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

Eighth Annual Interdisciplinary
Women's Health Research Symposium
November 17, 2011

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IN THE YEAR following the 20th anniversary of the establishment of the Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH) and the release of the new NIH Strategic Plan for Women's Health and Sex Differences Research, ORWH has begun working with a number of NIH Institutes and Centers (ICs) to begin the process of implementing its vision, goals, and objectives. As a first step, ORWH used the reissuance of the requests for applications (RFAs) for two of its major programs as an opportunity to address the goals of the strategic plan. These RFAs represent the sixth round of funding for the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program and the third round for the Specialized Centers of Research (SCOR) on Sex Differences, which was recently renamed in light of the increased focus of the new strategic plan on sex differences research and the translation of sex-specific findings to clinical practice.

Since its inception, ORWH has looked for innovative ways to encourage collaborative, interdisciplinary research to improve women's health and elucidate the differences and similarities between women and men in the presentation, treatment, and outcomes of disease. ORWH developed, implemented, and funded two innovative interdisciplinary career development and research programs—the BIRCWH program, launched in 1999, and the SCOR program, established in 2001. Through these programs, many interdisciplinary collaborations have been established that would not have been possible otherwise.

The Interdisciplinary Women's Health Research Symposium, now in its eighth year, showcases the research findings of BIRCWH scholars, who are early stage, junior faculty; and SCOR principal investigators (PIs), who are senior investigators. The abstracts for this symposium, which are compiled and presented on the following pages, cover a broad spectrum of research areas relevant to women's health and sex and gender differences.

BIRCWH, an innovative, institutional mentored career development program, was designed to increase the number of women's health researchers pursuing interdisciplinary research. BIRCWH is built on three pillars: career development, a supportive mentoring relationship, and interdisciplinary research. The program pairs junior faculty, who have recently completed clinical training or postdoctoral fellowships and who are beginning basic, clinical, or translational research related to women's health, with senior investigators in women's health. In July 2010, ORWH and cosponsors including the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institute on Aging (NIA), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Mental Health (NIMH), National Institute on Drug Abuse (NIDA), National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the NIH Office of Dietary Supplements (ODS) funded 13 new and continuing BIRCWH programs. Currently, there are 29 active BIRCWH programs nationwide and as of July 2011, 451 scholars have participated in the program, 81 percent of whom are women. The majority of BIRCWH scholars has achieved continued career success in research positions and obtained independent funding

from Federal and other sources, including academic, foundation, and industry grants. As of 2010, scholar success rates for NIH research grant applications (R, P, and U series) ranged from 31 to 40 percent, and scholars have been awarded over 475 NIH research grants. Awards from the NIH were primarily from the National Heart, Lung, and Blood Institute (NHLBI), National Institute of Allergy and Infectious Diseases (NIAID), NICHD, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIDA, and National Institute of Neurological Disorders and Stroke (NINDS). In addition, scholars have received Federal funding from the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, the Department of Defense, and the Department of Energy.

The SCOR program provides support for senior investigators who are looking at sex differences and major medical problems that affect women by integrating basic, clinical, and translational approaches to women's health. It is hoped that the requirement that the SCOR contain a basic and clinical component will lead to the transfer of findings to patients. Each SCOR is required to have a central theme related to the disease area to which at least three individual core projects relate and which serves as an integrating force. SCORs may be interdepartmental, intercollegiate, or interinstitutional. The currently funded SCORs are in the fifth year of their funding cycle and consist of 11 centers that continue to thrive and are conducting interdisciplinary research on sex and gender factors in depression, pain, substance abuse, osteoporosis, and urinary tract and reproductive health.

ORWH is the major funder of the SCORs with additional funding and programmatic support provided by five NIH ICs (NIAMS, NICHD, NIDA, NIDDK and NIMH) and the Food and Drug Administration (FDA) Office of Women's Health. The SCOR represents an excellent model for stimulating interdisciplinary and translational research, with significant applications to gender-specific human health. In the past five years, SCOR investigators have published 490 articles in a variety of journals, most commonly the *American Journal of Obstetrics and Gynecology*, *Journal of Urology*, *Journal of Clinical Endocrinology and Metabolism*, *PLoS ONE*, *Infection and Immunity*, *Gastroenterology*, *American Journal of Physiology*, *Drug and Alcohol Dependence*, and *Proceedings of the National Academy of Sciences of the United States of America*, demonstrating the diversity of research areas that is being conducted in the centers.

The Eighth Annual Interdisciplinary Women's Health Research Symposium will take place on November 17, 2011 on the NIH campus. The abstracts selected for oral or poster presentation represent the full spectrum of women's health research. The symposium will include, for example, cutting edge research on inherited genes that affect breast cancer susceptibility in Latinas; the role of pubertal hormones and their influence on cognition and stress reactivity in adulthood; sex differences in cocaine seeking behavior and risk of relapse; and the interplay of depressive symptoms and gender and how they affect the risk of cardiovascular disease in older adults. A poster session will promote networking and interactions among BIRCWH scholars and BIRCWH and SCOR PIs.

ORWH recognizes that the study of women's health across the lifespan can be enhanced by an interdisciplinary approach to research

that encourages team-based studies by bridging basic and clinical science and incorporating new models of collaboration, institutional support, and evaluation. The BIRCWH and SCOR programs are ORWH's signature initiatives dedicated to promoting interdisciplinary research and career development with the goal of reducing fragmentation in approaches to women's health and advancing research on the role of sex differences on health and disease. Goal 1 of the Strategic Plan is to "increase sex differences research in basic science studies" and it is hoped that the expansion of the SCOR program will help achieve this goal. Goal 6 of the Strategic Plan is to "employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce." An important part of this goal is to "lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs." A pillar of BIRCWH is effective mentoring—ensuring that mentors represent the diverse disciplines needed to carry out interdisciplinary projects and support the career development that will help BIRCWH scholars to bridge the transition to research independence.

The past two decades have seen major progress in women's health research and the understanding of how sex and gender factors affect the health of women and men. The BIRCWH PIs and scholars and the SCOR investigators now constitute groups of interdisciplinary researchers across the country that serve as a platform to further advances in women's health and sex differences research that will help to fill the remaining gaps in our knowledge of major health problems and translate research advances into findings that can be applied in the clinical setting. BIRCWH PIs from multiple institutions across the

United States have also formed a Writing Group and are beginning to publish about lessons learned from utilizing an interdisciplinary approach to women's health research and career development at their institutions. It is our hope that the presentations at the Interdisciplinary Women's Health Research Symposium, represented in these abstracts, will further emphasize the importance of interdisciplinary approaches to women's health research and the need to perform sex/gender analyses of scientific results. Three of the SCOR PIs made major contributions to the IOM workshop on *Sex Difference and Implications for Translational Neuroscience Research*, the summary of which was published in March 2011. It is encouraging to see the BIRCWH and SCOR programs serving as a model for scientific knowledge that is team-science oriented and takes variations due to sex into account as an integral part of the research enterprise.

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A Tribute to Vivian W. Pinn, M.D.

Vivian W. Pinn, M.D., founding director of the Office of Research on Women's Health (ORWH), retired from the National Institutes of Health (NIH) and the Federal Government on August 31, 2011 after 20 years of service. Under Dr. Pinn's leadership, ORWH has implemented inclusion policies for women and minorities in clinical trials, supported science-driven sex differences research, and collaborated with NIH Institutes and Centers to bring true trans-agency ownership to women's health research and career development programs.

Among many other accomplishments, Dr. Pinn co-chaired the NIH Working Group on Women in Biomedical Careers and launched the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program in 2000, followed by the Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health in 2001. She spearheaded a series of nationwide scientific meetings and public hearings to reexamine priorities for women's health research and inform ORWH's new strategic plan, *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research*, presented on ORWH's 20th anniversary in September 2010.

Dr. Pinn is a fellow of the American Academy of Arts and Sciences and was elected to the Institute of Medicine in 1995. The Foundation for Gender-Specific Medicine at Columbia University honored

Dr. Pinn in May 2011 with their Athena Award, which recognizes individuals who have contributed significantly to the understanding of human health and the pathophysiology of disease. She also received the Tufts University School of Medicine Dean's Medal. She has received 11 honorary degrees of laws and science since 1992 and, in 1989, she became the second woman to be named president of the National Medical Association. Her legacy also includes the University of Virginia (UVA) School of Medicine's Vivian W. Pinn Distinguished Lecture in Health Disparities, the Vivian Pinn College of UVA, Tufts University's Vivian W. Pinn Office of Student Affairs, and a Tufts University Medical School scholarship in her name for disadvantaged students.

Dr. Pinn has been an inspiration to all involved in women's health and sex and gender differences research. She has been a trailblazer and mentor par excellence. The progress we celebrate is thanks to Dr. Pinn's unrelenting creativity, resourcefulness, persistence, and her refusal to take "no" for an answer when it comes to advancing women's health and sex differences research and related career development. For these reasons and because of our appreciation of her, the staff of ORWH would like to dedicate this special issue to Vivian W. Pinn to showcase her accomplishments for all women and men.

BIRCWH Poster Abstracts

P-1: A New Method to Determine Vaginal Axis and Spatial Position Using a 3-D Anatomical Coordinate System

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Background and Objective: The position and orientation of the vagina using sagittal images has been used previously to quantify the degree of pelvic organ prolapse. While useful, analyses based on 2-D sagittal images are subject to tilt errors due to patient misalignment. The objective is to establish a 3-D coordinate system of the female pelvis based on MRI and use it to describe the position and orientation of the centroidal axis of the vagina.

Methods: Nine subjects with symptoms of pelvic floor dysfunction were scanned in the supine position. Three-dimensional reconstructions and anatomical coordinate systems were established using custom software written in Mathematica™ (Wolfram Research). Anatomical coordinate systems were established based on the location of the ischial spines and the length of the longitudinal axis of the pubic symphysis. Three-dimensional surface models of the vagina were created using custom segmentation software written in Mathematica™ (Wolfram Research). The centroidal axis of the surface model was then utilized to calculate changes in vaginal angle as it crossed the plane of the levator hiatus.

Results: Vaginal angle became more acute (toward the hiatal plane) in all but two women with changes ranging from 32 degrees toward the plane to 5.4 degrees away. A less acute angle suggests compromised apical support.

Conclusions: By quantifying anatomy relative to each patient's skeleton, this approach accounts for patient misalignment and is not subject to tilt error. In the future, this approach will be utilized to quantify differences in vaginal position and orientation in patients with prolapse to nulliparous controls.

P-2: Gender Differences in Body Mass Index and Physical Performance among Older Mexican Americans

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Background and Objective: Obesity is a major public health problem associated with reduced physical function in older adults. The purpose of this study was to examine gender differences between body mass index (BMI) and decline of physical performance at 2-year follow-up among older Mexican Americans.

Methods: Two-year prospective study of Mexican-American men and women aged >75 residing in five southwestern states in the United States. Data were collected on socio-demographic variables, physical performance (tandem stand balance, timed chair stand, and timed 8-foot walk), medical conditions, and BMI. Multiple regression analysis was used to test the effect of BMI on physical performance at 2-year follow-up.

Results: Out of 668 subjects, 31.3% of women and 18.4% of men had a BMI ≥ 30 kg/m² at baseline. Mean score of physical performance at baseline was 5.1 (SD=3.2) in obese women and 7.1 (SD=2.7) in obese men. Multiple regression analysis showed that women with a BMI of 30 < 35 kg/m² showed a decline of 0.8 points (SE=0.37; $p=0.04$) and those with a BMI ≥ 35 kg/m² showed a decline of 0.9 points (SE=0.47; $p=0.04$), after controlling for medical conditions and physical perfor-

mance at baseline. No significant association was found between BMI and physical performance in men.

Conclusions: The association between BMI and physical performance differed by sex in older Mexican Americans. Among women, high BMI (≥ 30 kg/m²) was associated with decline in physical performance after controlling for all covariates. Conversely, BMI does not seem to affect physical performance in men.

P-3: Cohort differences in Body Composition in Women: A Comparison of the Baltimore Longitudinal Study of Aging and Old Order Amish

Dawn Alley (presenting author),¹ Laura Yerges,¹ Michelle Shardell,¹ E. Jeffrey Metter,² Eleanor Simonsick,² Soren Snitker,¹ Sari Stenholm,² Alan R. Shuldiner,¹ Braxton Mitchell,¹ and Luigi Ferrucci²

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Background and Objective: It is unknown how age-related changes in body composition differ across birth cohorts in the context of rapidly rising obesity rates. The objective of this study is to compare cohort trajectories of body composition in adulthood (ages 20+) across birth cohorts and in two socioculturally distinct populations of women: the Old Order Amish (OOA, N=226) and non-Hispanic White women from the Baltimore Longitudinal Study of Aging (BLSA, N=413).

Methods: Mixed effects models predicted body mass index (BMI) and body composition (obtained from DXA scans conducted from 1991–2010) based on age, population (OOA vs. BLSA), birth cohort, and their interactions.

Results: More recent cohorts of women in the BLSA had higher BMI across the lifespan: Women in the most recent cohort (born after 1944) had an average BMI 4.5 kg/m² higher ($p<0.001$) than women in the earliest cohort (born before 1923). Percent body fat also differed, with the most recent cohort having an average percent body fat 5.2 percentage points higher than the earliest cohort ($p<0.001$). Cohort differences in body fat were not accounted for by increases in BMI. OOA women had higher BMI than BLSA women ($p<0.05$), but lower percent body fat ($p<0.05$) than BLSA women.

Conclusions: The association between BMI and body fat differs across birth cohorts and social environments. Although increases in body fat have exceeded those predicted by increases in BMI alone among women in Baltimore, analysis of Amish women suggests that high physical activity may result in lower percent body fat even at similar weights.

P-4: Beyond the Dyad: Gender, Distress, and Dementia Caregiving Patterns in Mexican-Heritage Families

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Background and Objective: Caregiver burden (i.e., stress and poor physical and mental health) is prevalent among chronic caregivers of individuals with dementia, if adequate caregiver support and resources are not available. Gender differences exist in caregiving. Women are more likely to be caregivers for persons with dementia and to incur greater caregiver burden than men. Compared to White Non-Hispanics, Latino caregivers (mostly women) report more depressive symptoms, smaller and less effective support networks, and more dissatisfaction with the support they receive. The objective of the study is to describe Mexican-heritage caregivers' perceptions of their social support network and explore gender differences in caregivers' perceptions of the nature of the support they receive.

Methods: Secondary qualitative analysis of in-depth interviews with 37 Mexican-heritage caregivers for persons with dementia from SALSA (Sacramento Area Latino Study on Aging, an NIH-funded longitudinal study).

Results: The total sample included 17 (46%) spouses (6 husbands) and 20 (54%) adult children (5 sons) as primary caregivers. All caregivers reported diverse distribution patterns of caregiving beyond the primary relationship (caregiver and informant). However, spousal caregivers (husbands and wives) reported having fewer kin involved in sharing the burden than non-spousal (adult children) caregivers. Further, among spousal caregivers, lower socioeconomic status (SES) and less acculturated wives expressed greater dissatisfaction, feelings of isolation and distress, discontent with available support, and reluctance to ask for assistance than their lower SES male spousal caregiver counterparts.

Conclusion: Social support networks differ for male and female caregivers of Mexican heritage, which should be considered in designing meaningful interventions.

P-5: Inflammatory Patterns in Placentas from Mothers with Preterm Premature Rupture of Membranes

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Background and Objective: Preterm premature rupture of membrane (PPROM) accounts for up to one-third of preterm births and is often associated with chorioamnionitis. Yet, studies of PPRM placental pathologies are limited and may give insight into neonatal consequences. Our objective is to determine patterns of inflammation in placentas of women with PPRM.

Methods: Placentas were collected from women enrolled in our prospective PPRM cohort study at the University of Colorado Hospital from July 1, 2010 to April 30, 2011. Placentas (n=19) underwent gross and microscopic examination for findings of fetal- and maternal-side inflammation.

Results: Median gestational age at membrane rupture was 30 2/7 weeks (range 24 4/7–33 4/7). Average time to delivery after rupture was 8.3 days (range 1–36). There were 11 pathologically confirmed chorioamnionitis cases (58%). There was no difference in mean time to delivery after rupture between placentas with and without chorioamnionitis (7.5 vs. 9.3 days; p=0.68). Funisitis was also present (n=7; 37%), often with chorioamnionitis (n=6/11; 55%). There was no difference in mean time to delivery after rupture between cases with and without funisitis (8.9 vs. 7.9 days; p=0.82). Seven placentas had chorionic plate vasculitis (37%); all of which were associated with chorioamnionitis. Three placentas had chronic villitis (16%); one placenta had deciduitis reflecting sites of maternal inflammation.

Conclusions: In our PPRM cohort, more inflammation was seen on the fetal side of the placenta. Time to delivery after rupture did not predict pathological inflammation. Our findings supply groundwork to further delineate the relationship of PPRM, inflammation and newborn brain injury.

P-6: The Transcriptional and Metabolic Response to Hypoxic Challenge

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Background and Objective: The availability of oxygen is inherently tied to metabolism, where nutrients obtained through dietary input are balanced with O₂ levels to meet cell- and tissue-specific requirements of energy production and expenditure. In limiting oxygen conditions, the integrity of DNA, proteins, and lipids can be compromised—all are susceptible to attack by elevated levels of reactive oxygen species. The cellular adaptive response to hypoxia is multifaceted, and relies on

shifts in transcription and metabolism. However, the processes underpinning conserved hypoxic-induced changes are not well understood. The objective of this study was to delineate the global transcriptional and metabolic changes that transpire in response to hypoxic insult and which are dependent upon the actions of HIF (hypoxia inducible factor) and ERR (estrogen-related receptor).

Methods: *Drosophila* display a robust hypoxic response that is mediated by conserved factors. We have used microarray analysis, GC/MS, and a variety of molecular genetic approaches (e.g., chromatin immunoprecipitation) to comprehensively define the hypoxic response in *Drosophila* larvae.

Results: Our approach has allowed us to determine, with high confidence and great resolution, those transcriptional and metabolic changes that occur in response to hypoxic challenge. Furthermore, we have defined the individual and collective roles of HIF and ERR in these transitions.

Conclusions: Our results indicate that HIF and ERR drive cellular behavior in hypoxia. Without either or both factors the adaptive hypoxic response cannot occur. Equally as important, our results suggest the existence of a novel, conserved hypoxic response pathway that is entirely HIF- and ERR-independent.

P-7: Elevated Psychological Stress and Poor Physical Function among HIV+ women on HAART

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Background and Objective: HIV infection is a risk factor that contributes to age-associated declines in physical function and psychological stress, despite effective HIV treatment. The objective of the study is to identify associations between physical function and psychological stress in women with HIV.

Methods: HIV-infected women aged 40 or older on stable HAART were enrolled. Psychological stress (Perceived Stress Scale [PSS]) and physical function testing (short physical performance battery [SPPB] and loaded stair climb) were assessed. Chi square, student T and correlation tests were performed (SAS version 9.1).

Results: Of 54 subjects enrolled to date, mean age is 50.5±6.9 years; 74% are Black, 50% are U.S. born, 31% are partnered, 40% are employed, and 52% graduated from high school. The median BMI is 27.4 (range 15.1–41.5); 28% have diabetes and 50% have hypertension. The median CD4 count is normal at 673 cells/mm³ (range 204–1320); while the median nadir CD4 count is low at 202 cells/mm³ (range 0–412); 94% have a HIV viral load ≤75 copies/mL. Seventy-six percent report higher levels of psychological stress (PSS score ≥14). While 33 of 41 (80%) had a high SPPB score ≥10, thirty-six completed the loaded stair climb demonstrating poor performance with mean power of 271.5±100.3 watts. Decreased power was associated with lower SPPB score and older age, but not higher psychological stress level.

Conclusions: HIV infection in these women was associated with a substantial burden of psychological stress despite viral suppression and CD4 restoration. Physical function as measured by power was poor, but not directly related to psychological stress level.

P-8: African-American Adolescent Girls: What Are the Environmental Factors that Influence Their Risk for Overweight/obesity?

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Background and Objective: Underlying causes for overweight/obesity are a complex interplay of individual, behavioral, social, and environmental factors related to physical activity (PA) and eating. Less research has been conducted on environmental dynamics. Because African-American girls experience higher rates of overweight than other youth and more likely live in environments that may inhibit healthy lifestyles, there is a need to understand what roles

different environments play in the obesity paradigm for this population. The objective of this study was to better understand the environmental factors associated with overweight/obesity in African-American adolescent girls.

Methods: Social factors within the home, neighborhood, and school environments that influence PA and eating were explored in six focus groups with 34 girls and four groups with 25 of the girls' mothers. Food, PA, and media inventories were completed to assess the availability of physical resources in 19 homes.

Results: Major themes about the home environment that surfaced were mothers' negative discussion about their daughter's and their own weight and inconsistent family rules regarding eating meals while watching television or eating in bedrooms. Girls expressed concern about being active outdoors in their neighborhoods (traffic, gangs); however, the visibility of peers increased their use of available neighborhood resources (parks, walking trails). Being the minority in predominantly white schools affected some girls' decisions to be on a sports team. Most homes had limited PA equipment, but many media-related resources.

Conclusions: Gaining perspectives about PA and food environments is the first step in creating innovative strategies to address the high rates of overweight/obesity in African-American girls.

P-9: Gene Expression Profile Selected Genetic Variants and Breast Cancer Survival

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Background and Objective: Two commercially available assays measure gene expression in tumor tissues to predict breast cancer prognosis. Many genes and loci included in these assays represent novel biological mediators of cancer progression. The objective of the study was to evaluate associations between gene expression profile selected (GEPS) genetic variants and breast cancer survival.

Methods: Variants within and correlated to the expression of GEPS loci, were identified from genotype data for 2,918 Chinese women with breast cancer, followed for a mean of 5.7 years. Associations with breast cancer survival were evaluated using Cox proportional hazards regression.

Results: Genotype data was available for 2,308 variants within, and 433 variants correlated to the expression of, 80 GEPS loci. A total of 1,956 variants with minor allele frequencies above 5%, within 861 independent loci ($r^2 < 0.6$), were evaluated. The observed number of nominally significant associations ($p \leq 0.05$) was greater than expected by chance for both genetic variants (256 vs. 98, $p < 0.001$) and independent loci (163 vs. 43, $p < 0.001$). Highly significant associations ($p \leq 0.001$) were seen for 10 variants in seven loci (within or correlated to the expression of AURKA, BCL6, BIRC5, C20orf108, COL4A2, DIAPH3, DHX58, EPR1, KAT2A, and TMEM235).

Conclusion: Associations for variants in genes known to influence cancer progression, as well as in genes and loci not previously studied in the context of breast cancer survival, were identified at a level greater than chance. These findings provide additional targets for investigations into the genetic mediators of breast cancer progression.

P-10: Living Life in "Survival Mode": Understanding the Links between Stress, "Strength," and Black Women's Health

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Background and Objectives: To cope with and survive daily stressors, black women may adhere to a model of "strength" that carries expectations that they will respond to stressors and demands without complaint or assistance, and put the needs of others above caring for self. A "strength adherence" model that explores the health consequences of black women's yielding to expectations of "strong black womanhood" may provide insight into gender- and race-based health disparities. The objective of the study was to develop a stress-

health model (driven by black women's own insight) that explains how "strength adherence" influences health behaviors and health outcomes.

Methods: We used narrative data from 10 Internet blogs and 20 magazine articles that targeted black women and included the term "strong black woman." Reports of stressors and gendered expectations for managing them, and resultant health behaviors and outcomes, were analyzed to understand women's views on the consequences of adhering to strength expectations as a form of survival.

Results: Reported stressors included racial and gender discrimination, family and community responsibilities, and intimate partner concerns. To be "strong" in the face of stressors, women were expected to rely on self, conceal emotional distress, and sacrifice personal needs. This mode of stress management was linked to emotional eating, decreased help seeking, and symptoms of anxiety and depression.

Conclusions: The model demonstrates links among stress, strength, health behaviors and outcomes. Next steps include developing and testing a tool to assess "strength adherence," and explore its links to intention for preventive health care, beginning with black women's plans for breast cancer screening.

P-11: The Effects of an Automated Stimulus to Promote Physical Activity Adherence

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Background and Objectives: Physical activity has been widely studied to reduce cardiometabolic risk, although adherence and long-term maintenance of this demanding health behavior is often difficult to achieve. This study evaluated the effects of an intervention providing an automated stimulus for physical activity based on: (1) adherence with physical activity goals and (2) biomarkers of energy expenditure in overweight (BMI 25–30 kg/m²) midlife women age 47–55 years (n=60) with increased cardiometabolic risk. The secondary objective was to evaluate the feasibility of the stimulus-response intervention for future physical activity research by examining subjects' perceptions.

Methods: The Dual System account provides the theoretical basis for the intervention. This includes the semi-automated, habit-based system involving a stimulus and response, and is relatively more efficient than the goal-directed system, which also requires consideration of goals and outcomes. A repeated measures design was used to examine adherence and biomarkers of energy expenditure pre- and post-intervention (6-week duration). An accelerometer worn at the waist during waking hours throughout the intervention provided a real-time automated stimulus by vibrating when energy was being conserved.

Results: Subjects responded by increasing activity minutes per week (min/wk), and kilocalories expended per week (kcal/wk) above the resting metabolic rate (RMR). Subjects increased the percent kilocalorie expenditure from 0–25% at baseline to near 100% of their goal. Subjects also reported positive perceptions of the intervention.

Conclusions: Testing this intervention has important implications for explaining and predicting physical activity adherence and for maximizing the benefits of physical activity over time.

P-12: Hot Flashes, Sleep Complaints, and Depressed Mood in Midlife Women

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Background and Objective: One-fifth of midlife women report that sleepiness interferes with daily life and can influence depressed mood. Here we examined the relations among hot flashes (HF), sleep complaints, and depressed mood as part of a larger study on midlife women's genital health.

Method: Cross-sectional data were obtained from 179 women (ages 35–60, 79% white). HF experience was coded as ever/never and ever/never within the past year. Sleep complaints were assessed with the Pittsburgh Sleep Quality Index (PSQI); depressed mood was

assessed with the Center for Epidemiological Studies-Depression scale (CES-D).

Results: The experience of HF was significantly related to the total PSQI score for both ever having HF ($p < .001$) and for HF within the past year ($p = .001$). Depressed mood was not significantly related to HF, but was correlated with PSQI total score ($p < .001$); 25% of the sample reported both elevated PSQI and CES-D scores (≥ 5 and ≥ 16 , respectively). Ever experiencing HF was related to shorter sleep duration ($p = .023$), longer sleep latency ($p = .041$), more frequent daytime dysfunction ($p = .008$), and greater sleep disturbance ($p = .015$). Focusing on HF within the past year, sleep duration and daytime dysfunction were no longer significant (p -values $> .05$), whereas longer sleep latency and greater sleep disturbance remained. Among HF sufferers, those reporting < 7 hours of sleep/night were more likely to report an elevated CES-D score, ($p = .007$).

Conclusion: Midlife women with HF reported numerous sleep complaints; these sleep complaints were not related to depressed mood. The combination of HF and insufficient sleep might trigger depressive symptoms.

P-13: Reintroduction of Amino Acids to the IUGR Fetus Increases Net Fetal Protein Accretion

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Background and Objective: Placental insufficiency results in decreased fetal amino acid (AA) uptake, decreased fetal plasma insulin, and poor fetal growth. We hypothesize that reintroduction of AA and/or insulin to the IUGR fetus will increase fetal protein accretion.

Methods: IUGR was produced using a sheep model of placental insufficiency. Late in gestation, IUGR and control (C) fetuses received acute infusions of either AA (IUGR, $n = 5$ and C, $n = 4$), insulin (IUGR, $n = 6$ and C, $n = 5$), or saline. Fetal leucine metabolism was measured followed by a muscle biopsy to quantify mTOR signaling.

Results: Fifty-five percent of fetuses were male; sex was not a significant variable for any outcome tested. In C, AA infusion increased leucine flux into fetal tissues by 35% ($p < 0.01$) and increased leucine oxidation more than in IUGR fetuses (100% vs. 25%, $p < 0.05$). In IUGR, AA infusion suppressed fetal protein breakdown by 90% and increased protein accretion by 150% ($p < 0.05$). Insulin infusion did not promote fetal protein accretion in either group, however activated mTOR-p70S6k-rpS6 signaling to a greater degree in C ($p < 0.05$).

Conclusion: Acute reintroduction of AA to the IUGR fetus suppressed fetal protein breakdown without increasing leucine oxidation, which increased fetal protein accretion. Use of AA to promote fetal growth in IUGR might be more effective than hormonal strategies if responsiveness to insulin within growth signaling pathways is limited.

P-14: Arthralgia and Patient-Reported Outcomes in Postmenopausal Women with Early Breast Cancer Taking Aromatase Inhibitors

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Background and Objective: To prevent cancer recurrence, each year over 100,000 U.S. women begin a 5-year course of aromatase inhibitors (AIs) for early-stage breast cancer. AI-related joint pain (arthralgia) may interfere with patients' well-being, leading to non-adherence. More information is needed about arthralgia and patient-reported outcomes (PROs) in these women. We sought to assess relationships of arthralgia with other PROs over the first 12 weeks of AI therapy in a longitudinal cohort study.

Methods: Postmenopausal female oncology outpatients with early-stage breast cancer ($n = 52$, pilot cohort) completed paper surveys prior to AI initiation, and every 2 weeks thereafter for 12 weeks. Pain was measured in 16 joint locations using a 0–10 numeric rating scale. Baseline covariates included age, comorbidities, major depressive disorder, social support, performance status, and menopausal symptoms. Time-varying PROs examined included physical function, sleep disturbance, pain interference, and emotional distress (depression). We used mixed models to analyze arthralgia and PROs.

Results: Mean age was 62 ± 10 years. The majority had active performance status ($n = 46$) and no major depression ($n = 47$) at baseline. Median worst pain in any joint prior to AI initiation was 1/10 (interquartile range = 0–5). Adjusting for baseline covariates, greater arthralgia at 12 weeks was associated with worse physical function ($\beta = -0.09[-0.13, -0.04]$), greater pain interference ($\beta = 0.15[0.09, 0.20]$), and greater emotional distress ($\beta = 0.06[0.01, 0.11]$) but not with sleep disturbance ($\beta = -0.01[-0.03, 0.004]$).

Conclusions: Our findings contribute to understanding how arthralgia relates to PROs over the first 12 weeks of AI therapy. We will build targeted AI adherence interventions from more comprehensive longitudinal PRO information.

P-15: Race Disparities in the Association between Preterm Birth and Maternal Cardiovascular Disease

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Background and Objective: Women with preterm births (PTB) have excess cardiovascular disease (CVD) risk perhaps related to metabolic, vascular, and lipid aberrations. How risk may differ according to race is unknown. We considered that both White and Black women with PTB would have elevated CVD risk, but risk factor profiles may vary.

Methods: Eight years after pregnancy (mean age 38) we measured total, LDL and HDL cholesterol, triglycerides, apolipoprotein-B, and glucose in women with prior PTB (< 37 weeks, White $n = 135$; Black $n = 46$) or term births (≥ 37 weeks, White $n = 203$; Black $n = 103$). Women also underwent a standardized evaluation of carotid intima media thickness (IMT), brachial flow mediated dilation (FMD), and pulse wave velocity (PWV). Women with preeclampsia or small for gestational age births were excluded.

Results: White women with PTB versus term births had higher total and LDL cholesterol, Apo-B, and glucose concentrations, adjusted for age, body size and smoking (p for all < 0.01). Black women with PTB versus term births had higher adjusted systolic blood pressure (beta 8.11 mmHg, $p = 0.04$). No lipid or metabolic markers were different in Black women according to PTB history. White women with PTB < 34 weeks versus term births had higher adjusted IMT (beta 0.03 mm, $p = 0.03$).

Conclusions: White women with a history of PTB had a pro-atherogenic profile in the decade after pregnancy compared to those with term births, and they had evidence of early atherosclerosis. Black women with PTB had higher blood pressure, but no other vascular or metabolic aberrations were detected.

P-16: Relationship between Exposed Vaginal Length, Genital Hiatus Size and Levator Ani Muscle Status

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Background and Objective: Birth-induced muscle injury is highly associated with pelvic organ prolapse but the fundamental mechanism linking them remains unknown. Theoretical work suggests that muscle damage could lead to an enlarged hiatus exposing the vagina to pressure differentials favoring cystocele development. This study tests

the hypothesis that exposed vaginal length, hiatus size and muscle injury are associated.

Methods: Thirty women were selected to represent a full spectrum of AVW support including women with normal support and AVW prolapse. Each underwent supine, static and dynamic MR imaging. On midsagittal slice at maximum Valsalva, the curved length of the exposed AVW from the distal urethra to the point of perineal body contact and hiatus size from the pubic bone to the perineal body were measured. Levator ani muscle injury was scored into "No Defect," "Minor Defects," and "Major Defects" based on the axial MR scans. Polynomial regression analyses and ANOVA were used for statistical analysis.

Results: There is a strong quadratic relationship between the exposed vaginal length and hiatus size ($R^2=0.87$, $p<0.001$). Women with major defects have significantly larger hiatus (major: 4.7 ± 1.5 cm vs. no defect: 2.6 ± 1.2 cm, $p=0.007$; major vs. minor: 3.0 ± 1.4 cm, $p=0.021$) and longer exposed vaginal length (major: 4.2 ± 2.6 cm vs. no defect: 1.2 ± 1.7 cm, $p=0.019$; major vs. minor: 1.4 ± 2.3 cm, $p=0.025$) than women with minor and no defects.

Conclusion: Exposed AVW length increases with increasing hiatus size. Major defect results in larger hiatus size and longer exposed vaginal length at the maximum Valsalva.

P-17: Association between Low Activity Levels and Falling in Women and Men with Parkinson's Disease

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Background and Objectives: Falling contributes to greater levels of disability. Low activity levels may contribute to falling. Women with Parkinson's are less active than men, potentially contributing to falling. The objective is to examine (1) whether lower activity was associated with falls among adults with Parkinson's and (2) whether the association between activity and falls differed among men and women.

Methods: Eighty-eight women and 121 men with Parkinson's participated in a multi-center longitudinal study. Fall history and activity level were evaluated at baseline and 6 months later. Mann-Whitney tests ($\alpha=0.05$) were used to compare activity levels between fallers and non-fallers. Logistic regression analysis was used to assess associations between activity level and gender with falls.

Results: Forty-one women (49%) and 53 men (44%) fell over a 6-month period. Fall rates did not differ by gender ($p=.58$). Baseline median activity levels were significantly lower ($p<.05$) among fallers than non-fallers among women (101.2 vs. 147.0) and men (109.1 vs. 166.9). Men had higher levels of activity than women for both fallers ($p=.08$) and non-fallers ($p=.10$). Women with low baseline activity levels were three times as likely to fall compared to women with high activity levels (OR=2.91, 95% CI=1.2-7.1). This relationship was not significantly different ($p=.69$) in men (OR=2.31, 95% CI=1.1-4.9).

Conclusion: Approximately half the sample with Parkinson's fell over a 6-month period. Both women and men fallers were less active than non-fallers. These results suggest that low activity levels contribute to falling.

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P-18: Effects of Behavioral Intervention on Caregivers of Individuals with Mild Cognitive Impairment

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Background and Objectives: Caregivers of individuals with mild cognitive impairment (MCI) experience significant distress and decreased quality of life (QOL) similar to that experienced by caregivers of dementia patients, but few studies have examined the effects of intervention programs on caregiver burden in MCI. Women are dis-

proportionately affected, i.e., 65% of persons with Alzheimer's disease (AD) and 60% of caregivers for persons with AD are women. The objectives were to determine if a memory compensation program, Healthy Action to Benefit Independence and Thinking (HABIT), could increase self-efficacy in individuals with amnesic MCI that could lead to improvement in functional status and less dependence on caregivers, and to see if men and women caregivers are differentially affected.

Methods: HABIT, a multicomponent, 2-week, behavioral intervention program, was delivered to individuals with MCI and their caregivers. Self- and informant-based mood and perceived burden survey data were collected at baseline, at intervention end, and 8 weeks post-intervention in 38 caregivers (18 women, 20 men; mean age 69) and MCI cases (26 women, 12 men; mean age 75).

Results: MCI cases reported significant improvement in QOL ($p=.001$) through 8-week follow-up even though an initial improvement in functional status was not sustained. Trends toward improvement in perceived burden ($p=.056$) and QOL ($p=.081$) were noted by caregivers. Further, while men reported no change from baseline to 8 weeks post-intervention ($t(19)=1.56$, $p=.14$), women reported decreased burden ($t(17)=2.89$, $p=.01$).

Conclusions: Programs such as HABIT can help MCI cases and their caregivers, particularly women, adjust to the disease and its consequences on well-being.

P-19: The Relationship of Violence to Weight Change, Pre-diabetes and Diabetes: Longitudinal Analyses from the Study of Women's Health Across the Nation (SWAN)

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Background and Objective: Several studies indicate that violence against women is associated with poorer health, as well as death. However, few studies have examined the longitudinal effects of violence during midlife on the risk of obesity and diabetes. The objective is to investigate the associations of violence with changes in weight, waist circumference, incident pre-diabetes and diabetes.

Methods: Ten years of data from the longitudinal cohort of women enrolled in the Study of Women's Health across the Nation (SWAN) were collected. An ethnically/racially and socially diverse group of 2,208 women between the ages of 42 and 52 years at baseline who did not have diabetes or pre-diabetes at baseline comprised the study sample. Data were collected annually for 10 years on violence, health outcomes and confounding variables, and annually collected fasting blood samples analyzed for blood glucose levels to detect the incidence of pre-diabetes and diabetes.

Results: At baseline more African-American women reported violence than Caucasian, Chinese and Japanese women. In bivariate analyses, being separated or divorced, smoking, reporting depressive symptoms and having no health insurance were positively associated with violence. Baseline violence was positively associated longitudinally with incident pre-diabetes ($p=.03$) and nonsignificantly with incident diabetes ($p=.06$); changes in weight and waist circumference were not associated with violence.

Conclusion: Violence in middle-aged women was associated with incident pre-diabetes; and while non-significant, results indicated that incident diabetes may be related to violence. Our findings suggest that violence in midlife may have an adverse effect on women's health, specifically related to pre-diabetes and diabetes.

P-20: The Impact of Pelvic Organ Prolapse on Emotional Well-Being

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Background and Objective: Women's emotive responses to having pelvic organ prolapse are poorly studied. Better understanding may

lead to improved patient-provider communication and outcomes. The objective of the study was to describe emotions experienced by women with prolapse before and after treatment.

Methods: Forty-two women with symptomatic prolapse participated in semi-structured focus groups or one-on-one phone interviews. The facilitator stimulated discussion about prolapse and emotional well-being by asking open-ended scripted questions. All groups and interviews were audiotaped and transcribed. Two members of the study team utilized a grounded theory approach to code the transcripts. Major themes were identified throughout this process. The codebook was amended until thematic saturation was achieved.

Results: Subject mean age was 60.7 ± 10.5 years. Twenty-five participated in focus groups and 17 in phone interviews. Women expressed annoyance, frustration, anger, fear, uneasiness, sadness, depression, anxiety, and feelings of getting older or "falling apart" as emotions associated with prolapse. Women expressed hope at the thought of surgery, and improvement in their emotional well-being after surgery. Other women struggled with "negative" emotions associated with recovering from surgery, fear of recurrence, or with persistent symptoms.

Conclusions: Women experience significant "negative" emotions associated with prolapse that appear to impact emotional well-being. Planned surgery can provide a sense of hope and improvement for some women. Postoperative followup will help us determine if surgical correction has a sustained improvement on emotional well-being related to prolapse. A better understanding of the range of women's emotions surrounding prolapse may help providers better meet patients' needs and improve patient-provider communication.

P-21: Differential Negative-Feedback Responses of Neurokinin B and Kisspeptin Expression Indicate Sensitivity Differences to Estrogen in the Arcuate Nucleus

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Background and Objective: In reproduction, neurokinin B (NKB) cooperatively contributes to kisspeptin (Kiss1) activity and GnRH secretion, but how the steroid hormone milieu affects NKB function remains poorly understood. NKB and Kiss1 are co-expressed within the arcuate (ARC), a hypothalamic region regulating negative-feedback by gonadal sex steroids. Developmental expression of mouse ARC NKB and Kiss1 suggested differences in sex steroid negative-feedback. The objective of the study was to elucidate the reproductive physiology of ARC negative-feedback by performing studies of Kiss1 and NKB sensitivity to estradiol (E2).

Methods: To achieve different physiological E2 levels, three doses (vehicle, Low E2, and High E2) were implanted subcutaneously for 7 days in ovariectomized adult (P60) WT females. Juvenile (P13) and P60 hypogonadal *hpg* mice, deficient in GnRH, were also treated. ARC tissues of each ($n = 10-13$) were processed for Kiss1 and NKB qRT-PCR.

Results: All groups had a negative-feedback response. Low E2 significantly suppressed Kiss1 expression, with further repression by High E2. In contrast, NKB expression was significantly suppressed only by High E2. The NKB response to E2 was similar between juvenile and adult *hpg*, suggesting negative-feedback is developmentally intact at prepubertal ages, but that higher levels of E2 are necessary to manifest E2 negative-feedback suppression of NKB.

Conclusions: These findings provide evidence of differential regulation of NKB and Kiss1 in the ARC by E2, possibly distinguishing NKB from Kiss1 contributions in puberty and reproductive function. Importantly, these results suggest that ARC Kiss1 and NKB regulation by E2 would establish distinct patterns of activation and repression across the estrous/menstrual cycle.

P-22: Perinatal Regionalization and Women's Health: Improving Area-Based Boundary Definitions for AHRQ Quality Indicator Evaluation

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Background and Objective: Statewide perinatal regionalization protects women's health through improved coordination of health-care within geographic areas. The Agency for Healthcare Research and Quality (AHRQ) recommends area-based indicators to evaluate healthcare quality within county and metropolitan census boundaries. For rare indicator-events, risk-adjusted rates are "smoothed" across census areas to improve rate reliability. Smoothed rates however, may be difficult to interpret when planning local-healthcare services. The objective of the study is to demonstrate the construction of indicator-specific boundary definitions from within which to calculate stable rates. The quality indicator "neonatal mortality" is evaluated in Michigan.

Methods: Vital statistics birth and linked infant death records on all live-singleton births to resident mothers 2004-2009 ($n = 600,540$) were used to calculate neonatal mortality rates. Individual records were assigned census tract identifiers ($n = 2,765$). Tracts were aggregated to meet case/population thresholds and maximum shape compactness using Automated Zone Matching (AZM) methodology. Maps of unadjusted and risk-adjusted neonatal mortality rates were created.

Results: Thirty-three zones were constructed that contained a mean 62.2 (range, 29-143) neonatal deaths. The unadjusted neonatal mortality rate for each zone ranged 2.0 to 7.6 neonatal deaths per 1,000 live births. Controlling for percent extreme low birth weight, mothers with chronic hypertension, black race and less than high-school education, neonatal mortality rates decreased in zones with large suburban populations, but remained elevated in certain zones with urban populations. Rural Michigan had low unadjusted and adjusted neonatal mortality rates.

Conclusions: Future healthcare evaluation should be conducted in selected urban areas of Michigan to reduce neonatal mortality, improve perinatal regionalization, and protect women's health in Michigan.

P-23: MSH-releasing Inhibitor Factor (pro-leu-gly-NH2) Acts as an Allosteric Activator for Oxytocin-induced MAPK Signaling but Does Not Affect Uterine Contractility

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Background and Objective: MSH-releasing inhibitor factor (pro-leu-gly-NH2) is an oxytocin fragment, containing the last three amino acids of the hormone oxytocin. The oxytocin receptor (OXTR) is a G-protein coupled receptor that is capable of both G-protein and β -arrestin-mediated signaling. Oxytocin-induced β -arrestin signaling occurs through the MAPK pathway. We determined whether the peptide, pro-leu-gly-NH2 affects oxytocin-mediated G-protein and β -arrestin-mediated signaling.

Methods: HEK-293 cells expressing the OXTR were stimulated with oxytocin at concentrations of 1nM to 1 μ M with or without pretreatment with pro-leu-gly-NH2. MAPK activation was measured with Western blot for phospho-ERK following oxytocin stimulation for five minutes at each concentration. To determine if pro-leu-gly-NH2 increased oxytocin-induced uterine contractions, uterine muscle strips from wild-type mice were suspended in a tissue organ bath and stimulated with oxytocin with or without pretreatment with pro-leu-gly-NH2 and the contraction responses measured.

Results: Pretreatment of HEK-293 cells expressing the OXTR with pro-leu-gly-NH2 increased oxytocin-induced phospho-ERK signaling compared to cells not receiving pro-leu-gly-NH2. Pretreatment of uterine muscle strips from wild-type mice did not affect oxytocin-induced uterine contractions. Stimulation of cells or uterine muscle strips alone with pro-leu-gly-NH2 did not activate MAPK signaling or induce uterine contractions.

Conclusions: The oxytocin fragment pro-leu-gly-NH2 acts as an allosteric activator for oxytocin-induced MAPK signaling, but does not increase G-protein-mediated oxytocin-induced contractions. Further work is needed to understand the molecular conformations of the OXTR that produce these findings.

P-24: Women Physicians: Choosing a Career in Academic Medicine

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Background and Objective: The development of opportunities and support of women researchers is important in women's health. Academic women physicians are an important component of women researchers. The pathway to a career in academic medicine (AM) is poorly understood despite recent attempts to understand the complex process of physician career development. This study attempted to better define how, when and why women choose a career in AM.

Methods: Fifty-three women physicians in AM were interviewed regarding how, when, and why they chose this career path. Transcripts were thematically analyzed by project investigators individually and then collectively. Emerging themes in the data were objectively identified.

Results: Academic medicine: *Why?* Five themes—Aspects of Academic Health Center Environment (14 subthemes); Fit (5 subthemes); People (7 subthemes); Exposure (4 subthemes) and Clinical Medicine. *How?* Five themes—Change in Specialty; Parental Influence; Dissatisfaction with Former Career; Decision-Making Styles (6 subthemes); Emotionality (2 subthemes). *When?* Four themes—Practicing Physician; Fellowship; Resident; Medical Student.

Conclusion: Choosing a career in AM is greatly influenced by the environment in which one trains and by people—be they faculty, mentors, role models, or family. An interest in teaching is a primary theme associated with women choosing a career in academic medicine. Many women physicians entering AM chose this career path in fellowship or after. Many became more aware of AM as a career path during residency and their decision was solidified during fellowship. For many women, choosing AM was not necessarily an active, planful decision; rather it was serendipitous or circumstantial.

P-25: An Integrated Metabolomic Profiling Approach to *E.coli* Urinary Tract Infections

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Background and Objectives: Urinary tract infections (UTIs) caused by uropathogenic *E. coli* (UPEC) disproportionately affect women. Metabolomic profiling of patients offers the prospect of differentiating disease states and better understanding pathophysiology based upon metabolic pathway activities. To date, few studies have been performed to characterize infectious disease-associated pathway changes. The objective of this study was to identify metabolic pathway changes in a population with recurrent urinary tract infection.

Methods: The optimized liquid chromatography-mass spectrometry method involves minimal sample preparation and uses a Fused-Core® phenyl-hexyl column interfaced with a hybrid triple quadrupole/linear ion trap instrument operating in negative ion ESI mode. PCA analysis of the approximately 2,300 features revealed this method to be reproducible and capable of distinguishing patients by diagnostic group. Multiple supervised chemometric analyses revealed substantial metabolomic shifts between control and urinary tract infection patients.

Results: A consensus scoring strategy, while conservative, identified nine metabolites that distinguish *E. Coli* UTI from control patient populations. These metabolites are biologically plausible and suggest multiple infection-associated biochemical processes.

Conclusions: This metabolomic approach suggests a robust strategy for distinguishing metabolomic shifts among patients with uro-

logical infectious diseases. Pathways identified by this method suggest new diagnostic, therapeutic and prophylactic approaches to UTI in women.

P-26: Persistent and Transient Supplemental Nutrition Assistance Program (SNAP) Participation and Adult Women's Body Mass Index Transitions

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Background and Objectives: High rates of overweight and obesity have been observed among low-income women. The high rates have lead researchers to question whether food assistance programs, such as the Supplemental Nutrition Assistance Program (SNAP) in which 66% of adult participants are women, is a contributing factor. Several studies have examined the association between SNAP participation and women's weight gain; however, isolating the effect of the program is difficult as results are biased by selection (who selects into the program). To address the selectivity concerns, propensity score matching techniques were used to investigate the association between SNAP participation and weight status and body mass index (BMI) transitions among a sample of reproductive-age women.

Methods: Data are from the Fragile Families and Child Well-being Study, a longitudinal study of socio-economically disadvantaged, urban families. Participants are 1,360 non-pregnant women between the ages of 20–39 whose income is <130% Federal Poverty Line at two time points, measured two years apart.

Results: Results from the propensity score matching methods suggest that neither persistent nor transient SNAP participation is related to higher levels of BMI; nor is SNAP participation related to women transitioning to higher (nor lower) BMI categories.

Conclusions: Results do not support the hypothesis that SNAP participation is contributing to overweight and obesity. The study is the first to use propensity score matching techniques to assess the association between SNAP and reproductive-age women's BMI transitions. Among this age-group of women, survey measures of SNAP participation may be serving as a proxy for "economically disadvantaged."

P-27: Factors Influencing the Views That Aging Women Have About Sexual Health Communication with Their Health Care Providers

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Background and Objectives: Mid- and late-life women report difficulty communicating with their health care providers about sexual health. According to the Integrated Model of Behavior Prediction (IMBP), which guided this study, communication can be predicted by attitudes, perceived behavioral norms, and perceived behavioral control. The objectives are to compare the relative importance of attitudes, perceived norms, and perceived behavioral control in aging and older women's views of communication with their providers about sexual health and to explore other factors that older women believe impact their communication about sexual health with their providers.

Methods: Qualitative interviews (N=12) were conducted with women aged 50 and older, recruited from the community. A semi-structured interview elicited women's views on communicating with providers about sexual health. Interviews were transcribed, coded, and analyzed using theory-based thematic analysis.

Results: Of the three constructs of interest, attitudes appeared to be the most salient theme for women, followed by perceived behavioral control, and then perceived norms. Women identified many advantages and few risks associated with communication with providers about sexual health. Other themes of importance included provider behavior and attitudes related to initiation of discussions of sexual health.

Conclusions: For mid-to-late-life women, attitudes and perceived behavioral control are important factors in sexual health communication with their health care providers. Normative pressure was a less salient theme for these women.

P-28: Sexual Dimorphism of Cardiomyocyte Size in Adult but Not Fetal Sheep

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Background and Objective: The capacity for cardiomyocyte enlargement (necessary for adaptive cardiac growth) influences progression of cardiac disease, a process that differs between men and women. The objective is to determine how cardiomyocytes differ between the sexes in adulthood, and if those differences are present near birth.

Methods: Adult (male n=4; female n=4) and near-term fetal (138 ± 1 of 145 days of gestation; male n=8; female n=9) sheep hearts were enzymatically dissociated. Cellular dimensions were measured from fixed isolated cardiomyocytes. In cells from fetal hearts, proliferative index (measured by Ki-67 immunoreactivity) and maturational index (measured by binucleation) were quantified.

Results: Adult male sheep were significantly larger than adult females (105 ± 2 vs. 69 ± 8 kg) and had larger hearts (444 ± 50 vs. 301 ± 40 g). In adult sheep, males had significantly longer (171 ± 9 vs. 139 ± 7 μm) and wider (45 ± 3 vs. 38 ± 4 μm) left ventricular cardiomyocytes, and longer (176 ± 15 vs. 142 ± 20 μm) right ventricular cardiomyocytes. In contrast, neither body weight, heart weight, nor cardiomyocyte dimensions were found to be different between male and female fetuses. Additionally, the proliferative index and cardiomyocyte maturation were similar between male and female fetuses.

Conclusions: Differences in cardiomyocyte dimensions in adult sheep reflect sexual divergence in body (and consequently heart) weights. In contrast, body weight, heart weight, and cardiomyocyte parameters are similar between males and females in late gestation. These results suggest that cardiomyocyte growth in the fetus does not presage adult sexual dimorphisms. Sex differences in cardiomyocyte morphology that are important for adaptive growth in the adult may arise during postnatal maturation.

P-29: The Estrogen Receptor 1 (ESR1) Gene and Blood Pressure Salt Sensitivity

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Background and Objective: Previous reports have documented increased blood pressure (BP) salt sensitivity in women compared to men. The objective of the study is to examine the association between 799 single nucleotide polymorphisms (SNPs) in 44 genes involved in sex hormone biosynthesis, bioavailability and metabolism for their association with BP responses to sodium intervention in men and women.

Methods: A 7-day low-sodium (51.3 mmol sodium/day) followed by a 7-day high-sodium feeding study (307.8 mmol sodium/day) was

conducted among 1,906 Han, Chinese participants. Nine BP measurements were obtained at baseline and the end of each intervention period using a random-zero sphygmomanometer.

Results: Among men, absolute BP responses to sodium interventions decreased with the number of minor alleles of ESR1 markers rs9340844, rs9397453 and rs9383951. For example, men with genotypes C/C, C/T, and T/T of rs9397453 had respective mean DBP responses (95% CI) of: -2.67 (-3.13, -2.22), -1.23 (-1.98, -0.48), and 0.08 (-2.31, 2.47) mmHg to low-sodium intervention (p=0.0001; adjusted-p=0.04); and 1.46 (1.03, 1.89), 0.19 (-0.54, 0.91), and -1.10 (-2.82, 0.61) mmHg to high-sodium intervention (p=0.0002; adjusted-p=0.04). In addition, mean SBP responses (95% CI) were: -5.70 (-6.19, -5.20), -4.34 (-5.37, -3.31), and -2.65 (-5.15, -0.16) mmHg, respectively, for low-sodium intervention (p=0.002; adjusted-p=0.17); and 4.56 (4.12, 4.99), 3.47 (2.63, 4.30), and 1.97 (-0.49, 4.43) mmHg, respectively, for high-sodium intervention (p=0.003; adjusted-p=0.40). Similar, non-significant trends for these SNPs were observed among women.

Conclusions: We identified strong, consistent relationships between genetic variants in the ESR1 gene and salt sensitivity in men. These findings support a role for sex-hormones in the etiology of this complex trait.

P-30: Cardiopulmonary Testing and Correlates of Breast and Cardiac Biomarkers in Breast Cancer Survivors

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Background and Objective: Cardiac events are the leading cause of death in long-term breast cancer (BrCa) survivors next to primary malignancy recurrence. BrCa treatment may increase the risk of cardiac dysfunction including other factors such as weight gain and genetics. Low cardiorespiratory (CR) fitness level (measured as VO_{2 peak}) is a measure of cardiac dysfunction and contributes to cardiovascular, BrCa, and all-cause mortality. Strategies preventing cardiovascular disease (CVD) in this high-risk population are necessary. CR testing may be a useful biomarker to identify asymptomatic cardiac dysfunction. The objective of the study is to explore biomarkers of cardiovascular and BrCa risk in cancer survivors.

Methods: The study included 30 postmenopausal female BrCa survivors, 6 months to 10 years post treatment with cardio-toxic chemotherapy, who had +/- left chest wall radiation along with ≥ 2 CVD risk factors, completed maximal and submaximal CR testing (treadmill), along with an echocardiogram (ECHO) or Multigated Acquisition Scan (MUGA), serum biomarkers, and quality of life measures.

Results: BrCa survivors were 50.5 ± 5.6 year old and approximately 4.5 years from initial treatment. Maximal and submaximal CR tests were VO_{2 peak} = 25.4 +/- 5.3 ml/kg/min and VO_{2 peak} = 20.5 +/- 4.3 ml/kg/min, respectively. Eighty-seven percent of participants were in a poor CR fitness category. ECHO/MUGA were normal (LVEF=60.5 +/- 5.0). Poor CR fitness was associated with higher weight, BMI, and percent body fat, use of anti-hypertensive and statin medications, and exposure to and duration of an aromatase inhibitor.

Conclusion: CR fitness may serve as a reliable, modifiable biomarker of CVD and BrCa risk and be used as a target in future cancer survivorship trials.

P-31: Natural Killer Cells and Preeclampsia

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Background and Objectives: Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality worldwide. Recent evidence suggests that decidual Natural Killer cells (dNKs) at the maternal-fetal interface may play an important role in the regulation of maternal spiral artery remodeling. This process is compromised in preeclampsia and believed to be important for its pathogenesis. In contrast to peripheral blood NK cells (pNKs), which are cytotoxic and non-angiogenic, first trimester human dNKs have been shown to secrete proangiogenic molecules and to have reduced cytotoxicity. The objective is to convert human pNKs into dNK-like cells using specific factors.

Methods: pNKs were cultured under hypoxia in the presence TGF- β 1 and tested for expression of dNK cell surface markers, for secretion of proangiogenic molecules by ELISA, for angiogenic potential in tube formation assays and for cytotoxic activity on K562 target cells.

Results: pNKs cultured under hypoxia secreted VEGF, a potent proangiogenic molecule, and induced tube formation by Human Umbilical Vein Endothelial Cells. Under hypoxia in the presence of TGF- β 1 they also expressed the dNK cell marker CD9 and showed reduced cytotoxicity. An animal model is being established to study *in vivo* the spiral artery remodeling capacity of these *in vitro* generated dNK-like cells.

Conclusions: A combination of hypoxia and TGF- β 1 converts pNKs into proangiogenic non-cytotoxic cells with similarities to dNKs. These observations may have applications in the development of novel therapeutic approaches for preeclampsia and related disorders.

P-32: MirSNPs and microRNA-mediated Regulation of Hepatic Drug Metabolism and Disposition

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Background and Objective: Several hepatic genes involved in absorption, distribution, metabolism, and elimination (ADME) of drugs are highly variable in expression and demonstrate significant differences between genders and ethnicities, leading to interindividual variation in drug efficacy and toxicity. MicroRNAs have increasingly been shown to modulate gene expression networks and SNPs that disrupt microRNA binding sites (mirSNPs) have been shown to dysregulate gene expression and introduce variation in gene expression. The objective of this *in silico* study was to identify hepatic microRNAs and potentially functional mirSNPs that may play important roles in ADME gene regulation and contribute to underlying gender and ethnic differences in ADME gene expression networks.

Methods: We evaluated microRNA binding sites in ADME genes using major microRNA-target prediction programs: Targetscan, MirBase and PITA. We filtered for hepatic microRNAs (n=81) and filtered out false positives by selecting for sites predicted by at least two prediction programs. Next, we screened for SNPs disrupting microRNA-mRNA binding sites, and prioritized these for their predicted effects on mRNA folding using the program RNA hybrid.

Results: Our preliminary analysis identified microRNA binding sites and mirSNPs in several ADME genes including: efflux transporters ABCA2 and ABCC5; uptake transporters SLC22A11, SLC22A3, SLC31A1, SLC3A2, SLC7A11, SLC7A5, and SLC01B1; Phase I enzymes CYP2A6, CYP2B6 and CYP2C9; and Phase II enzymes SUL2A1 and NAT1.

Conclusions: We identified microRNAs and mirSNPs that might contribute towards regulation and gender differences in ADME gene expression. Future work is directed towards experimental evaluation and validation of these microRNAs and mirSNPs for their therapeutic significance.

P-33: A Role of Two Novel GPCRs, FFAR2 and FFAR3, in Gestational Diabetes

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Background and Objective: Gestational diabetes occurs when pancreatic beta cells cannot meet the increased insulin resistance

during pregnancy. G protein coupled receptors (GPCRs) are important mediators of pancreatic beta cell function and we recently discovered two novel GPCRs, free fatty acid receptor 2 (FFAR2) and 3 (FFAR3), are expressed in pancreatic beta cells. Because of these data, we have begun to explore their role in glucose homeostasis, specifically during pregnancy.

Methods: Using control mice, we have examined changes in FFAR2 and FFAR3 expression in different insulin resistant states. We have also used global KO mice for FFAR2 and FFAR3 to begin to examine the effect of null mutations on glucose/insulin homeostasis during pregnancy.

Results: Using different mouse models of insulin resistance, including pregnancy, we observed changes in FFAR2 and FFAR3 expression in mouse islets during the development of insulin resistance. Peak expression of FFAR2 was on day 13.5 of gestation, while peak expression of FFAR3 was on day 16 of gestation through post-partum day 1. Using global KO mice for FFAR2, we have also observed that, during pregnancy, FFAR2 global KO mice are glucose intolerant as compared to control mice.

Conclusions: Expression of FFAR2 and FFAR3 in islets is altered in different insulin resistant states, suggesting a possible role in the metabolic changes associated with insulin resistance. Global KO models are being used to better define the roles of these receptors in glucose homeostasis in states of insulin resistance.

P-34: Gender Differences in Advanced Heart Failure Symptom Profiles

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Background and Objective: Advanced heart failure (HF) is characterized by symptoms that limit daily life despite optimal therapy. The objective of the study is to identify gender differences in symptom profiles in adults with advanced HF.

Methods: We analyzed data on 39 women and 69 men in an ongoing study of advanced HF symptoms. Physical symptoms were measured with the HF Somatic Perception Scale, daytime sleepiness was measured with the Epworth Sleepiness Scale, depression was measured with the Patient Health Questionnaire, and hostility and anxiety were measured with the Brief Symptom Inventory. Latent class mixture modeling was used to identify distinct profiles among these five symptoms scores in separate models stratified by gender.

Results: Two symptom profiles were identified for women. Women with a high symptom burden profile (36%) reported worse daytime sleepiness, more depressive symptoms, and greater anxiety and hostility compared with women with the low symptom burden profile (64%) (all $p < .01$); there was no difference in physical symptoms between women with high vs. low symptom burden. Three symptom profiles were identified for men (21.7% had high, 17.4% had medium, and 60.9% of men had low symptom burden). There was a graded increase in severity of physical symptoms, daytime sleepiness, depressive symptoms, anxiety, and hostility across the three symptom profiles for men (all $p < .01$).

Conclusions: Physical symptoms, often viewed as hallmarks of HF, are not helpful in identifying women with greater symptom burden in HF. Psychological distress and sleep disturbances are indices of greater distress in women with advanced HF and therefore warrant assessment and treatment.

P-35: Abnormal Vaginal Flora and Infection with *Trichomonas vaginalis*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*

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Background and Objective: Bacterial vaginosis (BV) is a risk factor for sexually transmitted infection (STI) acquisition. Intermediate

vaginal flora is abnormal flora which does not meet diagnostic criteria for BV, but may also impact STI risk. The objective of the study is to determine whether abnormal vaginal flora, including intermediate vaginal flora and BV, are associated with *Trichomonas vaginalis* (TV), *Chlamydia trachomatis* (CT), and *Neisseria gonorrhoeae* (GC) infection.

Methods: We conducted a cross-sectional analysis of 6,088 women enrolled in the Contraceptive CHOICE Project who had a satisfactory nucleic acid amplification test for CT and GC, a satisfactory culture for TV, and a vaginal smear Gram-stained and scored using Nugent criteria at enrollment. We defined intermediate flora as a Nugent score of 4–6 and BV as a Nugent score ≥ 7 . We investigated associations between any baseline STI (TV, CT, or GC) and participant characteristics using univariate and multivariable analyses.

Results: There were 482 women who tested positive for TV, CT, or GC at enrollment. The baseline prevalences were: TV 5.5%, CT 3.1%, and GC 0.5%. In the multivariable analysis, significant factors associated with baseline STI included race/ethnicity, marital status, education, socioeconomic status, number of sexual partners, douching, and abnormal vaginal flora. Women with intermediate vaginal flora and BV had more than a two-fold increase in the risk of baseline STI (OR_{adj} 3.6 (95% CI 2.7–4.8) and OR_{adj} 2.8 (95% CI 2.1–3.8), respectively).

Conclusion: Abnormal vaginal flora may increase the risk of STI acquisition even in the absence of BV. A longitudinal investigation of this association is warranted.

P-36: Association of Hexachlorobenzene (HCB), Dichlorodiphenyltrichloroethane (DDT), and Dichlorodiphenyldichloroethane (DDE) with *In Vitro* Fertilization (IVF) Outcomes.

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Background and Objective: Hexachlorobenzene (HCB), dichlorodiphenyltrichloroethane (DDT), and dichlorodiphenyldichloroethane (DDE), are persistent chlorinated pesticides with endocrine activity that may adversely affect the early stages of human reproduction. The objective is to determine the association of serum levels of HCB, DDT, and DDE with implantation failure, chemical pregnancy, and spontaneous abortion (SAB) in women undergoing IVF from 1994 to 2003.

Methods: Levels of HCB and congeners of DDT and DDE were measured in serum collected during the follicular phase. Multivariable-adjusted statistical models accommodating multiple outcomes and multiple cycles per woman were used to estimate the relation between serum pesticide levels and IVF outcomes.

Results: A total of 765 women with a mean age (SD) of 35.4 years (4.2) at enrollment contributed 827 IVF cycles. All samples had detectable levels of HCB, DDT, and DDE, with median levels of 0.87 ng/g serum for HCB, 1.22 ng/g serum for total DDT, and 1.09 ng/g serum for p,p'-DDE. Compared to the lowest quartile of HCB, the lipid- and multivariable-adjusted odds for failed implantation was significantly elevated for those with higher HCB quartiles [Adjusted Odds Ratio (aOR) for Q2: 1.71, 95% confidence interval (CI): 1.03, 2.82, aOR for Q3: 2.30, 95% CI: 1.39, 3.81; aOR for Q4: 2.32, 95% CI: 1.39, 3.90] and showed a significantly increasing trend ($p=0.001$). No sta-

tistically significant associations were observed between DDT/DDE and IVF outcomes or between HCB and chemical pregnancy or SAB.

Conclusions: Serum HCB concentrations were significantly associated with failed implantation among women undergoing IVF.

P-37: Sex Differences in the Impact of Arginine Vasopressin on Social Affiliation in Posttraumatic Stress Disorder

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Background and Objective: The neurohormone arginine vasopressin (AVP) plays a critical role in social behaviors used to regulate stress. Sex differences exist such that AVP leads men to respond aggressively towards men, but affiliatively towards women, whereas it leads women to respond affiliatively towards both sexes. Posttraumatic stress disorder (PTSD) occurs more frequently among women than men and poor social relations contribute to symptom severity. The objective of the study was to examine the ability of AVP to modulate the relation between PTSD and social affiliation in stressful context, including whether such modulation would be more pervasive for women than men.

Methods: Participants were seven heterosexual couples (14 individuals; data collection ongoing) in which at least one partner exhibited elevated PTSD symptoms. Following intranasal administration of 20 IU AVP or placebo, participants completed a measure of attention to facial expressions of fear portrayed by their partner and unfamiliar men and women (as an indicator of affiliation in stressful context).

Results: PTSD severity was significantly associated with less affiliation, as reflected in less attention to fearful expressions. AVP significantly increased attention to fear, and significantly decreased the negative relation between PTSD and attention to fear. This effect was stronger for men than women, particularly in response to partner expressions.

Conclusions: AVP enhances affiliative responses in PTSD, particularly among men. Sex differences may reflect greater sensitivity of men's AVP system. Although these results are preliminary and should be interpreted with caution, AVP may prove to be therapeutic for PTSD by decreasing avoidance of social interaction, especially with one's partner.

P-38: Regulation of Drug Efflux Transporters in Human Placental Cells by Prostaglandin E₂

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Background and Objective: The inflammatory response modulates the expression of placental drug transporters, which could impact the disposition of drugs during pregnancy. Prostaglandin E₂ (PGE₂) acts as an immunomodulator at the maternal-fetal interface during pregnancy. Its effects are mediated through G-protein coupled receptors, acting via second messengers. We sought to determine the impact of PGE₂ on the expression of P-glycoprotein (P-gp, MDR1) and breast cancer resistance protein (BCRP) in placental cells. We hypothesize that PGE₂ regulates MDR1 and BCRP expression via subtype-specific PGE₂ receptor (EP1–4) signaling mechanisms.

Methods: Human placental JAr cells were treated with PGE₂ [5–10 μ g/ml] and changes in MDR1 and BCRP gene and protein expression were monitored over time by quantitative real time PCR. In subsequent studies, placental cells were treated with 10 μ M selective EP receptor antagonists (EP1, SC-19220; EP1 and EP2, AH-6809; EP3, L-798106; EP4, L-161982) for 1 hour prior to stimulation with PGE₂ (5 μ g/ml). Transporter expression was then evaluated.

Results: Treatment of placental JAr cells with PGE₂ (5 μ g/ml) decreased the expression MDR1 for up to 72 hours. PGE₂ (5 μ g/ml) increased BCRP gene expression (Fold Change, 1.7 ± 0.13). At this concentration, BCRP expression levels remained elevated for up to 72 hours. The effects of PGE₂ on MDR1 and BCRP expression were mediated via multiple PGE₂ receptors.

Conclusion: PGE₂ alters the expression of MDR1 and BCRP in placental cells. Elucidating the signaling cascade that results in PGE₂-mediated transcription regulation may contribute to the development of strategies to manipulate drug transporters during pregnancy and disease.

P-39: "I Just Keep My Antennae Out"—How Primary Care Physicians Respond to Intimate Partner Violence in Rural Communities

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Background and Objectives: In rural communities, limited health services, poverty and social isolation compromise healthcare access, producing unique challenges for healthcare providers caring for women exposed to intimate partner violence (IPV). Using qualitative methods, we assessed the opinions of primary care physicians caring for rural women with regard to IPV identification, the scope and severity of IPV as a health problem, physician's response to IPV, and barriers to optimized IPV care.

Methods: Based on thematic saturation, 19 internist, family practice, and OB-GYN physicians were interviewed. Using grounded theory, interview transcripts were analyzed for major themes.

Results: Most physicians did not practice routine inquiry for IPV due to competing time demands, lack of provider training, low confidence in referral services, and concern that inquiry would harm the patient-doctor relationship. They identified IPV largely among patients with symptoms of mood, anxiety or somatic disorders. Response to IPV included reassurance, validation, danger assessment, safety planning, referral to services and follow-up planning. Physicians perceived that barriers preventing rural women from seeking care for IPV included traditional gender roles, lower education, economic dependence on an abusive partner, low self-esteem, and patient reluctance to discuss IPV. They also perceived inadequate mental health and other referral services for IPV. To overcome barriers, physicians created a "safe sanctuary" to discuss IPV and suggested improved public health education and referral services.

Conclusions: Interventions to improve IPV-related care in rural communities should address physician and patient comfort discussing IPV, through both provider training and community education programs.

P-40: Are Depression and Frailty Overlapping Syndromes in Later Life? A Latent Variable Analysis

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Background and Objective: Depression and frailty are common geriatric conditions. However, it is unclear to what extent these represent independent rather than overlapping syndromes. The objective of the study was to examine the degree to which depression and frailty indicate overlapping constructs.

Methods: Data come from 2004/5 wave of the Baltimore Epidemiologic Catchment Area Study and analysis is limited to participants aged 40 and older with complete data on frailty and depression indicators (N=683). Depression was measured using the Diagnostic Interview Schedule and frailty was indexed by modified Fried criteria. Exploratory and confirmatory latent class analyses (LCA) were used to assess the degree to which depression and frailty syndromes co-occur within individuals. A latent Kappa coefficient was calculated from joint class distributions to measure chance-corrected latent agreement between the two constructs.

Results: LCA analyses supported a three-class solution for depression, with 3.9% categorized as severe depression, 19.6% as mild/moderate depression, and 76.5% as not depressed. A two-class solution was the best fit for frailty, with 8.8% classified as frail. Modeling the

indicators of depression and frailty as a single latent construct provided comparable fit to treating them as separate but correlated latent constructs. There was a high degree of correspondence between the latent depression and frailty constructs (Kappa=0.66).

Conclusions: Results suggest that depression and frailty are interrelated concepts, and that the operational criteria of these constructs identify highly overlapping subpopulations. This construct overlap has implications for understanding factors that contribute to the etiology and prognosis of depression and frailty in later life.

P-41: Effects of Psychosocial Stress on Brain Activity in Cocaine-Dependent Men and Women

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Background and Objective: Sex/gender differences in substance-dependent individuals are well documented. However, little is known about the neural correlates that underlie stress-induced relapse. Brain activity was compared between cocaine-dependent men and women during the Montreal Imaging Stress Task (MIST). The purpose of the study was to compare brain activity between cocaine-dependent men and women during a psychosocial stressor.

Methods: Subjects (n=10 men; n=10 women) were placed in a 3T scanner and exposed to the MIST. A block design of three conditions (rest/control/stress) was utilized. Results are based on data from 16 subjects. Images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p = 0.05$. Mean group images were thresholded using clusters determined by a corrected threshold of $p = 0.05$. Subjective ratings of stress and craving were obtained at the end of each run.

Results: The MIST produced a significant increase in stress in cocaine-dependent men. However, the magnitude of subjective stress following the second run of the MIST was greater in women than men. There was no effect of the MIST on craving. The math task elicited activity in both men and women in the prefrontal, anterior cingulate and parietal cortices. The stress condition increased activity in the precuneus, anterior and posterior cingulate cortices of women, with no change observed in men.

Conclusion: The MIST produces sex/gender-specific changes in measurable brain activity related to stress, suggesting that it may be an ideal paradigm for exploring the neural correlates of stress in substance-dependent individuals.

P-42: CMV Seropositivity as a Risk Factor for Frailty and Osteoporosis among Older Adults in the U.S. NHANES III Study

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Background and Objective: Frailty and osteoporosis are significant predictors of morbidity and mortality in the elderly. Associations with inflammatory markers implicate chronic inflammation as a risk factor for both outcomes, and cytomegalovirus (CMV) may be a source of this inflammation. The objective was to evaluate CMV seropositivity as a risk factor for frailty and bone mineral density (BMD) and to determine whether associations differ by sex.

Methods: We included 5,161 participants ≥ 60 years old from the U.S. National Health and Nutrition Examination Survey III who had CMV IgG serology and data on the outcome measures of interest. Frailty categories were based on the number of the following criteria: BMI $\leq 18.5 \text{ kg/m}^2$, slow walking, and self-reported weakness, exhaustion, or low physical activity. Hip BMD was measured using dual-energy X-ray absorptiometry. For frailty, prevalence ratios (PR) and 95% confidence intervals (CI) were calculated. For BMD, linear regression was used. Many potential confounders were considered.

Results: CMV seroprevalence was 91%, increased with age, and was higher in women (93%) than in men (88%). CMV seropositivity

was associated with frailty in men (age-adjusted PR for frail vs. robust: 2.3 [CI: 1.1–4.9]) but not women (PR: 1.6 [CI: 0.8–3.3]). Mean BMD was 4% lower for CMV seropositive men ($p=0.01$) and women ($p=0.02$) than for seronegative participants and was consistent after multiple adjustment.

Conclusions: CMV seropositivity was highly prevalent but not independently associated with frailty in this large survey. However, mean BMD among CMV seropositive participants was lower in both sexes. CMV may play a role in osteoporosis.

P-43: Symptoms of Depressed Mood, Disturbed Sleep and Sexual Problems in Midlife Women: Cross-sectional Data from the Study of Women's Health across the Nation (SWAN)

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Background and Objective: Depression is associated with sleep disturbance and sexual problems in midlife women. These symptoms are commonly reported, but little has been reported on their covariance in individual women. The objective was to evaluate the inter-relatedness of depressed mood, disturbed sleep, and sexual problems in midlife women and to characterize these women's demographic, psychosocial, and clinical characteristics.

Methods: SWAN is a multi-site, multi-ethnic observational cohort study of the menopausal transition across the United States. Depression was assessed using the Center for Epidemiological Studies Depression Scale (CES-D). Sleep disturbance was defined as nighttime or early awakenings, or difficulty falling asleep in the past 2 weeks. Sexual problems were defined as self-reported problems in any one of five domains: desire, arousal, satisfaction, orgasm and vaginal dryness. Logistic regression models were used to estimate the association of the demographic, psychosocial and clinical characteristics with the symptom complex.

Results: Five percent ($N=90$ of total $N=1,716$) experienced all three symptoms. In multivariable models, these women were more likely to have lower incomes, less education, be surgically postmenopausal (OR 3.37 [95% CI: 1.56, 7.26]) or late peri-menopausal (OR 1.99 [95% CI: 1.06, 3.75]), have lower self-reported health status, more stressful life events, and lower social support. No effect was noted for race/ethnicity or hormone therapy.

Conclusions: In this cross-sectional analysis of the SWAN cohort, 5% of women were affected by the complex of symptoms of depressed mood, disturbed sleep and sexual problems. Late-perimenopause, surgical menopause, poor social support, and stressful life events were associated with having the symptom complex.

P-44: Sex Differences in Medication Use among Dementia Patients

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Background and Objectives: Medications for mitigating dementia symptoms have limited efficacy; they also have adverse effects. Women are more likely to manifest dementia symptoms than men. Describing medication use by sex is key toward determining sex differences in dementia treatment safety and effectiveness. The objective of the study is to determine population-based medication use patterns for dementia by sex.

Methods: Medicare beneficiaries with dementia during 2007–2008 were identified from administrative data for this retrospective study. Part D data were used to ascertain 2008 medication use. We report relative prevalence of selected medications in women versus men, adjusting for age, race/ethnicity and long-term nursing home stays (LTNH). Since dementia is likely more severe in LTNH, we considered effect modification of LTNH by testing sex*LTNH interaction.

Results: Mean age of 127,547 beneficiaries with dementia was 82.6 (± 7.7) years; 75.8% were female, 32.8% had LTNH. Medication prevalence was: cognitive-enhancers 39.1%; antidepressants 48.4%; antipsychotics 24.1%; mood-stabilizers 4.8%. LTNH modified the effect of sex on antidepressants and antipsychotics. Among non-LTNH beneficiaries, women were 33% and 14% ($p<0.01$) more likely to use antidepressants and antipsychotics than men, respectively, while in LTNH women were 11% ($p<0.01$) more likely to use antidepressants with no significant difference in antipsychotic use. Regardless of LTNH, women were 7% ($p<0.01$) more likely to use cognitive-enhancers and 21% ($p<0.01$) less likely to use mood-stabilizers.

Conclusions: For most dementia management drug classes, use prevalence was higher in women than men. Documenting population-based medication prevalence is the first step in quantifying risks and benefits of dementia symptom treatment and identifying important treatment heterogeneity by sex.

P-45: Effects of Menstrual Cycle Phase on Cognition in Schizophrenia

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Background and Objective: Preliminary reports indicate that high levels of endogenous estrogen and exogenous estrogen therapy relate to improved cognition in women with schizophrenia. The objective of the study was to characterize how individual variations in sex hormones in women with schizophrenia impact performance on cognitive abilities typically sensitive to sex differences. We hypothesized that, similar to healthy women, women with schizophrenia would show better performance on “female” tasks (verbal memory/fluency) and worse performance on “male” tasks (visuospatial) when estrogen levels were high versus low, and these changes would correlate with changes in estradiol.

Methods: Twenty-three women with schizophrenia and 31 women without (46% African-American) completed cognitive testing at two carefully controlled phases of the menstrual cycle: (1) early follicular (Days 2–4; low estrogen/progesterone) and (2) midluteal (Days 20–22; high estrogen/progesterone). Men were included to establish the expected pattern of sex differences on cognitive tests. We obtained plasma hormone assays of estrogen, progesterone, and testosterone.

Results: Women with schizophrenia performed worse than female controls on all tasks (all $p<0.05$). Unexpectedly, neither group of females showed a change in performance on “female” or “male” tasks across cycle phase. Individual variations in estradiol or progesterone did not relate to cognitive performance in either group.

Conclusions: Our results suggest that performance on cognitive tasks typically sensitive to sex differences did not vary across cycle phase in women with schizophrenia or controls. These results are in contrast to previous findings in healthy women. Natural fluctuations in estradiol and progesterone may not influence cognition in women with schizophrenia.

P-46: Association of NMDA Receptor Antibodies and Neurocognitive Dysfunction in Pediatric Lupus Patients

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Background and Objective: Systemic Lupus Erythematosus (SLE) is an episodic, multisystem autoimmune disease that is recognized worldwide. The incidence of SLE is dramatically higher in women than in men. Approximately 1/5 of all systemic lupus starts in childhood and central nervous system (CNS) dysfunction is more common in childhood-onset SLE (cSLE). Despite these findings, the diagnosis of CNS disease in SLE remains difficult. The objective is to assess the association between elevated anti-NMDA-NR2 subunit receptor antibodies and neurocognitive dysfunction in pediatric lupus patients.

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

Results: Thirteen lupus patients, ages 10–19, completed neurocognitive testing and NMDA receptor antibody testing (two males, eight African Americans, three Caucasians, two others). SLEDAI scores ranged from 0–19. Means for intellectual functioning were low (FSIQ=87.8) compared to the general population (50th percentile FSIQ=100). All other cognitive score means were in the average range, except working memory and math fluency (both low average). There were no significant correlations between neurocognitive functioning and NMDA receptor antibodies, although verbal fluency approached significance ($p=.097$).

Conclusions: A larger sample size with control group is necessary to make more definitive conclusions about the association of NMDA receptor antibodies and neurocognitive dysfunction in pediatric lupus patients. This study is ongoing and will include: 30 patients with cSLE, 30 patients with JIA, and 30 children born to mothers with lupus (first degree relatives).

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P-47: Transport of Dexamethasone-loaded Nanoparticles across an *In Vitro* Model of Placental Trophoblast Cells

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Background and Objectives: The administration of dexamethasone during pregnancy when treating fetal congenital adrenal hyperplasia can result in severe side effects in the mother. Nanoparticles for targeted fetal therapy may improve *in utero* treatment of congenital adrenal hyperplasia and reduce maternal dexamethasone exposure. These studies were carried out to compare the influence of particle size and nanoparticle surface modification on the transport of dexamethasone-loaded nanoparticles across an *in vitro* model of human placental trophoblast cells (BeWo b30 cells).

Methods: Nanoparticle characterization included x-ray diffraction, transmission electron microscopy, particle size, zeta potential, encapsulation efficiency, and drug release determinations. Transport studies were performed across BeWo cell monolayers cultured on Transwell® inserts, with drug concentrations measured by HPLC. Coumarin-6 was incorporated as a fluorescent marker in nanoparticle tracking experiments.

Results: The transport of dexamethasone across BeWo cells was greater in nanoparticle formulations as compared to dexamethasone dissolved alone in the transport medium (apparent permeability 4.4×10^{-6} cm/s). Dexamethasone transport was dependent on nanoparticle size, as the percent of drug added to the maternal compartment reaching the fetal compartment after 2 hours was $53.8 \pm 4.8\%$ when dexamethasone was formulated in smaller particles (146 ± 2 nm), compared to $13.3 \pm 3.4\%$ with larger particles (227 ± 5 nm). Experiments with fluorescent particles confirmed the size dependence of nanoparticle transport. Increasing nanoparticle surface PEGylation (to 10% density) resulted in reduced transport rates.

Conclusions: These results highlight the feasibility of nanoparticle-based targeted fetal dexamethasone therapy as a strategy to reduce maternal side effects.

P-48: Scenario-Based Electronic Learning to Teach Women's Gastrointestinal Health

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Background and Objective: Scenario-based electronic learning (SBeL) immerses learners in a contextualized situation. SBeL can complement learning through direct patient care, especially in topics in which appropriate patient exposure is limited and training is deficient. The objective is to assess user satisfaction, perceived value, and knowledge gained in women's gastrointestinal (GI) health using SBeL.

Methods: An interactive case illustrating a woman's GI health topic was developed using the Case Scenario Builder authoring platform. Second-year medical students were recruited to play the case. Pre-play surveys assessing prior experience with SBeL, its perceived value, and knowledge of the subject of the case were administered. Post-play, satisfaction and usability of the tool was assessed. Perceived value of SBeL and subject knowledge were reassessed. Responses were recorded using Likert Scales. Descriptive statistics were calculated.

Results: Pre- and post-surveys were completed by 38 and 31 subjects, respectively. Prior experience with SBeL was low (mean score 1.49 ± 0.6 , 1=no prior use and 6=daily use). Subjects were initially neutral about its value in learning and/or becoming proficient in the following: medical facts (3.8 ± 0.9), patient-provider interactions (3.1 ± 1.1), trainee-supervisor interactions (3.3 ± 1.0), 1=not valuable and 5=very valuable. Post-play surveys found subjects to be very satisfied with the tool. They also reported being more knowledgeable and prepared to handle a similar case. Ninety-four percent reported being likely to complete additional cases.

Conclusions: SBeL can be used to teach women's GI health. Although prior experience with SBeL among students is low, once exposed, they perceive it to be valuable and are interested in using it more.

P-49: Role of Gender in HIV-1 Associated Decline in Gut Mucosal Integrity

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Background and Objective: Human Immunodeficiency Virus (HIV) infection is one of the leading causes of death in women in Africa. HIV infection results in loss of CD4+ T-cells in Gut-Associated Lymphoid Tissue (GALT). HIV disease progression correlates with immune activation which is higher in women compared to men. Antiretroviral therapy (HAART) effectively suppresses viral replication and stimulates immune reconstitution. HIV+ women on HAART have higher levels of T-cell activation than men on HAART. We hypothesize that compromised mucosal integrity allows for increased microbial translocation in women which stimulates systemic immune activation, which has implications for increased morbidity and disease progression in women. The objective is to compare the effects of gender on mucosal integrity in HIV+ individuals on HAART.

Methods: We compared gene expression profiles in gut mucosa and plasma levels of microbial products in male and female HIV+ participants.

Results: A greater proportion of HIV+ women on HAART had sustained levels of GALT CD4+ T-cell activation (37.4% vs. 6.5%) and CD8+ T-cell activation (42.7% vs. 12.52%) than men ($p < .05$). Comparison of mucosal gene expression showed down-regulation of

epithelial regeneration pathways and tight junction protein ZO-1 (2-fold decrease) in women than men on HAART. Indicators of microbial translocation, such as plasma LPS, and bacterial 16S rRNA, were increased in women compared to men on HAART.

Conclusions: These preliminary data suggest that increased microbial translocation may explain why women have sustained CD4+ T-cell activation, despite effective control of viral replication. Studies investigating the effects of HAART in women should focus on the maintenance of mucosal integrity and health.

P-50: Maternal Periconceptional Folic Acid Intake and Risk for Autism Spectrum Disorders in the CHARGE Case-control Study

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Background and Objective: Periconceptional folate is essential for proper neurodevelopment. Maternal folic acid intake was examined in relation to risk for autism spectrum disorder (ASD) and developmental delay (DD).

Methods: Families enrolled in the CHARGE (Childhood Autism Risks from Genetics and Environment) Study from 2003–2009 were included if their child had a diagnosis of ASD (n=429), DD (n=130) or typical development (TD, n=278) confirmed at the UC Davis M.I.N.D. Institute using standardized clinical assessments. Average daily folic acid was quantified for each mother based on dose, brands, and intake frequency of prenatal vitamins, multivitamins, folic acid-specific vitamins, other supplements, and cereal reported through parental interviews.

Results: Mean folic acid intake was significantly greater for mothers of TD children than for mothers of children with ASD in the first month of pregnancy (P1) (779.0 and 655.0 mcg, respectively, $p < 0.01$). This difference primarily resulted from higher mean folic acid from prenatal vitamins among mothers of TD children. Women reporting average daily intake of 600 mcg folic acid or more during P1 had reduced estimated risk of having children diagnosed with ASD compared to mothers reporting less than 600 mcg (odds ratio=0.62, 95% CI 0.42, 0.92, $p=0.02$), and risk estimates decreased with increased folic acid ($P_d=0.001$). Mothers of DD children tended to report lower folic acid intake during the three months before pregnancy relative to mothers of TD children ($p=0.08$).

Conclusions: Folic acid in the periconceptional period may reduce the risk of ASD. Replication of these findings and investigations of mechanisms involved are warranted.

P-51: Development of a Bioluminescent Mouse Model of Metastatic Cervical Cancer

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Background and Objective: Metastatic cervical cancer develops in a predictable pattern that progresses through lymph node regions before involving the lungs. Previous studies in mice used fluorescence microscopy to monitor this process *ex vivo*. The objective is to use bioluminescence to track non-invasively mouse models of metastatic human cervical cancer *in vivo*.

Methods: Lentivirus was used to establish stable expression of EGFP/click beetle green (CBG) in human cervix cancer cell lines ME-180, SiHa and Caski (ATCC). To initiate *in vivo* growth, 10^6 cells were mixed with media/matrigel and injected subcutaneously into the flanks of 8–12 week old female SCID mice (Charles River). Flank tu-

mors 1 cm in size were excised and dissected under sterile conditions. Tumors were cut into 2 mm fragments and surgically implanted into the cervixes of anaesthetized mice (Cairns and Hill, 2004). Serial bioluminescence and magnetic resonance imaging were used to monitor the development of primary tumors and metastatic disease.

Results: Primary cervical tumors were successfully established from all three lines and grew at predictable rates within the pelvis. MRI data suggests primary tumors extend superiorly within the uterus and abdomen. Increases in local tumor burden were associated with leukocytosis and increased circulating hematopoietic progenitor cells after 2 weeks. Metastatic disease was identified by bioluminescence in lungs at 5 weeks post implant.

Conclusions: Bioluminescence can be used to monitor the development of metastatic cervical cancer in the mouse. This model will be used to test novel imaging strategies and therapeutic interventions for cervical cancer.

P-52: Sphingosine-1-phosphate Axis as a Novel Target for Metastatic Breast Cancer by Suppression of Angiogenesis and Lymphangiogenesis

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Background and Objectives: Sphingosine-1-phosphate (S1P), a lipid mediator, regulates processes important for breast cancer progression, and expression of sphingosine kinase 1 (SphK1) that produces S1P correlates with poor outcome. We demonstrated that ABC-transporters, ABCC1 and ABCG2, export S1P from breast cancer cells. The aim of this study is 1) to determine the expression of these transporters in patient samples and 2) to determine the role of SphK1 in angiogenesis and lymphangiogenesis.

Methods: Tissue microarrays from 290 breast cancer patients were constructed. An improved 4T1-luc2 syngeneic metastatic breast cancer model was used to explore the role of SphK1 and S1P. We developed a new method to quantify both angiogenesis and lymphangiogenesis by combining directed *in vivo* angiogenesis assays with fluorescence activated cell sorting.

Results: Triple negative cancer, which is known to have worse prognosis, showed significantly higher expression of ABCC1 and ABCG2. Utilizing a specific SphK1 inhibitor, SKI-I, we found that SphK1 contributes to increased S1P levels in the tumor and in the circulation that correlates with tumor progression. Similarly, stage IIIA breast cancer patients also had significantly higher levels of serum S1P compared to the matched controls. Lymph node and lung metastasis and overall tumor burden *in vivo* were inhibited by SKI-I. FACS analysis showed that SKI-I decreased angiogenesis and lymphangiogenesis not only in primary tumor, but also in lymph nodes.

Conclusion: S1P produced by SphK1 is an important factor in breast cancer-induced angiogenesis and lymphangiogenesis and the SphK1/S1P axis deserves consideration as a target for breast cancer treatment.

P-53: General Health Perception of Older African-American Breast Cancer Survivors

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Background and Objective: Impairment in health status is a major health concern for older African-American breast cancer survivors. The objective of this study was to examine the impact of aging on social function and general health perception of older African-American breast cancer survivors using data from the Medicare Health Outcome Survey. Other variables examined were comorbidity, socioeconomic status, and depressive symptoms.

Methods: General health perception and social functioning was examined in 189 breast cancer survivors using the SF-36 Health Survey from the Medicare Health Outcome Survey Questionnaire.

Participants were divided into two age groups: ages 60–70 and 71 and older. Multilinear regression was used to determine predictors of general health perception.

Results: There were no statistically significant differences in general health perception between the two age groups. Social functioning scores were moderately high for each age group. General health perception was positively associated with social functioning, physical functioning, and comorbidity.

Conclusions: Social functioning is a potential target for efforts aimed at the maintenance/improvement of physical health for older African-American breast cancer survivors.

P-54: Smart Therapy for Uterine Fibroids Enabled by the Hyperbranched Polyglycerol Platform

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Background and Objectives: Uterine fibroids are diagnosed in one-fourth of all women and contribute more than \$2.1 billion annually to health care costs. Despite the high cumulative incidence of fibroids, their etiology is elusive. Hysterectomy is the only treatment to permanently eliminate fibroids. It is obvious but rarely stated that hysterectomies lead to irrevocable loss of fertility. Furthermore, even without hysterectomy, fibroids, particularly subserosal fibroids, can lead to infertility. We have suggested that fibroids develop and grow by a fibrotic process and are not true neoplasms. Clearly, more fundamental knowledge is needed regarding the molecular biology of fibroids. Smart Therapy is needed to enable local delivery of a drug or a combination of drugs that will ablate or inhibit growth of fibroids and prevent hysterectomy. To this end, we have designed a drug delivery system that gels under physiological conditions and degrades over time to release entrapped therapeutic agents. The objectives are to (1) evaluate the degradation properties of the drug delivery system and (2) entrap model drugs in our multifunctional, biocompatible, injectable, thermoresponsive, biodegradable nanocarrier drug delivery system and evaluate drug release.

Methods: Solutions of the drug delivery system in PBS (16.7 wt %) were poured into 2 ml vials and incubated for different periods of time at 37 °C. At predetermined times, samples were quenched in liquid nitrogen and frozen until needed for further studies. The frozen samples were lyophilized and the molecular weights of the resulting products were determined by GPC. A model drug, pirfenidone, was dissolved in the 16.7 wt% drug delivery system solution (0.2 mg/mL in 10 mM PBS, pH 7.4) and incubated at 37 °C to create a gel. After 5 min, 3.5 mL of release medium (0.02 wt% NaN₃, 0.2 wt% Tween 20, 10 mM PBS) at 37 °C was added to the gel. Fresh medium were replaced at designated sampling intervals and subsequently analyzed by optical spectroscopy.

Results: Within the first 16.5 hours, the drug delivery system had lost 95% of its molecular weight. Spectral changes in the proton nuclear magnetic resonance spectroscopy confirmed hydrolytic degradation of delivery system. Pirfenidone release from the delivery system measured by optical spectroscopy showed bimodal kinetics and was consistent with the degradation studies.

Conclusions: Our drug delivery system is biocaptible and has attributes (injectable liquid that solidifies below 35 °C before degrading) to provide controlled local delivery of antifibrotic drugs. This localized, non-surgical intervention for fibroids is the first of its type and may prove to be a viable alternative to hysterectomies.

P-55: Mitochondrial Copy Number is Associated with Breast Cancer Risk

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Background and Objective: Mitochondrial DNA (mtDNA) copy number variation is common in breast tumors and reflects the effect of interaction between hereditary and environmental factors. Data on mtDNA copy number and breast cancer risk in prospective cohorts is lacking. We evaluated the association between mtDNA copy number in peripheral blood and breast cancer risk among female participants of the Singapore Chinese Health Study.

Methods: We conducted a nested case-cohort study of 262 breast cancer cases (91 incident cases with pre-diagnostic blood and 171 prevalent cases with post-diagnostic blood) and 324 control women who were free of breast cancer at blood draw. The mtDNA copy number was measured using real time PCR. Analysis of covariance and logistic regression methods were employed to examine the association between mtDNA copy number and breast cancer risk.

Results: mtDNA copy number was significantly lower among incident breast cancer cases than controls (geometric mean: 0.50 vs. 0.58, $p=0.03$) after adjustment for potential confounders. Among prevalent breast cancer cases, mtDNA copy number increased with decreasing time interval between cancer diagnosis and blood draw: 0.60 in 45 cases with <6 months, 0.58 in 69 cases with 6–12 months, and 0.46 in 57 cases with >12 months (P for trend=0.045). Lower mtDNA copy number was associated with increased breast cancer risk.

Conclusions: Breast cancer diagnosis and/or treatment could increase mtDNA copy number. Prospective studies with a larger study sample size are warranted to confirm the novel inverse association between mtDNA copy number and breast cancer risk.

P-56: Oophorectomy at Younger Age Increases the Risk of Glaucoma

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Background and Objective: Glaucoma is the leading cause of blindness worldwide; the majority of persons affected are women. Identifying sex-specific risk factors for glaucoma may support preventive interventions. One such risk factor is early estrogen deficiency, which may increase susceptibility of the optic nerve to glaucoma. The objective is to determine whether bilateral oophorectomy, which causes estrogen deficiency, increases the risk of glaucoma.

Methods: We used the Mayo Clinic Cohort Study of Oophorectomy and Aging, a population-based historical cohort study of all women who underwent oophorectomy from 1950–1987 in Olmsted County, MN. Glaucoma diagnostic codes were searched in the records-linkage system of the Rochester Epidemiology Project. Hazards ratios (HR) were calculated for women with bilateral oophorectomy compared with age-similar referent women without oophorectomy.

Results: Of 1,061 women who underwent bilateral oophorectomy before menopause 155 developed glaucoma, and of 2,361 referent women 279 developed glaucoma. We found no overall increased risk of glaucoma in women who underwent bilateral oophorectomy (HR 1.07, 95% CI 0.88–1.30). However, we found a significantly increased risk of glaucoma in women who underwent bilateral oophorectomy before age 43 years (first tertile of age distribution; HR 1.51, 95% CI 1.11–2.03). In this group, approximately 10% were treated with estrogen to age 50 and treatment did not modify the association (HR 1.47, 95% CI 0.75–2.85).

Conclusions: Our analyses suggest that bilateral oophorectomy at younger age increases the risk of glaucoma and estrogen treatment does not attenuate the risk. Further verification of glaucoma diagnoses and analyses adjusted for potential confounders is warranted.

P-57: Risk of Spontaneous Abortions Related to Nonsteroidal Anti-Inflammatory Drug Exposure in the First-Trimester Varies by Race

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Background and Objective: Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common medication exposures reported in the first-trimester. Prostaglandins play multiple biologic roles in early pregnancy and their synthesis is inhibited by NSAIDs. The objective was to estimate the association between NSAID exposure during the first-trimester and risk for spontaneous abortion (SAB, <20 weeks).

Methods: Women were enrolled in *Right from the Start* (2000–2009), a prospective cohort. Data about NSAID exposure was obtained from baseline and first-trimester interviews; miscarriages were self-reported and verified by medical records. We used Cox proportional hazards regression models to estimate association between NSAID exposure and SAB outcome.

Results: Among 4,137 pregnancies, 523 experienced an SAB and 3,614 did not. NSAID exposure was reported by 1,503 (36%) participants. Only maternal age remained in the model as a confounder and race was an effect modifier. NSAID exposure was not associated with SAB risk in unadjusted models (hazard ratio [HR]: 1.03, 95% confidence interval [CI] 0.86–1.22). However, adjusted race-stratified analyses indicated protection from SAB in Blacks (HR: 0.61, 95% CI 0.38–0.99) but not Whites (HR: 1.02, 95% CI 0.84–1.26) or Hispanics (HR: 1.55, 95% CI 0.75–3.21).

Conclusions: NSAID use appears to protect against pregnancy loss for Black but not White women. This finding could reflect confounding factors or a true causal association. It warrants pursuit of evidence about whether known differences in inflammatory pathways or other genetic factors are in play. Further investigation of dose, timing in gestation and indication may help identify biologic mechanisms to explain this disparity in SAB risk.

P-58: Neuron-specific Lipoprotein Lipase Knockout Mice: A Model to Study the Molecular Mechanism Underlying Gender Differences in Obesity Development

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Background and Objectives: Compared to men, women suffer from a disproportionate burden of many co-morbidities associated with obesity, e.g., cardiovascular disease, cancer and dementia. The underlying mechanism for this gender difference is not well understood. One problem is the lack of suitable animal models to conduct detailed and related mechanistic studies. The objectives of this study are to conduct extensive characterizations of the gender differences in obesity development and to explore the possible underlying mechanism.

Methods: This study employed a recently developed mouse model, neuron-specific lipoprotein lipase deficient mice (NEXLPL-/-)

(Wang et al., *Cell Metabolism*, 2011), in which both male and female NEXLPL-/- mice develop obesity on standard chow.

Results: Female mice developed obesity in a similar time course as males, but gained a higher percentage of excess body weight than the male counterparts. Female mice were also more glucose intolerant, initially at 3 months, and maintained their glucose intolerance over time. Furthermore, female mice displayed learning and memory deficits at a younger age than males.

Conclusions: NEXLPL-/- mice display gender differences in obesity development that mimic clinical observations, thus making them an excellent platform for mechanistic studies. Since NEXLPL-/- mice have disrupted lipid metabolism in the brain, gender differences in obesity development may be related to gender-based differences in the ability of the brain to sense how much fat is in the diet. In addition, behavioral abnormality plays a more important role in obesity development in females.

P-59: Short-Term High Dietary Salt Treatment Decreases Sex-Dependent Difference in Neuronal Activity in the Rat Hypothalamus

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Background and Objective: Neuronal activity in the paraventricular nucleus (PVN) of the hypothalamus plays a critical role in the central pathways mediating sympathetic regulation of cardiovascular function. Increased dietary salt triggers signaling pathways that increase oxidative stress and lead to the development and progression of hypertension. We conducted experiments to determine the effects of short term (7 days) high dietary salt (8% NaCl) on neuronal activity in the hypothalamus of male and female rats.

Methods: Expression of c-fos was used as an indirect marker of neuronal activity.

Results: The basal neuronal activity was higher in male hypothalamic tissue compared to age-matched females. High dietary salt treatment increased the neuronal activity in the hypothalamus of both males and females; however the sex-related difference in neuronal activity diminished. TRPV1 (transient receptor potential vanilloid type 1) is shown to play a role in the transduction of osmotic and mechanical stimuli and has multiple effects on the cardiovascular system. Moreover, TRPV1 is widely expressed in the brain. Total TRPV1 expression was higher in the PVN of male rats compared to females and the expression levels are increased after high dietary salt treatment. However, the basal difference between males and females also diminished similarly to the difference in neuronal activity.

Conclusions: The present findings demonstrate that there is a sex-dependent difference in basal neuronal activity and high-salt diet diminishes this difference. Moreover, short-term high-salt diet association with increased neuronal activity in the rat hypothalamus may indicate an early alteration contributing to the development of neurogenic hypertension.

BIRCWH and SCOR Presentation Abstracts

O-1: Gender Differences in Associations between Stress Response and Substance Use in Adolescents

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Background and Objective: Individual differences in adolescents' responses to stress may be a factor in their risk for substance use disorders and links between stress response and substance abuse may be different for girls versus boys. We examined associations between emotional and physiological response to stress and substance use in adolescents by gender.

Methods: We assessed heart rate (HR), blood pressure (BP), self-reported and observed emotion, and salivary cortisol arousal in response to the Trier Social Stress Test-Child version (TSST-C) in 120 (60 girls) low-income inner-city adolescents. Youth's lifetime substance use was determined based on self-report, interview, urine toxicology, and breathalyzer.

Results: Lower diastolic BP response to the stressor was associated with greater odds of being a substance user ($\text{Exp}[B] = .94$, $p = .02$). Lower observed anxiety responses to the stressor were associated with greater odds of being a substance user for girls but not for boys ($\text{Exp}[B] = .41$, $p = .04$). In contrast, lower self-reported anxiety responses showed a trend for an association with substance use for boys but not for girls ($\text{Exp}[B] = .77$, $p = .06$). Heart rate and cortisol responses were not related to substance use for boys or girls.

Conclusions: Findings suggest that dampened physiological (e.g., blood pressure) and emotional responses to stress may be a marker for substance abuse risk in adolescents. The profile of responding that is a marker for risk may differ by gender, highlighting the importance of considering sex differences in understanding substance abuse risk.

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O-2: Treatment, Prevention, and Reversal of Antibiotic Resistance in Urinary Tract Infection by Orally Active Mannosides

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Background and Objective: Over 15 million women suffer from urinary tract infections (UTI) annually in the U.S. and ~20–40% have multiple recurrences. This unique high prevalence of chronic/recurrent infections has led to long-term conventional prophylactic therapy which has contributed to an increased antibiotic-resistance of uropathogenic *E. coli* (UPEC) the causative agent of most UTIs. Elucidation of bacterial pathogenic pathways revealed that the adhesin of type 1 pili, FimH, is an essential virulence factor and thus a novel therapeutic target. We seek to develop FimH antagonists called mannosides to prevent and treat UTI.

Methods: Mannose derivatives were rationally designed using high-resolution structures of mannose bound FimH and synthesized. The resulting compounds were tested for potency in FimH-dependent hemagglutination and biofilm inhibition assays. The efficacy of orally delivered mannosides in treating and/or preventing acute and chronic cystitis was evaluated in a murine model. Specifically, we determined the ability of mannosides to prevent UPEC colonization,

invasion, and formation of recalcitrant intracellular bacterial communities within the bladder epithelium. Mass-spectrometry was utilized to determine bioavailability.

Results: We identified potent orally active mannosides that demonstrated fast-acting efficacy in the treatment and prevention of chronic UTI and potentiated first-line empiric UTI therapy of TMP-SMZ, reversing clinical resistance.

Conclusions: This work shows for the first time that an orally administered mannoside is a potent fast-acting therapeutic for the treatment and prevention of UTI *in vivo*. Use of mannoside FimH inhibitors promises to provide substantial benefit to women suffering from recurrent and chronic UTI.

O-3: Behavioral, Clinical, and Biological Factors Associated with Anal Human Papillomavirus (HPV) Infection among HIV-infected Women

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Background and Objective: HIV-infected women are at high risk for HPV-associated cancers due to immunosuppression and co-infection with HPV, but anal HPV infection is understudied. The study's objective is to estimate the prevalence of anal HPV infection and to assess factors associated with anal HPV infection among HIV-infected women.

Methods: HIV-infected women were recruited from five HIV/AIDS outpatient clinics. A behavioral survey was self-administered by the participants to collect information on socio-demographics, HPV-related knowledge, sexual history, and high-risk behaviors. Oral, vaginal, and anal swabs were collected by the clinicians and were tested for the presence of 37 type-specific HPV DNA using a PCR-based assay. Participants' sera were tested for antibody responses against 14 types of HPV virus-like particles (VLPs) by ELISA. Clinical information was obtained from the medical records.

Results: A total of 60 HIV-infected women were enrolled; they were mainly older than 40 years, non-Hispanic white, had low knowledge about HPV, and had been infected with HIV for more than 10 years. None had received HPV vaccination. High-risk sexual behaviors and substance use were commonly reported. Overall, HPV DNA was detected among 57% of women, and the prevalences of oral, vaginal, and anal HPV infections were 8%, 37% and 42%, respectively. About 18% had multiple-site infection (≥ 2 anatomical sites) or multiple-type infection (≥ 2 HPV types). Anal HPV infections with HPV16/18/6/11 were not common (9%). While most women (80%) had positive antibody responses to multiple HPV VLPs, they were either not currently infected or infected with different HPV types.

Conclusions: Anal HPV infection, especially with non-vaccine covered types, was common among HIV-infected women. Antibodies induced from natural infection may have protective effects against HPV re-infection.

O-4: Increasing First Trimester Use of Opioid Analgesics

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Background and Objective: Use of opioid analgesics has increased dramatically in recent years, but little research examines whether use of these medications in pregnancy has increased. Given that opioids may pose a risk for the developing fetus, information on early fetal exposure is urgently needed. The objective is to quantify whether the prevalence of prescribed opioid analgesics during the first trimester among pregnant women enrolled in Tennessee Medicaid increased from 1995 to 2009.

Methods: This is a retrospective cohort study of 268,987 pregnancies from 1995 to 2009 among Tennessee Medicaid-insured women. Pregnancies were identified from birth and fetal death certificates, and linked to previously validated computerized pharmacy records to determine medication use. Poisson regression was used to estimate trends over time, rate ratios, and 95% confidence intervals.

Results: During the study period, 14.5% of pregnancies filled at least one prescription for an opioid analgesic during the first trimester. Use increased from 8.6% of pregnancies in 1995 to 20.1% of pregnancies in 2009. After adjusting for maternal characteristics, the prevalence of any first trimester use in 2009 was 2.3 times greater than in 1995 (95% C.I. = 2.1 to 2.5). Older, white, non-Hispanic mothers with less than a high school education and one or more prior pregnancies were more likely to have filled at least one prescription for an opioid analgesic during the first trimester.

Conclusions: First trimester use of opioid analgesics increased from 1995 to 2009 among Tennessee Medicaid-insured pregnant women. Potential consequences of early fetal exposure to these medications warrant careful examination.

O-5: Admixture Mapping Identifies Regions on 6q25 and 11p15 Associated with Breast Cancer in U.S. Latinas

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Background and Objective: U.S. Latinas have lower breast cancer incidence compared to non-Hispanic Whites. Higher European genetic ancestry among Latinas is associated with increased risk of breast cancer. This suggests that there could be a genetic component to the observed difference in breast cancer incidence between populations. We used an admixture mapping approach to detect particular regions along the genome with strong departures in ancestry between Latina women with breast cancer and healthy controls which would indicate the presence of genetic risk variants within those regions.

Methods: Genome-wide association data from 1,461 U.S. Latinas with breast cancer and 1,280 U.S. Latina controls were used to estimate and test locus specific genetic ancestry for association with breast cancer risk in case-control analyses using logistic regression models.

Results: We identified two regions where genetic ancestry was significantly associated with breast cancer risk: 6q25 ($p = 8.2 \times 10^{-7}$) and 11p15 ($p = 2.9 \times 10^{-6}$). In both regions the risk of breast cancer increased with higher European ancestry. The peak of the 6q25 signal includes the estrogen receptor 1 gene (ESR1) and 5' region, which has been associated with breast cancer in previous studies. The 11p15 signal is within a region not previously implicated in breast cancer. Combined analysis of the SNPs genotyped and imputed in these regions found no single variant that explained the admixture signals.

Conclusions: Identification of the underlying biologically relevant variants responsible for the admixture mapping signals will contribute to the improvement of predictive models for breast cancer risk

assessment both in Latinas and non-Hispanic Whites, as well as to a better understanding of breast cancer etiology.

O-6: The Association of Pelvic Girdle Pain and Urinary Incontinence in Pregnancy

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Background and Objectives: Pelvic girdle pain (PGP) and urinary incontinence (UI) are common problems during pregnancy. The musculoskeletal changes, particularly of the pelvic floor musculature (PFM), that occur during this time may be an underlying risk factor in both these conditions. The study has two objectives: (1) to investigate the association between UI and PGP in pregnant women in the second trimester of pregnancy and (2) to determine the association between UI and PFM strength by PGP status.

Methods: Fifty-two pregnant women, 26 with and 26 without PGP, were recruited in the second trimester. Women were defined as having PGP if they reported pain intensity of 3/10 or higher on self-report and at least 2/4 positive physical examination tests. Following international guidelines, women were classified as having incontinence if they score 1 or higher on the International Consultation on Incontinence Questionnaire-Short Form (ICIQ). Vaginal PFM examination assessing for strength using the Modified Oxford scale was also performed on 48 women.

Results: There was not a statistically significant association between PGP status and continence status (Fishers Exact Test (FET) $p < 0.25$), in the second trimester. Women without PGP and strong PFM never reported incontinence. Women with PGP and/or weak PFM were equally likely to report incontinence.

Conclusion: There is no association with PGP and incontinence or PFM weakness and incontinence in these second trimester pregnant women. Further research of this possible link in the third trimester and postpartum is warranted.

O-7: Gene Expression Response of Luminal and Basal Breast Cancer Cell Lines to Ionizing Radiation

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Background and Objective: There are significant differences in how breast tumors respond to ionizing radiation. A growing body of data suggests that breast tumor biology (luminal, basal) contributes to the probability of locoregional control in women with breast cancer. We hypothesized that this may be, in part, due to molecular differences in radiation response among biologically diverse breast tumors exposed to ionizing radiation.

Methods: Six commercially available human breast cancer cell lines known to display gene expression patterns of distinct breast subtypes (luminal—ZR751, T47D, MCF7; basal—SUM159, SUM149, MDA-MB-231) were selected for further study. Cell lines were maintained in appropriate media and grown in triplicate to account for individual sample variability. After reaching confluence, RNA was harvested before and 24 hours after a single dose of 5Gy. Clonogenic cell survival assays were performed to assess the varying degree of radiosensitivity and compare with gene expression to identify markers and determinants of phenotypic responses.

Results: Resistance to ionizing radiation was significantly associated, but not in perfect agreement with, the basal type breast cells. Similarly, pre- and post-radiation gene expression mostly tracked with basal versus luminal cell types, but the distinct patterns of gene expression seen between the two cell types were tightly associated with varying degrees of radiosensitivity.

Conclusion: These data are the first to link patterns of gene activation to radiation response. Our long-term goal is to further

characterize radiation gene expression response to identify biomarkers of radiation resistance and novel approaches to enhance radiosensitivity.

O-8: Social and Environmental Enrichment Alter the Effects of Marijuana on Cocaine Reward in Male and Female Adolescent Rats

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Background and Objective: Marijuana is one of the most widely used illegal drugs, with adolescents being particularly vulnerable to its use and abuse. Use of marijuana during adolescence increases the likelihood of subsequent use of other substances such as cocaine. It is not known whether the environment can impact this effect. This study was done to investigate whether social and environmental conditions alter the effects of tetrahydrocannabinol (THC), the active ingredient in marijuana, on cocaine reward in adolescent male and female rats.

Methods: On postnatal day (PND) 23, rats were housed in either an isolated impoverished condition (alone with no toys, I) or social enriched (3/cage with toys, SE3). Starting on PND 30, 3 mg/kg THC was injected daily for 5 days and locomotor activity was measured. On PND 38, cocaine conditioned place preference (CPP) began.

Results: In isolated females but not males, THC increased the potency of cocaine. In enriched males, there was a large increase in cocaine reward after pretreatment with THC compared to vehicle, but this was not evident in females.

Conclusions: Cocaine reward is differentially altered in male and female adolescents exposed to THC depending upon social and environmental conditions. These data suggest that drug prevention and treatment strategies need to be specific to adolescent males or females, and need to take into account the different environments in which teenagers might live.

O-9: Gestational Weight Gain and Obesity: Is 20 Pounds Too Much?

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Background and Objective: Obesity increases the risk for adverse pregnancy outcomes. In 2009, the Institute of Medicine recommended that obese women gain 11–20 pounds (5.0–9.0 kg) during pregnancy regardless of obesity severity. Gestational weight gain (GWG) lower than these recommendations may improve outcomes in obese women and their neonates. The objective was to compare maternal and neonatal outcomes in obese women according to GWG and body mass index (BMI) class.

Methods: Multicenter data from 20,750 obese women (pre-pregnancy BMI ≥ 30 kg/m²) with singleton, term, live births were analyzed. Adjusted odds ratios (OR) with 95% CI were calculated for cesarean delivery, preeclampsia, small and large for gestational age (SGA, LGA) infants, and NICU admissions within BMI classes (I = 30.0–34.9, II = 35.0–39.9, III ≥ 40.0 kg/m²) and by GWG (weight loss, low 0–4.9 kg, normal 5.0–9.0 kg [referent], high >9.0 kg).

Results: Cesareans decreased for women in obesity class I who lost weight (OR 0.52, CI 0.37–0.73). Preeclampsia decreased for women in obesity classes I and III who lost weight (OR 0.22, CI 0.07–0.71; OR 0.51, CI 0.30–0.89). SGA infants increased, but still were $<10\%$, for women in obesity class II who lost weight (OR 1.99, CI 1.23–3.22). LGA infants decreased for women in obesity classes II and III who lost weight or had low GWG, $p < 0.05$. NICU admissions decreased in obesity classes I and II with low GWG, $p < 0.05$.

Conclusions: Weight loss in obese women reduced cesareans by 50% and preeclampsia by 80%, and improved other neonatal outcomes (LGA infants, NICU admissions) without increasing the expected occurrence of SGA infants. Lowering GWG guidelines in obese women may improve maternal and neonatal outcomes.

O-10: Hypoleptinemia in Anorexia Nervosa and Hypothalamic Amenorrhea is Associated with Symptoms of Depression, Independent of Body Mass Index

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Background and Objective: The fat-derived hormone leptin is anorexigenic, and levels are decreased in low-weight and high in obese women. Animal data suggest that leptin may have anxiolytic and anti-depressant properties. Depression and anxiety are common in anorexia nervosa (AN), an illness associated with low weight, body fat, and leptin levels. Similarly, there is an increased prevalence of anxiety and depression in normal-weight women with hypothalamic amenorrhea (HA), a disorder also characterized by hypoleptinemia. It is unknown whether low leptin levels contribute to the development of mood disorders in these populations. We performed a cross-sectional study to investigate the relationship between leptin levels and symptoms of anxiety and depression in AN and HA.

Methods: We studied 64 women: 15 AN, 12 normal-weight HA, 20 normal-weight healthy (HC), and 17 overweight or obese (OB) healthy controls. We measured fasting serum leptin levels and administered Hamilton Rating Scales for Anxiety (HAM-A) and Depression (HAM-D).

Results: HAM-D scores were higher in AN than other groups, higher in HA than OB, and lowest in HC. HAM-A scores were higher in AN than OB and HC, higher in HA than OB, and lowest in HC. Leptin was lowest in AN, higher in HC than HA, and highest in OB. Leptin levels were inversely associated with HAM-D scores ($r = -0.43$, $p = 0.0004$); this relationship remained significant after controlling for BMI. Leptin levels were inversely associated with HAM-A scores ($r = -0.34$, $p = 0.006$); this relationship was not significant after controlling for BMI.

Conclusions: Leptin may mediate symptoms of depression independent of BMI.

O-11: Exposure to Pubertal Hormones Influences Cognition and Stress Reactivity during Adulthood

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Background: Adolescence appears to be a period of enhanced vulnerability for psychiatric illness. While exposure to gonadal steroids during neonatal development profoundly organizes the brain and behavior, the potential contribution of these hormones during adolescence is not well understood. The objective is to determine whether pubertal hormones can organize cognitive behavior and stress reactivity, which are often disrupted in mental illness.

Methods: Half the rats were gonadectomized (GDX) prior to puberty, while the other half were GDX after puberty. As adults, all animals received replacement gonadal steroids via silastic implants (estradiol to females, testosterone to males) for two weeks prior to behavioral testing. Adult animals were tested on fear memory conditioning and extinction, acoustic startle response (ASR), and pre-pulse inhibition (PPI).

Results: The development of a conditioned fear memory, which is dependent on the amygdala, did not differ between groups. In contrast, the extinction of that memory, which is supported by the prefrontal cortex, was influenced by gonadal hormone deprivation during adolescence. Adult GDX males and females recapitulated the sex difference previously observed among intact animals (Markham et al., 2010), and this sex difference was reversed by pre-pubertal GDX in either sex (treatment*sex $p < .043$). While sex differences in PPI were not affected by adolescent gonadal hormone deprivation, females GDX before puberty showed enhanced ASR relative to females GDX as adults ($p < .05$), and were similar to males GDX as adults (adult GDX males $>$ females $p < .01$).

Conclusions: These findings demonstrate that pubertal gonadal steroids can organize prefrontal-supported cognition and stress reactivity.

O-12: Sex Differences in Orexin 1 Receptor Mediation of Reinstatement to Cocaine-seeking in an Animal Model of Relapse

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Background and Objective: Prior studies have demonstrated sex differences in reward-associated behaviors with drugs of abuse, including cocaine. The orexin/hypocretin system has recently been implicated in the conditioned cue-induced reinstatement of cocaine-seeking in male rats. Here, we assessed the effects of the selective orexin 1 receptor antagonist, SB-334867, on responding during cue- and stress-induced reinstatement to cocaine-seeking following chronic cocaine self-administration in female and male rats.

Methods: Rats self-administered intravenous cocaine (0.6 mg/kg/infusion; 2 hr/day) paired with stimulus cues (light + tone). Following self-administration and withdrawal, reinstatement of cocaine-seeking was triggered by presentation of the previously cocaine-paired cues, the pharmacological stressor, yohimbine (2.5 mg/kg), or a combination of cues + yohimbine. Thirty minutes prior to each reinstatement trial, rats received SB-334867 (0, 10, 20, or 30 mg/kg).

Results: Both sexes showed reinstatement to cocaine-seeking with cues, yohimbine, or cues + yohimbine. However, SB-334867 significantly attenuated cue-induced reinstatement only in males, but not females. While orexin 1 receptor blockade failed to affect cue-induced reinstatement in females, SB-334867 dose-dependently decreased stress-induced reinstatement, and abolished the potentiative effects of cues + yohimbine in both sexes.

Conclusions: Our results show a clear sexual dimorphism in orexin-mediated control of cocaine-seeking during relapse, whereby orexin regulation of conditioned cue-induced reinstatement occurs in males, but not females. However, stress activated reinstatement of cocaine-seeking is under the control of the orexin system in both males and females. These differences may be due to intrinsic sex differences in hypothalamic orexin-mediated signaling, providing a potential target for gender specific treatment of cocaine addiction.

Support: These studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, as adopted and promulgated by the National Institutes of Health. This research was supported by NIH grant P50 DA16511 (Specialized Center of Research on Sex and Gender Factors Affecting Women's Health).

O-13: Geriatric Syndromes Trigger Late-life Disability in Community-dwelling Older Women

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Background and Objective: Older women account for the majority of Americans living with disabilities and of Medicaid expenses due to disability-related nursing home placements. Thus, preventing or delaying the onset of disability will help older women remain in their homes longer and reduce Medicaid costs. Late-life disability develops from the accumulation of age-related syndromes. Therefore, this study aimed to identify geriatric syndromes associated with disability in community-dwelling older women.

Methods: Baseline and 2-year follow-up data collected from a random sample of female Medicare beneficiaries (N = 272, 98.5% white, age range 70–99) participating in a fall prevention randomized controlled trial was used. The SF-36 physical function subscale score at 2 years (mean 57.33 ± 25.76) measured disability. Predictors with $p < .10$ in univariate linear regression models were included in a multivariate model. Predictors were baseline measures except for falls, which were measured prospectively over 2 years.

Results: The regression coefficient, its 95% confidence interval and p value for predictors in the multivariate model were: urinary inconti-

nence $-7.74 (-13.62, -1.86)$, $p = .01$; frailty $-13.29 (-23.63, -2.94)$, $p = .01$; balance confidence score $.68 (.48, .88)$, $p < .01$; cognitive impairment score $1.33 (-.75, 3.41)$, $p = .21$; geriatric depression score $-1.20 (-2.72, .33)$, $p = .12$; age in years $-.28 (-.86, .30)$, $p = .34$; number of medications used weekly $.21 (-.72, 1.14)$, $p = .66$; number of diseases $-.33 (-1.70, 1.04)$, $p = .63$; osteoarthritis $-3.96 (-9.80, 1.87)$, $p = .18$; number of falls $-1.09 (-2.28, .10)$, $p = .07$.

Conclusions: Only urinary incontinence, frailty, and low balance confidence were independent predictors of functional disability at 2 years. Efforts to prevent or delay late-life disability in community dwelling older women should target multiple areas including urinary incontinence, frailty, and balance confidence.

O-14: Depressive Symptoms, Gender, and Cardiovascular Disease in Older Adults

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Background and Objectives: Depressive symptoms and cardiovascular disease influence life expectancy and quality of life in older adults and often co-occur. The direction of association between these conditions and the role of gender in these relationships is unclear. The objectives are to investigate (1) the relationship between depressive symptoms and incident cardiovascular disease, (2) the relationship between cardiovascular disease and incident depressive symptoms, and (3) whether these relationships are stronger in women than in men.

Methods: The Health and Retirement Study is a longitudinal study of adults in the U.S., born in 1931–1941. Respondents provided information on heart disease and depressive symptoms in 2002, 2004, 2006, and 2008. Information on other health and social characteristics was collected in 1992 and 2002. We used discrete-time hazard models to examine relationships in both directions between heart disease and depressive symptoms.

Results: In 2002, 10,344 individuals did not have heart disease, and 9,721 did not have depressive symptoms. In fully adjusted gender-stratified models, depressive symptoms were related to increased risk of incident heart disease only in women (OR = 1.21; 95% CI = 1.03, 1.42, p value for interaction between gender and depressive symptoms = 0.04). Heart disease in 2002 was associated with a moderate increase in risk of incident depressive symptoms in fully adjusted models (OR = 1.07; 95% CI = 0.99, 1.15). Gender did not modify this relationship.

Conclusions: Depressive symptoms are a risk factor for cardiovascular disease in women. Cardiovascular disease is related to subsequent depressive symptoms in men and women.

O-15: Compartment Involvement Patterns in Knee Osteoarthritis: The MOST Study

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Background and Objective: The knee joint is divided into the medial and lateral compartments, with a large majority of individuals with knee osteoarthritis (OA) having evidence of loss of articular cartilage in the medial compartment. Malalignment is associated with progression of knee OA. Few studies have examined the prevalence and epidemiology of lateral compartment involvement. The objective was to compare compartmental patterns of knee joint space narrowing (JSN) in women and men and assess whether these are related to knee alignment.

Methods: The NIH-funded Multicenter Osteoarthritis (MOST) Study is an observational study of persons aged 50 to 79 years with either symptomatic knee OA or at high risk of knee OA. JSN was defined as present or absent for each tibiofemoral compartment. Mechanical axis angle was measured using full-limb films. We compared the proportion of JSN in lateral compartments between women and men using a logistic regression model adjusting for covariates, and used generalized estimating equations to account for correlation between two knees within a person. We added in knee alignment as a further adjustment.

Results: Of 5,202 knees (2,652 participants), 1,532 (29.5%) had medial JSN, and 425 (8.2%) had lateral JSN. Lateral JSN was more prevalent in women than in men (prevalence odds ratio [pOR] = 1.9, 95% CI 1.5–2.4). After adjusting for malalignment, the gender association became insignificant (pOR = 1.1, 95% CI 0.9–1.5).

Conclusions: Women are more likely to have lateral JSN than men. Valgus malalignment may contribute to the higher prevalence in women.

O-16: Post-Separation Abuse of Children whose Mothers Divorce Intimate Partner Abusing Fathers

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Background and Objective: Perpetrators of intimate partner violence often do not limit their abuse to intimate partners: approximately 30 to 60 percent of children of abused mothers are also abused by their fathers. Mothers' efforts to gain safety for themselves and their children are complicated by court-ordered custody and parenting time decrees that require mothers and children to keep abusive fathers in their lives. This allows perpetrators opportunities to continue their abuse. This qualitative study examined whether custody and parenting time arrangements were used by fathers to facilitate abuse of their children and whether mothers detected negative mental health consequences due to the abuse.

Methods: Semi-structured interviews were conducted with 19 mothers who had experienced intimate partner violence by their ex-husbands and who had received custody determinations for shared children from family court. Qualitative data analyses were conducted using Analytic Induction.

Results: Ten of the nineteen (53%) mothers reported that their children (n = 20) had experienced either physical or emotional abuse or neglect by their fathers since the initial separation. For 17 of these children (85%), mental health symptoms following father-interactions were often severe and resulted in the children requiring counseling (n = 17), engagement in self-harm (n = 3), and even mental health hospitalizations (n = 2, with one child experiencing three hospitalizations).

Conclusions: Women's claims of intimate partner violence must be taken into consideration by courts when deciding custody and parenting time arrangements, not just for the safety of the mothers, but for the safety and mental well-being of the children as well.

Additional SCOR Abstracts

1: Internalizing Symptoms and Marijuana Involvement in African-American Youth: Sex/Gender Influences

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Background and Objective: Sex/gender differences in adolescent marijuana involvement have been understudied in African-American youth. The objective of the study was to examine male-female variation in marijuana involvement among African-American adolescents and to estimate the degree to which internalizing symptoms might predict marijuana smoking by mid-adolescence.

Methods: The sample was drawn from the longitudinal Miami Prenatal Cocaine Study (MPCS) cohort. Four hundred and seven African-American adolescents completed at least one exam at 12, 14–15, and/or 16–17 years, with marijuana use assessed by self-report and toxicology. Self-reported anxiety and depressive symptoms were measured at 12 years. Odds ratio estimates (OR) are from the generalized linear model with generalized estimating equations.

Results: Estimated across assessments, males were more likely to initiate marijuana use by mid-adolescence (OR = 4.4; $p < 0.05$). At 16–17-years, males were also more likely to exhibit greater marijuana involvement than females as indicated by repeated lifetime use and current use ($p < 0.01$). Males reported greater anxiety symptoms, and females reported more depressive symptoms at age 12 years ($p < 0.01$). However, neither symptoms of depression ($p > 0.3$) nor anxiety ($p > 0.1$) at age 12 predicted marijuana use through 16–17 years. Anxiety symptoms were related to marijuana use cross-sectionally at age 12 in females ($p = 0.002$) but not in males ($p = 0.577$). Prenatal cocaine exposure was not associated with marijuana smoking.

Conclusions: Within an urban African-American cohort, there was a male excess in marijuana involvement by mid-adolescence. Internalizing symptoms did not predict initiation of marijuana through mid-adolescence. Anxiety was linked with marijuana use during early adolescence only, with a stronger association for girls than boys.

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2: Early Gender-Related Motor Skills Differences in Female and Male Preterm Infants

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Background and Objective: Due to improvements in neonatal care, more extremely preterm infants now survive and these infants are at greater risk for neurodevelopmental disorders, placing caregiving burdens on mothers who must cope with the children's developmental uncertainties and possible lifelong impairments. The mental health of mothers of children with disabilities may be improved by early identification and intervention strategies that decrease the severity of developmental delays. As early screening is incompletely done at best, we designed this pilot trial to determine very early quantifiable abnormal motor and muscle patterns in preterm infants, and to compare these to brain imaging results by gender.

Methods: Infant motor tests, motion kinematics, and muscle ultrasound were performed on 10 female and male preterm infants at term, 6 weeks, and 12 weeks corrected gestational age to establish preliminary normative data on differences in motor skill acquisition between high- and low-risk preterm infants. Infants who scored at

risk on tests of infant motor performance at term had MRS/DTI for measures of brain injury.

Results: Kinematics can detect early atypical head movements of high-risk preterm infants in the first 3 months of life. Additionally, muscle ultrasound can detect abnormalities of the gastrocnemius muscle architecture at 6 weeks providing further support that muscles are affected at earlier time periods than previously thought.

Conclusion: Early identification of abnormal motor and muscle patterns in preterm high-risk infants will facilitate targeted intervention during early development, prior to the onset of significant clinical deficits associated with cerebral palsy.

3: Effects of Exogenous Progesterone on the Stress and Cue-related Craving State in Cocaine-Dependent Men and Women

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Background and Objective: Exogenous progesterone has been shown to attenuate the rewarding effects of cocaine. It may also reduce the stress and cue-related cocaine craving state and improve regulatory processes integral to resisting drug use in the face of challenge. The objective of this study was to conduct a double-blind placebo-controlled study assessing the efficacy of progesterone in strengthening emotional, biophysiological, and cognitive processes associated with the provoked craving state in cocaine-dependent men and women.

Methods: Forty-two early-abstinent treatment-seeking cocaine-dependent individuals were randomly assigned to either daily doses of placebo (12M/9F) or micronized progesterone (12M/9F) (200 mg, p.o.; b.i.d.) for 7 days. In a laboratory experiment, all were exposed to three 5-minute personalized guided imagery conditions (stress, cocaine cue, relaxing), one per day, consecutively in a random, counterbalanced order. Subjective craving, mood, Stroop performance, hypothalamic-pituitary-adrenal (HPA) and cardiovascular output were assessed repeatedly pre- and post-imagery.

Results: Participants receiving progesterone demonstrated significantly lower craving ($p < .05$), ACTH ($p = .04$) and cortisol ($p = .01$) following cocaine cue exposure compared with those receiving placebo. In addition, females receiving progesterone reported lower ratings of negative emotion ($p = .04$) and higher ratings of relaxed mood ($p = .03$) following stress imagery compared with females receiving placebo. Improved Stroop performance was also observed in all participants receiving progesterone ($p = .02$), across all conditions.

Conclusions: Progesterone is selectively effective in reducing aspects of the provoked cocaine craving state, and efficacy may be moderated by both the type of environmental cue exposure and gender.

Support: NIH grants P50-DA16556, K02-DA17232.

4: Hypoactivation of the Stress Response Circuitry in Depression Associated with Loss of Parasympathetic Control of the Heart and Dysfunction in the HPG Axis: A Combined Analysis of fMRI and Heart Rate Variability

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Background and Objective: The comorbidity of major depressive disorder (MDD) and cardiovascular disease (CVD) represents the fourth leading cause of morbidity and mortality worldwide, and women have higher rates. Thus, understanding the co-occurrence of these disorders will have major public health significance, particularly for women. Brain regions implicated in mood dysregulation also are implicated in the neural control of the heart through the autonomic nervous system (ANS). Additionally, MDD in women has been linked to dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis. In this functional magnetic resonance imaging (fMRI) study, we investigated whether abnormal hypoactivation in fronto-limbic stress response circuitry in women with MDD, demonstrated in our recent work, is associated with dysregulation of the ANS and disruption of the HPG axis.

Methods: Ten women with MDD in remission made comparable to 10 healthy controls were scanned during the late follicular/midcycle phase of the menstrual cycle on a 3T GE magnet using a visual stress challenge in tandem with acquisition of heart rate, from which we calculated the high frequency (HF) component of the R-R interval variability (RRV), a common measure of parasympathetic ANS. Baseline gonadal hormones included estradiol and progesterone.

Results: Using SPM2 with HF-RRV as a regressor in general linear modeling of brain activity of the stress response, we demonstrated that hypoactivations of anterior hypothalamus, hippocampus, anterior cingulate cortex (ACC), and orbitofrontal cortex were significantly associated with lower parasympathetic control of the heart in MDD women. MDD women had higher progesterone and lower estradiol than healthy controls. Inclusion of estradiol and progesterone levels as covariates attenuated the effect of HF-RRV on brain activity differences between groups in the hippocampus, ACC, and OFC, suggesting that gonadal hormone deficits accounted, in part, for the effect of HF-RRV on brain activity deficits in MDD. Thus, findings provide evidence that hypoactivity of the stress response circuitry in MDD is significantly associated with dysregulation of the ANS, specifically parasympathetic cardiac control, and with disruption of the HPG axis in women.

Conclusions: Findings have implications for understanding the relationship between mood, arousal, heart regulation, and hormonal status, and may provide insights into the co-morbidity of MDD and CVD in women.

5: Genome-wide Gene Expression Study of Peripheral Blood Monocytes for Osteoporosis

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Background and Objective: Osteoporosis is a disease of bone fragility, with an increased risk of low-trauma fracture. The disease has significant impact to the health of the elderly, especially old women. Bone mineral density (BMD) is a key parameter to characterize osteoporosis and genetics plays an important role in BMD variation. An important mechanism for osteoporosis is an excess of bone resorption by osteoclasts over bone formation by osteoblasts. Peripheral blood monocytes (PBMs) are precursors of osteoclasts and play an essential role in osteoclastogenesis by producing cytokines, such as TNF and IL-1. The objective of the study was to identify genes important to osteoporosis through analysis of PBMs.

Methods: A genome-wide expression profiling analysis of PBMs in 69 middle-aged Caucasian females (age 47–53) with extremely high ($n = 41$) or low ($n = 28$) hip BMD was performed using Affymetrix Human Exon 1.0 ST arrays.

Results: We identified a number of genes showing significant evidence of differential expression between high vs. low BMD subjects. Among the genes, some were known to be important factors for osteoclast differentiation (e.g., CTNBP1, $p = 2.89\text{E-}4$, fold-change = 1.45 in low- vs. high-BMD subjects) and some were previously associated with BMD variation (e.g., C1orf61, $p = 3.59\text{E-}5$, fold-change = 0.61, and NAMPT, $p = 6.13\text{E-}4$, fold-change = 1.58). Interestingly, we also identified some novel candi-

date genes for BMD variation, such as CCDC62 ($p = 2.95\text{E-}3$, fold-change = 0.83), which was known to have an estrogen receptor regulation function and may act on monocyte-mediated postmenopausal bone loss through that function.

Conclusions: Our findings, together with previous evidence, suggested interesting candidate genes for BMD regulation and risk of osteoporosis.

6: Peripheral Blood Monocyte-Expressed Anxa2 Gene is Involved in Pathogenesis of Osteoporosis in Humans

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Background and Objective: Low bone mineral density (BMD) is a risk factor of osteoporosis and has strong genetic determination. Peripheral blood monocytes (PBMs) could access to bone resorption surfaces and differentiate into osteoclasts to resorb bone. The objective of this study is to identify osteoporosis susceptibility genes and characterize their functions.

Methods: Three independent samples (Samples I, II, and III) containing Caucasians with extremely low vs. high hip BMD ($N = 28, 80, 44$, respectively) and one cohort of 1,000 unrelated Caucasians (Sample IV) were used. Proteomics analysis of PBMs was conducted in Sample I to discover proteins/genes functionally relevant to BMD. The identified proteins/genes were validated at mRNA level in PBMs from Sample II. Finally, the validated genes were tested for association with BMD in Samples III and IV.

Results: In proteomics analysis of PBMs, *Anxa2* was found to be upregulated 2.0-fold in subjects with low BMD, which was verified by Western blotting, and replicated at mRNA level. Three SNPs in *Anxa2* were found to be associated with BMD variation ($p < 0.05$). The above integrative evidence strongly supports that *Anxa2* is involved in the pathogenesis of osteoporosis in humans. Furthermore, monocyte migration across endothelial barrier *in vitro* was elevated up to 4.9-fold by *Anxa2* stimulation, suggesting that it may stimulate more PBMs to migrate from blood to bone resorption surfaces to differentiate into osteoclasts *in vivo*, hence leading to increased bone resorption and decreased BMD.

Conclusions: This study identified a novel osteoporosis susceptibility gene, and suggested a novel pathophysiological mechanism, mediated by *Anxa2*, for osteoporosis in humans.

7: Normal Ranges and Shape Analysis in 3-D Vaginal Morphology

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Background and Objective: Pelvic organ prolapse is associated with changes in vaginal size, shape, and position. The objective of the study was to develop a technique to quantify vaginal dimension and report preliminary findings on their relationship to body size.

Methods: MRI of 10 subjects of 10th percentile (age: 48.5 ± 6.7), 10 of 50th percentile (age: 48.3 ± 6.7), and ten of 90th percentile (age: 48.1 ± 7.3) height were selected from the control group of an ongoing case and control study. Supine, multi-planar MR imaging was performed. ImageJ v1.44 was used to establish the vaginal location and contour in both axial and middle sagittal scans. Width was assessed

at five equally spaced locations. A MATLAB™ program was used for data analysis.

Results: Vaginal widths at the five equally spaced locations from bottom to top vary with the 10th, 50th, and 90th percentile height. The corresponding p-values are 0.134, 0.077, 0.174, 0.702, and 0.789. Anterior vaginal lengths of the subjects with 10th, 50th, and 90th percentile height are 68.7 ± 10.3 (length unit: mm), 67.6 ± 10.5 , and 71.8 ± 9.8 . The corresponding p-value is 0.504. Posterior vaginal lengths of the subjects with 10th, 50th, and 90th percentile height are 122.1 ± 16.6 , 118.9 ± 12.3 , and 122.3 ± 10.0 . The corresponding p-value is 0.968. Cervix lengths of the subjects with 10th, 50th, and 90th percentile height are 36.4 ± 7.5 , 34.0 ± 7.0 , and 30.8 ± 5.7 . The corresponding p-value is 0.070. Average middle sagittal vaginal shapes of the three groups vary with each other and have overlaps over each other.

Conclusions: Vaginal dimension has large variation between individuals but it is not primarily explained by body height.

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