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

Eleventh Annual Interdisciplinary
Women's Health Research Symposium
November 6, 2014

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Joan Davis Nagel, MD, MPH

THE YEAR 2014 marks the Eleventh Annual National Institutes of Health (NIH) Interdisciplinary Women's Health Research Symposium. The Interdisciplinary Symposium emerged as a result of the collaboration between two signature Office of Research on Women's Health (ORWH) initiatives. In 2004, it was the first symposium of its kind at the NIH. The Interdisciplinary Symposium showcases the research findings from the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) scholars and the Specialized Centers of Research (SCOR) on Sex Differences principal investigators (PIs). ORWH designed, developed, and implemented the BIRCWH program in 2000 followed by the SCOR program in 2002. With the midyear mark of the release of the "NIH Strategic Plan for Women's Health Research (NIH SP), A Vision for 2020 for Women's Health Research"¹ approaching, these two programs will be evaluated in light of the NIH SP goals and accomplishments. Indeed, the BIRCWH is serving as a research model to illustrate why the NIH SP Objective 6.2, "lead the way in encouraging institutions to recognize mentoring" contributes to success in biomedical research careers and the SCOR has been a useful vehicle for expanding the NIH SP Goal 1.0, to "increase sex differences research in basic science studies."

BIRCWH Program

The BIRCWH is an innovative, trans-NIH institutional, interdisciplinary, mentored research career development program. To date, 77 BIRCWH awards have been made to 39 institutions in 25 states; over the course of the program's existence, 560 individuals have participated, and as of August 1, 2014, 114 scholars are active. BIRCWH supports junior faculty members who have recently completed clinical training or postdoctoral fellowships and who are beginning basic, translational, clinical, and/or health services research related to women's health research by pairing junior researchers with senior investigators.

When the program was first initiated, the majority of scholars had one mentor who served as their research mentor. The program evolved over the years with the reissuance of funding opportunity announcements from a single to a dual approach, and over the past 5 years, to an interdisciplinary team mentoring approach. Scholars under the BIRCWH

program now have an average of three mentors.² Scholars have a research mentor, a career mentor, and an additional mentor from, for example, a basic science field if the scholar comes from a clinical field. In this way, scholars acquire skills in working across disciplines to address complex women's health issues. In fiscal year 2013, twenty-seven BIRCWH programs are active and the majority of BIRCWH scholars have gone on to receive funding from NIH, other federal sources, foundations, and industry. Based on NIH Program data, 80% of scholars submitted at least one NIH grant within 1 year after their start date, and two-thirds of those went on to obtain funding that led to research independence.

SCOR Program

The SCOR was developed and implemented two years after the BIRCWH to serve as a complement but with a larger, interdisciplinary team science focus. The SCOR is a trans-NIH and bi-agency center initiative (with cofunding from the U.S. Food and Drug Administration). The SCOR supports accomplished scientists who conduct research that integrates basic, clinical, and translational research at large centers. SCORs are inherently translational in nature and are designed to increase the rapidity of transfer of basic research findings that account for sex as a biologic variable to sex- and gender-informed clinical practice. Current SCOR investigators are examining sex differences observed in pain, including visceral and pelvic floor dysfunction, developmental trajectories in major depressive disorders, sex differences in the brain's response to drug cues, addiction and stress, therapeutic targets for recurring urinary tract infections, vascular dysfunction and cognitive decline, metabolic disorders, and reproductive disorders. SCOR investigators have contributed to major Institute of Medicine reports on sex differences in pain and the importance of reporting sex as a variable in research findings.^{3,4}

Interdisciplinary Symposium

The NIH Strategic Plan for Women's Health Research calls for an expanded focus on sex and gender differences in basic science research to better understand their significance

in health and disease. This year's Interdisciplinary Symposium will feature interdisciplinary research presentations from BIRCWH scholars and SCOR PIs that examine complex women's health conditions as well as the role of sex/gender on health and disease. There will be presentations from BIRCWH scholars and SCOR PIs on a diverse, wide range of topics in women's health such as sex differences in drug and smoking cues, role of periconceptual folic acid supplementation and DNA methylation in developing autism and the impact of a pregnancy complication, placental abruption, on the risk for developing type 2 diabetes mellitus for women in later life. Moreover, in alignment with a recent *Nature* commentary⁵ from the director of NIH and director of ORWH, this year's symposium will include a special panel and workshop on sex differences methodology and a keynote address by Dr. David C. Page (Whitehead Institute at Massachusetts Institute of Technology). The panel will include discussions by clinical trialists, journal editors, and researchers on how the basic biological variable of sex can be incorporated in the entire biomedical research enterprise, as well as the impact of including or not including sex as a basic biological variable. Abstracts from both the oral and poster presentations are presented in this special journal edition. We hope that the abstracts will enhance understanding of the influence of sex as a fundamental variable and the importance of interdisciplinary approaches in helping us to better understand major health problems that affect women. For those of you who are fortunate enough to travel to the NIH campus to participate in this year's Interdisciplinary Symposium on November, we hope that you will be excited to hear the latest and greatest findings in women's health and sex differences

research. It is evident that the SCOR and BIRCWH research studies are contributing to an expanded translational knowledge base on how sex/gender affect basic biologic processes and pathogenic disease pathways as well as treatment responses that hold promise for improving the health of women and girls.

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BIRCWH and SCOR Poster Abstracts

P-1: Beta-Blocker Use and Ovarian Cancer Survival as Determined by Electronic Medical Records

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Background and Objective: Beta-adrenergic blocking agents (beta-blockers) are prescribed for arrhythmias and the secondary prevention of myocardial infarctions. Beta-blockers inhibit the action of adrenergic hormones, which may promote tumor growth. The use of beta-blockers has been associated with improved survival from several malignancies. The objective of this study was to determine if beta-blocker use is associated with improved survival from ovarian cancer.

Methods: Confirmed ovarian cancer cases were selected from identified electronic medical records (EMRs) from the Vanderbilt University Medical Center. Ever use of any beta-blocker was determined by MedEx, a natural-language processing system designed to capture medication use from EMRs. Linked tumor registry data was used to generate hazard ratios (HRs) and confidence intervals (CIs) for overall survival using proportional hazards regression; covariates included age, diagnosis year, race, disease stage, and histologic subtype.

Results: Most of the 1,147 confirmed ovarian cancer cases were Caucasian (87.0%); 53.6% had serous histologic subtypes; and 50.0% had late-stage disease (III or IV). Ovarian cancer cases with any beta-blocker use (142, 12.4%) had longer survival than non-users (mean: 5.8 vs. 5.0 years). This difference was significant in both unadjusted analyses (HR: 0.74, 95% CI, 0.58, 0.95) and when adjustment included covariates (HR: 0.66, 95% CI, 0.51, 0.85). In analyses by drug type, use of both nonselective ($P=0.033$) and beta-1 selective blockers ($P=0.002$) was associated with improved survival among ovarian cancer cases.

Conclusions: This retrospective analysis suggests that EMR-documented use of beta-blockers is associated with improved ovarian cancer survival. Further evaluation, which should include timing, dose, and duration of use as well as assessment of confounding by indication, is needed to further examine this apparent association.

P-2: Vulnerability to Functional Decline in Women Hospitalized With Cardiovascular Disease

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Background and Objective: Declining functional status in older women with cardiovascular disease (CVD) may contribute to their increased mortality compared with men. Hospitalization for an acute event can precipitate a decline, conferring a risk of future hospitalization and mortality. Currently, there is no widely used measure of vulnerability to decline to identify individuals at risk. Our objective was to assess a validated functional status tool, the Vulnerable Elders Survey (VES-13), to identify vulnerable CVD patients in the acute hospital setting.

Methods: We enrolled 445 individuals, men and women aged 65 years or older who were admitted to the hospital with acute coronary syndrome and/or decompensated heart failure. Participants completed an in-person interview during admission that included vulnerable functional status using the VES-13, sociodemographic characteristics, health-care utilization practices, and clinical patient-specific measures. A multivariable proportional odds logistic regression model examined the relationship of vulnerability to medical and psychosocial factors associated with poor outcomes in CVD.

Findings: Vulnerability was associated with a higher number of clinic visits, emergency room visits, and hospitalizations (all $P<.001$). A 1-point increase in VES-13 (vulnerability) was independently associated with being female (odds ratio [OR]: 1.5, $P=.032$), diagnosis of heart failure (OR: 3.1, $P<.001$), prior hospitalizations (OR: 1.3, $P<.001$), low social support (OR: 1.4, $P=.008$), and depression (non-linear association, OR: 1.7 corresponding to change from mild to moderate depressive symptoms, $P<.001$), while adequate health literacy was protective (OR: 0.69, $P=.001$).

Conclusion: Vulnerability to functional decline is highly prevalent in hospitalized older CVD patients, especially women, and is associated with patient risk factors for adverse outcomes and an increased use of health care services. The VES-13 provides for an easily administered screening tool that can be used to identify at-risk patients.

P-3: Angiotensin-Converting Enzyme Inhibitors Do Not Appear to Interact With Doxorubicin Pharmacokinetics in Women Undergoing Chemotherapy for Breast Cancer

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Background and Objective: Doxorubicin (DOX) chemotherapy can cause cardiac complications in breast cancer survivors. Studies suggest that angiotensin-converting enzyme inhibitors (ACEIs) may help prevent these complications, but little is known about whether ACEIs affect DOX efficacy. We performed a pharmacokinetics (PK) study to determine whether DOX exposure is altered in patients receiving DOX concurrently with an ACEI.

Methods: A total of 19 women with breast cancer who had been prescribed DOX 60 mg/m² every 14 days were enrolled; 2 women withdrew. Blood samples for PK (levels of DOX, its metabolite, and doxorubicinol) were drawn at baseline and at 0.5, 1.0, 2.0, 4.0, 24.0, and 48.0 hours after infusion with and without the ACEI (enalapril). Correlative laboratory values were obtained. PK data were analyzed using noncompartmental methods, and DOX and the doxorubicinol area under the curve (AUC)_{0-∞}, C_{max} (maximum concentration), and half-life were estimated. Paired, 2-tailed t-tests were used to determine whether DOX and its metabolite were altered with the use of the ACEI.

Results: A total of 17 women (median age: 45 years) completed the study. The mean (SD) AUC_{0-∞}s for DOX and doxorubicinol with ACEI exposure were 1185.56 (44.64) hr*ng/ml and 1040 (80.6) hr*ng/ml, respectively. AUC_{0-∞} values for DOX and doxorubicinol without the ACEI were 1167.73 (45.26) hr*ng/ml and 1056.32 (92.03) hr*ng/ml, respectively. There appeared to be no interaction between DOX and the ACEI. The ACEI was well tolerated (35% of the women had grade 1 dizziness).

Conclusions: The ACEI enalapril does not appear to alter the PK of DOX. Ongoing efforts to determine the effectiveness of ACEIs as cardioprotective agents in women receiving DOX chemotherapy should be continued.

Funding source: Masonic Cancer Center, University of Minnesota, NIH# K12-HD055887

P-4: Birth Weight Alters Associations Between Physical Activity and Blood Pressure

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Background and Objective: For a growing subgroup of children, cardiovascular risk is elevated due to fetal programming effects of maternal obesity. Behavioral risk factors for hypertension may vary according to the unique physiology of this subgroup, but this hypothesis has not been tested. The objective in this study was to test if associations between moderate to vigorous physical activity (MVPA) and blood pressure varied by birth weight (BW) in a nationally representative sample of adolescents.

Methods: Among adolescents in the National Health and Nutrition Examination Survey (1999–2006; ages 12–15 years; $n = 6,693$), we used gender-stratified multivariable linear regression to quantify associations between systolic and diastolic blood pressure (SBP and DBP) and self-reported MVPA (weekly metabolic equivalent [MET] hours), adjusted for sociodemographics and diet; we tested for interactions between MVPA and BW (low [LBW], normal [NBW], and high [HBW]).

Results: Among girls, MVPA was more strongly associated with lower DBP in the HBW subgroup than in the NBW subgroup (coefficients [95% confidence interval (CI)]: HBW, $-1.9 [-3.6, -0.1]$; NBW, $-0.2 [-0.8, 0.4]$; interaction significance: $P = .07$). MVPA was not associated with DBP in LBW girls. Boys exhibited a distinct patterning in which MVPA was most strongly associated with DBP in the LBW group (coefficients [95% CI]: LBW, $-2.1 [-4.4, 0.1]$; NBW, $-0.9 [-1.5, -0.3]$), but the interaction was not statistically significant. Associations between MVPA and SBP did not vary by BW for boys or girls.

Conclusions: DBP may be more responsive to MVPA in HBW (versus NBW) girls and in LBW (versus NBW) boys. These findings have implications for the potential role of early-life factors in gender differences in behavioral risk factors for cardiovascular outcomes.

P-5: Weight Status and the Ability to Transform Health Behavior Goals into Action in Midlife Women

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University of Kansas Medical Center

Background and Objective: The context for this work was the increased cardiometabolic risk of midlife women during the menopausal transition. There is a need for more effective interventions to promote desirable health behaviors, such as engaging in physical activity and maintaining a healthy diet; neuroimaging offers an alternative for investigating the connection between cognition and behavior. The objectives of this study were to identify differences in brain responses in midlife women ranging from “healthy weight” to obese during a goal-directed decision task. The ultimate goal was to develop new and effective interventions to achieve optimal outcomes.

Methods: Twenty non-diabetic, midlife (aged 47–55 years) women with a body mass index (BMI) ranging from 18.5 to 40 (weight in kg divided by height in m^2) were recruited from an internal medicine clinic. A descriptive, correlational design was used to assess the relationship between brain activations and weight status. Participants underwent a set of goal-directed behavior tasks in the scanner that consisted of a learning phase and an implementation phase. The task was designed to assess goal-directed behavior.

Results: The results indicated that overweight women activated cognitive control regions while they were learning associations between actions and outcomes. This was not the case for these women, however, during the implementation phase, which made it more difficult for this subgroup to transform goals into action (e.g., maintain physical activity, follow a healthy diet over time).

Conclusions: Overall, these results indicate that overweight midlife women will respond differently from other women during the implementation of learned actions that lead to positive outcomes during a general test of goal-directed behavior. Research is needed to assess these findings in behavioral interventions that focus on transforming health behavior goals into action.

P-6: Gestational Age of 36 Weeks at Birth Is Associated with Significant Changes in CpGs Methylation

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Background and Objective: Low gestational age at birth is a critical risk factor for morbidity throughout life. However, mechanisms for the increase in morbidity with decreasing gestational age are not well understood. Epigenetic investigation may identify some of the changes that occur at the molecular level as a consequence of being born preterm. Identifying differences in CpGs DNA methylation between preterm and term infants may provide insight into the relationships between preterm delivery and later morbidities. The objective of this study was to investigate CpGs with significant methylation differences across gestational age.

Methods: We profiled 348 samples (76 preterm, 272 term) from newborn cord blood using the Illumina HumanMethylation 27k bead array using the *Minfi* Bioconductor package in R. Statistical analysis was performed only on autosomal CpGs (27,578). To determine CpGs with significant methylation differences between preterm and term samples, linear regression was employed using the log ratio of methylation to unmethylation signal, with a *t*-test used to determine significance and the Benjamini-Hochberg method employed to correct for multiple testing.

Results: We found 1,764 differentially methylated CpGs at a 10% false discovery rate. In all, 809 of these showed decreased methylation in preterm infants, with a general increase at 36 weeks of gestation.

Conclusions: Significant changes in methylation on CpGs occur at a gestational age of 36 weeks. Cell composition of the cord blood may account for some of this difference. We are currently reanalyzing the data accounting for cell composition. The CpGs that remain significantly methylated after controlling for cell composition may provide important insights to long-term outcomes associated with prematurity.

P-7: Mesh Used for Pelvic Organ Prolapse Elicits a Chronic Pro-inflammatory Response in Primates and Humans

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Background and Objective: Surgical mesh is used to improve outcomes in pelvic organ prolapse (POP), but complications are sometimes observed. It is suggested that complications are attributable, in part, to an inflammatory process. However, a detailed investigation of the response to mesh in the vagina has never been performed. The objectives of this study were to (a) define the host inflammatory response to mesh in the rhesus macaque and (b) examine the host inflammatory response to mesh removed from human patients because of complications.

Methods: The host response to mesh implanted in 43 rhesus macaques and 27 women was examined by immunolabeling and enzyme-linked immunosorbent assay to determine the profile of immune cells present within the implant site and the M1/M2 phenotype (pro-inflammatory versus anti-inflammatory) of the macrophage population.

Results: Macrophages were the primary responders to mesh in both the primates and the humans. These cells were found to be of predominantly M1 phenotype. However, lighter-weight, higher-porosity mesh was associated with attenuated pro-inflammatory responses in a comparison with heavy-weight mesh in primates. Elevated levels of pro-inflammatory cytokines were observed in mesh-implanted animals and human patients in comparisons with controls matched by age, body mass index, and menopausal status.

Conclusions: The host response to mesh consists predominantly of activated, pro-inflammatory, M1 macrophages. This response can persist for years in human patients. While additional work is required to establish causal relationships, these results suggest a link between the host response and clinical outcome. An improved understanding of the host's response to mesh has the potential to drive the design of next-generation mesh, inform clinical practice, and improve outcomes.

P-8: Lipoprotein(a) and Cardiovascular Risk in Women With HIV

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Background and Objective: Chronic HIV infection is associated with increased risk of cardiovascular disease (CVD), although the underlying mechanisms are unclear. Elevated lipoprotein(a) (Lp[a]) is an independent risk factor for CVD in the general population, and a size polymorphism in the apo(a) gene confers this risk. We previously found in a cross-sectional study of HIV and CVD that HIV+ individuals who had higher CD4+ T-cell counts and lower viral loads had elevated Lp(a) levels, with atherogenic smaller apo(a) sizes. The objective of the contemplated study is to compare the relation of HIV infection and highly active antiretroviral therapy (HAART) to Lp(a) levels, apo(a) sizes, and CVD risk. First, we will assess the levels of Lp(a) longitudinally in HIV+ women on HAART and compare the levels with those in HIV- women while accounting for apo(a) size. Second, we will perform a cross-sectional analysis to determine if increased Lp(a) levels are associated with elevated CVD risk in HIV+ and HIV- women.

Methods: The study population will be drawn from the Women's Interagency HIV Study. For specific aim 1, Lp(a) levels will be assessed in 127 HIV+ women once before and twice after initiation of HAART and will be compared with those in HIV- women. For specific aim 2, 100 HIV- and 150 HIV+ women will have CVD risk assessed by carotid intima-media thickness (CIMT) at a single time point.

Results: We anticipate that exposure to HAART will increase Lp(a) levels, particularly those with atherogenic smaller apo(a) sizes in HIV+ women. We also anticipate that elevated Lp(a) levels, in particular those with atherogenic smaller apo(a) sizes, will be associated with a higher CIMT.

Conclusions: It is anticipated that elevated Lp(a) will be shown to be a risk factor for CVD in HIV+ women.

P-9: Oxytocin, Pregnancy, and Long-term Maternal Health

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Background and Objective: We have previously shown that after a normal pregnancy and lactation, mice had lower blood pressure, fasting glucose, and triglyceride levels than age-matched virgin mice. The neuropeptide oxytocin (OXT) is expressed during labor and in the ejection of milk. In addition, OXT has beneficial effects on blood pressure and adiposity. The objective of this study was to investigate the levels of OXT in primigravid (PG) and nulligravid (NG) female mice.

Methods: Virgin CD-1 female mice were allocated to breeding (PG) and non-breeding (NG) groups. PG animals proceeded through a normal pregnancy, delivery, and pup weaning. Plasma levels of OXT, mRNA expressions of *Oxt*, its receptor (*Oxtr*), *mmu-miR-29a*, and the level of *Oxtr* methylation in tissues were determined using Luminex magnetic bead technology and appropriate polymerase chain reaction methods. Student's T-test and the Mann-Whitney test were used for statistical analysis (significance: $P \leq .05$).

Results: Plasma OXT was significantly lower in NG mice ($P = .03$). *Oxt* gene expression was reduced significantly in the heart ($P = .05$) and aorta ($P = .03$) and increased in visceral adipose tissue (VAT; $P = .04$) from NG mice compared with PG mice. *Oxtr* expression was significantly reduced in VAT ($P = .008$), the heart ($P = .05$) and the aorta ($P = .04$) from NG animals. *Oxtr* was hypermethylated in the heart ($P = .03$) and, though not significantly, in VAT ($P = .6$) of NG mice. The *mmu-miR-29a* was significantly higher in the hearts of NG mice ($P = .04$).

Conclusions: Our data indicate that pregnancy has a long-term effect on OXT levels, *Oxt* and *Oxtr* gene expression, and epigenetic regulation of *Oxtr* in vascular and adipose tissue. These differences could mediate the protective effects of pregnancy on cardiometabolic health.

P-10: An Untargeted Metabolomic Approach to Identifying Biologic Pathways Significantly Altered by Treatment in Polycystic Ovary Syndrome

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Background and Objective: Polycystic ovary syndrome (PCOS) is a condition of androgen excess and anovulatory cycles that is associated with insulin resistance. The heterogeneity of PCOS in clinical presentation and therapeutic response presents a challenge for research on its pathophysiologic mechanisms. Previously, an untargeted metabolomics approach identified 19 significantly altered biologic pathways in PCOS when compared with controls. We sought to determine which biologic pathways were significantly altered after treatment for PCOS.

Methods: Twenty obese women with PCOS were compared with 18 women matched for age and body mass index. Five women with PCOS were retested 6 months after the use of metformin and oral contraceptives. Plasma samples were obtained during fasting. We utilized a liquid chromatography/mass spectrometry-based nontargeted metabolomics approach to identify differentially regulated metabolites in PCOS following treatment. Using principal component analysis and pathway enrichment analysis, metabolites were detected in at least 50% of the samples, with thresholds of a 1.5-fold difference between treatment groups, level of significance (P) less than .05, and false discovery rate less than 5%.

Results: In all, 328 metabolites were significantly changed after treatment. The known metabolites characterized 34 significantly altered pathways. Twelve of these pathways were also significantly altered pathways in PCOS in comparisons with controls, including vitamin D, branched chain amino acid, catecholamine and phospholipid metabolism, cholesterol biosynthesis, prostaglandin H2 and HETE/HPETE biosynthesis and metabolism, the N-acyltransferase and transcription PPAR pathways, and regulation of CFTR gating.

Conclusions: The effects of treatment can help identify biologically important metabolic pathways in PCOS. Large-scale metabolomics analysis may be an important tool for studying the pathophysiology of PCOS and appropriate therapeutic targets.

P-11: Differences by Sex in First Carpometacarpal Joint Motion

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Background and Objective: The prevalence of first carpometacarpal (CMC) joint osteoarthritis (OA) in women is more than double that in men across all ages. We hypothesize that this difference is a consequence of differences by sex in the motion patterns of the first CMC joint. The objectives of this study were to (a) develop a rapid MRI protocol for evaluating the first CMC joint during its continuous and realistic unassisted motion and (b) demonstrate that the resulting anatomical images enable the derivation of motion MRI metrics that can be compared between the sexes.

Methods: We optimized and evaluated advanced image reconstruction methods on a Siemens 3T MRI system, enabling us to capture approximately 15 to 20 frames per second. Four healthy men

(average age: 30 years) and three healthy women (average age: 28 years) were scanned using the imaging protocol.

Results: The protocol provided images of the moving first CMC joint with minimal artifacts and enabled the derivation of motion-based metrics associated with the joint. For example, trapezium translation during the thumb flexion-extension maneuver was (mean $\pm$ extrema) 2.0 ± 0.2 mm in men versus 2.4 ± 0.2 mm in women.

Conclusions: This novel MRI method to assess the motion of the first CMC joint holds promise. Our future work will involve detailed comparisons of the motion imaging metrics by sex and help researchers begin to determine if the derived imaging metrics correlate with the sex-specific prevalence of first CMC joint OA.

P-12: Increased Dosing Does Not Overcome the Intrauterine, Gender-Dependent Programmed Diuretic Response of Furosemide

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Background and Objective: The phenomenon of intrauterine growth restriction (IUGR) programs higher risk for chronic disease during adulthood via morphological and physiological changes in organ systems, including the kidney. We hypothesized that renal maladaptations result in altered pharmacologic patterns for life.

Methods: Maternal protein restriction during gestation and lactation was used to induce IUGR in the current study. Offspring were weaned onto lab chow. The diuretic response of furosemide (2 mg/kg or 10 mg/kg single intraperitoneal dose) in IUGR rats during adulthood was investigated, as was the expression status of select drug transporters, renal metabolic clearance of furosemide, serum protein binding, and renal function. Additionally, the expression of the pharmacodynamic target, sodium-potassium-chloride co-transporter, was determined.

Results: Diuresis, natriuresis, and renal excretion of furosemide were significantly reduced relative to controls, indicative of decreased efficacy for a 2 mg/kg dose. While baseline diuresis was similar, a modest 12% and a significant 26% decrease were observed in IUGR males and females, respectively, upon dosing with 2 mg/kg. The in vitro metabolism of furosemide, the in vivo urinary excretion of the metabolite, and the expression of renal drug transporters were all unaltered. Significant reductions in serum protein binding of furosemide were noted. Creatinine clearance was significantly reduced by 15% and by 19% in male and female IUGR rats, respectively. Further evidence of renal insufficiency was suggested by decreased uric acid clearance. There were no changes in the renal protein expression of sodium-potassium-chloride co-transporter. Similar changes were observed with a higher dose (10 mg/kg).

Conclusions: It appears that IUGR could permanently imprint pharmacokinetic processes in a gender-dependent manner that affects drug response.

P-13: Traditional Assay Methodology, Drug Species, and Perinatal Growth: A Perfect Storm for Oral Contraceptive Failure Among Obese Women

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Background and Objective: Pharmacokinetic explanations of oral contraceptive (OC) failure in obese women have been confusing. We tested the hypothesis that pharmacokinetic estimations are confounded by the bioanalytical assay chosen, the drug species, and the birth weight.

Methods: Serum levonorgestrel was measured by liquid chromatography-mass spectrometry (LCMS-MS), and compared with

traditional radioimmunoassay (RIA) in a clinical pharmacokinetic study of combination OC in normal (body mass index [BMI] < 25; n = 10) and obese (BMI > 30; n = 10) women (18–35 years), with BMI equaling weight in kg divided by height in m². Free and total concentrations were measured using LCMS-MS.

Results: Levonorgestrel concentrations determined by LCMS-MS were approximately 25% lower than those measured using RIA in all women ($P < .05$). The half-life (hr) computed using RIA (25 ± 9) and LCMS-MS (27 ± 19) was similar in normal women, but it was significantly longer in obese women per LCMS-MS than per RIA (107 ± 81 vs. 53 ± 29 ; $P < .05$). The measures of drug exposure were either overestimated (maximum concentration) or unchanged (area under the curve) by RIA in all women. Using LCMS-MS, there were no differences between normal and obese women in both measures of exposure expressed as total concentrations, but they were significantly smaller in obese women when expressed as free concentrations.

Conclusions: Estimation of pharmacokinetic parameters is accurate using novel LCMS-MS as compared to traditional RIA. The measures of drug exposure when expressed as free, but not total, concentrations explain a potential for OC failure among obese women. This may reflect differences in total plasma protein concentrations as suggested by animal experiments, especially in perinatal growth-restricted animals. The use of traditional bioanalytical methods and the drug species employed obfuscate pharmacokinetic explanations of OC failure.

P-14: Lamotrigine, Dosing, and the Bipolar Woman: Pharmacokinetics for Therapeutic Drug Monitoring and Dosing

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Background and Objective: Lamotrigine is a medication commonly used for the treatment of bipolar disorder (BD). Sex differences for the metabolism of lamotrigine are attributed to changes in the woman's hormonal milieu, including increased levels of estradiol during pregnancy. Rising estradiol levels are associated with increased lamotrigine metabolism, which has implications for therapeutic efficacy and the clinical management of BD in pregnancy. Information to guide therapeutic drug monitoring and algorithms for dosing lamotrigine during pregnancy are needed to maintain wellness of pregnant women with BD. A research strategy to determine a dosing algorithm for lamotrigine in pregnant women with BD is presented. This investigation aims to explore decreases in lamotrigine concentration as it relates to increased elimination in pregnancy. The study also investigates the association between lamotrigine concentration and worsening BD symptoms in pregnancy.

Methods: This is a prospective, observational study of women (n = 10) on lamotrigine for BD. Serial serum samples (n = 15) are obtained and banked for later pharmacokinetic analysis for six targeted 24-hour visits that include preconception, pregnancy, and postpartum time points. Assessments of depression, mania, anxiety, and function are completed at each visit and correlated with lamotrigine concentration changes.

Results: We expect significant decreases in lamotrigine concentration across pregnancy and a rapid increase in concentration postpartum. Decreases in lamotrigine concentration will result in worsening symptoms of depression, mania, anxiety, and function in women with BD.

Conclusions: Longitudinal pharmacokinetic analysis of lamotrigine in pregnancy will guide health care specialists in therapeutic drug monitoring and dosing for pregnant women with BD.

P-15: In Vivo Dopamine Responses Captured by Novel PET Method Reveal That Cigarette Smoking Induces Right Ventral Striatal Dopamine Release in Men but Not Women

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Background and Objective: Women have more difficulty than men in quitting smoking. The neurobiological basis for this difference is unknown. Dopamine is a critical neurochemical that is implicated in nicotine reinforcement and the success of treatment for smoking, with evidence supporting stronger associations for men than for women. A recent methodological innovation allows us to probe the dopamine response to smoking in highly localized areas of the striatum. In this study, the first investigation to examine sex differences in the dopaminergic signature of smoking, the objective was to identify sex differences in anatomical or temporal aspects of smoking-induced dopamine release.

Methods: Healthy smokers (8 men, 8 women) who were abstinent overnight participated in 1 [^{11}C]raclopride positron emission tomography (PET) scan. Subjects smoked their preferred brand of cigarette while being scanned. Brief dopamine responses (lasting only minutes) were extracted from the dynamic PET data. Voxel-wise analyses produced spatio-temporal patterns of dopamine release, visualized as "dopamine movies." Parametric images of the magnitude and timing of dopamine release were compared between the 2 groups.

Results: Men were significantly more likely than women to release dopamine in some fraction of the right ventral striatum in response to smoking. The male activation pattern in response to cigarettes was characterized by faster and greater peak response to cigarettes than was the female pattern.

Conclusions: This is the first demonstration of sex differences in the dopamine response to tobacco smoking in the living human brain. Differences in dopamine release patterns may explain sex differences in smoking behavior as well as the differential efficacy of nicotine replacement therapy for men over women.

P-16: Muscle Insulin Resistance in Adolescent PCOS Is Related to Serum Androgen Concentrations but Not to Markers of Mitochondrial Dysfunction

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Background and Objective: Polycystic ovarian syndrome (PCOS) is associated with insulin resistance and type 2 diabetes. Muscle insulin resistance in adults with type 2 diabetes has been linked to defects in mitochondrial oxidative capacity. Muscle mitochondrial function has not been studied in PCOS, especially youth with PCOS, who are early in this disease process. The objective of this study was to measure muscle mitochondrial oxidative function and peripheral insulin resistance in obese girls with or without PCOS.

Methods: Obese girls without PCOS ($n = 19$, mean age 14.5 years, body mass index [BMI] percentile 96 ± 1) and obese girls with PCOS ($n = 36$, mean age 14.9 years, BMI percentile 98 ± 2) were enrolled. In vivo muscle mitochondrial function was assessed with ^{31}P -magnetic resonance spectroscopy before, during, and after near-maximal isometric calf exercise, and peripheral insulin sensitivity was measured with an $80 \text{ mU/m}^2/\text{min}$ hyperinsulinemic euglycemic clamp.

Findings: Girls with PCOS had significantly more androgens (free androgen index 11.2 ± 1.1 vs. 3.9 ± 0.4 ; $P < .001$) and insulin resistance (glucose infusion rate $10.1 \pm 0.7 \text{ mg/kg lean/min}$ vs. 16.2 ± 1.42 ; $P < .001$). Markers of mitochondrial function were similar in the 2 groups (ADP time constant $22.9 \pm 1 \text{ sec}$ vs. $20.1 \text{ sec} \pm 1.4$, $P = .1$, oxidative phosphorylation rate $0.14 \pm 0.01 \text{ mmol/sec}$ vs. $0.30 \pm 0.12 \text{ mmol/sec}$, $P = .2$). Free androgen index was related to glucose infusion rate ($R = -0.638$, $P < .0001$). Neither androgens nor glucose infusion rate correlated with in vivo markers of mitochondrial function.

Conclusions: Obese girls with PCOS have significant peripheral insulin resistance, which is related to their serum androgen concentrations. However, mitochondrial function is not impaired in these girls relative to similar-weight controls. This finding may be due to the anabolic effect of testosterone in muscle. Further work is needed to understand the cause of peripheral resistance in girls with PCOS.

P-17: Mucosal Generation of Rheumatoid Arthritis-Related Autoantibodies in Women in the Preclinical Period of Rheumatoid Arthritis Development

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Background and Objective: Rheumatoid arthritis (RA) has a preclinical period of development characterized by serum positivity of disease-specific autoantibodies (e.g., anti-cyclic citrullinated peptide [CCP] antibodies) before the development of inflammatory arthritis. Proceeding from this fact, our central hypothesis was that autoimmunity in RA originates at an extra-articular mucosal surface. In prior work, we demonstrated that the lung generates anti-CCP in a high proportion of preclinical RA subjects, but it is not yet known why RA affects women 3 times more often than men. Further work is needed to link mucosal origination of RA to higher rates of RA in women. The objective of the present study was to evaluate the lung as a mucosal site of RA-related autoantibody generation in women.

Methods: Using enzyme-linked immunosorbent assays, we tested induced-sputum samples for anti-CCP in a total of 58 men and women with preclinical RA defined as the presence of 1 or more serum RA-related autoantibodies in the absence of inflammatory arthritis.

Results: Preclinical RA women were less likely than men to be positive for sputum anti-CCP (32% vs. 50%, $P = .17$). Furthermore, there was a trend, albeit not significant, for women 50 years or older to be more likely to have sputum anti-CCP positivity than women younger than 50 years (9/22 [41%] vs. 3/16 [19%]; $P = .18$); there was no such differential in men. Results were unaffected by smoking.

Conclusions: These findings suggest that the lung is not the site of generation of RA-related autoantibodies in a majority of women, especially premenopausal women. These data have led to a hypothesis that the cervicovaginal mucosa is a site of generation of RA-related autoimmunity, especially in premenopausal women. Ultimately, understanding where autoimmunity in RA originates in women can lead to novel strategies for preventing this disease.

P-18: Mapping Missing Heritability in PCOS Through Whole-genome Sequence Analysis in Multiplex PCOS Families

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Background and Objective: Polycystic ovary syndrome (PCOS) is a highly heritable non-Mendelian disorder. As in other complex genetic diseases, common susceptibility variants identified by genome-wide association studies do not account for all of the observed heritability. Rare variants (minor allele frequency [MAF] $< 1\%$) with larger biological effects may account for this "missing heritability." Using whole-genome sequences from PCOS probands and their families, we identified genes containing putatively deleterious coding mutations that segregate by disease status.

Methods: Whole-genome sequencing at a depth of 40x was performed on 77 PCOS probands diagnosed by National Institutes of Health criteria and on their parents (69 fathers, 71 mothers), affected sisters (13 PCOS, 4 elevated androgens with regular menses), and unaffected sisters (77) at Complete Genomics Inc. (CGI, Mountain View, California). Bioinformatic services at CGI were used to identify variants in these families that met a mixed parental dosage mode of inheritance.

Results: We identified 20,297,703 high-quality variants in the study subjects, of which 9,556 were coding variants in a total of 9,164 genes. At a 1% risk allele frequency threshold, 12 genes were found to contain at least 7 coding variants across at least 6 families. Prioritization for follow-up will be done by assessing the damaging

potential bioinformatically (e.g., by SIFT [scale-invariant feature transform], PolyPhen2 [Polymorphism Phenotyping version 2], etc.). Putative deleterious mutations will be confirmed by Sanger sequencing, genotyped in a larger set of PCOS cases and controls, and functionally investigated in appropriate cell systems or transgenic animal models.

Conclusions: Rare deleterious mutations identified will provide considerable insight into the etiology of PCOS because they are predicted to be physiologically relevant.

P-19: Payer-Level Differences in the Response to Regulatory Actions Regarding Withdrawal of Breast Cancer as an Indication for Bevacizumab

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Background and Objective: Based on promising results from early trials, the U.S. Food and Drug Administration (FDA) approved bevacizumab for use in breast cancer in February 2008. In November 2011, the FDA revoked this indication, as new findings suggested an unfavorable risk-benefit profile. The Centers for Medicare and Medicaid Services (CMS) announced its intention to continue covering bevacizumab for breast cancer for Medicare beneficiaries. At the same time, some private insurers announced their intention to cover bevacizumab for breast cancer only on a case-by-case basis. The objective of the present study was to examine payer-specific trends on the use of bevacizumab for breast cancer to determine the impact of coverage policies on such use following the FDA's revocation of this indication.

Methods: We used IMS Health LifeLink CMS-1500 claims from February 2008 through September 2012. We evaluated bevacizumab use as a proportion of infused chemotherapy by person-month for breast cancer claims paid by Medicare or commercial insurance (N=110,959 women). We used modified Poisson regression and generalized estimating equations (GEEs) for repeated measures.

Results: Before the FDA's action, the proportion of women with breast cancer receiving bevacizumab was higher among Medicare enrollees than among commercial enrollees (11% vs. 9%). Following the FDA's action, use of bevacizumab among commercially insured patients decreased by 73%, while use among Medicare patients decreased by 66% (risk ratio: 1.25, 95% confidence interval, 1.07, 1.46).

Conclusions: Although CMS and private payers differed in their public statements regarding policies for covering bevacizumab, we found significant declines in use among both payer groups. While there remain small differences in payer-specific bevacizumab use, it appears that physicians have rapidly reduced use of this therapy among women with breast cancer.

P-20: IgG Fc Glycosylation Favoring Less Inflammatory Variants Is Regulated by Estradiol in Men

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Background and Objective: Conserved IgG glycosylation at the Fc region modulates its affinity for Fc receptors and complement. Interestingly, IgG Fc glycans vary across the life span in a sex-dependent manner, and yet no mechanism regulating these glycans has been defined. Our unpublished data in women suggest that estradiol (E2) is a regulator of IgG galactosylation. We examined whether testosterone (T) modulates IgG galactosylation in men and whether these effects are directly due to T or via aromatization of T to E2.

Methods: As part of 2 randomized controlled trials, healthy men aged 20–50 years received various combinations of goserelin acetate, T, anastrozole, and/or placebo to create 3 groups (n=20 per group) with suppressed T and E2 (T–E–), suppressed E2 (T+E–) only, and no suppression (T+E+). We performed high-performance liquid chromatography-based serum N-glycan analysis in these groups at a pretreatment baseline and at 12 or 16 weeks.

Results: As expected, men in the T+E– and T–E– groups had suppression of E2 throughout the study, whereas men in the T+E+ group had no change in their E2 levels. Men in the T+E+ group had no change in agalactosylated IgG structures, while men in both the T–E– and T+E– groups had similar increases in agalactosylated IgG structures over baseline. The differential response arose from the absence of available E2.

Conclusions: These results establish E2 as a critical factor in the modulation of human IgG glycosylation in vivo. In the setting of low E2, T does not appear to influence IgG glycosylation. This effect is dependent on the availability of E2 via aromatization of T, reflecting gender-dependent regulation of immune function by sex steroid hormones.

P-21: Sexual Orientation Disparities in Unintended Pregnancies Among Adult Women: Results From a Nationally Representative Study

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Background and Objective: Unintended pregnancy is associated with adverse infant and maternal outcomes. Research suggests that bisexual and gay or lesbian women are at increased risk of teen pregnancy. No studies have examined disparities in sexual orientation among adults with unintended pregnancies. The objective of this study was to determine if lesbian women, bisexual women, and heterosexual WSW (women who have sex with women) are more likely to report mistimed and unwanted pregnancies than are heterosexual WSM (women with male sex partners only [referent]).

Methods: Data were taken from the National Survey of Family Growth 2006–2010, a nationally representative study of U.S. women and their pregnancy histories. The sample was restricted to pregnancies within 5 years of the survey (N=5,521; mean maternal age=27.9 years). Mixed-effects hazard models were used to assess disparities in sexual orientation in reports for pregnancies that were characterized as too soon, unwanted, or wanted. Analyses adjusted for socio-demographic characteristics, established risk factors (e.g., forced sex, age of debut), parity, and use of assisted reproductive technology.

Results: In all, 1% of the pregnancies were among lesbian women, 4.6% among bisexual women, and 10.2% among heterosexual WSW. Fully adjusted models revealed that heterosexual WSW were 1.5 times ($P<.01$) as likely as the reference group to report the pregnancy occurred “too soon.” Bisexual and lesbian women were 1.5 ($P<.10$) and 3 times ($P<.05$), respectively, as likely as the reference group to report that the pregnancy was unwanted. These results are robust as to whether the pregnancy ended in termination, miscarriage, or live birth.

Conclusions: Lesbian and bisexual women are engaging in sexual behaviors that result in an elevated risk of unwanted pregnancies, with implications for other possible sexual health risks. The contraceptive needs of the lesbian and bisexual populations are not being met.

P-22: Sleep Duration and Fasting Blood Glucose in Gestational Diabetics

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Background and Objective: Data from nonpregnant populations suggest that sleep disruption can negatively affect glucose metabolism. Moreover, several studies have found associations between shortened sleep and impaired glucose metabolism in pregnancy. However, interpretation of the pregnancy data is limited, given the lack of objective sleep measures. The objective of this study was to describe the relationship between objectively assessed sleep duration and fasting blood glucose in women recently diagnosed with gestational diabetes.

Methods: At the time that women recently diagnosed with gestational diabetes were enrolled, none of them were on insulin or glyburide, and all received the same standardized teaching by trained diabetic educators. The women were asked to wear an Actigraph and to complete a sleep log for 7 consecutive days. A linear mixed model analysis was used to estimate the effect of sleep duration on morning fasting blood glucose.

Results: A total of 17 participants provided sleep data and morning fasting blood glucose values; 68 nights of data were available for analysis. Median fasting glucose was 94.5 mg/dL (interquartile range [IQR], 89.5–102.5), and median sleep duration was 7.1 hours (IQR, 6.2–7.8). For 24% of the nights, sleep duration was less than 6 hours. Sleep duration was negatively associated with fasting blood glucose ($P = .038$). There was a 2 mg/dL decrease in fasting blood glucose for each additional hour of sleep.

Conclusions: A longer duration of sleep is associated with lower fasting blood glucose in women with gestational diabetes. Educating women on healthy sleep and screening for and treating sleep disorders during pregnancy may have roles in optimizing blood glucose control in gestational diabetes.

P-23: Protease Inhibitor-Based Highly Active Antiretroviral Therapy Is Associated with Decreased Plasma Folate and Increased Transferrin Receptor Concentrations in Lactating HIV-Infected Women

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Background and Objective: To optimize the health of lactating HIV-infected women, information is needed about the association between highly active antiretroviral therapy (HAART) and the micronutrient concentrations of these women. The objective of this study was to measure the associations of protease inhibitor-based HAART and micronutrient-fortified, lipid-based nutrient supplements (LNS) with concentrations of plasma folate, B12, selenium, retinol binding protein (RBP), hemoglobin, ferritin, and transferrin receptors (TfR) in lactating HIV-infected women at 24 weeks postpartum.

Methods: Prospectively enrolled Malawian women ($n = 690$) received (1) HAART containing lamivudine/zidovudine and either nelfinavir or lopinavir/ritonavir or (2) no HAART from delivery to 28 weeks postpartum. They were further assigned to LNS, which met the energy and micronutrient requirements of lactation, or to no LNS. Multivariable linear regression was used to test differences in micronutrient concentrations between groups while controlling for season, baseline viral load, and baseline CD4 count.

Results: Compared with the control group, LNS was associated with increased folate concentrations ($+7.2$ nmol/L, $P < .001$) and lopinavir/ritonavir with decreased folate concentrations (-3.0 nmol/L, $P < .05$). In the groups receiving both interventions, HAART eliminated the positive association of LNS with folate. LNS ($+73.2$ pmol/L, $P < .001$) and nelfinavir ($+59.9$ pmol/L, $P < .05$) were associated with increased B12 concentrations, but women who had both interventions did not differ from controls. Nelfinavir ($+1.6$ mg/L, $P < .001$), nelfinavir plus LNS ($+1.2$ mg/L, $P < .001$), and lopinavir/ritonavir ($+0.9$ mg/L, $P < .01$) were associated with increased TfR, indicating

poorer iron status. No differences between groups were detected in RBP, hemoglobin, ferritin, or selenium.

Conclusions: HAART appears to be negatively associated with folate and positively associated with TfR. It diminished positive associations of LNS with folate. These findings suggest that tailored nutritional interventions are needed in lactating HIV-infected women on lifelong HAART.

P-24: Sex Differences in Demand for Highly Palatable Food Rewards: Role of Orexin Neurons

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Background and Objective: Demand is a measure of reward consumption as a function of the reward's price—the effort required to earn a reward. Recent studies (including ours) have found that orexin signaling is involved in responding to highly salient rewards, particularly during high effort (Cason & Aston-Jones, 2012, *Psychopharmacology* 226, 155–165). Furthermore, orexin is sexually dimorphic (Johren et al., 2002, *Peptides* 23, 1177–1180). In the current study, demand for 3 types of highly palatable food (HPF) reward—low-fat, high-fat, and sucrose—were evaluated in male and female rats.

Methods: We used a within-session behavioral economics approach recently developed in our laboratory (Bentzley et al, 2013, *Psychopharmacology* 226,113–125) to evaluate the role of orexin signaling in demand for an HPF. With this method, an entire demand curve (consumption as a function of effort) is generated in each session, allowing for comparisons of demand following different manipulations.

Results: Female Sprague-Dawley rats revealed increased motivation (lower demand elasticity) for the high-fat and sucrose HPF compared with males; no sex differences in demand for the low-fat HPF were observed. Furthermore, administration of an orexin 1 receptor antagonist SB-334,867 prior to the behavioral economics session resulted in decreased demand for all rewards in male rats, but it altered demand only for the low-fat HPF reward in female rats.

Conclusion: These results indicate sex differences in the mechanisms that drive reward motivation for high-fat and sucrose rewards that should be evaluated in future studies.

P-25: Maternal Vitamin D Status, Preterm Birth, and Preeclampsia in a Multi-Site Trial of High-Risk Pregnancies

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Background and Objective: Poor maternal vitamin D status is associated with adverse pregnancy outcomes. Our objective was to examine the association between maternal vitamin D status and risk of preterm birth and preeclampsia in women at high risk for preeclampsia.

Methods: Pregnant women participated in a randomized trial of low-dose aspirin in 12 U.S. medical centers. In a subset of these women, we measured 25-hydroxyvitamin D (25[OH]D) concentrations from serum collected at 12–26 weeks of gestation ($n = 831$). Preeclampsia was rigorously defined by clinical criteria set by study investigators. Spontaneous preterm birth was defined as the spontaneous onset of labor or rupture of membranes at less than 37 weeks of gestation. Indicated preterm birth was defined as all preterm cases that were not spontaneous.

Results: Preterm birth occurred in 29% of births; 58% were indicated and 42% were spontaneous. Early preterm birth (< 35 weeks) occurred in 16% of births; half of these births were indicated and half were spontaneous. Preeclampsia occurred in 23% of pregnancies. We found that 25(OH)D concentrations were not associated with risk of overall, spontaneous, or indicated preterm birth (all $P > 0.05$). We also found that a 25(OH)D concentration of ≥ 75 nmol/L was

associated with a 50% reduced risk of early preterm birth (<35 weeks gestation) in comparison with <30 nmol/L (adjusted risk ratio: 0.50, 95% confidence interval, 0.26, 0.95). In this study, 25(OH)D concentrations were also inversely associated with risk of indicated, but not spontaneous, early preterm birth. We observed no association between 25(OH)D concentration and the risk of preeclampsia.

Conclusions: Maternal vitamin D status was inversely associated with risk of early preterm birth but not with later preterm birth or preeclampsia. Thus, vitamin D status deserves further attention in high-risk pregnancies.

P-26: Clinical and Biomarker Characterization of Inherited Frontotemporal Dementia

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Background and Objective: To date, clinically heterogeneous frontotemporal dementias (FTDs) have not been evaluated in terms of their genetic and molecular bases. We propose to identify the earliest presymptomatic changes in 5 families with dominantly inherited FTD in which this dementia was due to mutations in the tau (*MAPT*) or progranulin (*GRN*) genes. The objective is to develop a cohort of familial FTD cases and characterize them longitudinally in terms of clinical, behavioral, and molecular phenotypes.

Methods: Participants will be clinically evaluated, with a focus on changes in language, behavior, results of neuropsychological testing, and neurological findings. Molecular phenotype will be determined by measuring A β 40, A β 42, tau, and ptau181 in the cerebrospinal fluid (CSF) and using novel tau positron emission tomography (PET) imaging.

Results: In the *GRN* families, 15 clinical assessments have been completed, and CSF has been collected on 3 individuals. Four members of the *MAPT*^{R406W} family have completed clinical and cognitive assessments and CSF collection. A new *MAPT*^{P301L} family has been identified, and 4 clinical assessments have been completed; collection of CSF is pending. The majority of enrolled individuals are not symptomatic, further underscoring the need to evaluate biomarkers for early detection. We are adopting the new emerging technology of tau PET imaging to complement biofluid analysis and further characterize presymptomatic FTD.

Conclusions: Members of families with inherited FTD can be recruited and can complete clinical and behavioral assessments as well as submit biofluids to determine the biomarkers of presymptomatic disease. The immediate plan is to focus recruitment on our *MAPT*^{R406W} and *MAPT*^{P301L} families and assess their tau molecular phenotype using both CSF and tau PET imaging.

P-27: Relation of Gender and Cognitive Complaint to Neuropathological Evidence of Alzheimer's Disease in Mild Cognitive Impairment

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Background and Objective: Female sex and a memory complaint independently relate to a greater risk of pathological features of Alzheimer's disease (AD). Little is known, however, about the synergistic association of these factors with AD pathology. The objective of this study was to assess whether sex and memory complaint relate to greater AD pathology at autopsy in mild cognitive impairment (MCI), which is the prodromal phase of AD.

Methods: Participants from the National Alzheimer's Coordinating Center included 168 individuals (n=91 female) diagnosed with MCI approximately 1 year before death. At last clinical visit before death, participants and a loved one were asked if the participant had memory problems; a "yes" response represented a memory complaint. Complaint status was defined as no complaint (both the participant and the loved one answered "no") or mutual complaint (both

answered "yes"). Outcomes included autopsy-based AD pathology. Regression analyses related sex and complaint to neuropathology.

Results: At death, 43% of MCI individuals met the Consortium to Establish a Registry for AD criteria for AD. Compared with no complaint, mutual complaint showed more pathology, including diffuse (odds ratio [OR]: 6.6, $P < .01$) and neuritic (OR: 3.1, $P = .047$) amyloid plaques and a higher Braak stage (OR: 3.4, $P = .04$). More women than men met criteria for AD (OR: 1.2, $P = .04$). Women and men had similar frequencies of memory complaint, and no sex-by-complaint interaction was found.

Conclusions: Among older adults with MCI, a memory complaint and female sex independently relate to greater risk of AD pathology at death. However, the combination of these risk factors does not produce an additive risk of disease. In MCI, women and older adults with a memory complaint are ideal targets for early intervention strategies.

P-28: Menarche and Pediatric Multiple Sclerosis

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Background and Objective: Multiple sclerosis (MS) is an inflammatory disease of the central nervous system that predominantly affects women, with a sex ratio of 3:1 in most countries. Pre-pubertal onset of MS is rare, but it uniquely has a 1:1 sex ratio. Thus, puberty appears to influence the differential MS risk between males and females. How puberty may be associated with MS clinical features and disease course, however, is unknown. The objective of this study is to determine the association of menarche with disease course in girls with MS.

Methods: This is a longitudinal retrospective study using prospectively collected data from the University of California, San Francisco, Regional Pediatric MS Center database. As puberty onset is poorly defined, we used year of menarche as a reliable proxy for the onset of puberty. Poisson regression models were used for relapse analysis and adjusted for ethnicity and body mass index (BMI).

Results: Girls with prepubertal MS onset (n=23) and postpubertal onset (n=46) had similar ages at menarche, 12.2 years (± 1.6) and 12.0 years (± 1.4), respectively. Differences in MS symptoms at presentation included more cognitive symptoms in prepubertal patients (30% vs. 4%, $P = .005$) and more sensory symptoms in postpubertal patients (17% vs. 48%, $P = .018$). Females with prepubertal MS onset had a lower incidence of relapses (incidence rate ratio: 0.12, 95% confidence interval, 0.07, 0.2, $P < .001$) in a comparison with those having postpubertal onset after adjustment for ethnicity and BMI.

Conclusions: Pubertal status at disease onset may influence MS course, at least in female patients. Understanding how puberty influences the clinical features of MS may offer new insights into important factors regulating disease processes.

P-29: Enteric Glia Drive Neuron Death in Colitis

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Background and Objective: Gut dysfunction in women with Crohn's disease causes low quality of life and significant mortality. Permanent gut dysfunction is caused by neuron death in the enteric nervous system. Activation of neuronal P2X7 receptors (P2X7Rs) is the trigger for neuron death, but how this pathway becomes activated is unknown. Enteric glia surround enteric neurons and regulate their microenvironment. Our objective was to test the hypothesis that glial cells drive neuron death in Crohn's by activating P2X7Rs.

Methods: Glial mechanisms were manipulated with drugs in vitro or gene modifications in vivo, and neuron survival was quantified by immunohistochemistry. Dinitrobenzene sulfonic acid colitis was used to model Crohn's in vivo. Glial activity was monitored by

imaging Ca^{2+} and nitric oxide (NO). Analysis of variance (ANOVA) with Bonferroni's multiple comparisons was used to assess statistical differences.

Results: Activation of glial Ca^{2+} responses drove neuron death to the same extent as directly activating neuronal P2X7Rs (in both cases it was reduced by 25% vs. control; $n=5$, $P<.005$). Stimulation of glia promoted NO production during inflammation, and glial NO was required for P2X7R-driven neuron death. Exogenous NO was sufficient to drive neuron death (20% loss, $n=3$, $P<.0001$). Ca^{2+} responses and NO converged on glial connexin-43 (Cx43) hemichannels and blocked Cx43 activity with the mimetic peptide 43Gap26, or they deleted the channel in inducible and conditional Cx43 null mice, preventing neuron death in situ and in vivo, respectively.

Conclusions: Activation of enteric glial cells drives P2X7R-dependent neuron death in Crohn's disease. New therapies that target this novel glial-dependent mechanism could improve treatment for Crohn's.

P-30: Morphological and Diffuse Tensor Imaging-Based Brain Signatures Discriminate Obese and Overweight from Lean Subjects: Examining Sex Differences Within the Brain

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Background: Neuroimaging has identified similarities between brain mechanisms involved in maladaptive obesity-related ingestive behaviors and addictive behaviors, demonstrating that alterations in key regions of an extended reward network are linked to increased food-related behaviors in obesity. The objective of this study was to apply multivariate pattern analysis from machine-based learning approaches to identify obesity-related grey- and white-matter alterations.

Methods: Structural and diffusion tensor imaging were obtained from 120 healthy controls (64 females, 63 with high body mass index [BMI]). FreeSurfer was used for regional segmentation and parcellation, yielding 165 regions. Deterministic tractography was performed using TrackVis to provide normalized fiber density counts between regions. Each subject's structural values and connectivity matrices were entered into a sparse partial least squares discrimination analysis in order to examine differences between obese or overweight and lean individuals.

Results: *Grey Matter (GM):* The classification algorithm indicated that 2 multivariate brain signatures achieved 69% accuracy in discriminating obese or overweight from lean. For females, the accuracy was 73%; for males, the accuracy was 62%. Signatures were primarily composed of higher GM values in cognitive modulatory regions, motor function, and motivation or drive in those with higher BMI. *White Matter:* The classification algorithm indicated 97% accuracy in discriminating obese or overweight from lean. In subjects with higher BMIs, it mainly included higher values in the basal ganglia, dorsal striatum, frontal, and orbital regions.

Conclusions: A higher BMI in healthy subjects is associated with structural and anatomical connectivity brain changes, especially in females. These brain measurements alone can identify specific targets for future mechanistic studies and treatments aimed at abnormal ingestive behavior and obesity.

P-31: Food Access and Dietary Behaviors Among Urban Adolescent Girls

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Background and Objective: The built environment may increase risk for obesity by creating a climate that supports unhealthy eating. Low-income, urban, African American girls are at high risk for obesity. The objective in this study was to determine if adolescent girls living near a high density of corner stores (4 or more within 0.25 miles, no supermarket) are more likely to consume additional snacks or desserts than their counterparts living near a low density (1–3) of corner stores or near no corner stores at all.

Methods: Adolescent girls (sixth and seventh grade) recruited from urban, low-income, predominantly African American schools comprised the study group. Percentiles of body mass index (BMI) for age were plotted from measured height and weight. Servings per day of snacks or desserts were calculated from the Youth/Adolescent Food Frequency Questionnaire. Home addresses were provided by caregivers and geocoded using ArcGIS. The numbers and types of food stores (maps were provided by the local planning department) within a 0.25-mile radius of home were calculated, exported, and merged. Multilevel linear regression models were used to examine associations while adjusting for covariates.

Results: In all, 781 of 789 addresses were geocoded; 634 of the 789 girls had dietary data (80.4%). In this sample, 52.4% of the girls were overweight or obese (at or above the 85th percentile for BMI), mean age was 12.1 years (range: 10.1–14.7), 35% lived near a high density of corner stores, 32% lived near a low density of such stores, and 33% did not live near any corner stores. Mean servings consumed of snacks or desserts equaled 3.4 ± 2.5 . Participants living near a high density of corner stores consumed more servings of snacks or desserts (3.8 per day) than those living near a low density of such stores (3.4 per day; $b=0.22$, $P=.046$) or those living where there were no corner stores (3.2, $b=0.33$, $P=.001$) in an analysis that adjusted for age, overweight or obesity, and clustering within schools.

Conclusions: Adolescent girls living near a high density of corner stores are likely to consume more snacks or desserts than their counterparts living elsewhere. Dietary interventions should consider the built environment/food access when addressing adolescent dietary behaviors.

P-32: Adolescent Contraceptive Use 1 Month After Pregnancy: Variation by Pregnancy Type and Intention, USA, 2006–2010

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Background and Objective: Adolescents are at high risk of unintended and rapid repeat pregnancies. Patterns of adolescent contraception use by method type after pregnancy, however, are not well understood. The objective of this study was to evaluate the prevalence and predictors of effective contraceptive use by adolescents 1 month after pregnancy.

Methods: By using the National Survey of Family Growth (2006–2010), the most recent pregnancies of adolescents (ages 13–19) were identified, including live births ($n=356$), abortions ($n=77$), and losses ($n=102$). Contraceptive use 1 month after these pregnancies was categorized based on World Health Organization classifications as effective (hormonal and long-acting) versus less effective (barrier, natural family planning, withdrawal, and no method). To evaluate factors associated with effective contraceptive use at 1 month after pregnancy, a multivariable logistic regression was performed that included the following factors: type of pregnancy, pregnancy intention, instruction on contraception, age, and race or ethnicity.

Results: Use of effective methods at 1 month after pregnancy differed between women with pregnancies resulting in live births (30.5%, $P<.01$), abortions (6.5%, $P<.01$), and losses (3.3%, $P<.01$). With control for age and race or ethnicity, pregnancies ending in abortion (odds ratio [OR]: 0.11, $P<.001$) or loss (OR: 0.05, $P<.001$) were associated with lower use of effective contraceptives, as were intended versus unintended pregnancies (OR: 0.29, $P<.05$). Group

instruction about contraception was marginally associated with greater use of effective contraceptives (OR: 1.9, $P < .10$).

Conclusions: Based on this study, it is likely that more than 90% of adolescents whose pregnancies result in abortion or loss will fail to use effective contraception at 1 month after pregnancy. There is an urgent need for effective strategies to increase the use of contraception by adolescents after pregnancy.

P-33: The Implications of Unwanted Pregnancies for Women's Mental Health in Later Life

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Background and Objective: Despite decades of research on unintended pregnancy (UP), few studies have explored UP's mental health effects on the women who carry those pregnancies. Nor has research examined these long-term associations for pregnancies that occurred prior to the legalization of abortion. The objective of this study was to assess later-life depressive episodes and symptoms among women who reported UPs prior to Roe vs. Wade, while controlling for potential confounders.

Methods: Data were derived from the Wisconsin Longitudinal Study, an investigation of 1 in 3 Wisconsin high school graduates from the class of 1956. In 1975, participating women were asked whether each of their prior births was intended, unintended but mistimed, or unwanted. We explored associations between unwanted or mistimed pregnancies and both depression scores (Center for Epidemiologic Studies Depression [CES-D]) and episodes later in life, all while accounting for numerous pre-pregnancy factors such as early-life socioeconomic conditions, IQ, personality, educational attainment, and prior depressive episodes.

Results: Among 4,601 women, 55% reported having had at least 1 UP, and 22% reported at least 1 unwanted pregnancy. Compared with women whose pregnancies were all intended, those who had at least 1 unwanted pregnancy were more likely to have higher levels of psychological distress by their early 50s—even after controlling for confounders. For women with mistimed pregnancies, the effect was smaller and less robust.

Conclusions: Among women who completed their pregnancies prior to the legalization of abortion, unwanted pregnancies were strongly associated with mental health outcomes in later life, a fact that should be considered by the clinicians and therapists who treat these women. Children are a critical turning point and a sustained influence on women's health.

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P-34: Role of Race/Ethnicity in the Association Between Obesity and Cancer Screening Among Women

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Background and Objective: The effects of race or ethnicity on the association between obesity and cancer screening have not been adequately explored in the literature. We examined whether the association between body mass index (BMI) and cancer screening is similar for Hispanic, black, and white women.

Methods: Two cycles of the Health Information National Trends Survey (HINTS) were combined for this cross-sectional study. Weighted descriptive statistics were evaluated using chi-square, and multivariable logistic regression models were used to evaluate associations between women with a normal (<25), overweight (25–29.9), or obese (≥ 30) BMI and guideline-concordant cancer screening (Pap testing $\leq$ every 3 years for those aged ≥ 21 years; most recent mammography ≤ 2 years ago for those aged ≥ 40 years) in analyses stratified by race or ethnicity.

Results: The study of the association between BMI and Pap tests included 4,080 women, and 3,093 were included in the analysis involving mammography. BMI was associated with Pap testing ($P < .01$), but not with mammography ($P > .05$). In stratified analyses, obese white women (odds ratio [OR]: 0.67; 95% confidence interval [CI], 0.51, 0.89) and overweight black women (OR: 0.46; 95% CI, 0.21, 0.99) were less likely to report Pap testing no more than 3 years ago than were women with normal BMIs of corresponding race or ethnicity, while no association was observed among Hispanics. Overweight white women were more likely (OR: 1.37; 95% CI, 1.00, 1.88) and obese Hispanic women were less likely (OR: 0.42; 95% CI, 0.19, 0.92) to report mammography no more than 2 years ago than were normal-weight women of corresponding race/ethnicity, while no association was observed among black women.

Conclusions: The association between BMI and cancer screening appears to vary by race and ethnicity. The reasons underlying this observation are unknown, but they may be sociocultural in nature.

P-35: Changes in Gene Expression After Radiation in Human Breast Cancers: A Guide to Predicting and Modulating Radiation Response

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Background and Objective: Clinical data suggest that subtypes of breast cancer respond differently to therapeutic radiation. We previously identified an association between breast cancer subtype and gene expression profiles in 6 breast tumor cell lines. Here, we extend our initial findings to include 16 diverse breast tumor cell lines and a cohort of pre- and post-radiation tumor tissue from early-stage breast cancer patients.

Methods: Sixteen biologically diverse breast cancer cell lines were characterized. Microarray analysis was performed using RNA from treated cell lines (5Gy and 0Gy). A 2-way multiplicative linear mixed-effects model was used to identify interactions between gene expression and radiation treatment. In addition, RNA was harvested from paired pre- and post-radiation formalin-fixed paraffin-embedded breast cancer tissue in 9 patients.

Results: Striking differences were noted in radiation-induced gene expression. Four of the cell lines experienced significant changes in gene expression following radiation, while 12 of the lines had very little radiation response. Three of the 4 non-HER2+ luminal cell lines were in the radiation-responsive group. FAS, a critical modulator of programmed cell death, showed significant differential induction in the radiation-responsive lines versus the radiation-nonresponsive lines. Genome-wide analysis of the human tumor samples revealed the FAS gene to be among the top 10% of genes with significant variation across tumor samples.

Conclusions: Breast tumor cell lines have distinct gene expression profiles following radiation. Non-HER2+ luminal cell lines appear to be more radiation responsive overall and induce FAS. Induction of FAS seen in culture can also be observed in patients.

P-36: Maternal Cis-Vaccenic (18:1 Cis-11) Acid Measured in Pregnancy Negatively Predicts Maternal Central Fat Distribution

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Background and Objective: Epidemiologic data are mixed regarding the relationship between palmitoleic acid (PA) or cis-Vaccenic acid (cVA) and disease risk. The mechanism behind how a risk or benefit may be conferred is unknown, with no data reported during pregnancy. Both fatty acids are thought to be involved in the signaling pathways regulating de novo lipogenesis and gluconeogenesis. This study examined the relationship between PA or cVA and maternal fat distribution.

Methods: Fifty women had blood drawn at 36 weeks in pregnancy and dual energy x-ray absorptiometry (DXA; iDXA GE Healthcare) was completed at 2 weeks postpartum. Central fat mass (FM), peripheral FM, visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT; trunk region) were calculated by using enCORE software (version 13.5). Blood was analyzed for red blood cell phospholipid fatty acids using gas chromatography. Gestational weight gain (GWG) was included as a confounder in the regression analysis, and group differences were explored by maternal pre-pregnancy body mass index (BMI) group (women with normal BMIs formed the reference group).

Results: Maternal central FM (kg; $R^2=0.68$) was predicted by cVA ($\beta = -10.4$; $P=.019$) and GWG ($\beta = 0.18$; $P=.011$), and group differences were found for the overweight ($\beta = 4.02$; $P<.001$) and obese ($\beta = 11.11$; $P<.001$) groups. Maternal SAT (kg; $R^2=0.67$) was predicted by cVA ($\beta = -1.3$; $P=.048$) and GWG ($\beta = 0.03$; $P=.020$), and group differences were found for the overweight ($\beta = 0.56$; $P=.001$) and obese ($\beta = 1.68$; $P<.001$) groups. No relationships were found to PA.

Conclusions: cVA appears to be negatively related to maternal central FM, a relationship that seems to be driven by a relationship to maternal SAT. Studies are needed to explore how cVA relates to metabolic parameters during pregnancy.

P-37: Sex-Specific Differences in Disease Severity in Patients with Chronic Rhinosinusitis with Nasal Polyps

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Background and Objective: Up to 50% of patients with chronic rhinosinusitis (CRS) have comorbid asthma, and we have reported that a subset of CRS patients who have nasal polyps (CRSwNP) have elevated autoantigen-specific antibodies within their NP. While increases in the prevalence and/or severity of asthma and autoimmunity in women are well characterized, it is not known whether CRSwNP demonstrates a similar trend. We sought to determine whether CRSwNP demonstrated sex-specific differences in prevalence or severity.

Methods: Using a prospectively collected database of patients undergoing nasal surgery ($n>1,200$), we evaluated the effect of sex on the prevalence of CRSwNP, aspirin sensitivity, and asthma status. We further compared levels of eosinophil cationic protein (ECP) and anti-dsDNA antibodies in NP extracts from men and women by enzyme-linked immunosorbent assay (ELISA).

Results: Although women comprised about 50% of control and CRS patients without NP (CRSsNP), a significantly smaller proportion of CRSwNP patients were female (37%, $P<0.05$). Interestingly, women with CRSwNP were more likely than their male counterparts to have comorbid asthma ($P<0.01$), and 62% of patients with aspirin-exacerbated respiratory disease (CRSwNP plus asthma and aspirin sensitivity) were women ($P<0.001$). Asthmatic women with CRSwNP had the highest levels of autoantigen-specific IgG ($P<0.01$) and ECP ($P<0.05$), and they were more likely than men to have revision surgeries ($P<0.05$).

Conclusions: These data suggest that women with CRSwNP have more severe disease than their male counterparts. Future studies are needed to elucidate the mechanisms that drive this disease in men and women, and these studies may pave the way for the development of improved therapeutic strategies for the treatment of CRSwNP in both women and men.

P-38: Reproductive Aging Is Associated With Altered Prefrontal and Hippocampal Signaling During Working Memory

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Background and Objective: A rapidly growing body of work from rodents and nonhuman primates has established estradiol's influence on synaptic organization within the prefrontal cortex (PFC) and hippocampus. Consistent with these findings, previous work from our group and others has demonstrated significant estradiol-dependent effects on dorsolateral PFC (DLPFC) function and working memory performance in young women. Given estradiol's regulation of memory circuitry, the loss of ovarian estrogens during menopause likely plays a significant role in shaping age-related neural changes in midlife. To investigate this, healthy midlife men and women ($N=132$; ages 46–53 years) who are part of a prospective birth cohort study were enrolled in a functional magnetic resonance imaging (fMRI) study.

Methods: Menstrual cycle histories in conjunction with fasting serum samples were used to determine the premenopausal/perimenopausal/postmenopausal status of women per STRAW + 10 (Stages of Reproductive Aging Workshop + 10) guidelines. Participants performed a visual working memory task during fMRI scanning.

Results: Robust changes in DLPFC and hippocampal function were observed as a function of reproductive age, despite minimal variance in chronological age. During working memory performance, women exhibited greater DLPFC activity and weaker hippocampal activity as estradiol levels declined and follicle-stimulating hormone (FSH) levels increased.

Conclusions: These results are consistent with our previous work in young women, showing exaggerated DLPFC activity under low versus high estradiol conditions (despite indistinguishable performance), a putative marker of neural inefficiency. We see a similar inefficient DLPFC response in midlife women as ovarian estradiol levels decline. These data underscore the importance of studying adults early in the aging process in order to understand sex-specific mechanisms that may shape cognitive aging trajectories and ultimately disease risk.

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P-39: Perfluorinated Compounds in Colostrum and Vaccine Antibody Concentrations at Age 6 Months

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Background and Objective: Perfluorinated compounds (PFCs) are a class of chemicals that have numerous applications, such as nonstick coatings and surfactants or repellents in food packaging and textile impregnation. Some human studies suggest that developmental exposure to PFCs results in decreased vaccine-specific antibody concentrations in children. This pilot study assessed concentrations of 2 prevalent PFCs, perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA, both measured in colostrum), in relation to vaccine antibody concentrations.

Methods: The 79 mother-infant pairs in the present study were a subset of 1,134 pairs participating in an ongoing cohort study in eastern Slovakia. PFOS and PFOA concentrations were determined in milk collected before the mother's discharge from the maternity ward. From infant serum collected at age 6 months, antigen-specific IgG antibody concentrations were determined for tetanus, diphtheria, haemophilus influenzae type b, and Bacillus Calmette-Guérin

vaccines. Multivariable regression was used to assess the association between antibody and PFC concentrations, adjusting for ethnicity, and maternal lipid and PCB (polychlorinated biphenyl) 153 concentrations.

Results: All concentrations of PFOA (median: 35 pg/ml; IQR [interquartile range]: 26 pg/ml) and PFOS (median: 36 pg/ml; IQR: 28 pg/ml) were above the assay's limit of detection. An increase in colostrum PFOA concentration from the 25th to the 75th percentile was associated with a 27% reduction in tetanus (95% confidence interval [CI], -88%, +10%) and a 24% reduction in diphtheria antibody concentrations (95% CI, -62%, +13%). Results for PFOS were generally null, as were those for haemophilus influenzae type b and Bacillus Calmette-Guérin endpoints.

Conclusions: These preliminary data indicate that PFOA concentrations may lead to reduced vaccine response in this study population.

P-40: De Novo Generation of Adipocytes From Hematopoietic Stem Cells in Human Adipose Tissue

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Background and Objective: Loss of gonadal hormone production is associated with a redistribution of fat from the extremities to deep visceral adipose tissue and a concomitant increase in the incidence of chronic diseases. This association suggests that gonadal hormones, in part, regulate the distribution of body fat and the production of adipocyte subpopulations that promote metabolic dysfunction. We previously reported the de novo production of proinflammatory white adipocytes from hematopoietic stem cells (HSCs) and their preferential accumulation in the visceral adipose tissue of female rather than male mice. These cells may provide a model for the regulation of adipocyte production by sex hormones. The objective of this study was to obtain clinical evidence for hematopoietic transdifferentiation to adipocytes in human transplant recipients as a first step in testing the impact of gonadal hormones on the production of these cells.

Methods: Biopsies of abdominal subcutaneous adipose tissue were harvested from adult subjects from 12 to 53 months after transplant. DNA from flow cytometry-purified adipocytes was subjected to microsatellite analysis for highly polymorphic short tandem repeats to quantify donor cell chimerism.

Results: Up to 35% of adipocytes were generated from the transdifferentiation of donor HSCs in the absence of cell fusion. The percentage of HSC-derived adipocytes increased over time.

Conclusions: These studies provide the first evidence for the hematopoietic origin of a subpopulation of adipocytes in humans. These adipocytes likely exhibit the same detrimental phenotype as HSC-derived adipocytes previously described in mice, thereby providing a new mechanistic link between gonadal hormones, adiposity, and chronic metabolic dysfunction.

P-41: Hysterectomy With Conservation of Both Ovaries Increases the Risk of Subsequent Hypertension

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Background and Objective: Hysterectomy with conservation of both ovaries (H-OC) is often considered to have no effect on ovarian hormones or on long-term cardiovascular risk. However, our prior work demonstrated that H-OC increased the risk of subsequent

cardiovascular disease (CVD). The objective of the present study was to explore the mechanisms linking H-OC with CVD, and thus we investigated the risk of developing de novo hypertension following H-OC.

Methods: The Mayo Clinic Study of Uterine Disease and Health included 3,816 women who underwent H-OC between 1965 and 2002 in Olmsted County, Minnesota. Each woman was age-matched (+/- 1 year) to a referent woman who had her uterus and both ovaries intact as of the index date (the date of H-OC in the matched pair). Hypertension was identified using diagnostic codes from the electronic indexes of the Rochester Epidemiology Project records-linkage system. Analyses were stratified by age at H-OC and by indication for surgery. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards models.

Results: Overall, hypertension was increased in women following H-OC (HR: 1.08, 95% CI: 1.01, 1.06). This increased risk was driven by women who underwent H-OC at age 46 to 50 years (HR: 1.22, 95% CI: 1.00, 1.49). No other age strata showed significant associations. The association did not vary across the indication for surgery (fibroids, prolapse, or menstrual disorders).

Conclusions: There is an increased risk of hypertension in women who have undergone H-OC in comparison with age-matched referent women. Hypertension and other vascular changes may be the link between H-OC and CVD.

P-42: Neonatal Seizures or Serious Neurologic Dysfunction Recorded or Unascertained in Birth Certificates After Vaginal Breech Deliveries at Home Compared to Hospitals

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Background and Objective: Despite the higher risk of neonatal seizures among home births than hospital births, vaginal breech delivery (VBD), one of the most useful indicator conditions for neonatal seizures, was unspecified in recent studies or excluded altogether. We hypothesized that VBD at home was associated with more recorded or unascertained neonatal seizures or serious neurologic dysfunction (NSSND).

Methods: In a secondary analysis of VBD for the years 2010 to 2012 from the National Center for Health Statistics Natality File, we excluded multiple gestations and deliveries at <37 weeks or <2,500 grams. NSSND was abstracted from the 2003 U.S. Standard Certificate of Live Birth from at least 33 states and Washington, D.C. Logistic regressions were performed to control for maternal race or ethnicity and age and to calculate adjusted odd ratios (ORs) and 95% confidence intervals (CIs).

Results: Among 87,139 VBDs, 1,065 (1.22%) were delivered at home. NSSND was more likely to be recorded at both unintended (OR: 52.9; 95% CI, 8.3, 188.2) and intended (OR: 33.0; 95% CI, 10.4, 88.7) VBDs at home than in hospitals; unknown NSSND also was more likely to be recorded at unintended home VBDs (OR: 7.8, 95% CI, 1.9, 21.0) than in hospitals. NSSND at an intended home VBD by midwives other than certified nurse midwives was more likely to be recorded than a VBD by medical doctors in hospitals (OR: 84.8; 95% CI, 22.7, 261.8).

Conclusions: NSSND is recorded or unascertained more frequently among VBDs at home than in hospitals. Further research is needed to address the Institute of Medicine's calls to evaluate the effects of maternal care services in diverse settings and to improve the quality of birth certificates.

P-43: Childhood Risk Factors for Adult Hypertension—Sex Differences: The Bogalusa Heart Study

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Background and Objective: Childhood risk factors are predictive of adult hypertension (AHT). However, whether such relationships are sex- and/or race-specific is not known. The objective of this study was to examine sex- and race-specific associations between childhood risk factors and risk of AHT.

Methods: We included 3,065 participants (67% white, 33% black) who were examined as both children (aged 3.3–17.9 years) and adults (aged 18.0–50.3 years) in the Bogalusa Heart Study, with an average follow-up of 23.5 years. Odds ratios (ORs) derived from logistic regression models were used to represent AHT risk associated with an increase of 1 standard deviation in childhood risk factor variables, with adjustment for age, cigarette smoking, and race (in sex-specific analysis).

Results: The incidence of AHT was 22.1% (676/3,065). In the total sample, significant childhood predictors of AHT were systolic blood pressure (SBP) (OR: 1.62, 95% confidence interval [CI], 1.45, 1.82; $P < .0001$) and body mass index (BMI) (OR: 1.20, 95% CI, 1.08, 1.33; $P = .001$). The OR for childhood SBP as a predictor of AHT was 1.92 (95% CI, 1.61, 2.30; $P < .0001$) in males and 1.45 (95% CI, 1.25, 1.68; $P < .0001$) in females (P for interaction = .025). Childhood low-density lipoprotein cholesterol was a significant predictor only in males (OR: 1.23, 95% CI, 1.03, 1.46, $P = .022$) and BMI only in females (OR: 1.23, 95% CI, 1.07, 1.41, $P = .005$), but there was no significant interaction by sex for either of these risk factors ($P > .079$). There were no significant interactions for any of the risk factors by race ($P > .05$).

Conclusions: Sex modifies the relationship between childhood risk factors and the risk of AHT. The public health implications of these findings await further investigation.

P-44: Building a Community-Academic Partnership to Promote Healthy Weight in Wisconsin Women

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Background and Objective: Excess weight before and during pregnancy is increasingly common, disproportionately affects low-income and minority women, and results in tremendous health burdens. Thus, there is an urgent need for initiatives to promote healthy weight for low-income minority women before, during, and after pregnancy. Effective obesity prevention will require broad-based, coordinated efforts beyond the scope of traditional health care practice. Our long-term vision is to create innovative nutrition and physical activity programs for women planning a pregnancy or who are already pregnant, programs that are offered in partnership between community partners and academic health care practitioners.

Methods: We developed a collaborative partnership involving key stakeholders in a defined geographic area with significant cultural diversity, low economic status, and health disparities. Partners included health care providers, researchers, community organizations, health care administrators, public health workers, and community advocates. Together, we developed and implemented an asset-oriented, multi-component strategy to identify existing resources and determine the need for additional evidence-based, sustainable, and culturally appropriate interventions. Partnership strategies included regular coalition meetings, a community-academic partnership retreat, asset mapping, and interviews with community leaders and community members.

Results: We identified over 100 existing community resources for reproductive-aged women and their children, but there is still a clear need for better coordination to reduce duplication of services and improve women's access to the services they need. Where gaps exist, we have identified mutually agreeable, feasible, evidence-based community approaches that could be implemented.

Conclusions: Sustainable community-academic partnerships can be developed to identify and implement obesity prevention and intervention strategies for reproductive-aged women.

P-45: Women Who Run from Zombies: Is a Horror-Themed Active Mobile Game Acceptable to Adult Women?

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Background and Objective: Adult women are in need of novel interventions to increase their physical activity. Although active video games can be motivating, women may find them frightening or their violent content aversive. This pilot study investigated women's reactions to a zombie-themed active video game played on a smartphone. Specifically, the study sought to determine the acceptability of the smartphone game *Zombies, Run!* among adult women.

Methods: Ten sedentary, overweight women (age 52 ± 12 years, body mass index 31 ± 4) were recruited into a 12-week pre-experimental pilot study. Participants received a smartphone with the game application and weekly brief counseling phone calls. The game consisted of audio clips that told a post-apocalyptic story and randomized zombie chases that required brief higher-intensity activity intervals. Acceptability was measured via several self-report items and open-ended interview questions.

Results: Nine women completed the study (1 became pregnant). No participants reported a problem with the game's storyline or scary nature (0/9). These women agreed or strongly agreed that zombie chases made them go faster (9/9), the game encouraged them to view their steps (7/9), and that they would like to continue to play (6/9). A recurring theme from interviews was participants' preference for using their own phones rather than the ones provided.

Conclusion: Women can and do enjoy horror-themed narratives and active video games. However, the logistics involved in playing mobile games can present challenges to their acceptability. Although providing smartphones has benefits for investigators, future interventions may wish to use participants' own phones to improve acceptability.

P-46: Pre-Existing Obesity and Weight Loss Do Not Affect the Decline in Physical Activity That Results from the Loss of Ovarian Function

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Background and Objective: Menopause has been associated with a decline in physical activity and metabolic health. We hypothesized that obesity may protect against the decline at this transition, as adipose tissues become the primary source for local estrogens. The objective of this study was to examine the impact of pre-existing obesity and weight loss on spontaneous physical activity (SPA) after the loss of ovarian function.

Methods: Mature lean and obese female rats were fed a moderate-fat diet ad libitum (lean-AL, obese-AL) or one that was calorie restricted (lean-CR, obese-CR) for 8 weeks. CR rats lost approximately 15% of their body weight, the vast majority being from the loss in fat mass. All 4 groups were then ovariectomized (OVX) to model menopause. Subsequent responses in energy balance and physical activity were assessed before, during, and after 8 weeks of AL feeding in all groups.

Results: In AL rats, OVX induced a decline in SPA that became apparent only during the OVX-induced positive energy imbalance. In CR rats, this decline occurred prior to any weight gain. By the end of the study, SPA levels were approximately half of their pre-OVX levels in all groups. In CR rats, the decline in activity was accompanied by a reduction in mitochondrial respiration capacity, regardless of their pre-existing adiposity level.

Conclusions: These observations show that pre-existing obesity and weight loss do not affect the OVX-induced decline in SPA. Weight loss, however, appears to impart a reduction in mitochondrial respiration capacity that should remain after OVX-induced weight gain.

P-47: Disturbed Sleep During Pregnancy in Women with Systemic Lupus Erythematosus (SLE)

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Background: Sleep disruption, which is common in pregnancy, is predictive of poor pregnancy outcomes. Women with systemic lupus erythematosus (SLE) are at increased risk for pregnancy complications, and current literature suggests that disordered sleep is common in SLE, particularly during active disease. However, no studies have assessed sleep in pregnant women with SLE. The objective of the present study was to examine sleep patterns among pregnant women with SLE and compare them to pregnant women with other chronic diseases.

Methods: Third-trimester pregnant women recruited from obstetric clinics at a large tertiary medical center were included. Low-risk, healthy pregnant women were also recruited. All women completed a battery of sleep questionnaires. Cases were reviewed for diagnoses of SLE, chronic hypertension (CHTN), preeclampsia (PE), and gestational diabetes (GDM).

Results: To date, enrollment has included 12 women with SLE, 63 with CHTN, 119 with PE, and 195 with GDM. No SLE women were found to be obese, and their nonpregnant body mass index was lower than that of any other group except low-risk pregnancies: ($P = .003$ vs. the PE group; $P < .001$ vs. CHTN, GDM). Despite this, frequent fatigue and sleepiness were higher in SLE women than in any of the other groups, and SLE women were more likely to nap than others (64% vs. 27–32%). In addition, SLE women used more over-the-counter sleep aids (27 SLE% vs 10% CHTN, 15% PE, 6% GDM and 8% healthy) and were less likely to snore (8% among SLE; 27% of healthy controls; >40% of others).

Conclusions: Pregnant SLE women have disturbed sleep, as evidenced by their significantly increased use of sleep aids when compared with other pregnant women who have chronic diseases. These pilot data support a larger-scale effort to better characterize sleep in this population, which is known to be at risk for pregnancy complications.

P-48: Do Stress-Related Eating Behaviors Drive Observed Associations Between Childhood Abuse and Later Weight Status?

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Background and Objective: Women who experienced abuse in childhood are at increased risk for later obesity, but the mechanisms are not known. The objective of this study was to estimate the effect of childhood abuse on body mass index (BMI, calculated as mass in kilograms divided by the square of height in meters) in women aged 22 to 29 years and examine whether this effect is independent of 2 stress-related eating behaviors: binge eating and coping-motivated eating.

Methods: The Growing Up Today Study enrolled 9,039 9- to 14-year-old girls in 1996 and has followed them with questionnaires. The 2007 questionnaire ascertained childhood physical, sexual, and emotional abuse, and the 2010 questionnaire included the coping-motivated eating subscale of the Motivations to Eat Scale. Height and weight, as well as binge eating, have been collected over follow-up. We used linear marginal structural models to estimate (1) the effects of abuse on BMI in 2010, when participants were aged 22 to 29 years, and (2) these effects independent of coping-motivated and binge eating.

Results: Of 4,009 women in the analysis, 15% experienced at least 1 type of severe abuse, and 6% experienced at least 2 types. Women who experienced at least 2 types of severe abuse prior to age 11 years had a significantly higher BMI at age 22 to 29 years than non-abused women (difference = 1.10 BMI units; 95% confidence interval [CI], 0.30, 1.90). This difference was 0.89 BMI units (95% CI, -0.04, 1.82) after adjustment for binge eating and 0.61 BMI units (95% CI, -0.29, 1.51) after adjustment for coping-motivated eating.

Conclusions: Binge and coping-motivated eating only partially explain the impact of severe abuse on BMI. More research is needed to identify other potential pathways linking abuse and obesity.

P-49: Sex- and Disease-Related Alterations in Anterior Insula Functional Connectivity of the Resting Brain in Chronic Abdominal Pain

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Background and Objective: Resting-state functional magnetic resonance imaging has been used to investigate intrinsic brain connectivity in healthy subjects and in patients with chronic pain. Sex-related differences in the frequency power distribution within the human insula (INS), a brain region involved in the integration of interoceptive, affective, and cognitive influences, have been reported. We aimed to test sex- and disease-related alterations in the intrinsic functional connectivity of the dorsal anterior INS.

Methods: Because the anterior INS is engaged during goal-directed tasks and modulates the default mode and executive control networks, we compared the functional connectivity of dorsal anterior INS with other brain regions in age-matched female and male healthy control subjects and in patients with irritable bowel syndrome, a common chronic abdominal pain condition.

Results: We found evidence for sex- and disease-related alterations in the functional connectivity of the anterior INS: (1) compared with female patients, males had increased positive connectivity of dorsal anterior INS bilaterally with medial prefrontal cortex (PFC) and dorsal posterior INS; (2) compared with male patients, females had greater negative connectivity of the left dorsal anterior INS with left precuneus; (3) disease-related differences in the connectivity between bilateral dorsal anterior INS and dorsal medial PFC were observed only in female subjects; and (4) the functional connectivity between dorsal anterior INS and dorsal medial PFC was significantly correlated with a gastrointestinal-related worry index in male patients.

Conclusion: These findings suggest that the dorsal anterior sub-region of the INS plays an important role in modulating the intrinsic functional connectivity of major networks in the resting brain and that this role is influenced by sex and diagnosis.

P-50: Racial and Ethnic Differences in HPV Prevalence and Type Distribution Among Women in the United States

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Background and Objective: Human papillomavirus (HPV) types vary by geographical region, and evidence suggests that this may be attributable to the underlying racial and ethnic composition within a given area. The objective of this study was to examine whether the distribution of HPV types differs by race/ethnicity among women in the United States.

Methods: We used NHANES (National Health and Nutrition Examination Survey) data from 2003 to 2010 to examine the prevalence of 37 HPV types detected in cervicovaginal swabs from women aged 20 to 54 years. The prevalence of each genotype was determined for non-Hispanic white ($n = 2,543$), non-Hispanic black ($n = 1,216$), and Hispanic women ($n = 1,693$). Chi-square tests were used to compare individual and grouped HPV types by race or ethnicity. Logistic regression assessed associations between race or ethnicity and HPV types after adjusting for covariates.

Results: Overall HPV prevalence was higher in blacks (59.1%) and Hispanics (44.9%) than in whites (39.9%) ($P < .001$). Having any high-risk type, having a high-risk non-vaccine type (non-16 or 18), and having a low-risk type were all more common in blacks and Hispanics than whites ($P < .001$ each), and these associations remained significant after adjustment. HPV 53 was the most common high-risk type in whites and Hispanics, and both 52 and 53 were the most common types in blacks. The prevalence of HPV 31, 58, and 66 was higher in blacks and Hispanics than in whites ($P < .01$ each), and significant differences were also observed for other HPV types.

Conclusions: The distribution of high-risk HPV types in the United States varies by race and ethnicity, and this fact may play a role in the observed differences in geographical distribution of HPV types. The results of this study may have implications for the effectiveness of current and next-generation vaccines.

P-51: Sex Differences in Intrinsic Connectivity During fMRI Stroop in Cocaine-Dependent Individuals

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Background and Objective: We have previously used intrinsic connectivity distribution (ICD) analyses to assess functional connectivity during fMRI (functional MRI) Stroop performance in cocaine-dependent individuals. Versus controls, cocaine-dependent subjects showed less intrinsic connectivity diffusely but greater mean-adjusted connectivity in the ventral striatum, putamen, inferior frontal gyrus, anterior insula, thalamus, and substantia nigra. However, the extent to which cocaine-dependent women and men showed differences in functional connectivity was not previously examined. The objective of the present study was to examine sex differences in intrinsic connectivity in cocaine-dependent subjects during fMRI Stroop performance.

Methods: Thirty-three (13 female, 20 male) cocaine-dependent patients completed an fMRI Stroop Color-Word Interference task as described in our previously published work. Unadjusted and mean-adjusted ICD analyses were conducted to identify sex differences, with the latter analyses adjusting for individual differences in overall connectivity.

Results: No between-sex differences survived gray-matter correction in unadjusted maps. Mean-adjusted maps showed that cocaine-dependent women, relative to men, showed greater connectivity in the midbrain, hippocampus, temporal gyrus, and cerebellum and lesser connectivity in the insula, putamen, and dorsal cortical regions, including the inferior parietal lobule and post-central gyrus.

Conclusions: Cocaine-dependent women and men will display differences in mean-adjusted connectivity during a cognitive control task, with women showing relatively greater connectivity within ventral brain regions previously linked to drug abstinence and relatively lesser connectivity within insula, stratum, and dorsal brain regions linked to sensorimotor function. The extent to which these patterns of connectivity relate to clinically relevant measures of cocaine dependence warrants additional investigation.

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P-52: Impact of Endogenous Progesterone Levels on Reactivity to Yohimbine and Cocaine-Paired Cues

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Background and Objective: The long-term effects of cocaine use are more severe for women than men. Understanding the neurobiologic factors that underscore the motivation to use cocaine could improve treatment outcomes for cocaine-dependent women. In

a recent study, we found that cocaine-dependent women reported greater subjective responses to cues that were preceded by a stressor than did cocaine-dependent men. Of note, data from clinical and preclinical models of relapse suggest that progesterone attenuates cocaine-seeking behavior. The objective of the present study was to compare the impact of high (> 4 ng/ml) and low (< 2 ng/ml) plasma progesterone on reactivity to cues that are preceded by a stressor.

Methods: Cocaine-dependent women with high ($n = 10$) and low ($n = 15$) plasma progesterone received either the alpha-2 adrenergic receptor antagonist yohimbine (21.6 mg) or placebo before each of 2 cocaine-cue exposure sessions. Participants were tested under both treatments in a counterbalanced, double-blind fashion. Subjective data were collected after treatment, immediately and at 5, 30, and 60 minutes after the cue.

Results: Under yohimbine, women with high progesterone reported lower craving in response to the cue than did women with low progesterone (the group by time interaction was significant at $P = .05$). Also under yohimbine, women with high progesterone reported lower anxiety throughout the procedures than did women with low progesterone (there was a significant group effect; $P = .03$).

Conclusions: These preliminary data suggest that high levels of endogenous progesterone attenuate subjective anxiety and responses of craving to a cue that is preceded by a stressor. Importantly, these data support a growing literature demonstrating the protective effects of endogenous progesterone on the vulnerability to cocaine-seeking behavior.

P-53: Associations Between Ovarian Hormones and Multiple Facets of Anxiety and Depression

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Background and Objective: Although many claim that anxiety and depression are significantly influenced by ovarian hormones, surprisingly little supportive data exist. Research to date is limited by largely relying on the menstrual cycle as an indirect proxy for hormone levels, by the poor measurement of anxiety and depression symptoms, and by a lack of consideration of interactions between hormones. The objective of the present study was to examine associations between ovarian hormones and multiple facets of anxiety and depression measured daily across a full menstrual cycle.

Methods: Fourteen naturally cycling women between the ages of 18 and 25 years provided saliva samples for hormone extraction and also completed multiple measures of anxiety and depression symptoms – including mixed anxiety and mood, anhedonia, and worry – daily for 35 consecutive days. Analyses were conducted using multilevel modeling, the results of which reflect relationships both within women over time and across different women.

Results: Higher estradiol levels were independently associated with higher anhedonia ($P < .01$) and, to a lesser extent, with higher mixed anxiety and mood symptoms ($P < .06$). Higher progesterone levels, on the other hand, were related to lower worry symptoms, but only in the presence of higher estradiol levels ($P = .01$).

Conclusions: These findings shed new light on the relationships between ovarian hormones and anxiety and depression symptoms by demonstrating that different hormones, and their interactions, have unique associations with certain facets of anxiety and depression. Hormone effects on anxiety and depression are more nuanced than previously considered.

P-54: A Systematic Review of Interventions to Improve Physical Activity and Dietary Behavior During Pregnancy

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Background and Objective: Previous systematic reviews of interventions targeting physical activity (PA) and dietary behaviors

among pregnant women have found these interventions to have limited success in affecting primary outcomes such as prevention of excessive weight gain or gestational diabetes. However, the effectiveness of combined interventions on the intermediate outcomes of changing PA and dietary behaviors has not been systematically assessed. The objective of the present study was to review the effectiveness of combined PA and dietary interventions on increasing PA and improving dietary behaviors during pregnancy.

Methods: Two independent reviewers conducted searches in PubMed and Embase and screened the results to select eligible studies. The inclusion criteria were (a) a randomized controlled trial among pregnant women, (b) the intervention arm targeted both PA and diet, and (c) the results included baseline and follow-up measures of PA and diet.

Results: Of 136 relevant abstracts screened, 55 met criteria for full-text review and 12 studies met inclusion criteria. Among these, 1 study found significant improvement in PA only, 5 studies reported significant improvements in diet only, and 3 studies found significant improvements in both PA and diet in the intervention group compared with the control group. Among studies successful at changing both behaviors, 1 utilized techniques based in motivational interviewing, and 2 offered structured group exercise sessions with baseline individualized dietary counseling.

Conclusions: Previous intervention studies have had limited success at changing PA and diet during pregnancy. Theoretically designed interventions are needed to promote both PA and a healthy diet among pregnant women to improve maternal and fetal health.

P-55: Factors Influencing Patient-Physician Discussion of Mammography Choice: Examining Informed Decision Making Amidst Cancer Screening Controversy

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Background and Objective: In 2009, the U.S. Preventive Services Task Force recommended against routine mammograms for women aged 40 to 49 years. When a firestorm of controversy followed, the task force amended the guidelines, emphasizing the value of informed decision making for women younger than 50. Little is known, however, about whether and for whom informed decision making is taking place. The objective of the present study was to document the prevalence of patient-physician discussion of mammography choice and to examine sociodemographic and clinical factors associated with such discussion.

Methods: Data were obtained from the most recent iteration of the Health Information National Trends Survey (HINTS 4 Cycle 2), conducted from October 2012 to January 2013 by the National Cancer Institute.

Results: Among 391 women aged 40 to 49, only 38.4% reported that their doctor told them they could choose whether or not to have a mammogram; discussion was also infrequent among women aged 30 to 39 (26.3%) and 50 to 59 (33.9%). Additionally, among women aged 40 to 49, Hispanics and non-Hispanic Blacks were significantly less likely to have reported discussion of mammography choice with their doctor. Education, income, having insurance, and having a regular health care provider were not significantly associated with such discussion.

Conclusions: Many women aged 40 to 49 do not discuss choices about mammography with their physicians, and this may be particularly true for members of racial or ethnic minorities. Given the ongoing disagreement among experts about the use of mammography to screen for breast cancer—discord that increasingly plays out in the media—it is important for clinicians to help women understand screening's risks and benefits so that these women can make an informed choice.

P-56: Variations in the Delivery of Multidisciplinary Breast Cancer Follow-Up Care

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Background and Objective: Significant variation exists surrounding the delivery of breast cancer follow-up. Given that the number of different types of oncologists (medical, radiation, surgical) participating in follow-up is associated with follow-up frequency, we hypothesized that the inherent challenges associated with coordinating multidisciplinary care contribute to observed variations. The objective of this study was to examine patterns of multidisciplinary breast cancer follow-up, focusing on the distribution of visits over time.

Methods: We used the SEER (Surveillance, Epidemiology, and End Results)–Medicare database (2000–2006) to identify patients who underwent breast conservation for stage I to stage III breast cancer ($n = 12,139$). Follow-up frequency was defined as the number of visits over total time. Provider type was identified using Medicare specialty provider codes and the American Medical Association Physician Masterfile. Visit distribution was quantified using the coefficient of variation (CV) for time between oncologist follow-up visits. Ordinal logistic regression identified patient characteristics associated with more (low CV) versus less (high CV) regular visits.

Results: Median visit frequency was 3.0 (1.3–9.4) visits per year. Two-thirds (67%) of those with a high regularity of visits received follow-up from a single oncologist type, versus 8% with a low regularity of visits. The number of types of oncologists involved in follow-up had the greatest association with visits of low regularity (odds ratio: 7.4 [6.7–8.3] and 15.4 [13.6–17.6] for 2 and 3 oncologist types, respectively).

Conclusions: Based on our inquiry, which used a novel means of quantifying the regularity of clinic visits, it appears that follow-up with more than 1 oncologist type will be associated with more disordered breast cancer follow-up. Future research should focus on *who* provides breast cancer follow-up as a means of improving the quality of care and decreasing disparities.

P-57: Ovarian Hormones Increase IL-17A Production from Th17 Cells Through a Let-7f Mediated Pathway in Women with Severe Asthma

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Background and Objective: The prevalence of severe asthma is greater in women than men, but the mechanisms remain unclear. Interleukin 17A (IL-17A), produced by Th17 cells, is increased in the sputum of severe asthma patients as compared to patients with milder asthma. IL-17A production requires IL-23 receptor (IL-23R) signaling, and IL-23R is negatively regulated by Let-7f miRNA. The objective of this study was to determine whether 17 β -estradiol (E2) and progesterone (P4) increase IL-17A production by decreasing Let-7f and increasing IL-23R expression.

Methods: IL-17A levels were measured by flow cytometry in Th17 cells from women ($n = 16$) and men ($n = 15$) with severe asthma. Naïve T cells were differentiated ex vivo into Th17 cells from healthy women ($n = 16$) and men ($n = 17$). In select experiments, Let-7f was inhibited prior to Th17 cell differentiation. To determine the mechanism, 17 β -E2, P4, 17 β -E2 + P4, or placebo was administered to ovariectomized female mice for 3 weeks prior to Th17 cell differentiation. IL-17A levels were measured by enzyme-linked immunosorbent assay (ELISA) and IL-23R and Let-7f expression by qPCR (quantitative polymerase chain reaction) in Th17 cells from healthy individuals and mice.

Results: In Th17 cells from patients with severe asthma, IL-17A production was increased in women compared to men. In Th17 cells from healthy participants, IL-17A production and IL-23R expression

were increased and Let-7f expression was decreased in women compared to men, and inhibition of Let-7f increased IL-17A production. In ovariectomized mice, IL-17A production and IL-23R expression were increased, and Let-7f expression was decreased in the Th17 cells from mice administered 17 β -E2+P4 compared to placebo.

Conclusions: Ovarian hormones mediate IL-17A production, providing a potential mechanism for the greater prevalence of severe asthma in women than in men.

P-58: Placental Growth Factor Enhances TLR-Pathway-Induced Innate Immune Inflammatory Responses in Human Mononuclear Phagocytes

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Background and Objective: Epidemiologic studies have demonstrated an unexplained vulnerability to severe viral infections (e.g., influenza) during pregnancy, particularly in the third trimester. One physiologic change characteristic of middle to late gestation is a rise in circulating placental growth factor (PIGF) levels. Given these observations and reports of PIGF involvement in inflammatory conditions such as sickle cell anemia and rheumatoid arthritis, as well as the known role of specific toll-like receptor (TLR) ligands (TLR-7/8) in influenza infection, we hypothesized that PIGF contributes to an exaggerated pathologic proinflammatory state in response to TLR stimulation.

Methods: Primary human CD14⁺ cells were cultured in the presence of specific TLR ligands and/or PIGF. Conditioned culture media were harvested for tumor necrosis factor alpha (TNF- α) quantification by enzyme-linked immunosorbent assay (ELISA), and total RNA was prepared from CD14⁺ cells for real-time PCR (polymerase chain reaction).

Results: Although PIGF alone was not capable of inducing TNF- α secretion, PIGF significantly increased TNF- α production by primary human monocytes exposed to both PIGF and a TLR-7/8 ligand, enhancing both TNF- α protein and mRNA levels. This "PIGF/TLR" effect on TNF- α transcript and protein abundance was mediated through phosphorylation of MK2, a p38 substrate involved in TLR-mediated TNF- α production.

Conclusions: These results suggest that PIGF may directly contribute to an exaggerated pathologic proinflammatory state in response to activation by specific TLR agonists, mediated by increasing TNF- α mRNA abundance. We hypothesize that this PIGF/TLR effect contributes to a state of hyperinflammation in pregnant women infected by viruses that activate TLR-7/8 pathways, viruses such as influenza that are known to induce excessive morbidity and mortality in pregnancy.

P-59: Improving Efficacy of Targeted Therapies for the Treatment of Epithelial Ovarian Cancer Through Identification of Prognostic Markers of Drug Response

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Background and Objective: Epithelial ovarian cancer (EOC) is the leading cause of death from a gynecological malignancy among American women. Despite favorable response rates to primary therapy, a majority of women eventually experience tumor recurrence that ultimately becomes treatment resistant. A plethora of investigational drugs used following recurrence or as maintenance therapies have yet to improve the 5-year relative survival rate of patients with EOC. Given the time and vast resources required to identify and develop a new drug for clinical use, the objective in this study was to enhance the efficacy of existing drugs and build upon current therapeutic strategies by identification of prognostic markers associated with response to a given drug.

Methods: In vitro dose response studies were performed using a panel of 40 drugs against 14 EOC cell lines. The drug panel comprised front-line therapy for EOC patients, FDA-approved targeted tyrosine kinase inhibitors, and a selection of other targeted inhibitors that are currently in clinical trials for the treatment of EOC and other disease types at various phases of development. Gene expression of kinases and phosphatases was measured and correlated with drug sensitivity.

Results: Response to targeted therapies is variable across the EOC cell lines; correlation of these drug sensitivity data with gene expression is currently being conducted.

Conclusions: Identification of prognostic markers of drug response will indirectly improve drug efficacy by aiding the selection of patients most likely to benefit from a given drug, yielding improved personalized therapy.

P-60: Depression Symptoms in Obese Older Adults with Functional Limitations: Effects of a Weight-Loss Intervention

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Background and Objective: The obesity epidemic is detrimental to mental health, as shown by an increased risk of depression among obese individuals. Depression is more common in individuals with impaired physical function, and obesity may also increase risk of this problem. However, the causal relationships among depression, obesity, and function are poorly understood. This weight-reduction study in obese older adults with functional limitations offers a promising avenue for exploring these relationships and potentially preventing or lessening depression in this at-risk population. The objective is to determine the influence of weight reduction and the associated improvements in physical function on depression in an obese and functionally impaired pilot study cohort.

Methods: Individuals with mild to moderate physical impairment (Short Physical Performance Battery [SPPB] score 4–10, out of 12), aged 60 years or older, were enrolled in a 6-month intensive dietary weight-loss intervention. At baseline, 3 months, and 6 months, depression symptoms were evaluated with the Center for Epidemiologic Studies Depression (CES-D) scale, and weight and body composition (BodPod[®]) were also measured.

Results: Of the 51 subjects enrolled, 16 have completed the trial. Among those 16 persons, mean weight loss was 19.0 pounds (range: 2.4–51.1 pounds), and physical function was improved by 2.3 points. Depression scores were distributed across minimal, mild, and moderate ranges. In preliminary analyses, weight loss (in pounds) was not significantly associated with changes in depression scores ($P = .26$).

Conclusions: Initial results for the study being conducted are inconclusive and limited by the small sample. Continuation of this study may indicate that meaningful changes in depression symptoms can be influenced by weight loss in a physically impaired obese population.

P-61: Hyperandrogenism Is Associated With NAFLD and Metabolic Risk in Both Normal and Overweight Adolescent Girls

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Background and Objective: In adult women, hyperandrogenism connotes increased risk for metabolic syndrome and up to 3 times greater risk of nonalcoholic fatty liver disease (NAFLD) when compared to obesity alone, a difference attributed to elevated androgens. It is unclear, however, whether elevation in androgens in adolescents infers a similar increased risk. The objective of this study was to compare androgen levels with markers of metabolic syndrome and NAFLD in adolescent girls.

Methods: This was a cross-sectional study of 103 females aged 11 to 14 years. Fasting glucose, insulin, alanine transaminase (ALT),

total testosterone, free testosterone, sex hormone-binding globulin (SHBG), and body mass index (BMI) were measured. Hepatic fat fraction (HFF) was quantified using proton density fat fraction MRI. Hepatic steatosis (HS) was defined as an HFF greater than 5.5%. Normal weight (NW) was defined as a BMI below the 85th percentile and overweight (OW) as a BMI at the 85th percentile or above.

Results: Mean ages were 12.6 ± 1 year for the NW girls and 12.5 ± 1 year for the OW girls. HS was seen in 26% of the OW girls. HOMA-IR (homeostasis model assessment-estimated insulin resistance) correlated with SHBG (NW $r=0.27$, $P=.04$; OW $r=0.61$, $P<.001$) and free testosterone (NW $r=0.26$, $P=.05$; OW $r=-0.30$, $P=.01$). HFF correlated with SHBG (NW $r=-0.42$, $P=.001$; OW $r=-0.54$, $P<.001$) and with free testosterone in OW ($r=0.36$, $P=.02$). ALT correlated with free testosterone in OW ($r=0.32$, $P=.03$). Girls with HS and a free androgen index above the median had higher mean HFF and ALT than those below the median (HFF mean = 18.0 vs. 10.2, $P=.02$, ALT = 45.2 vs. 22.2, $P=.01$).

Conclusions: In adolescent girls, insulin resistance (IR) and HFF correlate with an increase in androgens prior to the development of hyperandrogenemia. The strong correlation of SHBG with IR and HFF in both normal and overweight adolescents suggests that hepatic IR may develop prior to obesity and may serve as an early indicator of disease risk. In girls with HS, higher androgens are associated with disease severity, suggesting that androgens may play a role in the progression of NAFLD in adolescent girls.¹¹

P-62: Progress in Increasing Awareness and Availability of the Intrauterine Device in Bonsaaso, Ghana

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Background and Objective: The intrauterine device (IUD) is an effective, yet underutilized, contraceptive method in low-resource settings. The level of IUD use in rural Bonsaaso, Ghana, was 0% in 2012. Research suggests that provider and patient barriers such as biased contraceptive counseling and lack of IUD knowledge and availability contribute to low uptake of this device. The objective of this study was to assess the long-term impact of a 3-day family planning workshop for providers on awareness and perceived availability of the IUD among women accessing family planning clinics within 1 year of training.

Methods: Semi-structured interviews and focus groups were conducted with 42 contraceptive users 1 year following the workshop, which included a review of contraceptive counseling techniques, eligibility criteria for contraceptive use, and insertion of the IUD. The content of the interviews and focus groups was analyzed, and emerging themes were identified.

Results: Twelve of the 42 contraceptive users were offered the IUD, and 2 selected this method. Although there was greater awareness about the IUD and its availability, uptake was affected by lack of comprehensive counseling specific to the IUD and poor understanding of IUD functionality and the benefits of this method. Of those who chose the IUD, the desire for spacing pregnancies and dissatisfaction with other methods led to IUD selection.

Conclusions: Provider training alone marginally increases awareness of the IUD and its availability. A more robust intervention that focuses on provider bias and community sensitization is needed to improve the quality of contraceptive counseling and to more aptly meet the needs of contraceptive users.

P-63: Adolescent Anemia Screening During Ambulatory Visits in the United States

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Background and Objective: The Centers for Disease Control and Prevention recommends anemia screening for reproductive-age women every 5 to 10 years but annually for those with risk factors. Because of the lower risk of anemia among males, screening for men

is recommended only if they have risk factors. The objective of this study was to examine health care professionals' current anemia screening patterns for male and female adolescents.

Methods: Data were taken from the 2001–2004 National Ambulatory Medical Care Survey, which had a nationally representative sample of ambulatory visits to primary care practices. The frequency of anemia screening during preventive care visits by 12- to 21-year-olds was estimated by sex using a reported hemoglobin/hematocrit or complete blood count as an indicator of screening. Multivariable logistic regression identified patient-, provider-, and practice-level factors associated with screening.

Results: During the study period, 1,263 preventive care visits were made by 12- to 21-year-olds. In bivariate analysis, a higher odds ratio (OR) for anemia screening was observed for both younger females (OR: 1.85; 95% CI [confidence interval], 1.09, 3.14) and older males (1.83 [1.02, 3.26]) compared to older females (> 16 years). In the multivariable model, odds of screening were increased with nonwhite race (OR: 3.29 [1.84, 5.88]), tobacco use (OR: 3.57 [1.94, 6.58]), longer visit (OR: 1.03 [1.01, 1.06]), and acceptance by practice site of managed care plans (OR: 2.08 [1.04, 4.14]). Patient sex and age were not significant predictors of screening.

Conclusions: Although anemia is more prevalent among older adolescent females, they do not seem more likely to be screened. This suggests that providers are not targeting groups at the highest risk of anemia for screening.

P-64: Gender Differences in Inpatient End-of-Life Discussions for Patients with Advanced Cancer

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Background: End-of-life (EOL) discussions facilitate the receipt of care consistent with patient preferences. Although gender differences exist in the information needs of patients with advanced cancer, little is known about whether gender differences exist in the content of inpatient EOL discussions. The objective of this study was to evaluate gender differences in inpatient EOL communication for advanced-cancer patients.

Methods: Via daily contact with oncology, hospitalist, and palliative care services, we identified metastatic cancer patients with a known upcoming EOL discussion. Discussions and post-discussion patient, family, and physician interviews were audiotaped, transcribed verbatim, de-identified, and coded.

Results: Recruitment is currently ongoing. Of 36 patients approached, 25 consented to have their discussion recorded (15 women and 10 men). Seventy-three percent of the women and 60% of the men completed post-discussion surveys and interviews. Among the women, 27% reported that their discussion covered prognosis; 91%, hospice; 73%, resuscitation preferences; and 45%, curability. Among the men, 67% reported discussing prognosis; 50%, hospice; 67%, resuscitation preferences; and 67%, curability. All male patients reported a preference for care that focused on comfort rather than prolonging life, as compared with 73% of women who reported this preference. Percent agreement between the physician's understanding of patient treatment preferences and expressed patient EOL preferences following the discussion was poor: 50% agreement for male patients and 23% agreement for female patients.

Conclusions: Gender differences may exist in the content of inpatient EOL discussions, and physicians may have a poorer understanding of the preferences of their female patients. Additional qualitative analysis of the discussions in this study will allow for further elucidation of differences in discussion content.

P-65: Sex Differences in the Mouse Lung Inflammatory miRNA Profile in Response to Ozone Inhalation

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Background and Objective: Exposure to ozone (O₃) induces airway inflammation and impairs lung function. Women are more susceptible than men to inflammatory lung diseases. We have previously reported an increased expression of inflammatory genes in the lungs of female mice (versus male mice) in response to O₃ exposure. We hypothesized that miRNAs, a class of small RNAs that repress gene expression, may be implicated in this differential regulation. The objective of the present study was to test whether O₃ exposure differentially affects expression of lung miRNAs in male and female mice.

Methods: Adult male mice (n=8) and females in all 4 stages of the estrous cycle (n=8/stage) were exposed to O₃ (2 ppm) or filtered air (control) for 3 hours (n=4/group). Lung tissue was collected 4 hours after exposure, and the expression of 84 miRNAs predicted to regulate inflammatory genes was assayed by real-time polymerase chain reaction (PCR).

Results: Exposure to O₃ significantly increased the expression of 22 lung miRNAs in male mice and of 2 miRNAs in female mice when compared with controls ($P < .05$). In the O₃-exposed group, the expression of 10 miRNAs was significantly higher in males than in females ($P < .05$). In O₃-exposed females, the expression of miRNAs was significantly higher in proestrus than in other stages ($P < .05$).

Conclusions: We found that O₃ inhalation differentially disrupts the expression of select miRNAs associated with inflammatory response signaling in male and female mice. Increased miRNA levels in males in response to O₃ may negatively affect the overall expression of lung inflammatory genes. Females lacking this negative regulatory mechanism may be at higher risk for developing exacerbated O₃-induced inflammation.

P-66: Varenicline Attenuates Gender Disparities in Smoking Cessation

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Background and Objective: A number of studies have found that women are less likely than men to successfully quit smoking cigarettes. Varenicline is the most effective FDA-approved medication for smoking cessation, yet potential gender differences in the efficacy of this medication are unknown. We conducted a meta-analysis of varenicline clinical trials, examining gender differences in cessation for both placebo and varenicline treatment groups. We also tested differential efficacy by gender.

Methods: Twenty-six investigations were included in the meta-analysis, covering 98% of published data (n=10,416). Point prevalence (PP) abstinence and continuous abstinence (CA) were evaluated as outcomes at week 12 (end of treatment), week 24 (6-month follow-up), and week 52 (1-year follow-up).

Results: Among those in placebo groups, women were significantly less likely to quit smoking than men as measured by PP at week 12 (odds ratio [OR]: 0.76, 95% confidence interval [CI], 0.62, 0.94) and CA at week 24 (OR: 0.73, 95% CI, 0.55, 0.98). Among those in varenicline groups, there were no gender differences for either PP abstinence or CA at any time point. Differential efficacy by gender was significant for PP abstinence at 12 weeks and for CA at week 12 ($P < .05$). Among women, varenicline use was associated with an OR of 4.96 for PP abstinence at week 12 (95% CI, 4.03, 6.11), well above the OR for men of 3.33 (95% CI, 2.91, 3.82).

Conclusions: Varenicline use appears to attenuate gender differences in smoking cessation, demonstrating greater efficacy among women than men. In the present study, these differences were most pronounced at 12 weeks after the quit date. Future preclinical and Phase II work will be directed towards identifying mechanisms underlying gender differences in varenicline's efficacy for smoking cessation.

P-67: What Is the Evidence for "Hardening"? Trends in Nicotine Dependence in the United States, 2002–2011

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Background and Objective: There has been considerable interest in determining whether declines in cigarette smoking in the U.S. have resulted in a population of "hardcore" (i.e., hardened) smokers. We analyzed data from the National Survey on Drug Use and Health (2002–2011) to study changes in nicotine dependence levels over this time period.

Methods: We used generalized nonlinear factor analysis and items from the Nicotine Dependence Syndrome Scale (NDSS) to generate an indicator for dependence that was psychometrically equivalent across years in the study. This approach also allowed us to use item response theory to evaluate changes in the performance of specific NDSS symptoms over time. All analyses were stratified by gender.

Results: The prevalence of cigarette smoking declined from 2002 to 2011. The proportion of smokers consuming >25 cigarettes per day also declined. Nicotine dependence as determined by the NDSS declined among male smokers, but it remained steady among female smokers. When the sample was categorized by daily cigarette consumption, however (0–15, 16–25, >25), we found slight increases in dependence among both male and female smokers who reported consuming 16–25 cigarettes per day. We also found this trend among women who reported smoking 0–15 cigarettes per day.

Conclusions: Dependence may be declining among male smokers, but it is likely due to reduced consumption; however, there may have been increases in dependence among both male and female "pack-a-day" smokers and female "light" smokers, suggesting higher levels of dependence at lower levels of cigarette consumption.

P-68: Predictors of Shoulder Range of Motion After Breast Cancer Surgery

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Background and Objective: Restricted shoulder range of motion (ROM) is common after breast cancer (BC) treatment and is associated with decreased function. The role of preoperative shoulder ROM in predicting changes in postoperative shoulder ROM has not been studied. Identification of preoperative predictors to target for early intervention may minimize the incidence and severity of treatment-related upper extremity impairments. The objective of this study was to evaluate predictors for changes in shoulder ROM during the first year following BC treatment.

Methods: Shoulder abduction ROM was assessed preoperatively and at regular intervals during the first year following BC surgery in 396 women. Using hierarchical linear modeling, demographic, clinical, and treatment characteristics were evaluated as predictors of postoperative shoulder abduction ROM at the initial postoperative assessment (intercept) and over the first year following surgery (trajectories/slopes).

Results: In all, 64% of the women were white; their mean age was 54.9 years (SD 11.6). There was a significant reduction in shoulder abduction ROM from the preoperative to 12-month postoperative assessment ($P < 0.001$). Predictors of inter-individual differences in the intercept for postoperative shoulder ROM were the type of BC surgery (mastectomy or breast conserving surgery), axillary lymph node dissection (ALND), neoadjuvant chemotherapy, ethnicity, and preoperative shoulder ROM. Predictors of inter-individual differences in the linear, quadratic, and cubic slope parameters for postoperative shoulder ROM were living alone, type of BC surgery, ALND, and chemotherapy during the first year after surgery.

Conclusions: Mastectomy, ALND, neoadjuvant chemotherapy, being nonwhite, and lower preoperative ROM are associated with greater reductions in ROM postoperatively. Living alone, mastectomy, ALND, and chemotherapy during the first year after surgery are associated with variability in ROM changes over time.

P-69: Sex Differences in the Impact of Adolescent Psychosocial Stress on Behavior and Body Weight Regulation

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Background and Objective: Social-defeat stress (i.e., stress resulting from bullying) is a common problem among adolescents and is linked with psychological (anxiety and depression) and metabolic conditions later in adulthood. Females are twice as likely as males to suffer from stress-related psychopathologies that emerge during the adolescent period. Despite this fact, most rodent studies use males. The goal of the present study was to determine whether there are sex differences in the behavioral and metabolic consequences of adolescent social-defeat stress.

Methods: To accomplish this goal, male and female rats were exposed to social-defeat stress or served as non-stressed controls during the adolescent period. Males and females were tested for anxiety-like and depression-like behavior during adolescence or adulthood. Body weight was also assessed during this time.

Results: Adolescent social-defeat stress significantly increased anxiety-like behavior in nonsocial settings during the adolescent period in male and female rats relative to their same-sex control counterparts. Notably, these behavioral changes persisted through adulthood in both sexes. Males, however, but not females, were more likely to demonstrate social deficits (e.g., social avoidance) characterized by heightened anxiety-like behavior in multiple social settings. These anomalies in social behavior persisted through adulthood in males. Adolescent social-defeat stress significantly decreased body weight gain during adolescence and adulthood in males, but it had no impact on females.

Conclusions: These data indicate that adolescent social-defeat stress induces sustained changes in behavior in rodents that are context dependent and sexually dimorphic. Future studies will examine sex differences in neuroendocrine and central (brain) responses following social defeat.

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P-70: Ovariectomy—With and Without Estrogen Therapy—and Incident Diabetes in a Genetically Susceptible Rodent Model

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Background and Objective: Type 2 diabetes is one of the most prevalent chronic diseases in postmenopausal women, but the contribution of postmenopausal estrogen loss to the risk of type 2 diabetes is unclear. The objective of the present study was to test several hypotheses: (1) Estrogen loss induced by ovariectomy (OVX) will increase gain in body weight, which will increase incidence and decrease time to onset of type 2 diabetes in comparison with estrogen-replete animals; (2) OVX-induced type 2 diabetes will be independent of gain in body weight; (3) estrogen treatment (ET) in OVX rats will reduce incidence and increase time to onset of type 2 diabetes.

Methods: Two-month-old UCD-T2DM rats were randomly assigned to one of several conditions: (1) Control: Sham surgery/placebo implants; (2) OVX: OVX/placebo implants; (3) OVX/weight-matched: OVX/placebo implants/weight-matched to controls via paired feeding; or (4) OVX/E (OVX/17 β -estradiol implants). Following surgery/implantation, blood glucose, plasma estrogen, food intake, and body weight were measured weekly. Incident type 2 diabetes was diagnosed when non-fasting blood glucose exceeded 200 mg/dl for 2 consecutive weeks.

Results: At 3 months after surgery, incident diabetes was 0% for all groups (n=8/group). Weight gain in OVX was higher ($P=.02$) and tended to be higher in OVX/E compared with the control group.

Plasma estradiol concentrations in OVX/E were 60% lower than in the control group ($P=.007$), and they decreased because of declining delivery of estrogen by the 90-day estrogen pellets.

Conclusions: The ET protocol did not provide adequate estrogen replacement. We will increase the estradiol dose and administer it via subcutaneous injection on a schedule that will provide comparable body weight gain and plasma estradiol concentrations in the OVX/E and control groups.

P-71: Personal, Financial, and Employment Burdens of Low-Wage-Earning Cancer Survivors

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Background and Objective: The impact of cancer on employment is an important research area. However, few studies focus specifically on low-wage-earning cancer survivors, a population vulnerable to economic and health insecurity. The purpose of this study was to examine personal, financial, and employment burdens among low-wage-earning women with a history of cancer.

Methods: Using a complex data-linkage methodology, National Health Interview Survey (NHIS)/Medical Expenditure Panel Survey (MEPS) (2011) data were linked to a cancer survivorship supplement dataset. There were 147 female cancer survivors with a history of employment (since they were first diagnosed with cancer); these women were dichotomized into low-wage and middle/high-wage groups based on family income as a percentage of poverty. We assessed differences between the 2 groups related to sociodemographics, comorbidities, perceived physical and mental health, paid sick leave, and financial burden due to cancer.

Results: Compared with middle/high-wage-earning cancer survivors, low-wage women were significantly more likely to be African American, to have lower rates of education, and to be widowed or never married. Low-wage-earning women were more likely to be diabetic, report fair/poor physical health, and report good/fair mental health. Additionally, low-wage-earning women were significantly less likely to receive paid sick leave, took more leave from work due to their cancer, and made more financial sacrifices because of their cancer in comparisons with middle/high-wage-earning women.

Conclusions: Low-wage-earning female cancer survivors experience more personal, financial, and employment-related burdens than their higher-earning counterparts, potentially exacerbating disparities in cancer survivorship and in long-term employment outcomes.

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P-72: Work-Treatment Conflict Among a Population-Based Sample of Female Cancer Survivors in North Carolina

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Background and Objective: Much has been reported in the literature about the impact of cancer on employment outcomes, but there is a paucity of research on the influence of work on receipt of recommended cancer care. The purpose of the present study was to document work-treatment conflict among a sample of female cancer patients.

Methods: Women diagnosed with either breast, colorectal, cervical, or endometrial cancer within the past 6 months were recruited from the North Carolina Central Cancer Registry to participate in a study focused on partner and family influences on cancer care outcomes. Additional survey questions inquired about employment history, wages/salary, and work-treatment conflicts. As of May 2014,

478 women had completed the study survey (mean age: 60 years); the 39% (n=187) of these women who were employed at the time of diagnosis (mean age: 55 years) served as our analytic population.

Results: Educational services (20%) and medical/health care/social assistance (26%) were the 2 most commonly reported industry groups. More than half (55%) of the women were paid hourly; 73% worked full time (≥ 35 hours/week). Almost one-third (32%) of the study population discussed with their health care provider how work might interfere with or affect their ability to get recommended cancer care. Nine women (5%) indicated that their work situation interfered with receiving recommended cancer care, with several qualitative responses centering on schedule conflicts. Thirteen women (7%) admitted to missing, canceling, or delaying their cancer treatment due to work.

Conclusions: A small, but notable, percentage of women with cancer have concrete evidence of work-treatment conflict. More research is needed to examine this phenomenon and its impact on cancer outcomes.

P-73: Liraglutide Reverses Hypertension and Improves Metabolic Perturbation in a Rat Model of Polycystic Ovarian Syndrome

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Background and Objective: Polycystic ovarian syndrome (PCOS) affects women of reproductive age and is linked to type 2 diabetes and cardiovascular disease. Targeted therapies addressing both these complications in PCOS are limited, however. Levels of glucagon-like peptide-1 (GLP-1) are low in PCOS patients. Moreover, GLP-1 agonists (known antidiabetic agents) can improve cardiovascular function in patients. Therefore, it is likely that GLP-1 agonists would be beneficial in PCOS patients. The objective of this study was to determine if liraglutide (a GLP-1r agonist) would improve both cardiovascular and metabolic perturbation in a rat model of PCOS.

Methods: Prepubertal female Sprague Dawley rats were implanted with subcutaneous dihydrotestosterone (DHT) pellets (90-day release; 83 μ g/day). Radiotelemeters were implanted at 12 weeks to measure blood pressure (n=25 DHT vs. 9 vehicle group). A subgroup of the telemetered DHT rats (n=13) received 0.2 mg/kg of liraglutide twice daily from 12 to 16 weeks. Cardiac echocardiography was conducted at 16 weeks.

Results: DHT-implanted rats had ovarian dysfunction and metabolic perturbation characteristic of PCOS. Liraglutide treatment significantly decreased body weight and also glucose excursion post-glucose load in DHT rats. DHT rats were hypertensive, and liraglutide significantly improved mean blood pressures (arterial: 107.6 vs. 103 mmHg, systolic: 128.4 vs. 122 mmHg, diastolic: 90 vs. 88 mmHg in DHT and DHT+liraglutide rats, respectively). Left ventricular dysfunction was observed in DHT-treated rats and was not reversed by liraglutide treatment.

Conclusion: These results suggest that GLP-1 likely plays a role in DHT-induced ovarian, metabolic, and blood pressure changes but not in ventricular dysfunction.

P-74: Beyond Bar Graphs: Time for a New Data Presentation Paradigm

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Background and Objective: The National Institutes of Health recently highlighted the critical problem of irreproducibility, especially in preclinical studies. Poor data presentation may contribute to irreproducibility. Bar graphs are intended for categorical data, but

when used for continuous variables, bar graphs provide little information about the distribution of the data and often distort data in studies with small samples. The objective of this study was to examine the types of figures used to present continuous outcomes in highly ranked physiology journals.

Methods: We performed a systematic review of all full-length original research articles (n=698) published in the top 20 physiology journals between January 1 and March 31, 2014. We examined the types of figures used to present continuous outcomes, sample size, and statistical methods.

Results: In all, 626 articles included figures depicting continuous outcomes; 85% included a bar graph for a continuous outcome, with 77% showing mean $\pm$ standard error. Line graphs or graphs showing means and error bars were common (61%). Scatterplots (13%), boxplots (5%), and histograms (8%) were used infrequently. The minimum and maximum sample sizes (median, interquartile range) for any group presented in a figure were 4 (3–6) and 10 (6–15). Despite these small samples, most articles used only parametric statistics (79%). Among the 17% of articles that performed any nonparametric analyses, 58% showed data that were analyzed nonparametrically as mean $\pm$ standard error or standard deviation.

Conclusions: Changes in journal policies are urgently needed to encourage investigators to use appropriate statistical methods and to select figures that show the distribution of data from small samples to ensure the validity of conclusions.

P-75: Incorporating the X Chromosome Into Genetic Data Analysis

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Background and Objective: Although the X chromosome is crucial for sex determination, it is routinely excluded from genetic analyses of common traits. Data-mining methods such as random forests (RF) can investigate complex genetic models, but they do not accommodate data on the X chromosome. The objective of this study was to extend RF to incorporate data from the X chromosome.

Methods: Using data from a case-control study of alcoholism, we sought to demonstrate that for traits associated with sex, inclusion of X chromosome single nucleotide polymorphisms (SNPs) in RF analysis would yield biased results. We developed 3 extensions of RF to include X SNPs, based on (1) the principle of X chromosome inactivation (XCI), (2) stratification of the forest by sex, and (3) incorporation of information on sex as the forest is built. We compared the performance in the alcoholism data and using simulated data.

Results: In the data on alcoholism, regular RF ranks the X SNPs highly, whereas the new approaches rank the X SNPs similarly to the autosomes. In simulated data, all methods do not inflate the importance of the X chromosome if sex is not associated with the trait. If sex is associated, the importance of the X chromosome is biased with regular RF. However, the stratified forests and XCI methods do not inflate the importance of the X chromosome, although its importance is slightly lower than the autosomes for unbalanced trait data.

Conclusions: Regular RF is not appropriate to analyze data on X chromosomes if sex is associated with the trait; either stratification of the forest or extension based on XCI will eliminate bias and rank X chromosome SNPs appropriately.

P-76: Identification of Signaling Pathways With Potential to Confer Resistance to Breast Cancer Chemotherapies

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Background and Objective: Resistance to anticancer therapies can be driven by genetic or epigenetic events occurring within cancer cells or by extracellular cues such as soluble growth factors or cell-cell contacts. Ultimately, these diverse upstream events lead to the activation of growth and survival signaling pathways within cancer cells that enable them to survive otherwise lethal drug treatments. By blocking these drug resistance pathways, it may be possible to

improve the potency and durability of anticancer drugs. Unfortunately, for most drugs, the number and identities of potential resistance pathways are unknown.

Methods: To address this problem, we engineered a library of pathway-activating mutant cDNAs, then used this library to perform pooled screens to identify those pathways whose activation enhances the survival of cancer cells in the presence of clinically relevant targeted therapies.

Results: Activation of the Ras-mitogen-activated protein kinase (Ras-MAPK), Notch1, and phosphoinositide 3-kinase-mammalian target of rapamycin (PI3K-mTOR) pathways is frequently capable of conferring resistance to drugs, including those with diverse mechanisms of action. Further, for a given drug, only a small number of screened pathways (≤ 5) are typically capable of conferring resistance in this assay. Using this screening strategy, we have identified previously unknown pathways of resistance to drugs including estrogen receptor, HER2, PI3K, and mTOR inhibitors in breast cancer. These pathways are frequently upregulated in drug-resistant tumors from human patients relative to their drug-sensitive counterparts. Furthermore, the inhibition of these pathways reverses resistance in multiple cellular models of evolved or intrinsic resistance.

Conclusions: This systematic approach enables the rapid identification of signaling pathways that drive resistance, and it may be useful also in the study of a range of additional oncogenic phenotypes.

P-77: Anti-Müllerian Hormone, a Noninvasive Biomarker for Primate Follicle Growth and Oocyte Maturation in Vitro

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Background and Objective: In vitro follicle maturation (IFM) techniques are under development to offer fertility preservation options to women, including female cancer patients. Because the process of human ovarian follicle development remains poorly understood, noninvasive biomarkers of follicle/oocyte health in vitro are not available. Monkey secondary (immature) follicles produce anti-Müllerian hormone (AMH) in culture during IFM, with levels correlating positively with growth rates. Therefore, studies were designed to evaluate the potential of AMH in predicting further follicle growth and oocyte maturation in vitro.

Methods: Ovaries were collected from rhesus macaques. Secondary follicles were isolated, encapsulated into alginate, and cultured for 5 weeks at 5% O₂ in α MEM (Minimal Essential Medium) supplemented with follicle-stimulating hormone (FSH) and insulin. Follicle growth was assessed. Follicles reaching the antral stage were treated with hCG (human chorionic gonadotropin). Oocytes retrieved were analyzed for meiotic status.

Results: AMH levels produced at week 1 by growing follicles were higher ($P < .05$) than those of no-grows. Ninety-five percent of secondary follicles producing > 0.9 ng/ml AMH at week 2 grew to the antral stage. Follicles that generated metaphase II oocytes secreted greater ($P < .05$) amounts of AMH at week 1 than did those yielding immature germinal vesicle oocytes.

Conclusions: The fact that AMH levels produced by secondary follicles during week 1 correlated positively with further follicle growth and oocyte maturation in vitro is encouraging. Week 2 AMH levels are able to predict further follicle development during IFM. These findings may be applied to human IFM to eliminate follicles that likely will not grow, thereby saving time and resources.

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P-78: Design of Biodegradable Poly Lactic-Co-Glycolic Acid (PLGA) Nanoparticles for Co-Delivery of Anti-HIV Protein Griffithsin and Dapivirine in the Vagina

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Background: Griffithsin (GRFT) is an anti-HIV protein that blocks viral gp120 binding to CD4 receptor by binding to its mannose-rich glycans. Dapivirine (DAP) is a most potent non-nucleoside reverse transcriptase inhibitor. The broad-spectrum anti-HIV activity and unique safety profile of these 2 agents support their development as topical microbicides. However, the proteinous nature and poor tissue permeability of GRFT and the quick tissue elimination of DAP pose limitations to their potential as topical microbicides. The objective of the present study was to develop PLGA nanoparticles (NPs) in order to enhance vaginal delivery of GRFT and DAP.

Methods: A double-emulsion method was utilized to manufacture PLGA NPs containing GRFT and DAP. NPs were characterized by particle size/distribution, zeta potential, and encapsulation efficiency (EE). The efficacy and toxicity of GRFT and DAP NPs were evaluated in a TZM-bl assay.

Results: GRFT-, DAP-, and GRFT/DAP-loaded PLGA NPs showed a spherical shape with a size range of 220 to 320 nanometers and a narrow distribution (polydispersity index < 0.2). Zeta potentials were -25 to -30 millivolts. EE was 60% and 90% for GRFT and DAP, respectively. The IC₅₀ (IC = inhibitory concentration) of GRFT and DAP in NPs was 0.4 nanomoles and 4.2 nanomoles, respectively. Cell viability was completely maintained after exposure to blank or drug-loaded NPs. The combination index of GRFT and DAP in NPs was less than 1.

Conclusions: This first attempt to co-deliver protein and hydrophobic small molecules into a PLGA NP system yielded encouraging results. NPs not only demonstrated efficacy and safety as individual drugs, but they also indicated a potential synergistic effect. Co-delivery of GRFT/DAP may enhance their tissue penetration, leading to increased protection.

P-79: Nervous System-Related Loci Determine Sex Differences in Blood Pressure Reactivity to Cold Stress in Both Chinese and Whites

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Background and Objective: Exaggerated blood pressure (BP) reactivity to stress is a risk factor for developing cardiovascular disease. Women exhibit greater BP reactivity to cold stress than do men. The objective of this study was to identify sex-specific genetic determinants for BP reactivity to cold stress.

Methods: A genome-wide association analysis was conducted to examine the interaction effect of SNPs (single nucleotide polymorphisms) and sex on BP reactivity during the cold pressor test (CPT) among 1,881 Han Chinese participants from the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study. The replication sample was from the Coronary Artery Risk Development in Young Adults Study (CARDIA), in which 1,448 participants of European ancestry completed a similar CPT.

Results: A total of 13 loci showed potential sex differences in the association with BP reactivity variables in the GenSalt study (P for interaction $< 1.0 \times 10^{-5}$). Five of the 13 loci identified in the GenSalt study (1p32.2, 2q33.1, 3q26.31, 5q15, and 13q33.3) showed potential trans-ethnic replication in the CARDIA study (P for interaction < 0.1). Four of the 5 loci (1p32.2, 3q26.31, 5q15, and 13q33.3) included nervous system-related genes that have been implicated in neurological disorders, such as Parkinson's disease (*CDCP2* in 1p32.2 and *CAST* in 5q15), bipolar disorder (*TMEM212* in 3q26.31), and cerebral calcification (*COL4A1* in 13q33.3).

Conclusions: Our study provides the first evidence for the trans-ethnic replication of sex-specific genetic factors for the BP response

to cold stress and implicates multiple potential nervous system-related genes in determining the sex differences in BP reactivity to stress.

P-80: Sex Differences in the Association Between Blood Pressure Reactivity to Cold Stress and Hypertension Incidence

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Background and Objective: Hyperreactivity of blood pressure (BP) to the cold pressor test (CPT) has been suggested as a risk factor for hypertension. Women exhibit greater BP reactivity during the CPT than do men. The objective in this study was to examine whether

the association between BP reactivity to the CPT and incidence of hypertension differed between men and women.

Methods: A total of 1,961 participants who were not receiving any antihypertensive treatment completed the CPT at the baseline examination of the Genetic Epidemiology Network of Salt Sensitivity study. Hypertension status was assessed by 9 BP measurements obtained during 3 consecutive days at baseline (2003–2005) and 2 follow-up visits (2008–2009 and 2011–2012).

Results: After adjustment for multiple covariates, BP reactivity variables were significantly associated with incidence of hypertension. Compared with the lowest quartile of the systolic BP (SBP) response, the odds ratios (ORs) with 95% confidence intervals for developing hypertension were 0.92 (0.66, 1.39), 1.42 (1.03, 1.97), and 1.45 (1.05, 2.00) for the second, third, and fourth quartiles, respectively (*P* for trend=0.004). In addition, the effect of SBP response on incident hypertension was more manifest in women than in men (*P* for interaction=0.02). Those with a hyperreactive SBP response (top quartile) exhibited greater risk for hypertension than normal reactors (the other 3 quartiles) in women (OR: 1.76 [1.23, 2.53], *P*=0.002) but not in men.

Conclusions: BP hyperreactivity to the cold stimulus may predict the risk of hypertension. Furthermore, the systolic BP reactivity during the CPT may be more effective in predicting hypertension in women than in men.

BIRCWH and SCOR Presentation Abstracts

O-1: Sex-Dependent Neurodevelopmental and Behavioral Consequences of Exposure to Concentrated Ambient Ultrafine Particles

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Background and Objective: Evidence suggests that air pollution can induce inflammation and oxidative stress in the brain; epidemiological studies report associations of air pollution with impaired cognition, reduced attention, and increased risk for autism. Considering that early neurodevelopment is a period of heightened vulnerability to xenobiotic exposures due to ongoing neurogenesis and gliogenesis, we examined the neurotoxicological consequences of early postnatal (PN) exposure to concentrated ambient ultrafine particulate matter (CAPS; < 100 nm).

Methods: Mice received CAPS or filtered air exposure by inhalation for 4 hr/day on PN days (PND) 4 to 7 and 10 to 13. Some animals received a rechallenge with CAPS in early adulthood (PND 55 to 59). Animals were euthanized at multiple time points following exposure to assess the effects on brain development, cumulative exposure, and persistence of effect. Locomotor activity, impulsivity, learning, and memory were examined.

Results: Mean particle counts in the exposure chamber averaged 200,000 particles/cm³, with a mass concentration of 96.4 µg/m³. CAPS produced male-specific lateral ventricle enlargement (ventriculomegaly) and also elicited a sex-dependent glial response. Males displayed reduced astrocytic, but increased microglial, presence in the corpus callosum and hippocampus. PN CAPS induced transient activation of astrocytes in females. Both sexes showed increased hippocampal glutamate, consistent with potential excitotoxicity. Behavioral deficits were persistent and sex-dependent and included deficits in learning, locomotor activity, and short-term memory.

Conclusions: Collectively, these findings demonstrate the sex-dependent vulnerability of the developing brain to environmental levels of air pollution. Moreover, these findings raise the possibility that such exposures contribute to the etiology of neurodevelopmental disorders, including autism.

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O-2: Sex Differences in Human Pancreatic Islets: Survival, Function, and Genetic Expression

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Background and Objective: We previously reported that human female pancreatic islets contain more insulin-producing beta-cells than do islets in males. This sex difference provides evidence of potential benefits of preferentially using female cells in human islet transplantation to cure type 1 diabetes. The objective of the present study was to investigate sex differences in the survival, function, and genetic expression of human islets.

Methods: Human islets were isolated from deceased donors. Survival was quantified in vitro by islet loss during culture and beta-cell apoptosis. Function was assessed in vitro by intracellular changes after glucose stimulation, and in vivo by the efficacy of human islet transplantation in curing type 1 diabetes in mice. Genetic ex-

pression was examined using microarrays. Multivariable regression was employed to analyze sex differences.

Results: Female advantage in cell survival (less islet loss during culture [$P=0.02$] and less beta-cell apoptosis [$P=0.03$]) and in cell function (greater calcium-influx “activating” islets following glucose stimulation [$P=0.004$]) was observed, although not in subsequent insulin secretion ($P=0.46$). Female advantage in human islets’ efficacy in curing type 1 diabetes in mice was demonstrated, particularly islets from non-obese donors (odds ratio: 7.2, $P=0.04$). Sex differences in genetic expression were evident in 2 genes ($P\leq 0.01$): female islets had higher *ABCC1* expression (this gene clears cellular toxins) and lower *AGBL4* expression (this gene modifies/shortens microtubules that transport insulin).

Conclusions: Human female islets appear to have advantages over their male counterparts in survival and in achieving functional cure in mice. Genetic data suggest improved survival might derive from enhanced toxin clearance, and improved cure might reflect more efficient adaptation of insulin transport to glucose using more complex microtubules. These findings further support the potential benefits of preferentially using female cells in human islet transplantation to cure type 1 diabetes.

O-3: Inhibition of Cyclooxygenase-2 Prevents Chronic and Recurrent Cystitis

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Background and Objective: The global spread of multidrug-resistant microorganisms has created an urgent need for novel therapeutic strategies to combat urinary tract infections (UTIs). Immunomodulatory therapy may provide clinical benefit, as treatment of mice with dexamethasone during acute UTI with uropathogenic *E. coli* (UPEC) improved UTI outcomes by reducing the development of chronic cystitis, which predisposes to recurrent infection. We hypothesized that, as was previously found in mice, biomarkers of recurrent UTI (rUTI) could be identified in the sera of young women presenting initially with acute UPEC cystitis. By identifying immune response pathways associated with rUTI, we hoped to identify new therapeutic targets for the treatment and prevention of rUTI in women.

Methods: We utilized clinical specimens from a clinical study of UTI performed at the University of Washington to generate hypotheses that we then tested in our animal model of rUTI.

Results: We discovered that soluble biomarkers engaged in myeloid cell development and chemotaxis were predictive of future UTI recurrence when they were elevated in the sera of young women with acute UTI. Translation of these findings revealed that moderation of the neutrophil response during acute UTI in mice, and specifically disruption of bladder epithelial transmigration of neutrophils by inhibition of cyclooxygenase-2, protected against chronic and recurrent cystitis.

Conclusions: Cyclooxygenase-2 expression during acute UTI appears to be a critical molecular trigger determining disease outcome, and drugs targeting cyclooxygenase-2 could help to treat and prevent recurrent UTI.

O-4: Placental Abruption and Type 2 Diabetes Risk in Women: The Danish Birth Registry, 1980–2010

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Background and Objective: Placental abruption (PA) is a premature complete or partial separation of the placenta before delivery that involves vascular dysfunction and chronic inflammation. Inflammation may signal a future risk of type 2 diabetes. Given ethnic differences in rates of PA and type 2 diabetes, we evaluated the association between PA and subsequent risk of type 2 diabetes in women by ethnicity.

Methods: We used data from 1,873,604 singleton deliveries to Danish women registered in the Danish Medical Birth Registry from 1980 to 2010. PA was defined as having an ICD (International Classification of Diseases)-8 or ICD-10 code for PA, placenta previa, or antepartum hemorrhage. Type 2 diabetes was defined as having an ICD-8 code of 250 or an ICD-10 code of E11. We considered maternal age, education, ethnicity, and immigrant status as potential confounders. We used Cox proportional hazards models to estimate age-adjusted and fully adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). We stratified by immigrant status.

Results: In age-adjusted models, PA was associated with a 40% increased risk of developing type 2 diabetes (95% CI, 1.18, 1.63). Associations were stronger in immigrants than in native-born Danes (age-adjusted HR: 1.70 [95% CI, 1.13, 2.53] for immigrants vs. 1.40 for native-born Danes [95% CI, 1.18, 1.66]). Adjustment for sociodemographic factors attenuated these associations, making the overall association borderline significant (fully adjusted HR: 1.14; 95% CI, 0.97, 1.35).

Conclusions: Having a PA could signal an increased risk of type 2 diabetes, particularly in immigrant women who come from the Middle East or East Africa. If these results are replicated, future studies should evaluate whether women with PA would benefit from lifestyle interventions to reduce their future risk of type 2 diabetes.

O-5: Pubertal Hormone Associations With Psychopathology: Dynamic Cyclic and Moderated Effects

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Background and Objective: Puberty is characterized by dynamic changes in gonadal hormone levels and a rapid increase in the prevalence of psychopathology (Sisk & Zehr, 2005, *Frontiers in Neuroendocrinology* 26, 163-174). Hormonal changes at puberty likely increase the risk for psychopathology by instantiating individual differences in temperament and environmental sensitivity to context (Del Giudice, Ellis, & Shirtcliff, 2011, *Neuroscience and Biobehavioral Reviews* 35, 1562-1592). The current study evaluated this idea.

Methods: Four studies were reviewed, 2 cross-sectional and 2 with a longitudinal design. For the cross-sectional studies, participants were 134 female (and 178 male) adolescents who were over-recruited for clinically significant attention problems, and 60 female undergraduate students, respectively. For the longitudinal studies, participants were 50 female college students and 40 female college students, respectively. Symptoms were assessed using a well-validated questionnaire or interviews, and hormones were measured using established and sensitive assays.

Results: Among the key cross-sectional findings was that higher levels of circulating testosterone during adolescence were associated with decreased inattention in females ($\beta = -.22$, $P < .01$), but not in males ($\beta = .02$, $P > .05$). Further, higher levels of binge eating in females were apparent during the luteal phase of the menstrual cycle ($\beta = .13$, $P < .05$). Longitudinal results suggested that a high level of ovarian hormones during the luteal phase was associated with increased depressive symptoms, but only for those with high trait perspective taking (interaction $\gamma = .05$, $P < .01$). Within-person cyclical increases in estradiol were associated with reduced symptoms of borderline personality disorder, but only for those characterized by high neuroticism ($\gamma = -.13$, $P < .01$) or those who had been exposed to sexual abuse ($\gamma = -.15$, $P < .01$).

Conclusions: Evolutionary theory suggests that hormone-based effects instantiate environmental influences and shape dispositional functioning so as to increase risk for psychopathology (Martel, 2013, *Psychological Bulletin* 139, 1221-1259). The results of the present study have utility for assessment and intervention that could be targeted to adolescence.

O-6: Sex Differences in Attenuation of Cocaine-conditioned Cue Reinstatement by the Central Oxytocin Receptor Agonist

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Background and Objective: Therapies for addiction to stimulants and the underlying neurobiology have typically focused on males. In both sexes, systemic oxytocin treatment attenuated reinstatement of cocaine seeking in a rodent model of relapse. However, the question remains as to whether enough systemic oxytocin crosses the blood-brain barrier to exert a central effect. Additionally, oxytocin binds vasopressin receptors, and so the involvement of this system remains unclear. We assessed the effects of systemic and centrally administered oxytocin and a novel oxytocin receptor agonist, FE-202739, on cocaine seeking in male and female rats. FE-202739 specifically binds to oxytocin receptors and does not have a central effect when administered systemically.

Methods: Rats underwent cocaine self-administration followed by extinction. FE-202739 was intraperitoneally injected before reinstatement of cocaine seeking, which was induced by cocaine prime or conditioned cues. In a separate experiment, oxytocin and FE-202739 were infused intracerebroventricularly (ICV).

Results: Unlike systemic oxytocin, systemic FE-202739 had no effect on reinstatement to cocaine seeking. Central administration of both compounds significantly attenuated cocaine-primed reinstatement. However, cue-induced reinstatement was reduced only in males.

Conclusions: A central action on the oxytocin receptor is necessary for the attenuation of response to a cocaine prime. However, in response to conditioned cues, central actions on the oxytocin receptor appear to be relevant only in males because in females, both ICV oxytocin and FE-202739 appear to have no effect. This sex difference in cue-induced cocaine seeking may relate to the well-known differences between females and males in the role of oxytocin on peripheral organ sites of action.

O-7: Periconceptional Folic Acid-Containing Supplements and LINE-1 DNA Methylation in the MARBLES Prospective Study of Autism Spectrum Disorder

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Background and Objective: In population-based studies, maternal periconceptional folic acid intake has been associated with reduced risk for autism spectrum disorder (ASD) in the child. In a prospective study of high-risk families, we examined whether folic acid supplementation decreased ASD risk in siblings. We also examined relationships with LINE-1 (long interspersed nucleotide element 1) DNA methylation as an indicator of potential epigenetic mechanisms, given the ties between folate and methylation.

Methods: Mothers in the MARBLES (Markers of Autism Risk in Babies - Learning Early Signs) study who had at least 1 child with ASD and who became pregnant with another child were included. LINE-1 methylation was measured in DNA extracted from maternal whole blood samples collected during each trimester and at delivery, and in the child's cord and peripheral blood using bisulfite conversion and pyrosequencing (averaged across 5 CpG sites). Maternal interviews were used to collect information on prenatal intake of vitamins and supplements. Final ASD clinical diagnoses were made at the MIND Institute using standardized assessments at 36 months.

Results: Children whose mothers did not report taking a prenatal vitamin and who consumed no supplemental folic acid during the first month of pregnancy were several times more likely to be diagnosed with ASD. Folic acid supplementation and ASD were also associated with trends in global DNA methylation in the child.

Conclusions: Taking folic acid supplements during the first month of pregnancy could reduce risk for ASD in subsequent children, and it could also affect the child's LINE-1 DNA methylation. Additional research is needed to confirm these results and to further explore dose thresholds.

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O-8: Sex Differences in the Brain Response to Smoking Cues in Adult Cigarette Smokers

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Background and Objective: Women have greater difficulty quitting smoking than do men, perhaps because their cigarette use is more strongly influenced by smoking-related cues (e.g., seeing someone else smoke). Currently, the mechanisms that underlie these differences remain unclear. The objective of this study was to test the hypothesis that female smokers would display a stronger response in brain areas linked to motivational drive, such as the orbitofrontal cortex (OFC), than male smokers.

Methods: Functional magnetic resonance imaging (fMRI) was used to measure brain activity associated with holding and viewing an unlit cigarette in 26 male and 21 female nicotine-deprived daily smokers (>15 cigarettes/day; 18–45 years old) recruited from the community. To increase their desire to smoke, participants were informed that they would be able to smoke the cigarette they were holding immediately following the fMRI session. An independent-samples t-test was used to compare cue-elicited activation throughout the entire brain in males versus females.

Results: Compared to male smokers, female smokers exhibited significantly greater cue-elicited activation of the OFC, as predicted. Females also displayed stronger activation of the left occipital cortex and weaker activation of the left precentral gyrus than males during exposure to cigarette cues ($P < .005$ for each comparison).

Conclusions: Greater cue-elicited activation of the OFC in female than in male smokers is consistent with the observation that cigarette-related stimuli play a greater role in maintaining smoking for female smokers. The strength of responses in the OFC to smoking cues may serve as a useful neurobiological marker for evaluating the effectiveness of smoking interventions tailored to women.