Abstracts from the
NIH Office of Research
on Women's Health

Ninth Annual Interdisciplinary
Women's Health Research Symposium
November 15, 2012

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Joan Davis Nagel, M.D., M.P.H. and Joyce Rudick

THE OFFICE OF RESEARCH ON WOMEN'S HEALTH (ORWH) recognizes that the study of women's health across the life span requires a new interdisciplinary approach to research that bridges basic and clinical science and incorporates new models of collaboration, institutional support, and ways of evaluating those who conduct research. The ORWH continues to support innovative ways to encourage collaborative, interdisciplinary, and team-based research to improve women's health through two signature programs: 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 announced in 1999, and the first programs were started in 2000; the SCOR program was established in 2001. Both programs were expanded in 2012 as part of the implementation of the new National Institutes of Health (NIH) Strategic Plan for Women's Health and Sex Differences Research, *Vision 2020*. Goal 1 of the new strategic plan is to "increase sex differences research in basic science studies," and it is hoped that the expansion of the SCOR program will help achieve this goal. Goal 6 is to "employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce." BIRCWH is now serving as an institutional model of how to support junior faculty research and career development in women's health.

The abstracts included in this issue will be presented at the NIH Interdisciplinary Women's Health Research Symposium, now in its ninth year. They showcase the research findings of BIRCWH scholars, who are early stage, junior faculty, and SCOR investigators. The abstracts represent only a small cross-section of the research findings from these programs that cover the full spectrum of research relevant to women's health and sex differences. BIRCWH pairs junior faculty, who have recently completed clinical training or postdoctoral fellowships and are beginning basic, clinical, or translational research related to women's health, with senior investigators in women's health. Each BIRCWH site has the mentors, career development environment, and programs that the peer review process found to have the greatest potential to enhance the careers of the cadre of junior faculty committed to working across professional and scientific boundaries to address complex conditions that affect women's health.

In fiscal year 2012, ORWH and cosponsors, including the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institute on Aging

(NIA), National Institute of Mental Health (NIMH), National Institute on Drug Abuse (NIDA), and National Cancer Institute (NCI), funded 14 new and continuing BIRCWH programs that will expand and maintain the cadre of men and women researchers available to conduct women's health research. Currently, there are 29 active sites nationwide, and as of August 2012, 488 scholars have participated in the program, 80% of whom are women. The majority of BIRCWH scholars have gone on to receive independent funding from federal and other sources, including academic, foundation, and industry grants.

Also in fiscal year 2012, ORWH funded the third round of the SCOR program, which provides support for senior investigators who are looking at sex differences and major medical problems that affect women by integrating basic, clinical, and translational approaches to women's health. Each SCOR is required to have a central theme related to a disease area that at least three individual core projects will investigate. The SCOR theme serves as an integrating force. The requirement that each SCOR contain both a basic and a clinical component is designed to increase the likelihood of findings that are relevant to patients. The newly funded SCORs will advance sex differences research in the areas of developmental trajectories in affective disturbances and depression, aging, tobacco dependence, substance use, pain and chronic pain, musculoskeletal diseases, urinary tract health, reproductive health, and gonadal function.

This third round of SCOR centers is funded by ORWH; six cosponsoring NIH Institutes and Centers: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NICHD, NIDA, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIMH, and NIA; and the Food and Drug Administration (FDA) Office of Women's Health. The SCOR represents an excellent model for stimulating interdisciplinary sex differences research with significant applications to gender-specific human health. In June 2012, ORWH, in collaboration with SCOR investigators, published the third edition of the *SCOR e-Newsletter*, which included a cross-section of the research highlights from the second round of SCOR centers. Of particular note was a press release from the Yale SCOR on how female and male addicts respond differently to stress and may benefit from different addiction treatment approaches. In addition, the newsletter included a section on "What a difference a SCOR makes." A recurring theme was the SCOR's impact—transforming research programs at many institutions into translational research programs that take sex differences into account and examine the role of sex and gender in health and

disease. Other highlights included treatment and prevention of urinary tract infection with new agents, orally active FimH inhibitors.

The Ninth Annual Interdisciplinary Women's Health Research Symposium will take place on November 15, 2012, on the NIH campus. The abstracts selected for oral or poster presentation represent a diversity of topics in women's health and sex differences research. The Symposium will include, for example, plenary talks on the variation in cesarean section rates across hospitals in the United States, gender differences in responses to oxytocin in cocaine-dependent individuals, the impact of air pollution exposure on the risk of uterine leiomyomata (fibroids) in the Nurses' Health Study, the influence of childhood anxiety trajectories on the chance of having disordered eating in adolescence, and the use of new technologies, such as nanoparticles, for delivery of drug treatments for epithelial ovarian cancer. The Symposium also will include poster presentations on a variety of women's health topics.

As ORWH implements the new strategic plan, the BIRCWH and SCOR programs continue to be major vehicles for advancing women's health and sex differences research that has potential to benefit the health of women and men. Researchers who participate in BIRCWH and SCOR actively

contribute to the momentum and impact of these programs. The BIRCWH principal investigators (PIs) have formed a writing group to publish about best practices and lessons learned from interdisciplinary mentoring and career development initiatives at their institutions. It is gratifying to see what these two ORWH programs have achieved in the past decade through their unique interdisciplinary approach to research and career development in women's health. They have also drawn much needed attention to the importance of sex and gender data in the meaningful interpretation of scientific findings.

Address correspondence to:

Joyce Rudick
Director, Programs and Management
Office of Research on Women's Health
National Institutes of Health
6707 Democracy Boulevard
Suite 400
Bethesda, MD 20892

E-mail: ORWH-Research@od.nih.gov

BIRCWH Poster Abstracts

P-1: Altered Loading Conditions Negatively Impact the Structural Properties of the Vagina-Supportive Tissue Complex in Rats

Steven Abramowitch (presenting author),¹ Bradley Edelman,² and Pamela Moalli³

¹Musculoskeletal Research Center, Department of Bioengineering, University of Pittsburgh; ²Department of Biomedical Engineering, University of Minnesota; and ³Magee-Womens Research Institute, Department of Obstetrics and Gynecology and Reproductive Sciences at Magee-Womens Hospital, University of Pittsburgh

Background and Objective: A multitude of clinical and epidemiological studies are pointing to altered mechanical forces as possible risk factors for pelvic organ prolapse. Non-physiologic forces are known to result in changes in the expression of proteins, growth factors, transcription factors, and cytokines that in turn alter tissue structure. The objective is to utilize a hind limb unloading cage design to determine if altered loading conditions change the structural properties of the VSTC in the rat model.

Methods: A custom-built hind limb unloading cage based on a model developed by NASA was developed. Two sets of bearings support the tail of the rat hanging at a 30-degree angle (torso to the floor). This bearing system permits rat movement in two axes in order to reach food and water using only their front paws. Five nulliparous Long-Evans rats were hung in this system for 4 weeks and compared to age-matched controls (n=13). Our established biomechanical testing protocol was then utilized to measure the structural properties of the vaginal-supportive tissue complex.

Results: While there was no change in stiffness between the two groups, the ultimate load and elongation at failure were decreased by 33% ($P < 0.012$) and 38% ($P < 0.0011$), respectively. This corresponded to an energy absorbed at failure that was 61% decreased in the unloaded group ($P < 0.00013$), demonstrating a dramatic loss in mechanical integrity.

Conclusions: These data indicate that the vagina and its supportive tissues are highly mechanosensitive. This should be recognized as a possible contributing mechanism to the development of prolapse and failure following surgical repair.

P-2: Fetal Cord Blood Thrombin and Plasmin Generation in Preterm Premature Rupture of Membranes

Jennifer Armstrong-Wells (presenting author),¹ Meghan Donnelly,² Miriam Post,³ Virginia Winn,² and Marilyn Manco-Johnson⁴

¹Department of Pediatrics (Neurology), ²Department of OB/GYN, ³Department of Pathology, and ⁴Department of Pediatrics (Hematology), University of Colorado Denver

Background and Objective: Studies of fetal coagulation disturbances in preterm premature rupture of membranes (PPROM) may give insight into mechanisms of adverse neonatal outcomes. An assay that simultaneously measures both clot formation (coagulation) and dissolution (thrombolysis) is ideal to characterize clotting profiles in this specialized population. The objective of this study is to characterize the thrombin and plasmin generation of fetal cord blood from pregnancies complicated by PPRM, compared with healthy term controls.

Methods: Fetal cord blood samples were taken from pregnancies of women with PPRM (n=9) and healthy term pregnancies (n=50) that were enrolled in an institutional prospective cohort study. Thrombin and plasmin enzymes were assayed by continuous fluorometric detection following activation by calcium, 5 pM tissue factor and 450 ng/mL tissue plasminogen activator. Distribution of data for each parameter, including lag time to initial generation (lag), maximal velocity (Vmax), and maximal amplitude (MA), were analyzed as % normal (%NL) of an established pediatric normative population,

then compared between groups by Mann-Whitney U. $P < 0.05$ was considered significant.

Results: PPRM fetal cord blood had shorter thrombin lag (49 vs. 83 %NL; $P = 0.002$), faster Vmax (76 vs. 58 %NL; $P = 0.002$), but comparable MA (91 vs. 89 %NL; $P = 0.27$). Plasmin MA was decreased in PPRM (60 vs. 72 %NL; $P = 0.003$), although Vmax was increased (27 vs. 45 %NL; $P = 0.02$); lag did not differ ($P = 0.38$).

Conclusions: PPRM fetal cord coagulates faster, but may have less thrombolytic capability, compared with healthy term controls. These coagulation disturbances may contribute to adverse neonatal outcomes associated with PPRM and warrant further investigation.

P-3: Depression and Gestational Weight Gain: Is There a Relationship?

Lyndsay Ammon Avalos (presenting author), Monique M. Hedderson, Jeannette R. Ferber, and De-Kun Li

Kaiser Permanente Division of Research

Background and Objective: An estimated 12% to 25% of pregnant women suffer from depression. Prenatal depression is known to negatively impact reproductive outcomes and may influence eating habits. Excess and inadequate weight gain during pregnancy are also associated with perinatal complications. However, the relationship between depression and gestational weight gain (GWG) is unknown. The objective of the study is to assess the relationship between depression during pregnancy and GWG.

Methods: We conducted a population-based retrospective cohort study among 44,783 pregnant Kaiser Permanente Northern California members between July 2009 and January 2012 who were screened for prenatal depression. Depression status, prepregnancy height and weight, last weight before delivery, and potential confounders were ascertained through electronic medical records. GWG was categorized into 3 categories based on IOM recommendations: inadequate, adequate, and excessive.

Results: Preliminary analyses suggest that overall the 17% (n=7,626) of pregnant women with depression were more likely to exceed the recommended weight gain during pregnancy compared to women without depression (53% vs. 49%, $P < .001$). However, these results varied by prepregnancy body-mass index (BMI). Among normal or underweight women, depressed women were more likely to exceed the recommended weight gain during pregnancy (Underweight: 32% vs. 21%, $P = .04$; Normal: 46% vs. 38%, $P < .001$). Among women who were overweight, women with depression were more likely to have inadequate GWG compared to women without depression (Overweight: 13% vs. 11%, $P < .001$). There was no difference in GWG among depressed women who were obese prior to pregnancy.

Conclusions: Our preliminary results suggest that depression may be associated with excessive or inadequate GWG. However, further research is needed.

P-4: Hypoxic Adaptation Requires the Estrogen-Related Receptor

Keith D. Baker,¹ Yan Li,¹ Divya Padmanabha,¹ Luciana B. Gentile,¹ I. Dumur,¹ and Robert B. Beckstead²

¹Virginia Commonwealth University; ²University of Georgia

Background and Objective: Low-oxygen tolerance is supported by an adaptive response that includes a concomitant shift in metabolic strategy and the activation of a transcriptional program that is driven by the hypoxia-inducible factor (HIF) pathway. The precise contribution that HIF-1 has in the adaptive response, however, has not been determined. We investigate here how HIF-1 influences adaptation by assessing transcriptional and metabolic responses to hypoxic challenge throughout development.

Methods: We use a genetics and biochemical approach that takes advantage of transcriptional profiling and metabolomic analysis. Our analysis utilizes the model organism *Drosophila melanogaster*, which maintains a robust hypoxic response that mirrors that seen in mammalian systems.

Results: We find that hypoxic-induced transcriptional changes are comprised of HIF-dependent and HIF-independent pathways that are distinct and separable. Contrary to expectations, we find that hypoxic up-regulation of glycolytic transcripts is non-HIF-dependent. We show that, although the normoxic set-points of carbohydrate catabolites are significantly altered in dHIF mutants, hypoxic-induced changes of individual metabolites occur normally. Furthermore, we find that the estrogen-related receptor (ERR) is required for a competent hypoxic response. ERR binds to dHIF and participates in the HIF-dependent transcriptional program in hypoxia; however, ERR also acts in the absence of dHIF in hypoxia. A significant portion of HIF-independent transcriptional responses can be attributed to ERR actions, including hypoxic up-regulation of glycolytic transcripts.

Conclusion: These results indicate that competent hypoxic responses are a patchwork of HIF-dependent and -independent actions, and that dERR provides a central role in both programs.

P-5: Prenatal Stress Is Associated With Masculinized Anogenital Distance in Infant Females

Emily S. Barrett (presenting author),¹ Sheela Sathyanarayana,² Fan Liu,³ J. Bruce Redmon,⁴ Christina Wang,⁵ and Shanna H. Swan³

¹Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry; ²Department of Pediatrics, Seattle Children's Research Institute, University of Washington; ³Department of Preventive Medicine, Mount Sinai School of Medicine; ⁴Departments of Medicine and Urologic Surgery, University of Minnesota Medical School; and ⁵Division of Endocrinology, Department of Medicine, Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute

Background and Objective: In animal models, prenatal stress programs reproductive development in the resulting offspring; however, little is known about effects in humans. Anogenital distance (AGD) is commonly used as a sexually dimorphic biomarker of prenatal androgen exposure in many species. In rodents, prenatally stressed males have shorter AGD than controls (suggesting lower prenatal androgen exposure), whereas prenatally stressed females have longer AGD than controls (suggesting greater prenatal androgen exposure). Our objective was to investigate the relationship between prenatal stress and infant AGD in humans.

Methods: In a prospective cohort study, pregnant women and their partners reported exposure to major adverse life events during pregnancy. Pregnancies in which the woman reported 2 or more life events or the couple reported 4 or more life events were considered high stress. Women also reported on difficulty conceiving and time to pregnancy. After birth, trained examiners measured AGD in the infants (142 males, 153 females).

Results: After controlling for age and body size, infant females born to couples with high life events stress had significantly greater (i.e., more masculine) AGD than females born to couples with low life events stress ($P=.03$). There was a trend, furthermore, toward associations between longer female AGD and high maternal stress, difficulty conceiving, and longer time to pregnancy ($P\leq .10$). Although high prenatal stress was associated with shorter AGD in males, the relationships were not statistically significant.

Conclusion: Our results suggest prenatal stress may masculinize female reproductive development in humans. More sensitive prenatal stress measures and additional measures of reproductive development are needed to better understand these relationships and clarify mechanisms.

P-6: Large Two-Stage Study Identifies Novel Associations Between Common Genetic Variants in *OncotypeDX*[®] Genes and Breast Cancer Survival

Alicia Beeghly-Fadiel (presenting author),¹ Wei Lu,² Xiangyu Ma,¹ Ryan J. Delahanty,¹ Ying Zheng,² Hui Cai,¹ Jirong Long,¹ Ben Zhang,¹ Qiuyin Cai,¹ Yutang Gao,² Wei Zheng,¹ and Xiao Ou Shu¹

¹Division of Epidemiology, Vanderbilt University Medical Center; and

²Shanghai Institute of Preventive Medicine, Shanghai Cancer Institute

Background and Objective: MammaPrint[®] and *OncotypeDX*[®] are commercially available gene expression assays used to predict breast cancer prognosis. Inherited genetic variation may influence the expression of these genes, and also breast cancer survival. The objective of the study was to comprehensively evaluate common genetic variants in MammaPrint[®] and *OncotypeDX*[®] genes for associations with breast cancer survival.

Methods: A 2-stage study design was employed. Genotyping was conducted using the Affymetrix Genome-Wide Array 6.0 (Stage 1) and iSELECT and Illumina platforms (Stage 2). Associations with disease-free survival (DFS) and overall survival (OS) were evaluated using Cox proportional hazards regression to generate hazard ratios (HR) and 95% confidence intervals (CI).

Results: In Stage 1, a total of 1,956 genetic variants in 861 independent loci were evaluated among 2,919 breast cancer patients followed for an average of 5.7 years; 58 variants in 34 loci were associated with DFS and/or OS ($P\leq .01$). In Stage 2, variants in 32 loci were successfully genotyped and further evaluated among 4,214 breast cancer patients followed for an average of 4.0 years. Two variants had consistent and highly significant associations: *AURKA/C20orf108 rs4811693* was associated with worse DFS (HR: 1.18, 95% CI: 1.08–1.29; $P=.0003$) and OS (HR: 1.18, 95% CI: 1.07–1.30; $P=.0011$) in an additive manner; *MKI67 rs9452221* was associated with worse DFS (HR: 1.18, 95% CI: 1.11–1.30; $P=.0007$) and OS (HR: 1.18, 95% CI: 1.07–1.46; $P=.0063$) in a dominant manner.

Conclusion: Genetic variants in 2 *OncotypeDX*[®] genes were associated with breast cancer survival; these germline variants may therefore influence gene expression in tumor tissue.

P-7: Feasibility of an Automated Real-Time Stimulus to Promote Physical Activity Adherence

Kelly A. Bosak (presenting author)

School of Nursing, University of Kansas

Background and Objective: Cardiometabolic risk increases with age, overweight, and obesity. Untreated, this condition leads to diabetes and cardiovascular disease. Physical activity (PA) has been widely studied and found to effectively reduce cardiometabolic risk; however, adherence to this demanding health behavior is difficult for most adults. The objective was to evaluate the effects of an intervention using the Gruve[®] accelerometer delivering an automated real-time stimulus to promote physical activity adherence as the basis for a future larger study.

Methods: Nondiabetic overweight (BMI = 25–29.9 kg/m²) midlife women aged 47 to 55 years ($n=25$) were randomly assigned to groups. The experimental group wore the Gruve[®] accelerometer during waking hours for 6 weeks and received a gentle vibration when energy expenditure (EE) fell below the resting metabolic rate. The attention control group wore the standard RT3 accelerometer for 1 week at baseline and week 6.

Results: Significant changes were found in the Gruve[®] group, including a decrease in sedentary time (–1.6 min/hr), an increase in low intensity PA (0.9 min/hr), and an increase in EE (3.1 kcal/hr). On average, the Gruve[®] was worn 68% of the time in 24 hours (16.32 hours/day). This was used to calculate the changes. Thus, the Gruve[®] resulted in a decrease in sedentary time (26.1 min/day and 182.7 min/wk), an increase in low intensity PA (14.6 min/day and 102.2 min/wk) and an increase in EE (50.3 kcal/day and 352.1 kcal/wk).

Conclusions: The results indicate that the intervention effectively improved PA outcomes, and the methods and measures used are feasible for a future larger study.

P-8: Prepregnancy Obesity and Long-Term Maternal Cardiovascular Function in a Mouse Model

Egle Bytautiene (presenting author), Esther Tamayo, Phyllis Gamble, Rheana Urrabaz-Garza, and George R. Saade

Department of Obstetrics and Gynecology, University of Texas Medical Branch

Background and Objective: Studies investigating the sole effect of maternal prepregnancy obesity on later maternal health are lacking. The objective of this study was to test the hypothesis that prepregnancy obesity alters maternal cardiovascular function later in life.

Methods: CD-1 female mice were placed on standard (SF, $n=13$) or high-fat (HF, $n=9$) diet 3 months before mating. After weaning, all dams were placed on an SF diet. At 6 months, postpartum mice were fitted with telemetric transducers for in vivo blood pressure recordings. After 7 days, the right carotid artery was excised for in vitro vascular reactivity studies. Concentration-response curves to phenylephrine (PE), thromboxane (TBX), serotonin (5-HT), acetylcholine (ACh), sodium nitroprusside (SNP), and isoproterenol (ISO) were obtained. Student *t*-test, Mann-Whitney rank sum, and 2-way ANOVA tests were used for statistical analysis (significance, $P < 0.05$).

Results: The HF mice were significantly heavier than SF group on day 1 of pregnancy and at the time of weaning. At 6 months postpartum, HF mice exhibited significantly higher adiposity, systolic blood pressure, heart rate, and impaired vascular responses to PE, TBX, and ACh than did SF mice. No other differences were observed.

Conclusions: Prepregnancy obesity results in impaired maternal cardiovascular function and is not affected by postpartum diet modification. This animal could be used to study effects of prepregnancy obesity on long-term maternal health.

P-9: Time Course of Arthralgia Among Women Initiating Aromatase Inhibitor Therapy Compared with Postmenopausal Women Without Cancer in a Prospective Cohort

Liana D. Castel (presenting author),¹ Katherine E. Hartmann,² Ingrid A. Mayer,¹ Chad S. Boomershtine,¹ Vandana G. Abramson,¹ Anuradha Bapsi Chakravathy,¹ David H. Johnson,³ and David F. Cella⁴

¹Department of Medicine, ²Department of Obstetrics and Gynecology, Vanderbilt University Medical Center; ³Department of Internal Medicine, University of Texas Southwestern Medical Center; and ⁴Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine

Background and Objective: More than 100,000 breast cancer patients begin a 5-year course of aromatase inhibitors (AI) each year to prevent recurrence. AI-related arthralgia (joint pain and/or stiffness) likely leads to nonadherence. Adequate prospective data are needed on arthralgia trajectories among women initiating AI and postmenopausal women without cancer. The study's objective was to describe longitudinal arthralgia trajectories and risk factors over the first 12 weeks of AI treatment.

Methods: Postmenopausal female outpatients initiating AI ($n=94$) completed baseline surveys prior to AI initiation, and follow-up surveys every 2 weeks for 12 weeks. A comparison group of postmenopausal females without cancer ($n=157$) completed concomitantly-timed surveys. We used a 0-to-10 numeric rating scales to measure mean pain over 16 joints. We also collected information on clinical and demographic characteristics and health-related quality of life. We used linear mixed regression models to analyze differences by group in arthralgia trajectories, adjusting for baseline and time-dependent factors.

Results: At weeks 6 and 12, women who had initiated AI experienced worsening arthralgia versus the comparison group. Among a set of baseline demographic and clinical variables, none were significant risk factors. Women with more severe menopausal symptoms over time had more severe arthralgia over time ($P < .001$).

Conclusions: Standard demographic and clinical risk factors are not helpful in identifying who will experience arthralgia. Adequate time (at least 12 weeks) for potential development of arthralgia should be taken into account when scheduling follow-up visits among women initiating AI. These findings will help inform decision making and adherence interventions toward ensuring the clinical effectiveness of AIs.

P-10: Sex-Based Differences in Posttraumatic Osteoarthritis Development Following Knee Injury in Mice

Blaine A. Christiansen (presenting author),¹ Dominik R. Haudenschild,¹ and Nancy E. Lane²

¹Department of Orthopaedic Surgery, ²Department of Internal Medicine, School of Medicine, University of California, Davis

Background and Objective: Posttraumatic osteoarthritis (PTOA) is observed in more than 50% of patients within 10 to 20 years following joint injuries such as anterior cruciate ligament (ACL) rupture. Female athletes are 4 to 6 times more likely to sustain an ACL injury. PTOA development may differ by sex; however, the specific mechanisms of PTOA development, and how these differ between men and women, are unclear. Using a noninvasive mouse knee injury model developed in our laboratory, we sought to determine short-term (0 to 14 days) and long-term (8 to 12 weeks) inflammation, subchondral bone, and articular cartilage changes in male and female mice following knee injury.

Methods: All mice were scanned with in vivo microcomputed tomography at days 0, 7, 14, 56, and 84 after injury to quantify subchondral bone mass and architecture. Blood samples were collected at each time point, and serum was analyzed for inflammatory biomarkers and biomarkers of cartilage remodeling. Both limbs were collected 84 days after injury for histological analysis of articular cartilage.

Results: Preliminary results show rapid trabecular bone loss (-40% to -44% trabecular bone volume) within 7 days after knee injury, with significant articular cartilage degeneration by 84 days ($P < .001$).

Conclusions: Following knee injury, we observed immediate inflammation and rapid subchondral bone turnover, followed by long-term degeneration of articular cartilage. Future data assessment will determine potential differences in PTOA development between male and female mice. Results from these studies will help to establish likely mechanisms contributing to the development of PTOA and will help explain the disparity in PTOA between men and women.

P-11: Longitudinal Assessment of Human Papillomavirus (HPV) Infections in HIV-Infected Women: Implications for HPV-Related Cancer Prevention

Ping Du (presenting author),^{1,2} John J. Zurlo,¹ Craig Meyers,³ Eugene J. Lengerich,² Andrew Read,⁴ and Neil Christensen⁵

¹Department of Medicine, ²Department of Public Health Sciences, ³Department of Microbiology and Immunology, Pennsylvania State University College of Medicine; ⁴Department of Biology and Entomology, Pennsylvania State University Eberly College of Science; and ⁵Department of Pathology, Pennsylvania State University College of Medicine

Background and Objective: The natural history of HPV infections in HIV+ women needs to be revisited in the era of highly active antiretroviral therapy. The study's objective was to examine the prevalence, incidence, and persistence of oral, vaginal, and anal HPV infections in a cohort of HIV+ women.

Methods: HIV+ women were recruited from 5 HIV/AIDS outpatient clinics and were followed at 4-month intervals to assess HPV infections over time. A behavioral survey; oral, vaginal, and anal swabs; and a blood sample were collected at each visit. The swabs were used to detect 37 types of HPV DNA, and the sera were tested for HPV 16/18 neutralizing antibodies. HIV/AIDS-related clinical information was obtained from the medical records.

Results: High-risk sexual behaviors and uses of tobacco/alcohol/drugs were commonly reported among 98 HIV+ women enrolled in this study. HPV DNA was detected among 55% of women at the first visit. The prevalence of oral, vaginal, and anal HPV infections was 7%, 40%, and 46%, respectively. During the follow-up visits, new types of HPV DNA in the oral cavity, the vagina, and the anus were detected among 9%, 12%, and 23% of women with repeated visits. Persistent oral, vaginal, and anal HPV infections were observed among 0%, 29%, and 13% of women, respectively. Multiple recent sexual partners and smoking were associated with persistent HPV infections.

Conclusions: New and persistent vaginal and anal HPV infections are common in HIV+ women. Further medical evaluations are needed for HIV+ women to detect HPV-related precancerous lesions at noncervical sites.

P-12: Impact of the Recent Economic Downturn on the Use of Mental Health Crisis Services by Youth in Tennessee

Richard A. Epstein (presenting author),¹ Sarah Hurley,² Jon S. Ebert,¹ William V. Bobo,¹ Wei Wang,³ Rameela Chandrasekhar,³ and Neil Jordan⁴

¹Department of Psychiatry, Vanderbilt University; ²Youth Villages, Inc.;

³Department of Biostatistics, Vanderbilt University; and ⁴Department of Psychiatry and Behavioral Sciences, Northwestern University

Background and Objective: Economic stress is associated with increased risk for adverse mental health outcomes and un-insurance. It is unknown whether the onset of economic recession is associated with increased use of safety-net services such as youth mental health crisis services. The study's objective was to test the hypothesis that the onset of the recent U.S. economic recession was associated with increased use of youth mental health crisis services in Tennessee.

Methods: We conducted a retrospective cohort study with an interrupted time series design and developed a segmented autoregressive integrated moving average model. We used aggregate data on the number of Tennessee crisis hotline calls and calls resulting in an inpatient hospitalization referral from the statewide provider (Youth Villages, Inc.), and publicly available data on the number of youth in Tennessee (U.S. Census Bureau) and economic indicators (National Bureau of Economic Research and U.S. Department of Labor).

Results: In the post- as compared to the pre-recession period, there was a significant increase in the rate of change in the monthly prevalence of total crisis calls ($\beta = 0.34$; 95% CI = 0.12, 0.57) but not of calls resulting in an inpatient hospitalization referral ($\beta = 0.06$; 95% CI = -0.05, 0.17), after adjusting for demographics and the pre-recession secular trend.

Conclusions: The recent economic downturn was associated with a significant increase in the rate of use of youth mental health crisis services in Tennessee. These data indicate increasing use of these important safety-net services concurrent with economic threats to public funding for them.

P-13: Multiple Juvenile Idiopathic Arthritis Subtypes Demonstrate Pro-inflammatory IgG Glycosylation

Altan Ercan (presenting author),¹ Michael G. Barnes,² Melissa Hazen,³ Heather Tory,³ Lauren Henderson,³ Fatma Dedeoglu,³ Robert C. Fuhlbrigge,³ Alexei Grom,⁴ Ingrid A. Holm,⁵ Mark Kellogg,⁶ Susan Kim,³ Barbara Adamczyk,⁷ Pauline M. Rudd,⁷ Mary Beth Son,³ Robert P. Sundel,³ Dirk Foell,⁸ David N. Glass,⁴ Susan D. Thompson,⁴ and Peter A. Nigrovic^{1,3}

¹Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital; ²Division of Rheumatology, Cincinnati Children's Hospital Medical Center; ³Division of Immunology, Children's Hospital Boston; ⁴Division of Rheumatology, Cincinnati Children's Hospital Medical Center; ⁵Division of Genetics, Program in Genomics, and The Manton Center for Orphan Disease Research, Children's Hospital Boston and Harvard Medical School; ⁶Department of Laboratory Medicine, Children's Hospital Boston; ⁷Dublin-Oxford Glycobiology Laboratory, National Institute for Bioprocessing Research and Training, University College, Dublin, Ireland; and ⁸Institute of Immunology, University of Muenster, Germany

Background and Objective: Alteration in the N-glycans of immunoglobulin G (IgG) affects its ability to engage inflammatory mechanisms via Fc receptors and complement. In particular, hypogalactosylation of this glycan translates into increased effector potency, and has been associated with adult rheumatoid arthritis. Recent studies from our group and others point to an effect of both gender and menopause on IgG Fc glycan structure. We examined whether changes in glycosylation with gender extended to healthy children and to children with juvenile idiopathic arthritis (JIA), a family of autoimmune diseases that affect girls more than boys. The study's objective was to characterize IgG glycans in young children and JIA patients to assess their potential contribution to the onset and gender distribution of JIA.

Method: We employed a well-established HPLC method to characterize serum N-glycans in normal children (n = 165) and in patients with new-onset untreated JIA (n = 141).

Results: JIA as a whole, as well as multiple JIA subtypes, is associated with hypogalactosylation of IgG. Surprisingly, healthy children in the first years of life also demonstrated aberrant glycosylation, although no gender differences could be discerned.

Conclusions: Aberrant glycosylation is associated with JIA, potentially implicating aberrant humoral immunity in the pathogenesis of this disease. Interestingly, in healthy children of both genders, aberrant glycosylation is also observed around the peak age of JIA onset (2 to 3 years). These findings raise the novel possibility that the remarkable predilection of JIA at early childhood may in part reflect particular characteristics of the pediatric immune system, in particular with respect to antibody glycans.

P-14: Pelvic Organ Prolapse: Women's Perceptions of Illness

Chiara Ghatti (presenting author),¹ Sallie Oliphant,¹ Laura Skoczylas,¹ Cara Nikolajski,² and Jerry Lowder¹

¹Division of Female Pelvic Medicine and Reconstructive Surgery, Department of Obstetrics, Gynecology, and Reproductive Sciences, Magee-Womens Hospital, University of Pittsburgh; and ²Center for Research on Health Care, Department of General Internal Medicine, University of Pittsburgh

Background and Objective: Pelvic floor disorders impact a large portion of the female population. The study's objective was to explore illness perception in women with symptomatic pelvic organ prolapse (POP).

Methods: Forty-two subjects participated either in semistructured focus groups or individual phone interviews as part of the IRB-approved study. A trained facilitator stimulated discussion using scripted questions. All dialogues were audio recorded and transcribed for analysis. For this study, transcripts were independently analyzed for themes related to illness perception using a grounded theory approach. Themes were identified and confirmed by consensus.

Results: Twenty-five women participated in the focus groups and 17 had phone interviews. Mean participant age was 61 ± 11 years and had median POP quantification stage III. POP illness perception-related themes fell into 3 broad categories: condition, treatment, and duration. Women endorsed a poor understanding of the condition and often did not differentiate POP from symptoms of other conditions such as urinary incontinence and pelvic pain. Anatomic and etiologic misconceptions were frequently expressed. Women associated concepts of poor health and aging with POP. Women reported ambivalence about treatment options and reported relying on guidance from providers or friends regarding when to seek treatment. Perceptions of when POP was recognized and its expected duration varied. Some women identified prolapse as a life-long problem; even following repair, women had concerns about recurrence.

Conclusions: The themes identified in this secondary analysis provide a framework to better understand women's cognitive perceptions of the condition of POP. These data and future research efforts will aid providers in education, support, and counseling of women with POP.

P-15: Maternal Characteristics of Extremely Low Birth Weight and Very Low Birth Weight Infants Born and Retained in Non-NICU Hospitals: Michigan 2004-2009

Sue C. Grady

Department of Geography, Michigan State University

Background and Objective: In Michigan from 2004 to 2009, 1,051 pregnant women delivered extremely low birth weight (ELBW) (<1,000 g) or very low birth weight (VLBW) (1,000-1,500 g) infants in Levels 1 and 2 birthing hospitals. Of these, 635 (60.4%) infants were retained—i.e., not transferred to Level 3 hospitals with neonatal intensive care units (NICUs). Of retained infants, 145 (22.8%) died prior to hospital discharge. The study's objective was to describe the

characteristics of mothers of ELBW/VLBW infants born and retained in Levels 1 and 2 hospitals to target future education and health care interventions to reduce infant mortality; and to assess the need for a regionalized system of perinatal care in Michigan.

Methods: Vital statistics birth and linked infant death records (2004–2009) on singleton ELBW/VLBW infants born in Level 1 ($n=32$; $n=362$) and Level 2 ($n=34$; $n=629$) hospitals and maternal characteristics were obtained from the Michigan Department of Community Health. Descriptive and analytical (Generalized Linear Models) analyses were conducted in SPSS v.19 and SAS v.9.2.

Results: Mothers residing in rural areas delivering infants in Level 2 hospitals were significantly ($OR=2.4$, $P=.00$) more likely to be retained than infants born in similar hospitals in metropolitan areas. Mother's age, race, and education (below high school level) were not significantly associated with retention. Infants of mothers with pregnancy-related complications (preeclampsia/eclampsia, $OR=4.2$, $P=.00$ or vaginal bleeding, $OR=5.9$, $P=.04$) were significantly more likely to be transferred than retained, controlling for infant sex and gestational age.

Conclusions: Future research should investigate rural hospital infant/maternal transport systems, other pregnancy-related complications and the postpartum health of women delivering in Level 1 and 2 hospitals.

P-16: An Interdisciplinary Approach Reveals a New Function for Yersiniabactin, a Uropathogen Virulence Factor

Jeffrey P. Henderson (presenting author), Kaveri S. Chaturvedi, Chia S. Hung, Jan R. Crowley, and Ann E. Stapleton

Department of Internal Medicine, Washington University School of Medicine

Background and Objective: Urinary tract infections (UTIs) caused by uropathogenic *E. coli* (UPEC) disproportionately affect women and can progress to kidney or bloodstream infections. Urinary tract virulence has been associated with bacterial secretion of yersiniabactin, a siderophore known for its ability to bind ferric iron. Why yersiniabactin confers a pathogenic advantage beyond the multiple UPEC siderophores has been unclear. The study's objective was to determine whether yersiniabactin binds nonferric metal ions during urinary tract infections.

Methods: Yersiniabactin was purified using liquid chromatography (LC). We configured a mass spectrometer (MS) to identify metal-yersiniabactin complexes based on a unique ion fragmentation signature. High resolution mass spectrometry was used to confirm molecular identities. We used a stable isotope dilution LC-MS approach to identify and quantify different metal-yersiniabactin complexes in urine samples from UTI patients. Bacterial viability in cell culture was determined by colony forming unit determination.

Results: Yersiniabactin binds physiologic copper (II) ion to form a stable complex (Cu-Ybt) that was present in the urine of female outpatients with UTI. Yersiniabactin was found to protect *E. coli* from copper-mediated growth inhibition. Urinary *E. coli* isolates exhibited greater copper resistance than rectal isolates.

Conclusions: These findings reveal that yersiniabactin is expressed during human infections, where it binds both iron and copper ions. Yersiniabactin's ability to protect uropathogenic *E. coli* strains from copper-mediated growth inhibition suggests a functional rationale for its pathogenic association. This adaptation to host-derived copper supports other recent findings that immune cells use copper as an antibacterial host defense, a function that may be particularly consequential in UTI.

P-17: Differential Activation of Cell Death Pathways After Ionizing Radiation in Luminal and Basal Breast Cancer Cell Lines

Janet K. Horton (presenting author),¹ Diane R. Fels,¹ Hsiu-Ni Kung,² Yingchun Zhou,¹ Kathleen Ashcraft,¹ Mark W. Dewhirst,¹ and Jen-Tsan Ashley Chi²

¹Department of Radiation Oncology, ²Department of Molecular Genetics, Duke University

Background and Objective: A growing body of data suggests that the intrinsic (luminal, basal) subtypes of breast cancer strongly influence the probability of locoregional control in women receiving radiation as a component of their treatment. Our preliminary data suggest that a distinct pattern of gene activation is seen in these subtypes in response to radiation. Further understanding of these unique patterns could identify biologically-based targets for treatment modulation.

Methods: Six commercially available human breast cancer cell lines known to display gene expression patterns of distinct breast subtypes (luminal: ZR751, T47D, MCF7; basal: SUM159, SUM149, MDA-MB-231) were utilized for further study of gene expression and phenotypic responses to ionizing radiation. Clonogenic assays to assess radiation sensitivity, in conjunction with stimulating and inhibiting antibodies, were utilized to assess the impact of pharmacologic modulation on radiation sensitivity.

Results: Multiple members of the programmed cell death pathway were strongly induced by radiation in the radiosensitive cell lines, both luminal. Among the cell death genes that were strongly induced in the radiosensitive cell lines was Fas, which is linked with radiation response in other cell types. Treatment of a resistant basal cell line, SUM159, with Fas-stimulating antibody (CH11) resulted in radiosensitization (dose modifying factor=2.5).

Conclusions: These data link patterns of gene expression response to radiation response and identify potential subtype-specific targets that can enhance radiation effect. Induction of the Fas pathway, in particular, was found to enhance the radiation sensitivity of resistant breast tumors.

P-18: Urinary Phthalate Metabolite Concentrations and Biomarkers of Diabetes Risk by Race/Ethnicity and Sex, the National Health and Nutrition Examination Survey 2001–2008

Tamarra James-Todd (presenting author),¹ Tianyi Huang,² Elvira Isganaitis,³ and Aditi Saxena¹

¹Department of Medicine, Brigham and Women's Hospital/Harvard Medical School; ²Department of Medicine, Brigham and Women's Hospital; and ³Department of Integrative Physiology and Metabolism, Joslin Diabetes Center

Background and Objective: Women and minorities are more likely to be exposed to higher levels of phthalates, endocrine-disrupting chemicals that may be associated with diabetes. The study's objective was to evaluate the relationship of urinary phthalate concentrations to biomarkers of diabetes, by sex and race/ethnicity.

Methods: Urinary phthalate metabolite concentrations and diabetes biomarkers (fasting blood glucose [FBG] and insulin) were analyzed by the CDC in a subset of 3,083 men and women aged 20 to 79 years who participated in NHANES 2001–2008. HOMA-IR was calculated from FBG and insulin. Median regression was used to calculate median change and 95% confidence intervals (CI). Models were stratified by race/ethnicity and sex and adjusted for urinary creatinine and potential confounders.

Results: In the overall population, MnBP, MiBP, MCP, and DEHP exhibited dose-response increases in FBG, insulin, and HOMA-IR levels. In women, MiBP and MnBP had stronger effects; the highest quartile had a median of 4.41 mg/dL higher FBG compared to the lowest quartile. The association between urinary phthalates and FBG was strongest for Mexican Americans, followed by blacks, then whites, with MiBP conferring the greatest increase in FBG (highest quartile compared with lowest quartile), as follows: for Mexican Americans, 5.72 mg/dL (95% CI, 3.83, 7.6); for blacks, 3.58 mg/dL (95% CI, 1.12, 6.03); for whites, 2.29 mg/dL (95% CI, 0.33, 4.25). The association of DEHP and HOMA-IR was stronger in blacks than in other racial/ethnic groups.

Conclusions: Higher levels of phthalates are associated with higher FBG and HOMA-IR, with varying relationships by sex and race. Reducing exposure to certain phthalates could benefit specific populations at increased risk of diabetes.

P-19: Pilot Study to Evaluate a Home-based Diet and Exercise Intervention on Markers of Cardiopulmonary Fitness and Breast Cancer Risk in Postmenopausal Breast Cancer Survivors

Jennifer R. Klemp (presenting author),¹ David Burnett,² Charles Porter,³ Katherine J. Schmitz,⁴ Patricia Kluding,² and Carol J. Fabian¹

¹Breast Cancer Survivorship Center, ²Physical Therapy and Rehabilitation Sciences, University of Kansas Medical Center; ³Mid-America Cardiology, University of Kansas Hospital; and ⁴Department of Epidemiology, University of Pennsylvania

Background and Objective: Breast cancer (BrCa) survivors have an estimated 4-fold increased risk for developing cardiovascular disease (CVD) compared to women never treated for breast cancer and a nearly 3-fold increase in breast cancer mortality in women with low cardiorespiratory fitness measured by VO₂ peak. Cardiac events are the second most common cause of death in long-term breast cancer BrCa survivors. We conducted a study to investigate the effects of a home-based diet and exercise (cardiovascular plus slow-progressive, resistance training) intervention in postmenopausal BrCa survivors on targeted CVD and BrCa outcomes.

Methods: Cross-sectional within group design. A total of 17 BrCa survivors, average age of 52.6±9.3 years and 23±9.6 months from diagnosis, were enrolled in the study. Participants underwent baseline and 17-week assessments including maximal exercise testing (VO₂ max and minutes on the treadmill), body composition measurements (weight, BMI, percentage of body fat), and assessment of quality of life.

Results: Significant improvements from baseline to 17 weeks were seen for all measures of body composition: pre-weight of 191.5±32 lbs decreased to post-weight of 178.0±32 lbs, approximately 9.5% of their starting weight ($P < .001$); pre-total percent fat mass of 47.4%±6.2% decreased to post-total percent fat mass of 43.5%±8.5% ($P < .01$). Measures of cardiorespiratory fitness (VO₂ peak and minutes on the treadmill) improved from 23.7±5.8 to 27.9±5.8 and from 699.6±273.7 minutes to 917.7±236.6 minutes, respectively ($P < .001$).

Conclusions: BrCa survivors participating in a home-based diet and exercise intervention were able to significantly improve measures of CVD and BrCa after completing a 17-week intervention.

P-20: Health Behaviors in Low-Income Minority Pregnant Women

Michelle A. Kominiarek (presenting author)¹ and Susan Vonderheid²

¹Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, College of Medicine, and ²Department of Women, Children, and Family Health Science, College of Nursing, University of Illinois at Chicago

Background and Objective: Research shows that behavioral interventions for gestational weight gain (GWG) are effective for normal-weight women but not for obese women. Non-Hispanic blacks and Hispanics have the highest prevalence of obesity, yet most interventions have targeted non-Hispanic whites. The objective of the study was to compare racial/ethnic differences in health behaviors in low-income pregnant obese and nonobese minorities.

Methods: A face-to-face 75-item survey was administered to 94 women (46% nonobese, 54% obese; 71% blacks, 29% Hispanics) at a prenatal visit to an inner-city clinic. Television-watching, exercise, and nutrition were compared between obese and nonobese women, and racial/ethnic differences were compared within each body-mass index (BMI) category using X² and Fisher's exact tests. We tested for interactions between BMI category and race/ethnicity for each health behavior.

Results: More obese women described their nutrition as "fair" or "poor" ($P = .02$) and missed more meals per day ($P = .03$) compared to nonobese women. Obese blacks were less likely to improve their nutrition during pregnancy compared to obese Hispanics. Nonobese blacks watched more television ($P = .03$) and exercised less during pregnancy ($P = .04$) than nonobese Hispanics. Except for dairy products, there were no differences in nutrition (fruit, soda, vegetables, chips)

among the BMI categories and racial/ethnic groups; however, less than 50% of all participants consumed fruits and vegetables every day. There was an interaction between BMI category and race/ethnicity: obese Hispanics exercised less before pregnancy ($P = .02$) but exercised more during pregnancy ($P = .01$) compared to nonobese Hispanics.

Conclusions: Interventions for GWG in obese women may have greater success if they considered racial/ethnic differences in health behaviors, especially related to exercise.

P-21: A Screen for Regulatory MicroRNAs Reveals a Potential Role for miR34a in Regulating Hepatic Drug Metabolism

Vishal Lamba (presenting author) and Yogita Ghodke

Department of Experimental and Clinical Pharmacology, University of Minnesota

Background and Objective: Hepatic drug metabolizing enzymes (DMEs), such as cytochrome P450A4, are highly variable in expression between individuals and show differential expression between sexes, often leading to either reduced efficacy or drug-related toxicity. Very little is known about the factors underlying this variation. MicroRNAs have been suggested to play an important role in regulation of hepatic DMEs, but a systematic screen for microRNAs that regulate the expression of hepatic DMEs and their upstream transcription factors is lacking. The objective of the study was to identify and evaluate the potential role of microRNAs in regulating expression of hepatic DME genes.

Methods: We screened the Targetscan database for predicted microRNAs binding sites in selected hepatic DMEs and transcription factors. Expression profiling was performed for candidate microRNAs and their target genes using Taqman-based real-time PCR quantitation in 48 human liver samples (24 female, 24 male).

Results: The expression of hepatic miR34a demonstrated significant negative correlation with expression of hepatic transcription factors (NR1I2 and HNF4a) and DMEs (CYP3A4, CYP2C19). Additionally, miR34a expression was significantly higher in males than in females; this result is in alignment with higher CYP3A4 in females than males.

Conclusions: Our preliminary results suggest that hepatic miR34a, which showed gender differences in its expression, may play a role in regulating the expression of hepatic transcription factors and DMEs. As miR34a is a tumor suppressor that is aberrantly expressed in several human cancers, dysregulation of miR34a may result in altered DME levels in these cancers.

P-22: The Effects of Narrative Transportation on Energy Intake and Expenditure During Screen Time: Gender Differences

Elizabeth J. Lyons

Institute for Translational Sciences, University of Texas Medical Branch

Background and Objective: Immersion in a story during screen time is positively associated with energy intake, likely due to distraction from satiety cues. In a study of snacking during screen time, energy intake was higher in men than in women, and higher during TV watching than during active gaming. The purpose of this secondary analysis was to investigate gender differences in narrative transportation, or the feeling of being immersed in a story, and to investigate possible effects of transportation on eating behavior.

Methods: Participants (N=120, 60 F, 24.1±4.4 years old, 24.3±4.1 kg/m² BMI) were randomized to watch TV, play sedentary video games, or play active video games for one hour while snack foods were available. Participants could choose their preferred shows/games from a wide variety of options. Narrative transportation was measured at the conclusion of the play period.

Results: Median (interquartile range) narrative transportation was significantly higher in men (44.1 [13.5]) compared with women (36.5 [12.13]; $P = .002$) and in TV (44.8 [11.8]) compared with gaming (37.8 [11.8] and 36.3 [13.6]; $P = .002$). Narrative transportation was associated with energy intake ($\rho = .205$, $P = .025$).

Conclusions: Men and those who watched TV were more immersed in the stories presented, and that narrative transportation was

associated with greater energy intake. Further study is needed to investigate why women were less narratively immersed than men, even when able to choose their preferred content. These results may have implications for preventing weight gain.

P-23: Association of Air Pollution Exposures and Risk of Endometriosis in the Nurses' Health Study II: A Prospective Study

Shruthi Mahalingaiah (presenting author),¹ Jaime E. Hart,² Francine Laden,^{2,3,4} and Stacey Missmer^{2,3}

¹Department of OB/GYN, Boston Medical Center, Boston University;

²Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School; ³Department of Epidemiology, ⁴Department of Environmental Health, Harvard School of Public Health

Background and Objective: Particulate matter and proximity to large roadways may promote disease mechanisms, including systemic inflammation, hormonal manipulation, and vascular proliferation, that underlie the development and severity of endometriosis. The objective of this study is to determine the association of air pollution exposures, including distance to road, particulate matter less than 10 microns (PM₁₀) and less than 2.5 microns (PM_{2.5}), and timing of exposure with risk of endometriosis in the Nurses' Health Study II.

Methods: Proximity to major roadways and outdoor levels of PM₁₀ and PM_{2.5} were determined for all residential addresses at all questionnaire time points. Multivariable-adjusted time-varying Cox proportional hazard models were used to estimate the relation between specific air pollution exposures and endometriosis risk.

Results: A total of 82,831 women were available for analysis, and 2,284 incident cases of surgically confirmed endometriosis were identified over 699,354 person-years of follow-up. No statistically significant associations were observed between distance to road, exposures to particulate matter at various time points (24 months, 48 months, and cumulative exposure) and endometriosis risk.

Conclusions: Traffic and air pollution exposures were not associated with incident endometriosis risk in this group of women.

P-24: Association of In Utero Exposure to Diethylstilbestrol and Risk of Uterine Leiomyomata in the Nurses' Health Study II: A Prospective Study

Shruthi Mahalingaiah (presenting author),¹ Jaime E. Hart,² Lauren Wise,³ Janet Rich-Edwards,^{4,5} Francine Grodstein,² Kathryn Terry,⁶ Renee Boynton-Jarrett,⁷ Karin Michels,⁶ and Stacey Missmer^{2,8,9}

¹Department of OB/GYN, Boston Medical Center, Boston University;

²Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School; ³Department of Epidemiology, Boston University School of Public Health; ⁴Department of Epidemiology, Harvard School of Public Health, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital; ⁵Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care; ⁶Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School; ⁷Division of General Pediatrics, Boston University School of Medicine; ⁸Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School; and ⁹Department of Epidemiology, Harvard School of Public Health

Background and Objective: Risk factors for uterine leiomyomata (UL) have been evaluated, including lifestyle, diet, anthropometric, hormonal, and genetic factors. Exposure to diethylstilbestrol (DES) has been previously evaluated with inconsistent results. A preliminary evaluation of DES exposure and UL incidence from 1989 to 1999 was performed in the Nurses' Health Study II, concluding no association. We re-evaluated the association of UL and DES with follow-up through 2007. Objective is to examine the associations of in utero DES exposure and incidence of uterine leiomyomata.

Methods: On the 1993 Nurses' Health Study II questionnaire, women were asked about their mothers' use of DES. All women who responded affirmatively were mailed a supplementary follow-up questionnaire to obtain additional information, including trimester of

initiation, duration of use, and their certainty of exposure. We excluded from analysis women who were unsure of exposure and those with a diagnosis of UL, cancer, or hysterectomy prior to 1993, leaving 102,165 premenopausal women available for analysis. Cases of ultrasound- or hysterectomy-confirmed UL were reported on biennial questionnaires starting in 1993 onward. Multivariable-adjusted time-varying Cox proportional hazard models were used to estimate the relation between DES exposure and UL risk. All models were adjusted for age, calendar time, race, current body mass index (BMI), smoking status, parity, oral contraceptive use, age at menarche, age at first and last birth, time since last birth, total months of exclusive breastfeeding, and antihypertensive medication use.

Results: During 1,226,269 person-years of follow-up, there were 20,609 incident cases of UL. Women exposed to DES in utero were at a higher risk of incident UL compared with the unexposed, with a multivariable-adjusted hazard ratio (HR) of 1.14 (95% CI: 1.00–1.30). When trimester of initiation was considered, risk was strongest for initiation in the first trimester, adjusted HR = 1.24 (95% CI: 1.04–1.48).

Conclusions: Similar to recent studies, these results suggest that in utero DES exposure is associated with an increased risk of UL. The association is strongest with initiation in the first trimester, corresponding to early stages of fetal müllerian tract development.

P-25: Circulating Endothelial Progenitor Cells and Low Density Granulocytes in Lupus Pregnancies Versus Control Pregnancies

Wendy Marder (presenting author),¹ Sri Yalavarthi,¹ Martha A. Ganser,¹ Emily C. Somers,^{1,2} W.J. McCune,¹ and Mariana J. Kaplan¹

¹Division of Rheumatology, Department of Internal Medicine, University of Michigan; ²Department of Environmental Health Sciences, University of Michigan School of Public Health

Background and Objective: Circulating endothelial progenitor cells (EPC) are decreased in systemic lupus erythematosus (SLE). SLE pregnancies are associated with increased complications, including preeclampsia. A proposed mechanism may involve increased numbers of low density granulocytes (LDG), a novel type of lupus neutrophil that is cytotoxic to EPCs and correlates with SLE disease activity. Our objective was to characterize vasculopathy of lupus pregnancy by examining LDG and EPC levels.

Methods: Serum from pregnant SLE and pregnant healthy women was obtained during second and third trimesters. For lupus patients, the SLE disease activity index (SLEDAI) was calculated. Cells were separated on Ficoll and peripheral blood mononuclear cells stained for EPCs and LDGs. EPCs were identified in lymphocyte population as CD34+ /CD133+ in the CD3-/CD79b-/CD56_ gate. LDGs were identified as CD10+ /CD15 high. Nonparametric statistics were used to compare LDG and EPC levels between groups.

Results: Thirteen SLE and 14 control pregnancies were analyzed. Nineteen were Caucasian, 4 Black, 1 Hispanic, 1 South Asian, and 2 Unknown. Median age was 30.8 [Interquartile range (IQR) 26.8–35.0]. Median LDGs for second trimester SLE patients were 0.29174 cells/mL blood [IQR 0.1984125–0.3676923] and 0.7658951 [IQR 0.1390356–1.006505] for healthy controls ($P=NS$). Median EPCs for second trimester SLE patients were 83.5 [IQR 11.885–315.47] and 114.2 [IQR 75.9–269.3] for healthy controls ($P=NS$). Third trimester values were similar. SLEDAI did not correlate with LDGs or EPCs.

Conclusions: This pilot study did not detect differences between SLE and normal pregnancies in numbers of EPCs or LDGs, although statistical power may be limited due to sample size at this point.

P-26: Change in Estradiol and Oxytocin During Couples' Interactions: Effects of Sex, Posttraumatic Stress Disorder, and Partner Behavior

Amy D. Marshall (presenting author)

Department of Psychology, Pennsylvania State University

Background and Objective: Posttraumatic stress disorder (PTSD) occurs more frequently among women than men, and poor social relations contribute to symptom severity. The neurohormone oxytocin augments the effects of positive social interactions to decrease

stress. Estrogens also contribute to the stress response and modulate oxytocin release. Sex differences exist such that these effects are stronger among women than men. The objective of the study was to examine whether positive partner behaviors stimulate release of oxytocin and estradiol, particularly among women with severe PTSD.

Methods: Participants were 24 individuals from 12 heterosexual couples in which at least one partner exhibited elevated PTSD symptoms. Participants provided urine samples before and after engaging in a 20-minute video-recorded discussion of a positive aspect of their relationship. Oxytocin and estradiol were assayed from the urine to measure change in these hormones during the interactions. Video recordings were coded for quality of intimate behaviors.

Results: For women with the most severe degree of PTSD symptoms, partner provision of intimacy was associated with greater change in estradiol and oxytocin levels.

Conclusions: Women with PTSD may be particularly sensitive to partner behaviors such that the nature of their relationship may play a significant role in the severity of their PTSD. If these results are replicated, they support the use of couples' therapy as a form of treatment for women's PTSD.

P-27: Help-seeking Among Rural Women Exposed to Intimate Partner Violence: What Prompts Use of the Health Care System?

Jennifer S. McCall-Hosenfeld (presenting author)^{1,2} and Amanda N. Perry²

¹Department of Medicine, ²Department of Public Health Sciences, Penn State College of Medicine

Background and Objective: Our previous research showed that IPV exposure in rural communities is common, but rural women are unlikely to access health services for mental health or other IPV-related health problems. The objective of the study was to understand when and how IPV-exposed rural women use health care.

Methods: Adult women receiving services at rural domestic violence shelters participated in focus groups and telephone interviews. The interview guide focused on help-seeking at the time of abuse. Thematic saturation determined the sample size. Transcripts were independently coded using NVivo8. Themes were derived by the investigators.

Results: Women aged 19 to 62 years from 11 rural counties participated in focus groups (n=31) or interviews (n=13). Half had experienced IPV within the last 6 months. The majority (86%) of rural women articulated numerous health problems arising from IPV, notably depression (45%), anxiety (41%), and substance abuse (30%). Despite these health concerns, few (5%) initially sought help from a health care provider. Many reported that they did not do so because they lacked knowledge about IPV and its medical consequences (39%) or because they believed that health care providers were not likely to be helpful (57%). Many (56%) reported fear of abuse disclosure to health care providers and noted that this was an important concern in rural communities, where doctors are likely to also know or treat the abuser.

Conclusions: Overcoming barriers to health care seeking among IPV-exposed rural women requires education regarding the health consequences of IPV, providers who are perceived as interested in addressing IPV, and attention to privacy and confidentiality concerns in rural communities.

P-28: Prospective Study of Police Officer Spouses/Partners: A New Pathway to Secondary Trauma and Relationship Violence?

Susan M. Meffert (presenting author),¹ Clare Henn-Hasse,² Thomas J. Metzler,¹ Suzanne Best,³ Ayelet Hirschfeld,⁴ Shannon McCaslin,¹ Sabra Inslict,¹ Thomas C. Neylan,¹ and Charles R. Marmar¹

¹Department of Psychiatry, University of California, San Francisco;

²Department of Psychiatry, New York University; ³Pacific University;

⁴Veterans Administration Medical Center, San Francisco

Background and Objective: It has been reported that posttraumatic stress disorder (PTSD) is associated with secondary

spouse/partner (S/P) emotional distress and relationship violence. This prospective study examines secondary trauma among S/Ps of police officers.

Methods: Two hypotheses were tested in 71 S/Ps: (1) officer reports of greater PTSD symptoms after 12 months of police service will be associated with greater secondary trauma symptoms among S/Ps; and (2) greater secondary trauma symptoms among S/Ps at 12 months will be associated with S/P reports of greater relationship violence.

Results: Neither of these traditional understandings was replicated.

Conclusions: A novel pathway toward S/P secondary trauma and relationship violence was identified which implicates S/P perception of PTSD.

P-29: Health Disparities Among Women: Examining the Role of Sexism

Lisa Molix (presenting author),¹ Janet B. Ruscher,¹ Alison Blodorn,¹ and Susan T. Fiske²

¹Department of Psychology, Tulane University; and ²Department of Psychology, Princeton University

Background and Objective: Despite considerable progress in recent years, sex and gender disparities in health persist. Indeed, in the United States, the majority of preventable deaths are in women. Some research suggests that experiencing sex-related prejudice is a chronic stressor that influences health. To date, research has primarily focused on hostile sexism. Nevertheless, stereotypes about women tend to be more positive compared to men, with men as well as women attributing highly favorable traits to women. Favorable stereotypes and attitudes can also be a form of prejudice in that they serve to justify and maintain the subordination of women. This form of sexism, referred to as benevolent sexism, is theorized as being complementary to hostile sexism. The primary objective of the present work was to examine the relationship between individual levels of hostile and benevolent sexism toward women and regional health outcomes among women.

Methods: Individual participant data were collected via an online survey and were aggregated with regional data from a variety of public health databases.

Results: In accord with previous research, hostile and benevolent sexism were positively correlated. Hostile and benevolent sexism toward women scores also varied significantly by participant sex, race, and region of residence. Further, levels of sexism toward women were associated with regional health outcomes including obesity, heart disease, and cancer mortality rates.

Conclusion: This initial investigation of the influence of both hostile and benevolent forms of sexism on women's health supports the notion that future research should incorporate broader definitions of sexism.

P-30: Sex Differences in Functional Connectivity Within the Limbic Circuitry Between Cocaine-dependent Men and Women Exposed to the Montreal Imaging Stress Task

Megan M. Moran-Santa Maria (presenting author),¹ Kevin Johnson,² James Pfeiffer,¹ and Kathleen T. Brady¹

¹Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina; and ²Department of Anesthesia, Stanford University

Background and Objective: Cocaine-dependent women are more likely to report negative affect prior to relapse than cocaine-dependent men. Altered functional connectivity within the limbic circuitry has been implicated in disorders of negative affect; however, few studies have directly compared limbic connectivity between cocaine-dependent men and women. The purpose of the study was to compare functional connectivity between limbic brain regions between cocaine-dependent men and women during the stress.

Methods: Blood oxygen level-dependent (BOLD) functional magnetic resonance imaging data were collected from cocaine-dependent subjects (9 men, 7 women) exposed to corticotropin-releasing hormone and the Montreal Imaging Stress Task. A block design of 3 conditions (rest, mental arithmetic, and stressful mental

arithmetic) was utilized. Functional connectivity was assessed by correlating the time course of changes in the BOLD signal between the anterior cingulate cortex and the amygdala (ACC-AMYG). The mean Pearson's correlation coefficients (r) were compared between groups using independent samples t -tests.

Results: During the rest condition, men (left $r=0.241$ and right $r=0.225$) and women (left $r=0.188$ and right $r=0.117$) exhibited similar ACC-AMYG connectivity. During stressful mental arithmetic, men ($r=0.323$) exhibited significantly ($P=.05$) greater connectivity between the left ACC-AMYG than women ($r=0.180$). A similar trend ($P=.07$) was observed between men ($r=0.385$) and women ($r=0.222$) during mental arithmetic. Men ($r=0.341$) exhibited significantly greater connectivity ($P<.05$) between the right ACC-AMYG during mental arithmetic than women ($r=0.01$).

Conclusion: These preliminary findings suggest that cocaine-dependent women exhibit lower functional connectivity between the ACC and the amygdala than cocaine-dependent men during tasks of cognitive and emotional demand.

P-31: Influence of Sex and Disease Severity on Cartilage Thickness in Patients with Knee Osteoarthritis

Melissa M.B. Morrow (presenting author)¹ and Kenton R. Kaufman²

¹Department of Orthopedic Surgery, ²Department of Physiology and Biomedical Engineering, Mayo Clinic

Background and Objective: Women have a higher incidence of knee osteoarthritis (KOA) compared with men, but investigations of disease sexual dimorphism are relatively unexplored. It is unclear how knee cartilage thickness differs between sexes and across OA disease severity in the medial and lateral tibiofemoral (TF) and patellofemoral (PF) compartments. The objective of the study was to characterize differences in cartilage thickness during early and advanced KOA between men and women in all three knee compartments.

Methods: The study cohort consisted of 306 adult subjects (234 women) with KOA. Bilateral knee x-rays were performed. OA radiographic severity was stratified into early (KL grades 1, 2) and advanced (KL grades 3, 4). Minimum cartilage thickness (mm) in each compartment was determined from x-ray. A 2-way analysis of variance was used to test the main effects of sex and severity and their interaction on minimum cartilage thickness. Results were adjusted to age and body mass index (BMI).

Results: There was no difference in disease severity, age, or BMI across sexes. There was a significant decrease in cartilage thickness in advanced OA for both sexes. Significant effects of sex on cartilage thickness existed in the lateral TF and PF compartments but not in the medial TF. Women had a 1-mm decrease in cartilage thickness in the lateral TF and PF compartments compared to men.

Conclusions: Women have decreased cartilage in the lateral TF and PF compartments in early and advanced KOA. Similarity in the medial TF compartment may be related to loading during gait and knee alignment. Further studies into the mechanisms of loading and disease progression are required.

P-32: Transcriptional Control of the Response to Diet in *Drosophila*

Laura P. Musselman (presenting author), Jill L. Fink, and Thomas J. Baranski

Division of Endocrinology, Metabolism, and Lipid Research, Department of Medicine, Washington University School of Medicine

Background and Objective: Women's health can be adversely affected by diet, leading to diseases such as diabetes and cardiovascular disease. Transcriptional mechanisms, in part, control an animal's ability to accommodate changes in the diet. 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. Network analyses revealed many transcriptional control nodes, including several nuclear hormone receptors (NHRs). NHRs are highly conserved transcription factors, some of which are

known to function in metabolic disease in mammals. Our objective was to define the roles of NHRs in nutrient metabolism in the fat body. Mammalian NHR orthologs have been described that regulate adipose or liver biology, but downstream factors are poorly understood. Flies offer a rapid, genetically dissectible system in which to study conserved metabolic pathways in a tissue-specific manner.

Methods: All 18 *Drosophila* NHR ligand binding domains (LBDs) were screened for activity using the GAL4-LBD ligand sensor system. Activity was tested under control or high sugar conditions.

Results: GAL4-LBD studies showed increased activity of several LBDs upon transfer to high-sugar diets. Also selected for further study were those receptors expressed in a diet- or genotype-dependent manner in the fat body. Tissue-specific loss of function revealed specific roles for some NHRs in metabolic homeostasis in this tissue.

Conclusions: Our studies reveal previously undescribed functions for NHRs in the adipose-like fat body of the fly. Future work will test the pathways downstream of these receptors to identify critical biochemical mediators of diabetes-like pathophysiology in this organ.

P-33: IL-17A Protein Expression Is Increased by CD4+ Th17 Differentiated Cells From Females Compared With Males

Dawn C. Newcomb (presenting author),¹ Madison G. Boswell,¹ Kimberly Woodward,¹ Carla M. Sevin,¹ Dan E. Dulek,² Kasia Goleniewska,¹ and R. Stokes Peebles, Jr.¹

¹Department of Medicine, ²Department of Pediatrics, Vanderbilt University Medical Center

Background and Objective: Women have a higher prevalence of severe asthma, multiple sclerosis, and lupus. CD4+ Th17 cells are associated with these diseases. Th17 cells require the transcription factor RORC2 for differentiation and produce IL-17A. Sustaining Th17 cells requires IL-23 signaling through the IL-23 receptor (R). Our objective was to determine whether IL-17A protein expression is increased in Th17 cells from females compared with males.

Method: Naive T cells were isolated from the blood of healthy men and women (aged 18 to 45 years). Naive T cells were also isolated from the spleens of male, female, and ovariectomized BALB/c mice. T cells were activated and differentiated into Th17 cells for 4 days in vitro. IL-17A protein expression was measured by ELISA, and RORC2 and IL-23R mRNA was measured by qPCR.

Results: IL-17A protein expression by Th17 cells was increased in women compared with men ($n=12$ for females, $n=16$ for males, $P<0.05$). RORC2 mRNA expression was similar in Th17 cells from women and men, but IL-23R mRNA expression was increased in women compared with men. In mice, IL-17A protein expression by Th17 cells was significantly increased in female mice compared with male and ovariectomized mice ($n=9$ mice per group, $P<0.05$). IL-23R mRNA expression in Th17 cells was also significantly increased in female mice compared with male and ovariectomized mice.

Conclusions: These data suggest that ovarian hormones enhance IL-17A production and provide a possible explanation for a higher prevalence of Th17-mediated diseases in women compared with men.

P-34: Decreasing Prenatal Alcohol Use: A Randomized Clinical Trial of Motivational Interviewing

Robin L. Osterman (presenting author),¹ Robert T. Ammerman,² Donna Gates,¹ and John Schafer¹

¹College of Nursing, University of Cincinnati; ²College of Medicine, University of Cincinnati and Cincinnati Children's Hospital Medical Center

Background and Objective: Fetal Alcohol Spectrum Disorders (FASD) are the consequence of intrauterine alcohol exposure affecting 2% to 5% of live births in the United States. Theory-based interventions that decrease prenatal alcohol use are essential to preventing FASD. Motivational interviewing (MI) is a method that strengthens a person's motivation for behavior change. This study determined the effectiveness of MI to decrease prenatal alcohol use and examined mechanisms of behavior change based on self-determination theory, such as basic psychological needs satisfaction.

Method: Women attending a prenatal visit (n=185; 66% African American, mean age 25.4, mean weeks gestation 24.3) completed the AUDIT and quantity/frequency measures of alcohol use. Those who reported any drinking in the previous year completed the Basic Psychological Needs Scale (BPNS) and other measures. Women were randomized to an MI or comparison group (n=122), with both groups completing 30-day follow-ups.

Results: Generalized estimating equations analysis showed significant main effects of MI on total BPNS and dichotomized AUDIT scores. Exact nonparametric testing showed greater between-group increases in BPNS scores for the intervention group (mean baseline BPNS score=5.64/follow-up=6.11) versus the comparison group (5.52/5.83, respectively) ($P=.021$). While no between-group differences in drinking behaviors were found, both groups demonstrated significant within-group decreases in AUDIT scores ($P=.000$), with only the intervention group demonstrating significant decreases in quantity of alcohol use ($P=.031$).

Conclusions: In the prevention of FASD, preliminary findings demonstrated MI's effectiveness in decreasing alcohol use and increasing basic psychological need satisfaction in pregnant women.

P-35: What Midlife Women Want From Their Gynecologist: A Survey of Patients in Specialty and Private Practices

Beth A. Prairie (presenting author),¹ Marcia Klein-Patel,¹ MinJae Lee,¹ Katherine L. Wisner,^{2,3,4} and Judith L. Balk¹

¹Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh School of Medicine; ²Department of Epidemiology, University of Pittsburgh; ³Department of Psychiatry, University of Pittsburgh; ⁴Women's Behavioral HealthCARE, Western Psychiatric Institute and Clinic, University of Pittsburgh

Background and Objective: Community-based cohort studies demonstrate that the majority of midlife women experience vasomotor symptoms but only a subset experience a broad range of additional symptoms attributed to menopause, including mood changes, sleep, and sexual problems. Women presenting to academic menopause centers likely represent a self-selected subset experiencing this broad range of non-vasomotor symptoms. Our objective was to characterize the reason for a single gynecology visit among midlife women in an academic menopause clinic compared to urban and suburban private practices. We hypothesize that women seeking subspecialty care will report more non-vasomotor concerns.

Method: Women aged 40 to 60 were surveyed using self-administered waiting room questionnaires at 3 sites: an urban academic midlife center (MLHC) and urban (A) and suburban (B) locations of a generalist practice. Women weighted the reason for their visit as "very much," "somewhat," or "not at all" for 15 common gynecologic and menopausal complaints. Comparisons between groups were made using parametric and nonparametric tests as appropriate.

Results: Women presenting to the MLHC were significantly younger and more likely to present for vasomotor symptoms, moodiness, sexual problems, sleep problems, and to learn more about menopause, and less likely to present for annual exams. Site A had significantly more African American women. The groups did not differ in educational attainment or ability to pay for basics, or in visits for vaginal discharge, breast problems, or irregular periods.

Conclusions: Women seeking care in a menopause subspecialty center had significantly more vasomotor and non-vasomotor complaints than those seeing general gynecologists, representing a distinct subset of the midlife population.

P-36: Cardiovascular Risk Factors of the Intravascular Compartment Associate With White Matter Hyperintensity Progression in Postmenopausal Women

Limor Raz (presenting author),¹ Muthuvel Jayachandran,¹ Nirubol Tosakulwong,² Timothy Lesnick,² Samantha Wille,³ Matthew Murphy,³ Matthew Senjem,⁴ Prashanthi Vemuri,³ Clifford Jack,⁵ Virginia M. Miller,⁶ and Kejal Kantarci⁷

¹Department of Physiology and Biomedical Engineering, ²Department of Biomedical Statistics and Informatics, ³Center for Advanced Imaging Research, ⁴Department of Information Technology, ⁵Department of

Diagnostic Radiology, ⁶Departments of Surgery, Physiology and Biophysics, and ⁷Department of Neuroradiology, Mayo Clinic

Background and Objective: White matter hyperintensities (WMH) on brain MRI are associated with cardiovascular (CV) risk factors in the elderly, but this relationship is not established in younger populations. Our objective was to investigate the relationship between conventional CV risk factors and thrombogenic platelet microvesicles (MV) of the intravascular compartment with WMH load and progression in recently menopausal women.

Method: Women (n=101) enrolled in the Kronos Early Estrogen Prevention Study at Mayo Clinic underwent MRI at baseline, 36, and 48 months post-randomization to hormone treatments. Conventional CV risk factors, carotid intima-medial thickness, coronary arterial calcification, and factors of the intravascular compartment were measured at baseline. WMH volumes were calculated using a semi-automated segmentation algorithm based on Fluid Attenuated Inversion Recovery (FLAIR) MRI. Correlations of these parameters with baseline WMH and longitudinal change in WMH were adjusted for age, months past menopause, APOE $\epsilon 4$ status, and treatment group in linear regression analysis.

Results: At baseline, WMH were present in all women; median (interquartile range) volume was 1,909 (1,537, 2,655) mm³. WMH volume increased by 122.1 (-164.3, 539.5) mm³ at 36 months and 155.4 (-92.13, 599.4) mm³ at 48 months. These increases correlated with numbers of platelet-derived and total thrombogenic MV at baseline ($P=.04$).

Conclusions: Associations of baseline platelet-derived, thrombogenic MV within the vascular compartment and increases in WMH suggest that platelet activation may contribute to the cascade of events leading to development of WMH in recently postmenopausal women.

P-37: Improving Sexually Transmitted Infection Results Notification in a Pediatric Emergency Department

Jennifer L. Reed (presenting author),¹ Jill S. Huppert,² Gordon Gillespie,³ Regina Taylor,¹ Jessica Kahn,⁴ and Evaline Alessandrini^{1,5}

¹Division of Emergency Medicine, ²Division of Adolescent Gynecology, Cincinnati Children's Hospital Medical Center; ³College of Nursing, University of Cincinnati; ⁴Division of Adolescent Medicine, and ⁵Anderson Center for Quality Health Care, Cincinnati Children's Hospital Medical Center

Background and Objective: Inadequate communication of positive sexually transmitted infection (STI) results to emergency department (ED) patients is a significant barrier to STI treatment. Our objective was to improve notification of female adolescent ED patients regarding positive STI tests (gonorrhea, chlamydia, and/or trichomoniasis) using mobile phone texting technology.

Methods: A randomized intervention study among 14- to 21-year-olds (n=319) using a 2x3 factorial design to evaluate the effectiveness of 6 combinations of 2 factors on the proportion of STI-positive females contacted within 7 days of testing. The factors include method of patient notification (call, text message, or both) and provision of an STI information card with or without an ED phone number to obtain results. Covariates in a logistic regression model included age, presumptive STI treatment, and documentation of a confidential phone number.

Results: The odds of successful contact were significantly greater using both a call and a text message as compared with calling alone (OR 2.4 [95% CI, 1.02, 5.66]). Texting alone or the type of STI information card distributed to patients was not significantly related to patient notification rates. Documenting a confidential phone number (OR 3.6 [95% CI, 1.68, 7.93]) was independently associated with successful notification; 94% of those with a documented confidential phone number who received both a call and a text message were successfully contacted.

Conclusions: Using a combination of a phone call and text messaging improved contact for STI-positive ED adolescents. Documentation of a confidential phone number is also important for reaching ED patients with positive STI results.

P-38: Oxytocin Differentially Decreased 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: Notable sex differences exist in methamphetamine (meth) addiction patterns; however, meth effects and potential therapeutic treatments are typically only studied in males. Our objective was to determine whether oxytocin could be an effective pharmacotherapeutic agent for meth addiction. To provide a comprehensive assessment, we determined whether oxytocin was effective at reducing meth seeking in both males and freely cycling females.

Methods: We used a drug self-administration and relapse model to determine oxytocin's impact on meth seeking. Rats self-administered meth or sucrose pellets. Following stable daily intake, lever responding was extinguished and rats underwent a series of conditioned cue, meth-primed, and yohimbine-primed reinstatement tests with oxytocin (1 mg/kg) or saline administered 30 minutes before each test in a counterbalanced order.

Results: Females reinstated more than males to meth-conditioned cues, and oxytocin decreased responding in females only. Females had greater meth-primed reinstatement, and oxytocin decreased meth seeking in both sexes. Oxytocin decreased yohimbine-induced reinstatement in both males and females. Females reinstated more than males to sucrose-conditioned cues, and oxytocin decreased this responding in females only. Oxytocin decreased sucrose-primed reinstatement in both sexes but was ineffective on yohimbine-induced reinstatement of sucrose seeking.

Conclusions: Oxytocin differentially attenuated meth and sucrose seeking in males and females. The primary difference was oxytocin's ability to reduce responding in the presence of conditioned cues in females only. These findings indicate sex-specific effects of oxytocin on conditioned drug and natural rewards. These data suggest that oxytocin may be a potential treatment for prevention of relapse in meth addiction for males and females.

P-39: Gender Differences in Blood Pressure Control Among Older Adults: Findings From the Cohort Study of Medication Adherence in Older Adults

Lovie Lewis Rodgers (presenting author),¹ Elizabeth Holt,² and Marie Krousel-Wood^{2,3}

¹College of Pharmacy, Xavier University of Louisiana; ²Center for Health Research, Ochsner Clinic Foundation; ³Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine

Background and Objective: Previous studies indicate that gender disparities exist in blood pressure control among hypertensive adults. The purpose of this study is to determine if there are gender differences in blood pressure control in a sample of older adults with hypertension and to explore factors contributing to these differences.

Methods: A cross-sectional analysis of baseline data from the Cohort Study of Medication Adherence in Older Adults (CoSMO) treated for hypertension was conducted. Data for socio-demographic and clinical characteristics were obtained from patient surveys. Blood pressure measures were obtained from outpatient medical records. Antihypertensive medications filled and comorbid conditions were obtained from administration database utilization. Three categories of blood pressure control were assessed: SBP < 120 and DBP < 80, SBP 120 to 139 or DBP 80 to 89, and SBP ≥ 140 or DBP ≥ 90. Blood pressure control rates were compared between genders.

Results: The mean age of 1,957 participants was 75.0 ± 5.6; 30.5% were African American and 58.7% were women. Female gender was consistently associated with higher blood pressure levels. After adjustment for socio-demographic characteristics, women had a 1.94 (95% CI 1.31, 2.89) higher odds of SBP ≥ 140 or DBP ≥ 90 than men. Gender differences in blood pressure control remained significant even after additional adjustment for clinical characteristics, the number and type of antihypertensive medication filled, and self-reported adherence to antihypertensive medications.

Conclusions: Gender disparities exist in blood pressure control for older adults with hypertension. Further research to identify gender-specific determinants of blood pressure control is needed.

P-40: The Association of NMDA Receptor Antibodies and Neurocognitive Dysfunction in Pediatric Lupus Patients and in the Offspring of Adult Patients With Lupus

Natasha M. Ruth (presenting author), Mary C. Kral, Stephanie Slan, Tamara K. Nowling, Murray H. Passo, and Gary S. Gilkeson

Division of Pediatric Rheumatology, Medical University of South Carolina

Background and Objective: Central nervous system (CNS) disease is second only to nephritis as a cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). Anti-NMDA receptor antibodies are anti-double-stranded DNA antibodies that cross-react with the NMDA receptors NR2a and NR2b. The activation of the NMDA receptor is critical in learning and memory and is expressed on neurons throughout the hippocampus and cortex. Our objective was to measure the prevalence of anti-NR2 glutamate receptor antibodies in patients with childhood onset SLE and juvenile idiopathic arthritis (JIA), and to assess the association between elevated anti-NMDA-NR2 subunit receptor antibodies and neurocognitive dysfunction in pediatric patients with SLE and patients with JIA.

Methods: Patients diagnosed with SLE prior to age 18 were recruited along with a JIA control patient. Each patient underwent neurocognitive testing, assessing a range of cognitive domains and NMDA receptor-NR-2 subunit antibody testing.

Results: T-test comparison of lupus cohort to JIA cohort revealed that there were group differences for Full Scale IQ ($P = .007$), single word reading skills ($P = .013$), and math calculation skills ($P = .039$). JIA patients performed better in these areas than did SLE patients. SLE patients also had higher NMDA receptor antibody levels and NMDA receptor antibodies correlated significantly ($P = .005$) with reaction time.

Conclusions: Findings suggest that pediatric patients with SLE had greater cognitive dysfunction than JIA patients and also had higher NMDA receptor antibody levels than did JIA controls. Higher antibody levels correlated with reaction time. These preliminary results suggest that NMDA receptor antibody levels may be helpful in patients where there is concern for CNS lupus.

P-41: Developmental Programming of Fetal Loss in Adult Female Common Marmosets (*Callithrix jacchus*)

Julienne Rutherford (presenting author),¹ Corinna Ross,² and Suzette Tardif²

¹Department of Oral Biology, University of Illinois at Chicago;

²Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio

Background and Objective: The impact of a female's fetal development on her later reproductive function is largely unknown. The marmoset monkey provides a unique opportunity to study how the prenatal environment affects later fertility. Female common marmoset monkeys (*Callithrix jacchus*) produce litters of variable size and birthweight. Marmoset triplets are a useful clinical translational model of a growth-restricted human fetus, because they experience a nutritionally-restricted prenatal environment compared with twins. Our objective was to assess whether a marmoset female's birthweight and litter size at birth contributes to her adult fertility as measured by fetal loss.

Methods: The effect of litter size on fetal loss was examined in 56 adult female marmosets (Southwest National Primate Research Center). Differences in loss rates between twins ($n = 29$) and triplets ($n = 27$) were measured using *t*-tests. Linear regression was used to determine the extent to which litter size predicted fetal loss even after accounting for the lower birthweight of triplets.

Results: Triplet females lost 3 times more fetuses than did twins (38% vs. 13%, $P = .0007$) across all categories of birthweight. Litter size

explained 18% of the variance in total loss rate, whereas birthweight explained only 7%.

Conclusions: The high rate of fetal loss in triplet marmoset females may result from disruption of the growth and development of the reproductive system, a process that is seemingly decoupled from prenatal growth as reflected by birthweight. Using this primate model, we find support for our view that fetal loss in women stems from their own adverse prenatal environments.

P-42: A Nanomedicine Approach for Fetal Digoxin Therapy

Erik Rytting (presenting author)¹ and Norah Al-Bekairi²

¹Department of Obstetrics and Gynecology, ²Department of Pharmacology and Toxicology, University of Texas Medical Branch

Background and Objective: Fetal arrhythmias complicate 1% to 2% of all pregnancies and may lead to serious consequences such as hydrops fetalis. Current practices for transplacental digoxin therapy may result in a number of adverse side effects for the pregnant mother. The purpose of this study was to test the rationale for a nanoparticle-based approach to improve fetal digoxin therapy and reduce maternal side effects. This involved the preparation of digoxin-loaded nanoparticles using biocompatible polymers, validation of an HPLC analytical method to determine drug encapsulation efficiency, and optimization of process parameters to maximize drug loading.

Methods: Nanoparticles were prepared using the modified solvent displacement technique. Due to the limited solubility of digoxin in acetone, the solvent dissolving the polymer (PEGylated poly(lactic-co-glycolic acid)) and drug was changed to tetrahydrofuran. Particle size and polydispersity index were measured by photon correlation spectroscopy; zeta potential was determined using laser Doppler velocimetry. HPLC was used to quantify both tetrahydrofuran evaporation as well as nanoparticle drug loading.

Results: Complete evaporation of tetrahydrofuran resulted in aqueous nanoparticle suspensions. Digoxin-loaded nanoparticles ranged in size from 64 to 131 nm, with polydispersity indices between 0.16 and 0.25, and negative zeta potential values. The selected HPLC parameters resulted in no overlap of chromatographic peaks for digoxin and nanoparticle excipients. Encapsulation efficiency ranged from 87.2% to > 99.9%.

Conclusions: The successful encapsulation of digoxin in biocompatible nanoparticles—together with our lab's previous work demonstrating the transplacental transport of fluorescently-labeled polymeric nanoparticles in vitro—demonstrates the feasibility of a nanomedicine approach for fetal digoxin therapy.

P-43: Dysmenorrhea in Women With Crohn's Disease: A Case-Control Study

Sumona Saha (presenting author),¹ Emilie Midtling,¹ Erica Roberson,² Veena A. Nair,³ Arnold Wald,¹ and Mark Reichelderfer¹

¹Department of Medicine, Gastroenterology and Hepatology, University of Wisconsin School of Medicine and Public Health; ²Department of Medicine, Gastroenterology, Oregon Health and Sciences University; ³Department of Radiology, University of Wisconsin School of Medicine and Public Health

Background and Objective: Dysmenorrhea and Crohn's disease (CD) have overlapping symptoms; however, their relationship is poorly understood. The objectives of this study were to examine: (1) the impact of dysmenorrhea on pain severity and pain medication use in CD and (2) the relationships between dysmenorrhea, CD activity, and health-related quality of life (HRQOL).

Methods: This was a case-control study of menstruating women with and without CD. Subjects were assessed for dysmenorrhea, pain severity, medication use, menstrual distress, and HRQOL. CD activity scores were calculated. The correlation between menstrual distress and CD activity was assessed. Linear regression analysis was performed to determine the effects of dysmenorrhea and CD on pain severity.

Results: The study had 110 subjects; 40% of cases had dysmenorrhea. Dysmenorrhea was associated with higher pain scores among cases. Compared with controls, cases with dysmenorrhea reported

similar pain severity but lower nonsteroidal anti-inflammatory drug (NSAID) use. After adjusting for medication use, cases had significantly greater distress due to menstrual pain. CD activity scores were not higher in women with dysmenorrhea; however, menstrual distress scores correlated positively with disease activity. HRQOL was significantly lower in cases with dysmenorrhea by some measures.

Conclusions: Dysmenorrhea is common in women with CD and has an additive effect on overall pain severity. It is not, however, associated with greater NSAID use. Menstrual distress is positively correlated with CD activity scores and associated with lower HRQOL by some measures. Treatment of dysmenorrhea may improve the perception of CD activity and HRQOL in women with CD.

P-44: Is There a Role for Ovarian Stromal Tissue Remodeling Leading to Precocious Ovarian Aging Subsequent to Doxorubicin-Induced Chemotoxicity?

Sana M. Salih (presenting author),¹ Elon C. Roti Roti,¹ Karris Tilbury,² Scott Leisman,¹ Paul Campagnola,² and David H. Abbott³

¹Department of Obstetrics and Gynecology, ²Department of Biomedical Engineering, ³Wisconsin National Primate Research Center, University of Wisconsin

Background and Objective: Doxorubicin (DXR) chemotherapy provokes precocious primordial follicle (PF) depletion leading to premature ovarian aging (POA) and infertility in cancer survivors. Mechanisms underlying such accelerated DXR-induced POA are not known. Using a mouse model, we show that DXR is initially sequestered in the central core of ovarian stromal tissue and then gradually diffuses to the follicles (Roti Roti and Salih, *Biology of Reproduction*, 2012; Roti Roti et al., *PLoS One*, 2012). DXR causes extensive loss of ovarian stroma within 48 hours. Stromal cell DNA double strand breaks (DSBs) precede granulosa cell DNA damage in DXR-treated mouse ovaries contributing to 50% ovarian weight loss (Roti Roti et al., 2012; Ben-Aharon et al., *Reproductive Biology and Endocrinology: RB&E*, 2010). We hypothesize that DXR-induced stromal cell loss results in extracellular matrix (ECM) remodeling of surviving stroma cells and leads to POA. Here, we investigate DXR-induced ovarian stromal toxicity and remodeling.

Methods: TUNEL assay was used to assess DXR-induced DNA DSBs in in vivo-treated murine ovaries. We used second-harmonic generation (SHG) microscopy to image collagen fibers in formalin-fixed control and DXR-treated mice ovaries.

Results: TUNEL assay showed that unlike granulosa cells, apoptosis was not detected in stroma cells despite appreciable stroma cell loss. Qualitative image analysis of SHG images showed that the collagen in the control mouse seems to be more abundant and less organized than DXR-treated mice; at 4 weeks, 10 mg/kg DXR-treated mice had less dense collagen than 5 mg/kg DXR and control mice.

Conclusions: DXR causes early and extensive ovarian stroma loss in murine ovaries. Ovarian stroma surviving DXR-induced toxicity display profound ECM remodeling. The role of ECM remodeling in DXR-induced accelerated ovarian aging warrants further investigation.

P-45: Estradiol Protects Gut Mucosa by Reducing HIV Infection Associated Barrier Dysfunction

Sumathi Sankaran (presenting author),¹ Katie Coolidge, Michael George,¹ Irina Grishina,¹ Larissa Goulart,¹ Mary K. Miller,² Jason Flamm,⁴ Thomas J. Prindiville,³ and Satya Dandekar¹

¹Department of Medical Microbiology and Immunology, University of California, Davis; ²Department of Obstetrics and Gynecology, ³Department of Internal Medicine, University of California, Davis, School of Medicine; ⁴Kaiser Permanente Medical Group

Background and Objective: Human Immunodeficiency Virus (HIV) infection is one of the leading causes of death in women in Africa. HIV disease progression correlates with immune activation, which is higher in women compared with men, in the blood and gut. Compromised mucosal integrity allows for increased microbial translocation in women, which stimulates systemic immune activation. Estradiol improves epithelial integrity, but its effects during HIV

infection are unknown. The objective of the study is to determine if low levels of exogenous estradiol protect mucosal integrity during HIV infection in an in-vitro model.

Methods: Epithelial cells, grown in a monolayer, were treated with 17 β Estradiol (β E2). The monolayer was exposed to lymphocyte cell lines infected with SIV (simian equivalent of HIV). Epithelial integrity and tight junction protein expression were analyzed.

Results: Epithelial cells grown in the presence of β E2 had increased proliferation (up to 40% higher) in a dose-dependent manner. Cells grown in the presence of SIV had a decrease in proliferation of > 50%, which was abrogated in the presence of β E2. Epithelial integrity measured by the transepithelial resistance (TER) also decreased by 25% in the presence of SIV infection; however, low basal levels of exogenous β E2 restored the TER. Increase in TER was associated with increased expression of the tight junction protein, ZO1.

Conclusions: These preliminary data suggest that low levels of β E2 may help overcome the HIV-associated decline in epithelial integrity in women. Studies investigating sex differences during treatment for HIV infection should focus on the role of hormones in the maintenance of mucosal integrity and health.

P-46: Selected Vitamin D Metabolic Gene Variants and Risk for Autism Spectrum Disorders in the CHARGE Study

Rebecca J. Schmidt (presenting author),^{1,2} Robin L. Hansen,^{2,3} Jaana Hartiala,⁵ Hooman Allayee,⁵ Linda C. Schmidt,⁴ Flora Tassone,^{2,4} and Irva Hertz-Picciotto^{1,2}

¹Department of Public Health Services, ²Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, ³Department of Pediatrics, University of California, Davis, School of Medicine; ⁴Department of Biochemistry and Molecular Medicine, University of California, Davis; ⁵Department of Preventive Medicine and Institute for Genetic Medicine, Keck School of Medicine, University of Southern California

Background and Objective: Causes of autism are unclear, though genetic contributions are well accepted. Vitamin D is essential for neurodevelopment. The objective of the study is to examine for the first time associations between autism spectrum disorder (ASD) and common, functional polymorphisms involved in vitamin D uptake and metabolism.

Methods: Children aged 24 to 60 months enrolled from 2003 to 2009 in the population-based CHARGE case-control study were evaluated clinically and confirmed to have ASD (n=474), or typical development (TD, n=281). Maternal, paternal, and child DNA samples for 384 (81%) families of children with ASD and 234 (83%) families of TD children were genotyped for *TaqI*, *BsmI*, *FokI*, and *Cdx2* in the vitamin D receptor (*VDR*) gene and *CYP27B1* rs4646536, *VBP* rs4588, and *CYP2R1* rs10741657. Case-control logistic regression analyses, family-based log-linear analyses, and hybrid log-linear analyses were conducted to produce risk estimates and 95% confidence intervals (CI).

Results: Homozygous variant genotypes in paternal *VDR* (*TaqI* and *BsmI*) and *CYP27B1* genes were significantly associated with ASD in the case-control analysis (odds ratio (OR)=6.3, CI: 1.9–20.7; OR=4.7, CI: 1.6–13.4; and OR=2.2, CI: 1.0–4.9, respectively). Log-linear analyses detected parental imprinting effects for several *VDR* gene variants, and paternal *VDR FokI* and *Cdx2* homozygous genotypes were associated with ASD in the child; paternal *VDR Cdx2* was also associated with ASD in the hybrid analysis. A significant association between decreased risk for ASD and child *CYP2R1* homozygous variant genotype was also found in hybrid log-linear analysis.

Conclusion: This study provides preliminary evidence that paternal and child vitamin D metabolism might play a role in the etiology of ASD.

P-47: Clinical Characteristics Associated With the Use of Opioid Analgesics in Pregnancy

Megan V. Smith (presenting author), Nathan Gotman, and Kimberly A. Yonkers

Department of Psychiatry, Yale School of Medicine

Background and Objective: Use of opioid analgesics for chronic noncancer pain has increased considerably among women in the United States in recent years. However, prior research has not determined the extent of prescription opioid use and its associated characteristics among pregnant women. The objective of the study was to examine characteristics associated with the use of opioids in pregnancy.

Methods: Data were derived from a prospective cohort study of pregnant women. Participants were administered the Composite International Diagnostic Interview to identify depressive and anxiety disorders. Data on medication use were gathered at 3 assessment points. Participants included 2,654 English- or Spanish-speaking pregnant women who had a singleton live birth.

Results: Six percent (n=161) used opioid analgesics at any point in pregnancy. More women using opioids met diagnostic criteria in pregnancy for major depressive disorder (16% vs. 8% for non-users), generalized anxiety disorder (19% vs. 9% for non-users), posttraumatic stress disorder (11% vs. 4% for non-users; $P < .001$), and panic disorder (6% vs. 4% for non-users). Women who reported opioid use were also significantly more likely than non-users to report using illicit drugs and almost 3 times as likely to report smoking in the second or third trimester of pregnancy (22%) as compared to non-opioid users (8%).

Conclusion: The use of opioids in pregnancy was associated with higher levels of psychiatric comorbidity and use of other substances as compared to non-opioid users. Understanding of maternal drug use patterns is essential to tailoring care for drug-exposed women and their neonates.

P-48: Development of FTY720 as a Novel Treatment That Targets Obesity-Associated Breast Cancer

Kazuaki Takabe (presenting author)

Division of Surgical Oncology, Department of Surgery, Virginia Commonwealth University School of Medicine

Background and Objective: Given the rapid epidemic of obesity in the United States, treatment targeting obesity-associated breast cancer is urgently needed. Sphingosine-1-phosphate (S1P) is a lipid mediator that plays important roles in breast cancer progression. FTY720, an FDA-approved drug for multiple sclerosis, is a functional antagonist of S1P specific receptor-1 (S1PR1) that blocks the S1P signaling pathway. The objective of the study is preclinical evaluation of FTY720 in obesity-associated breast cancer.

Methods: Both a syngeneic orthotopic model with mouse 4T1-luc2 cells implanted in chest mammary fat pad, and MMTV-PyVT transgenic mice that develop metastatic breast cancer spontaneously were used. Metastatic lesions and the tumor burden were quantified using bioluminescence imaging for syngeneic model. S1P was measured using mass spectrometry. FTY720 was dosed orally every day for treatment.

Results: Progression of breast tumor and metastasis were significantly worse in the high-fat-diet obese group, compared with the normal-diet lean group in both models. Serum S1P levels were significantly higher in the obese group. *S1PR1* gene expression was highest in the lung metastasis, followed by the primary tumor, and then the cells in vitro. Oral administration of FTY720 daily suppressed the overall tumor burden more in the obesity group, compared with the control group. Further, the growth of the metastatic lesions was also suppressed by FTY720.

Conclusion: Increased serum S1P levels in obese mice and higher *S1PR1* gene expression in metastatic lesions implicates that targeting S1P signaling pathway by FTY720 may be effective against advanced obesity-associated breast cancer.

P-49: Feasibility of Recruiting for the Defeating Urinary Incontinence With Exercise Training (DUET) Study

Kristine M.C. Talley (presenting author),¹ Jean F. Wyman,¹ Ulf G. Bronas,¹ Becky J. Olson-Kellogg,² Teresa C. McCarthy,³ and Patricia L. Schaber⁴

¹School of Nursing, ²Physical Medicine and Rehabilitation, ³School of Medicine, ⁴Allied-Occupational Therapy, University of Minnesota

Background and Objective: Frail older women are at risk for developing toileting disabilities and subsequent nursing home placement because of urinary incontinence and functional impairments. The Defeating Urinary Incontinence with Exercise Training (DUET) intervention (nondrug treatments for urinary incontinence, exercise, and bathroom modifications) may prevent toileting disabilities. The objective of the study is to identify the feasibility of recruiting frail older women living in a continuing care community to enroll in a 12-week single-arm development study of DUET.

Methods: The goal was to enroll 8 women aged ≥ 60 years. Participants were frail (Vulnerable Elders Survey score ≥ 3), were cognitively intact (pass Mini-Cog), had urinary incontinence unrelated to neurological disorders, and did not exercise regularly. Recruitment strategies included flyers announcing weekly recruitment presentations to residents, letters to family members, and personal encouragement of select residents by the facility's recreational therapist.

Results: During 9 weeks of recruitment in one facility with 88 potential participants, recruitment events yielded 24 attendees (including 2 caregivers), 12 screened participants, 8 eligible participants, and 5 enrolled participants. Ineligible participants had cognitive impairment ($N=3$) or used medication for urinary retention ($N=1$). Eligible refusers reported the hospitalization of a spouse, being too busy, and disliking exercise. Six percent of potential participants were enrolled. Women refusing screening made statements minimizing the impact of urinary incontinence or about incontinence being untreatable at their age.

Conclusions: Recruiting this population is time consuming, and complicated by beliefs that incontinence is an inevitable part of aging. Different approaches in accessing the target population and simplifying the intervention may be needed.

P-50: Adult Role and Smoking Initiation Sequencing Order: Does Order Matter to Smoking Cessation Disparities Among Black and White Women Adult-Onset Smokers?

Azure B. Thompson (presenting author)

Department of Psychiatry, Yale University School of Medicine

Background and Objective: Black-white disparities in smoking cessation are greatest in young adulthood and among women who initiate smoking within that developmental period. During the young adult years a decline in rates of smoking begins to occur and the decline is thought to be associated with transitions into first adult roles. Yet black women who smoke may be precluded from the more favorable smoking cessation outcomes associated with these transitions. Black women's average age at first birth is earlier than their average age of initiation. The objective of the study was to identify among women adult-onset smokers whether there are black-white differences in the ordering of smoking initiation, first marriage, and birth of first child (ages 18 to 25) and whether order predicts smoking duration.

Methods: Multivariate linear regression models were used to analyze data from the National Longitudinal Survey of Young Women ($n=5,159$).

Results: Black women adult-onset smokers had a smoking duration three years longer than white women adult-onset smokers (22 vs. 19 years, respectively). A majority (55%) of black women adult-onset smokers gave birth to their first child before smoking initiation compared to 28% of white women adult-onset smokers. White women adult-onset smokers who gave birth to their first child before smoking initiation had a smoking duration two years longer than those who did not give birth before smoking initiation ($\beta=2.15$, $P=.010$). This relationship did not hold for black women adult-onset smokers ($\beta=-0.29$, $P=.831$).

Conclusions: More black than white women adult-onset smokers are parenting when they start smoking. However, these differences do not explain smoking cessation disparities.

P-51: Genetic Determinants of Mitochondrial DNA Copy Number

Bharat Thyagarajan (presenting author),¹ Weihua Guan,¹ Renwei Wang,² Helene Barcelo,¹ Woon-Puay Koh,³ and Jian-Min Yuan²

¹University of Minnesota; ²University of Pittsburgh; ³National University of Singapore

Background and Objective: There is a sex-specific association between mitochondrial DNA (mtDNA) copy number and colorectal cancer risk. Higher mtDNA copy number is associated with increased colorectal cancer risk in men, and lower mtDNA copy number is associated with increased colorectal cancer risk in women. Since genetic variants in the mitochondrial D-loop region have been associated with mtDNA copy number, we hypothesized that mitochondrial genetic variants may have a sex-specific effect on mtDNA copy number. The objective of the study is to comprehensively evaluate the sex-specific associations between mitochondrial genetic variation and mtDNA copy number.

Methods: We measured mtDNA copy number in 83 cancer-free individuals (42 women and 41 men). We genotyped 64 tagSNPs (minor allele frequency (MAF) $>1\%$) in the non-D loop region and sequenced the hypervariable mitochondrial D-loop region.

Results: We identified 214 polymorphic sites in the D-loop region (median=8; range 2–24). Two polymorphisms, mt16297 (MAF=11%; $P=.04$) and mt16304 (MAF=19%; $P=.04$) were significantly associated with mtDNA copy number. The number of mitochondrial deletions in the D-loop region (median=1; range=0–6) showed an inverse borderline association with mtDNA copy number ($P=.05$). There were no sex differences among any of the observed associations. There were 18 polymorphic tagSNPs in the non D-loop region (median=1; range=0–4). The non D-loop tagSNPs were not associated with mtDNA copy number in men or women.

Conclusions: Our preliminary findings suggest a modest association between genetic variants in the mitochondrial D-loop region and mtDNA copy number that is similar across both sexes.

P-52: Heightened Food Craving and Consumption of High-Calorie Foods in Obese Men and Women

Tomoko Udo (presenting author) and Sherry A. McKee

Yale University School of Medicine

Background and Objective: Mood-induced craving plays a critical role in addictive behaviors. Yet, the relationship between food craving, as conceptualized as urge to eat, and mood-induced eating behaviors has not been well-studied in relation to obesity. The objective of this pilot study was to adapt a well-established drug self-administration paradigm to examine whether a positive or negative mood induction affected eating behaviors and food craving differently by obesity status and by gender.

Methods: Obese ($n=15$; 40.0% women, BMI=35.1 $\pm$ 3.70) and nonobese individuals ($n=15$; 46.7% women, BMI=23.0 $\pm$ 1.96) completed 2 laboratory sessions (positive vs. negative mood conditions) consisting of a 3-hour period of food deprivation, followed by a positive or negative mood induction, and a 3-hour ad-lib eating period, where they were asked to choose between favorite high-calorie snacks and monetary reinforcement. Food craving was assessed throughout.

Results: Obese men and nonobese women showed increased food craving after negative mood induction. Obese women showed no changes in food craving following negative mood induction, but showed significant decreases following positive mood induction. Food craving was elevated upon decision to eat across mood conditions. In the negative mood condition, greater food craving upon decision to eat was correlated with less ability to resist eating in obese men and women, and greater calorie consumption in obese women. Food craving was positively correlated with calorie consumption in obese women.

Conclusions: Our preliminary findings suggest that heightened food craving may be important for susceptibility to overconsumption of high-calorie foods in obese individuals, particularly obese women.

P-53: Male-Female Differences in Nutrient Densities of Antioxidants

Thasarat S. Vajaranant (presenting author)¹ and Charlotte E. Joslin^{1,2}

¹Department of Ophthalmology and Visual Sciences, College of Medicine, University of Illinois, Chicago; and ²Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois, Chicago

Background and Objective: Increased antioxidant intake is associated with decreased risks for diseases, including cancer, cardiovascular disease, Alzheimer's disease, and age-related eye disease. In light of male-female differences in these diseases, it is of interest to evaluate possible gender differences in antioxidant intake. The objective of the study is to determine male-female differences in dietary antioxidant intake using a validated 90-item modified Block Food Frequency Questionnaire in the Age-Related Eye Disease Study (AREDS), a 10-year, NIH-funded randomized clinical trial of antioxidants for aging eye diseases.

Methods: We analyzed data from 2,260 female and 1,856 male AREDS participants (95.8% white and 3.6% African American; mean age=69.4±5 years). We examined male-female differences in baseline dietary intake of beta-carotene and vitamins C and E, assessed as nutrient density—a ratio of the selected nutrient to total energy intake.

Results: Compared with men, women had higher nutrient densities of beta-carotene (2.2 vs 1.9 µg/kcal), vitamin C (83.6 vs 66.4 µg/kcal), and vitamin E (68.6 vs 66.0 µg/kcal). All *P*-values were less than .0001.

Conclusions: Our findings provide new information about male-female differences in antioxidant intake and suggest that older women have a higher intake compared with older men. These findings raise questions about the extent to which such variations contribute to differences in disease outcomes for men and women. Future research related to gender disparities in antioxidant intake and therapy would improve our knowledge about risk factors for blinding eye diseases of aging, in which women carry higher burden of blindness.

P-54: Early Age-at-Menarche Is Associated with Fibroid Presence and Number in a Prospective Cohort

Digna R. Velez Edwards (presenting author)^{1,2,3,4} and Katherine E. Hartmann^{1,2,3}

¹Vanderbilt Epidemiology Center; ²Institute of Medicine and Public Health, Vanderbilt University; ³Department of Obstetrics and Gynecology, Vanderbilt University; ⁴Center for Human Genetics Research, Vanderbilt University

Background and Objective: Age-at-menarche varies by race and has been associated with several reproductive health conditions, including the development of uterine fibroids. Racial differences independent of age-at-menarche also impact risk for uterine fibroids. The objective of the study is to comprehensively examine the relationships among uterine fibroids, fibroid characteristics, age-at-menarche, and race.

Methods: Women were prospectively enrolled in *Right from the Start* (2001–2010) and had an endovaginal ultrasound to determine fibroid presence, number, type, volume, and diameter using repeated measurements and standardized definitions. Generalized estimating equations were used to estimate associations between age-at-menarche, presence of fibroids, and fibroid characteristics, as well as to test for interactions with race.

Results: Among 5,023 participants, 11% had fibroids, 19% were African American, and 70% were European American. Average age of participants was 29. Seven percent had age-at-menarche before 11 years, 13% at 11 years, 55% between 12 and 13 years, 14% at 14 years, and 11% after 15 years. Age-at-menarche did not interact with race to modify risk. Older age-at-menarche was associated with protection from fibroids (adjusted Odds Ratio [aOR]=0.84, 95% confidence interval [CI] 0.79, 0.89) and protection from having 2 or more fibroids (aOR=0.73, 95% CI 0.65, 0.81). The highest risk for fibroids was for age-at-menarche less than 11 years (aOR=1.58, 95% CI 1.14, 2.21).

Conclusions: Overall our findings show that early menarche is a strong risk factor for fibroids and race does not interact with age-at-menarche to modify fibroid risk. Furthermore, age-at-menarche may contribute to the number of fibroids a woman develops.

P-55: Brain Lipid Sensing and Gender Difference in Obesity Development: A Preliminary Study Using Neuron-Specific Lipoprotein Lipase Knockout Mice

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

Division of Endocrinology, Metabolism, and Diabetes, Anschutz Medical Campus, University of Colorado Denver

Background and Objective: Compared to men, women suffer more comorbidities associated with obesity. Our goal was to characterize and explore mechanisms of sex differences in obesity development in murine model, neuron-specific, lipoprotein lipase-deficient (NEXLPL^{-/-}) mice (Wang et al., *Cell Metabolism*, 2011).

Methods: A pair-feeding experiment, in which the daily food intake for the experimental mice is limited to the average daily food intake for control ad libitum feeding mice, is conducted in both male and female NEXLPL^{-/-} mice. Expressions of candidate genes in various brain regions are examined by RT-PCR.

Results: Pair feeding delayed but did not prevent obesity in male NEXLPL^{-/-} mice with significant body weight gain starting at 28 weeks. In contrast, pair feeding delayed obesity development in female mice up to 38 weeks despite AgRP up-regulation. Estrogen receptor alpha (ER- α) is known to be involved in central nervous system energy balance regulation in a sex-specific way. GPR30 has been suggested as a possible estrogen receptor and a receptor for fatty acids with controversial role in energy balance regulation. Both ER- α and GPR30 gene expression were significantly reduced in the hypothalamus in 3-month-old male NEXLPL^{-/-} mice, but slightly increased in female mice.

Conclusions: The sex difference in obesity development revealed by pair feeding suggests a more important role of energy intake in female vs. male mice. The differential expression of ER- α and GPR30 in the hypothalamus in male vs. female NEXLPL^{-/-} mice suggests a relationship between brain lipid sensing and sex differences that warrants further exploration.

P-56: Functional Impairment, Sex and Knee Replacement in the Multicenter Osteoarthritis Study

Barton L. Wise (presenting author),¹ Jingbo Niu,² Nancy E. Lane,¹ Michael Nevitt,³ David T. Felson,² Jean Hietpas,⁴ Alesia Sodosky,⁴ James Torner,⁵ C.E. Lewis,⁶ and Yuqing Zhang²

¹University of California, Davis, School of Medicine; ²Boston University School of Medicine; ³University of California, San Francisco; ⁴Pfizer, Inc.; ⁵University of Iowa; and ⁶University of Alabama, Birmingham

Background and Objective: Functional impairment may influence an individual to receive a knee replacement (KR), but few studies have explored this assumption. The objective of the study was to evaluate the association between functional impairment and risk of KR and the distribution of KR by sex.

Methods: The NIH-funded Multicenter Osteoarthritis Study (MOST) is an observational study of persons aged 50 to 79 years with or at high risk of symptomatic knee OA. We performed a repeated measures analysis using baseline Western Ontario McMaster (WOMAC) physical function score to predict the risk of KR from baseline to 30 months, and WOMAC score at 30 months to predict risk of incident KR from 30 months to 60 months. We used generalized estimating equations to account for the correlation between two knees within an individual and across the two periods. We calculated relative risk of KR over 30 months by WOMAC function, using a score of 0–5 as referent in multiple binomial regressions with log link.

Results: Our sample consisted of 2,890 individuals with 5,780 native knees; 1,738 (60%) were women. We observed 445 incident KR in 10,506 30-month knee-periods (4.3%); 311 (69.8%) were in women. Those with the greatest functional impairment (WOMAC scores 40–68) had 18.0 times (95% CI 8.4–38.3) the risk of KR over 30 months compared with the referent group, adjusting for covariates.

Conclusions: Women disproportionately receive KR in the MOST. Baseline physical function strongly predicts KR over a 30-month period.

P-57: The Safety of Mothers During Child Exchanges With Former Abusive Partners

April M. Zeoli (presenting author),¹ Echo A. Rivera,² and Cris M. Sullivan²

¹*School of Criminal Justice, Michigan State University; and* ²*Psychology Department, Michigan State University*

Background and Objective: When a woman shares a child with her abusive former partner, he often stays in her life through his involvement with their child. Limited research suggests that partner-abusive men use their access to children to continue abusing former partners. The objective of the study was to investigate whether and how perpetrators of intimate violence use child exchanges, the time when a child passes between parents for visits or shared custody, to continue to abuse.

Methods: Forty-one partner-abused mothers were recruited for this longitudinal study just before or in the beginning stages of es-

tablishing a child custody order through family court. The results use data from Time 1 interviews. Twenty-one women experienced child exchanges with former abusive partners. These women were asked about occurrences during child exchanges of the following: emotional abuse, physical abuse, stalking, threats to themselves, and threats to children or other loved ones.

Results: Of the 5 abusive tactics considered, women experienced a mean of 2.71 (s.d. 1.45) tactics. The most frequently used tactic was emotional abuse, which was used during an average of half of the exchanges. Nine women (43%) were physically assaulted during exchanges, 7 of whom were injured. Nineteen women (90%) stated there was at least a little risk of danger to themselves during exchanges, with 7 (33%) rating themselves at extremely high risk.

Conclusions: Abusive ex-partners use child exchanges to continue to abuse and threaten the mothers of their children. The possibility of continued abuse must be taken into account in safety planning, policy, and family court practice.

BIRCWH and SCOR Presentation Abstracts

O-1: Fetal Inflammatory Response Patterns in Preterm Premature Rupture of Membranes, Preeclampsia, and Healthy Term Pregnancies

Jennifer Armstrong-Wells (presenting author),¹ Meghan Donnelly,² Miriam Post,³ Marilyn Manco-Johnson,⁴ and Virginia Winn²

¹Department of Pediatrics (Neurology), ²Department of OB/GYN, ³Department of Pathology, and ⁴Department of Pediatrics (Hematology), University of Colorado Denver

Background and Objective: Studies of the fetal inflammatory response (FIR) in preterm premature rupture of membranes (PPROM), preeclampsia, and normal term pregnancies are limited but may give insight into mechanisms of adverse pregnancy outcomes. The objective of the study is to characterize the fetal inflammatory response, as measured by fetal cord blood cytokines, of placentas from pregnancies complicated by PPRM and preeclampsia, compared with healthy term controls.

Methods: Women with PPRM (n=20), preeclampsia (n=15), and healthy term pregnancies (n=50) were enrolled in an institutional prospective cohort study. Fetal cord blood was tested for IL-1 β , IL-6, IL-8, and TNF- α . Kruskal-Wallis and Mann-Whitney U were used to compare median distribution between groups, with $P < 0.05$ considered significant.

Results: Overall, there was a significant difference in median cytokine levels between all three groups (IL-1 β , $P = 0.0001$; IL-6, $P = 0.0001$; IL-8, $P = 0.0001$; IL-18, $P = 0.03$; TNF- α , $P = 0.01$). By group, median IL-1 β was higher in PPRM compared with preeclampsia (0.5 vs. < 0.2 pg/ml; $P = 0.007$) and controls (< 0.2 pg/ml; $P = 0.00001$). Median PPRM IL-6 (71.9 pg/ml) and IL-8 (43.85 pg/ml) were also higher than in preeclampsia (14.4 pg/ml, $P = 0.03$; 9.8 pg/ml; $P = 0.02$) and controls (3.65 pg/ml, $P = 0.00001$; 5.8 pg/ml, $P = 0.0001$). Additionally, median PPRM TNF- α was higher than controls (19.8 vs. 14.4 pg/ml; $P = 0.003$). Median preeclampsia IL-6 and IL-8 were higher than controls ($P = 0.001$ and 0.0002 , respectively) as well as with IL-18 (82.65 vs. 57 pg/ml; $P = 0.003$).

Conclusions: This study demonstrates distinct patterns of FIR, with FIR most robust in PPRM, then to a lesser extent in preeclampsia, compared with healthy term controls.

O-2: Development of Biomarkers in Endometrial Cancer and Its Precursor Lesions

Jamie N. Bakkum-Gamez (presenting author),¹ Jeremy Chien,² Amy C. Clayton,³ Kevin C. Halling,³ William A. Cliby,¹ Sean C. Dowdy,¹ Benjamin R. Kipp,³ Abimbola Famuyide,⁴ Andrea Mariani,¹ Ann L. Oberg,⁵ Nicolas Wentzensen,⁶ Mark Sherman,⁶ Karl C. Podratz,¹ and Viji Shridhar²

¹Division of Gynecologic Surgery, ²Division of Experimental Pathology, ³Department of Laboratory Medicine and Pathology, ⁴Division of Medical Gynecology, ⁵Division of Biomedical Statistics and Informatics-Cancer Center Statistics, Mayo Clinic; and ⁶Hormonal and Reproductive Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Background: Endometrial cancer (EC) is the most common gynecologic malignancy in the United States. Most ECs arise from pathologically defined precursor lesions that develop slowly over years, providing ample opportunities for early detection. However, research to develop early detection approaches is limited. The study's objective was to determine the feasibility of collecting biospecimens from the lower genital tract fluid (the vaginal pool) via intravaginal tampon and endometrial brushings via Tao brush for analysis of cell-free DNA methylation.

Methods: Tampon and Tao brush biospecimens were collected from 37 women with biopsy-proven EC and 37 age-matched women with benign conditions all scheduled to undergo hysterectomy.

Pyrosequencing of a panel of genes (7 selected based on gynecologic oncology literature and 4 novel genes identified via tissue-based profiling of 180 separate ECs and 25 benign endometrial tissues using the Illumina GoldenGate platform) was performed; methylation status was correlated with disease status.

Results: Both collection modalities yielded sufficient amounts of DNA (median 4.7 μ g [interquartile range (IQR) 2.5–10.7 μ g] and 33 μ g [IQR 8.1–62.6 μ g] via tampon and Tao brush, respectively) for analyses. Within the 11 genes, we identified a preliminary panel of 11 CpG sites with consistent differential methylation between EC and control for both collection specimens. Using this panel, 83% of ECs had hypermethylation of at least 1 CpG site while 83% of controls had hypermethylation at 0 CpG sites. The AUC for the 11-site panel ROC curve was 0.85.

Conclusions: A methylation-based biomarker panel distinguishes between EC and control utilizing a highly accepted method of biospecimen collection, the tampon.

O-3: Targeted Polymer Therapeutics to Treat Lead-Induced Osteoporosis

Danielle S.W. Benoit (presenting author),^{1,2,3,4} Chris Schmitt,^{1,2} Ian Marozas,¹ Deborah Cory-Slechta,⁵ and J. Edward Puzas^{3,4}

¹Department of Biomedical Engineering, ²Department of Chemical Engineering, University of Rochester; ³Department of Orthopaedics, ⁴Center for Musculoskeletal Research, and ⁵Department of Environmental Medicine, University of Rochester Medical Center

Background and Objective: Environmental toxins, particularly lead, are major contributors to bone loss associated with osteoporosis. Lead exposure reduces Wnt/ β -catenin signaling within osteoblasts, reducing overall bone formation. Therefore, bone-acting therapeutics that restore Wnt/ β -catenin signaling should enhance bone production, serving as potential new treatments for lead-induced osteoporosis. Our objective is to develop highly specific, targeted bone anabolics, based on the Wnt/ β -catenin agonist, 6-bromindirubin-3'-oxime (BIO). BIO will be incorporated into polymer therapeutics targeted specifically to bone and that release BIO over time with control over dose and rate to demonstrate therapeutic efficacy.

Methods: Osteoblasts were treated with lead or BIO (5 μ M each). Polymers that incorporate releasable BIO have been synthesized and released BIO with zero-order kinetics over 4 to 15 days, depending upon the chemistry employed. To target polymer therapeutics specifically to sites of bone resorption, a peptide that specifically binds to tartrate resistant acid phosphatase (TRAP), a molecule found within resorption pits, was incorporated.

Results: Peptide alone has high affinity towards TRAP (approximately 1 nM), while peptide-modified polymers have favorable, albeit lower, affinities (1–150 μ M). Lead treatment reduced osteoblast β -catenin and alkaline phosphatase (ALP) expression to approximately 30% and 60%, respectively, compared with untreated cells. In contrast, BIO treatment increased β -catenin and ALP expression approximately 70% and 200%, respectively, compared with untreated controls, highlighting BIO's therapeutic potential.

Conclusions: The designed polymer therapeutic shows great promise to home to bone and release the bone anabolic drug, BIO, over time to treat lead-induced osteoporosis. Current efforts focus on circulation time, biodistribution, and safety/efficacy profiles of polymer therapeutics in vivo.

O-4: Gender Differences in Response to Oxytocin in Cocaine-dependent Individuals

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

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

Background and Objective: Stress is a significant factor in relapse to cocaine use. Oxytocin is a hypothalamic neuropeptide that has been shown to mediate behavioral responding to stress as well as play a role in neuroadaptations that occur as a consequence of long-term drug use. Given these effects, oxytocin may have a therapeutic role in ameliorating the negative affect commonly observed prior to relapse in cocaine-dependent individuals. As estrogen appears to enhance oxytocin's effects, women may have an enhanced response to oxytocin. The objective was to evaluate the impact of oxytocin pretreatment on stress and craving responses following a psychosocial stress task in cocaine-dependent men and women.

Methods: In a laboratory setting, baseline measurements of craving, stress, and anxiety were collected in men ($n=8$) and women ($n=5$) meeting DSM-IV criteria for cocaine dependence. Participants were then administered oxytocin 40IU nasal spray 40 minutes prior to completion of the Trier Social Stress Task (TSST). Measurements were repeated pre-TSST, immediately post-TSST, and 5, 15, and 60 minutes post-TSST.

Results: A significant gender by task interaction was found for stress ($P=0.01$) and anxiety ($P=0.03$), indicating greater attenuation in women as compared to men in response to the TSST. A significant gender by task interaction was not noted for craving ($P=0.12$).

Conclusions: Although preliminary, these results suggest that oxytocin may help ameliorate stress-induced negative affect in cocaine-dependent individuals, and that this response may be greater in cocaine-dependent women.

O-5: Influences of Cocaine and Sex on the Neural Correlates of Impulsivity-Related Constructs

Elise E. DeVito (presenting author), Hedy Kober, Kathleen M. Carroll, and Marc N. Potenza

Department of Psychiatry, Yale University School of Medicine

Background and Objective: Sex differences have been widely demonstrated in the clinical presentation of addiction. Growing evidence supports sex differences in brain structure and function, and in aspects of impulsivity and impaired decision making, that may contribute to the development or maintenance of addiction. Despite substantial literature on functional magnetic resonance imaging (fMRI) in addiction, very few studies have directly assessed sex differences. The study's objective was to investigate sex differences in the influence of cocaine dependence on the neural correlates of cognitive control and relationship to impulsivity and risky decision making.

Methods: Twenty-three individuals meeting DSM-IV criteria for current or past cocaine dependence (CD; 11 women) and 24 age-matched healthy controls (HC; 12 women) completed an event-related fMRI Stroop task, decision-making measures, and self-reported impulsivity. fMRI analyses assessed sex and diagnostic group differences in Stroop effect (i.e., incongruent > congruent) and were whole-brain familywise error-corrected ($P_{FWE} < .05$). Impulsivity and decision-making measures were included in fMRI correlation analyses.

Results: The CD group scored higher on self-reported impulsivity, and sex differences were found on a measure of risky decision making. Differences between cocaine-dependent and healthy control groups on Stroop effect-related BOLD signal showed sex-specific patterns and correlated with out-of-scanner measures of impulsivity and risky decision making.

Conclusions: Sex differences in cocaine addiction may arise in part from sex differences in the neural underpinnings of cognitive control and decision making.

O-6: Cesarean Delivery in the United States: Variation Across Hospitals

Katy Backes Kozhimannil (presenting author),¹ Jason C. Borah,² Michael R. Law,³ Beth A. Virnig,¹ and David Van Riper²

¹Division of Health Policy and Management, University of Minnesota School of Public Health; ²Minnesota Population Center, University of Minnesota; and ³Centre for Health Services and Policy Research, School of Population and Public Health, University of British Columbia

Background and Objective: Cesarean delivery is the most common operating room procedure in the United States, with rates having increased dramatically in recent years. This study analyzed variation in hospital rates of cesarean delivery in a national sample of hospitals.

Methods: We used data from the 2009 Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project to determine hospital-based cesarean delivery rates. The NIS, a 20% sample of U.S. hospitals in 44 states, contained data on 593 hospitals with at least 100 obstetric deliveries in 2009. We measured hospital-level rates of both cesarean deliveries overall and cesarean deliveries among low-risk women (those with full-term, singleton, vertex pregnancies and no prior cesarean deliveries).

Results: We found substantial variation in hospital rates of cesarean delivery, both overall and for low-risk deliveries. The mean cesarean rate was 32.8%, and rates ranged from 7.1% to 69.9%. Among low-risk women, the mean cesarean delivery rate was 12.0%, ranging from 2.4% to 36.4%. This variation remained, both nationally and within individual states, after stratification by hospital size, teaching status, and geographic location.

Conclusions: Cesarean delivery rates varied 10-fold across hospitals, and cesarean rates for low-risk women varied 15-fold. These wide variations imply potential quality concerns; efforts to decrease variation should focus on policy determinants of hospital obstetric care, including state and federal regulation and Medicaid payment policy.

O-7: Insulin Sensitizer Use May Attenuate the Loss in Gait Speed for Older Women With Diabetes

Christine G. Lee (presenting author),¹ Ann V. Schwartz,² Kristine Yaffe,³ Teresa A. Hillier,⁴ Erin S. LeBlanc,⁴ and Peggy M. Cawthon⁵

¹Department of Medicine, Oregon Health & Science University;

²Department of Epidemiology and Biostatistics, ³Department of Psychiatry, University of California San Francisco; ⁴Center for Health Research, Kaiser Permanente Northwest; and ⁵California Pacific Medical Center Research Institute for the Study of Osteoporotic Fractures Research Group

Background and Objective: Insulin resistance is present in type 2 diabetes and is associated with disability in older adults. The objective is to determine whether older, diabetic women have a greater loss in physical performance and whether these changes differ by insulin sensitizer (IS; metformin/thiazolidinediones) use.

Methods: In the Study of Osteoporotic Fractures, 2,864 women (mean age 78.5 ± 3.6 years) had physical performance measured from 1997 to 1998 and 4.9 ± 0.6 years later. Least squares mean changes in usual and rapid walk speed and grip strength were estimated from separate multivariate linear regression models for diabetic women not using IS and using IS and were compared with results from non-diabetic women (referent). Postestimation testing with nonlinear constraints was used to compare diabetic women not on IS with those on IS.

Results: Estimates from fully adjusted models showed that women with diabetes had greater declines in usual walk speed (-0.16 [95% CI: $-0.19, -0.14$]) and rapid walk speed (-0.21 [95% CI: $-0.24, -0.17$]) than women without diabetes (usual: -0.11 m/s [95% CI: $-0.12, -0.11$]; rapid: -0.15 m/s [95% CI: $-0.16, -0.14$]), $P < .05$ for both comparisons. Diabetic women on IS had significant attenuation in the loss of usual walk speed compared to diabetic women not on IS ($P < .05$). Declines in grip strength were not significantly different across groups. Results were unaltered after excluding women on insulin at either visit.

Conclusions: Older, diabetic women experience a greater decline in gait speed, and insulin sensitizer use may attenuate this loss. Further studies to assess whether insulin sensitizers can attenuate the decline in mobility for older, diabetic adults are needed.

O-8: Association of Air Pollution Exposures and Risk of Uterine Leiomyomata in the Nurses' Health Study II: A Prospective Study

Shruthi Mahalingaiah (presenting author),¹ Jaime E. Hart,² Francine Laden,^{2,3} Katie Terry,⁴ Lauren Wise,⁵ Renee Boynton-Jarrett,⁶ Janet Rich-Edwards,^{7,8} and Stacey Missmer^{2,9}

¹Department of OB/GYN, Boston Medical Center, Boston University; ²Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School; ³Departments of Epidemiology and Environmental Health, Harvard School of Public Health; ⁴Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School; ⁵Department of Epidemiology, Boston University School of Public Health; ⁶Division of General Pediatrics, Boston University School of Medicine; ⁷Department of Epidemiology, Harvard School of Public Health, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital; ⁸Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care; ⁹Department of Epidemiology, Harvard School of Public Health

Background and Objective: Risk factors for uterine leiomyomata (UL) have been evaluated, including lifestyle; diet; and anthropometric, hormonal, and genetic factors. Air pollution (AP), particularly that from vehicle exhaust, has been shown to have hormonal activity and to be associated with systemic and local inflammation. Furthermore, smaller sizes of particulate matter (PM), such as PM_{2.5}, can cross into the blood stream and deposit at distant tissues. Recent literature correlating AP with cardiac and pulmonary morbidity and mortality has shown stronger associations with smaller size fractions. At present, it is unknown whether air pollution exposure is associated with the occurrence of UL. The objective is to examine the associations of distance to road (as a measure of traffic exposure) and particulate matter over varying time intervals with incidence of UL.

Methods: Proximity to major roadways and outdoor levels of particulate matter (PM₁₀, PM_{2.5}) were determined for all residential addresses at all questionnaire time points for 67,487 women in the Nurses' Health Study II. Exposures were modeled from data from 1989 to 2007. Women were included in the current study if they were alive, premenopausal, free of cancer, did not have a diagnosis of UL prior to 1993, and had at least one address from 1993 to 2007 geocoded to the street segment level. Cases of ultrasound or hysterectomy confirmed UL were reported on biennial questionnaires. Multivariable-adjusted time-varying Cox proportional hazard models were used to estimate the relation between distance to road and PM exposures and UL risk. All models were adjusted for age, calendar time, race, current body mass index (BMI), smoking status, parity, oral contraceptive use, age at menarche, age at first and last birth, time since last birth, total months of exclusive breastfeeding, antihypertensive medication use, census tract level median income, and median home value.

Results: During 629,960 person-years of follow-up, there were 5,814 incident cases of UL. Living close to a major road and 24-month, 48-month, and cumulative exposures to PM₁₀ were not associated with an increased risk of UL. However, each 10 µg/m³ increase in 24-month average, 48-month average, and cumulative average PM_{2.5} was associated with adjusted hazard ratios of 1.09 (95% CI: 0.98–1.18), 1.09 (95% CI: 0.98–1.20), and 1.12 (95% CI: 1.03–1.22), respectively.

Conclusions: Long-term exposure to PM_{2.5} may be associated with a modest increase in risk of UL.

O-9: Integrating Social Science and Behavioral Genetics: Testing the Causation Versus Selection Hypotheses of Social Disparities in Major Depression Using a Genetically Informed Design

Briana Mezuk (presenting author),^{1,2} John M. Myers,² and Kenneth S. Kendler²

¹Department of Epidemiology and Community Health and ²Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University

Background and Objective: To test three hypotheses regarding the origin of socioeconomic disparities in major depression (MD): social causation, social drift, and common (social or genetic) cause.

Methods: Data come from a population-based sample of female twins (N=2153). Logistic regression and structural equation twin models were used to evaluate the relative importance of these competing hypotheses.

Results: Consistent with the social causation hypothesis, education (OR=0.78, *P*<0.01) and income (OR=0.93, *P*<0.01) were significantly related to past year MD. There was no evidence that parental SES—a common social cause—was related to MD (OR=0.98, *P*>0.10). Consistent with a common genetic cause, a modest negative genetic correlation was found between MD and education (*r*²=−0.22). Co-twin control analyses indicated a protective effect of education and income on MD even after accounting for genetic effects. Upward social mobility was associated with lower risk of MD.

Conclusions: This genetically informative study addresses the fundamentally sociological question as to how social position relates to MD, and demonstrates conceptual and methodological aspects of examining the joint action and interaction of genetic propensity and the environment.

O-10: Systemic Vaccination With the Uropathogenic *E. coli* Bladder Adhesin FimH Protects Previously Infected Mice That Are Predisposed to Severe, Recurrent Cystitis

Valerie P. O'Brien (presenting author),¹ Thomas J. Hannan,² and Scott J. Hultgren¹

¹Department of Molecular Microbiology and Center for Women's Infectious Disease Research, ²Department of Pathology and Immunology, Washington University School of Medicine

Background and Objective: The high rate of recurrent urinary tract infections (rUTIs) and the rise of multidrug-resistant uropathogens indicate the urgent need for new therapeutics, such as a UTI vaccine. We recently developed a mouse model of recurrent cystitis that is useful for studying the molecular basis of rUTIs and testing novel therapeutics. In this model, C3H mice that are allowed to develop chronic bladder infection with uropathogenic *E. coli* (UPEC) prior to antibiotic therapy become predisposed to severe, recurrent cystitis. Our objective was to determine whether C3H mice with a history of chronic cystitis are sensitized to challenge with other UPEC strains and whether vaccination can protect from challenge.

Methods: C3H/HeN mice were infected by intravesical inoculation with the clinical UPEC isolate UTI89, and urines were collected over 2 weeks to identify chronically infected mice. Four weeks after initiation of antibiotics, mice were challenged with UPEC or were vaccinated, boosted, and challenged with UTI89. The outcomes of the infections were determined by longitudinal urinalysis and analysis of tissue bacterial load at sacrifice.

Results: Sensitized mice were highly susceptible to severe, recurrent chronic cystitis when challenged with other UPEC strains, but not with MG1655. After vaccination with FimCH, only 8% of sensitized mice developed chronic cystitis upon challenge with UTI89, compared with 38% of mock-vaccinated, sensitized mice.

Conclusions: FimCH protected sensitized mice from recurrent chronic cystitis upon challenge with UTI89. Sensitization is not limited to UTI89, and we are now investigating whether the FimCH vaccine also protects mice from challenge with other UPEC strains.

O-11: Combination Therapy Using Targeted Nanoparticles in Preclinical Models of Epithelial Ovarian Cancer

Harsh B. Pathak (presenting author),¹ Smruthi Murthy,¹ Ryan Moulder,² Shuang Cai,² Laird Forrest,² and Andrew K. Godwin¹

¹Department of Pathology and Laboratory Medicine, University of Kansas Medical Center; ²Department of Pharmaceutical Chemistry, University of Kansas

Background and Objective: In a phase 2 clinical trial for the treatment of an unselected cohort of patients with epithelial ovarian carcinoma (EOC), dasatinib, a small molecule SRC-kinase inhibitor,

had minimal activity as a single agent (RECIST criteria) (Schilder et al., *Gynecol Oncol*, 2012). Our objectives were to (1) identify second-site molecular targets that synergize with inhibition of SRC kinase to improve the clinical efficacy of dasatinib and (2) develop a nanoparticle formulation for delivery of a combination of siRNA + dasatinib suitable for in vivo therapeutic use in an orthotopic mouse model of EOC.

Method: We used RNAi approaches to perform gene silencing studies in combination with dasatinib using a siRNA library recently described by Aptsaturov et al. (*Science Signaling*, 2010) targeting 638 genes related to signaling through tyrosine kinase receptors across a panel of EOC cell lines and nontumorigenic human immortalized ovarian (HIO) epithelial cell lines. For the second objective, we modified a recently published high-density lipoprotein nanoparticle formulation by Shahzad et al. (*Neoplasia*, 2011).

Results: Thirty-eight dasatinib-sensitizing hits were identified and validated from our initial screening efforts. Additional screening across multiple EOC and HIO cell lines refined this list further and provided two dasatinib-sensitizing targets to evaluate in mouse models using a nanoparticle delivery system. This nanoparticle formulation is being optimized to provide targeted delivery of both siRNA and dasatinib for combination therapy.

Conclusions: Development of an efficient nanoparticle drug delivery vehicle will allow us to evaluate the in vivo efficacy of the combination therapies identified from our in vitro studies.

O-12: The Impact of Menopausal Anxiety Symptoms on Verbal Learning Is Greater in HIV-Seropositive Versus HIV-Seronegative Midlife Women

Leah H. Rubin (presenting author),¹ Erin E. Sundermann,² Eileen M. Martin,¹ Elizabeth T. Golub,³ Kathleen Weber,⁴ Mardge Cohen,⁵ Howard Crystal,⁶ Julie Cederbaum,⁷ Kathryn Anastos,⁸ Mary Young,⁹ Ruth M. Greenblatt,¹⁰ and Pauline M. Maki²

¹Department of Psychiatry, ²Departments of Psychiatry and Psychology, University of Illinois at Chicago; ³Department of Epidemiology, Johns Hopkins School of Public Health; ⁴The Core Center, Bureau of Health Services of Cook County; ⁵Department of Medicine, Stroger Hospital and Rush University; ⁶Department of Neurology, SUNY Downstate Medical Center; ⁷University of Southern California, School of Social Work; ⁸Departments of Medicine and Epidemiology and Population Health, Albert Einstein College of Medicine; ⁹Georgetown University School of Medicine; ¹⁰Departments of Clinical Medicine and Epidemiology, University of California, San Francisco

Background and Objective: Menopausal symptoms—particularly mood changes, sleep disturbance, and hot flashes—negatively impacted cognition in the Study of Women's Health Across the Nation (SWAN). Using data from the Women's Interagency HIV Study (WIHS), we evaluated the individual and interactive effects of menopausal mood symptoms, menopausal stage, and HIV-serostatus on cognition.

Methods: HIV-seropositive (n=710) and HIV-seronegative (n=280), pre-, peri-, or post-menopausal WIHS participants (64% African American; aged 30 to 65) completed a neurocognitive test battery including measures of verbal learning, verbal memory, attention, and executive function. The SWAN menopausal symptom questionnaire was used to assess anxiety, sleep, and vasomotor symptoms, and the Center for Epidemiological Studies depression scale to assess depressive symptoms.

Results: After adjusting for relevant demographic and behavioral characteristics, HIV-serostatus and menopausal mood symptoms negatively impacted cognition ($P < .05$). Persistent anxiety and depressive symptoms were associated with lower verbal memory and learning ($P < .05$) but only depressive symptoms were associated with lower attention and executive function ($P < .05$). The impact of persistent anxiety symptoms on verbal learning was greater in HIV-seropositive ($\beta = -5.26$, $SE = 1.62$, $P = .001$) than in HIV-seronegative women ($\beta = 0.73$, $SE = 2.36$, $P = .75$).

Conclusions: HIV-infection and menopausal mood symptoms were independently associated with lower cognitive function. For anxiety, this relationship was stronger in HIV-seropositive women than HIV-seronegative women. This finding underscores the importance of screening and treating anxiety in HIV-seropositive midlife

women, as it may increase vulnerability to cognitive dysfunction and decrease treatment adherence. Ongoing longitudinal assessments are under way to determine the robustness of these associations.

O-13: E545K Mutation in PI3KCA Is Associated With Recurrence in Cervical Cancer Patients Treated With Chemoradiation

Ramachandran Rashmi,¹ Cynthia Helms,² Anne M. Bowcock,² Perry W. Grigsby,³ and Julie K. Schwarz (presenting author)⁴

¹Department of Radiation Oncology, ²Division of Human Genetics, Biotechnology Center, ³Department of Radiation Oncology, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Mallinckrodt Institute of Radiology, Division of Nuclear Medicine, and Alvin J. Siteman Cancer Center, ⁴Departments of Radiation Oncology, Cell Biology and Physiology, and Alvin J. Siteman Cancer Center, Washington University School of Medicine

Background and Objective: We recently reported that alterations in expression of genes from the PI3K/Akt pathway are associated with incomplete metabolic response after chemoradiation in carcinoma of the cervix. The objective of the current study was to test for common mutations in the PI3K/Akt pathway using 8 human cervical cancer cell lines and 103 fresh frozen pretreatment tumor biopsies.

Methods: Tumor biopsies were obtained as part of a cervical cancer registry at Washington University School of Medicine. Human cervical cancer cell lines were obtained from ATCC. Sequenom mass array MALDI-TOF (matrix assisted laser desorption/ionization time of flight mass spectrometry) was used to identify common cancer mutations in *PI3KCA*, *PTEN*, and *AKT1/2* (*PI3KCA* R88Q, N345K, C420R, E545/2K, H701P, H1047L, N1068K, Y1021C; *PTEN* R173C; *AKT1* E17K; *AKT2* S302G, R371H). This method uses PCR amplification to generate allele-specific products that separate based on unique mass differences using chip-based mass spectrometry.

Results: Eight mutations were identified in 5 human cervical cancer cell lines. The most common mutations were E545/2K (n=2) and H1047L (n=4) in *PI3KCA*. Cell lines with mutations in the PI3K/Akt pathway had increased pAkt versus total Akt by Western blot, and demonstrated increased cell migration in vitro. E545/2K mutation was identified in 6 pretreatment tumor biopsies. Patients with *PI3KCA* E545/2K tumors had increased distant metastasis and decreased 3-year progression-free survival after chemoradiation (21% vs. 50%, $P = 0.18$).

Conclusions: Oncogenic mutations in *PI3KCA* were identified in human cervical cancer. *PI3KCA* E545/2K was associated with decreased progression-free survival after chemoradiation.

O-14: Childhood Adversities and Subsequent Risk of One or Multiple Abortions

Julia R. Steinberg (presenting author) and Jeanne M. Tschann

Department of Psychiatry, University of California, San Francisco

Background and Objective: Although many studies have found an association between childhood adversities and mental health problems, few have examined whether childhood adversities are linked to having abortions. The objective of this research is to investigate the association between a range of childhood adversities and risk of abortion to identify which adversities are important to consider when examining the association between abortion and mental health.

Methods: Using the National Comorbidity Survey-Replication (NCS-R), we test the association between 10 childhood adversities and risk of 0, 1, or multiple abortions among 1,511 U.S. women 18 to 41 years old. We employed multinomial logistic regression to also look at the independent association between each childhood adversity and number of subsequent abortions, controlling for socio-demographic factors, total number of pregnancies, and each adversity.

Results: Women who had experienced 2 or more personal safety threats [OR=9.87, 95% CI: 2.45–39.72; OR=13.33, 95% CI: 2.48–71.68], 1 parental mental illness [OR=2.81, 95% CI: 1.27–6.21; OR=2.17, 95% CI: 1.03–4.56], or 2 or more parental mental illnesses

[OR=5.28, 95% CI: 1.60–17.38; OR=3.67, 95% CI: 1.15–11.76] were more likely to have multiple versus no abortions, and multiple versus 1 abortion, respectively. Women who had experienced childhood physical abuse [OR=2.00; 1.19–3.34] were more likely to have 1 compared with no abortions.

Conclusions: These results suggest that some childhood adversities may partially explain the association between abortion and mental health. Accordingly, they should be considered in future research examining the link between abortion and mental health.

O-15: Novel Theranostic Nanoparticle Use for Efficient Administration of Doxorubicin in Breast Cancer Cell

Dinesh Vyas (presenting author), Arpita Vyas, Puliur S. Mohanhumar, and Xuefei Huang

Michigan State University

Background and Objective: Triple negative human breast cancer (TNBC) cell line MBA-MD-231 has overexpression of CD44. TNBC is associated with worse prognosis and metastasis. The objective of the study is to determine whether presence of CD44 on the TNBC will help in targeted therapy of doxorubicin (DOX) with the help of multifunctional nanoparticles (NP).

Methods: TNBC and MCF-7 were treated in vitro with DOX and NP-HA-DOX at various time periods, and cellular uptake was analyzed by confocal microscopy.

Results: TNBC and MCF-7 breast cancer cells treated with NP-HA-DOX for 1 and 5 hours showed statistically significant drug uptake in cytoplasm compared to nuclei. The same study showed TNBC had a statistically significant drug uptake in cytoplasm and nuclei compared to cytoplasm and nuclei of MCF-7 breast cancer cells. TNBC and MCF-7 treated with DOX for 5 hours showed statistically significant drug uptake in nuclei compared to cytoplasm. NP-HA-DOX has more uptake of DOX in cell.

Conclusion: Use of DOX liganded to NP-HA was more effective in cytoplasmic uptake than DOX alone in both TNBC and MCF-7 cells after 5 hours of treatment. NP-HA-DOX shows more uptake of DOX by TNBC cells than MCF-7 cells for both 1- and 5-hour treated cells.

There is a need for further in vivo studies to evaluate its application for treatment.

O-16: Childhood Anxiety Trajectories Predict Disordered Eating in Adolescence

Stephanie Zerwas (presenting author), Ann Von Holle, and Cynthia M. Bulik

Department of Psychiatry, University of North Carolina, Chapel Hill

Background and Objective: Theories of eating psychopathology have long implicated childhood anxiety as a risk factor for the development of disordered eating. In retrospective studies, adults with eating disorders report that their struggles with childhood anxiety predated the onset of disordered eating behaviors. However, no prospective studies have examined whether anxiety in childhood predicts disordered eating in adolescence. The aim of the present study was to describe childhood anxiety trajectories and disordered eating in adolescence using latent growth mixture modeling (LGMM). We hypothesized 4 trajectories of childhood anxiety (low stable, increasing, high stable, and decreasing) and that increased childhood anxiety would predict adolescent disordered eating behaviors.

Methods: Data were collected as part of the prospective longitudinal NICHD Study of Early Child Care and Youth Development (N=462 girls). Childhood anxiety was assessed yearly via maternal report on the Child Behavior Checklist at 54 months and at kindergarten through ninth grade. Adolescent girls self-reported disordered eating behaviors on the Eating Attitudes Test (EAT) at 15 years. We conducted LGMM to define anxiety trajectories and included maternal education as a covariate.

Results: The best-fitting model included 3 trajectories of childhood anxiety: low stable (77% of girls), middle increasing (20%), and high increasing (3%). Girls in the middle increasing trajectory class had significantly increased odds of scoring above risk thresholds on the EAT in comparison to the low stable trajectory class (OR=1.78, $P<.01$).

Conclusions: Childhood anxiety predicts disordered eating in adolescence.

Additional SCOR Abstracts

1: Role of Orexin/Hypocretin in Conditioned Sucrose Seeking: A Comparison Between Female and Male Rats

Angie M. Cason (presenting author) and Gary Aston-Jones

Department of Neurosciences, Medical University of South Carolina

Background and Objective: Accumulating evidence implicates the orexin/hypocretin system in reward-seeking for highly salient food rewards. Increased reward seeking contributes to the overconsumption of palatable foods that in turn contributes to obesity. Like other eating disorders, obesity affects more women than men. We recently demonstrated that signaling at the orexin 1 receptor (OxR1) is involved in sucrose reinforcement and cue-induced reinstatement of extinguished sucrose seeking, particularly in food-restricted subjects. We reasoned that the orexin system may be strongly engaged during periods of food restriction. The present study compared the involvement of OxR1 activation in sucrose reinforcement, and cue-induced reinstatement of extinguished sucrose seeking in female and male rats.

Methods: Food-restricted and ad lib-fed rats were trained to self-administer sucrose pellets, and we determined the effects of pretreatment with the OxR1 receptor antagonist SB 334867 (SB) on self-administration and cue-induced reinstatement of extinguished sucrose-seeking.

Results: In females, SB (20–30 mg/kg) decreased responding during self-administration, but not during cue-induced reinstatement. In males, SB decreased responding for sucrose (10–30 mg/kg) and the number of reinforcers earned (20–30 mg/kg) during self-administration. Furthermore, SB attenuated cue-induced reinstatement to sucrose seeking. In both sexes, the effects were greatest in food-restricted subjects.

Conclusions: These results indicate that signaling at the OxR1 receptor is involved sucrose reinforcement and lead us to consider that conditioned activation of Orx neurons may increase motivation for food reward during food restriction. Additionally, the findings that SB is less effective at inhibiting responding for sucrose in females suggest that signaling at the OxR1 receptor is sexually mediated.

2: GSN: A Novel Susceptibility Gene for Female Osteoporosis

Yao-Zhong Liu (presenting author),¹ Fei-Yan Deng,¹ Wei Zhu,² Yong Zeng,² Yong-Jun Liu,¹ and Hong-Wen Deng¹

¹Center for Bioinformatics and Genomics, Tulane University School of Public Health and Tropical Medicine; and ²College of Life Sciences, Hunan Normal University

Background and Objective: Osteoporosis is a public health problem, especially in women. Low bone mineral density (BMD) is a risk factor for osteoporosis and has strong genetic determination. Genes influencing the majority of variation of BMD are largely unknown. Peripheral blood monocytes (PBMs) can serve as progenitors of bone-resorbing osteoclasts and are involved in bone metabolism. Herein, we attempted to identify osteoporosis susceptibility gene(s) through initial proteome profiling of PBMs in vivo, and using a strategy of multidisciplinary and integrative studies.

Methods: We recruited 3 independent case-control samples (n = 34, 29, and 40 in Samples 1–3, respectively), including premenopausal women with extremely low vs. high hip BMD in a white population, and two random population samples, including 2,286 white and 1,627 Chinese women, respectively. We utilized quantitative proteomics methodology to profile PBM proteomes in Sample 1 to discover proteins, and thus gene(s), functionally relevant to low BMD. Differentially expressed protein(s) identified were verified by western blotting (WB). Then, mRNA expression in PBM was ana-

lyzed in Samples 2 and 3. For gene(s) also differentially expressed at mRNA level, we tested association of SNPs with hip BMD in populations.

Results: In Sample 1, gelsolin (GSN) was down-regulated 3.0-fold in subjects with low BMD ($P < .05$). Down-regulation of GSN gene expression in low-BMD subjects was verified by WB and was further replicated at mRNA level in Samples 2 and 3 ($P < .05$). Four SNPs within the GSN locus were associated with hip BMD in both populations ($P < .05$).

Conclusions: We conclude that GSN is a significant susceptibility gene involved in the pathogenesis of female osteoporosis.

3: Monocyte Apoptosis, a New Mechanism for Female Osteoporosis Suggested by a Microarray Study

Yao-Zhong Liu (presenting author), Yu Zhou, Yong-Jun Liu, Ji-Gang Zhang, and Hong-Wen Deng

Center of Bioinformatics and Genomics, Department of Bioinformatics and Biostatistics, Tulane University School of Public Health and Tropical Medicine

Background and Objective: Osteoporosis is caused by excessive bone resorption (by osteoclasts) over bone formation (by osteoblasts). Monocytes are important to osteoporosis by serving as progenitors of osteoclasts and produce cytokines for osteoclastogenesis. The objective is to identify osteoporosis genes by microarray analyses of monocytes in high vs. low BMD (bone mineral density) subjects.

Methods: Microarray analyses of monocytes were performed using Affymetrix 1.0 ST arrays in 73 white women (aged 47–56) with extremely high (n = 42, 16 pre- and 26 postmenopausal subjects) or low hip BMD (n = 31, 15 pre- and 16 postmenopausal subjects). Differential gene expression analysis in high- vs. low-BMD subjects was conducted in the total cohort, as well as pre- and postmenopausal subjects. Focusing on the top 200 differentially expressed genes identified in the total, the pre- or the postmenopausal subjects (with a $P \leq E-3$), we performed replication of the findings in three independent datasets of microarray analyses of monocytes in (1) 80 white women (40 high- vs. 40 low-BMD subjects); (2) 19 white women (10 high- vs. 9 low-BMD subjects); and (3) 26 Chinese women (14 high- vs. 12 low-BMD subjects).

Results: We identified and successfully replicated 7 genes (*DDX18*, *VDAC1*, *DAXX*, *PKD1*, *ACSL3*, *RABGGTB* and *CLCN4*) in both the 80 and the 19 (or the 26) women, with a $P \leq .10$. Importantly, two genes, *VDAC1* and *DAXX*, are both apoptosis induction genes, and both down-regulated in low-BMD subjects.

Conclusions: Our findings support a lower apoptosis rate of monocytes as a novel mechanism for female osteoporosis.

4: Multi-Stage Genome-wide Association Meta-analyses Identified Gender-specific Loci Associated With Bone Mineral Density

Lei Zhang,^{1,2} Jian Li,² Yu-Fang Pei,^{1,2} Yong Lin,¹ Hui Shen,² Karol Estrada,^{3,4,5} Fernando Rivadeneira,^{3,4,5} André Gutterlinden,^{3,4,5} Chan Soo Shin,⁶ Hyung Jin Choi,⁶ Emma L. Duncan,^{7,8} Paul J. Leo,⁹ Matthew A. Brown,⁷ Yao-Zhong Liu,² Yongjun Liu (presenting author),² Ji-Gang Zhang,² Qing Tian,² Yu-Ping Wang,² Xue-Zhen Zhu,¹ Shuyan Wu,¹ Christopher J. Papasian,⁹ and Hong-Wen Deng^{1,2}

¹Center of System Biomedical Sciences, University of Shanghai for Science and Technology; ²Center for Bioinformatics and Genomics, Department of Biostatistics and Bioinformatics, Tulane University; ³Department of Internal Medicine, Erasmus Medical Center; ⁴Department

of Epidemiology, Erasmus Medical Center; ⁵Netherlands Consortium for Healthy Aging, Netherlands Genomics Initiative; ⁶Department of Internal Medicine, College of Medicine, Seoul National University; ⁷Human Genetics Group, Diamantina Institute, University of Queensland; ⁸Department of Endocrinology, Royal Brisbane and Women's Hospital; and ⁹Department of Basic Medical Science, University of Missouri, Kansas City

Background and Objective: Osteoporosis is a public health problem predominantly affecting women. Bone mineral density (BMD), a major risk factor for osteoporosis, has strong genetic determination. Genes affecting BMD variation are largely unknown. The objective of the study was to identify genetic variants important for BMD and investigate potential gender-specific effects.

Methods: We conducted multi-stage meta-analyses of genome-wide association (GWA) datasets that comprise 17,655 females and 9,333 males. In Stage 1, we meta-analyzed seven GWA datasets (with 7,738 females and 3,402 males) for BMDs at the lumbar spine, hip, and femoral neck. In Stage 2, a subset of single nucleotide polymorphisms (SNPs) selected from Stage 1 was analyzed in silico in three independent samples comprising 6,076 females and 3,109 males. Significant SNPs in joint analyses of Stages 1 and 2 were replicated de novo in two additional samples comprising 3,841 females and 2,822 males.

Results: We identified novel loci (genes) important for BMD, some with gender-specific effects. Female-specific loci (genes) include 21q22.13 (*CLDN14*), 9q31.2 (*KLF4*), and 11p15.1 (*HPS5*). Analyses of gene expression data in osteogenic cells showed these genes were differentially expressed in females with high versus low BMD. We also identified two male-specific loci (genes), 3q25.1 (*IGSF10*) and 8q21.3 (*TMEM64*). Additional 13 loci were found to have general effects in both genders, including 1p36.12 (*ZBTB40*), 1p31.3 (*GPR177*), 4p16.3 (*FGFRL1*), 5q14.3 (*MEF2C*), 6q25.1 (*C6orf97*, *ESR1*), 7q21.3 (*FLJ42280*, *SHFM1*), 7q31.31 (*FAM3C*, *WNT16*), 8q24.12 (*TNFRSF11B*), 11p15.3 (*SOX6*), 11q13.4 (*LRP5*), 13q14.11 (*AKAP11*), 14q24.2 (*SMOC1*), and 16q24 (*FOXL1*).

Conclusions: Our findings provided valuable insight into the gender-specific genetic architecture of osteoporosis.

5: Positively Selected FimH Residues Confer Enhanced Virulence for Uropathogenic *Escherichia coli*

Drew J. Schwartz (presenting author),¹ Caitlin N. Spaulding,¹ Patrick D. Olson,² Swaine L. Chen,³ and Scott J. Hultgren¹

¹Department of Molecular Microbiology, Center for Women's Infectious Disease Research, Washington University School of Medicine;

²Department of Pediatrics, Washington University School of Medicine;

³Department of Medicine, Division of Infectious Diseases, Yong Loo Lin School of Medicine, National University of Singapore, and Infectious Diseases Group, Genome Institute of Singapore

Background and Objective: Urinary tract infections (UTI) affect 50% of women at least once during their lifetime. Up to 40% of these women suffer recurrent UTI, leading to further use of antibiotics, which promotes rising resistance. This vicious cycle can lead to chronic UTI by prolonging bacteriuria and symptoms. The most common cause, uropathogenic *E. coli* (UPEC) invades bladder tissue and establishes intracellular bacterial communities (IBCs) in both mice and humans. UPEC binding to epithelial cells and subsequent invasion relies on the FimH adhesin, which binds mannosylated residues on the bladder surface. Specific residues in FimH are under positive selection among UPEC compared to fecal *E. coli*.

Methods: We determined the effect of these residues on acute and chronic infection caused by two prototypical UPEC strains: UTI89, a cystitis isolate, and CFT073, a urosepsis isolate. The whole genomes of UTI89 and CFT073 are 99% identical; however, FimH has two differences in positively selected residues. To test the effects of these differences, we swapped the *fimH* alleles between UTI89 and CFT073 and assessed their pathogenesis in mouse models.

Results: We found that UTI89 formed more IBCs and had higher bladder titers than CFT073 at 6 hpi. CFT073 with UTI89 FimH caused chronic cystitis while wild-type CFT073 did not. Additionally, in co-infection experiments, UTI89 FimH outcompeted strains with CFT073 FimH in both backgrounds.

Conclusions: These data show that FimH is crucial in determining UPEC virulence and may suggest a prognostic test to predict the potential severity of a UTI based on FimH sequence.

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