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Longitudinal changes in reproductive hormones, reproductive organs, and anogenital distance in infant boys: does soy formula affect minipuberty? Helen Chin Andrea Kelly Donna Baird Walter Rogan David Umbach

Soy formula feeding is common in infancy and is a source of high exposure to phytoestrogens, documented to influence vaginal cytology in female infants. The influence of soy on the emergence and progression of minipuberty in males is unknown. We used data from the Infant Feeding and Early Development study to assess differences in reproductive hormones and hormone-responsive tissues in infant boys exclusively fed soy formula, cow-milk formula, or breastmilk. In this longitudinal cohort study, we followed 147 infant boys from birth to age 28 weeks with up to 9 data-collection visits. Infants participating in the study were normal birthweight (2500-4500 grams) and term gestational age (37-42 weeks). Over the study period we assessed serum testosterone concentrations, serum luteinizing hormone (LH) concentrations, stretched penile length, anogenital distance, and testis volume. We examined feeding-group differences in age trajectories for these outcomes using mixed-effects regression splines. We adjusted anatomical outcomes for weight-for-length z-score to account for age and body size changes. Our main comparison was between the two formula groups because women who breastfed differed from women who formula fed in multiple and likely unmeasured ways. Testosterone concentrations were in the mid-pubertal range at age 2 weeks (median: 176 ng/dL, quartiles:124, 232) and remained "pubertal" through age 12 weeks. Trajectories of testosterone, LH, and anatomical measures did not differ between boys fed soy formula (n=55) and boys fed cow-milk formula (n=54). Our findings suggest that these measures of early male reproductive development do not respond to infant phytoestrogen exposure, in contrast to the response observed in infant girls. More research is needed to understand infant hormone production and individual variability for these outcomes.

Maternal caffeine consumption during pregnancy and longitudinal child growth Jessica Gleason Stephen Gilman Rajeshwari Sundaram Susanna Mitro Stefanie Hinkle Cuilin Zhang Katherine Grantz

Greater caffeine consumption in pregnancy has been associated with reduced infant size at birth, but little is known about potential effects of in utero caffeine exposure on child growth. A few studies have found links between maternal caffeine consumption and excess weight gain in infancy and increased adiposity and risk for obesity in children, but all rely on self-reported caffeine consumption, and most evaluated outcomes at only 2-3 time points limiting ability to assess longitudinal trajectories. In 2,734 mother-child pairs from the Collaborative Perinatal Project pregnancy cohort (1959-66), serum caffeine and paraxanthine were evaluated in relation to child BMI and WHO-based BMI z-scores at birth, 4, 8, 12, 36, and 48 months. We fit generalized linear mixed models with age modeled quadratically and as cubic splines to compare BMI curves between caffeine quartiles. We also estimated relative risk (RR) of excess infant weight gain, defined as an increase in weight z-score ≥ 0.67 from birth to 12 months, using Poisson regression with robust standard errors. Models were adjusted for maternal demographics and smoking. Median caffeine concentration (IQR) was 792 (2067) ng/mL, which is high compared to a contemporary cohort with median (IQR) of 157 (631) ng/mL, where mean consumption was half a cup of coffee per day. Compared to the first quartile (<116.8ng/mL) of serum caffeine, there was no differences in child BMI or BMIz for any caffeine quartile at any assessment point. Results were similar for paraxanthine. We also found no difference in excess infant weight gain (q4 v q1 RR=0.98; 95% CI 0.85, 1.12), though 44% of the sample had an increase in weight z-score ≥ 0.67 in the first 12 months. In a cohort of high caffeine consumers, there was no association with later child growth. Results should be interpreted with caution, as the sample BMIz was well below the WHO mean for all quartiles (z=-0.70 to -0.72) at birth and above the mean at 48 months (z=0.41 to 0.44).

Large-for-gestational age, leptin, adiponectin and adiposity in infancy Rong Huang Yu Dong Anne Monique Nuyt Emile Levy Shu-Qin Wei Pierre Julien William Fraser Zhong-Cheng Luo

Background: Large-for-gestational-age (LGA) has been associated with elevated leptin concentrations at birth. It is unknown whether this association remains in infancy. We aimed to evaluate whether LGA is associated with circulating leptin and adiponectin levels in infancy, and assess their determinants.

Methods: In the prospective Canadian 3D birth cohort, we studied 70 LGA (birth weight >90th percentile) and 140 optimal-for-gestational-age (OGA, 25th-75th percentiles) control infants matched by maternal ethnicity, smoking and gestational age at delivery. We assayed circulating leptin, total and high molecular weight (HMW) adiponectin concentrations, and assessed adiposity indicators [body mass index (BMI), triceps and subscapular skinfold thickness] at age 2 year.

Results: LGA infants had higher BMI (P=0.008) and subscapular skinfold thickness (P=0.039) than OGA infants. However, there were no differences in leptin, total and HMW adiponectin concentrations (all P>0.25). Leptin concentrations were positively associated with female sex (P<0.001), current BMI (P=0.021) and the sum of triceps and subscapular skinfold thickness (P=0.014), and negatively associated with maternal age (P=0.031) and white ethnicity (P<0.001). Female sex was associated with lower total (P=0.019) and HMW (P=0.054) adiponectin concentrations. Current BMI was positively associated with total adiponectin (P=0.005) in LGA infants only.

Conclusion: The study is the first to reveal that LGA is not associated with altered circulating levels of both leptin and adiponectin in infancy, maternal age is negatively associated with leptin in infancy, and there may be a LGA-specific association between BMI and adiponectin in infancy. Females may have lower adiponectin concentrations in infancy.

Child health and development

Associations of Early Antibiotic Exposure with Childhood Body Mass Index Trajectory Milestones Izzuddin Aris Pi-I Debby Lin Sheryl Rifas-Shiman L. Charles Bailey Janne Boone-Heinonen Ihuoma Eneli Anthony Solomonides David Janicke Sengwee Toh Christopher Forrest Jason Block

Objectives: Few studies have documented alterations to body mass index (BMI) trajectory milestone patterns during childhood following early antibiotic exposure. We investigated this relationship using data from PCORnet, a National Patient-Centered Clinical Research Network.

Methods: We abstracted information on antibiotic use at ages 0–5, 6–11, 12–23, 24–35 and 36–47 months from electronic health record data from 26 institutions participating in PCORnet between 2009 and 2016. We also included children with at least one valid same-day height and weight measurements at each of the following age periods: 0–5, 6–11, 12–23, 24–59 and 60–131 months. We fitted individual BMI trajectories using mixed-effect models with natural cubic spline functions to estimate age and magnitude of BMI peak in infancy and rebound in early childhood, and used multivariable regression to examine associations of antibiotic use with these BMI trajectory milestones.

Results: Of 183,444 children included in the study, 78% received ≥1 episode of any antibiotic, 51% had ≥1 episode of broad-spectrum and 65% had ≥1 episode of narrow-spectrum antibiotics at any time before age 4 years. Exposure to any antibiotics at 0–5 months (vs. no exposure) was associated with later age (β 0.05 months; 95% CI 0.02, 0.08) and higher BMI at peak (0.09 kg/m^2; 0.07, 0.11). Exposure to any antibiotics at 0–47 months (vs. no exposure) was associated with an earlier age (-0.60 months; -0.81, -0.39) and higher BMI at rebound (0.02 kg/m^2; 0.01, 0.03). These associations were strongest for children receiving ≥4 antibiotic episodes. The associations with age at BMI rebound were more pronounced for those exposed to antibiotics at 24–35 or 36–47 months, than those exposed at earlier periods.

Conclusion: Antibiotic exposure was associated with small differences in BMI trajectory milestones in infancy and early childhood.

Triangulating approaches to estimate the effect of prenatal exposure to trans fatty acids on brain development in fetal life and childhood Runyu Zou Jeremy Labrecque Sonja Swanson Hanan El Marroun Henning Tiemeier

Introduction: Dietary trans fatty acids (TFAs) are primarily industrially produced and have been associated with poor cardio-metabolic health. Little is known about intrauterine exposure to TFAs in relation to brain development. We aimed to investigate the effect of prenatal TFAs exposure on brain development in fetal life and childhood.

Methods: In total 3295 mother-child dyads from a prospective population-based study in Rotterdam, the Netherlands were included. Maternal plasma TFAs concentration was assessed using gas chromatography in mid-gestation. Offspring head circumference (HC) in fetal life was repeatedly measured using ultrasonography; brain morphology in childhood was assessed using magnetic resonance imaging. We performed regression and instrumental variable (IV) analyses adjusting for several sociodemographic covariates. Our proposed IV leveraged a local policy change at recruitment starting from 2002-2003.

Results: After adjusting for covariates, maternal TFAs concentration was inversely related to fetal HC in the third trimester [mean difference =-0.37, 95% confidence interval (CI) -0.62 to -0.11, cm] and to fetal HC growth from the second to the third trimester (mean difference=-0.04, 95% CI -0.07 to -0.02, cm/week). Similar estimates were obtained with the IV analyses (mean difference=-0.40, 95% CI -0.74 to -0.06, cm; and mean difference=-0.10, 95% CI -0.12 to -0.07, cm/week, respectively). Maternal TFAs concentration was not predictive of offspring HC in the second trimester, nor global brain volume at age 10 years.

Conclusion: Higher maternal TFAs concentration during pregnancy was associated with suboptimal offspring brain development such as lower HC and slower HC growth in fetal life. These findings were consistent across regression and IV analyses, strengthening a causal interpretation. Our findings are of important public health relevance as TFAs levels in food remain high in many countries.

Sleep, 24-hour activity rhythm and cardiometabolic risk factors in school-age children Victoria A.A. Beunders M. Elisabeth Koopman-Verhoeff Marijn J. Vermeulen Pauline W. Jansen Annemarie I. Luik Irwin K.M. Reiss Koen F.M. Joosten Vincent W.V. Jaddoe

INTRODUCTION: Disturbed sleep and 24-hour activity rhythms have been linked to adverse cardiometabolic profiles in adults and adolescents. Yet research in school-age children, using objective sleep measures as well as other cardiometabolic risk factors besides adiposity, is scarce. Our aim was to study associations of sleep and 24-hour activity rhythms, as assessed by actigraphy, with cardiometabolic outcomes in school-age children.

METHODS: This cross-sectional population-based study comprised 894 children aged 8-11 years from the Generation R Study. Sleep (duration, efficiency, arousals) and 24-hour activity rhythm (social jetlag, intradaily variability (IV)) were assessed using a tri-axial wrist accelerometer for nine subsequent nights. Cardiometabolic outcomes included adiposity (BMI Z-score, fat mass index (FMI) using dual-energy X-ray absorptiometry, visceral fat mass (vFM) and liver fat fraction using magnetic resonance imaging), blood pressure and blood markers (glucose, insulin, lipids). We adjusted for season, age, sex, gestational age, ethnicity, maternal education, and in a separate model also for lifestyle (sport, television viewing, sugar intake).

RESULTS: Longer sleep duration was associated with lower BMI (-0.09 SD, 95% confidence interval (CI): -0.18;-0.00) and FMI (-0.03 kg/m^2, 95% CI: -0.06;-0.00). The number of arousals was negatively associated with all adiposity outcomes, whereas greater IV was associated with higher FMI (0.05 kg/m^2, 95% CI: 0.02;0.07) and vFM (0.06 grams, 95% CI: 0.02;0.11), all independent of lifestyle. Sleep efficiency and social jetlag were not associated with outcomes. We found no associations with blood pressure or blood markers.

CONCLUSIONS: In school-age children, sleep and 24-hour rhythm parameters are associated with increased adiposity, but not with blood pressure or metabolic blood markers. Although follow-up is needed to assess causality, optimizing sleep and 24-hour rhythm in children may help to prevent obesity.

Folate, vitamin B12 and homocysteine concentrations during pregnancy and early signs of atherosclerosis in childhood Giulietta Monasso Janine Felix Sandra Heil Romy Gaillaird Vincent Jaddoe

Background Early signs of atherosclerosis develop from childhood onwards. We hypothesized that fetal exposure to lower circulating folate and vitamin B12 concentrations and higher circulating homocysteine concentrations are associated with early signs of atherosclerosis in childhood.

Methods This study among 3,826 school-age children and their mothers was embedded in the Generation R Study, a population-based prospective cohort study from early pregnancy onwards. We examined the associations of early pregnancy and cord blood plasma folate, serum total and active B12 and plasma homocysteine concentrations with common carotid artery intima-media thickness (cIMT) and distensibility in the children aged ten years.

Results Early-pregnancy circulating folate, total and active B12 and homocysteine concentrations measured continuously were not associated with cIMT or distensibility in the children. However, as compared to normal early-pregnancy serum total B12 concentrations ($\geq$145 pmol/L) , low serum total B12 concentrations (<145 pmol/L) were associated with higher childhood cIMT (difference 0.09 standard deviations score (SDS); 95% confidence interval (CI): 0.01, 0.16). As compared to normal early-pregnancy plasma folate concentrations ($\geq$8 nmol/L), low plasma folate concentrations (<8 nmol/L) were associated with lower childhood common carotid artery distensibility (difference -0.16 SDS; 95% CI: -0.28, -0.04). In cord blood at birth, one SDS higher plasma homocysteine concentrations was associated with a -0.05 SDS (95% CI: -0.09, -0.02) lower distensibility in childhood. Cord blood folate, total and active B12 concentrations were not associated with cIMT or distensibility in childhood.

Conclusions Circulating folate, total B12 and homocysteine concentrations during fetal life seems to be associated with markers of subclinical atherosclerosis in childhood. Further studies need to examine the causality and mechanisms underlying these associations.

Pregnancy outcomes

The Association Between Diet Quality Indices and Gestational Age and Birth Weight among Latinas Megan Harvey Sofija Zagarins Bess Marcus Milagros Rosal Penelope Pekow JoAnn Manson Katherine Tucker Tiffany Moore Simas Glenn Markenson Lisa Chasan-Taber

Prior studies of the impact of maternal diet on birth outcomes have not typically assessed compliance with recommended dietary guidelines and have not focused on Latinas, a group with poorer diet quality and more adverse maternal outcomes, relative to non-Latina White women. Therefore, we evaluated the association between four established diet indices and gestational age (GA) and birth weight among 168 predominantly Puerto Rican participants enrolled in Estudio PARTO, a randomized trial of a lifestyle intervention in Western Massachusetts from 2013-2017. Diet was measured at a mean of 28.1 (SD=6.6) weeks GA by trained bicultural/bilingual personnel via three 24-hour recalls. The Healthy Eating Index 2015 (HEI 2015), Alternate Healthy Eating Index 2010 (AHEI 2010), alternate Mediterranean Diet Score (aMED), and Healthy Plant-Based Diet Index (HPDI) were calculated, with higher scores indicating better quality. Mean GA at delivery was 39.2 wks (SD=1.5) and mean birth weight was 3446.1g (SD=523.3). Participants reported mean intakes of 1856 kcal (SD=555) per day. Mean diet quality scores were 54.9 (SD=14.6, HEI 2015), 36.6 (SD=11.6, AHEI 2010), 24.4 (SD=5.5, aMED), and 51.8 (SD=7.7, HPDI). Women who were married, older than 35, non-smokers, with lower total energy intake and who preferred speaking Spanish had significantly higher diet quality (all $p<0.05$). After adjusting for age, history of preterm birth, energy intake, activity level, and intervention arm, higher diet quality scores were not associated with gestational age (HEI 2015 $\beta=0.10$ $p=0.20$; AHEI 2010 $\beta=0.11$ $p=0.17$; aMED $\beta=0.07$ $p=0.38$; HPDI $\beta=-0.03$ $p=0.74$), nor birth weight (HEI 2015 $\beta=0.03$ $p=0.73$; AHEI 2010 $\beta=0.06$ $p=0.50$; aMED $\beta=-0.01$ $p=0.98$; HPDI $\beta=0.04$ $p=0.64$). Future research should seek to elucidate relevant diet patterns for Latinas and the association between dietary quality and birth outcomes among this ethnic group.

Effects of mother's plasma cortisol on infant birth weight: a Mendelian Randomiza-tion study Madeline Travers Mary Schooling

In the United States, low birth weight (LBW) is a leading cause of infant death overall, and the leading cause of death for African American infants. Understanding and preventing adverse birth outcomes is a major public health priority in the United States. Observationally, there is some evidence to support the hypothesis that cortisol may be associated with LBW. To clarify the effect of cortisol exposure on LBW, we used separate-sample instrumental variable analysis with genetic instruments (Mendelian randomization) based on 3 single nucleotide polymorphisms (SNP), from a genome wide association study, strongly (p-value $< 5 \times 10^{-6}$) and independently associated with morning plasma cortisol. These SNPs were applied to a large, extensively genotyped study of birth weight conducted by the Early Growth Genetics Consortium (EGGC), which contains mother's genetic effect on offspring birth weight, after adjusting for the correlated offspring's genotype (n =179,360). SNP-specific Wald estimates were meta-analyzed to obtain inverse variance weighted and MR-Egger estimates, taking into account correlations between SNPs. Higher genetically instrumented plasma cortisol was associated with lower birth weight using inverse variance weighting. Birth weight decreased by about 29 grams (0.057 standard deviation (SD)) for every unit increase of log transformed effect size of plasma cortisol (beta = -.057 (95% confidence interval (CI) -0.103, -0.021). More investigation is required into the role of cortisol in LBW, a leading cause of morbidity and mortality among infants, as a potential target of intervention.

Pre-pregnancy BMI and gestational age-specific rates of perinatal death: Do singleton and twin pregnancies differ? Jeffrey Bone KS Joseph Lauren Yearwood Chantal Mayer Laura Magee Sarka Lisonkova

Background

High pre-pregnancy body-mass-index (BMI) associated with adverse birth outcomes including perinatal death; however, these associations are understudied in multiple pregnancies. Our aim was to estimate the effects of pre-pregnancy BMI on gestational age specific rates of perinatal death in twin versus singleton pregnancies.

Methods

This was a retrospective cohort study of all births at ≥20 weeks' gestation in British Columbia, Canada (2000-2017). Data were from the British Columbia Perinatal Database Registry. Cox models with robust standard errors were used to estimate adjusted hazard ratios (AHR) and 95% confidence intervals (CI) and to test interaction between plurality (singletons vs. twins) and BMI class (underweight <18.5 kg/m^2, normal BMI 18.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2, and obese ≥30 kg/m^2). Models were adjusted for demographic characteristics and prior obstetric history.

Results

Among all 517,845 women, 12.4% were obese, 20.5% overweight and 6.2% underweight; 3.1% had twin pregnancies. Women with twins delivered at earlier gestation (median 36 vs 39 weeks). Gestational age- specific rates of perinatal death increased with gestation in both twin and singleton pregnancies; twins had higher rates overall (AHR=8.08, 95% CI: 6.69-9.75). The effect of BMI was modified by plurality (p = 0.05). Perinatal death rates were higher among singletons born to overweight (AHR=1.25, 95% CI: 1.13- 1.40) and obese women (AHR=1.61, 95% CI: 1.42-1.82). In contrast, perinatal death rates were not elevated in twins born to overweight (AHR=1.02, 95% CI: 0.73-1.43) and obese women (AHR=1.06, 95% CI: 0.71-1.59), but increased among twins born to underweight women (AHR=1.98, 95% CI: 1.23-3.20).

Conclusions

The association between pre-pregnancy BMI and perinatal mortality may differ between singleton and twin pregnancies. Elevated rates of perinatal death were observed in underweight women with twin pregnancies, and in overweight and obese women with singletons.

Caffeine intake across pregnancy and timing of delivery in the NICHD Fetal Growth Studies-Singletons Stefanie Hinkle Jessica Gleason Samrawit Yisahak Sifang Zhao Jagteshwar Grewal Sunni Mumford Katherine Grantz Cuilin Zhang

Objective: Pregnant women are advised to limit caffeine intake to <200 mg/d. Much of the prior research on caffeine and preterm birth has been limited to a single self-reported measure of intake. We examined associations of self-reported caffeinated beverage intake across pregnancy and 1st trimester plasma caffeine with timing of delivery.

Methods: For 2784 pregnant women, self-reported daily caffeine intake from beverages in the past week was estimated at 10-13, 16-22, 24-29, 30-33, 34-37 gestational weeks. Plasma caffeine and paraxanthine were measured at 10-13 weeks. Gestational age was estimated from ultrasound verified last menstrual period date. Associations of time-varying self-reported caffeine with time to delivery and preterm birth (<37 weeks) were estimated using Cox proportional hazard models. Associations of caffeine and paraxanthine with time to delivery and preterm birth were estimated using Cox proportional hazard models and Poisson regression with robust variance, respectively. Covariates included demographics, parity, pre-pregnancy body mass index, hyperemesis, and lifestyle factors.

Results: Mean gestational age at delivery was 39.2 (standard deviation 1.9) weeks with 6% delivered preterm. Across pregnancy, 1% of women reported caffeine intake >200 mg/d, which was associated with an increased hazard for earlier delivery (adjusted hazard ratio [aHR; 95% confidence interval]: 1.5 [1.0,2.3]) and higher preterm birth risk (aHR 5.1 [1.5,17.0]) compared to 0 mg/d; intakes <200 mg/d were not associated with either outcome. Further, higher levels of 1st trimester total plasma caffeine and paraxanthine concentrations were related to greater preterm birth risk; aHR across increasing quartiles were 1.00, 1.6 (0.9,2.6), 1.9 (1.2,3.1), and 1.6 (1.0,2.6), whereas no association was observed with time to delivery.

Conclusions: Caffeinated beverage intake above recommendations was associated with an earlier time to delivery and increased risk for preterm birth.

Long-term neuropsychiatric risk across gestational age subgroups: a Danish population-based cohort study Jingyuan Xiao Yuntian Xia Yongfu Yu Wan-Ling Tseng Eli Lebowitz Andrew DeWan Lars Pedersen Jørn Olsen Jiong Li Zeyan Liew

Abstract

Importance: Previous studies have indicated children born at non-optimal gestational durations are at risk for neurodevelopmental disabilities, yet evidence regarding finer classification of gestational age groups and the risk for multiple major neuropsychiatric disorders beyond childhood is limited.

Objective: To comprehensively evaluate the associations between six gestational age groups and the risk of nine major types and eight subtypes of childhood and adult-onset neuropsychiatric disorders.

Design: Nationwide register-based cohort study.

Setting: Denmark**.**

Participants: Danish individuals born between January 1, 1978 and December 31, 2016 (N=2,327,639).

Exposure: Gestational age subgroups classified based on data obtained from the Danish Medical Birth Register. (in completed weeks): very preterm (20-31), moderately preterm (32-33), late preterm (34-36), early term (37-38), term (39-40, reference), and late/post-term (41-45).

Main Outcomes and Measures: Neuropsychiatric diagnostic records up to August 10, 2017, ascertained from the Danish Psychiatric Central Register using ICD-10 codes F00-F99. We used Poisson regression to estimate the incidence rate ratio (IRR) and 95% confidence interval (CI) for neuropsychiatric disorders in childhood and adulthood, adjusting for selected sociodemographic factors.

Results: For the three preterm groups, a gradient of decreasing IRRs was found from very preterm to late preterm groups for having any or each of the nine neuropsychiatric disorders (e.g., very preterm: IRR=1.49 ,95% CI=1.43-1.55; moderately preterm: IRR=1.23, 95% CI=1.18-1.28; late preterm: IRR=1.17, 95% CI=1.14-1.19 for any disorders) compared with term birth. Individuals born early term had 7% higher rates (IRR=1.07, 95% CI=1.06-1.08) for any neuropsychiatric diagnoses and 31% for mental retardation (IRR=1.31, 95% CI=1.25-1.37) when compared to those born at term. The late/post-term group had lower IRRs for most disorders, except childhood autism in which the rate was higher for individuals born post-term compared with the term.

Conclusions and Relevance: Higher incidences of all major neuropsychiatric disorders were observed not only in the spectrum of preterm but also beyond the traditional threshold of fetal maturity. Early term and late/post-term births might not share a homogeneous low risk for neuropsychiatric disorders with individuals born at term. Intervention strategies aimed at perinatal risk factors contributing to nonoptimal gestation might reduce long-term risks for neuropsychiatric disorders in the population.

Racial/ethnic disparities in adverse birth outcomes among women living in public housing in New York City Melanie Baker Lorna Thorpe

New York City (NYC) is home to the largest public housing authority in the United States. More than 400,000 residents live in approximately 370 public housing developments; median household income is $20,000 and approximately 90% of residents are non-Hispanic Black or Hispanic. We examined within-public housing racial/ethnic disparities in preterm birth and low birthweight among a population of women giving birth while living in NYC public housing between the years of 2013-2016 (n=45,890). Data for analysis were obtained from birth records provided by the NYC Office of Vital Records. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were reported. Among women residents, there was a higher proportion of low birthweight and preterm birth among non-Hispanic Black women (10% and 11%) than Hispanic (7% and 9%) and non-Hispanic White (4% and 6%) women. Non-Hispanic Black women were 50% more likely to deliver a low birthweight infant [AOR=1.5, 95% CI (1.3, 1.6)] and 20% more likely to deliver a preterm infant [AOR=1.2, 95% CI (1.2, 1.3)] compared to Hispanic women. Non-Hispanic White women were 30% and 40% less likely to deliver a low birthweight and preterm infant, [AOR=0.7, 95% CI (0.5, 0.8); AOR=0.6, 95% CI (0.5, 0.8)] respectively, compared to Hispanic women. When stratified by maternal age, non-Hispanic Black women had elevated adjusted odds ratios of low birthweight and preterm birth for all age groups compared to Hispanic women but declined from 2013-2016 in women older than 35 years. Our findings show profound differences in adverse birth outcomes by race/ethnicity and maternal age, even when analyses were restricted to the public housing resident population. Further studies are warranted to identify important contributors to disparities in birth outcomes among women living in public housing.

Paternal Characteristics and Associated Pregnancy and Birth Outcomes Ashley Hill Guru
Rajesh Jammy Kalpana Betha P.S. Reddy Brandie D. Taylor Elizabeth Miller Catherine Haggerty

Background

Paternal biological factors influence the growth and development of the fetus and may play a
significant role in the fetal environment influencing pregnancy outcomes, although not well
investigated. This study aims to explore paternal demographic and behavioral factors associated
with preterm birth in a sample of rural to peri-urban Indian women and their husbands.

Methods

A retrospective analysis of cohort data from the Longitudinal Indian Family hEalth (LIFE) study were
included. Women (n=1227) aged 15 to 35 years and their husbands were recruited before pregnancy
or in their first trimester from 2009 – 2016 and followed through pregnancy, labor and delivery, and
postpartum. Questionnaire and laboratory data were collected at study registration including
demographics, environmental exposures and mental health. The main outcome was overall preterm
birth. An initial exploratory analysis of paternal factors and preterm birth was conducted; crude
odds ratios are reported.

Results

This sample included 385 fathers linked to singleton pregnancies, excluding multiparous births.
Fathers were primarily Hindu (89%) and were on average 27 years old. Majority had attended school
(90%) and could read (88%) and write (90%) in English. Fathers primarily reported good health
(84%) and did not have chronic conditions. Roughly 21% of fathers smoked tobacco or and 71%
drank alcohol during the pregnancy. Paternal fasting blood sugar was marginally associated with
preeclampsia (1.02 CI 95% 1.00-1.04), and the drinking alcohol (0.85 CI 95% 0.74-0.96) and storing
fuel in the home (0.73 CI 95% 0.56-0.95) were associated preterm birth.

Conclusion

These intriguing findings suggest the need for additional complex analyses that investigate paternal
social and behavioral factors. This may include examining complex interactive relationships between
maternal and paternal characteristics that influence adverse pregnancy outcomes in diverse cohorts
to understand potentially modifiable risk factors.

Child health and development

Gestational age and siblings' literacy: spillover effects in the family David Mallinson Felix Elwert Deborah Ehrenthal

Contemporary research findings on early-life health and development suggest that a child's health shock may harm their siblings' academic performance. These insights are guided by resource reallocation theory: parental investments shift from healthier children to affected siblings to compensate for the health shock's deleterious effects, which may impair unaffected siblings' development. Using a longitudinal birth cohort from Wisconsin, we investigate whether a child's gestational age affects their older sibling's literacy at kindergarten. We sampled 20,014 sibling pairs that were born during 2007-2010 and took Phonological Awareness Literacy Screening-Kindergarten (PALS-K) tests during 2012-2016. Exposures were gestational age (completed weeks), preterm birth (<37 weeks), and very preterm birth (<32 weeks). To estimate spillover, we use gain-scores, a fixed effects estimator that differences siblings' school year-standardized PALS-K scores to offset family-level, sibling-invariant confounding. We first regress the gain-score on siblings' exposures, and we then sum the exposures' partial regression coefficients to generate a "spillover coefficient." The resulting spillover coefficient yields a lower-bound spillover effect estimate of the younger siblings' gestational age on their older siblings' PALS-K score. Multivariate regressions indicate that a one-week increase in younger siblings' gestational age improves the older siblings' PALS-K score by 0.011 standard deviations (SD) (95% confidence interval [CI]: 0.001, 0.021 SD). This lower-bound spillover estimate was greatest among siblings whose mothers reported having a high school diploma/equivalent only (0.024 SD; 95% CI: 0.004, 0.044 SD). With evidence that children's shorter gestation harms older siblings' literacy, our findings underscore the relevance of early-life health shocks and their spillover effects on family members.

Risk of adverse neonatal outcomes among pregnant women with disabilities Jessica Gleason Jagteshwar Grewal Zhen Chen Alison Cernich Katherine Grantz

Women with disabilities are at risk of maternal and obstetric complications, including cesarean and preterm delivery, but whether neonatal morbidity is increased is unknown. We performed a comprehensive analysis of neonatal outcomes among 223,385 singleton deliveries in the Consortium on Safe Labor, a retrospective cohort study of maternal and neonatal electronic medical records at 12 clinical sites (2002-2008). Physical (n=1,733), sensory (n=250), or intellectual disabilities (n=91) were defined using International Classification of Diseases-9 codes with 221,311women defined as having no disability. Relative risk (RR) of 22 outcomes was calculated using adjusted log-linear regression models with generalized estimating equations. Compared to no disability, neonates of women with any disability had higher risk of nearly all neonatal outcomes, including preterm birth (RR=1.69; 95% CI 1.55, 1.85), small-for-gestational age (SGA) (RR=1.21; 95% CI 1.07, 1.36), NICU admission (RR=1.64; 95% CI 1.50, 1.80), seizures (RR=2.50; 95% CI 1.37, 4.56), cardiomyopathy (RR=4.26; 95% CI 1.01, 17.98), respiratory morbidities (RR ranged from 1.34-1.91) and death (RR=2.14; 95% CI 1.30, 3.51). When examining outcomes as a composite, neonates of women with disability had higher risk of experiencing any adverse outcome (RR=1.54; 95% CI 1.41, 1.68). Increased risk varied but was generally consistent across all disability categories. When restricting the sample to neonates born at term (37+ weeks; n=198,846), compared to women without disabilities, neonates of women with any disability (n=1609) maintained higher risk of low birthweight (<2500g), SGA, and NICU admission, with increased risk of neonatal death (RR=4.60; 95% CI 1.87, 11.33). They also had higher risk of any adverse outcome (RR=1.34; 95% CI 1.16, 1.54). Neonates of women with disabilities were at higher risk of a broad range of adverse neonatal outcomes, including death, and risks were not fully explained by preterm birth.

Childhood autism spectrum disorder diagnosis and household food insecurity Gabrielle Gutierrez Melanie Adkins Kristen Upson Claire Margerison Nicole Talge

The health care needs of children with autism spectrum disorder (ASD) are resource intensive and can lead to household financial strain. However, it is unclear whether these hardships also include food insecurity. To address this issue, we used data from the National Survey for Children's Health (NSCH: 2016-2018) in which ASD diagnostic status (yes, no) and household food insecurity information (none, mild, moderate/severe) were collected via parent administered surveys. We restricted analyses to NSCH participants ages 2-17 years with available data (n=86,401) and used multinomial logistic regression, accounting for survey sampling, to estimate ORs and 95% CIs. We also investigated the impact of state-level mandates in ASD insurance benefits, stratifying by "less generous" and "more generous" mandates defined using algorithms that incorporate information on beneficiary eligibility and spending caps.

Childhood ASD diagnosis was associated with both mild and moderate/severe food insecurity (OR 1.9, 95% CI: 1.5, 2.3; OR 2.6, 95% CI: 1.9, 3.5, respectively). However, the magnitude of the association differed by the generosity of the state's ASD insurance mandate. In more generous states, ASD diagnosis was associated with mild insecurity, but not moderate/severe insecurity (mild: OR 2.1, 95% CI: 1.3, 3.3, moderate/severe: OR 1.3, 95% CI: 0.7, 2.3). In less generous states, ASD diagnosis was associated with both mild and moderate/severe insecurity (mild: OR 1.7, 95% CI 1.4, 2.2; moderate/severe: OR 3.3, 95% CI 2.4, 4.6). We observed similar results after adjustment for household, caregiver, and child characteristics.

Our results indicate that childhood ASD diagnosis is associated with household food insecurity, particularly in states with less generous ASD insurance mandates. Future research is needed to identify the causal mechanisms that drive these findings as well as whether food insecurity relates to health outcomes in children with ASD

Other

Temporal trends in cerebral palsy rates in children born in the province of Ontario, Canada, 2002-2013: A population-based retrospective cohort study Asma Ahmed Laura Rosella Seungmi Yang

Background: Studies in Europe and Australia have examined temporal trends in cerebral palsy (CP) rates with inconsistent findings, and corresponding figures from North America are still scarce. Little is known about changes in CP rates by important sociodemographic characteristics over time.

Methods: We identified 1,587,087 live births born in the province of Ontario, Canada between 2002 – 2013 and ascertained CP diagnosis made before age 5 in health administrative databases. We examined differences in CP rates overall and by child, maternal, and area-based socioeconomic characteristics over time.

Results: CP rates increased from 3.72 (95% confidence interval: (3.49, 3.96)) per 1000 live births in 2002 to 4.16 (4.00, 4.33) in 2007 before starting a steady decline afterward, reaching a low of 3.19 (2.98, 3.41) in 2013. As expected, CP rates were considerably higher in children with low gestational age (GA) and birth weight (BW), although rates in the low BW/GA categories were steadily decreasing over the study period. CP rates were higher in boys, multiples, children with congenital malformations, and in those delivered by caesarean section; these gaps have narrowed over time. Children of young (<20 years), old (>35 years), primiparous, and grand multiparous (4+) mothers had higher rates of CP over time. We also observed socioeconomic disparities in CP rates that mostly remained stable over the study period.

Conclusion: This is the first population-based study to examine not only overall CP rates over time but stratified by important birth and sociodemographic characteristics. It is encouraging that CP rates were decreasing in recent years both overall and across GA and BW categories, which may suggest a potential positive impact of advances in obstetric and neonatal care together with neuroprotective strategies. The persistence of socioeconomic disparity over time warrants further investigation.

Association of sweetened carbonated beverage consumption during pregnancy and ADHD symptoms in the offspring. A study from the Norwegian, Mother, Father and Child Cohort Study (MoBa). Liv Kvalvik Kari Klungsøyr Jannicke Igland Ida Henriette Caspersen Anne Lise Brantsæter Berit Skretting Solberg Catharina Hartman Lizanne Johanna Stephanie Schweren Henrik Larsson Lin Li Ingeborg Forthun Stefan Johansson Alejandro Arias Vasquez Jan Haavik

Purpose: Intrauterine exposures influence offspring health and development. We investigated maternal intake of sweetened carbonated beverages (SCB) during pregnancy and its association with ADHD symptoms in children.

Methods: This study was based on the Norwegian Mother, Father and Child Cohort Study (MoBa) and the Medical Birth Registry of Norway. Maternal diet mid-pregnancy was assessed using a food frequency questionnaire (FFQ). All women who responded to the FFQ and a questionnaire when children were 8 years of age were included (n=39 870). The exposure was defined as maternal intake (daily servings) of SCB, using no daily intake as reference. Outcome was offspring ADHD symptoms, evaluated as a continuous standardized ADHD score and as a binary outcome of six or more ADHD symptoms vs. five symptoms or less. Associations were analysed using linear mixed regression models and log-binomial regression, adjusted for relevant confounders.

Results: The adjusted regression coefficients for the standardized ADHD offspring symptom score were 0.003 (95% confidence intervals (-0.47 to 0.48)), 0.54 (0.08 to 1.00) and 0.39 (-0.24 to 1.01) for maternal intake of 1 glass, 2-3 glasses and 4 or more glasses of SCB, respectively. The adjusted relative risks were 1.01 (0.78 to 1.29), 1.27 (1.04 to 1.56) and 1.18 (0.92 to 1.51), for drinking 1, 2-3 and 4 or more glasses daily, respectively compared to women with no daily intake of SCB.

Conclusion: In a large pregnancy cohort with offspring followed up until 8 years of age, we found a positive association between high maternal intake of SCB and offspring ADHD symptoms. The results suggest a weak underlying relationship between maternal intake of SCB and offspring ADHD.

The association between assisted reproductive techniques and offspring childhood asthma Chen Wang Anna Johansson Sonia Hernández-Díaz Catarina Almqvist Sara Öberg

Objective To examine the previously reported association between ART and childhood asthma independent of infertility and other measured parental factors, as well as all stable parental factors. **Methods** All live births between 1997 and 2013 identified in the Swedish Medical Birth Register were linked to other national registers. Infertility and ART use were ascertained from IVF clinic reporting, clinical diagnosis, and maternal self-report at the first antenatal visit. Childhood asthma was identified from diagnosis in medical records and dispensation of asthma medication, with follow-up through 2018. Cox proportional hazard regression was used to estimate the association of ART and asthma in the population, in children of couples with known infertility, and in a sample of siblings conceived with and without ART. **Results** Of the 1,671,532 live births in the cohort, 11.7% were born to couples with known infertility, and 3.5% were conceived with ART. Compared with all other children, children conceived by ART had a small elevated risk of asthma (adjusted hazard ratio (aHR)=1.14, 95% Confidence interval (CI) 1.11-1.16). When the comparison was restricted to children of couples with known infertility, the risk of asthma was reduced (aHR=1.07, 95% CI 1.05-1.10), and in the comparison of siblings conceived with and without ART no difference in risk was seen (aHR=0.98, 95% CI 0.86-1.13). Among children conceived with ART, those in which intra-cytoplasmic sperm injection (ICSI) had been used had a slightly lower risk of asthma (aHR= 0.93, 95% CI 0.90-0.97), whereas no difference in risk was seen between use of fresh and frozen-thawed embryo transfer. **Conclusion** This study found a modestly elevated risk of asthma in children conceived with ART to be largely explained by confounding from parental background factors. There were further no indications of harm from increasingly utilized ART procedures such as ICSI or embryo-freezing, with respect to children's risk of asthma.

Prevalence and Treatment of Balance and Dizziness Problems among U.S. Children Aged 3-17 Years – A Healthy People 2020 Update Chuan-Ming Li Howard J. Hoffman Christa L. Themann Devin L. McCaslin Anne E. Hogan Bryan K. Ward

Purpose To examine trends in prevalence and treatment of balance and dizziness problems (BDPs) among U.S. children aged 3-17 years in accordance with Healthy People 2020 objectives.

Methods Data from the 2012 and 2016 National Health Interview Surveys were analyzed to evaluate Healthy People 2020 objective 13.1, which sought to increase the proportion of children who have tried recommended methods for treating BDPs. Parents/caregivers reported whether their child had experienced BDPs (including vertigo, poor balance, coordination problems, frequent falls, light-headedness/fainting, or blurred vision) in the preceding 12 months, and whether they had tried treatments recommended by a doctor, physical or occupational therapist, or other health care professional. Estimates were weighted to represent the U.S. childhood population.

Results BDP prevalence increased slightly but not significantly from 5.3% (3.3 million; 5.6% females, 5.0% males) in 2012 to 5.6% (3.5 million; 5.8% females, 5.5% males) in 2016. The increase in reported prevalence was significant among Hispanic children (4.5% to 6.2%; p=0.05). The proportion of children who received treatment for BDPs during the preceding 12 months also increased slightly but not significantly between 2012 and 2016 (30.6% to 33.3%). Significant or marginally significant changes in BDP treatment were observed among females (29.0% to 36.0%; p=0.09), non-Hispanic (NH) black (26.8% to 46.1%; p=0.005), and Hispanic (20.4% to 29.0%; p=0.05). Among children with "moderate/big/very big" BDPs, significant changes in treatment rates were observed among NH black (43.6% to 64.3%; p=0.05) and Hispanic (33.2% to 58.1%; p=0.007).

Conclusions BDPs in childhood may have lifelong adverse sequelae. Although increases in treatment prevalence were observed in Hispanic and NH black children, overall access to treatment for children with BDP remains low. Increased efforts to address this childhood public health issue are warranted.

Association between past negative experience with emotional or behavioral problems among US children: Evidence from the 2016-2019 National Survey of Children's Health Qiping Fan Qiping Fan

Objectives: We aimed to investigate the prevalence of emotional or behavioral problems among US children and examine the association between past negative childhood experience with the attention-deficit hyperactivity disorder (ADHD), depression, anxiety, and behavioral problems, accounting for the sociodemographic, family characteristics, and other developmental disabilities and chronic health conditions.

Methods: A cross-sectional analysis of the four-year data from the 2016-2019 National Survey of Children's Health (n= 131, 774 children) was conducted. We examined several measures of lifetime history of emotional and behavioral problems reported by parents/caregivers based on healthcare provider diagnosis, including ADHD, depression, anxiety, and behavioral problems. Negative childhood experience included victim of violence, being treated unfairly because of race, parent's divorce or service in jail, and living with people with substance abuse problems or mental illnesses. Weighted multivariate logistic regression was employed to examine the association between past negative experience with the emotional and behavioral problems, accounting for other confounders.

Results: Among US children, 16.11% of them had lifetime history of emotional or behavioral problems. Specifically, the prevalence of ADHD, depression, anxiety, and behavioral problems were 8.4%, 3.5% 7.1%, and 8.1% respectively. Children's any negative experience was significantly associated with lifetime history of ADHD (aOR=2.0, 95% CI=1.7-2.4, P<.001), depression (aOR=3.5, 95% CI=2.8-4.5, P<.001), anxiety (aOR=2.3, 95% CI=1.9-2.8, P<.001), and behavioral problems (aOR=2.5, 95% CI=2.1-3.1, P<.001).

Conclusion: Negative childhood experience is significantly related to children's emotional and behavioral problems. Prevention and treatment programs for children with special emotional or behavioral needs should provide stronger support and special care for children with negative experience.

Prevalence of dementia by age among privately-insured adults with and without congenital heart defects, 2015-2017 Karrie Downing Matthew Oster Sherry Farr

Neurocognitive issues are common among individuals with congenital heart defects (CHD). However, less is known about prevalence and onset of dementia among adults with CHD. Our objectives were to determine if prevalence of diagnosed dementia among adults ages 26-64 years differs by presence and severity of CHD and if these relationships are modified by age group (26-55, 56-64 years). Using IBM MarketScan Commercial claims databases, we identified adults with CHD (defined as ≥2 outpatient CHD diagnosis codes >30 days apart or ≥1 inpatient code documented in 2007-2017) continuously enrolled from 2015-2017 in employer-sponsored health insurance. Those with Down syndrome diagnosis codes documented from 2007-2017 were excluded. Severe CHDs were those typically requiring intervention in the first year of life. Dementia was defined as ≥2 outpatient dementia diagnosis codes ≥1 day apart or ≥1 inpatient code and identified between 2015 and 2017. Log-binomial regression models estimated adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for associations between presence and severity of CHD and dementia. All models included sex, region, age as of January 2015, and an interaction term for age and CHD presence or severity, respectively. There were 20,072 adults with CHD diagnoses and 7,121,951 adults with no CHD diagnosis. Overall, 0.2% of adults with CHD and 0.1% without were diagnosed with dementia [aPR=2.2 (CI: 1.6-2.9)]. Stratifying by age, the aPR among 26-55 year-olds was 2.3 (CI:1.5-3.6) and among 56-64 year-olds was 2.0 (CI: 1.4-3.0). For CHD severity, the overall aPR comparing severe CHD to no CHD was 4.0 (CI: 2.2-7.3); comparing non-severe CHD to no CHD was 1.9 (CI:1.4-2.7); and comparing severe to non-severe CHD was 2.3 (CI:1.1-4.5). Across all age groups, dementia is more prevalent among adults with both severe and non-severe CHD compared to those without CHD and also among adults with severe CHD compared to those with non-severe CHD.

Health Profile of Preterm Males with Duchenne Muscular Dystrophy Aida Soim Bailey Wallace Nedra Whitehead Michael Smith Joshua Mann Shiny Thomas Emma Ciafaloni Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet)

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder with a prevalence of 1 in 3600-6000 live male births and is the result of the disruption of dystrophin in the dystrophin-glycoprotein complex. Males with DMD experience progressive muscle weakness and wasting resulting in decline in mobility and eventual need for a wheelchair by age 12, limitations in performing daily activities, and respiratory and/or cardiac complications. Babies born prematurely are vulnerable to a wide array of long-term conditions, such as neurodevelopmental disabilities, chronic diseases including chronic respiratory complications, cognitive impairment, visual and hearing impairments, behavioral and socio-emotional problems, and poor health and growth. In this retrospective cohort study, major clinical milestones (ambulation cessation, assisted ventilation use, and onset of left ventricular dysfunction [LVD]) and corticosteroids use in 399 males with DMD (365 full-term and 43 preterm) identified through a population-based surveillance system were analyzed using Kaplan-Meier survival curves and Cox proportional hazards modeling. The adjusted risk of receiving any respiratory intervention among preterm males with DMD was 87% higher than among the corresponding full-term males with DMD; adjusted Hazard Ratio (aHR)=1.87; 95% Confidence Intervals (CI):1.02, 3.42. The adjusted risks for ambulation cessation and LVD were modestly elevated among preterm compared to full-term males, but the 95% CI contained the null (aHR=1.28 and aHR=1.13, respectively). No difference in the start of corticosteroid use between preterm and full-term DMD males was observed. Overall, the disease course seems to be similar between preterm and full-term males with DMD; however, pulmonary function seems to be affected earlier among preterm males with DMD. Clinicians may need to have heightened awareness of the potential need for respiratory support in males with DMD born preterm.

County-level Environmental Quality and Gastroschisis in the National Birth Defects Prevention Study Alison K. Krajewski Achal Patel Christine L. Gray Lynne C. Messer Peter H. Langlois Jennita Reefhuis Suzanne M. Gilboa Martha M. Werler Gary M. Shaw Suzan Carmichael Wendy Nembhard Tabassum Z. Insaf Marcia L. Feldkamp Danelle T. Lobdell Tania A. Desrosiers National Birth Defects Prevention Study

The etiology of gastroschisis is not well understood. Genetic factors, young maternal age, low BMI, and isolated environmental exposures have been linked to this birth defect of the abdominal wall, but the contribution of combined exposures across socio-environmental domains has not been comprehensively examined. We used the Environmental Quality Index (EQI), a county-level estimate of cumulative exposures in five domains – air, water, land, sociodemographic, and built environment – developed by the US Environmental Protection Agency (EPA), to assess the association between environmental quality and gastroschisis in the National Birth Defects Prevention Study, a population-based case-control study conducted in multiple US states. We analyzed data for 594 infants with gastroschisis and 4105 non-malformed controls delivered between 2006 and 2011. Maternal residence at conception was geocoded and linked to the EQI, yielding exposure data for 369 counties. We used logistic regression to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI) for gastroschisis and EQI tertiles (referent = T1 = "best" environmental quality), adjusted for maternal age at conception (<20 or ≥20 years), race/ethnicity, periconceptional cigarette smoking, alcohol use, and maternal country of birth (US or non-US). Overall, the aORs for T2 and T3 were 1.11 (95% CI: 0.88,1.40) and 1.02 (0.80,1.29), respectively. For the individual domains, the aORs for the "worst" environmental quality (T3) were: air 1.04 (0.82,1.33); water 1.31 (0.99,1.73); land 0.99 (0.75,1.30); sociodemographic 1.20 (0.86,1.67); and built environment 1.28 (0.96,1.70). While some socio-environmental factors have previously been associated with gastroschisis, we did not observe strong associations with cumulative county-level exposures across environmental domains. These findings and conclusions are those of the authors and do not necessarily represent the official position of the EPA or the CDC.

Maternal asthma in relation to infant adiposity and growth Danielle Stevens Edwina Yeung Andrew Williams Stefanie Hinkel Leah Lipsky Marion Ouidir Jenna Kanner Seth Sherman Matt Rohn William Grobman Zhen Chen Pauline Mendola

Background: Maternal asthma and poor asthma control are associated with intrauterine growth restriction and could thereby influence newborn adiposity and postnatal growth.

Objective: We examined maternal asthma and asthma control in relation to infant adiposity and anthropometry at birth and 4 months among pregnant women with (n=311) and without asthma (n=107) and their infants in the B-WELL-Mom study.

Methods: Asthma control (poorly- versus well-controlled) was determined based on symptomology collected in daily diaries. Infant adiposity (percent fat mass) was assessed by air displacement plethysmography at birth. Infant anthropometry included weight, length, weight-for-length, body mass index (BMI), head and arm circumferences, and triceps and subscapular z-scores at birth and 4 months. Rapid infant growth was defined as a 0.67 increase in z-scores for weight between birth and 4 months. Linear models estimated mean differences (95% confidence interval (CI)) in anthropometry and adiposity, and Poisson models estimated the relative risk (RR (95% CI)) of rapid infant growth by maternal asthma status and asthma control. Models were adjusted for maternal characteristics and study site.

Results: Maternal asthma status was not associated with any study outcomes. Infants of women with poorly-controlled asthma had higher weight (0.34 (0.01, 0.67)), weight-for-length (0.52 (0.15, 0.88), BMI (0.49 (0.15, 0.82)), and head circumference (0.65 (0.19, 1.10)) z-scores at birth compared to infants of women with well-controlled asthma. Infants of women with well-controlled asthma had similar anthropometry and adiposity as infants of women without asthma. No difference in outcomes at 4 months or risk of rapid infant growth were evident by maternal asthma control.

Conclusions: Contrary to expectations, infants of mothers with poorly-controlled asthma were larger than infants of mothers with well-controlled asthma. Further research is needed to elucidate these associations.

Diabetes risk status and meeting United States physical activity recommendations by race/ethnicity in reproductive-age women: 2011, 2013, 2015, 2017 BRFSS Bethany Rand Samantha Ehrlich Tammie Johnson James Churilla

Background: Women with history of gestational diabetes or prediabetes can reduce their diabetes risk by engaging in physical activity (PA). This study examined the association of diabetes risk status with meeting recommendations for aerobic activity (AA), muscle strengthening activity (MSA), or both PA recommendations, and potential modification of these associations by race/ethnicity. ***Methods:*** Non-pregnant women ages 18-44 years, free of diagnosed diabetes who completed the 2011, 2013, 2015, or 2017 Behavioral Risk Factor Surveillance System survey (N= 211,114) were categorized no diabetes (ND; n= 202,766) versus at risk for diabetes (RD; n= 8,348). Logistic regression models were adjusted for age, race/ethnicity, BMI class, education, alcohol consumption, and smoking. ***Results:*** In the full cohort, 29% met the AA recommendation, 9.3% the MSA, and 22% both PA recommendations. Compared to ND, there was the suggestion that RD women had significantly greater odds of meeting the AA recommendation (OR 1.09; 95% CI 1.00, 1.20; P=0.06). RD women were found to have significantly lower odds of meeting the MSA recommendation alone (OR 0.81; 95% CI 0.70, 0.95) and of meeting both PA recommendations (OR 0.87; 95% CI 0.78, 0.97) compared to ND. Effect modification by race-ethnic was detected (P < 0.10). Upon stratification, similar associations were observed for Whites, but there were none among Blacks, Hispanics, Asians, or Other. Prevalence of meeting recommendations varied by race/ethnicity; 24-31% met the AA, 8-11% met the MSA, and 19-25% met both. In the RD group, Whites had the highest (35%) and Blacks the lowest (25%) prevalence of meeting the AA recommendation. ***Conclusions:*** Reproductive-aged women in the U.S. at risk for diabetes, stand to benefit from increasing PA, particularly MSA, as good evidence suggests MSA may improve glucose regulation and meeting the MSA recommendation was rare. Strategies are needed to increase AA in U.S. minority women at risk for diabetes.

Is cesarean delivery a risk factor for childhood cancer before 14 years? Safiya Soullane
Sophie Marcoux Ga Eun Lee Nathalie Auger

Background: Cesarean delivery may predispose children to mucosal dysbiosis, impaired immunosurveillance, and the risk of hematologic or solid tumours. We evaluated the association between cesarean delivery and childhood cancer.
Methods: We followed a longitudinal cohort of 1,034,049 children born in hospitals of Quebec, Canada from birth up to 14 years of age. The exposure was delivery mode, namely cesarean, operative vaginal (forceps, vacuum), and nonoperative vaginal delivery. The outcome included hematopoietic or solid tumours. We evaluated a range of cancers, including lymphoma, leukemia, sarcoma, neuroblastoma and central nervous system tumours. We calculated hazard ratios (HR) and 95% confidence intervals (CI) for the association between mode of delivery and childhood cancer, adjusted for potential confounders.

Results: 249,415 (24.1%) children were born by cesarean and 97,411 (9.4%) by operative vaginal delivery. Compared with nonoperative vaginal delivery, cesarean was associated with 1.16 times the risk of any cancer (95% CI 1.04-1.30), 1.12 times the risk of hematopoietic cancer (95% CI 0.92-1.36), and 1.21 times the risk of solid tumours (95% 1.05-1.38). Associations appeared at 2 years of age, and were greatest between 2 and 4 years of age. Between 2 and 14 years, cesarean delivery was associated with lymphoma (HR 1.80, 95% CI 1.11-2.92) and sarcoma (HR 1.77, 95 % CI 1.27-2.48), but not leukemia, neuroblastoma and central nervous system tumours. Operative vaginal delivery was not associated with the risk of any cancer.

Conclusions: Cesarean delivery was associated with the risk of childhood cancer up to 14 years, especially lymphoma and sarcoma. Associations were strongest between 2 and 4 years of age. Operative vaginal delivery was not associated with the risk of childhood cancer. Further study is needed to determine if mucosal dysbiosis and altered immunity from reduced exposure to maternal flora could explain the findings.

Impact of COVID-19 shelter-in-place policies on child abuse Corinne Riddell Kriszta Farkas Krista Neumann Jeanie Santaularia Jennifer Ahern Susan Mason

Background: Families in the US are facing increased unemployment, school closures, movement restrictions, and social isolation due to the COVID-19 pandemic, all of which are risk factors for child abuse. Allegations of child abuse to Child Protective Services (CPS) have starkly declined due to reduced contact between children and mandated reporters, but there are concerns that actual child abuse may have increased. The study objective was to estimate the effect of COVID-19 shelter in place (SIP) policies on child abuse using data independent of CPS.

Methods: We linked data on state-level SIP policies to outcome data from the Google Health Application Programming Interface. The outcome was a scaled proportion of searches for child abuse-related phrases (proportionateto total search volume). Between 914–1512 abuse phrases were included for each abuse sub-domain (physical, sexual, and emotional). We applied a differences-in-differences design using Poisson regression to estimate the extent that changes in child abuse search volume after the introduction of SIP policies differed in states that introduced SIP vs. those that did not in the same week.

Results: Eight states and DC were excluded because of suppressed outcome data. Of the remaining states, 37 introduced a SIP policy between March 19, 2020 and April 7, 2020 and 5 states (AR, IA, NE, OK, UT) did not. The introduction of SIP led to a slight reduction in relative child abuse search volume, net of changes experienced by states that did not introduce SIP at the same time (relative change for weeks 1-5 after SIP: 0.97, 95% CI: 0.92-1.02, relative change for weeks 6-10: 0.99, CI: 0.95-1.04).

Conclusions: We found evidence consistent with no change or a possible slight reduction in relative child abuse search volume associated with the introduction of SIP. This finding may reflect a real null or slight decrease, however an increase in total search volume during the pandemic could complicate the interpretation.

Roles of income and acculturation in the Hispanic paradox: Breastfeeding among Hispanic women Soojung Kim Andrew Williams

Background: Hispanic paradox suggests Hispanics have better health outcomes despite relatively low socioeconomic status. U.S. Hispanic mothers have the highest prevalence of breastfeeding compared to other racial/ethnic groups, yet contributing factors remain unclear. This study examines the relationship between Hispanic nativity, acculturation and breastfeeding using Fragile Families Child Wellbeing Study baseline and Year 1 data.

Methods: 4,603 women (1,019 non-Hispanic White, 2,311 non-Hispanic Black, 385 US-born Mexicans [UM], 344 US-born other Hispanics [UH], 364 foreign-born Mexicans [FM], and 180 foreign-born other Hispanics [FH]) were included in analyses. Logistic regression estimated odds ratios (OR) and 95% confidence intervals (CI) for the association between race/ethnicity and breastfeeding initiation (self-reported any breastfeeding), accounting for acculturation (Spanish language use, cultural engagement, religiosity, and traditional gender role attitudes), demographics, income, and health behaviors. Models were run for the overall sample and stratified by low vs. high income (high above overall median: $21,873).

Results: Overall, FM(2.35 95%CI:1.33,4.15) and FH(2.28 95%CI:1.23,4.24) had higher odds, while UM(.55 95%CI:.41,.73) and UH(.50 95%CI:.37,.67) had lower odds of breastfeeding, compared to white women. In stratified models, low income FM(2.61 95%CI:1.12,6.05) and FH(3.73 95%CI:1.43,9.74) women had higher odds of breastfeeding than high income FM(2.11 95%CI:0.96, 4.65) and FM(1.97 95%CI:0.86, 4.52) women. Spanish language use and religiosity were stronger predictors of breastfeeding among low-income women than high-income women.

Discussion: The Hispanic paradox applies differentially among Hispanic women due to nativity, income, and acculturation. Compared to white women, low-income FM and FH are more likely to breastfeed. Also, acculturation may more strongly influence breastfeeding among FM and FH women than women in other racial/ethnic groups.

Substance Use

Cannabis Use and Mental Disorders Among Canadian Children & Youth: a population-based study Asmita Bhattarai Jeanne VA Williams Tamara Pringsheim Andrew GM Bulloch Scott Patten

Background:

Prior studies have reported that cannabis use has long-term mental health consequences, however most of the studies are conducted among adults. The study examined the association between cannabis use and common mental disorders among children and youth.

Methods:

The Ontario Child Health Survey 2014 assessed mental disorders among children and youth residing in private households (aged 12-17 years, n=2,728) using the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). Any cannabis use was also self-reported. Odds Ratios (OR) and 95% Confidence Intervals (CI) were estimated to further characterize the associations. Sampling weights and bootstrap procedures were used to address the survey design effects.

Results:

The prevalence of cannabis use among children and youth was 8.25% (95%CI 7.96-8.54). Prevalence of mental disorders was higher among cannabis users than non-users. Associations were significant with the mental disorders, namely generalized anxiety disorder (OR 2.00, 95% CI 1.75-2.29), major depressive episode (OR 3.15, 95% CI 2.74-3.62), attention deficit hyperactive disorder (OR 3.02, 95% CI 2.61-3.49), oppositional/conduct disorder (OR 4.00, 95%CI 3.51-4.56), and social/specific phobia (OR 1.58, 95%CI 1.34-1.85), which persisted after adjustment for a variety of covariates such as age, sex, education, chronic conditions, alcohol use etc. However, the association (for each mental illness) weakened substantially when adjusted for nicotine use.

Conclusion:

The results reinforce that cannabis use is associated with poor mental health among children and youth, suggesting that this is a high-risk population. Weakening of the associations with adjustment for nicotine use suggests that the effects of cannabis are intermixed with those of extraneous factors (e.g., genetics, coping styles) that may determine the use of both substances. However, the cross-sectional nature of the study does not allow confirmation of causality.

Social determinants of health

Epigenetics and Neighborhood Environment among Pregnant Black Women Jazib Gohar
Dawn Misra Alexandra Nowak Carmen Giurgescu

Epigenetic changes may explain how maternal residence in disadvantaged neighborhoods during pregnancy relates to higher rates of adverse births outcomes. We examined the association between neighborhood-level characteristics and maternal DNA methylation in a cohort of Black pregnant women. This study reports data on a subsample of 64 women who participated in the Biosocial Impacts on Black Births (BIBB), an ongoing longitudinal cohort study conducted in metropolitan Detroit, MI and Columbus, OH. Women completed questionnaires and had blood drawn at 8-29 weeks gestation. Neighborhood-level characteristics were abstracted from the 2018 American Community Survey (ACS) for the zip codes where the study participants resided, including median neighborhood income, high school graduation rates, and neighborhood poverty rate. We extracted DNA from leukocytes and measured genome-wide DNA methylation using the Infinium MethylationEPIC BeadChip array. Using linear regression, associations between nine neighborhood-level characteristics and maternal DNA methylation were tested by regressing β values for each cytosine-phosphate-guanine dinucleotide (CpG) site on each neighborhood-level factor while adjusting for covariates. We used a false discovery rate (FDR) threshold <0.05. Three of the CpG sites (cg13149677, cg15228451, cg18905866) were found to be associated with neighborhood median household income after adjusting for maternal age, ever-smoking status, and batch effects. We identified novel associations between neighborhood-level factors and the DNA methylome. Further analysis could strengthen our findings, reinforcing the notion that improving neighborhood conditions could, downstream, improve health outcomes.

Utilization of the Electronic Medical Records to Initiate change in Provider Habits Jagjit Singh Teji Amy Smolucha

Background:

After cesarean section, 1 in 300 opiate-naïve women exposed to opioids will become persistent opioid users. With the majority of misused prescription pain relievers being provided by a friend or family member for free (2) as a result of excess tablets at home, the need to standardize postpartum analgesic regimens is crucial.

Objectives:

The main study objective is to assess the average number of opioid tablets prescribed at discharge following cesarean section by anonymous provider types before and after a grand rounds intervention utilizing data extraction and analytics from the electronic medical record system.

Methods:

Data extraction and analysis using the Mercy Hospital and Medical Center electronic medical records (EMR) system from 10/1/2017 to 12/31/2018. Patients had to be eighteen years or older and have undergone cesarean section during their current admission as identified by patient room location and opioid tablets on discharge by provider type as attending physicians (AP), resident physicians (RP), and certified nurse midwives (CNM). Baseline results were presented at a grand rounds. Primary outcomes included the number of opioid tablets prescribed by provider type before and after a grand round intervention. Secondary outcomes included the average number of opioid tablets prescribed by individual anonymous providers and between provider type.

Results:

There were 597 patients (492 before and 106 after grand rounds intervention). Initially prescriptions ranged from 6 to 42 tablets at discharge. AP were 43.75% and 75% of RP who attended grand rounds. There was a 31% decrease in the number of opioid tablets prescribed overall (p=0.001). AP decreased their average number of opioids tablets at discharge by 27% or 6 tablets (p=0.007) less than RP decreased by 31% or 6.1 tablets (p=0.001).

Conclusions:

Lack of standardized clinical practice was noted in prescribing opioids by all three types providers. After grand round intervention prescriptions for opioid tablets declined among attending physicians and residents. Data extraction and analysis using the EMR database utility appears effective and can be applied to multiple specialties across the board improve quality improvement.

Substance Use

Developing a Statewide Equity Dashboard to Drive Quality Improvement in Substance Addiction Treatment during Pregnancy Hafsatou Diop Sarah Stone Samantha Parker Rachel Applewhite Munish Gupta

Objectives: Medication-assisted treatment (MAT) for opioid use disorder (OUD) remains underutilized among racial and ethnic minorities, including in pregnant people. Inequities in maternal treatment and outcomes require increased efforts to achieve equitable care. Since 2017, the Perinatal-Neonatal Quality Improvement Network of Massachusetts has led a statewide effort to improve outcomes for opioid-exposed newborns and their families. We sought to use the database from this effort to develop an equity dashboard examining key outcomes by race/ethnicity over time, first focusing on MAT at delivery.

Methods: We analyzed mother-newborn dyads in the database from 1/2017 to 10/2020. MAT was defined as prescribed methadone, buprenorphine, or naltrexone at time of delivery. We calculated the prevalence of MAT in two-year intervals (2017/2018, 2018/2019, 2019/2020) and examined trends, prevalence ratios (PRs), and prevalence differences (PDs) with 95% confidence intervals (CI) for MAT by race/ethnicity using White non-Hispanic (WNH) as the reference.

Results: Twenty-five Massachusetts hospitals contributed data on 2,901 dyads, of which 87.1% were WNH, 3.8% were Black non-Hispanic (BNH), and 9.2% were Hispanic. Using two-year averages, the prevalence of MAT ranged from 63%-67% [95% CI (50%, 78%)] among BNH and 64%-68% [95% CI (56%, 76%)] among Hispanic compared to 82-84% [95% CI (80%, 86%)] among WNH. PRs were similar for BNH and Hispanic mothers relative to WNH, ranging from 0.75 to 0.8 with 95% CI from 0.62 to 0.96. PDs were similar for BNH and Hispanic mothers relative to WNH, ranging from 0.16 to 0.19 with 95% CI from 0.04 to 0.33. PRs and PDs remained similar over time.

Conclusion: Significant racial/ethnic inequities in MAT persisted during our study period, despite ongoing improvement efforts. Future research should focus on understanding treatment experiences of BNH and Hispanic women. Equity dashboards can be effective tools for perinatal quality collaboratives.

Association of Neighborhood Walkability, as Measured by Walk Score, with Perinatal Outcomes Helen Gao Lindsay Cheu Daniel Block Borko Jovanovic Michelle Kominiarek

Introduction: Few studies have evaluated the association of neighborhood walkability and perinatal outcomes. Walk Score® is a validated tool that rates zip code walkability from 0-100 based on amenity density. This study examines the association of Walk Score rating and early and adequate prenatal care, first trimester prenatal care, preterm birth, and low birth weight.

Methods: Perinatal outcome data for Chicago's 77 community areas were abstracted from the Chicago Health Atlas, a database with vital statistics from all birth certificates issued 2013-2017. The following outcomes were assessed: early and adequate prenatal care (care by month 4 with ≥80% recommended visits completed), first trimester prenatal care, preterm birth (<37 weeks gestation), and low birth weight (<2500g). The 2017 Walk Score data for Chicago zip codes were derived from WalkScore.com. Areal interpolation using ArcGIS generated Walk Score ratings for each community area based on the weighted mean of zip code Walk Scores. Getis-Ord Gi* statistic identified geographic hot spots for perinatal outcomes. Linear and logistic regression models in STATA examined the relationship of Walk Score with perinatal outcomes and hot spots.

Results: Chicago Walk Score ratings range from 28.1 to 94.4. A 10-point higher Walk Score rating is associated with 2.3% higher early and adequate prenatal care (p=0.03) and 2.3% higher first trimester prenatal care (p<0.01). One-point higher Walk Score rating is associated with an increased odds that an area is a hot spot for early and adequate prenatal care (OR 1.14, 95% CI 1.07-1.23) and for first trimester prenatal care (OR 1.38, 95% CI 1.17-1.63), as well as a decreased odds for preterm birth (OR 0.93, 95% CI 0.89-0.98) and low birth weight (OR 0.93, 95% CI 0.89-0.98).

Conclusions: Higher Walk Score is associated with increased early and adequate prenatal care and first trimester prenatal care and decreased preterm births and low birth weights.

Serum per- and polyfluoroalkyl substance concentrations and common cold among children and adolescents in NHANES 2013-2014 Yu Zhang Vicente Mustieles Yang Sun Stelios Vagios Angela Slitt Yixin Wang Carmen Messerlian

Background

Per- and polyfluoroalkyl substances (PFAS) exert immunosuppressive effects in experimental animals. Few epidemiologic studies investigated PFAS in relation to the common cold as a marker of immune function during development.

Methods

This study included 517 children aged 3-11 years and 394 adolescents aged 12-19 years in the National Health and Nutrition Examination Study (NHANES) 2013 – 2014 cycle. Serum concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS) were quantified. Common cold was self-reported by the participant or parent as having a head cold or chest cold in the last month. Multivariable logistic regression was utilized to examine the adjusted association between individual PFAS and common cold. The joint effect of PFAS mixture was evaluated using Probit Bayesian Kernel Machine Regression (BKMR).

Results

Per doubling of serum PFHxS concentration was associated with a 31% (OR=1.31, 95%CI: 1.06, 1.62) and a 23% (OR=1.23, 95%CI: 0.96, 1.59) increased odds of common cold for children and adolescents, respectively. Serum PFNA concentration was positively associated with common cold in children (OR=1.36, 95%CI: 1.04, 1.79) while an inverse association was observed for adolescents (OR=0.42, 95%CI: 0.22, 0.80). A suggestive positive association for PFOA and common cold was found in both age groups. No association was observed for PFOS in either group. BKMR confirmed the individual associations and showed a clear increasing trend of common cold estimates across quantiles of the total PFAS mixture concentration among children, with no obvious pattern in the adolescents.

Conclusion

Serum PFHxS and PFNA concentrations were associated with increased odds of common cold in young children. Using common cold as a general measure of immunosuppression, this study may have important implications for the immunotoxicity of selected PFAS in childhood.

Real-time characterization of personalized air pollution exposure in pregnant women participating in a birth cohort study Akhgar Ghassabian Yelena Afanasyeva Keunhyung Yu Terry Gordon Mengling Liu Leonardo Trasande

Air pollution is a health risk in pregnant women and young children. Despite the importance of refined exposure assessments particularly at low exposure levels, characterization of personalized air pollution exposure remains a challenge in pediatric and perinatal epidemiology. Our objective was to use small and portable personal monitors to characterize exposure to indoor and outdoor air pollutants in pregnant women. We recruited 253 pregnant women from the New York University Children's Health Study (November 2019-November 2020). We provided women with a monitor, Flow by Plume Labs, which measures concentrations of particulate matter (PM), nitrogen dioxide (NO_2), and volatile organic compounds (VOC) in the personalized air inhaled by individuals. Women were instructed to wear the device for ≥2 weeks in each trimester of pregnancy. For 157 women (62%), real-time air pollution data and geolocation were stored in the secure database via HTTPS synchronization with a smart phone application. Compared to women with no pollution data (n=96, 38%), women with effective use of monitors were older (32.8±5.5 vs 31.8±6.1) and more likely to be Non-Hispanic White (47% vs 21%), married/partnered (94% vs 85%), and highly educated (75% vs 43%). As of November 2020, 30 women used air monitors twice or more, with no differences in average concentrations of pollutants between periods of use (p for paired comparison >0.05). The median for duration of air monitor use was 8 days [interquartile range (IQR): 3-15]. Median daily mean air pollution concentrations was 1.4 µg/m^3 for PM≤1µm (IQR=1.1-3.5), 3.2 µg/m^3 for PM≤2.5µm (IQR=2.4-6.9), 12.5 µg/m^3 for PM≤10µm (IQR=7.4-23.0), 12.1 ppm for NO_2 (IQR=7.0-19.1), and 165.5 ppb for VOC (IQR=150.6-187.3). Average hourly levels during night and day times were similar, except for NO_2(lower 8 pm-8 am). Small wearable devices represent a promising method for assessment of short- and long-term exposure to air pollution in epidemiological settings.

Associations between preterm birth and particulate matter or ozone vary by a combination of individual- and census tract-level indicators of race and poverty Kevin Park Kristen Rappazzo Josh Warren Adrien Wilkie Fanny Njie Tom Luben

Gestational exposure to air pollution is associated with adverse pregnancy outcomes, including preterm birth (PTB), and these associations may differ across both individual- and area-level strata of race/ethnicity and poverty. We used a cohort (2006–2014) of North Carolina live births combined with concentration estimates of ozone (O_3) and fine particulate matter ($PM_{2.5}$) from EPA's Community Multi-scale Air Quality model to estimate associations with PTB. Census tract-level data on race and poverty from the US Census Bureau's 2009 and 2013 American Community Survey were used as stratification variables. Geocoded residential locations from birth records were linked to daily air pollutant estimates at the census tract centroids. PTB was associated with 1st and 2nd trimester O_3 exposure [odds ratio (95% confidence interval) for an interquartile range increase: 1.09 (1.07, 1.10), 1.03 (1.02, 1.04), respectively]. When stratified by individual race and census-tract majority race, the odds of PTB associated with O_3 in the 1st trimester was greater for non-Hispanic (NH) Black mothers living in majority NH non-Black census tracts [1.12 (1.08, 1.16)] compared to NH Black mothers living in majority NH Black census tracts [1.08 (1.05, 1.11)]. When stratified by individual-level socio-economic status (SES) and census tract-level SES indicators, odds of PTB associated with 1st trimester O_3 exposure was greater for subjects with Medicaid living in census tracts with majority of residents under the poverty level [1.11 (1.06, 1.16)] compared to subjects without Medicaid living in the same census tracts [1.05 (1.03, 1.08)]. Odds of PTB associated with $PM_{2.5}$ exposure were similar in both trimesters [1.07 (1.07, 1.08); 1.06 (1.05, 1.06)] and in stratified analyses. Air pollutant exposure is associated with increased odds of PTB; however, the magnitude of association varies based on individual and neighborhood race and poverty indicators. This abstract does not reflect EPA policy.

Flame Retardants and Adverse Pregnancy Outcomes (FRAPO): First trimester PBDE-47 concentrations in maternal plasma increases the risk of in the first trimester increases the risk of post-partum depression Darios Getahun Michael Fasset Yuko Arita Harpreet Takhar Vicki Chiu Morgan Peltier

Darios Getahun[1,2], Michael J. Fasset[3], Yuko Arita[4], Harpreet.S.Takhar[1], Vicki Y Chiu[1], Morgan R. Peltier[4]. [1]Department of Research and Evaluation; Kaiser-Permanente Southern California, Pasadena, CA; [2]Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine; [3]Department of Obstetrics and Gynecology, West Los Angeles Medical Center, Kaiser-Permanente Southern California, Pasadena, CA; [4]Department of Foundations of Medicine, NYU-Long Island University, Mineola, NY

Background: Postpartum depression (PPD) affects up to 19.1% of pregnancies and is associated with inflammation, increased levels of proinflammatory cytokines and reductions in Brain-Derived Neurotrophic Factor (BDNF). Previous work by our lab suggests that environmental toxins such as polybrominated diphenyl ethers (PBDEs) enhance placental inflammation and reduce BDNF production. Nearly 100% of women have some level of exposure to these compounds due to their extensive use as flame retardants but their impact on risk of perinatal depression is unclear.

Methods: We quantified PBDE-47 concentrations in first-trimester maternal plasma in a subset of samples (n=348) from the FRAPO study by immunoassay. Levels were compared between women who had antenatal or post-partum depression with those that reported no depressive symptoms.

Results: In this cohort, 22 patients had PPD, 20 had antenatal depression only, and the remaining patients (n=326) had no evidence of depression. Pregnancies that were later complicated by PPD had significantly increased PBDE-47 levels in their plasma (P = 0.031), but no correlation with antenatal depression was detected. Groups were similar with regard to PTB rate, race-ethnicity, parity, child's sex, maternal pre-pregnancy BMI, maternal age, family income and center where samples were collected (P > 0.16 for all). Multinomial regression analysis suggested that each 2-fold increase in PBDE-47 concentrations increased the risk of PPD by ~15% (OR = 1.15, 95% CI: 1.01, 1.31) but no association was detected for antenatal depression (OR = 1.01, 95% CI: 0.90, 1.14). Patient's maximum recorded PHQ9 score also tended to increase with PBDE-47 levels but the results did not reach statistical significance.

Conclusion: These results suggest that PBDE-47 exposure in the first trimester increases the risk of post-partum, but not antenatal, depression. Further work is needed confirm these findings and identify the molecular mechanisms behind this association.

A systematic review of the epidemiologic evidence supporting the association between prenatal exposure to toxic and essential metals and preterm birth Lauren A. Eaves Alexander P. Keil Radhika Dhingra Julia E. Rager Tracy Manuck Rebecca Fry

Aim: In order to provide an updated and comprehensive summary, we systematically reviewed the epidemiologic evidence of the associations between prenatal exposure to arsenic, cadmium, chromium, copper, mercury, manganese, lead, zinc and preterm birth (PTB) or gestational age at delivery.

Methods: The Medline/PubMed database was searched in April 2020 for epidemiologic studies published in peer-reviewed journals after January 1, 1995. A total of 1029 studies were identified and screened utilizing the title and abstract. Of these, 104 were assessed for further eligibility by reading the full-text and 60 studies were ultimately included. A Risk of Bias (ROB) assessment will be conducted using the preliminary Risk Of Bias In Non-randomized Studies of Exposures tool.

Results: The included studies were primarily United States-based cohort studies using biomarker-based exposure assessment and the number of studies varied by metal: arsenic (24), cadmium (16), chromium (6), copper (9), mercury (14), manganese (7), lead (25) and zinc (8). There is strong evidence that prenatal exposure to either cadmium or lead is associated with higher risk of PTB and weaker evidence that exposure to arsenic or mercury may also be associated with higher risk. Evidence regarding exposure to remaining metals and PTB and/or delivery gestational age remains limited. Despite likely co-exposure, joint effects of multiple metals have been assessed in only two studies to date. We expect that the ROB assessment will highlight a lack of appropriate control for confounding by co-occurring metals and potential bias from biomarker-based exposure measurement at delivery. Further, we note a need to disaggregate by preterm birth phenotype, given different biological pathways.

Conclusions: Future research would benefit from disaggregation of phenotypes and thorough consideration of co-occurring metals, including investigations of metal-mixtures.

Associations of a Metal Mixture with Verbal Learning and Memory in Italian Adolescents Samantha Schildroth Donatella Placidi Megan Horton Roberta White Thomas Webster Donald Smith Robert Wright Roberto Lucchini Birgit Claus Henn

Background: Many metals are known neurotoxicants, affecting several domains of cognition. Research on metal mixtures, which may have additive or interactive effects, remains limited in relation to verbal learning and memory, an important cognitive domain. Further, few studies have focused on adolescence, a period characterized by rapid brain maturation.

Methods: We measured manganese (Mn), lead (Pb), copper (Cu), and chromium (Cr) in biomarkers from 403 Italian adolescents residing near ferroalloy industry. Verbal learning and memory were assessed using the California Verbal Learning Test (CVLT) for Children. Sociodemographic data were collected in baseline questionnaires. We used quantile-based g-computation to estimate individual and joint associations (β, per quartile increase in concentrations) between z-standardized metals and CVLT scores, adjusting for age, sex, HOME score and socioeconomic status.

Results: Median metal concentrations for hair (μg/g) Mn, Cu, and Cr were 0.07, 9.6 and 0.04, and for blood Pb was 12.7 μg/L. After adjustment, Cu was positively associated with several CVLT sub-tests: short delay recall (β=0.19, 95% CI=0.09,0.28), long delay recall (β=0.23, 95% CI=0.13,0.32), and perseverations (β=0.14, 95% CI=0.05,0.24). Hair Mn was negatively associated with short (β=-0.10, 95% CI -0.20,-0.004) and long (β=-0.11, 95% CI=-0.21,-0.02) delay recall. Jointly, metals were positively associated with perseverations (β=0.20, 95% CI=0.06,0.35), and short (β=0.11, 95% CI=-0.03,0.26) and long (β=0.10, 95% CI=-0.04,0.25) delay recall. Modest interactions were observed for hair Cu*blood Pb for short (β=0.05, 95% CI=-0.03,0.13) and long (β=0.04, 95% CI=-0.04,0.12) delay recall.

Conclusions: In our cross-sectional analysis, the metal mixture, driven by the association of Cu, was positively associated with aspects of verbal learning and memory (i.e., declarative learning), which may contribute to our understanding of the role of metals on cognition in adolescence.

Prenatal Per- and Polyfluoroalkyl Substances (PFAS) Exposure on Infant Birth Outcomes Within the MADRES Pregnancy Cohort Alicia Peterson Thomas Chavez Rima Habre Shohreh Farzan Sandrah Eckel Brendan Grubbs Theresa Bastain Carrie Breton

Introduction

Per- and polyfluoroalkyl substances (PFAS) are persistent synthetic chemicals found in many household products that can cross the placenta during pregnancy. We investigated whether exposure to PFAS during pregnancy was associated with adverse birth outcomes.

Methods

Serum concentrations of five PFAS (PFOS, PFHxS, PFNA, PFDA and PFOA) were measured in 340 prenatal specimens (mean gestational age: 21±9 weeks) from participants in the ongoing Maternal And Developmental Risks from Environmental and Social Stressors (MADRES) pregnancy cohort. PFAS analytes were modeled continuously and categorically. Birth outcomes assessed were birth weight and gestational age at birth. Linear regressions were performed to evaluate associations between PFAS exposures and birth outcomes adjusting for key covariates.

Results

Maternal participants (N=340) were on average 29±6 years old at study entry and were predominantly Hispanic (76%). Infants were born at a mean of 39±2 weeks gestation and weighed on average 3,280±523 grams. PFOS and PFHxS were detected in all samples, while PFNA, PFOA, and PFDA were detected in 70%, 65% and 57% of samples, respectively. Median concentrations were 1.34 nanograms per milliliter (ng/mL) for PFOS, 1.09 ng/mL for PFHxS, 0.07 ng/mL for PFNA, 0.12 ng/mL for PFOA and 0.04 ng/mL for PFDA. Levels were lower than comparable cohorts within California. Infants born to women with detectible levels of PFOA weighed 107 grams less on average at birth than infants born to women with non-detected levels of PFOA (p=0.03). We did not find significant adjusted associations with the remaining PFAS analytes and the birth outcomes assessed.

Conclusion

Prenatal exposure to PFOA was associated with lower birthweight in infants, suggesting that exposure to these chemicals during critical periods in development may have important implications for children's health.

Severe maternal morbidity and cardiovascular disease Ugochinyere Vivian Ukah Natalie Dayan Aimina Ayoub Brian Potter Nathalie Auger

Introduction: The relationship between severe maternal morbidity and cardiovascular disease is not well studied. Severe maternal morbidity consists of life-threatening complications around pregnancy that may affect cardiac function. Our objective was to examine the long-term risks of cardiovascular disease after a pregnancy complicated by severe maternal morbidity.

Methods: We used a longitudinal cohort of women who delivered in the province of Quebec, Canada between 1989 and 2019. The exposure was severe maternal morbidity, defined according to the Canadian Perinatal Surveillance System, and included conditions such as acute renal failure, and severe preeclampsia. The outcome was hospitalization for cardiovascular disease beginning 42 days after delivery, with follow-up extending up to thirty years later. We used time-varying adjusted Cox regression models to estimate hazard ratios (HR) with 95% confidence intervals (CI) for cardiovascular outcomes, comparing severe maternal morbidity with no severe morbidity.

Results: In a total of 1,336,846 women, severe maternal morbidity occurred in 66,537 (5.0%) women. Severe maternal morbidity was associated with an increased risk of cardiovascular hospitalization during follow-up (HR 1.78, 95% CI 11.73-1.83), compared with no morbidity. The association was strongest the first year after delivery (HR 4.44, 95% CI 3.79-5.21), but persisted beyond 15 years (HR 1.45, 95% CI 1.38-1.52). The morbidities most strongly associated with cardiovascular hospitalization were cardiac conditions (HR 5.39, 95% CI 4.67-6.23), cerebrovascular accidents (HR 3.82, 95% CI 2.94-4.96), and acute renal failure (HR 2.64, 95% CI 2.19-3.18).

Conclusion: Severe maternal morbidity is associated with a greater risk of cardiovascular hospitalization after the postpartum period, compared with no morbidity. Women with severe maternal morbidity may benefit from clinical surveillance after delivery, to prevent the development of cardiovascular disease.

Mode of birth by type of antenatal education: a prospective observational study Antonia Shand Bronwyn Lewis-Jones Timothy Nielsen Jane Svenssen Anne Lainchbury Amanda Henry Natasha Nassar

Background: Antenatal education aims to prepare expectant parents for pregnancy, birth, and parenthood. Some studies have reported antenatal classes teaching breathing and relaxation methods for pain relief, termed psychoprophylaxis, reduce the rate of caesarean section compared with general birth and parenting classes. Given the rising rates of caesarean section, we aimed to determine whether there was a difference in caesarean section rates in women based on the type of antenatal education attended.

Methods A cross-sectional antenatal survey of nulliparous women ³28 weeks gestation with a singleton pregnancy was conducted in 2 maternity hospitals in Sydney, Australia in 2018. Women were asked what type of antenatal education they attended and sent a follow-up survey post-birth. Hospital birth data was also obtained. Education classes were classified into 4 groups: psychoprophylaxis, birth and parenting, other or none.

Results: 505 women with birth data were included. A higher proportion of women who attended psychoprophylaxis education had a vaginal birth (instrumental or spontaneous birth) (79%) compared with women who attended birth and parenting, other or no classes (69%, 67%, 60%, respectively p=0.045). After adjusting for maternal characteristics, birth and hospital factors, the association was attenuated due to small numbers (Odds ratio 2.03; 95% confidence interval 0.93-4.43).

Conclusion: Women who attended psychoprophylaxis couple-based education had a trend towards higher rates of vaginal birth. Randomised trials comparing different types of antenatal education are required to determine whether psychoprophlaxis education can reduce caesarean section rates and improve other birth outcomes.

Pre-pregnancy BMI associated with placental dysfunction in early but not late preterm birth Alexander J. Layden Marnie Bertolet W. Tony Parks James M. Roberts Janet M. Catov Jennifer Adibi

Background: Maternal obesity is a risk factor for preterm birth (PTB), particularly before 32 weeks' gestation. Obesity may increase the risk of PTB through placental damage, but heterogeneity in PTB etiology hinders efforts to find key placental pathways.

Objective: We applied latent class analysis to identify placental pathology phenotypes in early (<32wks) and late PTBs (32 to <37wks) associated with pre-pregnancy BMI using placental pathology data.

Methods: Women with a singleton PTB at Magee-Womens Hospital (Pittsburgh, PA) in 2008-2012 and a placental evaluation (89% of PTBs) were stratified into early (n=900, 61% spontaneous) and late PTBs (n=3362, 57% spontaneous). Pre-pregnancy BMI was self-reported at first prenatal visit and 15 abstracted placental features were included. Placental features were clustered in early and late PTBs separately by latent class analysis. The optimal number of clusters was selected by comparing model fit statistics. The probability of cluster membership across BMIs was estimated in early PTBs and in late PTBs by latent class regression adjusting for race, smoking, education and parity.

Results: Early PTBs clustered into 4 groups: acute inflammation (38% of cases), maternal malperfusion with chorioamnionitis (29%), maternal malperfusion (25%), and fetal malperfusion (8%). As BMI increased from 20 to 50kg/m^2 the predicted probability of maternal malperfusion steadily increased while the probability of maternal malperfusion with chorioamnionitis decreased. There was minimal change in the probability of acute inflammation or fetal malperfusion with increasing BMI. Late PTBs also clustered into 4 groups: maternal malperfusion (22%), acute inflammation (12%), fetal malperfusion (9%) and low risk pathology (58%). Unlike early PTBs, the predicted probabilities for all 4 clusters were relatively unchanged with increasing BMI in late PTBs.

Conclusions: Obesity may predispose women to PTB through placental dysfunction but mainly in early PTBs.

Placental Pathology in the Context of Maternal Congenital Heart Disease Donna Pham Mana Parast Ana Rodriguez

Maternal congenital heart disease (CHD) during pregnancy plays an important role in maternal and fetal morbidities (Schlichting et al., 2019). For women with CHD, many complications arise in pregnancy, including as pre-eclampsia and preterm labor (Hayward et al., 2017); however, little is known about the underlying pathophysiology of these disorders in the setting of CHD. As the "diary of intrauterine life," the placenta can provide insight into such pregnancy complications if evaluated thoroughly, both macroscopically and microscopically. In order to evaluate associations between maternal CHD, placental pathology, and pregnancy outcomes, a retrospective cohort study was performed on 38 women with CHD, each of whom were matched with 2 non-CHD patients based on BMI, maternal age, and delivery date. Placental findings were extracted from placental pathology reports for both groups. BMI, maternal age, gestational age, mode of delivery, birth weight, fetal sex, birthweight percentiles (adjusted for fetal sex and gestational age), Apgar scores, and NICU admission data were also collected from medical records on EPIC. Placentas of women with CHD were more likely to show meconium staining of fetal membranes ($p=0.001$), normoblastemia ($p=0.007$), small placenta size ($p=0.022$), chorioamnionitis ($p=0.042$), hypermaturity ($p=0.000?$), intervillous thrombosis ($p=0.043$), and hematoma ($p=0.044$), compared to placentas of women without CHD. These findings highlight increased incidence of placental pathology, as well as evidence of in utero fetal hypoxic stress, in women with CHD. Further studies are needed to correlate these findings with pregnancy outcomes, and explore the underlying etiology of this pathology in order to improve management of pregnancy in women with CHD.

Patterns of anti-hypertensive medication use in pregnancy and risk of SMM in individuals with pre-pregnancy hypertension Shalmali Bane Suzan Carmichael Elizabeth Wall-Wieler Maurice Druzin

Chronic hypertension is a known driver of severe maternal morbidity (SMM). Anti-hypertensive medications (Anti-HT meds) like ACE-inhibitors and ARBs are not recommended during pregnancy due to risk of adverse fetal outcomes; medications like Labetalol or Methyldopa are recommended instead. The impact of specific classes of anti-HT meds during pregnancy on the fetus is documented; there is limited research on the impact on maternal health.

Our objective was to assess the impact of patterns of anti-HT med use in pregnancy (not recommended, safe, no use) on risk of SMM in those with chronic hypertension. Our cohort consisted of pregnancies (resulting in live birth or stillbirth) in Optum's de-identified Clinformatics® Data Mart Database from July 2007-Oct 2017 with adequate coverage, a chronic hypertension diagnosis and a prescription for anti-HT meds 6 months prior to pregnancy (n = 11,759). SMM from birth to 42 days postpartum was defined per CDC definition of 21 indicators. RRs were computed using modified Poisson regression with robust standard errors and adjusted for maternal age, education and birth year.

Overall, 83% of births were associated with filling an anti-HT prescription during pregnancy, and 6.3% with SMM. For no medication use in pregnancy, the 95% CI crossed 1 for pre-pregnancy safe (adjusted RR: 0.91, 95% CI 0.67, 1.23) and not recommended med use (1.20, 95% CI 0.91, 1.58). Compared to those using safe anti-HT meds pre- and in pregnancy (42% of births), risk of SMM was higher when switching from safe to not recommended (2.7, 95% CI 1.8, 4.1, 1% of births), not recommended to safe (1.4, 95% CI 1.2, 1.8, 14%), and using not recommended meds pre- and in pregnancy (1.5 95% CI 1.2, 1.7, 26%).

This study supports that choice of anti-HT meds before and during pregnancy is associated with SMM, in addition to known impact on fetal outcomes. Further work is needed to establish if this is due to hypertension severity, pregnancy planning, or quality of care.

History of infertility and adverse pregnancy outcomes in Project Viva Diana C. Soria-Contreras Wei Perng Sheryl Rifas-Shiman Jorge Chavarro Marie-France Hivert Emily Oken

Background. Infertility and adverse pregnancy outcomes are both highly prevalent among women, but it remains unclear whether the former is a risk factor for the latter.

Objective. To evaluate the associations of history of infertility with adverse pregnancy outcomes, and to identify whether the associations, if present, are attributed to underlying physiology or use of medical treatment.

Methods. N=2201 women from the Boston-area Project Viva cohort 1999-2002. The exposure was history of infertility for the index pregnancy based on: self-reported time to pregnancy ≥12 mo (or ≥6 mo if ≥35 y) or use of medical treatment to become pregnant; a diagnosis of infertility or claims for infertility treatments from medical records. We ascertained outcomes from outpatient/delivery charts, including: gestational glucose tolerance (impaired tolerance, gestational diabetes, isolated hyperglycemia, normal), hypertensive disorders (gestational hypertension/preeclampsia, normal), birth outcome (miscarriage, live birth), gestational weight gain (inadequate, excessive, adequate), birth weight-for-gestational age z-score, preterm birth, and systolic blood pressure (SBP). We performed generalized regression analyses adjusted for age, race/ethnicity, and age at menarche (Model 1), and additionally adjusted for pre-pregnancy BMI (Model 2).

Results. Nineteen percent of women had a history of infertility; 6% sought medical treatment to become pregnant. SBP was 0.92 (95% CI: 0.16,1.66) mmHg higher across pregnancy in women with vs. without infertility (Model 1); this estimate was somewhat attenuated in model 2 (0.65 mmHg, 95% CI: [-0.07,1.36]). These associations were stronger among women who received medical treatment for infertility (Model 2: 1.19 mmHg [0.05,2.33]). Other outcomes were not associated with infertility.

Conclusion. Infertility may be associated with higher prenatal blood pressure. Women with infertility may benefit from a more intensive monitoring during pregnancy.

Female Infertility Treatment, Maternal Characteristics, and Adverse Birth Outcomes Danielle Uribe Sarah Nechuta Peterson Haak

Background: Data from the 2015-2017 National Survey of Family Growth indicates that 13% of women in the United States between the ages of 15 and 49 reported difficulty becoming pregnant or staying pregnant. As the age at first birth has increased and fertility medicine has advanced, the popularity of fertility treatments has risen. The potential health risks of these treatments for both mother and child are not fully known. Our objective was to determine the association between fertility treatments and adverse birth outcomes using the Pregnancy Risk Assessment Monitoring System (PRAMS) data.
Methods: Using PRAMS, we conducted a serial cross-sectional analysis using data from 2009-2016 of 30,221 intended pregnancies, of which 3,969 reported using fertility treatments to conceive. Specific fertility treatments included ovulation stimulation drugs, artificial insemination, and assisted reproductive technology. Present analyses were limited to singleton births (n=28,525). Odds ratios (OR) and 95% confidence intervals (CIs) were adjusted for maternal age, race, education level, state of residence, parity, level of prenatal care, diabetes, and hypertension. All analyses accounted for the PRAMS complex sampling strategy and are appropriate for weighted data.
Results: Use of any kind of fertility treatment was associated with 1.3 higher odds of a cesarean delivery (95% CI: 1.16-1.45). Infants were 1.38 times more likely to born preterm (95% CI: 1.18-1.62), 1.16 times more likely to be small for gestational age (95% CI: 0.98-1.38) and 1.37 times more likely to have a hospital stay longer than 5 days (95% CI: 1.14-1.64).
Conclusions: The use of fertility treatments during intended pregnancies was associated with higher odds of cesarean-section, preterm delivery, small for gestational age, and a longer hospital stay. While further research is needed to understand mechanisms, women and their partners should be counseled on potential health risks associated with fertility treatments.

Birthweight by gestational age, preterm delivery and preeclampsia in a first pregnancy and subsequent risk of Gestational diabetes: A population-based study using sib-ship design Linn Marie Sorbye Nils-Halvdan Morken Kari Klungsoyr Liv Grimstvedt Kvalvik Ellen Aagaard Nohr Roy Miodini Nilsen Janne Mannseth Rolv Skjaerven

Background: Higher birthweight, preterm delivery and preeclampsia are factors associated with both Gestational diabetes mellitus (GDM) and maternal long-term mortality, however underlying mechanisms have not been fully described. We aimed to investigate if the combination of these factors in a woman's first pregnancy predicted the risk of GDM in the subsequent pregnancy. Methods: In sibling linked data from the population-based Medical Birth Registry of Norway 552,559 mothers with their first and second singleton pregnancy (1985-2019) were analysed. Mothers with any diabetes prior to second pregnancy were excluded. The exposure variable was categorized into 16 categories according to outcomes in first pregnancy: Z-scores of birth weight by gestational age in quartiles (Q1-4), preterm delivery (yes/no) and preeclampsia (yes/no). Relative risks (RR) with 95% confidence interval (CI) for GDM in second pregnancy were estimated, and mothers with a fetus in Q1, term delivery and without preeclampsia were the reference category. Results: Mothers with a term and non-preeclamptic pregnancy with a fetus in Q3 and Q4 had a RR 1.3 (95% CI: 1.1-1.5) and 2.2 (1.9-2.5) for GDM, respectively. The corresponding RR for mothers with a preterm delivery were 2.3 (1.7-3.2) and 4.3 (3.3-5.5), for a preeclamptic term pregnancy RR 3.0 (2.1-4.2) and 7.5 (6.0-9.3) and for mothers with both preterm delivery and preeclampsia RR 6.2 (3.5-11.0) and 15.5 (9.9-24.3). Conclusion: Mothers with a fetus in the highest birthweight by gestational age quartile had the highest risk of GDM across all categories. The most pronounced risk of GDM was found among mothers with a combination of preterm delivery, preeclampsia and a fetus in the highest birthweight by gestational age quartile.

TORCH Infections among Very Low Birth Weight and Very Preterm Infants Admitted to Neonatal Intensive Care Units in the United States, 2018 and 2019 Erika Edwards Lucy Greenberg Tatiana Lanzieri Jeffrey Horbar

Background: TORCH infections, which include toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes simplex virus, cause short- and long-term sequalae in infants. Prevalence of TORCH infections among very low birth weight and very preterm infants are largely unknown.

Objective: To describe prevalence of TORCH infections among very low birth weight and very preterm infants in the United States by maternal race and ethnicity.

Methods: Vermont Oxford Network receives data on all infants 401 to 1500 grams or 22 to 29 weeks' gestational age born or admitted within 28 days from birth. Maternal race and ethnicity were obtained by the reporting hospitals from personal interview with the mother, review of the birth certificate, or medical record and were categorized as Hispanic (any race) or non-Hispanic Black, white, Asian American or Pacific Islander, American Indian or Alaska Native, or other.

Results: In 2018 and 2019, 764 hospitals in the United States reported 87,205 very low birth weight or very preterm infants to Vermont Oxford Network of which 630 infants, or 7.2 per 1000, were diagnosed with a TORCH infection. Syphilis, cytomegalovirus, and herpes simplex were the infections reported most frequently, with an overall prevalence of 1.8, 3.3, and 1.9 per 1000 infants, respectively. Prevalence of syphilis, cytomegalovirus, and herpes simplex (7.1, 4.2, and 2.8 per 1000 infants, respectively) were highest among Native American infants.

Conclusions: Prevalence of TORCH infections among very low birth weight and very preterm infants varied by race and ethnicity. Understanding the social determinants responsible for these disparities, current testing practices, and health outcomes among infants with TORCH infections will inform public health strategies for prevention and screening.

Infectious disease

Early-Onset Sepsis Epidemiology Among Very Preterm Infants, 2018-2019 Erika Edwards Dustin Flannery Karen Puopolo Jeffrey Horbar

Background: Early-onset sepsis (EOS) is a significant cause of morbidity and mortality among very preterm infants. Nationally representative, contemporary, large-scale EOS epidemiology data can inform empiric antibiotic guidance, highlight risk factors for infection, and aid in prognostication for infected infants.

Design/Methods: Prospective observational study of very preterm infants born 401 to 1500 grams or 22 to 29 weeks' gestational age reported by 753 Vermont Oxford Network members in the United States. EOS was defined as a culture-confirmed blood or cerebrospinal fluid bacterial infection in the first 3 days after birth.

Results: Overall, 84,190 infants were included of which 1136 had EOS (13.5 per 1000 (99% CI [12.5, 14.6]). Incidence was highest for infants born ≤23 completed weeks (45.4 per 1000 (99% CI [38.3, 53.7]). Group B Streptococcus (217/1155; 18.8%) and E. coli (538/1155; 46.6%) were the most common pathogens identified, although 200/1155 (34.6%) were other bacteria. Infected infants were more often born vaginally to mothers with chorioamnionitis and without hypertension or multiple gestation, were less often SGA, and had lower birthweights and gestational ages compared to uninfected infants. Infected infants had longer lengths of stay (median 92 vs 66 days), higher rates of all neonatal morbidities, and lower rates of survival (67.5% vs 90.4%) and survival without major morbidity (26.2% vs 59.4%).

Conclusion(s): In a nationally representative sample of very preterm infants from 2018-2019, E. coli was the most common infecting pathogen, but approximately one third of isolates were neither GBS nor E. coli. Very preterm infants with EOS died at higher rates, and survivors had only half the rate of survival with major morbidity compared to uninfected infants. The profoundly negative impact of EOS on very preterm infants highlights the need for novel preventative strategies among such infants.

Characteristics and outcomes of pregnant women with SARS-CoV-2 infection and other severe acute respiratory infections (SARI) in Brazil from January to November 2020. Lisiane Leal Joanna Merckx Deshayne Fell Ricardo Kuchenbecker Angelica Miranda Wanderson de Oliveira Robert Platt Lívia Antunes Mariângela Silveira Natália Barbieri

Background: Knowledge about COVID-19 in pregnancy is limited, and evidence on the impact of the infection during pregnancy and postpartum is still emerging.

Aim: To analyze maternal morbidity and mortality due to severe acute respiratory infections (SARI), including COVID-19, in Brazil.

Methods: This population-based study used surveillance data from the SIVEP-Gripe *(Sistema de Informação de Vigilância Epidemiológica da Gripe)*. Currently and recently pregnant women aged 10-49 years hospitalized for severe acute respiratory infection (SARI) from January through November, 2020 were selected. SARI cases were grouped into: COVID-19; influenza or other detected agent SARI; and SARI of unknown etiology. Characteristics, symptoms and outcomes were presented by SARI type and region. We used descriptive statistics to profile the study population. Binomial proportion and 95% confidence intervals (95% CI) for outcomes were obtained using the Clopper-Pearson method.

Results: Of 945,460 hospitalized SARI cases in the SIVEP-Gripe, we selected 11,074 women aged 10-49 who were pregnant (7,964) or recently pregnant (3,110). COVID-19 was confirmed in 49·4% cases; 1·7% had influenza or another etiological agent; and 48·9% had SARI of unknown etiology. The *pardo* race/ethnic group accounted for 50% of SARI cases. Hypertension/Other cardiovascular diseases, chronic respiratory diseases, diabetes, and obesity were the most common comorbidities. A total of 362 women with COVID-19 (6·6%; 95%CI 6·0-7·3) died. Mortality was 4·7% (2·2-8·8) among influenza patients, and 3·3% (2·9-3·8) among those with SARI of unknown etiology. The South-East, Northeast and North regions recorded the highest frequencies of mortality among COVID-19 patients.

Conclusion: Mortality among pregnant and recently pregnant women with SARIs was elevated among those with COVID-19, particularly in regions where maternal mortality is already high.

A case study and proposal for publishing pre-analytic directed acyclic graphs: The effectiveness of the quadrivalent HPV vaccine in perinatally HIV exposed girls Ruby Barnard-Mayers Hiba Kouser Jamie Cohen Katherine Tassiopoulos Ellen Caniglia Anna-Barbara Moscicki Nicole Campos Michelle Caunca George Seage III Eleanor Murray

Developing a causal graph is an important step in etiologic research planning and can be used to highlight data flaws and irreparable bias and confounding. However, there has been little guidance on how to build or report a causal graph for applied health research. Here, we present a step-by-step approach to constructing and reporting a causal graph, using as a case study the effectiveness of the quadrivalent human papillomavirus (HPV) vaccine in girls with perinatal HIV.

Recent findings have suggested that the human papillomavirus (HPV) vaccine is less effective in protection against HPV associated disease for people living with HIV. In order to understand the relationship between HIV status and HPV vaccine effectiveness, it is important to outline the key assumptions of the causal mechanisms before designing a study to either corroborate or challenge these findings.

We describe the process of building a causal graph and determining the resulting analytic approach required to investigate this relationship. We outline a format for justifying the inclusion and omission of arrows and nodes from the causal graph and discuss the key assumptions made by the graph, as well as implications for the analysis. We differentiate between a causal graph based on general knowledge and one designed for our specific dataset of interest, which can introduce additional nodes and arrows to consider. Finally, we outline a process for requesting peer feedback on assumptions prior to conducting data analysis.

Does respiratory syncytial virus infection cause pediatric asthma? Examining the relationship between birth timing relative to respiratory syncytial virus peak and subsequent asthma in Ontario, Canada Michelle Dimitris Daniel Feikin Erin Sparrow Sue Schultz Jeffrey Kwong Deshayne Fell

Most infants are exposed to respiratory syncytial virus (RSV) in their first year of life, and studies find higher risk of asthma among infants with early severe RSV infection. Yet, it is unclear whether this relationship is causal or due to susceptibility to both conditions. We leveraged random variation in week of birth relative to RSV season to investigate the relationship between RSV infection and pediatric asthma. We used province-wide health administrative databases to identify all births from April 2002-March 2013 in Ontario, Canada. Infant age at RSV peak was calculated by subtracting the week of birth from the calendar week during the infant's first RSV peak, defined as the week with the highest proportion of RSV-related hospitalizations among infants ≤1 year. Asthma was identified using ICD-9/10 codes for ≥1 inpatient and/or ≥2 outpatient visits for asthma by 5 years, with ≥1 visit from 3-5 years. We analyzed the relationship between infant age at RSV peak and asthma using logistic regression, adjusting for infant sex, year of birth, baseline maternal characteristics, and fitting splines for continuous variables. We plotted risk of asthma alongside population-level RSV and influenza surveillance data by infants' week of birth. Marginally higher risk for asthma was observed at approximately 13-16 weeks' infant age at RSV peak, and did not change in sensitivity analyses that broadened/restricted the asthma definition. When plotted by infant week of birth offset by 13 weeks, the peaks of asthma followed population-level seasonality of both RSV and influenza. Our results replicate a similar study from the United States, which found highest risk of asthma at 17 weeks' infant age at winter virus peak. We add that the magnitude of temporal peaks in pediatric asthma follows those of both RSV and influenza, suggesting that both viruses and/or other seasonal factors may play a causal role. If causal, RSV appears to be only one minor contributor to pediatric asthma.

Infectious disease

Differential and age-dependent seropositivity for SARS-CoV-2 in elementary versus early year high school-aged children from areas with low versus high community transmission Joanna Merckx Lise Boey Mathieu Roelants Niel Hens Isabelle Desombere Els Duysburgh Corinne Vandermeulen

Background

Community transmission levels are thought to impact transmission dynamics of SARS-CoV-2 in children. It is unclear how transmission severity translates in infection rates in the pediatric population and if there are differences between elementary school children and young teenagers. Repetitive evaluation in the pediatric population requires child friendly sampling methods for seroprevalence studies. Our objective was to validate saliva testing for antibody detection and simultaneously to assess to which extent community transmission is reflected in pediatric infection.

Methods

We designed a representative cross-sectional seroprevalence survey that compared the SARS-CoV-2 attack-rate in a sample of 362 children recruited from September 21 to October 6, 2020 in primary (ages 6-12) or lower secondary schools (ages 12-15), in a municipality with low (142/100,000 inhabitants/14-days) versus high (946/100,000/14-days) peak cumulative community transmission during the first epidemic wave in Belgium. The sample size was designed to detect a 6-8% difference in the prevalence for a baseline prevalence of 5-8% with a power of 80% and was determined by the diagnostic performance characteristics of the enzyme-linked immunosorbent assay. Blood and oral fluid samples were tested in pairs.

Results

We found anti-SARS-CoV-2 antibodies in 4.4% (95%CI 0.7-8.1) and 14.4% (95%CI 8.2-20.5) of children in the low and high transmission region, respectively. None of the primary schoolchildren were seropositive in the low transmission region, whereas the seroprevalence among primary and secondary schoolchildren did not differ in the high transmission region. Data-analysis on the validation of the oral samples is still pending.

Conclusion

High level SARS-CoV-2 circulation is reflected in the pediatric population with similar seroprevalence in children aged 6-12 and 12-15 years and differs from the distribution of the seroprevalence in low-transmission areas.

Evaluating sexually transmitted infections and hypertensive disorders of pregnancy in older women Brandie Taylor Akaninyene Noah Ashley Hill Maria Perez-Patron Tyne Hernandez

Hypertensive disorders of pregnancy (HDP) are increasingly common, and the most severe forms can lead to serious maternal morbidity and mortality. Genital infections are not typically considered major risk factors for HDP and often these conditions are not examined in perinatal studies of common sexually transmitted infections including *Chlamydia trachomatis* (CT), syphilis, and *Neisseria gonorrhoeae* (GC). Our prior research suggested that CT may increase preeclampsia risk at term in young adults. Trends were observed in older women, but these women are not typically screened for CT and GC and thus excluded from studies. To expand on this work, we restricted this analysis to older women > 25 years. We used data from 27,442 single pregnancies without HIV enrolled in Peribank between July 2011 and September 2020. STIs were measured in 98.5% of women and 4% had CT, 0.7% had syphilis, and 0.4% had GC. Most women are Hispanic, on Medicaid, and are overweight/obese with a mean age of 32 years. Outcomes included gestational hypertension, mild preeclampsia, severe preeclampsia, superimposed preeclampsia, and preeclampsia with a preterm delivery. Logistic regression was used to calculate ORs and 95% CIs, the penalized likelihood approach was used when necessary. Analyses were adjusted for race, age, foreign born status, sociodemographic variables, substance use, other infections, and prior complications. E-values were calculated to examine robustness to unmeasured confounding. Syphilis was associated with gestational hypertension (OR 1.8, 95% CI 1.1-2.9). GC was associated with preterm preeclampsia (OR 5.6, 95% CO 1.7-18.4) and severe preeclampsia (OR 4.1, 95% CI 1.3-13.2). CT was associated with superimposed preeclampsia (OR 1.7, 95% CI 1.0-2.5). With the striking reemergence of STIs and lack of universal screening for GC and CT among older women, there is a need to revisit the burden of STIs in pregnant women.

The Variations in the Effect of Foreign-Born Status (FBS) on Sexually Transmitted Infections among Expecting Mothers by Race/Ethnicity. Akaninyene Noah Ashley Hill Maria Perez-Patron Camillia Comeaux Brandie Taylor

Prior research on the epidemiological paradox and healthy migrant effect show foreign-born status (FBS) offers some protective effect against adverse birth outcomes—although the effect's magnitude can differ by race/ethnicity. Sexually transmitted infections (STI) are associated with adverse birth outcomes such as preterm birth and growth restriction. However, studies have yet to examine (1) the link between FBS and common STIs among pregnant women and (2) if these associations vary by race/ethnicity. Our study population included 38,786 singleton pregnancies, mean age of 29.3 years, enrolled in Peribank between July 2011 and September 2020. The population was 21% non-Hispanic (NH) White, 15% NH Black, 58% Hispanic, and 6% other race. Fifty-two percent were born outside the US. We examined the association between FBS and *Neisseria gonorrhoeae* (GC), syphilis, and *Chlamydia trachomatis* (CT), prevalent in 0.5%, 4% and 0.7% of the cohort, respectively. We conducted a stratified analysis using logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI) for the entire population and subgroups by race/ethnicity, the penalized likelihood approach was used when needed. Our model was adjusted for age, socioeconomic variables, substance use, mental health status, chronic health conditions, co-infections, and prior maternal complications. We examined all three STIs, combined and individually, and noticed similar results. Before stratification, FBS was associated with lower odds of combined infection (OR 0.8, 95% CI 0.7 – 0.9) compared to US born women. After stratification, FBS was only associated with lower odds of infection among NH Blacks (OR 0.6, 95% CI 0.4 – 0.8). NH Whites (OR 0.5, 95% CI 0.2 – 1.2) and Hispanics (OR 0.9, 95% CI 0.7 – 1.0) did not show statistically significant association with infection. Future studies should examine factors that may reduce STI odds, especially among Foreign-Born NH Black women to shape prevention strategies.

Prenatal antidepressant medication usage patterns and delivery outcomes among preconception users Nerissa Nance Sylvia E. Badon Kathryn K. Ridout De-Kun Li Lyndsay Avalos

Introduction

Antidepressant medication use is common and effective in reproductive-aged women. Little is known about antidepressant use patterns in pregnancy and their effects on delivery outcomes among women with preconception use. This study described patterns of antidepressant use among these women and examined associations between usage patterns and delivery outcomes.

Methods

We conducted a retrospective cohort study of women with live births at Kaiser Permanente Northern California (2014-2017) and an antidepressant fill in the 6 months prior to pregnancy that overlapped with the 8th week of pregnancy. Using electronic health records, we identified whether women continued use (refilled throughout pregnancy), stopped and reinitiated (refill after 30+ day gap in supply), or discontinued (no refills). We used Poisson regression to examine the association between these patterns and preterm birth and Neonatal ICU (NICU) admission, adjusting for demographic characteristics and depression severity.

Results

Among 3,246 women with preconception antidepressant use, 33% continued use throughout pregnancy, 20% stopped and reinitiated, and 47% discontinued after early pregnancy. A greater proportion of women who continued use were college graduates and non-Hispanic white. Women who stopped and reinitiated or discontinued use had 38-46% lower risk of preterm birth and NICU admission than women who continued use (Table).

Conclusions

Nearly half of women with preconception antidepressant medication use discontinued use during early pregnancy. Early pregnancy antidepressant users who continue use may be at higher risk of adverse delivery outcomes, which may reflect underlying depression severity and should be considered alongside risk of depression relapse in pregnant women.

Mental health

Opportunities for Prevention of Pregnancy-Related Deaths from Mental Health Conditions: Data from 14 US Maternal Mortality Review Committees, 2008–2017 Susanna Trost Jennifer Beauregard Ashley Smoots Jean Ko Sarah Haight Tiffany Moore Simas Nancy Byatt Sabrina Madni David Goodman

Each year, approximately 700 persons die in the United States from pregnancy-related complications. Maternal Mortality Review Committees (MMRCs) are uniquely positioned to evaluate the events in a pregnant or postpartum person's life and surrounding their death. We describe the characteristics of pregnancy-related deaths due to mental health conditions and identify opportunities for prevention based on MMRC recommendations. Data voluntarily shared by 14 state MMRCs for 2008-2017 were analyzed. Pregnancy-related mental health deaths were defined as deaths during or within one year of the end of pregnancy from a pregnancy complication, a chain of events initiated by pregnancy, or an aggravation of an unrelated condition by the physiologic effects of pregnancy, where mental health conditions were the underlying cause, including all suicides, as well as overdoses of unintentional or unknown intent where substance use disorder was indicated. Chi-square or Fisher's Exact tests were used to assess differences between pregnancy-related mental health deaths and pregnancy-related deaths from all other causes. Substance use, mental health conditions, and life stressors were identified through review of abstracted records. Among 421 pregnancy-related deaths from 2008-2017 with an underlying cause of death determination, 46 (11%) were classified as pregnancy-related mental health deaths. Compared to deaths from other causes, pregnancy-related mental health deaths were more likely to be determined preventable (100% vs 64%), occur among non-Hispanic White persons (86% vs 45%), and occur 43-365 days postpartum (65% vs 18%). Among the pregnancy-related mental health deaths, 63% were suicides, 24% were unintentional overdoses, and 13% were classified as *other causes.* MMRC recommendations can be used to prioritize strategies for eliminating future pregnancy-related deaths from mental health conditions, and for broader improvements in maternal mental health.

Mental health

Social Isolation among Mothers Caring for Infants in Japan: Findings from the Nationwide Survey of Healthy Parents and Children 21 Sayaka Yamazaki Zentaro Yamagata

Objectives: Child-rearing isolation may increase the risk of child abuse and negatively affect child development; however, the prevalence of this phenomenon has increased owing to increased urbanization and declines in family and community support systems. **Methods:** This study aimed to identify the prevalence of child-rearing isolation and related sociodemographic factors among mothers in Japan using data from the Final Survey of Healthy Parents and Children 21. Respondents were mothers of young children attending their 3–4 month, 18-month, and 3-year health examinations. **Results:** Data from 69,337 women were analyzed using logistic regression analysis. In total, 0.2% of mothers experienced child-rearing isolation. Mothers who were 35- to 39-years-old at childbirth (OR = 1.6, 95% CI[1.0, 2.4], p = .036), unemployed (OR = 1.7, 95% CI[1.3, 2.4], p = .001), experiencing financial difficulty (OR = 1.8, 95% CI[1.3, 2.5], p < .001), having husbands who had limited participation in child-rearing (OR = 5.7, 95% CI[4.2, 7.9], p < .001), and those living in special wards in Tokyo Metropolis (OR = 4.2, 95% CI[2.2, 8.3], p < .001), having concerns regarding abusing their child (OR – 2.1, 95% CI [1.5, 2.9], p < .001) and having no time to relax with their child (OR = 4.5, 95% CI [3.1-6.7], p < .001) had higher odds for child-rearing isolation, compared to those not meeting those criteria. **Conclusions for Practice:** The results highlight the importance of fathers' involvement in child-rearing and need for support to mothers to reduce child-rearing isolation.

Mental health

Early childhood exposure to food insecurity and adolescent mental health in the United States Marine Azevedo Da Silva Sara Mohammadi Frank Elgar

Although evidence suggests that food insecurity (FI) has a detrimental impact on a range of psychosocial outcomes for children, it is unclear if early childhood FI itself is associated with long-term mental health problems. Previous research has relied on measures of household FI, which may not accurately reflect the degree of FI experienced by a child. Indeed, children are often shielded from experiencing FI by their parents. We investigated the association between child FI and adolescent depression and anxiety symptoms.

We used data from the Fragile Families and Child Wellbeing Study, a birth cohort study of 4898 children born in large U.S. cities between 1998-2000. Household and child FI measures were assessed at ages 3-5 using the 18-items US Department of Agriculture Food Security Module. Symptoms of depression and anxiety were respectively measured at age 15 by the Center for Epidemiologic Studies Depression Scale and the Brief Symptom Inventory. Negative binomial regression models were used to estimate the association between early childhood FI and adolescent mental health.

The final analytic samples were nearly 3000 children. After controlling for sociodemographic factors, health-related behaviors, and caregiver depression, household FI at age 3-5, but not child-specific FI, was associated with higher rates of depressive symptoms and anxiety at year 15. In a sensitivity analysis, disaggregating the household food security status in food-secure household, food-insecure household with shielded child, and food-insecure household with non-shielded child, we surprisingly found that only shielded children living in food-insecure households had higher rates of symptoms of depression and anxiety in adolescents compared to child living in a food-secure household.

Shielding could have negative social consequences on families (such as partners or family conflicts, scapegoats) that might be alleviated when every family member suffers from FI.

Policy

A Narrative Review of State-level Health Policies and their Association with Perinatal and Infant Outcomes Jessica Webster David Paul Jonathan Purtle Robert Locke Neal Goldstein

Introduction: Rates of preterm birth and infant mortality are alarmingly high in the U.S. Legislated efforts to reduce adverse perinatal and infant outcomes in the U.S. include the enactment of certain economic and social policies.

Methods: We conducted a narrative review to summarize the associations between perinatal and infant outcomes and four state-level U.S. policies. The four selected policy measures included 1) tax credits including the Earned Income Tax Credit, childcare, and child and dependent care, 2) paid parental leave, 3) minimum wage, and 4) tobacco or cigarette tax. The outcomes of interest included but were not limited to pregnancy loss, infant mortality (including Sudden Infant Death Syndrome), and (low) birth weight. A latent profile analysis was conducted to operationalize an unobserved categorical variable based on the observed policy indicators.

Results: Out of 26 articles identified, eight focused on child or dependent tax credits, eight on paid parental leave, four on minimum wage, and six on cigarette tax. All but three studies found that the implementation of each of these policies was associated with an improvement in perinatal or infant outcomes. The latent profile analysis revealed three policy profiles, with the most expansive policies in Western and Northeastern U.S. states, and the least expansive policies in the U.S. South.

Conclusion: These four legislative efforts have the potential to improve perinatal and infant outcomes in the U.S. Future research should examine how the combination of these legislative efforts has collectively impacted perinatal and infant outcomes in the U.S.

Pregnant in a pandemic: Mental well-being and associated health behaviors among California pregnant people during COVID-19 Jennifer Phipps Mackenzie Whipps Indira D'Souza Kirby Lee Leigh Ann Simmons

Perinatal mental health disorders are the most common complications of pregnancy. The recommended COVID-19 mitigation behaviors (e.g., social distancing, limiting interactions to one's "pod") make the social supports typically recommended for individuals with mental health disorders and birthing people less accessible. Pregnant people are limiting healthcare visits due to worry of COVID-19 infection, reducing the likelihood that they are screened for mood disorders. The purpose of this investigation was to better understand how COVID-19 has affected the mental health and associated health behaviors of pregnant people in California in order to identify risks and opportunities for intervention.

We performed a cross-sectional survey of 465 pregnant people in California from June 6 through July 29, 2020. Average maternal age was between 25-34 (58.9%), 34.4% identified as Hispanic and 46.2% identified as non-White; 47.8% of our cohort was primiparous and 49.7% was multiparous. Using the PHQ-2 and GAD-2 surveys, we found that 22% of our cohort reported clinically significant depression and 31% reported clinically significant anxiety. Multiparous women worried more about their birth experience and their own health than primiparous women ($p=0.040$ and $p=0.044$, respectively). We assessed sleep, nutrition and physical activity and found that each were associated inversely with anxious-depressive symptomology ($p<0.001$, for each), while controlling for maternal age, urbanicity, financial insecurity, race, and ethnicity, though this relationship did not differ significantly between primiparous and multiparous people.

This study demonstrated higher rates of depression and anxiety than previously reported; health behaviors were poor and worries significant. While concerning, the pandemic also may offer opportunities to leverage technology to increase remote access to mental health screening and intervention resources, including those that increase health-promoting behaviors.

Using an Intersectional Approach to Examine the Relationship Between Early Adolescent Substance Use and Later Depressive Symptoms Tess Marusyk Colleen Davison

Substance use has been associated with depression in adolescence and earlier initiation may be especially problematic. Social locations, such as those defined by gender, race, or socioeconomic status (SES), have been associated with early adolescent substance use and adolescent depression. However, their effects have primarily been examined independently, whereas Intersectionality Theory suggests they work synergistically. In a Canadian context, the objectives are to (1) provide a descriptive analysis of early substance users considering intersecting social locations (gender, race, and SES); (2) examine the overall association between early substance use and depressive symptoms later in adolescence; and (3) evaluate potential differences in the relationship at varying intersections of gender, race, and SES. This contemporary analysis uses a nationally representative sample of adolescents in grades 9 and 10 (n=7,933) from the 2018 Health Behaviour in School-aged Children Study. Reported alcohol, cigarette, or cannabis use prior to age 14 is considered early substance use. Depressive symptoms are measured by asking, "During the past 12 months, did you ever feel so sad or hopeless almost every day for two weeks or more in a row that you stopped doing some usual activities?". A descriptive and multilevel, multivariable analysis is being conducted, using two- and three-way stratification by gender, race, and SES. Preliminary results have shown that approximately one in four adolescents reported early substance use and over one-third reported experiencing recent depressive symptoms. Early substance use was associated with later depressive symptoms (p<0.0001). The forthcoming regression model will estimate the relative risk for the overall sample and each stratified subgroup. This analysis using an intersectional lens may help better explain the relationship between early substance use and later adolescent depression and help identify particular subgroups at greater risk.

Maternal serotonergic antidepressant use in pregnancy and risk of seizure outcomes in children Kelsey Wiggs Ayesha Sujan Martin Rickert Patrick Quinn Paul Lichtenstein Sara Oberg Brian D'Onofrio

Objective: To evaluate whether children born to women who use serotonergic antidepressants during pregnancy have higher risk of newborn convulsions or epilepsy.

Methods: We used Swedish register-based data to examine associations between maternal-reported first trimester use of selective-serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and ICD-9 and ICD-10 diagnoses of 1) newborn convulsions in a sample of 1,469,875 offspring (born January 1st, 1996 to November 30th, 2013) and 2) epilepsy in a sub-cohort of 1,285,056 offspring (born January 1st, 1996 to December 31st, 2011). In the sub-cohort with available prescribed drug data (born 2006-2013), first trimester reports showed 98.5% of agreement with the filling of a prescription in the second or third trimester, supporting our assumption that these drugs are used throughout pregnancy. We fit logistic regression models that accounted for a wide range of measured confounders, including pregnancy-related characteristics, maternal and paternal individual characteristics, and family socioeconomic characteristics.

Results: Overall, maternal use of SSRIs/SNRIs in pregnancy was associated with an elevated risk of newborn convulsions (odds ratio [OR]=1.41, 95% confidence interval [CI]=1.03-1.94). After adjustment for maternal indications, parental epilepsy, and other covariates, the association was almost entirely attenuated (OR=1.10, 95% CI=0.79-1.53). Similarly, we observed increased risk of epilepsy diagnosis in children related to SSRIs/SNRI use in an unadjusted model (hazard ratio [HR]=1.21, 95% CI=1.03-1.43), though this association was completely attenuated after adjustment for maternal indications, parental epilepsy, and the remaining covariates (HR=0.96, 95% CI=0.81-1.14).

Conclusions: The present study found no evidence of a causal association between maternal use of either SSRIs or SNRIs in pregnancy and neonatal convulsions, and epilepsy in children.

Vitamin D and semen quality in an infertility treatment-seeking population Sunni Mumford Lindsey Sjaarda Douglas Carrell Jim Hotaling Brad Van Voorhis Abey Eapen James Mills Zhen Chen Enrique Schisterman Erica Johnstone

Background: Vitamin D is hypothesized to play a key role in male reproduction as vitamin D receptors and metabolizing enzymes are expressed in the testis and prostate and have been shown to impact the male androgenic hormone axis. However, reported associations between vitamin D levels and semen quality are inconsistent.

Methods: In a longitudinal study of men (n=2369) seeking infertility care, serum 25(OH)D was measured at baseline and semen quality was assessed using standardized procedures by quantification of sperm concentration, volume, motility, morphology, count, and total motile count at baseline and 6-months post-enrollment and with DNA fragmentation at 6-months. The data were analyzed using weighted linear regression adjusted for age, body mass index, race, season at enrollment, abstinence time, income, and multivitamin use. Vitamin D status was categorized as deficient (<20 ng/mL, reference), insufficient (20-29.9 ng/mL), or sufficient ($\geq$30 ng/mL).

Results: Overall, 29% of men had deficient levels of 25(OH)D at baseline, 41% were insufficient, and 30% were sufficient. 25(OH)D status was not associated with semen quality parameters assessed at baseline. 25(OH)D was also not associated with semen quality parameters at 6-months post-enrollment (percent change in total motile sperm count: 4%, 95% CI: -31%, 57% sufficient vs deficient; -13% (-39%, 25%, insufficient vs deficient). No associations were observed with sperm DNA fragmentation (β=0.1, 95% CI: -3.8, 3.9 sufficient vs deficient; β=1.6, 95% CI: -1.6, 4.7 insufficient vs deficient).

Conclusions: 25(OH)D levels were not associated with semen quality parameters in a cohort of men seeking infertility care who underwent multiple, standardized assessments of semen quality. Future research should investigate whether 25(OH)D in the male partner is related to pregnancy and its outcomes, irrespective of semen quality metrics.

A descriptive study of prescription and over-the-counter medication use among pregnancy planners in the United States and Canada Holly Crowe Amelia Wesselink Lauren Wise Elizabeth Hatch

Pregnancy planners may seek to decrease their medication use to minimize potentially harmful exposures before pregnancy detection. However, most research focuses on medication use during pregnancy or use of known teratogens. We used data from an online preconception cohort study to describe medication use among women trying to conceive, a hard-to-reach population. From 2013 through 2020, we enrolled 12,467 eligible female pregnancy planners. At baseline, women reported ever-diagnoses of several common conditions: urinary tract infection, depression, anxiety, migraine, asthma, bacterial vaginosis, polycystic ovarian syndrome, hayfever, chlamydia, thyroid disorder, gastroesophageal reflux disease, herpes, genital warts, endometriosis, fibroids, diabetes and pelvic inflammatory disease. Urinary tract infections (59%), depression (25%), and anxiety (25%) were the most frequently reported conditions. Although medication for these conditions are generally safe to use during pregnancy, some antibiotics and psychiatric medications are of unknown risk or contraindicated. Women reported prescription or over-the-counter medication use for these conditions or other indications during the past 4 weeks. Overall, 81% of women reported any recent medication use; 29% used pain medication, 36% used medication for a common condition and 18% used medication for other indications. Of the women using medication for a common condition, 18% used medication for migraines (9% of the overall cohort), 15% used medication for depression (8% of the overall cohort) and 15% used medication for anxiety (8% of the overall cohort). Of the women using medication for other indications, 17% used antihistamines, 6% used decongestants, 6% used antidepressants, 5% used steroids, and 5% used stimulants. Additional research into potential reproductive effects of migraine medications, depression and anxiety medications, antihistamines, and other commonly used medications among pregnancy planners is warranted.

History of infertility and long-term weight, body composition, and blood pressure among women in Project Viva Diana C. Soria-Contreras Emily Oken Martha M. Téllez-Rojo Sheryl L. Rifas-Shiman Wei Perng Jorge E. Chavarro

Background. In cross-sectional and case-control studies, infertility has been associated with higher body mass index and waist circumference. Evidence from prospective studies in a general-risk setting is limited.

Objective. To evaluate the association of a history of infertility with long-term weight, body composition, and blood pressure.

Methods. 1581 women participating in the Boston area cohort Project Viva**.** We assessed history of infertility before the index pregnancy based on: self-reported time to pregnancy ≥12 months or use of medical treatment to conceive for the index or any prior pregnancy; a diagnosis of infertility; claims for infertility treatments or prescriptions abstracted from medical records. The outcomes were weight, waist circumference, and body fat assessed at study visits from 6 months through 12 years postpartum; and blood pressure assessed at 6 months and 3 years postpartum. We used linear mixed-effect models accounting for age at the time of outcome assessment, and adjusted for age at study enrollment, race/ethnicity, annual household income, education, marital status, parity, age at menarche, and BMI before the index pregnancy.

Results. 342 women (21.6%) had a history of infertility. We found that women with vs. without a history of infertility had higher average weight (3.27 kg, 95% CI: 1.33, 5.22), waist circumference (2.45 cm, 95% CI: 0.77, 4.12) and body fat (1.76 kg, 95% CI: 0.09, 3.42) across 12 years of follow-up. Among younger (18-29 years), but not older (≥30 years) women, a history of infertility was associated with higher SBP (4.07 mmHg, 95% CI: 0.91, 7.23) and DBP (2.15 mmHg, 95% CI: 0.11, 4.20) through 3 years of follow-up.

Conclusion. Among parous women, a history of infertility is positively associated with weight, waist circumference, body fat, and blood pressure through 12 years of follow-up. A history of infertility may serve as a marker to identify women at higher risk of cardiometabolic disease.

Men's health

A North American prospective cohort study of sugar-sweetened beverages consumption and semen quality Marlon Joseph Lauren Wise Amelia Wesselink Tanran Wang Michael Eisenberg Greg Sommer Kenneth Rothman Sherri Stuver Elizabeth Hatch

Background: In the United States, the amount of sugar in the American diet increased by 19% between 1970 and 2005, mainly due to the consumption of sugar-sweetened beverages (SSB). Dietary factors, including high sugar intake from SSB, may have adverse effects on male reproductive health. Few studies have examined the consumption of SSB in relation to semen quality.

Objective: We prospectively evaluated the association between male SSB consumption and semen parameters.

Methods: We analyzed data from 375 men (654 samples) participating in a semen testing substudy of Pregnancy Online Study (PRESTO), a preconception cohort of North American couples. After enrollment, male participants aged ≥21 years were invited to perform at-home semen testing using the Trak™ system. SSB consumption and covariate data were obtained via baseline questionnaire. We estimated the percent difference in mean log-transformed semen parameter values (%D) and 95% confidence intervals (CI) for associations between SSB intake and semen volume (mL), total sperm count (TSC, million), sperm concentration (million/mL), motility (%) and total motile sperm count (TMSC, million), adjusting for potential confounders.

Results: Adjusted %Ds (CIs) comparing seven or more (7+) SSB per week vs. none were -1.8 (-12.5, 10.1), -32.1 (-51.1, -5.9), -33.3 (-51.5, -8.5), -10.2 (-23.0, -0.6) and -40.2 (-58.4, -14.1) for semen volume, sperm concentration, TSC, motility, and TMSC, respectively. Adjusted risk ratios (95% CIs) for the association between SSB consumption and World Health Organization low semen parameters cut-points, comparing 7+ SSB per week vs. none were 0.67 (0.35, 1.27), 1.72 (1.05, 2.80), 2.00 (0.96, 4.18), 1.67 (1.05, 2.64), and 2.06 (1.02, 4.31) for low semen volume (<1.5 ml), low sperm concentration (<15 million/ml), low TSC (<39 million), low motility (<40%), and low TMSC (<16 million), respectively.

Conclusion: Greater total SSB consumption was associated with reduced semen quality.

Methods

Feasibility of app-based recruitment for a time-to-pregnancy (TTP) study Anne Marie Jukic
Donna Baird Danielle Bradley

Menstrual cycle tracking apps (MCTAs) are commonly used by young, reproductive-aged women. MCTA-based populations have great potential for TTP studies due to their millions of users, accessibility by women across geography and income strata, and their detailed collection of menstrual cycle characteristics. However, little is known about the demographic characteristics of MCTA users, their reproductive history, their health conditions related to fertility, and their pregnancy attempt time when they begin using the app. Moreover, response rates to directed questionnaires would also be important for approximating sample size in research studies. Given the potential of MCTAs to contribute to TTP studies, characterization of MCTA-based study populations is crucial. We administered a questionnaire to approximately 300 MCTA users that characterized multiple factors for both women and their partners, including demographics and their decision-making around attempting pregnancy. In 12 days, a total of 90,725 emails were delivered, 10,193 were opened, and ultimately 605 women answered the survey. Of these, 56% were currently attempting pregnancy and 86% were doing so without medical interventions. Of the women who were not currently trying, 12% cited COVID19 as a reason; 12% planned to try in 3 months. Of those attempting pregnancy without medical treatments, 70% were of white race, 13% were black/African-American, 6% were Asian, and 13% were Hispanic. Most respondents had at least a college degree (56%), were married or living with a partner (74%), and had a total income of $100,000 or less (62%). A single survey provides enough TTP information for a current duration analysis. The mean duration of attempt time was 13 months, the median was 5 months; 25% had been trying for two months or less; 40% of partners agreed to participate. This study provides fundamental information for recruiting women and their partners into a prospective or cross-sectional TTP study using an MCTA.

Factors associated with enrollment and retention in a North American internet-based preconception cohort Ruth J. Geller Olivia R. Orta Renée Boynton-Jarrett Amelia K. Wesselink Tanran Wang Jessica Sara Levinson Maya Thirkill Martha Rose Koenig Marlon D. Joseph Sydney Willis Mary Willis Elizabeth E. Hatch Lauren A. Wise

Background: Racial and socioeconomic disparities in fertility exist in the US, yet most fertility research is conducted in high-socioeconomic status, majority-white cohorts. Internet-based studies provide an opportunity to recruit more diverse participants into preconception cohorts.

Methods: We analyzed data collected in 2013-2020 from Pregnancy Study Online, a North American internet-based prospective cohort study of women age 21-45 years who are not using contraception or fertility treatments. We examined demographic characteristics (age, race/ethnicity, educational attainment, and annual household income [HHI]) of participants and tabulated them against factors related to study participation: pregnancy attempt time at enrollment, enrollment source, survey breakoff (starting but not completing the enrollment survey), and loss to follow-up.

Results: Among 13,470 women, the mean (SD) age at enrollment was 30 (4.2) years; 18% identified as women of color (e.g., Latina, 7%; non-Hispanic Black, 5%); 8% had ≤12 years of education, and 24% had HHI <$50,000. Age 40-45, non-Hispanic Black or American Indian/Alaska Native race/ethnicity, ≤12 years of education, and HHI <$50,000 were associated with longer pregnancy attempt time at enrollment. Recruitment via Facebook yielded the highest proportion of women with ≤12 years of education and HHI <$50,000 compared with other sources (e.g., pregnancy-related websites and other social media). Survey breakoff was highest among non-Hispanic Black women (36%, compared with 17-32% in other race/ethnicity groups). The majority (54%) of women with HHI <$50,000 were lost to follow-up, compared with 16% of women with HHI ≥$150,000.

Conclusions: Sustainable commitments from fertility researchers are needed to recruit and retain women of color and women across a wide range of educational backgrounds and income in order to advance reproductive health equity. Future qualitative work will examine factors related to study participation in depth.

Added sugar intake as measured by ecological momentary assessment versus 24-hour dietary recall during pregnancy Yu-Hsuan Lai Serwaa Omowale Meredith Wallace Stephen Rathbun Tiffany Gary-Webb Esa Davis Lora Burke Dara Mendez

Background: The literature examining dietary intake in real-time compared to other methods that require recall is very limited. We compared the use of ecological momentary assessment (EMA) with smartphone technology and 24-hour dietary recalls (24h recalls) in assessing the consumption of added sugar intake during pregnancy.

Methods: Data were obtained from a prospective longitudinal study that examines factors associated with racial disparities in postpartum weight retention and cardiometabolic health. Participants completed two 24h recalls (one self-administered and one interviewer-administered) that were approximately one to six weeks apart during the second to third trimester of pregnancy. The mean of added sugar in teaspoon equivalents was obtained from the two recalls. Over each 28-day block, EMA end-of-day surveys assessed the intake of added sugar foods and drinks on 10 weekdays and 4 weekend days. We examined EMA responses between the first 24h recall and two weeks after the second recall. This analysis includes descriptive statistics, correlations, and cross-classification of tertiles describing the relationship between the EMA and 24h recall data measuring added sugar intake.

Results: There were 1,125 EMA assessments. The sample (N = 222) was on average 29.9 years of age, 63.1% White, 58.6% college-educated or higher, and 55.9% employed full time. The mean number of added sugar items consumed per day was moderately positively correlated with the mean added sugar in teaspoon equivalents (ρ=0.38, p<0.0001). The percentage of exact agreement between the two measures, where participants were classified in the same tertile, was 44.1%. The percentage of extreme disagreement (classified in opposite tertiles) was 9.5%.

Conclusions: EMA measures of added sugar intake captured key elements that were measured in 24h recalls. These findings contribute to current gaps in knowledge regarding assessment of added sugar intake in pregnant populations.

A prospective study of the Dietary Inflammatory Index and fecundability Sydney Willis Elizabeth Hatch Amelia Wesselink Ellen Mikkelsen Anne Sofie Laursen Katherine Tucker Kenneth Rothman Sunni Mumford Lauren Wise

The current global dietary trend toward greater consumption of added sugars and saturated fat coupled with insufficient consumption of fruits, vegetables, and whole grains has been associated with elevated inflammatory markers. The Dietary Inflammatory Index (DII) was designed to measure the effect of diet on inflammation in the body. There is accumulating evidence that dietary exposures associated with inflammation (e.g., high glycemic load) are associated with reduced fertility. We evaluated the association between the DII and fecundability, the per-cycle probability of conception, in two preconception cohorts of pregnancy planners not using fertility treatment or contraception at baseline: Snart Foraeldre in Denmark and Pregnancy Study Online (PRESTO) in North America. Participants completed a baseline questionnaire to ascertain data on demographic and lifestyle factors. Ten days later they were invited to complete a validated food frequency questionnaire (FFQ). We used each respective FFQ to calculate the DII. Participants completed bimonthly follow-up questionnaires for up to 12 months or until pregnancy, whichever came first. We restricted our analyses to 3,429 Snart Foraeldre and 5,803 PRESTO participants attempting pregnancy for ≤6 cycles at entry. We used proportional probabilities regression models to estimate fecundability ratios (FR) and 95% CIs, adjusted for lifestyle and demographic factors. Greater DII, indicative of a diet associated with greater inflammation (i.e., poorer diet quality), was associated with reduced fecundability in both Snart Foraeldre and PRESTO (DII ≥-1.5 vs <-3.3: FR=0.83, 95% CI: 0.71-0.97 and FR=0.82, 95% CI: 0.73-0.93, respectively). We observed a monotonic inverse relation between DII and fecundability when modeled using restricted cubic splines. These results support the hypothesis that an inflammatory mechanism may explain, in part, how diet quality influences fecundability.

Racial and Ethnic Disparities in Low Birthweight and very Low Birthweight Infant Mortality in the US 1995-2017 Yousra Mohamoud Charlan Kroelinger Ruben Smith Tiffany Riehle-Colarusso Cynthia Ferre

Despite declines in infant mortality rates (IMR) for low birthweight (LBW, <2,500 grams) and very low birthweight (VLBW, <1,500 grams), racial/ethnic disparities persist, particularly for Black and American Indians/Alaska Natives (AIAN) infants. However, there continues to be a need to examine disparities in all racial/ethnic groups to provide a clearer picture of more recent patterns of inequities. We used Joinpoint regression analysis to examine trends in LBW and VLBW IMRs by maternal race/ethnicity using US period-linked birth/infant death data for 1995-2017. IMRs were calculated as deaths per 1000 live births during a year, stratified by maternal race/ethnicity: non-Hispanic white (NHW), non-Hispanic black (NHB), Hispanics, American Indians/Alaska Natives (AIAN), and Asian/Pacific Islander (API). We estimated rate ratios and 95% confidence intervals (CI). IMRs for LBW and VLBW declined significantly across all racial/ethnic groups. For LBW, NHB saw the largest declines 2006-2010, but the NHB-NHW disparity ratio remained constant at 1.4 (95% CI 1.3-1.4) 1995-2017. The gaps between AIAN or Hispanics and NHW increased from 1.0 (95% CI 0.8-1.2) and 1.0 (95% CI 0.9-1.1) in 1995, respectively, to 1.4 (95% CI 1.2-1.6) and 1.2 (95% CI 1.1-1.2) in 2017. For VLBW, while the NHB-NHW gap remained constant at 1.2 (95% CI 1.1-1.2), the IMR for AIAN surpassed that for NHB from 2012 to 2017 to have the highest rate (NHB: 216 per 1000; AIAN: 232 per 1000) and a similar disparity ratio (1.2, 95% CI 1.0-1.4) in 2017. There was no difference in IMRs between API and NHW for VLBW or LBW. Disparities in mortality rates for VLBW and LBW infants varied by race/ethnicity and over time. Persistent disparities for NHB and AIAN infants warrant further review, as factors such as implicit bias or structural racism, may impact access, provision and utilization of healthcare and community services.

Birth Outcomes Among Women with Congenital Physical Disabilities Michelle Huezo Garcia Martha Werler Julie Peterson Samantha Parker

Introduction: Some literature suggests that women with congenital physical disabilities (CPD) are at an increased risk for pregnancy complications and adverse birth outcomes (e.g. low birthweight, preterm birth), however research is limited. We sought to describe maternal characteristics and birth outcomes among women with and without CPD.

Methods: Data were retrieved from the Boston University Slone Epidemiology Center Birth Defects Study, which included maternal report of personal and family history of birth defects as well details of the study pregnancy. Exposure status was defined as mothers who reported themselves having one of the following: spina bifida, cerebral palsy, muscular dystrophy, contractures, or arthrogryposis and were matched to unexposed mothers by interview year and study site. Log binomial regressions estimated relative risks (RR) for low birthweight, macrosomia, preterm birth and small/large for gestational age (SGA/LGA) in the study pregnancy. Because of overrepresentation of pregnancies affected by birth defects, the data were weighted to mimic 3% infant birth defect prevalence.

Results: Women with CPD were more likely to be white, nulliparous prior to study pregnancy, report a cesarean section, have an unplanned pregnancy, have a BMI $\geq$25kg/m^2, smoke during pregnancy, and report a vaginal or bladder infection during pregnancy. Women with CPD had a lower mean birthweight (3297 vs 3405 grams) and a shorter mean gestational length (267 vs 275 days) compared to the control group. Deliveries to women with CPD were associated with having a preterm birth (RR=4.08, 95% CI:2.64, 6.34) and SGA infant (RR=1.74, 95% CI:1.22, 2.48). There were no observed differences for other birth outcomes.

Conclusion: Women with CPD were more likely to experience adverse pregnancy outcomes, specifically preterm birth and having a SGA infant, highlighting the need for further research to identify ways to reduce adverse experiences and birth outcomes in this population.

Prevalence and correlates of learning disability among children with special healthcare needs: Evidence from the 2016-2019 National Survey of Children's Health Qiping Fan Qiping Fan Ping Ma

Background: Approximately 20% of the US children are considered as children with special healthcare needs (CSHCN). Although learning disability has been considerably studied among general US child population, less is known about learning disability among CSHCN and how it compares to healthy US child population

Objectives: To investigate the prevalence of learning disability among US children with and without special healthcare needs, and examine the correlated factors including the sociodemographic, family characteristics, and past negative childhood experience.

Methods: A cross-sectional analysis of the four-year data from parent or caregiver's responses in the 2016-2019 National Survey of Children's Health (n= 131, 774 children) was conducted. We examined several measures of learning disability reported by parents/caregivers based on healthcare provider diagnosis, including lifetime history of learning disability, current learning disability, and severity of learning disability. Negative childhood experience included victim of violence, being treated unfairly because of race, parent's divorce or service in jail, and living with people with substance abuse problems or mental illnesses. Weighted logistic regression was employed to examine the correlates of lifetime history of learning disability.

Results: Lifetime history of learning disability was significantly higher among CSHCN than non-CSHCN (24.0% vs 1.9%, *P*<.001). Among children with current learning disability, CSHCN showed a significantly higher proportion of moderate/severe learning disability comparing that among non-CSHCN (64.7% vs 31.0%, *P*<.001). Children who were male (aOR=1.7, 95% CI=1.4-2.0, *P*<.001), living in suppressed areas ((aOR=1.3, 95% CI=1.1-1.5, *P*=.005), or had any negative experience (aOR=1.3, 95% CI=1.1-1.6, *P*=.009) were more likely to report history of learning disability.

Conclusion: Intervention are warranted targeting at US children with special healthcare needs who had negative childhood experience in rural areas. Better care should be provided, and more resources should be allocated to children with high risks of developing learning disabilities to reduce health disparities.

Maternal diabetes and infant hospitalizations in Cree, other First Nations and Non-Indigenous populations in rural communities in Quebec Zhong-Cheng Luo

Objective: First Nations are at high risk for diabetes in pregnancy, including pre-gestational diabetes (PGD) and gestational diabetes (GD). Cree communities have the highest reported rate of diabetes in pregnancy in Canada. It is unknown whether diabetes in pregnancy is linked to infant morbidities. We sought to assess whether maternal diabetes is associated with infant hospitalizations in Cree, other First Nations and non-Indigenous populations in rural communities in Quebec.

Methods: In a population-based linked birth cohort study, singleton infants of Cree (n=5070), other First Nations (9,910) and non-Indigenous (48,200) mothers in rural communities in Quebec were identified by residential postcode. Maternal diabetes (pre-gestational diabetes (PGD) or gestational diabetes (GD)) and infant (<=1 year) hospitalizations were captured through linkage by medical insurance number.

Results: Maternal diabetes and infant hospitalization rates were much higher in Cree (23.7% and 29.0%) or other First Nations (12.4% and 34.1%) vs. non-Indigenous (5.9% and 15.5%) communities (all p<0.001). Compared with no diabetes, PGD was associated with an increased risk of any infant hospitalization to a greater extent in Cree [RR=1.56 (95% CI 1.28-1.91)] or other First Nations [RR=1.56 (1.32-1.85)] than non-Indigenous [RR=1.26 (1.15-1.39)] communities. PGD was associated with increased risks of infant hospitalizations due to diseases of multiple systems (respiratory system diseases, etc.) in all communities (Cree, other First Nations or non-Indigenous). The associations between gestational diabetes and the risks of infant hospitalizations were weak and non-significant. Adjustment analyses showed that the high prevalence of maternal diabetes might partly explain the excess infant hospitalizations in Cree and other First Nations communities.

Conclusions: PGD was associated with elevated risks of infant hospitalizations due to diseases of multiple systems, while GD was not. High prevalence of maternal diabetes could partly account for the elevated burdens of severe infant morbidities in Cree and other First Nations populations in rural communities in Quebec.

Caesarean sections among immigrant women compared to Canadian born women Erin
Hetherington Kamala Adhikari Natalie Scime Amy Metcalfe

Background: The global rise in caesarean sections (CS) has led to concerns about overuse of this
medical intervention. In higher income countries, CSs are generally higher among immigrant
women, but medical history and women's expectations, which may differ by country of origin, are
not adequately addressed. This study examines differences in CS rates between immigrants to
Canada compared to Canadian born women according to time in Canada and rates of CS in country
of origin.

Methods: This study uses linked data from hospitalization records and the Canadian Community
Health Survey for women who delivered a baby in a hospital between 2002 and 2017 in Canada
(excluding Quebec). Descriptive statistics are provided for the entire sample, and then broken down
by Canadian-born, recent immigrants and non-recent immigrants. Odds of CS in immigrants (recent
and non-recent) compared to Canadian born women were calculated using logistic regression and
stratified by parity. Immigrants were further categorized by the CS rate in their country of origin as
low (<10%), medium (≥10 to <35%) or high (≥35%). All statistics were calculated using weights and
bootstrapping to account for sampling design.

Results: Of the 53,505 women included, 89% were Canadian born, 4% were recent immigrants (<5
years) and 7% were non-recent immigrants. Overall, 28.6% had a CS, and this was slightly higher
among recent immigrants (30%), non-recent immigrants (31%) than Canadian born women(28%).
After adjusting for medical and socio-economic factors, the odds of caesarean section among recent
immigrants (1.12 95%CI 0.95, 1.34) and non-recent immigrants (1.11 95%CI 0.98, 1.25) did not
statistically differ from Canadian born women. Recent immigrants from countries with lower CS
rates had higher odds of CS (1.34, 95%CI 1.05, 1.70), whereas recent immigrants from medium and
high CS rate countries did not differ from Canadian born women.

Discussion: After accounting for demographic and medical factors, few differences remained in CS
rate between immigrants and Canadian born women. Country of origin practices are unlikely to
reflect preferences for CS in immigrant women to Canada.

Health equity

Reproductive and sexual healthcare for women with intellectual and developmental disabilities: A scoping review Eric Rubenstein Jade Ransohoff Prisha Kumar David Flynn

Background: Intellectual and developmental disabilities are conditions that present before 18 years of age and impair cognitive and adaptive functioning. Despite past injustice, women with IDD have the same reproductive and parenting rights as peers. Because of disparity and inequity, women with IDD face poorer reproductive and pregnancy outcomes. Less is known about how reproductive health care services are allocated in women with IDD, which may have major implication for interventions.

Objective: To conduct a scoping review of the literature surrounding reproductive healthcare use among women with IDD.

Methods: We searched PubMed, Embase, and Web of Science using the following keywords: intellectual disability; cerebral palsy; autistic disorder; autism spectrum disorder; fertility; family planning services; prenatal education; prenatal care; doulas; midwives; and their related terms. Our search was limited to papers in English. Two reviewers manually reviewed abstracts and extracted articles based on inclusion criteria. We compiled findings and identified themes common between papers.

Results: Our search identified 5464 articles and 48 met inclusion criteria. We focused on 6 common topics: fertility; family planning/contraceptive use; prenatal care; midwives/doulas; and outcomes after delivery. Research shows that while women with IDD are able to become pregnant, the overall fertility rate among this population is lower than women without IDD. Women with IDD have a higher rate of rapid repeat pregnancy, indicating that women with IDD may not receive proper information about family planning and contraceptive use. Women with IDD were less likely to receive adequate prenatal care or pregnancy-related information compared to peers. While midwives/doulas are a possible way to increase support surrounding pregnancy, many providers were not prepared to provide treatment to this population.

Conclusion:

We found a small but consistent literature surrounding reproductive and sexual health care for women with IDD. These women face a disproportionate burden when accessing sexual and reproductive health care, directly affecting health, pregnancy experience, and postnatal outcomes. With growing cohorts of reproductive-age women with IDD, it is necessary to begin acting to reduce these disparities.

Changes in Perceived Quality of Prenatal Care Following COVID-related changes at Grady Memorial Hospital Kaitlyn Stanhope Kendra Piper Peg Goedken Tatyana Johnson Naima Joseph Angeline Ti Franklyn Geary Sheree Boulet

Background: In response to the COVID-19 pandemic, many health systems changed the structure of prenatal care, including reduced in-person visit schedules and incorporation of phone-based visits. Our goal was to understand differences in perceived quality of and satisfaction with prenatal care following changes in care modality (in-person v. phone-based).

Methods: We conducted a mixed-methods study with 67 postpartum women who initiated prenatal care at Grady Memorial Hospital prior to March 2020 and had at least one phone-based prenatal visit. All completed a web-based survey and 16 completed semi-structured in-depth interviews. We measured quality of and satisfaction with in-person and phone-based visits using the Quality of Prenatal Care Questionnaire. Here we present descriptive statistics for quantitative results and thematic analysis of qualitative data.

Results: Reported quality was high for both in-person and phone visits (median subscale responses: 5, the highest quality). 17 participants (38.6%) reported at least one barrier to in-person care, compared to 13 (26.5%) who reported at least one barrier to phone-based care. Though quality assessments overall were similar for both visit types, 49.1% (27) of participants reported one or more positive changes from in-person to phone visits, slightly higher than the 42.1% (24) who reported one or more negative changes. While most interview participants preferred in-person visits for the opportunity to hear the fetal heartbeat, some described dissatisfaction with the ban on visitors at appointments.

Conclusions: Despite overall high reported quality, quantitative scales may not accurately reflect patient experiences, as qualitative results suggest nuance and room for improvement in visitor policies and remote appointments.

Mental health, emotional support, and managing parenting demands among grandparent and multigenerational caregivers compared to parents in the U.S. Sarah Keim Andria Parrott

INTRODUCTION

About 10% of US children live with a grandparent; 2.7 million grandparents serve as primary caregivers. However, up-to-date knowledge about how grandparent caregivers are faring remains largely unknown because shifts in societal factors and policy (e.g. substance abuse trends, incarceration and foster care policies) have placed more children with grandparents than before, especially preschool-aged children.

METHODS

Using 4 cycles of National Survey of Children's Health data (2016-19), we compared grandparent-headed and multi-generational households to parent-headed households in terms of caregiver mental health, receipt of emotional support, and managing parenting demands. Survey weighted logistic regression models were built, adjusted for confounders selected *a priori* (number of caregivers, caregiver(s) age, receipt of cash welfare, SNAP benefits receipt, and child's race).

RESULTS

Among 30673 families with a child aged 1-5 years, 3464 (3.9%) were grandparent-headed, 4075 (4.7%) were multigenerational, 108547 (91.4%) were parent-headed. Grandparents and multigenerational caregivers were no more likely than parents to rate their mental health as good/fair/poor rather than excellent/very good ($aPR_{grandparents}$(prevalence ratio)=1.26, 95% CI: 0.82, 1.94). Grandparents were much less likely to lack a source of emotional support (aPR=0.52, CI: 0.28, 0.95) and to report they could not handle the demands of raising children (aPR=0.51, CI: 0.33, 0.79) compared to parents. No differences by caregiver type were observed in terms of usually/always feeling their child was harder to care for than most, that child does things that bother a lot, or feeling angry with the child.

CONCLUSIONS

Despite rising demands on grandparent caregivers, they reported faring at least as well as parent-headed households. It is possible their prior parenting experience and social ties make them more resilient. Multigenerational households fared similar to parent-headed households.

The association between established diet quality indices and gestational weight gain in Hispanic women Sofija Zagarins Megan Harvey Katherine Tucker Bess Marcus Milagros Rosal Tiffany Moore Simas JoAnn Manson Glenn Markenson

Maternal diet is a contributing factor to gestational weight gain (GWG). However, it remains unclear whether adherence to recommended dietary guidelines or healthful dietary patterns is associated with adequate GWG, as defined by the Institute of Medicine (IOM). Hispanic women in the US have higher rates of excess GWG than the general population, and dietary quality tends to be lower in certain US Hispanic groups, including Puerto Ricans. We evaluated these associations using data from 168 Hispanic (predominantly Puerto Rican) participants enrolled in Estudio PARTO, a randomized controlled trial conducted in Western Massachusetts (2013-17). Trained bicultural/bilingual personnel assessed diet at a mean±SD of 28.6±6.3 weeks gestation via 3 24-hour recalls. We calculated the Healthy Eating Index 2015 (HEI-2015), Alternate Healthy Eating Index 2010 (AHEI-2010), alternate Mediterranean Diet Score (aMED), and Healthy Plant-Based Diet Index (HPDI). Mean GWG was 27.9±16.0 pounds, with 22.8% of participants meeting the IOM guidelines for adequate GWG, and 56.9% exceeding guidelines. Mean diet scores were 54.9±14.6 (HEI-2015), 36.5±11.6 (AHEI-2010), 24.4±5.5 (aMED), and 51.8±7.7 (HPDI). Diet scores were all higher (indicating better dietary quality) in women who were less acculturated; among those reporting Spanish, vs. English as their primary language, scores ranged from 2.14 (HPDI; P=0.03) to 7.7 (HEI-2015; P=0.003) points higher. Diet scores were not significantly associated with GWG in linear regression models adjusted for age, pregnancy activity level, energy intake, and intervention arm. Each one-SD increase in diet score was associated with a 0.55 to 1.02-pound decrease in GWG (all P>0.05). Findings suggest that existing diet indices may have limited utility in predicting GWG in Hispanic women. Future research should explore the association between acculturation and dietary quality, as well as the development of diet indices specific to a Hispanic population.

Genomic study of early pregnancy maternal lipid traits revealed four known adult lipid loci
Marion Ouidir Suvo Chatterjee Jing Wu Fasil Tekola-Ayele

Blood lipids during pregnancy are known risk factors for cardiovascular diseases and adverse pregnancy outcomes. Genome-wide association studies (GWAS) in predominantly male European ancestry populations have identified genetic loci associated with blood lipid levels. However, the genetic architecture of blood lipids in pregnant women remains poorly understood. Our goal was to identify genetic loci associated with blood lipid levels among pregnant women from diverse ethnic groups via trans-ethnic GWAS meta-analysis and to evaluate whether previously known lipid GWAS loci are transferable to pregnant women.

The trans-ethnic GWAS were conducted on serum level of cholesterol, HDL, LDL, triglycerides and total lipids during first trimester among pregnant women from four population groups (501 White-, 470 African-, 450 Hispanic- and 233 Asian-Americans) recruited in the NICHD Fetal Growth Studies cohort, adjusting for maternal age and population stratification. The four GWAS summary statistics were combined using trans-ethnic meta-analysis approaches based on random effects accounting for genetic heterogeneity among populations.

In the trans-ethnic GWAS meta-analyses, 13, 9, 33 and 1 SNPs were associated ($P<5\times10^{-8}$) with cholesterol, HDL, LDL and total lipids, respectively. The lead SNPs annotated to *CELSR2*, *APOE*, *CETP* and *ABCA1* genes and overlapped with known lipids-related loci. Novel low-frequency loci (*GALNT7*, *SLAIN2*, *LOC101928274*, *NRXN3*, and *ANKRD27*) were associated with triglycerides, primarily driven by one population. 429 out of 454 known lipids-related loci in previous GWAS studies, were evaluated in our data and 143 (33%) loci were significant (p<0.05).

This trans-ethnic GWAS meta-analysis in pregnant women of diverse populations identified four known lipid-loci. Replication of 1/3rd of the known loci from predominantly European study populations underlines the need for genome-wide lipids-related association studies in diverse populations.

Sex-specific placental gene expression signatures of small for gestational age at birth Suvo Chatterjee Xuehuo Zeng Marion Ouidir Cuilin Zhang Fasil Tekola-Ayele

Background: Small for gestational age at birth (SGA), often a consequence of placental dysfunction, is an established risk factor for later life cardiometabolic diseases. Accumulating evidence suggests sex differences in placental gene expression. We hypothesized that there may be distinct placental gene expression signatures of SGA in male and female neonates.

Method: Placental gene expression data spanning 14285 protein coding genes was obtained from ethnic diverse pregnant women in the NICHD Fetal Growth Studies cohort (n=80). SGA status (birthweight $<10^{th}$ percentile) and appropriate for gestational age (AGA: $\geq 10^{th}$ and $<90^{th}$ percentile) were defined based on sex-specific reference for United States. In total, 12 SGA and 27 AGA males, and 9 SGA and 26 AGA females were identified. Differential gene expression between SGA and AGA was identified separately in males and females using a weighted mean of log ratios method with adjustment for mode of delivery and ethnicity.

Result: At 5% false discovery rate (FDR), we identified 58 differentially expressed genes (DEGs) related to SGA status among males (93.1% up- and 6.9% down-regulated) and 318 DEGs among females (39.3% up- and 60.7% down-regulated). The DEGs in males were significantly enriched for immune response and inflammation signaling pathways while DEGs in females were enriched for organ development signaling pathways (FDR<0.05). The DEGs also differed in tissue enrichment for expression quantitative loci (whole blood, spleen and lung for males; heart, brain and adipose tissues for females) and genome-wide association study phenotypes (blood protein levels for males; obesity, blood pressure and cognitive ability for females).

Conclusion: We identified distinct placental gene expression changes and molecular pathways associated with SGA in male and female neonates. The findings facilitate understanding of SGA pathology, and suggest the need for sex-tailored molecular diagnostic and therapeutic interventions.

Genetics

Maternal perceived stress exposure and DNA methylation in newborn cord blood Kristen Polinski Diane L. Putnick Sonia L. Robinson Sunni L. Mumford Karen Schliep Robert Silver Enrique Schisterman Edwina Yeung

Objective: Maternal stress is associated with physiologic and mental health outcomes in the offspring, but the underlying biologic mechanisms are unknown. We examined the associations of maternal perceived stress with DNA methylation (DNAm) alterations in the cord blood buffy coat of 378 singleton neonates.

Methods: Maternal perceived stress was measured prior to and throughout pregnancy in a cohort of women enrolled in the EAGeR trial. During the first two menstrual cycles while attempting pregnancy, daily stress assessment scores based on a standardized Likert-scale were averaged. Cumulative early and mid- to late-pregnancy stress was estimated by calculating the predicted area under the curve of stress reported in early gestation (up to 8 weeks) and between 12-36 weeks of gestation. DNAm was measured by the Infinium MethylationEPIC BeadChip. Multivariable robust linear regression was used to assess associations of perceived stress with DNAm β-values. Ingenuity Pathway Analysis was used to evaluate biologic implications.

Results: On average, women reported little to no preconception and early pregnancy stress and moderate stress in mid- to late pregnancy. Preconception and early pregnancy perceived stress were not associated with individual CpG sites in neonatal cord blood (all false discovery rate [FDR] >5%). Higher maternal stress during the 2nd and 3rd trimester was associated with differential DNAm at cg22255634 near the *PARP15* gene (FDR p=0.005), which is a transcription regulator with roles in DNA repair. Pathway analysis of the top-100 CpGs impacted by maternal stress identified several molecular pathways involved in immune responses related to this set of loci including gene expression, cellular development and lipid metabolism.

Conclusion: Limited effects of maternal perceived stress exposure on array-wide neonatal methylation differences were found in leukocytes. Further studies should examine epigenetic modifications from stress exposure in other tissues.

Molecular

Maternal serum cotinine in association with poly-unsaturated fatty acids and autism spectrum disorder: a case control study Anna Bostwick Gayle Windham Nathaniel Snyder Kristen Lyall

We sought to investigate the potential relationship between prenatal smoking exposure and maternal polyunsaturated fatty acids (PUFAs), as two environmental factors acting on an immune-mediated pathway (generally positively and negatively influencing inflammation, respectively), and to consider their joint effects on risk of offspring autism spectrum disorder. Participants (n=1001) were from a California case-control study utilizing archived prenatal serum specimens. ASD case status was obtained from the California Department of Developmental Services, and both PUFA and cotinine levels measured in mid-pregnancy serum. We first examined whether cotinine levels influenced PUFAs, overall and stratified by ASD status, using adjusted linear regression. Associations were also examined by environmental and direct smoke exposure ($\leq$10 and >10 ng/mL serum cotinine, respectively). Next, to assess potential joint effects of prenatal PUFAs and cotinine on ASD, we tested interaction terms in adjusted logistic regression models predicting ASD, and examined risk associated with low PUFA (levels below the median) and high cotinine (>10 ng/mL). Overall, PUFA levels did not significantly differ by cotinine levels, nor were significant associations observed in regression models overall or stratified by case status. Suggestions of reductions in certain PUFAs were observed with higher cotinine levels among those with cotinine levels indicative of environmental or second-hand exposure, though estimates were not significant (adjusted ß, linoleic acid: -1.63, 95% CI: -3.69, 0.43; total n-6 and total PUFA similar). In analyses of joint effects, there was no evidence of interactions, nor was the combination of low PUFA and high cotinine associated with ASD. Thus, strong associations were not observed here, but future work should further consider the potential effects of environmental cigarette exposure on PUFA levels, and whether other combinations of such factors may impact ASD risk.

Physical Activity Before and During Pregnancy and Placental DNA Methylation – An Epigenome Wide Association Study Sifang Zhao Edwina Yeung Marion Ouidir Stefanie Hinkle Katherine Grantz Jagteshwar Grewal Susanna Mitro Jing Wu Danielle Stevens Suvo Chatterjee Fasil Tekola-Ayele Cuilin Zhang

Objectives: Physical activity (PA) prior to and during pregnancy may influence offspring health through epigenetic modifications in the placenta. Prior studies had a single PA assessment in pregnancy limiting the ability to account for PA changes during pregnancy. We evaluated associations between multiple assessments of PA during pregnancy and genome-wide methylation changes in the placenta.

Methods: Placental tissues were obtained at delivery and DNA methylation was measured using the Illumina Human Methylation450 Beadchip for 301 mothers in the NICHD Fetal Growth Studies–Singleton cohort. Total PA (MET-min/wk) was assessed using the Pregnancy PA Questionnaire targeted for 8-13 (visit0), 16-22 (visit1), 24-29 (visit2), 30-33 (visit3), 34-37 (visit4), 38-41 (visit5) weeks' gestation. For associations of PA at each visit with methylation, we conducted linear regression adjusting for potential confounders such as maternal age, race/ethnicity, and pre-pregnancy body mass index. Genes annotating significant CpG sites (false discovery rate adjusted P<0.05) were queried for enrichment of functional pathways using Ingenuity Pathway Analysis.

Results: PA in the 12 months prior to visit 0 was not significantly associated with methylation whereas PA since last visit for visits 1-5 were associated with methylation of 1, 0, 2, 29, 30 CpG sites, respectively (P values ranging from 3.07×10^{-9} to 3.35×10^{-6}). Thirteen CpG sites significantly related to PA overlapped at visits 4&5, with the most significant associations at cg21385047 located in *S1PR1* (P=3.07×10^{-9}, P=7.45×10^{-9}, respectively). Five enriched pathways overlapped at visits 4&5 (P<0.05): inositol pyrophosphates biosynthesis, gustation pathway, choline biosynthesis III, cAMP-mediated signaling, G-protein coupled receptor signaling.

Conclusions: Findings suggest that PA during pregnancy is associated with placental methylation changes at loci potentially related to cardiovascular and neurological system development/function.

Placental miRNAs associate with early childhood growth characteristics Elizabeth Kennedy Karen Hermetz Amber Burt Dong Pei Devin Koestler Ke Hao Jia Chen Diane Gilbert-Diamond Margaret Karagas Carmen Marsit

Poor placental function is the most common cause of intrauterine growth restriction and is associated with perinatal morbidity, mortality and long-term health outcomes. Our prior work suggests that birthweight and childhood obesity-associated genetic variants functionally impact placental function. To further demonstrate the role of the placenta in developmental programming, we assessed the role of placental miRNAs in early childhood growth. We have utilized small RNA sequencing to assay placental miRNAs from the New Hampshire Birth Cohort Study (NHBCS, n=238), and **S**uper**I**mposition by **T**ranslation **A**nd **R**otation (SITAR) modeling to generate estimates of average size and growth intensity during the first five years from medical record-based and in person weight assessments. Using negative binomial generalized linear models, we identified five placental miRNAs that are associated with growth intensity and one miRNA with average size (FDR<0.05), while accounting for sex, gestational age at birth, and maternal parity. One doubling of miR-155 transcript abundance, our most robust association, corresponds to a 0.6% increase in growth intensity (95% CI: 0.17-1.03), compared to the average. The miRNAs identified to associate with growth intensity are predicted to target over 3,000 placental mRNAs. Among growth intensity associated miRNAs, 65 mRNAs are targeted by more than two miRNAs. Genes targeted by growth intensity associated miRNAs are enriched (FDR<0.02) in pathways for TGF/beta signaling (miR-155, miR-1290), EGF/R signaling (miR-1290, Let-7a), aldosterone synthesis (miR-1246), notch signaling and apidogenesis (miR-629). The only size-associated miRNA, miR-216a, targets genes enriched in EGFR1 signaling. These pathways are known to function in placental invasion, differentiation and function. Our results support the hypothesis that fetal environment, specifically placental function guided by miRNA expression, can have impacts beyond birth, into early childhood.

Omics

Deconvolution of an epidemiologic preeclampsia dataset reveals cell type proportion differences that largely drive gene expression differences Kyle Campbell Justin Colacino Muraly Puttabyatappa Saher Hammoud Steven Domino Dana Dolinoy Vasantha Padmanabhan Jaclyn Goodrich Rita Loch-Caruso Kelly Bakulski

Many adverse pregnancy outcomes are mediated by placental dysfunction. Placental tissue is a highly heterogeneous mixture of multiple cell types. Epidemiology studies often measure molecular biomarkers in bulk placental tissue. To provide mechanistic insight into how exposures cause adverse pregnancy outcomes, methodological approaches are needed to account for cell type proportions in bulk placental tissue.

We subjected healthy placental villous tissues to single-cell RNA-sequencing. 15,532 single-cell libraries across 36,601 genes from five biological and two technical replicates clustered into 19 fetal and 8 maternal cell types. We applied cell type-specific gene expression profiles via deconvolution to estimate cell type proportions in previously published placental bulk tissue studies of preeclampsia totaling 157 preeclamptic mothers and 173 controls.

Hofbauer cells (odds ratio=0.81, p=5.8×10-10) and mesenchymal cell types were less abundant among preeclamptic cases compared to controls, whereas extravillous trophoblasts were more abundant (odds ratio=1.82, p=1.08×10-18). Adjustment for cell type proportion in differential expression analysis dramatically attenuated gene expression differences between preeclampsia cases and controls from 1,224 differentially expressed genes (padj<0.05) to 39 (padj<0.1). Gene enrichment analysis of cell type-adjusted results identified microRNA hsa-miR-6768-5p (padj=0.04) and VEGFR1 (padj=0.04) as potential cell type-independent factors in preeclampsia etiology.

Our study of term placentae provides cell type-specific gene expression profiles to serve as a deconvolution reference. Application to an epidemiologic preeclampsia dataset revealed biologically important cell type proportion differences largely drive gene expression differences. Accounting for cell type proportions in molecular assays of tissue samples is essential to reveal causal mechanisms of adverse pregnancy outcomes.

Fetal loss/stillbirth/infant mortality

Preconception sleep hygiene and risk of pregnancy loss Joshua Freeman Brian Whitcomb Elizabeth Bertone-Johnson Laura Balzer Lindsey Sjaarda Keewan Kim Robert Silver Alexandra Purdue-Smithe Enrique Schisterman Sunni Mumford

Sleep prior to conception may be important for pregnancy. Clock genes, which partly regulate sleep, play a role in embryo implantation and placentation, and thus may be related to pregnancy loss. However, epidemiological evidence on sleep and pregnancy loss is limited to studies of women recruited during pregnancy after which many pregnancy losses have occurred. We addressed this gap by evaluating sleep behaviors prior to conception among 1,228 reproductive aged women with 1-2 prior pregnancy losses who were prospectively followed for ≤6 cycles while attempting to conceive and throughout pregnancy if they conceived. Pregnancies were identified via urinary hCG and confirmed by clinical ultrasound; losses were identified as subsequent absence of pregnancy. We calculated sleep duration, sleep midpoint (median time between going to bed and waking up corrected for sleep debt), and social jet lag (difference in weekend-weekday sleep midpoints) from baseline self-report. We used Log-Poisson models to estimate RRs of sleep characteristics with pregnancy loss, controlling for demographics, caffeine, exercise, parity, and weighting to account for conditioning on pregnancy. Overall, 23.6% (188/797) of pregnancies ended in a loss. Sleep duration was not associated with pregnancy loss (<7 hrs vs 7-9 hrs: RR 0.99, 95% CI: 0.65-1.49; ≥9 hrs vs 7-9 hrs: RR 1.25, 95% CI: 0.8-1.97). Preconception sleep midpoint and social jet lag were also not associated with pregnancy loss. Results did not differ when considering hCG-detected and clinical losses separately. In our prospective cohort of pregnancy planning women, we observed no associations between preconception sleep and pregnancy loss. These findings expand on prior studies by following women from preconception to capture early pregnancy losses and suggest that preconception sleep may not be related to pregnancy loss.

Support: NICHD, NIH.

Long-term mortality in women with pregnancy loss and modification by race/ethnicity Sonia M. Grandi Sonia M. Grandi Stefanie N. Hinkle Sunni L. Mumford Lindsey A. Sjaarda Katherine L. Grantz Pauline Mendola James L. Mills Anna Z. Pollack Edwina Yeung Cuilin Zhang Enrique F. Schisterman

Background: Pregnancy loss is a common reproductive complication but the association between pregnancy loss and long-term mortality and whether this association varies by maternal race/ethnicity is not well understood.

Methods: A racially diverse cohort of 48,188 pregnant women enrolled at 12 U.S. clinical sites in the Collaborative Perinatal Project (CPP) from 1959-1966 was used for this study. CPP records were linked to the National Death Index (NDI) and the Social Security Death Master File for deaths prior to 2016. Pregnancy loss was defined as the total number of self-reported losses, including ectopic pregnancies, abortions, and stillbirths/fetal deaths, that occurred prior to or during enrollment in the CPP. The outcomes were all-cause mortality and underlying mortality defined in the NDI. Stratified Weibull models with maternal age as the underlying time scale were used for all analyses.

Results: Among 48,188 women (46.0% White, 45.8% Black, 8.2% Other), 25.6% reported ≥ 1 pregnancy loss with a slightly higher proportion among Black (27.4%) versus White women (23.6%). Over a median follow-up of 52 (IQR: 47, 54) years, 18,789 (39.0%) women died. Overall, women with a history of pregnancy loss had a higher relative risk of all-cause mortality (HR 1.07, 95% CI 1.04, 1.11), and deaths due to coronary heart disease (CHD) (HR 1.14, 95% CI 1.05, 1.25) compared to women with no history of loss. Stratified by race/ethnicity, an increased risk of all-cause and CHD deaths associated with pregnancy loss was observed in White women (All-cause: HR 1.12, 95% CI 1.06, 1.19; CHD: HR 1.32, 95% CI 1.16, 1.52) but not in Black women (All-cause: HR 1.04, 95% CI 0.98, 1.09; CHD: HR 1.04, 95% CI 0.93, 1.17).

Conclusions: Pregnancy loss increases the risk of all-cause and cardiovascular mortality. These findings support pregnancy loss as a risk factor for long-term mortality and the need to assess reproductive history as part of routine screening in women.

Impact of COVID-19 on Physical Activity in Pregnant Women using Objective Measures Susan Park John Staudenmayer Robert Marcotte Scott Strath Patty Freedson Lisa Chasan-Taber

PURPOSE: Physical activity has been shown to decline throughout pregnancy. In March of 2020, restrictions due to the COVID-19 pandemic led to drastic changed in the work-life balance for many U.S. women. We examined the impact of the COVID-19 pandemic on patterns of physical activity in women at various stages of pregnancy.

METHODS: We used data was from the prospective Physical Activity in Pregnancy Study conducted from April 2019 to January 2021. Pregnant women (N= 46) wore an ActiGraph GT3X on the non-dominant wrist for three weeks, once during early, middle, and late pregnancy. After March 2020, participants were asked in each measurement session to self-report whether and how their lifestyle was significantly affected by the COVID-19 pandemic. Steps per day were downloaded from the ActiGraph at the end of each week. ActiGraph wear time was based upon self-report or, if missing, using the Choi wear time algorithm. Only participants with 10 hours of wear time for at least 4 days were included. Linear mixed effects regression models adjusted for gestational age, pre-pregnancy BMI, parity, and age were used to estimate the effects of COVID-19 on steps per week.

RESULTS: Women had a mean age of 32.7 years (SD 4.14), 52% were overweight/obese, and 1.17 (1.40) children. In early, middle, and late pregnancy, 17%, 35%, and 61% of the women reported being significantly affected by COVID-19, respectively. Compared to those not significantly affected by the pandemic, women who were affected accumulated 600 fewer steps/day (95% CI: -1,214, 5) in adjusted analyses (p=0.05).

CONCLUSIONS: Findings suggest the negative impact of the pandemic on steps during pregnancy. Given the benefits of maintaining adequate physical activity during pregnancy, findings may have important implications for intervening to prevent subsequent adverse maternal and fetal health outcomes among women who were pregnant during COVID-19.

Do tall mothers have lower risk of perinatal death irrespective of body-mass-index? Lauren Yearwood Jeffrey Bone Emma Wen Giulia Muraca Janet Lyons KS Joseph Sarka Lisonkova

Background: The adverse effects of obesity on perinatal outcomes are well known, however, the independent effect of maternal stature is understudied.

Objective: To examine the association between maternal stature and perinatal death, independent of pre-pregnancy body-mass-index (BMI), race and other risk factors.

Methods: Our retrospective cohort study included all singleton live births and stillbirths in the USA, 2016-2017 (N= 7,361,713). Data were obtained from the US National Center for Health Statistics. Short and tall stature were defined as <10th and >90th percentile of maternal height distribution; perinatal death included stillbirth and neonatal death (birth to 28 days of age). Logistic regression was used to obtain adjusted odds ratios (AOR) and 95% confidence intervals (CI); with adjustment for pre-pregnancy BMI, race, age, education, parity, health insurance provider, congenital anomalies, and other factors.

Results: The rates of perinatal death per 1000 total births were 7.66 among tall women (>172.7 cm), 7.60 among women of average stature, and 8.58 among short women (<154.9 cm). Tall women were more likely to be white or African-American, nulliparous, underweight, older, and with private medical insurance, chronic diabetes and hypertension as compared with average stature women. Short women were more likely to be Hispanic or Native American, multiparous, obese, younger, and without medical insurance. Adjusted for potential confounders, tall women had a 7% lower rate of perinatal death (AOR=0.93, 95% CI 0.88-0.99) and short women had a 15% higher rate (AOR=1.15, 95% CI 1.10-1.21) as compared with women of average stature.

Conclusion: Tall and short women had lower and higher risk, respectively, compared to women of average stature independent of other known risk factors. Further studies are required to identify mechanisms underlying the association between height and perinatal mortality, including potential residual confounding by socioeconomic status.

Copy number changes and placental abnormalities in stillborn fetuses Tsegaselassie Workalemahu Tsegaselassie Workalemahu Susan Dalton Amanda Allshouse Jessica Page Robert Silver

Introduction: Maternal vascular supply abnormalities are among the most common placental pathological causes of death in stillborn fetuses (SB). While chromosomal microarray (CMA) identified copy number changes (CNCs) in 9.5% of SB, the association between CNCs and placental pathological lesions (PPLs) in SB is uncertain. We evaluated the association between specific CNCs and PPLs.

Methods: We conducted a secondary analysis of the Stillbirth Collaborative Research Network study among SB (n=385) with CMA and postmortem examinations of the fetus and placenta. Using standard definitions, we categorized PPLs by type including maternal and fetal vascular, inflammatory and immune/idiopathic lesions. We used single-nucleotide polymorphism array with ≥500 kb to detect CNCs. We classified CMA into two groups: Normal, defined as no CNC/benign CNC, and Abnormal, defined as pathogenic CNC (including aneuploidy) or variants of unknown clinical significance. We compared proportions of Abnormal and Normal CNC between SB with and without PPLs using the Wald Chi-squared test.

Results: We observed a higher proportion of SB with maternal vascular lesions in the placenta among Abnormal CNCs (83.0%) in comparison to those with Normal CNCs (65.7%; p=0.003). The proportion of SB with fetal vascular lesions and Abnormal CNCs (78.6%) was not significantly different compared with those with Normal CNCs (76.4%; p=0.7). The proportions of SB with maternal/fetal inflammatory or immune/idiopathic lesions were similar among those with Abnormal CNCs compared with Normal CNCs. We identified CNCs that were pathogenic deletions (n=9) and duplications (n=20) in several genes in samples with placental vascular lesions.

Conclusion: Our data suggest that CNCs are associated with PPLs involving maternal vascular lesions in SB. Identification of CNCs related to placental abnormalities may shed light on the specific pathophysiology of placental function and SB

Early-life exposure to secondhand smoke and childhood adiposity: Identifying windows of susceptibility Brianna Moore Kimberly Kreitner Anne Starling Sheena Martenies Sheryl Magzamen Maggie Clark Dana Dabelea

Background: Secondhand smoke is a common early-life exposure that may contribute to obesity. However, prenatal and postnatal exposures are rarely assessed in the same study. Therefore, the most susceptible developmental periods are unknown.

Methods: We followed 568 mother-child pairs in Healthy Start who were born ≥37 weeks. Mothers reported smoking pre-conception, at 17 weeks gestation, and at delivery. Self-report of household smokers was collected at age 5 and 18 months. Cotinine was measured in maternal urine collected at 27 weeks gestation and child urine collected at age 5 years. Offspring adiposity (fat mass percentage) and fat mass (kg) were measured via air displacement plethysmography at birth and age 5 years. Multiple informant models estimated the associations between the repeated measures of secondhand smoke with childhood adiposity (fat mass percentage), fat mass and fat-free mass, as well as changes in adiposity, fat mass, and fat-free mass from birth to age 5 years. To determine whether the associations depend on timing, we included an interaction term between secondhand smoke and time in all models.

Results: We observed strong evidence that the association between secondhand smoke and changes in adiposity or fat mass depends on the timing of exposure (p for interaction=0.01 and 0.02, respectively). For example, maternal smoking pre-conception and at delivery were associated with increased adiposity accretion from birth to age 5 years (3.1%; [95% CI: 1.0, 5.1] and 4.0% [95% CI: 0.4, 7.6], respectively), as compared to offspring with no exposure during these exposure windows. Moreover, offspring living with household smokers during the first 5 months of life experienced a 1.7% increase (95% CI: 0.1, 3.2) in childhood adiposity, as compared to non-exposed offspring.

Conclusions: Exposure to secondhand smoke immediately before pregnancy, during late gestation, and in early infancy may have the greatest impact on childhood adiposity.

Joint effects of prenatal exposure to per- and poly-fluoroalkyl substances and psychosocial stressors on corticotropin releasing hormone during pregnancy Stephanie Eick Dana Goin Lara Cushing Erin DeMicco Amy Padula Tracey Woodruff Rachel Morello-Frosch

Background: Prenatal exposure to per- and poly-fluoroalkyl substances (PFAS) and psychosocial stressors has been associated with adverse pregnancy outcomes, including preterm birth (PTB). Previous studies have suggested joint exposure to environmental chemical and social stressors may explain even greater differences in risk of PTB. Elevated corticotropin releasing hormone (CRH) during mid-gestation may represent one biologic mechanism linking chemical and non-chemical stress exposures to PTB.

Methods: Using data from a prospective birth cohort (N=497), we examined the associations between individual PFAS (ng/mL) and CRH (pg/mL) using linear regression. PFAS and CRH were measured during the second trimester in serum and plasma, respectively. Coefficients were standardized to reflect change in CRH associated with an interquartile range (IQR) increase in natural log transformed PFAS. We additionally examined if the relationship between PFAS and CRH was modified by psychosocial stress using stratified models. Self-reported depression, stressful life events, perceived stress, food insecurity, and financial strain were assessed using validated questionnaires during the second trimester and included as binary indicators of psychosocial stress.

Results: An IQR increase in PFNA was associated with elevated CRH (β=5.17, 95% CI=1.79, 8.55). Increased concentrations of PFOA were also moderately associated with CRH (β=3.62, 95% CI=-0.42, 7.66). The relationship between PFNA and CRH was stronger among women who experienced stressful life events, depression, food insecurity, and financial strain compared to women who did not experience these stressors (Figure).

Conclusions: This study is the first to examine the relationship between PFAS exposure and CRH levels in mid-gestation. We found these associations were stronger among women who experienced stress, which aligns with previous findings that chemical and non-chemical stressor exposures can have joint effects on health outcomes.

Residential Green Space and Fecundability North American Preconception Cohort Study Mary Willis Amelia Wesselink Perry Hystad Kipruto Kirwa Elizabeth Hatch Lauren Wise

Background: A growing body of literature suggests that exposure to green space (natural vegetation) may have positive effects on human health, including reproductive health. Residential green space may improve health via reduced exposure to traffic-related air pollution, reduced depressive symptoms or stress levels, and increased physical activity. We hypothesize that increased exposure to green space may also promote fecundability, a sensitive marker of fertility.

Methods: In a large North American preconception cohort study (Pregnancy Study Online, PRESTO), we examined associations between residential green space (measured by satellite normalized difference vegetation index [NDVI] at a 30m resolution) and fecundability (per-cycle probability of conception). From 2013 through 2019, women aged 21-45 years who were trying to conceive without fertility treatment completed online questionnaires every 8 weeks for up to 12 months. We followed participants until reported pregnancy or a censoring event (end of pregnancy attempt, loss to follow-up, initiation of fertility treatment, or 12 menstrual cycles) whichever came first. Using geocoded residential addresses over follow-up, we calculated seasonal NDVI within 50-500 meter buffers around each residence to quantify green space exposure. We used proportional probabilities regression models to estimate fecundability ratios (FR), adjusting for sociodemographic and lifestyle characteristics.

Results: Among 7,644 pregnancy planners, adjusted models show an FR of 1.07 (95% CI: 0.98, 1.13) when comparing the top quintile (most green space) to the bottom quintile (least green space) within 250m of a residence. Results are similar for other distance buffers.

Conclusion: We present the first epidemiologic evidence that residential greenness is positively associated with fecundability. Future work will examine the role of key pathways that may mediate this relationship.

Changes in behavior among pregnant women after Hurricane Michael Ke Pan Leslie Beitsch
Elaina Gonsoroski Samendra Sherchan Christopher Uejio Maureen Lichtveld Emily Harville

Background

A severe disaster is a stressful event often resulting in unhealthful behaviors. Among pregnant
women, an increase in smoking and alcohol could contribute to adverse birth outcomes.

Method

Using vital statistics data for 2017-2019 from Florida, we compared smoking and alcohol use among
pregnant women before and after Hurricane Michael (October 2018). We categorized counties into
12 most-affected counties (Area A) or less-affected counties (Areas B and C). We examined whether
the proportion of women who smoked before pregnancy and during pregnancy and drank alcohol
during pregnancy changed after Michael. Lastly, we examined whether changes in those behavior
might have contributed to increasing the proportion of adverse perinatal outcomes using the Baron-
Kenny method to assess mediation. Logistic regression models were used, controlling for maternal
characteristics.

Result

In area A, women whose pregnancies started within 3 months after Michael were more likely to
smoke in 3 months prior to pregnancy compared to women whose pregnancies started before
Michael (adjusted Odds Ratio (aOR):1.423, 95% confidence interval (CI):1.209, 1.675); women who
were pregnant during Michael were more likely to smoke during pregnancy compared to women
whose pregnancies ended before Michael (aOR:1.187, 95%CI:1.015, 1.388). Changes in other areas
were not significant. The proportions of pregnant women who drank alcohol during their
pregnancies were not significantly different after Michael compared to before. The increase in low
birth weight (LBW) and small for gestational age (SGA) births after Michael might be partially
explained by the increasing proportion of women who smoked during pregnancy (0.23% of LBW and
0.16% of SGA).

Conclusion

Smoking prevalence before and during pregnancy increased after Michael. Future studies should
investigate mechanisms to explain post-disaster changes in smoking behavior and develop relevant
interventions.

Ambient air pollution exposure assessments in fertility studies: A guide for reproductive epidemiologists Johanna Jahnke Kyle Messier Melissa Lowe Anne Marie Jukic

Many studies have examined how ambient air pollution may be associated with fertility and pregnancy loss. We review the exposure assessments of ambient air pollution used in studies of fertility and pregnancy loss. We find that air pollution exposure models have vastly improved over the past decade with better predictive accuracy, precision, increased spatiotemporal variability and resolution, and incorporation of physiochemical properties. Despite the improvements, the fertility literature has yet to fully incorporate these methods. Specifically, 7% of fertility and pregnancy loss studies have used proximity models to assess air pollution, 60% have used surface monitor data, 4% have used land-use regression models, 9% have used dispersion/chemical transport models, 20% have used fusion models, and none have used personal air monitors. We provide descriptions of each of these air pollution exposure models and assess the strengths and limitations of each model. Finally, we summarize the findings of the literature on ambient air pollution and fertility, taking into account these disparate models. This review clarifies the details of air
pollution exposure assessment methods in fertility studies, helping researchers interpret existing findings. It also serves as a guide for reproductive epidemiologists in utilizing air pollution exposure models and embracing the new technologies available in air pollution exposure assessment.

Prenatal Phthalate Exposure and Maternal Chronic Pain in The Infant Development and Environment Study (TIDES) Anika M. Lovgren Allison C. Dona Grace R. Lyden Emily S. Barrett Sheela Sathyanarayana Nicole R. Bush Shanna H. Swan Ruby H.N. Nguyen

Background: Female reproductive chronic pain conditions may be influenced by environmental hormone disruptors such as phthalates, which are ubiquitous anti-androgenic chemicals. Hormone disruption may increase inflammation through oxidative stress pathways associated with the development of endometriosis and chronic pain conditions, yet the role of phthalates in these processes is largely unknown.

Objective: To evaluate cross-sectional associations between prenatal urinary phthalate metabolite concentrations and chronic pain diagnoses in a multi-center pregnancy cohort study, TIDES.

Methods: Early pregnancy urinary concentrations of 11 phthalate metabolites were measured (n=725 women). We reviewed prenatal medical records for past or present history of 12 chronic pain conditions (ICD-9) noted during pregnancy including migraine and vulvodynia. We used logistic and ordinal regression models to examine associations between log-transformed, specific-gravity adjusted urinary phthalate concentrations and 1) presence of any chronic pain condition and 2) number of chronic pain diagnoses, adjusted for race/ethnicity, age and study center.

Results: Higher monoethyl phthalate (MEP) was associated with higher odds of having any pain diagnosis (Adjusted Odds Ratio (AOR): 1.34; 95% CI: 1.03, 1.73) per IQR increase in log MEP; and odds of an increased number of pain diagnoses (AOR: 1.34; 95% CI:1.04, 1.74) per IQR increase in log MEP. No strong associations between other phthalate metabolites and pain diagnoses were observed.

Conclusions: Women with higher urinary MEP concentrations had increased odds of a chronic pain diagnosis and a greater number of chronic pain conditions. Evidence suggests MEP may be associated with oxidative stress biomarkers, thereby increasing inflammation associated with chronic pain, yet mechanisms for MEP and pain are largely unknown. Future research should examine whether a temporal relationship exists between MEP concentrations and chronic pain.

Data pooling and harmonization across pre-conception studies: The PrePARED Consortium Ke Pan Brittany Charlton Jorge E. Chavarro Danielle Symons Downs Erica P. Gunderson Catherine L. Haggerty Hong Jiang Anne Marie Jukic Sylvia Ley Gita D. Mishra Sunni L. Mumford Christina A. Porucznik Donna Santillan Karen Schliep Jeffrey G. Shaffer Sara Simonsen Daniela Sotres-Alvarez Joseph B. Stanford Lauren A. Wise Emily Harville

Background

Sample size in single cohorts is usually limited for study of rare risk factors or diseases or detect small effects. Our objective was to combine cohorts with pre-conception health information and to describe a data pooling and harmonization approach.

Methods

Individual-level data were pooled from women who were followed up after age of 18 from 10 prospective cohorts from the United States, Canada, and Australia. The crosswalk-cataloging-harmonization procedure was used to guide the harmonization process. Common data elements from the PhenX toolkit were used when possible.

Findings

The pooled dataset included 112,473 women. Harmonized variables included age, race/ethnicity, education, income, parity, gravidity, and pre-pregnancy body mass index, substance use, chronic conditions, and perinatal outcomes. Overall, 87% of participants self-reported their race as white. At baseline, mean age was 12.0±2.8 years in the two cohorts recruiting participants from childhood and 28.7±8.2 years in the remaining 8 cohorts. Gravidity was 0 for 48%, 1 for 23%, 2 for 9%, and 3+ for 20%; corresponding proportions for parity were 71%, 12%, 11% and 6%. A total of 24,816 (22%) women reported at least one pregnancy lasting more than 20 weeks during the study; 65% of those had their first pregnancy ever during the study. Mean age at the first pregnancy after enrollment was 29.6±4.8. If BMI was recorded multiple times during study, the most recent BMI before the first pregnancy after enrollment was harmonized. 22% of participants were overweight, and 15% were obese (recorded 2 years before pregnancy on average). Income collected in a single year and country was categorized into quantiles and harmonized with quantiles from other years and countries.

Conclusions

Harmonization of data presents an efficient approach and unique opportunity to study rare pre-conception risk factors and pregnancy-related events. Pooling data requires careful attention to time-varying covariates, secular trends, and data from different countries.

Treatments for primary dysmenorrhea: an umbrella review of systematic reviews and meta-analyses of randomized controlled trials Stefania Papatheodorou Evangelos Evangelou Ines Belaroussi

Background: Dysmenorrhea has a significant negative impact on the quality of life, productivity, and workdays lost of affected females. Numerous meta-analyses and systematic reviews have claimed that several types of pharmacological and non-pharmacological interventions are effective in treating primary dysmenorrhea.

Objective: The aim of this umbrella review was to identify systematic reviews and meta-analyses on the effectiveness of pharmacologic and nonpharmacologic interventions for primary dysmenorrhea, to summarize available evidence for these treatments and to evaluate if there is evidence for biases in this literature and assess the robustness of epidemiologic evidence.

Study design: A systematic literature search was carried out in PubMed, EMBASE, Web of Science, and the Cochrane Database of Systematic Reviews from inception to 6 March 2020 to identify systematic reviews and meta-analyses of studies examining the effectiveness of pharmacologic and non-pharmacologic therapies for primary dysmenorrhea.

Results: From the 847 eligible articles, forty-two articles were included. Twenty-two out of the 42 eligible papers (52%) provided quantitative synthesis corresponding to 50 unique comparisons investigating pharmacological (70%) and nonpharmacological (30%) interventions for primary dysmenorrhea covering six domains (medication, acupuncture, physical activity, herbal therapy dietary supplementation, and other non-pharmacological treatments, e.g heat, manual therapy). Only two out of 22 articles were rated as high quality using the AMSTAR 2 tool.

Forty-four out of 50 (88%) comparisons reported a nominally statistically significant summary result ($P < 0.05$) as per random-effects, suggesting the superiority of the investigated intervention compared to an active or inactive control group, or a mix of both. GRADE approach demonstrated a low level of evidence in 90% of the comparisons while no association was supported by high-level evidence. Comparisons with a moderate level of evidence were NSAIDS versus placebo, acupoint therapy vs no treatment, and manual acupuncture vs NSAIDs.

Conclusion: This umbrella review demonstrates that there is a wide range of treatment comparisons showing the benefit of some interventions, but high-quality evidence is lacking.

Association of preterm birth with risk of early natural menopause Christine R. Langton Brian W. Whitcomb Alexandra C. Purdue-Smithe Lynnette L. Sievert Susan E. Hankinson JoAnn E. Manson Bernard A. Rosner Elizabeth R. Bertone-Johnson

Early menopause, defined as the cessation of ovarian function before the age of 45 years, affects approximately 10% of women in Western populations. Current research suggests that women who experience early menopause are at increased risk of cardiovascular disease (CVD). Research examining maternal pregnancy outcomes and their relation to CVD has demonstrated a strong positive association between preterm birth and CVD risk. Preterm birth has a complex etiology, and underlying pregnancy-related vascular factors may contribute to, and thus influence, menopause timing. We evaluated the association of preterm birth with early natural menopause among 66,031 parous participants in the prospective Nurses' Health Study II.

Nurses were 25 to 42 years old at baseline (1989) and provided information on menopause status and age at menopause every 2 years through 2017. In 2009, participants reported their complete pregnancy history including the gestational age of each birth and type of delivery. Preterm birth was defined as a singleton gestation <37 weeks. We used logistic regression models to estimate risk via odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for age at first birth (18 to 45 years), race/ethnicity, and prepregnancy lifestyle factors including smoking and body mass index.

During 28 years of follow-up, 1,664 women experienced early natural menopause. In multivariable models, women whose first pregnancy ended in preterm birth had a 13% higher risk of early menopause compared to women with a term pregnancy (OR=1.13, 95% CI, 0.95-1.34). Risk was higher for women whose first birth was preterm with spontaneous labor and vaginal delivery versus term (OR=1.21, 95% CI, 0.90-1.64).

In this large, prospective study, preterm birth was associated with a modestly but non-significant higher risk of early menopause. Further research is needed to evaluate this finding and determine if menopause timing contributes to the association of preterm birth with CVD risk.

The Impact of a Lifestyle Intervention on Pregnancy and Postpartum Cardiovascular and Insulin Resistance Biomarkers among At-Risk Latinas Kathryn Wagner Vrinda Prakash Christine St. Laurent Bess Marcus Penelope Pekow Milagros Rosal Caren Solomon Barry Braun Lisa Chasan-Taber

Women with abnormal glucose tolerance during pregnancy are at elevated risk for the development of type 2 diabetes and cardiovascular disease; Latinas experience higher rates of these disorders compared to non-Latina whites. Prior lifestyle interventions were often limited to non-Latina whites, required travel to a gym, and did not utilize a theoretical framework. Therefore, we evaluated the effect of a culturally modified, individually-tailored lifestyle intervention on biomarkers of CVD risk and insulin resistance among 131 pregnant Latinas with abnormal glucose tolerance in Estudio PARTO. Women were randomly assigned at 24-28 weeks of gestation (baseline) to a Lifestyle Intervention (LI; n=60), focused on achieving Institute of Medicine guidelines for postpartum weight loss through physical activity and diet, or to a Health and Wellness comparison arm (HW; n=71). Follow-up assessments occurred at 6 weeks, 6 months, and 12 months postpartum. Participants had a mean age of 27.3 years, 77% were overweight or obese and 45% were born outside the US. Almost half of participants (45%) had isolated hyperglycemia, 18% had impaired glucose tolerance and 37% had gestational diabetes mellitus. There were no significant differences between arms at baseline. In intent to treat analysis, we observed a significantly greater decrease in insulin (β = -4.52, 95% CI: -9.36, 0.32) in the LI arm compared to the HW arm, across the first year postpartum. We also observed a significant decrease in HDL cholesterol (β = -4.32, 95% CI: -8.35, -0.28), which may be due to differences in change in weight across the arms. There were no significant differences in change between arms in total cholesterol, LDL cholesterol, triglycerides, blood glucose and HbA1c. In this randomized trial among high-risk Latinas, findings suggest that a lifestyle intervention may have a beneficial impact on postpartum insulin but not on HDL cholesterol but require replication in larger studies.

INFERTILITY DIAGNOSES AND AGE AT NATURAL MENOPAUSE Samantha Davidson Melanie L. Bell Stacey A. Missmer Allison Vitonis Kathryn L. Terry Leslie V. Farland

Background: Women who experience an earlier age at menopause may be at increased risk of cardiovascular disease and mortality. Reproductive and hormonal conditions may influence age at menopause, but research has been limited.

Methods: Women who received fertility treatments from three Boston infertility clinics and participated
in a prior study (1995-2004) were recontacted in 2018 to participate in the AfteR Treatment Study. Participants reported their menopausal status and among women who had undergone natural (non-surgical) menopause, their age at menopause. Participants who self-reported their primary infertility diagnosis in 2018 as ovulatory infertility, endometriosis, uterine factor, tubal factor, and other infertility,
were compared to women whose infertility was attributed to their male partner. Among postmenopausal women, we utilized linear regression with 95% confidence intervals (CI) to determine
the difference in age at natural menopause and adjusted for body mass index at the time of fertility treatment.

Results: Of the 808 participants, 536 experienced natural menopause. Mean age at natural menopause
was 50 years (SD 4.4). Women whose primary infertility was attributed to uterine (U) and tubal (T) factors experienced natural menopause approximately two years earlier than women whose infertility
was attributed to their male partners (U: -2.1 years, CI: -4.0, -0.2; T: -1.8 years, CI: -3.1, -0.4). We observed no difference in age at natural menopause for women with ovulatory infertility (0.2 years, CI: –
0.8, 1.2), endometriosis (-1.0 years, CI: -2.3, 0.2), or other infertility diagnoses (-0.8 years, CI: -1.9, 0.2).

Conclusions: Among infertile women who utilized fertility treatment, specific infertility diagnoses of uterine factor infertility and tubal factor infertility were associated with an earlier age at natural menopause. Future research is needed to further investigate the association between reproductive factors and natural menopause.

Association between hypertensive disorders of pregnancy and dementia: A systematic review and meta-analysis Karen Schliep Hailey McLean Bin Yan Fares Qeadan Shinyoung Ju Lauren Theilen Surrendra Sharma Michael Varner

The last 5 years have seen an increased focus on maternal hypertensive disorders of pregnancy (HDP) and subsequent chronic disease risk, including cardiovascular disease and cognitive decline. While several systematic reviews and meta-analyses have reported on the risk of cardiovascular disease in relation to HDP, no formal evaluation has been conducted for cognitive decline. Therefore, we aim to summarize the evidence for the impact of HDP on dementia, taking into account unique associations between HDP and dementia subtypes. A comprehensive search in Medline, Embase, and Pubmed was conducted to identify relevant studies. The exposure was all-cause HDP and HDP subtypes: gestational hypertension, preeclampsia/eclampsia, or other HDP. Outcomes were all-cause dementia and dementia subtypes: Alzheimer's disease, vascular dementia, or other dementias. Sensitivity analyses were done to examine the influence of individual studies. We included 7 studies (1 case-control, 6 retrospective cohorts), with a total of 194,694 HDP exposed women and 2,583,716 HDP non-exposed women, with exposure window 1939–2012, and outcome window 1939–2017. Pooled analysis found no difference in all-cause dementia among women with versus without all-cause HDP exposure (adjusted hazard ratio [aHR]: 1.16; 95% CI: 0.80; 1.68). However, when examining association by subtype, we found that women with all-cause HDP had a three-fold higher risk of vascular dementia (aHR: 2.93; 95% CI: 2.19; 3.92) compared to those without: and women with preeclampsia/eclampsia had a 36% higher risk of all-cause dementia (aHR: 1.36; 95% CI: 1.04; 1.78) compared to those without. Our findings indicate that maternal history of HDP is an important risk factor for later development of vascular dementia, but not Alzheimer's disease. Further research quantifying the magnitude of effect of preeclampsia/eclampsia on vascular dementia is warranted, in addition to unraveling impact of mid-life mediating factors.

Phthalate metabolites exposure among healthy pregnant women in an ethnically diverse nulliparous pregnancy cohort in the United States Shabnaz Siddiq Shabnaz Siddiq Autumn M Clemons John Meeker Virginia Rauh Ronad Wapner Pam Factor-Litvak

Background: Phthalate exposure varies by geographic region, race, sex and other factors. Evidence suggests that phthalates are associated with reproductive and developmental toxicity. Few data consider exposure differences throughout pregnancy in racially/ethnically diverse women. Here we examine determinants of phthalate metabolites during pregnancy in a cohort of nulliparous pregnant women.

Methods: We analyzed urinary metabolites of 4 parent phthalates: Butyl benzyl phthalate (BBzP), Di-isobutyl phthalate (DiBP), Diethyl phthalate (DEP), Di-(2-ethylhexyl) phthalate (∑DEHP) from urine collected in each trimester from 960 women enrolled in the Nulliparous Mothers To Be Study. Phthalate metabolites were adjusted for specific gravity; concentrations below the limit of detection (LOD) values were replaced with LOD/√2. Metabolite exposure for each woman was calculated as the geometric mean of the values in each trimester. We fit generalized linear models to examine characteristics that predicted average levels of phthalate metabolites in pregnancy.

Results: 57.7% of the women were non-Hispanic white, 14.5% were non-Hispanic black, 18.2% were Hispanic, 5.5% were Asian and 4.1% were Other race. Race, education and clinical site were significant predictors for all metabolites (p-value <.1). Compared to non-Hispanic White women, higher concentrations of BBzp were found in non-Hispanic Black women, DiBP in Hispanic women, and DEP in Asian women, respectively. Lower educational attainment and higher BMI values predicted higher mean concentrations phthalate metabolites. Overall, BBzP, DiBP and ∑DEHP concentrations were similar throughout the US except for one site in the Midwest.

Conclusion: Race, education attainment, BMI and clinical site are significant predictors phthalate exposure during pregnancy in this diverse cohort. These findings may indicate different product use patterns and imply the need for messaging targeted toward specific groups to reduce exposure.

A mixed-method study of social support among low-income pregnant people during the COVID-19 pandemic. Bridgette Blebu Martha Tesfalul Kimberly Coleman-Phox Jazmin Fontenot Deborah Karasek Charles McCulloch Lauren Lessard Miriam Kuppermann

Objective: Lack of prenatal social support (SS) is a known risk factor for decreased maternal well-being and poor pregnancy outcomes. SS is thought to optimize pregnancy outcomes by reducing stress and anxiety and improving stress coping mechanisms. In light of the COVID-19 pandemic, which may further decrease SS, we sought to explore maternal factors associated with SS and describe how the pandemic impacts SS.

Methods: Publicly insured pregnant participants enrolled in a study of enhanced prenatal care in Fresno, CA, were surveyed during their third trimester. The modified Medical Outcomes Social Support survey, an 8-item instrument measuring the availability of emotional and instrumental support, was used to assess prenatal SS. After transformation, scores range from 0 – 100, where higher scores indicate high SS. Multivariate linear regression was performed to explore SS and maternal factors. Open-ended survey responses regarding changes in SS during the pandemic were analyzed using qualitative methods.

Results: 86 participants were surveyed, and their mean SS score was 81.1 (SD = 21.7, range: 15 – 100). Being married or living with a partner was associated with more SS (β = 19.7, p < .01) while having at least one foreign-born parent (β = -19.1, p < .01) or a mental health disorder (β = -9.1, p < .10) was associated with less SS. Among 19 (22%) participants who experienced changes in SS during the pandemic, 15 (79%) reported reduced availability of SS, strained relationships, increased social isolation, and fewer opportunities to connect during the pandemic, although 4 (20%) developed closer relationships and greater availability of SS.

Conclusions: SS was associated with relationship status, having foreign-born parents, and mental health status. Given the need for social distancing during the pandemic, more attention should be paid to developing alternate vehicles for pregnant people to receive this form of SS. These exploratory findings can inform initiatives seeking to improve outcomes of low-income pregnant people during the pandemic.

Trends in initiation of hormonal contraceptive methods among teenagers born between 1989 and 1997 in Norway and the United States Katherine Ahrens Finn Egil Skjeldestad

Background: The teen birth rate in the United States (US) continues to fall, but remains higher than other developed nations. Early initiation of effective contraceptive methods is one recommended strategy for reducing teen pregnancy rates.

Objective: To assess initiation of hormonal contraception among women aged 15-19 in the US and Norway, a country with historically low rates of teen births.

Methods: We used population-based survey (US) and administrative (Norway) data to estimate the cumulative probability of age at first use of hormonal contraception for female residents born between 1989 and 1997 in 3-year birth cohorts. Differences between countries were assessed using confidence intervals, and differences between birth cohorts were assessed using survival analysis.

Results: At age 15, first use of any hormonal method was higher among US respondents (16-17% US vs. 10-12% Norway), whereas for ages 16 to 19 use was higher among Norwegian women (by age 19, 60-64% US vs. 74-77% Norway). Similar patterns were observed for pill use; however, depot medroxyprogesterone acetate (DMPA), implant, and intrauterine device (IUD) use tended to be higher among US women. In both countries, cumulative first use of the pill, patch, ring, and DMPA declined across birth cohorts while first use of implants and IUDs increased. In 2018, teen abortion rates were similar, but the US teen birth rate was nearly 6 times higher.

Conclusion: Age at initiation and type of first hormonal method use differed between US and Norwegian teenagers. These differences may contribute to the lower teen birth rate in Norway.

Methods for Modeling the Trajectory of Gestational Weight Gain: A Review of the Literature
Anna Booman Rachel Springer Jennifer Lucas Miguel Marino Jean O'Malley Amy Palma Teresa Schmidt Kristin Scott Kalera Stratton Jonathan Snowden Sarah-Truclinh Tran Kimberly Vesco Janne Boone-Heinonen

Gestational weight gain (GWG) has been investigated as a determinant of perinatal and maternal health outcomes, most typically using measures of the total amount of weight gained during pregnancy. However, women can follow different trajectories of gain and reach the same total weight gain, and prior evidence suggests that the timing of the weight gain may be important. There is no consensus on the appropriate way to assess weight gain trajectories. The objective of this study was to review methods used to model trajectories of GWG and discuss their advantages and disadvantages.

We performed a literature search in PubMed for studies that evaluated GWG as an exposure or an outcome. Articles were included in the review if they used methods that modeled weight gain patterns throughout pregnancy and included three or more weight datapoints per pregnancy.

Thirty-nine studies were included in the review. Several methods differentiate weight gain among trimesters, including trimester-specific models of linear GWG, rate of GWG, and the GWG adequacy ratio. Methods that model weight gain throughout pregnancy include the area under the GWG curve method, which estimates additional pound-days carried through pregnancy; calculation of z-scores, which is uncorrelated with the length of pregnancy; latent trajectory groups; and application of a super-imposition by translation and rotation model. Methods varied with regard to differentiation between body mass index classification, number of requisite time points, estimation of first trimester GWG, and flexibility of the GWG curve.

Numerous methods for modeling GWG trajectories have been used in prior studies, enabling investigation of the relationship between patterns of GWG and health outcomes. Further research will apply these techniques on an identical dataset to determine if they result in similar strengths of association between GWG and a health outcome. This research will help identify recommended techniques for modeling GWG.

The utility and feasibility of using threshold regression to study the causes of preterm birth Sara Conroy Jonathan Race Michael L. Pennell Erinn M. Hade William C. Miller Courtney D. Lynch

Background: Despite years of research, the causes of preterm birth remain largely unknown. Threshold regression (TR) is a well-established statistical model that has not been widely employed in reproductive and perinatal epidemiology. TR can be used to estimate the rate of change in latent fetal growth/development processes. We used 1959-1965 data from the Collaborative Perinatal Project (CPP) to examine the association between smoking during pregnancy and gestational age (GA) at delivery to assess what TR analysis might add to the literature.

Methods: Inclusion criteria were: first pregnancy in the study, regular cycles, enrollment <14 weeks, Black or White race, GA at delivery 18-46 weeks, and plausible birth weight for GA. The exposure was smoking status (smoker or non-smoker) as reported at enrollment. The outcome was GA at birth (days). Covariates were chosen based on a directed acyclic graph. Overall conclusions from logistic regression, Cox proportional hazards regression, and TR were compared.

Results: Of the 59,392 pregnancies in the CPP, 6,617 (11.1%) met the study eligibility criteria. Among included women, 42% smoked and 15% delivered preterm. The odds of preterm birth were higher for smokers compared to non-smokers [Odds Ratio (OR): 1.54 95% CI:(1.34, 1.77)]. The live birth rate was higher for smokers compared to non-smokers until 37 weeks [Hazard Ratio (HR): 1.45, 95% CI: (1.24, 1.70)], after which, there was no evidence of a difference [HR: 1.00, 95% CI: (0.94, 1.06)]. TR suggested that the fetal growth/development process had a greater rate of change for smokers compared to non-smokers [Drift difference 0.079, 95% Credible interval: (0.03, 0.13)], with smokers delivering two days earlier.

Conclusions: TR offers a new perspective for the study of preterm birth. Estimates from TR may be helpful in elucidating the factors underlying other maternal and child health-related events, like time to pregnancy loss or time to maternal or infant death.

Remote Recruitment and Data Collection with Postpartum Women during COVID-19: An Example from a Safety-Net Institution in Atlanta, Georgia Kaitlyn Stanhope Kendra Piper Tatyana Johnson Naima Joseph Angeline Ti Franklyn Geary Sheree Boulet

During the COVID-19 pandemic, many research studies suspended or quickly pivoted to remote recruitment and data collection. However, there is little evidence on the effectiveness of remote recruitment, particularly among populations with low health literacy and low-income. We describe remote recruitment and data collection metrics among postpartum women who delivered in a safety-net institution during the COVID-19 pandemic (March – August 2020).

Methods

Potentially eligible individuals were identified through the medical record and contacted via the listed phone number, 1 to 6 months following delivery. The research coordinator called women up to three times to invite them to participate and sent a follow-up text message if there was no response. Individuals interested in participation were texted a link to a REDCap-based consent form and short survey to complete independently. Following survey completion, women received a $20 e-gift card via text. We sent reminder texts weekly for up to 4 weeks or until survey completion.

Results

Of 277 individuals approached, 98 agreed to participate when contacted by phone (35%) and 17 agreed after receiving a text (15% of women who received a follow-up text), for a total response rate of 42%. Of refusals (162/277), we received no response by phone or text for 94 women (34%). The most common refusal reasons given were not speaking English (23%, 42/162), followed by not interested (14%, 24/162). Of 115 individuals who agreed to participate, 65 (57%) completed the survey. Of survey completers, 30 agreed to be contacted for a follow-up interview, leading to 15 completed interviews. Response rates were lower than previous in-person recruitment in our women's clinic (42% v. 50%) and survey completion was low (57%).

Conclusion

Remote recruitment is feasible in low-income postpartum women; however, future researchers should explore barriers to remote participation and consider strategies to improve survey completion rates.

Obstetric health

Cesarean Delivery, Labor Duration and Risk of Future Mothers' Mortality After More Than 50 Years of Follow-up
Katherine Grantz Rajeshwari Sundaraum Stefanie Hinkle James Mills Pauline Mendola Sunni Mumford Yan Qiao Chunming Zhu Cuilin Zhang Enrique Schisterman

Pregnancy complications like preeclampsia predict future cardiovascular disease (CVD) but whether obstetric factors such as labor duration and delivery route are associated with long-term health and mortality is unknown. We examined whether labor duration and cesarean delivery were associated with subsequent total and underlying cause-specific mortality among mothers from the Collaborative Perinatal Project (1959-1966; n=41,058 women, last delivery only). Vital status as of 2016 was determined by linkage to National Death Index and Social Security Death Master File. Hazard ratios (HR) were estimated using Cox models stratified by parity and adjusted for age, race, smoking, marital status, socioeconomic factors, pre-pregnancy chronic conditions, delivery gestational age, and pregnancy year.

Mortality rates for cesarean and vaginal delivery were 43.3% (219/506) and 27.1% (3219/11885) for nulliparas and 54.5% (1070/1965) and 43.5% (12,121/27,883) for multiparas. All-cause mortality was increased for women with cesarean compared to vaginal delivery (nulliparas, HR 1.27; 95%CI 1.09-1.47 and multiparas, HR 1.13; 95%CI 1.06-1.21). Cause-specific rates from diabetes (nulliparas, HR 2.86; 95%CI 1.53-5.34; multiparas HR 1.63; 95%CI 1.28-2.08) were higher in all women with cesarean, and kidney disease (HR 1.49; 95%CI 1.01-2.21), CVD (HR 1.13; 95%CI 1.01-1.27) and infection (HR 1.79; 95%CI 1.32-2.42) were high in multiparas with cesarean. Increased risk of all-cause mortality and death specifically from diabetes and infection remained for multiparas after adjusting for diabetes and hypertension in pregnancy. Labor duration was not significantly related to mortality.

In a U.S. cohort, cesarean was associated with subsequent development of CVD, diabetes, infection-related and overall mortality. Whether cesarean is a marker for poor medical care leading to more delivery problems, or there is something intrinsic about cesarean that increases future mortality risk is unknown.

Obstetric health

Evaluating the effect of changes in maternal, infant, and obstetric practice factors on cesarean delivery trends in Sweden and Canada using the Robson classification system Giulia Muraca K.S. Joseph Neda Razaz Linnea Ladfors Sarka Lisonkova Olof Stephansson

Background: The Robson classification system, which stratifies populations based on obstetric factors, is used widely in spatio-temporal comparisons of cesarean delivery (CD) rates. However, important determinants of CD including maternal, infant and obstetric practice factors are not integrated into the Robson scheme.

Objective: To compare temporal trends in CDs in Sweden and British Columbia (BC), Canada using the Robson classification, and to estimate the influence of maternal, infant, and practice factors on variations in CD rates.

Methods: We carried out a cohort study of all deliveries in Sweden and BC (2004-2016) with data obtained from population-based birth registers. Temporal trends in the contribution of each Robson group to the overall CD rate were compared. Log-binomial regression was used to study the effect of changes in maternal (e.g., age, BMI), infant (e.g., birth weight) and practice factors (e.g., epidural) on CD rates.

Results: The study included 1,952,700 deliveries. CDs in Sweden were stable at 17% from 2004 to 2016, while CDs increased in BC from 29.4% to 33.9%. Groups 5 (vertex fetus at term, previous CD) and 1 (nullipara, term, vertex fetus, spontaneous labor) were the main contributors to the CD rate and accounted for most of the excess CDs in BC vs Sweden. In BC, CDs in Group 1 increased from 19.7% to 22.6% (rate ratio [RR] 2014-16 vs 2004-07=1.15, 95% CI 1.12-1.20) and this increase was abolished by adjustment for maternal and practice factors (adjusted RR 2014-16 vs 2004-07=1.00, 95% CI 0.97-1.04). Such adjustment did not attenuate the increase in CDs observed in Sweden in Group 5 (adjusted RR 2014-16 vs 2004-07=1.09, 95% CI 1.05-1.12).

Conclusion: Maternal and practice factors, which are not part of the Robson classification, explained the temporal increase in CD rate in some Robson groups. Inferences regarding CD rates and trends based on the Robson classification should account for such maternal, infant and obstetric practice factors.

Maternal Prenatal Psychosocial Phenotypes and Associated Diurnal Cortisol Throughout Pregnancy Hannah Murphy Amber Kautz Emily Barrett Rich Miller Tom O'Connor

Background

Maternal prenatal stress physiology, indexed by HPA axis activity and its downstream element cortisol, is a natural target for human research because of substantial evidence from experimental animal studies. We leverage data from a prospective longitudinal study that characterizes maternal prenatal diurnal cortisol at each trimester to examine the changing intrauterine environment and its association with relevant psychosocial phenotypes. We test the hypothesis that elevated maternal prenatal anxiety and depression is positively associated with increased levels of prenatal cortisol throughout pregnancy.

Methods

Understanding Pregnancy Signals and Infant Development (UPSIDE) is a longitudinal pregnancy cohort study in Rochester, NY with 326 mothers recruited in their first trimester. 294 mothers (90%) have been retained through birth. UPSIDE is well positioned to examine prenatal impacts on child development with the collection of repeated biological and psychosocial measures.

Prenatal diurnal salivary cortisol samples were collected at each trimester following standard passive drool protocols at wake, 45 minutes post-wake, 2.5 hours, 8 hours, and 12 hours post-wake. Samples were analyzed in duplicate using a high-sensitivity enzyme immunoassay. Cortisol parameters were derived from diurnal slope, cortisol awakening response, and area under the curve.

Diurnal cortisol metrics will be adjusted for gestation, time of collection, and key covariates, as well as evaluated for potential mediation by sleep quality and medication use. Analyses with the maternal prenatal diurnal cortisol pattern will be adjusted for relevant covariates, including socio-economic status, race/ethnicity, sex, early pregnancy BMI, parity, and maternal age.

Feasibility

Collection of prenatal diurnal cortisol data and psychosocial symptoms is complete, as is data on pre- and perinatal covariates. Analyses of data has begun and will be complete by early spring.

Obstetric health

Cesarean delivery among birthing people of minority race/ethnic groups in rural counties
Mekhala Dissanayake Robert Hummer Whitney Robinson

Background
Current research on mode of delivery in rural U.S. settings includes mostly Non-Hispanic Whites (NHW); outcomes for minority race/ethnicity groups are less known.
Objective
Describe variation in cesarean delivery by race/ethnicity for people residing in rural counties and whether this varies by racial composition of counties.
Methods
We linked North Carolina live birth certificates (2014-2018) with U.S. population data and Rural-Urban Continuum Codes (RUCC). Counties with RUCC>3 were considered rural. We calculated maternal race/ethnicity-stratified (NHW; Non-Hispanic Black (NHB); Hispanic) percentages of cesarean delivery. We used mixed-effects logistic regression to determine the association between county percentage (%) of NHW residents in maternal county of residence and cesarean delivery, stratified by maternal race/ethnicity. Models were adjusted for adequacy of prenatal care, obesity, maternal age >35 years, gestational hypertension, gestational diabetes, nulliparity, and prior cesarean delivery.
Results
We included 115,577 births in 54 rural counties. The county percentage of NHW residents ranged from 26% to 95% (median 63%). Percentage of live birth delivered by cesarean was 31.1% in NHWs, 34.0% in NHBs, and 25.1% in Hispanics. Greater % NHW was associated with increased cesarean delivery for both NHB and Hispanic mothers in rural counties (Hispanic OR: 1.39, 95% CI: 0.94, 2.05; NHB OR: 1.51, 95% CI: 1.07, 2.14) and decreased cesarean delivery for NHW mothers (OR: 0.92, 95% CI: 0.74, 1.14). Covariate adjustment strengthened the association in Hispanics (OR: 1.63, 95% CI: 1.01, 2.62) but slightly attenuated it in NHBs (OR: 1.42, 95% CI: 0.93, 2.17) and rendered it null in NHWs (OR: 1.01, 95% CI: 0.82, 1.25).
Discussion
Cesarean delivery among minority race/ethnicity people increased with the % NHW in maternal county of residence in rural counties. This may reflect increased barriers to care or institutional discrimination in majority NHW rural areas.

Maternal inflammation and metabolic health: associations between bioactive lipids and blood glucose during pregnancy Barrett Welch Madeline Somers Alexander Keil Thomas Van t' Erve Leesa Deterding Jason Williams Fred Lih David Cantonwine Thomas McElrath Kelly Ferguson

Background. Glycemic regulation in pregnancy is critical for both maternal and fetal health. Elevated systemic inflammation can disturb normal glucose levels in pregnant women, but the role of specific inflammatory pathways is uncertain. Oxylipins, an important class of bioactive lipids that mediate inflammation, are generated through several distinct pathways. We aimed to estimate associations between plasma oxylipins and blood glucose among pregnant women.

Methods. Data come from a study of 90 pregnant women nested within the LIFECODES cohort in Boston, MA. Blood glucose was measured at mid-pregnancy using a standard glucose loading test to screen for gestational diabetes. Maternal plasma samples collected at early and mid-pregnancy were analyzed for 61 oxylipins, which were grouped into biosynthetic pathways defined by upstream fatty acid precursors and enzymes. Associations were examined using weighted multiple linear regression models. We also evaluated effect measure modification by the ratio of omega-6 to omega-3 (n6:n3) polyunsaturated fatty acids in plasma, as higher n6:n3 can be a risk factor for elevated lipid inflammation.

Results. Among the overall population we observed weak to null associations between blood glucose and plasma oxylipins from most biosynthetic pathways. However, significant positive associations were observed for 19-HETE and 20-HETE, which are important pro-inflammatory lipids produced from the oxidation of arachidonic acid by cytochrome P450 enzymes. A doubling in plasma 19-HETE was associated with 10.3 mg/dl (95% CI: 3.5, 17.4) higher blood glucose at mid-pregnancy. Importantly, we observed evidence that associations were modified by diet, as women with the highest tertile of plasma n6:n3 had associations among more oxylipin pathways and of greater magnitude.

Conclusion. Our results indicate that higher pro-inflammatory oxylipins from specific metabolic pathways are associated with elevated blood glucose among pregnant women. Further, results suggest dietary-related factors may be influencing these associations, which represents a potential modifiable factor to mitigate effects of inflammation on glucose levels during pregnancy. These findings can provide deeper insight into the pathways through which systemic inflammation may increase blood glucose during pregnancy.

Baseline Characteristics of Hispanic women with Pregnancy Hyperglycemia: Estudio Parto Madhuri Palnati Megan Harvey

Women who develop glucose intolerance during pregnancy are at high risk for the subsequent development of type 2 diabetes. Thus, pregnancy and postpartum are critical time-periods for interventions designed to prevent subsequent onset of diabetes in vulnerable populations. We investigated the prevalence of diabetes risk factors using baseline data from Estudio Parto, a randomized controlled trial of 204 Hispanic women with pregnancy hyperglycemia conducted from 2013-17 in Western Massachusetts. The Pregnancy Physical Activity Questionnaire was used to assess meeting ACOG guidelines for physical activity. Depression was measured using the Edinburgh Postpartum Depression Scale (EPDS) and diet was assessed by three 24-hour dietary recalls. Acculturation was assessed via the Psychological Acculturation Scale and sleep quality via the Pittsburgh Sleep Quality Index (PSQI). Participants were young (mean age = 27.7 years), 77% were overweight or obese, 44% were born outside the US, 76% had low acculturation; mean PSQI score was 6.9 (SD 4.3) indicating poor sleep quality and 15% had at least probable minor depression (EPDS>13). Almost half of participants (45%) had isolated hyperglycemia, 20% had impaired glucose tolerance and 35% had gestational diabetes mellitus. One-third (34%) met ACOG guidelines for physical activity and 8% planned to exclusively breastfeed. Diet quality was low, with only one quarter of participants meeting the American Diabetes Association recommendations for total fat (26%); fewer met guidelines for saturated fat (22%), fiber (4%), and sodium (19%). Of the 25% participants who smoked before pregnancy, 6% continued smoking. Of the 50% who consumed alcohol before pregnancy, 26% continued consumption. Findings demonstrate the need to support this at-risk population in making healthy lifestyle changes during pregnancy, thereby ultimately decreasing diabetes risk.

Women's health

Impact of inflammation on estimated iron deficiency prevalence in women ages 23-35 years with high body mass index Kristen Upson Parminder Suchdev Lisa Tussing-Humphreys Elizabeta Nemeth Quaker Harmon Gregory Travlos Ralph Wilson Donna Baird

Accurate diagnosis of iron deficiency (ID) is critical for clinical management and public health prevention. Yet, the widely used definition of iron deficiency in adults, plasma or serum ferritin <15 µg/L may underestimate ID as ferritin is elevated with inflammation. Several approaches have been proposed to adjust ferritin for inflammation using C-reactive protein (CRP) and ferritin adjustment is now recommended by the World Health Organization in areas of widespread infection or inflammation. Since obesity induces low-grade inflammation and is common in the U.S., we investigated the impact of inflammation on ID prevalence estimation in the context of high body mass index (BMI). We used enrollment data from the Study of Environment, Lifestyle & Fibroids, a cohort of 1693 African-American women ages 23-35 years among whom 59% have a BMI of ≥30 kg/m^2. Among a subset of participants (n=626) with data on serum ferritin (SF) and high-sensitivity CRP, we estimated ID prevalence using three approaches compared to the unadjusted SF<15 µg/L: (1) correction factor if CRP>5 mg/L (0.81, geometric mean ratio of SF with CRP≤5 and >5), (2) higher SF cut-off value (<70 µg/L) if CRP>5 mg/L, and (3) the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) internal regression correction (IRC). Among participants, CRP >5 mg/L was common (33%). The unadjusted ID prevalence was 14%. After accounting for inflammation, ID prevalence ranged from 16% (correction factor) to 22% (BRINDA IRC) and 32% (higher cut-off value). Among women with BMI ≥40 kg/m^2 (n=145), ID prevalence varied from 14% (unadjusted) and 19% (correction factor) to 30% (BRIND IRC) and 48% (higher cut-off value). Our results indicate higher ID prevalence after accounting for inflammation using CRP, particularly among women with a high BMI. Given the global obesity epidemic, further investigation of the impact of obesity-induced inflammation on the estimation of ID prevalence is warranted.

Maternal diet quality during pregnancy is associated with biomarkers of metabolic risk among male offspring Ellen Francis Dana Dabelea Kartik Shankar Wei Perng

Background: Limited data exists on the association between maternal diet quality during pregnancy and metabolic traits during early childhood, which is a sensitive period for risk of obesity-related disorders later in life.

Objective: To examine the association of maternal diet quality, as indicated by the Healthy Eating Index (HEI)-2010, in pregnancy with offspring metabolic biomarkers and body composition at age 4-7 years.

Design: We used data from 761 mother-offspring pairs from the Healthy Start Study to examine sex-specific associations of HEI >57 vs. ≤57 with offspring fasting glucose, leptin, cholesterol, HDL, LDL, % fat mass, BMI z-score, and log transformed insulin, 1/insulin, HOMA-IR, adiponectin, triglycerides, triglycerides:HDL, fat mass, waist circumference, and sum of skinfolds. Multivariable linear regression models accounted for maternal race/ethnicity, age, education, smoking habits during pregnancy, and physical activity, and child's age.

Results: During pregnancy, mean (SD) HEI score was 55.0 (13.3), and 43.0% had a HEI score >57. Among boys, there was an inverse association of maternal HEI and offspring glucose, insulin, HOMA-IR, and adiponectin. For instance, maternal HEI >57 was associated with lower fasting glucose (-0.12; 95% CI: -0.20, -0.03 mg/dL), and lower concentrations of: insulin by 15.7% (95% CI: -0.29, -0.06), HOMA-IR by 16.8% (95% CI: -0.30, -0.07), and adiponectin by 9.1% (95% CI: -0.17, -0.02). Among girls, there was an inverse association of maternal HEI with insulin and HOMA-IR, and a positive association with LDL. However, following covariate adjustment, all estimates among girls were attenuated to the null.

Conclusion: A better quality diet in pregnancy as reflected by a higher HEI-2010 score may improve the maternal-fetal milieu and decrease susceptibility for poor metabolic health among offspring, particularly boys. Future studies are warranted to confirm these associations and determine the underlying mechanisms.

Preconception dietary folate intake and risk of spontaneous abortion Anne Sofie D. Laursen Elizabeth E. Hatch Lauren A. Wise Kenneth J. Rothman Henrik T. Sørensen Ellen M. Mikkelsen

Previous studies suggest a beneficial effect of supplemental folic acid use and dietary folate intake on fertility, while results for fetal loss are conflicting. Most previous research on fetal loss focused on folic acid supplement use. We investigated the association between dietary folate intake and spontaneous abortion (SAB) in a Danish preconception cohort of couples trying to conceive. Pregnancies were ascertained through bimonthly follow-up questionnaires up to 12 months after study entry. SABs were identified by self-report on the follow-up questionnaires and through the Danish National Patient Registry. Baseline dietary folate intake was estimated using a validated food frequency questionnaire (FFQ). Folate intake was adjusted for energy intake using the residual method and categorized as <250, 250-399 and >=400µg/day. We used Cox proportional hazards regression models with gestational weeks as time scale to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for SAB, adjusting for age, partner's age, educational attainment, smoking status, anthropometry, physical activity, alcohol intake, folic acid supplement use, time-to-pregnancy, gravidity and parity. In sensitivity analyses, we stratified by folic acid supplement use, body mass index (BMI) and alcohol intake. Of the 2,957 women who became pregnant within 12 months of study entry and completed the FFQ, we identified 432 SABs. HRs for 250-399 and >=400 compared with <250 µg/day of folate intake were 0.83 (95% CI: 0.53; 1.29) and 0.87 (95% CI: 0.54; 1.39), respectively. Comparing intake >=400 with <250 µg/day, the association was stronger when the analysis was restricted to folic acid supplement users, 0.74 (95% CI: 0.39; 1.40), to BMI>=25, 0.67 (95% CI: 0.31; 1.43), and to alcohol intake >4 drinks/week, 0.66 (95% CI: 0.16; 2.66). Our study may suggest that high dietary folate intake among folic acid supplement users is associated with a lower risk of SAB, although our estimates are imprecise.

Nutrition/obesity

Urinary preconception phenolic compounds and fecundability among women attempting pregnancy Keewan Kim Alexandra Purdue-Smithe Joshua Freeman Samrawit Yisahak Enrique Schisterman Sunni Mumford

Background/Aim: Diets rich in plant-derived phenolic compounds may be beneficial for reproduction through antioxidant and anti-inflammatory effects. However, it is unknown whether these compounds that are abundant in vegetables, fruits, seeds, teas, and herbs, may have a role in improving fecundability. Therefore, we evaluated associations between preconception dietary phenol biomarkers and fecundability among women attempting pregnancy.

Methods: In a prospective cohort study following 1,228 women for up to 6 menstrual cycles while trying to conceive, concentrations of 28 dietary phenols were measured in urine at baseline. Pregnancy was assessed using urine hCG. Discrete Cox regression models, accounting for left-truncation and right-censoring, were used to estimate fecundability odds ratios (FORs) and 95% confidence intervals (CIs) for associations between dietary phenols and fecundability. Models were adjusted for urinary creatinine concentrations and potential confounders.

Results: Levels of most of urinary phenols were well above the limit of quantification, except catechin and resveratrol where only trace amounts were measured. We observed increased fecundability with higher levels of preconception 3,4-dihydroxyhydrocimmanic acid (FOR 1.23, 95% CI 0.97, 1.57; Quartile 4 vs 1), enterolactone (FOR 1.36, 95% CI 1.06, 1.75; Quartile 4 vs 1), and p-coumaric acid (FOR 1.29, 95% CI 1.00, 1.65; Quartile 4 vs 1). In contrast, comparing the highest to the lowest quartile, 3,4-dihydroxyphenylacetic acid (FOR 0.72, 95% CI 0.51, 1.00) and gallic acid (FOR 0.71, 95% CI 0.52, 0.97) were associated with reduced fecundability. No other dietary phenols were associated with fecundability.

Conclusions: A few dietary phenolic compounds measured in urine were associated with fecundability, highlighting their potential role among women attempting pregnancy. Further study of foods rich in these compounds may be beneficial to provide more useful guidance to women trying to conceive.

The Bidirectional Association Between Depression and Excess Body Weight: marginal structural modeling Ashenafi Cherkos Ann Vander Stoep Daniel Enquobahrie Isaac Rhew Elizabeth McCauley

Background and aims – The evidence on bidirectional associations between excess body weight (EBW) and depression during adolescence is equivocal. We examined effects of cumulative depression during early adolescence (age 12-14) on likelihood of excess body weight during late adolescence (age 17-18), and vice versa. We also examined potential effect modification by sex. Design: The study sample included 521 adolescents from public middle schools in Seattle, Washington, USA. Measured height and weight from five waves, from 6th to 12th grades, were used to determine EBW based on body mass index percentiles and CDC standards. The child-report version of the Mood and Feelings Questionnaire from the five waves was used to assess depressive symptoms. Covariates, including sex, race/ethnicity, and household income were taken into account. Marginal structural models (MSMs) with stabilized inverse probability weighting (SIPW) were used to estimate RRs and 95% CIs.
Result: Median BMI percentile and median MFQ score ranges were 68.00–72.27 and 8.51–10.51 across the five assessments. Cumulative depression score across the four early adolescent waves had no statistically significant effect on late adolescent EBW (RR=1.08; 95% CI: 0.72, 1.62; p-value=0.70). Cumulative EBW had no statistically significant effect on later depression (RR=1.01; 95% CI: 0.66, 1.53; p-value=0.98). Likewise, there was no statistically significant lagged effect of depression on EBW at the subsequent time point (RR=1.17; 95% CI: 0.88, 1.55; p-value=0.27) or lagged effect of EBW on depression at the subsequent time point during adolescence (RR=1.13; 0.85, 1.51; P-value=0.39). Sex did not modify the associations (interaction p-value > 0.05). Conclusion: We found no bidirectional cumulative or lagged association between overweight and depression in adolescence.

Obstetric health

Characterizing Self-reported Systemic Infection and Inflammatory Markers in Pregnancy
Allison Ciesla Kristin Scheible Hannah Murphy Ana Vallejo Sefair Richard Miller Jessica Brunner Emily Barrett Thomas O'Connor

Prenatal maternal infection has been linked with multiple child health disturbances, particularly neurodevelopmental disorders. However, there remains considerable variation in how infection is measured in pregnancy cohorts. Many studies rely on self-reported infections, but that is often based on a single time point or retrospective recall, sometimes long after birth. We are not aware of any studies linking reports of infection to biological measures of inflammation, the presumed mechanism. For this study, we describe infection data from self-report and measures of immune activation from analyses of blood samples taken throughout pregnancy.

The Understanding Pregnancy Signals and Infant Development (UPSIDE) cohort study in Rochester, NY has enrolled 326 pregnant women in their first trimester and followed 294 subsequent term-birth children, with continued follow-up through age 4. Women were asked in the third trimester of pregnancy to recall several systemic infections (i.e. flu, urinary tract, respiratory) they may have had, along with the months in the current pregnancy in which the infection occurred. Blood samples at each trimester were assayed for immune markers using a multiplex platform.

Forty-six percent reported at least one infection in pregnancy (and the 3 months leading up to conception), with 15% and 21% reported infections in the first and second trimesters, respectively. The highest reported infections were respiratory (17%), urinary tract (15%), yeast (7%) and flu (7%). Initial analyses found higher levels of IL-7 (in the 7th month), IL-23 (in the 7th month), and TNFα (in the 8th month) for participants reporting an infection in that month of pregnancy, compared to those without an infection in the same corresponding month of pregnancy. The utilization of both self-reported infection and repeated measures of inflammatory markers in pregnancy will help to determine infections in pregnancy for use in associations with peri- and post-natal outcomes.

Perinatal HIV exposure and its association with executive functioning among six- to ten-year-old Ugandan children Sarah Brewer Nicole Talge Claudia Holzman Alla Sikorskii Amara Ezeamama

In the post combined antiretroviral therapy (cART) era, there remains limited information on cognitive function in children exposed perinatally to human immunodeficiency virus (HIV). Previous literature has focused on younger children, neglected the populations most affected (sub-Saharan Africa), or included large age ranges. Our study worked to fill these gaps in the literature.

We compared group differences in executive function (EF) among 3 groups of children with known HIV exposure status during the perinatal period and 6-10 years of age (study enrollment): children HIV-infected perinatally (CPHIV, n=99), children born to HIV-infected mothers, but were HIV negative at enrollment (CHEU, n=97), and HIV-unexposed, uninfected community controls (CHUU, n=98). Caregiver report of EF was collected using the Behavior Rating Inventory of Executive Function (BRIEF) which assesses two dimensions of EF (BRI: Behavioral Regulation Index; MCI: Metacognition Index) and an index reflecting a combination of these dimensions (General Executive Composite). The BRI captures a child's ability to shift cognitive set and modulate emotions and behavior, and the MCI captures the ability to cognitively self-manage tasks and to monitor performance. Age- and sex-standardized z-scores were derived for all BRIEF measures using the CHUU group as the reference. We used linear regression models to estimate mean differences among the HIV exposure groups.

The CPHIV and CHEU groups did not differ from the CHUU group on the GEC or MCI. However, the CPHIV group scored lower than CHUU on the BRI, which is indicative of better functioning in this domain (β=-.40, 95% CI -0.77, -0.03). Results were unaffected following adjustment for maternal sociodemographic and child health factors.

EF scores did not differ substantially across perinatal HIV exposure groups, though we observed some evidence that CPHIV may thrive in the BRI domain. Further research is needed to fully understand this finding.

Caregiver and household predictors of stunted child growth in the Asenze cohort, South Africa

Rachel Gruver Nonhlanhla Myeza Claude Mellins Jane Kvalsvig Shuaib Kauchali Silvia Martins Saloshni Naidoo Myra Taylor Chris Desmond Jeremy Kane Leslie Davidson

Background:

Stunted growth (low height for age) indicates chronic undernutrition or illness, and has irreversible effects on child development, health and cognition. In South Africa, prevalence of stunting in children under 6 is 27%, well above national/WHO targets. Here we identify factors associated with stunting at age 7 in a peri-urban area with high HIV prevalence.

Methods:

The community-based Asenze cohort study measured child growth at average ages 5 and 7 years (n=1404). At age 5, HIV status was assessed for the child and their primary caregiver using rapid test or caregiver report, and caregivers completed measures of depression and anxiety (Client Diagnostic Questionnaire); experience of intimate partner violence (IPV); alcohol use (AUDIT scale); household food insecurity, measured as running out of food on one or more days in the past month; and the CHAOS scale measuring disorganization of home environment. We calculated stunting, defined as height-for-age <-2 SD of the WHO Child Growth Standards median. We used chi-squared tests to identify factors associated with stunting at age 7. Multivariable analysis and analysis of stunting trajectories from ages 5-7 will also be presented.

Results:

Caregiver HIV infection, major depression, and experience of IPV each predicted stunted child growth 2 years later (11% of children whose caregiver had HIV were stunted, vs. 8% with HIV-negative caregiver; 14% whose caregiver had major depression were stunted, vs. 8% without; 10% with caregiver IPV were stunted, vs. 6% without), as did child HIV infection (35% with HIV were stunted, vs. 8% of those HIV-negative); all significant at p<0.05. Notably, household food insecurity did *not* predict stunting, nor did caregiver anxiety, caregiver alcohol misuse, caregiver mild/moderate depression, or household chaos.

Conclusions:

Further research should investigate the hypothesized roles of caregiver factors (major depression, IPV and HIV) in stunting to inform potential interventions.

Gestational age, birth weight and adolescent neurocognitive development in Tanzania Nandita Perumal Karim P. Manji Anne Marie Darling Rodrick R. Kisenge Ingrid Kvestad Mari Hysing David C. Belinger Willy Urassa Tor A. Strand Christopher P. Duggan Wafaie Fawzi Christopher R. Sudfeld

Objectives: To investigate the association between gestational age (GA), birthweight, and birthweight adjusted for GA, with domains of adolescent neurocognitive development and behavioral problems in Tanzania.

Study Design: Data from a long-term follow-up of adolescents aged 11 to 15 years born to women previously enrolled in a randomized controlled trial of prenatal multiple micronutrient supplementation in Dar es Salaam, Tanzania, were used. A battery of neurodevelopmental tests were administered to measure adolescent general intelligence, executive function, and behavioral problems. The INTERGROWTH-21st newborn anthropometric standards were used to derive birthweight-for-GA z-scores (BWGA z-scores). We assessed the shape of relationships using restricted cubic splines, and estimated the associations of GA, birthweight, and BWGAZ with adolescent development using multivariable linear regressions. We used inverse probability censoring weights to account for loss-to-follow-up.

Results: Among adolescents studied (n = 421), higher GA (per week), birthweight (per 100 grams), and BWGAz (per standardized z-score) were linearly associated with higher intelligence score (adjusted standardized mean difference (aSMD): 0.05 SD (95% CI: 0.01, 0.09), 0.04 SD (95% CI: 0.02, 0.06), and 0.09 SD (95%CI: 0.01, 0.17), respectively). Birthweight and BWGA z-score, but not GA, were also associated with improved executive. Low birthweight (<2500 grams) was associated with lower intelligence and executive function scores, but higher behavioral problem score. Associations between birthweight and executive function were stronger among adolescents born to women with higher education.

Conclusion: Duration of gestation and birthweight were positively associated with adolescent neurodevelopment in Tanzania. These findings suggest that interventions to improve birth outcomes may also benefit adolescent cognitive function.

COVID-19 and preterm birth: Understanding the relationship Louisa Smith Camille Dollinger Diego Wyszynski Sonia Hernandez-Diaz

Background: Evidence has accumulated throughout the COVID-19 pandemic suggesting that the disease is associated with increased risk of preterm birth. However, prior studies were conducted exclusively in hospitalized patients, lacked appropriate comparison groups, and/or only included infection late in pregnancy.

Methods: Participants enrolled in the International Registry of Coronavirus Exposure in Pregnancy while pregnant or within 6 months postpartum. Via online questionnaires, they provided demographic and health history information; COVID test results, symptoms, and treatments; and details on pregnancy outcomes. We compared risk of preterm delivery between those with COVID and those who tested negative. We used several study designs to assess risk after severe disease and throughout pregnancy.

Results: Over 17,000 participants were tested for SARS-CoV-2 or reported clinical diagnosis of COVID during pregnancy. 41% had a positive test or diagnosis. The majority (54%) joined before end of pregnancy, and 31% have reported pregnancy outcomes so far. Of 5,214 live births, 8% were delivered before 37 completed weeks of gestation. Of those with severe COVID, 67% reported cesarean delivery, compared to 41% of those testing negative. We estimated an adjusted OR of 1.7 (95% CI 1.3, 2.4) for preterm birth comparing COVID at any time during pregnancy to those without it. Among those with symptomatic COVID, the OR for preterm comparing severe to mild disease was 1.4 (1.2, 1.6) and moderate to mild was 1.0 (0.9, 1.1). From a case-time-control analysis comparing COVID exposure in the month prior to delivery vs. earlier in pregnancy and adjusting for time trends, we estimated an OR of 2.8 (CI 1.1, 7.5). A time-to-event analysis, which included participants still under follow-up, supported our findings.

Conclusion: Increased risk of preterm birth after COVID was primarily after severe disease in the third trimester. We continue to collect outcomes on thousands of participants.

"CODE LABOR": An Evidence Based and Interdisciplinary Approach to Managing Women Experiencing Precipitous Labor Outside of the Labor and Delivery Unit Rachel Wooten

"CODE LABOR": An Evidence Based and Interdisciplinary Approach to Managing Women Experiencing Precipitous Labor Outside of the Labor and Delivery Unit

Structured Abstract

LOCAL PROBLEM
Precipitous delivery refers to childbirth that occurs within 3 hours of the commencement of labor. Despite the commonality of childbirth, precipitous deliveries can incite adverse obstetrical events that can result in poor obstetrical outcomes. In a 346-bed, rural hospital in northern Alabama, the Director of Women's and Children's Service report 75 to 100 babies are currently delivered monthly with a reported average of two precipitous deliveries occurring monthly.

OBJECTIVE
The intent of the present work was to address a cohort (n=75) of obstetrical (OB) and emergency department (ED) nurses' knowledge gaps regarding the care of women experiencing precipitous labor outside of the labor and delivery unit by introducing an evidence based and interdisciplinary organizational policy for quality improvement, "CODE LABOR", and an OB assessment and care algorithm called the "CODE LABOR Care Pathway".

DESIGN
A non-probability, quota sampling method was used for nurses working in the ED Women's and Children's Department. This quasi-experimental design aims at quality improvement from the healthcare system's level and influencing improved organizational and patient outcomes.

PARTICIPANTS
Fifty-seven staff nurses employed in the ED and the labor and delivery unit participated in this interdisciplinary quality improvement project.

INTERVENTION/MEASUREMENTS
Pre- and post-educational surveys were conducted to evaluate perceived limitations and improvements in interdisciplinary communication and care of women experiencing precipitous labor. Using 12 sessions, 57 nurses were presented with education specific to managing women experiencing precipitous labor outside of the labor and delivery unit while including concepts of interdisciplinary communication and teamwork. Evaluation of Hospital Consumer Assessments of Healthcare Providers and Systems (HCHAPS) reports, retrospective chart reviews of women who have experienced precipitous deliveries, and post-hoc interviews were conducted to evaluate patient satisfaction outcomes, neonatal indicators, and use of CODE LABOR policy.

RESULTS
Using multi-variate analyses, pre-educational data revealed (a) moderate to well communication was felt to occur between the OB and ED nurses prior to the CODE LABOR education ($\bar{x}$=3.84), (b) the average ages of the research population were 31-40 years ($\bar{x}$=35.5) with an average level of nursing experience of 5-10 years ($\bar{x}$=7.5), and (c) 50.8% of participating nurses felt comfortable or neutral when caring for an obstetrical patient experiencing precipitous labor and delivery ($\bar{x}$=29). The pre-educational research was significant with a P-value of .005181.

Post-educational data revealed (a) feelings of interdisciplinary communication improved ($\bar{x}$=4.42 on a Likert scale 1-5) and (b) the nurses' overall level of comfort improved with 56.1% reporting very comfortable and 31.5% reporting comfortable (p= .00001).

While performing retrospective chart reviews, it was determined that 393 obstetrical clients presented to the emergency department for initiation of care during the project's time frame. It was determined that nine women experienced precipitous labor and delivery (1.8%). Seven women delivered within 7 to 40 minutes after arriving to the labor and delivery unit and two deliveries occurred outside of the labor and delivery unit (0.5%). Post-hoc interviews revealed positive utilization of the CODE LABOR policy and the "CODE LABOR Care Pathway" 50% of the time. The CODE LABOR kit and precipitous delivery tray were transferred to the ED triage area instead of the ED trauma room. Retrospective chart reviews of the precipitous deliveries (n=9) revealed one neonatal Apgar score below seven at 5 minutes after birth (11% below goal of Apgar scores of seven or greater at 5 minutes).

HCHAPS data specific to the OB unit were evaluated for process improvement related to patient experience as reported by patient observation. Criteria evaluated included nurse communication and likelihood to recommend the hospital to friends and family, a component of patient satisfaction. Published fourth quarter 2018 data disclosed an 84.3% satisfaction rate of nurse to patient communication and a 70.6% recommendation of the hospital to friends and family (n=17) (GRMC HCHAPS Inpatient Report, 2018). First quarter 2019 data revealed an 80.2% satisfaction rate of nurse to patient communication and 71.7% that would recommend the hospital to friends and family (n=10) (GRMC HCHAPS Inpatient Report, 2019).

CONCLUSION

Incorporating evidence based practice by instituting an interdisciplinary institutional policy helps nurses increase their assessment skills, critical decision making processes, collaborative communication, and teamwork. The influence of the CODE LABOR Policy on the OB and ED units' cultures and patient outcomes is evident. Both clinical administrators and nurses of the OB and ED units must fully harness the guidelines set forth by the CODE LABOR Policy to continue to capture knowledge gaps and improve communication and teamwork.

Keywords: code labor, precipitous labor, evidence-based practice,interdisciplinary

Age of juice introduction and childhood weight status at 7-9 years old Sonia Robinson Rajeshwari Sundaram Diane L. Putnick Akhgar Ghassabian Jessica L. Gleason Danielle Stevens Erin M. Bell Edwina H. Yeung

In 2017, the American Academy of Pediatrics (AAP) recommended delaying juice introduction until 12 months (mo.), revising a previous guideline to not introduce juice until 6 mo., due to concerns of weight gain. However, few studies have evaluated prospectively if juice introduction is related to childhood weight status.

We aimed to assess the relation of juice introduction with child weight status at 7-9 years (y) in the Upstate KIDS cohort. Women and their children were enrolled at 4 mo. postpartum (n=4989). Sociodemographics were obtained from questionnaires or birth certificates. At 4-18 mo., women reported if they had introduced juice and the age of introduction, which was categorized as <6, 6-12, and ≥12 mo. At 7-9 y, women reported their child's height and weight at their last doctor's visit (n=1283). Body mass index-for-age z-scores (BMIz) were calculated using the CDC reference for age and sex. Controlling for sociodemographics and maternal BMI, we assessed the association of juice introduction with childhood BMIz using generalized linear mixed models with inverse probability weights to account for non-response to follow-up, multiple imputations for missing exposure and covariates, and an autoregressive correlation matrix for correlations between repeated outcomes.

Prevalence of childhood obesity (>95th percentile) at 7, 8, and 9 y was 16.8, 18.2, and 21.3%, respectively; mean (SD) BMIz was 0.4-0.5 (1.4-1.5). After adjustment, the risk of childhood obesity was 2.43 (95% CI 1.28, 4.59) times higher in children with juice introduction at <6 versus ≥12 mo. Further, juice introduction at <6 versus ≥12 mo. was related to a 0.35 higher BMIz (95% CI 0.09, 0.61) at 7-9 y. Juice introduction at 6-12 versus ≥12 mo. was not significantly related to childhood obesity or BMIz.

While the AAP recently updated their guidelines for juice introduction, childhood obesity was most starkly associated with introduction at <6 mo. with less observed benefit of delaying until 12 mo.

Pre- and perinatal correlates of ideal cardiovascular health (ICVH) during early childhood: a prospective analysis in the Healthy Start Study Wei Perng Ellen Francis Caylor Schuldt Gregory Barbosa Dana Dabelea Katherine Sauder

Objectives: To characterize prevalence of ideal cardiovascular health (ICVH) during early childhood (4-7 years), and to identify pre- and perinatal biological, sociodemographic, metabolic, and behavioral correlates of ICVH.

Methods: Among 350 mother-child pairs in the Healthy Start Study, we defined ICVH as no exposure to second hand smoke (SHS), ≥1 h/day of moderate-to-vigorous physical activity, BMI≤85th percentile; systolic and diastolic blood pressure<90th percentile; cholesterol<170 mg/dL, fasting glucose<100 mg/dL; and healthy diet, per the American Heart Association. Pre- and perinatal characteristics were obtained from questionnaires, medical records, and in-person visits. Due to low prevalence of ICVH, we focused on prevalence of meeting ≥6 metrics in the analysis. We examined bivariate associations of each characteristic with % meeting ≥6 metrics and included those that were significant (*P*<0.05) in a multivariable logistic regression model.

Results: ICVH prevalence at mean±SD age 4.7±0.6 years was 6.9%; boys had twice the prevalence as girls (9% vs. 4.4%). Most (>85%) children met criteria for SHS, BMI, blood pressure, cholesterol, and glucose, while only 1/3 met criteria for physical activity (31.4%) and diet (35.1%). In multivariable analyses, key correlates of ICVH were maternal weight status ($OR_{overweight/obese\ vs.\ non-overweight/obese}$=0.41 [0.23, 0.73]) and offspring sex ($OR_{male\ vs.female}$=2.14 [1.22, 3.65]).

Conclusions: At age 4-7 years, ICVH prevalence is already low, with diet and adequate physical activity being the limiting factors. Healthy maternal weight prior to pregnancy and male sex are potential determinants of childhood ICVH. Additional work is required to explore associations of early-life ICVH with future health outcomes.

Nutrition/obesity

Rapid Infant Weight Gain: infant predictor of adult disease Margaret Bosenbark

Rapid infant weight gain (RIWG) has been established as an infant predictor of adult diseases such as, coronary artery disease, hypertension, obesity, and diabetes type two. RIWG is well established in the literature with several key contributing factors, including infant feeding modality, ethnicity, maternal basal metabolic rate, socioeconomic status, timing of solid food introduction, and parenting response to infant temperament. The objective of this cross sectional retrospective quantitative study is to identify if parenting beliefs have an effect on infant growth. By better understanding the link between parenting and infant growth, this study will help to add evidence to the state of the science which seeks to establish a predictor set of variables surrounding RIWG. The specific aims of the study are to, identify where along a spectrum of parenting beliefs a participant falls, demonstrate infant growth patterns retrospectively across the first year of life, and understand the impact that parenting beliefs have on infant growth after controlling for a set of predictor variables; maternal age, BMI, highest level of education, socio-economic status, ethnicity, infant gender, breastfeeding status, timing of solid food introduction, parenting style, and infant weight gain. The sample included English-peaking, first-time moms whose infant is between 12 and 24 months old. The infant must be a singleton, term infant with no medical diagnosis that would impact growth and development. Each mother completed a demographic and parenting survey, had their height and weight measured and then granted HIPPA access to their infant's growth chart data for review. Logistic regression analysis was performed with the current sample. Each predictor variable was analyzed separately to determine if it should be included in the model. Variables meeting a significance threshold were included in the overall model showing a moderate ability to predict rapid infant weight gain

Nutrition/obesity

Dietary Correlates of Periconceptional and First Trimester Ultra-Processed Food Intake
Samrawit Yisahak Stefanie N. Hinkle Sunni L. Mumford Katherine L. Grantz Cuilin Zhang Jagteshwar Grewal

Objective: Characterizing diet by the extent of processing rather than nutrients/food groups has gained recent attention as a more translatable framework for nutritional counseling. Ultra-processed food (UPF) intake has been described in the general population, but is understudied among pregnant women. We described UPF intake in a diverse multisite US pregnancy cohort, and examined whether it is a marker of poor dietary quality by estimating the correlation with commonly used diet quality scores.

Methods: Women with singleton pregnancies (n=1605) completed a 145-item food frequency questionnaire (FFQ) at gestational weeks 8-13, reflecting diet in the past 3 months. Quantity of intake of 29 food and beverage items identified as UPFs was ranked into quartiles. Characteristics across quartiles of UPF were compared using chi-squared tests and ANOVA. Correlation and agreement between UPF and diet quality (continuous and quartiles) was examined using Pearson correlation coefficients (r) and weighted kappa statistics (κ), respectively.

Results: Median (IQR) UPF intake in the sample was 1139 (64, 2674) grams/day. Women with higher UPF intakes were more likely to identify as non-Hispanic black (p <.0001) and nonvegetarian (p <.005) as well as be younger (p <.0001), have lower income (p <.05), and have higher BMI (p <.05). UPF intake was inversely correlated with Healthy Eating Index-2010 (r = -0.26, κ = -0.17 (-0.20, -0.14)), Alternative Healthy Eating Index-2010 (r = -0.22, κ = -0.15 (-0.18, -0.12)), Dietary Approaches to Stop Hypertension (r = -0.23, κ = -0.13 (-0.16, -0.10)), but not alternate Mediterranean diet score (r = -0.01, κ = -0.003 (-0.04, 0.03)).

Conclusions: UPF intake among pregnant women had an inverse and minor correlation with some healthy diet quality scores. Future work should examine if this translates to associations of UPF with adverse pregnancy outcomes to ultimately inform dietary counseling during prenatal care.

The effect of sleep duration on the association between food insecurity and childhood obesity. Wendemi Sawadogo Tilahun Adera

Background: Childhood obesity has increased globally during the past four decades. Multiple studies have reported an association between food insecurity and obesity. However, little is known about the impact of sleep duration on this association specially among children. The purpose of this study was to examine the association between food insecurity and childhood obesity and to investigate whether sleep duration mediate such association.

Method: Data was obtained from the 2018 National Survey of Children's Health (NSCH). The study included children age 10 to 17 years. The exposure variable was food insecurity during the past year, the mediator variable was sleep duration during the past week, and Body Mass Index at the time of the survey was used to classify participants as with/without obesity. Covariates included age, sex, race/ethnicity, education, poverty ratio and physical activity. We employed logistic regression models to investigate the association between food insecurity and childhood obesity. Utilizing causal mediation analysis within a counterfactual framework, we decomposed the total effect of food insecurity into natural direct and indirect effect.

Result: The prevalence of obesity was estimated at 15.11% in our study population. The total effect of food insecurity on obesity was (OR=1.88; 95% CI: 1.68-2.07), the controlled direct effect of food insecurity on obesity was (OR=1.85; 95% CI: 1.65-2.04), and the natural indirect effect was (OR=1.02; 95% CI: 1.00-1.03). The proportion mediated by sleep duration was 3.65 (1.56-5.74).

Conclusion: Food insecurity increases the risk of obesity among children. Although the mediation effect of sleep duration is significant, the percentage mediated is relatively small. These results suggest that the association between food insecurity and obesity may develop mostly through pathways that do not involve sleep duration.

Gestational weight gain trajectories by pregnancy obesity class and infant size at birth Julie
Petersen Lisa Bodnar Katherine Ahrens Samantha Parker Martha Werler Jennifer Hutcheon

Background: The current US recommendations for gestational weight gain (GWG) were derived
primarily from studies examining total gain (weight change from start to end of pregnancy). Our
understanding of how GWG trajectory affects health outcomes remains limited, especially within
classes of prepregnancy obesity.

Methods: We investigated GWG in the 2nd and 3rd trimester in relation to small- and/or large-for-
gestational age (SGA/LGA) among women with prepregnancy obesity. Data were from a case-cohort
study of medical records (Pittsburgh, PA, 1998-2010). Serial antenatal weights (median±std 9±2.7
measurements per participant) informed group-based latent GWG trajectories. We used modified
Poisson regression to estimate risk ratios for SGA/LGA, defined as livebirths 90th percentile,
respectively, according to ultrasound-based standards. The trajectory most closely approximating
the US maternal weight gain recommendations in the 2nd and 3rd trimester (0.4-0.6 lbs/wk) served
as the reference. All analyses were stratified by obesity class.

Results: The class I, II, and III subcohorts included 1071, 1031, and 991 women, plus 199, 134, and
101 SGA cases and 306, 248, and 217 LGA cases. We identified four GWG trajectories: low
(median±std 0.2±0.3 lbs/wk), (approximately) as recommended (0.7±0.2 lbs/wk), higher (1.1±0.2
lbs/wk), and highest (1.7±0.3 lbs/wk). Low gain was associated with a 10-30% reduction in LGA risk
in all classes, a 60-70% increase in SGA risk in classes I and II, but only a 20% increase in SGA risk
in class III. Higher/highest gain was associated with increased LGA risk in all classes and highest
gain increased SGA risk in class III, although the estimate was imprecise.

Conclusion: Our findings suggest lower than recommended gain may reduce risk of LGA, while not
substantially increasing risk of SGA, for women with class III obesity. This could be clinically
significant given the increased risk of childhood obesity associated with being born LGA.

Adolescent Pregnancy correlates on Offspring Nutritional Status from Childhood to Early Adolescence: Longitudinal evidence from Peru Daniel Antiporta Alvaro Munoz David Celentano Laura Caulfield Robert Blum

Background: Limited evidence, primarily from high-income countries or cross-sectional data, links adolescent pregnancy and early childhood nutrition. We quantified the association of adolescent, young adult, and older adult childbearing with their offspring's nutritional status from one year of age to early adolescence in Peru.

Methods: We analyzed data of first- and second-born offspring across five study visits, representing 14 years of follow-up, from the Young Lives Study. We assessed three nutrition indicators: height for age z-score (HAZ), BMI for age z-score (BMIAZ), and dietary diversity index, as well as their categorical forms: stunting, overweight/obese, minimum dietary diversity. We estimated, stratified by birth order, differences in nutrition indicators by maternal age of delivery (adolescent vs. young adult, adolescent vs. adult) using mixed-effects models and doubly robust estimation. We reported average marginal effects at ages 1, 5, 9, and 13; to quantify the gap between children born to adolescent and adult mothers throughout childhood and early adolescence.

Findings: The total eligible sample included 1,311 children, representing 6,229 observations in the five assessment rounds. Most children were firstborn, lived in the Andean region and urban areas. Firstborn children to adolescent mothers showed substantial lower HAZ (β: -0.29, 95% CI: -0.50, -0.08) and higher stunting rates (PR: 1.66, 95% CI: 1.11, 2.47) compared to their adult counterparts. Stunting average marginal effects exceeded nine percentage points even at age 13 in detriment to children born to adolescent mothers (PD: 9.18, 95% CI 3.89, 14.46). No associations were found for BMIAZ, overweight/obesity, and dietary diversity by maternal age or among second-born children.

Interpretation: Firstborn children born to adolescent mothers had worse growth outcomes than children born to young adult or adult mothers, which start during early childhood and remain until early adolescence. Our findings represent an opportunity to prioritize adolescent mothers in safety net programs during sensitive periods of development and nutrition as well as through adolescence.

Associations of dietary glycemic index and load during pregnancy with blood pressure, placental hemodynamic parameters and the risk of gestational hypertensive disorders. Clarissa Wiertsema Rama J. Wahab Annemarie G.M.G.J. Mulders Romy Gaillard

Background: In non-pregnant populations, adherence a low-glycemic index or low-glycemic load diet seems to lower blood pressure. We hypothesized that maternal adherence to a lower dietary glycemic index and load during pregnancy improves gestational hemodynamic adaptations and reduces the risk of gestational hypertensive disorders.

Aim: To examine the associations of dietary glycemic index and load with maternal blood pressure, placental hemodynamic parameters and the risk of gestational hypertensive disorders.

Methods: In a population-based cohort among 3378 pregnant Dutch women, dietary glycemic index and load were assessed from food frequency questionnaires at median 13.4 (95% range 9.9-22.9) weeks gestation. Blood pressure was measured in early, mid and late pregnancy and placental hemodynamic parameters were measured in mid and late pregnancy. Data on gestational hypertensive disorders was acquired from medical records.

Results: Mean dietary glycemic index (sd) was 58 (3) and mean dietary glycemic load (sd) was 155 (47). Dietary glycemic index was not associated with blood pressure, placental hemodynamic parameters and the risk of gestational hypertensive disorders. Higher dietary glycemic load SDS was associated with a higher diastolic blood pressure in early-pregnancy, remaining after adjustment for socio-demographic and lifestyle factors ((0.98 (95% CI 0.35-1.61) mmHg per SDS increase in glycemic load). No other associations of glycemic load with blood pressure or placental hemodynamic parameters and the risk of gestational hypertensive disorders were present.

Conclusion: Within this low-risk pregnant population, we did not find consistent associations of dietary glycemic index and load with blood pressure, placental hemodynamic parameters and the risk of gestational hypertensive disorders. Further studies need to assess whether the effects on gestational hemodynamic adaptations are more pronounced among high-risk women with an impaired glucose metabolism.

Glycemic Control Trajectories and Associated Risk Factors among Women with Gestational Diabetes Yeyi Zhu Mara Greenberg Amanda Ngo Juanran Feng Assiamira Ferrara

Background: Gestational diabetes mellitus (GDM) affects over 350,000 U.S. pregnant women annually, posing significant economic and healthcare burden. Although glycemic control (GC) is the cornerstone of GDM management, population-based data on GC trajectories after GDM diagnosis are lacking.

Objectives: We aimed to identify GC trajectories from GDM diagnosis to delivery and examine their associations with patient, social-contextual, and healthcare level factors.

Methods: In a multi-racial/ethnic cohort of 28,026 women with GDM in Kaiser Permanente Northern California (2007-2017), self-monitored blood glucose (SMBG) levels were recorded by a universal, centralized monitoring program. Optimal GC was defined as ≥80% of SMBG meeting the American Diabetes Association goals (fasting ≤95 mg/dL; 1-hr postprandial ≤140 mg/dL). Latent class models profiled GC trajectories using serial SMBG measurements.

Results: On average, women with GDM had 19.9 (standard deviation 13.4) counts of SMBG values per week over 11.8 (6.6) weeks. Four distinct GC trajectories were identified: stably optimal [group (G)1: 47.3%], low to optimal (G2: 26.4%), moderate with fluctuations (G3: 9.3%), and low to moderate (G4: 17.1%). Over 90% of patients improved their GC across pregnancy and 75% of patients reached optimal GC by 10 weeks after diagnosis of GDM. Compared to G1 (stably optimal GC), non-white race/ethnicity, pre-pregnancy obesity, alcohol use in pregnancy, and GDM severity by oral glucose tolerance test results were positively associated with less optimal trajectories G2-4, whereas adherence to the monitoring program and daily frequency of SMBG were inversely associated with G2-4 (all P <0.05). Compared to G2 (those that started with poor but improved to optimal GC), neighborhood poverty, Medicare/Medicaid, multiparity, smoking in pregnancy, GDM severity, and GDM diagnosis at <24 weeks of gestation were positively associated with G4 (those that started with poor but improved to moderately optimal GC; all P <0.05).

Conclusions: Our findings illustrated distinct phenotypes of GC among women with GDM. Several patient, socio-contextual, and healthcare level factors were associated with GC trajectories, which may inform future multi-component interventions to optimize GC and improve GDM care and management.

Associations between gestational weight gain adequacy and obstetric intrapartum interventions: observational population-based study in France Melissa Amyx Jennifer Zeitlin Béatrice Blondel Camille Le Ray

Gestational weight gain (GWG) guidelines were published by the Institute of Medicine (IOM), as excessive GWG is associated with gestational complications. However, GWG as a risk factor for intrapartum interventions is understudied. Our objective was to evaluate associations between GWG adequacy and obstetric interventions (cesarean section [CS]; oxytocin administration; episiotomy use). Using nationally-representative French National Perinatal Survey 2016 data, we included term cephalic singleton pregnancies with trial of labor (N=9724). GWG was calculated as end of pregnancy minus prepregnancy weight and categorized as inadequate, adequate, or excessive by prepregnancy BMI (under-[<18.5], normal [18.5-24.9], over-[25-29.9] weight; obese≥$30kg/m^2$) using 2009 IOM thresholds. Intervention use by GWG adequacy was determined. Multilevel GEE logistic regression models, adjusted for *a priori* confounders, evaluated intervention-GWG adequacy associations. Analyses were stratified by BMI (under+normal weight; overweight; obese) and parity (primiparas; multiparas). Among under+normal weight women, excessive GWG was associated with increased CS (primiparas: 15.3% vs 12.7% for adequate GWG; multiparas: 6.3% vs 3.5% for adequate GWG); following adjustment, the association persisted among under+normal weight multiparas (aOR 1.8, 95%CI 1.2, 2.7). Similarly, excessive GWG was associated with increased oxytocin use among under+normal weight women (primiparas: 65.0% vs 60.8% for adequate GWG; multiparas: 36.2% vs 29.1% for adequate GWG), an association which persisted among under+normal weight multiparas (aOR 1.3, 95%CI 1.1, 1.6). Further, oxytocin use was increased among overweight primiparas with excessive GWG (72.5% vs 58.7% for adequate GWG; aOR 1.8, 95%CI 1.1, 2.9). No consistent associations were found for episiotomy. Excessive GWG may be a more important risk factor for specific intrapartum obstetric interventions for under+normal weight women than for obese women.

Prenatal exposure to perceived stress, maternal asth¬¬ma, and placental size Sadia Saizy Pauline Mendola William Grobman Akila Subramaniam Danielle Stevens Sunni Mumford Kate Larson Zhen Chen Lynne Messer Virginia Duncan Ona Faye-Petersen Rajesh Kumar Andrew Williams

Background: Prenatal exposure to stress is associated with poor pregnancy outcomes, yet evidence linking stress and placental size is limited. Asthma is associated with worse pregnancy outcomes and women with asthma may be more susceptible to stress. We examined the association between stress and placental size among women by asthma status in the B-WELL-Mom study, a prospective cohort study focused on asthma in pregnancy.

Methods: 293 women (221 with asthma) had measures of placental weight (gm), length (cm), width (cm), and thickness (cm) measured by a pathologist. Stress was measured using the Perceived Stress Scale (PSS) at 30 weeks gestation on average (range: 27-36). PSS scores were categorized into quartiles (lowest-score quartile used as reference). Linear regression models estimated associations (95% confidence intervals (CI)) between stress and placental measures. Models were adjusted for maternal demographic and medical factors, health behaviors and gestational age at birth, and were run for the overall sample and by asthma status.

Results: Overall, high levels (Quartile 4) of perceived stress were associated with lower placental weight (-53.61 (CI: -94.21,-12.99)), width (-1.10 (CI: -1.79,-0.34)), and length (-1.11 (CI: -2.03,-0.19)), but not thickness (0.02 (CI: -0.19,0.25)). This association was stronger among women with asthma for placental weight (asthma: -65.22 (CI: -113.18,-17.26); no asthma: -24.15 (CI: -109.00,60.69)), width (asthma: -1.16 (CI: -2.00,-0.31); no asthma: -0.80 (CI: -2.29,0.67)), and length (asthma: -1.36 (CI: -2.45,-0.26)); no asthma: -0.30 (CI: -2.15,1.54)), but not thickness (asthma: 0.09 (CI: -0.16,0.34); no asthma:-0.19 (CI: -0.69,0.31)).

Discussion: Higher levels of perceived stress were associated with smaller placental size, particularly among women with asthma. More research is needed to understand how prenatal exposure to perceived stress restricts placental size, and to further explore the effect of maternal asthma.

Obstetric health

Cesarean delivery in nulliparous, singleton, cephalic, term pregnancies, and recurrence in Norway, 1967-2014: A register-based study Yeneabeba Tilahun Sima Rolv Arnold Skjærven Liv Grimstvedt Kvalvik Nils-Halvdan Morken Kari Klungsøyr Linn Marie Sørbye

Background: Advanced maternal age may increase the risk of cesarean delivery (CD), and a high CD recurrence may increase risk of later complications. The aims were to describe long-term changes in CD and estimate recurrence risk related to changing sociodemographic patterns in Norway from 1967 to 2014.

Methods: Data from the Medical Birth Registry of Norway was used to describe CD by maternal age groups (years): <20 (reference), 20-24, 25-29, 30-34, >=35 and onset of labor: spontaneous (reference), induced and pre-labor CD. Nulliparous women with singleton, cephalic, term deliveries were followed through their first and second births. Seven risk factors in first pregnancy (abruptio placenta, diabetes mellitus, hypertension, preeclampsia, postdate, premature rapture of membrane and placenta previa) were used to group women into lower (no factors) and higher (one or more factors) risk of CD. Risk estimates were stratified by periods: 1967-1982, 1983-1998 and 1999-2014. Multivariable regression models were used to estimate relative risk (RR) with 95% confidence interval (CI), adjusting for sociodemographic factors.

Results: A total of 952,643 women were included and the prevalence of CD in the first birth across periods increased from 3.3% to 10.2% and from 6% to 20.5% in lower and higher risk women, respectively. Overall, women >= 35 years had the highest risk of CD, however, CD risk increased in women < 35 years across periods. Compared to women with spontaneous onset, the RR of CD in women with induced onset of labor increased from 3.2 (95% CI 3.0-3.3) to 5.4 (95% CI 5.2-5.5) across periods. Overall CD recurrence risk was 57.6%. The RR of CD recurrence, compared to women without CD in first birth, decreased from 22.4 (95% CI 21.9-23.1) to 8.8 (95% CI 8.6-9.1) from the first to the last period.

Conclusion: CD increased in Norwegian women <35 years both in the higher- and lower risk group. CD recurrence risk declined over period of 47 years.

Associations of duration of the second and active first stages of labor Louise Lundborg
Katarina Åberg Xingrong Liu Anna Sandström Olof Stephansson Ellen Tilden Mia Ahlberg

Background One important question in obstetrics is how fast labor progresses and when to
intervene due to slow labor. Historically labor is divided into phases despite the fact that is a
continuum. The relationship between the first and second stage of labor is surprisingly unexplored.
Objective To evaluate the associations of the duration of the active first stage with the duration of
the second stage and mode of delivery. **Design** Cohort study **Setting** Electronic medical records of
women delivering in Stockholm, Sweden 2008-2014. **Methods** Population-based data from 13 379
women with spontaneous onset of labor. The association was examined using both univariate and
multivariable quantile regressions. Active first stage was analyzed by quartiles. Linear regression
was used for the mean difference. Important confounders were adjusted for in the regression
analysis. Nonlinearity was tested by restricted cubic splines. The risk of instrumental delivery was
examined using logistic regression. The cumulative incidence of mode of delivery were estimated
using a multi-state model. **Results** The unadjusted median duration of active first stage was 6.3
hours, 90th and 95th being 12 and 14 hours respectively. Median duration of the second stage was 96
minutes, 95th percentile 270 minutes. A positive association was seen between the duration of the
second and active first stage of labor across all quantiles. The estimated regression curves showed
an increasing trend, followed by a plateau at 12 hours or more. Further, a higher likelihood of
operative vaginal delivery (adjusted odds ratio 3.3, 95% CI 2.9-3.9) and a 3.5-fold (95% CI: 2.9-4.4)
increased risk of cesarean delivery for women stratified into the fourth quartile compared to women
in the first quartile. **Conclusion** Increasing active first stage was associated with the duration of the
second stage and increased risk of instrumental delivery. Future research should take these
associations into account in the analyses.

Obstetric health

Counterfactuals in etiologic studies of interpregnancy intervals: "What ifs" and "buts" Julie Petersen Jennifer Hutcheon Kimberly Dukes Samantha Parker Martha Werler Katherine Ahrens

Adverse neonatal outcomes are more likely following short interpregnancy intervals. Yet, it remains unclear whether these associations are causal. It is unlikely a single biologic mechanism explains all observations and only minimal empirical data support proposed hypotheses. Interpregnancy interval length results from many factors, including fecundity, prior pregnancy/infant outcomes, health/childcare policies and access, and financial stability. Such data are minimal in vital statistics, on which most US research is based. In the Safe Passage cohort, we investigated propensity for short intervals (<6 months) versus the conventional reference group (18-23 months) by 7 domains (pregnancy planning, reproductive history, comorbidities, demographics, finances, living conditions, behaviors/lifestyle; each measured by 2-13 factors) stratified by self-identified racial group and study setting: American Indian ancestry and white (Northern Plains, US) and mixed ancestry (Western Cape, South Africa). Covariate profiles differed greatly, with little overlap in propensity scores for women with 0.2) differed by race/study setting. Among women of mixed ancestry, 5 domains had 1+ predictive factors; reproductive history was most important. In the US, all domains had 1+ predictive factors, but standardize differences were greater among white women compared to those of American Indian ancestry. Based on these data, it may be difficult to identify women in the reference group whose outcomes can stand in for what would have happened to women with short intervals had they instead, counterfactually, had longer intervals without comprehensive confounder data. Consideration of the full array of factors contributing interpregnancy interval length and how they may differ across populations may aid the design and validity of future interpregnancy interval research with causal questions.

Perceived stress during pregnancy and serum placental hormone levels Andrew Williams Siri Bardwell Kate Larson Sadia Saizy Pauline Mendola William Grobman Akila Subramaniam Sunni Mumford Zhen Chen Danielle Stevens Rajesh Kumar

Background: The association between prenatal exposure to perceived stress and placental function is not well understood. Maternal serum placental hormone concentrations reflect placental function, with lactogenic hormones of interest for their role in lactation. We examined the association between perceived stress during pregnancy and serum placental hormones in participants enrolled in the B-WELL-Mom study.

Methods: Serum drawn at 30 weeks (range 27-36 weeks) gestation was available for 329 women. Prolactin (ng/mL), lactogen (ng/mL), placenta growth hormone (PGH; pg/mL), IGF-1 (pg/mL) and IGF-2 (ng/mL) concentrations were measured via enzyme-linked immunosorbent assay method in duplicate and averaged. Stress scores were categorized into quartiles ("low" stress the referent). Linear regression models estimated associations and 95% confidence intervals (CI) for the association between stress and 3rd trimester average hormone levels. Models for each hormone were adjusted for demographic and medical factors, health behaviors, and infant sex, and .

Results: Women with higher stress (Quartile 4) had greater prolactin (6.01, CI: 2.72,0.67) and lactogen (19.51 CI: 4.81,34.22) concentrations. Higher stress early in pregnancy (11 weeks and 20 weeks) was also associated with greater prolactin and lactogen. At 30 weeks on average, higher stress may have a plateau effect on lower PGH (quartile 3: -243.11 CI: -459.45,-26.78); quartile 4: -189.46 CI: -434.02,55.10). Stress was not associated with IGF-1 or IGF-2.

Discussion: High stress early in pregnancy was associated with increased levels of lactogenic hormones (prolactin, lactogen) which play a role in lactation. Late in pregnancy, greater perceived stress is associated with lower PGH, which may be linked to placental development.

Tdap vaccination among pregnant women in the United States: whom are we missing? Rachel Smith Erinn Hade Mona Prasad Courtney Lynch

Newborns are at the highest risk of death due to pertussis, but providing Tdap boosters to pregnant women at 27 to 36 weeks of gestation decreases the risk by 80-91%. Thus, in 2013 the CDC's Advisory Committee on Immunization Practices (ACIP) recommended that women receive a Tdap booster during each pregnancy. To examine the impact of this recommendation and identify subgroups less likely to be vaccinated, we used data from Phases 7 (2012-2015) and 8 (2016-2018) of the CDC's Pregnancy Risk Assessment Monitoring System (PRAMS), a population-based complex sample survey of women who recently delivered a liveborn infant. We analyzed data from the 27 reporting areas with available Tdap data. We used Stata 15.1 incorporating survey stratification and sampling weights, producing population-based estimates. Prior to the recommendation (2012-2013), 24.5% (23.6-25.5%) reported receiving a Tdap during pregnancy, whereas after (2014-2018) the proportion was 67.2% (66.7-67.7%). In examining the most recent data during which Tdap vaccination status has stabilized at about 75% (2016-2018), some demographic subgroups have an increased odds of not receiving a Tdap during pregnancy after confounding adjustment. This includes, most notably: mothers 35+ years [odds ratio (OR)=1.16; 95% confidence interval (CI)=(1.04, 1.30)], Non-Hispanic Black women [OR=1.40; 95% CI=(1.24, 1.58)], women whose delivery was paid for by Medicaid [OR=1.51; 95% CI=(1.35, 1.68)]; women with <12 years of education [OR=1.69; 95% CI=(1.42, 2.01)], and women who reported receiving no prenatal care [OR=1.68; 95% CI=(1.07, 2.65)]. It is unclear if these findings reflect differences in offering Tdap vaccination or differences in uptake. The incidence of pertussis among infants <1 year has decreased, from 100.9 per 100,000 in 2014 to 52.8 in 2018. Despite this success, more work is needed to examine why infants of women, who are commonly considered underserved, are still not receiving the benefit of vaccination.

Natural history of fibroids in pregnancy: NICHD Fetal Growth Studies – Singletons cohort Susanna Mitro Zhen Chen Shyamal Peddada Germaine M. Buck Louis Jagteshwar Grewal Jessica L. Gleason Cuilin Zhang Katherine L. Grantz

Background: Up to 60% of women may have uterine leiomyomas (fibroids) by age 35, but prior studies of fibroid changes in pregnancy have been small and shown inconsistent findings. We investigated the natural history of fibroids in pregnancy in a racially diverse cohort.

Methods: Pregnant women (n=2774; 27% non-Hispanic (NH) white, 28% NH Black, 29% Hispanic, 17% Asian/Pacific Islander) had up to 6 study ultrasounds (US) in gestational weeks 10-41. Sonographers recorded fibroid number and volume of the 3 largest fibroids at each visit. Latent class models grouped trajectories of total fibroid volume and number. Chi-square tests compared predicted latent groups by race/ethnicity, body mass index (BMI), and age. US without observed fibroids were recorded as 0 in number and volume, or as missing if occurring between US with observed fibroids.

Results: Visualized fibroid prevalence was 9.6% (n=266 affected women, of whom 95% had ≥2 US). There were 3 volume trajectories, which did not differ by race, age, or BMI: Most women (83%) had constant small fibroid volume; 12% had larger, decreasing volume; and 5% had larger, constant volume. There were 3 trajectories of fibroid number, which varied significantly by race (p<0.01) and age (p=0.04): 57% of women had on average 1 fibroid; 30% started with 1 fibroid and ended with 0 (more likely to be NH white and <30 years old); and 13% had on average 4 fibroids and decreased to 2 (more likely to be NH Black and >30 years old). Sensitivity analyses limited to women with only anterior fibroids (n=120) and women with ≥5 US (n=199) were similar, indicating that difficulty visualizing most fibroids and the pattern of missing data did not substantially alter results.

Conclusion: Total fibroid volume and number were stable or decreased in pregnancy. Race and age were associated with fibroid number changes; NH Black women were more likely than others to have multiple fibroids.

Longitudinal semen quality in an infertility treatment-seeking population Elizabeth DeVilbiss Lindsey Sjaarda C. Matthew Peterson Jim Hotaling James Mills Pauline Mendola Douglas Carrell Erica Johnstone Zhen Chen Neil Perkins Ginny Ryan Amy Sparks Rachel Whynott Traci Clemons Sunni Mumford Enrique Schisterman

Background: Semen analyses are the cornerstone of male infertility treatment. While guidelines recommend two semen analyses due to inter-test variability, there is a lack of robust data on how semen parameters change over time.

Methods: In a longitudinal study of men (n=2369) seeking infertility care, semen quality was assessed using standardized procedures by quantification of sperm concentration, volume, motility, morphology, count, and total motile count at baseline and 2-, 4- and 6-months post-randomization. The data were analyzed using weighted generalized linear models accounting for repeated study visits per participant; adjusted models accounted for study site, randomized treatment, infertility treatment stratum, male fertility diagnosis at baseline, physical activity, age, BMI, abstinence duration, smoking status, and fever since last visit.

Results: Sperm concentration, morphology, count, and total motile count did not change significantly over 6 months of follow-up. Motility was reduced by 0.9-1.0% at 2- and 4- months follow-up, but did not differ at 6 months relative to baseline. Only semen volume was reduced 0.1 to 0.2 mL from baseline at each of the three follow-up visits. Semen quality parameters were missing for 14%, 27%, and 31% of men at the 2-, 4-, and 6-month study visits, respectively.

Conclusions: Semen parameters did not seem to meaningfully vary over 6 months of follow-up. In similar populations, a single assessment may be sufficient to guide fertility care. While a small decrement in semen volume was observed, the clinical importance of this requires further evaluation.

Longitudinal semen quality and live birth among an infertility treatment-seeking population Elizabeth DeVilbiss Lindsey Sjaarda C. Matthew Peterson Jim Hotaling James Mills Pauline Mendola Douglas Carrell Erica Johnstone Zhen Chen Neil Perkins Ginny Ryan Amy Sparks Rachel Whynott Traci Clemons Sunni Mumford Enrique Schisterman

Background: While a semen analysis remains the cornerstone of the evaluation of male fertility potential, relations between semen quality across the spectrum of male fertility and live birth are not well understood. Prior studies report mixed findings, and no prior work has examined relations between longitudinal semen quality and live birth.

Methods: Couples seeking fertility consultations in a large clinical trial (n=2369) received *in vitro* fertilization (IVF), intrauterine insemination (IUI), or ovulation induction (OI) medications only or no fertility treatment over follow-up. Semen quality was assessed at baseline and 2-, 4- and 6-months post-enrollment by quantification of sperm concentration, volume, motility, morphology, count, and total motile count. Adjusted identity-binomial models estimated risk differences between quartiles of semen parameters across all study visits and live birth, stratified by fertility treatment received. Stabilized inverse probability weights accounted for men who missed study visits and multiple imputation addressed additional missingness. Live birth was ascertained for all participants from pregnancies occurring within 9 months of enrollment.

Results: Among couples utilizing OI only or no treatment (n=1377), the lowest quartile of each semen parameter was associated with 13 to 22 fewer live births per 100 couples, relative to the highest quartile. Among couples utilizing IUI (n=613), the lowest quartile of concentration, count, and total motile count, were associated with 6 to 9 fewer live births per 100 couples. Associations were largely null among participants utilizing IVF (n=380). Thirty-five percent of couples attained a live birth.

Conclusions: In this large study of couples intending fertility treatment, low semen quality was associated with reduced probabilities of live birth among couples utilizing non-IVF treatments or no fertility treatment. IVF appeared to overcome the impact of reduced semen quality.

Exposure to environmental chemicals and infertility among U.S. women of reproductive age Valerie Martinez Irene Yen Camila Alvarez Sandie Ha

Background: Global production of potentially dangerous chemicals increased 23.5 times from 1947 to 2007. These ubiquitous environmental chemicals have endocrine disruption properties and may affect female infertility but evidence is limited.

Objectives: We explored sociodemographic variations in exposures to 32 common chemicals and examined their relationship with self-reported infertility among U.S. women.

Methods: Non-pregnant women ages 18-49 years without history of hysterectomy or oophorectomy (N= 2,535) were identified from the National Health and Nutrition Examination Survey (NHANES, 2013-2016). Socio-demographic factors and infertility were self-reported. Environmental chemicals were analyzed from blood, serum, or urine samples, and were dichotomized as high and low based on the median. Kruskal Wallis test examined the differences in chemicals exposures by sociodemographic factors. Logistic regression models estimated the odds ratio (OR) and 95% confidence intervals (CI) for the association between high chemical exposures and infertility. Models adjusted for potential confounders and complex probability sampling.

Results: Heavy metals and some pesticides had positive associations with infertility after adjusting for confounders, but the estimates were not statistically significant ($OR_{arsenic}$: 1.17 (0.77-1.76); $OR_{cadmium}$: 1.35 (0.98-1.85); $OR_{N, N-diethyl-3-methylbenzamide}$: 1.13 (0.62-1.89); $OR_{hexachlorobenzene}$: 1.25 (0.71-2.21). Compared to younger women, those who were ages 40-49 had significantly higher concentrations of polybrominated biphenyls, heavy metals, some pesticides, and per- & polyfluoroalkyl substances. Women with lower incomes (<45k) had significantly higher urine and blood concentrations of heavy metals, N, N-diethyl-3-methylbenzamide, and Bisphenol A compared to those with higher incomes.

Conclusions: There is no significant association between the chemical exposures and infertility, but exposures varied by sociodemographic characteristics.

Air pollution and fecundability: Results from a Danish preconception cohort study Amelia Wesselink Tanran Wang Matthias Ketzel Ellen Mikkelsen Jorgen Brandt Jibran Khan Ole Hertel Lauren Wise Anne Sofie Dam Laursen Jonathan Levy Kenneth Rothman Henrik Sorensen Elizabeth Hatch

A growing literature indicates that air pollution may adversely influence human reproduction. Yet most existing epidemiologic studies on air pollution and fertility are small or restricted to infertile study populations. We examined the association between residential exposure to air pollution and fecundability – the per cycle probability of conception – in a preconception cohort of 10,183 Danish couples. During 2007-2019, women aged 18-45 years who were trying to conceive completed an online baseline questionnaire and bi-monthly follow-up questionnaires for up to 12 months. We geocoded time-varying residential addresses during the year before baseline and used the DEHM/UBM/AirGIS dispersion modelling system to estimate the annual mean concentrations of nitrogen dioxide, nitrogen oxides, carbon monoxide, ozone, sulfur dioxide, $PM_{2.5}$ and PM_{10} (particulate matter with diameters <2.5 μm and <10 μm, respectively). We used proportional probabilities regression models to estimate fecundability ratios (FRs) with 95% CIs, adjusting for potential confounders and co-pollutants. We followed women until pregnancy or censoring event (stopped trying, loss to follow-up, fertility treatment initiation, or 12 menstrual cycles). Individual pollutants were positively correlated with one another (Spearman correlations: 0.41-0.96), except for ozone, which was inversely correlated with other pollutants. Annual average $PM_{2.5}$ concentrations were associated with slightly reduced fecundability: in comparison with the reference group (<8.0 μg/m^3), FRs for $PM_{2.5}$ concentrations of 8.0-9.9, 10.0-11.9, 12.0-12.9, and ≥13.0 μg/m^3 were 0.89 (95% CI: 0.82, 0.97), 0.87 (95% CI: 0.78, 0.96), 0.89 (95% CI: 0.73, 1.08), and 0.84 (95% CI: 0.62, 1.14), respectively. Associations were stronger among nulliparous women. Other pollutants were not appreciably associated with fecundability. Our results indicate that long-term air pollution exposure may be related to reduced fertility.

Examining the Co-occurrence and Risk Factors of Endometriosis and Polycystic Ovarian Syndrome Karen Schliep Felicity Hughes Joseph Stanford Germaine Buck Louis Amber Kiser C. Matthew Peterson

Polycystic Ovarian Syndrome (PCOS) and endometriosis are the two most common female reproductive disorders; however, limited research has assessed prevalence and risk factors for the co-occurrence of both conditions. We examined the overlap between prevalent PCOS and incident endometriosis, as well as risk factors for both. The study population includes 473 women, ages 18–44 years, who underwent a diagnostic and/or therapeutic laparoscopy or laparotomy. Women with a history of endometriosis were excluded. Endometriosis was diagnosed via surgical visualization and captured on operative reports completed by surgeons and PCOS by women's reporting ≤9 cycles/year along and history of polycystic ovaries, excessive body/facial hair, or inflammatory acne during the in-person enrollment interview prior to surgery. Age and site adjusted multinomial regression models were used to estimate prevalence ratios (aPR) and 95% confidence intervals (CI) of reproductive history characteristics by disease status (endometriosis only, PCOS only, or both endometriosis and PCOS), with estimated prevalence rates of 26%, 17% and 14%, respectively. A history of subfertility was associated with a higher probability of having both conditions (aPR 3.62; 95% CI, 1.97–6.62), followed by only endometriosis (aPR 2.64; 95% CI, 1.59–4.38) or PCOS (aPR 1.17; 95% CI, 0.63–2.20) compared to women with neither disease. Dysmenorrhea within the past 12 months was also associated with a higher probability of having both conditions (aPR 2.33; 95% CI, 1.32–4.12) followed by only endometriosis (aPR 2.15; 95% CI, 1.36–3.41) or PCOS (aPR 1.24; 95% CI, 0.72–2.15) compared to unaffected women. Our findings support that endometriosis co-morbid with PCOS is not uncommon, and that having both conditions is associated with higher subfertility than having either disease alone. Consideration of endometriosis among women with PCOS who continue to have difficulty conceiving after ovulation is restored is warranted.

Pesticide residue intake from fruit and vegetable consumption and risk of uterine fibroids Colette Davis Nichole Garzia Kara Cushing-Haugen Kathryn L. Terry Yu-Han Chiu Jorge E. Chavarro Stacey A. Missmer Holly R. Harris

Objective: Dietary factors may play a role in uterine fibroids etiology due to their potential to modify endogenous hormones and their inflammatory effects – these processes may be influenced by food contaminants including pesticides. We sought to examine the association between pesticide residue intake from consumption of fruits and vegetables and risk of ultrasound or hysterectomy-confirmed fibroids.

Design: Prospective cohort study using data collected from 52,982 premenopausal women from 1999-2009 in the Nurses' Health Study II.

Methods: Every four years, diet was assessed with a validated food frequency questionnaire. We classified fruits and vegetables into high- or low-pesticide-residues using a validated method based on surveillance data from the U.S. Department of Agriculture. Multivariable Cox proportional hazards models were used to calculate RR and 95% CIs for the association between high and low PRBS and fibroids.

Results: During 10 years of follow-up (median age at baseline 42 years), 4,285 incident cases of ultrasound or hysterectomy-confirmed fibroids were reported. No association was observed between intake of high-pesticide residue (RR for 5th vs 1st quintile=0.91; 95% CI=0.80-1.03; p_{trend}=0.12) nor the low-pesticide residue (RR for 5th vs 1st quintile=1.01; 95% CI=0.88-1.14; p_{trend}=0.84) fruits and vegetables and fibroids.

Conclusions: No clear associations were observed between intake of high or low pesticide residue fruits and vegetables and risk of uterine fibroids. These results suggest that pesticide residues on fruits and vegetables are not strong contributors to fibroid risk among women in their 30s, 40s, and 50s. Additional studies examining an exposure window more proximal to fibroid initiation among younger women and assessing class specific pesticides are needed.

Associations of gestational hypertensive disorders and maternal blood pressure with offspring blood pressure, and early markers of atherosclerosis at the age of 10. Clarissa J. Wiertsema Vincent W.V. Jaddoe Annemarie G.M.G.J. Mulders Romy Gaillard

Background: Gestational hypertensive disorders and a higher maternal gestational blood pressure are associated with higher offspring blood pressure. We hypothesized that exposure to an adverse in utero environment might lead to vascular alterations in the offspring of affected pregnancies, predisposing them to a higher blood pressure.

Aim: To examine the associations of gestational hypertensive disorders and maternal gestational blood pressure with offspring blood pressure and early atherosclerotic changes, and whether these associations are explained by gestational age and weight at birth, breastfeeding status and child adiposity.

Methods: In a population-based cohort among 4777 mother-offspring pairs, offspring blood pressure, carotid intima media thickness and distensibility were measured at the age of 10.

Results: Compared to normotensive pregnancies, offspring of mothers with gestational hypertension, but not preeclampsia, had higher systolic and diastolic blood pressure (difference: 0.17 (95% CI 0.02,0.31) and 0.23 (95% CI 0.08, 0.38) SDS in offspring systolic and diastolic blood pressure, respectively), which was not explained by birth and child factors. Higher maternal systolic and diastolic blood pressure in early, mid and late pregnancy were associated with higher offspring systolic and diastolic blood pressure and lower carotid distensibility (all p-values <0.05), persisting after correction for birth and child factors. No associations were found with offspring carotid intima media thickness.

Conclusion: Gestational hypertension and already a higher maternal blood pressure across the full range during pregnancy are associated with higher blood pressure in the offspring. Higher maternal blood pressure is also associated with decreased offspring carotid distensibility, indicating increased arterial stiffness. Further studies need to assess whether these associations reflect intrauterine mechanisms, or family-based shared lifestyle and genetic predisposition.

Associations of maternal angiogenic factors during pregnancy with alterations in cardiac development in childhood Meddy Bongers-Karmaoui

Reduced maternal placental growth factor (PlGF) and higher soluble fms-like tyrosine kinase (sFlt-1) levels in pregnancy may have persistent effects on offspring cardiac development. We examined the associations of maternal first and second trimester PlGF and sFlt-1 concentrations across the full range with childhood cardiac ventricular structure and function.

In a population-based prospective cohort among 2415 women and their offspring, maternal first and second trimester serum PlGF and sFlt-1 concentrations were measured.

Maternal angiogenic factors were not associated with childhood cardiac outcomes in the total population. In children born small-for-their-gestational-age, higher maternal first trimester PlGF was associated with a lower childhood left ventricular mass (-0.24 SDS (95%CI -0.42, -0.05 per SDS increase in maternal PlGF)), whereas higher sFlt-1, was associated with higher childhood left ventricular mass (0.22 SDS (95%CI 0.09, 0.34 per SDS increase in maternal sFlt-1)). Higher second trimester maternal sFlt-1 was also associated with higher childhood left ventricular mass (p-value<0.05). In preterm born children, a higher maternal first and second trimester sFlt-1/PlGF ratio was associated with higher childhood left ventricular mass (0.30 SDS (95%CI 0.01, 0.60), 0.22 SDS (95%CI -0.03, 0.40) per SDS increase in maternal sFlt-1/PlGF ratio in first and second trimester respectively). No effects on other childhood cardiac outcomes were present within these higher-risk children.

In a low-risk population, maternal angiogenic factors are not associated with childhood cardiac ventricular structure and function within the normal range. In children born small for their gestational age or preterm, an imbalance in maternal angiogenic factors in the first half of pregnancy was associated with higher childhood left ventricular mass only.

Child health and development

Treatment received mediates the association between race/ethnicity and survival in children diagnosed with central nervous system tumor types: An analysis of the National Cancer Database (NCDB) Kristin Moore Linday Williams Christopher Moertel

Central nervous system (CNS) tumors are the most common solid childhood malignancy comprising 25% of cancers in individuals aged 0-19 and are the leading cause of death from disease in this group. Racial and ethnic minority children have poorer outcomes than Non-Hispanic White (NHW) children, however studies have yet to investigate how much of this association is mediated by treatment received. Using the National Cancer Database (NCDB; 2004-2016), we identified children (age 0-19) diagnosed with brain and central nervous system tumors. Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated by race/ethnicity using a multivariable Cox proportional hazards model for 16 histologic types. Using an inverse odds weighting mediation analysis, we estimated the association between race/ethnicity and death with treatment received as a mediator. We included 22,469 cases. The association between race/ethnicity and death was partially mediated by the treatment received for all CNS tumors in Black (indirect HR 1.11; 95% CI 1.07, 1.14) and Hispanic children (indirect HR 1.06; 95% CI 1.01, 1.11) compared to NHW. Even when accounting for mediation by treatment, the direct effect of race/ethnicity on death was still higher for Black (direct HR 1.16; 95% CI 1.15, 1.17) and Hispanic (direct HR 1.26; 95% CI 1.24, 1.29) compared to NHW children. Treatment received did not mediate the associations between Black race and death after glioblastoma or API race in medulloblastoma. These findings suggest that while the type of treatment received may mediate some associations in CNS tumors, there are still complex societal and biologic factors experienced by minority children that also likely contribute to the observed survival disparities.

Child health and development

Early Life Household Pesticide Exposures and Infant Motor Development in the MADRES Cohort Study in Urban Los Angeles Ixel Hernandez Sandrah P. Eckel Thomas Chavez Mark Johnson Claudia Toledo-Corral Shohreh F. Farzan Rima Habre Genevieve F. Dunton Carrie V. Breton Theresa M. Bastain

Background

The development of motor skills in infancy is a vital neurodevelopmental milestone tied to various lifelong outcomes. Although previous studies have explored the neurotoxic effects of agricultural pesticides on infants' motor development, limited research has examined early household pesticide use on infants' motor development, particularly among urban communities.

Objective

This study examined the association between early life household pesticide use and infants' motor development at 6 months of age.

Methods

Questionnaires were administered via telephone to a subset of 277 mother-infant dyads in the Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) pregnancy cohort. Early life household pesticide use was assessed within a battery of questionnaires administered when infants turned 3 months old and motor development was assessed by the Ages and Stages Questionnaire (ASQ3) at 6 months old. Infant motor scores were reverse coded so that higher scores indicated lower gross motor performance. Negative binomial regressions were used to assess the relationship between household pesticide use and infant motor development.

Results

Infants were predominantly Hispanic (79.1%) and full term (gestational age at birth: 39.1⊞6 weeks), with 25.3% of participants reporting any household use of pesticides (e.g., rodent/insect, flea, and weed pesticides), with the majority reporting household use of rodent/insect pesticides (89.0%). Infants with maternal reported household use of any pesticides had 1.3 times higher expected gross motor scores (p-value=0.01) than infants with no reported use of household pesticides, with higher scores indicating decreasing gross motor performance.

Conclusion

Our results suggest household pesticide use may harm infants' gross motor development in early childhood. Future research should evaluate this association by measuring biomarkers of specific household pesticide chemicals and infants' motor development.

Children's blood lead screening tests in North Carolina – who is tested, who is missed? Elizabeth M. Kamai Julie L. Daniels Paul L. Delamater Bruce P. Lanphear Jacqueline MacDonald Gibson David B. Richardson

Identifying children with subclinical lead poisoning is done by testing their blood for elevated lead concentrations. Not every child receives a blood lead screening test, and many children with elevated blood lead levels (EBLLs) may not be identified because they are not screened. We investigated determinants of children receiving lead screening tests in North Carolina (NC) in 2011-2018 and estimated the number of children with EBLLs who were not identified.

We geocoded NC birth certificates from 2011-2017, spatially linked them to 2010 Census tracts and block groups, and linked to NC blood lead test results from 2011-2018 using names, birth dates, and addresses. We compared distributions of characteristics at birth between the total cohort and those with a blood lead test result. We used a logistic regression model to estimate the predicted probability of being screened for lead and created inverse probability (IP) of testing weights. We applied these weights to the screened children to estimate the number of additional children with EBLLs expected if all NC children were tested.

Of 633,159 children with geocoded NC birth certificates, 402,002 (63.5%) were linked to a blood lead test result at <30 months of age. Mothers of children tested for lead were more likely to be ≤25 years old, Hispanic, Black or American Indian, covered by Medicaid, and born in NC. Residential addresses at birth of the tested children were more likely to be in rural areas, with greater proportions of Black and low-income residents and older housing. Among the screened children, 39,855 (9.9%) had a maximum EBLL ≥3 µg/dL; 10,066 (2.5%) had an EBLL ≥5 µg/dL. After applying IP weights, we estimate complete blood lead screening would identify an additional 17,857 and 4,544 children with EBLLs ≥3 µg/dL and ≥5 µg/dL, respectively, over the study period.

Our results indicate that current lead screening strategies in NC are failing to identify many children with elevated blood lead concentrations.

Gestational age specific birth weight curve for Asian Indian newborns from lowest risk pregnancies Arpita Bhriguvanshi Jagjit Singh Teji

BACKGROUND:

The number of newborns of the Asian Indian (AI) origin have increased in the last decade to over 80,000 per year in the US, according to the National Center for Health Statistics (NCHS). In order to accurately assess the effects of the gestational pathologies such as gestational diabetes and preeclampsia etc. on the fetus, there needs to be a gestational age (GA) specific birth weight (BWT) curve for the normal AI babies.

OBJECTIVE:

To create a GA specific BWT curve for AI newborns from the lowest risk pregnancies and compare it to the non-Hispanic white (NHW) newborns.

METHODS:

The linked birth/infant death perinatal data files from NCHS by CDC for 2014-2017 was used to create GA specific BWT curves for AI newborns. The curves were created for singleton births delivered by mothers without any medical risk factors during pregnancy, with birth weights for each specific GA >=23 through 47 weeks. Maternal risk factors excluded in our study were chronic hypertension, pre-pregnancy hypertension, gestational hypertension, pre-pregnancy diabetes, gestational diabetes, history of tobacco smoking, age groups of <20 and >35, and BMI <18.5 & >30. NHW and AI were compared and curves were constructed for AI group for GA and BWT for both genders.

RESULTS:

Out of total births 15,752,573 in 2014 to 2017 where lowest risk pregnancies were 2,424,527 were NHW and 108,311 were AI newborns. Preterm births were significantly higher in the AI group 5.52%, P<0.001 where as low birthweight, LBW, in AI were about 2 times the percentage noted in the NHW, P<0.001. C-Section, CS, rate in AI was 2.5 times than that seen NHW. AI newborns at birth weighed lower than NHW particularly greater than 30 weeks gestation and the difference was higher in the non-risk associated pregnancies compared to risk associated in both groups with maximum over 300 grams.

CONLCUSIONS:

This is the first-time presentation of gestation age specific birth weight curve created for the Asian Indian babies born in the United States of America to lowest risk pregnancies and should serve as a standard for assessing the adequacy of the intrauterine growth for weight of the Asian Indian newborns born anywhere in the world.

Maternal lifetime surgery and prenatal exposure to fluorinated anesthetics and offspring neurodevelopment Melissa Kravets Mark Klebanoff Sarah Keim

Background: A transgenerational, epigenetic effect of anesthesia, particularly fluorinated agents, has been examined in rat models, but translation to humans is unclear. The present study examined associations of maternal anesthesia with child neurodevelopment.

Methods: Women in the US Collaborative Perinatal Project (1959-63) reported lifetime history of surgeries and pregnancy exposure to anesthetics. Offspring were followed to age 7 for assessments categorized as global cognitive ability; externalizing, internalizing and stereotypic behaviors; perseveration or rigidity; social and communication; and educational outcomes. Logistic and linear regression adjusted for child birth year; study site; maternal race, smoking, birth year, education, parity.

Results: Among 49985 offspring, many individual outcomes were unassociated with exposure to maternal surgery. However, maternal surgery in early childhood was associated with greater odds of perseveration or rigidity during infancy (adj (odds ratio) OR=2.4, 95% CI 1.1, 5.2) and, at age 7, poorer educational outcomes (adj OR =1.4, CI 1.0, 2.0) but slightly better global cognitive ability (adj β=0.6, CI 0.2, 1.0). Maternal surgery in mid-childhood was associated with decreased odds of stereotypic behaviors at age 4 (adj OR=0.4, CI: 0.2, 0.8) but increased odds at age 7 (adj OR=1.7, CI 1.1, 2.8). Maternal surgery in puberty was associated with poorer global cognitive ability (adj β=-0.5, CI -0.6, -0.2) and increased odds of externalizing behaviors at age 7 (adj OR=1.1, CI 1.0, 1.2). Offspring prenatal exposure to fluorinated anesthetics was positively associated with internalizing behaviors (adj OR=1.7, CI 1.3, 2.3) and social and communication problems at age 4 (adj OR=2.7, CI 1.1, 6.7).

Conclusion: Offspring exposure to maternal surgery and fluorinated agents displayed mixed, timing-specific associations with outcomes including those relevant to Autism Spectrum Disorder. Residual confounding by indication is possible.

Variation in Pregnancy-Related Mortality Ratio by Socio-spatial Indicators, US, 2011–2016 Chloe Barrera Michael Kramer Peter Merkt Emily Petersen Mary Brantley Lindsay Eckhaus Jennifer Beauregard David Goodman

Background: Pregnancy-related mortality in the US has not improved in over a decade, and substantial disparities by race/ethnicity and geography persist. Social determinants of health are thought to influence the rate of pregnancy-related deaths; however, few studies have looked at county-level socio-spatial indicators that may contribute to pregnancy-related mortality. **Objective:** To characterize county-level differences in pregnancy-related mortality as a function of contextual health environment, social capital and support, and economic opportunity and deprivation. **Methods:** Cross-sectional analysis characterizing the absolute difference (RD) in pregnancy-related mortality ratios for people living in US counties with higher versus lower levels of select socio-spatial indicators overall and by race/ethnicity. All pregnancy-related deaths with available ZIP code or county data in CDC's Pregnancy Mortality Surveillance System during 2011-2016 among people who were Hispanic and non-Hispanic American Indian/Alaska Native, Asian/Pacific Islander, Black, White, and ages 15–44 years were included. **Exposures:** A set of 31 county-specific, socio-spatial indicators were assembled from publicly available data sources that could hypothetically influence the health of people before, during, and following pregnancy. **Results:** Pregnancy-related mortality varied across geographical area and by race/ethnicity. Many indicators, including county-level percent of low birthweight births (RD: 6.61; 95% Confidence Interval (CI): 5.53, 7.69) and food insecurity (RD: 5.01; 95% CI: 4.25, 5.76), are associated with county-specific pregnancy-related mortality ratios independent of maternal age, population size, and census region. The magnitude of these associations varies by indicator and by race/ethnicity stratifications. **Conclusions**: This analysis identifies socio-spatial indicators associated with pregnancy-related mortality, demonstrating the influence of place in pregnancy-related deaths.

The Association Between Neighborhood Crime and Adverse Birth Outcomes in Latina Women
Brittany Griffin Penelope Pekow Brian Whitcomb Qian Yu Lisa Chasan-Taber

Women of Puerto Rican descent have disproportionately high rates of low birthweight (LBW), preterm birth, and small-for-gestational age (SGA) infants compared to non-Latina Whites. Established individual-level risk factors only account for a portion of these birth disparities. Previous studies on neighborhood-level risk factors are inconsistent. Therefore, we evaluated the association between neighborhood crime and adverse birth outcomes in Proyecto Buena Salud, a prospective cohort study of 1,195 predominantly Puerto Rican women conducted from 2006-10 in Western Massachusetts. Residential address data was used to place participants in neighborhoods based on census block group at enrollment. Overall and violent neighborhood crime within census blocks were defined using FBI Uniform Crime data. Adverse birth outcomes were abstracted from medical records. Ten percent of women experienced preterm birth, 8.2% had LBW, and 12.3% had SGA infants. Women in the highest quartile of violent neighborhood crime reported lower education and income, higher levels of depression, and Spanish preference (all $p < 0.05$).

Women in the highest quartile of violent neighborhood crime had higher odds of SGA (odds ratio [OR] 2.1, 95% confidence interval [CI] 1.2-3.4) compared to women in the lowest quartile after adjusting for parity, age, BMI, gestational weight gain, education level, and smoking. We did not observe statistically significant associations between violent neighborhood crime and preterm birth (OR 0.9, 95% CI 0.5-1.5) or LBW (0.9, 95% CI 0.5-1.6) in adjusted analyses. We did not observe statistically significant associations between women in the highest quartile of overall neighborhood crime and adverse birth outcomes.

This study was the first, to our knowledge, to study neighborhood crime and adverse birth outcomes among Latinas. Future studies with larger samples are warranted to address the impact of neighborhood disadvantage in high-risk groups.

Out-Of-Hospital Births, Rural Maternal Residence, and Infant Mortality in the United States Elora Way Jenny Carwile Erika Ziller Katherine Ahrens

Background: Out-of-hospital births have been increasing in the United States, and home births are almost twice as common in rural as compared to urban counties. Home births and births in rural areas may increase the risk of infant mortality but their combined effect has rarely been considered in studies that estimate the association between birth setting and infant mortality.

Objectives: To estimate the combined effect of birth setting and rural-urban maternal residence on infant mortality in the US.

Methods: We conducted a population-based cohort study of all infants born in the US during 2010-2017 using the National Center for Health Statistics' period-linked birth-infant death files. Unadjusted and adjusted Poisson regression models with an offset for the number of births were used to calculate infant mortality rate ratios and 95% confidence intervals for rural vs. urban maternal residence, overall and stratified by birth setting, and for out-of-hospital births vs. hospital births, overall and stratified by maternal residence.

Results: The rate of infant deaths was higher in rural (6.53 per 1,000 live births) than in urban areas (6.00 per 1,000 live births); rate ratio [RR]=1.09 (95% CI: 1.08, 1.11). Rates were higher for rural vs. urban areas for births in hospitals (RR=1.09 [95% CI: 1.07, 1.10]), birth centers (RR=1.89, 95% CI=1.43, 2.51) and planned home births (RR=1.60, 95% CI=1.37, 1.86). After adjusting for maternal demographics, and infant and obstetric characteristics, the rural-urban rate ratio for hospital births was attenuated (RR=1.07, 95% CI=1.06, 1.09) and rate ratios were no longer significantly higher for rural areas among births in out-of-hospital birth settings.

Conclusions for Practice: Our findings emphasize the need for policy and public health outreach to improve the safety of rural hospital and community birth options and continued research on the effect of reduced maternity care access on infant health.

Gestational Exposure to Fatal Police Violence and Pregnancy Loss in US Core Based Statistical Areas, 2013-2015 Jaquelyn Jahn Nancy Krieger Madina Agénor Michael Leung Brigette Davis Marc Weisskopf Jarvis Chen

Background: Fatal police violence in the United States disproportionately affects Black, Native American, and Hispanic people, and for these groups is a racially oppressive population-level stressor that we hypothesize to increase the risk of pregnancy loss. Focusing on core based statical areas (CBSAs) surrounding small and large urban centers, we accordingly tested whether gestational exposure to fatal police violence decreased the number of live births, which is reflective of a rise in lost pregnancies.

Methods: We linked microdata for all births (N=7,709,300) in 520 CBSAs with at least one incident of fatal police violence in 2013-2015 to Fatal Encounters, a database that prospectively identified 2,594 police-related fatalities using online media reports and public records. We estimated the association between month-to-month changes in fatal police violence and conceptions resulting in live births using distributed lag quasi-Poisson models with CBSA-level fixed effects, accounting for seasonality and stratified by maternal race/ethnicity.

Findings: For each additional police-related fatality that occurred in the first through sixth months of gestation, we observed a 0.14% decrease (95% confidence interval: 0.05%, 0.23%) in the total number of live births within CBSAs, and a 0.29% decrease in births to Black women (95% CI: 0.11%, 0.48%). The association was null for births to White women.

Interpretation: Our findings suggest fatal police violence may have population-level consequences for pregnancy loss and adds to the evidence regarding the importance of preventing these fatalities.

Birth outcomes following unexpected job loss: a matched sibling design Tim Bruckner
Samantha Gailey Laust Mortensen Elias Knudsen

Involuntary job loss serves as a potent and undesirable stressor. Research also documents social and economic antecedents of adverse birth outcomes. This work suggests the hypothesis that involuntary job loss in a household adversely affects birth outcomes. Previous work on this topic, however, lacks high-quality individual data on, and variation in, plausibly exogenous job loss during pregnancy and therefore cannot rule out strong confounding. We exploit unique linked registries in Denmark, from 1980 to 2017, to test whether a father's involuntary job loss during his spouse's pregnancy increases the risk of a low weight (i.e., <2,500gm) and/or preterm (i.e., < 37 weeks of gestational age) birth. We applied a matched sibling design to 743,574 sibling pairs. Results indicate an increased risk of low weight birth among siblings exposed in utero to fathers' unexpected job loss (Odds Ratio [OR] = 1.37, 95% confidence interval [CI]: 1.07, 1.75). Sex-specific analyses indicate that this result holds for males in utero (OR= 1.70, 95% CI: 1.14, 2.53) but not females (OR=1.24, 95% CI: 0.80, 1.91). We find no relation with preterm birth. Findings in Denmark support the inference that a father's unexpected job loss adversely affects the course of pregnancy, especially among males in utero.

Exposure to endocrine disrupting chemicals (EDCs) and cardiometabolic health during pregnancy: the HOME Study Ann Vuong Joseph Braun Andreas Sjodin Antonia Calafat Kimberly Yolton Bruce Lanphear Aimin Chen

Toxicology studies have identified pregnancy as a window of susceptibility for endocrine disrupting chemicals (EDCs) and women's cardiometabolic health. No study in humans, however, has examined EDC mixtures and cardiometabolic health during pregnancy. We used the Health Outcomes and Measures of the Environment (HOME) Study to examine whether bisphenol A (BPA), polybrominated diphenyl ethers (PBDEs), per- and polyfluoroalkyl substances (PFAS), and phthalates are associated with blood pressure, fasting plasma glucose, and lipids in 388 pregnant women. We measured PBDEs and PFAS in serum at 16 weeks gestation, while BPA and phthalates were quantified in urine at 16 and 26 weeks. We used linear regression and Bayesian Kernel Machine Regression (BKMR) to estimate associations of individual EDCs and their mixtures with cardiometabolic health during pregnancy. A 10-fold increase in BDE-28 was associated with a 13.1 mg/dL increase in glucose (95% CI 2.9, 23.2) in linear regression. The BKMR model also identified BDE-28 as having a positive association with glucose. BDE-28, BDE-47, and BDE-99 were positively associated with cholesterol in both single- and multi-pollutant models, whereas a suggestive negative association was noted with BDE-153. Mono-n-butyl phthalate (β=-7.9 mg/dL, 95% CI -12.9, -3.0) and monobenzyl phthalate (MBzP) (β=-6.3 mg/dL, 95% CI -10.6, -2.0) decreased cholesterol in linear regression, but only MBzP was an important contributor with BKMR. Overall, we observed positive associations of PBDEs with glucose and cholesterol levels during pregnancy, while negative associations were found between some phthalates and cholesterol. No relationship was noted for BPA or PFAS with cardiometabolic health during pregnancy.

Fluoride exposure and asthma among children and adolescents in NHANES 2013-2014 Yu Zhang Vicente Mustieles Yang Sun Stelios Vagios Francine Laden Yixin Wang Carmen Messerlian

Background: Fluoride is shown to be immunotoxic in animal studies. Particulate fluoride exposure has been linked to asthma in occupational settings. Population-based studies of fluoride exposure in relation to asthma among children and adolescents are lacking.

Methods: We examined fluoride concentrations in plasma and household water in relation to asthma among 2,133 participants aged 6 to 19 years from the National Health and Nutrition Examination Study (NHANES), 2013-2014 cycle. Asthma was self-reported by the participant or parent as ever been diagnosed with asthma. Multivariable logistic regression was utilized to calculate the adjusted odds ratios of asthma associated with continuous and tertiles of natural log transformed fluoride concentrations. We further stratified the analyses by participant age category (6-11 years and 12-19 years).

Results: The 2,133 included participants had a mean (SD) age of 12.8 (4.0) years. Prevalence of asthma was 18.9%. Per ln-unit increase in plasma fluoride concentration was associated with a 35.0% increase (95% CI: 1.00, 1.81) in the odds of asthma. Compared to the 1st tertile, the 3rd tertile (OR: 1.51, 95% CI: 1.07, 2.12), not the 2nd tertile (OR: 1.11, 95% CI: 0.77, 1.59) of plasma fluoride concentration was associated with increased odds of asthma. No association was found for water fluoride concentration and asthma. In age stratified analysis, the positive association for plasma fluoride concentration and asthma was observed in adolescents aged 12-19 years (3rd vs 1st tertile: OR 1.62, 95%CI: 1.01, 2.62) and not in children aged 6-11 years (3rd vs 1st tertile: OR: 1.02, 95%CI: 0.63, 1.63).

Conclusion: Plasma fluoride concentration was positively associated with asthma in adolescents in the general U.S. population. Given widespread fluoride exposure, prospective studies are needed to confirm the findings.

Mixture effects of prenatal exposure to per- and polyfluoroalkyl substances and polybrominated diphenyl ethers on maternal and newborn telomere length Stephanie Eick Dana Goin Lara Cushing Erin DeMicco June-Soo Park Amy Padula Tracey Woodruff Rachel Morello-Frosch

Background: Per- and polyfluoroalkyl substances (PFAS) and polybrominated diphenyl ethers (PBDEs) are endocrine disrupting chemicals that are widespread in the U.S. given their abundance in consumer products. PFAS and PBDEs have been associated with reproductive toxicity and adverse health outcomes, including certain cancers. It is possible that PFAS and PBDEs influence adverse health outcomes through alternations in telomere length. We examined joint associations between prenatal exposure to PFAS, PBDEs, and maternal and newborn telomere length using mixture analyses, to better reflect cumulative exposures.

Methods: Study participants were enrolled a demographically diverse cohort of pregnant women and children in San Francisco, CA. PFAS (ng/mL) and PBDEs (ng/g lipid) were measured in maternal serum samples obtained during the 2nd trimester. Newborn and maternal telomere length (T/S ratio) were measured in delivery cord blood of 292 newborns and 110 second trimester maternal whole blood samples, respectively. Quantile g-computation was used to assess the joint association between groups of PFAS and PBDEs and newborn and maternal telomere length. Groups considered were: (1) all PFAS and PBDEs combined, (2) PFAS and (3) PBDEs. Maternal and newborn telomere length were treated as separate outcomes and modeled separately.

Results: In mixtures analyses, a simultaneous one quartile increase in all PFAS and PBDEs was associated with a small increase in newborn (mean change per quartile increase =0.03, 95% CI=-0.03, 0.08) and maternal telomere length (mean change per quartile increase =0.03 (95% CI=-0.03, 0.09). When restricted to maternal-fetal paired samples (N=76), increasing all PFAS and PBDEs in the mixture was associated with a strong, positive increase in newborn telomere length (mean change per quartile increase=0.12, 95% CI=0.02, 0.27).

Conclusions: Our findings suggest that PFAS and PBDEs may be positively associated with newborn telomere length.

The association between living near wildfire before and during pregnancy and spina bifida risk in offspring Bo Park Arriel Alvarez Mie Phan Shivani Patel Maria Acosta de Gonzales Dan Curtis Ruofan Yao

Background: Climate change continues to increase the severity and prevalence of natural disasters. California wildfires have increased significantly over time and produced air pollutants that have been associated with complications during the pregnancy period. Spina bifida is a condition where the spine and spinal cord form a neural tube defect on the embryo during the early stages of pregnancy. The purpose of this study is to determine the association between wildfire exposure before and during pregnancy and the odds of spina bifida in the offspring.

Methods: This was a retrospective cohort study using the California Office of Statewide Health Planning and Development Linked Birth File and the California Department of Forestry and Fire Protection data between 2007 and 2010. Pregnancies complicated by spina bifida were identified by the International Classification of Diseases Clinical Modification, 9th Revision. Pregnancies were considered exposed to wildfire if the mother's primary residence zip code was within 15 miles to the closest edge of a wildfire. The initial wildfire exposure was further broken into four timeframes: first, second, third trimester, or within 4 weeks before the last menstrual period. Multivariate logistic regression models were used to estimate the association between wildfire exposure by trimester and spina bifida compared to pregnancies without wildfire exposure.

Results: Between 2007 and 2010, 1,904,344 births were analyzed in the study. Compared to births without wildfire exposure, those with first-trimester exposure were associated with higher odds of spina bifida (adjusted odds ratio (aOR) 1.43, 95% confidence interval (CI): [1.11 – 1.84]). Whereas, pre-pregnancy aOR 1.43, 95% CI: [1.11 – 1.84]), second aOR 0.81, 95% CI: [0.64 – 1.03]) and third trimester aOR 0.83, 95% CI: [0.65 – 1.07] wildfire exposure were not associated with higher spina bifida risk.

Conclusions: Wildfire exposure during the critical window of neural tube development appears to increase the odds of developing spina bifida in the offspring.

Associations between air pollution and preterm birth: a time-stratified case-crossover study Sandie Ha Valerie Martinez

Background: The San Joaquin Valley (SJV) of California has one of the worst air quality in the nation and significantly higher rate of preterm birth (PTB) compared to California. The extent of impact air pollution has on preterm birth rate of this region is unclear. We investigated the acute associations between air pollution and preterm birth, and estimated the excess number of preterm birth attributed to air pollution exposures in the SJV.

Methods: In this time-stratified case crossover study, we identified 198,503 singleton preterm (<37 weeks) and early term births (37-39 weeks) in the SJV (2007-2015) from Vital Statistics and spatiotemporally linked them to daily zip-code level air quality data obtained from the SJV Air District. Conditional logistic regression models calculated the odds ratio (OR) and 95% confidence intervals (CI) for the associations between preterm birth and an interquartile range (IQR) increase in exposures to a) ozone during the warm season (May-Oct), and b) particulate matter <2.5 microns (PM$_{2.5}$) during the cold season (Nov-Apr) after adjustment for co-pollutants. We further calculated the excess number of preterm births associated with air pollution exposures.

Results: An IQR increase in ozone exposures at lag 2 (i.e., two days prior) was associated with 6% increase in preterm birth odds and this effect progressively increased to 26% at lag 7. These associations were equivalent to about 5 and 21 excess PTB cases per 1,000 live births, respectively. In the cold season, an IQR increase in PM$_{2.5}$ exposures was associated with 2% to 5% increase in the odds of having a very preterm birth (VPTB, <34 weeks) from lags 3-7, equivalent to about one additional VPTB every 1000 live births.

Conclusion: Acute air pollution exposures during the prior week may trigger preterm birth and contribute to the high preterm birth rates in the SJV. While awaiting larger studies, it is pertinent to continue exposure reduction efforts for pregnant women.

Environment/climate change

Maternal bisphenol urine concentrations, fetal growth and adverse birth outcomes. A population-based prospective cohort. Chalana Sol Charissa van Zwol-Janssens Elise Philips Alexandros Asimakopoulos Maria-Pilar Martinez-Moral Kurunthachalam Kannan Vincent Jaddoe Leonardo Trasande Susana Santos

Background: Exposure to bisphenols may affect fetal growth and development. The trimester-specific effects of bisphenols on repeated measures of fetal growth remain unknown. Our objective was to assess the associations of maternal bisphenol urine concentrations with fetal growth measures and birth outcomes and identify potential critical exposure periods.

Methods: In a population-based prospective cohort study among 1,379 pregnant women, we measured maternal bisphenol A, S and F urine concentrations in first, second and third trimester. Fetal head circumference, length and weight were measured in the second and third trimester by ultrasound and at birth.

Results: An interquartile range increase in maternal pregnancy-averaged bisphenol S concentrations was associated with larger fetal head circumference (difference 0.18 (95% confidence interval (CI) 0.01 to 0.34) standard deviation scores (SDS), p-value<0.05) across pregnancy. When focusing on specific critical exposure periods, an interquartile range increase in maternal first trimester bisphenol S concentrations was associated with 0.10 (95% CI 0.03 to 0.17, p-value<0.020) SDS larger fetal head circumference in the second trimester and 0.07 (95% CI 0.01 to 0.14, p-value<0.05) and 0.07 (95% CI 0.00 to 0.14, p-value<0.05) SDS higher fetal weight in second and third trimester, respectively. An interquartile range increase in maternal first trimester bisphenol S concentrations was associated with a lower risk of small size for gestational age at birth (Odds Ratio 0.72 (95% CI 0.54 to 0.96), p-value<0.05). Maternal bisphenol S concentrations were not associated with fetal length or risk of preterm birth. None of the other bisphenols were consistently associated with fetal growth outcomes.

Conclusions: Higher maternal bisphenol S urine concentrations, especially in the first trimester, seem to be related with larger fetal head circumference, higher weight and a lower risk of being small size for gestational age at birth.

High blood pressure and bacteriuria as risk factors for preterm birth: a comparison of risk factor analysis and population intervention effects Rachael Ross Stephen Cole Joan Price Jeffrey Stringer

Conclusions of traditional risk factor analyses often point to modifiable factors strongly associated with the outcome as targets for intervention, implying that intervention would have a meaningful impact. But many risk factor analyses do not provide evidence sufficient for such conclusions. Population intervention effects can provide the expected impact of an intervention. We illustrate estimation of intervention effects and compare the assumptions, results, and interpretation to a typical risk factor analysis.

We examined the risk factors high blood pressure (BP) and bacteriuria and the outcome preterm birth in a prospective cohort of pregnant women in Lusaka, Zambia. For intervention effects, we used g-computation to estimate the outcome risk under 3 interventions: elimination of bacteriuria alone, high BP alone, or both. Risk ratios (RR) were calculated compared to the natural course (i.e., under no intervention). For risk factor analysis, RRs were estimated by modified Poisson regression.

Of 1270 women, 4.9% had bacteriuria and 3.3% had high BP; 13% of pregnancies ended in a preterm birth. Risk factor analysis produced RRs well below 1 (e.g., normal BP 0.57, 95% CI 0.31, 1.05) indicating that not having each risk factor was protective. Conversely, intervention effect RRs were close to 1 (e.g., normal BP 0.99, 95% CI 0.98, 1.00) indicating elimination of each risk factor had little impact on the outcome. Intervention on both factors together was estimated to prevent 4 outcomes.

Risk factor analyses may not provide informative estimates as they do not consider the observed prevalence of the risk factor and the reference group reflects the unrealistic scenario where all women have the risk factor. Conversely, population intervention effects directly answer a question of scientific interest: How would the outcome risk change under an intervention to eliminate this factor? Both analyses assumed no unmeasured confounding; risk factor analysis also assumed homogeneity.

Neurodevelopmental symptoms in children according to parental time-to-pregnancy and conception by assisted reproductive technologies Maria Magnus Alexandra Havdahl Alice Goisis

Neurodevelopmental symptoms in children according to parental time-to-pregnancy and conception by assisted reproductive technologies

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Background: Previous studies suggest that children conceived by assisted reproductive technologies (ART) might have an altered neurodevelopment. What the role of underlying parental subfertility might be remains unclear.

Methods: We examined differences in motor and language skills development, autism-related social communication difficulties and repetitive behaviours, and attention and hyperactivity problems up to 8 years of age according to parental time-to-pregnancy (TTP) and conception by ART in 91,260 singletons participating in the Norwegian Mother, Father and Child Cohort Study. Mean differences in neurodevelopmental problems according to TTP ≤3 months (reference), TTP 4-11 months, TTP ≥12 months and conception by ART were estimated using linear regression.

Results: We observed modestly lower language skills measured using the ages and stages questionnaire (ASQ) among children of parents with TTP ≥12 months and among ART children. The mean difference in the standardized scores at 36 months were -0.05 (95% CI: -0.08, -0.02) for non-ART children of parents with TTP>12 months, while it was -0.05 (95% CI: -0.11, 0.01) for ART children. We also observed lower motor skills among both children of parents reporting a TTP ≥12 months and among non-ART children. At 6 months, the decrease was -0.06 (95% CI: -0.09, -0.03) among children of parents with TTP >12 months and -0.10 (-0.15, -0.04) among ART children. Lower scores for autistic traits using the modified checklist for autism in toddlers (M-CHAT) at 18 months

-0.045 (95% CI: -0.083, -0.008) and the social communication questionnaire (SCQ) 36 months -0.062 (95% CI: -0.117, -0.007) were seen among ART children only. No differences were seen in attention and hyperactivity symptoms.

Conclusion: We observed a modest decrease in both language and communications skills and motor development among ART children which is likely to be explained by underlying parental subfertility and not the ART procedure. The modest decrease in the scores for autistic traits among ART children did not appear to be explained by underlying parental subfertility and should be further examined in future studies.

Health equity

The role of wealth accumulation in Black-White preterm delivery disparities: a causal mediation analysis approach Collette Ncube Michael Kramer Savanah Rumbika Lori Lyn Price Ashley Naimi Lorraine Lacroix-Williamson

Introduction: The US has striking and persistent Black-White disparities in preterm delivery (PTD). The causal inference potential outcomes framework can be leveraged to further understanding of racial disparities mechanisms. *Methods:* Using a modification of g-estimation, the objective of our study was to estimate the effect on PTD racial disparities of a population-level intervention (Child Development Accounts (CDA)) to change the distribution of family wealth. We selected individuals (G1) from the Panel Study of Income Dynamics (PSID), born into a PSID family unit (G0), who reported delivering at least one live-born singleton infant in 2013, 2015 or 2017 waves. Black or White family racial group was the exposure, the outcome was PTD (< 37 weeks), and family wealth at G1 age 18 years was the mediator. Longitudinal sample weights were applied in order to make inference at the national level. *Results:* Overall, 10.1% of livebirths were preterm, with an excess PTD risk among individuals from Black families compared with White of 7.6 per 100 livebirths (95%CI: 1.3, 13.9). The PTD racial disparity that would remain under an intervention such as the CDA, is estimated at 7.9 per 100 livebirths (95%CI: -5.0, 20.8). *Conclusion:* The findings of our study suggest either an intervention the magnitude of a CDA is unlikely to have much of an effect on PTD racial disparities, or it may even contribute to a widening of these disparities. The latter may occur if the effect of family wealth on PTD is stronger for White families than for Black families.

Policy

Respiratory syncytial virus bronchiolitis hospitalizations in young infants after the introduction of paid family leave in New York State Jennifer Hutcheon Teresa Janevic Katherine Ahrens

Background: Respiratory syncytial virus (RSV) bronchiolitis is a leading cause of hospitalization among infants in the United States. Infants who receive childcare at home are less likely to be hospitalized with lower respiratory tract infections such as RSV than those who receive out-of-home childcare, but it is unknown whether provision of paid parental leave reduces RSV-associated hospitalizations.

Objective: To determine if the implementation of a paid 8-week family leave policy in New State on Jan 1, 2018 reduced the number of hospitalizations for respiratory syncytial virus (RSV) bronchiolitis and other acute lower respiratory tract infections in infants ≤8 weeks of age in New York State.

Methods: We conducted an interrupted time series analysis using all-payer hospital discharge records from New York State, Oct 1 2015 to Dec 31, 2019. Our outcomes were the rates of monthly hospitalizations with International Classification of Diseases 10 codes for RSV bronchiolitis (narrow definition) or any acute lower respiratory tract infection (broader definition) among infants aged ≤8 weeks at admission. We implemented our design using negative binomial regression, estimating the change in hospitalization rates after January 2018 controlling for underlying temporal trends and seasonality.

Results: There were 6808 hospitalizations with acute lower respiratory tract infection to infants aged ≤8 weeks (excluding newborn hospitalization), including 4733 with RSV bronchiolitis. Hospitalization rates for RSV bronchiolitis and acute lower respiratory tract infection decreased by 30% after the introduction of paid family leave (rate ratios= 0.7 [95% CI: 0.5 to 0.9] and 0.7 [95% CI: 0.6 to 0.9], respectively). No such reductions were observed in our control group of one-year olds (rate ratios=1.0 [95% CI: 0.7 to 1.3] and 1.2 [95% CI: 1.0 to 1.3], respectively).

Conclusions: Paid family leave may reduce RSV-associated hospitalizations in young infants.

Pre-pregnancy overweight and diabetes, and their relationship with gestational hypertension and preeclampsia: a mediation analysis approach. Jesus Serrano-Lomelin Brittany Matenchuk Graeme N. Smith Sandra T. Davidge Radha Chari Meghan Riddell Susan Crawford Jeffrey Bakal Maria B. Ospina

Introduction. Diabetes mellitus (DM) and pre-pregnancy overweight are known risk factors of gestational hypertension (GH) and preeclampsia (PE). Overweight is also a risk factor for DM. Therefore, DM could be in the intermediary pathway between overweight and GH or PE, acting as a mediator. The mediating effect of DM on GH and PE among women with pre-pregnancy overweight remains unclear. We examined the direct effects of pre-pregnancy overweight and pre-pregnancy DM on GH and PE, and the mediating role of pre-pregnancy DM on GH and PE among women with pre-pregnancy overweight.

Methods. We are conducting a case-control study using data from the Alberta Perinatal Health Program for the years 2010-2013. Cases are nulliparous women aged >16 years having GH or PE. Controls are a random sample of pregnant women in their first pregnancy with no diagnosis of GH or PE, matched by gestational age for a ratio of 1:3 cases/controls. Structural equation models were used for the mediation analysis, with smoking during pregnancy, maternal age, and socioeconomic status as covariates. We reported odds ratios (OR) with 95% confidence intervals (CI) for direct effects and the proportional effect for the DM-mediation component.

Results. Data from 19,075 women were analyzed (controls=14,307; GH=4,768; PE=1,213). For GH, the direct effect of pre-pregnancy overweight (OR 3.2; CI 2.8-3.4) was greater than the direct effect of pre-pregnancy DM (OR 1.6, CI 1.2-2.1). For PE, the direct effect of both pre-pregnancy overweight (OR 2.4; CI 2.1-2.8) and pre-pregnancy DM (OR 2.1; CI 1.4-3.1) were similar. The mediating effect of pre-pregnancy DM accounts for 44% of the total effect of pre-pregnancy overweight on PE compared to 27% for GH.

Conclusion. Pre-pregnancy overweight plays a direct role on GH, while in PE, both direct and mediating roles of DM are important. Diabetes management has important but different implications for overweight women at risk of developing GH and PE.

Feeding Problems as an Indicator of Developmental Delay in Early Childhood Diane Putnick
Erin Bell Akhgar Ghassabian Sonia Robinson Rajeshwari Sundaram Edwina Yeung

Feeding problems are discussed the longest of all topics at well-child visits. High proportions of children with developmental disabilities have feeding problems, but it is unclear to what extent feeding problems indicate developmental delays in the general population.

In the Upstate KIDS cohort study (n=3,597), mothers reported the frequency of children's behavioral feeding problems from 0 (*never)* to 3 (*often)* on 9-12 questions (e.g., crying during meals, pushing food away, gagging on food) and developmental delays in 6 domains (i.e., total, fine and gross motor, communication, personal-social, and problem-solving skills) using the Ages and Stages Questionnaire (ASQ) at 18, 24, and 30 months. A subset of children (n=516) were objectively assessed at 4 years using the Battelle Developmental Inventory (BDI-2).

Feeding problems (per point increase on a continuous scale) were increasingly associated with failure on the ASQ from 18 months (Odds Ratios (ORs) = 1.50 – 2.35) to 24 months (ORs = 2.44 – 3.04) to 30 months (ORs = 4.41 – 6.44). Children with persistently high feeding problems, $\geq 90^{th}$ percentile at all time points (2% of the sample), were more than four times as likely to fail the ASQ (ORs = 4.24 – 5.58), and children with high feeding problems at one or two time points (20%) were more than twice as likely to fail the ASQ (ORs = 2.18 – 2.57), than children who never experienced high feeding problems (**Figure 1**). Children with one-point higher feeding problems at 30 months scored 3-4 points lower on all subscales of the BDI-2 at 4 years.

The American Academy of Pediatrics recommends developmental screening at 9, 18, and 30 months, but recent data suggests that over one-third of pediatricians did not screen all children under 3. Given that feeding problems are regularly discussed at well-child visits, frequent feeding problems that persist into the third year, could be used to identify children at risk for developmental delay for more targeted screening.

Child health and development

Examining the effect of maternal pre-pregnancy body-mass index on allergic disease development in offspring: a population-based study using health administrative databases in Ontario, Canada Sebastian A. Srugo Deshayne B. Fell Daniel Corsi Romina Fakhraei Yanfang Guo Laura Gaudet

Introduction: Overweight and obesity are the most common pre-existing morbidities in pregnancy. Studies suggest excess pre-pregnancy weight may impact fetal immunological development through metabolic dysfunction and inflammation. We sought to examine the effect of maternal pre-pregnancy body mass index (BMI) on incidence of four common pediatric allergic diseases.

Methods: We conducted a retrospective, population-based cohort study of all singleton live births in Ontario between 2012–14, using maternal-newborn records from the provincial birth registry linked with health administrative databases. Neonates (N=248,017) were followed up to 7 years of age for anaphylaxis, asthma, dermatitis, and rhinitis, identified though validated algorithms based on healthcare-encounter diagnostic codes. Ten multiply imputed datasets were created to address missingness. Cox proportional-hazards models were employed to calculate adjusted hazard ratios (aHR) with 95% confidence intervals, overall and stratified by infant sex to assess effect-measure modification.

Results: 14,235 (5.7%) infants were born to underweight mothers, 129,091 (52.1%) to normal weight, 59,958 (24.2%) to overweight, and 44,733 (18.0%) to obese mothers. Incidence rates (per 100,000 person-days) for anaphylaxis, asthma, dermatitis, and rhinitis were 0.22, 6.80, 12.41, and 1.54, respectively. Compared to normal weight, maternal obesity was associated with increased hazard of asthma in offspring (aHR=1.08, 1.05–1.11), but decreased hazard of anaphylaxis (aHR=0.83, 0.69–0.99) and dermatitis (aHR=0.97, 0.94–0.99). Maternal underweight was associated with increased hazard of dermatitis in offspring (aHR=1.06, 1.02–1.10). Stratification revealed similar directions of associations by infant sex, though higher magnitudes for males.

Conclusion: Maternal pre-pregnancy BMI may have weak but important effects on pediatric allergic disease in offspring.

Child health and development

Prenatal oxidative stress and autism spectrum disorder Meghan Carey Nathaniel Snyder Stepan Melnyk Jill James Carolyn Salafia Irva Hertz-Picciotto Lisa Croen Daniele Fallin Craig Newschaffer Kristen Lyall

Oxidative stress (OS) is a pathway implicated in adverse neurodevelopment. However, research assessing prenatal OS and autism spectrum disorder (ASD)-related traits in the child is lacking. We therefore sought to examine the association between prenatal OS and child ASD-related traits. Participants (n=152) were drawn from the Early Autism Risk Longitudinal Investigation (EARLI), a study following families with a child with ASD through a subsequent pregnancy. Biomarkers of OS, including glutathione (GSH), glutathione thiol/disulfide (GSSG), and 3-nitrotyrosine were measured in third trimester maternal plasma samples, and 8-oxo-deoxyguanine (8-OHdG) in maternal DNA. ASD-related traits were assessed via the Social Responsiveness Scale at 36 months. Associations were examined using crude and adjusted linear regression, accounting for child's sex and several maternal characteristics. Quantile regression was used to explore relationship differences by levels of ASD-related traits. Results indicated a marginal, modest positive association between GSH/GSSG, a ratio indicating redox balance, and raw total SRS scores in adjusted linear regression models (β: 1.72, 95%CI: -0.35, 3.78). In quantile regression analysis, this relationship appeared strongest for those in the highest quantile of SRS scores (90th percentile, β: 4.92, 95%CI: -.40, 10.22). Slightly higher SRS scores, consistent with greater ASD-related traits, were also associated with lower levels of oxidative stress according to 8-OHdG, an indicator of DNA oxidative damage, in those with the lowest percentiles of SRS scores (10th percentile, β=-0.50, 95%CI: -0.83, -0.17). Associations with other markers were not observed. Overall, results from this high familial risk cohort do not support a strong relationship between markers of OS in the third trimester and ASD-related traits. Future work should consider these and other markers of OS at other time points and in populations whose background ASD risk is not elevated.

Sex-specific patterns of the infant microbiome in relation to early-childhood behavioral outcomes Hannah E. Laue Margaret R. Karagas Modupe O. Coker David C. Bellinger Emily R. Baker Susan A. Korrick Juliette C. Madan

BACKGROUND: A link between the gut microbiome and behavior is hypothesized, but the literature is mostly cross-sectional and animal studies. The potential modifying role of sex is unknown.

METHODS: In a subset of the New Hampshire Birth Cohort Study, infant gut microbiome diversity and taxa were captured with 16S rRNA sequencing at 6 weeks (6W, n=190), 1 year (1Y, n=187), and 2 years (2Y, n=146). Species and gene pathways were inferred from metagenomic sequencing at 6W (n=116) and 1Y (n=118). When subjects were 3 years old, parents completed the Behavioral Assessment System for Children, 2nd edition (BASC-2). We analyzed composite scales (Internalizing and Externalizing Problems, Behavioral Symptoms, Adaptive Skills) and scales that likely relate to the microbiome (Depression, Anxiety, Hyperactivity, Attention Problems, Developmental Social Disorders, Social Skills). Missing covariate data was multiply imputed. BASC-2 T-scores were regressed against bacterial diversity. We used Microbiome Multivariable Association with Linear Models to relate BASC-2 scores to individual taxa, species, and bacterial functions. We obtained sex-specific estimates from interaction models.

RESULTS: Higher diversity at 6W was significantly associated with better Internalizing Problems and its component scales (Depression and Anxiety) among boys, but not girls [β_{Boys}=-1.86 points/standard deviation Shannon diversity; 95% confidence interval (-3.29, -0.42), p_{Boys}=0.01, β_{Girls}=0.22 (-1.43,1.87), p_{Girls}=0.8, $p_{interaction}$=0.06]. Among other taxa-specific associations, we found *Bifidobacterium* at 6W was associated with better Adaptive Skills scores in a sex-specific manner, whereas *Blautia* at 2Y years was associated with worse Hyperactivity scores in the full population. We evaluated and observed relationships between microbial functional features and BASC-2 scores.

CONCLUSIONS: This study advances our understanding of microbe-host interactions with implications for childhood behavioral health.

Associations between cord blood telomere length and adiposity in the first two decades of life Farah Qureshi Izzuddin Aris Sheryl Rifas-Shiman Wei Perng Emily Oken Janet Rich-Edwards Andres Cardenas Michelle Enlow Mandy Belfort Henning Tiemeier

Background: Research on telomere length (TL) and chronic disease risk focuses mostly on adults, but emerging evidence suggests initial settings at birth may be a biomarker of future disease susceptibility. We examined if newborn TL is related to early adiposity measures that precede adult disease.

Methods: Participants were 375 children in Project Viva (born in 1999-2002). TL was measured in cord blood via duplex quantitative PCR and assessed as a binary variable with shorter TL defined as those smaller than the sample mean. Height and weight were measured repeatedly from birth to age 18y in study visits and via medical records. Body mass index (BMI) trajectories were fit to estimate age and magnitude of BMI peak in infancy and rebound in early childhood. In a subsample of 214 children, total and truncal fat mass index (FMI) were assessed via whole-body DXA scans in mid-childhood and early adolescence.

Generalized estimating equations tested if shorter TL was associated with greater BMI magnitude, later age of peak, and earlier age of rebound, which are all related to poorer cardiometabolic health later in life. Analyses adjusted for prenatal and birth characteristics. Sex differences were tested via interaction. Sensitivity analyses assessed associations with direct FMI measures.

Results: TL was not associated with magnitude of BMI peak or rebound but was related to timing of BMI milestones. Shorter TL was associated with a 0.9-month later age of BMI peak for girls only (95% CI=0.03, 1.75; $p_{\text{sex interaction}}$=0.02), and with a 5.0-month earlier age of BMI rebound for both girls and boys (95% CI=-9.04, -0.93). No substantial associations were noted with either FMI measure in mid-childhood. In early adolescence, shorter TL was related to higher total (β=0.91, 95% CI=0.15, 1.68) and truncal FMI (β=0.42, 95% CI=0.01, 0.82).

Conclusion: Initial TL settings may be an early indicator of future adiposity risk, highlighting a need to understand telomere biology starting at birth.

Case-control study of adiposity measures and adenomyosis risk: The impact of control selection on results Kristen Upson Sawsan As-Sanie Holly Harris Victoria Holt

Adenomyosis, characterized by the presence of endometrial glands and stroma within the myometrium, is associated with substantial morbidity. Given the historic reliance on hysterectomy for diagnosis, epidemiologic understanding of adenomyosis has been hampered by bias from control selection, resulting in inconsistent results across studies. This includes mixed results for body mass index (BMI), the only adiposity measure examined in prior studies, and adenomyosis risk. We investigated overall adiposity (BMI, weight) and central adiposity (waist circumference (WC), waist-to-hip ratio (WHR)) using a novel case-control design in a study of female enrollees ages 18-59 of a large, integrated healthcare system in Washington State. We identified incident, pathology-confirmed adenomyosis cases diagnosed 2001-2006 (n=386) and employed two control groups: 1) randomly selected age-matched enrollees with intact uteri ("population controls", n=323) and 2) hysterectomy controls (n=233). Self-reported weight and BMI at the reference date (first visit for symptoms leading to adenomyosis diagnosis) and measurements of WC and WHR were collected during in-person interviews. We used logistic regression to estimate ORs and 95% CIs, adjusting for age, reference year, menarche age, education, and gravidity. In analyses using population controls, weight and BMI were associated with increased adenomyosis risk (weight ≥190 vs. <135 lbs: OR 2.2, 95% CI: 1.3, 3.6; BMI ≥30.0 vs. <25.0: OR 1.8, 95% CI: 1.2, 2.7). We also observed increased adenomyosis risk with increased WC and WHR (WC > 35 vs. ≤35 inches: OR 1.6, 95% CI: 1.1, 2.2; WHR >0.88 vs. ≤0.88: OR 1.3, 95% CI: 0.9, 2.1). In contrast, we observed attenuated associations for weight and BMI and null associations for WC and WHR in analyses using hysterectomy controls. Our results highlight the impact of control selection in the epidemiologic study of adenomyosis and contributes new data on this understudied condition.

Long-term Cardiovascular Mortality in Mothers with Singleton and Twin Births: A Family-Based Approach Prativa Basnet Rolv Skjærven Linn Marie Sørbye Nils-Halvdan Morken Kari Klungsøyr Janne Mannseth Allen Wilcox Quaker Harmon Liv Grimstvedt Kvalvik

Preeclampsia and preterm delivery are associated with higher lifetime risk of cardiovascular disease (CVD) in mothers. CVD risk is especially high among women with only one life-time pregnancy. Twin pregnancies have increased risk of preeclampsia and preterm birth, but their CVD risk has not been fully described. Using maternally linked sibling data (847 664 women) from the Norwegian Medical Birth Registry and Cause of Death Registry, we estimated the risk of long-term CVD mortality in women who stop or continue reproduction after a first singleton or twin birth delivered in 1967-2007, with follow-up for maternal deaths until 2014. Adjusted hazard ratios (aHR) and 95% confidence intervals (CI) for CVD mortality in women aged 40-69 years were estimated for various reproductive patterns: 1) women with only a singleton birth, 2) women with only a twin birth, 3) women with twins and another birth, 4) women with 2 or 3 singleton births (reference group). We also studied if first pregnancy complicated by preterm birth (<37 gestational weeks) was associated with an increased aHR for CVD mortality. Women with only one singleton pregnancy who stopped reproduction had an aHR of 1.9 (95% CI, 1.8-2.1) for CVD mortality. Women with only a twin pregnancy who stopped reproduction had an aHR of 2.1 (1.4-3.1), both compared to women with 2 or 3 singleton births. Risks increased to 3.5 (2.9-4.2) and 2.7 (1.6-4.9) when first birth was preterm. Women who had twins and an additional singleton had no indication of increased risk 0.9 (0.7-1.3). These findings suggest that women with only one birth, singleton or twin, have a two-fold risk of CVD mortality compared to women with 2 or 3 singleton births. In all comparisons, women with a twin pregnancy had no excess CVD risk.

Gestational age trends in placental dysfunction among women with preeclampsia using a novel clustering approach Alexander J. Layden Marnie Bertolet James M. Roberts W. Tony Parks Janet M. Catov Jennifer Adibi

Introduction: Preeclampsia is a life-threatening pregnancy syndrome hypothesized to have 2 subtypes with distinct placental pathogenesis: early (<34weeks) and late-onset (>34 weeks). Placental pathology evaluations are routinely conducted for preeclampsia, which may help elucidate subtypes. Few systematic methods exist to summarize the variables generated from pathology review.

Objective: Using the clustering method, latent class regression (LCR), we characterize placental features of preeclampsia across gestation.

Methods: We included 2863 women with preeclampsia determined by ICD-9 codes who delivered at Magee-Womens Hospital (Pittsburgh, PA) in 2008-2012 with a singleton pregnancy and an available pathology review (91% of preeclampsia cases). Gestational age was determined by best obstetric estimate and 15 abstracted placental features from pathology reviews were included. LCR simultaneously clustered placental features and estimated the likelihood of cluster membership with increasing gestational age. The optimal number of clusters was determined by comparing fit statistics.

Results: Placental findings in women with preeclampsia clustered into 4 groups: "maternal malperfusion" (22% of cases), "fetal malperfusion" (10%), "acute inflammation" (13%) and "low risk pathology" (55%). The most prevalent cluster before 34 weeks was maternal malperfusion (78%) while low risk pathology (66%) was most prevalent after 34 weeks. A 1-week increase in gestational age at delivery was associated with a lower odds of maternal malperfusion (OR: 0.55, 95% CI: 0.47,0.63) and fetal malperfusion (OR 0.79, 95% CI: 0.72,0.86), but a higher odds of acute inflammation (OR: 1.34, 95% CI: 1.26, 1.41) relative to the low risk pathology group.

Conclusions: In support of a 2-subtype hypothesis, we identified distinct placental clusters in women with early and late-onset preeclampsia. Our novel application of LCR offers a framework for studying preeclampsia and perhaps other placental conditions.

Menstrual cycle irregularities and adverse pregnancy outcomes in Project Viva Diana Soria-Contreras Wei Perng Sheryl Rifas-Shiman Jorge Chavarro Marie-France Hivert Emily Oken

Background. Retrospective evidence suggests that menstrual cycle irregularities may be a marker for risk of adverse pregnancy outcomes, but these studies are susceptible to bias.

Objective. To evaluate the association between menstrual cycle irregularities and adverse pregnancy outcomes in a prospective cohort of pregnant women**.**

Methods. N=2046 women from Project Viva. In early pregnancy, women reported their usual menstrual cycle length (<21 days, 21-25 days, 26-34 days (reference), ≥35 days, and too irregular to estimate). For the analysis, we combined <21 days with 21-25 days, and ≥35 days with too irregular to estimate. We ascertained outcomes from outpatient/delivery charts, including: gestational glucose tolerance (impaired glucose tolerance/gestational diabetes (IGT/GDM), normal, isolated hyperglycemia), hypertensive disorders of pregnancy (gestational hypertension/preeclampsia, normal), birth outcome (live birth, intrauterine fetal demise/miscarriage), gestational weight gain (inadequate, excessive, adequate), birth weight-for-gestational age z-scores, preterm birth (<37 weeks at delivery), and systolic blood pressure during pregnancy. We performed linear, multinomial, or logistic regression adjusted for age, race/ethnicity, parity, age at menarche, and pre-pregnancy BMI.

Results. Most women (74.3%) had a menstrual cycle of 26-34 days, 16.2% reported cycles <25 days, and 9.5% reported cycles ≥35 days/too irregular to estimate. A menstrual cycle length of <25 days was associated with lower odds of IGT/GDM (OR 0.51, 95% CI: [0.29, 0.90]) and higher odds of preterm birth (OR 1.57, [1.00, 2.48]). A menstrual cycle of ≥35 days/too irregular to estimate was associated higher odds of IGT/GDM (OR 1.80, [1.09, 2.95]) and preterm birth (OR 2.22, [1.33, 3.70]). No other associations were evident.

Conclusion. Irregular menstrual cycles may predict some adverse pregnancy outcomes, and thus may serve as an important marker of women to monitor closely during pregnancy.

Metformin and Risk of Adverse Pregnancy Outcomes Among Pregnant Women with Gestation Diabetes in The United Kingdom: A Population-Based Cohort Study Ya-Hui Yu

Robert Platt Oriana Yu Kristian Filion

Objectives

To compare the rate of adverse pregnancy outcomes with metformin versus insulin among women with GDM in the United Kingdom.

Methods

We conducted a retrospective cohort study using linked data from the Clinical Practice Research Datalink, its pregnancy register, and Hospital Episode Statistics. We included pregnancies of women without diabetes history and initiated metformin or insulin between a gestational age of 20 weeks and the end of pregnancy from 1998 to 2018. We defined exposure using an intention-to-treat approach, with person-time classified into either the metformin or insulin group based on the treatment prescribed at cohort entry. The primary outcome was a composite outcome of large for gestational age (birthweight> 90th percentile) and macrosomia (birthweight> 4000 grams). The secondary endpoints were preterm birth, Cesarean delivery, and hypertensive disorders during pregnancy. We used inverse probability weighted-Cox proportional hazards models with a time scale of time since treatment initiation to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for the association between the risk of adverse pregnancy outcomes and the use of metformin versus insulin, accounting for baseline covariates.

Results

Our cohort included 2,330 pregnancies from 2,231 women with GDM. A total of 42% of women were prescribed insulin and 58% were prescribed metformin at cohort entry. The mean gestational age at treatment initiation was 31.8 weeks (standard deviation: 4.4). Compared to insulin use, metformin use was associated with a decreased risk of a composite endpoint of large for gestational age and macrosomia (HR:0.61, 95% CI: 0.50, 0.75). Metformin use was also associated with decreased risks of Cesarean delivery (HR:0.82, 95% CI: 0.72, 0.92), and preterm birth (HR: 0.82, 95% CI: 0.61, 1.09). The HR for hypertensive disorders during pregnancy was 0.90 (95% CI: 0.64, 1.27). In sensitivity analyses that used gestational age as the underlying time axis, we observed similar trends.

Conclusions

Our study suggests that, compared to the use of insulin, the use of metformin is associated with decreased risks of large for gestational age and macrosomia and of Cesarean delivery among women with GDM.

Obstetric comorbidity scores and evaluating disparities in severe maternal morbidity Stephanie Leonard Elliott Main Deirdre Lyell Suzan Carmichael Chris Kennedy Christina Johnson Mahasin Mujahid

Background. We previously developed and validated a comorbidity scoring system in unselected state and national birth data to predict severe maternal morbidity (SMM) – a well-established indicator of serious complications at birth. Our objectives were to evaluate the validity of the scoring system across racial-ethnic and socioeconomic groups and to determine the effect of standardizing for the comorbidity score on disparities in SMM. **Methods.** We analyzed live births in California during 2011-2017 with linked birth certificate and birth hospitalization discharge data (n = 3,308,554). We assessed the performance of the comorbidity scoring system in subpopulations (groups) defined by race-ethnicity, nativity, payment method, and education. We then calculated the risk-standardized incidence of SMM in each group, and estimated SMM disparities before and after adjustment for the comorbidity score using logistic regression models. **Results.** The comorbidity scoring system performed well across groups (area under the ROC curve ranged from 0.79-0.87 and minimal variation in precision-recall curves; calibration curves demonstrated goodness of fit). All nonwhite groups had elevated SMM incidence, compared with white, before and after comorbidity score standardization; however, standardization increased the disparity for the Asian and Latinx groups and decreased the disparities for the other racial-ethnic groups. Standardization for comorbidities also increased disparities for the foreign-born group and the non-commercial insurance groups. Increasing education was associated with decreasing SMM incidence, which was largely unaffected by comorbidity score standardization. **Conclusion.** These results support the use and validity of a newly developed comorbidity scoring system to evaluate disparities in SMM. Differences in comorbidities partially explained disparities in SMM for some racial/ethnic and socioeconomic groups and masked the magnitude of disparities for others.

Neighborhood-level Racial/Ethnic and Socioeconomic Inequality and Severe Maternal Morbidity in the State of California: Employing the Index of Concentration at the Extremes Christine Board Xing Gao Elleni Hailu Rachel Berkowitz Suzan Carmichael Mahasin Mujahid

Structural racism has emerged as a root cause of racial/ethnic disparities in severe maternal morbidity (SMM), however, empirical investigations remain limited. We examined associations between the Index of Concentration at the Extremes (ICE), which quantifies area-level racial and economic inequality, and SMM to address this important gap in knowledge. We leveraged linked vital statistics and hospital discharge records from the Office of Statewide Health Planning and Development in California (OSHPD) from 1997 to 2012 to identify occurrences of SMM (as defined by the 21 Centers for Disease Control indicators). Three ICE measurements (ICE-race/ethnicity; ICE-income; ICE-race/ethnicity & income) were used to capture the individual and joint influence of racial and economic spatial polarization, based on residential census tract (n= 8057 tracts; average= 897 participants within tracts) at time of giving birth (categorized into quartiles; Q1=most inequality, Q4=least inequality). Mixed effects logistic regression models (i.e. participants nested within neighborhoods) were used to compare estimates before and after adjustment for sociodemographic factors (age, education, insurance, race/ethnicity), pregnancy-related behaviors (parity, singleton/multiple birth), and a comorbidities index. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported as approximations of relative risk, given that SMM is a rare outcome. Of the 8,147,839 participants who gave birth, 1.0% experienced SMM (1.6% Black; 1.0% Hispanic; 1.0% Asian/Pacific Islander; 0.8% White; 1.2% American Indian/Alaska Native or "Other"). In the adjusted models, greater (Q1 vs. Q4) racial/ethnic inequality (OR=1.13, 95% C.I. 1.11-1.16), economic inequality (OR=1.04, 95% C.I. 1.02-1.07), and combined racial and economic inequality (OR=1.12, 95% C.I. 1.09-1.15) were associated with a higher odds of SMM. These results provide support for the harmful effects of structural racism on SMM.

Drivers of Postpartum Readmissions with and without Severe Maternal Morbidity, Oregon All Payer All Claims 2012-2018 Menolly Kaufman Jonathan Snowden

Background: Given the rise in maternal morbidity in the US, substantial research and health policy focus have been given to "near misses" of maternal mortality – often classified as severe maternal morbidity (SMM). However, readmissions *without* evidence of SMM are also common, and are significant markers of maternal morbidity in ways that are not yet fully understood. We assessed which demographic, clinical, and system-level factors are associated with postpartum readmission without evidence of SMM and if they differ from risk factors for postpartum readmissions with evidence of SMM.

Methods: We conducted a retrospective cohort study using All Payer All Claims Data (APAC) among persons age 15-44 with a hospital delivery in Oregon from 2012-2017. We estimated the associations between demographic (i.e. age and rurality), clinical (i.e. delivery route, comorbidities), and system-level factors (i.e. insurance type, hospital rurality) and postpartum readmissions up to 12 months from delivery discharge. We created two outcome measures – postpartum readmissions with evidence of SMM and without evidence of SMM. For each factor, we built multivariate models to estimate cumulative incidence ratios, controlling for confounders identified using directed acyclic graphs.

Results: The overall postpartum readmission rate within 12 months of delivery discharge was 1.8%. Of these, 84% had no evidence of SMM. Age was not associated with the risk of SMM-related readmissions. In contrast, people under the age of 24 were 44% more likely to be readmitted without evidence of SMM compared to those aged 25-29 (RR: 1.44; 95% CI: 1.32 – 1.57). Medicaid insurance at delivery was strongly associated with readmissions with SMM (RR: 12.87; 95% CI: 8.76, 18.92) and without SMM (RR: 9.85; 95% CI: 8.46, 11.46).

Conclusion: Drivers of postpartum readmissions differ depending on the presence of SMM. Our research shows that policies aimed at reducing postpartum morbidity delivery must address system level factors that lead to maternal health inequities.

Health equity

Abstract: Driving distance to maternity hospitals and risk of adverse perinatal outcomes and maternal morbidity: an analysis of Pennsylvania birth records from 2011-2015 Sarah Minion Catherine Haggerty Dara Mendez Elizabeth Krans Maria Brooks

Objective: To quantify associations between driving distance from maternal residence to delivery hospital and adverse perinatal outcomes

Methods: We used live births ≥20 weeks gestation without missing data or maternal hospital transfer (N = 603,997 infants to 593,504 mothers) in Pennsylvania birth records (2011-2015). We calculated associations between the shortest driving distance from maternal residence to the delivery hospital in ArcGIS and small-for-gestational age (SGA), preterm birth <37 weeks (PTB), infant neonatal intensive care unit (NICU) admission, and maternal morbidity (blood transfusion, unplanned operation, ruptured uterus, unplanned hysterectomy, or intensive care unit admission). All models controlled for maternal characteristics, pregnancy risk factors, hospital NICU level, and residence rurality.

Results: In multivariable analyses, greater distance to the delivery hospital was associated with increased risks for all outcomes, although nadirs varied by outcome. For SGA and PTB, risk patterns were U-shaped with increasing risks at both short and long distances. For maternal morbidity and NICU admission, risk patterns directly increased as driving distance increased. As compared to the referent category of traveling 0km to the delivery hospital, relative risks (95% confidence intervals) of maternal morbidity, NICU admission, PTB, and SGA when traveling 80km were 1.41 (1.24, 1.58), 1.63 (1.57, 1.69), 1.34 (1.30, 1.39), and 1.04 (1.01, 1.07), respectively.

Conclusions: Longer driving distance to the delivery hospital was associated with a greater risk of adverse pregnancy outcomes in Pennsylvania mothers, although elevated risks at the shortest distances signify a complex relationship. Driving distance may serve as a proxy of inadequate healthcare spatial accessibility for rural mothers in Pennsylvania. Optimizing healthcare facility location and increasing awareness of risks associated with living far from the delivery hospital may help address inequities.

Risk of recurrent severe maternal morbidity in an urban safety net health system Sheree Boulet Kait Stanhope Nikkia Worrell Denise Jamieson

Severe maternal morbidity (SMM) in the US has increased over time and disproportionately affects Black and low-income women. Although there is some evidence that history of certain maternal complications is associated with recurrent adverse outcomes in subsequent pregnancies, only one study to date has assessed risk of SMM recurrence. We conducted a population cohort study to estimate the risk of recurrent SMM in an urban, medically underserved population in Atlanta, Georgia. We abstracted electronic medical record data for all deliveries at Grady Memorial Hospital between 2011 and 2020 and included all women with two singleton deliveries (live and stillborn) during the study period, selecting the first two births for women with more than two deliveries. We defined SMM during using International Classification of Disease codes and included diagnoses at delivery through 42 days postpartum. We used multivariable generalized linear models to estimate adjusted risk differences (aRD), adjusted risk ratios (aRR) and 95% confidence intervals (CI) for SMM at the second birth, controlling for age, parity, self-reported race/ethnicity, insurance type, and chronic hypertension or diabetes at first birth. Among 4,564 women with two singleton births, 4.8% (n=217) had SMM during the index birth and 5.8% (n=265) had SMM during the second birth. In crude and adjusted models, having SMM during the index birth was associated with a 3-fold higher risk of SMM during the subsequent birth (aRR 3.21, 95% CI: 2.33-4.44, aRD 11.8 per 100 births, 95% CI: 8.6-15.1). History of SMM may be an important indicator of SMM risk in future births.

Adherence to traditional Chinese postpartum practices and postpartum depression: a cross-sectional study in Hunan, China Pengfei Guo Roman (Dong) Xu Zeyan Liew Hua He Peter Brocklehurst Beck Taylor Chao Zhang Xin Jin Wenjie Gong

Background: The relationship between adherence to traditional Chinese postpartum practices (known as 'doing-the-month') and postpartum depression (PPD) remains unknown. Practices include restrictions on diet, housework and social activity, personal hygiene, and cold contact.
Methods: The cross-sectional study included 955 postpartum women in obstetric clinics in Hunan Province of China between September 2018 to June 2019. Thirty postpartum practices were collected by a self-report online structured questionnaire. PPD symptoms were assessed by the Chinese version of the Edinburgh Postnatal Depression Scale (EPDS). Multivariable linear regression was used to estimate the differences in EPDS scores according to adherence to postpartum practices. Firth's bias-reduced logistic regression was employed to analyze the binary classification of having PPD symptoms (EPDS >=10).
Results: Overall, both moderate and low adherence to postpartum practices appeared to be associated with higher EPDS scores (adjusted difference 1.07, 95%CI 0.20, 1.94 for overall moderate adherence; and adjusted difference 1.72, 95%CI 0.84, 2.60 for overall low adherence). In analyses by practice domain, low adherence to housework-related and social activity restrictions was associated with having PPD symptoms compared with high adherence (OR 1.61, 95%CI 1.07, 2.43).
Conclusions: Low adherence to traditional Chinese postpartum practices is associated with PPD, especially in the domain of housework-related and social activity restrictions. The influence of low adherence to postpartum practices on PPD may relate to psychosocial stress and the lack of satisfactory practical support. Longitudinal study and clinical assessment would be needed to confirm these findings.

Mental health

Prenatal exposure to bisphenols and phthalates and postpartum depression: Examining the role of neuroactive sex steroid hormone disruption Melanie Jacobson Cheryl Stein Leonardo Trasande

Postpartum depression (PPD) is a serious psychiatric disorder that affects up to 20% of childbearing women. While etiology remains largely unknown, perinatal sex steroid hormone fluctuations have been identified as an important factor. In particular, the neuroactive progesterone metabolite, allopregnanolone, has recently emerged as a key driver. Synthetic environmental chemicals such as bisphenols and phthalates are known to affect sex steroid hormones; however these toxicants have not yet been examined in relation to hormonal changes relevant to PPD. The objective of this study was to investigate associations of prenatal exposure to bisphenols and phthalates with serum sex steroid hormones in mid-pregnancy and PPD symptoms at four months postpartum. In a prospective cohort study of 139 pregnant women, bisphenols and phthalate metabolites were measured in early- and mid-pregnancy urine samples and serum allopregnanolone, progesterone, pregnanolone, and pregnenolone were measured in mid-pregnancy. PPD was assessed at 4 months postpartum using the Edinburgh Postnatal Depression Scale. To evaluate the associations of chemical exposures with sex steroid hormones and PPD, multiple informant models were fit using generalized estimating equations. Di-n-octyl phthalate (DnOP) and diisononyl phthalate (DiNP) metabolites were associated with reduced progesterone concentrations. In adjusted models, log-unit increases in ∑DnOP and ∑DiNP predicted 8.1% (95% Confidence Interval (CI): -15.2%, -0.4%) and 7.7% (95% CI: -13.3%, -1.7%) lower progesterone, respectively. ∑DnOP was also associated with increased odds of PPD (odds ratio=1.48 (95% CI: 1.04, 2.11)). Bisphenols and other phthalates were not associated with other hormone outcomes or PPD. This study highlights the biologic plausibility of phthalate-induced sex steroid hormone disruption on the pathway for PPD pathogenesis and the potential for pregnancy as a critical window of exposure.

Early pregnancy exposure to metals and maternal mid-pregnancy depressive symptoms in Project Viva Lisa B. Rokoff Sheryl L. Rifas-Shiman Andres Cardenas Pi-I D. Lin Brent A. Coull Michelle Bosquet Enlow Susan A. Korrick Emily Oken

Background: Pregnancy may be a period of heightened susceptibility to neurotoxicant stressors. However, prenatal chemical exposures have not been well explored in relation to maternal depression. We evaluated the extent to which blood levels of essential and non-essential metals were prospectively associated with mid-pregnancy depressive symptoms.

Methods: Participants were 1129 women in Project Viva, a longitudinal cohort recruited during pregnancy (1999-2002) in the greater Boston area. We measured levels of 11 metals in maternal first trimester erythrocytes. We assessed depressive symptoms via the Edinburgh Postnatal Depression Scale (EPDS+13; 0-30 scale) at mid-pregnancy. Adjusting for maternal sociodemographics and co-exposures, we used logistic regression to evaluate odds of EPDS+ with each chemical, and quantile g-computation to examine joint associations with the metal mixture.

Results: In our cohort of moderately high socioeconomic status participants (e.g., 73% college graduate), the prevalence of EPDS+ was 9%. Correlations between metals were moderately positive (Spearman: 0.02-0.59), except for weak, negative correlations between barium and all other metals. First trimester metal levels were largely not associated with EPDS+ at mid-pregnancy. In the mixtures analysis, the odds ratio (OR) for a joint quartile increase in all metals was 0.92 [95% confidence interval (CI) 0.56, 1.51]. Although CIs were imprecise, copper (Cu) and lead (Pb) were weakly associated with higher odds of EPDS+ [OR (95% CI) 1.44 (0.43, 3.91), 1.24 (0.83, 1.84) per two-fold exposure; respectively], whereas arsenic (As) was associated with lower odds [OR (95% CI) 0.87 (0.78, 1.00)]. Direction and relative magnitude of ORs and quantile g-computation weights were similar for As, Cu, and Pb.

Conclusion: In this first study to investigate associations of an early pregnancy metal mixture with subsequent prenatal depressive symptoms, we did not observe strong evidence of associations.

Circulating miRNA associated with depressive symptoms in pregnant mothers and effect on birthweight Helen Foley Caitlin Howe Carrie Breton

MicroRNA (miRNA) circulating in plasma have been proposed as biomarkers for a variety of conditions and diseases, including complications during pregnancy. These 20-24nt segments of RNA have been also associated with depression. However, few studies have addressed miRNA associated with depression during pregnancy and examined the relationship between depressive symptoms, miRNA, and birthweight. In this study, we examined miRNA in early and late pregnancy from the MADRES cohort of primarily low-income Hispanic women based in Los Angeles, CA. miRNA, including those from extracellular-vesicles (EVs), were isolated from maternal blood plasma samples collected during pregnancy and quantified using Nanostring Ncounter, a fluorescence- and hybridization-based miRNA analysis method. In this study, we identified miRNA previously associated with depression were also present in circulating plasma of expectant mothers with depressive symptoms and differed between early and late pregnancy. We also used linear mixed models to explore the effects of miRNA associated with depression on birthweight and whether socioeconomic factors could also contribute to altered miRNA profiles in this health-disparities cohort of Hispanic women.

COVID-19 outbreak-related stress, coping mechanisms, and symptoms of depression and anxiety in pregnant women Sylvia E Badon Lisa A Croen Assiamira Ferrara Jennifer L Ames Monique M Hedderson Kelly C Young-Wolff Yeyi Zhu Lyndsay A Avalos

Background: COVID-19 outbreak-related stress has been reported to be associated with depression and anxiety. We examined the impact of coping mechanisms on the association between COVID-19 outbreak-related stress and symptoms of depression and anxiety in pregnant women.
Methods: 54,326 members of Kaiser Permanente Northern California who were pregnant between June 22 and September 30, 2020 were invited to complete an online survey about stress (modified Acute Stress Disorder questionnaire) and coping mechanisms since the start of the COVID-19 outbreak, and current depression (8-item Patient Health Questionnaire [PHQ-8]) and anxiety (Generalized Anxiety Disorder screener [GAD-7]). We categorized stress into tertiles (low, moderate, high). We used regression to estimate mean differences in depression and anxiety symptoms for stress categories stratified by coping mechanisms, adjusted for sociodemographics.
Results: 6,628 (12%) pregnant women completed the survey. The most common coping mechanisms were talking with friends and family (77%), outdoor exercise (57%), and watching television (49%). In women who talked with friends and family, high (vs low) stress was associated with 4.9 greater PHQ-8 score (95% CI: 4.7, 5.1) and 5.4 greater GAD-7 score (95% CI: 5.2, 5.6). In women who did not talk with friends and family, high (vs low) stress was associated with 6.6 greater PHQ-8 score (95% CI: 6.1, 7.1) and 7.2 greater GAD-7 score (95% CI: 6.7, 7.6). Outdoor exercise similarly modified associations between high stress and depression and anxiety symptoms (both P for interaction <0.001). Watching television did not modify associations between high stress and depression or anxiety symptoms (P for interaction=0.34 and 0.17, respectively). Patterns of associations were similar for moderate stress.
Conclusions: Talking with friends and family and outdoor exercise may mitigate depression and anxiety symptoms associated with COVID-19 outbreak-related stress in pregnant women.

COVID-19 and Perinatal Intimate Partner Violence: A cross-sectional survey of pregnant and post-partum individuals in the early stages of the COVID-19 pandemic Katherine Muldoon Kathryn Denize Robert Talarico Carlie Boisvert Olivia Frank Alysha Harvey Ruth Rennicks-White Deshayne Fell Meagan Ann O'Hare-Gordon Malia Murphy Yanfang Guo Daniel Corsi Kari Sampsel Shi-Wu Wen Mark Walker Darine El-Chaâr

Background: The COVID-19 pandemic has caused extreme societal stress and concern for rising risk of intimate partner violence (IPV). This study was designed to investigate the prevalence, patterns and risk factors for perinatal IPV among those who gave birth since COVID-19 began.

Methods: We conducted a cross-sectional survey of patients who gave birth at The Ottawa Hospital and were >20 days post-partum between March 17th-June 16th 2020. Perinatal IPV was defined as psychological, physical, and/or sexual abuse in the 12 months pre-pregnancy, during pregnancy or post-partum. Log-binomial multivariable regression models were used to compute adjusted risk ratios (aRR) and 95% CI to quantify relationships with potential risk factors for IPV: maternal age, parity, household income, post-partum depression, and increase in partner substance use.

Results: Of 1568 patients who gave birth during the study period, 572 were contacted, 261 completed the survey and 216 had complete data for analyses. Median maternal age was 33 years (IQR: 30-36) and median infant age was 76 days (IQR: 66-90). In total, 52 (24.1%) reported perinatal IPV: 37 (17.1%) had controlling partners; 13 (6.0%) reported abuse in the 12 months pre-pregnancy, 11 (5.1%) during pregnancy, and 15 (6.9%) post-partum. Household income below the municipal median was the strongest risk factor for any IPV (aRR: 3.24, 95% CI: 1.87-5.59). There was no apparent association between maternal age (aRR: 0.99, 95% CI: 0.94-1.04), nulliparity (aRR: 1.18, 95% CI: 0.71-1.97), post-partum depression (aRR: 1.03, 95% CI: 1.00-1.07), or partner substance use increase since COVID-19 began (aRR: 0.73, 95% CI: 0.42-1.25) with IPV.

Conclusion: A quarter of our study population experienced perinatal IPV. Household income was the strongest risk factor for perinatal IPV, and surprisingly, many hypothesized risk factors (e.g., mental health, increased partner substance use etc.) were not associated with perinatal IPV in this sample.

Risk factors for Severe Coronavirus Disease 2019 (COVID-19) during pregnancy Sonia Hernandez-Diaz Louisa H. Smith Camille Dollinger Diego Wyszynski

Background: The risk for severe COVID-19 in pregnant women with SARS-CoV-2 infection is at least as high as in non-pregnant women. Comorbidities can further increase that risk. We describe characteristics associated with a severe clinical course of COVID-19 during pregnancy.

Methods: Since June 2020, the International Registry of Coronavirus Exposure in Pregnancy (IRCEP) follows up pregnant women 18 years of age and older tested for SARS-CoV-2 or clinically diagnosed with COVID-19. Participants self-enroll and administer online questionnaires on demographics, COVID-19 clinical course, comorbidities, and other factors. We classified symptomatic participants with positive tests as having mild, moderate, or severe COVID-19 and compared their demographic and clinical characteristics.

Results: Of 17174 enrolled participants, 6958 had a positive test, and 5540 had symptoms, of whom 2291 (41%) were mild, 3173 (57%) were moderate, and 154 (2%) were severe. Among the moderate cases, 8.5% were hospitalized for an average of 5 days. Among the severe cases, 73.4% were hospitalized for an average of 9 days and 70.0% required respiratory assistance, ventilation or ECMO. Olfactory symptoms were most common in mild disease (74.0%), upper respiratory symptoms in moderate (88.0%), and shortness of breath (88.0%) in severe. The highest proportion of moderate and severe cases were reported from Brazil (72.9%). The proportion of moderate or severe COVID-19 was higher in those with underlying asthma (73.0%), diabetes (70.9%), hypertension (67.2%) and obesity (64.4%). In an adjusted model, asthma, diabetes, and obesity remained important predictors of COVID-19 severity. Maternal age, thyroid disease, smoking or vaping were not associated with severity.

Conclusion: Underlying asthma, diabetes and hypertension are associated with an increased risk of severe clinical course in pregnant women with symptomatic COVID-19. These subpopulations could benefit from closer clinical observation.

Validity of electronic medical records for measuring maternal COVID-19 infection Annette Regan Sheena Sullivan Onyebuchi Arah

Validity of electronic medical records for measuring maternal COVID-19 infection

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Background: Large-scale evaluation of maternal SARS-CoV-2 infection and prenatal COVID-19 vaccination based on electronic medical information will rely on the quality of ICD coding. However, little is known about the validity of ICD-coded COVID-19 diagnoses.

Methods: We used data from a national cohort of pregnant women with a date of delivery since 1 January 2020 in the OptumLabs® Data Warehouse (OLDW). OLDW is a longitudinal, real-world data asset with de-identified administrative claims and electronic health record data. We identified all services with an ICD-10-CM diagnostic code of U07.1. For comparison, laboratory claim records were extracted to identify SARS-CoV-2 diagnostic testing within 3 days of the COVID-19 diagnosis. We compared ICD-coded diagnoses to SARS-CoV-2 test results ("gold standard") to calculate sensitivity, specificity and predictive values.

Results: Of 81,210 pregnancies identified, 1,391 pregnant women had an ICD-10-CM diagnosis of COVID-19 and 3,247 women had a record of a laboratory test for SARS-CoV-2. Agreement between ICD-coded diagnosis and laboratory testing records was high 92% (95% CI 91, 93%), as was the specificity (95%; 95% CI 94, 96%). However, sensitivity of ICD-code diagnosis was low (22%; 95% CI 15, 30%) and the positive predictive value was 16% (95% CI 12, 21%).

Conclusions: Results from a national cohort of pregnant women suggest that the use of diagnostic coding alone would miss 78% of maternal COVID-19 infections. Rather than relying exclusively on diagnostic coding, perinatal epidemiology research and surveillance should draw from multiple sources of COVID-19 diagnostic information.

Associations between neighborhood COVID-19 pandemic stress, SARS-CoV-2 infection, and preterm birth in New York City Teresa Janevic Erona Ibroci Jezelle Lynch Stephanie Sestito Nina Molenaar Lotje De-Witte Joanne Stone Veerle Bergink Elizabeth Howell

Concern exists that the COVID-19 pandemic will increase risk of preterm birth (PTB), potentially due to inflammatory processes related to SARS-CoV-2 infection or "pandemic stress" due to the social and economic crisis. We analyzed data from an ongoing prospective pregnancy cohort of SARS-CoV-2 infection during pregnancy in New York City to examine the association between neighborhood pandemic stress (defined as increased in unemployment rates from January-December 2020 and COVID-19 mortality rates) and PTB, taking into account SARS-CoV-2 IgG status. The current analyses include 762 women who delivered at two hospitals between April-November 2020. We used publicly available zip code estimates of unemployment rate increases, COVID-19 mortality, and baseline neighborhood vulnerability. SARS-CoV-2 serologic enzyme-linked immunosorbent assay was performed on a blood sample obtained during pregnancy. We ascertained preterm birth (<37 weeks) and covariates from the electronic medical record. We used log-binomial regression with robust standard error by zip code to estimate associations between neighborhood pandemic stress and PTB, adjusting for baseline neighborhood vulnerability, SARS-Cov-2 IgG+ status, race-ethnicity, insurance status, age, and parity. 132 (17%) women were SARS-CoV-2 IgG positive. SARS-CoV-2 infection during pregnancy was not associated with PTB (adjusted relative risk (aRR)=1.1, 95% Confidence Interval (CI)=0.6, 2.1). Women in neighborhoods with high unemployment rate increase had 60% higher risk of PTB than those in other neighborhoods (aRR=1.6, 95%CI=1.0, 2.7). Neighborhood COVID-19 mortality was not associated with PTB (aRR=1.1, 95%CI=0.6, 1.9). Multiplicative or additive interaction between SARS-CoV-2 IgG+ and pandemic stress was not present. We found modest evidence of associations between neighborhood pandemic stress and PTB, even after adjusting for baseline disadvantage and neighborhood demographic composition.

Global health

Pregnancy outcomes during the COVID-19 pandemic in Canada, March to August 2020 Shiliang Liu Susie Dzakpasu Chantal Nelson Shu Qin Wei Julian Little Heather Scott K.S. Joseph

Background: Several studies have documented changes in preterm birth and stillbirth during the COVID-19 pandemic. We carried out a study to examine obstetric intervention, preterm birth and stillbirth rates in Canada from March-August 2020.
Methods: The study included all singleton hospital deliveries in Canada (excluding Quebec) from March-August 2020 (and March-August 2015-2019) with information obtained from the Canadian Institute for Health Information. Data for Ontario were examined separately because this province had the highest rates of COVID-19 in the study population. Rates and odds ratios with 95% confidence intervals (CI) were used to quantify pregnancy-related outcomes.
Results: There were 136,445 and 717,905 singleton hospital deliveries in Canada (excluding Quebec) in March-August 2020 and March-August 2015-19, respectively. Rates of obstetric intervention declined at early gestation. Odds ratios for labour induction and cesarean delivery at <32 weeks' gestation contrasting March-August 2020 vs March-August 2015-19 were 0.84 (95% CI 0.74-0.95) and 0.92 (95% CI 0.85-1.00), respectively. Preterm birth rates increased in Canada (excluding Quebec) from 6.42% in March-August 2015 to 6.74% in March-August 2019 but were unchanged in March-August 2020 (6.74%). Stillbirth rates were stable between March-August 2015 and March-August 2020. However, stillbirth rates peaked in Ontario in April 2020 due to higher rates of stillbirths at 20-27 weeks and 37-41 weeks' gestation.
Conclusion: Changes in labour induction and cesarean delivery at early gestation, and in other perinatal outcomes, during March to August 2020, highlight the need for timely perinatal surveillance, and for further study of the use and impact of obstetric services in pandemic circumstances.

Outcomes after controlled ovarian stimulation and embryo transfer in women with cancer: a systematic review and meta-analysis Clare Meernik Charles Poole Stephanie Engel Mary Peavey Barbara Luke Hazel Nichols

Cancer and its treatment can increase infertility risk and may necessitate assisted reproductive technology (ART) to achieve pregnancy. However, current evidence gaps may contribute to lack of knowledge and utilization of ART. We conducted a systematic review and meta-analysis of studies comparing ART outcomes between women with and without cancer after controlled ovarian stimulation and embryo transfer. PubMed, Embase, and Scopus were searched for studies that evaluated any of the following: length of ovarian stimulation; gonadotropin dose; peak estradiol; total or mature oocytes retrieved; fertilization; embryos obtained; oocyte/embryo survival after thaw; implantation; cycle cancellation; pregnancy; or live birth. Of 5,241 unique records identified, 40 studies met inclusion criteria, representing a median per study of 52 women with cancer and 114 women without cancer. Random-effects models were used to calculate mean differences (MD) (continuous outcomes) and risk ratios (RR) (binary outcomes) with 95% prediction intervals (PI). Preliminary analyses of stimulation length, gonadotropin dose, peak estradiol, total and mature oocytes, and cycle cancellation indicate substantial among-study heterogeneity. No differences were observed in the number of embryos obtained among women with vs. without cancer (k=8; MD= -0.18, 95% PI: -1.15, 0.79), nor in the clinical pregnancy rate (k=7; RR=0.75, 95% PI: 0.36, 1.57) or live birth rate (k=8; RR=0.77, 95% PI: 0.30, 1.98). Further analyses are ongoing, including subgroup analysis and meta-regression to examine the influence of study characteristics, such as cancer type, indication for ART among controls, age at ART, and timing of ART initiation relative to cancer treatment. This review will provide an updated and comprehensive synthesis of ART outcomes among women with cancer, which can aid clinicians and cancer patients in more informed discussion of the expected success of ART relative to a non-cancer population.

Miscarriage history and subsequent fecundability: Results from the Norwegian Mother, Father and Child Cohort Study Lise A. Arge Siri E. Håberg Allen J. Wilcox Øyvind Næss Olga Basso Maria C. Magnus

Background: A link between miscarriage and later fecundability is debated, with studies reporting both lower and higher fecundability after miscarriage. We examined the association between number of prior miscarriages and subsequent fecundability within the Norwegian Mother, Father and Child Cohort Study (MoBa).

Method: We used information on time to pregnancy (TTP) and prior pregnancy outcomes from 48 152 planned MoBa pregnancies conceived without treatment among women with at least one prior pregnancy. TTP was calculated using trying time in months adjusted for cycle length. We estimated fecundability ratios (FRs) and 95% confidence intervals using proportional probability regression, with cycles as the unit of analysis and the cycle number included as an indicator variable. We compared women with 1, 2 and 3 or more prior miscarriages to women with no prior miscarriages. The analysis was adjusted for maternal age, education, income, body mass index and smoking during pregnancy.

Preliminary results: Compared to the reference group with no prior miscarriages, FRs and confidence intervals were 0.92 (0.90-0.95), 0.83 (0.78-0.87) and 0.76 (0-69-0.84) for 1, 2 and 3 or more miscarriages respectively. A sensitivity analysis including women with unplanned pregnancies showed similar results.

Conclusion: The results suggest that women with a higher number of prior miscarriages have reduced fecundability. This may reflect a contribution of occult pregnancy losses to TTP, or the presence of shared underlying causes for fecundability and miscarriage.

Disability status

Fertility rates in women with intellectual and developmental disabilities in Wisconsin Medicaid Eric Rubenstein Deborah Ehrenthal Jenna Nobles David Mallinson Lauren Bishop Marina Jenkins Hsiang-Hui Kuo Maureen Durkin

Background

Women with intellectual and developmental disabilities (IDD) face stigma and inequity surrounding pregnancy and raising children. With a growing number of women with IDD entering reproductive age and relying on Medicaid services, it is important to understand patterns in fertility to better support this population and allocate services within Medicaid.

Objectives

To calculate the general fertility rate (GFR), age-specific fertility rates (ASFR), and the total fertility rate (TFR) for women with IDD and compare to women without IDD in 10 years of Medicaid-linked birth records from Wisconsin. We investigated ASFR in each year and evaluated differences by three prevalent IDDs: intellectual disability, cerebral palsy, and autism spectrum disorder.

Study design

We used data from the Big Data For Little Kids project, a longitudinal cohort of administratively-linked birth records for in-state, resident deliveries during 2007-2016. Our sample was Medicaid-enrolled women with live births in Wisconsin. We identified IDD through one year of pre-pregnancy Medicaid claims. The Wisconsin Department of Health Services provided Medicaid enrollment data for all women in the state in each year, which was the denominator in analyses. We calculated the GFR, ASFR, and the TFR and corresponding 95% confidence intervals (95% CI) for women with and without IDD. We calculated rate ratios to compare the two groups. We examined ASFR and TFR by year and generated estimates stratified by IDD-type.

Results

From 2007-2016, Wisconsin women aged 15-44 were enrolled in Medicaid for 3.5 million person-years, of which 28,203 person-years were to women diagnosed with IDD. There were 1,751 live births to 1,026 unique women with IDD and 272,839 live births to 176,428 unique women without IDD. GFR in women with IDD was 62.1 births per 1000 women with IDD (95% CI 59.2, 64.9). For

women without IDD, general fertility was 77.1 per 1,000 (95% CI: 76.8, 77.4), resulting in a general fertility rate ratio of 0.81 (95% CI: 0.7, 0.9). Women with IDD had comparatively lower fertility rates in the younger age strata. The TFR in women with IDD (1.80 births per woman) was 11% lower than that of women without IDD (2.05 births per woman) (rate ratio: 0.89 95% CI: 0.5, 1.5). Over time, there was a significant reduction in fertility among women aged 20-24 years with and without IDD. Autistic women and women with cerebral palsy had lower ASFRs in younger age strata compared to women without IDD. Peak fertility for autistic women was 30-34 years, less than the peak of 20-24 years for other IDD types. In the 20-24 years strata, ASFR of women with intellectual disability was 4 times that of autistic women and 2.5 times that of women with cerebral palsy.

Conclusion

In the Wisconsin Medicaid system, the GFR of women with IDD was lower than women without IDD, but this difference was not evident when accounting for differing age distributions. It is important to describe the fertility trends in women with IDD to understand disparities, access to care, and to plan and allocate pregnancy-related care within Medicaid.

Concordance of self-reported sexual intercourse frequency between members of heterosexual couples attempting conception Julia Bond Lauren Wise

Background

Many research questions require accurate information on sexual behaviors. However, there is no "gold standard" for assessing sexual behavior. Concordance of inter-partner reports of sexual behavior has been proposed as one method of estimating the reliability and, indirectly, validity of self-report data.

Methods

We analyzed data from Pregnancy Study Online (PRESTO) among heterosexual dyads attempting conception. Self-reported sexual frequency at baseline was assessed using the same question in both partners: "In the past month, about how often did you have sexual intercourse with your partner?" Response options were: <1 time/month, 1 time/month, 2-3 times/month, 1 time/week, 2-3 times/week, 4-6 times/week, or daily. We used weighted and unweighted Kappas to assess the intra-partner concordance of reported frequency and log-binomial regression to estimate probability ratios (PRs) and 95% CIs) for predictors of discordance.

Results

Our sample included 2,127 couples. 1,374 reported concordant sexual frequency (64.6%), while men reported less frequent sex in 497 (23.4%) couples and more frequent sex in 256 (12.0%) couples. Unweighted and weighted Kappas were 0.51 (95% CI 0.48-0.54) and 0.63 (95% CI 0.61-0.66), respectively. Longer relationship length was associated with men underreporting relative to their partners (PR=1.19, 95% CI 0.96-1.49). Being unmarried and more educated than one's female partner were associated with men overreporting relative to their partners (PR=1.44, 95% CI 1.00-2.08; PR=1.45, 95%CI 1.07-1.96, respectively).

Discussion

Our study highlights challenges of accurate measurement of a construct with no gold standard. We found that sexual frequency had only moderate concordance among couples planning to conceive, and that selected social factors affected concordance.

Willingness to use the 'male' birth control pill: Demographic and reproductive health correlates among a community-based sample of U.S. men Summer Martins Christy Boraas

Introduction: The prospect of a 'male' birth control pill (MBCP) has garnered national news headlines and high levels of public support. Empirical data on U.S. men's willingness to use MBCP, however, are sparse.

Methods: Non-sterilized cisgender men ages 18-45 with female sex partners were recruited at the 2019 Minnesota State Fair (>2 million attendees) for a cross-sectional survey about novel male birth control methods under development. Using modified Poisson regression, we estimated adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for being "very" willing to use the MBCP by key demographic and reproductive health characteristics.

Results: Participants (n=185) had a mean age of 29 years and 74% were non-Hispanic white. Overall, 62% reported being very willing to use the MBCP. Independent correlates of high willingness included age (30-39 vs. 18-29 years old, aPR=1.29, 95% CI 1.01-1.64), high importance of religion in daily life (aPR=0.65, 95% CI 0.42-1.00), and identifying with a non-Christian vs. no religious denomination (aPR=1.48, 95% CI 1.07-2.07). Willingness to use MBCP was not independently associated with race/ethnicity, education level, urbanicity, current relationship status, or prior involvement in a pregnancy.

Conclusions: Age and religiosity were the most prominent drivers of men's willingness to use MBCP. Efforts to ascertain demand for novel male-controlled contraceptive methods should focus on these characteristics. Additional research on MBCP attitudes in racially, ethnically, and socioeconomically diverse populations is sorely needed.

Association Between Perceptions of Harm and Opioid Use During Pregnancy Among Louisiana Women Ayzsa Tannis Rosaria Trichilo-Lucas, MPH Andrei Stefanescu, MS

Introduction Opioid use during pregnancy poses health risks to both mothers and infants. We examine associations between perception of harm from opioid use, discussions with healthcare workers about opioid use risks, and opioid use during pregnancy using data from the 2019 Louisiana Pregnancy Risk Assessment Monitoring System (PRAMS) Opioid Supplement.

Methods The Louisiana PRAMS Opioid Supplement collected data from April-September 2019. Perception of harm from opioid use was categorized as not harmful at all, not harmful if taken as prescribed, and harmful even if taken as prescribed. Weighted percentages are reported. Rao-Scott chi square tests are used to assess associations between perception of harm, discussions with healthcare workers, and opioid use during pregnancy.

Results Of 460 respondents, 36 (7.7%) reported opioid use while pregnant. Among these mothers, 16.5% perceived use as not harmful at all to a mother's health, 73.1% as not harmful if taken as prescribed, and 10.4% as harmful even if taken as prescribed compared to 5.9%, 49.1%, and 45.0% in mothers who did not use opioids during pregnancy (p=0.0009). Results were similar for perception of harm to infants (p<0.0001). We found no significant association between discussions with healthcare workers about opioid risks and opioid use during pregnancy (p=0.90) and no significant association between discussions with healthcare workers and perception of harm to maternal health (p=0.85) and to infant health (p=0.47).

Discussion Perception of harm differed between mothers who used opioids during pregnancy and those that did not. However, discussions with healthcare workers about opioid use risks were not associated with either perception of harm or opioid use during pregnancy. Qualitative studies examining the content, quality, and effectiveness of these discussions are needed. Different approaches may be more effective at communicating opioid-related risks and improving opioid management during pregnancy.

COVID-19 and parental substance use in the perinatal period: A cross-sectional survey of substance use among post-partum women and their partners in the early stages of the COVID-19 pandemic Olivia Frank Katherine A. Muldoon Kathryn M. Denize Robert Talarico Carlie Boisvert Alysha LJ Harvey Ruth Rennicks White Deshayne B. Fell Meagan Ann O'Hare Gordon Yanfang Guo Malia SQ Murphy Daniel Corsi Kari Sampsel Shi Wu Wen Mark Walker Darine El-Chaâr

Background: There is concern about the rise in substance use caused by the stress of the COVID-19 pandemic, however little is known about patterns among the perinatal population and their households. Our objective was to assess patterns and risk factors of substance use among women who gave birth during the COVID-19 pandemic, and their partners.

Methods: This is a cross-sectional survey of obstetrical patients from The Ottawa Hospital that delivered since the COVID-19 pandemic (March 17-June 16, 2020) and were >20 days post-partum. Participants reported on changes in their own substance use (i.e., alcohol, tobacco, cannabis) and that of their partners since the pandemic began. Modified Poisson multivariable models were used to estimate adjusted risk ratios (aRR) and 95% confidence intervals (CI) for associations with potential risk factors including: parity, post-partum depression, immigration status, household income, and job loss.

Results: Complete data was available for 216 women. The median maternal age was 33 years (IQR:30-36) and infant age was 76 days (IQR:66-90). Any substance use was reported by 113 (50%) women; 15 (6.9%) reported increases in use since the pandemic began. A total of 162 (75%) women reported partner substance use; 45 (20.8%) reported increases in their partner's substance since COVID-19 began. Adjusting for all risk factors, the risk factor most strongly associated with increased maternal substance use was post-partum depression (aRR:5.78, 95%CI:2.22-15.05) and the factor most strongly associated with increased partner substance use was changes in childcare (aRR:2.46, 95%CI:1.38-4.39).

Conclusion: In our sample 7% of mothers and 21% of partners reported an increase in substance use. Increased substance use was 5 times higher among mothers with post-partum depression and 2 times higher among partners with changes in childcare. Our findings highlight the importance of childcare support and perinatal mental health screening during the pandemic.

Prenatal opioid analgesic exposure and risk of birth defects: a population-based study Alexa C. Bowie Martha M. Werler Maria P. Velez Wenbin Li Andi Camden Astrid Guttmann Susan B. Brogly

Background: The teratogenic effect of opioid analgesics is unclear. We sought to quantify the risk of birth defects after prenatal opioid analgesic exposure.

Methods: Using universal coverage administrative health data for Ontario, we assembled a cohort of mother-infant pairs without opioid use disorder with an estimated date of confinement April 2013-March 2018 ($N = 623,182$). The Ontario Narcotics Monitoring System database, which records all prescribed opioid analgesics from July 2012 on, was used to ascertain exposure. Birth defects were identified with the Metropolitan Atlanta Congenital Defects Program classification. Risk ratios (RR) for any and 1st trimester exposure (any opioid analgesic, codeine, morphine, oxycodone) in relation to any defect, organ system defects (cardiovascular, gastrointestinal, genitourinary, CNS), and specific defects were estimated. High dimensional propensity scores (HDPS) including *a priori* confounders with inverse probability treatment weighting was used for confounding adjustment.

Results: Defect prevalence was 2.2%. Overall, 4.1% of pairs were exposed to opioid analgesics during pregnancy (2.0% 1st trimester), mainly to codeine (2.3%), morphine (1.1%), and oxycodone (0.9%). Compared with unexposed, the risk of any birth defect was higher with any opioid analgesic exposure (RR_{adj} 1.16, 95% CI: 1.07-1.25) but not with 1st trimester exposure (RR_{adj} 1.05, 95% CI: 0.92-1.19). An elevated risk of any defect was observed for 1st trimester morphine (RR_{adj} 1.32, 95% CI: 1.05-1.67) but not other agents. Only a higher risk of gastrointestinal intestinal defects was observed with any opioid analgesic exposure (RR_{adj} 1.35, 95% CI: 1.12-1.62) or 1st trimester exposure (RR_{adj} 1.46, 95% CI: 1.11-1.93).

Conclusions: Prenatal exposure to opioid analgesics and morphine in the 1st trimester was associated with an elevated risk of birth defects after accounting for confounding.

Social determinants of health

Racial discrimination, marijuana use, mental health in pregnant African American women Liying Zhang Rhonda Dailey Ana Wong Emily Dove-Medows Mercedes Price Dawn Misra Carmen Giurgescu

Background: Racial discrimination has been related to perceived stress and depressive symptoms among pregnant African American women. However, data are limited regarding the mediation effect of marijuana use on the associations of racial discrimination with stress and depressive symptoms among pregnant African American women. We hypothesized that marijuana use mediates the effects of racial discrimination on perceived stress and depressive symptoms. **Method**: A sample of 615 pregnant African American women aged 18-45 years participated in the Biosocial Impact on Black Births (BIBB) study between 8-29 weeks gestation. Women completed the Experiences of Discrimination Scale (EOD, 9 situations, score 0-9), Perceived Stress Scale (PSS, 10 items, score 0-40), Center for Epidemiological Studies-Depression Scale (CES-D, 20 items, score 0-60), a question about marijuana use during pregnancy (yes vs no) and a sociodemographic questionnaire. Descriptive and path analysis were performed. **Results**: The mean maternal age was 26.6 (SD=5.7) years and the mean gestational age at data collection was 17.1 (SD=6.0) weeks. Fifty-one percent of women reported one or more situations of racial discrimination, 27% had CES-D scores $\geq$ 23 which have been related to depression diagnosis, and 8% reported marijuana use. Compared with women who did not use marijuana, women who used marijuana reported more situations of racial discrimination (1.7 vs. 2.4; $p<0.05$), and had higher levels of perceived stress (18.6 vs. 21.1; $p<0.01$) and depressive symptoms (16.6 vs. 20.5; $p<0.05$). Marijuana use mediated the effect of racial discrimination on perceived stress (standardized indirect effect=0.006; $p<0.05$) and CES-D scores (standardized indirect effect=0.005; $p<0.05$) after controlling for other covariates. **Conclusion**: Women who reported racial discrimination were more likely to use marijuana during pregnancy and reported higher levels of perceived stress and depressive symptoms. Further research is needed to explore the mechanism by which racial discrimination and marijuana use relate to perceived stress and depressive symptoms among pregnant African American women.

Key Words: Racial discrimination, Marijuana use, Stress, Depression, African American

Accuracy of Maternal Opioid-related Diagnosis Codes among Infants with NAS, Florida 2017

Amanda L. Elmore Jason L. Salemi Joseph Lowry Heather Lake-Burger Russell S. Kirby Jean Paul Tanner

Background: The opioid crisis has negatively impacted women and children, as evidenced by increases in maternal opioid use disorder (OUD) and Neonatal Abstinence Syndrome (NAS). Previous studies have shown maternal opioid-related diagnoses at delivery increased by 100% from 2010-2017 in Florida. However, prevalence estimates of maternal opioid use are often based upon unverified ICD-10-CM codes and evaluations of such codes are limited. Therefore, we investigated the accuracy of ICD-10-CM codes related to opioid use documented during delivery hospitalization.

Methods: To identify women with opioid use during pregnancy, we used a sample of infants (N=240) born during 2017 with a diagnosis code indicative of NAS (P96.1). Maternal delivery diagnosis codes for opioid use (F11.2X, F11.1X, F11.9X, Z279.891) were obtained through hospital discharge data. Infant birth and maternal delivery record were reviewed to collect drug screen results and reported drug use. Accuracy of each opioid-related code, as determined by evidence of opioid use in the infant or maternal record, was measured using the positive predictive value (PPV).

Results: We found that 60% of mothers of infants with NAS were diagnosed with an opioid-related diagnosis code at delivery. Of which, 47% were diagnosed with a code indicating OUD. When any opioid-related diagnosis code was used, the PPV was 99% and sources of drug confirmation included reported use (91%), maternal prescription (66%), maternal screening results (61%), and infant screening results (54%). The PPV of codes indicating OUD was 100% and the PPV for codes indicative of opioid use was 97%.

Conclusion: Overall, we found high accuracy of maternal opioid-related diagnoses at delivery. However, our findings suggest that 40% of mothers with prenatal opioid use may not be diagnosed with opioid related codes at delivery. Understanding the accuracy of ICD-10-CM codes indicative of maternal opioid use is paramount for public health surveillance.

History of pandemic H1N1-containing influenza vaccination and risk for spontaneous abortion and birth defects Celeste Romano Clinton Hall Zeina Khodr Anna Bukowinski Gia Gumbs Ava Marie Conlin

Background: One recent study suggested a possible association between receipt of pandemic H1N1 (pH1N1)-containing vaccines in consecutive influenza seasons and spontaneous abortion, but corroborating scientific evidence is limited. We leveraged a population of vaccine-compliant, pregnant military women to examine history of pH1N1-containing influenza vaccination and adverse pregnancy outcomes.

Methods: Pregnancies and live births from Department of Defense Birth and Infant Health Research program data were linked with military personnel immunization records to identify women vaccinated with a pH1N1-containing vaccine in pregnancy prior to 21 6/7 weeks' gestation, October 2009–April 2015. Cox and modified Poisson regression models estimated associations between vaccination with pH1N1- vs non–pH1N1-containing influenza vaccine in the season prior to the index pregnancy, and spontaneous abortion and birth defects, respectively. Cox models were calculated for two periods of follow-up: vaccination through 1) 21 6/7 weeks' gestation and 2) 28 days postvaccination.

Results: Of 26,264 pregnancies, 21,736 (82.8%) were among women who received a pH1N1-containing vaccine in the prior influenza season and 4,528 (17.2%) were among women who received the non–pH1N1-containing vaccine in the prior influenza season; among 23,121 infants, 19,365 (83.8%) and 3,756 (16.2%) had mothers exposed and unexposed to pH1N1-containing vaccine in the prior influenza season, respectively. The adjusted hazard ratio (aHR) for spontaneous abortion approximated 1.0 across the complete follow-up period [95% confidence interval (CI): 0.89–1.13] and was slightly elevated when censored at 28 days postvaccination, though the CI was imprecise (aHR: 1.19, 95% CI: 0.97–1.46). No associations with birth defects were observed.

Conclusion: This work lends additional support for the safety of vaccination against pH1N1 in pregnancy, regardless of the vaccine received in the prior influenza season.

Preconception migraines and spontaneous abortion: a prospective cohort study Holly Crowe Amelia Wesselink Lauren Wise Elizabeth Hatch

Migraines affect nearly a quarter of reproductive-aged women. Previous research has shown a modest increase in risk of spontaneous abortion (SAB) among migraineurs. We used data from a preconception cohort study in the U.S and Canada to examine the association between physician-diagnosed migraines and SAB risk. From 2013-2020 we enrolled 13,043 women; 6,325 conceived during 12 cycles of follow up and 1,208 (19%) reported SAB. At baseline, we collected data on migraine history, frequency, and medication use. Pregnancy losses <20 weeks of gestation were reported on bimonthly follow-up and early (~8 weeks) and late pregnancy (~32 weeks) questionnaires. We used Cox proportional hazards models, with gestational weeks as the time scale, to estimate hazard ratios (HR) and 95% CIs, adjusting for demographics, lifestyle, and reproductive history. Overall, 1332 (21%) of women reported a history of migraines, 45% of whom took migraine medication in the past 4 weeks. Of the 605 women taking medication, 91% took medication only when experiencing symptoms, most commonly over-the-counter pain relievers (75%). While 42% of migraineurs reported no migraines in the past 4 weeks, 29% reported 1 migraine, 14% reported 2 migraines, and 16% reported ≥3 migraines. Overall, a history of migraines was not appreciably associated with risk of SAB (HR=1.04, CI: 0.91-1.20). Among migraineurs, recent use of migraine medication showed little association with SAB (HR=1.08, CI: 0.84-1.38). There was also little association between migraine frequency and SAB: HRs for 1, 2, or ≥3 vs. 0 migraines in the past 4 weeks were 0.88 (CI: 0.65-1.19), 0.98 (CI: 0.65-1.40), and 0.94 (CI: 0.65-1.36), respectively. Our findings provide little support for the hypothesis that a history of migraine or use of migraine medications are associated with SAB risk.

Fetal mortality in the context of the COVID-19 pandemic Andrew Williams

Background: The COVID-19 pandemic was declared a public health emergency in the United States in February 2020. Data suggest a pronounced decrease in the birth rate in in Fall 2020, 36 to 40 weeks after February. What can we learn about the health of pregnancies during the pandemic? Fetal Mortality Rate (FMR) [(fetal deaths/(fetal deaths + live births))x1000] in the U.S. has been approximately 6.0 for the past 20 years. Changes to monthly FMR may provide insight into population-level prenatal health during the pandemic.

Methods: Publicly available monthly provisional data on live births and fetal deaths (pregnancy loss ≥20 weeks gestation) were obtained for Florida, Oregon, and North Carolina for 2019-2020. FMR was calculated by month and percent change in FMR was calculated by month for 2019-2020. Results are presented by state. Data are current on January 28, 2021.

Results: In Florida, FMR was 6.0, 6.2, 5.9, and 4.7 in September, October, November, and December 2020, respectively. Compared to the same months in 2019, Florida's 2020 FMR declined 8.3 percent in September, 10.3 percent in October, 21.5 percent in November, and 27.4 percent in December. Similarly, North Carolina had 10.6 percent reduction in FMR in September 2020 compared to September 2019, and approximately 40 percent reductions in FMR in October and November 2020 compared to 2019. In contrast, Oregon's FMR increased approximately 5.1 percent in August 2020 compared to 2019, and only decreased by 1.1 percent in September 2020 compared to 2019.

Discussion: Lower FMR in Fall 2020 compared to Fall 2019 may suggest pregnancies conceived after onset of the COVID-19 pandemic are healthier compared to prior years. However, this differs by state. Oregon is less diverse (75% white) than Florida (53% white) and North Carolina (62.7% white). Median income is higher in Oregon ($67,058) than Florida ($59,227) or North Carolina ($57,341), suggesting the pandemic may differentially effect pregnancy by demographics.

Interpregnancy interval and adverse pregnancy outcomes among pregnancies following miscarriages Gizachew Tessema Siri Haberg Gavin Pereira Maria Magnus

The World Health Organization recommend woman to wait at least 6 months before attempting a subsequent pregnancy after a miscarriage or pregnancy termination. However, the evidence that led to the development of this guideline has been critised for not making distinction between miscarriages and induced abortions pregnancies, which may cause heterogeneity in the study group. The objective of our study was to investigate the risk of adverse pregnancy outcomes after short IPI among women with previous miscarriages using population based registries – Birth Register, the General Practitioner and Patient Register- that contain comprehensive information of all recognised pregnancies in Norway. We identified 50,347 births that with prior miscarriages between 2008 and 2016 in Norway. We investigated the associations between IPIs and four pregnancy outcomes – preterm birth, small-for-gestational age (SGA), large-for-gestational age (LGA), and pre-eclampsia. Generalised linear models were used to estimate adjusted relative risks (aRR) and 95% confidence interval (CI).We adjusted for maternal age, parity, and birth year, smoking during pregnancy and pre-pregnancy body-mass index. In the study, the median IPI after a miscarriage was 4 months (IQR=2-9). After miscarriage, 61% (n=30,828) were conceived within six months and 20% (n=10,266) were between 6-12 months. There were 6% PTB, 9.5% SGA births, 10.3% LGA births and 3.2% pre-eclampsia. In the adjusted analysis, compared to births with an IPI of 6-12 months for births after miscarriages, except for SGA (aRR = 0.88, 95 % CI: 0.82, 0.94), there was no evidence of risk of short IPI on pregnancy complications included in the study. We found no association between IPI and all of the included outcomes. Our study indicated that there were less or no increased risk of pregnancy complications after short IPIs following miscarriages. Whenever women decide to get pregnant shortly after miscarriages, they should not necessarily be discouraged to do so.

Live Birth Bias in Estimating Effects of Time-Varying Prenatal Exposures: A Simulation Study Yuyuan Lin Tram Nguyen Onyebuchi Arah Zeyan Liew

Background: In perinatal and pediatric epidemiology, prenatal exposure effect studies are subject to live-birth-bias (LBB) when the analyzed sample is restricted to live births. This bias structure was previously proposed as a form of collider bias in which conditioning on live birth status induces a non-causal association between exposure and outcome. In this study, we explored the impact of LBB on the estimation of the effects of time-varying prenatal exposures on offspring health outcome.
Method: We use directed acyclic graphs to illustrate the structural relationships between trimester-specific exposures, covariates, pregnancy losses, and child health outcome. We then used Monte Carlo simulations to investigate multiple hypothetical scenarios that assumed trimester-specific prenatal exposures affect pregnancy losses but do not cause the child health outcome. We estimated the impact of LBB in these scenarios when estimating the effects of trimester-specific exposures on child health.
Results: When the trimester-specific exposure variables are positively correlated because of a common exposure source and pregnancy losses can be induced by the exposures throughout gestation, the magnitude of LBB tends to increase. However, the bias direction and magnitude change when the trimester-specific exposures are negatively correlated e.g. a seasonal exposure if it occurs in early gestation the likelihood for an exposure in late pregnancy is lower. The overall direction and magnitude of bias also vary when exposures affect subsequent exposures later in pregnancy.
Conclusion: The magnitude and direction of LBB can be uncertain when the bias structure is complex and time-varying, making heuristics misleading here. There is need for the development of analytic methods that can estimate causally interpretable quantities in the presence LBB following pregnancy losses in complex time-varying exposure effects, mediation and confounding settings.

Is prenatal diet associated with the composition of the vaginal microbiome? Emma Rosen
Anna Maria Siega-Riz Chantel Martin Kim Ludwig Patricia Basta Gregory Buck Myrna Serrano
Jennifer Fetweiss Michael Wu Shan Sun Anthony Fodor Stephanie Engel

Background: The vaginal microbiome is a constellation of bacterial species whose balance helps
maintain a woman's health. Shifts away from a *Lactobacillus*-dominated microbiome have been
associated with adverse pregnancy outcomes such as preterm birth and miscarriage, though high
levels of *Lactobacillus iners* may indicate a transition to an unhealthy microbiome. The effects of diet
on vaginal microbiota and differences by race remain largely unexamined, though it represents an
important and modifiable influence on vaginal health.

Methods: For this study, we leveraged a racially diverse prenatal cohort of North Carolina women
enrolled between 1995-2001. Women completed food frequency questionnaires about diet over the
previous 3 months and foods were categorized into subgroups: fruits, vegetables, nuts/seeds, whole
grains, low-fat dairy, sweetened beverages, and red meat. Vaginal swabs collected in mid-pregnancy
were sequenced using 16S metagenomics. We divided women into 3 groups based on species
predominance: *Lactobacillus iners, Lactobacillus* miscellaneous, and Bacterial Vaginosis (BV)-
associated bacteria. Adjusted Poisson models with robust variance estimators were run to assess the
risk of being in a specific vagitype compared to the referent. Models were stratified on maternal
race (black/white).

Results: In this study of 634 women, higher consumption of dairy was associated with increased
likelihood of membership in the *L. crispatus* group compared to the *L. iners* group in a dose-
dependent manner (RR for quartile 4 vs. 1: 2.01 [95% CI: 1.36, 2.95]). Results were stronger among
black women compared to white women (3.04 [1.42, 6.53] vs. 1.62 [1.06, 2.49]). There were no
detected associations between any other food groups or risk of membership in the BV-group.

Conclusions: Higher consumption of low-fat dairy was associated with increased likelihood of
vagitype dominated by *L. crispatus*. These results should be cautiously interpreted given the cross-
sectional design

Iron and folic acid and multiple micronutrient supplementation strategies during pregnancy and adverse birth outcomes in Botswana Ellen Caniglia Rebecca Zash Sonja Swanson Emily Smith Christopher Sudfeld Julia Finkelstein Modiegi Diseko Gloria Mayondi Mompati Mmalane Joseph Makhema Shahin Lockman Roger Shapiro

Background: Iron and folic acid supplementation (IFA) and multiple micronutrient supplementation (MMS) that includes IFA may reduce the high risk of adverse birth outcomes in Sub-Saharan Africa. However, there is limited evidence from clinical settings on the effectiveness of supplementation in women with HIV and in those at increased risk for malnutrition.

Methods: The Tsepamo Study captured data at up to 18 large delivery sites in Botswana from August 2014-November 2020. We compared 4 program-driven antenatal supplementation strategies among women who presented for care prior to 24 weeks gestation: no supplementation, iron alone, IFA, and MMS. We calculated risk differences (RDs) for any adverse birth outcome (stillbirth, preterm delivery [PTD], small-for-gestational-age [SGA] or neonatal death) and any severe birth outcome (stillbirth, very PTD, very SGA, or neonatal death). We adjusted for confounding by trimester of presentation to care, maternal HIV status, early pregnancy weight and hemoglobin (Hb), age, urban residence, year, and socioeconomic position via IP weighting. RDs were calculated separately by trimester of presentation to care, maternal HIV status, weight, Hb, age, and urban residence.

Results: 136207 women presented to care (23% with HIV) and received either no supplementation (6.1%), iron only (37.3%), IFA (23.2%), or MMS (33.4%). Compared to iron only, RDs (95% CIs) for any adverse birth outcome were 6.0% (4.7%, 7.3%) for no supplementation, -2.5% (-3.1%, -1.8%) for IFA, and -2.0% (-2.6%, -1.3%) for MMS (overall risk 28.9%). RDs were similar by trimester of presentation to care but larger in magnitude among women with HIV (-3.0% [-4.5%, -1.6%] for IFA and -3.3% [-4.7%, -1.8%] for MMS), women <50kg, women with anemia (Hb <11 g/dL), and women <20 or ³35 years. Findings were similar for any severe birth outcome.

Conclusions: Antenatal IFA or MMS may improve birth outcomes compared with iron supplementation alone, particularly among women with HIV.

Preconception caffeine metabolites and fecundability among women attempting to conceive Alexandra Purdue-Smithe Keewan Kim Stefanie Hinkle Karen Schliep Neil Perkins Lindsey Sjaarda Robert Silver Enrique Schisterman Mumford Sunni

Caffeine is the most frequently used psychoactive substance in the United States and more than 90% of reproductive-age women report some level of intake daily. Women are often counseled to limit caffeine intake while attempting pregnancy despite conflicting evidence on associations between caffeine and fecundability. Importantly, prior studies examining caffeine intake and fecundability measured exposure via self-report only, which is subject to measurement error and does not account for factors that influence caffeine metabolism. We therefore evaluated associations of preconception serum caffeine metabolites (i.e., caffeine, paraxanthine, and theobromine) and self-reported intake of caffeinated beverages, with fecundability among 1,228 women aged 18-40 years who were attempting to conceive in the EAGeR trial. Using Cox proportional hazards models, we estimated fecundability odds ratios (FOR) and 95% confidence intervals (CI) according to each metabolite. At baseline, 84%, 73%, and 90% of women had detectable levels of serum caffeine, paraxanthine, and theobromine, respectively. 797 women became pregnant during 6 months of preconception follow-up. After adjusting for age, BMI, smoking, and other potential confounders, neither serum caffeine (Tertile 3 vs 1 FOR=0.87; 95% CI=0.71-1.08), paraxanthine (Tertile 3 vs 1 FOR=0.92; 95% CI=0.75-1.14), nor theobromine (Tertile 3 vs 1 FOR=1.15; 95% CI=0.95-1.40) were associated with fecundability. Intakes of total caffeinated beverages (>2 vs 0 servings/d FOR=0.94; 95% CI=0.73-1.21), coffee (>2 vs 0 servings/d FOR=0.87; 95% CI=0.58-1.30), soda (>2 vs 0 servings/d FOR=0.93; 95% CI=0.71-1.21), and tea (>1 vs 0 servings/d FOR=1.03; 95% CI=0.49-2.20), were also not associated with fecundability. Our findings suggest that preconception caffeine exposure, as measured by both serum metabolites and self-report, do not appear to play an important role in conception.

Fertility and fecundity

Biomarkers of iron status and reproductive outcomes Kerry Flannagan Lindsey Sjaarda Elizabeth DeVilbiss Sonia Grandi Robert Silver Enrique Schisterman Sunni Mumford

Iron deficiency (ID) and ID anemia are major health concerns among women of reproductive age, affecting up to 15% of these women in the US. Maternal ID is linked to maternal and infant death and pregnancy loss. However, most studies have focused on ID during pregnancy rather than before conception, and few have assessed iron status in relation to fertility. Therefore, we examined associations of biomarkers of preconception iron status with fecundability and pregnancy outcomes in a well-characterized preconception cohort.

We followed 1228 healthy women for up to six menstrual cycles while they were attempting conception, as part of a trial of low-dose aspirin. We measured assessed three biomarkers of iron status: serum iron, ferritin, and soluble transferrin receptor (sTFR). We estimated fecundability odds ratios (FOR) and 95% confidence intervals (CI) using Cox proportional hazards models, and risk ratios (RR) of live birth and pregnancy loss using log binomial regression models. Models were adjusted for age, body mass index, race, physical activity, season of blood draw, treatment assignment in the original trial, vitamin use, and number of prior losses and live births.

Median serum concentrations of iron, ferritin, and sTFR were 78 ug/dL, 43 ug/L, and 2.7 mg/L, respectively; 9% of women had ID (defined as ferritin <15 ug/L). Higher serum iron was associated with higher fecundability, but this relationship was attenuated after adjustment (aFOR per 1 SD: 1.06; 95% CI: 0.98, 1.16). Higher serum ferritin was associated with higher risk of pregnancy loss, but this was again attenuated after adjustment (aRR per 1 SD: 1.09; 95% CI: 0.99, 1.21). ID was imprecisely associated with lower fecundability (aFOR: 0.78; 95% CI: 0.57, 1.08).

We did not find strong evidence for associations between iron status and reproductive outcomes in a relatively healthy population of women, although further studies should investigate whether ID is related to reduced fertility.

Folate intake and ovarian reserve among women attending a fertility center Mumta Kadir Robert Hood Lidia Minguez-Alarcon Ana Belen Maldonado-Carceles Jennifer Ford Irene Souter Jorge Chavarro Audrey Gaskins

Background: Higher folate intake has been linked to shorter time to pregnancy and greater success of infertility treatments; however, the mechanisms underlying the beneficial effects of folate on female fertility have been less studied. Antral follicle count (AFC) is a well-accepted measure of ovarian reserve associated with female fertility potential and reproductive aging. Factors such as diet may affect ovarian reserve, although the research is sparse.

Methods: Our analysis included 552 women attending the Massachusetts General Hospital Fertility Center (2007-2019) who participated in the Environment and Reproductive Health Study. We measured folate intake using a validated food frequency questionnaire and AFC using transvaginal ultrasonography performed on the third day of an unstimulated menstrual cycle or on the third day of a progesterone withdrawal bleed. Multivariable Poisson regression models with robust standard errors were used to estimate the association of folate intake (total, supplemental, and food intakes) with AFC adjusting for calorie intake, age, BMI, physical activity, education, smoking status, year, and vitamin B12, iron, and vitamin D intake.

Results: Among the 552 women (median age 35.0 years, median folate intake 1,003 micrograms/day), higher intakes of total, supplemental, and food folate intake were unrelated to AFC. The multivariable adjusted percent difference in AFC (95% confidence interval) for women in the fourth quartile compared to the first quartile was 6.5% (-6.8, 21.7) for total folate intake (p-trend=0.48), 6.6% (-5.6, 20.5) for supplemental folate intake (p-trend=0.32), and 5.2% (-4.8, 16.2) for food folate intake (p-trend=0.33).

Conclusions: Folate intake was unrelated to AFC among women presenting to a fertility center. Given the high average intake of folate in our cohort, particularly from supplements, our findings should be further investigated in more diverse populations.

Violence or abuse victimization

Association of Adverse Childhood Experiences and Household Food Insecurity in Washington State Ashenafi Cherkos Jessica Marcinkevage Susmitha Nambuthiri Daniel Enquobahrie

Background: Adverse childhood experiences (ACEs) can potentially cause adulthood financial hardships and food insecurity by affecting neurological, physical, and behavioral coping strategies, which result in poor school and job performance. We assessed the association between ACEs and adult household food insecurity in Washington State. Effect modification by sex or race/ethnicity was also examined.

Methods: This study was a cross-sectional study among 14,769 adult Washington State residents who had landline and cell phones. Data source was the 2011 Behavioral Risk Factor Surveillance System conducted by the department of health (DOH) and CDC. Sampling weight provided by the Washington State DOH was used to correct for systematic differences in probability sampling. Multivariable logistic regression (odds ratios and related 95% confidence intervals [CI]) was used to assess the association between ACEs (including abuse, neglect, and household dysfunction) and household food insecurity. Effect modification by ethnicity/race and sex of respondents were tested using stratified analyses and the Breslow-Day test for homogeneity.

Result: About 14.6% of the population had household food insecurity, and approximately 60.65% had at least one of the 11 ACEs where 40.35% head of the households had 1-3 ACEs, and 20.29% had four or more ACEs. Individuals who had 1-3 ACEs and ≥ 4 ACES had had 2.57-fold (95% CI: 2.00, 3.29) and 5.21-fold (95% CI: 4.00, 6.78) higher odds of household food insecurity compared to individuals who didn't have ACEs. Estimates for non-Hispanic Whites and Blacks who had ≥ 4ACEs were OR=6.29 (95% CI: (4.57, 8.67) and OR=17.29 (95% CI: 3.51, 85.25), respectively (p-value for interaction <0.001). Estimates for males and females who had ≥ 4ACEs were OR=6.38 (95% CI: 4.14, 9.83) and OR=4.42 (95% CI: 3.19, 6.13), respectively (p-value for interactions <0.001).

Conclusion: ACEs are associated with subsequent adult household food insecurity. This association is stronger among non-Hispanic Blacks and males.