, and the Cochrane Database of Systematic Reviews, were searched. The initial screen identified articles within the years and topics of interest. Two reviewers assessed full-text articles for eligibility. Then 2 reviewers utilized the quality rating and strength of evidence systems published by the Agency for Healthcare Research and Quality's Evidence-based Practice Centers Program to evaluate 53 risk factors related to lymphedema.

Results: We assessed 112 articles published between 2003 and 2012. Body mass indices (BMI) greater than 30 kg/m^2 and regional and radical lymph node dissections had high strength of evidence (SOE) scores as risk factors for lymphedema. High SOE scores refuted the role of smoking, diabetes, and strength training in increasing the risk of lymphedema. Moderate SOE scores were reported for 19 risk factors.

Conclusions: Cancer-associated lymphedema is a multi-factorial condition, but higher BMIs and more aggressive cancer treatment may be the best predictors of risk.

P-73: Altered Cardiac Insulin Signaling in a Sheep Model of Polycystic Ovarian Syndrome

Arpita Vyas (presenting author)

Michigan State University

Background and Objective: Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder amongst reproductive aged women with increased risk of peripheral insulin resistance and hyperinsulinemia due to defects in insulin signaling. There is increasing prevalence of cardiovascular dysfunction in women with PCOS, but the mechanisms leading to cardiovascular disorders are not clear. The purpose of the study was to determine if peripheral insulin resistance disrupts cardiac insulin signaling contributing to the cardiovascular abnormalities seen in PCOS.

Methods: Offspring of Suffolk sheep exposed to testosterone in utero (days 30–90 of gestation, term: 147 days) develop PCOS and cardiometabolic disturbances by 2 years of age. Left ventricle tissue was harvested from the 2-year-old female offspring (n = 4) that developed PCOS and control (n = 4). Changes in expression of cardiac genes and proteins related to insulin signaling were quantified by RT-PCR and Western blot analyses.

Results: Preliminary findings indicate that prenatal T excess increased insulin inducible glucose transporter 4 (GLUT 4), IRS-1, and AKT-1 mRNA levels. No difference was seen in protein concentration of GLUT 4, AKT, P-AKT (ser 473), P85 PI3K, AMPK and P-AMPK and GLUT 1.

Conclusions: Accentuated insulin signaling at the mRNA level of cardiac tissue in PCOS may be related to chronic systemic hyperinsulinemia. Elevated IRS-1 and AKT-1 mRNA may lead to cardiac hypertrophy through the mitogenic pathway, a feature also considered in diabetic cardiomyopathy. Alternatively, these effects may be compensatory changes. Further studies are needed to investigate the mitogenic pathway and cardiac function and relate these to the metabolic perturbation seen in PCOS.

P-74: A Theranostic Nanoparticle/Curcumin Combination Decreases Doxorubicin-Induced Cytokine Production in MDA-MB-231 Breast Cancer Cells via IL-6/NF-kB Pathway

Dinesh Vyas (presenting author)

Michigan State University

Background and Objective: Triple negative breast cancer (TNBC) cells, with a high metastatic potential, exhibit an elevated baseline

pro-inflammatory status which is further aggravated by doxorubicin (DOX) treatment. We studied the effect of treatment with a novel nanoparticle (hyaluronic acid [HA] and DOX [NP-DOX]) designed to target TNBC cells; HA is a ligand for CD44, which is overexpressed in TNBC cells. Curcumin (CUR) is a known anti-inflammatory modulator. We hypothesized that the targeted NP-DOX treatment would reduce toxicity and the pro-inflammatory response to treatment in these cells and that the addition of curcumin would further decrease inflammation.

Methods: The TNBC cell line MDA-MB-231 was treated with DOX, NP-DOX, and CUR. IL-6 production, NF-kB promoter activity, and proliferation were measured by ELISA, Cignal Lenti NF-kB reporter luciferase, and MTS assay, respectively (n = 3).

Results: DOX therapy increased supernatant IL- 6 levels (2783 ± 23 pg/mL vs. 1005 ± 23 pg/mL at baseline). However, IL-6 production was much lower (1477 Â ± 29 pg/mL) after NP-DOX treatment. Addition of CUR decreased IL-6 levels in both the DOX and NP-DOX-treated cells to 2,126 ± 19 pg/mL and 1,335 ± 50 pg/mL, respectively. Similar trends were seen with NF-kB. CUR also decreased proliferation in the NP-DOX treatment group by 35%, but had no effect in cells treated with DO.

Conclusions: The NP-DOX and CUR combination synergistically decreases TNBC cell proliferation, possibly via inhibition of a pro-inflammatory pathway. These preliminary results indicate that CUR could be added to our NP-DOX, thus generating a single delivery drug for TNBC that is targeted and less toxic and that reduces angiogenesis and metastasis.

P-75: The Link Between Brain Lipid Sensing and Sex Differences in Obesity Development

Hong Wang (presenting author), Yongping Wang, Matthew D. Taussig, and Robert H. Eckel

University of Colorado Anschutz Medical Campus

Background and Objective: Neuron-specific lipoprotein lipase deficient mice (NEXLPL-/-) (Wang et al., *Cell Metabolism* 2011) exhibit sex differences in obesity development. We want to explore mechanisms underlying these differences in search of sex-specific approaches for prevention and treatment.

Methods: Pair feeding was conducted in 10-week-old male and female NEXLPL-/- and littermate WT mice. Daily food intake for the pair-fed mice was limited to the average daily food intake for WT ad libitum fed mice. Body weight was monitored daily; body composition, metabolic phenotype, and candidate gene expression in hypothalamus were examined at the end of the feeding period.

Results: Pair feeding up to 38 weeks of age prevented obesity in female NEXLPL-/- mice only. Reduction of estrogen receptor alpha (ER-α) level in the hypothalamus led to obesity in female mice only (Xu et al., *Cell Metabolism* 2011). Under ad libitum feeding conditions, ER-α expression was increased two-fold in female NEXLPL-/- mice with no change in male. ER-α expression was also increased 50% in both female and male WT mice after 8 weeks of pair feeding. The effect of pair feeding and LPL deficiency on ER-α expression was additive in pair-fed female NEXLPL-/- mice (2.5-fold increase).

Conclusions: The sex difference in obesity development in pair-fed NEXLPL-/- mice suggests a more important role of energy intake in female than in male mice. The increase of ER-α in female NEXLPL- /- mice appears to protect them from weight gain under pair feeding conditions. ER-α could provide the link between brain lipid sensing and sex differences in obesity development.

P-76: Sex Moderates the Association Between Volume of the Striatum and Interest in Quitting Smoking in Adult Cigarette Smokers

Stephen Wilson (presenting author),[1] Robert MacLean,[2] and Joshua Muscat[2]

[1]*Penn State College of Medicine, and* [2]*Pennsylvania State University*

Background and Objective: Compared to male cigarette smokers, female smokers express less interest in quitting and are less confident in their ability to achieve abstinence. Non-human animal research suggests that these effects may be linked to the structure and function of a brain region called the striatum (an area strongly implicated in the development of addiction). The goal of the study was to test the hypothesis that sex differences in the structure (specifically, gray matter [GM] volume) of the striatum are associated with sex differences in self-reported interest in quitting smoking.

Methods: The sample included 108 male and 42 female smokers (>15 cigarettes/day). Interest in quitting was measured via self-report during a baseline session that preceded the experiment using a single item (0–10 scale). High-resolution brain images were acquired within 2 weeks of the baseline session using magnetic resonance imaging. Voxel-based morphometry (a brain imaging data analysis technique) was used to measure GM volume in the striatum and control regions.

Results: Striatal GM volume was higher in female than male smokers, while interest in quitting was lower in the former (Ps < .001). Sex moderated the relation between striatal GM volume and interest in quitting, such that there was a substantially stronger negative association between the two for females than males (P = .03).

Conclusions: Findings extend preclinical data by indicating that the striatum may play a greater role in maintaining cigarette use in female relative to male smokers. Additional research further characterizing these sex-specific effects would provide insight into the unique factors that maintain cigarette use in female smokers.

P-77: Notch1 Activation Confers Broad-spectrum Drug Resistance in Breast Cancer

Kris C. Wood (presenting author),[1] Colin A. Martz,[2] Kathleen A. Ottina,[2] Jeff S. Jasper,[1] Ashley Peraza-Penton,[2] and David M. Sabatini[2]

[1]*Whitehead Institute for Biomedical Research, Department of Biology, and Howard Hughes Medical Institute; and* [2]*Department of Pharmacology and Cancer Biology, Duke University School of Medicine*

Background and Objective: Drug resistance is a significant clinical problem in breast cancer, particularly because we have only a basic understanding of the signaling events that confer resistance to relevant therapies. We sought to catalog the signaling pathways whose activation confers resistance to targeted therapies relevant to breast cancer: tamoxifen and fulvestrant (ER modulators), lapatinib (HER2i), BKM120 (PI3Ki), MK2206 (AKTi), BEZ235 (PI3K/mTORi), Torin1 (mTORC1/2i), and rapamycin (mTORC1i).

Methods: We developed a library of lentiviral genetic constructs that individually activate every major oncogenic signaling pathway. Using this library, we screened each of the drugs above to identify the pathways whose activation confers resistance to each drug.

Results: Resistance is typically driven by either the activation of classical pro-growth pathways (Ras-MAPK, PI3K-mTOR) or pathways that control differentiation (Notch1). Interestingly, Notch1 activation confers resistance to all drugs in question as well as cytotoxic agents like doxorubicin. Notch1 activation causes an epithelial-mesenchymal transition which results in a stem cell–like phenotype that decreases proliferation rates and drug sensitivities in breast cancer cells. Breast cancer cell lines evolved in vitro to exhibit resistance to tamoxifen expressed higher levels of Notch1 and Notch pathway members than their parental counterparts, and RNAi knockdown of Notch1 reversed resistance in these cells. Finally, in human breast cancer patients, Notch1 expression predicts for significantly worse survival outcomes following treatment with doxorubicin.

Conclusions: Notch1 activation confers broad-spectrum drug resistance in breast cancer. Additionally, pathway-centric screening has the potential to accelerate the search for drug resistance pathways in many other cancer types.

P-78: Role of Anti-Mullerian Hormone (AMH) in Regulating Primate Follicle Growth and Function During Encapsulated 3-Dimensional (3D) Culture

Jing Xu (presenting author), Alison Y. Ting, Mary B. Zelinski, and Richard L. Stouffer

Division of Reproductive and Developmental Sciences, Oregon National Primate Research Center

Background and Objectives: In vitro follicle maturation (IFM) provides options for fertility preservation in women, including female cancer patients. During encapsulated 3D culture, monkey preantral follicles grow to the antral stage, with steroid hormone and AMH production correlated positively with growth rates. Studies were designed to investigate the local role(s) of AMH in promoting primate preantral follicle development and steroid production.

Methods: Ovaries were collected from rhesus macaques. Secondary follicles were isolated, encapsulated into alginate, and cultured for 5 weeks at 5% O_2 in αMEM supplemented with FSH and insulin. Follicles were assigned randomly to 3 groups: (a) media-only control, (b) 30 ng/ml anti-human AMH antibody (AMH-Ab) during week 0–3 (before antrum formation), and (c) 30 ng/ml AMH-Ab during week 3–5 (after antrum formation). Follicle survival, growth, and steroid production were assessed.

Results: AMH-Ab exposure during weeks 0–3 decreased follicle survival rates and diameters of growing follicles at week 5, but not week 3. Growing follicles formed an antrum at week 3 with increased ($P < .05$) steroid production. At the end of culture, estradiol levels were lower ($P < .05$) in follicles exposed to AMH-Ab during weeks 0–3. In contrast, follicles cultured with AMH-Ab during weeks 3–5 had no difference in any parameters analyzed compared with controls. AMH ablation during the preantral stage negatively impacts follicle survival and growth, as well as estradiol production, after antrum formation.

Conclusions: The current study suggests stage-dependent, local roles of AMH that influence primate follicular development, with relevance to human IFM.

JOURNAL OF WOMEN'S HEALTH
Volume 22, Number 10, 2013

BIRCWH and SCOR Presentation Abstracts

O-1: Exposure to Prenatal Life Events Stress Is Associated With Masculinized Play Behavior in Girls

Emily S. Barrett (presenting author),[1] Fan Liu,[2] Christina Wang,[3] and Shanna H. Swan[2]

[1]Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry; [2]Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai; and [3]Division of Endocrinology, Department of Medicine, Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute

Background and Objective: Previous research on humans and animal models suggests that exposure to prenatal stress not only affects fetal development, but also can do so in different ways in males and females. Only one published study has prospectively examined the relationship between exposure to prenatal stress and gender-specific play behavior during childhood, finding masculinized play behavior in girls who experienced high prenatal life events stress, but no associations in boys. Here we examine the relationship between exposure to prenatal stress and play behavior during childhood in a second prospective cohort from the Study for Future Families.

Methods: Pregnant women completed questionnaires on stressful life events during pregnancy, and those who reported 1 or more stressors were considered highly stressed. Families were re-contacted several years later (mean age of index child: 4.9 years), and mothers completed a questionnaire including the validated Preschool Activities Inventory (PSAI), which measures sexually dimorphic play behavior.

Results: In sex-stratified analyses, after adjusting for child's age, parental attitudes toward gender-atypical play, age and sex of siblings, and other relevant covariates, girls (n = 72) exposed to high prenatal life events stress had higher scores on the PSAI masculine sub-scale ($\beta = 3.48$, $P = .006$) and showed a trend towards higher (more masculine) composite scores ($\beta = 2.63$, $P = .08$). By contrast, in males (n = 74), prenatal stress showed a trend towards association with higher PSAI feminine sub-scale scores ($\beta = 2.23$, $P = .10$), but no association with masculine or composite scores.

Conclusions: These data provide further evidence that prenatal stress may have androgenic effects on female fetuses and anti-androgenic effects on male fetuses.

O-2: Urinary Biomarkers of Lower Urinary Tract Symptoms in Women With Cystoceles

Mitchell B. Berger (presenting author),[1] Daniel M. Morgan,[1] and Andrew Johnston[2]

[1]Department of Obstetrics and Gynecology and [2]Department of Dermatology, University of Michigan

Background and Objective: Although poorly understood, women with cystocele often have lower urinary tract symptoms (LUTS), and LUTS frequently resolve after prolapse reduction. The aims of this pilot study are to compare levels of urinary biomarkers in 1) women with and without cystoceles, and 2) women whose LUTS do or do not improve after prolapse repair.

Methods: This is a case-control study of women with cystoceles (cases) and controls with normal support undergoing benign gynecologic surgery. Baseline demographics were recorded. All subjects completed the MESA and PFDI-20 questionnaires preoperatively. Intraoperative urine specimens were obtained, processed, and the supernatants frozen. Cases repeated the surveys at the 6 week postoperative time point. Urinary biomarker concentrations were assayed and normalized to creatinine concentration.

Results: Ninety-three cases and 61 controls were recruited. Cases were significantly older, of higher parity, and slightly lower body mass index (BMI) than controls. Cases reported more severe LUTS and had significantly higher urinary levels of MCP-1 than controls. Cases were then stratified into those whose LUTS improved (responders) and those whose symptoms worsened/did not significantly improve (non-responders). Demographics were similar in responders and non-responders. Responders had higher concentrations of IL-6 ($P = .01$), IL-10 ($P = .09$), and MIP-1β ($P = .02$), and lower NGF concentrations ($P = .03$) than non-responders.

Conclusions: Women with cystocele have more severe LUTS and higher urinary MCP-1 concentrations than women with normal support. Prolapse repair leads to improved LUTS for nearly 70%. Urinary biomarkers associated with postoperative improvement of LUTS include higher levels of IL-6, IL-10, and MIP-1β, and lower levels of NGF, suggesting new targets for research and treatment.

O-3: Why Normal Pregnancy Is Protective Against Maternal Hypertension Later in Life

Egle Bytautiene (presenting author), Michael Wen, Talar Kechichian, Phyllis Gamble, Esther Tamayo, and George R. Saade

Department of Obstetrics and Gynecology, University of Texas Medical Branch

Background and Objective: We have previously shown that a normal pregnancy is protective against hypertension later in life in both obese and non-obese animals. The objective was to investigate if alterations in the renin-angiotensin system could explain the protective effect of pregnancy.

Methods: Virgin CD-1 female mice were placed on standard fat (SF) or high fat (HF) diets. After 3 months, mice were randomly allocated to a breeding versus non-breeding group, resulting in 4 groups: primigravid on SF (SF-PG) or HF (HF-PG) and nulligravid on SF (SF-NG) or HF (HF-NG). The primigravid group proceeded through a normal pregnancy and delivery. After weaning, all animals were contemporaneously placed on a SF diet. Visceral adipose tissue (VAT) and kidneys were collected from PG at 6 months post partum and from age-matched NG mice. Protein expressions of angiotensin (ANG) and its receptors, angiotensin receptor 1 and 2 (AT1 and AT2, respectively), were determined using Western blot analysis. One-way ANOVA and Kruskall Wallis tests with appropriate posthoc tests were used for statistical analysis (significance $P < 0.05$).

Results: There were no differences in ANG protein expression between groups, neither in VAT nor kidneys. AT1 was significantly higher in VAT from SF-NG groups than from SF-PG. In kidneys, AT1 was significantly higher in both NP groups compared with the PG groups. AT2 was significantly lower in both NG groups in VAT and kidney compared with PG.

Conclusions: The protective effect of a normal pregnancy could be mediated by a decrease in AT1 receptors and an increase in AT2 receptors in the kidney and VAT.

O-4: Sex and Pubertal Stage Moderate the Association Between Negative Life Events and Telomere Length in African American Youth

Stacy S. Drury (presenting author),[1] Zoe Brett,[1] Emily Mabile,[2] and Katherine Theall[2]

[1]Department of Psychiatry and [2]School of Public Health, Tulane University

Background and Objective: Negative early life stress (ELS) is associated with cardiovascular disease, cognitive decline, and psychopathology. One biomarker of ELS, associated in adults with both negative health and ELS, is telomere length (TL). The utility of this biomarker in children has rarely been examined. The objective was to

examine the association between ELS and TL in African American youth and whether the relation is moderated by sex or pubertal stage.

Methods: Fifty-six African American youth (mean age, 9.64 years) were recruited from at-risk neighborhoods in New Orleans, Louisiana. Salivary DNA was extracted, and adjusted telomere length (sTL) was determined using qPCR. sTL was calculated controlling for parental age at conception and child age and subsequently standardized. Negative early life events were determined by parental report. Pubertal stage was determined by parent and child self-report.

Results: Mean number of early life events was 4.4 for boys and 4.8 for girls (range 0 to 13). sTL was significantly different between sex ($P = .01$). For boys, z-score transformed sTL = −.12 (n = 32) and for girls, sTL = .02 (n = 24). ELS was associated with sTL in both sexes. Pubertal stage was not associated in girls ($P = .18$), but was associated with sTL among boys ($P = .005$) and mediated the association between ELS and sTL. The full model, with both genders, predicted 37% of the variance in sTL ($P < .0001$, r = .37. f = 10.51, n = 56)

Conclusions: In African American youth, exposure to ELS is significantly associated with decreased sTL. TL may represent a biological indicator of ELS mediated by pubertal stage in boys.

O-5: Early Life Adversity Increases Risk of New Onset Depression During the Menopause Transition

C. Neill Epperson (presenting author)

Perelman School of Medicine, University of Pennsylvania

Background and Objective: There is an increased risk for new onset depression during the menopause transition, even in women without previous psychiatric history. Childhood adversity has lasting effects on neurotransmitter systems, which are also modulated by estrogen. We sought to determine whether early life adversity contributes to the increased risk of incident menopause depression.

Methods: In a 15-year longitudinal study of women undergoing a natural transition to menopause, participants (n = 390) completed the Clinical Epidemiologic Scale for Depression (CES-D). A CES-D score higher than 16 was used to denote a probable major depressive episode. The Adverse Childhood Events (ACE) questionnaire was used to assess the presence of abuse, neglect, and serious family dysfunction experienced prior to the age of 18. Of the 390 participants with at least 2 mood assessments, 206 of the women who remain in the study have been contacted to collect ACE information. The impact of number of ACEs (0, 1, 2, or more) on new onset depression across the five stages of menopause (premenopause, late premenopause, early transition, late transition, postmenopause) was determined.

Results: There were 1,033 observations with each individual contributing on average 12 observations. Using generalized estimating equations and controlling for age, menopause stage was associated with a 2.7-fold risk ($P = .02$) of new onset depression as women progressed from the pre- to postmenopause.

Conclusions: Childhood adversity, defined broadly, is a risk factor for first episode depression during the menopause transition when ovarian sources of estrogen are waning. These data suggest an environment by hormone interaction predicting depression risk in menopausal women.

O-6: Varenicline Versus Nicotine Patch for Smoking Cessation in Women: Efficacy Findings from a 4-Week Double-blind Trial

Kevin M. Gray (presenting author)[1], Michael E. Saladin,[1] Nathaniel L. Baker,[1] Erin A. McClure,[1] Karen J. Hartwell,[1,2] and Matthew J. Carpenter[1]

[1]Medical University of South Carolina; and [2]Ralph H. Johnson Veterans Affairs Medical Center

Background and Objective: Women may have more difficulty quitting smoking than men; comparative evaluation of cessation pharmacotherapies in women may be critical to inform clinical practice. Within a parent study examining ovarian hormone effects on smoking cessation, we conducted the first double-blind trial directly comparing the efficacy of varenicline versus nicotine patch.

Methods: Treatment-seeking nicotine-dependent female smokers (aged 18–45, n = 137) were randomized to receive a 4-week course of (a) varenicline tablets and placebo patches or (b) placebo tablets and nicotine patches, via a double-blind, double-dummy design. All participants received a 1-week titration lead-in (tablets only) before a targeted quit date, followed by goal dosing (tablets and patches) for an additional 4 weeks. All participants received 2 brief cessation counseling sessions. Abstinence was assessed at weekly visits and analyzed via an intent-to-treat approach.

Results: During the last week of the 4-week treatment, 46.9% of varenicline participants achieved 7-day point prevalence abstinence, compared with 20.6% of nicotine patch participants (OR 3.3 [95% CI 1.5–6.9]; $P = .002$). At the end of a 4-week post-treatment follow-up, 7-day point prevalence abstinence numerically favored varenicline, but did not meet statistical significance (23.4% vs. 13.7%, OR 1.9 [95% CI 0.8–4.7]; $P = 0.15$).

Conclusions: Varenicline, compared with nicotine patch, more than doubled the odds of abstinence at end of 4-week treatment. Absolute abstinence rates with both treatments were lower than those in a prior open-label trial inclusive of both men and women (Aubin et al., 2008). Nonetheless, these preliminary findings support varenicline as a preferred pharmacotherapy for smoking cessation in women.

Funding sources: NIDA P50DA16511 Component 4 (KMG & MES), NIDA K23DA020482 (MJC), and NCRR UL1RR029882 (MUSC Clinical and Translational Research Center). Varenicline and matched placebo were supplied by Pfizer, Inc.

O-7: Early Adverse Life Events: Influence on Resting State Connectivity in Patients With Chronic Abdominal Pain

Arpana Gupta (presenting author)

University of California, Los Angeles

Background and Objective: Early adverse life (EAL) events and female sex have been identified as a vulnerability factor for the development of several stress-sensitive disorders, including irritable bowel syndrome (IBS). Methylation of genes related to the central stress system have been implicated as an epigenetic mechanism mediating this association. We aimed to identify disease- and sex-based differences in resting state (RS) connectivity associated with EALs in IBS subjects.

Methods: Resting state functional magnetic resonance imaging was used to identify patterns of intrinsic brain oscillations in the form of RS networks in 168 subjects (58 IBS; 28 females and 110 healthy controls, 72 females). Partial least squares (PLS) multivariate analysis was used to identify possible correlations between functional connectivity in seven identified RS network components (pain, emotion, salience/executive control, cognition, cognition and language, cognitive control, and the default mode network) and a history of EAL. Disease- and sex-related effects of EAL on RS networks were observed.

Results: While a history of EALs was associated with altered connectivity in the salience/executive control network to a similar extent in male and female IBS patients, male IBS patients demonstrated additional EAL-related alterations in the cerebellar network. This study is the first to identify correlations between RS networks and EALs in IBS subjects.

Conclusions: These results suggest that exposure to EALs before age 18 can shape adult RS in both male and female patients in the salience network, a brain network that has been implicated in the pathophysiology of central pain amplification.

O-8: Targeting the Noradrenergic System for Gender-sensitive Treatment Development for Tobacco Dependence

Sherry A. McKee (presenting author)

Yale University School of Medicine

Background and Objective: Tobacco use is the leading cause of preventable morbidity and mortality in the United States. Women, compared with men, have poorer rates of smoking cessation, exacerbated health risks, and appear to have less success with available first-line treatments. However, few attempts have been made to develop gender-sensitive smoking cessation treatments. The

considerable body of data suggesting that women are more likely to smoke to regulate negative affect and stress, while men are more likely to smoke for the reinforcing properties of nicotine, suggests an important direction in the development of a new approach to smoking cessation treatments. Substantial preclinical evidence demonstrates that noradrenergic transmission is involved in stress-induced relapse and nicotine-related reinforcement, yet there is a surprising lack of clinical investigations translating these findings to humans.

Methods: Using a hybrid human laboratory and clinical outcome design, we have evaluated effects of noradrenergic targets including guanfacine (alpha2a agonist), prazosin (alpha1 antagonist), and carvedilol (combined alpha1 and beta antagonist) on stress-reactivity, smoking-related reinforcement, and reductions in cigarette use.

Results: There were notable differences in results across the noradrenergic targets with guanfacine producing the most promising findings to date. Guanfacine significantly reduced smoking behavior during the treatment phase in both women and men, but preferentially improved laboratory-based assessments of stress-reactivity in women and smoking-related reinforcement in men.

Conclusions: Noradrenergic agonists, especially alpha2a noradrenergic agonists, are a highly promising neurobiological target for the development of gender-sensitive therapeutics for smoking cessation.

O-9: The Role of Loading Mechanics in Sex Differences of Knee Osteoarthritis

Melissa M. B. Morrow (presenting author),[1] Mary I. O'Connor,[2] and Kenton R. Kaufman[1]

[1]Department of Orthopedic Surgery, Mayo Clinic (Rochester, MN); and [2]Department of Orthopedic Surgery, Mayo Clinic (Jacksonville, FL)

Background and Objective: Women have a higher incidence of knee osteoarthritis (KOA) than men do. Mechanisms attributing to this difference are unclear. We hypothesize that the difference could result in part from loading mechanics placed on the knee during walking. The objective was to characterize and compare knee loading mechanics between adult men and women with medial KOA.

Methods: Adults (221 women and 73 men) with medial compartment KOA underwent bilateral knee x-rays to determine radiographic OA severity and cartilage thickness. Gait analysis was performed during level walking to determine measures of cadence, magnitude of knee loading, rate of knee loading, and timing of peak loads during the gait cycle. ANCOVA analyses were performed to test the main effects of sex on gait. Results were adjusted for OA severity, age, body mass index, and knee alignment.

Results: Medial compartment cartilage thickness and estimated loading during walking were lower in women compared with men. There was no sex difference in the ratio of medial compartment cartilage thickness to medial compartment loading or in loading rates. Women walked with a faster cadence, and women applied peak loads during terminal stance, while men tended to apply peak loads during the initial loading response after heel strike.

Conclusions: Knee loading rate and magnitude are not indicated as risk factors in women; however, over a constant distance, women take more steps than men and experience peak loading later in the gait cycle. Differences in cumulative loading mechanics could contribute to sex differences in the onset and progression of KOA.

O-10: The Dek Oncogene Drives Breast Cancer Progression and Chemotherapeutic Resistance

Lisa M. Privette Vinnedge (presenting author),[1] Purnima K. Wagh,[1] Juana Serrano-Lopez,[1] Susan E. Waltz,[1] and Susanne I. Wells[2]

[1]Cincinnati Children's Hospital Medical Center, and [2]University of Cincinnati

Background and Objective: Late-stage breast cancer (BC) patients are faced with poor survival rates, drug resistance, and risk of tumor recurrence. Novel drivers of advanced disease must be identified that also may be targets of new therapies. This study was needed to investigate an oncogene that may determine disease progression and drug resistance. The goal was to determine if the Dek oncogene was required for breast cancer progression in vivo and drug resistance. Furthermore, we studied the role of Dek in maintaining the breast cancer stem cell population, which has been implicated as the causative factor for drug resistance and disease recurrence.

Methods: Dek-/- mice were bred to the MMTV-Ron breast cancer model. Histological and biochemical analyses were performed on tissues and cell lines derived from murine tumors.

Results: Dek expression is upregulated upon Ron receptor activation. Loss of the Dek oncogene significantly delayed tumor initiation in vivo due, in part, to decreased proliferation in pre-neoplastic glands. In cell lines derived from the murine model, Dek loss was associated with decreased BCSC numbers, fewer overt lung metastases, and Wnt pathway inhibition. Finally, the loss of Dek enhanced the cytotoxicity of cisplatin.

Conclusions: Dek is an important driver of BC progression and supports the maintenance of the BCSC population, which is thought to be responsible for disease recurrence and drug resistance. Targeted genetic inhibition of Dek may enhance therapeutic response to several classes of drugs. Pre-clinical testing of DEK inhibition should proceed as a method to enhance drug sensitivity in BCSCs, thus resulting in improved survival.

O-11: Sex Differences in Anticipatory Negative Contrast and Binge-like Eating Behaviors in Mice

Tomoko Udo (presenting author), Darren M. Opland, and Ralph J. DiLeone

Department of Psychiatry, Yale University of School of Medicine

Background and Objective: Women may be more susceptible to maladaptive eating behaviors, such as binge eating disorder, than men. However, due to primary focus on female sample, there are few preclinical and clinical studies on sex differences in binge-like eating behaviors. The study aimed to examine sex differences in adaptation of feeding behaviors under limited access to palatable food in mice, using anticipatory negative contrast (ANC). In addition to binge-like eating, ANC models behavioral inhibition, and thus allows modeling regulation of food intake in general as well.

Methods: In ANC, male and female C57BL/6J mice are given access to food for two consecutive 5-minute periods. They received either regular chow only (chow/chow [CC]; n = 5 per sex) or chow followed by palatable chocolate pellets (chow/sucrose [CS]; n = 5 per sex). Following several pairings, CS mice learn to decrease chow intake in anticipation of palatable food and consequently binge-eat the palatable food, compared with CC mice.

Results: For all mice, daily calorie intake was restricted to maintain 80% to 85% free-feeding body weight. The first feeder and second feeder intakes were compared by feeding condition and by sex. In anticipation of access to palatable foods, both male and female CS mice showed significantly less intake of regular chow, compared with their CC counterparts. Across sex, the CS group also developed binge-like eating of preferred food. Although there was no significant difference in the level of suppression of the first feeder intake (i.e., regular chow) by sex, female CS mice consumed significantly more preferred food than male CS mice during the second 5-minute feeding period. Thus, while no sex differences were found in the ability to inhibit food intake, female mice appeared to have developed more escalated binge-like eating behaviors than male mice.

Conclusions: This is the first study to demonstrate greater vulnerability to binge-like eating in females than in males using the ANC paradigm. This project will be followed by characterizing the neural circuitry underlying sex differences in behavioral adaptations observed in ANC. Identifying neurobiological systems involved in self-regulation of food intake and binge eating behaviors may ultimately lead to new sex-specific therapeutic targets for intervention against binge eating and eating disorders in general.

O-12: Drug Treatment for Type 2 Diabetes Modifies Fibroid Risk

Digna R. Velez Edwards (presenting author),[1] Katherine E. Hartmann,[2] Anushi Shah,[3] Hua Xu,[4] and Todd L. Edwards[1]

[1]*Center for Human Genetics and* [2]*Department of Obstetics and Gynecology, Institute for Medicine and Public Health, Vanderbilt Epidemiology Center;* [3]*Department of Biomedical Informatics, Vanderbilt University; and* [4]*School of Biomedical Informatics, University of Texas Health Science Center, Houston*

Background and Objective: Uterine fibroids (UFs) affect 77% of women by menopause, and account for $9.4 billion in yearly health care costs. Studies have shown that type 2 diabetes (T2D) associates with UF protection. Whether protection derives from having T2D or T2D pharmacologic management (treatment) is unclear. The objective was to further evaluate the relationship between UFs and T2D treatment.

Methods: UF status was determined from pelvic imaging. Women with T2D were identified from their clinical records and had not been diagnosed with UFs at T2D diagnosis. Cox regression, adjusted for confounders, was used to test for association between UF presence and T2D treatments (metformin [n = 1,089], thiazolidinedione [n = 353], insulin [n = 1,477], or other treatment [n = 332]). We also tested for interactions between T2D treatment and race and body mass index.

Results: We identified 2,321 women with T2D, with average age of diagnosis of 47. Seventeen percent developed UFs after T2D diagnosis. Insulin, compared with other treatments, conferred protection from UFs in European Americans (EAs) and African Americans (AAs) (EAs, adjusted hazard ratio [aHR] = 0.50, 95% confidence interval [CI] 0.36–0.69; AA, aHR = 0.53, 95% CI 0.37–0.74). We observed increased UF risk with metformin treatment among EAs (aHR = 1.94, 95% CI 1.37–2.74), but not among AAs (aHR = 1.07, 95% CI 0.76–1.51). Normal weight and overweight T2Ds had the most protection from UFs due to insulin compared with obese T2Ds. Thiazolidinedione and other T2D treatments did not associate with UFs.

Conclusions: These data support the hypothesis that protection from UFs linked to T2D diagnosis may derive from T2D treatments, specifically insulin. Further research is required to dissect the biological mechanisms of this effect, as well as the link between metformin and UF risk.

JOURNAL OF WOMEN'S HEALTH
Volume 22, Number 10, 2013

Abstract Author Index
by abstract number